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ORIGINAL RESEARCH

Solid-state synthesis of isostructural tetrachlorometallate salts of amodiaquine: crystal structure of $[CdCl_4][C_{20}H_{24}ClN_3O]$

Adedibu C. Tella[1] · Samson O. Owalude[1] · Nzikahyel Simon[2] · Rotimi O. Arise[3]

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Abstract Tetrachlorometallate salts $[AMDH^{2+}][CoCl_4]^{2-}$ **1a** and $[AMDH^{2+}][CdCl_4]^{2-}$ **2a** ($AMDH^{2+}$ = amodiaquine dication) were obtained by ball milling of amodiaquine with inorganic salts $CoCl_2{\cdot}6H_2O$ and $CdCl_2{\cdot}6H_2O$, respectively, in the absence of solvent. Solution-based synthesis of $[AMDH^{2+}][CoCl_4]^{2-}$ **1b** and $[AMDH^{2+}][CdCl_4]^{2-}$ **2b** were also carried out by reaction of amodiaquine with the corresponding metal salts under reflux in methanol for 1 h. The analytical and spectroscopic data (IR, UV–Vis and NMR spectra) obtained for the compounds prepared via the two different routes are identical. The XPRD pattern of **1a** closely matched the simulated pattern obtained from its reported single-crystal data. Single crystals of **2b** suitable for X-ray structural analysis were obtained. The X-ray structure of **2b** revealed an ionic compound with formula unit comprising of one protonated dicationic amodiaquine molecule and a tetrachlorocadmate(II) anion. The crystals are triclinic with space group P-1 and unit dimensions $a = 9.3272(8)$ Å, $b = 11.1418(9)$ Å, $c = 12.482(10)$ Å, $V = 1191.89$ Å^3, and $Z = 2$. The amodiaquine molecule is protonated both at the quinoline and quinuclidine nitrogen atom. Antimalarial efficacy of **1a** on *Plasmodium berghei*-infected mice were investigated, and the results revealed an enhanced activity of the compound by significantly ($p < 0.05$) improving the suppression of parasitemia in established infection when compared with the controls.

Keywords Ball mill · Solvent-free synthesis · Amodiaquine · Tetrachlorometallate salts · XRPD patterns

Introduction

Amodiaquine belongs to the class of 4-aminoquinoline which have been applied as prophylactic and therapeutic drugs in combating strains of malaria parasite, such as *P. ovule*, *P. vivax*, and *P. falciparium* (Naisbitt *et al.*, 1997; Watkins *et al.*, 1984). Amodiaquine is an effective antimalaria drug, and its mode of action is equal to that of chloroquine on strains of *P. falciparium* resistant to chloroquine (Watkins *et al.*, 1984; Neftek *et al.*, 1986). Recent reports have shown that amodiaquine is now only used for the treatment of acute phase of malaria due to the severe side effects including agranulocytosis and hepatitis (Neftek *et al.*, 1986). Its clinical use has been restricted because it is hepatotoxic and salty. It is very useful in the pediatrics treatment and in combination therapy with other antimalarial agents such as artesunate and artemisinin (WHO, 2001). It is available in form of its chloride salt dihydrochloride 4-[(7-chloroquinolin-4-yl)amino]-2-[(diethylamino)methyl]phenol (Fig. 1). The parent compound quinine is an alkaloid derived from cinchona bark which is a blood schizonticidal drug and very effective against the erythrocytic forms of all four species of plasmodia (Laurent *et al.*, 1993). Malaria is by far the most serious and widespread parasitic disease occurring in man. It is estimated that about two billion people are at risk of this disease in tropical and subtropical areas of the world. Due

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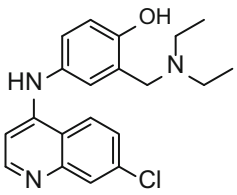


Fig. 1 Chemical structure of amodiaquine

to increased vector resistance to the existing antimalarial drugs, the need for new drugs therefore becomes critical (Obaleye *et al.*, 2007). In search for novel drugs against chloroquine-resistant malarial parasites, the modification of existing antimalarial drugs by incorporation of transition metal into molecular structure of the drugs has attracted considerable attention in recent years (Arancibia *et al.*, 2010; Biot *et al.*, 2010, 2012; Navarro *et al.*, 2012). This of course enhanced antimalarial activities of such compounds (Arancibia *et al.*, 2010). The reaction by complexation is usually performed in solution by use of organic solvents, which may end up as residual solvents in the final products or released into the environment as pollutants. The presence of residual organic solvent in drugs is highly undesirable due to their toxicity, and therefore a limit to their concentration in drugs has been placed (Amin *et al.*, 2010). It is therefore desirable that the drug substances be made free from toxic organic solvents. Recently, methods have been developed to prepare these compounds without solvents. Solvent-free mechanochemical method which involves grinding of reactants in a mortar with a pestle or ball milling without solvent represent viable green routes for preparation of these compounds. Solvent-free synthesis has many advantages over solution synthesis. The method is simple, eliminates, and minimizes the use of organic solvents, thereby reducing environmental contamination. The reaction is usually carried out at room temperature, thereby making the method to be energy efficient with short reaction time. Synthesis of metal complexes of amodiaquine using traditional solvent-based techniques has been reported (Biot *et al.*, 2000; Dormale *et al.*, 1998; Hubel *et al.*, 1999; Ajibade and Kolawole, 2008; Obaleye *et al.*, 2009; Tella and Obaleye, 2010; Wasi *et al.*, 1987).

