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ABSTRACT BOOK

NEW HYDROPHILIC RIMINOPHENAZINES AS POTENT ANTIPROTOZOAL AGENTS

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Malaria and leishmaniasis are life-threatening human parasitosis caused by protozoa-infected insect vectors. In most of affected countries, the expansive and hazardous therapies available to fight protozoan infections are generally harmed by the spread of drug resistance phenomena upon prolonged treatments. This scenario highlights the need of novel antiprotozoal agents hopefully able to act trough new mechanism(s) of action.

Interestingly, the fat-soluble antimycobacterial drug Clofazimine (**Figure 1**) was reported to exhibit a moderate antiprotozoal action and some interesting antileishmanial *in vitro* and *in vivo* effects were reported in few preliminary, yet promising, studies.[1,4]

Intrigued by these results, we have previously prepared a series of basic Clofazimine analogues which demonstrated the beneficial effects of the introduction of a basic head on the antiprotozoal activity.[5] Here, to further investigate the role of balancing between the lipo- and hydrophilicity on the antiparasitic activity of these riminophenazines, we report the synthesis and the *in vitro* evaluation as leishmanicidal (*L. tropica* and *L. infantum* promastigotes) and antiplasmodial (chloroquine sensitive and resistant *P. falciparum* strains) agents of a family of hydrophilic C-2 aminopyridinyl substituted riminophenazines, bearing in C-3 differently decorated basic side chains (**Figure 1**).

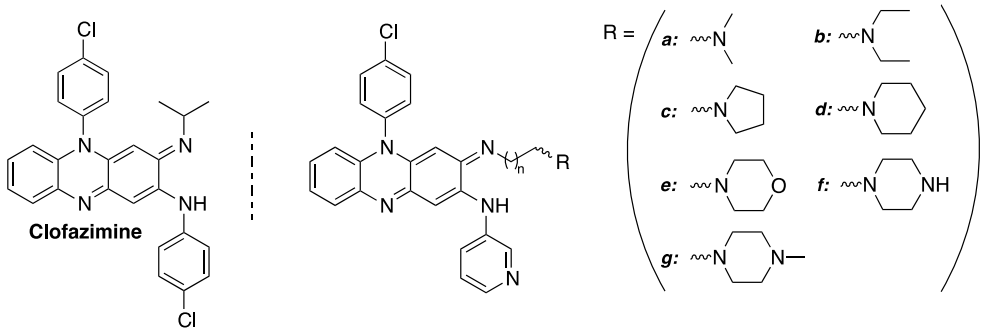

Figure 1: Structures of Clofazimine and C-2 aminopyridine substituted riminophenazine analogues.

Results showed that most of the new compounds potently inhibited the growth of protozoa with IC_{50} in the high nanomolar range and underlined the key role of the hydrophilic C-2 aminopyridinyl moiety to improve the leishmanicidal activity. In addition, the length and the nature of the basic side chain differently influenced the antiprotozoal activity and the selectivity index versus mammalian cells, providing useful information for further structural optimizations.

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