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Theoretical Study of Partial Agonist Ligands of Vitamin D Receptor (VDR): 19-nor Vitamin D₃ Analogues

Sayaka MOTOYOSHI^{1*}, Kenji YAMAGISHI², Makoto MAKISHIMA³,
Sachiko YAMADA^{2,3}, and Hiroaki TOKIWA^{1,2,3}

- 1) Department of Chemistry, Faculty of Science, Rikkyo University, 3-34-1 Nishi-ikebukuro, Toshima-ku, Tokyo 171-8501, Japan
- 2) Research Information Center for Extremophile, Rikkyo University, 3-34-1 Nishi-ikebukuro, Toshima-ku, Tokyo 171-8501, Japan
- 3) Department of Biochemistry, Nihon University of Medicine, Oyagichi-kamicho, Itabashi-ku, Tokyo 173-8610, Japan

**motoyoshi@rikkyo.ac.jp*

1. Introduction

Agonists of the human Vitamin D Receptor (hVDR) are capable of inhibiting the proliferation and cell differentiation. The activated vitamin D₃ hormone, 1 α , 25-dihydroxyvitamin D₃ (1 α ,25-(OH)₂D₃)(**1**) plays important role in not only a key regulator of calcium homeostasis but also malignant cell proliferation. However, toxicity of hypercalcemia has limited the use of natural ligand for the hVDR, 1 α , 25-(OH)₂D₃, in clinical trials. A lot of vitamin D₃ analogues were synthesized in order to develop partial agonist ligands, which have only one target activity, that is, inhibition of the proliferation. These analogues mediate the bioactivities through specific binding to the hVDR. It is significant to estimate correctly direct interactions between the hVDR and ligands to design the significant partial agonists.[2] The hydrogen bonds between the residues in the ligand binding pocket (LBP) and the ligand is an important factor for forming the protein-ligand binding.

Lack 19-carbon (19-nor) VD₃ analogue, 19-nor-1 α ,25-dihydroxyvitamin D₃ (19-nor-1 α ,25(OH)₂D₃)(**2**) has significantly less calcemic, and greater or equivalent potencies to 1 α ,25-(OH)₂D₃ for inhibiting the proliferation and inducing the cell differentiation.[1] In this study, we theoretically analyze the difference of the interactions between the analogue and the residues in hVDR-LBP with comparing the case of natural ligand, 1 α , 25-(OH)₂D₃.

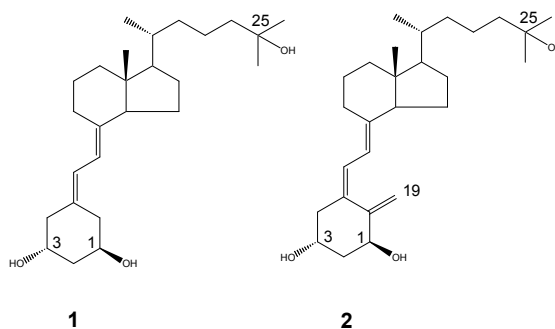


Fig.1 Structures of 1 α ,25(OH)₂D₃(**1**), and 19-nor-1 α ,25(OH)₂D₃(**2**)

2. Computational Method

Although a large number of 3-D structures for protein-ligand complexes have been determined by the X-ray crystal analysis and the X-ray crystal structure for the complex of the natural ligand ($1,25(\text{OH})_2\text{D}_3$) and the hVDR LBD (120-423, Δ 165-215; PDB code: 1DB1) were obtained, no experimental structural data on the hVDR LBD/19-nor- $1\alpha,25(\text{OH})_2\text{D}_3$ complex existed. So that the structures of the complex was built as follows: (1) the isolated 19-nor- $1\alpha,25(\text{OH})_2\text{D}_3$ ligand molecule was optimized at the conventional HF/6-31G(d) level, (2) the ligand was superimposed onto natural ligand, $1\alpha,25(\text{OH})_2\text{D}_3$ in the crystal structure (1DB1) and $1\alpha,25(\text{OH})_2\text{D}_3$ was then removed, (3) missing hydrogen atoms and side chains in the PDB file were complemented automatically by using the molecular modeling software SYBYL7.3, (4) the positions of all hydrogen atoms were optimized by the molecular mechanics (MM) procedure with the SYBYL force field with the other heavy atoms fixed at the initial positions of the PDB data, (5) the hydrogen atoms of two hydroxyl groups in the A ring of the ligand and the hydrogen atoms in residues (Tyr143, Tyr147, Ser237, Arg274, Ser275, Asn276, and Ser278, etc.) in the LBP were optimized at several small models in order to determined the stable hydrogen bond network system between the ligand and the hVDR. The entire hVDR LBD consists of 253 amino acid residues. The number of atoms in the complex is 4129. All fragment molecular orbital (FMO) calculations[3] were carried out by using the ABINIT-MP and Gaussian03 programs on the Xeon PC clusters.

3. Results and Discussion

We have already found the functions of key residues in the hVDR-LBP and the origin of type II hereditary rickets by the FMO-interfragment interaction energy (IFIE) calculations for the hVDR/ $1\alpha,25(\text{OH})_2\text{D}_3$

complex.[4] In this study, we determined the hydrogen bond network systems between 19-nor- $1\alpha,25(\text{OH})_2\text{D}_3$ and residues in the LBP. Fig. 2 shows typical models A and B for the hydrogen bonds around 1- and 3-OH group in the ligand. Partial geometrical optimizations were performed for *ab initio* docking of the ligand into the hVDR-LBP including “*induced-fit effect*”.

References

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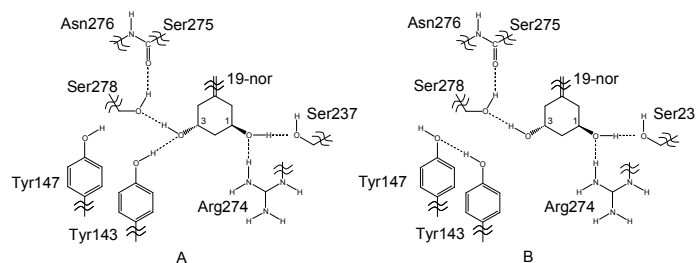


Fig.2 Models A and B around 1- and 3-OH groups in 19-nor- $1\alpha,25(\text{OH})_2\text{D}_3$