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Fleroxacin hydrochloride hydrate

Xiang-Jun Zheng, Hui-Chun Zhao and Lin-Pei Jin*

Department of Chemistry, Beijing Normal University, Beijing 100875, People's Republic of China
Correspondence e-mail: lpjin@bnu.edu.cn

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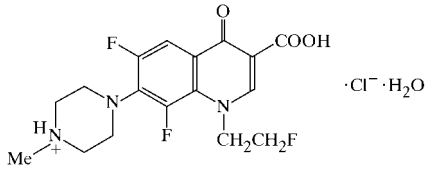
In the structure of the title compound, 4-[3-carboxy-6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-4-oxo-7-quinolyl]-1-methylpiperazinium chloride hydrate, $C_{17}H_{19}F_3N_3O_3^+\cdot Cl^-\cdot H_2O$, the quinoline and its substituents, except for the fluoroethyl group, are coplanar, while the piperazinium moiety exists in a chair form. There are π–π-stacking interactions between the quinoline rings, and intra- and intermolecular hydrogen bonds in the crystal.

Comment

6,8-Difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-quinoline-3-carboxylic acid, trivially known as fleroxacin, is one of the fluoroquinolone antibiotic drugs, and is certified as the best choice for curing infections caused by susceptible bacteria (Drakopoulos & Ioannou, 1997). It affords powerful broad-spectrum antisepsis, long effectiveness, few side effects and no interference with other antibiotics (Weidekamm *et al.*, 1987). It has been widely used for the treatment of bacterial infections, such as those of the respiratory system, the urinary tract, skin, soft tissue, bones and joints, the gastro-intestinal tract and the central nervous system (Krisztina *et al.*, 1990). Photolysis (>320 nm) of fleroxacin results in the loss of the fluorine substituent at C9 (Fig. 1) as fluoride (Martinez *et al.*, 1997). Fleroxacin has the highest DNA photocleaving activity among the fluoroquinolones; DNA damage probably results from the generation of a carbene at C9 as a result of the photoinduced loss of atom F2 as fluoride upon UVA irradiation (Martinez & Chignell, 1998). Therefore, it is important to know the molecular structure of fleroxacin to investigate this reaction better.



(I)

To this end, the title compound, (I), the hydrochloride hydrate of fleroxacin, has been prepared and its structure is reported here.

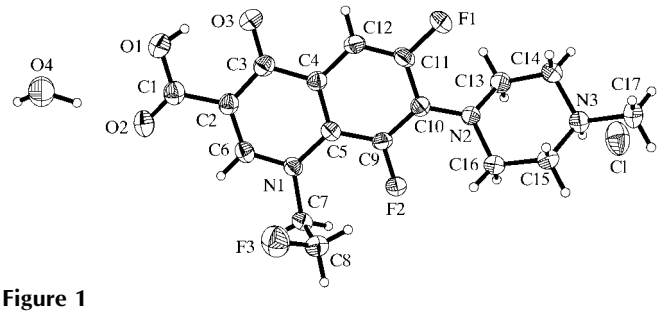


Figure 1
The molecular structure of (I), showing the atom-numbering scheme and 50% probability displacement ellipsoids. H atoms are drawn as small spheres of arbitrary radii.

In (I), the quinoline and its substituents, except for the piperazinium moiety and the fluoroethyl group attached to atom N1, are nearly coplanar, with a mean deviation of 0.052 (2) Å, while the quinoline itself is planar, with a mean deviation of 0.032 (2) Å. The piperazinium moiety is in a chair form.

There are three C—F bonds in (I). The C8—F3 bond is apparently longer than the C—F bonds to the quinoline, C11—F1 and C9—F2 (Table 1). This can be attributed to the conjugation of the electrons of atoms F1 and F2 with the quinoline. The C9—F2 bond is longer than C11—F1 and the photoinduced C—F breakage is easier for the former under UV irradiation (Zhang *et al.*, 2000). In the molecule of (I), the nine C—N bonds can be divided into two groups, of which six, falling in the range 1.455 (3)–1.501 (3) Å, characterize C—N single bonds. Two short C—N bonds, C5—N1 [1.407 (3) Å] and C6—N1 [1.349 (3) Å], result from the delocalization of their electrons on the quinoline. The other short C—N bond, C10—N2 [1.377 (3) Å], arises from the conjugation of the lone pair of electrons on N2 with the quinoline. The bond angles at N1 and N2 are different (Table 1).

In (I), the fleroxacin is in a cationic form, with atom N3 of the piperazinium group being protonated. The C1—O2 and C1—O1 bond lengths (Table 1) of the carboxyl group agree with those found in *N*,*N*,*N*′,*N*″,*N*‴,*N*‴-triethylenetetraminehexacetic acid (Finnen & Pinkerton, 1997), *N*-(2-hydroxyethyl)ethylenediaminetriacetic acid (Kettmann *et al.*, 1993) and some derivatives or complexes of betaine (Ilczyszyn, Barnes *et al.*, 1995; Ilczyszyn, Lis & Ratajczak, 1995; Ratajczak *et al.*, 1994), and show that the carboxyl group is in the acid form. The C3—O3 bond length is intermediate between that expected for single and double bonds. The intramolecular hydrogen bond between atoms O1 and O3 (Table 2) may account for this phenomenon.

