Journal of Applied Crystallography

Volume 47 (2014)

Supporting information for article: KK5170

Elucidating the crystal structure of the antimalarial drug mefloquine hydrochloride: a tetragonal hydrated species

Table S1 Final coordinates and equivalent isotropic displacement parameters ($U_{iso} = B_{iso}/8\pi^2$) for all atoms in the hydrated mefloquine hydrochloride crystal structure.

Atom	*x/a*	*y/b*	*z/c*	U_{iso} (Å^2)	*Occ*
N(1)	0.3752(8)	0.4111(7)	0.334(3)	0.098(2)	1
C(2)	0.3939(11)	0.4527(14)	0.440(4)	0.098(2)	1
C(3)	0.3833(10)	0.5075(11)	0.393(3)	0.098(2)	1
C(4)	0.3488(10)	0.5206(11)	0.235(4)	0.098(2)	1
C(5)	0.2909(8)	0.4848(9)	−0.056(3)	0.098(2)	1
C(6)	0.2713(10)	0.4418(10)	−0.162(3)	0.098(2)	1
C(7)	0.2839(9)	0.3881(10)	−0.109(3)	0.098(2)	1
C(8)	0.3170(11)	0.3773(11)	0.057(5)	0.098(2)	1
C(9)	0.3410(12)	0.4218(15)	0.171(4)	0.098(2)	1
C(10)	0.3269(12)	0.4767(15)	0.114(4)	0.098(2)	1
C(11)	0.3387(9)	0.5801(10)	0.178(3)	0.098(2)	1
C(12)	0.3769(9)	0.5992(9)	0.003(4)	0.098(2)	1
N(13)	0.3640(7)	0.6563(7)	−0.049(2)	0.0987(2)	1
C(14)	0.3968(8)	0.6777(9)	−0.226(3)	0.098(2)	1
C(15)	0.4577(9)	0.6728(8)	−0.185(3)	0.098(2)	1
C(16)	0.4724(9)	0.6140(10)	−0.125(3)	0.098(2)	1
C(17)	0.4369(7)	0.5947(9)	0.058(3)	0.098(2)	1
C(18)	0.3332(11)	0.3196(14)	0.105(3)	0.098(2)	1
C(19)	0.4327(12)	0.4393(10)	0.616(4)	0.098(2)	1
O(20)	0.3458(5)	0.6160(5)	0.3495(18)	0.098(2)	1
F(21)	0.3108(5)	0.2835(5)	−0.0261(17)	0.098(2)	1
F(22)	0.3869(6)	0.3125(5)	0.0921(13)	0.098(2)	1
F(23)	0.3178(5)	0.3056(5)	0.2989(17)	0.098(2)	1
F(24)	0.4834(5)	0.4392(5)	0.5565(17)	0.098(2)	1
F(25)	0.4257(4)	0.3899(5)	0.6930(19)	0.098(2)	1
F(26)	0.4297(5)	0.4727(5)	0.7750(17)	0.098(2)	1
Cl(27)	0.2587(3)	0.6167(2)	0.7083(7)	0.098(2)	1
O(44)	0.2170(8)	0.7327(10)	0.726(3)	0.098(2)	0.5
H(28)	0.2858(8)	0.5208(9)	−0.112(3)	0.118(2)	1
H(29)	0.2705(9)	0.3594(10)	−0.197(3)	0.118(2)	1
H(30)	0.3975(10)	0.5379(11)	0.469(3)	0.118(2)	1
H(31)	0.3007(9)	0.5854(10)	0.153(3)	0.118(2)	1
H(32)	0.2534(10)	0.4497(10)	−0.292(3)	0.118(2)	1
H(33)	0.3185(5)	0.6104(5)	0.4605(18)	0.118(2)	1

H(34)	0.3609(9)	0.5795(9)	−0.111(4)	0.118(2)	1
H(35)	0.3297(7)	0.6621(7)	−0.069(2)	0.118(2)	1
H(36)	0.4455(7)	0.5568(9)	0.088(3)	0.118(2)	1
H(37)	0.4447(7)	0.6160(9)	0.179(3)	0.118(2)	1
H(38)	0.3882(8)	0.7150(9)	−0.246(3)	0.118(2)	1
H(39)	0.3883(8)	0.6573(9)	−0.350(3)	0.118(2)	1
H(40)	0.4667(9)	0.5908(10)	−0.244(3)	0.118(2)	1
H(41)	0.5103(9)	0.6121(10)	−0.085(3)	0.118(2)	1
H(42)	0.4676(9)	0.6964(8)	−0.070(3)	0.118(2)	1
H(43)	0.4777(9)	0.6832(8)	−0.307(3)	0.118(2)	1
H(45)	0.2451(8)	0.7172(10)	0.631(3)	0.118(2)	0.5
H(46)	0.2109(8)	0.7076(10)	0.845(3)	0.118(2)	0.5

Table S2 Some selected bond distances for hydrated mefloquine hydrochloride.

