Journal of Molecular Structure 983 (2010) 27–31

Contents lists available at ScienceDirect

Journal of Molecular Structure

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

Growth, characterization and crystal structure analysis of rifapentine

K. Zhou [a], J. Li [b,*], D.S. Zheng [b]

[a] College of Materials and Chemical Engineering & Chemistry, Chengdu University of Technology, Chengdu, Sichuan 610059, PR China
[b] College of Chemical Engineering, Sichuan University, Chengdu, Sichuan 610065, PR China

ARTICLE INFO

Article history:
Received 12 January 2010
Received in revised form 17 August 2010
Accepted 17 August 2010
Available online 21 August 2010

Keywords:
Rifapentine
Crystal structure
Characterization
Crystallization

ABSTRACT

Single crystals of rifapentine have been grown by cooling technique. The crystal structure analysis and the molecular arrangement of these crystals have been determined using X-ray diffraction (XRD) method. From single-crystal XRD studies, it is found that the compound crystallizes in the monoclinic system with a space group $P2_1$, and the corresponding lattice parameters were calculated (a = 12.278(3) Å, b = 19.768(4) Å, c = 12.473(3) Å, Z = 2, beta = 112.35(3)°). FT-IR spectra are recorded to identify the various functional groups present in the compound. The UV–Vis spectrum of rifapentine takes place at a wavelength of 236, 255, 334 and 474 nm, respectively. The thermal stability of the crystal is determined from TG/DTA curves.

1. Introduction

Rifapentine is a potent antibiotic marketed by Sanofi–Aventis under the brand name Priftin. Rifapentine and rifabutin are commonly used to treat tuberculosis acquired in HIV-positive patients. A very important feature of rifapentine is its ability to prevent drug resistance. Rifapentine is a rifamycin derivative with excellent activity against mycobacterium tuberculosis in vitro and in animals [1,2]. It is not only one of the most effective antibiotic, but it is especially very effective low-dosage and long-term treatment of pulmonary tuberculosis [3]. The drug has an advantage of five times longer half-life than rifampicin and it is recommended for use in intermittent therapy [4]. A crystal structure of rifapentine in complex with its bacterial target, RNA polymerase, is known (Protein Data Bank ID 2A69). It is highly probable that the small molecule structure of rifapentine does also exist but may not be available for the general scientific community. In any case, study of the polymorphism in drugs is of high importance since the drug solubility and bioavailability may depend on the administered crystal polymorph of the compound, that also presents patent issues for pharmaceutical companies.

In the previous work, two different crystal modifications of rifapentine were identified [5]. In this paper, the single crystal of rifapentine was obtained from methanol solvent and basic data including crystal structure and physical characteristic are reported.

2. Experimental procedure

2.1. Crystal growth of rifapentine

A brick red crystalline rifapentine power ($C_{47}H_{64}N_4O_{12}$, molecular weight 877.04) used to experiment was purchased from Leshan San Jiu-Long March Pharmaceuticals Co., Ltd., China. Its mass fraction determined by HPLC, is better than 99.0%. Fig. 1 shows the chemical structure of this compound. The known amount of rifapentine solid was dissolved in methanol at 30 °C above the saturation temperature in the 300 ml-jacket vessel. The saturation temperature was determined by the solubility curve for the known solution concentration [6]. After the clear solution was obtained, the supersaturation was generated by cooling the solution from the initial temperature to 25 °C at cooling rate of 1 °C/d to yield single crystals. Parallelepiped shaped crystals of rifapentine were obtained.

2.2. Crystal structure determination

X-ray diffraction from an air-dried crystal of rifapentine (0.33_0.30_0.26 mm^3) was measured using a Rigaku MM-007 four-circle X-ray diffractometer operating at 50 kV and 20 mA, using Mo Kα radiation (λ = 0.71073 Å) at 293 K. The cooling device is Enraf–Nonius FR558. The θ range is between 1.77° and 27.87°. Image processing and data reduction were done by using the Rigaku/MSC software. Intensities 23,270 reflections, among which 12,944 are independent, were scaled and corrected using ABSCOR. The structure was solved by direct methods using SHELXS-97 and refined by SHELXL-97 using least-squares on F^2 [7]. In the

* Corresponding author. Tel./fax: +86 028 85460936.
E-mail address: lijun@scu.edu.cn (J. Li).

0022-2860/$ - see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.molstruc.2010.08.023

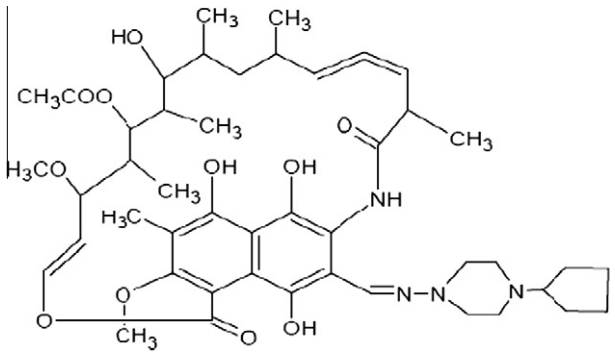

Fig. 1. Chemical structure of rifapentine.

Table 1
Bond lengths (Å) for rifapentine–methanol.

