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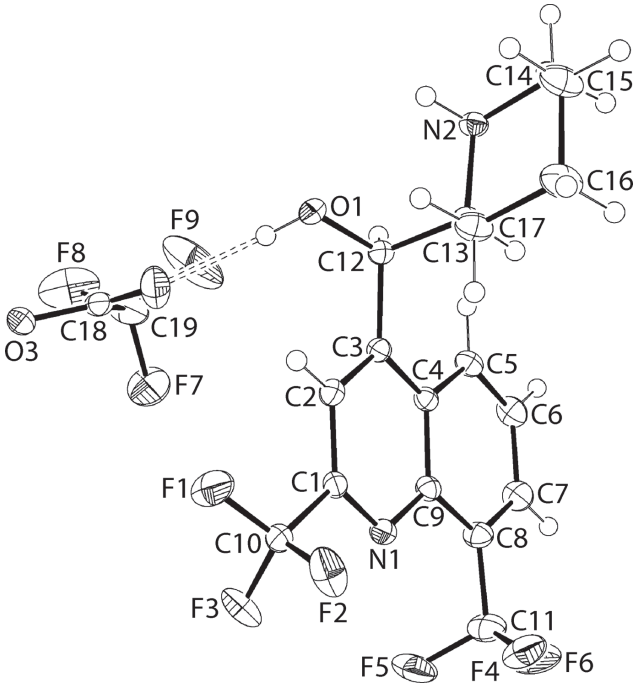
Crystal structure of 2-((2,8-bis(trifluoromethyl) quinolin-4-yl)(hydroxy)methyl)piperidin-1-ium trifluoroacetate, $[C_{17}H_{17}F_6N_2O][C_2F_3O_2]$



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Abstract

$[C_{17}H_{17}F_6N_2O][C_2F_3O_2]$, triclinic, $P\bar{1}$ (no. 2), $a = 7.9873(1)$ Å, $b = 11.0534(2)$ Å, $c = 13.2380(3)$ Å, $\alpha = 105.617(1)°$, $\beta = 102.189(1)°$, $\gamma = 106.075(1)°$. $V = 1028.76(3)$ Å^3, $Z = 2$, $R_{gt}(F) = 0.0403$, $wR_{ref}(F^2) = 0.1086$, $T = 120(2)$ K.

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The title crystal structure is shown in the figure. Tables 1 and 2 contain details on crystal structure and measurement conditions and a list of the atoms including atomic coordinates and displacement parameters.

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Table 1: Data collection and handling.

Crystal:	Colourless slab
Size:	0.44 × 0.26 × 0.18 mm
Wavelength:	Mo $K\alpha$ radiation (0.71073 Å)
μ:	0.16 mm^{-1}
Diffractometer, scan mode:	Bruker-Nonius Roper, φ and ω
θ_{max}, completeness:	27.5°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	21617, 4704, 0.029
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 4151
$N(param)_{refined}$:	307
Programs:	SHELX [1–3], WinGX/ORTEP [4], COLLECT [5] and DENZO [6]

Source of material

Solutions of mefloquine (0.38 g, 1 mmol) in ethanol (10 mL) and trifluoroacetic acid (0.13 g, 1.3 mmol) in ethanol (10 mL) were mixed and refluxed for 20 min. On leaving the open reaction mixture at room temperature, colourless crystals were collected after 4 days. M.pt: 503−505 K. ^{1}H NMR (400 MHz, d_6-DMSO): δ: 1.18−1.32 (2H, m), 1.57−1.80 (4H, m), 3.00−3.10 (1H, m), 3.30−3.38 (1H, br, d), 3.47−3.67 (1H, br, d), 5.96 (1H, s), 6.23 (1H, br, s), 7.10 (1H, s), 7.94 (1H, t, J = 8.0 Hz), 8.14 (1H, s), 8.33 (1H, d, J = 8.0 Hz), 8.75 (1H, d, J = 8.0 Hz) ppm. ^{13}C NMR, d_6-DMSO): δ: 21.38, 21.38, 21.79, 44.71, 59.18, 68.08, 115.68, 117.24 (q, $J_{C,F}$ = 296 Hz), 121.38 (q, $J_{C,F}$ = 274 Hz), 123.81 (q, $J_{C,F}$ = 272 Hz), 126.59, 127.55 (q, $J_{C,F}$ = 29.4 Hz), 128.31, 128.91, 129.86 (q, $J_{C,F}$ = 4.7 Hz), 143.05, 147.03 (q, $J_{C,F}$ = 34Hz), 151.25, 159.59 (q, $J_{C,F}$ = 32 Hz) ppm. ^{19}F NMR (d_6-DMSO): δ: −59.2, −67.0, −74.1 ppm.

