外 国 語 要 約

学位論文題目「Development of novel specific modulators of vitamin D and androgen nuclear receptor」

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Nuclear receptors are members of ligand-dependent transcription factors, and their endogenous ligands such as steroid hormones, vitamin A and vitamin D regulate specific gene transcription related to development, metabolism, immune function and homeostasis of the organism. Nuclear receptors and their ligands have been shown to be closely related to the pathogenesis and treatment of diseases such as cancer, metabolic diseases and autoimmune diseases, and nuclear receptors are important target molecules for the development of therapeutic agents for these diseases. In this study, I focused on the vitamin D receptor (VDR) and the androgen receptor (AR), and have developed and synthesized novel compounds that regulate the function of these nuclear receptors.

In chapter 2, I describes the development of novel vitamin D receptor (VDR) agonists. Most of the VDR ligands so far developed have the same secosteroid skeleton as the natural ligand, active vitamin D_3 (VD3). The secosteroid skeleton is useful backbone for development of highly active derivatives, while it has some disadvantages, such as the complicated synthesis, and poor chemical stability. Therefore, development of non-secosteroid type VDR ligands is desired for further clinical application of vitamin D derivatives. Lithocholic acid (LCA, Fig. 1) was a secondary bile acid, and was identified as the second endogenous VDR ligand by Makishima et al. in 2002. The VDR agonistic activity of LCA is much weaker compared to VD3. In this study, I tried to develop novel LCA derivatives with higher activity.

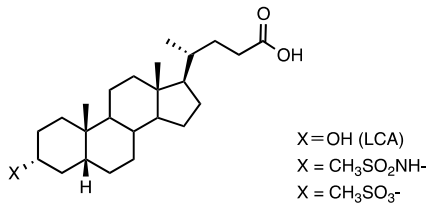

Fig.1　Structures of lithocholic acid and 3-position derivatives

Based on the crystal structure of a complex of lithocholic acid and VDR ligand binding domain (LDB), several lithocholic acid derivatives with various substituents at the 3-position or the side chain were designed and synthesized. VDR agonistic activities of the synthesized compounds were examined by using differentiation-induction assay of human promyelocytic leukemia HL-60 cells. For the 3-position derivatives of LCA, introduction of nitrogen functional group was examined. Among the nitrogen-containing derivatives synthesized, the 3-sulfonamide derivative had the differentiation-inducing activity of HL-60 cells. Although the activity was lower than the compound having the corresponding oxygen functional group (sulfonate group), it had higher activity than LCA. The sulfonamide bond is chemically stable, compared to the sulfonate group, and I believe that it is possible to develop higher active non-secosteroid-type vitamin D derivatives by optimizing the structure of this compound.

In chapters 3 and 4, I described the development of novel androgen receptor (AR) antagonists. AR antagonists

have been used as drug for the prostate cancer. A number of AR antagonists with steroid or non-steroidal skeleton have been developed, and some of them are clinically applied. However, AR antagonists in clinical use have a problem of causing drug resistance or cancer progression (castration-resistant prostate cancer; CRPC) after their long-term treatment. The mutation of AR is significant factors for CRPC, and therefore, development of AR antagonists effective towards mutated AR is desired.

In Chapter 3, I designed diarylcarborane derivatives (Fig. 2) as AR antagonists with carborane as the hydrophobic backbone, and evaluated their activity as AR antagonists. Various carborane derivatives were synthesized by introducing aromatic rings into *p*-carborane by Ulmann type coupling reactions. Some of the synthesized compounds showed moderate AR antagonistic activity, and I found unique compound showing both agonistic activity and antagonistic activity. Based on the structural information obtained in this study, I would like to design and synthesize more active compounds in the future, and to examine the detailed functions as AR antagonists.

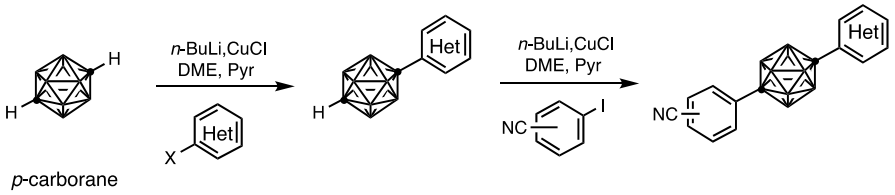

Fig. 2. General structure and synthesis method of diarylcarborane derivatives

In Chapter 4, I designed and synthesized AR antagonist candidates with a phenoxyphenol skeleton, designed based on the structure of curcumin. Various derivatives including compounds with the various substituents on the aromatic ring, *N*-alkylated amide derivatives, and sulfonamide derivatives were systematically synthesized. Among the synthesized compounds, **4-71** and **4-73** exhibited the most potent growth-inhibitory activity toward androgen-dependent cells LNCaP and 22Rv1, having mutated ARs. These compounds inhibited also the growth of AR-independent PC-3 cells, which means that they has AR-independent activity besides AR antagonistic functions.

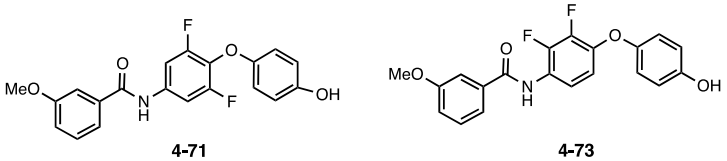

Fig. 3 Structures of compounds **4-71** and **4-73** having AR antagonist activity

In conclusion, I designed and synthesized various ligands for vitamin D receptor and androgen receptor with unique structures. As a result, I found novel VDR agonists and AR antagonists and obtained the significant structural information on these nuclear receptor ligands. In particular, AR antagonists **4-71** and **4-73**, can act as antagonists towards the mutated ARs causing clinical problems, and therefore they can be lead compounds for the development of drug candidates by further structural optimization and detailed functional analyses.