Acta Crystallographica Section C
**Crystal Structure Communications**
ISSN 0108-2701

# Almotriptan, an antimigraine agent, and its malate salt

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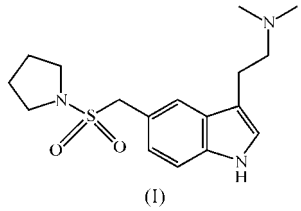
Received 1 November 2007
Accepted 18 November 2007
Online 14 December 2007

The crystal structures of almotriptan {systematic name: *N*,*N*-dimethyl-2-[5-(pyrrolidin-1-ylsulfonylmethyl)-1*H*-indol-3-yl]-ethanamine}, $C_{17}H_{25}N_3O_2S$, and almotriptan malate {systematic name: *N*,*N*-dimethyl-2-[5-(pyrrolidin-1-ylsulfonylmethyl)-1*H*-indol-3-yl]ethanaminium malate, $C_{17}H_{26}N_3O_2S^+\cdot C_4H_5O_5^-$, a novel selective serotonin 1B/D agonist, have been determined in order to gain further insight into the structure–activity relationships of triptans. The two structures differ in the orientation of their sulfonylpyrrolidine side chains. A comparison with other triptans reveals that molecules of almotriptan, sumatriptan, zolmitriptan and rizatriptan can adopt two principal conformations. N—H···N, N—H···O and O—H···O hydrogen bonds are responsible for the molecular packing.

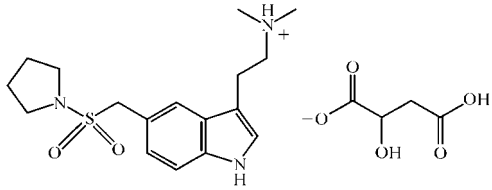
## Comment

Triptans are the first class of drugs designed to relieve migraine symptoms by targeting the disease pathology (Perry & Markham, 1998; Humphrey *et al.*, 1990). Unlike nonspecific medications that increase a patient's tolerance to pain, nausea and associated symptoms, triptans act specifically *via* receptor-mediated binding in the central nervous system and its vascular system. Triptan medications are selective 5-hydroxytryptamine (5-$HT_{1B/D}$) receptor agonists that share a basic indole ring structure with different side chains. Almotriptan, (I), is a novel selective serotonin 1B/D agonist developed for the abortive treatment of migraine (De Vries *et al.*, 1999). Over the past decade, seven triptans have become available in the USA, *viz.* sumatriptan, zolmitriptan, naratriptan, rizatriptan, frovatriptan, eletriptan and almotriptan. They are believed to constrict the blood vessels by acting on the 5-$HT_{1B/D}$ receptors, which makes them the best amongst the listed acute antimigraines. The present study is a continuation of our ongoing programme on structure elucidation of drug molecules.

The molecular structures of (I) and its malate salt, (II), are shown in Figs. 1 and 2, respectively. The bond distances and angles in (I) and (II) are similar and agree well with the



(I)



(II)

values found in the related structures sumatriptan (Ravikumar *et al.*, 2006), sumatriptan succinate (Ravikumar *et al.*, 2004), zolmitriptan (Ravikumar *et al.*, 2007*a*) and rizatriptan benzoate (Ravikumar *et al.*, 2007*b*).

The conformation of the molecules in both structures can be defined by the dihedral angle between the mean planes of the indole system and the pyrrolidine ring [30.0 (1)° in (I) and 27.0 (1)° in (II)]. The ethylamine side chain is in an extended conformation in both structures. The pyrrolidine ring is in an envelope conformation in (I), whereas it is planar in (II). As seen in other triptan salts, the dimethylammonium atom N2 in (II) also shows quaternary character as a result of proton transfer from the malate anion and consequently bears the positive charge in the molecular cation. The malate anion, in an (−)antiperiplanar conformation, lies perpendicular [dihedral angle = 88.9 (1)°] to the indole system.

An overlay of the triptans (Fig. 3) superimposing the planar indole systems, reveals the significant orientation differences. The solid-state conformation found in the triptans can be characterized in terms of the torsion angles $\tau1$ (C1—C2—C9—C10) and $\tau2$ (C5—C13—S1—N3) (Table 3). Two principal orientations can be noted here for both the side chain substituted at atom C2 {synperiplanar [±(0–30)°] and anticlinal [±(90–150)°]} and that at C5 {synclinal [±(90–150)°] and

