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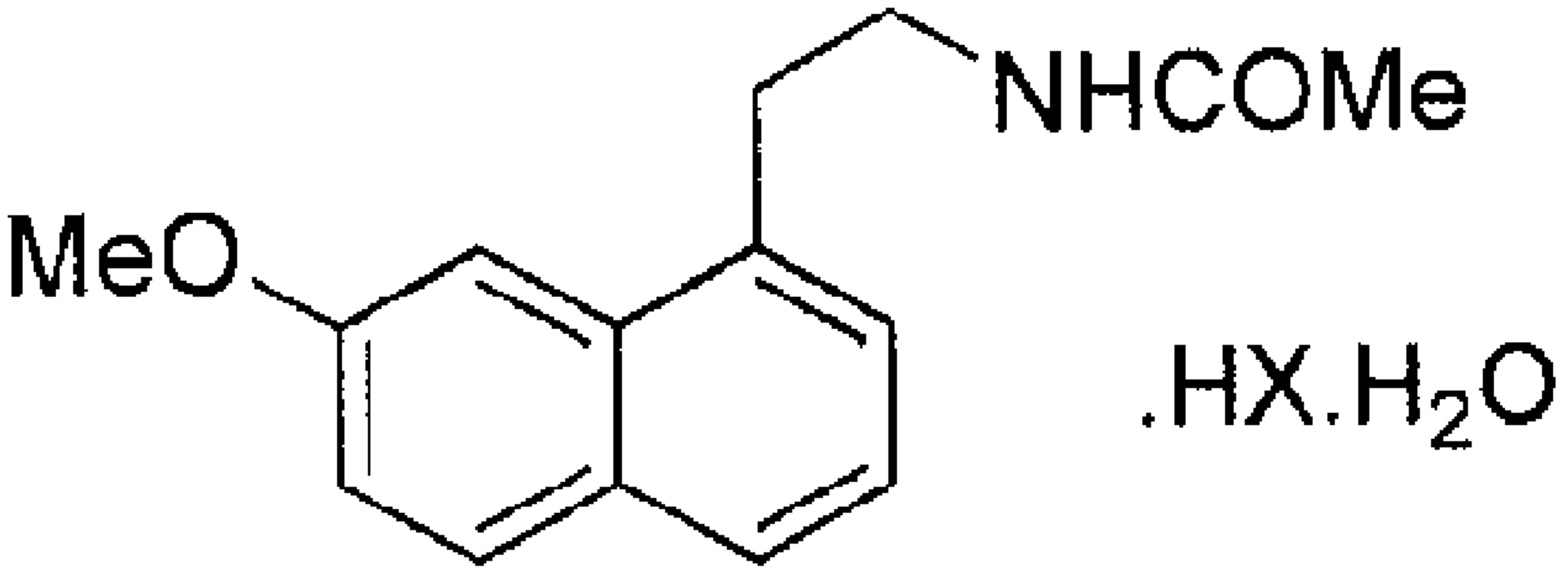
(54) Titre : BROMHYDRATE D'AGOMELATINE HYDRATE ET SA PREPARATION
(54) Title: AGOMELATINE HYDROBROMIDE HYDRATE AND PREPARATION THEREOF



(I)

(57) **Abrégé/Abstract:**

An agomelatine hydrobromide hydrate of formula (I), in which X is Br, preparation method and use thereof as well as pharmaceutical composition containing it are provided. The solubility of the agomelatine hydrobromide hydrate obtained by the present method is significantly higher than that of agomelatine. Therefore, it is more suitable for manufacturing pharmaceutical formulations. In addition, the product has higher stability and purity. The present product of high purity can be obtained through a simple process, rather than process with complicated steps.

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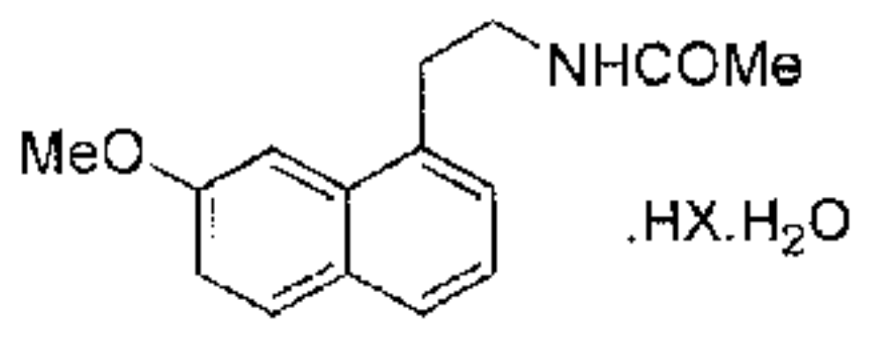
**(54) Title**: AGOMELATINE HYDROBROMIDE HYDRATE AND PREPARATION THEREOF



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**(57) Abstract**: An agomelatine hydrobromide hydrate of formula (I), in which X is Br, preparation method and use thereof as well as pharmaceutical composition containing it are provided. The solubility of the agomelatine hydrobromide hydrate obtained by the present method is significantly higher than that of agomelatine. Therefore, it is more suitable for manufacturing pharmaceutical formulations. In addition, the product has higher stability and purity. The present product of high purity can be obtained through a simple process, rather than process with complicated steps.