The first solvent-free synthesis of Zn(II) and Cu(II) complexes of gabapentin simply by grinding of the corresponding metal salts and solid gabapentin was reported by Braga and co-workers (Braga *et al.*, 2008). Recently, our team reported solvent-free synthesis of metal complexes of some active pharmaceutical ingredients (API) (Tella *et al.*, 2011, 2012, 2014). In continuation of our studies on interaction of metal ions with API in solvent-free media, we now wish to report a simple but highly efficient procedure for the synthesis of Co(II) and Cd(II) compounds of amodiaquine drug under solvent-free grinding technique. The experiments described herein demonstrate the utility of mechanochemical method for rapidly achieving complete reactions between divalent metal ions and amodiaquine in 15 min. The analytical and spectroscopic data of the products obtained from this method are then compared with those of the free ligand and the product obtained from conventional solution-based technique. To the best of our knowledge, this represents the first solid-state preparation, crystal structure, and X-ray powder diffraction studies of tetrachlorocadmate compound of amodiaquine.

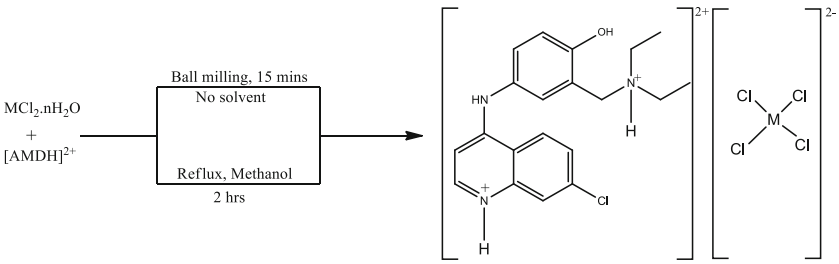
Experimental

All reagents and chemicals were commercially sourced from Aldrich and were not further purified. The amodiaquine ligand was a gift from Tuyil Pharmaceutical Company, Ilorin, Nigeria. A total of 20 male albino mice (*Mus musculus*) of average body weight of 26.01 ± 0.21 g were obtained from the Animal Breeding Unit of Biochemistry Department, University of Ilorin, Nigeria. *Plasmodium berghei* were collected from IMRAT, University of Ibadan, Nigeria. FTIR spectra were recorded on a SHIMADZU Scientific model 500 FITR spectrophotometer as KBr pellets. Thin-layer chromatography was carried out using TLC plates coated with silica gel, while the AAS analysis was carried out on an Atomic Absorption Spectrophotometer Model 6503 Jenway. X-ray diffraction analysis was carried out on a Bruker AVS D8 graphite diffractometer. High-resolution ^{1}H NMR spectra were recorded on a Bruker Avance 600-MHz spectrometer at 298 K. The chemical shifts were calibrated to solvent peaks, which are reported relative to TMS. Elemental analysis was performed on a PerkinElmer CHN Analyzer 2400 Series II.

Solvent-free synthesis of 4-[(7-chloroquinolin-4-yl)amino]-2-[(diethylamino)methyl]phenol tetrachlorocobaltate(II) salt ($[AMDH^{2+}][CdCl_4]^{2-}$) (1a) and 4-[(7-chloroquinolin-4-yl)amino]-2-[(diethylamino)methyl]phenol tetrachlorocadmate(II) salt ($[AMDH^{2+}][CdCl_4]^{2-}$) (2a)

The two compounds were prepared by modification of the literature procedures (Adams *et al.*, 2010). A typical synthetic route is described here for **1a**. $CoCl_2.6H_2O$ (0.240 g, 1 mmol) and amodiaquine. HCl (0.788 g, 2 mmol) was weighed into Retsch MM200 stainless-steel ball-mill vessel equipped with steel balls (20 g), and the vessel was closed and the milling was carried out at room temperature at a speed of 25 HZ. After every 5-min milling cycles, the progress of the reaction was monitored by thin-layer chromatography. The milling continued for 15 min after which no traces of the reactants were found. The procedure is depicted in scheme 1 below:

