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

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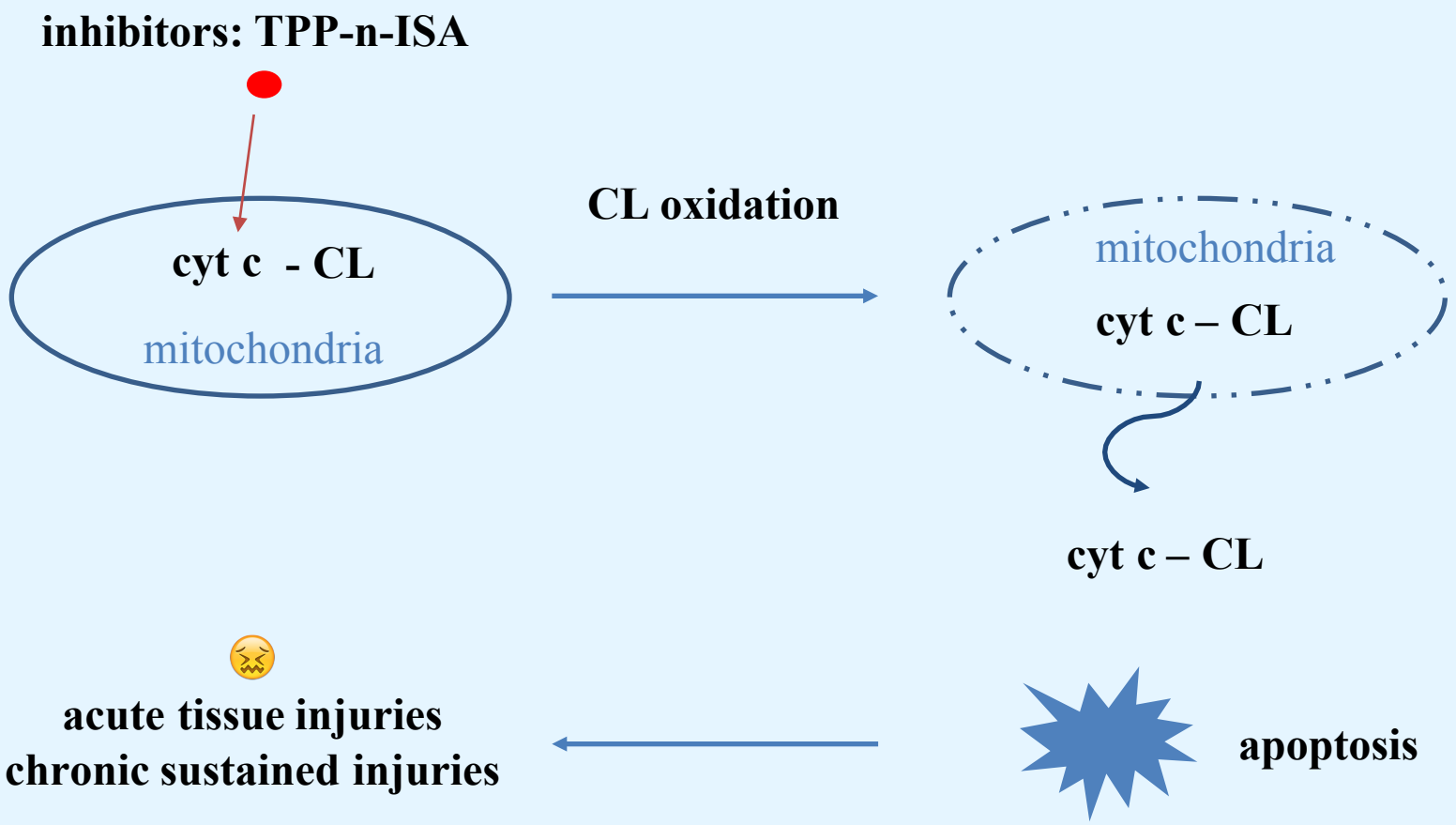
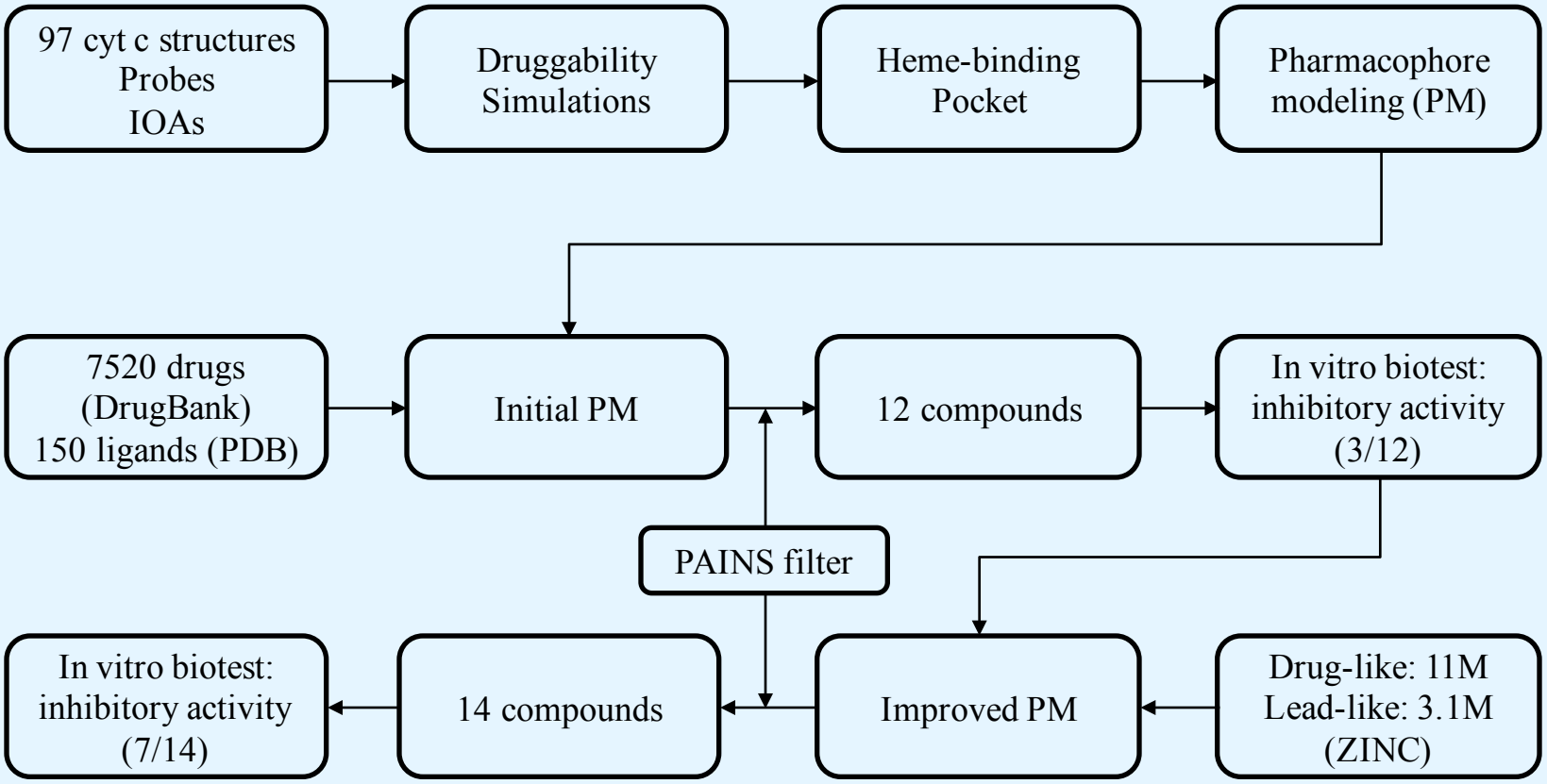
*Bakan, A., et al. (2015). "Inhibition of Peroxidase Activity of Cytochrome c: De Novo Compound Discovery and Validation." Mol Pharmacol **88**(3): 421-427.*