There are four intermolecular hydrogen bonds in the crystal of (I) (Table 2). The water molecule, as a hydrogen donor, is hydrogen bonded to the Cl^- anion, as well as to the two O atoms of the carboxyl group, forming a three-centre hydrogen bond. In addition, the Cl^- anion is also hydrogen bonded to the protonated fleroxacin N atom. Although flourine is the most electronegative element in (I), no hydrogen bonds are observed around the F atoms. The quinoline rings are oriented to give alternate π–π-stacking interactions of 3.375 (3) and 3.392 (3) Å (Fig. 2).

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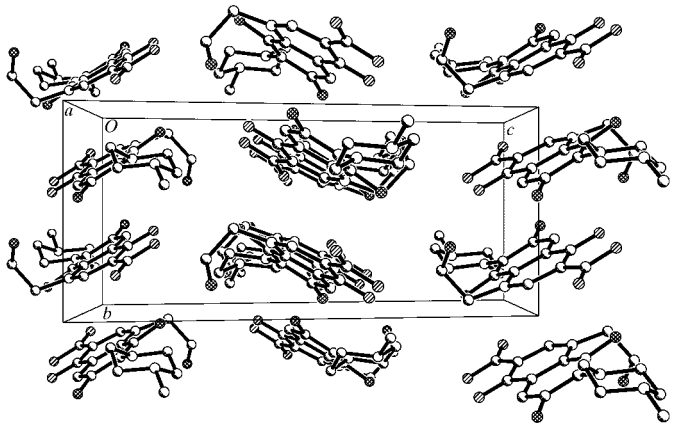

Figure 2
A packing diagram for (I), showing the π–π-stacking interactions between the quinoline rings of the fleroxacin. All H atoms, lattice water molecules and Cl^- anions have been omitted for clarity.

Experimental

Fleroxacin was kindly donated by Qingdao Pharmaceutical Factory. Fleroxacin (0.185 g, 0.5 mmol) was dissolved in distilled water (5 ml) and the pH adjusted to 5 with dilute hydrochloric acid under heating. The mixture was sealed in a 20 ml stainless-steel reactor with a Teflon liner and heated at 373 K for 76 h. Yellow crystals of (I) were obtained (m.p. 553 K).

Crystal data

$C_{17}H_{19}F_3N_3O_3^+\cdot Cl^-\cdot H_2O$
M_r = 423.82
Monoclinic, $P2_1/c$
a = 12.961 (8) Å
b = 7.979 (5) Å
c = 18.113 (11) Å
β = 104.184 (10)°
V = 1816.1 (19) Å^3
Z = 4
D_x = 1.550 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 7320 reflections
θ = 1.6–25.0°
μ = 0.27 mm^{-1}
T = 293 (2) K
Plate, light yellow
0.30 × 0.25 × 0.20 mm

Data collection

Bruker *SMART* 1000 CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.923, T_{max} = 0.948
7320 measured reflections
3209 independent reflections
2103 reflections with $I > 2\sigma(I)$
R_{int} = 0.032
θ_{max} = 25°
$h = -15 \rightarrow 14$
$k = -9 \rightarrow 6$
$l = -19 \rightarrow 21$

Table 1
Selected geometric parameters (Å, °).

F1—C11	1.348 (2)	N2—C13	1.465 (3)
F2—C9	1.364 (2)	N3—C17	1.490 (3)
F3—C8	1.390 (3)	N3—C14	1.497 (3)
N1—C6	1.349 (3)	N3—C15	1.501 (3)
N1—C5	1.407 (3)	C1—O2	1.216 (3)
N1—C7	1.490 (3)	C1—O1	1.326 (3)
N2—C10	1.377 (3)	C3—O3	1.265 (3)
N2—C16	1.455 (3)		
C6—N1—C5	119.25 (18)	C17—N3—C14	111.39 (17)
C6—N1—C7	116.37 (18)	C17—N3—C15	111.20 (18)
C5—N1—C7	123.74 (17)	C14—N3—C15	110.97 (17)
C10—N2—C16	123.92 (18)	O2—C1—O1	120.8 (2)
C10—N2—C13	121.02 (18)	O2—C1—C2	123.1 (2)
C16—N2—C13	112.10 (17)	O1—C1—C2	116.1 (2)

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

D—H···A	D—H	H···A	D···A	D—H···A
N3—H3A···Cl^{i}	0.91	2.23	3.067 (3)	152
O1—H1···O3	0.82	1.76	2.524 (3)	154
O4—H41···Cl^{ii}	0.98 (2)	2.13 (2)	3.111 (3)	175 (3)
O4—H42···O2	0.97 (2)	1.87 (2)	2.842 (3)	178.2 (14)

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

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.100
S = 1.01
3209 reflections
263 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.049P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.006
$\Delta\rho_{max}$ = 0.32 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}

H atoms of the cation were generated geometrically and allowed to ride on their parent atoms, with N—H = 0.91 Å, O—H = 0.82 Å and C—H = 0.93–0.97 Å. The water H atoms were located from difference maps and refined with isotropic displacement parameters, which can introduce high U_{iso} parameters for water H atoms. Therefore, the ratio of U_{eq}(max):U_{eq}(min) is relatively high.

Data collection: *SMART* (Bruker, 1998); cell refinement: *SMART*; data reduction: *SHELXTL* (Sheldrick, 1998); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: TA1382). Services for accessing these data are described at the back of the journal.

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