Bonds	Lengths (Å)
N(1)–C(2)	1.31(4)
N(1)–C(9)	1.36(3)
C(2)–C(3)	1.40(4)
C(2)–C(19)	1.51(4)
C(3)–C(4)	1.36(3)
C(4)–C(10)	1.43(4)
C(4)–C(11)	1.53(3)
C(5)–C(6)	1.34(3)
C(5)–C(10)	1.41(3)
C(6)–C(7)	1.40(3)
C(7)–C(8)	1.36(3)
C(8)–C(9)	1.44(4)
C(8)–C(18)	1.50(4)
C(9)–C(10)	1.44(4)
C(11)–C(12)	1.53(3)
C(11)–O(20)	1.42(2)
C(12)–N(13)	1.48(3)
C(12)–C(17)	1.52(3)
N(13)–C(14)	1.48(2)
C(14)–C(15)	1.52(3)
C(15)–C(16)	1.54(3)
C(16)–C(17)	1.53(3)
C(18)–F(21)	1.34(3)
C(18)–F(22)	1.33(3)
C(18)–F(23)	1.34(2)

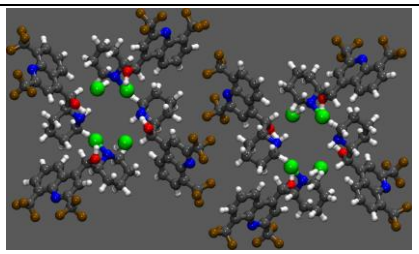
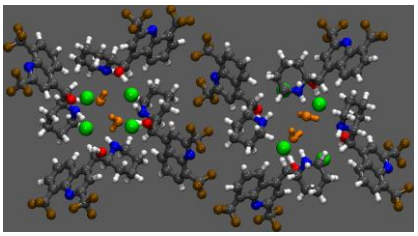
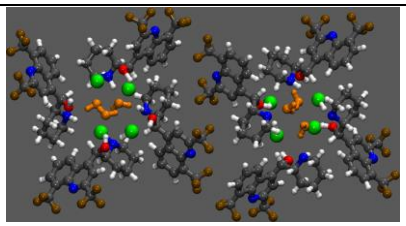
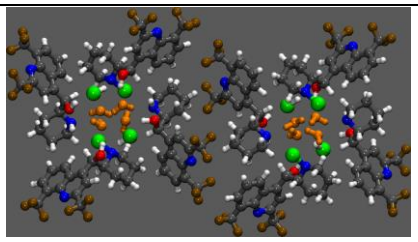
C(19)–F(24)	1.30(3)
C(19)–F(25)	1.32(3)
C(19)–F(26)	1.31(3)

Table S3 Some selected bond angles for hydrated mefloquine hydrochloride.

Bonds	Angles (°)
C(2)–N(1)–C(9)	117(2)
N(1)–C(2)–C(3)	125(3)
N(1)–C(2)–C(19)	116(2)
C(3)–C(2)–C(19)	119(2)
C(2)–C(3)–C(4)	120(2)
C(3)–C(4)–C(10)	117(2)
C(3)–C(4)–C(11)	120(2)
C(10)–C(4)–C(11)	122(2)
C(6)–C(5)–C(10)	120(2)
C(5)–C(6)–C(7)	123(2)
C(6)–C(7)–C(8)	120(2)
C(7)–C(8)–C(9)	119(3)
C(7)–C(8)–C(18)	120(2)
C(9)–C(8)–C(18)	120(3)
N(1)–C(9)–C(8)	119(3)
N(1)–C(9)–C(10)	121(3)
C(8)–C(9)–C(10)	119(3)
C(4)–C(10)–C(5)	123(3)
C(4)–C(10)–C(9)	119(3)
C(5)–C(10)–C(9)	118(3)
C(4)–C(11)–C(12)	112(2)
C(4)–C(11)–O(20)	113(2)
C(12)–C(11)–O(20)	107(2)
C(11)–C(12)–N(13)	109(2)
C(11)–C(12)–C(17)	114(2)
N(13)–C(12)–C(17)	109(2)
C(12)–N(13)–C(14)	113(2)
N(13)–C(14)–C(15)	112(2)
C(14)–C(15)–C(16)	110(2)
C(15)–C(16)–C(17)	110(2)
C(12)–C(17)–C(16)	111(2)
C(8)–C(18)–F(21)	113(2)
C(8)–C(18)–F(22)	112(2)
C(8)–C(18)–F(23)	111(2)
F(21)–C(18)–F(22)	106(2)
F(21)–C(18)–F(23)	107(2)
F(22)–C(18)–F(23)	108(2)

