DISCOVERY OF NOVEL ANTI-MALARIAL AGENTS: 1-[(ARYL)(4-ARYL-1*H*-PYRROL-3-YL)METHYL]-1*H*-IMIDAZOLES TARGETED TO FARNESYL TRANSFERASE

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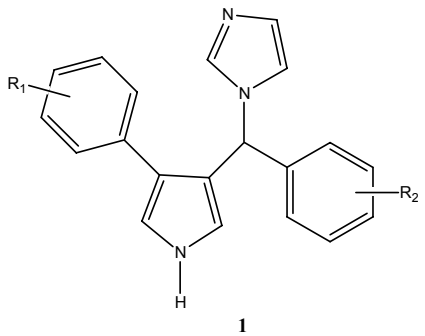
Malaria is one of the most important infectious diseases that causes about 500 million clinical cases resulting in over one million deaths annually, especially small children in disease endemic countries. The fatal cases are generally caused by the most virulent human malaria parasite *Plasmodium falciparum*. Current clinical treatment involves the use of antifolates and the quinoline-containing drugs. The antifolates include diaminopyrimidines (such as pyrimethamine, trimethoprim), the biguanides of which proguanil is a representative, and sulfa drugs, namely sulfonamides and sulfones. The quinoline-containing drugs are represented by quinine, aryl aminoalcohols related to quinine such as mefloquine, 4-aminoquinolines (such as chloroquine), and 8-aminoquinolines like primaquine. These drugs are currently failing at an accelerating rate in most malaria-endemic regions, with consequent increases in malaria-related morbidity and mortality. Therefore, to combat malaria new drugs are needed. Other malaria control efforts have focused on new drug targets such as isoprenoid biosynthetic pathway inhibitors. Pursuing our decennial studies on azole derivatives as chemotherapeutic agents [1-3], we discovered the inhibitory activity against the enzyme farnesyl transferase (FT) of a series of 1-[(aryl)(4-aryl-1*H*-pyrrol-3-yl)methyl]-1*H*-imidazoles **1**. Derivatives **1** showed anti-*Plasmodium falciparum* activity at micromolar concentrations. SAR studies of these new antimalarials targeted to FT will be reported.



1

R_1 = H, alkyl, aryl
R_2 = H, F, Cl,

[1] Artico, R. Di Santo, R. Costi, et al. *J. Med. Chem.* **1995**, *38*, 4223.
[2] A. Tafi, M. Artico, R. Costi, R. Di Santo, et al *J. Med. Chem.* **1996**, *39*, 1227.
[3] A. Tafi, R. Costi, M. Botta, R. Di Santo, et al. *J. Med. Chem.* **2002,** *45*, 2720.