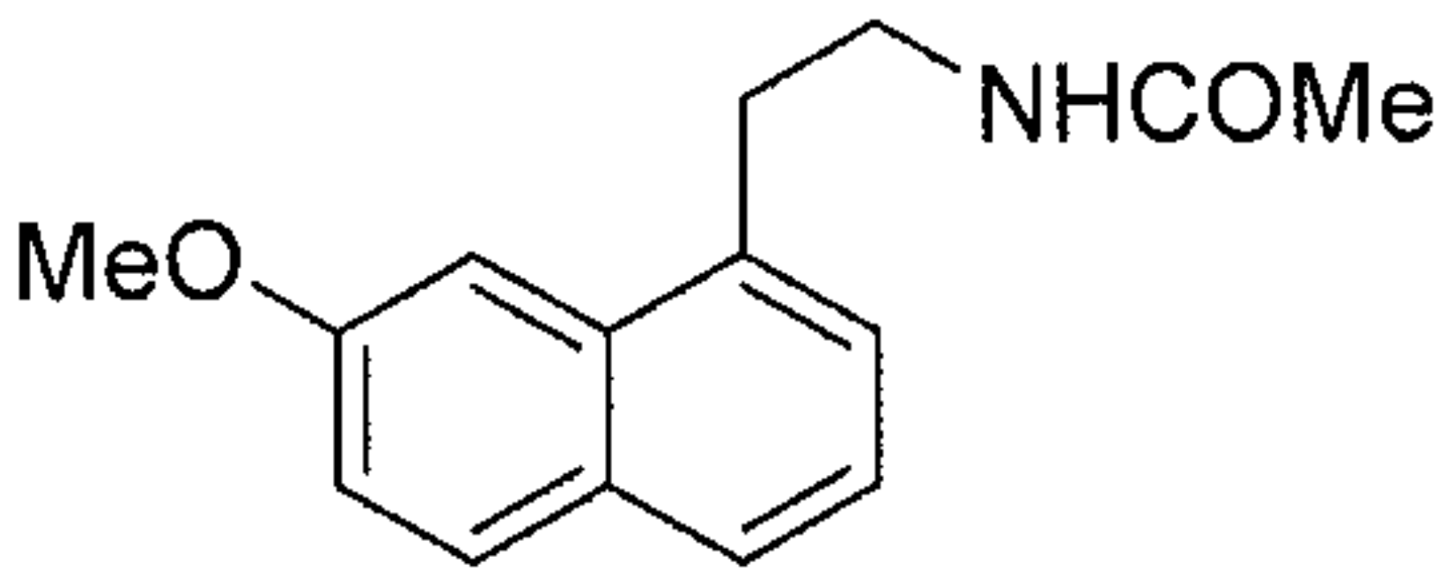
# AGOMELATINE HYDROBROMIDE HYDRATE AND PREPARATION THEREOF

## Technical Field

The present invention relates to an agomelatine hydrobromide hydrate and preparation and use thereof, and to pharmaceutical composition containing it.

## Technical Background

Agomelatine, or N-[2-(7-methoxy-1-naphthyl)ethyl]-acetamide, has the structure of formula II. It is marketed under the trade name of Valdoxan by the French company Servier as a melatonin agonist and antagonist of 5HT$_{2C}$ receptor. It is the first melatonin type anti-depressant, indicated for depression, improving sleep and sexual function.



( II )

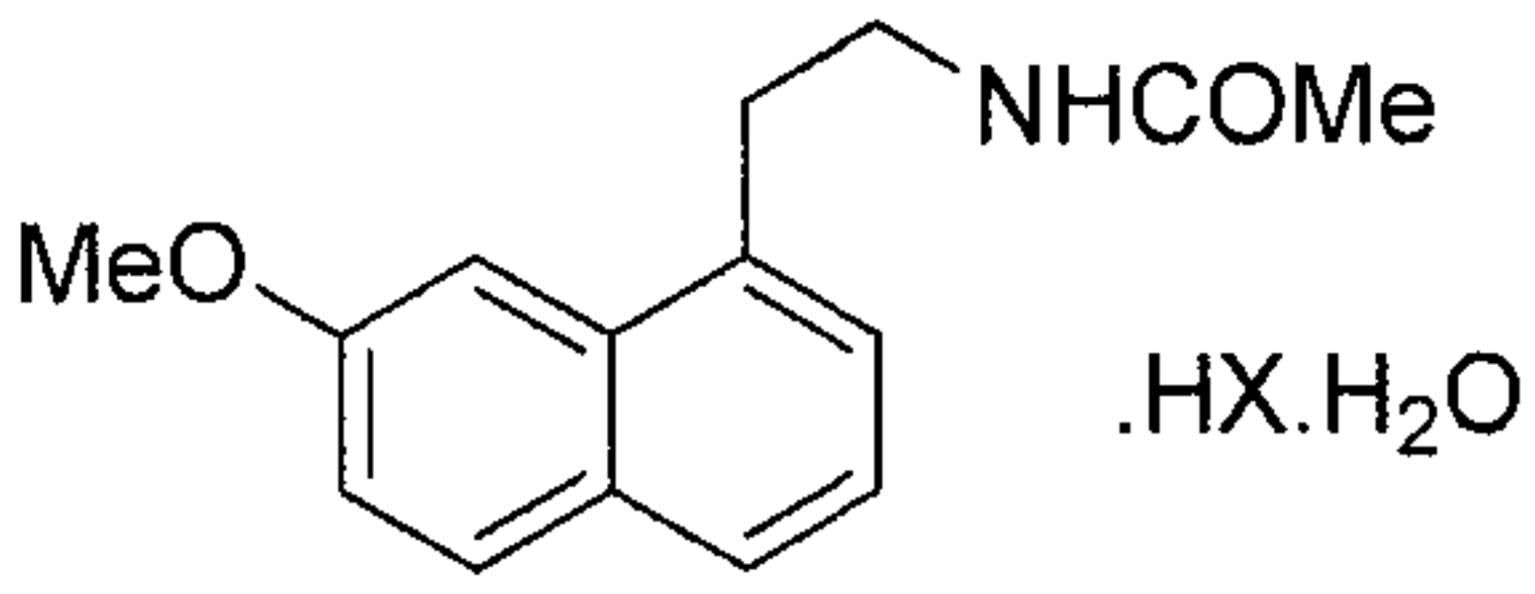
In view of its pharmaceutical value, it is important to produce the compound or a complex thereof with better purity, solubility and reproducibility.

