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Abstract

Development of new drugs to treat tuberculosis based on the dinitrobenzamide scaffold †

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Abstract: Despite the efforts made to stop the tuberculosis (TB) epidemic, it still remains one of the leading causes of death from an infectious disease. Previous work in the group uncovered a new family of amides which showed promising activities against *Mycobacterium tuberculosis*. A closer look at the literature showed that these compounds are structurally related to the DNB family of inhibitors of DprE1, an essential epimerase for the formation of a vital precursor of the arabinogalactan biosynthesis, one of the components of the mycobacterial cell wall. Following those results, we decided to study a wide range of substituted amides and determine their activity, focusing on unexplored structures related to the dinitrobenzamides (DNB) found in the literature. To synthesize our library of compounds we started from 3,5-dinitrobenzoic acid to form the nitroaromatic core that is characteristic of the DNB's, to which we then added linear or cyclic amine moieties. Additionally, the impact of terminal aromatic moieties was also assessed for some derivatives, via an ether, ester or amide bond. In order to obtain the desired derivatives, multiple synthetic approaches were used, mainly focused in nucleophilic addition/elimination reactions, S_N2 reactions and Mitsunobu reactions. The most interesting compounds exhibited activities in the 100-200 nM range, and we're currently developing an extended family of compounds based in those structures. Additionally, computational studies were performed aimed at further understanding their interactions with DprE1 and comparing it to known DNB's.

Keywords: Tuberculosis; DprE1; DNB; TB; Nitrobenzamides

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