XXIX Symposium on Bioinformatics and Computer-Aided Drug Discovery

IBMC Institute of Biomedical Chemistry

In Silico Screening of Commercial Drug-like Compounds for Covalent Inhibition of Tc80: Insights into Mechanism and Promising Candidates for the Treatment Against Chagas Disease

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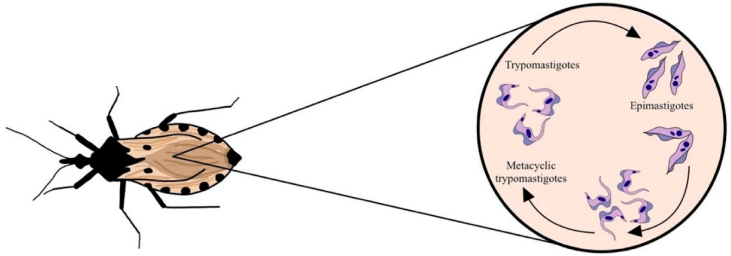
Speaker: Mly Huiza

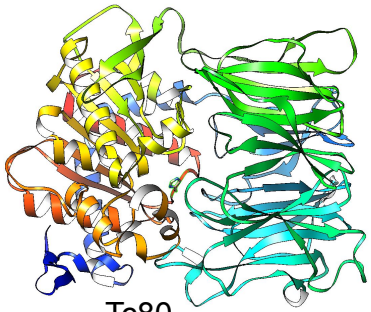
BioSolveIT expect actives!

CSSR Chemistry Student Society for Research

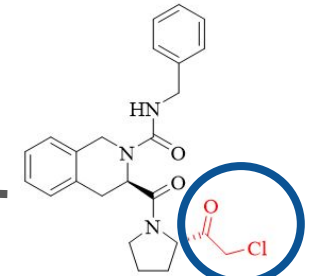
Hypothesis

- Chagas disease is a endemic tropical illness prevalent in Latin American.
- Tc80, a serine protease enzyme in T. cruzi, is involved in parasite maturation and invasion.
- 1A is a Tc80 selective covalent inhibitor.



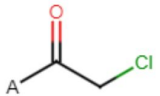


Tc80



Chloromethyl ketone Tic Derivatived (1A)

