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Ropinirole hydrochloride, a dopamine agonist

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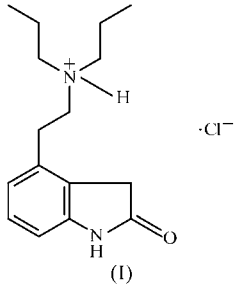
Ropinirole hydrochloride, or diethyl[2-(2-oxo-2,3-dihydro-1*H*-indol-4-yl)ethyl]ammonium chloride, $C_{16}H_{25}N_2O^+\cdot Cl^-$, belongs to a class of new non-ergoline dopamine agonists which bind specifically to D2-like receptors with a selectivity similar to that of dopamine (D3 > D2 > D4). The N atom in the ethylamine side chain is protonated and there is a hydrogen bond between it and the Cl^- ion. In the crystal structure, two cations and two anions form inversion-related cyclic dimers *via* N—H···Cl hydrogen bonds.

Comment

Ropinirole hydrochloride (ReQuip; SmithKline Beecham) is a second-generation non-ergoline dopamine agonist (DA) that selectively activates postsynaptic dopamine receptors (Eden *et al.*, 1991). It mimics the role of dopamine in the brain, causing the neurons to react as they would to dopamine. All of the agonists contain a dopamine-like ring structure which is believed to be the portion of the molecule that actually stimulates the dopamine receptor (Tulloch, 1997). *In vitro* studies have shown that ropinirole binds with high affinity to cloned human D2, D3 and D4 receptors. The activity of ropinirole against Parkinson's disease is believed to be due to its stimulatory effects on central postsynaptic dopamine D2 receptors within the candate-putamen (Kuzel, 1999). Clinical



(I)

studies have shown that ropinirole can be used for both early and late treatment of Parkinson's disease. Ropinirole, launched as Requip, was recently cleared for marketing by the US Food and Drug Administration for treatment of the signs and symptoms of Parkinson's disease, both as initial therapy and as an adjunctive treatment with levodopa (Rascol *et al.*, 1996). It was well tolerated and patient withdrawal from clinical trials was rare (Brooks *et al.*, 1995). In a continuation of our ongoing programmes on the structural elucidation of drug molecules and in order to gain further insight into structure–activity relationships, the crystal structure determination of ropinirole

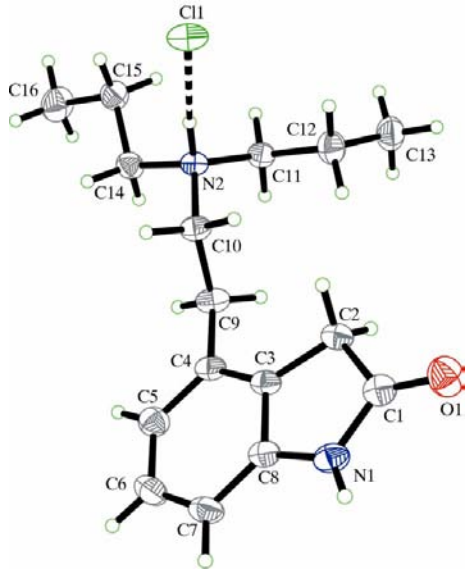


Figure 1
A view of (I), with the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. The intramolecular hydrogen bond is drawn as a dashed line.

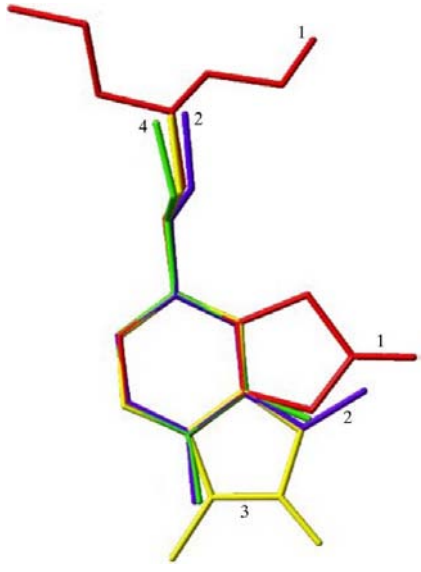


Figure 2
An overlay of dopamine with the title compound (labelled 1) and other dopamine derivatives, *viz*. the methoxy derivative of dopamine perchlorate (Okabe & Mori, 1992) (labelled 2, r.m.s. deviation = 0.028 Å), benzoxazole derivative (Boivin *et al.*, 1987) (labelled 3, r.m.s deviation = 0.040 Å) and dopamine HCl (Klein, 1991) (labelled 4, r.m.s. deviation = 0.023 Å), superimposing the aromatic moieties. H atoms have been omitted for clarity.

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hydrochloride, (I), has now been carried out and the results are reported here (Fig. 1 and Table 1).

Viewed from an overall perspective, the bond lengths and angles in compound (I) are comparable with those in similar closely related structures (Boivin *et al.*, 1987; Eyley *et al.*, 1986). Ropinirole crystallizes as the HCl salt with one molecule in the asymmetric unit (Fig. 1). The hybridization of the side-chain atom N2 appears to be characteristically sp^3 from its bond lengths [mean N2—C = 1.500 (2) Å] and angles [mean C—N2—C = 113.2 (1)°], indicating the protonation site of the molecule (Table 1).

