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New Ligands and New Insights for Vitamin D Receptor from Charge Density

M. Malińska[1], A. Kutner[2], K. Woźniak[1]

[1]University of Warsaw, Faculty of Chemistry, Warsaw, Poland, [2]Pharmaceutical Research Institute, Warsaw, Poland

Vitamin D protective effects result from its role as a nuclear transcription factor that regulates cell growth, differentiation, and a wide range of cellular mechanisms crucial to the development and progression of cancer.[1] Many academic investigators and pharmaceutical companies try to develop calcitriol analogs that exhibit equal or even increased anti-proliferative activity while exhibiting a reduced tendency to cause hypercalcemia. Analysis of 24 Vitamin D analogs bearing similar molecular structures with a complex of a Vitamin D Receptor (VDR) enabled the design of new agonists (TB1, TB2, TB3 and TB4). Undertaken approach was to minimize the electrostatic interaction energies available after the reconstruction of charge density with the aid of the pseudoatom databank (UBDB[2]). Comprehensive studies revealed 29 residues crucial for agonist binding. Trp286, which is specific to VDR among the representatives of the Nuclear Receptor Family, plays the crucial role of positioning the ligand forming dispersive interactions, mostly C-H...π, with an average strength of -4 kcal mol-1. The ligand binding pocket is primarily composed of hydrophobic residues, however there are 6 hydrogen bonds characteristic for all the ligands. They electrostatic interaction energies strongly contribute to the total interaction energy, with an average strength of -8, -19, -11 and -12 kcal mol-1 for hydrogen bonds to Ser237, Arg274, Ser278 and Tyr143. The aliphatic chain of the Vitamin D analogs adopt an extended conformation and the 25-hydroxyl group is hydrogen bonded to His305 and His397 with electrostatic interaction energies of -13 and -11 kcal mol-1. The geometries of complexes of the proposed ligand with VDR were obtained by the docking procedure implemented in Autodock4.3[3]. New agonsits form all mentioned before interactions with VDR. The final results of electrostatic interaction energy for TB1 and TB2 are -153 and -120 kcal mol-1, and this results are the smallest among all studied Vitamin D analogs.

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