Studies on the interactions of the enzyme InhA from *Mycobacterium tuberculosis* with small drug-like molecules

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**Background**

Enzymes involved in fatty acid biosynthesis are attractive targets for the design of new antibacterial agents [1]. In most bacteria, fatty acid biosynthesis is catalyzed by a set of distinct, monofunctional enzymes collectively known as type II Fatty Acid Synthase (FAS-II) [2]. They differ significantly from the type I FAS (FAS-I) in mammalians, in which all of the enzymatic activities are encoded in multifunctional polypeptides [3]. This distinctive difference in the FAS molecular organization makes possible the design of specific inhibitors of increased selectivity and lower toxicity. The *inhA* gene from *Mycobacterium tuberculosis* (Mt), encodes for an enoyl carrier protein reductase, InhA, a key enzyme of the mycobacterial fatty acid elongation cycle and has been validated as an effective target for the development of anti-microbial agents [4]. InhA catalyzes the NADH-dependent reduction of the trans double bond between positions C2 and C3 of fatty acyl substrates [5]. It is the target of isoniazid, a first line drug in the tuberculosis treatment. Mutations in InhA structural gene are associated with isoniazid resistance *in vivo*, and currently, five InhA mutations have been observed in clinical isolates of isoniazid-resistant Mt: I16T, I21V, I47T, V78A, I95P and S94A [6,7]. Even though mutations within the *inhA* gene are known to facilitate isoniazid resistance [6], InhA remains a good candidate for drug design because: (i) the vast majority of the mutations found in isoniazid-resistant clinical isolates are associated with the isoniazid activator (KatG catalase-peroxidase) [6]; (ii) only one enoyl-ACP reductase is found in Mt, unlike some of the other enzymes of bacterial FAS-II systems [6]; and (iii) the longer substrate chain length specificity of InhA distinguishes it from the enoyl-ACP reductases from other sources, such as the enoyl-ACP reductase component of the human FAS-I system [7].

**Objectives**

We aimed analyze in detail all 31 *Mt* InhA structures deposited in the Protein Data Bank (PDB) and also to develop and apply a virtual screening methodology for the identification of new lead compounds against Mtb InhA.

**Materials and methods**

We utilized public data banks of molecules, PDB [8], AutoDock 3.0.5 [9], ProgramQ [10].

**Results and Conclusions**

We report the identification of key features involved in Mtb InhA drug binding that may be crucial to the rational design of new antitubercular drugs having InhA as target. We also established an efficient Virtual Screening (VS) protocol that was able to identify a set of new potential InhA inhibitors.

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**References**


