4·2 kJ mol^{-1}) above the global minimum found for a conformer, in which C2–C1–N14–C13 is −60°. The energy barriers between the conformers do not exceed 4 kcal mol^{-1}, and both of the conformers – as well as others – will no doubt be accessible in solution (Liljefors & Bøgesø, 1988).

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Redetermination of the Crystal and Molecular Structure of the Antimalarial Chloroquine Bis(dihydrogenphosphate) Dihydrate

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Abstract. N^4-(7-Chloro-4-quinolinyl)-N',N'-diethyl-1,4-pentanediamine bis(dihydrogenphosphate) dihydrate, $C_{18}H_{28}ClN_3^{2+}.2H_2PO_4^-.2H_2O$, $M_r = 551{\cdot}8$, monoclinic, $P2_1/c$, $a = 9{\cdot}830$ (2), $b = 16{\cdot}879$ (3), $c = 15{\cdot}783$ (4) Å, $\beta = 105{\cdot}51$ (2)°, $V = 2523{\cdot}2$ Å^3, $Z = 4$, $D_x = 1{\cdot}452$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71073$ Å, $\mu = 2{\cdot}78$ cm^{-1}, $F(000) = 1168$, room temperature, final $R = 5{\cdot}5\%$ for 2431 reflections with $|F_o| > 3\sigma$. The chloroquine molecule is a dication with a hydrogen atom from each of the phosphate moieties residing on the quinoline and the terminal chain nitrogen atoms. Neighboring phosphate chains are bridged by chloroquine molecules *via* hydrogen bonding. Each hydrogen atom on each nitrogen atom, on each phosphate oxygen atom, and in each water molecule participates in hydrogen bonding. The helical manner in which the side chains of the chloroquine molecules wrap around phosphate chains and the stacking interval of the quinoline rings between the phosphate groups may be indicative of the interaction of chloroquine molecules with cellular constituents important to antimalarial action.

Introduction. Chloroquine (Fig. 1), first developed for human use during World War II, was the drug of choice for the treatment of *Plasmodium falciparum* (Webster, 1985). However, in the 1960's resistant strains of *P. falciparum* appeared in Asia and South America which have now spread across all of the

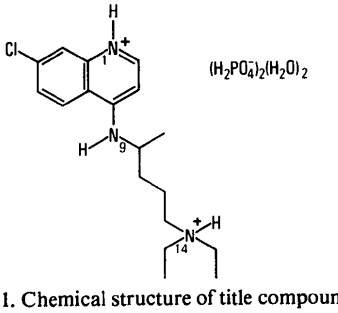

Fig. 1. Chemical structure of title compound.

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Table 1. *Fractional coordinates* ($\times 10^4$) *and thermal parameters* U_{eq} ($Å^2 \times 10^3$) *with e.s.d.'s in parentheses*

