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Enoxacin trihydrate

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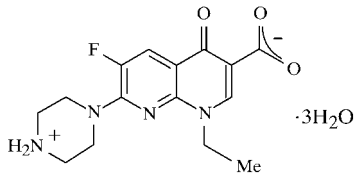
The structure of the title compound, 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-4-ium-1-yl)-1,8-naphthyridine-3-carboxylate trihydrate, $C_{15}H_{17}FN_4O_3\cdot 3H_2O$, has a zwitterion of enoxacin and three water molecules in the asymmetric unit. The zwitterions form sheets lying parallel to each other and are hydrogen bonded in a head-to-tail manner. The crystal structure is stabilized by the involvement of O and H atoms from all the water molecules in strong hydrogen bonds. The naphthyridine ring system is essentially planar, with the carboxylate group lying out of this plane at an angle of 26.13 (6)° and the ethyl group oriented at approximately right angles to this plane. The piperazinium ring adopts a chair conformation.

Comment

Enoxacin belongs to the second-generation fluoroquinolone antimicrobial agents (Smith, 2000). Its structure–activity relationships (Koga *et al.*, 1980; Domagala *et al.*, 1986; Domagala, 1994; Gootz & Brighty, 1996) and pharmacokinetics (Wise *et al.*, 1986) have been extensively studied. Like other quinolone antimicrobials, it exerts its action by inhibiting the enzyme DNA-gyrase, which is responsible for the continuous introduction of negative supercoils into DNA (Alfred *et al.*, 1996; Gootz *et al.*, 1994). Enoxacin, the naphthyridone analogue of norfloxacin, possesses roughly similar antibacterial activity but improved bioavailability over the latter (Gaja, 1992; Child *et al.*, 1995). There are a number of reported drug interactions of enoxacin with milk, food, antacids and H2-receptor antagonists. Drug interactions have been reported when enoxacin is co-administered with magnesium and aluminium hydroxide, resulting in decreased levels of enoxacin in plasma and urine (Jaehde *et al.*, 1994). There is additional evidence of the formation of complexes with Mg and Ca cations at pH 7.4, the binding sites being first the carbonyl and carboxyl groups, and then the piperazine N4 atom (Lecomte & Chenon, 1996). In this paper, we report the structure of enoxacin trihydrate, (I).



(I)

The asymmetric unit of (I) is composed of a zwitterion of enoxacin (Fig. 1) and three molecules of water of solvation, which form a strong network of hydrogen bonds (Fig. 2). The zwitterion is composed of an essentially planar naphthyridine ring system [maximum deviation for C6 of 0.0269 (10) Å], which is substituted with ethyl, fluoro, oxo, carboxyl and piperazinium groups. The carboxylate group lies out of the plane of the naphthyridine ring system, with an angle of 26.13 (6)° between the mean planes formed by the two entities. The ethyl group attached to N1 is oriented approximately at right angles to the plane of the naphthyridine ring [80.80 (11)°]. The piperazinium ring adopts a chair conformation, with puckering parameters (Cremer & Pople, 1975) Q = 0.571 (1) Å, θ = 175.4 (1)° and φ = 357 (2)°.

The zwitterions are stacked in sheets lying parallel to each other and are hydrogen bonded *via* a piperazinium ammonium H atom and a carboxylate moiety in a head-to-tail manner. The crystal structure of (I) is further strengthened by the involvement of the other ammonium H atom in a hydrogen bond with a hydration water molecule, which is also hydrogen bonded to another zwitterion through its carbonyl function. In fact, the O and H atoms of all the water molecules are involved in strong hydrogen bonding; details of the hydrogen bonding are given in Table 2.

A search of the Cambridge Structural Database (Version 1.6, 2003 release; Allen, 2002) yielded only one entry containing the piperazinyl-oxo-naphthyridine-carboxylate moiety, namely nalidixic acid (Datta *et al.*, 1995), while there are 32 structures in the database containing the quinoline ring system instead of the naphthyridine ring system.

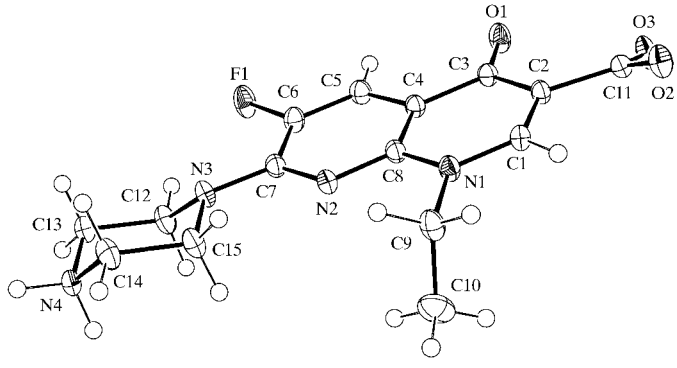


Figure 1
A view of the zwitterion of enoxacin in (I), with displacement ellipsoids plotted at the 50% probability level.

