Scaffold hopping for new bioactive cruzain inhibitors

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Introduction and Objectives

Chagas disease is a neglected tropical disease caused by the protozoa ***Trypanosoma cruzi*** **(Tc)**. Its main cysteine protease, **cruzain (Cz)**, has been extensively targeted in drug discovery efforts to find new treatments for this disease. The essentiality of this enzyme for the parasite has been established, still, **many cruzain inhibitors fail as trypanocidal agents**.

We expand on previous works[1,2] that aimed at **rationalizing** this phenomenon using chemical space analysis and predictive models in a **virtual screening** context.

By using machine learning and structure-based methods we intend to find **novel scaffolds** for cruzain inhibitors that are also within the chemical space of trypanocidal compounds, while not presenting undesired characteristics.

Methodology

Compound activity data
Cz, Tc, TcCYP51
Kd, Ki, IC50

Descriptors
Phys-chem
Morgan FPs
ErG FPs

Predictive models
Cz activity
TcCYP51 activity
(XGBoost)

VS Libraries
RealSpace (Enamine)
GalaXi (WuXi)
eXplore (eMolecules)

Filters
ADME
Tc chemical space
TcCYP51
Cz activity

Selected compounds
Potential activity
Novelty
Structure-based activity prediction

Partial Results and Discussion

Goals achieved:

- Selected 11 trypanocidal compounds as starting points for the scaffold hopping pipeline.
- Used BioSolveIT infiniSee 5.0.0 to select 100k compounds from each library, with Tanimoto similarities to the seed compounds between 0.9 and 0.6.
- Created TcCyp51 model with data from online databases and literature mining.
- Re-trained models for cruzain inhibition: Morgan fingerprint → Pharmacophoric fingerprint.

The models achieved excellent metrics on cross-validation and on a separate test set, but the previous cruzain model could not identify potential active compounds.

The new cruzain model trained on pharmacophoric features showed improved metrics on cluster and AVE splits of data, suggesting improved generalizability.

Next steps:

- Use the pipeline on the selected libraries and identify promising scaffold hops.
- Predict binding pose using docking.
- Purchase most promising compounds, test on enzyme and on parasite.

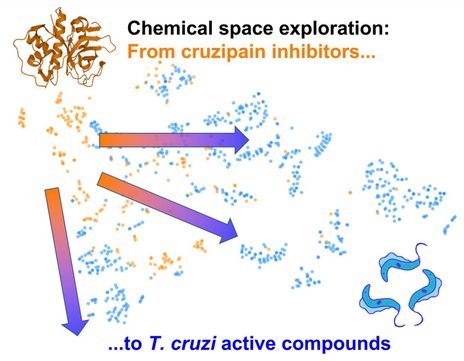
Conclusion

Previous works have shown a significant difference between the chemical spaces of cruzain inhibitors and *T. cruzi* active compounds.

Scaffold hopping can expand the chemical space of known cruzain inhibitors. Combining this approach with machine learning and structure-based methods should improve our chances of developing cruzain inhibitors that are **within the chemical space** of trypanocidal compounds and, therefore, with improved *T. cruzi* activity.

Future works

- Online platform for activity prediction
- Explore multitask models and alternative representation (GNN)
- Cheminformatics tutorials (in Portuguese) at github.com/rflameiro



References

1. Lameiro, R. F.; Montanari, C. A. **ChemMedChem.** 2023, 18, e202200434.
2. Cianni, L; de Vita, D; Montanari, C. A. et al. **Chem Biol Drug Des.** 2020, 96: 948– 960.

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