Title: *In silico* evaluation of new isoniazid derivatives with antitubercular activities

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Tuberculosis (TB) is the infectious disease with the highest number of fatalities in the world and it is estimated that about a quarter of the world population is currently infected with TB [1]. The treatment of TB, in most cases, is based on isoniazid (INH), one of the two most effective compounds in the fight against the disease. However, resistance to INH has been increasing in a very worrying way and is mainly due to mutations in the catalase-peroxidase (KatG) enzyme that interfere with the activation of this prodrug. Several promising derivatives of INH have already been reported in the literature, and in particular, a derivative with a long alkyl chain (INH-C_{10}) proved to be more effective than INH for S315T, one of the most relevant mutations of Mycobacterium tuberculosis, the causative agent of TB [2]. From a combination of experimental and computational data, we found that INH-C_{10} compensates for a lower reactivity, compared to INH, with a significantly higher membrane permeability [3]. Recent attempts to conjugate the higher activity of INH with the better lipophilicity of $INHC_{10}$ were unsuccessful probably due to the instability of the resulting compound in water [4].

In this work, we propose a series of computational approaches to study the impact of derivatizing INH with different alkylating groups. We will evaluate the new compounds in terms of: (i) membrane permeability, where higher lipophilicity will be beneficial; (ii) propensity to spontaneously form the IN* radical, which is essential for the antitubercular activity; and (iii) the ability to reach the KatG heme site pocket, an important step in the enzyme-catalyzed process.

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[4] C. Faria, et al. *Biomed. Pharmacother.* (2022) 144, 112362.