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# In search of next generation antimalarials

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ABSTRACT

Compounds **7**–**10** displayed potency without any apparent toxicity, in animal models of both relapsing and non-relapsing forms of malaria offering hope of a single molecule that can cure both relapsing and non relapsing forms of malaria.



Malaria remains a global scourge. According to the latest report (December, 2013) from World Health Organization (WHO), an estimated 3.4 billion people are at risk of malaria, of whom 1.2 billion are at high risk.[1] Malaria killed an estimated half-a-million children less than 5 years of age in the year 2012, equivalent to one child almost every minute. Though eradicated from most of the western hemisphere, it remains rampant in parts of Asia and sub-Saharan Africa. The toll of the disease on the socio-economy of the affected regions is staggering.

Malaria is a mosquito-borne illness.[2] The disease is caused by protozoan parasites of the genus *Plasmodium*. There are various species of the parasite pathogenic to human, of which *Plasmodium vivax* (benign tertian malaria) and *Plasmodium falciparum* (malignant tertian malaria) together cause majority of the cases. If left untreated, the recurring symptoms of benign malaria include high fever, chills, sweats, headaches, nausea and vomiting. In malignant case, the patient ultimately succumbs to death.[2] While quinine, a natural product had been the drug of choice for the treatment of the disease from the ancient time, the treatment of the various forms of the disease, in modern times, relied heavily on quinoline based synthetic molecules, for example, primaquine (compound **1**), chloroquine (compound **2**) and mefloquine (compound **3**) (Fig. 1), to name a few. In recent years, a natural product artemisinin (compound **4**, Fig. 2) and its synthetic analogs emerged as a new generation of antimalarials from an entirely different chemical class. However over time, the parasite developed resistance to each of this drug making their future use in peril. Thus the discovery of new generations of antimalarials remains an ongoing urgent endeavor.[3]

While the efforts to uncover new chemical classes of antimalarials have been ongoing,[4] various groups have been attempting to modify the established drugs also.[5] In the past, a promising series based on compound **1**, with modification at sites 4 and 5 of the quinoline nucleus, that culminated in compound **5** (Fig. 3) was reported from our laboratories.[6] Compound **5** displayed potency in animal models of both relapsing and non-relapsing forms of malaria. However, at increasing higher doses in the mouse model, increasing number of deaths in the treated animals was also observed (*vide infra*). This raised the issue of any unforeseen toxicity in a clinical setting. Thus efforts continued to modify the series by annexing an aryl or a heteroaryl moiety at the terminus of the 5-alkoxy chain of compound **5** to generate a next generation series represented by compounds **6**–**14** (Fig. 3 and Scheme 1). Herein, we report our current progress from this additional effort.

In step A (Scheme 1) an appropriate lithium aryl/heteroaryl reagent, compound **15** was reacted with the dibromo agent **16** to generate compound **17**. In step B, compound **18**[7] was coupled with newly generated compound **17** to produce compound **19**. The nitro group in compound **19** was reduced to generate corresponding 8-amino derivative **20** that was condensed with 4-bromo-1-phthalimidopentane producing compound **21**. The phthalimido group in compound **21** was subsequently removed by hydrazine and the

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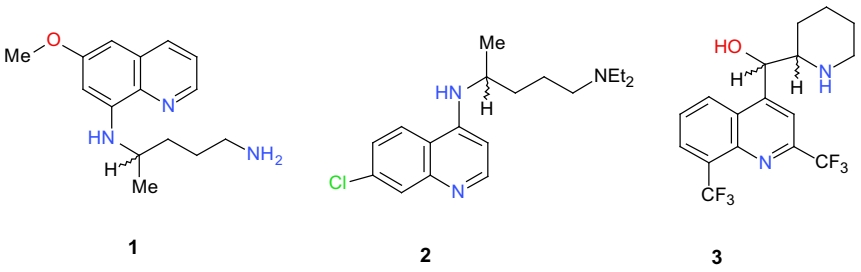


