

## [P16] Nonpeptide ligands of Arginine Vasopressin receptor (V2R): Docking study and conformational analysis.

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8-Arg-Vasopressin (AVP) is the endogenous nonapeptide antidiuretic hormone. It regulates body's water retention by interacting with the Arginine Vasopressin Receptor 2 (V2R), a renal G protein-coupled receptor<sup>1</sup>. Mutations in the V2R gene cause a deficient renal response to arginine vasopressin (AVP), leading to a rare disease called X-linked nephrogenic diabetes insipidus (NDI)<sup>2</sup>.

V2 receptor protein structure is not yet determined by X-ray crystallography. Therefore, the 3D model of V2 receptor was built by homology modeling using the neurotensin receptor structure as template (PDB ID: 4GRV)<sup>3</sup>. The aim of our study was to analyze the interactions between V2 receptor and its natural or synthetic ligands.

For a better understanding of the structure-activity relationship, we used two reference non-peptide ligands<sup>4</sup> showing micromolar and nanomolar affinities towards V2 receptor. These ligands were docked into the V2 receptor model using GOLD software. The best ligand/receptor complexes were optimized by molecular dynamics simulations. A detailed analysis of their interactions was carried out (figure 1).

In parallel, representative 8-Arg-Vasopressin conformations resulting from 1 microsecond molecular dynamics simulations (University of Portsmouth), were docked into V2R binding site. These AVP/V2R docking solutions were then compared to the non-peptide ligands/V2R complexes.

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Figure 1. Non-peptide ligand with V2R complex

[1]. Goodman & Gilman's The pharmacological Basis of Therapeutics, 12th edition (2011), Chapter 25

[2]. Metabolism Clinical and Experimental 61 (2012): 922-93

[3]. Nature, 490 (2012): 508-513

[4]. Bioorganic & Medicinal Chemistry 7 (1999) : 1247-1254