



Contribution ID: 32

Type: Poster

## Does Size Really Matter? Structural Fragmentation and Efficacy in Lead Drug Design and Optimization – A Computational “Proof-of-Concept”

Despite the potency embedded in natural products with regards to multiple disease treatment, the numerous challenges of toxicities and undesirable biological ‘off-targeting’ have limited its clinical transition. More recently, the synthetic reduction of complex natural products into simpler fragments has been identified as a viable strategy to develop next-generation leads with improved potencies and minimal toxic effects. Therefore, to validate the efficacy of this method, we employed combinatorial molecular modeling and cheminformatics techniques to describe the differential pharmacological and antagonistic activities of a selected fragment, SB640 and its parent compound, Anguinomycin D towards their target protein, Exportin Chromosome Region Maintenance 1 (CRM1), involved in pro-carcinogenic chemotherapeutic resistance. Our findings revealed that the fragment exhibited improved pharmacokinetics with minimal toxicities and off-target activities compared to the parent compound. Furthermore, truncation into a smaller fragment enabled optimal positioning and binding with crucial residues at the protein target site which in turn accounted for a more prominent CRM1 inactivation as compared to the parent compound that had minimal structural effects due to motion and dynamical constraints caused by its long polyketide tail. Our findings, therefore, indicate that the “size does not matter” and that reduction of complex bioderived compounds to fragments could be an essential strategy for improving potency and minimizing associable adverse drug reactions.

### Supported Student

**Primary author:** Dr OLOTU, Fisayo Andrew (University of KwaZulu-Natal)

**Co-authors:** Dr MUNSAMY, Geraldene (University of kwa-zulu natal); 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 OLOTU, Fisayo Andrew (University of KwaZulu-Natal)

**Session Classification:** SIG Poster

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