80th International Scientific Conference of the University of Latvia 2022

Contribution ID: **11** Type: **Oral presentation**

Exploring aspartic protease inhibitor binding to design selective antimalarials

Friday, 11 February 2022 11:40 (15 minutes)

Selectivity is a major issue in the development of drugs targeting pathogen aspartic proteases. Here we explore the selectivity determining factors by studying specifically designed malaria aspartic protease (plasmepsin) open-flap inhibitors. 2-Aminoquinazolin-4(3H)-one based plasmepsin inhibitors with various flap pocket substituents are synthesized and their potencies against several aspartic proteases are determined. Metadynamics simulations are used to uncover the complex binding/unbinding pathways of these inhibitors, and describe the critical transition states in atomistic resolution. Our findings demonstrate that plasmepsin inhibitor selectivity can be achieved by targeting the flap loop with hydrophobic substituents that enable ligand binding under the flap loop, as such behaviour is not observed for several other aspartic proteases. The ability to estimate compound selectivity before they are synthesized is of great importance in drug design, therefore, we expect that our approach will be useful in selective inhibitor design not only against aspartic proteases, but other enzyme classes as well.

Primary authors: Prof. JIRGENSONS, Aigars; Dr RASINA, Dace; Ms ZELENCOVA-GOPEJENKO, Diana; Mr BASENS, Emils Edgars; BOBROVS, Raitis; Mr LEITIS, Gundars; Mrs KANEPE, Iveta; Mr VELINS, Karlis Kristofers; Prof. JAUDZEMS, Kristaps; Mrs DRUNKA, Laura; Mrs MATISONE, Sofija; Dr ANDRIANOV, Victor

Presenter: BOBROVS, Raitis

Session Classification: Physical Chemistry and Analytical Chemistry. Joint session

Track Classification: Fizikālās ķīmijas un Analītiskās ķīmijas kopējā sēde