Experimental details

The C-bound H atoms were geometrically placed (C—H = 0.95–1.00 Å) and refined as riding with U_{iso}(H) = 1.2–1.5U_{eq}(C). The O- and N-bound H atoms were located in a difference Fourier map and were refined with distance restraints of O—H = 0.84 ± 0.01 and N—H = 0.88 ± 0.01 Å, respectively, and with U_{iso}(H) set to 1.5U_{equiv}(O) and 1.2U_{equiv}(N), respectively.

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

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
F1	0.02951(15)	0.37548(13)	0.38214(8)	0.0493(3)
F2	0.24872(13)	0.52419(9)	0.52189(9)	0.0385(2)
F3	0.07811(13)	0.35051(10)	0.53895(9)	0.0361(2)
F4	0.68301(14)	0.41825(10)	0.73814(8)	0.0408(3)
F5	0.46179(15)	0.24409(12)	0.72416(8)	0.0423(3)
F6	0.74099(17)	0.25665(13)	0.78058(8)	0.0521(3)
O1	0.27515(13)	0.17013(11)	0.11193(8)	0.0239(2)
H1O	0.1761(18)	0.1277(18)	0.1191(16)	0.036*
N1	0.39162(15)	0.30406(11)	0.52565(9)	0.0181(2)
N2	0.62889(15)	0.20936(11)	0.08180(9)	0.0185(2)
H1N	0.646(2)	0.1342(12)	0.0828(14)	0.022*
H2N	0.5280(16)	0.1840(16)	0.0269(11)	0.022*
C1	0.28884(17)	0.31996(12)	0.44213(10)	0.0171(2)
C2	0.29300(17)	0.27831(13)	0.33286(10)	0.0179(2)
H2	0.2188	0.2974	0.2774	0.021*
C3	0.40643(17)	0.20954(12)	0.30800(10)	0.0161(2)
C4	0.51298(17)	0.18144(12)	0.39366(10)	0.0158(2)
C5	0.62722(18)	0.10427(13)	0.37625(11)	0.0196(3)
H5	0.6313	0.0656	0.3039	0.024*
C6	0.7309(2)	0.08547(14)	0.46279(12)	0.0241(3)
H6	0.8045	0.0321	0.4498	0.029*
C7	0.7302(2)	0.14432(15)	0.57128(12)	0.0250(3)
H7	0.8063	0.1329	0.6309	0.030*
C8	0.62047(19)	0.21783(14)	0.59121(11)	0.0217(3)
C9	0.50491(17)	0.23564(12)	0.50262(10)	0.0168(2)
C10	0.16075(18)	0.39259(13)	0.47126(11)	0.0204(3)
C11	0.6245(2)	0.28366(17)	0.70762(12)	0.0311(3)
C12	0.42225(17)	0.16880(13)	0.19225(10)	0.0175(2)
H12	0.4292	0.0768	0.1715	0.021*
C13	0.59788(17)	0.26909(12)	0.18944(10)	0.0170(2)
H13	0.7034	0.2787	0.2510	0.020*
C14	0.7893(2)	0.29819(15)	0.06226(13)	0.0274(3)
H14A	0.7937	0.2554	−0.0127	0.033*
H14B	0.9041	0.3092	0.1161	0.033*
C15	0.7754(2)	0.43488(16)	0.07357(14)	0.0326(3)
H15A	0.6672	0.4251	0.0150	0.039*
H15B	0.8859	0.4935	0.0648	0.039*
C16	0.7578(2)	0.49892(15)	0.18635(13)	0.0314(3)
H16A	0.7470	0.5876	0.1929	0.038*
H16B	0.8686	0.5128	0.2449	0.038*
C17	0.5886(2)	0.40794(13)	0.20090(12)	0.0242(3)
H17A	0.5790	0.4497	0.2746	0.029*
H17B	0.4776	0.3988	0.1448	0.029*
F7	−0.08877(16)	−0.11720(14)	0.25094(9)	0.0527(3)
F8	−0.2559(2)	−0.25218(11)	0.08871(10)	0.0584(4)
F9	0.0247(2)	−0.13334(18)	0.11646(14)	0.0802(5)
O2	−0.06241(14)	0.08467(11)	0.13035(10)	0.0345(3)
O3	−0.35082(13)	−0.03455(10)	0.10914(8)	0.0235(2)
C18	−0.18437(19)	−0.01618(14)	0.12451(10)	0.0213(3)
C19	−0.1253(3)	−0.13127(19)	0.14389(14)	0.0367(4)

