BRANDON UNIVERSITY

February 2023 – Issue 2(2)

RESEARCH CONNECTION

Using computational and synthetic chemistry to design selective carbonic anhydrase inhibitors

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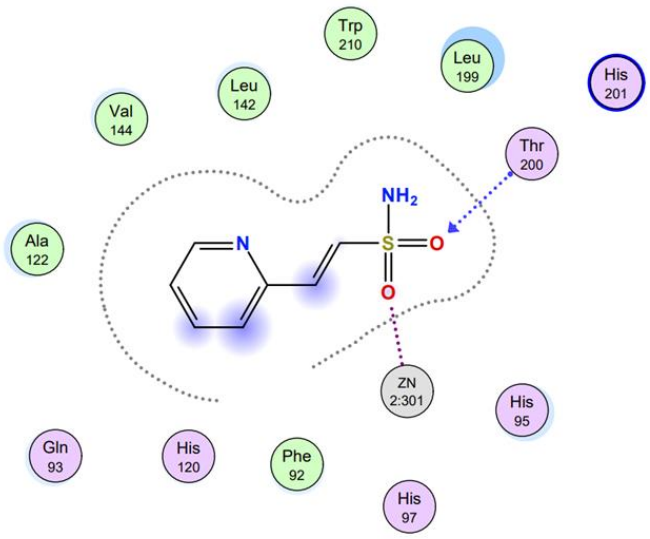
What you need to know

The carbonic anhydrase enzyme converts carbon dioxide and water into carbonic acid. If it is malfunctioning, it can cause numerous conditions, including glaucoma and epilepsy. With limited treatments available, we investigated novel therapeutics using a combination of computational and synthetic chemistry, resulting in promising leads.



Drug interaction map of a novel sulfonamide within the carbonic anhydrase active site

Why this research is important

The carbonic anhydrase enzyme is found in many cells in the body, including blood, and is fundamental to breathing—something we all need to do to live. As different forms of this enzyme are located in many different areas of the body, it has been difficult to develop selective inhibitors for one specific action. For example, to prevent glaucoma without adversely affecting other body functions such as the liver or kidney. Developing selective inhibitors of carbonic anhydrase would allow for possible treatments without significant side effects elsewhere.

How the research was conducted

The research was a combination of computational chemistry and synthetic organic chemistry. Computationally, the carbonic anhydrase enzyme was loaded into the Molecular Operating Environment (MOE) software package. Several small novel sulfonamide-based inhibitors (i.e., drugs) were "docked" within the active site using MOE. The binding energies were then calculated between each of the inhibitors and the active site zinc ion and surrounding amino-acid residues. By comparing the binding energy of the various inhibitors, we could predict the effectiveness of each compound as a potential drug. In

addition to the novel inhibitors, two known inhibitors, one a prescription drug (i.e., acetazolamide), were docked in the active site to generate a baseline binding energy for comparison. Experimentally, the next step is synthesizing the best-scoring inhibitors using a new methodology developed in the lab.

What the researchers found

Three of the four proposed novel inhibitors showed a stronger binding energy to the active site than the two known inhibitors and, therefore, legitimate synthetic targets. One of the target inhibitors is nearly synthesized in the lab requiring one final step to be complete, thus validating the new synthetic strategy.

How this research can be used

The novel inhibitors need to be tested biologically to determine their selectivity and efficacy as the next step. With that information, potential therapeutics could be developed, and this approach could be applied to other biochemical systems.

About the researchers

Christian Lozeau graduated from Brandon University with a 4-year Honors Degree in Chemistry (with CO-OP) in 2022 and is now a master's student at the University of Manitoba in Dr. Frank Schweizer's research group.

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Publication based on this research

Lozeau, C. (2022, June 13-17). *Insights into the design of human carbonic anhydrase inhibitors*. [Poster presentation]. 105th Canadian Society for Chemistry Conference and Exhibition 2022, Calgary, Canada. https://www.xcdsystem.com/cic/program/bMlXk1m/index.cfm?pgid=2690&sid=24559&abid=90988

Keywords

Carbonic anhydrase, computational chemistry, MOE, sulfonamides

Acknowledgements

Eric Bushnell thanks NSERC for funding. Bryan Hill thanks the Dean of Science for funding associated with this project. Christian Lozeau thanks the Manitoba Métis Federation for their financial support.

Research Connection is a periodical publication intended to provide information about the impact of Brandon University's academic research and expertise on public policy, social programming, and professional practice. This summary is supported by the Office of Research Services, the Centre for Aboriginal and Rural Education Studies, and the federally funded Research Support Fund.

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