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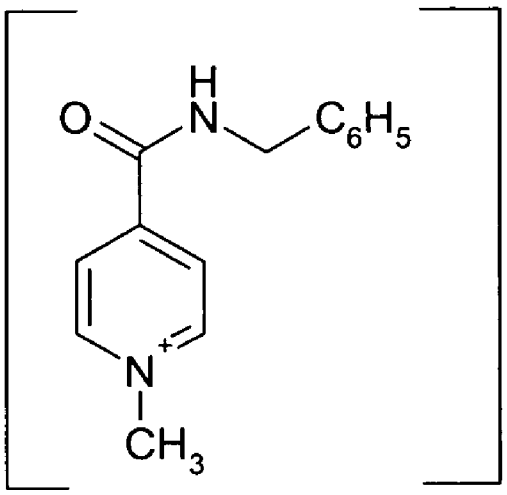
(54) Title: α-CRYSTALLINE FORM OF CARBABENZPYRIDE



(I)

(57) Abstract: The present invention relates to a new crystalline form of carbabenzpyride of formula (I) and the process for its preparation.

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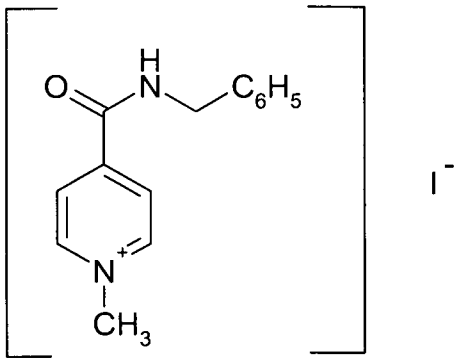
α-Crystalline Form of Carbabenzpyride

Field of the Invention

The present invention relates to a new crystalline form of carbabenzpyride and to a method for its preparation. Further, the invention relates to a pharmaceutical composition comprising the new crystalline form, i.e., the α-crystalline form of carbabenzpyride. Finally, the invention relates to the use of the α-crystalline form of carbabenzpyride for the preparation of a medicinal product for the treatment or prevention of viral infections.

Carbabenzpyride has the formula (I):



and is also known as Amizon.

Background of the Invention

The pharmaceutically acceptable salts of carbabenzpyride have valuable pharmacologically properties.

Their principal property is the treatment and prevention of viral infections more specifically those caused by influenza A viruses.

For the pharmaceutical use it is of major interest to have a highly pure substance. In addition it is advisable to use a stable, robust and scalable industrial process resulting in a very consistent quality of the product which should be suitable for pharmaceutical formulations.

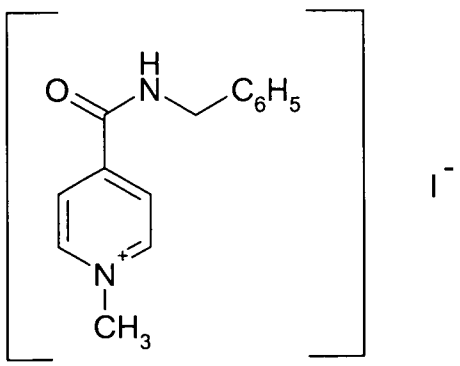
Description of the Prior Art

SU 583612 (1975) describes the synthesis of carbabenzpyride as a use for pharmaceutical purposes but there is no sufficient description on obtaining the drug substance in a reproducible manner.

Hence, there was a need for a route of synthesis which provides a highly pure material complying with the requirements for a pharmaceutical use.

Summary of the Invention

The present invention relates to α-crystalline form of carbabenzpyride of formula (I):



exhibiting essentially the following powder X-ray diffraction data, measured using a diffractometer (copper anticathode) and expressed in terms of inter-planar distance d, Bragg's angle 2 theta, and relative intensity (expressed as a percentage with respect to the most intense ray) as shown in the table below listing the following reflex positions of high and medium intensity:

No	Angle 2 theta (°)	Inter-planar distance d (Å)	Relative Intensity
1	2.3925	36.92687	5.23
2	10.2105	8.66366	5.95
3	11.3179	7.81828	5.70
4	12.3706	7.15527	10.86
5	13.9617	6.34318	3.67
6	16.2837	5.44354	6.62
7	17.4171	5.09177	8.45
8	17.6238	5.03251	66.93
9	19.8858	4.46489	100.00
10	20.3088	4.37284	7.36

This new α-crystalline form of carbabenzpyride is obtainable by the process according to the present invention comprising the following steps:

(i) condensation of isonicotinic acid with benzylamine at elevated temperatures,

(ii) crystallisation and isolation of the condensation product obtained in step (i) above,

(iii) reaction of the crystalline product obtained in step (ii) above with methyl iodide and

(iv) re-crystallisation of the crude product obtained in step (iii) from aqueous alcohol.

Brief Description of the Drawings

Fig. 1 represents a powder X-ray diffraction diagram of the α-crystalline form of carbabenzpyride according to the present invention.

Fig. 2 represents a differential scanning calorimetry curve of the α-form.

Fig. 3 represents an infrared spectrum of the α-form.

Fig. 4 represents a view of a molecule of carbabenzpyride from the crystal structure showing the numbering scheme employed. Anisotropoic atomic displacement ellipsoids for the non-hydrogen atoms are shown at the 50% probability level. Hydrogen atoms are displaced with an arbitrarily small radius.

Fig. 5 shows a view of the molecular packing for the α-crystalline form of carbabenzpyride obtained from the crystal structure. (Final cell constants: a = 9.27390(10)Å, b = 10.7187(2)Å, c = 14.2161(2)Å, α = 90°, β = 90°, γ = 90°, volume = 1413.14(4)Å^3. Final residuals: R1 [for 4152 I> 4σ(I)] = 1.87 % wR2 [for all 4309 data] = 4.40 %).

Fig. 6 schematically shows a preferred embodiment of the process for the preparation of the α-crystalline form of carbabenzpyride according to the present invention.

Detailed Description of the Invention

According to the process of the present invention a new crystalline form of carbabenzpyride (Amizon) can be obtained which is highly pure. As shown in the experimental section hereinafter, the new crystalline form according to the present invention has a purity of at least 99.5% and preferably of at least 99.9% as determined by HPLC.

This new crystalline form of carbabenzpyride, i.e. the α-form, is characterised by its X-ray spectrum as defined in claim 1 listing reflex positions of high and

medium intensity. For the sake of completeness, Table 1 below also includes the remaining peaks as shown in the X-ray spectrum according to Fig. 1.