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

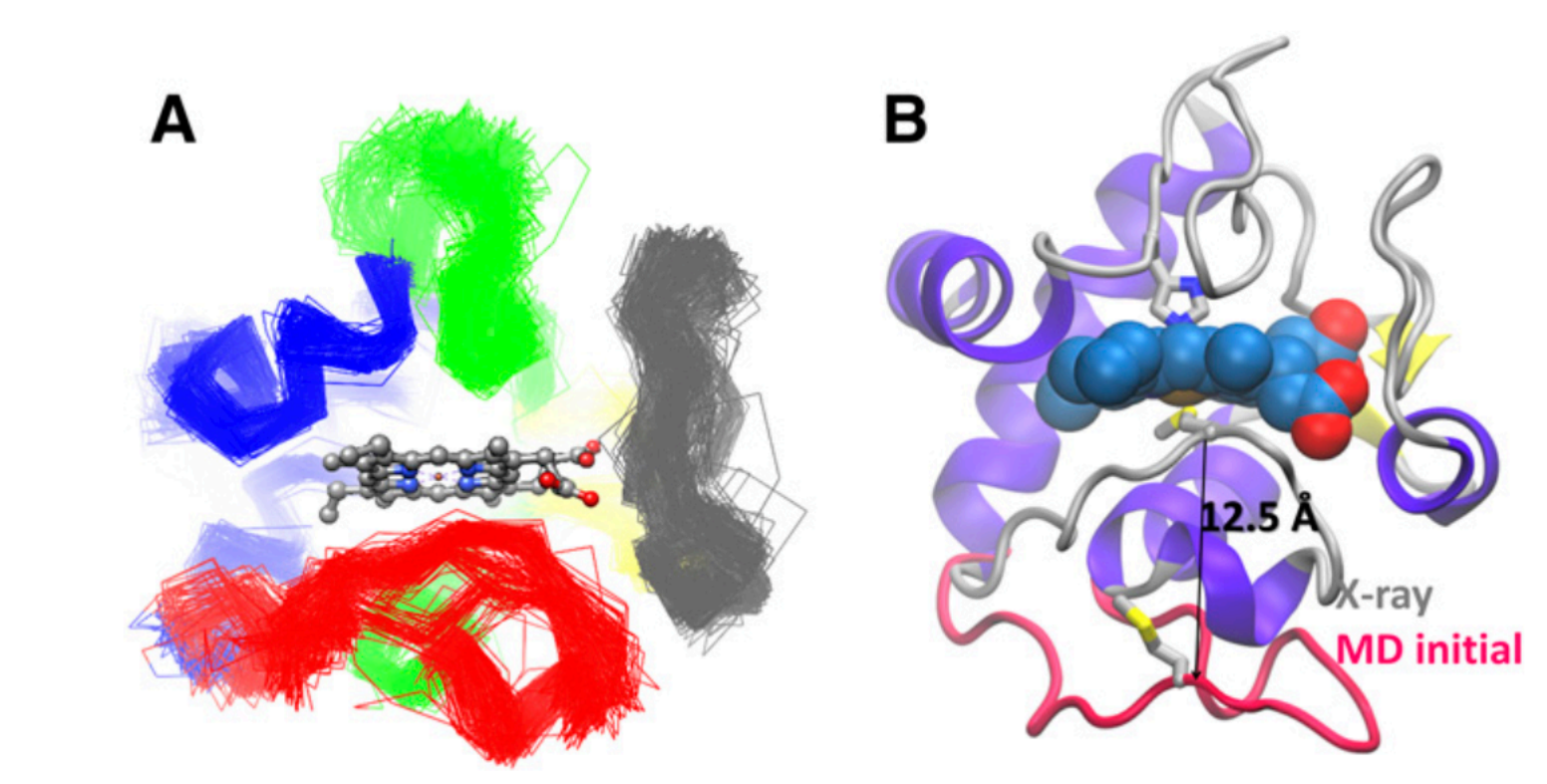


**Workflow: discovering de novo inhibitors**

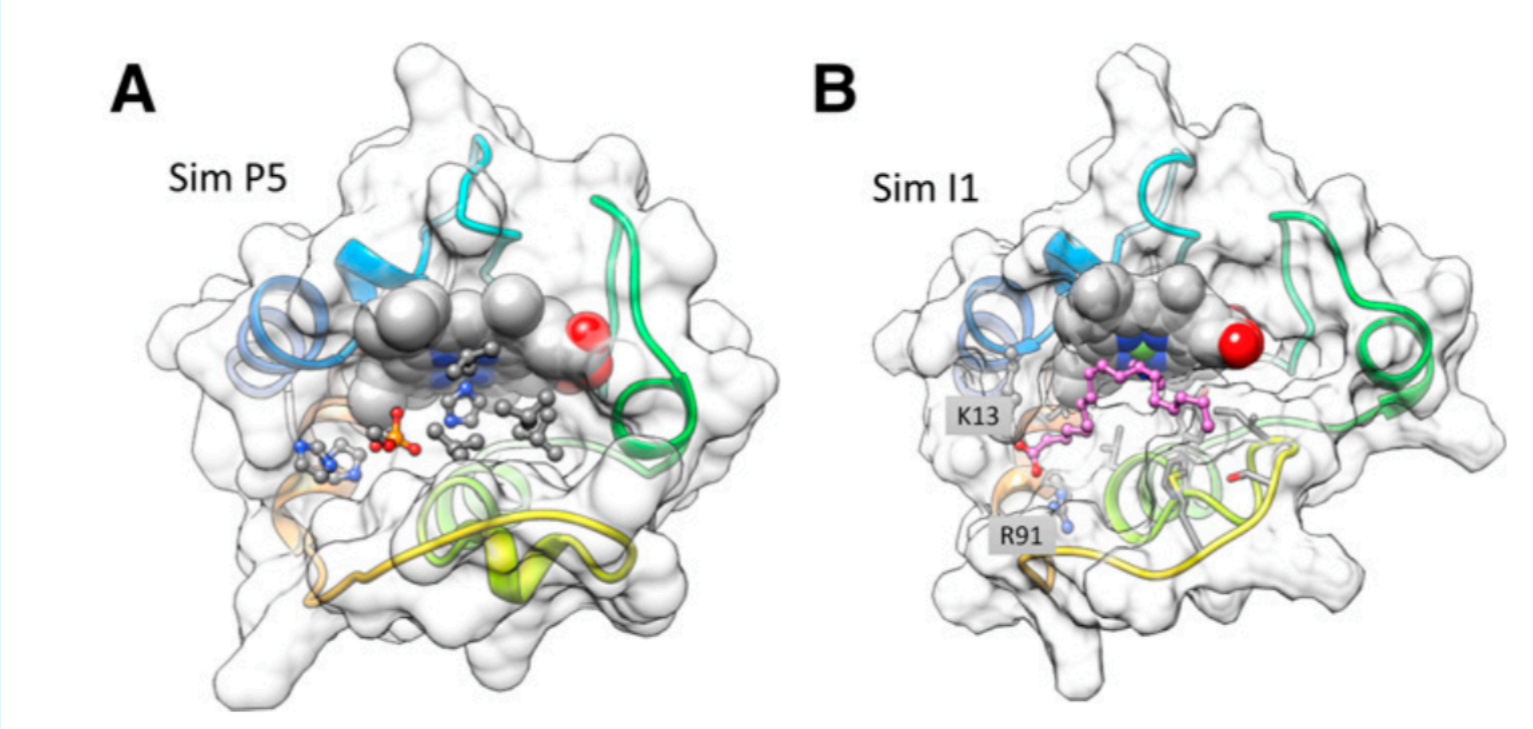



Two rounds of screening: 3 repurposable drugs & 7 novel inhibitors

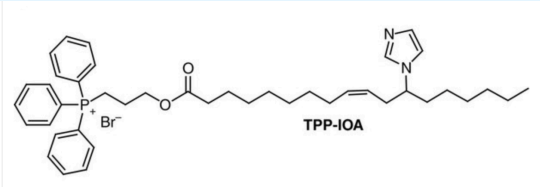
## Closed native structure *vs* open conformer



