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Halide salts of antimigraine agents eletriptan and naratriptan

K. Ravikumar,[a]* B. Sridhar,[a] Harihara Krishnan[b] and A. N. Singh[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: sshiya@yahoo.com

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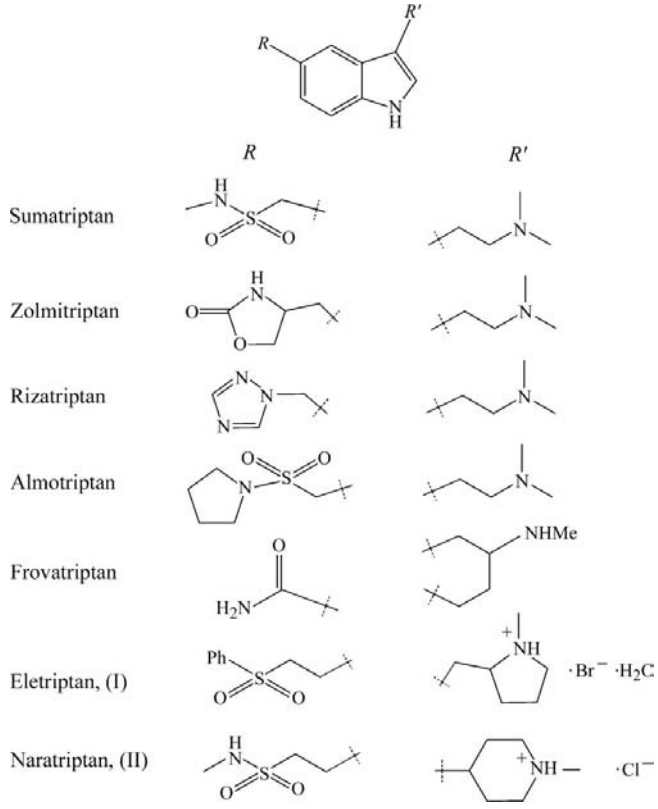
Molecules of eletriptan hydrobromide monohydrate (systematic name: (1*S*,2*R*)-1-methyl-2-{5-[2-(phenylsulfonyl)ethyl]-1*H*-indol-3-ylmethyl}pyrrolidinium bromide monohydrate), $C_{22}H_{27}N_2O_2S^+\cdot Br^-\cdot H_2O$, (I), and naratriptan hydrochloride (systematic name: 1-methyl-4-{5-[2-(methylsulfamoyl)ethyl]-1*H*-indol-3-yl}piperidinium chloride), $C_{17}H_{26}N_3O_2S^+\cdot Cl^-$, (II), adopt conformations similar to other triptans. The C-2 and C-5 substituents of the indole ring, both of which are in a region of conformational flexibility, are found to be oriented on either side of the indole ring plane in (I), whilst they are on the same side in (II). The N atom in the C-2 side chain is protonated in both structures and is involved in the hydrogen-bonding networks. In (I), the water molecules create helical hydrogen-bonded chains along the *c* axis. In (II), the hydrogen bonding of the chloride ions results in macrocyclic $R_4^2(20)$ and $R_4^2(24)$ ring motifs that form sheets in the *bc* plane. This structural analysis provides an insight into the molecular structure–activity relationships within this class of compound, which is of use for drug development.

Comment

Migraine headache is a severe throbbing pain over one or both halves of the scalp and is accompanied by nausea, vomiting, photophobia and/or phonophobia. Triptans are the family of tryptamine-based drugs specifically designed to alleviate migraine headaches, which they do by blocking serotonin receptors in blood vessels in the brain (Saxena & Tfelt-Hansen, 2001). They are designer drugs obtained by modifying the serotonin molecule (Goadsby, 1998). Triptan drugs were first introduced during the 1990s and are now available in different types under a variety of commercial names: sumatriptan (Imitrex), zolimitriptan (Zomig), rizatriptan (Maxalt), almotriptan (Axert), naratriptan (Amerge), eletriptan (Relpax) and frovatriptan (Frova). All triptans share a basic indole ring, with the side chains being different. These side chains affect the pharmacokinetics of these agents in ways that may be clinically significant as they may make them more, or less, effective (Isaac & Slassi, 2001).



Eletriptan and naratriptan, the second-generation drugs of Pfizer and Glaxo Wellcome, respectively, are more lipophilic and have higher oral bioavailability than sumatriptan (Tepper *et al.*, 2002). We have been studying the structural characteristics of a series of triptans (Ravikumar *et al.*, 2004, 2006, 2007*a*,*b*, 2008), and the present study of eletriptan hydrobromide monohydrate, (I), and naratriptan hydrochloride, (II), is a continuation of our investigation into the three-dimensional structural correlation of triptans.

