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1-(2-{4-[6-Hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiol-3-ylcarbonyl]phenoxy}ethyl)piperidinium chloride

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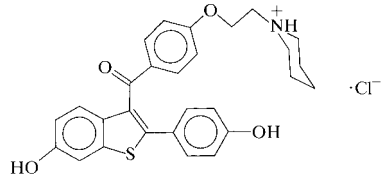
The title compound, raloxifene hydrochloride, $C_{28}H_{28}NO_4S^+\cdot Cl^-$, belongs to the benzothiophene class of antiosteoporotic drugs. In the molecular cation, the 2-phenol ring sustains a dihedral angle of 45.3 (1)° relative to the benzo[*b*]thiophene system. The benzo[*b*]thiophene and phenyl ring planes are twisted with respect to the carbonyl plane, with the smallest twist component occurring between the phenyl and carbonyl planes. The N atom bears the positive charge in the molecular cation and the piperidine ring adopts an almost perfect chair conformation. The Cl^- anion is involved in the formation of N—H···Cl and O—H···Cl intermolecular hydrogen bonds, which lead to the formation of a layer of molecular cations.

Comment

Many non-steroidal compounds (antiestrogens or selective estrogen-receptor modulators) are used clinically for the management of osteoporosis in women because they cause estrogen-like effects in a number of physiological systems without an increase in the risk of cancer. They act by binding with high affinity to the estrogen receptor, a nuclear transcription factor which controls the differentiation of the precursors of the macrophage cells that resorb bone tissue, the osteoclasts. The estrogen receptor action is now better understood following novel X-ray crystallographic studies on different ligand/receptor complexes (Brzozowski *et al.*, 1997; Pike *et al.*, 1999, and references therein). The accepted model states that the tissue-selective agonistic and/or antagonistic effects of the antiestrogens depend on the structural feature of each drug and are originated by the conformational change that takes place in the estrogen receptor upon binding of each individual ligand (McDonnell, 2000; Rodan & Martin, 2000). The mixed agonist/antagonist antiosteoporotic raloxifene hydrochloride is efficacious in preventing bone loss, and exerts beneficial effects on the cardiovascular system and breast tissue in the absence of significant secondary events in mammary tissue and the uterus (Bryant & Dere, 1998; Bryant *et al.*, 1999; Goldstein *et al.*, 2000).

A number of antiestrogens have been crystallographically studied, including the raloxifene-related compound {3-[4-(tetrahydropyrrolylethoxy)benzoyl]-2-*p*-hydroxyphenyl}-6-hydroxybenzo[*b*]thiophene acetone solvate (Kym *et al.*, 1993). Data of the latter compound (refcode PIDXIJ; Kym *et al.*, 1993) were retrieved from the Cambridge Structural Database (Allen *et al.*, 1983), and then used to compare the structures of both antiestrogens.

The solid-state X-ray analysis of raloxifene hydrochloride was undertaken as part of our ongoing study of the crystal and molecular structures of different chemical compounds that affect osseous metabolism and are used as therapeutic agents to treat a variety of bone disorders (Vega *et al.*, 1996, 1998).



(I)

The asymmetric unit of raloxifene hydrochloride, (I), consists of benzo[*b*]thiophene, *i.e.* a five-membered heterocycle fused across the C4—C9 bond to the benzo ring, substituted at the 2-position with phenol and at the 3-position with an arm containing phenyl and piperidine rings (see Fig. 1). The molecule bears a net positive charge due to proton transfer from HCl to the N atom of the piperidine ring (N41), so hereinafter it will be referred to as the molecular cation.

The benzo[*b*]thiophene system is essentially planar, with the maximum deviation from the least-squares plane through S1/C2–C9/O7 occurring at O7 [0.067 (1) Å]. The dihedral angle between the least-squares planes of the benzo[*b*]-thiophene and 2-phenol units [45.3 (1)°] is equal in raloxifene and PIDXIJ (Kym *et al.*, 1993), suggesting that benzo[*b*]-thiophene and the phenol ring are arranged in a structural motif which is common to both antiestrogens. As the phenol ring at the 2-position does not show any interatomic contact other than that involving the O24 atom, its orientation relative to benzo[*b*]thiophene could be the result of the minimization of steric hindrance.

The carbonyl C30 atom assumes sp^2 character and has a trigonal angle configuration with a bond-angle sum of 360° (see Table 1). The two bond angles made by the five-membered heterocycle with the carbonyl group, C2—C3—C30 124.99 (15)° and C4—C3—C30 121.60 (15)°, compare well with those in PIDXIJ (124.2 and 121.7°, respectively). Those formed by the phenyl ring and the carbonyl group, C32—C31—C30 122.77 (15)° and C36—C31—C30 118.70 (16)°, differ from the corresponding values in PIDXIJ (121.2 and 119.6°), suggesting that the attractive interaction involving C36—H36···O30 in raloxifene hydrochloride is greater than that present in PIDXIJ.

