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**Discovery of TAK-700, a highly selective oral 17,20-lyase inhibitor for the treatment of prostate cancer**

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17,20-lyase is a key enzyme in androgen synthesis that converts 17α-hydroxypregnenolone to dihydroepiandrosterone (DHEA). Its inhibitors can suppress androgens produced in both testicular and adrenal organs, and are expected to be a new treatment for castration-resistant prostate cancer, especially since their involvement in adrenal androgen proliferation has been suggested. In addition, 17,20-lyase is an enzyme belonging to the CYP family, and high selectivity for drug-metabolizing enzymes such as CYP3A4 was considered essential for its inhibitor profile. Therefore, we initiated research on non-steroidal inhibitors with the aim of creating highly selective 17,20-lyase inhibitors with less concern for drug interactions.

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Based on the structure of 17-α hydroxypregnenolone, the substrate of 17,20-rease, we designed and synthesized *de novo* inhibitors with various steroidal pseudoskeletons. As a result, we found that compound **1** with a naphthalene skeleton and its peripheral derivative 2 showed strong 17,20-rease inhibitory activity (Figure 1). Subsequent close examination of lead compound 2 showed that it increased liver weight after continuous administration to rats for 5 days, raising concerns about its hepatotoxicity. On the other hand, docking studies of compound 2 using a homology model of 17,20-rease suggested that introduction of a fat-soluble or polar group at the benzyl position and introduction of a polar group at the naphthalene ring 6 position are permissible (Figure 2).



In order to find a highly selective inhibitor that avoids hepatotoxicity concerns, we investigated the introduction of a substituent at the benzyl position. As a result, we found that **S-3**, a compound with a hydroxyl group at the benzyl position, exhibits strong 17,20-rease inhibitory activity and has no effect on liver weight gain (Figure 3). While **S-3, which** avoids hepatotoxicity concerns, exhibits strong 17,20-rease inhibitory activity, it also exhibits strong inhibitory activity against drug-metabolizing enzymes such as CYP3A4, indicating the need to further improve enzyme selectivity. In order to improve the enzyme selectivity, modification of the benzyl and naphthalene 6-positions, which were suggested to have potential for structural optimization based on a docking study using a homology model, was continued, and a novel 17,20-lyase inhibitor (**TAK-700**) with a fused imidazole ring was successfully identified. The result was the discovery of a new 17,20-lyase inhibitor (TAK-700) with a fused imidazole ring.



TAK-700 exhibits strong 17,20-rease inhibitory activity and high selectivity for drug-metabolizing enzymes, and has demonstrated potent testosterone- and DHEA-lowering effects in *in vivo* studies in monkeys. A Phase II study to evaluate the safety and efficacy of TAK-700 is currently underway in the United States.

In this presentation, we will show the research process from *de novo* design to the creation of **TAK-700**, the structure-activity relationship on enzyme selectivity, and the profile of TAK-700.

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