Bonds	Lengths	Bond	Angle
C(13)–H(13B)	0.9800	H(18A)–C(18)–H(18B)	109.5
C(13)–H(13C)	0.9800	H(18A)–C(18)–H(18C)	109.5
C(15)–H(15)	0.9500	H(18B)–C(18)–H(18C)	109.5
C(16)–H(16)	0.9500	C(23)–C(24)–H(24A)	109.5
C(18)–H(18)	0.9800	H(24A)–C(24)–H(24B)	109.5
C(21)–H(21)	0.9800	H(24A)–C(24)–H(24C)	109.5
C(27)–H(27)	0.9800	H(50AM)–C(50M)–H(50BM)	109.5
C(29)–H(29)	0.9800	H(50AM)–C(50M)–H(50CM)	109.5
C(31)–H(31)	0.9800	H(50BM)–C(50M)–H(50CM)	109.5
C(32)–H(32)	0.9500	H(39A)–C(39)–H(39B)	108.0
C(33)–H(33)	0.9500	H(41A)–C(41)–H(41B)	108.0
C(38)–H(38)	0.9500	H(42A)–C(42)–H(42B)	108.2
O(4)–C(26)	1.338(3)	H(44A)–C(44)–H(44B)	109.2
O(5)═C(26)	1.209(4)	H(45A)–C(45)–H(45B)	108.5
O(10)–H(10)	0.8400	H(46A)–C(46)–H(46B)	108.6
O(11)–H(11)	0.8400	H(47A)–C(47)–H(47B)	109.3

measurement, the R(int) value was 0.0353, the goodness-of-fit on F^2 1.048. A single weighting scheme was applied, and the refinement continued until the final deviation factors, R_1 and R_w, were 0.0631 and 0.1698, respectively.

2.3. Physical characterization

The spectra were recorded on an IR spectrophotometer (FT-IR, 670 NEXUS, USA) after respective samples were mixed with dried KBr powder and compressed to a 12 mm disc by a hydraulic press at 10 ton compression for 30 s.

The cavity of the metal sample holder of X-ray diffractometer (XRD) was filled with ground sample powder and then smoothed out with a spatula. XRD pattern of rifapentine crystals was obtained with the XRD (X′ Pert Pro MPD) operated at 40 kV and 40 mA. Cu Kα radiation was utilized in the measurements. The diffraction angles 2θ ranged from 5° to 50°. All XRD measurements were performed at ambient temperature.

The UV–Vis absorption spectrum of rifapentine was recorded using Shimadzu UV2100 spectrophotometer in the wavelength range 200–1000 nm. Thermal analysis of rifapentine was carried out using EXSTAR 6000 simultaneous thermo-gravimetric/differential thermal (TG/DTA) analyzer. The sample was scanned in the temperature range 25–450 °C at a rate of 10 °C/min.

3. Results and discussion

3.1. Crystal structure

The selected bond lengths and angles of rifapentine–methanol are given in Table 1. The molecular configuration of rifapentine and the atom numbering scheme are shown in Fig. 2, and the projection along the a-axis is shown in Fig. 3. The hydrogen-bonding data are listed in Table 2.

Fig. 2 is a perspective view of the molecular structure of rifapentine. The crystal packing is a stacking. In the molecules of the compound, the five-membered ring of furan and naphthalin are planar. At the same time, the six-membered ring of piperazine and the five-membered of cyclopentyl have a chair conformation. The data in Table 1 show that C(13), C(18), C(21), C(27), C(29) and C(31) are all equal to 0.98 Å. The C–H bond lengths for C(15), C(16), C(32), C(33) and C(38) are shortened to 0.95 Å due to the intensive attraction by double bonds. For the same reason, the C═O double bond lengths are shorter than C–O bond lengths due to the intensive attraction by double bonds. The O–H bond lengths are all 0.84 Å

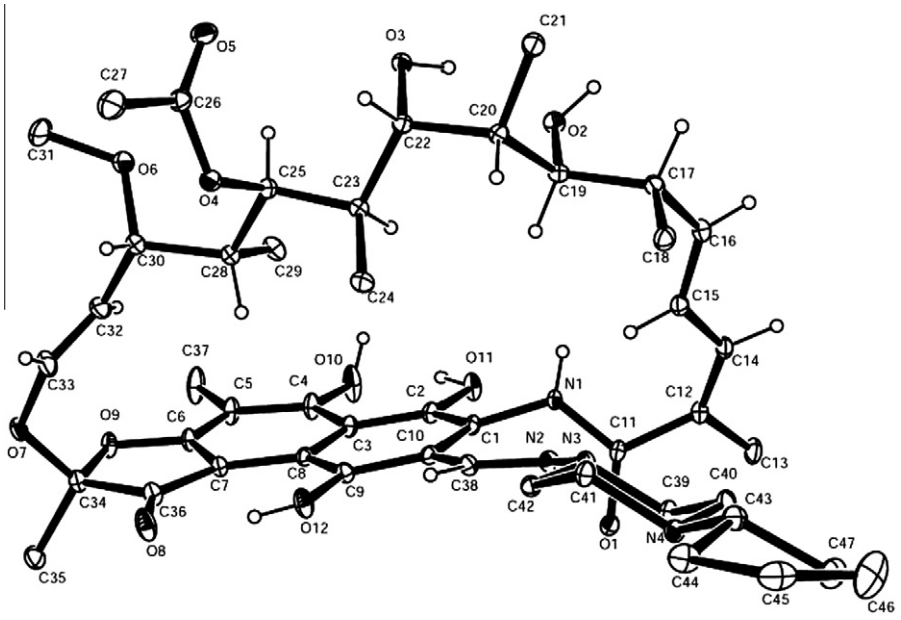

Fig. 2. Molecular structure of rifapentine.