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Jean Guillon, Noël Pinaud, Solène Savrimoutou, Mathieu Marchivie, Stéphane Moreau, et al.. Crystal structure of 1-(3-ferrocenyl-2-methylpyrrolo[1,2-a]quinoxalin-4-yl)piperazin-4-ium chloride. X-Ray Structure Analysis Online, 2021, 37, pp.65-67. 10.2116/xraystruct.37.65 . hal-03467904

**HAL Id: hal-03467904**

**<https://hal.science/hal-03467904>**

Submitted on 16 Sep 2024

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## Crystal Structure of 1-(3-Ferrocenyl-2-methylpyrrolo[1,2-*a*]quinoxalin-4-yl)-piperazin-4-ium Chloride

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The X-ray crystal structure of the antimalarial 1-(3-ferrocenyl-2-methylpyrrolo[1,2-*a*]quinoxalin-4-yl)piperazin-4-ium chloride has been established. It crystallizes in the tetragonal space group  $P-42_1c$  with cell parameters  $a = 24.6705(19)\text{Å}$ ,  $b = 24.6705(19)\text{Å}$ ,  $c = 7.4533(6)\text{Å}$ ,  $\alpha = 90^\circ$ ,  $\beta = 90^\circ$ ,  $\gamma = 90^\circ$   $V = 4536.3(8)\text{Å}^3$  and  $Z = 8$ . The crystal structure was refined to final values of  $R1 = 0.0354$  and  $wR2 = 0.0837$ . An X-ray crystal structure analysis revealed that each molecule features intermolecular N-H...Cl hydrogen bonds interactions between the ammonium group and the chloride anion to form tetramers.

(Received May 3, 2021; Accepted June 12, 2021; Published on web October 10, 2021)

According to WHO, malaria remains a major public health problem, all the more worrying nowadays as epidemiological data show that no significant progress in reducing malaria cases was registered for the period 2015 – 2017.<sup>1,2</sup> Indeed, about 229 million cases and 409000 related deaths worldwide of malaria were reported in the year 2019.<sup>1</sup> The increase in global drug resistance in the malaria endemic areas has significantly reduced the potency of most current used antimalarial compounds. Therefore, new antimalarial agents based on the novel mode of action are required to overcome the emergence of resistance and to control an ever-increasing number of epidemics caused by the malaria parasite.<sup>3–5</sup> For several years, a strategy for developing of organometallic-based antimalarial drugs was proposed. Given the avidity of *Plasmodium* for free iron, it was postulated that an effective way to remove the chloroquine resistance of parasites might be the addition of iron to a chloroquine molecule, and that a ferrocene moiety will permit one to vectorize the drug to the selected target. Hence, some new organometallic compounds including a ferrocene nucleus (dicyclopentadienyl iron) incorporated on chloroquine were designed, which led to the discovery of ferroquine (FQ) and of structural analogues.<sup>6–8</sup>

In the course of our work on the synthesis of new antimalarials, we have focused our interest on the synthesis of new ferrocenyl-substituted pyrrolo[1,2-*a*]quinoxaline derivatives,<sup>9,10</sup> new structural analogues of ferroquine (FQ), ferrocenyl quinine and ferrocenyl mefloquine analogues.<sup>6–8</sup> We report herein on the structural characterization of one of them, *i.e.* the 1-(3-ferrocenyl-2-methylpyrrolo[1,2-*a*]quinoxalin-4-yl)piperazin-4-ium chloride, an interesting antimalarial agent (Fig. 1), that shows antimalarial activity *in vitro* upon the *P. falciparum* chloroquine-sensitive strain F32/Tanzania ( $IC_{50} = 4.71\ \mu\text{M}$ ) and the chloroquine-resistant strains FcB1 and K1 ( $IC_{50} = 3.78$  and  $2.86\ \mu\text{M}$ ,

respectively).<sup>10</sup> This ferrocenic pyrrolo[1,2-*a*]quinoxaline was synthesized by treating 4-chloro-3-ferrocenyl-2-methylpyrrolo[1,2-*a*]quinoxaline with an excess of piperazine in ethylene glycol, and was isolated as its hydrochloride salt.<sup>10</sup>

Red crystals having dimensions of  $0.35 \times 0.080 \times 0.050\ \text{mm}^3$ , suitable for X-ray diffraction analysis, were obtained from a chloroform-ethanol solution (65/35) by slow evaporation of the solvent at  $+20^\circ\text{C}$  in the dark. The molecular structure of 1-(3-ferrocenyl-2-methylpyrrolo[1,2-*a*]quinoxalin-4-yl)piperazin-4-ium chloride is depicted in Fig. 2. Crystal and experimental data are given in Table 1.

