Área: MED
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Investigating the lack of cruzain to *Trypanosoma cruzi* activity with chemical space analyses and machine learning

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Highlights

Cruzain is an essential enzyme to the parasite *T. cruzi*, but many of its inhibitors are not bioactive. We try to rationalize this using chemical space analyses on calculated molecular descriptors.

Resumo/Abstract

Chagas disease is a neglected tropical disease caused by the protozoa *Trypanosoma cruzi*. Cruzain, its main cysteine protease, is commonly targeted in drug discovery efforts to find new treatments for this disease. Even though the essentiality of this enzyme for the parasite has been established, many cruzain inhibitors fail as trypanocidal agents. This lack of translation from biochemical to biological assays can involve several factors, including suboptimal physicochemical properties. In this work, we aim to rationalize this phenomenon through chemical space analyses of calculated molecular descriptors. These include statistical tests, visualization of projections, scaffold analysis, and creation of machine learning models coupled with interpretability methods. Our results demonstrate a significant difference between the chemical spaces of cruzain and *T. cruzi* inhibitors, with compounds with more hydrogen bond donors and rotatable bonds being more likely to be good cruzain inhibitors, but less likely to be active on *T. cruzi*. In addition, cruzain inhibitors seem to occupy specific regions of the chemical space that cannot be easily correlated with *T. cruzi* activity, which means that using predictive modeling to determine whether cruzain inhibitors will be trypanocidal is not a straightforward task. We believe that the conclusions from this work might be of interest for future projects that aim to develop novel trypanocidal compounds.

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