Pertinent bond lengths and angles for (I) and (II) are listed in Tables 1 and 3, respectively, and the molecular structures are depicted in Figs. 1 and 2. Protonation of the molecules occurs in both structures at atom N2, *viz*. of the pyrolidine ring in (I) and the piperidine ring in (II); the sum of the angles at this atom is 334.0 (2)° in (I) and 334.4 (1)° in (II). An overlay of the triptans superimposing the planar indole systems (Fig. 3) reveals the significant similarities and orientational differences.

The use of the substituents at C2 and C5 of the indole ring is believed to provide binding selectivity and affinity for 5-HT_{1D} receptors (Slassi *et al.*, 2000) and provides a region of conformational flexibility in the molecule. The conformational difference between the structures of (I) and (II) is in the orientation of the substituents at C2 [pyrrolidiniomethyl in (I) and piperidiniomethyl in (II)] and C5 [phenylsulfonylethyl in (I) and methylsulfamoylethyl in (II)] of the indole ring (Fig. 3). In (I), the two substituents are oriented on either side of the indole ring plane, whereas in (II) they are on the same side. Furthermore, the orientation of the side chain at C2 can be

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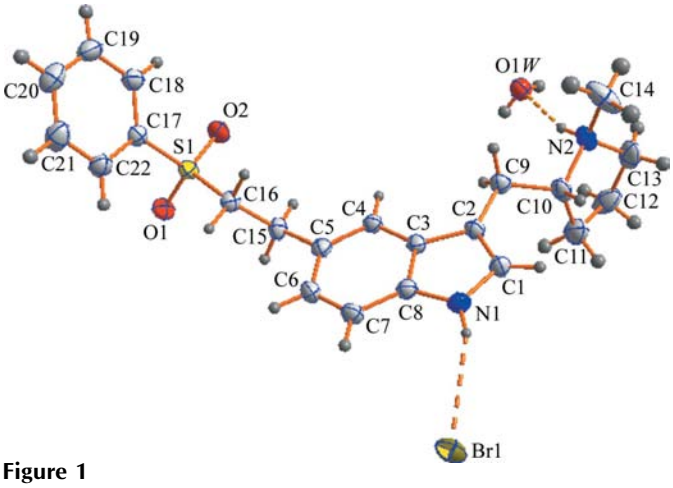

Figure 1
The asymmetric unit of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. Dashed lines indicate hydrogen bonds.

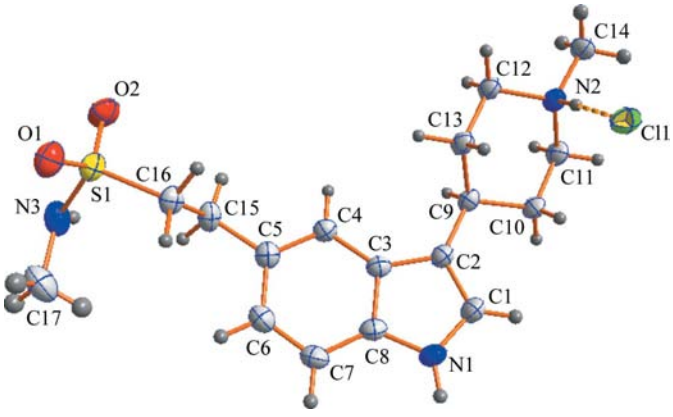

Figure 2
The asymmetric unit of (II), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. The dashed line indicates the hydrogen bond.

visualized in terms of the torsion angle $\tau1$ [C1—C2—C9—C10 = 24.5° (2) in (I) and 4.3 (3)° in (II)], which is synperiplanar in both molecules. The corresponding angles in other triptans are listed in Table 5, from which the two principal orientations, *viz.* synperiplanar and anticlinal, can be noted in the solid-state structures.

An interesting comparison between the structures of (I) and (II) is in the position of protonated atom N2 relative to the indole ring system. In (I) it is intra, being almost coplanar with the indole ring plane [0.080 (2) Å], whereas in (II) it is extra, 1.123 (2) Å above the plane. The distance between atom N2 and the centroid of the C3–C8 aromatic ring remains almost equal in both structures [6.48 Å in (I) and 6.76 Å in (II)]. The corresponding distances, a parameter correlating the 5-HT_{1B}-like receptor model (Moloney *et al.*, 1999), deduced for other triptans are listed in Table 5, which also indicates whether atom N2 is coplanar or not.