C(2)–C(19)–F(24)	113(2)
C(2)–C(19)–F(25)	113(2)
C(2)–C(19)–F(26)	114(2)
F(24)–C(19)–F(25)	103(2)
F(24)–C(19)–F(26)	106(2)
F(25)–C(19)–F(26)	106(2)

Table S4 Structural arrangements calculated using the semi–empirical PM6 method for different contents of water molecules and corresponding binding energies.

# of Water Molecules	Relaxed Structure	Binding Energy of Water molecules [eV]
0		0.00
4		–5.05
6		–5.20
8		–4.98

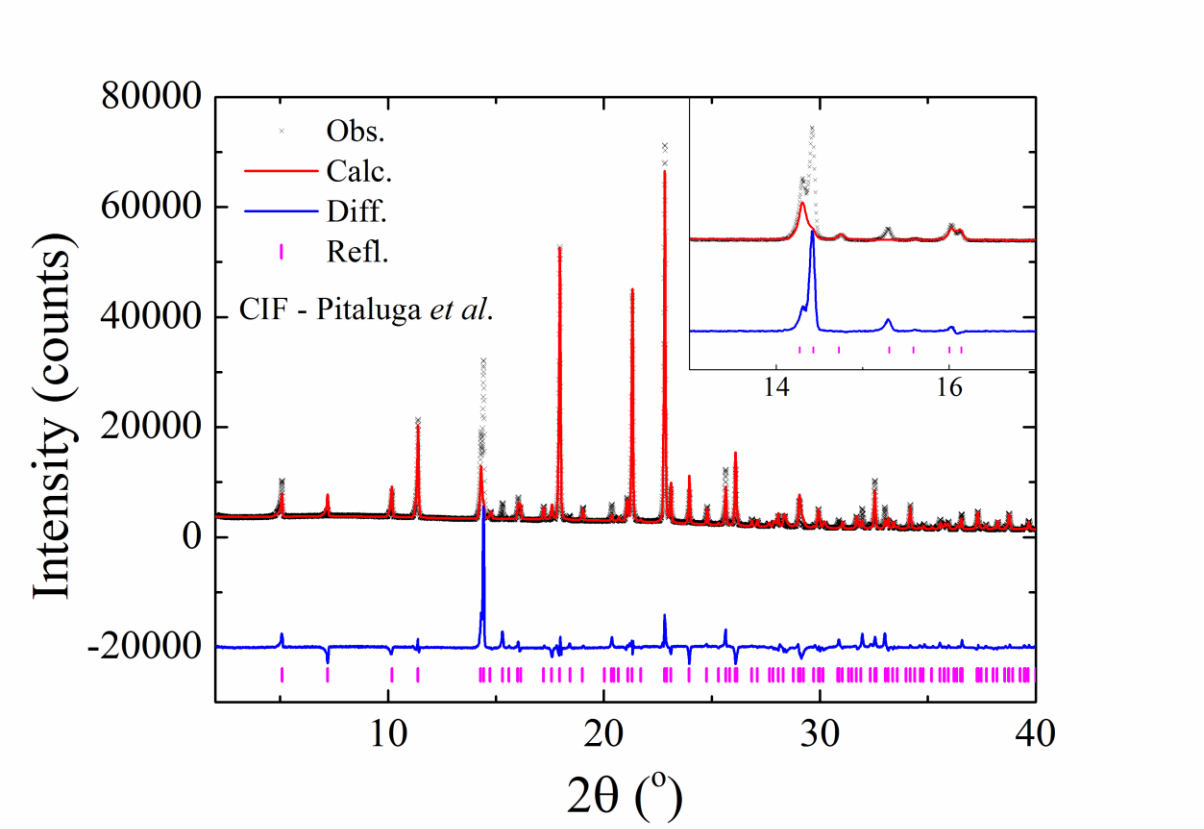


Figure S1 Rietveld plot of hydrated (±)–mefloquine hydrochloride taking into account the crystallographic information file (cif) described by Pitaluga *et al*. (CSD Refcode: SOJPOW01) (Pitaluga *et al.*, 2010). Measured pattern (black crosses), calculated pattern (solid line), and difference profile (blue bottom line). Tick marks (magenta vertical bars) at the bottom of the pattern indicate the peak positions allowed by the unit cell parameters and space group. Magnified region, from 13° to 17° (2θ) of the Rietveld refinement, clearly displays the lack of agreement between some observed and calculated reflections.

