## *Abstract*

**Inhibitors against Mycobacterial Fatty Acid Synthesis Enzymes FabG4 and HtdX: Design, Synthesis and Biochemical Studies**

This thesis is a compilation of research work aimed towards: a) selection of FabG4 (Rv0242c) and HtdX (Rv0241c), two less explored β-ketoacyl-CoA reductase and β-hydroxyacyl-CoA dehydratase of *M. tuberculosis*, as anti-tuberculosis drug target; b) design, synthesis and characterization of novel inhibitors of FabG4 and c) design, synthesis and characterization of dual inhibitors against FabG4-HtdX pair.

Two new fatty acid synthesis enzymes FabG4 and HtdX have been selected as anti-tuberculosis drug targets. Interdisciplinary approaches consisting of crystal structure analysis of target enzymes, inhibitor design, organic synthesis and biochemical studies, have been utilized to provide novel 1,4-triazole linked polyphenol-gallol (**1-2, Figure 1**) and polyphenol-aminobenezne (**3-8**) hybrids as inhibitors of FabG4. Polypharmacology strategy has been adopted to obtain novel compounds (**9-11**) as dual inhibitors of FabG4 and HtdX. These inhibitors have potencies in low micromolar concentrations and showed good antimycobacterial activities (**Table 1**). This work is an important addition to tuberculosis drug discovery because it selects two new fatty acid synthesis enzymes as drug targets and presents their inhibitors as potential candidates for pre-clinical trials.


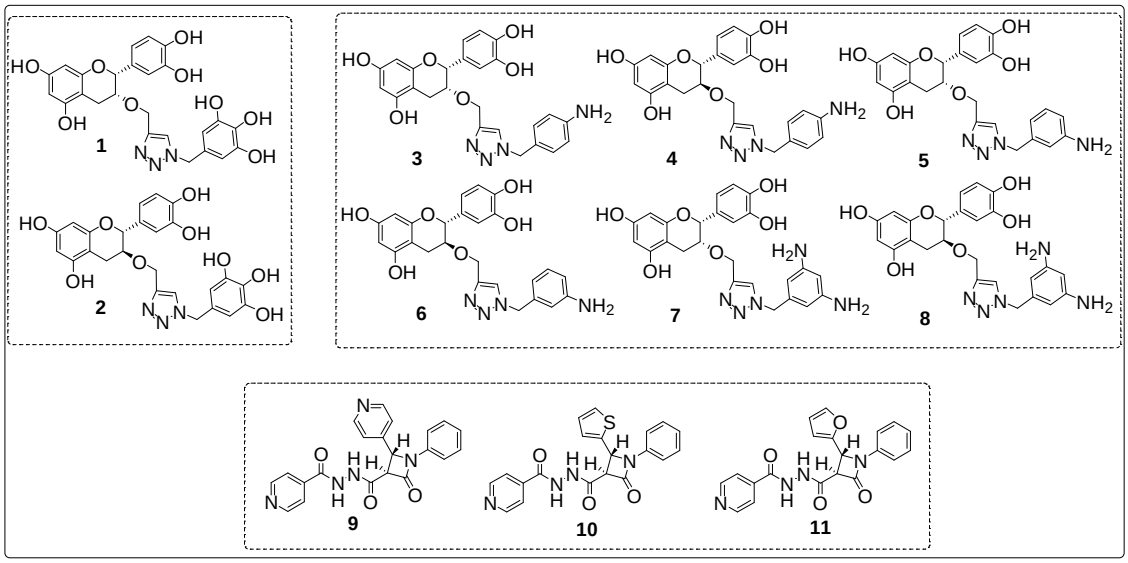


**Figure 1**

**Table 1**

| Compound number | $IC_{50}$ against FabG4 (in μM) | $IC_{50}$ against HtdX (in μM) | MIC against *M. smegmatis* (in μg/mL) | Compound number | $IC_{50}$ against FabG4 (in μM) | $IC_{50}$ against HtdX (in μM) | MIC against *M. smegmatis* (in μg/mL) |
|---|---|---|---|---|---|---|---|
| **1** | 44.7 | -- | 20 | **7** | 73.5 | -- | N.D. |
| **2** | 34.9 | -- | 5 | **8** | 61.6 | -- | N.D. |
| **3** | 73.2 | -- | N.D. | **9** | 15.2 | 22.3 | 15 |
| **4** | 59.3 | -- | N.D. | **10** | 26.1 | 10.3 | N.D. |
| **5** | 79.1 | -- | N.D. | **11** | 27.6 | 17.6 | N.D. |
| **6** | 58.7 | -- | N.D. | '--' = No inhibition; N.D. = Not determined | | | |


Key words: Tuberculosis, New targets, FabG4, HtdX, Inhibitor