$U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
P(1)	5163 (1)	−1415 (1)	−2247 (1)	39 (1)
P(2)	5454 (1)	−3935 (1)	−2477 (1)	40 (1)
O(1)	5633 (4)	−807 (2)	−1530 (2)	50 (1)
O(2)	6355 (3)	−1830 (2)	−2498 (2)	43 (1)
O(3)	4232 (5)	−2034 (3)	−1940 (3)	61 (2)
O(4)	4213 (4)	−1017 (3)	−3080 (3)	54 (2)
O(5)	5830 (4)	−4535 (2)	−1744 (2)	61 (2)
O(6)	4143 (3)	−3458 (2)	−2522 (2)	53 (2)
O(7)	6737 (4)	−3365 (2)	−2380 (3)	49 (2)
O(8)	5318 (4)	−4365 (2)	−3375 (2)	47 (1)
Cl	8704 (2)	882 (1)	2143 (1)	54 (1)
N(1)	12042 (4)	989 (2)	195 (3)	39 (2)
C(2)	12341 (5)	996 (3)	−574 (3)	38 (2)
C(3)	11326 (5)	1059 (3)	−1349 (3)	38 (2)
C(4)	9894 (5)	1091 (3)	−1363 (3)	32 (2)
C(4a)	9553 (5)	1066 (3)	−528 (3)	32 (2)
C(5)	8166 (5)	1067 (3)	−432 (3)	38 (2)
C(6)	7911 (5)	1017 (3)	378 (3)	42 (2)
C(7)	9050 (5)	966 (3)	1132 (3)	40 (2)
C(8)	10416 (5)	986 (3)	1076 (3)	38 (2)
C(8a)	10675 (5)	1018 (3)	250 (3)	32 (2)
N(9)	8881 (5)	1122 (3)	−2118 (3)	38 (2)
C(10)	9134 (5)	1169 (3)	−3001 (3)	37 (2)
C(11)	7931 (5)	763 (3)	−3667 (3)	39 (2)
C(12)	7854 (5)	−123 (3)	−3531 (3)	44 (2)
C(13)	6689 (5)	−489 (3)	−4250 (3)	40 (2)
N(14)	6514 (4)	−1356 (2)	−4155 (3)	39 (2)
C(15)	5179 (5)	−1613 (3)	−4823 (3)	49 (2)
C(16)	4776 (6)	−2460 (3)	−4745 (4)	68 (3)
C(17)	7776 (6)	−1841 (3)	−4177 (4)	53 (2)
C(18)	8153 (7)	−1847 (4)	−5036 (5)	88 (3)
C(19)	9308 (6)	2023 (3)	−3242 (4)	56 (2)
W(1)†	8837 (7)	4800 (4)	−806 (4)	151 (4)
W(2)†	8338 (9)	3118 (5)	−1006 (5)	189 (3)
H(*n*1)	12711 (51)	966 (28)	671 (32)	42 (15)
H(*n*9)	8071 (50)	1202 (27)	−2109 (30)	37 (16)
H(*n*14)	6513 (74)	−1486 (44)	−3445 (52)	135 (28)
H(*o*3)	4190 (91)	−2358 (43)	−2177 (53)	99 (36)
H(*o*4)	4227 (62)	−567 (35)	−3129 (38)	61 (22)
H(*o*7)	6610 (73)	−2867 (41)	−2468 (45)	104 (27)
H(*o*8)	4996 (96)	−5027 (51)	−3401 (59)	177 (36)

Coordinates and U_{iso} values have been refined only for hydrogen atoms in the phosphate molecules and those bonded to N(1), N(9), and N(14).

† O atom of water molecule.

Table 2. *Bond lengths* (Å), *bond angles* (°), *and torsion angles* (°) *with e.s.d.'s in parentheses*

P(1)–O(1)	1·506 (3)	P(1)–O(2)	1·506 (3)
P(1)–O(3)	1·550 (5)	P(1)–O(4)	1·547 (4)
P(2)–O(5)	1·508 (4)	P(2)–O(6)	1·504 (4)
P(2)–O(7)	1·560 (4)	P(2)–O(8)	1·566 (4)
Cl–C(7)	1·723 (5)	N(1)–C(2)	1·323 (6)
N(1)–C(8a)	1·370 (6)	C(4)–C(4a)	1·445 (6)
C(2)–C(3)	1·360 (6)	C(3)–C(4)	1·403 (6)
C(4a)–C(5)	1·412 (6)	C(5)–C(6)	1·369 (7)
C(4)–N(9)	1·334 (6)	C(4a)–C(8a)	1·416 (6)
C(6)–C(7)	1·401 (7)	C(7)–C(8)	1·370 (6)
C(8)–C(8a)	1·394 (6)	N(9)–C(10)	1·481 (6)
C(10)–C(11)	1·519 (6)	C(10)–C(19)	1·513 (7)
C(11)–C(12)	1·516 (6)	C(12)–C(13)	1·513 (6)
C(13)–N(14)	1·485 (6)	N(14)–C(15)	1·511 (6)
N(14)–C(17)	1·495 (6)	C(15)–C(16)	1·499 (7)
C(17)–C(18)	1·498 (8)		