Table 1

No	Angle 2 theta (°)	Inter-planar distance d (Å)	Relative Intensity
1	2.3925	36.92687	5.23
2	10.2105	8.66366	5.95
3	11.3179	7.81828	5.70
4	12.3706	7.15527	10.86
5	13.9617	6.34318	3.67
6	16.2837	5.44354	6.62
7	17.4171	5.09177	8.45
8	17.6238	5.03251	66.93
9	19.8858	4.46489	100.00
10	20.3088	4.37284	7.36
11	20.5068	4.33105	5.19
12	20.7785	4.27505	7.36
13	21.6883	4.09772	5.43
14	22.4553	3.95946	4.96
15	22.6282	3.92959	14.19
16	25.1931	3.53505	4.53
17	25.9608	3.43222	3.74
18	26.6025	3.35087	8.50
19	26.7790	3.32918	8.32
20	27.5071	3.24270	1.17
21	27.9630	3.19085	34.11
22	28.0126	3.18531	21.03
23	29.1890	3.05956	42.84
24	30.6379	2.91809	7.69
25	30.9488	2.88949	4.47
26	31.4818	2.84177	11.23
27	31.9139	2.80427	4.62
28	32.4529	2.75892	10.21
29	32.8634	2.72539	5.97
30	33.4828	2.67638	8.52
31	33.7418	2.65642	2.46

32	34.3000	2.61446	1.16
33	34.8705	2.57298	5.13
34	35.2361	2.54712	12.94
35	35.5986	2.52201	1.36
36	36.5494	2.45855	9.04
37	36.7967	2.44260	1.16
38	37.7826	2.38110	1.78

The α-form of carbabenzpyride is further characterised by its DSC curve as shown in Fig. 2 (this figure also includes the measuring conditions). The α-crystalline form exhibits an endothermic maximum in its DSC curve in the range of 187 to 199°C and, in particular, 189.0 to 191.0°C.

In addition, the α-form of carbabenzpyride is characterised by its IR-spectrum as shown in Fig. 3 exhibiting characteristic peaks listed in the following Table 2.

Table 2

Wave number [cm^{-1}]	vibration
3236	N–H
3040	C–H
2934	C–H
1622	C=O
1600 / 1502	C=C
760 / 704	C–H

As mentioned above, the α-crystalline form of carbabenzpyride has a purity of at least 99.5% and preferably of at least 99.9% as determined by HPLC.

Such a high purity could not be achieved in the prior art. In particular, it is possible by using the process according to the present invention to considerably reduce the content of the known genotoxic substance methyl iodide in the final product.

As mentioned above, the process according to the present invention comprises four basic steps, namely

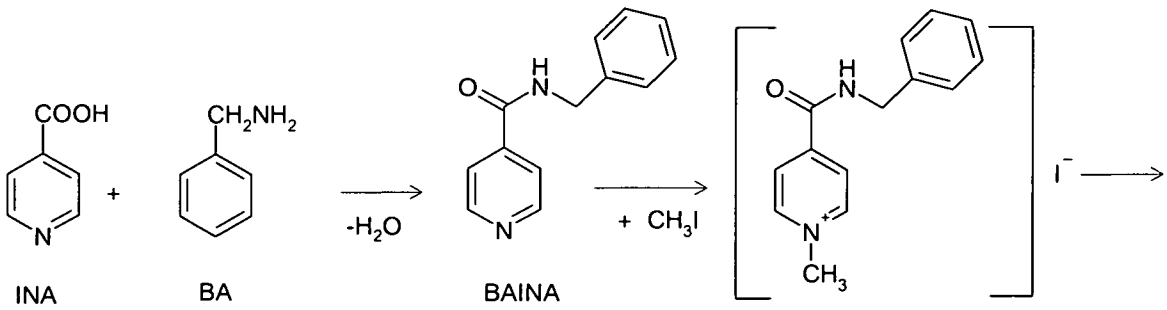
(i) condensation of isonicotinic acid with benzylamine at elevated temperatures,

(ii) crystallisation and isolation of the condensation product obtained in step (i) above,

(iii) reaction of the crystalline product obtained in step (ii) above with methyl iodide and

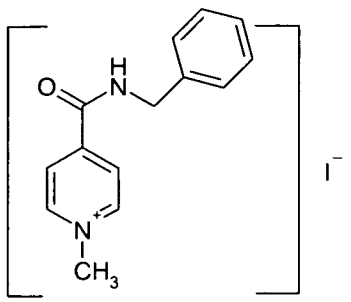
(iv) re-crystallisation of the crude product obtained in step (iii) from aqueous alcohol.

This process is exemplified in the scheme below:



INA BA BAINA

Carbabenzpyride crude



Carbabenzpyride purified

wherein INA denotes isonicotinic acid, wherein BA denotes benzylamine and wherein BAINA denotes benzylamide isonicotinic acid.

The condensation of isonicotinic acid with benzylamine is carried out at elevated temperatures, i.e., at temperatures in the range of 160 to 220°C.

The most preferred temperature is in the range of 200 to 210°C.

The mole ratio of isonicotinic acid and benzylamine is in the range of 1: (1.1 - 1.25).

The most preferred ratio is about 1:1.23.

In the reaction of isonicotinic acid and benzylamine, water is generated which is removed by distillation with benzylamine excess.

The condensation product, namely benzylamide isonicotinic acid (BAINA) is isolated from the reaction mixture by adding a solvent selected from the group consisting of ethyl acetate, acetonitrile and isopropanol.

The most preferred solvent is ethyl acetate.

According to a preferred embodiment of the process according to the present invention the BAINA-solution comprising the above solvent, and preferably ethyl acetate, is treated with activated carbon.

The activated carbon is used in the amount of 0.5% to 1.5% of the volume of solvent, preferably about 1%.

The treating time with activated carbon is 20 to 40 min, preferably about 30 min.

The treating temperature with activated carbon is 65 to 75°C, preferably about 70°C.

Next, the activated carbon or charcoal is filtrated off and the filtrate is spontaneously cooled to a temperature in the range of 25 to 35°C, preferably about 30°C.

Spontaneous cooling means that the solution is simply left standing until it reaches the desired temperature without any additional measures or means been taken to accelerate the cooling process.

After this spontaneous cooling to the aforementioned temperature, a cooling agent is used to lower the temperature to about 0 to 5°C.

Following stirring, the obtained crude product is collected.

It is in the form of a paste which is treated with water. The mass ratio of BAINA paste and water is in the range1:2 to 1:3, preferably about 1:2.

This aqueous system is heated to a temperature in the range of 30 to 40°C, and preferably 32 to 35°C. The stirring time is in the range of 1.5 to 2.5 hours, and preferably about 2 hours.

After filtration, the precipitate is rinsed two times with cold water and subsequently dried, for example, at 25°C for 18 hours.

The above mentioned process steps result in a BAINA product which is a homogeneous crystalline powder having a yellow to yellow-green colour and a content of impurities of not more than 0.5%.

This high degree of purity makes it possible to accurately calculate the amount of methyl iodide for use in the third step of the process according to the present invention.

Generally, the quaternization reaction of BAINA and methyl iodide is carried out using an excess of methyl iodide in a range of 5 to 15% and preferably 8 to 12%.

The most preferred excess of methyl iodide is about 10%.