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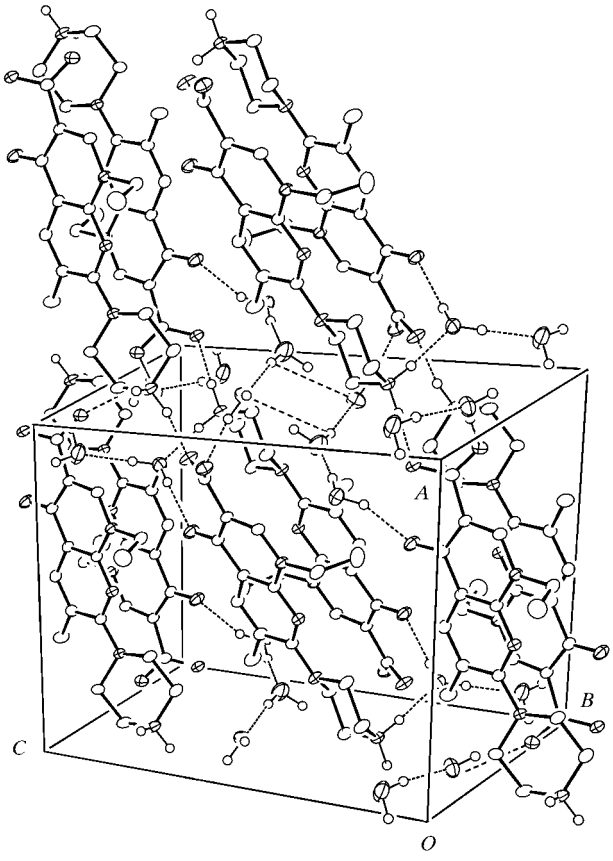

Figure 2
A view of the unit cell of (I), showing the hydrogen bonding (dashed lines).

Experimental

Enoxacin was obtained as a gift from Rhône–Poulenc Röhrer Pakistan (Pvt) Ltd, Wah Cant., Pakistan. It was recrystallized from dimethylformamide, affording colourless needles of (I) [m.p. 497–498 K (decomposition)].

Crystal data

$C_{15}H_{17}FN_4O_3\cdot 3H_2O$
$M_r = 374.37$
Monoclinic, $P2_1/c$
$a = 13.618\ (3)$ Å
$b = 7.2963\ (13)$ Å
$c = 18.316\ (5)$ Å
$\beta = 108.282\ (12)^\circ$
$V = 1728.0\ (7)$ Å^3
$Z = 4$
$D_x = 1.439$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 7267 reflections
$\theta = 3.1$–27.5°
$\mu = 0.12$ mm^{-1}
$T = 173\ (2)$ K
Needle, colourless
0.32 × 0.06 × 0.05 mm

Data collection

Nonius KappaCCD area-detector diffractometer
ω and φ scans
Absorption correction: multi-scan (*SORTAV*; Blessing, 1997)
$T_{min} = 0.95$, $T_{max} = 0.99$
7267 measured reflections
3945 independent reflections
3146 reflections with $I > 2\sigma(I)$
$R_{int} = 0.023$
$\theta_{max} = 27.5^\circ$
$h = -17 \rightarrow 17$
$k = -8 \rightarrow 9$
$l = -23 \rightarrow 23$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.036$
$wR(F^2) = 0.097$
$S = 1.04$
3945 reflections
328 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.0458P)^2 + 0.3941P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.27$ e Å^{-3}
$\Delta\rho_{min} = -0.21$ e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.011 (2)

Table 1
Selected geometric parameters (Å, °).

F1—C6	1.3581 (15)	N2—C7	1.329 (2)
O1—C3	1.2471 (16)	N2—C8	1.344 (2)
O2—C11	1.2593 (16)	N3—C7	1.382 (2)
O3—C11	1.259 (2)	N3—C15	1.466 (2)
N1—C1	1.351 (2)	N3—C12	1.474 (2)
N1—C8	1.384 (2)	N4—C13	1.486 (2)
N1—C9	1.481 (2)	N4—C14	1.489 (2)
C1—N1—C8	119.23 (10)	C7—N3—C15	115.41 (10)
C1—N1—C9	120.05 (11)	C7—N3—C12	119.64 (10)
C8—N1—C9	120.64 (10)	C15—N3—C12	112.49 (10)
C7—N2—C8	119.81 (11)	C13—N4—C14	109.48 (10)

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

D—H···A	D—H	H···A	D···A	D—H···A
O5—H051···O2	0.94 (2)	1.80 (3)	2.726 (2)	170 (2)
O5—H052···O2^{i}	0.87 (3)	1.89 (3)	2.740 (2)	162 (2)
O6—H061···O5^{ii}	0.88 (3)	1.95 (3)	2.821 (2)	171 (2)
O6—H062···O5	0.94 (3)	1.96 (3)	2.900 (2)	178 (2)
N4—H41···O4	0.96 (2)	1.82 (2)	2.767 (2)	169 (2)
N4—H42···O3^{iii}	0.97 (2)	1.72 (2)	2.676 (2)	168 (2)
O4—H041···O6^{iv}	0.92 (2)	1.86 (2)	2.779 (2)	173 (2)
O4—H042···O1^{v}	0.90 (2)	1.96 (2)	2.809 (2)	157 (2)

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

The H atoms were located from a difference Fourier synthesis and were allowed to refine with isotropic displacement parameters. The final difference map was free of any chemically significant features.

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *HKL DENZO* (Otwinowski & Minor, 1997); data reduction: *SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SAPI*91 (Fan, 1991); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1468). Services for accessing these data are described at the back of the journal.

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