

In Silico Evaluation of Cyclic Dipeptides Targeting Cancer-Associated GPCRs

S. Jafari¹, P. Söderhjelm², J. Bojarska¹, W. Wolf¹

¹ *Institute of General and Ecological Chemistry, Faculty of Chemistry, Lodz, University of Technology, Lodz, Poland,* ² *Department of Chemistry, Lund University, Lund, Sweden*

Sepideh.jafari@dokt.p.lodz.pl, Joanna.bojarska@p.lodz.pl

G protein-coupled receptors (GPCRs) are deeply involved in key physiological processes and have increasingly been recognized for their roles in cancer development and progression. Among them, CXCR4, NK1R, and AT2R have been linked to tumor growth, metastasis, and inflammation-related pathways, making them attractive targets for therapeutic intervention [1, 2].

In this study, we performed molecular docking simulations to investigate the binding potential of a series of cyclic dipeptides (also known as diketopiperazines, DKPs) with these three cancer-associated GPCRs. The goal was to explore how well these small, structurally stable ligands could interact with the receptor binding sites and evaluate their potential as selective modulators [3, 4].

The results showed that several of the compounds had strong binding affinities and formed stable hydrogen bonds within the active sites of the receptors. This indicates that cyclic dipeptides (DKPs) have great potential as scaffolds for developing peptide-based drugs to regulate GPCR activity in cancer-related pathways [5, 6].

This computational study serves as an important first step in exploring how cyclic dipeptides (DKPs) interact with GPCRs relevant to cancer. It paves the way for future work focused on optimizing these interactions and developing new drug candidates.

- [1] Venkatakrisnan, A.J., et al., Diverse activation pathways in class A GPCRs converge near the G-protein-coupling region. *Nature*, 2016. 536(7617): p. 484-487.
- [2] Wu, B., et al., Structures of the CXCR4 chemokine GPCR with small-molecule and cyclic peptide antagonists. *Science*, 2010. 330(6007): p. 1066-1071.
- [3] Wallace, A.C., R.A. Laskowski, and J.M. Thornton, LIGPLOT: a program to generate schematic diagrams of protein-ligand interactions. *Protein engineering, design and selection*, 1995. 8(2): p. 127-134.
- [4] Morris, G.M., et al., AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *Journal of computational chemistry*, 2009. 30(16): p. 2785-2791.
- [5] Bojarska, J., et al., Cyclic dipeptides: The biological and structural landscape with special focus on the anti-cancer proline-based scaffold. *Biomolecules*, 2021. 11(10): p. 1515.
- [6] Apostolopoulos, V., et al., A global review on short peptides: frontiers and perspectives. *Molecules*, 2021. 26(2): p. 430.