According to a preferred embodiment of the process according to the present invention the quaternisation reaction is carried out in an aqueous alcohol solution. The content of water in the alcohol is in general in the range of 5 to 15% and preferably 8 to 12%.

Most preferably the water content is about 10% and the alcohol is ethanol.

The crude product of the quaternisation reaction can be isolated by filtration and is preferably washed with an aqueous alcohol solution. Most preferably 96% ethanol is used.

The pure α-form of carbabenzpyride according to the present invention is obtained by means of re-crystallisation of the crude product obtained in step (iii) from aqueous ethanol.

In general, the amount of water present in the ethanol ranges from 5 to 15% and preferably 7 to 13%.

Most preferably 90% ethanol is used in step (iv).

According to a preferred embodiment of the claimed process the ratio of solvent to crude product used in step (iv) is in the range of 1:2 to 1:4.

The most preferred ratio is about 1:3.

After dissolving the crude product in the solvent, preferably in 90% ethanol, the solution is spontaneously (i.e. without a cooling agent) cooled from the reflux temperature of the solvent to a temperature in the range of 30 to 40°C.

Most preferably the hot solution is cooled spontaneously (i.e. without a cooling agent) to a temperature of about 30°C.

Subsequently, the temperature is further lowered to 10 to 15°C.

After stirring for a period of time in the range of 1 to 3 hours, the pure product can be filtered off and rinsed, for example, two times with cold 96% alcohol.

According to a preferred embodiment of the re-crystallisation process, activated charcoal is added to the solution of the crude product.

The invention also relates to pharmaceutical preparations containing as active ingredient the α-crystalline form of formula (I) together with one or more pharmaceutically acceptable, inert excipients. The formulation may be used as oral, nasal, rectal or parenteral administration in form of tablets, coated tablets, gelatin capsules, lozenges, drinkable solutions, nasal sprays, injectable solutions, suppositories, inhalable solution or powder, etc.

The useful dosage can be varied from 125 mg up to 2500 mg per day either in one or up to 4 individual doses.

The following examples illustrate the invention but do not limit it in any way.

Experimental part

Preparation of BAINA

Example 1.

A mixture of 91.4 g (0.7424 M) of isonicotinic acid and 97.9 g (0.9136 M) of benzylamine (1 : 1.23) is heated to a temperature of 180°C using a reflux condenser and stirred for 1 h. The temperature of the reaction is reduced to 160°C herewith. The reaction mass is then heated to a temperature of 210°C for 2 h using a direct condenser to distil off hydrous benzylamine. The reaction is heated to a temperature of 220°C for 1.5 h using a direct condenser to distil off excess benzylamine. The content of the reactor is cooled to a temperature of 100°C, and 240 ml of ethyl acetate are added, the reaction is further stirred for 20 min, and 2.4 g of charcoal are added, and the reaction is stirred at a temperature of 70 – 75° C for 30 min, filtrated from the charcoal, and the obtained solution is spontaneously cooled to 30°C, then with a cooling agent to 0 –+5°C, stirred for 1 h and filtrated.

The BAINA paste is dissolved in 180 ml of water, heated to a temperature of 32-35°C and stirred for 2 h.

The reaction is filtrated, and the precipitate in the filter is rinsed 2 times in 50 ml of cooled water. The product is dried at 25°C for 18 h.

Quantity of BAINA: 136.5 g (86.6 %).

Analytic control:

Assay: 101.44 %

Content of related substances:

BA, %	INA, %	Any impurity (total), %
0.1	absent	0.1

Example 2.

This Example differs from Example 1 in that :

1. A mixture of 294 g (2.39 M) of isonicotinic acid and 316.0 g (2.95 M) of benzylamine is heated.

2. 772 ml of ethyl acetate are added.

3. The BAINA paste is dissolved in 500 ml of water.

Quantity of BAINA: 413.6 g (81.6 %).

Example 3.

This Example differs from Example 1 in that :

1. A mixture of 45.7 g (0.3715 M) of isonicotinic acid and 49.1 g (0.4589 M) of benzylamine is heated.

2. 120 ml of ethyl acetate are added.

3. The BAINA paste is dissolved in 80 ml of water.

Quantity of BAINA: 65.1 g (82.6 %).

Preparation of crude carbabenzpyride

Example 4.

106.1 g (0.5 M) of BAINA are placed in a reactor fitted with a stirrer, reflux condenser and a dropping funnel, 230 ml of 90 % alcohol are added, and the reaction is heated to 38 – 40°C and stirred for 30 min upon obtaining a solution. 2.3 g of charcoal are added, and the reaction is heated at a temperature of 60 – 70°C for 30 min, after which time the reaction is filtrated and the charcoal on the filter is rinsed 2 times with 5 ml of 90% alcohol. The obtained solution is heated to a temperature of 40 – 41°C, and 78.1 g (0,55 M) of methyl iodide were added

dropwise. The reaction was stirred at a temperature of 40 – 41°C for 1 h, heated to boiling and boiled for 1 h. The reaction is spontaneously cooled to a temperature of 40°C, then to a temperature of 10-15°C in a water bath, and stirred for 1.5 h at this temperature (without seed crystals).The reaction is filtrated and the precipitate is rinsed on the filter 2 times with 55 ml of cooled 96% alcohol.

The product is dried at 25° C for 18 h and weighed.

Quantity of crude carbabenzpyride: 164.6 g (92.9 %)

Analytic control:

Assay: 102.05 %

Content of related substances:

BA, %	BAINA, %	INA, %	Any other impurity, %
absent	0.3	absent	0.05

Example 5.

This Example differs from Example 4 in that for the reaction of quaternization 398 g of BAINA (1.88 M), 868 ml of 90 % alcohol and 292.0 g (2.06 M) of methyl iodide are used.

Quantity of crude carbabenzpyride paste: 586.8 g

Example 6.

This Example differs from Example 4 that for reaction of quaternization 30 g (0.14 M) of BAINA, 63.5 ml of 90 % alcohol, 21.42 g (0.15 M) of methyl iodide are used.

Quantity of crude carbabenzpyride paste: 42.9 g

Preparation of the pure α-crystalline form of carbabenzpyride

Example 7.

580 g of crude carbabenzpyride are dissolved in 1744 ml of 90 % alcohol (1 : 3) (m/V), and 17 g of activated charcoal are added. The reaction is heated to boiling temperature, stirred at boiling for 30 min and filtrated. The obtained solution is spontaneously cooled to a temperature of 30°C, then to a temperature of 10-15°C in a cooling water bath, then stirred for 1 h at this temperature (without seed crystals), filtrated to obtain a solution and the filter is rinsed 2 times with 105 ml of cooled 96 % alcohol.

The product is dried at 25° C for 18 h and weighed.

Quantity of purified carbabenzpyride: 502.8 g (62.5 % based on isonicotinic acid).

