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Sumatriptan, an antimigraine drug

K. Ravikumar,[a]* B. Sridhar[a] and Harihara Krishnan[b]

[a]Laboratory of X-ray Crystallography, Indian Institute of Chemical Technology, Hyderabad 500 007, India, and [b]SMS Pharma Research Centre, Hyderabad 500 038, India

Correspondence e-mail: ravikumar_iict@yahoo.co.in

Key indicators

Single-crystal X-ray study
T = 273 K
Mean σ(C–C) = 0.003 Å
R factor = 0.045
wR factor = 0.127
Data-to-parameter ratio = 14.1

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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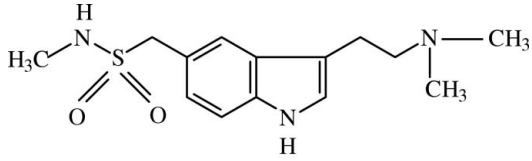
Sumatriptan, {3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl}-*N*-methylmethanesulfonamide, $C_{14}H_{21}N_3O_2S$, is reported in its parent form. The molecular geometry is similar to that of sumatriptan succinate, but the two differ in their side-chain orientations. Intermolecular N—H···O and N—H···N hydrogen bonds form a glide-symmetric chain along the *c* axis.

Comment

Sumatriptan (with trademarks Imitrex and Imigran) is a triptan drug originally developed by Glaxo for the treatment of migraine headaches. Several dosage forms for sumatriptan have been approved, including tablets, solution for injection and nasal inhalers. Migraine headaches are believed to result from dilatation of the blood vessels in the head. Sumatriptan causes constriction of the blood vessels, thus relieving the headache. While it is very effective in relieving migraine, it does not prevent or reduce the number of attacks. The drug is generally well tolerated. However, up to 15% of patients consistently report chest symptoms, including chest pressure, tightness and pain, often mimicking angina pectoris (Brown *et al.*, 1991; Plosker & McTavish, 1994; Visser *et al.*, 1996). The biological and pharmacological aspects of sumatriptan have been studied extensively (Evers *et al.*, 2003; Dahlof, 2003; Diener, 2003). Recently, the crystal structure of sumatriptan succinate (Ravikumar *et al.*, 2004) was published from our laboratory. The present report provides, for the first time, a precise structure determination of this pharmaceutically important compound in its parent form, (I) (Fig. 1).



(I)

In all essential details, the molecular geometry (Table 1) is in good agreement with that of sumatriptan succinate (Ravikumar *et al.*, 2004). The O═S═O angle is widened from the regular tetrahedral value.

The indole system is planar; the dihedral angle between the mean planes of the pyrrole and benzene rings is 1.2 (1)°. The torsion angles of the *N*-methylsulfamoyl side chain (Table 1) indicate anticlinal (−*ac*), antiperiplanar (−*ap*) and synclinal (−*sc*) conformations. The corresponding conformations are −*ac*, −*ap* and +*sc*, respectively, for sumatriptan succinate. In addition, the C9—C10 bond is in a *trans* disposition with respect to the C1—C8 bond (Table 1), whereas it is in a *gauche* conformation [74.2 (1)°] in sumatriptan succinate. An r.m.s.

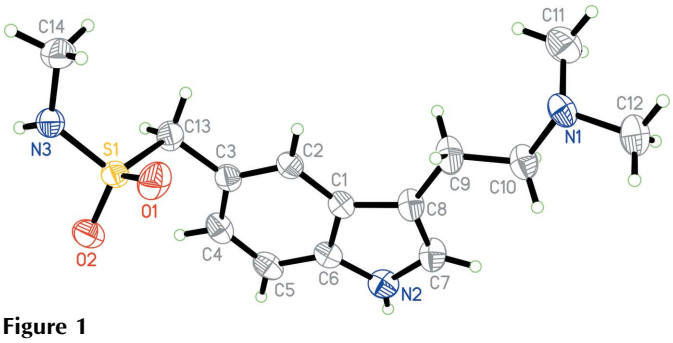


Figure 1
The molecular structure of (I), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

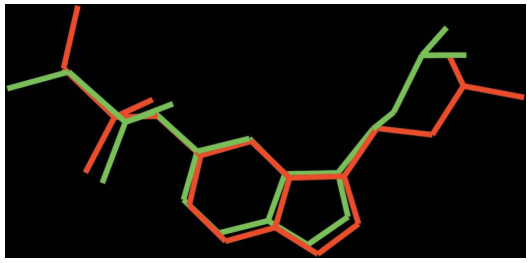


Figure 2
An r.m.s. overlay of sumatriptan (red) and sumatriptan succinate (green), showing the orientation differences in both the side chains.

