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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- Chagas disease is an 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.
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

3DDU

Homology Modelling

SWISS-MODEL

3D model of Tc80

Data Warrior
Ftrees similarity
PASS online

ProTox-II
SwissADME

Toxicity and ADME filter

Structure-activity filter

Similarity filter

Warhead filter

Covalent Molecular Docking

SeeSAR

Inhibition Mechanism

Gaussian 16

1A (Selective covalent inhibitor of Tc80)

Covalent bond

His

BioSolveIT

expect actives
Virtual Screening

**Results**

<table>
<thead>
<tr>
<th>76,496 covalent compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life Chemicals, ChemDiv, Enamine, ChemSpace, and CovalentInDB</td>
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**2842 compounds**

- **warhead**
- **FTrees**
- **PASS**
- **TOX PREDICTION**

**Bioactivity threshold >= 1a**

**1542 compounds**

**589 compounds**

- Hepatotoxicity
- Immunotoxicity
- Cytotoxicity
- Carcinogenicity
- Mutagenicity

**Pharmacokinetics**

**426 compounds**

**121 compounds**
Homology modelling

Results

Tc 80 3D model
Protein structure homologated
Compound 1794
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

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