Computational design of novel DPP8 and DPP9 inhibitors using cosolvent molecular dynamics simulations

Olivier Beyens[1], Sam Corthaut[2], Sarah Peeters[1], Pieter Van Der Veken[1], Ingrid De Meester[2], and Hans De Winter[1]

[1]Laboratory of Medicinal Chemistry, Department of Pharmaceutical Sciences, University of Antwerp, Antwerp, Belgium
[2]Laboratory of Medical Biochemistry, Department of Pharmaceutical Sciences, University of Antwerp, Antwerp, Belgium

Dipeptidyl peptidase 8 and 9 (DPP8 and DPP9are highly similar cytosolic serine proteases. DPP9 is an interesting drug target as DPP9 inhibition leads to pyroptotic cell death in acute myeloid leukemia [1] and HIV-1 infected cell lines [2]. The role of DPP8 is still being researched, however a novel selective inhibitor would accelerate this research. We applied a computational drug design methodology called cosolvent molecular dynamics (MD) to these two targets of interest. The application of cosolvent MD simulations serves the purpose of investigating three research objectives: insight in important ligand binding features, exploration of alternative binding pockets and novel scaffold discovery.

Cosolvent MD simulations are simulations that allow computing preferred binding locations of small organic fragments. This is achieved by simulating a box in which the target protein, water, ions and small organic fragments of interest (also called the cosolvent molecules or probes) are present. By tracking the locations of the probes throughout the simulations we can calculate fragment affinity maps of the probes in the targets. We made use of isopropanol (hydrogen bond donor/acceptor), isopropyl ammonium (positive charge), acetate (negative charge), isobutane (hydrophobic) and benzene (aromatic) as cosolvent molecules. Note that the use of lipophilic probe types (isobutane and benzene) leads to an additional challenge of preventing phase separation, which was addressed in this work by developing a novel cosolvent MD setup tool called “PART” [3]. The choice of the previously mentioned probes leads to maps of the most important intermolecular interactions used in drug design. Consequently, the use of these maps enables structure based drug design, as decisions for novel compound modifications can be rationalized using the maps.

Qualitative fragment affinity maps were computed, and these fragment affinity maps have been made freely available [4]. A virtual screening calculation was performed based on the computed maps, with the aim of discovering new DPP8 and DPP9 inhibitors. Resulting inhibitors were weak binders, but explored new binding pockets of DPP9. Additionally, *in silico* optimization of the inhibitors was performed.

References

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