Scheme 1 Mechanochemical synthesis of tetrachlorometallate salts of amodiaquine



M = Co(II) or Cd(II); $[AMDH]^{2+}$ = amodiaquine cation

1a. Yield 94.8 %; mp 278 °C; IR (KBr, cm^{-1}): 3460–3209 υ(O–H stretch, H-bonded), 3553 υ(N–H^+), 3068 υ(C–H aromatic), 2985 υ(C–H aliphatic), 1583 υ(C=N) 1583, 669 υ(Co–Cl); ^{1}H NMR (DMSO-d_6): $\delta = 9.62$ (1H, d, $J = 7.5$ Hz, H-2), 7.12 (1H, d, $J = 7.5$ Hz, H-1), 7.09–7.01 (4H, m, H-7, H-9, H-10, H-11), 6.84 (1H, dd, $J = 7.4$, 1.9 Hz, H-17), 6.69 (1H, s, O–H), 6.25 (1H, d, $J = 7.5$ Hz, H-16), 5.95 (1H, s, H-13), 4.50 (2H, d, $J = 0.9$ Hz, H-18), 3.28 (4H, q, $J = 6.3$ Hz, H-20, H-22), 1.19 (6H, t, $J = 6.3$ Hz, H-23, H-24); ^{13}C NMR (DMSO-d_6): 156.52 (C-13), 155.50 (C-7), 144.07 (C-16), 139.64 (C-12), 138.80 (C-19), 128.49 (C-23), 116.17 (C-8), 100.84 (C-14); Anal. Calc. for $C_{20}H_{24}N_3Cl_5OCo$: C 42.97; H 4.30; N 7.52; Co 10.56. Found: C 42.86; H 4.21; N 7.58, Co 10.26.

2a. Compound **2a** was prepared by a procedure similar to the synthesis of **1a** described above except that $CdCl_2 \cdot 2^1/_2H_2O$ (0.228 g, 1 mmol) was used instead of $CoCl_2 \cdot 6H_2O$. Yield: 88.4 %, mp 275 °C, IR (KBr, cm^{-1}): 3460–3311 υ(O–H stretch, H–bonded), 3563 υ(N–H^+), 3032 υ(C–H aromatic), 2980 υ(C–H aliphatic), 1585 υ(C=N), 640 υ(Cd–Cl), Anal. Calc. for $C_{20}H_{24}N_3Cl_5OCd$: C 39.25, H 3.92, N 6.87, Cd 18.37, Found: C 40.86; H 4.42; N 6.26. Cd 18.20.

Solvent-based synthesis of 4-[(7-chloroquinolin-4-yl)amino]-2-[(diethylamino)methyl]phenol tetrachlorocobaltate(II) salt ($[AMDH^{2+}][CdCl_4]^{2-}$) (1b) and 4-[(7-chloroquinolin-4-yl)amino]-2-[(diethylamino)methyl]phenol tetrachlorocadmate(II) salt ($[AMDH^{2+}][CdCl_4]^{2-}$) (2b)

The two compounds were prepared by a reported procedure (Semeniuk *et al.*, 2008) as described here for **1b**. $CoCl_2.6H_2O$ (0.240 g, 1 mmol) and amodiaquine. HCl (0.788 g, 2 mmol) was dissolved in methanol (10 ml). The two solutions were mixed together and refluxed at 70 °C for 2 h. The reaction solution thus obtained was filtered and allowed to evaporate slowly at room temperature to give blue crystals of **1b** suitable for X-ray diffraction studies.

1b. Yield: 76.2 %, mp 274 °C; Anal. Calc. for $C_{20}H_{24}N_3Cl_5OCo$: C 42.97; H 4.30; N 7.52; Co 10.56. Found: C 43.08; H 4.46; N 7.43, Co 10.30.

2b. Compound **2b** was prepared by a similar procedure to the synthesis of **1b** described above except that $CdCl_2 \cdot 2^1/_2H_2O$ (0.228 g, 1 mmol) was used instead of $CoCl_2 \cdot 6H_2O$. Yield: 74.2 %, mp = 277 °C, IR (KBr, cm^{-1}): Anal. Calc. for $C_{20}H_{24}N_3Cl_5OCd$: C 39.25, H 3.92, N 6.87, Cd 18.37. Found: C 42.86; H 4.21; N 6.26., Cd 18.48.

Antimalarial screening and safety evaluation of amodiaquine–cobalt compound 1a

Mice for experiment were infected as described by Sanchez-Delgado *et al.* (1996). Swiss mice were divided into four groups of five mice each, kept in metal cages and fed with mice cubes and water ad libitum.

