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Chemogenomic approaches to drug design: Docking-based virtual screening of nematode G-protein coupled receptors for potential anthelmintic agents

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Nematode (Helmintic) infections are major problems in veterinary medicine and human health. The pathogens affect 550-750 million people worldwide, and have broad effects on childhood growth, pregnancy, and cognitive and intellectual development. The genomic sequence of nematode Caenorrhabdtis elegans has been published and the primary sequence of the G-Protein Coupled Receptor (GPCR) made available. GPCRs play a significant role as targets for therapeutics and are responsible for signal transduction in cells. However, the three dimensional (3D) structure of the GPCR and the interactions with the peptides are not known. In this work, the 3D structure of nematode GPCR receptor (FLP18R1) was determined using homology modeling using the beta-2-adrenergic receptor as a template. Explicit membrane molecular dynamic simulations were used to optimize and refine the model over 100 ns. The homology model was of acceptable quality. In addition, solution structures of four known agonist neuropeptides that bind to FLP18R1; AF3, AF4, AF20 and FLP18-6 were determined using NMR-restrained molecular dynamics in DPC. Cyclic conformations of the neuropeptide structures were observed. Blind docking of the neuropeptides into FLP18R1 model was performed using AutoDock4.2 and Glide using SP-peptide docking. The docked complexes with Glide scores of -11.2, -10.9, -14.1 and -9.9 kcal/mol respectively were further optimized in explicit POPC membrane molecular dynamics simulations for 100 ns. The optimized complexes were used in docking-based virtual screening of the NCI database to identify potential FLP18R1 inhibitors. *In vitro* evaluation of the top 10% compounds confirmed three FLP18R1 inhibitors with IC50 below 10μM.

Biography

Raban Masuka is a PhD Chemistry candidate at the University of Cape Town under the supervision of Prof. Graham Jackson and Prof. Kelly Chibale. He obtained his BSc (Hons) Chemical Technology from the Midlands State University, LLB at the University of Zimbabwe and LLM at Africa University in Zimbabwe. He previously worked as a synthetic organic chemist and in-house Intellectual Property Counselor at the Scientific and Industrial Research and Development Centre (SIRDC, Zimbabwe). The focus of research at UCT is to use chemogenomic approaches to identify potential anthelmintic agents. These approaches include homology modeling, NMR-restrained molecular dynamic simulations, docking and structure-based virtual screening.

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