Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 142 (2015) 311–319

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Synthesis and structural elucidation of a novel polymorph of alcaftadine

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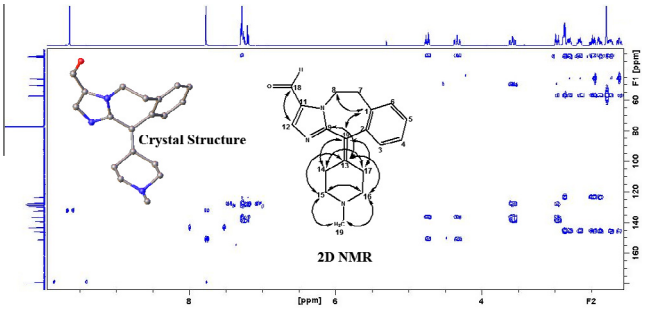
HIGHLIGHTS

- Alcaftadine is characterized in solution as well as in the solid state.
- The structural ambiguity of CH_2 protons is solved using 2D NMR spectra.
- The SCXRD and Hirshfeld surface helped to understand intermolecular interactions.
- PXRD and DSC data is in agreement with novel polymorph.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 7 October 2014
Received in revised form 16 January 2015
Accepted 29 January 2015
Available online 9 February 2015

Keywords:
Polymorph
Alcaftadine
Single crystal structure
2D NMR
Thermal study

ABSTRACT

In this study, we have synthesized and elucidated the structure of the H1 histamine antagonist, 2-(1-methylpiperidin-4-ylidene)-4,7-diazatricyclo[8.4.0.0$^{(3,7)}$]tetradeca-1(14),3,5,10,12-pentaene-6-carbaldehyde in the solution and solid-state. We have also studied the thermal dilapidation of the compound. Solution structure analysis was achieved by employing NMR spectroscopy including 2D experiments NOESY, HSQC and HMBC, while solid state investigations were undertaken using SXRD, PXRD, TGA, DSC, and IR spectroscopy. For the first time the single crystal structure of alcaftadine has now been solved. Crystallographic data are as follows: monoclinic, Cc, $a = 11.5694(6)$ Å, $b = 14.5864(6)$ Å, $c = 10.2688(4)$ Å, $\alpha = 90°$, $\beta = 111.793(3)°$, $\gamma = 90°$, $V = 1609.07(13)$ Å^3, $Z = 4$. The Hirshfeld surface analyses also have been performed using the crystal structure.

Introduction

Antihistamines are a pharmaceutical drug that inhibit the action of histamine by either blocking attachment to the appropriate receptors, or inhibiting the enzymatic activity of histidine decarboxylase which catalyzes the transformation of histidine into histamine. These synthetic molecules are commonly used for the relief of allergies caused by intolerance of proteins. Benzazepines and their derivatives constitute the majority of commercially available antihistamines [1–7]. Alcaftadine was discovered by Janssens et al. [8] and approved by the USFDA in 2010 for allergic conjunctivitis (commercial name Lastacaft). It is mainly an H1 antagonist, but also has a reduced effect on the H2 and H4 histamine receptors. Other synthetic methodology and polymorphs are also reported for alcaftadine (R89674) [9–11].

A number of tricyclic antihistamine (dibenzazepine, cyproheptadine, loratadine, desloratadine, mirtazapine, rupatadine, olopatadine) agents have been synthesized, characterized and developed for medicinal use. The majority of these have some reported analytical data available such as NMR, PXRD, or IR in literature [12–20]. These analyses aid in the further development of medicinal science. Physical data for alcaftadine is very scant, however, so we undertook to report the NMR, IR, DSC, TGA, PXRD and SXRD analyses for the title compound.

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http://dx.doi.org/10.1016/j.saa.2015.01.090
1386-1425/

Experimental

Materials

The chemical agents were purchased in reagent grade and used without further purification. Melting points were recorded on an Ernst Leitz Wetzlar hot-stage microscope and are uncorrected. For the synthesis of alcaftadine the methodology reported by Janssens et al. was followed, M.p. = 440–443 K [8]. A suitable crystal for the X-ray diffraction study was obtained by the slow evaporation method from a solution of dichloromethane and tetrahydrofuran at room temperature.

Methods

NMR spectroscopy

^{1}H NMR, ^{13}C NMR, COSY, NOESY, HSQC, HMBC spectra were recorded employing a Bruker Avance 400 MHz instrument with $CDCl_3$ as the solvent.

