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## Pyrazolylpyrazolines: Design, Synthesis and Biological Evaluation as Dual Acting Antimalarial-Antileishmanial Agents

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Abstract: Malaria and leishmaniasis have emerged as serious universal health problems throughout history of mankind. According to the WHO 2008 malarial report, half of the world population is at risk of malarial infection with an estimate of 1 million deaths occurring annually mainly in the African region. Furthermore, 12-15 million people are infected with Leishmaniasis worldwide. Despite the continuous introduction of a large number of agents for the treatment of malaria, there is still unmet medical needs due to the emergence of resistance. Resistance has occurred for almost all therapeutic agents approved for the treatment of malaria. Accordingly, it was the aim of this work to design and synthesis a group of antimalarialantileshmanial agents that would show inhibitory activity against chloroquine-resistant strain of Plasmodium falciparum. The synthesized compounds were designed to contain a pyrazolylpyrazoline moiety having an aromatic group (p-tolyl or pchlorophenyl) at N1-position of one pyrazoline ring due to the reports of promising activities of such compounds. A formyl or acyl substituent was introduced at the N1-position of the other pyrazoline ring, to investigate the effect of bulkiness of acyl substituents at this position. The synthesized compounds were evaluated for their in-vivo antimalarial activity against Plasmodium berghei infected mice at dose levels of 20 and 30 mg/Kg, the two most active compounds were evaluated for their antimalarial activity against chloroquin-resistant strain (RKL9) of Plasmodium falciparum. In addition, the synthesized compounds were tested for their in-vitro antileshmanial activity against Leishmania aethiopica promastigotes and amastigotes. For both antimalarial and antileishmanial activities, compounds having an N1-p-tolyl group at the first pyrazoline ring did not require bulkiness at the second pyrazoline ring nitrogen where the compound bearing an acetyl group proved to be the most active of the whole series. On the other hand, bulkiness at the N1-position of the second pyazoline ring was necessary in case of compounds carrying the p-chlorophenyl group, where the two derivatives having an N1-butanoyl and an N1-benzoyl moieties at the second pyrazoline showed the best activity. Furthermore, the toxicity of the active compounds were tested and were proved to be non-toxic at 125, 250 and 500 mg/Kg. In addition, docking of the most active compound (having a p-tolyl group at the first pyrazoline-N and an acetyl moiety on the other pyrazoline-N) was performed against dihydrofolate reductase enzyme.

Keywords: pyrazoline derivatives, in-vivo antimalarial activity, docking, dihydrofolate reductase

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