Analytic control:

Assay: 100.97 %

Content of related substances:

BA, %	BAINA, %	Total impurity, %
absent	0.01	0.01

Example 8

This Example differs from Example 7 in that for the re-crystallisation reaction 30 g of crude carbabenzpyride, 90 ml of 90% alcohol, and 0.1 g of activated charcoal are used.

Quantity of purified carbabenzpyride: 25.6 g (60.3% based on isonicotinic acid).

Analytic control:

Assay: 100.58 %

Content of related substances:

BA, %	BAINA, %	Total impurity, %
0.005	absent	0.005

Example 9

This Example differs from Example 7 in that for the re-crystallisation, 500 g of carbabenzpyride crude, 1500 ml of 90 % alcohol, 15 g of activated charcoal is used.

Quantity of purified carbabenzpyride: 425.79 g (75.4% based on isonicotinic acid).

Analytic control:

Assay: 99.48%

Content of related substances:

BA, %	BAINA, %	Total impurity, %
0.01	0.015	0.03

Example 10.

50 g of crude carbabenzpyride are dissolved in 150 ml of 90% alcohol (1 : 3) (m/V), 1.5 g of activated charcoal are added and the reaction is heated to boiling temperature, stirred at boiling for 30 min and filtrated. The obtained solution is spontaneously cooled to a temperature of 30°C, then to a temperature of 10-15°C in a cooling water bath, stirred for 1 h at this temperature (without seed crystals), filtrated to obtain a solution and the filter is rinsed 2 times with 20 ml of cooled 96% alcohol.

The product is dried at 25°C for 18 h and weighed.

Quantity of purified carbabenzpyride: 44 g (70.8% based on isonicotinic acid).

Analytic control:

Melting point: 191.3°C

Assay: 99.81%

Content of related substances:

BA, %	BAINA, %	Total impurity, %
absent	0.01	0.03

Example 11.

This Example differs from Example 10 in that 70% alcohol is used as solvent.

Quantity of purified carbabenzpyride: 33 g (53.1% based on isonicotinic acid).

Analytic control:

Melting point: 191.5°C

Assay: 101.01%

Content of related substances:

BA, %	BAINA, %	Total impurity, %
absent	0.03	0.05

Example 12.

This Example differs from Example 10 in that water is used as the solvent.

Quantity of purified carbabenzpyride: 40.6 g (65.4 % based on isonicotinic acid).

Analytic control:

Melting point: 191.4°C

Assay: 100.19%

Content of related substances:

BA, %	BAINA, %	Total impurity, %
absent	0.14	0.2

Example 13.

This Example differs from Example 10 in that crude carbabenzpyride was purified, and carbabenzpyride was subjected to a second re-crystallisation using water as solvent. 40 g of purified carbabenzpyride are dissolved in 460 ml of water at a temperature of 30 – 35°C, stirred for 20 min, and then spontaneously cooled to a temperature of 22 – 25°C, further stirred for 1 h, then cooled for 2 h to a temperature of 7 – 10°C and filtrated.

Quantity of purified carbabenzpyride: 29.5 g (73.8%, based on purified carbabenzpyride)

Analytic control:

Melting point: 191.1°C

Assay: 99.11 %

Content of related substances:

BA, %	BAINA, %	Total impurity, %
absent	0.007	0.04

Crystal structure information (α-crystalline form of carbabenzpyride)

A yellow prism of $C_{14}H_{15}IN_2O$, approximate dimensions 0.26 mm x 0.34 mm x 0.40 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 173(2) K on a Bruker SMART APEX II system equipped with a graphite monochromator and a MoKα fine-focus sealed tube (λ = 0.71073Å) operated at 1250 W power (50 kV, 25 mA). The detector was placed at a distance of 60 mm from the crystal. 458 frames were collected with a scan width of 1.5° in ω and an additional 211 frames were collected with a scan width of 1.5° in ϕ. All frames were collected with an exposure time of 20 sec/frame. The total data collection time was 5 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Orthorhombic cell yielded a total of 18403 reflections to a maximum θ angle of 30.54° (0.7Å resolution), of which 4309 were independent (redundancy 4.27, completeness = 99.7%, R_{int} = 2.67%, R_{sig} = 2.29%) and 4152 (96.4 %) were greater than 4 $\sigma(F^2)$. The final cell constants of a = 9.27390(10)Å, b = 10.7187(2)Å, c = 14.2161(2)Å, α = 90°, β = 90°, γ = 90°, volume = 1413.14(4)$Å^3$, are based upon the refinement of the XYZ-centroids of 9894 reflections above 20 σ(I) with 2.38° < 2θ < 30.54°. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the numerical technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.79. The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.4625 and 0.5872.

The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group P2(1)2(1)2(1), with Z = 4 for the formula unit, $C_{14}H_{15}IN_2O$. The final anisotropic full-matrix least-squares refinement on F^2 with 164 variables converged at R1 = 1.87%, for the observed data and wR2 = 4.40% for all data. The goodness-of-fit was 1.117. The largest peak on the final difference electron density synthesis was 0.260 $e^-/Å^3$ and the largest hole was -0.752 $e^-/Å^3$ with an RMS deviation of 0.093 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.665 g/cm^3 and F(000), 696 e^-.

The results of the X-ray crystal graphic analysis is summarised in the following tables below:

Table 3. Sample and crystal data

Identification code	BatchNo38	
Compound Name	BatchNo38	
Empirical formula	C14 H15 I N2 O	
Molecular formula	C14 H15 I N2 O	
Formula weight	354.18	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal size	0.40 x 0.34 x 0.26 mm	
Crystal habit	yellow prism	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.27390(10) Å	α= 90°
	b = 10.7187(2) Å	β= 90°
	c = 14.2161(2) Å	γ = 90°
Volume	1413.14(4) $Å^3$	
Z	4	
Density (calculated)	1.665 Mg/m^3	
Absorption coefficient	2.257 mm^{-1}	
F(000)	696	

Table 4. Atomic coordinates and equivalent isotropic atomic displacement parameters ($Å^2$).

