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Synthesis of novel triazole-linked mefloquine derivatives: Biological evaluation against *Plasmodium falciparum*

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ABSTRACT

Using 2,8-*bis*(trifluoromethyl)quinoline, the pharmacophore of mefloquine, as scaffold, eleven novel triazole-linked compounds have been synthesised by the application of CuAAC chemistry. The *in vitro* biological activity of the compounds on the *Plasmodium falciparum* chloroquine-sensitive strain NF54 was then determined. The compounds all showed IC_{50}s in the lower μM range with (1*R*,3*S*,5*R*)-*N*-{[1-(2,8-*bis*(trifluoromethyl)quinoline-4-yl)-1*H*-1,2,3-triazol-4-yl]methyl}adamantan-2-amine (**29**) exhibiting the best activity of 1.00 μM.

Since the 1940s, the development of synthetic antimalarial drugs has played a vital role in the control and treatment of malaria. However, the widespread use of antimalarials has caused the spread of resistant *Plasmodium falciparum* parasites which has resulted in an increased malaria morbidity and mortality.[1] To highlight the extent of the problem, between 200 to 500 million malaria related cases occur annually, with an estimated 1.7 to 3 million deaths the vast majority of whom are children.[2] For decades, the general treatment of malaria depended on chloroquine (**1**), a 4-aminoquinoline analogue that is known for its rapid efficacy, ready availability, low toxicity and affordability.[3] After the discovery of chloroquine, a number of quinoline derivatives such as amodiaquine (**2**), primaquine (**3**) and mefloquine (**4**) emerged (Fig.1).

The understanding of the mode of action of quinoline-based antimalarials has advanced in the recent years, but remains incomplete. The quinolines are known to inhibit heme aggregation and prevent the formation of hemozoin. This leads to intraparasitic accumulation of free heme that is toxic to the parasite.[4]

Mefloquine has a high inhibitory activity against chloroquine-resistant *P. falciparum* and is currently one of the drugs used to treat chloroquine-resistant malaria. Unfortunately, the use of mefloquine is usually associated with neuropsychiatric side effects.[5] The development of novel *bis*(trifluoromethyl)quinoline analogues may thus provide a fruitful avenue for further exploration.[6]

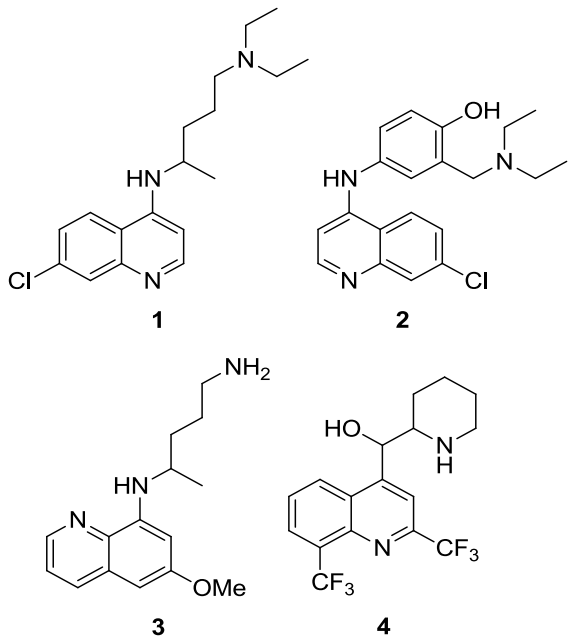

Figure 1: Structures of the early antimalarials

One of the attractive options to use in medicinal chemistry is the use of 1,2,3-triazole functional group as a structural feature.[7-10] This functional group can be incorporated by means of well-defined copper-catalyzed azide-alkyne cyclization (CuAAC) methods,[11, 12] and facilitates the introduction of structural