

MOLECULAR DYNAMICS SIMULATIONS OF THE GLIAL CELL LINE-DERIVED NEUROTROPHIC FACTOR (GDNF) FAMILY RECEPTOR $GFR\alpha_1$ – LIGAND INTERACTIONS

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Glial cell line-derived neurotrophic factor (GDNF) family ligands (GFLs) regulate the development and maintenance of the nervous system. GDNF has the ability to support the survival of brain dopamine-producing neurons, which degenerate in Parkinson's disease, and motoneurons, which die in amyotrophic lateral sclerosis [1].

The aim of the current work was to explore the possible binding site and interactions of small-molecule ligands BT-13 and BT-18 with protein $GFR\alpha_1$, which makes a complex with proteins RetA and GDNF. Compounds BT-13 and BT-18 are known to have an effect on $GFR\alpha_1$ and RetA function [2].

Three possible regions were examined: the interface between $GFR\alpha_1$ and GDNF, the RetA interface with $GFR\alpha_1$, and a possible allosteric site in $GFR\alpha_1$, using AutoDock Vina 1.1.2 [3] for the molecular docking studies and Desmond simulation package of Schrödinger LLC [4] for the molecular dynamics (MD) simulations.

The results obtained by the docking calculations and the MD simulations indicate that the preferable binding occurs at the allosteric site. The analysis of the MD simulations shows significant hydrophobic interaction between the ligands and the receptor $GFR\alpha_1$.

References

1. H. Sariola, M. Saarma, 2003, *J. Cell Sci.*, 116, 3855-3862.
2. (a) Y. A. Sidorova, et al., 2017, *Front Pharmacol.*, 8, Article 365, 1-18; (b) M. M. Beshpalov, et al., 2016, *BioRxiv* [10.1101/061820](https://doi.org/10.1101/061820).
3. O. Trott, A. J. Olson, 2010, *J. Comp. Chem.*, 31, 455-461.
4. Schrodinger Release 2017-3: Desmond Molecular Dynamics System; D. E. Shaw Research: New York, NY, 2017.



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