O(2)–P(1)–O(1)	114·2 (2)	O(3)–P(1)–O(1)	108·2 (3)
O(3)–P(1)–O(2)	109·6 (2)	O(4)–P(1)–O(1)	109·7 (2)
O(4)–P(1)–O(2)	108·3 (2)	O(4)–P(1)–O(3)	106·6 (3)
O(6)–P(2)–O(5)	115·3 (2)	O(7)–P(2)–O(5)	108·3 (2)
O(7)–P(2)–O(6)	109·6 (2)	O(8)–P(2)–O(5)	109·1 (2)
O(8)–P(2)–O(6)	109·9 (2)	O(8)–P(2)–O(7)	104·2 (2)
C(8a)–N(1)–C(2)	121·3 (5)	C(3)–C(2)–N(1)	122·4 (5)
C(4)–C(3)–C(2)	120·6 (5)	C(4a)–C(4)–C(3)	117·5 (4)
N(9)–C(4)–C(3)	121·4 (5)	N(9)–C(4)–C(4a)	121·1 (4)
C(5)–C(4a)–C(4)	124·4 (4)	C(8a)–C(4a)–C(4)	118·4 (4)
C(8a)–C(4a)–C(5)	117·2 (4)	C(6)–C(5)–C(4a)	121·6 (4)
C(7)–C(6)–C(5)	119·5 (5)	C(6)–C(7)–Cl	118·7 (4)
C(8)–C(7)–Cl	120·1 (4)	C(8)–C(7)–C(6)	121·2 (5)
C(8a)–C(8)–C(7)	119·3 (4)	C(4a)–C(8a)–N(1)	119·8 (4)
C(8)–C(8a)–N(1)	119·0 (4)	C(8)–C(8a)–C(4a)	121·2 (4)
C(10)–N(9)–C(4)	124·7 (4)	C(11)–C(10)–N(9)	109·4 (4)
C(19)–C(10)–N(9)	110·3 (4)	C(19)–C(10)–C(11)	112·0 (4)
C(12)–C(11)–C(10)	113·9 (4)	C(13)–C(12)–C(11)	110·7 (4)
N(14)–C(13)–C(12)	114·3 (4)	C(15)–N(14)–C(13)	108·3 (4)
C(17)–N(14)–C(13)	114·7 (4)	C(17)–N(14)–C(15)	113·4 (4)
C(16)–C(15)–N(14)	114·6 (4)	C(18)–C(17)–N(14)	115·6 (5)

C(8a)–N(1)–C(2)–C(3)	−177·6*	C(2)–N(1)–C(8a)–C(4a)	−0·9*
C(2)–N(1)–C(8a)–C(8)	178·1	N(1)–C(2)–C(3)–C(4)	−2·4
C(2)–C(3)–C(4)–C(4a)	0·9	C(2)–C(3)–C(4)–N(9)	−177·3
C(3)–C(4)–C(4a)–C(5)	−177·8	C(3)–C(4)–C(4a)–C(8a)	0·6
N(9)–C(4)–C(4a)–C(5)	0·4	N(9)–C(4)–C(4a)–C(8a)	178·8
C(3)–C(4)–N(9)–C(10)	−3·4	C(4a)–C(4)–N(9)–C(10)	178·5
C(4)–C(4a)–C(5)–C(6)	177·9	C(8a)–C(4a)–C(5)–C(6)	−0·5
C(4)–C(4a)–C(8a)–N(1)	−0·6	C(4)–C(4a)–C(8a)–C(8)	−179·5
C(5)–C(4a)–C(8a)–N(1)	177·9	C(5)–C(4a)–C(8a)–C(8)	−1·0
C(4a)–C(5)–C(6)–C(7)	0·2	C(5)–C(6)–C(7)–Cl	−178·7
C(5)–C(6)–C(7)–C(8)	1·7	Cl–C(7)–C(8)–C(8a)	177·2
C(7)–C(8)–C(8a)–N(1)	−176·1	C(7)–C(8)–C(8a)–C(4a)	2·8
C(4)–N(9)–C(10)–C(11)	149·6	C(4)–N(9)–C(10)–C(19)	−86·8
N(9)–C(10)–C(11)–C(12)	−66·2	C(19)–C(10)–C(11)–C(12)	171·2
C(10)–C(11)–C(12)–C(13)	−176·6	C(11)–C(12)–C(13)–N(14)	−178·4
C(12)–C(13)–N(14)–C(15)	170·9	C(12)–C(13)–N(14)–C(17)	−61·3
C(13)–N(14)–C(15)–C(16)	−173·9	C(17)–N(14)–C(15)–C(16)	57·6
C(13)–N(14)–C(17)–C(18)	−66·2	C(15)–N(14)–C(17)–C(18)	58·9