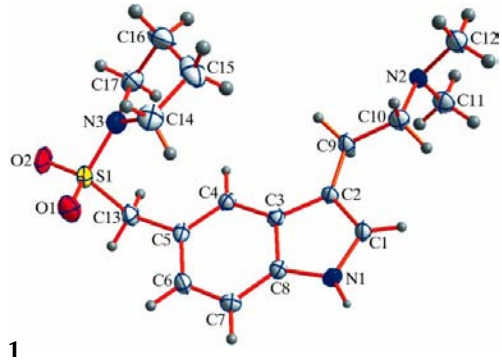



**Figure 1**
A view of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

 DOI: 10.1107/S0108270107060507  

antiperiplanar [±(150–180)°]}, indicating the flexibility of the molecule. Structural features were correlated using the theoretical 5-$HT_{1B}$-like receptor model (Moloney *et al.*, 1999), on parameters describing the benzene ring and two terminal N atoms (N2 and N3). The distance between the centre of the benzene ring and atom N2 is 6.45 Å in (I) and 6.37 Å in (II). The corresponding distances are 6.41 Å in sumatriptan, 5.82 Å in sumatriptan succinate, 5.24 Å in zolmitriptan and 5.71 Å in rizatriptan benzoate. The distance between the centre of the benzene ring and atom N3 is 4.14 Å in (I) and 5.31 Å in (II), the corresponding distances in the above-mentioned triptans being 5.34, 5.30, 4.13 and 3.70 Å, respectively.

In (I), N—H···N hydrogen bonds (Table 1) form the primary motif of crystal packing (Fig. 4), resulting in an infinite chain along the *b* axis. On the other hand, in (II), both the almotriptan cation and the malate anion, each having two potential hydrogen-bond donors, are engaged in O—H···O and N—H···O hydrogen bonds (Table 2). The association of the malate ions forms $R_2^2(10)$ and $R_4^4(20)$ rings (Bernstein *et al.*, 1995) along the *c* axis (Fig. 5). Further analysis of the crystal packing reveals possible C—H···O and C—H···$\pi$ interactions in both the structures. Indole system stacking [3.665 (2) Å] is seen in (I).

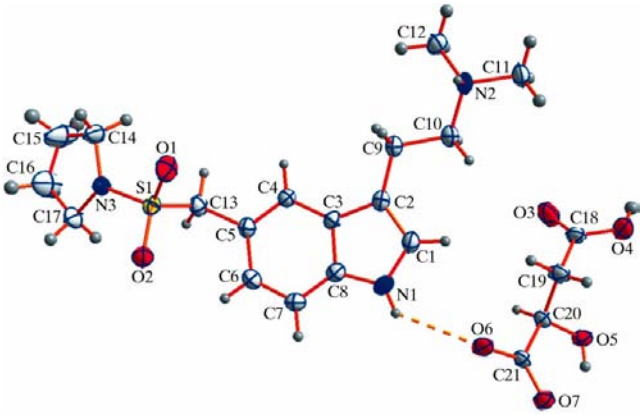



**Figure 2**
A view of (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. The intramolecular hydrogen bond is shown as a dashed line.

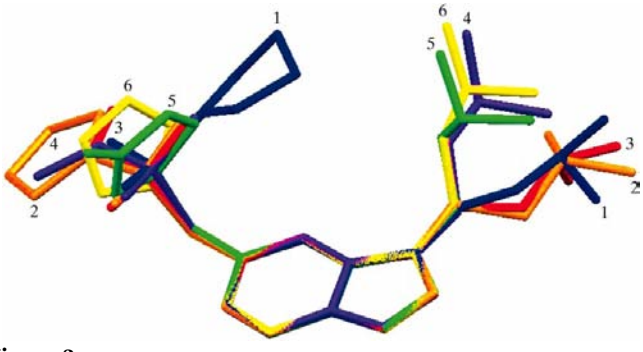



**Figure 3**
An overlay of triptans *viz.* almotriptan, (I) (labelled 1), almotriptan malate, (II) (labelled 2, r.m.s. deviation = 0.013 Å), sumatriptan (labelled 3, r.m.s. deviation = 0.017 Å), sumatriptan succinate (labelled 4, r.m.s. deviation = 0.021 Å), zolmitriptan (labelled 5, r.m.s. deviation = 0.016 Å) and rizatriptan benzoate (labelled 6, r.m.s. deviation = 0.012 Å).