The sulfonylethyl side chains of both (I) and (II) show a similar orientation, as indicated by the torsion angles $\tau2$ (C6—C5—C15—C16) of 65.9 (3) and 67.0 (2)°, and $\tau3$ (C5—C15—C16—S1) of 168.7 (2) and −168.50 (14)°, respectively. It is interesting to note that the corresponding torsion angles found in other triptans (Table 5) all favour a similar synclinal orientation for $\tau2$ but only some of them do for $\tau3$. The terminal groups, phenyl in (I) and methylamino in (II), attached with this chain are antiperiplanar [C15—C16—S1—C17 = −175.86 (15)°] and synclinal [C15—C16—S1—N3 = 56.39 (17)°], respectively.

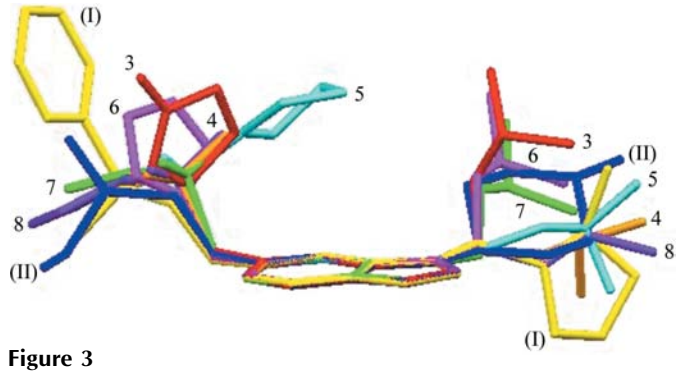

Figure 3
A superposition of the molecular conformations of triptans. The overlay was made by making a least-squares fit through the indole ring of eletriptan, (I). The labels and r.m.s. deviations (Å) are as follows: naratriptan, (II), 0.022; zolmitriptan (labelled 3), 0.028; sumatriptan (labelled 4), 0.017; almotriptan (labelled 5), 0.19; rizatriptan benzoate (labelled 6), 0.013; sumatriptan succinate (labelled 7), 0.017; almotriptan malate (labelled 8), 0.023.

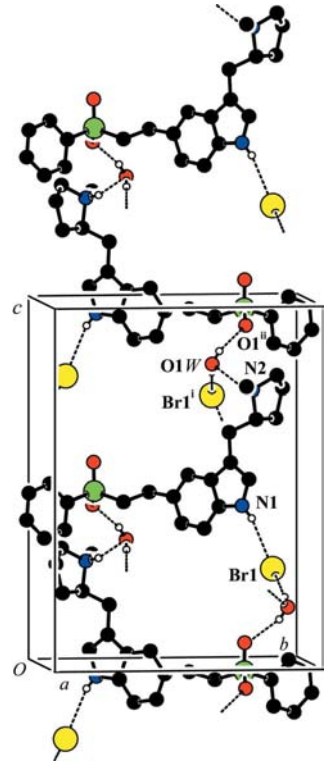

Figure 4
A view of part of the crystal structure of (I), showing the formation of helical chain along the *c* axis. Hydrogen bonds are drawn as dashed lines and H atoms not involved in hydrogen bonding have been omitted for clarity. [Symmetry codes: (i) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+1$; (ii) $-x+\frac{1}{2}, -y+1, z+\frac{1}{2}$.]