* E.s.d.'s for the torsional angles range from 0·4 to 0·5°.

equatorial continents. The resistant strains have necessitated the development of new antimalarials which will treat the resistant chloroquine strains. Although chloroquine has been used for four decades, neither the mechanism of action nor the mechanism of resistance of chloroquine has been fully elucidated (Ginsburg & Geary, 1987). Chloroquine uptake studies have demonstrated no significant difference in the rate of intracellular accumulation or in the steady state intracellular concentration of chloroquine between sensitive and resistant strains of *P. falciparum* suggesting the presence of an intracellular 'effector' (Geary, Jensen & Ginsburg, 1986). Knowledge of the three-dimensional structure of chloroquine may lead to insights into the mechanisms of action and resistance of chloroquine. Such insights would be expected to aid in the development of antimalarials active against chloroquine-resistant *P. falciparum*.

The crystalline structure of chloroquine diphosphate was first determined by Preston & Stewart (1970). Since the atomic coordinates were not published with the structure and are not available from the author, we recrystallized and redetermined the structure of chloroquine. Although the cell parameters are very similar between the two crystals, our structure is a dihydrate whereas the original structure was reported as a monohydrate.

Experimental. N^4-(7-Chloro-4-quinolinyl)-N',N'-diethyl-1,4-pentanediamine diphosphate (chloroquine, WR 1544) was obtained from Sterling–Winthrop (Albany, NY) and was crystallized by placing an aqueous solution of chloroquine inside dialysis tubing (Pope Scientific, Inc., Menomonee Falls, WI), tying the ends, and placing the tubing in a beaker of acetone. Plate-shaped crystals grew on the inside walls of the

dialysis tubing. Diffraction data were collected from a clear needle, 0·20 × 0·07 × 0·06 mm, in the θ–2θ mode to a maximum 2θ value of 45° on the $R3m$/micro Nicolet four-circle diffractometer (Nicolet Corp., Madison, WI) using Mo $K\alpha$ radiation with a graphite monochromator. Range of indices: h 0→10, k 0→18, and l −17→16. The total number of independent reflections was 3321. The standard reflections (006, 0,10,0 and 330) were monitored after every 60 intensity measurements. The standards varied by up to 6·3%. The lattice parameters were based on 25 centered reflections with 2θ values between 11° and 25°. No correction for absorption or extinction was used. The structure was solved routinely by direct phase determination (Karle & Karle, 1966). All but 5 of the non-hydrogen atoms were found in the first E map. The remaining non-hydrogen atoms which included 3 carbon atoms and the 2 water molecules were found in the first difference map. All of the hydrogen atoms attached to the nitrogen atoms and the phosphate oxygen atoms were found in subsequent difference maps. The hydrogen atoms attached to the carbon atoms were placed in idealized positions. Least-squares refinement was performed using 2431 reflections with $|F_o| > 3\sigma|F_o|$ ($R_{merge} = 0{\cdot}011$). Coordinates for all atoms except the hydrogen atoms on the carbon atoms were refined (on F) by a blocked cascade program in the *SHELXTL* system (Sheldrick, 1980). Anisotropic thermal parameters for the C, Cl, N, O, and P atoms and isotropic thermal parameters for hydrogen atoms were refined for a total of 333 parameters. Final $R = 5{\cdot}5\%$ and $wR = 5{\cdot}1\%$, $w = 1/[\sigma^2(|F|) + 0{\cdot}0007|F_o|^2]$. $(\Delta/\sigma)_{max} = 0{\cdot}2$. Final difference electron density $|\Delta\rho| < 0{\cdot}35$ e Å^{-3}. Atomic scattering factors were those incorporated in *SHELXTL*.*

