

Development of Novel Vitamin D Derivatives with Clinical Utilities in the Field of Skin Diseases

Aya Tanatani

Ochanomizu University

Active vitamin D₃ (**1**) plays important roles in many physiological processes, including calcium and phosphate homeostasis, bone metabolism, and immune regulation, via binding to vitamin D nuclear receptor (VDR). Since VDR is involved in the pathogenesis of various diseases, many VDR ligands have been developed as candidate therapeutic agents. Structurally, almost all of the developed VDR ligands with high potency have the same secosteroidal skeleton, while non-secosteroidal VDR ligands are promising candidates for many clinical applications. In this study, we synthesized several derivatives of lithocholic acid (**2**) that was identified as the second endogenous VDR agonist. Novel compounds were designed by using a lithocholic acid derivative **4** with potent vitamin D activity as the lead compound. Among compounds **3–7** with a different 3-substituent, the compound **5** was more potent inducer of the HL-60 cell differentiation than the lead compound **4**. The SAR study indicated the size and shape of 2-ethyl-2-hydroxy-1-butyl group as the 3-substituent are proper for potent activity. Then, the replacement of the carboxyl group of compound **4** with other functional group was examined. The compounds **8–10** bearing the amide group in the side chain were as potent as active vitamin D₃ (**1**). Further, compounds **11** and **12** with acyclic 1, 3-diol structure, instead of the carboxyl group of compound **4** also showed potent activity in HL-60 cell assay. Since these novel lithocholic acid derivatives are one of the most potent non-secosteroidal VDR agonists reported to date, and would have unique vitamin D functions and different pharmacological properties, compared with the conventional vitamin D derivatives, they would be promising lead for development of novel drug candidates.