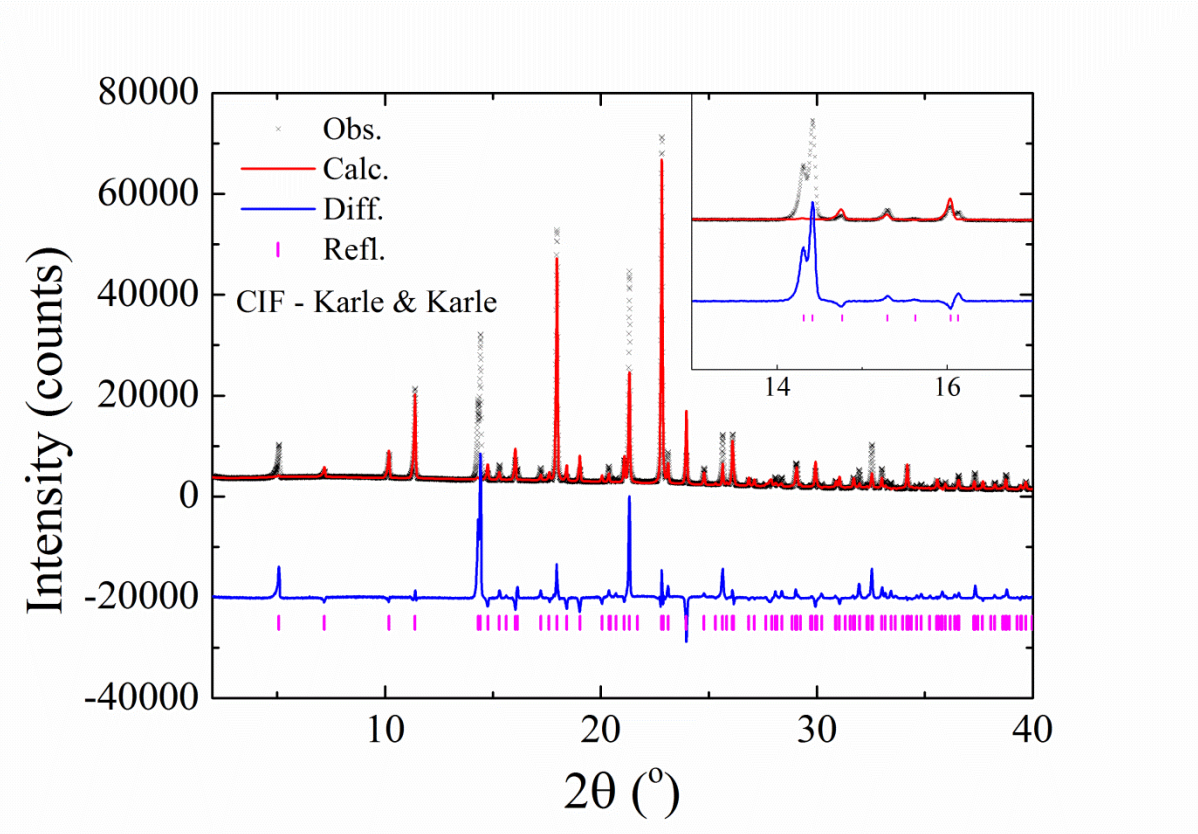


Figure S2 Rietveld plot of hydrated (±)–mefloquine hydrochloride taking into account the crystallographic information file (cif) described by Karle e Karle (CSD Refcode: SOJPOW) (Karle & Karle, 1991). Measured pattern (black crosses), calculated pattern (solid line), and difference profile (blue bottom line). Tick marks (magenta vertical bars) at the bottom of the pattern indicate the peak positions allowed by the unit cell parameters and space group. Magnified region, from 13° to 17° (2θ) of the Rietveld refinement, clearly displays the lack of agreement between some observed and calculated reflections.

