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(*R*)-4-(4-Fluorophenyl)-1-[2-hydroxy-2-(3-methyl-1-benzofuran-2-yl)ethyl]-piperazinium chloride propan-1-ol solvate

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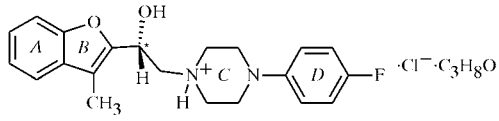
The title compound, $C_{21}H_{24}FN_2O_2^+\cdot Cl^-\cdot C_3H_8O$, is a potential drug designed as a hybrid compound with antihypertensive, antioxidant and β-adrenolytic activity. The cation contains nearly planar benzofuran and fluorophenyl ring systems, as well as a piperazine ring adopting an almost perfect chair conformation. The benzofuran and piperazine moieties are connected by an ethyl chain, the moieties forming a dihedral angle of 163.12 (13)°. In the crystal structure, ions and propanol solvent molecules are linked *via* N—H···Cl and O—H···Cl bonds into linear (010) chains.

Comment

Increased blood pressure is one of the major diseases of the cardiovascular system, leading to various organ disfunctions, for example, left ventricular hypertrophy, ischemic heart disease, renal failure and cerebrovascular damage (Pinkey & Yudkin, 1994). The title organic salt [(I), in pharmacological literature labelled as (4/1)] was designed and synthesized as a potential antihypertensive drug combining β-adrenolytic, vasodilating and antioxidant activities. It belongs to a group of heteroarylaminoethanol derivatives that are known as drugs affecting the sympathetic nervous system (Ruffolo *et al.*, 1995). Structurally, (I) is also an analogue of aryloxypropanolamines (Mokrý *et al.*, 2003) in which the oxymethylene group of the linking moiety becomes a part of the furan ring. Although this modification apparently decreases β-adrenolytic activity (Tumová *et al.*, 1997), the arylpiperazine substitution gives rise to a vasodilating effect. As revealed in recent years, reactive oxygen species (ROS) could play an important role in pathogenesis of hypertension (Friedman *et al.*, 2003). Active compounds that, besides the direct hypotensive effect, also have the ability to scavenge ROS should be more effective and useful in long-term antihypertensive therapy. The complete pharmacological evaluation of the title compound has not yet been completed, but the preliminary findings show promising vasodilating and β-adrenolytic activity, as well as significant antioxidant potency.



(I)

The structure of the (4/1) cation in (I) (Fig. 1 and Table 1) is similar to that in fluorophenylpiperazinylmethylbenzoxazolines (Köysal *et al.*, 2004), and contains a nearly planar benzofuran ring system, with deviations from the planes of six-membered ring *A* and five-membered ring *B* of up to 0.005 and 0.008 Å, respectively. Methyl atom C21 lies almost in the plane of ring *B* [the deviation from the plane is 0.048 (2) Å]. The interplanar angle between aromatic rings *A* and *B* is 2.06 (6)°. The benzofuran moiety is connected by an almost linear ethyl chain [the C1—C9—C10—N1 torsion angle is −163.12 (14)°] to the piperazine ring, *C*, which adopts an almost perfect chair conformation [the Cremer & Pople (1975) puckering parameters for ring *C* are Q = 0.572 (2) Å, Θ = 177.5 (2)° and φ_2 =

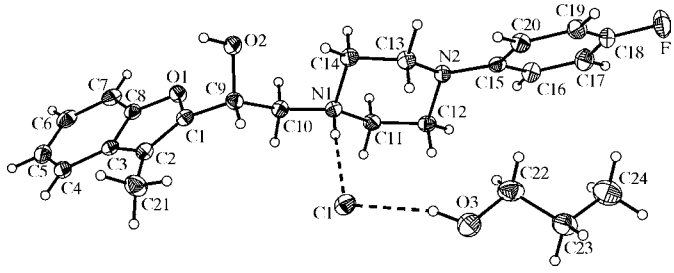


Figure 1
A view of the title compound. Non-H atoms are drawn as 50% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii.

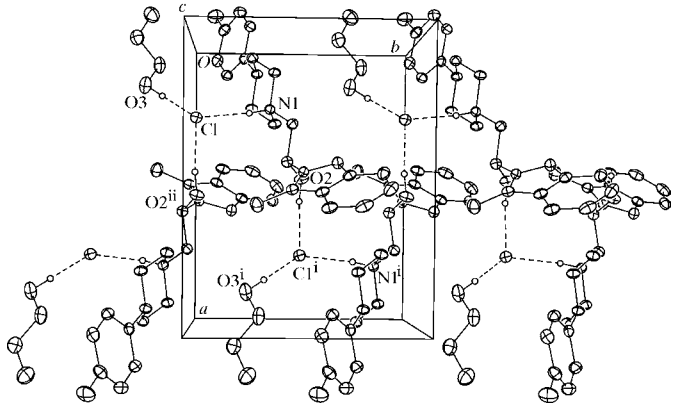


Figure 2
Part of the crystal structure of (I), showing the formation of a chain of N—H···Cl- and O—H···Cl-bonded (4/1) cations, Cl^- anions and propanol solvent molecules. H atoms not involved in hydrogen bonding have been omitted for clarity. [Symmetry codes: (i) $1-x$, $y+\frac{1}{2}$, $-z$; (ii) $1-x$, $y-\frac{1}{2}$, $-z$.]