Group 1—Infected but not treated (IBNT);
Group 2—Infected and treated with chloroquine (ITCQ);
Group 3—Infected and treated with amodiaquine (ITAM);
Group 4—Infected and treated with amodiaquine-Co **1a** (ITAC).

The mice were inoculated intravenously with 0.2 ml of 1×10^6 parasitized erythrocytes suspended in buffered physiological saline (pH 7.4). The mice were left for 4 days and their levels of parasitemia were monitored daily by counting parasites in blood smear fixed with 70 % methanol and Giemsa stain. The slides were viewed under the microscope with magnification of 100. The level of parasitemia was then determined by counting the number of infected erythrocytes/1000 erythrocytes in tail blood smears stained with Giemsa. 0.2 ml of each drug solution (corresponding to 7.7 mg/kg body weight) was daily and orally administered to the mice in each group from day 0 to day 3 of infection. Level of parasitemia was determined on day 4. The results were expressed as the percentage of infected cells or inhibition of parasites and percentage chemo-suppression of parasite multiplication by the drugs.

Results and discussion

Manual grinding of a mixture of amodiaquine and cobalt(II) chloride in a ball mill gave **1a** in quantitative yield. Compound **2a** was obtained in a similar manner but using cadmium(II) chloride in place of cobalt(II) chloride. Each reaction is completed within 15 min at room temperature as compared to **1b** and **2b** obtained through solvent-based technique which required 1 h of refluxing a solution of the starting materials in methanol at 70 °C. The products from the mechanochemical grinding (**1a** and **2a**) were obtained with no waste, and no further purification processes were needed unlike those obtained from the solvent-based technique (**1b** and **2b**) which required purification through recrystallization. The elemental analysis data indicates that both compounds are pure and consistent with the proposed formulae. The two compounds, **1a** and **2a**, are non-hygroscopic solids with sharp melting points. They are soluble in methanol, ethanol, and DMSO, but insoluble in chloroform and water. The two compounds were further characterized using techniques such as UV–visible spectra analyses, XRPD studies, and ^{1}H NMR spectroscopy.

IR studies

Figure S1 shows a comparison of the FTIR spectra of the free amodiaquine ligand with compounds **1a** and **1b** obtained via the two methods. Infrared spectra of the two products **2a** and **2b** shown in Fig. S2 indicate that the two materials are identical. The IR spectrum of the free amodiaquine exhibited a strong band at 1618 cm^{-1} due to the υ(C=N) group. In the spectra of all the complexes, this band generally experienced a small shift but not sufficiently large to indicate coordination through this group. It can also be observed from figures S1 and S2 that the band due to υOH at 3358 cm^{-1} in the free amodiaquine ligand has shifted to around 3319 cm^{-1} in **1a** and 3321 cm^{-1} in **2a**. This may not be as a result of coordination but due to hydrogen bonding between this group and the chlorine atoms on the metal center. Also the band at 3363 cm^{-1} due to υNH in the free amodiaquine ligand changed to 3345 cm^{-1} in **1a** and 3338 cm^{-1} in **2a**; this may also not connected to coordination, but instead may be due to protonation of the quinoline and quinuclidine nitrogen atom on the free ligand (Obaleye *et al.*, 2007; Semeniuk *et al.*, 2008). Similar trends were observed for the products obtained via the solvent-based technique. The observation of the FTIR spectra data for the compounds suggests that there is no direct metal–ligand coordination in their structures. The absorption bands at 2985 cm^{-1} is quite intense, with a shoulder at 2945 cm^{-1} due to the υ(C–H) stretching vibration of the methylene group present in the quinuclidine molecule. The absorption band at 1093 cm^{-1} in **1a** and 1096 cm^{-1} in **2a** due to υ(C–Cl) in amodiaquine retains its position and intensity in the spectra of the compounds indicating that this part of the molecule is unmodified in the compounds. The same trend was observed in **1b** and **2b**. This mode of coordination was observed in a related salt containing cinchoninine as the pharmaceutical ligand (Weselucha-Birczynska *et al.*, 1990). From this study and the literature evidence, it can be concluded that both compounds **1** and **2** are ionic salts with no direct metal–ligand bond.

