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Development of Novel Nuclear Receptor Ligands Based on Receptor-Folding Inhibition Hypothesis

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Nuclear receptors (NRs) are ligand-inducible transcription factors that regulate the specific gene expression, and have become significant molecular targets for drug discovery in various clinical fields. I proposed the "Receptor-Folding Inhibition Hypothesis", in which the ligand-inducible conformational alteration of helix 12 of NR ligand-binding domain would determine the unique activities of ligands, depending on the assay conditions or receptor mutations. This hypothesis has been experimentally verified (at lease in part) by applying it to the design of the novel ligands for NRs of vitamin D_3 (VDR) and androgen (AR).

More than three thousands of VDR agonists have been synthesized so far, while only two kinds of VDR antagonists were reported. I designed the lactam derivatives (DLAM series) of 1□,25-dihydroxyvitamin D_3 as VDR antagonist candidates, in which the N-substitution and configulation of the lactam ring would affect the folding structure of helix 12. Among them, (23*S*, 25*S*)-DLAM-1P, bearing an *N*-benzyl group, showed the potent VDR antagonistic activity. Further, during the development of non-*seco*-steroidal type VDR agonists, I found the novel aniline derivatives with dual VDR agonist/AR antagonist activity.

Then I developed novel non-steroidal AR antagonists, based on an isoxazolone or a pyrrolecarboxamide skeleton. These compounds were effective also in the androgen-independent prostate cancer cells with a mutated AR. Thus, the hypothesis was proven to be useful for the development of NR ligands with specific or unique activities.