Contribution ID: **146** Type: **Poster**

ng Against Tuberculosis Drug Resistance: Dual target Extirpation through a "Double-Edged" Antifolate Derivative

Despite the availability of clinically approved drugs and the incessant flurry of innovative research techniques, tuberculosis has escalated to the leading cause of death in its category, worldwide. The increasing prevalence of multidrug and extensively drug-resistant tuberculosis strains, due to target-specific inhibitors, have created an imperative need for new antibiotics that can overcome bacterial resistance and still maintain efficiency. In recent years, multi-target modulation or, "polypharmacology", has been a focal point in drug discovery. Polypharmacology is broadly defined as the affinity of a variety of biological targets toward a single "master-key" molecule. One of the key beneficial outcomes of multi-facetted inhibitors against bacteria, such as Mycobacterium tuberculosis, is its ability to overcome resistance by inhibiting an alternate target within the network of metabolic pathways. A recent study elucidated on one such antifolate derivative, which demonstrated inhibitory characteristics against DHFR and RV2671 within the folate pathway. However, a clear understanding of UCP1172's structural mechanism of action and molecular characteristics allowing for inhibition of the enzymatic dyad was not established. In this study, we conducted predictive pharmacokinetic profiling of UCP1172, as well as demonstrated a comparative structural mechanism of inhibition against the above-mentioned enzymes. It was evident from the pharmacokinetic analysis that the molecular characteristics of UCP1172, including its increased lipophilicity permitted increased GIT absorption. Predictive analysis also exposed UCP1172 as an antagonist against drug-metabolizing enzymes CYP3A4 and P-gp, thus extrapolating an enhanced biological half-life of the compound. Subsequent to molecular dynamic simulations, free-energy analysis and molecular interaction plots of the enzyme complexes revealed distinct similarity in the energy contribution of UCP1172 to both enzymes, with increased enzymatic contribution from RV2671. Catalytic residues (Serine, Threonine and Aspartate), common to both enzymes, also participated in key molecular interactions with UCP1172. This indicated a common molecular mechanism of inhibition of enzymatic dyad. By elucidating on the structural and molecular mechanism of UCP1172's inhibitory characteristics, inhibiting folate production and combating drug resistance can be sustained in tuberculosis therapy. This study could also act as a model in the design of effective polypharmacological inhibitors against drug-resistant diseases.

Supported Student

Primary author: Dr RAMHARACK, Pritika (Molecular Bio-Computation and Drug Design Laboratory)

Co-authors: Mr AGONI, Clement (Molecular Bio-computation and Drug Design Research Laboratory, School of Health Sciences, University of KwaZulu-Natal, Westville Campus, Durban 4001, South Africa.); Prof. SOLIMAN , Mahmoud (Molecular Bio-computation and Drug Design Laboratory, School of Health Sciences, University of KwaZulu-Natal, Westville Campus, Durban 4001, South Africa)

Presenter: Dr RAMHARACK, Pritika (Molecular Bio-Computation and Drug Design Laboratory)

Session Classification: SIG Poster

Track Classification: SIG Seminar: Chemistry, Material Science and Health Science