Insight into binding mode and crucial interaction of tetrahydropyran derivatives as potential InhA inhibitors using molecular docking calculations

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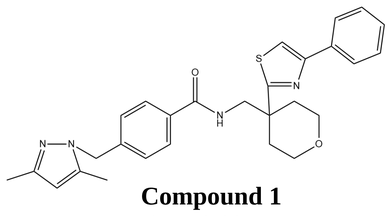
Introduction

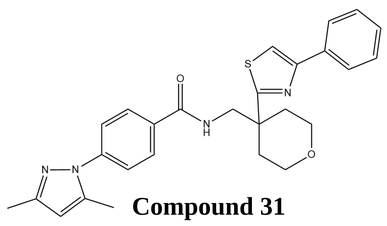
Tuberculosis (TB) remains a major global health problem, caused by *Mycobacterium tuberculosis (M. tuberculosis)*. Enoyl-ACP reductase or InhA is an attractive target responsible for biosynthesis of mycolic acid. Tetrahydropyran derivatives were selected to study because it is a classical substructure for glycomimetics inhibition of proteins and exhibits good InhA inhibitory potency. In this work, molecular docking calculations were applied to investigate binding mode and binding interactions of tetrahydropyran derivatives using Glide XP program.

Material and Methods

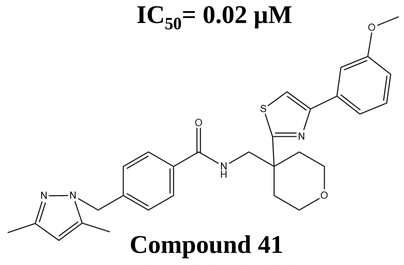
The structures of tetrahydropyran derivatives and their biological activity



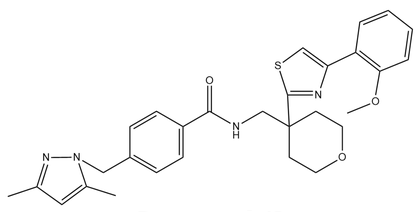
Compound 1
IC_{50}= 0.02 µM



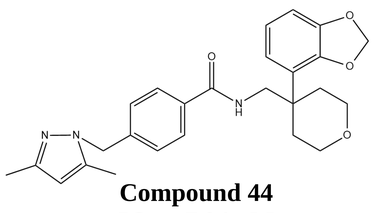
Compound 31
IC_{50}= >100 µM



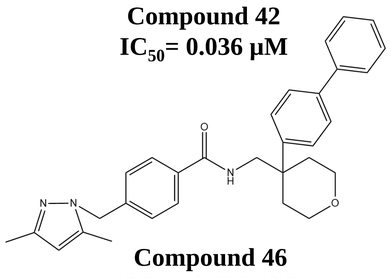
Compound 41
IC_{50}= 0.323 µM



Compound 42
IC_{50}= 0.036 µM



Compound 44
IC_{50}= 7.94 µM



Compound 46
IC_{50}= 0.029 µM

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Full optimized

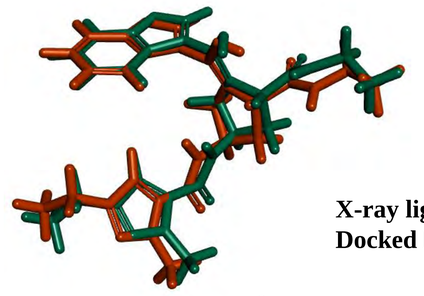
The structures were built by Gaussview 5.08 program and were optimized by M062X/6 31G(d,p) method using Gaussian09 program.

Molecular docking calculations

Tetrahydropyran derivatives were docked in InhA binding site (PDB code: 4COD) to predict binding mode and binding interactions using Glide XP program.

