Synthesis of Biologically Active Phosphorus Heterocycles

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Abstract
This dissertation work is divided into two parts. The first part is focused in the development of methodology for the synthesis of phostones and phosphonosugars and advancement thereof. The second part is focused in the development of affinity probes based the analogs of the natural product cyclophostin and the cyclipostins.

Phostone (3) and phosphonosugars are cyclic phosphonates. The anomeric carbon of sugar is replaced by the phosphorus atom. The synthesis of phostones has been achieved starting form the key intermediate γ, δ- epoxy vinyl phosphonate (1). The palladium catalyzed ring opening of γ, δ- epoxy vinyl phosphonates by a nucleophile results in the formation of δ-hydroxy phosphonates (2), which on further reduction and cyclization yields phostones (3). Various primary alcohols have been used as the nucleophile for the opening of γ, δ- epoxy vinyl phosphonate (1).

The synthesized phostones have been further functionalized and submitted to test their potency as LPS antagonist. Sugar-based methylene phosphonates have been prepared and tested as well.

Cyclophostin (4) and the cyclipostins (5) are bicyclic organophosphates. From previous study analogs of cyclophostin (4) and the cyclipostins (5) have shown to inhibit the growth of Mycobacterium tuberculosis either in infected macrophage or in the broth medium. This suggests that these analogs could represent class of multi-target inhibitors. To assist in the study of the mode of action and target identification of the analogs, two series of compounds were synthesized as the affinity probes. The synthesized compounds were submitted to study the activity against Mycobacterium tuberculosis.

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