## Summary of the Invention

The object of the present invention is to provide an agomelatine hydrobromide hydrate featuring excellent solubility, stability and purity, making it favourable for use in the manufacture of pharmaceutical formulations containing agomelatine.

When the present inventors attempted to purify agomelatine product, we surprisingly found that agomelatine can form a physically and chemically stable agomelatine hydrobromide hydrate when mixed with hydrobromic acid (HBr). Said agomelatine hydrobromide hydrate is suitable for the manufacture of pharmaceutical formulations. When other conventional inorganic acids (such as sulphuric acid, phosphoric acid, perchloric acid) or organic acids (such as acetic acid, oxalic acid, tartaric acid, fumaric acid) were used, it was not easy to produce a hydrate or hydrates with unstable physical and chemical properties were obtained.

The present invention provides an agomelatine hydrobromide hydrate with the following structure of formula I:



( I )

wherein X is Br.

The present invention further provides a method for the preparation of said agomelatine hydrobromide hydrate, wherein agomelatine is reacted with HBr in any form to produce the agomelatine hydrobromide hydrate. There can be two processes: agomelatine can be dissolved in aqueous organic solvent before HBr gas is bubbled through and the precipitated crystal is rinsed and dried; or agomelatine can be added to an solvent containing HBr and then the precipitated crystal is rinsed and dried. The results from repeated experiments show that in the first method, the oversupply of HBr only results in lower yield, while in the second method, it is easier to control the amount of HBr in the solvent. Therefore, the second method is preferred.

Specifically, agomelatine can also be added to an aqueous organic solvent before a solvent containing HBr is added dropwise, and the precipitated crystal is rinsed and dried.

Alternatively, agomelatine is dissolved in organic solvent before aqueous HBr solution is added dropwise, and the precipitated crystal is rinsed and dried.

The reaction temperature in the present invention can be conventional temperatures for such reactions in the art as long as it is lower than the boiling point of the solvent. In order to increase yield, room temperature or below is preferred, a temperature below the room temperature is more preferred, and 0-20°C is most preferred.

In the above-mentioned preparation method for said agomelatine hydrobromide hydrate, the organic solvent is not specifically limited so long as it can dissolve the starting materials agomelatine and HBr and meanwhile allows said agomelatine hydrobromide hydrate to be precipitated. Suitable solvent can be used includes ethyl acetate, methyl acetate, n-butyl acetate, acetone, acetonitrile and the like, and ethyl acetate is preferred. Organic solvents with higher polarity such as alcohols (ethanol and methanol etc.), DMF, DMSO are less preferred.

The present invention is advantageous in that the inventors found that among so many conventional acids, agomelatine can react with HBr to form a stable agomelatine hydrobromide hydrate, the physical properties of which, such as stability, solubility, and hygroscopicity, are better than those products of agomelatine with any other conventional acid. The process is also less complicated than if other acid is used.

The agomelatine hydrobromide hydrate produced according to the present method has significantly increased solubility than agomelatine *per se*, and therefore is more suitable for manufacturing pharmaceutical formulations. The product enjoys higher stability, purity and solubility. In addition, product with high purity can be obtained through a simple process, free of any complicated steps.

Pharmacological tests of the agomelatine hydrobromide hydrate demonstrated that it can be used for the treatment of melatoninergic system disorders, sleep disorders, stress, anxiety, seasonal affective disorder, major depression, cardiovascular diseases, digestive system diseases, insomnia and fatigue caused by jet lag, schizophrenia, phobia or depression disorders.

The present invention further provides a pharmaceutical composition, comprising an agomelatine hydrobromide hydrate of the invention in associated with pharmaceutically acceptable adjuvants or excipients.

The pharmaceutical composition can be formulated for various routes of administration, especially for oral administration or for injection.

The useful dosage can be adjusted depending on the nature and severity of the diseases to be treated, the mode of administration, and age and weight of the patients. The daily dosage varies from 0.1 mg to 1 g and may be administrated in a single dose or in several divided doses.

## Brief Description of Drawings

Representative examples of the present invention are illustrated with the drawings in order to better convey the objects, features, and advantages of the present invention.

Fig. 1 shows the TGA thermogram of the product of Example 1 in the present invention.
Fig. 2 is the projection chart of single-crystal 3-D structure of an agomelatine hydrobromide hydrate in the present invention.
Fig. 3 shows the projection chart of unit cell packing of an agomelatine hydrobromide hydrate in the present invention.

## Examples

### Example 1

1 g of agomelatine was dissolved in 10 ml of EtOAc with stirring, and aqueous HBr solution (0.92g, 40%) was added dropwise at 10 °C. The mixture was stirred for 1h, and then filtered, and the solid was rinsed twice with 1 ml of EtOAc and dried at 40 °C to afford 1.1 g of white solid (purity: 99.6%; yield: 78.2%).

Analytical results: ($C_{15}H_{17}NO_2 \cdot HBr \cdot H_2O$):
Calculated: Br% (23.35 wt%)
Found: Br% (23.27 wt%)
Mp: 88-90℃

### Example 2

10 g of agomelatine was dissolved in 100 ml of EtOAc with stirring, and aqueous HBr solution (8.32g, 40%) was added dropwise at low temprature. The mixture was stirred for 1h, and then filtered, and the solid was rinsed twice with 10 ml of EtOAc and dried at 40 °C to afford 11.2g of white solid (purity: 99.7%; yield: 84%).

