

Sildenafil citrate monohydrate

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Key indicators

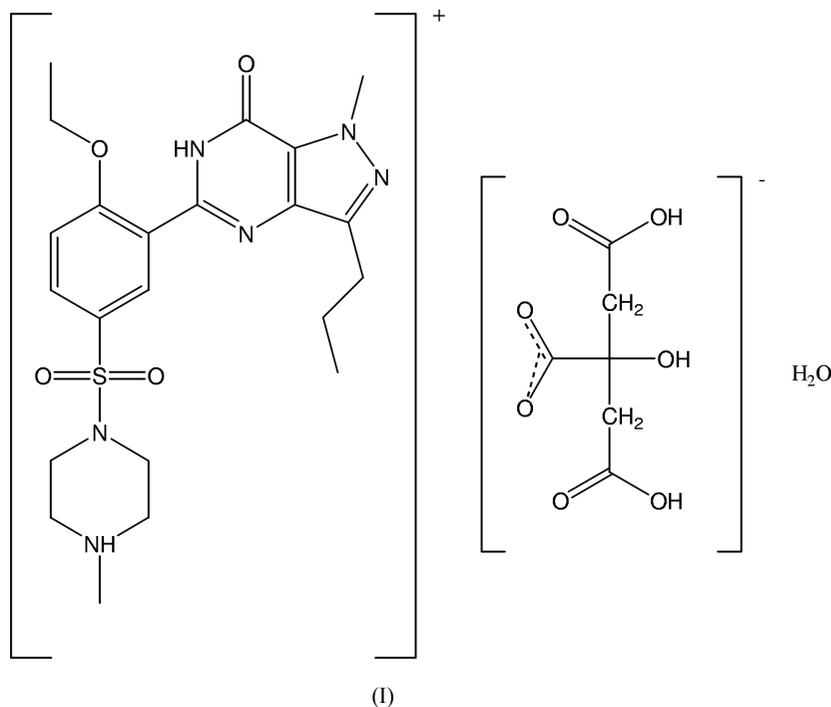
Single-crystal X-ray study
 $T = 173\text{ K}$
Mean $\sigma(\text{C}-\text{C}) = 0.008\text{ \AA}$
 R factor = 0.079
 wR factor = 0.154
Data-to-parameter ratio = 13.7For details of how these key indicators were automatically derived from the article, see <http://journals.iucr.org/e>.

Sildenafil citrate is well known as Viagra for the treatment of erectile dysfunction. In the title compound (systematic name: 1-[[3-(6,7-Dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazinium citrate monohydrate), $\text{C}_{22}\text{H}_{31}\text{N}_6\text{O}_4\text{S}^+\cdot\text{C}_6\text{H}_7\text{O}_7^- \cdot \text{H}_2\text{O}$, the pyrazolopyrimidone ring system and the benzene ring are almost coplanar, enabling an intramolecular hydrogen bond between the pyrazolopyrimidone NH group and the O atom of the ethoxy group. One of the N atoms of the piperazine ring is protonated and the citrate molecule exists as an anion. The crystal packing is stabilized by several hydrogen bonds.

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Comment

Sildenafil citrate is used to treat male erectile dysfunction under the trade name Viagra. The parent base, sildenafil, is a potent selective inhibitor of the enzyme phosphodiesterase (PDE-5), which destroys cyclic guanosine monophosphate (cGMP), itself a dilator of blood vessels in the body (Terrett *et al.*, 1996). The discovery and development of sildenafil has been a revolutionary event in medicine and society. A detailed review of sildenafil citrate has been published by McCullough (2002).