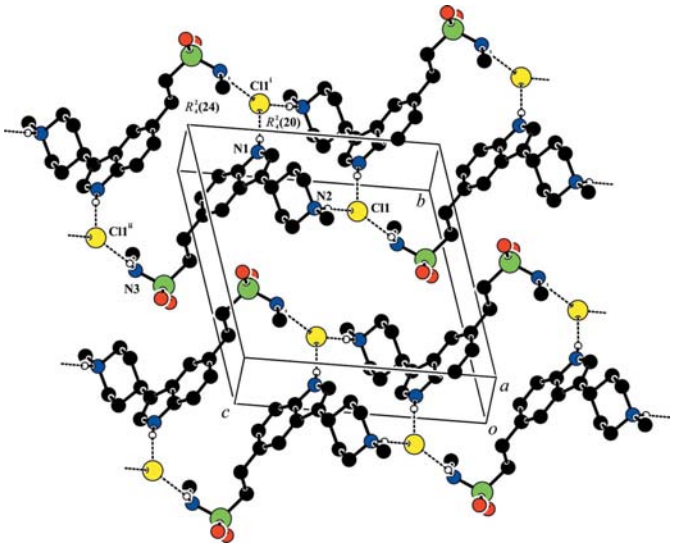

Figure 5
A view of part of the crystal structure of (II), showing the aggregation of $R_4^2(20)$ and $R_4^2(24)$ ring hydrogen-bonding motifs forming sheets in the *bc* plane. H atoms not involved in hydrogen bonding have been omitted for clarity. Dashed lines indicate hydrogen bonds. [Symmetry codes: (i) $-x+1, -y+2, -z+1$; (ii) $x-1, y, z+1$.]

The conformation of the pyrrolidine ring in (I) can be best described as an envelope, with the twofold axis through atom C13. The piperidine ring in (II) adopts a chair conformation. The dihedral angles formed by the mean plane of the pyrrolidine or phenyl ring with the mean plane of the indole ring are 82.8 (1) and 71.1 (1)°, respectively, indicating near perpendicularity in (I).

In (I), the water molecule plays a key role in the hydrogen-bonding network. It acts as both donor and acceptor, creating a helical chain along the *c* axis (Fig. 4 and Table 2). The sulfonyl O and Br atoms participate in the hydrogen-bonding network. In (II), the chloride ion plays a central role in the hydrogen-bonding network (Fig. 5 and Table 4). All three N atoms (N1, N2 and N3) form hydrogen bonds only with the Cl atom, even though the sulfonyl O atoms are available. N2—H···Cl and N3—H···Cl hydrogen bonds link the molecules into a chain running along the *c* axis. An N1—H···Cl hydrogen bond links to a chain related by centrosymmetry, along the *b* axis, resulting in a supramolecular macrocycle that may be described in graph-set notation as $R_4^2(20)$ and $R_4^2(24)$ (Etter, 1990; Etter *et al.*, 1990; Bernstein *et al.*, 1995), forming sheets in the *bc* plane. Since these two rings are edge fused, they form an overall macrocylic $R_6^3(37)$ ring in the sheets.

In conclusion, such crystal structures provide useful information on the overall conformation of molecules, the orientations of the two indole ring substituents and the molecular interactions influencing crystal packing. A word of caution may be exercised regarding the C2 side-chain orientation, since in solid-state structures it is probably governed largely by the position of the counter-ions, *viz.* halide, succinate, malate, benzoate, *etc.*, and may not be significant for activity in view of the flexibility of the chain.

Experimental

Crystals of eletriptan hydrobromide monohydrate and naratriptan hydrochloride (SMS Pharma Research Centre, Hyderabad) suitable for X-ray diffraction were obtained from solutions in a mixture of methanol and water (85:15) by slow evaporation.

Compound (I)

Crystal data

$C_{22}H_{27}N_2O_2S^+\cdot Br^-\cdot H_2O$
$M_r = 481.44$
Orthorhombic, $P2_12_12_1$
$a = 9.4019$ (6) Å
$b = 13.4089$ (8) Å
$c = 18.0173$ (11) Å
$V = 2271.4$ (2) Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 1.93$ mm^{-1}
$T = 294$ (2) K
0.16 × 0.12 × 0.07 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2001)
$T_{min} = 0.75$, $T_{max} = 0.86$
21861 measured reflections
3984 independent reflections
3761 reflections with $I > 2\sigma(I)$
$R_{int} = 0.066$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.024$
$wR(F^2) = 0.066$
$S = 1.06$
3984 reflections
279 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.36$ e Å^{-3}
$\Delta\rho_{min} = -0.25$ e Å^{-3}
Absolute structure: Flack & Bernardinelli (2000), with 1707 Friedel pairs
Flack parameter: −0.007 (5)

Table 1
Selected geometric parameters (Å, °) for (I).