Analytical results: ($C_{15}H_{17}NO_2 \cdot HBr \cdot H_2O$)
Calculated: Br% (23.35%)
Found: Br% (23.19%)
Mp: 87-89℃

### Example 3

1 g of agomelatine was dissolved in 10 ml of EtOAc with stirring, and concentrated $H_2SO_4$ was added dropwise at room temperature. No solid precipitated during the entire process.

### Example 4

1 g of agomelatine was dissolved in 10 ml of EtOAc with stirring, and concentrated $H_2SO_4$ was added dropwise at -10°C. No solid precipitated during the entire process.

### Example 5

1 g of agomelatine was dissolved in 10 ml of EtOAc with stirring, and glacial acetic acid was added dropwise at -10°C. No solid precipitated during the entire process.

**Example 6**
1 g of agomelatine was dissolved in 10 ml of EtOAc with stirring, and fumaric acid was added dropwise at -10°C. No solid precipitated during the entire process.

**Example 7**
100 g of agomelatine was dissolved in 800 ml of EtOAc with stirring, and aqueous HBr solution (84g, 40%) was added dropwise at a temperature below the room temperature. The mixture was stirred for 1h, and then filtered, and the solid was rinsed twice with 100 ml of EtOAc and dried at 40 °C to afford 120g of white solid (purity: 99.9%; yield: 85.3%).

Analytical results: ($C_{15}H_{17}NO_2{\cdot}HBr{\cdot}H_2O$)
Calculated: Br% (23.35%)
Found: Br% (23.21%)
Mp: 88-90℃

Agomelatine used in the above examples is commercially available or can be prepared according to methods known in the art.

**Example 8: Pharmaceutical Composition**

| Formulation for the preparation of 1000 capsules each containing a dose of 25 mg (agomelatine) | |
|---|---|
| Compound of Example 7 | 35.2 g |
| Lactose(Spherolac 100) | 80.6 g |
| Starch 1500 | 25.5 g |
| CMS-Na | 8.5 g |
| Ac-Di-Sol ®（FMC） | 17 g |
| Stearic Acid | 3.4 g |

**Detection Methods and Results**

1. Purity of Samples
Chromatographic conditions: C18 column; mobile phase: 10 mmol/L phosphate buffer (adjusted to pH 7.0 with NaOH): acetonitrile = 2 : 7 (v/v); column temperature: 40°C; detection wavelength: 220 nm; internal standard method was used on the products of examples 1 and 2.

Solutions of the products at 1 mg/mL were prepared with the mobile phase. 10 µL of each solution was injected into the liquid chromatograph system and chromatograms were recorded. The results of the purity are shown in examples 1 and 2.

2. Stability Test

The product of example 1 was placed in an incubator at 40°C for 30 days to determine its stability with HPLC. The results are shown in the following table 1:

Table 1

| Product of Example 1 | Day 0 | Day 5 | Day 10 | Day 30 |
|---|---|---|---|---|
| AG·HBr·$H_2O$ | 99.7% | 99.7% | 99.6% | 99.6% |

AG = Agomelatine $C_{15}H_{17}NO_2$

3. Water Solubility

Using external standard method, the product of example 1 was tested with HPLC, compared with agomelatine crystalline form II. The results are shown in the following table 2.

Table 2

| Sample | Agomelatine content (mg/ml) | | |
|---|---|---|---|
| | In water | In 0.1N HCl | In pH7.0 buffer |
| AG crystalline form II | 0.26 | 0.30 | 0.25 |
| AG·HBr·$H_2O$ | 0.33 | 0.37 | 0.31 |

As can be seen, the agomelatine hydrobromide hydrate of the present invention has better solubility than agomelatine *per se* in water, 0.1N HCl, which is similar to human gastric fluid, or in pH 7.0 buffer. This means the former enjoys the potential of higher bioavailability than the latter.

4. Crystal Water Analysis

Calculated water content in $C_{15}H_{17}NO_2$·HBr·$H_2O$ is 5.26 wt%.

4.1 Fischer's Method (Appendix VIII M, Chinese Pharmacopoeia, 2010)

The product of example 1 was analyzed according to said Fischer's method and water content was found to be 5.10 wt%.

The product of example 7 was analyzed according to said Fischer's method and water content was found to be 5.25 wt%.

4.2 Thermal Gravity Analysis (Appendix VIII Q, Chinese Pharmacopoeia, 2010)

The product of example 1 was analyzed according to said TGA method and water loss was found to be 5.70 wt%, meaning crystal water content in the product is 5.70 wt%. Fig 1 shows TGA thermogram.

The measurement condition for TGA method is as follows:

| | |
|---|---|
| Type of Instrument: | NETZSCH TG 209F1 |
| Type of Crucible: | $Al_2O_3$ |
| Flushing gas: | $N_2$ 20 ml/min; |
| Protective gas: | $N_2$ 10 ml/min |
| Temperature range: | Room temperature ~300℃ |
| Heat rate: | 10℃/min |

5. Crystal Structure Analysis

5.1 Diffraction Analysis

Preparation of crystal: a saturated solution of agomelatine hydrobromide hydrate in methanol was allowed to crystallize spontaneously and the crystal needed for the test was picked out.

White transparent solid crystal of size 0.10 x 0.20 x 0.40 mm was used in the diffraction analysis. The crystal belongs to the monoclinic crystal system, space group $P2_1/c$, with lattice parameters a = 7.5943 (7), b = 23.4046 (19), c = 9.6438 (8) Å, β = 1613.9 (2)°, V (volume)= 1476.28 (5) $Å^3$, Z (formula units per unit cell) = 4.