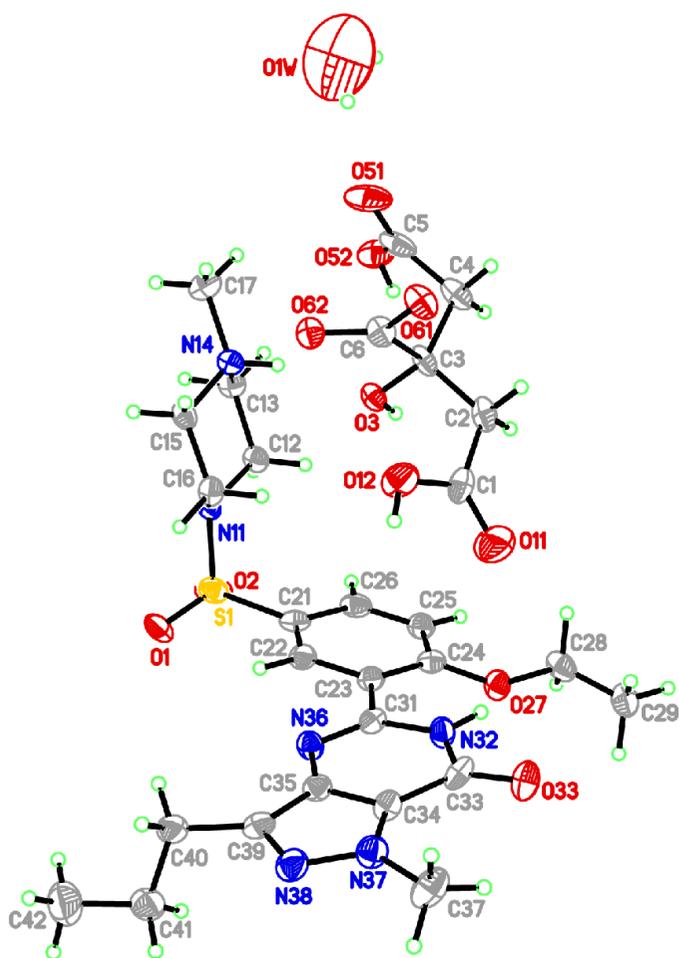


Figure 1
Perspective view of the title compound, with the atom numbering; displacement ellipsoids are drawn at the 30% probability level.

and angles can be regarded as normal (Cambridge Structural Database, Version 1.6 plus three updates; *MOGUL* Version 1.0; Allen, 2002). The piperazine ring shows the expected chair conformation, with the methyl and sulfonyl groups attached equatorially. The propyl and ethoxy side chains are in a *trans* conformation.

The crystal structure of isosildenafil, an isomeric compound of sildenafil, methylated at N2 of the pyrazolopyrimidone ring system, has been reported by El-Abadelah *et al.* (1999). The main difference between (I), the sildenafil cation of (I), the pyrazolopyrimidone ring system and the benzene ring are almost coplanar. The dihedral angle between the two cyclic groups is $11.6(3)^\circ$, whereas this angle is $43.3(1)^\circ$ in isosildenafil. As a result, in (I), there is a hydrogen bond between the pyrazolopyrimidone NH group and the O atom of the ethoxy group (Table 2). In isosildenafil, however, this interaction is significantly weaker ($N-H = 0.95 \text{ \AA}$, $H \cdots O = 2.35 \text{ \AA}$, $N \cdots O = 2.767 \text{ \AA}$ and $N-H \cdots O = 106.1^\circ$). Furthermore, the conformation of the propyl chains differ. The conformation is *trans* [$-173.4(6)^\circ$] in (I) and *gauche* in isosildenafil [$-60.6(7)^\circ$]. A least-squares fit of (I) with isosildenafil is shown in Fig. 2. Apart from the intramolecular

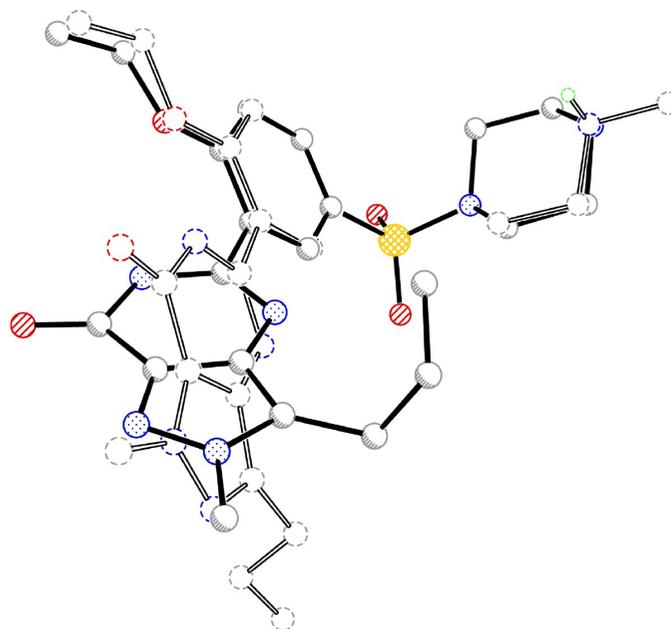


Figure 2
Least-squares fit of sildenafil (open bonds) and isosildenafil (closed bonds). The benzene ring, the SO_2 group and the piperazine ring were fitted (r.m.s. deviation = 0.122 \AA).

hydrogen bond, there are several intermolecular hydrogen bonds. It is interesting to note that there is no direct hydrogen bond between the sildenafil molecules, but the citrate anions function as a link between them. The water molecule does not act as an acceptor but just as a donor to a citrate anion and to sulfonyl atom O1 of a sildenafil cation (Table 2). The deprotonated carboxy group of the citrate molecule shows a significantly different geometry than the two other carboxyl groups: the two C—O bonds have the same length and the O—C—O angle is enlarged (Table 1).

