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Chemical synthesis of an indomethacin ester prodrug and its metabolic activation by human carboxylesterase 1

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ABSTRACT

It is necessary to consider the affinity of prodrugs for metabolic enzymes for efficient activation of the prodrugs in the body. Although many prodrugs have been synthesized with consideration of these chemical properties, there has been little study on the design of a structure with consideration of biological properties such as substrate recognition ability of metabolic enzymes. In this report, chemical synthesis and evaluation of indomethacin prodrugs metabolically activated by human carboxylesterase 1 (hCES1) are described. The synthesized prodrugs were subjected to hydrolysis reactions in solutions of human liver microsomes (HLM), human intestine microsomes (HIM) and hCES1, and the hydrolytic parameters were investigated to evaluate the hydrolytic rates of these prodrugs and to elucidate the substrate recognition ability of hCES1. It was found that the hydrolytic rates greatly change depending on the steric hindrance and stereochemistry of the ester in HLM, HIM and hCES1 solutions. Furthermore, in a hydrolysis reaction catalyzed by hCES1, the V_{max} value of *n*-butyl thioester with chemically high reactivity was significantly lower than that of *n*-butyl ester.

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In recent years, many types of prodrug have been developed for improvement of bioavailability and reduction of side effects. Since various enzymes including carboxylesterases (CESs) participate in the metabolic activation of prodrugs, there has been much discussion about the properties of these enzymes. By catalyzing the hydrolysis of various ester, amide and thioester derivatives, CESs are involved in the metabolic inactivation or activation of many drugs, biological materials, natural products, foods and environmental materials.[1] CESs are categorized into five groups (CES1–CES5) based on the amino acid sequence homology, and the CES1 or CES2 group is the major group of CESs in mammals.[2–4] Substrates with a small alcoxy group, such as methyl ester derivatives (cocaine[5] and methylphenidate)[6] and ethyl ester derivatives (meperidine,[7] temocapril,[8] and oseltamivir),[9] are mainly catalyzed by the CES1 isozyme. Conversely, substrates with a small acyl group, such as benzoate derivatives (cocaine),[5] (1,4′-bipiperidin)-1′-ylate derivatives (CPT-11 with a huge alkoxy group)[10] and acetate derivatives (heroin),[11] are mainly catalyzed by the CES2 isozyme. The organ distribution of CESs has also been investigated, and it has been shown that CESs have ubiquitous tissue distribution profiles.[12,13] The CES1 family is mainly distributed in the liver and lung, whereas the CES2 family is mainly distributed in the small intestine and kidney. Therefore, it has been suggested that the substrates catalyzed by CES1 or CES2 are specifically metabolized in each tissue. Previous experiments by our group showed that atorvastatin prodrugs are not hydrolyzed in human intestine microsomes (HIM) or human CES2 (hCES2) solution but are hydrolyzed in human liver microsomes (HLM) and human CES1 (hCES1) solution[14]

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, diclofenac, ibuprofen and indomethacin are one of the most widely prescribed group of drugs. However, long-term use of NSAIDs might cause gastroduodenal mucosal injury.[15] For decreasing the side effects of indomethacin, prodrugs such as acemethacin[16,17] and indomethacin farnecil[18] have been developed. Recently, results of studies on an oral prodrug of indomethacin in which a cilexetil, pivoxil[19] or glycosyl[20] group was substituted have also been reported. Some studies have suggested that an indomethacin-conjugated anticancer prodrug is effective for targeting cancer cells.[21,22] Thus, many researchers have attempted to synthesize indomethacin prodrugs. However, there has been little study on the design and synthesis of an indomethacin prodrug activated by hCES1.

The purpose of the present study was to synthesize a new indomethacin ester prodrug activated by hCES1 and to investigate the

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detailed substrate specificity of hCES1 for theoretical design of prodrugs. First, the chemical synthesis of indomethacin ester and thioester prodrugs was carried out. Then the synthesized prodrugs were subjected to hydrolysis reactions in HLM, HIM and hCES1 solutions, and the hydrolysis rates of these prodrugs were evaluated.

Indomethacin derivatives (**2a**–**2g**) were prepared according to the reported synthetic method (Scheme 1).[23] Treatment of indomethacin and alcohol compounds with dicyclohexylcarbodiimide (DCC) in the presence of dimethylaminopyridine (DMAP) provided the *n*-butyl ester **2a**,[23,24] *sec*-butyl ester **2b**, isobutyl ester **2c** and neopentyl ester **2e** in moderate yields. Although the yields were low, other esters such as *tert*-butyl ester **2d**,[25] 1-phenylpropyl ester **2f** and *n*-butyl thioester **2g** were synthesized by the same method. Substrates with a chiral center, such as *sec*-butyl ester **2b** and 1-phenylpropyl ester **2f**, were synthesized using their respective chiral alcohol compounds. The structures of the synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR, and IR analyses.