**Figure 1.** Structures of compounds **1**–**3**.

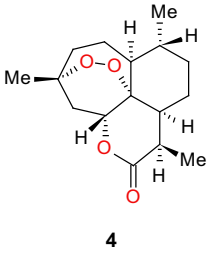


**Figure 2.** Structure of compound **4**.

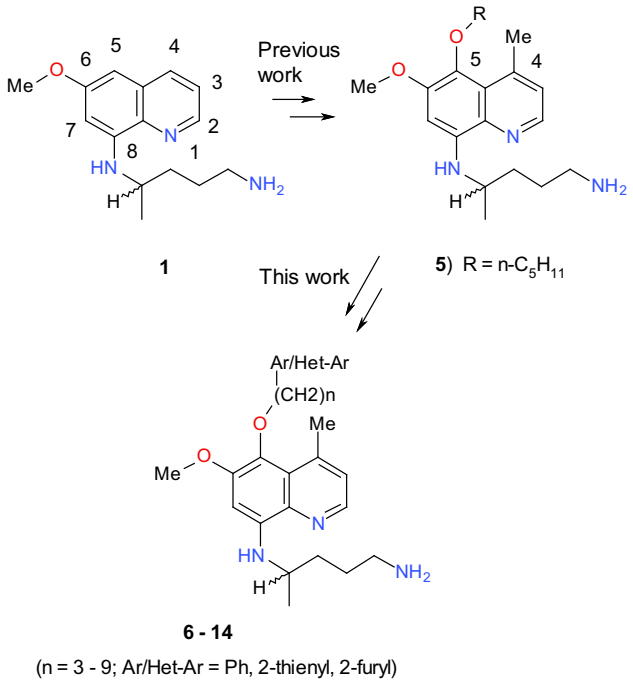


**Figure 3.** Evolution of current series.

free bases were converted to corresponding fumarate salt generating compounds **6**–**14** (Scheme 1).

Malaria parasites undergo a complex life cycle.[2] Thus, various in vivo protocols had been developed to assess the antimalarial efficacy of a compound at specified stages in the life cycle. Accordingly, the target compounds were initially profiled in the suppressive, blood schizonticidal test (trophozoite-induced *Plasmodium berghei* infection in mice).[8] Results are displayed in Table 1.

As shown in Table 1, in mouse model the parent compound **5** displayed potency at the low dose of 5 mg/kg maintaining it up to 40 mg/kg. However, starting at a dose of 80 mg/kg and upwards, the toxicity of the compound became apparent. In the current series, the initial compound **6** displayed potency up to a dose of 80 mg/kg, but at a dose of 160 mg/kg and upwards, it offered the hint of toxicity. Increment of the length of the alkoxy chain by one carbon atom in compound **7** revealed the attenuation of toxicity. This raised the anticipation that lengthening of the chain might be beneficial. This was borne out in compounds **8**–**12** when compounds maintained their potency without displaying any inherent toxicity up to a dose of 640 mg/kg (cf. compound **5** that displayed death in animals at a dose of 80 mg/kg). In order to extend the scope of the investigation, the terminal phenyl group in compound **8** was replaced by heterocyclic 2-thienyl and 2-furyl groups to generate compounds **13** and **14**, respectively. Though both compounds displayed potency, compound **14** revealed some toxicity at the highest level of dosing.

A set of selected compounds were also profiled (Table 2) in the radical curative tissue schizonticidal test (sporozite-induced *Plasmodium cyanomolgi* infection in rhesus monkey).[9]

In the rhesus monkey model (Table 2), compounds **6**–**10** displayed similar pattern of potency to that of the parent compound **5** over a range of doses confirming that the addition of the terminal phenyl group maintains the potency of the series without bringing any undue toxicity in a higher species. Thus, based on their behavior in both animal models, compounds **7**–**10** remained under active investigation.

In conclusion, in this *Letter*, we offered a brief account from our search for a next generation of antimalarials. Several members of the current series displayed potency in animal models of both relapsing and non-relapsing forms of malaria without any associated toxicity offering the hope of the possibility of a single molecule that can cure both relapsing and non relapsing forms of malaria. Recent work involves the exploration of the effect of various substituents on both aryl and hetero-aryl moieties on activity of the series.[10]

*Note added in the proof:* While this manuscript was under review, Professor François H. Nosten (Oxford University, UK) offered an alternate unique strategy to eradicate the disease in an affected region in a recent commentary.[11]

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