The cell parameters of sildenafil citrate without any solvent, determined by powder diffraction (Melnikov *et al.*, 2003), are totally different from those of the title compound: $a = 26.98 \text{ \AA}$, $b = 11.95 \text{ \AA}$, $c = 16.68 \text{ \AA}$, and $\beta = 106.96^\circ$ $V = 5143.9 \text{ \AA}^3$.

Experimental

Sildenafil citrate was obtained as a gift sample from CIPLA, Mumbai, India, and used without further purification. Recrystallization from dimethylformamide yielded needles of (I) after slow evaporation of the solvent. The title compound melts at 460 K . IR (KBr, $\nu \text{ cm}^{-1}$): $3616 (m)$, $3478 (m)$, $3300 (s)$, $3029 (m)$, $2962 (m)$, $2870 (m)$, $2563 (w)$, $2362 (m)$, $1702 (vs)$, $1581 (s)$, $1491 (m)$, $1462 (m)$, $1394 (m)$, $1359 (m)$, $1280 (m)$, $1250 (m)$, $1172 (s)$, $1096 (w)$, $1027 (m)$, $995 (s)$, $940 (m)$, $808 (m)$, $736 (s)$, $690 (m)$, $657 (m)$, $617 (m)$, $588 (s)$, $557 (m)$; $^1\text{H NMR}$ (DMSO- d_6 , p.p.m.): $0.86\text{--}0.90 (t, 3\text{H}, \text{CH}_3-)$, $1.27\text{--}1.31 (t, 3\text{H}, \text{CH}_3-)$, $1.64\text{--}1.73 (m, 2\text{H}, \text{CH}_2-)$, $2.29 (s, 4\text{H}, \text{CH}_2-)$, $2.55\text{--}2.75 (t, 2\text{H}, \text{CH}_2-)$, $2.96 (bs, 1\text{H}, \text{NH-})$, $3.94 (bm, 13\text{H}, \text{N-CH-})$, $4.11\text{--}4.2 (s, 3\text{H}, \text{N}^+-\text{CH}_3-)$, $7.34\text{--}7.36 (d, 1\text{H}, \text{ArH-})$, $7.79\text{--}7.83 (d, 2\text{H}, \text{ArH-})$, $12.19 (bs, 1\text{H}, \text{N}^+\text{H-})$; $^{13}\text{C NMR}$ (DMSO- d_6 , p.p.m.): $14.24 (q, \text{C42}, \text{CH}_3-)$, $14.67 (q, \text{C29}, \text{CH}_3-)$, $22.13 (t, \text{C41}, \text{CH}_2-)$, $27.53 (t, \text{C2}, \text{CH}_2-)$, $38.3 (t, \text{C40}, \text{CH}_2-)$, $39.1\text{--}40.35 (t, \text{C12}, \text{C13}, \text{C15}, \text{C16}, \text{CH}_2-)$, $43.64 (q, \text{C37}, \text{CH}_3-)$, $44.71 (d, \text{C35}, \text{C}=\text{C-})$, $53.34 (d, \text{C34}, \text{C}=\text{C-})$, $65.39 (t, \text{C28}, \text{CH}_2-)$, $72.59 (q, \text{C17}, \text{CH}_3-)$, 124.03

(*d*, C26, ArCH—), 124.82 (*d*, C22, ArCH—), 126.52 (*s*, C23), 130.43 (*d*, C25, ArCH—), 132.02 (*s*, C24, ArC—), 138.18 (*s*, C21, ArC), 145.45 (*s*, C39, C=N—), 148.55 (*s*, C6, COO[−]—), 154.24 (*s*, C5, HOOC—), 160.45 (*s*, C33, C=O—), 171.87 (*s*, C31), 175.81 (*s*, C3, citrate C—). Analysis calculated for C₂₈H₄₀N₆O₁₂S: C 49.11, H 5.89, N 12.27%; found: C 49.31, H 5.81, N 12.4%.

