Novel Fragment Inhibitors of PYCR1 from Docking-Guided X-Ray Crystallography

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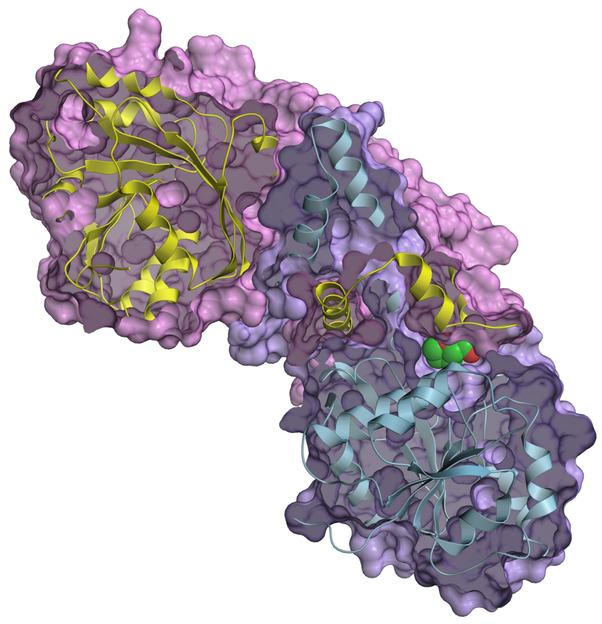
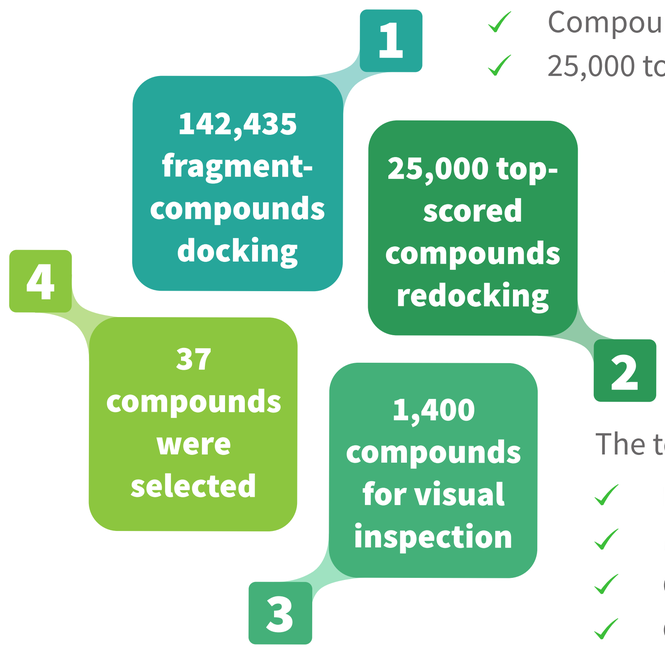
PYCR1 enzyme



Molecular docking of fragment-like set from Chemspace database

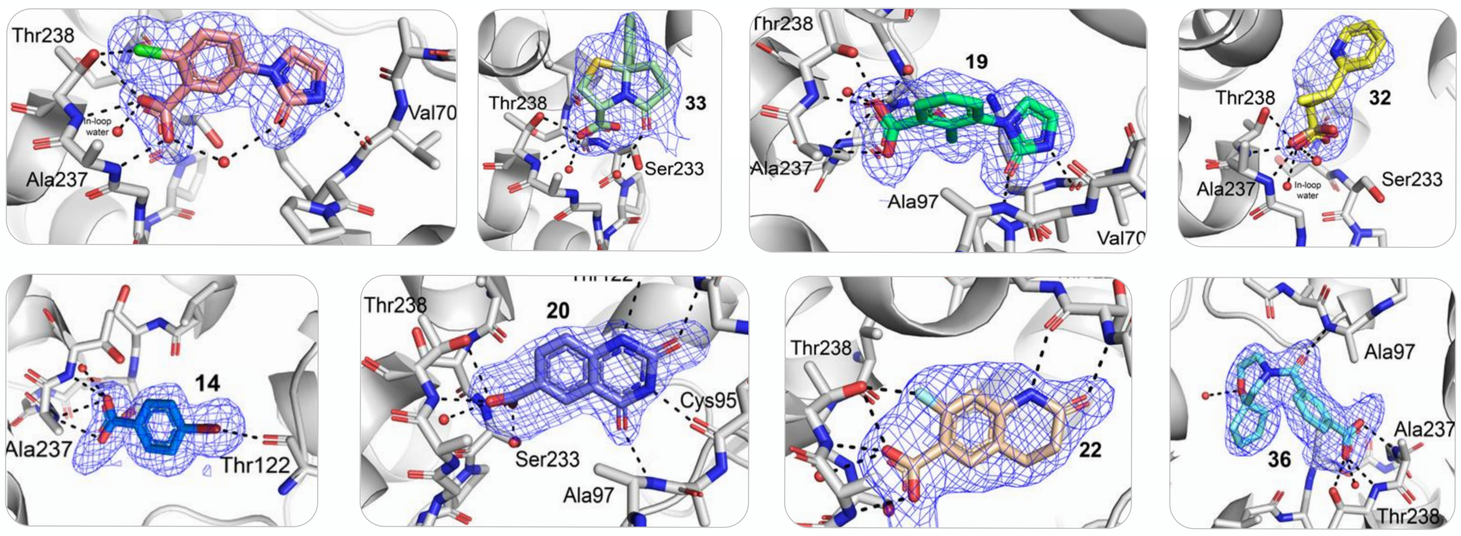


- ✓ The first docking stage was performed by utilizing a docking effort of 1.0
- ✓ Compounds with docking score < -20.0 were selected
- ✓ 25,000 top-scored compounds were selected
- ✓ The second docking stage was performed by utilizing a docking effort of 5.0
- ✓ 1,400 top-scored compounds were selected for visual inspection

