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Research paper

Design, synthesis, and structure-activity relationship study of glycyrrhetinic acid derivatives as potent and selective inhibitors against human carboxylesterase 2

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ABSTRACT

Human carboxylesterase 2 (hCE2), one of the major carboxylesterases in the human intestine and various tumour tissues, plays important roles in the oral bioavailability and treatment outcomes of ester- or amide-containing drugs or prodrugs, such as anticancer agents CPT-11 (irinotecan) and LY2334737 (gemcitabine). In this study, 18β-glycyrrhetinic acid (GA), the most abundant pentacyclic triterpenoid from natural source, was selected as a reference compound for the development of potent and specific inhibitors against hCE2. Simple semi-synthetic modulation on GA was performed to obtain a series of GA derivatives. Structure-activity relationship analysis brought novel insights into the structure modification of GA. Converting the 11-oxo-12-ene of GA to 12-diene moiety, and C-3 hydroxyl and C-30 carboxyl group to 3-O-β-carboxypropionyl and ethyl ester respectively, led to a significant enhancement of the inhibitory effect on hCE2 and the selectivity over hCE1. These exciting findings inspired us to design and synthesize the more potent compound **15** (IC_{50} 0.02 μM) as a novel and highly selective inhibitor against hCE2, which was 3463-fold more potent than the parent compound GA and demonstrated excellent selectivity (>1000-fold over hCE1). The molecular docking study of compound **15** and the active site of hCE1 and hCE2 demonstrated that the potent and selective inhibition of compound **15** toward hCE2 could partially be attributed to its relatively stronger interactions with hCE2 than with hCE1.

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1. Introduction

Carboxylesterases (CEs, E.C.3.1.1.1) are members of the serine hydrolase superfamily that cleaves carboxyesters into the corresponding carboxylic acid and alcohol via a proton transfer hydrolysis mechanism by a catalytic Ser-His-Glu triad. These enzymes are widely distributed in metazoan and especially common in mammalian tissues associated with the metabolism of xenobiotics and endobiotics [1–3]. As an important class of phase I metabolizing enzymes in mammals, CEs efficiently mediate the detoxification of environmental toxins and the metabolism of ester compounds [4–6]. In human, most CEs identified to date belong to two isoforms, human carboxylesterase 1 (hCE1) and human carboxylesterase 2 (hCE2) [7]. hCE1 is expressed in many organs, especially in the liver, but its expression in the gastrointestinal tract is markedly low, whereas hCE2 is the major CEs distributed in intestine but at relatively lower level in liver [8–10]. The selective expression of hCE2 in enterocytes may represent a defensive barrier that esterified xenobiotics need to breech before the organism is exposed following ingestion [11]. Thus, hCE2 is considered to be an important modulator of oral ester-containing drugs and other ester-containing xenobiotics during the first-pass metabolism.

Furthermore, hCE2 is the major CE in many tumour tissues and also plays an important role in the treatment outcomes of ester anticancer agents [9,12]. For example, CPT-11 (irinotecan), a

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carbamate prodrug prescribed for the treatment of colorectal cancer, is hydrolyzed by CEs to yield its active form SN-38 (ethyl-10-hydroxy-camptothecin) [13,14]. However, CPT-11 induced delayed diarrhoea is strongly associated with the activation of the prodrug by hCE2 in the small intestine [13,15]. Therefore, it is hypothesized that the co-administration of the potent and selective hCE2 inhibitor may alleviate CPT-11 associated toxicity. Such a strategy could block the hydrolysis of CPT-11 in the human intestine and thus reduce the exposure of intestinal SN-38, which may alleviate CPT-11 associated diarrhoea [16–18]. Therefore, it is highly desirable to find potent and selective hCE2 inhibitors which may have wide applications in either the alleviation of prodrug associated toxicities or increasing the bioavailability of oral ester-containing drugs that are inactivated by hCE2.

Glycyrrhetinic acid (GA), the major bioactive ingredient of the roots and rhizomes of licorice (*Glycyrrhiza* species), is a famous herbal medicine component in both eastern and western countries [19,20]. Over the past decade, GA has been used as an effective structural template in searching for more potent lead compounds with diverse pharmacological properties, such as anti-inflammation, anti-ulcer, anti-tumor, anti-virus, and anti-hepatotoxic activities [21–26]. Despite these sporadic reports, the potential applications of GA and its derivatives for developing novel pharmacological properties are far from being comprehensively exploited. As a safe natural product, the anti-inflammatory and anti-bacterial activities of GA could reduce CPT-11 associated diarrhoea and improve the life quality of irinotecan prescribed patients [27–30]. In recent years, screening of the specific and potent inhibitors toward hCE2 from medicinal plants and their extracts for translational applications has attracted increasing attentions [31–34]. However, to the best of our knowledge, there is no literature concerning with GA and its derivatives in the aforementioned field. Here, we select GA as the scaffold and focus on its structural modifications by the following strategies: (a) building up a 3-one or ester moiety in ring A of GA; (b) converting the 11-oxo-12-ene of GA in ring C to 12-diene moiety; (c) altering the C-30 carboxyl group to ester, amide, or nitrile functionality. The purpose of this study was to explore the detailed structure-activity relationship (SAR) of a series of GA derivatives as hCE2 inhibitors, which was then used to design more potent and selective hCE2 inhibitors based on GA skeleton.