Crystallographic data of this key intermediate compound were collected at 298 K on a Bruker APEX Duo diffractometer using monochromatic Mo- $K\alpha$  radiation ( $\lambda = 0.71073\ \text{Å}$ ). The collected data were reduced using SAINT software (SAINT, Bruker AXS Inc., Madison, Wisconsin, USA), and all reflections were used for unit-cell refinement. The crystal structure was solved by direct methods and successive Fourier difference syntheses with the SHELXS program.<sup>7</sup> Refinement of the crystal structure was performed on  $F^2$  by weighted anisotropic full-matrix least-squares methods using two inversion twin domains with a respective ratio of 0.48(2)/0.52(2) using the SHELXL program.<sup>11</sup> An absorption correction was performed

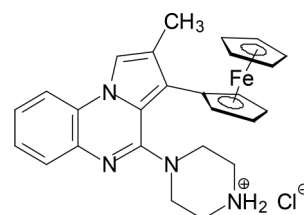


Fig. 1 Chemical structure of 1-(3-ferrocenyl-2-methylpyrrolo[1,2-*a*]quinoxalin-4-yl)piperazin-4-ium chloride.

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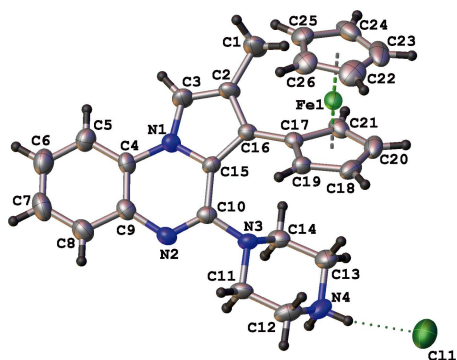


Fig. 2 Asymmetric unit ORTEP view of the crystal structure of the title compound with our numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

Table 1 Crystal and experimental data for the title compound

Chemical formula: $C_{26}H_{27}ClFeN_4$	
Formula weight: 486.81	
$T = 298(2)K$	
Crystal system: tetragonal	
Space group: $P-42_1c$	
$a = 24.6705(19)\text{\AA}$	$\alpha = 90$
$b = 24.6705(19)\text{\AA}$	$\beta = 90$
$c = 7.4533(6)\text{\AA}$	$\gamma = 90$
$V = 4536.3(8)\text{\AA}^3$	
$Z = 8$	
$D_x = 1.426\text{ Mg/m}^3$	
Radiation: Mo $K\alpha$ ( $\lambda = 0.71073\text{ \AA}$ )	
$F(0\ 0\ 0) = 2032$	
Crystal size = $0.35 \times 0.080 \times 0.050\text{ mm}^3$	
No. of reflections collected = 86624	
No. of independent reflections = 4655	
No. of reflections used [ $I > 2\sigma(I)$ ] = 4113	
$\theta$ range for data collection: $1.651$ to $26.387^\circ$	
Data/Restraints/Parameters = 4656/0/291	
Goodness-of-fit = 1.025	
$R$ indices [ $I > 2\sigma(I)$ ]: $R1 = 0.0354$ , $wR2 = 0.0837$	
$R$ indices (all data): $R1 = 0.0439$ , $wR2 = 0.0882$	
$(\Delta/\sigma)_{\max} = 0.002$	
$(\Delta\rho)_{\max} = 0.242\text{ \AA}^{-3}$	
$(\Delta\rho)_{\min} = -0.286\text{ \AA}^{-3}$	
Measurement: Bruker Kappa CCD diffractometer	
Structure determination: SHELXS <sup>11</sup>	
Refinement: SHELXL <sup>11</sup>	
CCDC deposition number: 2074486	

by semi-empirical methods using the SADABS program.<sup>11</sup> All parts of program were used within the OLEX2 package.<sup>12</sup> All non-H atoms were refined anisotropically, and the positions of the H atoms were deduced from the coordinates of the non-H atoms to which they are linked, confirmed by Fourier synthesis and treated according to the riding model during refinement. H atoms were included for structure factor calculations, but not refined.