Bruker SMART APEX-II diffractometer with CuKα emission and graphite momochromater is used to record diffraction intensity data (single-vessel diameter: Φ = 0.50 mm; distance between crystal and CCD detector: d = 60.3 mm; vessel voltage: 40 kV; vessel current: 30 mA; scanning mode: Φ/ω mode; 2154 independent reflection points were recorded, 2074 points observable ($|F|^2 \geq 2\sigma|F|^2$)).

5.2 Structural Analysis

The crystal structure was determined according to direct method (Shelxs97). The positions of all 20 non-hydrogen atoms were obtained from E Graph. The structure parameters were refined and the atom category was identified by least-square method. The positions of all hydrogen atoms were obtained with geometric calculation and difference Fourier method with $R_1$=0.0302, $wR_2$ = 0.0868 ($w=1/\sigma|F|^2$), S = 1.092. The chemical formula was determined to be $C_{15}H_{17}NO_2 \cdot HBr \cdot H_2O$ in an asymmetrical unit. Density of the crystal was calculated to be 1.404 g/$cm^3$.

The projection chart of 3-D molecular structure is shown in Fig. 2, and the projection chart of the unit cell packing is shown in Fig. 3.

6. Stability Test of the Agomelatine Hydrobromide Hydrate

The method for stability test as described in Chinese Pharmacopoeia was used in this test.

1) Affecting factors test (in open container for 10 days): high temperature (60 ℃), photostability under strong light (4500lx), high humidity (92.5%RH at 25℃)
2) Accelerated test (in closed container for 6 months): at 40 ℃, humidity: 75%RH
3) Long-term test (in closed container for 9 months): at 25℃, humidity: 60%RH

The results are shown in the following table 3.

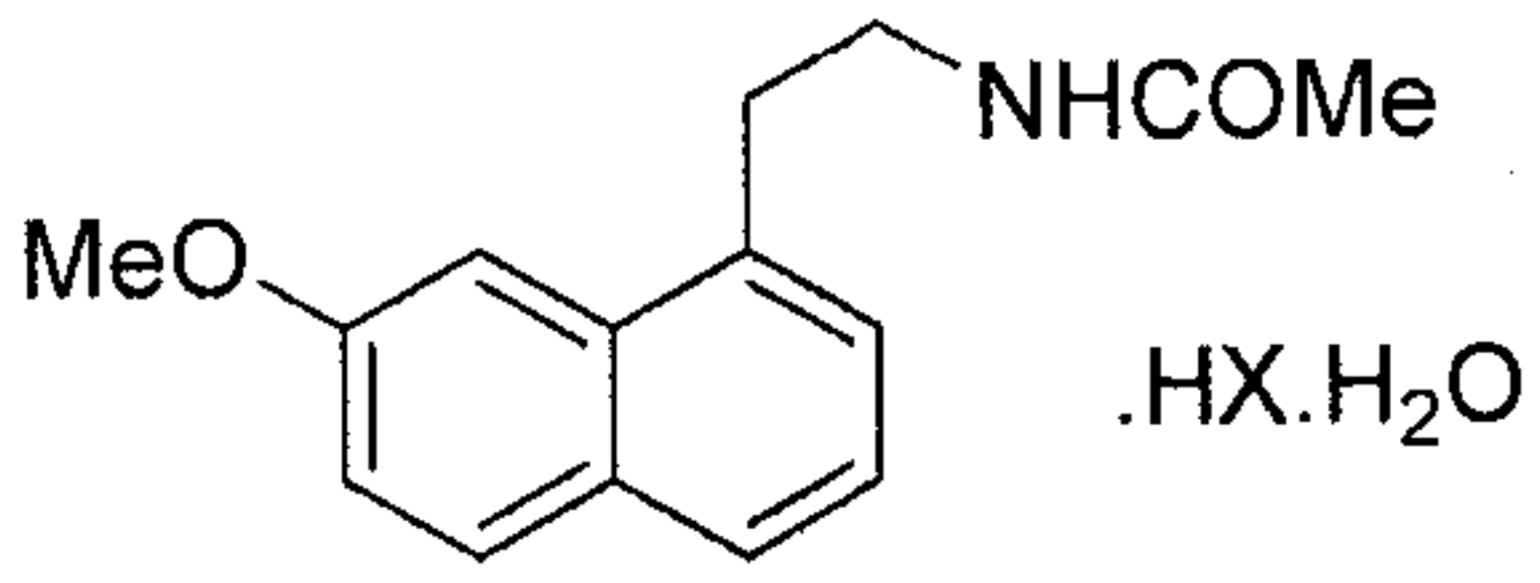
Table 3

| Sample | | Water (5.25%) | Br (23.21%) | Purity of agomelatine hydrobromide hydrate of Example 7 (initial value: 99.89%) |
|---|---|---|---|---|
| Affecting factors | High temperature | 5.18 | 21.95 | 99.87 |
| | Strong light | 5.22 | 22.61 | 99.71 |
| | High humidity | 5.45 | 23.11 | 99.83 |
| Accelerated test | | 5.41 | 23.07 | 99.83 |
| Long-term test | | 5.18 | 22.52 | 99.84 |

Therefore agomelatine hydrobromide hydrate in the present invention is stable, which is advantageous to preparations thereof.

Claims:

1. An agomelatine hydrobromide hydrate of formula I:



(I)

wherein X is Br.

2. An agomelatine hydrobromide hydrate of formula I according to claim 1 in the form of crystalline form, exhibiting the following crystal parameters: space group $P2_1/c$, lattice parameters a = 7.5943 (7), b = 23.4046 (19), c = 9.6438 (8) Å, β = 1613.9 (2)°.

3. A method for the preparation of the agomelatine hydrobromide hydrate according to claim 1 or 2, wherein agomelatine is reacted with HBr to produce the agomelatine hydrobromide hydrate.