## Druggability simulations: heme binding site is a nanomolar druggable site



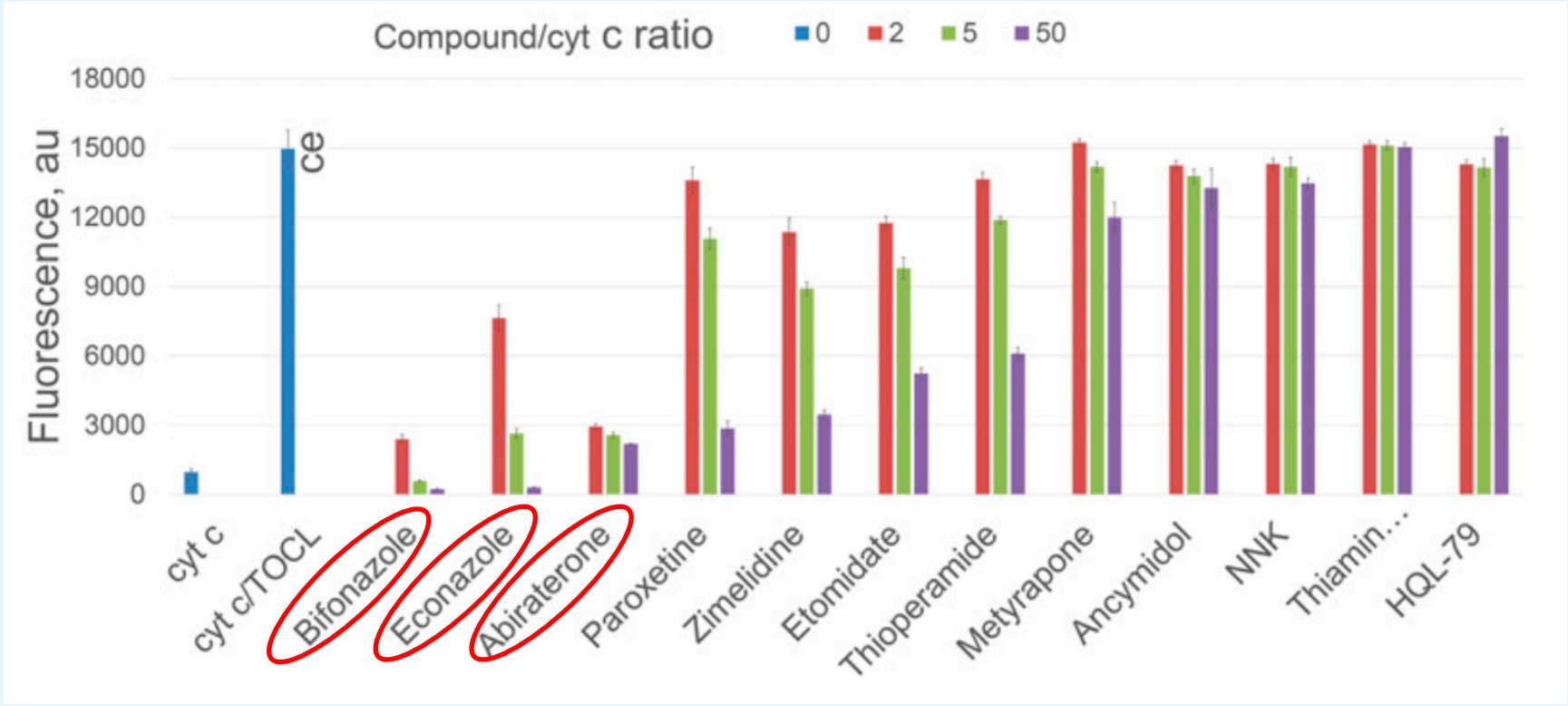

- Center of the pocket: isopropanol, isobutene (hydrophobic)
- Peripheries of the pocket: acetate, imidazole, methyl phosphate (positively charged residues)
- Imidazole coordinate the iron