The protonated amine and the N1—H1N group in a *meta* position relative to the ethylamine side chain comprise the two possible important sites of interaction with the DA receptor (McDermed *et al.*, 1976). An overlay of dopamine with the title compound and other dopamine derivatives, superimposing the aromatic moieties clearly reveals the conformational similarities (Fig. 2). The functional groups superimpose well, *viz*. the ethylamine side chain, the aromatic ring and the *meta*-hydroxy O atom of dopamine hydrochloride with the N atom of the pyrrolidinone, (I).

The solid-state conformation of the ethylamine side chain in (I), which is associated with the area of greatest conformational flexibility, is significantly similar and closely related to the conformations previously found in the dopamine derivatives (Table 3). It is apparent that the ethylamine side chain is in an almost extended conformation [C4—C9—C10—N2 = τ_1 = −177.5 (1)°] and also lies in a plane that is nearly orthogonal [C3—C4—C9—C10 = τ_2 = −68.9 (2)°] to the benzene ring plane, a situation that appears to favour biological activity (Fig. 3). However, in the structure of a methoxy derivative of dopamine hydrochloride (Okabe *et al.*, 1991), the side chain is fully extended but oriented in the same plane as the aromatic ring [τ_2 = −175.8 (6)°]. Incidentally, in the structures of dinitrobenzoate salts of dopamine (Ohba & Ito, 2002*a*,*b*), the side chain is in a *gauche* conformation, perhaps due to the presence of the bulky counter-ions and crystal packing.

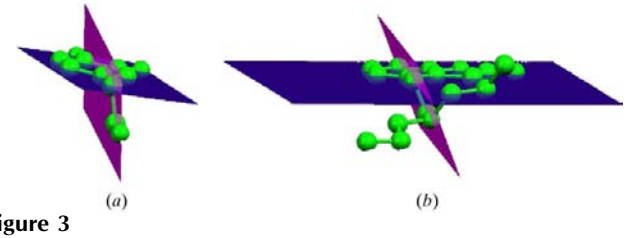

Figure 3
Orthogonal orientations of the ethylamine side chain to the plane of the aromatic ring for (*a*) dopamine hydrochloride and (*b*) ropinirole hydrochloride. H atoms have been omitted for clarity.

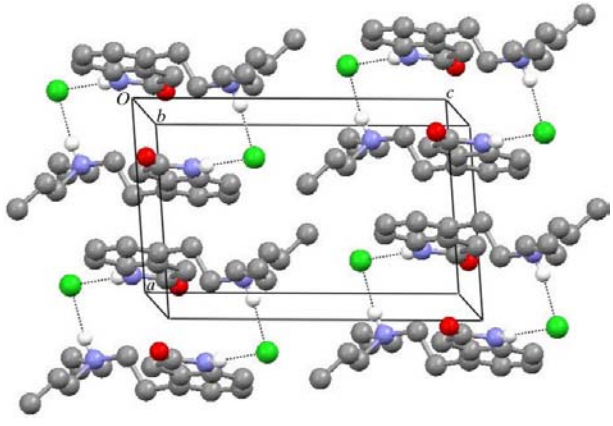

Figure 4
A packing diagram for (I), viewed down the *b* axis, showing the hydrogen-bond networks (dashed lines) involving two Cl^- ions that bridge two molecules of the cation to form centrosymmetric dimers. H atoms not involved in hydrogen bonding have been omitted for clarity.

The substituted propyl side chains at N2 are in an extended conformation [N2—C11—C12—C13 = −175.4 (1)° and N2—C14—C15—C16 = 175.1 (2)°] and are inclined at an angle of 69.4 (2)° to each other. This orientation of the propyl chains may also facilitate the binding of atom N2 at the receptor site through possible hydrophobic interactions. As in dopamine hydrochloride, the Cl^- ion is central to the hydrogen-bonding network, stabilizing the structure by forming covalent bonds with both N atoms, one each from the ethylamine chain and the indole ring (Table 2). In the crystal structure, two cations and two anions form inversion-related cyclic dimers *via* N—H···Cl hydrogen bonds. The dimers also form stacks along the *a* axis (Fig. 4).

In an attempt to map the pharmacophoric requirements for dopamine activity, distances describing the position of the protonated amine atom N2 in relation to the aromatic ring (d_1) and to the *meta*-substituted atom (d_2), along with the dihedral angle (φ) between the aromatic ring and the ethylamine side-chain least-squares planes, have been derived and are listed in Table 3. Significant similarities in these structural parameters can be seen. However, it is difficult from this limited set of data to suggest what structural or conformational parameters contribute to the observed pharmacological differences. It is difficult to come to any firm conclusion about the relationships between conformation and biological activity when dealing with agonists. Since they produce a response from living tissue, their activity not only depends upon their ability to activate receptors (efficacy) but also to bind to them (affinity). However, some ideas may be speculated by considering the derived structural features. Firstly, there appears to be some preference for the extended conformation of the ethylamine side chain and also for the plane of the ethylamine to lie at near right angles to the plane of the aromatic ring. Also, a favourable disposition (∼3.9–5.2 Å) of the charged N atom relative to the aromatic ring, and an optimal distance (∼5.6–7.4 Å), may be preferred between the charged N atom and the *meta*-substituted hydrogen-bonding atom on the aromatic ring.

