

QSAR Virtual Screening Identifies Repurposed Drugs as Direct InhA Inhibitors for Drug-Resistant Tuberculosis

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1. INTRODUCTION

Tuberculosis (TB) remains one of the deadliest infectious diseases globally, killing over 1.3 million people annually, with drug-resistant strains posing an escalating therapeutic crisis. Enoyl-acyl carrier protein reductase (InhA), an essential enzyme in the fatty acid synthesis pathway (FAS-II) of *Mycobacterium tuberculosis*, is the primary target of isoniazid, the frontline anti-TB drug.

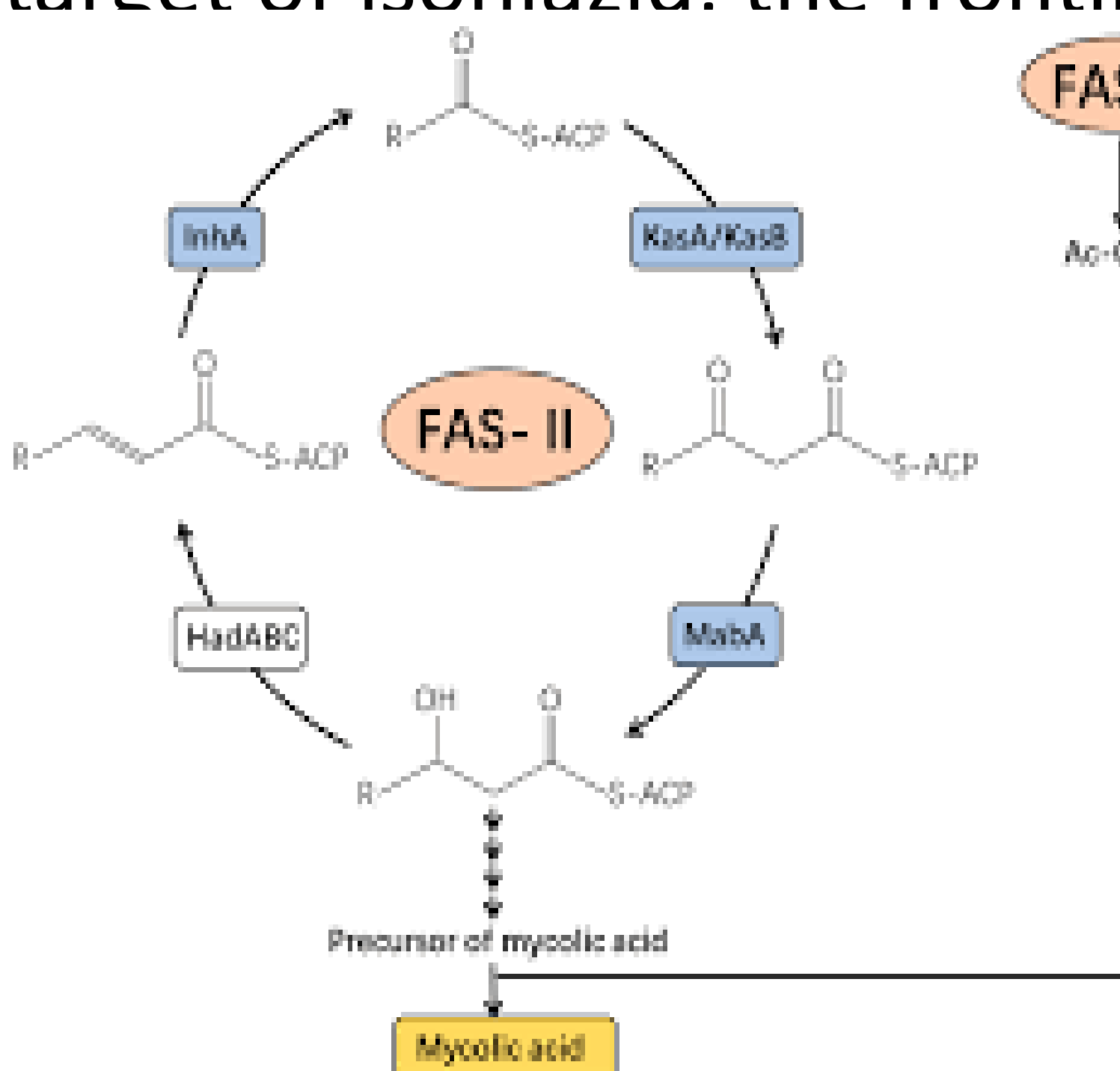


Fig 1: InhA in the FAS-II Pathway

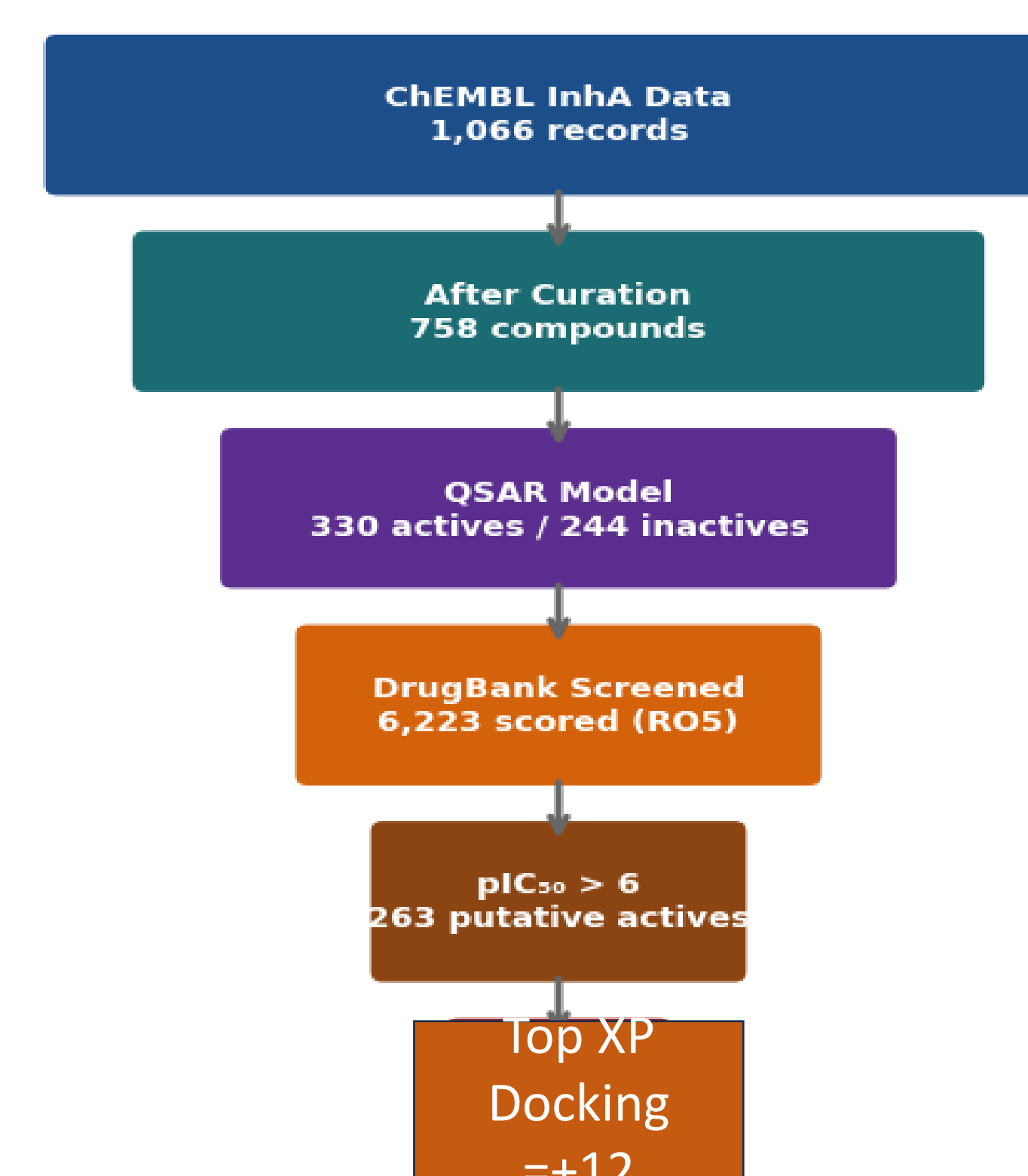


Fig 2: Schematic Representation of Pulmonary Tuberculosis

This study presents an integrated computational pipeline combining machine learning-based Quantitative Structure-Activity Relationship (QSAR) modelling, virtual screening, and molecular docking to identify high-affinity direct InhA inhibitors from an approved drug library, enabling drug repurposing opportunities with potential for accelerated clinical translation.

2. METHODOLOGY

Fig 3 Virtual Screening Funnel



Experimentally validated InhA inhibitor data were retrieved from the ChEMBL database (1,066 records; 758 unique compounds) and categorized using IC₅₀ thresholds ($\leq 1,000$ nM = active; $\geq 10,000$ nM = inactive), yielding 330 actives and 244 inactives for model development.