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According to Benassi *et al.* (1987), the five-membered heterocycle in benzo[*b*]thiophene derivatives possesses a higher degree of conjugative ability than the phenyl ring, so the former is less twisted than the latter from the carbonyl plane. Also, the same authors showed that the exocyclic $C_{thiophene}-C_{CO}$ bond [1.476 (2) Å] is shorter than the $C_{Ph}-C_{CO}$ bond [1.483 (2) Å], suggesting that the bond distance is shorter when the respective ring is less twisted with respect to the carbonyl plane (Benassi *et al.*, 1987). However, a very different conjugative ability is observed in PIDXIJ and raloxifene hydrochloride. In PIDXIJ, the five-membered heterocycle is twisted more from the carbonyl plane than is the phenyl ring, as can be seen from the values of the dihedral angles of 69 and 12°, respectively. Moreover, the $C_{thiophene}-C_{CO}$ bond (1.492 Å) is longer than the $C_{Ph}-C_{CO}$ bond (1.476 Å), clearly showing that the conjugative ability was transferred from the five-membered heterocycle to the phenyl ring. An intermediate situation occurs in this work, where the angular relationships involving the benzo[*b*]thiophene, the phenyl ring and the carbonyl planes [dihedral angles of 16.9 (1) and 53.4 (1)°, respectively] indicate that the phenyl ring plane is slightly more twisted from the carbonyl plane and the five-membered heterocycle is less than 15° less twisted than the corresponding values in PIDXIJ. Although the exocyclic $C_{thiophene}-C_{CO}$ bond [C3—C30 1.490 (2) Å] compares well with that in PIDXIJ, the $C_{Ph}-C_{CO}$ bond [C30—C31 1.487 (2) Å] is not significantly shorter. By another way, the carbonyl group is able to rotate around the $C_{thiophene}-C_{CO}$ bond and the torsion angle C2—C3—C30—O30, which in raloxifene has a value of 124.0 (2)°, is −66.2° in PIDXIJ.

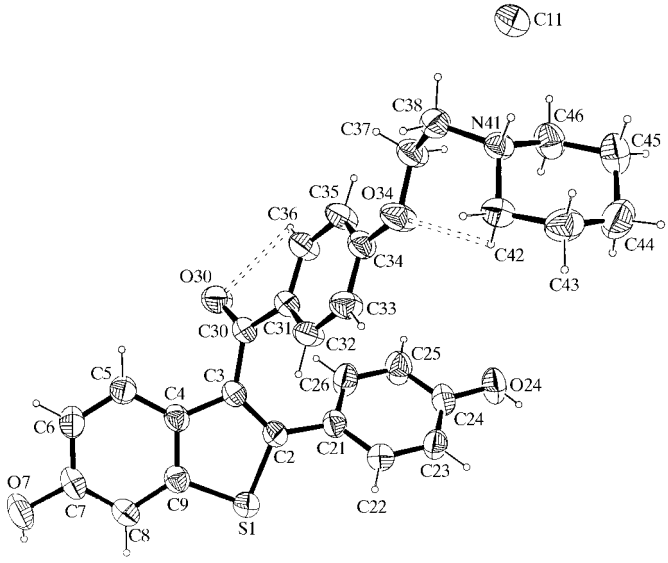

Figure 1
View of the title structure showing the numbering scheme used and displacement ellipsoids drawn at the 50% probability level. Intramolecular C—H···O contacts are shown as dashed lines.

The O34—C37—C38—N41 chain of atoms linking the phenyl group to the terminal ring assumes, as in PIDXIJ, a *gauche* conformation, the torsion angles being 67.5 (2) and 59°, respectively. The bond lengths and angles of the chain show differences when comparing both structures. In raloxifene hydrochloride, the geometry of the atoms within the chain could be significantly affected by the ability of the C42 atom of the piperidine ring to act as a hydrogen-bond donor to O34, in such a way that the C42—H421···O34 intramolecular contact forms a six-membered ring, as is apparent in Fig. 1. The terminal piperidine ring suffers considerable deviation from planarity and adopts an almost perfect chair conformation, the ring-puckering parameters (Cremer & Pople, 1975) being Q_T = 0.578 (2) Å, θ = 175.6 (2)° and φ = 221 (3)°. Asymmetry parameters (Nardelli, 1983) show the ring is close to D_{3d} local pseudosymmetry.