The team conducted comprehensive analysis, including:

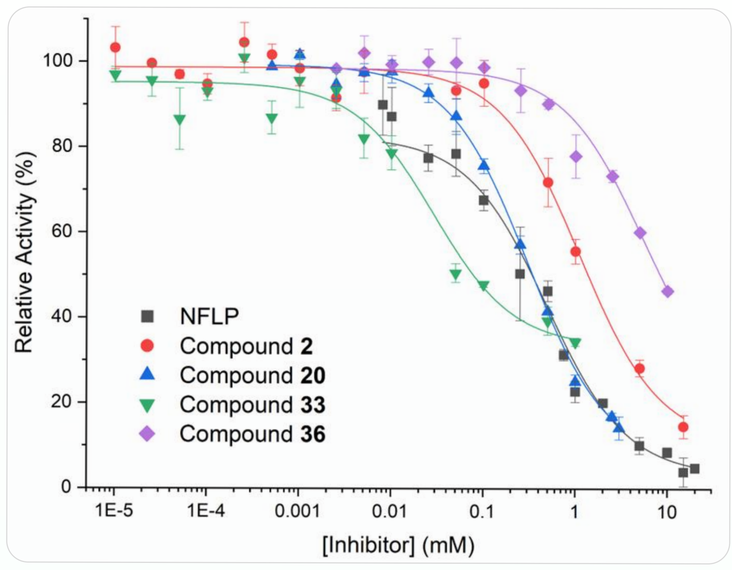
- ✓ Hydrogen bonds analysis
- ✓ Binding modes native-likeness analysis
- ✓ Overlapping with the NAD(P)H coenzyme
- ✓ Chemical diversity analysis
- ✓ In-stock availability analysis
- ✓ Carboxylic acid derivatives only were selected

Primary screening by X-ray crystallography

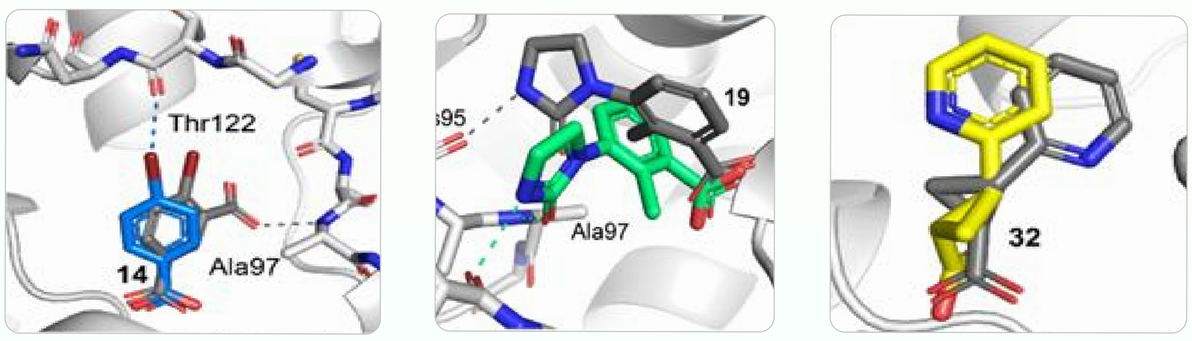


After primary screening using X-Ray crystallography clear electron density was observed for eight compounds, corresponding to a crystallographic hit rate of 22%. Four of the hit compounds showed inhibition of PYCR1 in kinetic assays, and one has a lower apparent IC50 than NFLP (N-formyl L-proline).

Enzyme activity assays



Poses and interactions of the compounds bound to PYCR1



The fragments are novel compared to existing proline analog inhibitors in that they block both the P5C substrate pocket and the NAD(P)H binding site and some form interactions mimicking those of the coenzyme. Halogen bonding to Thr238 was discovered as a new element of ligand recognition by PYCR1, and hydrogen bonding patterns that mimic that of the nicotinamide ribose of NADPH appeared to contribute to affinity. These results show proof-of-concept for our inhibitor discovery approach and provide a basis for fragment-to-lead optimization.

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Chemspace approaches to fragment-to-lead optimization

Custom Space Generation

We utilize cutting-edge tools like FTrees, Spacelight, SpaceMACS to name a few to tailor custom chemical spaces utilizing fragment hit features while addressing practical challenges in fragment growing such as physiochemical properties and synthetic accessibility.

Focused Library Generation

Relying on the structural information of the hit fragment bound to the target, we will proceed with the selection of synthons from Enamine xREAL with the exit vector for growing directed within the pocket while maintaining the key interactions with the target. Using such synthons for enumeration we will get the focused library enriched with the potential small molecule hits.

“Crystal Structure First” Approach

Combining crystallographic fragment hit discovery with rapid template docking of the synthetically accessible compounds within Enamine xREAL's extensive library (2.7T). The approach seamlessly integrates with REAL for efficient fragment-to-lead optimization.

APF Molecular Docking

This approach is driven by crystal structures with high ligand confidence to reveal key interactions in the active site, which are used to build the Atomic Property Fields (APF) template and utilized for molecular docking to select full-size hit molecules with more confidence and accuracy.

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