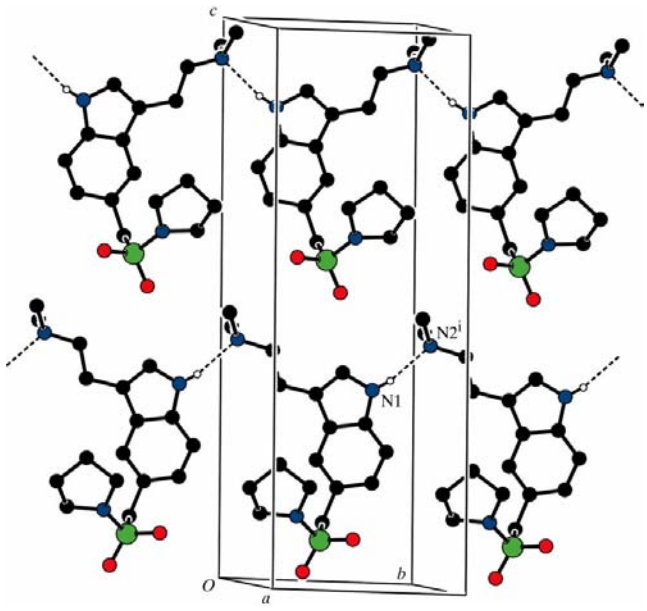



**Figure 4**
Part of the crystal packing for (I), viewed down the *a* axis, showing the N—H···N hydrogen-bonded (dashed lines) chains running along the *b* axis. H atoms not involved in hydrogen bonding have been omitted for clarity. [Symmetry code: (i) *x*, *y* + 1, *z*.]

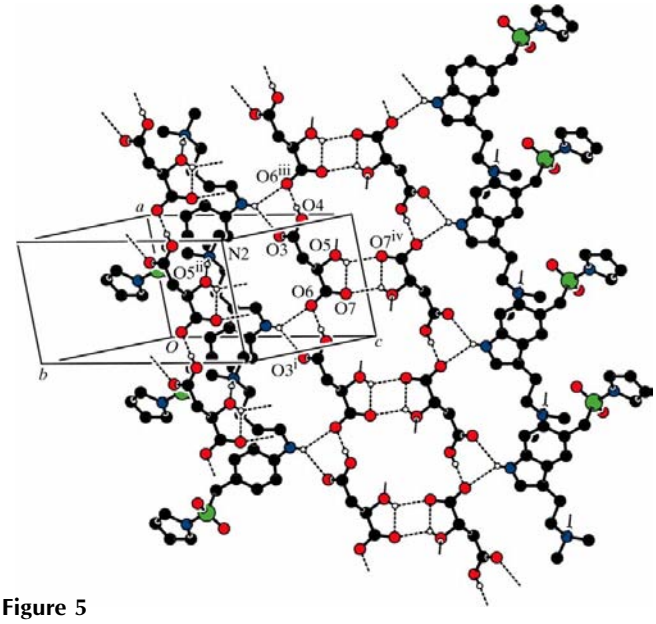



**Figure 5**
Part of the crystal packing for (II), showing the N—H···O and O—H···O hydrogen-bonded (dashed lines) networks, highlighting the association of malate ions *via* $R_2^2(10)$ and $R_4^4(20)$ ring formation along the *c* axis. H atoms not involved in hydrogen bonding have been omitted for clarity. [Symmetry codes: (i) *x* − 1, *y*, *z*; (ii) *x*, *y* + 1, *z*; (iii) *x* + 1, *y*, *z*; (iv) −*x* + 1, −*y*, −*z* + 2.]

## Experimental

Crystals of (I) and (II) (SMS Pharma Research Centre, Hyderabad) suitable for X-ray diffraction analysis were obtained from methanol solutions.

### Compound (I)

*Crystal data*

$C_{17}H_{25}N_3O_2S$
$M_r$ = 335.46
Monoclinic, $C2/c$
$a$ = 20.5023 (17) Å
$b$ = 7.6894 (6) Å
$c$ = 22.8470 (19) Å
$\beta$ = 104.904 (2)°
$V$ = 3480.7 (5) Å$^3$
$Z$ = 8
Mo $K\alpha$ radiation
$\mu$ = 0.20 mm$^{-1}$
$T$ = 294 (2) K
0.22 × 0.16 × 0.09 mm

*Data collection*

Bruker SMART APEX CCD area-detector diffractometer
16157 measured reflections
3057 independent reflections
2285 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.068

*Refinement*

$R[F^2 > 2\sigma(F^2)]$ = 0.078
$wR(F^2)$ = 0.162
$S$ = 1.17
3057 reflections
214 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.37 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.24 e Å$^{-3}$

**Table 1**
Hydrogen-bonding and contact geometry (Å, °) for (I).

*Cg*2 is the centroid of the C3–C8 ring.

