Inhibition of Peroxidase Activity of Cytochrome c: De Novo Compound Discovery and Validation

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Background: Inhibition of Peroxidase Activity of Cytochrome c (cyt c)

Inhibitors: TPP-n-ISA

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CL oxidation

Cyt c – CL

Mitochondria

Cyt c – CL

Mitochondria

Acute tissue injuries
Chronic sustained injuries

Apoptosis
Workflow: discovering de novo inhibitors

97 cyt c structures
Probes IOAs → Druggability Simulations → Heme-binding Pocket → Pharmacophore modeling (PM)

7520 drugs (DrugBank)
150 ligands (PDB) → Initial PM → 12 compounds

In vitro biotest: inhibitory activity (3/12)

PAINS filter

14 compounds → Improved PM

Drug-like: 11M
Lead-like: 3.1M (ZINC)

In vitro biotest: inhibitory activity (7/14)

Two rounds of screening: 3 repurposable drugs & 7 novel inhibitors
Closed native structure vs open conformer
Druggability simulations: heme binding site is a nanomolar druggable site

- Center of the pocket: isopropanol, isobutene (hydrophobic)
- Peripheries of the pocket: acetate, imidazole, methyl phosphate (positively charged residues)
  - Imidazole coordinate the iron
  - Salt bridges with Lys13 and Arg91
Initial pharmacophore model (PM) and first round of virtual screening

- probe and water molecules
Refined PM and second round of virtual screening

- Remove: anionic features based on the carboxyl head of IOA, donor/acceptor features based on isopropanol and water molecules
- Add: cation feature (weight 5)

In vitro biotest: inhibition of peroxidase activity

Drug-like: 11M
Lead-like: 3.1M (ZINC database)
Summary

- Provided a rational strategy for de novo drug discovery
- Developed a pharmacophore model for cyt c inhibitors
- Identified 3 repurposable drugs and 7 novel compounds for cyt c inhibition
- Gained insights in structure-activity relationships between inhibitors and binding domain
Thank you