C1—N1	1.369 (3)	C13—N2	1.473 (3)
C10—N2	1.516 (3)	C17—S1	1.759 (2)
C13—N2—C14	114.5 (3)	C14—N2—C10	113.4 (2)
C13—N2—C10	106.1 (2)	C17—S1—C16	104.28 (9)

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1N···Br1	0.80 (2)	2.71 (2)	3.4747 (19)	159 (2)
N2—H2N···O1W	0.81 (3)	1.96 (3)	2.740 (3)	162 (2)
O1W—H1W···Br1^{i}	0.78 (4)	2.47 (4)	3.244 (2)	175 (3)
O1W—H2W···O1^{ii}	0.78 (4)	2.08 (4)	2.827 (3)	162 (3)

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

Compound (II)

Crystal data

$C_{17}H_{26}N_3O_2S^+\cdot Cl^-$
$M_r = 371.92$
Triclinic, $P\overline{1}$
$a = 6.1914$ (5) Å
$b = 12.2298$ (10) Å
$c = 12.9948$ (11) Å
$\alpha = 78.348$ (1)°
$\beta = 76.338$ (1)°
$\gamma = 86.033$ (1)°
$V = 936.18$ (13) Å^3
$Z = 2$
Mo $K\alpha$ radiation
$\mu = 0.33$ mm^{-1}
$T = 294$ (2) K
0.18 × 0.15 × 0.08 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
9097 measured reflections
3301 independent reflections
3006 reflections with $I > 2\sigma(I)$
$R_{int} = 0.018$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.036$
$wR(F^2) = 0.097$
$S = 1.03$
3301 reflections
231 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.24$ e Å^{-3}
$\Delta\rho_{min} = -0.34$ e Å^{-3}

Table 3
Selected geometric parameters (Å, °) for (II).

C1—N1	1.363 (3)	C12—N2	1.502 (2)
C11—N2	1.492 (2)	N3—S1	1.6116 (19)
C14—N2—C11	111.69 (14)	C11—N2—C12	110.27 (14)
C14—N2—C12	112.41 (14)	N3—S1—C16	107.69 (10)

Table 4
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1N···Cl1^{i}	0.87 (2)	2.34 (2)	3.2045 (18)	173 (2)
N2—H2N···Cl1	0.89 (2)	2.21 (2)	3.0978 (16)	174 (2)
N3—H3N···Cl1^{ii}	0.78 (2)	2.53 (2)	3.2601 (19)	157 (2)

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

Table 5
Selected topographical solid-state features of triptans (°, Å).

$\tau1$ = C1—C2—C9—C10; $\tau2$ = C6—C5—C15—C16; $\tau3$ = C5—C15—C16—S1; $d1$ = displacement distance of N2 from the mean plane of the indole ring; $d2$ = distance of N2 from the centre of the aromatic ring.

Compound	$\tau1$	$\tau2$	$\tau3$	$d1$	$d2$	Reference
Sumatriptan	3.1 (4)	79.5 (2)†	−179.6 (2)‡	−0.166 (2)	6.41	(*a*)
Almotriptan	−23.7 (6)	87.7 (4)†	59.3 (3)‡	0.162 (3)	6.45	(*b*)
Almotriptan malate	22.9 (3)	79.8 (2)†	−174.8 (2)‡	−0.021 (2)	6.37	(*b*)
Eletriptan hydrobromide monohydrate	24.5 (3)	65.9 (3)	168.71 (15)	−0.080 (2)	6.48	This work
Naratriptan hydrochloride	4.3 (3)	67.0 (2)	−168.50 (14)	1.123 (2)	6.76	This work
Rizatriptan benzoate	−100.5 (2)	80.2 (2)§	85.4 (2)¶	1.456 (2)	5.71	(*c*)
Sumatriptan succinate	−112.1 (3)	83.1 (3)†	−177.1 (2)‡	0.884 (1)	5.82	(*d*)
Zolmitriptan	108.8 (3)	−84.4 (3)	65.8 (3)§	2.433 (2)	5.24	(*e*)

† C—C—C—S. § C—C—C—N. ‡ C—C—S—N. ¶ C—C—N—N. References: (*a*) Ravikumar *et al.* (2006); (*b*) Ravikumar *et al.* (2008); (*c*) Ravikumar *et al.* (2007*b*); (*d*) Ravikumar *et al.* (2004); (*e*) Ravikumar *et al.* (2007*a*).

All N- and O-bound H atoms of (I) and (II) were located in difference-density maps and refined isotropically. All other H atoms were positioned geometrically and were treated as riding on their parent C atoms, with C—H = 0.93–0.98 Å and $U_{iso}(H) = 1.5U_{eq}(C)$ for methyl and $1.2U_{eq}(C)$ for the other H atoms. The methyl groups were allowed to rotate but not to tip. For (I), the absolute configuration of the procured material was known in advance and was confirmed by unambiguous refinement of the absolute structure parameter (Flack & Bernardinelli, 2000).

For both compounds, data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *DIAMOND* (Brandenburg & Putz, 2005) and *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN3101). Services for accessing these data are described at the back of the journal.

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