NMR spectroscopy

The proton NMR spectrum of amodiaquine and its cobalt(II) salt $[AMDH^{+2}][CoCl_4]$ (**1a**) formed after ball milling for 15 min show that there is a little or no change in the chemical shifts of each proton signals (Fig. S3). Also comparison of the proton signals of free $AMDH^{+2}$ and $[AMDH^{+2}][CoCl_4]$ obtained from the solvent-based technique shows that the change in chemical shifts is not sufficiently large to indicate direct metal–ligand bonding in these compounds. The two compounds on the other hand showed new proton signals at δ 7.88 ppm in **1a** and 7.60 ppm in **2a** attributed to N6-H^{+} resulting from the protonation of the N atom in the quinoline group in the free ligand. New proton signals were also observed in **1a** at δ 4.10 ppm and in **2a** at 4.20 ppm assigned to N1-H^{+} as a results of the protonation of N atom on the quinuclidine in amodiaquine ligand. The proton signals attributable to OH group at δ 11.20 ppm in the free amodiaquine have disappeared in both compounds. These shifts in proton signals are as a result of strong hydrogen bonding interaction between relatively large amodiaquine molecule and the chlorine atoms on the metal center (Wasi *et al.*, 1987; Chaabane *et al.*, 2008). The ^{13}C NMR spectrum of **1a** (Fig. S5) consists of distinct lines between 126 and 138 ppm attributable to the aromatic carbons in the amodiaquine moiety, while the C–Cl of the quinoline ring in this molecule was observed as a single line at 139.64 ppm. The C=N was observed at 144.07 ppm, C–N at 155.50 ppm, and C–OH at 156.52 ppm (Casabianca and de Dios, 2004).

X-ray powder diffraction (XPRD) analysis of 1a

Figure 2 shows a comparison of the X-ray diffraction patterns of **1a** and the starting materials. It can be observed from the figure that the X-ray diffraction pattern of product **1a** was different from the XPRD patterns of the starting materials. New peaks were observed in the XPRD pattern of **1a** at $2\theta = 16°$, 17°, 23°, and 24° indicating formation of a new phase. This is an evidence of formation of new

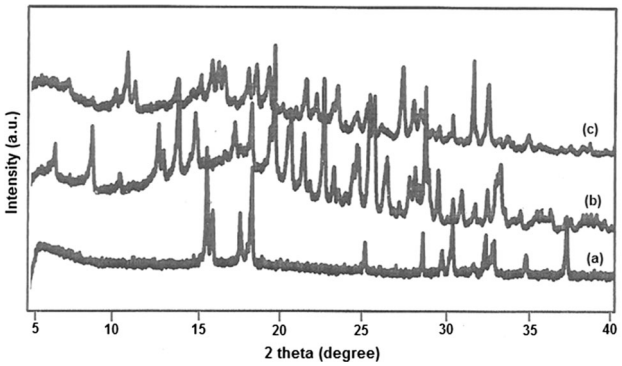


Fig. 2 Powder X-ray diffraction patterns of reactants *a* $CoCl_2$. $6H_2O$ *b* Amodiaquine HCl and the reaction product (*c*) **1a**

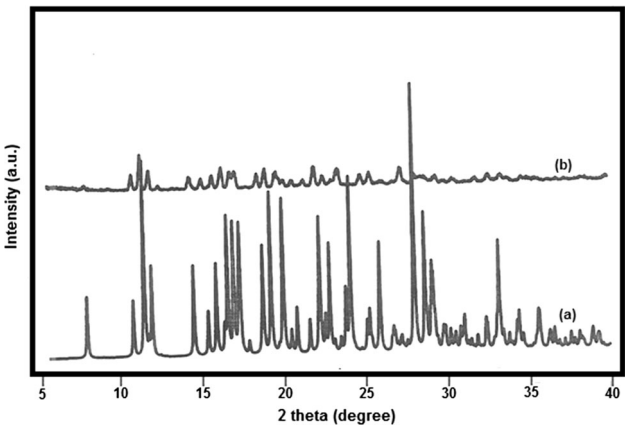


Fig. 3 PXRD patterns of *a* simulated patterns of single-crystal X-ray data of **1b**, *b* ball-milling product (**1a**)

product. Furthermore, the XRPD pattern of **1a** obtained from the computer simulation of its single-crystal X-ray data and the XPRD pattern of **1b** closely matched as shown in Fig. 3.

