Tetrazole-based deoxyamodiaquines: Synthesis, ADME/PK profiling and pharmacological evaluation as potential antimalarial agents

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Abstract

A series of new deoxyamodiaquine-based compounds was synthesized via the modified TMSN3-Ugi multi-component reaction and evaluated in vitro for antiplasmodial activity. The most potent compounds, **6b**, **6c** and **6j**, showed IC50 values in the range of 6–77 nM against chloroquine-resistant K1- and W2-strains of Plasmodium falciparum. In vitro ADME characterization of frontrunner compounds **6b** and **6c** indicates that these two compounds are rapidly metabolized and have a high clearance rate in human and rat liver microsomes. This result correlated well with an in vivo pharmacokinetics study, which showed low bioavailability of **6c** in rats. Tentative metabolite identification was determined by LC–MS and suggested metabolic lability of groups attached to the tertiary nitrogen. Preliminary studies on **6b** and **6c** suggested strong inhibitory activity against the major CYP450 enzymes. In silico docking studies were used to rationalize strong inhibition of CYP3A4 by **6c**. Full characterization and biological evaluation of the metabolites is currently underway in our laboratories.

Graphical abstract