Computational Drug Design for ICL1 in Tuberculosis

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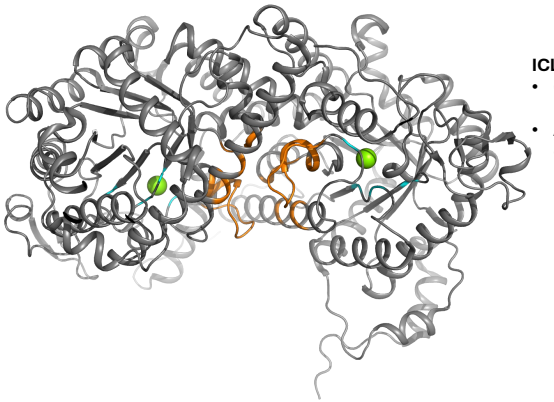
Abstract

Despite extensive drug-development efforts targeting *Mycobacterium tuberculosis* (Mtb), tuberculosis (TB) remains a leading cause of death worldwide. One way to combat TB is to target isocitrate lyase 1 (ICL1), an enzyme involved in the glyoxylate shunt in Mtb.

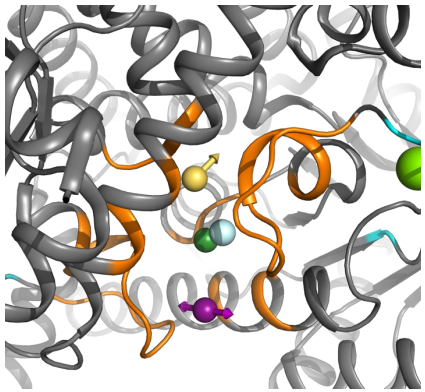
Although ICL1 is an attractive drug target, previous efforts to inhibit ICL1 have not yielded any viable drugs. ICL1 is known to form a dimer and tetramer, which play roles in regulating catalytic activity. Here we used a computational drug design pipeline and molecular dynamics to find new compounds to target the central cavity of the ICL1 dimer.

By targeting the central cavity, we can potentially inhibit ICL1 by altering the dimer structure, which could disrupt tetramerization and allosterically reduce catalytic activity. In addition, the central cavity is fairly large and deep, making it a desirable drug binding site. Targeting this cavity, rather than the conserved catalytic site, has the potential of achieving high specificity and reducing off-target side effects.

Through this approach we obtained multiple candidates that will be pursued in future studies.

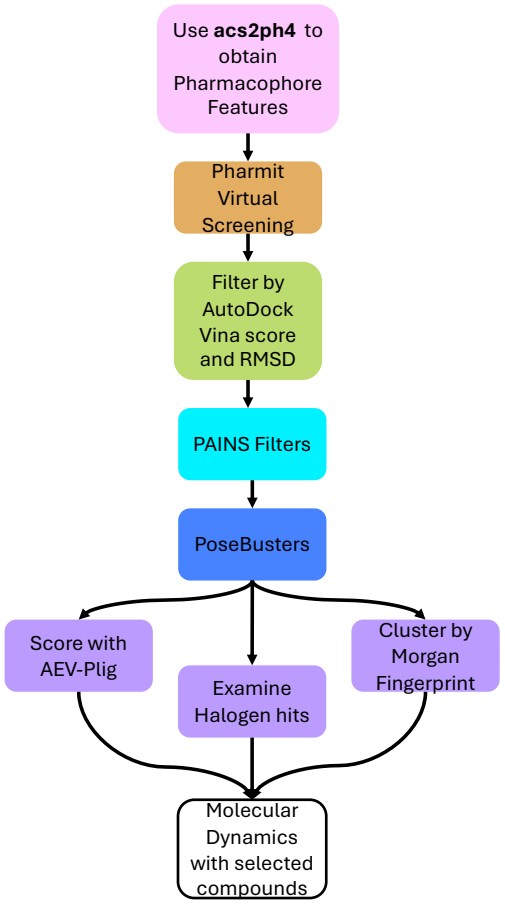


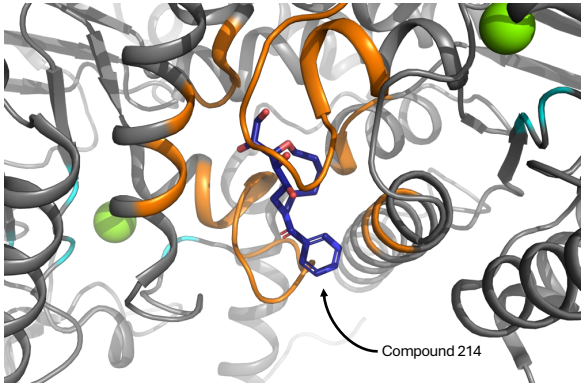
ICL1 Dimer
- Central cavity residues in orange
- Active site residues in cyan.



Selected Pharmacophore Features
- Yellow – h-bond acceptor
- Light blue – h-bond donor
- Purple – aromatic
- Green – hydrophobic

Drug Design Pipeline





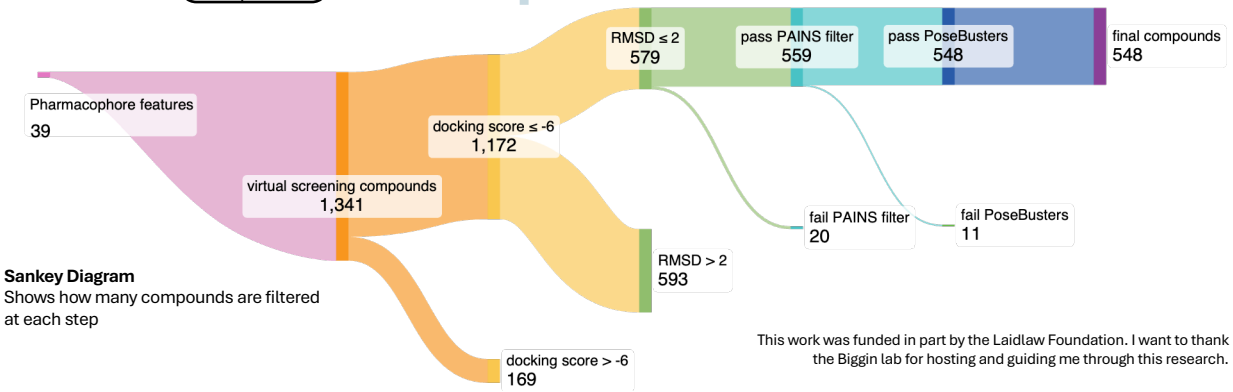
Binding Pose of Compound 214

Conclusion

- We developed acs2ph4, a package that converted apo state features from E-FTMap to pharmacophore features compatible with Pharmit for virtual screening
- We created a pipeline to filter candidates from virtual screening to make selection for MD more efficient
- High scoring compounds were obtained and further validated with RMSD scores

Future Directions

- More compounds will be screened with different pharmacophore features using the established pipeline
- Selected compounds will be sent for experimental validation by collaborators
- Experimentally validated compounds can be further tested in clinical trials



Sankey Diagram
Shows how many compounds are filtered at each step

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