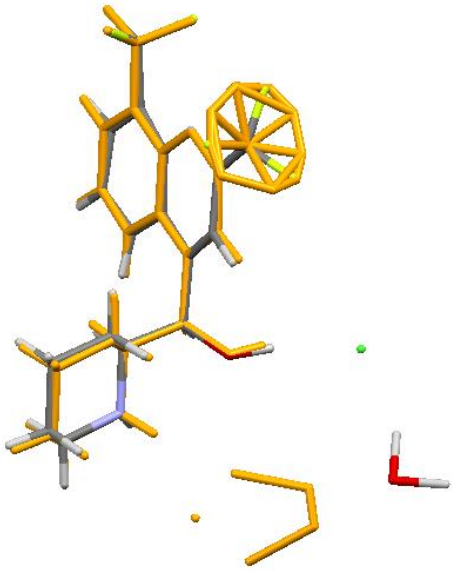


Figure S3 Comparison between the crystal structures determined by Karle and Karle (CSD Refcode: SOJPOW01) (Karle & Karle, 1991) (displayed in orange) and the one determined in the present work [carbon (grey), oxygen (red), nitrogen (light blue), fluorine (yellow), chloride (green), hydrogen (light grey)].

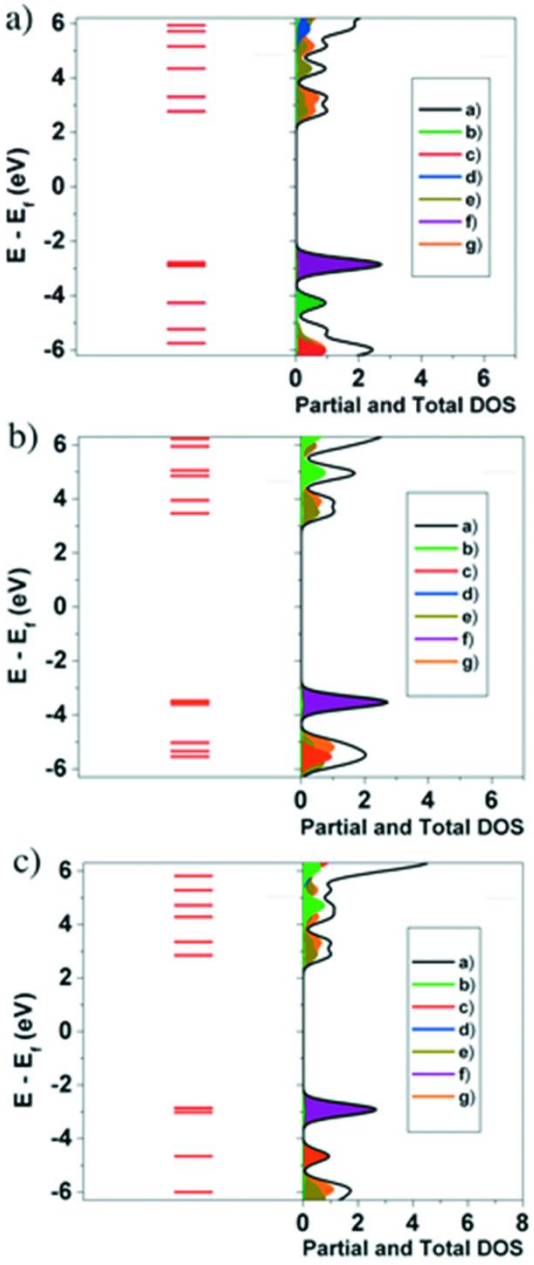


Figure S4 Energy levels and projected density of states for (±)–Mefloquine Hydrochloride. (a) Our results. (b) Results by Pitaluga *et al.* (Pitaluga *et al.*, 2010) (c) Results by Karle and Karle (Karle & Karle, 1991). The colour code corresponds to black–a) Total Density of States. green–b) Contribution from the ring far from the F atoms; c) Contribution from solvent molecules; d) Contribution from F atoms; e) Contribution from the ring close to F atoms; f) Contribution from Cl atom, g) Contribution from the aromatic ring.

S1. Results and discussion

S1.1. PM6 calculations

Following the procedure described in the main text, we performed a series of calculations for mefloquine hydrochloride crystals containing different numbers of water molecules in the voids. We started our calculations considering the configuration obtained by Rietveld refinement, introduced water in different initial configurations and allowed the system to relax. The binding energy was calculated considering the difference the total energy of the systems containing water – after relaxation – and the energies of the system without water, and the corresponding number of isolated water molecules. Table S4 shows selected configurations and the corresponding binding energy for different numbers of water molecules within the voids of the unit cell. We notice that, for all initial configurations, we obtained a negative binding energy, which indicates that it is favourable for water to fill the voids.

We also calculated the electronic structure of the different arrangements available in the literature and compared to our resolved structure. Fig. S4 shows that, albeit the structures are similar, the frontier orbitals as well as the HOMO–LUMO gap are significantly different.