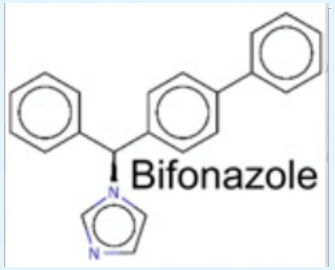


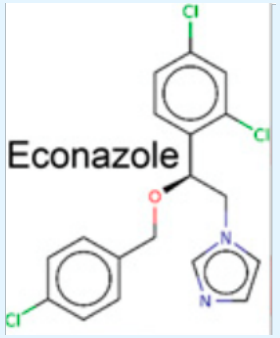

- Salt bridges with Lys13 and Arg91

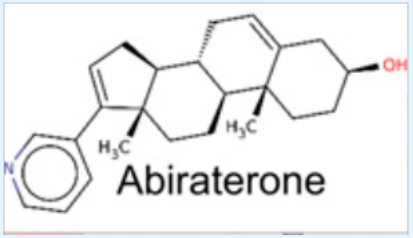
# Initial pharmacophore model (PM) and first round of virtual screening

- probe and water molecules



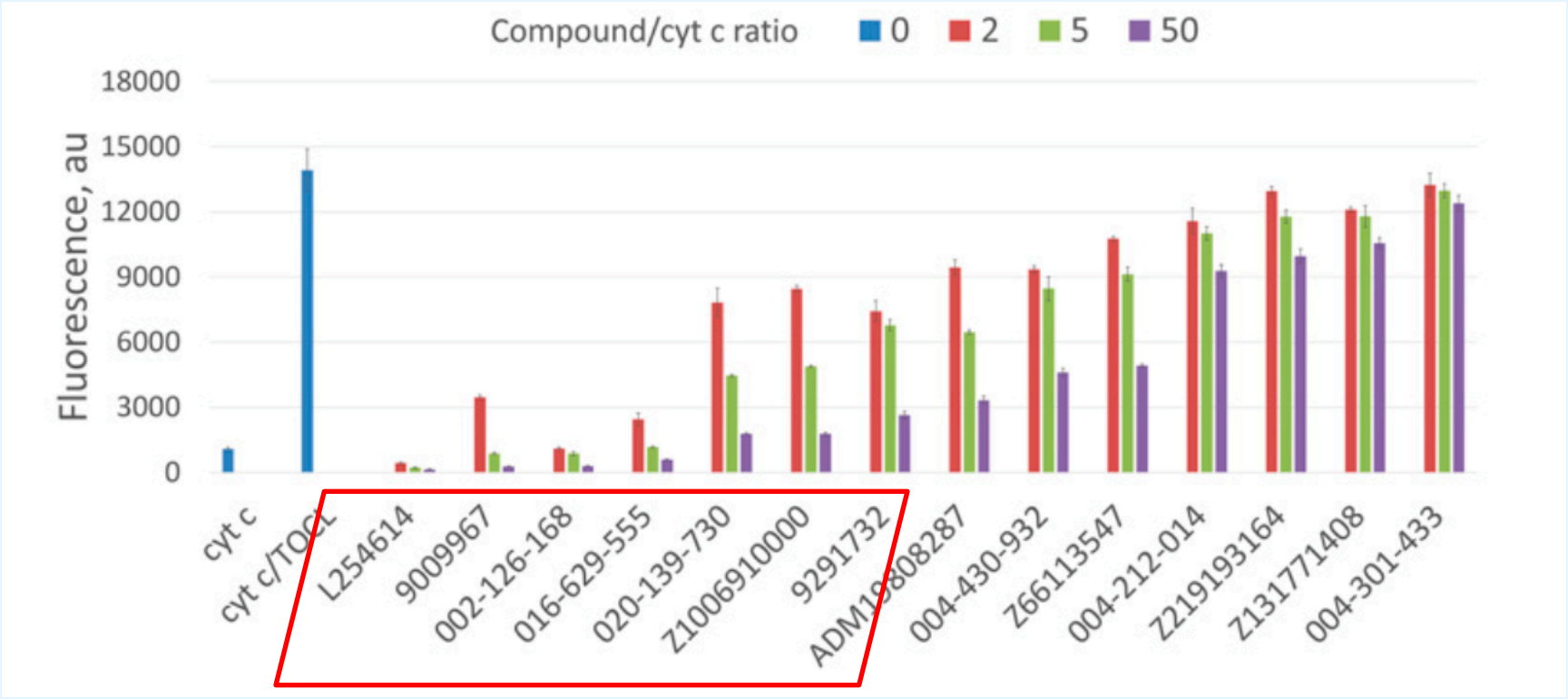



## Refined PM and second round of virtual screening

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



## 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***