Development of nature inspired antiplasmodial hits possessing the thiazinoquinone pharmacophore

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Malaria accounts globally for more than 200 million new cases and 438,000 deaths per year. Since malaria is a disease of worldwide implications, combating it is one of the highest priority programs of the WHO. A worrisome increase in the number of fatal cases has been registered in recent years and it is principally due to the diffusion of multi-drug resistant strains of Plasmodium, making less effective the limited armamentarium of available drugs.[1] Therefore, there is an urgent need of new antimalarial drugs with high efficacy against resistant strains and broad stage mode of action. To reach these challenging aims, the identification and selection of new lead compounds constitutes a crucial point. In this regard, nature remains an ever evolving resource. Recently, the antiplasmodial activity of marine secondary metabolites characterized by a quinone scaffold has been reported.[2] In particular, it is worth to point out that a number of quinones have been shown to be effective antimalarials. The observed effects are most likely related to the most prominent chemical feature of these kind of molecules, that is their ability to undergo redox reaction i) shuttling electrons from reduced flavoproteins to acceptors such as hemoglobin-associated or free Fe(III)-protoporphyrin IX or ii) inhibiting the mitochondrial electron transport chain. In this context, recently, we were inspired by two marine metabolites Aplidinone A and B (figure 1) isolated from the Mediterranean ascidian *Aplidium conicum,*[3] and we developed a series of synthetic analogues featuring the thiazinoquinone chemotype present in the natural metabolites with simplified side chains and different substituents. Manipulation of this chemical scaffold afforded additional analogues with improved pharmacological proprieties compared to the starting hits identified in the previous series (figure 1).

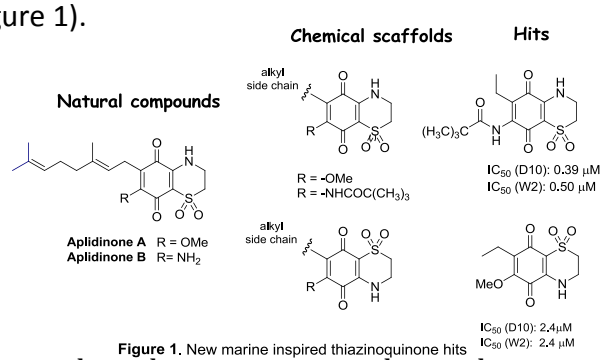

Figure 1. New marine inspired thiazinoquinone hits

Keywords: bioactive natural products, quinones, electrochemistry, reactive radical species, cytotoxic activity.

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