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1-[2-Ethoxy-2-(3-methyl-1-benzofuran-2-yl)ethyl]-4-(*o*-tolyl)piperazin-1-ium chloride

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Key indicators

Single-crystal X-ray study
T = 120 K
Mean σ(C–C) = 0.002 Å
R factor = 0.033
wR factor = 0.085
Data-to-parameter ratio = 14.8

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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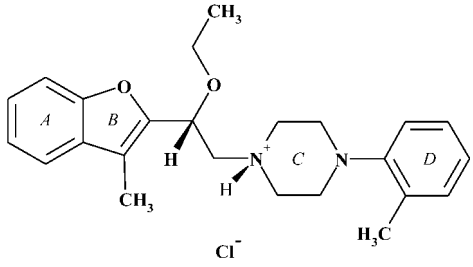
The title compound, $C_{24}H_{31}N_2O_2^+\cdot Cl^-$, is a potential drug designed as a hybrid molecule with antihypertensive, antioxidant and β-adrenolytic activity. It contains nearly planar benzofuran and benzene ring systems, and a piperazine ring which adopts an almost perfect chair conformation.

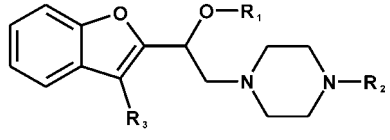
Comment

The title compound, (I) [in pharmacological literature also denoted as (24/4)] is a member of a group of potential antihypertensive drugs combining β-adrenolytic, vasodilating and antioxidant activities. These compounds were found during structure–activity relationship (SAR) studies on heteroarylethanolamine derivatives containing a substituted benzofuran moiety as a heteroaromatic part and an arylpiperazine moiety as a basic part of the bioactive molecule (Ecker *et al.*, 1996).



(I)

Previously studied compounds (*e.g.* Kurfürst *et al.*, 2004) contained a characteristic free secondary hydroxy group and an ethylene linking moiety (R_1 = H in the scheme below), and some of them showed significant pharmacological effects, such as β-antiadrenergic, vasodilating and antioxidant activities (Tumová *et al.*, 1997), or modulatory effects on tumor cell multidrug resistance (Ecker *et al.*, 1996).



R_1, R_3 = H or linear alkyl substituent (C_1 - C_2)
R_2 = methylated or halogenated phenyl substituent

Current targeted structural modifications of the linking moiety involve the replacement of the hydroxy group with an ethoxy group. Alkylation of the secondary hydroxy group of heteroarylethanolamines is assumed to modify the action of prepared potential drugs. Regardless of the changes in

receptor affinity and specificity, the alkoxy derivatives, in comparison with alcohols, are more lipophilic, and therefore different pharmacokinetic parameters are expected in processes such absorption, distribution, metabolism, and elimination. The increased lipophilicity could also influence hematoencephalic barrier transport and affect the action of compounds acting on the central nervous system. Our expectations are supported by interesting changes in adrenergic and dopaminergic activities of β-alkoxyarylethylamines shown after synthetic modification of studied derivatives (Katerinopoulos *et al.*, 1995; Torres *et al.*, 1998) or altered α_1-antiadrenergic activity of hydroxylated and ethoxylated heteroarylethanolamines (Bonacchi *et al.*, 1988). However, the hypotheses should be validated after substantial pharmacological evaluation.

The structure of the title cation (Fig. 1 and Table 1) is similar to that in compounds of fluorophenylpiperazine with benzofuran (Kurfürst *et al.*, 2004) and benzoxazole (Köysal *et al.*, 2004), or the antihypertensive flunazirine usually used in pharmacological evaluation as a reference standard (Prasanna & Guru Row, 2001).

The title cation contains a nearly planar benzofuran ring system, with maximum deviations from the planes of six-membered ring *A* and five-membered ring *B* (see the first scheme) of 0.0068 (17) and 0.0048 (15) Å, respectively. The interplanar angle between rings *A* and *B* is 1.64 (5)°. The benzofuran moiety is connected by an ethylene chain [C1—C9—C10—N1 = −174.01 (11)°] to piperazine ring *C*, which adopts an almost perfect chair conformation. The Cremer & Pople (1975) puckering parameters for ring *C* are q = 0.5830 (14) Å, Θ = 174.88 (13)° and φ_2 = −8 (2)°. The second piperazine N atom (N2) is bonded to tolyl ring *D*. Ring *D* is also nearly planar, with a maximum deviation from the plane of 0.0049 (17) Å. The plane through the C atoms of ring *C* makes dihedral angles with rings *B* and *D* of 49.01 (5) and 48.80 (4)°, respectively. Methyl atom C21 is located almost in the plane of ring *B* [the deviation from the plane is 0.013 (2) Å], while methyl atom C24 is slightly displaced out of the plane of ring *D* [the deviation from the plane is 0.028 (2) Å].

The positive charge of the title cation is compensated by the negative charge of the Cl^- anion, which is connected to the cation *via* N—H···Cl hydrogen bonding (Fig. 1 and Table 2). In the crystal structure of (I), the Cl^- anion is further involved in an extensive network of H···Cl contacts (some of them with Cl···H distance shorter than 3 Å are listed in Table 2).