4. The method for the preparation of the agomelatine hydrobromide hydrate according to claim 3, wherein agomelatine is reacted with HBr in an aqueous organic solvent to produce the agomelatine hydrobromide hydrate.

5. The method for the preparation of the agomelatine hydrobromide hydrate according to claim 4, wherein agomelatine is dissolved in organic solvent before aqueous HBr solution is added to precipitate the crystal of the product.

6. The method for the preparation of the agomelatine hydrobromide hydrate according to claim 5, wherein said aqueous HBr solution is added dropwise.

7. The method for the preparation of the agomelatine hydrobromide hydrate according to claim 4, wherein agomelatine is added to an aqueous organic solvent containing HBr to precipitate the crystal of the product.

8. The method for the preparation of the agomelatine hydrobromide hydrate according to claim 5 or 7, which further includes rinsing and drying the solid after crystallisation.

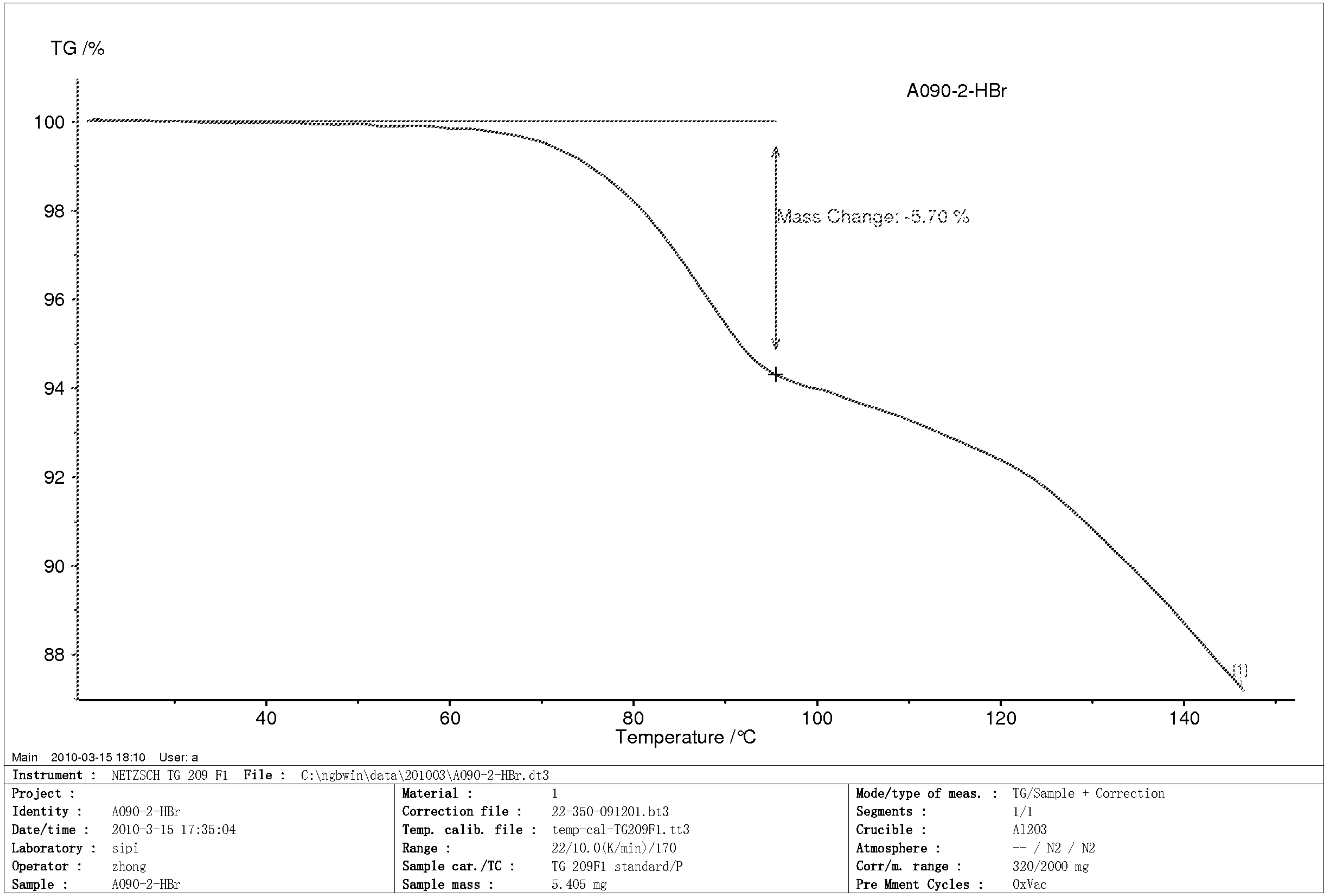
9. The method for the preparation of the agomelatine hydrobromide hydrate according to claim 5 or 7, wherein the reaction temperature is 0-20°C.

10. The method for the preparation of the agomelatine hydrobromide hydrate according to claim 5 or 7, wherein said organic solvent is ethyl acetate, methyl acetate, n-butyl acetate, acetone or acetonitrile.

11. The method for the preparation of the agomelatine hydrobromide hydrate according to claim 10, wherein said organic solvent is ethyl acetate.

12. A pharmaceutical composition, comprising an agomelatine hydrobromide hydrate according to claim 1 or 2 in associated with pharmaceutically acceptable adjuvants or excipients.

13. Use of an agomelatine hydrobromide hydrate according to claim 1 or 2 for the treatment of melatoninergic system disorders, sleep disorders, stress, anxiety, seasonal affective disorder, major depression, cardiovascular diseases, digestive system diseases, insomnia and fatigue caused by jet lag, schizophrenia, phobia or depression disorders.