Crystallographic data have been deposited in the Cambridge Crystallographic Data Centre (CCDC 2074486). Copies of these data can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk or [http://www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif)).

The title compound crystallizes in the tetragonal  $P-42_1c$  space

Table 2 Short-contact geometry in the title compound—hydrogen interactions ( $\text{\AA}$ ,  $^\circ$ )

D-H...A	H-A ( $\text{\AA}$ )	D-A ( $\text{\AA}$ )	D-H...A ( $^\circ$ )
N4-H4A...Cl1 <sup>a</sup>	2.18	3.051(4)	164.2
N4-H4B...Cl1	2.23	3.084(4)	160.2
C12-H12A...Cl1 <sup>b</sup>	2.60	3.476(5)	149.7

a.  $1-Y, -1+X, 1-Z$ .

b.  $1-Y, -1+X, 2-Z$ .

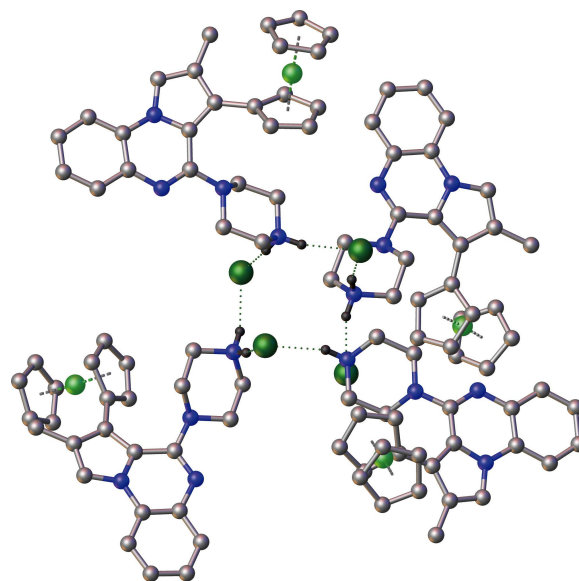


Fig. 3 View of the supramolecular tetramers formed by charge-assisted H-bonding.

group. The pyrroloquinoxaline moiety is almost planar; a derivation of the C(16) atom was noticed at  $-0.236(3)\text{\AA}$  from the plane defined by the tricyclic system (total RMSD calculated on the 13 non-H atoms of the pyrroloquinoxaline moiety =  $0.110\text{ \AA}$ ). The structural parameters for the ferrocenyl substituent in the pyrroloquinoxaline compound is within the normal ranges, and the iron atom is sandwiched almost perfectly centrally between the two cyclopentadienyl rings. Thus, the distances of the Fe atom from the centroids of the substituted and unsubstituted cyclopentadienyl systems (Cp) are  $1.656(2)$  and  $1.656(2)\text{\AA}$ , respectively. The  $Cg1-Fe-Cg2$  angle is  $176.8(1)^\circ$ , where  $Cg1$  (C17 to C21) and  $Cg2$  (C22 to C26) are the centroids of substituted and unsubstituted Cp rings, respectively. Thus, the Cp rings in the ferrocene system are almost parallel, since the dihedral angle between the Cp ring planes is  $7.3(2)$ . In addition, in this structure, the Cp rings display a nearly eclipsed conformation with a slight deviation, as demonstrated by the average  $C-Cg1-Cg2-C$  torsion angle of  $5.4(3)^\circ$ . The C-C bond distances in the Cp rings range from  $1.399(7)$  to  $1.436(6)\text{\AA}$ , while the Fe-C bond lengths range between  $2.022(4)$  and  $2.093(4)\text{\AA}$ . The piperazine ring has the chair conformation, the nitrogen atoms are alternately displaced from the least-squares plane by  $-0.652(6)$  and  $0.680(5)\text{\AA}$ , respectively.

Short intermolecular charge assisted H-bonding is found between the ammonium group and the chloride leading to a supramolecular tetramer (Table 2 and Fig. 3). Tetramers are linked together by a weaker H-bond interaction between a

carbon atom of the piperazine moiety (C12) and the chloride anion and  $\pi$ - $\pi$  stacking between pyrroloquinoxaline rings (centroid-centroid distance = 4.09 Å) that insure the global crystal cohesion (Fig. S1).

### Supporting Information

This material is available free of charge on the Web at <http://www.jsac.or.jp/xraystruct/>.

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