Abstract

HYBRIDS OF (2R, 3S)-N-BENZOYL-3-PHENYLISOSERINE AND ANTIMALARIAL PHARMACOPHORES: DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION

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Tubulin is an essential protein in all eukaryotic cells, and a well known anticancer and anthelmintic drug target1. It is a major structural component of microtubules. Microtubules are necessary organelles involved in cell division, maintenance of cell shape and integrity, and intracellular trafficking. Previous studies have shown that taxanes possess high antiplasmodial potency by disrupting microtubular structures of intraerythrocytic plasmodia.
Paclitaxel, a prototypical taxane, comprises two major pharmacophoric groups: the diterpenoid baccatin nucleus which forms the core of the molecule, and the (2R,3S)-N-benzoyl-3-phenylisoserine side chain attached via an ester bond at carbon 13 of the diterpene moiety.

Previous studies indicate that both the (2R,3S)-N-benzoyl-3-phenylisoserine and the baccatin nucleus are essential for the antimicrotubular and anticancer activity of paclitaxel, whereas individually they are devoid of any appreciable activity3. This suggests that the side chain plays a critical role in the pharmacology of taxanes. We hypothesized that the contribution of (2R,3S)-N-benzoyl-3- phenylisoserine to the anticancer activity of paclitaxel can be replicated when hybridized with antimalarial scaffolds.
Drug hybridization is a commonly used and successful drug discovery practice in which two or more pharmacophores are hybridized into one molecule with superior pharmacology. In the present work, molecular hybrids of (2R,3S)- N-benzoyl-3-phenylisoserine with antimalarial scaffolds were designed, synthesized and evaluated for their in vitro antiplasmodial activities. The results of this work will be presented and discussed.