
Isoniazid (INH) is still one of the two most effective antitubercular drugs and is included in all recommended multitherapeutic regimens. Because of the increasing resistance of Mycobacterium tuberculosis to INH, new INH-based compounds have been proposed to circumvent this problem. The KatG enzyme is known to activate INH, leading to a potent antitubercular drug. The S315T enzyme mutant is very common and interferes with this “drug production” process. In this work, we present a detailed comparative molecular study of the interactions between the normal enzyme or its S315T mutant form and either INH or INH-C10, a new acylated INH derivative. Our results indicate that the aliphatic tail in INH-C10 brings the compound closer to the active site. INH-C10 is able to counterbalance most of the conformational restrictions introduced by the mutation, which are thought to be responsible for the decrease in INH activity in the mutated strain. Therefore, INH-C10 appears to be a very promising lead compound and a new hope against tuberculosis.