First, the synthesized prodrugs (**2a**–**2g**) were subjected to hydrolysis reaction in HLM solution, and the hydrolysis rates were investigated (Fig. 1). The results showed that *n*-butyl ester **2a** had the highest hydrolysis rate among all of the prodrugs (**2a**–**2g**). A comparison of the C4-alkyl ester derivatives (**2a**–**2d**) showed that the hydrolysis rate greatly differs depending on the structure and configuration of carbon atoms of the alkoxy group. Although neopentyl ester **2e** has a bulky quaternary carbon, the hydrolysis rate of **2e** was not significantly reduced in comparison with that of *tert*–butyl ester **2d**. Therefore, it was thought that the hydrolysis rate in HLM solution is greatly influenced by steric hindrance of the neighboring carbon of the ester. In the *sec*-butyl ester derivative **2b** with a chiral center, the hydrolysis rate of the (*S*)-isomer was 2.1-times higher than that of the (*R*)-isomer. Surprisingly, 1-phenylpropyl ester **2f**, in which the hydrolysis rate of the (*R*)-isomer was 8.2-times higher than that of the (*S*)-isomer, has a reversed enantioselectivity from *sec*-butyl ester **2b**. Even for substrates with the same *n*-butyl group, it was found that the hydrolysis rate of thioester **2g** was 2.7-times lower than that of ester **2a**. The results suggested that indomethacin ester derivatives are more effectively hydrolyzed than are indomethacin thioester derivatives in HLM solution.

Next, prodrugs (**2a**–**2g**) were subjected to hydrolysis reaction in HIM solution, and the hydrolysis rates were investigated (Fig. 2). The data showed that the hydrolysis rates of C4-alkyl ester prodrugs (**2a**–**2d**) in HIM solution are similar to those in HLM solution. In the *sec*-butyl ester derivative **2b**, the hydrolysis rate of the (*S*)-isomer was 1.9-times higher than that of the (*R*)-isomer. Despite the high enantioselectivity in HLM solution, the hydrolysis rates of 1-phenylpropyl ester isomers **2f** were almost the same as those in HIM solution. The hydrolysis rate of *n*-butyl thioester **2g** was slightly higher than that of *n*-butyl ester **2a**. In terms of enantioselectivity or functional group selectivity, different results were obtained for the hydrolytic rates of indomethacin prodrugs in HLM and HIM solutions. On the whole, the hydrolytic rates of all of the prodrugs (**2a**–**2g**) in HIM solution were significantly lower than those in HLM solution. The results therefore suggested that all of the prodrugs (**2a**–**2g**) are efficiently hydrolyzed not in the human intestine but in the human liver.

Finally, the prodrugs (**2a**–**2g**) were subjected to hydrolysis reaction in hCES1b solution, and the kinetic parameters were determined (Table 1). hCES1b is also referred to as CES1A1, which is mainly expressed in the human liver. The K_m and V_{max} values were

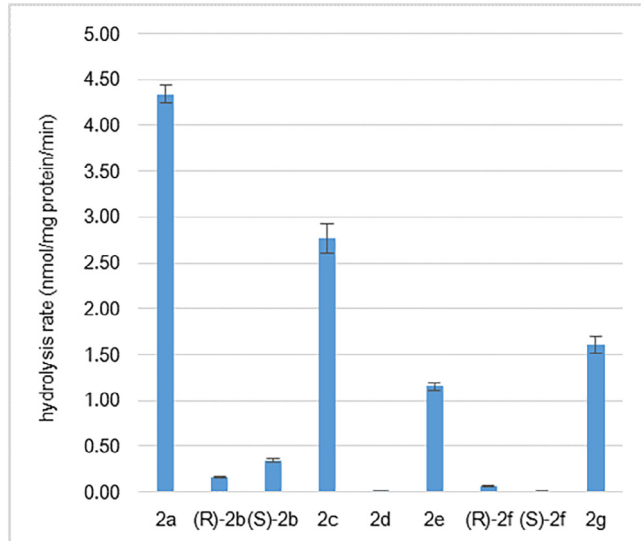
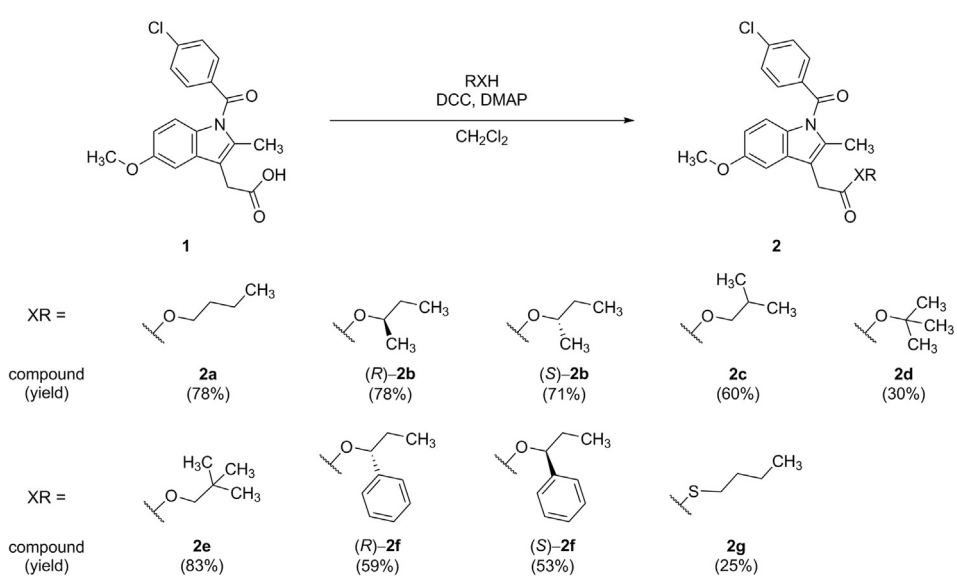


Fig. 1. Hydrolysis rates of indomethacin ester derivatives (**2a**–**2f**) and a thioester derivative (**2g**) in HLM solution. Values are means ± S.D. (n = 3).



Scheme 1. Synthesis of indomethacin ester derivatives (**2a–2f**) and a thioester derivative **2g**.

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