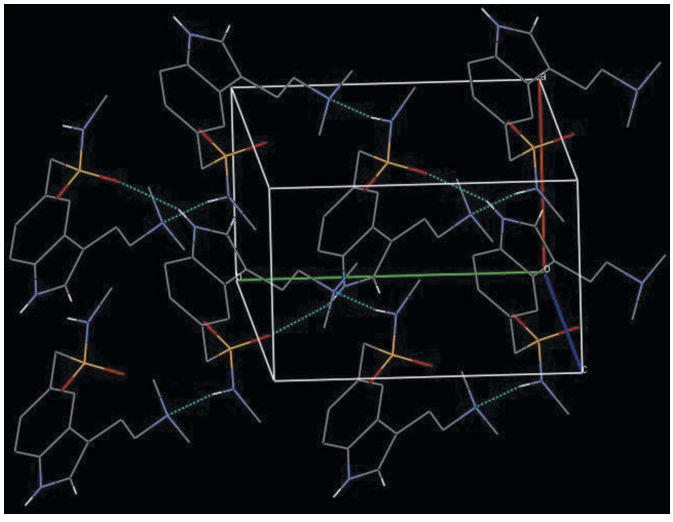


Figure 3
A packing diagram for (I). Intermolecular N—H···O and N—H···N hydrogen bonds, indicated by dashed lines, produce glide-symmetric chains along the *c* axis.

overlay fitting the indole system (r.m.s. deviation = 0.010 Å) of sumatriptan and sumatriptan succinate shows a difference in the orientations of both side chains (Fig. 2).

The ethylamine side chain is in an extended antiperiplanar (+*ac*) conformation, while in sumatriptan succinate the corresponding torsion angle is 176.7 (2)°. In the present structure, the *N*-methylsulfamoyl and ethylamine side chains have dihedral angles of 69.0 (1) and 43.2 (1)°, respectively, with the indole plane.

The atom N2 of the indole system is linked to sulfonyl atom O1 of the *N*-methylsulfamoyl group, through an intermolecular N—H···O hydrogen bond (Table 2). Furthermore, atom N3 of the *N*-methylsulfamoyl side chain forms an intermolecular N—H···N hydrogen bond with the ethylamine side chain. These hydrogen bonds lead to the formation of a glide-symmetric chain running along the crystallographic *c* axis (Fig. 3).

Experimental

Crystals of sumatriptan (SMS Pharma Research Centre, Hyderabad) suitable for X-ray diffraction were obtained from methanol solution.

Crystal data

$C_{14}H_{21}N_3O_2S$
M_r = 295.40
Monoclinic, $P2_1/n$
a = 6.3216 (3) Å
b = 10.1290 (5) Å
c = 24.1541 (12) Å
β = 96.318 (1)°
V = 1537.23 (13) Å^3
Z = 4
D_x = 1.276 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 7659 reflections
θ = 2.1–27.9°
μ = 0.22 mm^{-1}
T = 273 (2) K
Needle, yellow
0.22 × 0.11 × 0.08 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
ω scans
Absorption correction: none
14386 measured reflections
2709 independent reflections
2494 reflections with $I > 2\sigma(I)$
R_{int} = 0.021
θ_{max} = 25.0°
$h = -7 \rightarrow 7$
$k = -12 \rightarrow 12$
$l = -28 \rightarrow 28$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.127
S = 1.04
2709 reflections
192 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0686P)^2 + 0.667P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.52 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

S1—O2	1.4212 (17)	S1—C13	1.786 (2)
S1—O1	1.4251 (17)	C7—C8	1.361 (3)
S1—N3	1.5924 (19)		
O2—S1—O1	118.90 (11)	C10—N1—C12	109.2 (2)
C11—N1—C10	113.9 (2)	N1—C10—C9	112.78 (19)
C11—N1—C12	110.1 (2)		
C13—S1—N3—C14	−68.0 (2)	C2—C3—C13—S1	−100.4 (2)
C1—C8—C9—C10	−176.4 (2)	N3—S1—C13—C3	−179.62 (16)
C12—N1—C10—C9	158.1 (2)		

Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2N···O1^{i}	0.79 (3)	2.15 (3)	2.899 (2)	158 (2)
N3—H3N···N1^{ii}	0.85 (3)	2.06 (3)	2.893 (3)	167 (2)

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

N-bound H atoms were located in a difference density map and refined freely. All other H atoms were positioned geometrically and treated as riding atoms, with C—H distances in the range 0.93–0.97 Å and with U_{iso}(H) values of $1.5U_{eq}$(C) for methyl H and $1.2U_{eq}$(C) for other H atoms. The methyl groups were allowed to rotate but not to tip.

Data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL/PC* (Sheldrick, 1990), *QMOL* (Gans & Shalloway, 2001) and *MERCURY* (Bruno *et al.*, 2002); software used to prepare material for publication: *SHELXL97*.

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