Indole, Naphthalene and Triazolo-Quinoline Derivatives as Potent Inhibitors of MTB InhA - Virtual Screening

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Abstract:

Tuberculosis (TB), caused by Mycobacterium tuberculosis (MTB), is the ninth major cause of death worldwide surpassing HIV/AIDS. TB accounts for an estimated 1.7 million deaths reported in 2016. The emergence of multi-, extensively- and totally-drug resistant tuberculosis (MDR-, XDR-, TDR-TB), makes most of drugs in use today ineffective, which has created new challenges in the management of TB. Isoniazid (INH), the frontline anti-TB drug targeting enoyl-acyl carrier protein reductase (InhA) is the most prescribed drug for prophylaxis and TB treatment and together with rifampicin, form the pillars of current chemotherapy. A high percentage of INH resistance is linked to mutations in the pro-drug activating enzyme catalase-peroxidase (KatG), so the discovery of direct inhibitors of the InhA would be a promising approach for the identification of newer agents active against INH resistant TB. In this pursuit, structure based virtual screening of 2,94,847 molecules from ASINEX database against MTB InhA is performed using Glide HTVS, SP and XP docking methodologies of Schrodinger suite. A total of 70 compounds with the best binding energies (-8.54 to -10.19 kcal/mol) were then selected and screened for absorption, distribution, metabolism, excretion, and toxicity (ADMET) analysis. Twelve of those compounds containing Indole (binding energies from -9.67 to -10.14 kcal/mol), Naphthalene (binding energies from -9.32 to -9.62 kcal/mol) and Triazolo-Quinoline (binding energies from -8.91 to -9.49 kcal/mol) scaffolds (Figure 1) were found to satisfy all of the ADME and toxicity criteria and hydrogen bonding interaction with the Tyr158 which is considered as a key interaction residue of InhA enzyme. Thus the results of the present studies may provide a good starting point for the synthesis, evaluation and development of direct inhibitors of InhA, which are likely to be potent against MDR and XDR TB.

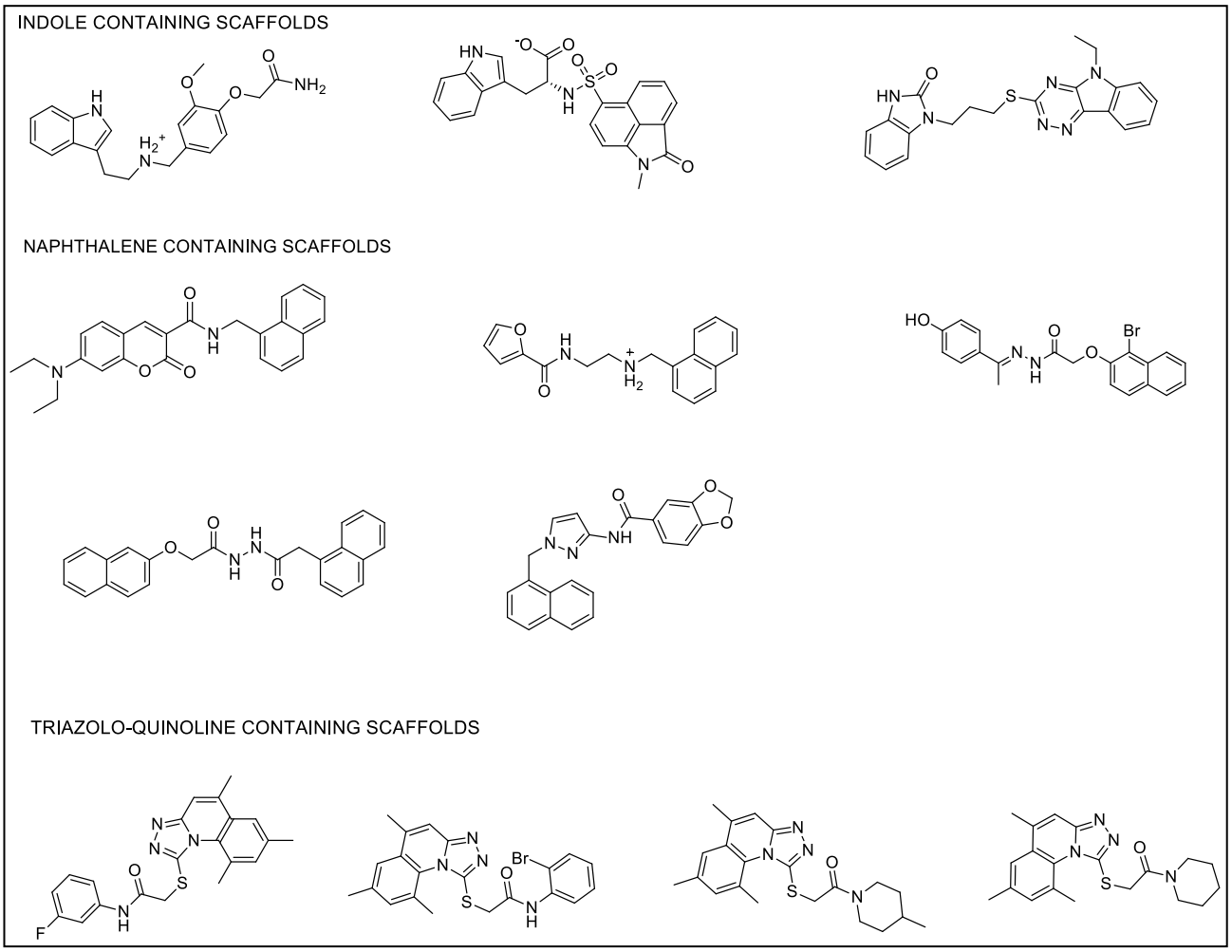

Figure 1: Structures of promising virtual hits obtained from Virtual screening

KEYWORDS

Tuberculosis, Mycobacteria, Enoyl-acyl carrier protein reductase, InhA, Isoniazid, Virtual screening