Molecular and Crystal Structure of Sildenafil Base

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Sildenafil citrate monohydrate, well known as Viagra®, is a drug for the treatment of erectile dysfunction. Here we present the X-ray crystal structure of the sildenafil base, $C_{22}H_{30}N_6O_4S$. The compound crystallizes in the monoclinic system, space group $P2_1/c$ with the unit cell parameters $a = 17.273(1)$, $b = 17.0710(8)$, $c = 8.3171(4)$ Å, $\beta = 99.326(2)$, $Z = 4$, $V = 2420.0(3)$ Å^3. A comparison with the known crystal structures of sildenafil citrate monohydrate and sildenafil saccharinate is also presented.

Key words: X-Ray, Crystal Structure, Sildenafil, Viagra

Introduction

Sildenafil, 5-[2-ethoxy-5-(4-methylpiperazin-1-yl) sulfonyl-phenyl]-1-methyl-3-propyl-6*H*-pyrazolo[4,3-*d*]pyrimidin-7-one, improves penile erections in men with erectile dysfunction by selectively inhibiting the cGMP-specific phosphodiesterase type 5 [1]. The crystal structures of sildenafil citrate monohydrate (**1**) and sildenafil saccharinate (**2**) have been reported earlier [2, 3]. Both salt structures comprise the sildenafil base (Fig. 1) protonated at the methylated nitrogen atom of the piperazine ring. In a study of the physicochemical properties of sildenafil citrate and base, Melnikov *et al.* presented the powder X-ray diffraction pattern of the sildenafil base (**3**) and calculated the crystal lattice parameters of **3** [4]. However, the three-dimensional crystal structure of the sildenafil base (Fig. 1) has not been determined yet. The aim of this study was to determine the crystal and molecular structure of sildenafil base (**3**) by single-crystal X-ray diffraction analysis.

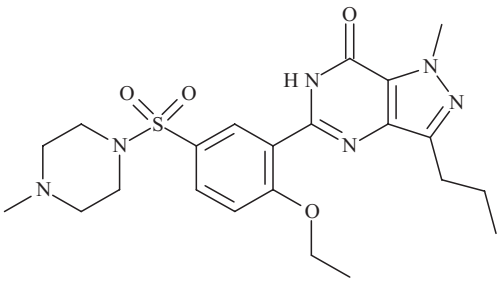


Fig. 1. Molecular structure of the title compound sildenafil base (**3**).

Results and Discussion

The bond lengths and angles in **3** are close to their standard values [5, 6]. For convenience we denote the pyrimidine, pyrazole, phenyl, and piperazine rings in the sildenafil molecule by capital letters A, B, C, and D, respectively (Fig. 2).

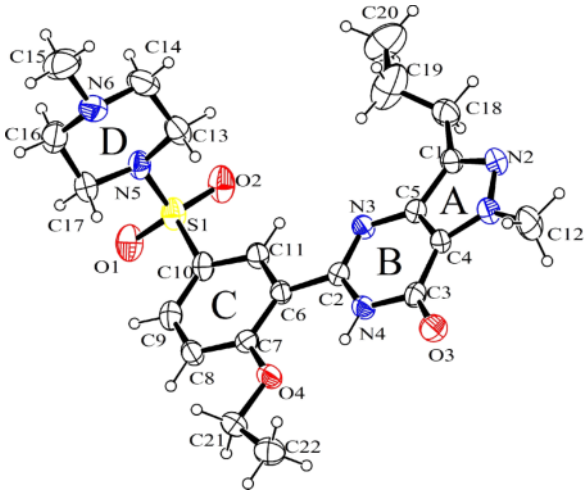


Fig. 2 (color online). ORTEP-III [7] drawing of the molecular structure of **3** in the crystal showing the adopted atom labeling scheme.

Table 1. Selected torsion angles in the structures of compounds **1** – **3** (deg) with estimated standard deviations in parentheses.

Torsion angle	**1**	**2**	**3**
C1–C18–C19–C20	−173.5(6)	−178.2(3)	−174.5(6)
C5–C1–C18–C19	97.4 (8)	−160.1(4)	−45.1(6)
C7–O4–C21–C22	179.8(5)	175.0(2)	175.8(2)
C8–C7–O4–C21	7.2(8)	13.0(4)	6.5(4)
C10–S1–N5–C13	−61.7(4)	−68.2(2)	−64.2(3)
N5–S1–C10–C11	94.4(5)	89.6(2)	84.9(2)

