Health

Development of a synthetic route towards N^4,N^9-disubstituted 4,9-diaminoacridines: On the way to multi-stage antimalarials

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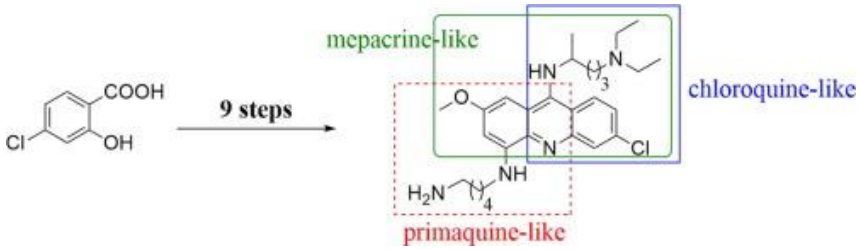
Malaria is one of the deadliest infectious diseases in the world and was responsible for 435 000 deaths in 2017, namely by *Plasmodium falciparum* species.[1] Antimalarial drugs are the unique weapon to fight this disease once there is no vaccine yet. Generally antimalarial chemotherapy targets mainly the pathogenic blood stage in humans. However, there is an urgent need of new, economic and safe drugs in order to: (i) block parasite transmission to the vectors, (ii) target parasite forms that, for some species, remain transiently dormant in the liver, and (iii) overcome the resistance against artemisinin-based treatments emerging in some vulnerable population in Africa. Consequently, malaria eradication is only possible with the discovery of new multi-targets drugs.[2] Mepacrine (MP, **Scheme 1**), the first synthetic antimalarial drug, was widely employed but it was rapidly superseded by chloroquine (CQ, **Scheme 1**), whose efficiency, bioavailability, and safety were far superior. By "dissecting" the chemical structure of QN, the acridine moiety of MP can be seen as the fusion between CQ and the heterocycle core of primaquine (PQ, **Scheme 1**), another emblematic antimalarial, active against all liver forms of the parasite, and gametocytes. In this context, and based on the fact that one fast and low-cost strategy to accelerate antimalarials development is to recycle classical pharmacophores, the aim of this work is the development a yet unexplored multi-step synthetic route towards 4,9-diaminoacridines (**Scheme 1**).[2] These can be regarded as respectively corresponding to the fusion between CQ and PQ derivatives. As expected, the preliminary *in vitro* results showed that the new compounds preserved the activity of the parent drugs, with activity against blood-stage, as in CQ, as well as against all liver forms and gametocytes, similarly to PQ.



Scheme 1: Schematic representation of the synthesis of the target compound.

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References:

1. World Health Organization, *World Malaria Report*, **2017**. 2. Teixeira, C. et al. *Chem Rev.* **2014**, *114*, 11164-11220. 3. Fonte, M. et al. *Tetrahedron Lett.*, **2019**, *60*, 1166-1169.