X-ray crystallographic analysis of 2b

The molecular structure of **2b** is shown in Fig. 4, while the packing diagram showing the hydrogen bonding is depicted in Fig. 5. The crystal data and refinement details of the complex are listed in Table 1 with the selected bond distances and angles summarized in Table 2. From Fig. 4, it is observed that there is no direct bonding of amodiaquine with Cd(II) in the salt. The formula unit of the compound consists of a tetrachlorocadmate(II) anion and one amodiaquine cation. The amodiaquine molecule is protonated at both the quinuclidine nitrogen (N1) and the quinoline nitrogen (N6). The third nitrogen N3 covalently bonds the H2N atom and forms an intermolecular hydrogen bond (N–H–Cl) with one of the chloride ions in the unit cell. The anionic $[CdCl_4]^{2-}$ and cationic $AMDH^{2+}$ are linked by this hydrogen bond which ensures the junction between amodiaquine cation and $CdCl_4^{2-}$. The compound is isostructural to the previously reported tetracobaltate amodiaquine salt (Semeniuk *et al.*, 2008). The Cd atom is coordinated to four Cl atoms in a tetrahedral environment with the Cd–Cl bond distances in the range 2.45(7)–2.48(5) Å. Bond distances found in this structure correspond to related values from other similar structure previously reported (Neve *et al.*, 2002). The tetrahedral coordination geometry of the cadmium atom in **2b** is slightly distorted with Cl–Cd–Cl bond angles in the range 105°–114.0°. This phenomenon can also be found in similar organic–inorganic salts of bis(4-nitroanilinium) tetrachlorocadmate and cinchonium tetrachlorocadmate(II) dihydrate (Azumi *et al.*, 1995; Oleksyn *et al.*, 1978). These structural differences could be explained by intermolecular interaction with involvement of the Cl^- atoms. In compound **2b**, the amodiaquine moiety is protonated at N1 and N6 positions. This is noticeable in quinoline fragment. The protonation at N6 results in increase in bond angle of C16–N6–C19 from 116.31° in free amodiaquine to 121.51(15)° in the compound. This is in agreement with the literature report that protonation of quinoline moiety results to unusual increase in C–N–C bond angle (Semeniuk *et al.*, 2008). The average N–C distance of 1.356 Å in compound **2b** is very close to that of amodiaquine dication (1.352 Å) but higher than that of unprotonated quinoline moiety (1.342 Å) (Semeniuk *et al.*, 2008). This may be attributed to the electron-withdrawing ability of the proton leading to increase in C–N–C bond angle and weakening of the N10–C bond strength. The bonding between the organic and the inorganic moieties is established by three different hydrogens N6–H6–C15, N3–H3–C12, and N1–H1–C16. In the crystal structure of **2b**, the anion and the cation are linked by N–H–Cl hydrogen bonds and Van der Waals interaction to form $[CdCl_4]$[AMDH] salt (Table 3).

Antimalarial activity

Table 4 represents percentage parasitamia in infected mice treated with amodiaquine and compound **1a**. There was a significant increase ($p < 0.05$) in parasitemia on days 5 and 6 post-inoculation in the mice that were infected and not treated (IBNT) when compared to parasite level on day 4 post-inoculation. The parasite level in mice treated with chloroquine (ITCQ) and **1a** declined below 5 % by the fifth day post-inoculation, while those treated with amodiaquine declined by 6 %. The percentage reduction of parasitamia in groups treated with chloroquine and compound **1a** on day 6 post-inoculation showed no significant difference ($p > 0.05$) when compared. However, all the animals in all the test groups survived beyond the experimental period.

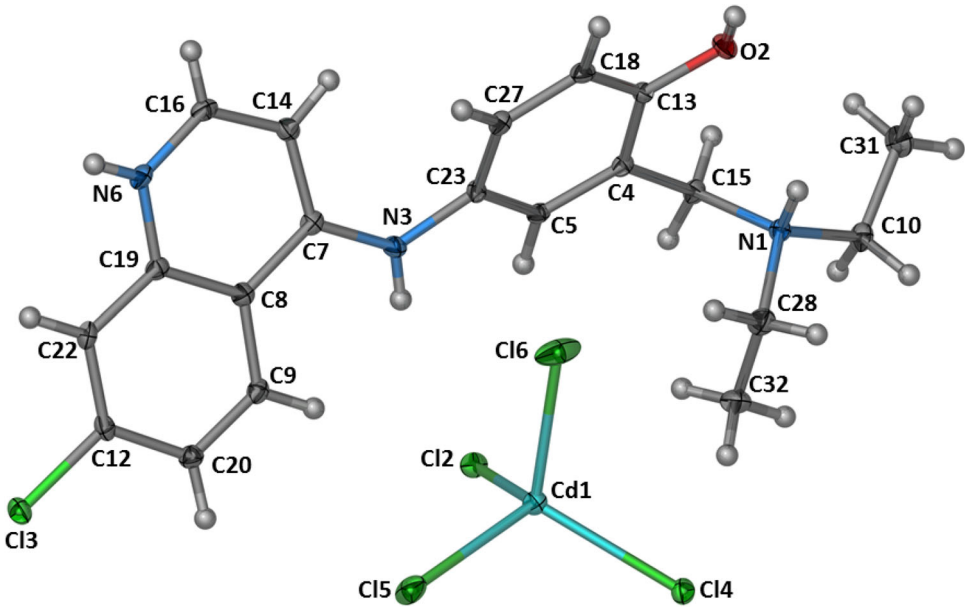


Fig. 4 ORTEP diagram showing the protonated amodiaquine molecule and the tetrachlorocadmate ion in **2b**, with thermal ellipsoids drawn at the 50 % probability level