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| N1—H1N···N2$^{i}$ | 0.80 (3) | 2.12 (3) | 2.906 (4) | 167 (3) |
| C15—H15$B$···$Cg2^{ii}$ | 0.97 | 2.96 | 3.909 (5) | 166 |

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

### Compound (II)

*Crystal data*

$C_{17}H_{26}N_3O_2S^+\cdot C_4H_5O_5^-$
$M_r$ = 469.55
Triclinic, $P\overline{1}$
$a$ = 7.5542 (7) Å
$b$ = 9.3561 (9) Å
$c$ = 17.3608 (17) Å
$\alpha$ = 104.081 (2)°
$\beta$ = 101.121 (2)°
$\gamma$ = 92.681 (2)°
$V$ = 1162.13 (19) Å$^3$
$Z$ = 2
Mo $K\alpha$ radiation
$\mu$ = 0.19 mm$^{-1}$
$T$ = 294 (2) K
0.19 × 0.14 × 0.08 mm

*Data collection*

Bruker SMART APEX CCD area-detector diffractometer
11188 measured reflections
4062 independent reflections
3743 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.017

*Refinement*

$R[F^2 > 2\sigma(F^2)]$ = 0.049
$wR(F^2)$ = 0.133
$S$ = 1.03
4062 reflections
307 parameters
2 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.43 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.33 e Å$^{-3}$

All N- and O-bound H atoms of both (I) and (II) were located in a difference density map and refined isotropically. In (II), the O4—H4O distance was restrained with a set value of 0.82 (1) Å. A distance restraint was also applied for the C15—C16 bond of the pyrrolidine ring in (II). All other H atoms were positioned geometrically and treated as riding on their parent C atoms [C—H = 0.93–0.98 Å and $U_{iso}$(H) = 1.5$U_{eq}$(C) for methyl H or 1.2$U_{eq}$(C) for other H atoms]. The methyl groups were allowed to rotate but not to tip.

For both compounds, 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) and *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97*.

**Table 2**
Hydrogen-bonding and contact geometry (Å, °) for (II).

*Cg*1 and *Cg*2 are the centroids of the N1/C1–C3/C8 and C3–C8 rings.

| $D$—H···$A$ | $D$—H | H···$A$ | $D$···$A$ | $D$—H···$A$ |
|---|---|---|---|---|
| N1—H1N···O3$^{i}$ | 0.81 (2) | 2.39 (3) | 3.034 (3) | 138 (2) |
| N1—H1N···O6 | 0.81 (2) | 2.47 (2) | 3.087 (2) | 135 (2) |
| N2—H2N···O5$^{ii}$ | 0.86 (2) | 1.88 (2) | 2.731 (2) | 173 (2) |
| O4—H4O···O6$^{iii}$ | 0.83 (1) | 1.67 (1) | 2.503 (2) | 178 (4) |
| O5—H5O···O7 | 0.80 (3) | 2.11 (3) | 2.623 (2) | 122 (3) |
| O5—H5O···O7$^{iv}$ | 0.80 (3) | 2.19 (3) | 2.811 (2) | 135 (3) |
| C11—H11$C$···O4$^{v}$ | 0.96 | 2.38 | 3.276 (3) | 156 |
| C14—H14$A$···O1$^{vi}$ | 0.97 | 2.55 | 3.301 (3) | 134 |
| C11—H11$B$···$Cg1^{iii}$ | 0.96 | 2.87 | 3.819 (3) | 172 |
| C12—H12$A$···$Cg2^{iii}$ | 0.96 | 2.83 | 3.767 (3) | 164 |
| C13—H13$A$···$Cg2^{vii}$ | 0.97 | 2.91 | 3.577 (1) | 127 |

Symmetry codes: (i) $x-1, y, z$; (ii) $x, y+1, z$; (iii) $x+1, y, z$; (iv) $-x+1, -y, -z+2$; (v) $-x+2, -y+1, -z+2$; (vi) $-x, -y+2, -z+1$; (vii) $-x, -y+1, -z+1$.

**Table 3**
Solid-state conformation of triptans indicated by torsion angles $\tau$1 and $\tau$2.

| Reference | $\tau$1 (°) | $\tau$2 (°) |
|---|---|---|
| 1 | −23.7 (6) | 59.3 (3) |
| 2 | 22.9 (3) | −174.8 (2) |
| 3 | 3.1 (4) | −179.6 (2) |
| 4 | −112.1 (1) | −177.1 (2) |
| 5 | −108.8 (3) | −65.8 (3)$^{*}$ |
| 6 | −100.5 (2) | 85.4 (2)$^{**}$ |

Notes: (1) Almotriptan free base (I) (this work); (2) almotriptan malate (II) (this work); (3) sumatriptan free base (Ravikumar *et al.*, 2006); (4) sumatriptan succinate (Ravikumar *et al.*, 2004); (5) zomitriptan (Ravikumar *et al.*, 2007*a*); (6) rizatriptan benzoate (Ravikumar *et al.*, 2007*b*). (*) C—C—C—N; (**) C—C—N—N.

The authors thank Dr J. S. Yadav, Director, IICT, Hyderabad, for his kind encouragement.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN3071). Services for1 accessing these data are described at the back of the journal.

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