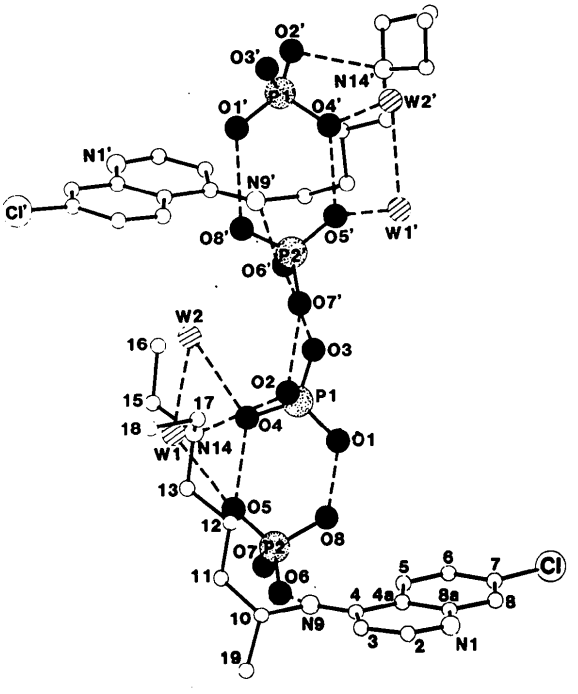

Fig. 2. Diagram of two chloroquine molecules whose side chains are wrapped around the same phosphate chain. The chain of dihydrogenphosphate ions is parallel to the b axis. Only non-hydrogen atoms are shown. The numbering scheme for the chloroquine, phosphate, and water molecules is indicated. The phosphate oxygen atoms are solid black, the phosphorus atoms are shaded, and the oxygen atoms of the water molecules are striped. Hydrogen bonds are depicted by dashed lines. The two hydrogen bonds not shown are the hydrogen bonds between N(1) and O(1) of a neighboring phosphate chain and $W(1)$ to $W(1)''$. The size of the circles was arbitrarily chosen to correspond approximately to the atomic weight of the atom.

Discussion. Coordinates and U_{eq} values for the non-hydrogen atoms and coordinates for the refined hydrogen atoms are listed in Table 1. Bond lengths, bond angles, and torsion angles are listed in Table 2. The bond length of the hydrogen atoms attached to the carbon atoms was kept fixed at 0·96 Å throughout the refinement procedure.

As described by Preston & Stewart (1970), the phosphate ions form continuous chains parallel to the b axis (Fig. 2) within which all four of the phosphate oxygen atoms are hydrogen bonded to two of the

* Lists of anisotropic temperature factors, hydrogen coordinates and temperature factors, and observed and calculated structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44972 (24 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

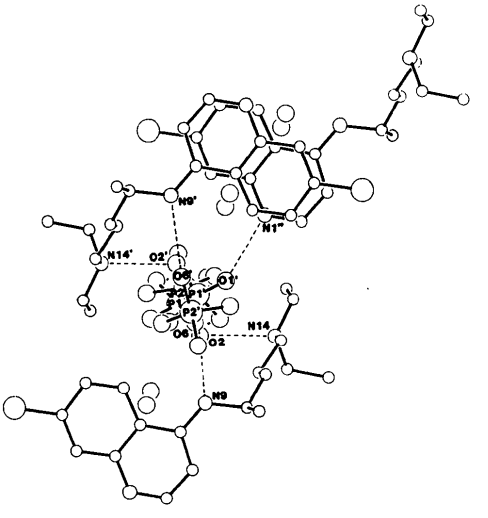

Fig. 3. View of chloroquine bis(dihydrogenphosphate) dihydrate down the b axis. The stacking of quinoline rings from the chloroquine molecules whose side chains are wrapped around the neighboring phosphate chains is illustrated. Only non-hydrogen atoms are shown. The isolated circles represent water molecules. Hydrogen bonds are depicted by dashed lines. The size of the circles was arbitrarily chosen to correspond approximately to the atomic weight of the atom.