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
I1	0.059362(13)	0.220079(11)	0.681751(8)	0.02914(4)
N1	0.69454(18)	0.05287(15)	0.58001(10)	0.0271(3)
N2	0.28947(17)	0.02738(14)	0.81732(11)	0.0264(3)
O1	0.46021(17)	-0.10841(13)	0.86668(9)	0.0349(3)
C1	0.7327(2)	-0.0307(2)	0.64696(15)	0.0364(5)
C2	0.6437(2)	-0.0549(2)	0.72023(15)	0.0345(4)
C3	0.5104(2)	0.00550(17)	0.72769(12)	0.0237(3)
C4	0.4756(2)	0.09259(18)	0.65976(12)	0.0264(4)
C5	0.5688(2)	0.11448(17)	0.58631(12)	0.0276(4)
C6	0.7919(2)	0.0751(2)	0.49994(13)	0.0373(5)
C7	0.4168(2)	-0.02994(16)	0.81034(12)	0.0255(4)
C8	0.1835(2)	-0.00506(18)	0.88881(12)	0.0297(4)
C9	0.1874(2)	0.07944(16)	0.97341(12)	0.0238(3)
C10	0.2960(2)	0.06614(17)	1.04050(13)	0.0264(4)
C11	0.2997(2)	0.1429(2)	1.11906(13)	0.0326(4)
C12	0.1953(3)	0.2329(2)	1.13172(14)	0.0395(5)
C13	0.0859(3)	0.2455(2)	1.06617(16)	0.0429(5)
C14	0.0835(2)	0.1694(2)	0.98697(14)	0.0355(4)

Table 5. Bond lengths (Å)

	N1-C5	1.343(2)	N1-C1	1.354(2)
	N1-C6	1.472(2)	N2-C7	1.335(2)
5	N2-C8	1.456(2)	N2-H2N	0.8800
	O1-C7	1.229(2)	C1-C2	1.354(3)
	C1-H1	0.9500	C2-C3	1.400(3)
	C2-H2	0.9500	C3-C4	1.381(2)
	C3-C7	1.509(3)	C4-C5	1.376(3)
10	C4-H4	0.9500	C5-H5	0.9500
	C6-H6A	0.9800	C6-H6B	0.9800
	C6-H6C	0.9800	C8-C9	1.506(2)
	C8-H8A	0.9900	C8-H8B	0.9900
	C9-C14	1.377(3)	C9-C10	1.394(3)
15	C10-C11	1.388(3)	C10-H10	0.9500
	C11-C12	1.378(3)	C11-H11	0.9500
	C12-C13	1.385(3)	C12-H12	0.9500
	C13-C14	1.391(3)	C13-H13	0.9500
	C14-H14	0.9500		

20

Table 6. Bond angles (°)

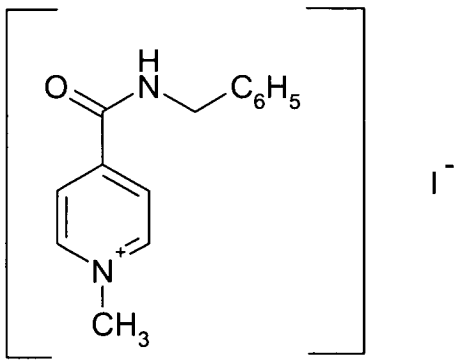
C5-N1-C1	120.36(17)	C5-N1-C6	120.29(16)
C1-N1-C6	119.35(17)	C7-N2-C8	122.64(16)
C7-N2-H2N	118.7	C8-N2-H2N	118.7
C2-C1-N1	120.51(19)	C2-C1-H1	119.7
N1-C1-H1	119.7	C1-C2-C3	120.56(18)
C1-C2-H2	119.7	C3-C2-H2	119.7
C4-C3-C2	117.77(18)	C4-C3-C7	125.45(17)
C2-C3-C7	116.78(16)	C5-C4-C3	119.93(17)
C5-C4-H4	120.0	C3-C4-H4	120.0
N1-C5-C4	120.82(16)	N1-C5-H5	119.6
C4-C5-H5	119.6	N1-C6-H6A	109.5
N1-C6-H6B	109.5	H6A-C6-H6B	109.5
N1-C6-H6C	109.5	H6A-C6-H6C	109.5
H6B-C6-H6C	109.5	O1-C7-N2	123.79(18)
O1-C7-C3	119.43(17)	N2-C7-C3	116.79(16)
N2-C8-C9	113.40(15)	N2-C8-H8A	108.9
C9-C8-H8A	108.9	N2-C8-H8B	108.9
C9-C8-H8B	108.9	H8A-C8-H8B	107.7
C14-C9-C10	118.77(17)	C14-C9-C8	121.04(17)
C10-C9-C8	120.18(17)	C11-C10-C9	120.54(18)
C11-C10-H10	119.7	C9-C10-H10	119.7
C12-C11-C10	120.17(19)	C12-C11-H11	119.9
C10-C11-H11	119.9	C11-C12-C13	119.71(19)
C11-C12-H12	120.1	C13-C12-H12	120.1
C12-C13-C14	119.9(2)	C12-C13-H13	120.0
C14-C13-H13	120.0	C9-C14-C13	120.87(19)
C9-C14-H14	119.6	C13-C14-H14	119.6

Table 7. Torsion angles (°)

C5-N1-C1-C2	1.1(3)	C6-N1-C1-C2	-178.5(2)
N1-C1-C2-C3	0.4(3)	C1-C2-C3-C4	-2.0(3)
C1-C2-C3-C7	178.4(2)	C2-C3-C4-C5	2.0(3)
C7-C3-C4-C5	-178.38(17)	C1-N1-C5-C4	-1.0(3)
C6-N1-C5-C4	178.63(18)	C3-C4-C5-N1	-0.6(3)
C8-N2-C7-O1	-5.2(3)	C8-N2-C7-C3	174.76(15)
C4-C3-C7-O1	-179.47(19)	C2-C3-C7-O1	0.1(2)
C4-C3-C7-N2	0.6(3)	C2-C3-C7-N2	-179.81(18)
C7-N2-C8-C9	97.4(2)	N2-C8-C9-C14	104.6(2)
N2-C8-C9-C10	-76.5(2)	C14-C9-C10-C11	-0.5(3)
C8-C9-C10-C11	-179.44(17)	C9-C10-C11-C12	0.3(3)
C10-C11-C12-C13	0.6(3)	C11-C12-C13-C14	-1.4(3)
C10-C9-C14-C13	-0.2(3)	C8-C9-C14-C13	178.67(19)
C12-C13-C14-C9	1.2(3)		

CLAIMS

1. α-Crystalline form of carbabenzpyride of formula (I):



exhibiting essentially the following powder X-ray diffraction data, measured using a diffractometer (copper anticathode) and expressed in terms of inter-planar distance d, Bragg's angle 2 theta, and relative intensity (expressed as a percentage with respect to the most intense ray) as shown in the table below listing the following reflex positions of high and medium intensity:

No	Angle 2 theta (°)	Inter-planar distance d (Å)	Relative Intensity
1	2.3925	36.92687	5.23
2	10.2105	8.66366	5.95
3	11.3179	7.81828	5.70
4	12.3706	7.15527	10.86
5	13.9617	6.34318	3.67
6	16.2837	5.44354	6.62
7	17.4171	5.09177	8.45
8	17.6238	5.03251	66.93
9	19.8858	4.46489	100.00
10	20.3088	4.37284	7.36

2. The α-crystalline form of carbabenzpyride according to claim 1 having a degree of purity of at least 99.5% as determined by HPLC.

3. The α-crystalline form of carbabenzpyride according to claim 2 having a degree of purity of at least 99.9% as determined by HPLC.

4. The α-crystalline form of carbabenzpyride according to claim 1 having a single endothermic maximum in its DSC curve in the range of 187 to 193°C.