Experimental

Compound (I) was prepared by the alkylation of 2-[4-(*o*-tolyl)piperazin-1-yl]-1-(3-methyl-1-benzofuran-2-yl)ethanol (10 mmol, 3.5 g) with sodium hydride (20 mmol, 0.5 g) and diethyl sulfate (20 mmol, 3.4 ml) in dimethyl sulfoxide (20 ml) at room temperature (295 K) and pressure. When the reaction was complete, the reaction mixture was poured into 10% NaOH water solution (100 ml) and extracted three times with chloroform (3 × 20 ml). The combined chloroform layers were washed three times with water, dried over K_2CO_3 and the chloroform was evaporated. The resulting oil was dissolved in ether and afterwards etheric HCl solution was added. The hydrochloride salt precipitate (0.5 g) was recrystallized from propan-2-ol (50 ml). After cooling, ether (50 ml) was added and the solution was left at 278 K for one week. CHN analysis (Carlo–Erba 1180 instrument) calculated for $C_{24}H_{31}ClN_2O_2$: C 69.47, H 7.53, N 6.75%; found: C 69.80, H 7.60, N 6.88%.

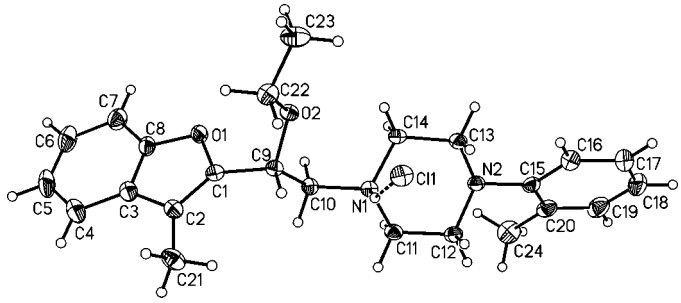


Figure 1
A view of the title compound. Non-H atoms are drawn as 50% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii.

Crystal data

$C_{24}H_{31}N_2O_2^+\cdot Cl^-$	D_x = 1.234 Mg m^{-3}
M_r = 414.96	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 3591 reflections
a = 17.446 (2) Å	θ = 2.7–28.1°
b = 10.4855 (9) Å	μ = 0.19 mm^{-1}
c = 13.0224 (14) Å	T = 120 (2) K
β = 110.304 (11)°	Prism, white
V = 2234.2 (4) Å^3	0.50 × 0.50 × 0.50 mm
Z = 4	

Data collection

Kuma KM-4 CCD area-detector diffractometer	3431 reflections with $I > 2\sigma(I)$
	R_{int} = 0.029
ω scans	θ_{max} = 25.0°
Absorption correction: none	$h = -20 \rightarrow 19$
8342 measured reflections	$k = -12 \rightarrow 10$
3918 independent reflections	$l = -12 \rightarrow 15$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.04P)^2 + P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.033	
$wR(F^2)$ = 0.085	
S = 1.02	$(\Delta/\sigma)_{max}$ = 0.001
3918 reflections	$\Delta\rho_{max}$ = 0.20 e Å^{-3}
265 parameters	$\Delta\rho_{min}$ = −0.23 e Å^{-3}
H-atom parameters constrained	

Table 1
Selected geometric parameters (Å, °).

O1—C8	1.3777 (17)	N1—C10	1.5039 (17)
O1—C1	1.3934 (16)	N1—C14	1.5070 (17)
O2—C9	1.4189 (16)	N2—C15	1.4274 (18)
O2—C22	1.4333 (16)	C1—C2	1.351 (2)
N1—C11	1.5017 (17)	C1—C9	1.5039 (19)
C11—N1—C10	109.05 (10)	C11—N1—C14	109.53 (10)
O1—C1—C9—C10	−72.94 (14)	C9—C10—N1—C11	148.68 (11)
C1—C9—C10—N1	−174.01 (11)		

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···Cl1	0.93	2.26	3.1145 (12)	152
C13—H13B···Cl1	0.99	2.86	3.5870 (15)	131
C9—H9···Cl1^{i}	1.00	2.97	3.6879 (14)	130
N1—H1···Cl1^{i}	0.93	2.96	3.4592 (12)	115
C21—H21A···Cl1^{i}	0.98	2.96	3.8621 (18)	154
C11—H11B···Cl1^{i}	0.99	2.74	3.4852 (15)	132
C10—H10B···Cl1^{ii}	0.99	2.87	3.7878 (14)	154
C14—H14B···Cl1^{ii}	0.99	2.61	3.5647 (15)	161

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

H atoms attached to C and N atoms were positioned with idealized geometry (N—H = 0.93 Å, aromatic C—H = 0.95 Å, methylene C—H = 0.99 Å and methyl C—H = 0.98 Å) and were refined with fixed isotropic displacement parameters [U_{iso}(H) = 1.5U_{eq}(C) for methyl H atoms and 1.2U_{eq}(C,N) for all other H atoms] using a riding model.

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, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*III (Burnett & Johnson, 1996); software used to prepare material for publication: *SHELXL*97 and *PARST* (Nardelli, 1995).

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