Table 3. *Hydrogen-bond distances and angles*

Donor atom	Hydrogen atom	Acceptor atom	Distance donor to acceptor* (Å)	Distance hydrogen to donor* (Å)	Distance hydrogen to acceptor* (Å)	Donor–hydrogen–acceptor angle (°)†	Symmetry equivalent of donor
N(1)	H(*n*1)	O(1)	2·680	0·86	1·84	167	$2-x,-y,-z$
N(9)	H(*n*9)	O(6)	2·959	0·81	2·17	163	$1-x,0·5+y,-0·5-z$
N(14)	H(*n*14)	O(2)	2·779	1·14	1·65	169	x,y,z
O(3)	H(*o*3)	O(6)	2·567	0·66	1·93	162	x,y,z
O(4)	H(*o*4)	O(5)	2·516	0·77	1·75	177	$1-x,-0·5+y,-0·5-z$
O(7)	H(*o*7)	O(2)	2·618	0·86	1·77	172	x,y,z
O(8)	H(*o*8)	O(1)	2·559	1·16	1·45	171	$1-x,-0·5+y,-0·5-z$
W(1)	‡	*W*(1)	3·008	‡	‡	‡	$1-x,1-y,-z$
W(1)	§	O(5)	3·138	§	§	§	x,y,z
W(2)	§	*W*(1)	2·885	§	§	§	x,y,z
W(2)	§	O(4)	2·926	§	§	§	$1-x,0·5+y,-0·5-z$

* E.s.d.'s for the donor–acceptor, the hydrogen–donor, and the hydrogen–acceptor distances are near 0·004, 0·07, and 0·04 Å, respectively.

† E.s.d.'s for the donor–hydrogen–acceptor angle are near 0·5°.

‡ The hydrogen atom attached to *W*(1) appears on the center of symmetry between two water molecules related by a center of symmetry.

§ Hydrogen not located in difference map.

phosphate oxygen atoms in each of the adjacent phosphate groups (Table 3). The quinoline ring system is nearly perpendicular to the phosphate chain. The quinoline nitrogen atom and the terminal chain nitrogen atom are positively charged with one hydrogen atom from each of the two coordinated phosphate groups being found on the nitrogen atoms. The N(1) and N(14) atoms from different chloroquine molecules are hydrogen bonded to the same phosphate group. The side chain wraps around the phosphate chain in a helical manner such that both nitrogen atoms in the side chain are hydrogen bonded to neighboring phosphate groups (Fig. 3). Neighboring phosphate chains are bridged by chloroquine molecules *via* hydrogen bonding of the quinoline nitrogen atom to one phosphate chain and hydrogen bonding by N(9) to the neighboring phosphate chain.

The crystalline structure of chloroquine dihydrogenphosphate dihydrate includes 11 hydrogen bonds (Fig. 2 and Table 3). Each hydrogen atom attached to a nitrogen atom or a phosphate oxygen is involved in hydrogen bonding. Although none of the hydrogen atoms associated with the water molecules were found in the difference maps, the water molecules are positioned such that they form hydrogen bonds among themselves and with the phosphate chain. The relatively short distances of 2·52–2·62 Å between all of the donor and acceptor atoms in the phosphate ion chains indicate a strong attraction between phosphate moieties.

The phosphorus to oxygen bond length ranges from 1·504–1·508 (4) Å for O(1), O(2), O(5), and O(6) (P=O bonds) and from 1·547–1·566 (5) Å for O(3), O(4), O(7), and O(8) (P–OH bonds). These values are consistent with the reported values for (–)-ephedrine dihydrogenphosphate, imidazole$H^+.H_2PO_4^-$, and histidine$H^+.H_2PO_4^-.H_3PO_4$, which range from 1·489–1·518 (3) Å for the P=O bonds and 1·544–1·578 (5) Å for the P–OH bonds (Hearn & Bugg, 1972; Blessing, 1986).

Suggested mechanisms of action of chloroquine include formation of a membrane-toxic chloroquine–ferriprotoporphyrin IX complex, accumulation of chloroquine into the lysosomal compartments of the parasite resulting in alkalinization and disruption of function, interaction with DNA, and interaction with membrane phospholipids (see commentary, Ginsburg & Geary, 1987). In addition, chloroquine acts as an inhibitor of protein phosphorylation in yeast cells (Kalisz, Pohlig & Holzer, 1987). Since most of these hypotheses involve interaction of chloroquine with cellular constituents, the geometry of the association of chloroquine with the phosphate chains in the crystalline structure may demonstrate the manner in which chloroquine interacts with cellular constitutents important to antimalarial action. This interaction may include intercalation of DNA. The distance between the stacked quinoline rings in the crystal (Fig. 3) ranges from 3·43 to 3·56 Å which approximates the 3·4 Å distance between DNA base pairs.

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