POTENTIAL GFRα_1 RECEPTOR AGONISTS

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

The aim of the current work was to identify potential binding sites in GDNF-GFRα_1-RET complex, using molecular docking, and to find out several low molecular weight compounds (MW < 500), i.e. GFRα_1 receptor agonists, which could activate the aforementioned complexes in the region between GDNF and GFRα_1 as well between RET and GFRα_1.

Methodology was based on the structure-based drug design (SBDD) approach [2], as the three-dimensional structure of biomolecular target is known. AutoDock Vina 1.1.2 [3] was used for the molecular docking studies to find out binding modes and binding energies of ligands (designed small molecules) to the receptor (GFRα_1).

Important hints about suitable molecular structure of possible agonists were obtained as a result of molecular docking. Thereafter, similar compounds (similarity ≥ 80%) were searched from ZINC and MolPort databases. One of these scaffolds demonstrated high activity according to phosphorylation and luciferase assays carried out by M. Saarma's research group in Helsinki University. The further study includes the development of structural modifications of this scaffold to improve its biological activity.

References

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