Comment

While originally developed as anti-malarial agents, derivatives of mefloquine continue to be pharmacologically relevant [7]. These studies are augmented by crystallographic investigations which are motivated by reasons more than the confirmation of molecular structure. Thus, two out of approximately 30 crystal structures of mefloquine derivatives [8] exhibit kryptoracemic behaviour [9]. The two unusual examples were isolated during attempts at chiral resolution of racemic mefloquine (which has two chiral centres) with different carboxylic acids. In the crystal of the first example, two mefloquinium cations are related across a non-crystallographic centre of inversion, with the charge balance being provided by a pair of crystallographically independent and chiral 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate anions [10]. In the second example, it was proven not necessary to have chiral carboxylate counter-ions to induce kryptoracemic behaviour. This structure arises as a result of incomplete substitution of chloride in the original salt by 4-fluorobenzenesulfonate [11]. Here, the asymmetric unit comprises a pair of pseudo-enantiomeric mefloquinium cations with the charge balance being provided by equal numbers of chloride and 4-fluorobenzenesulfonate anions [11]. As a continuation of studies in this area [8, 10, 11], the title salt, $[C_{17}H_{17}F_6N_2O][C_2F_3O_2]$, was characterised.

The molecular structures of the constituents of the title salt are shown in the figure (50% probability displacement ellipsoids). Proof that protonation occurred during crystallisation is at least two-fold. Thus, the C—O bond lengths of the carboxylate group, i.e. C18—O2, O3 of 1.2320(18) and 1.2507(17) Å, are very similar. Also, the pattern of hydrogen bonding and difference Fourier maps confirm the presence of two protons on the N2 atom of the piperidin-1-ium ring. The cation exhibits familiar characteristics: an approximate L-shape with the dihedral between the quinolinyl plane [r.m.s. deviation = 0.0385 Å] and the best plane through the piperidin-1-ium ring being 69.28(4)°. The hydroxyl-O1 and ammonium-N2 atoms are orientated to the same side of the cation with the O1—C12—C13—N2 torsion angle of −69.08(12)° indicating a – syn-clinal relationship. This proximity enables the formation of an intramolecular ammonium-N^+—H···O(hydroxy) hydrogen bond [N2—H2n···O1: H2n···O1 = 2.500(14) Å, N2···O1 = 2.8672(17) Å with angle at H2n = 105.8(10)°].

The most prominent feature of the molecular packing is the formation of supramolecular chains along the *a*-axis. These are mediated by charge-assisted hydrogen bonding. Each ammonium-N^+—H atom connects to a symmetry-related carboxylate-O3 atom *via* ammonium-N^+—H···O^-(carboxylate) hydrogen bonds and through a centre of inversion generate eight-membered $\{\cdots O\cdots HNH\}_2$ synthons [N2—H1n···$O3^i$: H1n···$O3^i$ = 1.994(14) Å, N2···$O3^i$ = 2.8580(17) Å with angle at H1n = 166.5(15)° and N2—H2n···$O3^{ii}$: H2n···$O3^{ii}$ = 2.001(15) Å, N2···$O3^{ii}$ = 2.7711(15)Å and angle at H2n = 145.5(15)°; symmetry operations (i): 1−*x*, −*y*,

1−*z* and (ii): −*x*, −*y*, −*z*]. The ensuing four-ion aggregates just described are connected into the supramolecular chain *via* charge-assisted hydroxyl-O—H···O$^-$(carboxylate) hydrogen bonds [O1—H1o···O2: H1o···O2 = 1.880(16) Å, O1···O2 = 2.6856(17) Å with angle at H1o = 160.4(19)°].

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