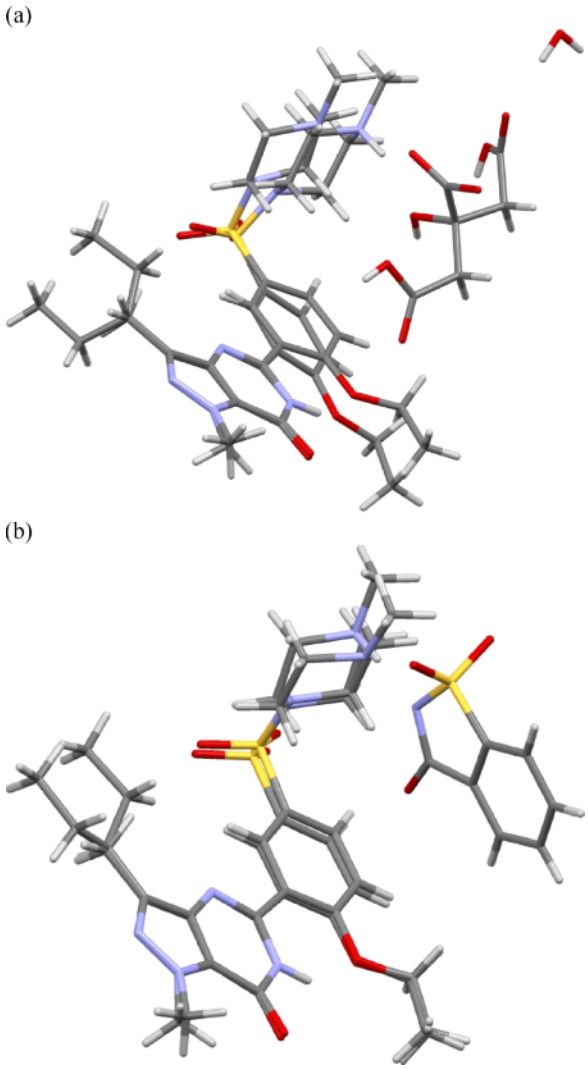


Fig. 3 (color online). Superimposed structures of the molecular structure of **3** with **1** (sildenafil citrate) (a) and **2** (sildenafil saccharinate) (b).

The pyrazolopyrimidine bicyclic system (A + B) and the phenyl ring (C) in **1**–**3** are almost coplanar. The dihedral angle between least-squares planes of the pyrazolopyrimidine system and the phenyl ring (A + B/C) is 11.6° in **1**, 2.4° in **2** and 5.6° in the molecular structure of **3**. The ethoxy groups in **1**–**3** lie also almost in the A + B + C plane. In sildenafil saccharinate (**2**) the propyl group lies close to the A + B + C average plane. In sildenafil citrate **1** the propyl group is situated out of the A + B + C plane and at the side opposite to the methylpiperazine fragment. In the sildenafil base (**3**) the propyl group is also situated out of the A + B + C plane but on the same side as the methylpiperazine fragment. In all three crystal structures the piperazine ring is in a chair conformation with methyl and sulfonyl groups attached equatorially. The values of selected torsion angles for **1**, **2** and **3** are given in Table 1.

Table 2. Intramolecular hydrogen bonding geometry (Å, deg).

Compound	D–H···A	D–H	H···A	D···A	∠D–H···A
1	N4–H···O4	0.88	1.94	2.622(6)	134
2	N4–H···O4	0.88	1.94	2.653(3)	137
3	N4–H···O4	0.86	1.95	2.645(3)	137

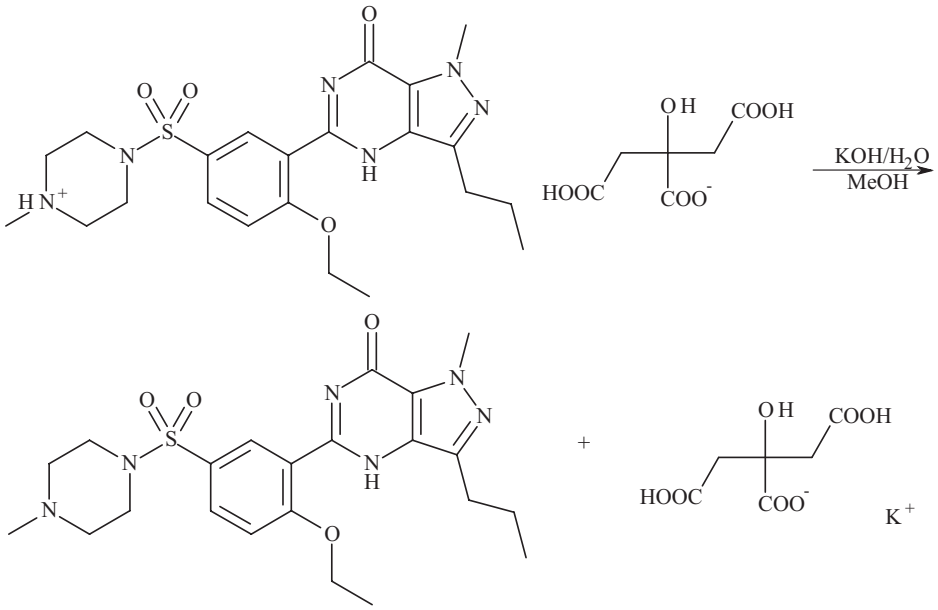
A graphical comparison of the molecular structures of **1**, **2** and **3** by means of the superimposed pyrazolopyrimidone ring systems is shown in Fig. 3.