Molecular descriptors (1D and 2D) were generated using DrugBank compounds, identifying 263 putative actives (predicted pIC₅₀ > 6) after Lipinski filtering. The trained QSAR model screened 10,051 DrugBank compounds, identifying 263 putative actives (predicted pIC₅₀ > 6) after Lipinski filtering. These compounds were subsequently docked against the InhA crystal structure (PDB ID: 2X23).

5. FUTURE WORK

This includes molecular dynamics simulations, DFT calculations, and *in vitro* validation of top candidates, with the overarching goal of advancing a direct InhA inhibitor that circumvents KatG-dependent resistance.

3. RESULTS

Fig 4 RF-QSAR Model Performance

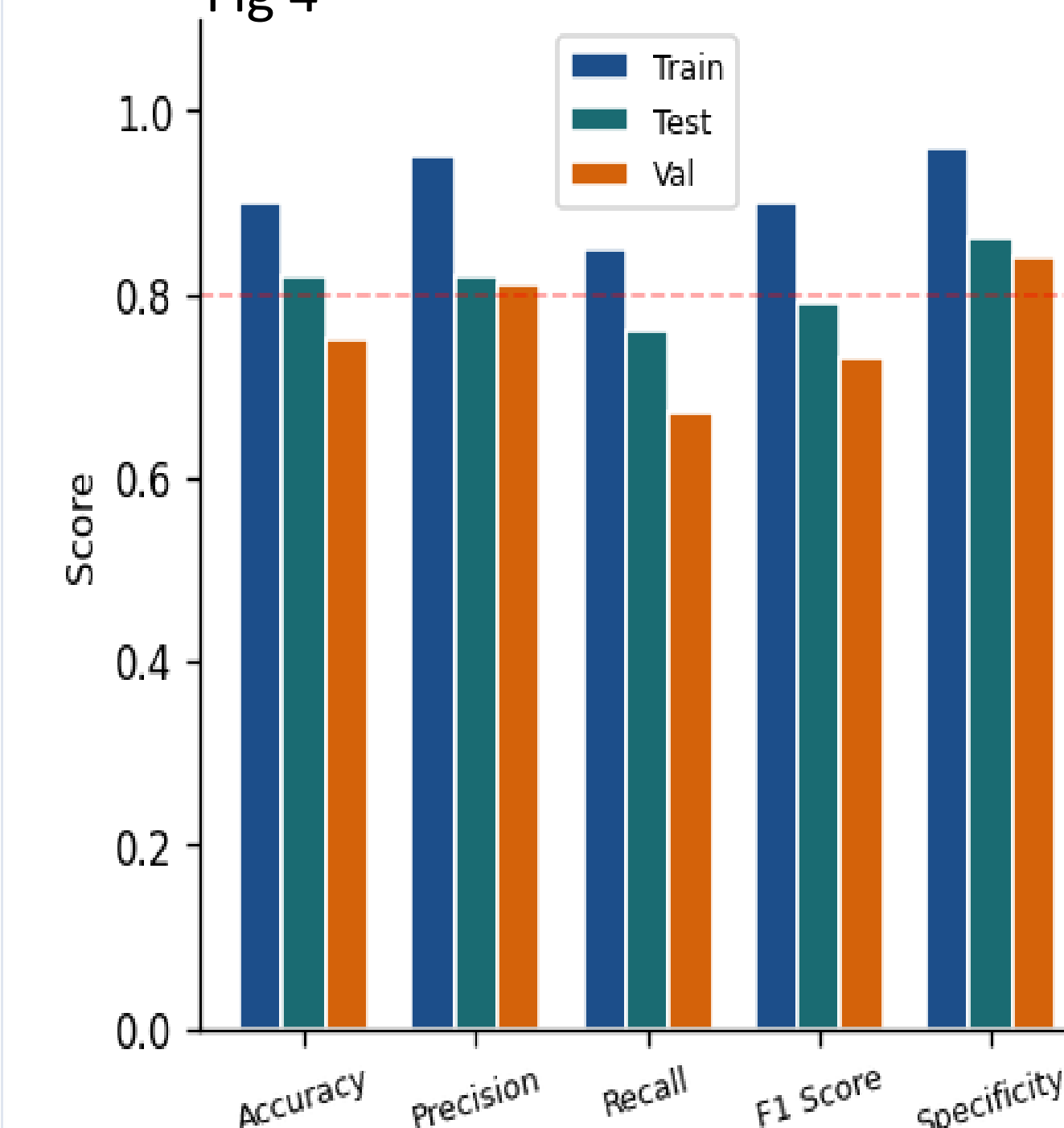
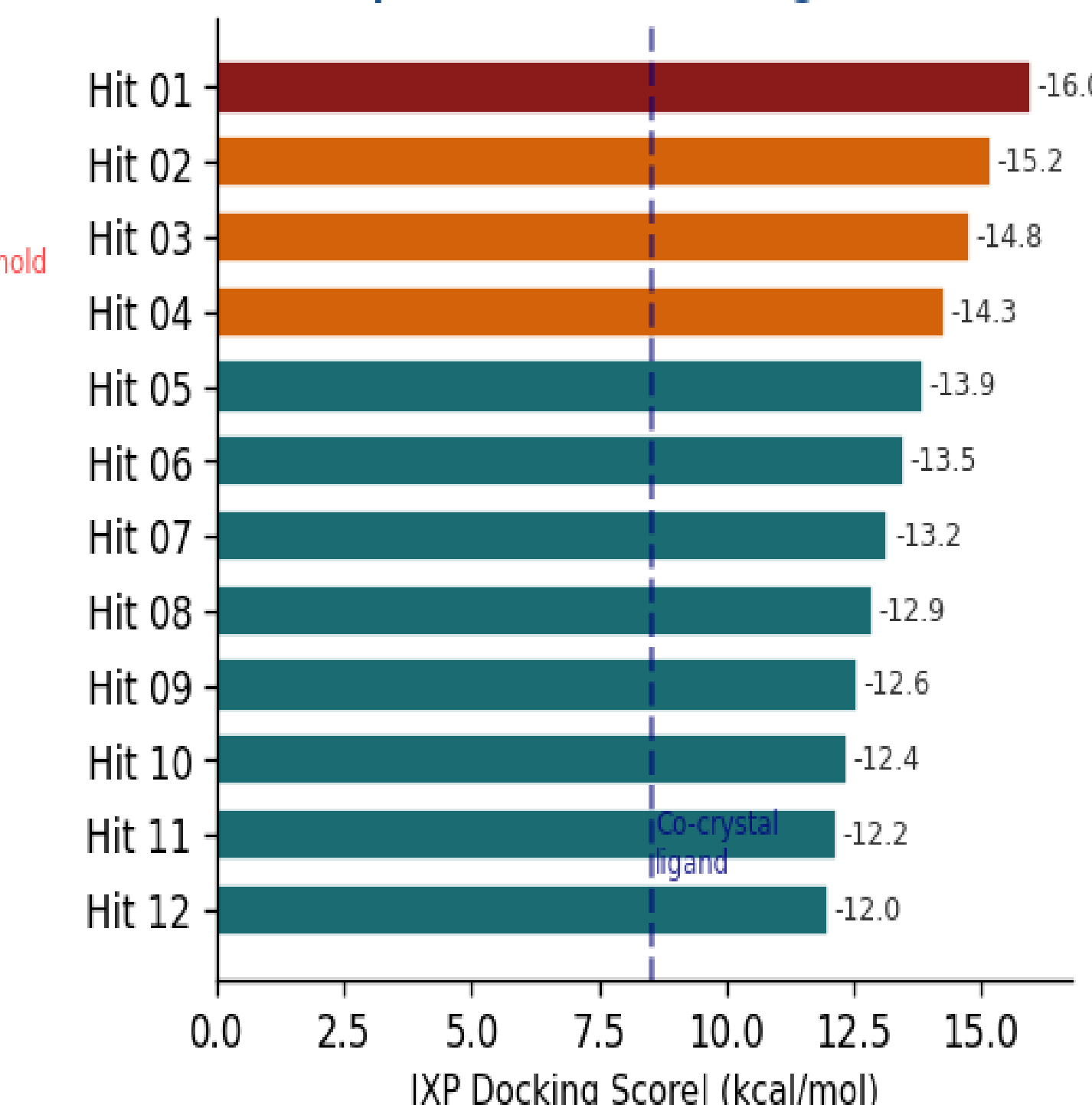


Fig 5 Top 12 Hits - XP Docking Scores



The virtual screening identified several high-affinity DrugBank compounds, including experimental bisphosphonate analogs DB07426, DB07410, and DB07409, as potential direct InhA inhibitors.

4. CONCLUSION

These compounds were originally investigated for non-tuberculosis targets, mainly enzymes involved in bone and metabolic pathways. Our computational study identified them as potential direct InhA inhibitors, suggesting a possible new application against drug-resistant tuberculosis.

6. References

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- [3] Vilchèze C. Mycobacterium tuberculosis is extraordinarily sensitive to killing by a vitamin C-induced Fenton reaction. Nat Commun. 2013;4:1881.