Antimalarial activity of 3-alkylpyridine alkaloid analogues: molecular modeling and interaction studies of inhibiting haemozoin formation.

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Introduction

During the erythrocytic cycle, *Plasmodium falciparum* (*Pf*) consumes, inside its digestive vacuole (DV), great amounts of haemoglobin as a source of amino acids. As result of haemoglobin digestion, haeme group is released as Fe^{3+}-protoporphyrin IX (Fe^{3+}-PIX), a compound toxic to parasite. *Pf* induces haemepolimerization converting dimers of Fe^{3+}-PIX into crystals (haemozoin) as a strategy to protect itself. The mode of action of many antimalarial drugs, including chloroquine, is related to a direct interference on the haemoglobin metabolism. Despite the emergence and subsequent spread of resistance to therapeutic arsenal employed against malaria parasites, haemepolimerization continues an attractive target for antimalarial development. In recent years, our research group has investigated the synthesis and antimalarial activity of 3-alkylpyridine marine alkaloid analogues (3-APA)[1]. In order to investigate a possible mechanism of action for this class of compounds preliminary data on interactions between Fe^{3+}-PIX and two active 3-APA were determined by molecular modeling and UV-Vis.

Results and Discussion

3-APA analogs **TEOC-5b** and **10b** are represented in Figure 1.

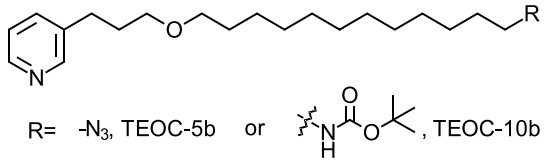

Figure 1. 3-APA synthesized analogs **TEOC-5b** and **10b**.

Both compounds were active against *Pf in vitro* and presented high selective index (SI) (Table 1). In order to investigate the parasite target, UV-Visible titration experiments for both compounds and Fe^{3+}-PIX were performed. In both cases, they clearly indicated a complex formation between the synthetic molecules and Fe^{3+}-PIX, by a change in the absorbance spectra, which presented a pattern of a saturation binding curve when **TEOC-5b** and **10b** were added to a solution containing the Fe^{3+}-PIX group.

Table 1. *In vitro* antimalarial and cytotoxic activity of two 3-APA analogues and Binding Energy (ΔE) calculated for the 2:1 ratio (2 Fe^{3+}-PIX + 1 analogue) by DFT level of theory.

Compounds	IC_{50} (μM) ± SD[a]			ΔE (kcal.mol$^{-1)}$
	Pf	WI-26VA4[b]	SI[c]	
TEOC-5b	4.3 ± 0.87	45.5 ± 2.7	10.6	-59,0
TEOC-10b	<4.8	46.8 ± 4.6	>9.7	-56,3
Chloroquine	0.6 ± 0.003	>100	>166	ND[d]

(a) average ± standard deviation; (b) fibroblast human cell line; (c) Selective Index = IC_{50}WI-26VA4 / IC_{50}*Pf*;(d)ND: Not Determined.

A molecular modeling based on DFT calculations was also performed in order to investigate the interaction between the APA-analogues with Fe^{3+}-PIX. The molecular modeling showed that, indeed, an effective chemical interaction occurs between the 3-APA analogues and haeme groups, leading to the formation of 1 to 2 stable complexes, as can be seen by the ΔE values in Table 1. In Figure 2 is shown the optimized geometry for the [**TEOC-5b**…Fe^{3+}-PIX] complex.

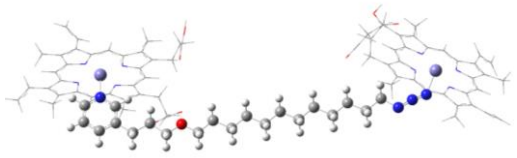

Figure 2. DFT optimized geometry for [**TEOC-5b**…Fe^{3+}-PIX].

Conclusions

The preliminary data indicate that **TEOC-5b** and **10b** interacts with Fe^{3+}-PIX, a classical antimalarial target.

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[1]Hilário, *et. al. Chem. Biol. Drug Des.*, **2011**, *78, 477.*