Synthesis and properties of a cholesterol targeting mycobactericidal drug

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Mycobacterial cells are enclosed by a complex lipid rich-cell wall containing mycolic acids amongst other membrane components. Antigenic cross-reactivity between mycolic acid and cholesterol suggest a possible mimicry between these molecules. This observation created new opportunities for Tuberculosis (TB) drug development in order to combat multi-drug resistance and latent infection of *Mycobacterium tuberculosis*. It has been shown that a combination of a cell wall synthesis inhibitor with a membrane active drug increases the efficiency of the therapy against *Candida*. Various cholesterol binding drugs could be utilized in the treatment of mycobacterial infections to target mycolic acids on the cell wall. Thus a cholesterol binding drug such as Amphotericin B (AmB)-a membrane porator- linked to Isoniazid (INH) -a mycobacterial cell wall synthesis inhibitor- may improve the efficiency of the latter dramatically.

In preliminary studies, the chemical synthesis of a hybrid molecule via a non-covalent construct, of AmB (as haptophore) and INH as (toxophore) did not provide reproducible results. In this study AmB and INH were covalently linked by Schiff base formation using terephthalaldehyde as linker molecule. Further experiments showed that the Schiff base was rapidly hydrolysed in aqueous environments which made the compound unsuitable for biological testing. Reduction of the Schiff base to the substituted amine increased the stability of the molecule and made it suitable for testing. Preliminary characterization of the functional properties of the INH-AMB conjugate will be reported and may include: Binding to cholesterol and mycolic acids and in vitro testing of Mycobacterium Tuberculosis cell cultures.