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104 (4)°]. The second piperazine N atom, N2, is bonded to the fluorophenyl ring, *D*. The planarity of ring *D* is deformed by the F atom; the deviations of atoms F and C18 from the plane of the remaining five ring atoms are 0.0501 (13) and 0.0223 (19) Å, respectively, while the out-of-plane deviations of the remaining five atoms are up to 0.006 Å. The plane through the C atoms of ring *C* makes dihedral angles with rings *B* and *D* of 81.92 (6) and 32.43 (6)°, respectively.

The positive charge of the (4/1) cation is compensated by the Cl^- anion, leading to the formation of N—H···Cl and O—H···Cl bonds (Table 2) connecting the Cl^- ion to two neighbouring cations and a propanol molecule. In the crystal structure of (I), ions and propanol molecules thus form linear (010) chains (Fig. 2). Two weaker C—H···O interactions involving the propanol O3—H moiety further link the molecular network.

Experimental

Compound (I) was prepared by the reduction of 2-[4-(4-fluorophenyl)piperazin-1-yl]-1-(3-methylbenzofuran-2-yl)ethanone using $NaBH_4$ in methanol. The methanol was evaporated and the residue was dissolved in chloroform, washed three times with water and dried over K_2CO_3. The chloroform was evaporated and the solid residue obtained was recrystallized from propan-2-ol. The recrystallized product was dissolved in $CHCl_3$ and an etheric HCl solution was added in order to obtain the HCl salt. Well developed white crystals were obtained by recrystallization of the hydrochloride salt (1.1 g) from propan-1-ol (100 ml). Analysis (Carlo–Erba 1180 instrument) calculated for $C_{24}H_{32}ClFN_2O_3$: C 63.92, H 7.15, N 6.21%; found: C 63.80, H 7.20, N 6.28%.

Crystal data

$C_{21}H_{24}FN_2O_2^+\cdot Cl^-\cdot C_3H_8O$
M_r = 450.97
Monoclinic, $P2_1$
a = 10.6052 (6) Å
b = 8.3553 (6) Å
c = 13.0588 (10) Å
β = 94.167 (6)°
V = 1154.08 (14) Å^3
Z = 2
D_x = 1.298 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4744 reflections
θ = 2.6–29.0°
μ = 0.20 mm^{-1}
T = 120 (2) K
Prism, white
0.50 × 0.40 × 0.30 mm

Data collection

Kuma KM-4-Plus CCD diffractometer
ω scans
7674 measured reflections
3317 independent reflections
3194 reflections with $I > 2\sigma(I)$
R_{int} = 0.031
θ_{max} = 25.0°
$h = -12 \rightarrow 12$
$k = -7 \rightarrow 9$
$l = -15 \rightarrow 15$

Table 1
Selected geometric parameters (Å, °).

O1—C8	1.3693 (19)	N1—C14	1.4983 (19)
O1—C1	1.388 (2)	N1—C11	1.5043 (17)
O2—C9	1.421 (2)	N2—C15	1.410 (2)
N1—C10	1.494 (2)		
C10—N1—C11	109.87 (12)	O1—C1—C9	113.95 (13)
C14—N1—C11	109.25 (11)	C1—C9—C10	108.75 (12)
C2—C1—O1	112.45 (14)		
C1—C9—C10—N1	−163.04 (14)	C2—C1—C9—C10	127.83 (18)
C9—C10—N1—C11	174.39 (13)		

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.025
$wR(F^2)$ = 0.066
S = 1.09
3317 reflections
290 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.045P)^2 + 0.05P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.15 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}
Absolute structure: (Flack, 1983), 1144 Friedel pairs
Flack parameter = 0.05 (4)

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···Cl	0.93	2.15	3.0806 (15)	174
O3—H3O···Cl	0.937 (18)	2.245 (19)	3.1546 (15)	163 (3)
O2—H2O···Cl^{i}	0.923 (15)	2.172 (15)	3.0906 (11)	173 (2)

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

Friedel pairs were not merged but were used for the determination of the chemical absolute configuration. H atoms attached to C and N atoms were positioned geometrically, with N—H = 0.93 Å and C—H = 0.95–0.99 Å, and with U_{iso}(H) values of 1.2U_{eq}(C,N) [1.5U_{eq}(C) for methyl atoms]. The parameters of H atoms attached to O atoms were refined with O—H distances restrained to 0.95 (2) Å.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2004); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2004); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*III (Johnson & Burnett, 1996); software used to prepare material for publication: *SHELXL*97 and *PARST* (Nardelli, 1995).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG1217). Services for accessing these data are described at the back of the journal.

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