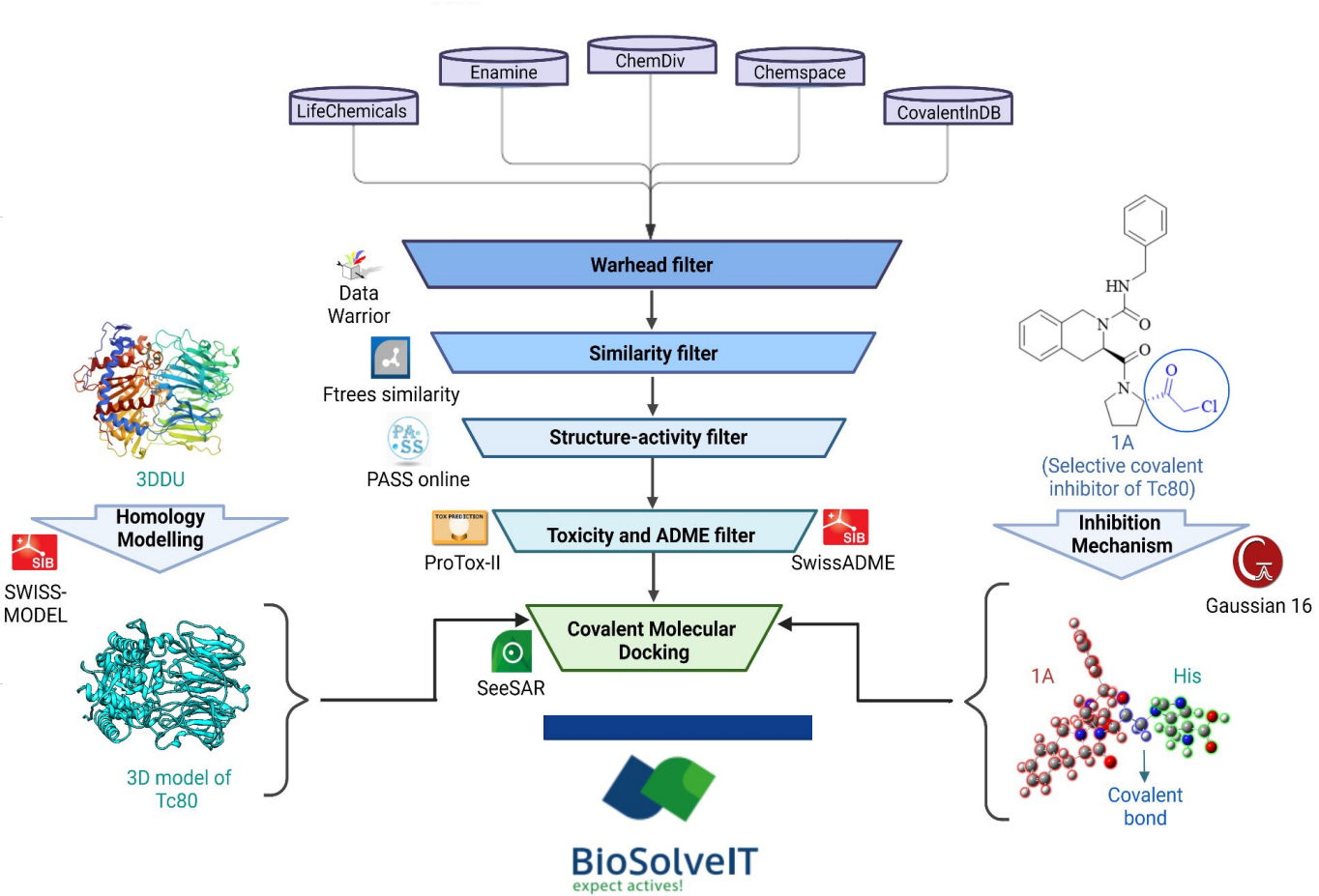
Chloromethyl ketones



Objective

Study the covalent inhibition potential of commercial drugs against Tc80 through in silico screening, with the goal of identifying promising candidates for the treatment of Chagas disease.

Methodology



Virtual Screening

Results

76 496 covalent compounds

Life Chemicals, ChemDiv, Enamine, ChemSpace, and CovalentInDB

warhead

2842 chloromethyl ketone compounds

2842 compounds

FTrees

Similarity 0.7 to 1A

1542 compounds

1542 compounds

PASS

Bioactivity threshold >= 1a

589 compounds

589 compounds

Toxicity

- Hepatotoxicity
- Inmunotoxicity
- Cytotoxicity
- Carcinogenicity
- Mutagenicity