Crystal data

C₂₂H₃₁N₆O₄S⁺·C₆H₇O₇[−]·H₂O

M_r = 684.72

Orthorhombic, *Pbca*

a = 24.002 (4) Å

b = 10.9833 (17) Å

c = 24.364 (3) Å

V = 6422.9 (17) Å³

Z = 8

D_x = 1.416 Mg m^{−3}

Mo *K*α radiation

Cell parameters from 8732

reflections

θ = 2.0–23.1°

μ = 0.17 mm^{−1}

T = 173 (2) K

Rod, colourless

0.26 × 0.12 × 0.11 mm

Data collection

Stoe IPDS-II two-circle diffractometer

ω scans

Absorption correction: multi-scan

(*MULABS*; Spek, 2003;

Blessing, 1995)

T_{min} = 0.937, *T_{max}* = 0.951

44385 measured reflections

5856 independent reflections

1970 reflections with *I* > 2σ(*I*)

R_{int} = 0.098

θ_{\max} = 25.4°

h = −28 → 28

k = −13 → 13

l = −29 → 27

Refinement

Refinement on *F*²

R [*F*² > 2σ(*F*²)] = 0.079

wR (*F*²) = 0.154

S = 0.78

5856 reflections

428 parameters

H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0407P)^2]$

where $P = (F_o^2 + 2F_c^2)/3$

(Δ/σ)_{max} < 0.001

$\Delta\rho_{\max} = 0.38 \text{ e } \text{Å}^{-3}$

$\Delta\rho_{\min} = -0.42 \text{ e } \text{Å}^{-3}$

Table 1

Selected geometric parameters (Å, °).

S1—O1	1.428 (4)	C34—C35	1.385 (8)
S1—O2	1.443 (4)	C35—N36	1.361 (7)
S1—N11	1.630 (5)	C35—C39	1.417 (8)
N11—C16	1.470 (7)	N37—N38	1.352 (6)
N11—C12	1.485 (6)	N37—C37	1.450 (7)
C13—N14	1.507 (7)	C1—O11	1.204 (7)
N14—C17	1.486 (7)	C1—O12	1.293 (7)
N14—C15	1.504 (7)	C3—O3	1.423 (6)
C31—N36	1.295 (7)	C5—O51	1.224 (8)
C31—N32	1.383 (7)	C5—O52	1.318 (8)
N32—C33	1.367 (7)	C6—O61	1.258 (7)
C33—C34	1.447 (8)	C6—O62	1.259 (7)
C34—N37	1.359 (7)		
O11—C1—O12	120.6 (7)	O61—C6—O62	126.3 (6)
O51—C5—O52	119.9 (7)		

Table 2

Hydrogen-bonding geometry (Å, °).

<i>D</i> —H··· <i>A</i>	<i>D</i> —H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> —H··· <i>A</i>
N14—H14···O3	0.93	1.88	2.764 (6)	159
N14—H14···O62	0.93	2.30	2.911 (6)	123
N32—H32···O27	0.88	1.94	2.622 (6)	134
O12—H12···N38 ⁱ	0.84	1.98	2.771 (7)	157
O3—H3···O61 ⁱⁱ	0.84	1.77	2.605 (5)	173
O52—H52···O62 ⁱⁱ	0.84	1.73	2.490 (6)	149
O1W—H1WA···O1 ⁱⁱⁱ	0.84	2.11	2.946 (13)	179
O1W—H1WB···O51	0.84	1.84	2.678 (16)	179

Symmetry codes: (i) 1 − *x*, 2 − *y*, 1 − *z*; (ii) $\frac{3}{2} - x, y - \frac{1}{2}, z$; (iii) $\frac{1}{2} + x, y, \frac{1}{2} - z$.

H atoms were located in a difference map, positioned geometrically and refined with fixed individual displacement parameters [set to 1.2 times *U_{eq}* value of the parent atom (1.5 for methyl groups)] using a riding model, with N—H = 0.88 Å, O—H = 0.84 Å and C—H distances ranging from 0.93 to 0.99 Å. In addition, the torsion angles about the hydroxyl groups and the methyl group at the pyrazolopyrimidone ring system were refined.

Data collection: *X-AREA* (Stoe & Cie, 2001); cell refinement: *X-AREA*; data reduction: *X-AREA*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *XP* in *SHELXTL-Plus* (Sheldrick, 1991); software used to prepare material for publication: *SHELXL97*.

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