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Metal-Atovaquone Complexes: Synthesis, Characterization, Inhibition of β-Hematin Formation, DNA Interaction, and Antimalarial Activity.

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The complexes $[Zn(ATV)_2(H_2O)_2]$ **(1)**, $[Zn(ATV)_2(CH_3OH)_2]\cdot H_2O$ **(2)** and $[Zn(ATV)_2]n$ **(3)** were synthesized by coordinating the antimalarial atovaquone (ATV) with the precursors $Zn(OAc)_2\cdot 2H_2O$ and $ZnCl_2.2H_2O$, respectively. These coordination compounds **(1-3)** were fully characterized in the solid state and in solution using various analytical and spectroscopic techniques. X-ray diffraction precisely confirmed the coordination mode of ATV to the metal, which can be mono or bidentate, depending on the metal center[1-2]. Notably, both coordination modes showed high stability in both solid and solution states. Regarding lipophilicity, the complexes exhibited negative logD values at pH 5 (**table 1**), while at neutral pH (7.4) the logD values were positive except for ATV and compound **(2)**, indicating a more hydrophilic character for this compound. These zinc-ATV complexes interact with ferriprotoporphyrin (FePPIX) in a manner similar to chloroquine (CQ)[3] (**table 1**). Additionally, the compound-DNA interaction constant (Kb) was determined using the neighbor-exclusion method, revealing that all synthesized metal complexes had interaction constants higher than the order of 10^3 (**table 1**), indicating a strong reversible interaction with DNA[3]. Molecular docking analysis reveals that complexes **1**-**3** bind to DNA through the major groove, while ATV and CQ bind through semi-intercalation with the minor groove. The most favorable binding poses of the metal complexes suggest a potential ligand exchange reaction, resulting in the coordination of the base pairs (Guanine) to Zn. The antimalarial activity assessment showed that these metal complexes could inhibit the growth of *P. falciparum* parasites with potency and selectivity comparable to ATV. These results provide significant insights into the synthesis of new biologically active metal complexes.

Table 1: Experimental Data for the Compounds

Compound	Lipophilicity LogD		Interaction with FePPIX	Interaction with DNA	*P. falciparum*, IC_{50} (±S.E.M) nM		Mammalian cells CC_{50} (± S.E.M) µM	
	pH 5	pH7	LogK	Kb	3D7	W2	J774	HepG2
CQ	-1.25	0.98	4.78 ± 0.01	8.57E+05	23.8± 5,5	526±126	50.5±8.9	~ 80
ATV	-1.17	-1.15	3.64 ± 0.10	1.47E+04	2.4 ± 1.2	2.1 ± 0.9	19.8±1.6	32.4±4.8
(1)	-2.62	0.28	4.14 ± 0.02	3.09E+05	9.2 ± 5.1	7.1 ± 2.1	5.5±1.1	14.0±1.6
(2)	-0.71	-1.05	4.68 ± 0.02	9.39E+04	7.6 ± 3.3	8.2 ± 1.6	18.1±1.2	34.2±2.0
(3)	-4.32	1.27	4.49 ± 0.02	3.09E+04	11.4± 3.4	14.6±4.1	-	-

*Estimated Free Energy of Binding in kcal/mol using molecular docking.

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