Experimental

To obtain crystals of (I) suitable for X-ray studies, ropinirole hydrochloride (Pharmacology Department, IICT, Hyderabad) was dissolved in a mixture of methanol and water (95:5) and the solution was allowed to evaporate slowly.

Crystal data

$C_{16}H_{25}N_2O^+\cdot Cl^-$
M_r = 296.83
Triclinic, $P\overline{1}$
a = 7.5388 (11) Å
b = 8.9545 (13) Å
c = 12.1647 (18) Å
α = 80.005 (2)°
β = 85.968 (2)°
γ = 83.504 (2)°
V = 802.5 (2) Å^3
Z = 2
D_x = 1.228 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4700 reflections
θ = 2.3–28.0°
μ = 0.24 mm^{-1}
T = 273 (2) K
Needle, colourless
0.21 × 0.11 × 0.08 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
ω scans
7757 measured reflections
2825 independent reflections
2582 reflections with $I > 2\sigma(I)$
R_{int} = 0.021
θ_{max} = 25.0°
$h = -8 \rightarrow 8$
$k = -10 \rightarrow 10$
$l = -14 \rightarrow 14$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.101
S = 1.05
2825 reflections
191 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0547P)^2 + 0.173P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

C10—N2	1.5035 (17)	C14—N2	1.4962 (19)
C11—N2	1.4996 (19)		
N2—C10—C9	114.15 (12)	C14—N2—C11	110.81 (11)
N2—C11—C12	114.32 (12)	C14—N2—C10	112.04 (11)
N2—C14—C15	112.97 (13)	C11—N2—C10	114.73 (11)

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1N···Cl1^{i}	0.770 (19)	2.43 (2)	3.1955 (15)	173.9 (18)
N2—H2N···Cl1	0.913 (19)	2.180 (19)	3.0701 (13)	164.7 (15)

Symmetry code: (i) $-x+2, -y+2, -z$.

H atoms on N atoms were located in a difference density map and were refined freely with isotropic displacement parameters. All other H atoms were included in calculated positions, with C—H = 0.93–0.97 Å, and refined using a riding model, with U_{iso}(H) values set at 1.2 (C atoms) or 1.5 (CH_3) times U_{eq} of the parent 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) and *MERCURY* (Bruno *et al.*, 2002); software used to prepare material for publication: *SHELXL97*.

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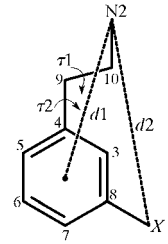
Table 3
Selected topographical X-ray structural features of the title compound and dopamine derivatives (Å, °).



τ_1 = torsion angle C4—C9—C10—N2, τ_2 = torsion angle C3—C4—C9—C10, d_1 = distance between the aromatic ring centroid and atom N2, d_2 = distance between N2 and X (X = N or O), and φ = dihedral angle between the ethylamine (C1/C7/C8/N) plane and the aromatic ring plane.

Ref	τ_1	τ_2	d_1	d_2	φ
a	−177.5 (1)	−68.9 (2)	5.214	6.946	67.4 (1)
b	−168.32	−120.92	5.172	7.268	64.36
c†	178.98/−177.24	−94.47/137.00	5.122/5.196	6.874/7.165	84.49/43.99
d	−171.78	−76.66	5.119	6.808	77.04
e	−179.27	−72.68	5.134	6.894	72.55
f	178.71	−175.83	5.202	7.415	4.27
g	179.78	73.19	5.118	6.824	74.20
h	60.47	68.98	3.940	5.745	77.76
i	55.49	58.39	3.975	5.620	89.17

† Two molecules in the asymmetric unit. Notes: (*a*) ropinirole hydrochloride, (I) (present work); (*b*) 5-(2-aminoethyl)-2-hydroxyphenyl hydrogen sulfate (Eggleston *et al.*, 1985); (*c*) 4-(2-aminoethyl)-2-hydroxyphenyl hydrogen sulfate (Eggleston *et al.*, 1985); (*d*) dopamine hydrochloride (Klein, 1991); (*e*) 6-(2-aminoethyl)-3-methyl-2,3-dihydro-1,3-benzoxazol-2-one hydrochloride (Boivin *et al.*, 1987); (*f*) 2-(4-hydroxy-3-methoxyphenyl)ethylammonium chloride (Okabe *et al.*, 1991); (*g*) 2-(4-hydroxy-3-methoxyphenyl)ethylammonium perchlorate (Okabe & Mori, 1992); (*h*) 2-(3,4-dihydroxyphenyl)ethylammonium 3,5-dinitrobenzoate (Ohba & Ito, 2002*a*); (*i*) 2-(3,4-dimethoxyphenyl)ethylammonium 3,5-dinitrobenzoate (Ohba & Ito, 2002*b*).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SJ2022). Services for accessing these data are described at the back of the journal.

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