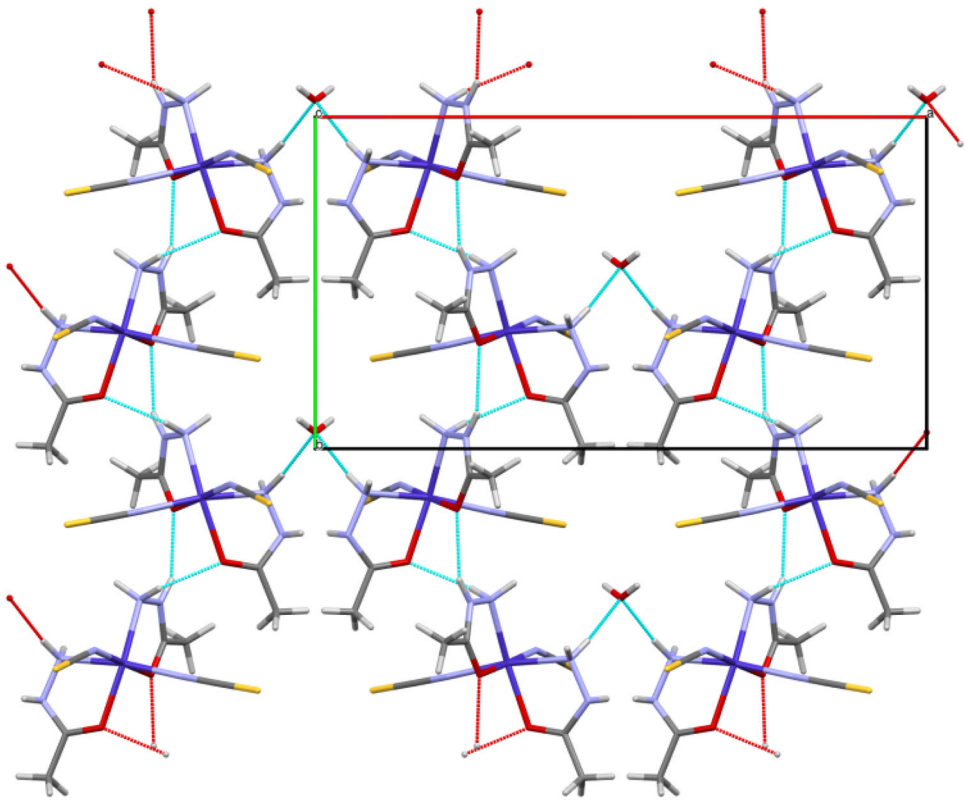


Fig. 5 Packing diagram of the crystal structure of **2b**

The percentage chemo-suppression of parasite multiplication following administration of amodiaquine and compound **1a** is presented in Table 5. The percentage chemo-suppression of mice treated with compound **1a** is relatively similar to that of the chloroquine group which increased significantly ($p < 0.05$). Amodiaquine attained 85.42 % by day 6, while **1a** attained 90.85 %.

The observed effects may be ascribed to the fact that **1a** was more permeative into parasitized erythrocytes than its amodiaquine ligand and chloroquine. Compound **1a** may

Table 1 Crystal data and structure refinement for **2b**

Empirical formula	$C_{20}H_{24}CdCl_5N_3O$
Formula weight	612.07
Temperature (K)	100
Crystal system	Triclinic
Space group	P-1
a (Å)	9.3272(8)
b (Å)	11.1418(9)
c (Å)	12.4824(10)
α (°)	87.875(2)
β (°)	77.319(2)
γ (°)	70.4800(10)
Volume (Å^3)	1191.89(17)
Z	2
ρ_{calc} (mg/mm^3)	1.705
m (mm^{-1})	1.494
$F(000)$	612.0
Crystal size (mm^3)	0.417 × 0.23 × 0.067
2θ range for data collection	3.346°–64.744°
Index ranges	$-13 \le h \le 14$, $-13 \le k \le 16$, $-18 \le l \le 17$
Reflections collected	10587
Independent reflections	7190[R(int) = 0.0161]
Data/restraints/parameters	7190/0/359
Goodness of fit on F^2	1.035
Final R indexes [$I \ge 2\ \sigma(I)$]	$R_1 = 0.0263$, $wR_2 = 0.0621$
Final R indexes [data]	$R_1 = 0.0288$, $wR_2 = 0.0637$
Largest diff. peak/hole/ e (Å^{-3})	0.74/−0.53