5. The α-crystalline form of carbabenzpyride according to claim 1 having an IR-spectrum exhibiting the following characteristic peaks shown in the table below:

Wave number [cm^{-1}]	vibration
3236	N–H
3040	C–H
2934	C–H
1622	C=O
1600 / 1502	C=C
760 / 704	C–H

6. A process for the preparation of the α-crystalline form of carbabenzpyride according to claim 1 comprising the following steps:

(i) condensation of isonicotinic acid with benzylamine at elevated temperatures,

(ii) crystallisation and isolation of the condensation product obtained in step (i) above,

(iii) reaction of the crystalline product obtained in step (ii) above with methyl iodide and

(iv) re-crystallisation of the crude product obtained in step (iii) from aqueous alcohol.

7. The process according to claim 6 wherein the condensation reaction between isonicotinic acid and benzylamine according to step (i) is carried out using an excess of benzylamine ranging from 10 to 25%.

8. The process according to claim 6 wherein the product of the condensation reaction between isonicotinic acid and benzylamide, i.e. benzylamide of isonicotinic acid (BAINA) is crystallised from the reaction mixture using a solvent selected from the group consisting of ethyl acetate, acetonitrile and isopropanol.

9. The process according to claim 8 further comprising the use of activated carbon.

10. The process according to claim 6, 8 or 9 wherein the product of step (ii), i.e. BAINA, is treated with water.

11. The process according to claim 6 wherein in step (iii) the quaternisation reaction of benzylamide isonicotinic acid and methyl iodide is carried out using an excess of methyl iodide in the range of 5 to 15%.

12. The process according to claim 11 wherein the quaternisation reaction is carried out in an aqueous alcohol.

13. The process according to claim 12 wherein the aqueous alcohol is 90% ethanol.

14. The process according to claim 6 further comprising the step of washing the crude product obtained from step (iii) with an aqueous alcohol.

15. The process according to claim 14 wherein the aqueous alcohol is 96% ethanol.

16. The process according to claim 6 wherein the aqueous alcohol used in step (iv) is ethanol comprising water in an amount of 5 to 15% v/v.

17. The process according to claim 16 wherein the aqueous ethanol is 90% ethanol.

18. The process according to claim 6 wherein the ratio of the crude product and the aqueous alcohol used in step (v) is in the range of 1:2 to 1:4.

19. The process according to claim 18 wherein the ratio of the crude product and the aqueous alcohol used in step (v) is 1:3.

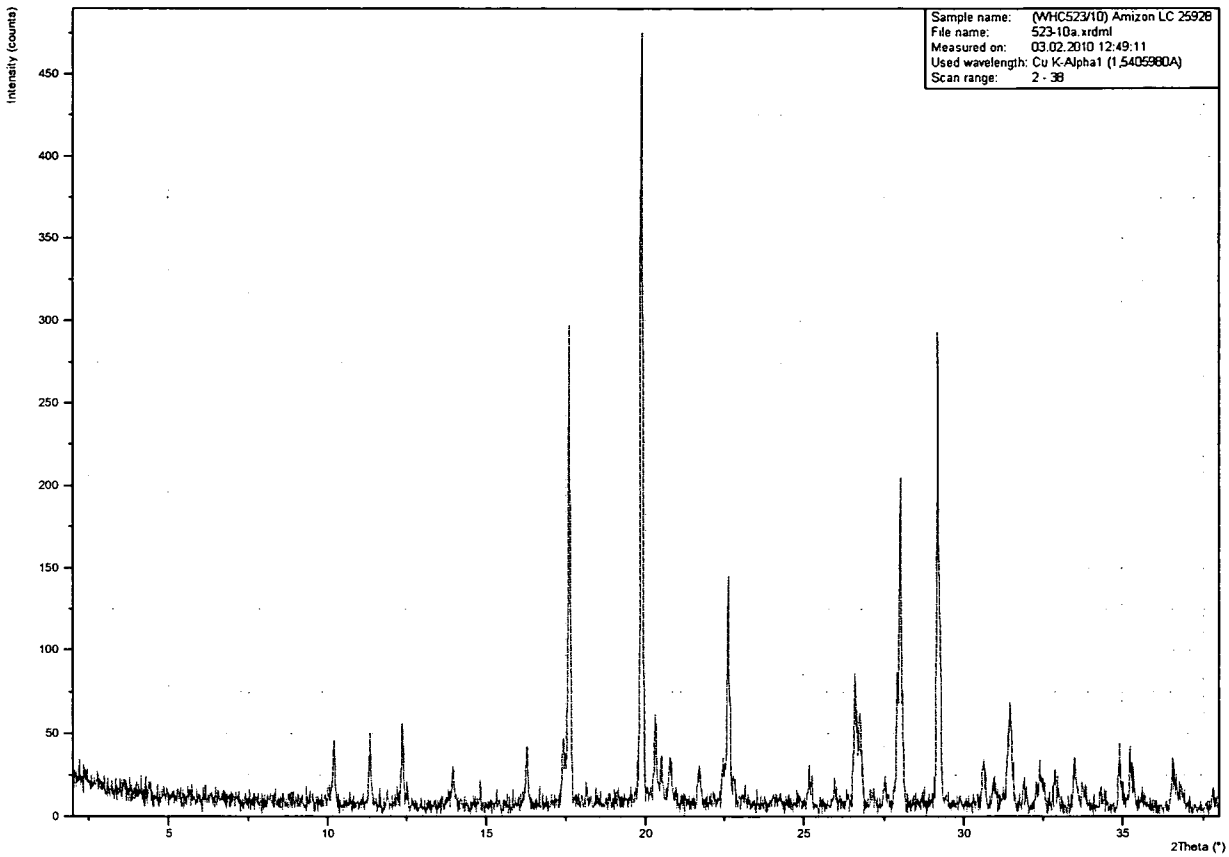
20. The process according to claim 6 wherein the re-crystallisation in step (iv) is carried out by spontaneously cooling the boiling aqueous ethanol solution of the crude product to a temperature in the range of 30 to 40°C and further cooling the solution to a temperature in the range of 10 to 15°C with further stirring over a period of time in the range of 1 to 3 hours.

21. A pharmaceutical composition comprising the α-crystalline form of carbabenzpyride of formula (I) according to any of claims 1 to 5 and a pharmaceutically acceptable carrier.

22. Use of the α-crystalline form of carbabenzpyride of formula (I) according to any one of claims 1 to 5 for the preparation of a medicament for the treatment and prevention of viral infections.