Single crystal X-ray analysis (SCXRD) and Hirshfeld analysis

A crystal of alcaftadine suitable for single crystal X-ray diffraction studies was mounted in a stream of cold nitrogen at 100(1) K. The crystal evaluation and data collection were performed on a Bruker Smart *APEXII* diffractometer with Mo Kα radiation (λ = 0.71073 Å). The detector to crystal distance was set at 4.00 cm. The reflections were successfully indexed by an automated indexing routine contained in the *APEXII* program suite [21]. The data collection method involved ω scans of width 0.5. Data reduction was carried using the program *SAINT+* [22]. The structure was solved by direct methods using *SHELXS* and refined [23]. Non-H atoms were first refined isotropically and then by anisotropic refinement with full-matrix least-squares calculations based on F^2 using *SHELXL SHELXS* [23]. All H atoms were positioned geometrically and allowed to ride on their respective parent atoms. The program *OLEX2* was used to prepare molecular graphic images [24]. To investigate the molecular contacts between the molecules Hirshfeld surface calculations of the crystal data and fingerprint analysis was carried out using the Crystal Explorer 3.0 program [25,26]. The bond lengths for hydrogen atoms were set to typical neutron values (C–H = 1.083 Å).

Powder X-ray diffraction (PXRD)

The PXRD of the sample was recorded at room temperature on a Bruker D8 advance diffractometer (Bruker AXS, Karlsruhe, Germany) with Cu Kα radiation (0.15406 nm), at 40 kV, 40 mA. 300 mg of alcaftadine was loaded in a 25 mm poly-methyl methacrylate (PMMA) holder and gently pressed by a clean glass slide to ensure coplanarity of the powder surface with the surface of the holder.

Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA)

Conventional DSC and TGA experiments were conducted to determine melting point and thermal behavior using a SDT Q600 V20.9 (TA Instruments, USA) equipped with Universal Analysis 2000 software (version 4.5A). Accurately, 3.5540 mg was weighed into a crimped aluminum pan and subjected to a thermal scan from 30 to 1000 °C at the heating rate of 10.0 °C/min. A dry nitrogen purge was maintained at 50 mL/min. We also repeated the experiment by purging air at 50 mL/min to examine aerial oxidation degradation with respect to temperature. The presence of solvent, moisture or any degradation during heating was examined.

IR spectroscopy (ATR)

The Fourier transformed infrared spectra were recorded using the attenuated total reflectance (ATR) technique on a PerkinElmer Universal spectrometer at room temperature.

Results and discussion

Chemistry

The alcaftadine was synthesized using the procedure reported by Janssens et al. [8] up to the penultimate stage. In the oxidation step of the synthesis of alcaftadine, various oxidizing agents were claimed [8–11,27], but we used a novel agent. The title compound (Scheme 1) was thus synthesized by using Dess–Martin periodinane (DMP) as the oxidizing agent in place of a metal oxide. In this improved process there is no need for double or triple repeats of the oxidation and purification steps, in addition the method also gives a novel polymorph.

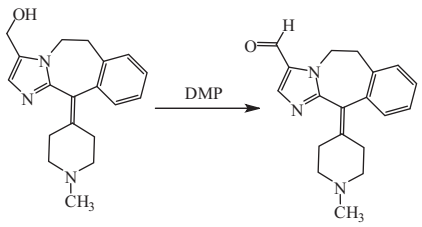
NMR spectroscopy

Prominent peaks were observed in the ^{1}H NMR spectrum of alcaftadine as shown in Fig. 1. Examination of the spectrum confirmed the presence of the aldehyde group at 9.64 ppm, as well as the imidazole proton at 7.76 ppm as singlets, each corresponds to one proton. The aromatic protons 3–6 are confirmed at 7.17–7.28 ppm as multiplet peaks. The N–CH_3 protons appear as a singlet at 2.29 ppm corresponding to three protons. The CH_2 protons of 7, 8 and 14–17 give signals between 2.11 and 4.75 ppm. Each signal corresponds to only one proton except that at 2.35–2.52 ppm, which corresponds to two protons and appears as a multiplet. This may be due to the piperidine methyl group being on one side of the horizontal plane through the piperidine ring, while the CH_2 protons are alternatively above and below this plane.

Further 2D NMR studies were carried out to resolve the ambiguity of the CH_2 protons in the structure. The 2D ^{1}H–^{1}H NOESY (Fig. 2) measurements for alcaftadine were performed, the NOE cross peaks are the result of cross relaxation between neighboring protons that are spatially close to each other (roughly, less than 4 Å). These correlations support the result depicted from the ^{1}H NMR peaks for the aldehyde (H18) and imidazole protons (H12). A noticeable relationship was observed between the H6 (phenyl ring) and the seven membered ring proton H7b. Other associations were also found between the *N*-methyl protons and the piperidine ring protons H15a/b, H16a/b.

The correlation obtained from NOESY experiments (Fig. 2) was found to be unsatisfactory in resolving the complicated piperidine protons 14 through 17. Next we employed HSQC experiments (see ESI) to study the ambiguity of these proton signals, but to no avail.

To identify the piperidine carbon atoms we applied a DEPT experiment. Then we chose HMBC to ascertain the proton signal assignments. From this latter experiment (Fig. 3) we found that carbon C14 at δ = 31.6 ppm (H14a/b: δ = 2.48/2.38 ppm) exhibited HMBC correlation with two proton signals at δ = 2.87 ppm ascribed



Scheme 1. Synthesis of alcaftadine.