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**Instrument :** NETZSCH TG 209 F1 **File :** C:\ngbwin\data\201003\A090-2-HBr.dt3

| | | | | | |
|---|---|---|---|---|---|
| **Project :** | | **Material :** | 1 | **Mode/type of meas. :** | TG/Sample + Correction |
| **Identity :** | A090-2-HBr | **Correction file :** | 22-350-091201.bt3 | **Segments :** | 1/1 |
| **Date/time :** | 2010-3-15 17:35:04 | **Temp. calib. file :** | temp-cal-TG209F1.tt3 | **Crucible :** | Al2O3 |
| **Laboratory :** | sipi | **Range :** | 22/10.0(K/min)/170 | **Atmosphere :** | -- / N2 / N2 |
| **Operator :** | zhong | **Sample car./TC :** | TG 209F1 standard/P | **Corr/m. range :** | 320/2000 mg |
| **Sample :** | A090-2-HBr | **Sample mass :** | 5.405 mg | **Pre Mment Cycles :** | OxVac |

Fig. 1

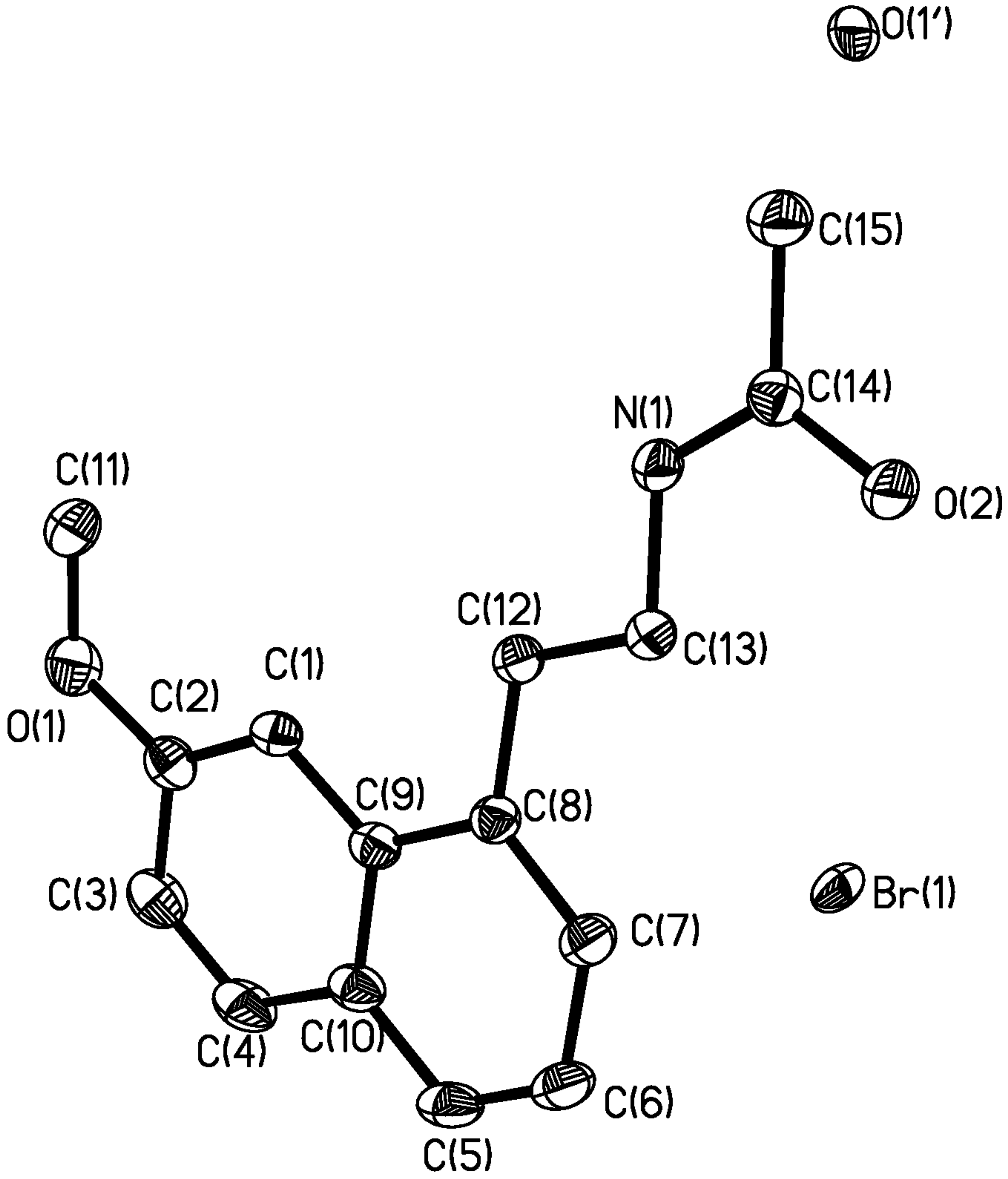


Fig. 2

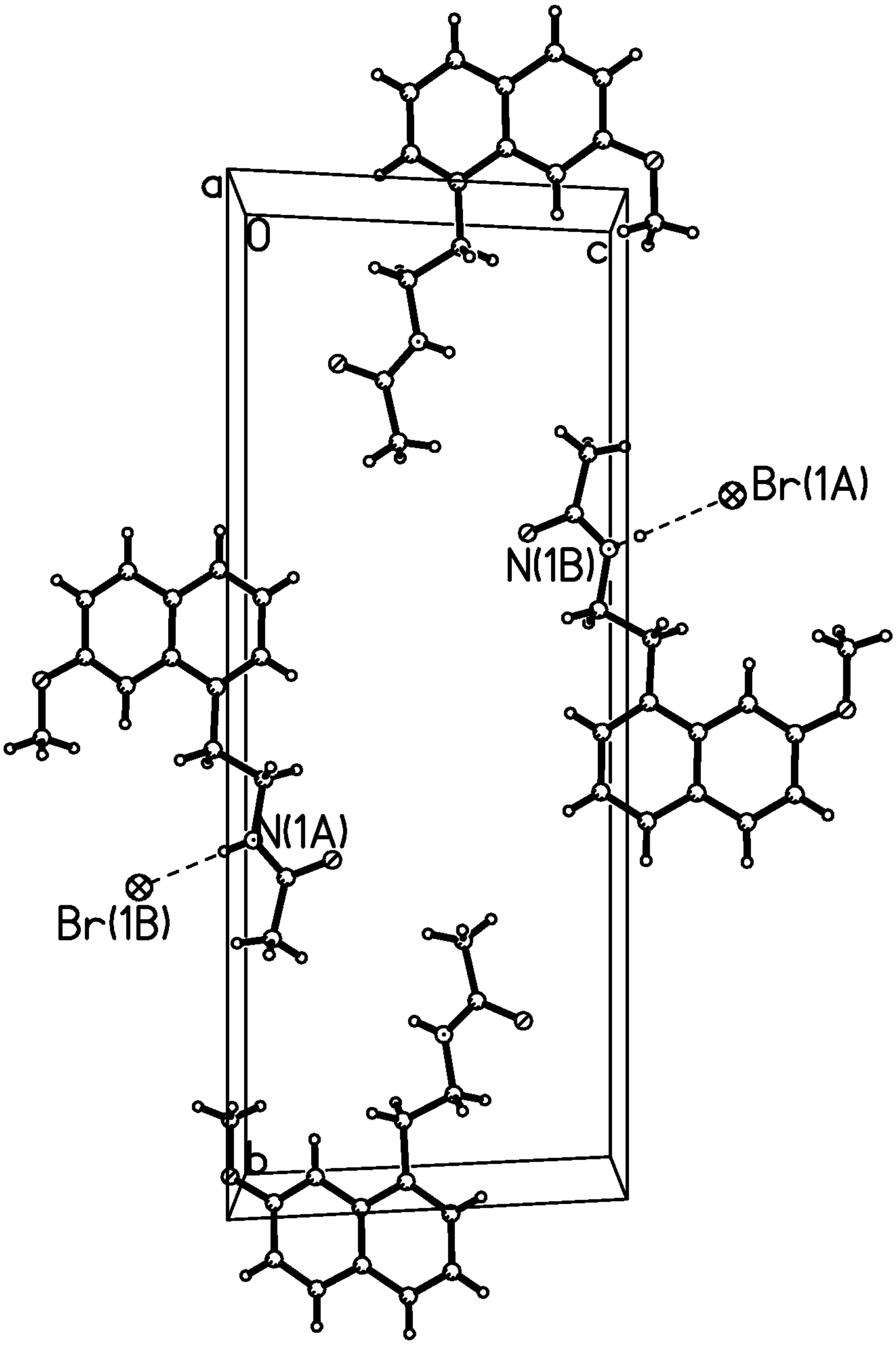
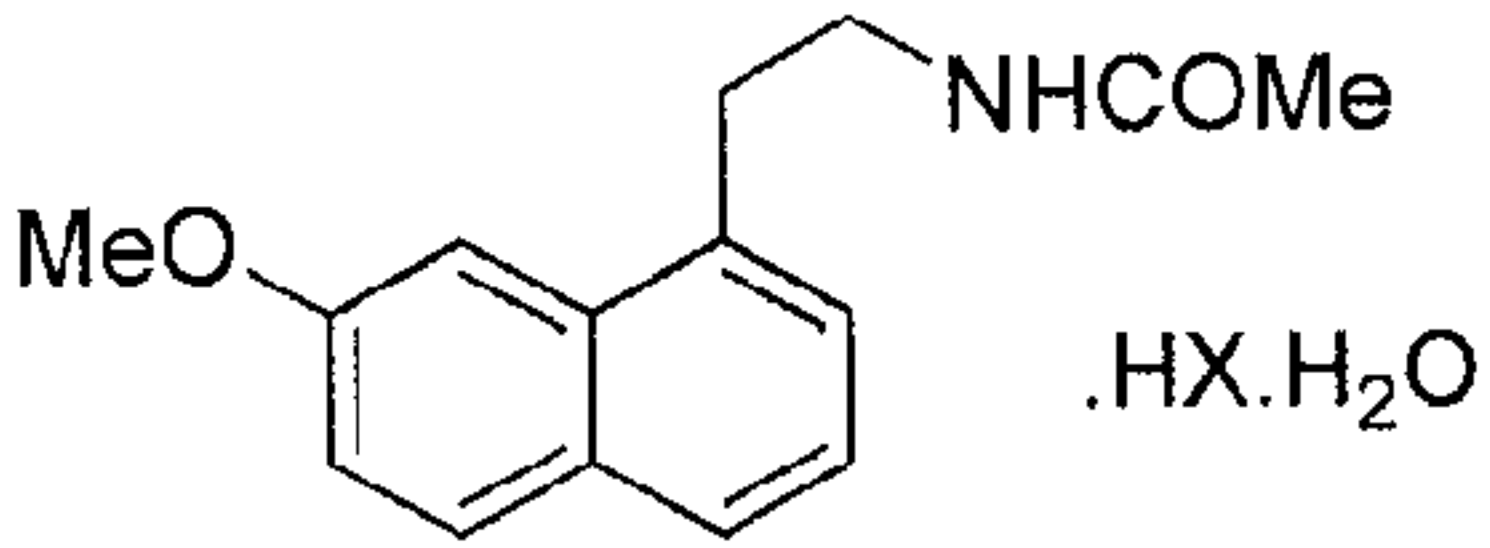


Fig. 3



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