426 compounds

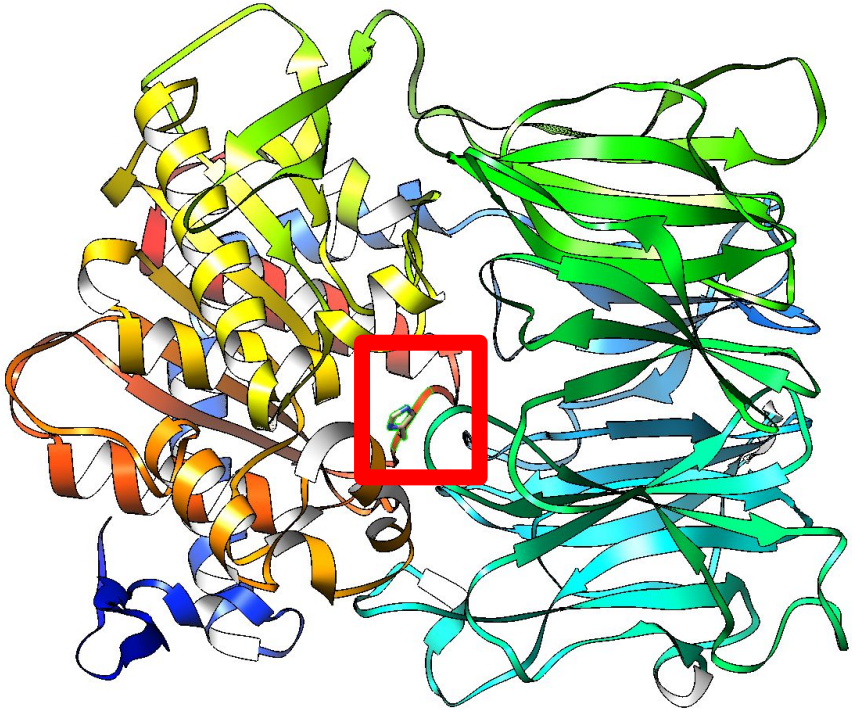
426 compounds

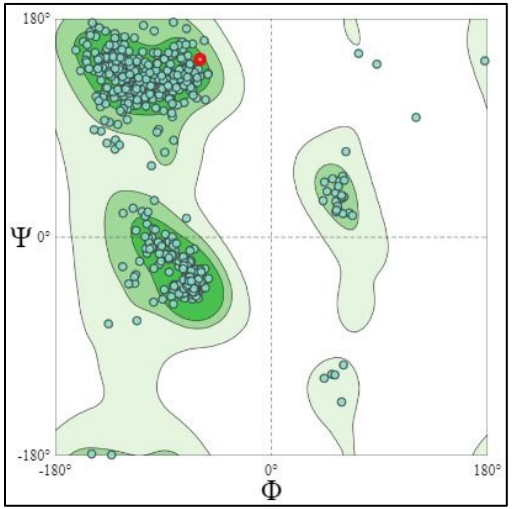
Pharmacokinetics

121 compounds

Homology modelling

Results

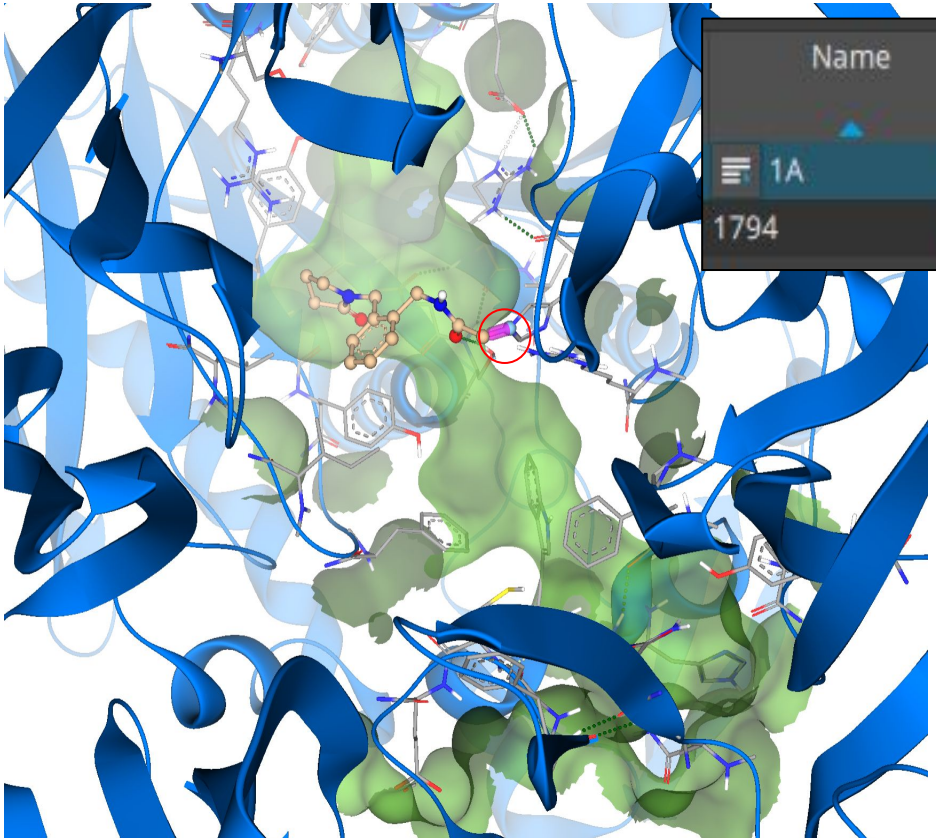




Tc 80 3D model
Protein structure homologated

Compound 1794

Results



Name	Estimated Affinity
	pM nM μM mM
1A	
1794	

Conclusion

We obtained promising compounds with better-estimated affinity than 1A, highlighting compound C1794 that presented multiple interactions with residues of the active site, including a hydrogen bond with the residue SER548 of the catalytic triad of Tc80.

Acknowledgments

- My partners and I especially thank BioSolveIT for giving us the opportunity to participate in the contest and win the SeeSAR software license.
- Special thanks to the Chemistry Student Society for Research (CSSR-PERÚ) for supporting the work.

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