23. The use according to claim 22 wherein the viral infections are infections caused by influenza (A) viruses.

Fig. 1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File name: 523-10a.xrdml
Measured on: 03.02.2010 12:49:11
Used wavelength: Cu K-Alpha1 (1,5405980A)
Scan range: 2 - 38
Intensity (counts)
0
50
100
150
200
250
300
350
400
450
5
10
15
20
25
30
35
2Theta (°)

Fig. 2

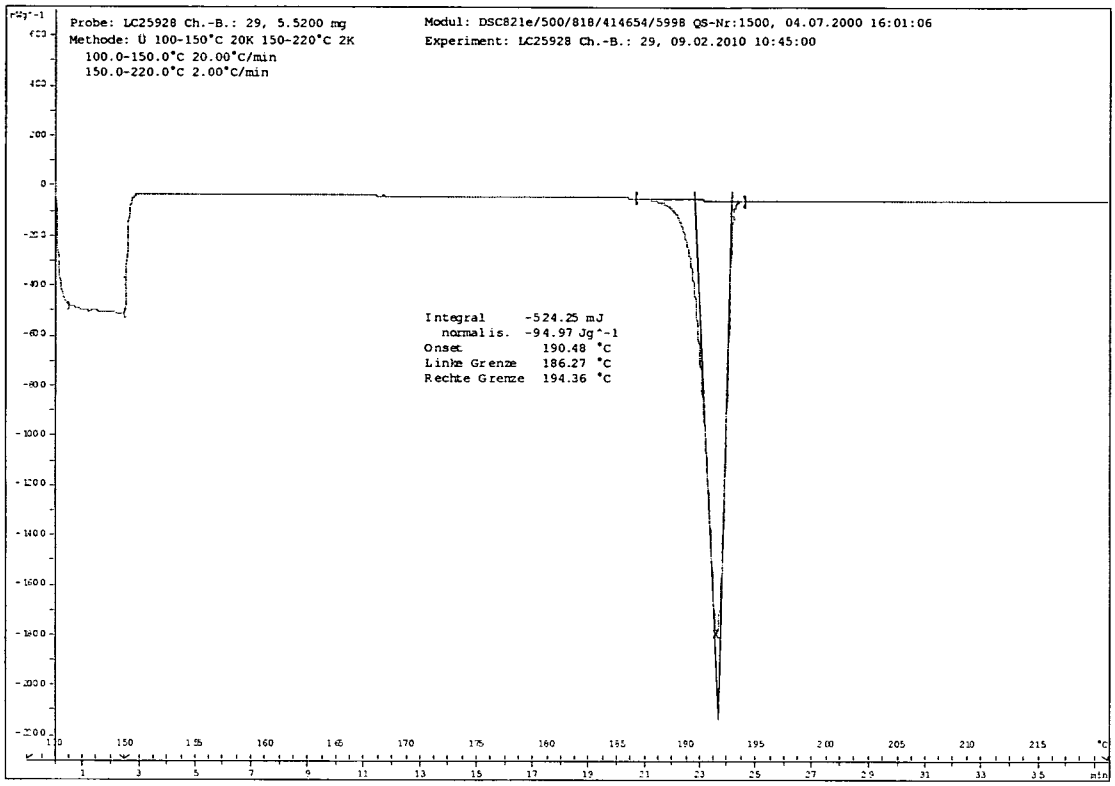

Probe: LC25928 Ch.-B.: 29, 5.5200 mg
Methode: Ü 100-150°C 20K 150-220°C 2K
100.0-150.0°C 20.00°C/min
150.0-220.0°C 2.00°C/min
Modul: DSC821e/500/818/414654/5998 QS-Nr:1500, 04.07.2000 16:01:06
Experiment: LC25928 Ch.-B.: 29, 09.02.2010 10:45:00
Integral -524.25 mJ
normalis. -94.97 Jg^-1
Onset 190.48 °C
Linke Grenze 186.27 °C
Rechte Grenze 194.36 °C
mW/mg^-1
°C
min

Fig. 3

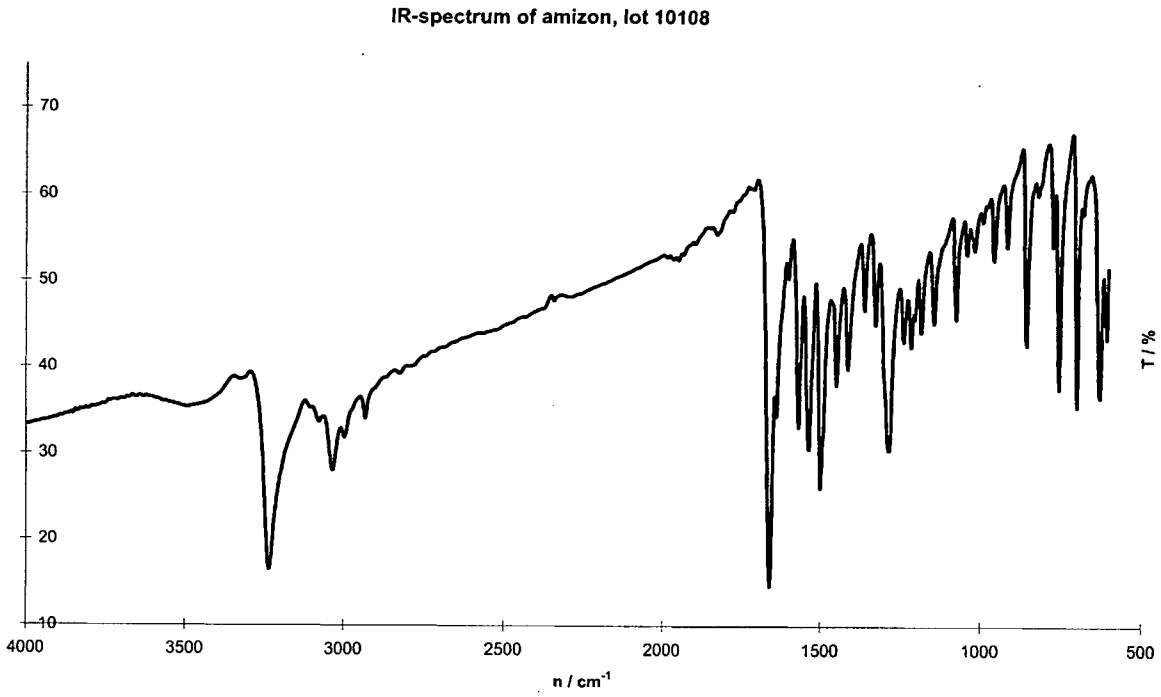

IR-spectrum of amizon, lot 10108
70
60
50
40
30
20
10
T / %
4000
3500
3000
2500
2000
1500
1000
500
n / cm-1

