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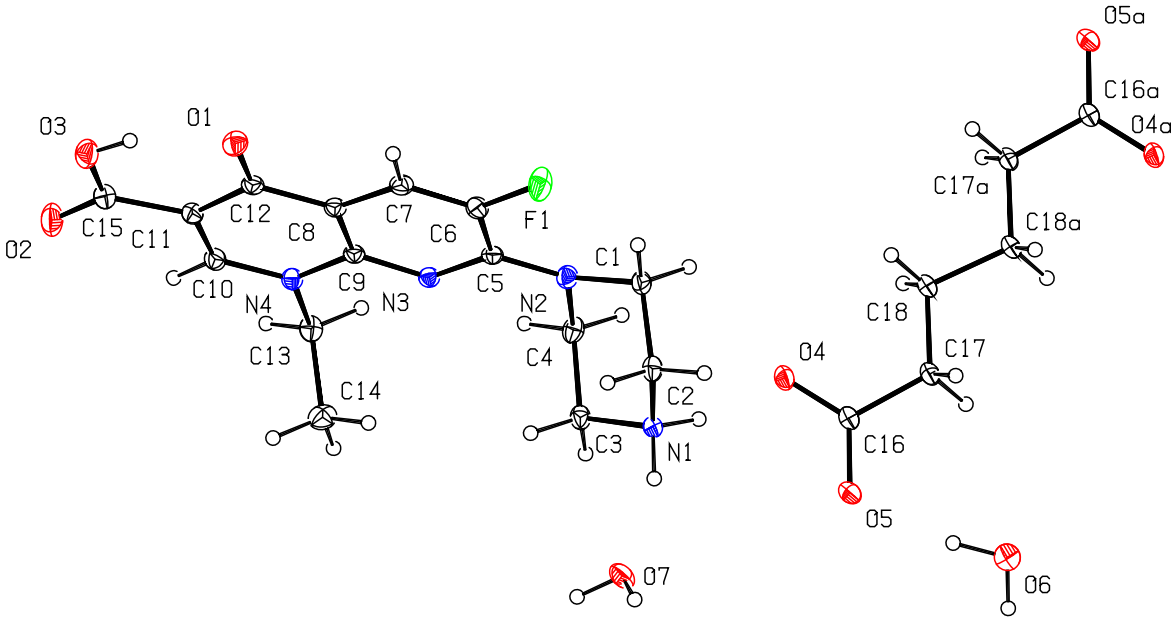
The crystal structure of bis(4-(6-carboxy-8-ethyl-3-fluoro-5-oxo-5,8-dihydro-1,8-naphthyridin-2-yl)piperazin-1-ium) adipate tetrahydrate, $C_{36}H_{52}F_2N_8O_{14}$



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Abstract

$C_{36}H_{52}F_2N_8O_{14}$, triclinic, $P\bar{1}$ (no. 2), a = 6.9775(4) Å, b = 9.0785(6) Å, c = 16.8942(10) Å, β = 92.778(2)°, V = 990.91(11) Å^3, Z = 1, $R_{gt}(F)$ = 0.0397, $wR_{ref}(F^2)$ = 0.1088, T = 170 K.

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The molecular structure is shown in the figure. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

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Table 1: Data collection and handling.

Crystal:	Colourless needle
Size	0.32 × 0.04 × 0.03 mm
Wavelength:	Mo *K*α radiation (0.71073 Å)
μ:	0.12 mm^{-1}
Diffractometer, scan mode:	Bruker D8 venture, φ and ω
θ_{max}, completeness:	27.1°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	16926, 4372, 0.032
Criterion for I_{obs}, $N(hkl)_{gt}$:	I_{obs} > 2 σ(I_{obs}), 3462
$N(param)_{refined}$:	282
Programs:	Bruker [1], Olex2 [2], SHELX [3, 4]

Source of material

The mixture of enoxacin (160 mg, 0.5 mmol) and adipic acid (36.5 mg, 0.25 mmol) was dissolved in 8 mL of deionized water. The resulting mixture was stirred and dissolved in a constant temperature water bath at 50 °C to obtain a clear solution, which was filtered and placed in a

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2).