Results

❑ Validation method



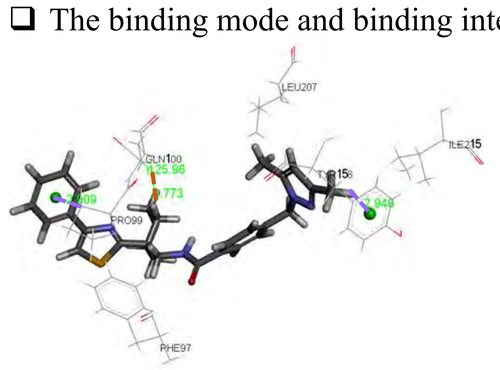
X-ray ligand = Green
Docked ligand = Red

RMSD = 0.6773 Å

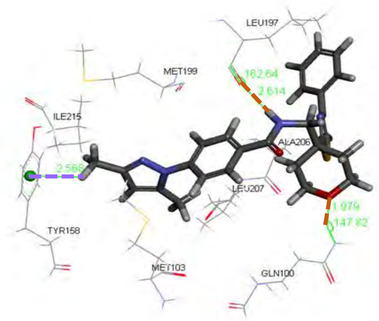
Figure 1. The superimposition between X-ray ligand and docked ligand

❑ Molecular docking calculations

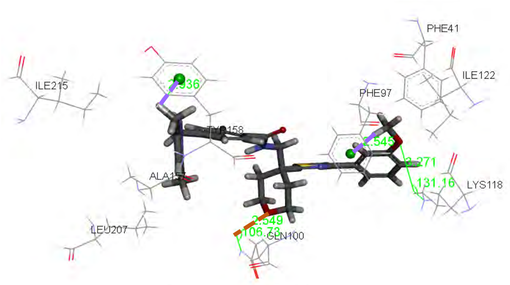
❑ The binding mode and binding interaction of selected compounds in InhA pocket



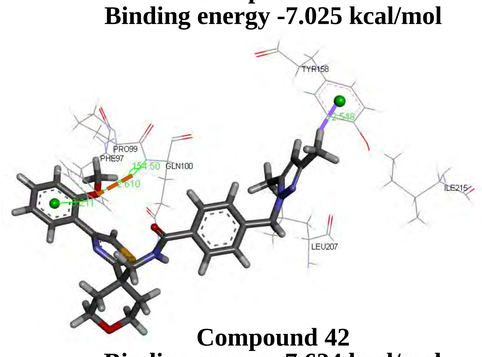
Compound 1
Binding energy -7.535 kcal/mol



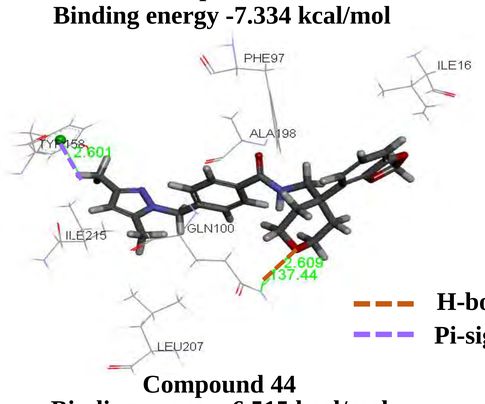
Compound 31
Binding energy -7.025 kcal/mol



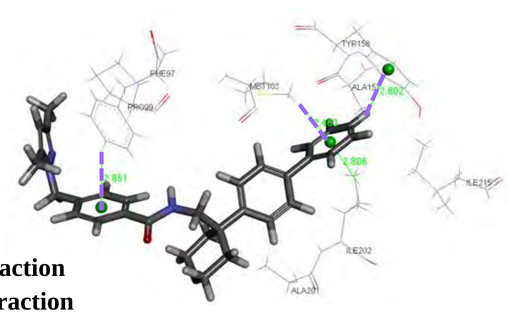
Compound 41
Binding energy -7.334 kcal/mol



Compound 42
Binding energy -7.624 kcal/mol



Compound 44
Binding energy -6.515 kcal/mol



H-bond interaction
Pi-sigma interaction

Compound 46
Binding energy -9.261 kcal/mol

Figure 2. The binding mode and binding interactions of the selected compounds

Conclusions

- ❑ Hydrogen bond interaction were found between oxygen atom of tetrahydro-2H-pyran ring with Gln100 residue.
- ❑ Aromatic ring of ligand formed pi-sigma interaction with Tyr 158 residue.
- ❑ Hydrophobic interactions were found with Phe97, Met103, Ala201, Leu207 and Ile215 residues.
- ❑ The obtained results provide beneficial guideline to rational design new and effective inhibitor against *M. tuberculosis.*

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