Fig. 4

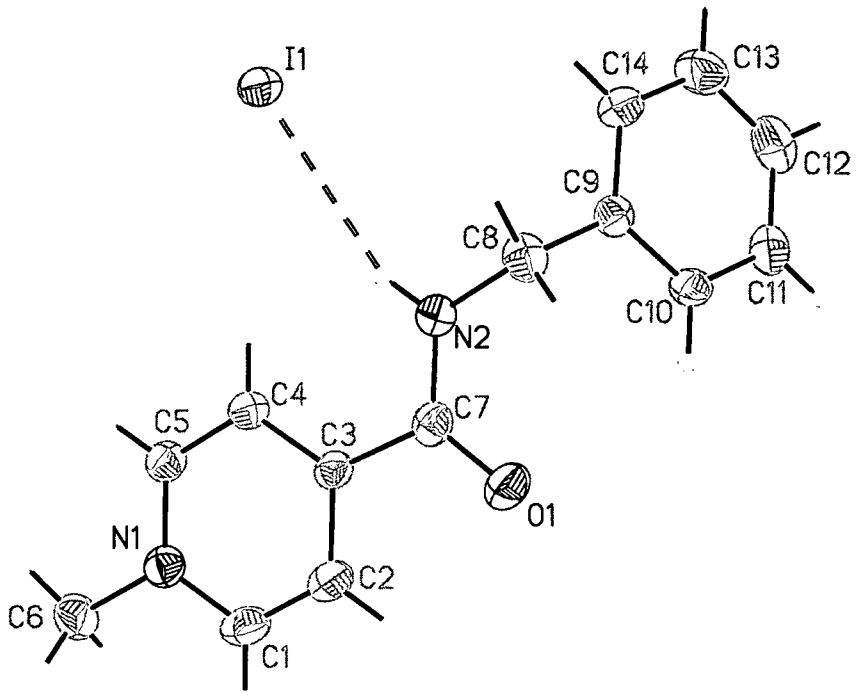


Fig. 5

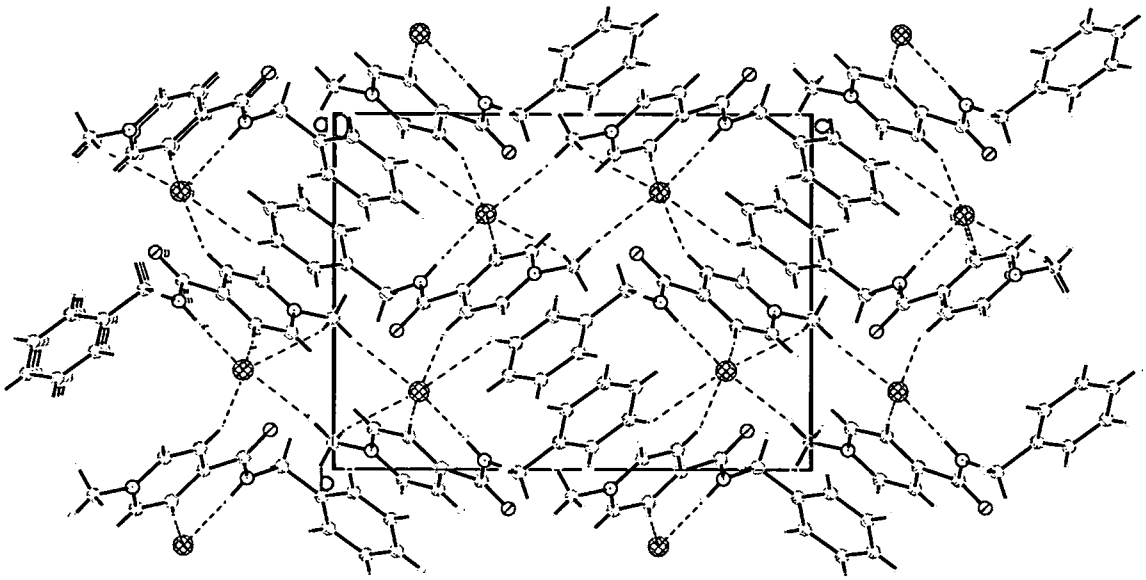
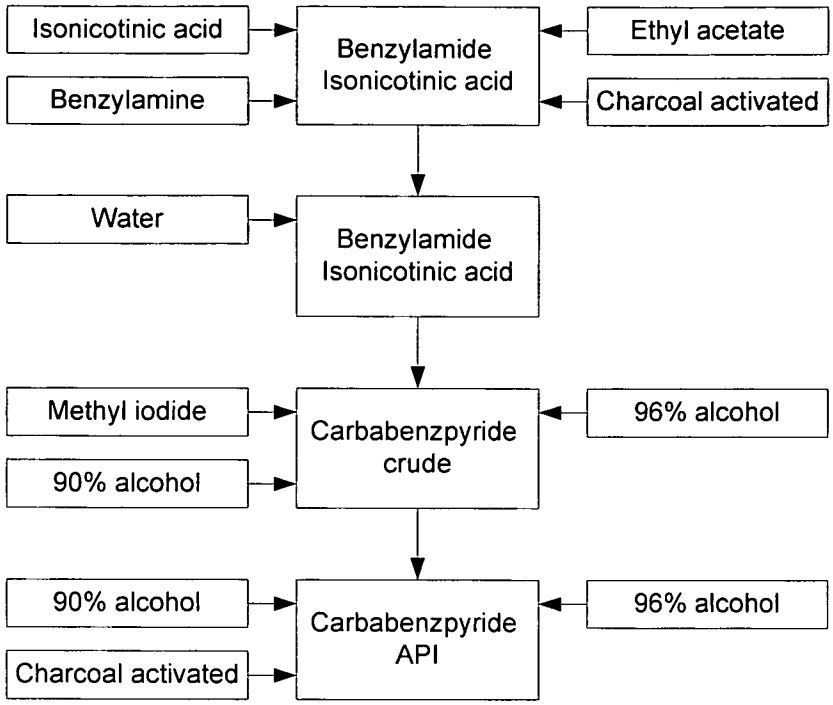


Fig. 6


Isonicotinic acid
Benzylamine
Benzylamide Isonicotinic acid
Ethyl acetate
Charcoal activated
Water
Benzylamide Isonicotinic acid
Methyl iodide
90% alcohol
Carbabenzpyride crude
96% alcohol
90% alcohol
Charcoal activated
Carbabenzpyride API
96% alcohol

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/001956

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/81 A61P31/16 A61K31/4425
ADD.

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)
C07D

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)
EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NESTEROVA ET AL: "Studying of Anti-Epstein-Barr Virus Activity of Amizon and their Derivative", ANTIVIRAL RESEARCH, ELSEVIER BV, NL, vol. 78, no. 2, 19 March 2008 (2008-03-19) , page A61, XP022541825, ISSN: 0166-3542, DOI: DOI:10.1016/J.ANTIVIRAL.2008.01.130 the whole document ----- -/--	1-23

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 February 2011	11/03/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Seelmann, Ingo

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/001956

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BUKHTIAROVA T A ET AL: "Structure and antiinflammatory activity of Isonicotinic and Nicotinic Amides", PHARMACEUTICAL CHEMISTRY JOURNAL, SPRINGER NEW YORK LLC, US, vol. 31, no. 11, 1 January 1997 (1997-01-01), pages 597-599, XP002501345, ISSN: 0091-150X, DOI: DOI:10.1007/BF02464277 table 1; compound 1 -----	1-23