Table 2 Selected bond distances (Å) and angles (°) for **2b**

Bond distances (Å)			
Cd(1)–Cl(2)	2.4542(2)	Cd(1)–Cl(4)	2.4642(4)
Cd(1)–Cl(5)	2.4749(5)	Cd(1)–Cl(6)	2.4454(7)
N(3)–C(7)	1.336(2)	N(3)–C(23)	1.419(2)
N(1)–C(10)	1.506(2)	N(1)–C(15)	1.506(2)
N(1)–C(28)	1.515(3)	N(6)–C(16)	1.339(3)
N(6)–C(19)	1.373(3)	C(4)–C(5)	1.388(2)
Bond angles (°)			
Cl(6)–Cd(1)–Cl(4)	110.056(18)	Cl(6)–Cd(1)–Cl(2)	105.350(16)
Cl(6)–Cd(1)–Cl(2)	105.350(16)	Cl(6)–Cd(1)–Cl(5)	108.680(2)
C(7)–N(3)–C(23)	128.190(14)	C(19)–N(6)–C(16)	121.510(15)
C(15)–N(1)–C(28)	112.860(13)	C(28)–N(1)–C(10)	112.280(13)

have exchanged its bound cobalt for ferric ions rendering the cobalt to be unavailable for vital parasite functions, thus suggesting **1a** may have a better therapeutic activity

Table 3 Hydrogen bond parameters for **2b**

D–H···A	H···A (Å)	D···A (Å)	D–H···A (°)
N(1)–H(1)···O(2)	2.36(3)	2.934(2)	126(2)
N(1)–H(1)···Cl(6)	2.42(2)	3.1313(16)	142(2)
O(2)–H(2)···Cl(2)	2.36(3)	3.0993(14)	174(3)
N(3)–H(3)···Cl(2)	2.76(3)	3.5553(17)	164(2)
N(6)–H(6)···Cl(5)	2.33(3)	3.1318(17)	168(2)
C(9)–H(9)···Cl(2)	2.83(3)	3.7309(18)	171(18)
C(9)–H(9)···N(3)	2.59(3)	2.891(2)	100(2)
C(15)–H(15)···Cl(15)	2.82(3)	3.5937(18)	135(2)

Table 4 Parasitemia levels in *P. berghei* NK-65-infected mice treated with chloroquine, amodiaquine, and **1a**

Treatments	Day 4	Day 5	Day 6
IBNT	19.99 ± 0.72^a	31.40 ± 0.59^c	42.86 ± 0.82^b
ITCQ	19.38 ± 0.43^a	12.60 ± 0.32^b	10.06 ± 0.62^a
ITAM	19.41 ± 0.64^a	15.84 ± 0.46^a	10.71 ± 0.61^c
ITAC	19.37 ± 0.58^a	15.99 ± 0.59^a	9.32 ± 0.60^a

Each value is a mean of five replicates ± SEM. Rows with different superscripts are significantly different ($p < 0.05$)

IBNT infected but not treated, *ITCQ* infected and treated with chloroquine, *ITAM* infected and treated with amodiaquine, *ITAC* infected and treated with amodiaquine-Co (**1a**)

Table 5 Percentage chemo-suppression of parasite multiplication in *P. berghei* NK-65-infected mice treated with chloroquine, amodiaquine, and **1a**

Treatments	Day 5	Day 6
Chloroquine	59.87	76.53
Amodiaquine	49.55	75.01
Amodiaquine-Co **1a**	49.07	78.25

against malaria than chloroquine (Ogunlana *et al.*, 2012) and amodiaquine (Biot *et al.*, 2000).

Conclusion

Tetrachlorometallate salts of amodiaquine have been synthesized via simple mechanochemical grinding and solvent-based techniques. The structure of the products obtained from the two methods was characterized by elemental analysis, AAS, conductivity measurements, TLC, FTIR, UV–Vis, and ^{1}H NMR spectroscopic analyses as well as powder X-ray diffraction studies. The comparison of analytical and spectroscopic data of all the two products showed they are identical. The solvent-free synthesis in this context is simple, fast, and clean. The first crystal structure

of tetrachlorocadmate compound of amodiaquine **2b** was reported. Compound **1a** demonstrated to be more effective than pure amodiaquine, while its ability in malaria parasite clearance was comparable with that of chloroquine. The result indicates that incorporation of cobalt into amodiaquine by mechanical induction improved its antimalarial activity. The amodiaquine–cobalt compound may have exchanged its bound cobalt for ferric ions rendering the iron to be unavailable for vital parasite functions.

Supporting information

CCDC 956880 contains the crystallographic data for the structure reported in this paper and has been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail for deposition: deposit@ccdc.cam.ac.uk).

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