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
F1	0.54391 (18)	0.08485 (10)	0.08471 (6)	0.0433 (3)
O1	0.78452 (16)	0.38446 (12)	−0.12696 (6)	0.0286 (2)
O2	0.9589 (2)	0.86045 (14)	−0.11739 (8)	0.0439 (3)
O3	0.91400 (18)	0.61436 (14)	−0.19045 (7)	0.0349 (3)
H3	0.869493	0.522204	−0.184385	0.052*
N1	0.76033 (17)	0.35227 (14)	0.37883 (7)	0.0213 (3)
H1A	0.665036	0.333659	0.413165	0.026*
H1B	0.882142	0.369992	0.407378	0.026*
N2	0.54156 (19)	0.33030 (14)	0.22750 (7)	0.0238 (3)
N3	0.66426 (17)	0.51109 (13)	0.15404 (7)	0.0199 (2)
N4	0.77448 (17)	0.70845 (13)	0.08743 (7)	0.0209 (3)
C1	0.5295 (2)	0.18633 (17)	0.25458 (9)	0.0261 (3)
H1C	0.509316	0.094903	0.206168	0.031*
H1D	0.413130	0.163290	0.285818	0.031*
C2	0.7214 (2)	0.20890 (17)	0.30832 (9)	0.0244 (3)
H2A	0.709065	0.113885	0.329137	0.029*
H2B	0.835791	0.221342	0.275473	0.029*
C3	0.7582 (2)	0.49702 (17)	0.35203 (9)	0.0244 (3)
H3A	0.872950	0.526568	0.320767	0.029*
H3B	0.772422	0.586740	0.400732	0.029*
C4	0.5625 (2)	0.46521 (18)	0.29861 (9)	0.0254 (3)
H4A	0.447922	0.440893	0.330597	0.030*
H4B	0.562315	0.560574	0.279870	0.030*
C5	0.6047 (2)	0.35929 (16)	0.15643 (8)	0.0202 (3)
C6	0.6043 (2)	0.23981 (16)	0.08407 (9)	0.0244 (3)
C7	0.6601 (2)	0.27632 (17)	0.01412 (9)	0.0234 (3)
H7	0.659342	0.194720	−0.033083	0.028*
C8	0.7197 (2)	0.43658 (16)	0.01162 (8)	0.0202 (3)
C9	0.7176 (2)	0.54752 (16)	0.08445 (8)	0.0193 (3)
C10	0.8334 (2)	0.75503 (17)	0.02061 (9)	0.0233 (3)
H10	0.874117	0.865640	0.024276	0.028*
C11	0.8383 (2)	0.65234 (17)	−0.05282 (9)	0.0229 (3)
C12	0.7808 (2)	0.48434 (17)	−0.06104 (9)	0.0215 (3)
C13	0.7742 (2)	0.82801 (17)	0.16431 (9)	0.0250 (3)
H13A	0.653363	0.787528	0.190421	0.030*
H13B	0.766842	0.926942	0.150991	0.030*
C14	0.9600 (3)	0.86489 (19)	0.22403 (10)	0.0333 (4)
H14A	1.079962	0.904474	0.198286	0.050*
H14B	0.964654	0.768135	0.239229	0.050*
H14C	0.955917	0.945997	0.273334	0.050*
H6A	0.613 (3)	0.199 (2)	0.6641 (11)	0.050*
C15	0.9083 (2)	0.71961 (19)	−0.12192 (10)	0.0293 (3)
O4	0.43462 (15)	0.27607 (12)	0.45897 (6)	0.0269 (2)
O5	0.62103 (16)	0.27011 (13)	0.56760 (7)	0.0312 (3)
C16	0.4586 (2)	0.22506 (16)	0.52098 (9)	0.0209 (3)
C17	0.2825 (2)	0.10104 (17)	0.54002 (9)	0.0241 (3)
H17A	0.318657	0.001184	0.533308	0.029*
H17B	0.264444	0.137634	0.598421	0.029*
C18	0.0825 (2)	0.06374 (17)	0.48852 (9)	0.0263 (3)
H18A	0.098142	0.027198	0.429838	0.032*
H18B	0.041942	0.161861	0.496040	0.032*
O6	0.5790 (2)	0.15812 (16)	0.70852 (8)	0.0443 (3)
H6B	0.664408	0.219882	0.750489	0.066*
O7	1.15544 (15)	0.43331 (13)	0.43775 (7)	0.0312 (3)
H7A	1.238263	0.378885	0.442282	0.047*
H7B	1.222447	0.527083	0.433637	0.047*

10 mL glass bottle. The bottle was sealed with a film with a puncture hole. The filtrate was slowly evaporated at room temperature. Crystal of the title compound were obtained after two days.

Experimental details

Absorption corrections were applied by using multi-scan program [1]. Using Olex2 [2], the structure was solved with the ShelXT [3] structure solution program and refined with the ShelXL [4] refinement package. The H atoms were fixed, fixed U_{iso} were set to 1.2 times of all C(H) groups, C(H,H) groups and N(H,H) groups; 1.5 times of C(H,H,H,H) groups, O(H) groups and O(H,H) groups.

Comment

As a third-generation quinolone antibiotic, enoxacin has antibacterial effects on Staphylococcus, *Escherichia coli*, Streptococcus, Helicobacter, etc., which has no cross with other antibiotics [5]. Although enoxacin has good permeability as a BCS class II drug, its solubility is extremely poor, which made it difficult to achieve optimal antibacterial activity. Recently, many studies on quinolone antibiotics with enoxacin-like structures have reported that solubility, permeability and efficacy was improved through the formation of drug salts/co-crystals [6]. For example, the solubility of enrofloxacin with the pharmaceutical salts/co-crystals of maleic, succinic, and oxalic acids was significantly higher, the solubility and stability of the drug [7]. Thus, we believe that the medicinal salt/co-crystal of enoxacin can also be prepared by drug co-crystal technology, which will improve the solubility and permeability of enoxacin and improve the clinical efficacy.

The title crystal was formed by connecting the raw materials enoxacin, adipic acid and water molecules through a protonation/deprotonation reaction of the starting materials followed by crystallisation. The

asymmetric unit consists of one monoprotonated enoxacine cation, one half of an adipate and two water molecules. N1H1A in the piperazinium group participates in a classical N1–H1A···O4 hydrogen bond to the oxygen atom of the adipate (see the figure). Furthermore the N1H1B in the piperazine group is involved in a N1–H1B···O7 hydrogen bond with water molecule (d(N1···O7) = 2.7180(16) Å; N1–H1B···O7 = 161.5°). Two oxygen atoms in a molecule of the adipate dianion form three hydrogen bonds with two water molecules: O6–H6A···O5 (d(O6···O5) = 2.7989(17) Å; angle: O6–H6A···O5 = 167(2)°); O7–H7A···O4^1(^{1} = 1 + x, +y, +z; d(O7···O4) = 2.7726(15) Å; angle: O7–H7A···O4 = 174.9°); O7–H7B···O5^2 (^{2} = 2–x, 1–y, 1–z; d(O7···O5) = 2.7340(15) Å; angle: O7–H7A···O5 = 175.5°). Bond lengths and angles derived from the title crystal structure are in the expected ranges.

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