The molecule of sildenafil in the structures of **1**, **2** and **3** has one intramolecular hydrogen bond with the geometric parameters given in Table 2. There are some short intermolecular C–H···O contacts in the crystal structure of **3**, which can be characterized as weak hydrogen bonds with electrostatic or mostly electrostatic nature [5].

The crystal structure determination of the sildenafil base (**3**) allows the inspection of the correctness of the powder diffraction pattern indexing of **3** as published by Melnikov *et al.* [4]. The theoretical diffraction pattern calculated from the atomic coordinates of **3** is consistent with the experimental powder diffraction pattern published in ref. [4]. Unfortunately, the lattice parameters of **3** as calculated in ref. [4] ($a = 8.66$, $b = 34.27$, $c = 8.93$ Å, $\beta = 96.63°$, $V = 2632.5$ Å^3) are far from the correct values, giving a wrong calculated crystal density of 1.18 g cm^{-3} instead of the correct value of 1.30 g cm^{-3}

Conclusion

The molecular and crystal structure of sildenafil base have been determinated by single-crystal X-ray structure analysis. The sildenafil molecule is built from a rigid central core fragment consisting of a π-conjugated bicyclic pyrazolopyrimidone and a phenyl ring. The bulky methylpiperazine-sulfonyl fragment seams to be insensitive to its rotation with respect to the central core fragment. The only flexible part of the molecule is the propyl group which adopts three different positions in the three known derivatives of silde-



Scheme 1. Synthesis of the sildenafil base **3**.

nafil. The molecule of the sildenafil base has one intramolecular hydrogen bond, and in the crystal structure the sildenafil molecules are connected only by van der Waals forces.

Experimental Section

The sildenafil base **3** was obtained from sildenafil citrate by reaction with a stoichiometric amount of aqueous KOH solution as shown in Scheme 1. Single crystals were grown from an acetone solution by slow evaporation of the solvent at room temperature. Experimental and refinement details of the X-ray diffraction study are summarized in Table 3.

X-Ray structure determination

The reflection intensities were measured at 190 K on a Bruker Nonius KappaCCD diffractometer with graphite-monochromatized MoK_α radiation ($\lambda = 0.71073$ Å). The data collection was performed using the KappaCCD Server Software [8], cell refinement was done with SCALEPACK [9], and the data were reduced by DENZO and SCALEPACK [9]. The structure was solved by Direct Methods (SHELXS-97 [10]) and refined anisotropically on F^2 values using SHELXL-97 [10]. All hydrogen atoms were positioned geometrically and refined with the riding model on the adjacent non-hydrogen atoms.

CCDC 853915 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 3. Crystallographic data and numbers pertinent to data collection and structure refinement for **3**.

Formula	$C_{22}H_{30}N_6O_4S$
M_r	474.59
Crystal size, mm^3	$0.40 \times 0.30 \times 0.05$
Crystal system	monoclinic
Space group	$P2_1/c$
a, Å	17.273(7)
b, Å	17.0710(8)
c, Å	8.3171(4)
β, deg	99.326(7)
V, Å^3	2420.0(2)
Z	4
D_{calcd}, g cm^{-3}	1.30
μ(MoK_α), cm^{-1}	1.7
F(000), e	1008
hkl range	$\pm 22, -18 \rightarrow +21, \pm 10$
$((\sin\theta)/\lambda)_{max}$, Å^{-1}	0.6475
Refl. measured / unique / R_{int}	9580 / 5384 / 0.098
Param. refined	298
$R(F)$ / $wR(F^2)^a$ (all refl.)	0.069 / 0.172
GoF $(F^2)^a$	0.96
$\Delta\rho_{fin}$ (max / min), e Å^{-3}	0.19 / −0.26

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