Hydrogen bonding determines the packing of the crystal of raloxifene hydrochloride, which comprises stacking of layers (the hydrogen-bond geometry is given in Table 2). Within a layer, the molecular cations are arranged in a chain running along the crystallographic *b* axis through N41—H41···Cl1 and O7—H7···Cl1^{i} hydrogen bonds, and, at the same time, parallel chains are held together *via* O24—H24···Cl1^{ii} hydrogen bonds. As shown in Table 2, the intermolecular C38—H381···O30^{iii} contacts seem to contribute to the interlayer stability of the structure (symmetry codes are given in Table 2).

Experimental

The title compound was obtained from Laboratorios Gador SA, Buenos Aires, Argentina. Crystals suitable for X-ray diffraction were obtained by slow evaporation from a water solution.

Crystal data

$C_{28}H_{28}NO_4S^+\cdot Cl^-$
M_r = 510.02
Monoclinic, $P2_1/c$
a = 13.4836 (3) Å
b = 13.1345 (3) Å
c = 14.6532 (3) Å
β = 102.0570 (13)°
V = 2537.84 (10) Å^3
Z = 4
D_x = 1.335 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 42516 reflections
θ = 1.0–27.5°
μ = 0.27 mm^{-1}
T = 120 (2) K
Prism, yellow
0.36 × 0.18 × 0.08 mm

Data collection

Nonius KappaCCD diffractometer
φ and ω scans with κ offsets
55970 measured reflections
5835 independent reflections
4580 reflections with $I > 2\sigma(I)$
R_{int} = 0.1
θ_{max} = 27.5°
$h = -17 \rightarrow 17$
$k = -15 \rightarrow 17$
$l = -19 \rightarrow 19$
Intensity decay: negligible

Refinement

Refinement on F^2
$R(F)$ = 0.044
$wR(F^2)$ = 0.142
S = 1.09
5835 reflections
429 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0810P)^2 + 0.3926P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.35 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.017 (2)

Table 1
Selected geometric parameters (Å, °).

S1—C9	1.7387 (18)	N41—C42	1.500 (2)
S1—C2	1.7496 (18)	N41—C38	1.503 (2)
O7—C7	1.371 (2)	C2—C3	1.358 (2)
O24—C24	1.366 (2)	C2—C21	1.475 (2)
O30—C30	1.222 (2)	C3—C30	1.490 (2)
O34—C34	1.363 (2)	C30—C31	1.487 (2)
O34—C37	1.419 (2)	C37—C38	1.503 (3)
N41—C46	1.489 (3)		
C9—S1—C2	91.85 (8)	C36—C31—C30	118.70 (16)
C34—O34—C37	118.13 (14)	C32—C31—C30	122.77 (15)
C46—N41—C42	110.98 (16)	O34—C37—C38	109.24 (16)
C46—N41—C38	113.61 (16)	C37—C38—N41	116.83 (17)
C42—N41—C38	114.52 (15)	N41—C42—C43	109.10 (16)
C2—C3—C30	124.99 (15)	C44—C43—C42	111.06 (19)
C4—C3—C30	121.60 (15)	C43—C44—C45	110.7 (2)
O30—C30—C31	120.43 (16)	C46—C45—C44	112.1 (2)
O30—C30—C3	119.15 (15)	N41—C46—C45	110.40 (18)
C31—C30—C3	120.34 (15)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N41—H41···Cl1	0.92 (2)	2.25 (2)	3.136 (2)	161 (2)
O7—H7···Cl1^{i}	0.95 (4)	2.19 (4)	3.112 (2)	165 (3)
O24—H24···Cl1^{ii}	0.95 (4)	2.15 (3)	3.038 (2)	156 (3)
C36—H36···O30	0.95 (3)	2.51 (2)	2.794 (2)	97 (2)
C38—H381···O30^{iii}	1.00 (3)	2.50 (3)	3.012 (3)	111 (2)
C42—H421···O34	0.97 (2)	2.57 (2)	3.043 (3)	110 (2)

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

All H atoms were located in a Fourier difference map and were refined freely with individual isotropic displacement parameters. C—H bond distances range from 0.88 (3) Å for C26—H26 to 1.02 (2) Å for C46—H462.

Data collection: *COLLECT* (Nonius, 1997–2000); cell refinement: *HKL SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *HKL DENZO* and *SCALEPACK*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997); software used to prepare material for publication: *PARST* (Nardelli, 1995), CSD (Allen *et al.*, 1983) and *WinGX* (Farrugia, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1487). Services for accessing these data are described at the back of the journal.

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