2. Results and discussion

2.1. Chemistry

GA derivative compounds **2**–**13** were synthesized according to Scheme 1. The GA (**1**) was reduced with zinc in the presence of concentrated hydrochloric acid to afford the 11-deoxo compound **2**. 3-Keto compounds **3** and **4** were obtained with the Jones' reagent in high yield from GA and compound **2** respectively. Reaction of the corresponding haloalkane with GA furnished the target compounds **5**–**7**, in over 80% yields. GA was acetylated in C-3 with acetic anhydride in pyridine to obtain ester **9** with high yield (95%). Compound **12** was synthesized from **7** by the same method as compound **9**, with only 37% yield. Compound **9**, the acetate of GA, was then treated with oxalyl chloride without isolation, and further reacted with concentrated ammonia to afford amide **10** in a yield of 94% over two steps. Compound **10** was hydrolyzed by NaOH to afford compound **8** in 90% yield. The 3β-hydroxy group of **6** was reacted with succinic anhydride in the presence of 4-dimethylaminopyridine (DMAP) to obtain the target product **13** in 75% yield.

2.2. SAR study

GA and its derivatives were evaluated for their inhibitory activities against human CEs (including hCE1 and hCE2). The bioassay results are summarized in Table 1. The parent compound GA (**1**) exhibited poor inhibitory effect on those two hCEs. The 11-ketal moiety of the GA, surprisingly, was found to markedly influence the compound inhibitory effect on hCE2. The compound **2**, 11-deoxo-GA derivative, showed promising inhibitory activity against hCE2 with IC_{50} value to be as low as 6.95 μM and 10-fold more efficient than the parent compound, whereas the inhibitory effect toward hCE1 was only slightly increasing. Compounds **3** and **4** exhibited relatively low inhibitory activities against hCEs as compared with GA and compound **2**, respectively, suggesting that the introduction of carbonyl group at C-3 results in a loss of potency. Further modifications to the 30-position including esters, amides and nitriles are listed in Table 1. Esterified compounds **5** and **6**, with small alkyl groups such as methyl and ethyl, are potent selective inhibitors of hCE2 instead of hCE1. Compound **7** bearing a bulky hydrophilic ester showed enhanced inhibitory effect but poor selectivity toward hCE2, in contrast to compounds **5** and **6**. The amide derivative, compound **8**, displayed moderate inhibitory effect on hCE2, and its inhibition against hCE1 was significantly reduced, compared with ester derivatives **5**–**7**. Compound **11** could inhibit neither hCE1 nor hCE2 ($IC_{50} > 100$ μM), indicating that the nitrile group introduced in such a position is not beneficial for compound inhibitory property toward hCEs. Replacements of the C-3 hydroxyl group with ethyl ester in compounds **9** and **10** led to an increase of the inhibitory effects on hCE2 and a considerable selectivity toward hCE2 rather than hCE1, as compared with GA and compound **8**. Compound **12** had a similar range of activity as compound **7**, while replacement of the C-3 ethyl ester group with 3-O-β-carboxypropionyl in compound **13** led to a dramatic increase of the inhibitory effect and specificity toward hCE2. Compound **13** exhibited potent inhibitory effect on hCE2 with the relatively low IC_{50} (0.66 μM) and strict selectivity toward hCE2. These results are summarized in Fig. 1 and enable us to better understand the SAR of GA-derived hCE2 inhibitors. The structure modifications of GA, i.e., converting the 11-oxo-12-ene to 12-diene moiety, as well as C-3 hydroxyl and C-30 carboxyl group to 3-O-β-carboxypropionyl and ester respectively, led to a dramatic increase of the inhibitory effect on hCE2 and selectivity over hCE1.

2.3. Design of a novel potent inhibitor

With these SAR results, we next designed and synthesized a novel GA derivative compound **15** that may exhibit more potent and higher selective inhibitory effect on hCE2. The synthetic route is described in Scheme 2. Compound **2** was introduced with ethyl ester in C-30 with ethyl bromide in the presence of potassium carbonate to obtain compound **14**, and its yield was 80%. The 3β-hydroxy group of **14** was reacted with succinic anhydride to harvest the target product **15** in 75% yield. The novel compound **15** showed unusually potent inhibitory activity against hCE2 with much lower IC_{50} value of 0.02 μM and was 3463-fold more potent than the parent compound GA, and it was 1020-fold more selective over hCE1. For comparison, two reported positive inhibitors (BNPP and bavachinin) were tested [34,35]. The result indicated that both compounds showed inferior inhibitory activity and selectivity compared to compound **15**. Furthermore, our results indicated that compound **15** acted as a competitive inhibitor of hCE2 and exhibited a K_i value of 0.042 μM in the human liver microsomes (HLMs) (Supporting Information (SI) Fig. 1). To the best of our knowledge, compound **15** is the most potent hCE2 inhibitor that can work in human tissue preparations. Compound **15** could be

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