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Structure-based optimization of free fatty acid receptor 1 agonists bearing thiazole scaffold

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ABSTRACT

The free fatty acid receptor 1 (FFA1) plays an important role in amplifying insulin secretion in a glucose dependent manner. We have previously reported a series of FFA1 agonists with thiazole scaffold exemplified by compound **1**, and identified a small hydrophobic subpocket partially occupied by the methyl group of compound **1**. Herein, we describe further structure optimization to better fit the small hydrophobic subpocket by replacing the small methyl group with other hydrophobic substituents. All of these efforts resulted in the identification of compound **6**, a potent FFA1 agonist (EC_{50} = 39.7 nM) with desired ligand efficiency (0.24) and ligand lipophilicity efficiency (4.7). Moreover, lead compound **6** exhibited a greater potential for decreasing the hyperglycemia levels than compound **1** during an oral glucose tolerance test. In summary, compound **6** is a promising FFA1 agonist for further investigation, and the structure-based study promoted our understanding for the binding pocket of FFA1.

1. Introduction

Type 2 diabetes mellitus (T2DM), a chronic metabolic disease, is associated with insufficient insulin secretion and tissue insulin resistance [1,2]. Besides the healthy lifestyle, the common administration emphasizes oral glucose-lowering drugs, especially in combination treatment, until the levels of blood glucose are in good control [3–5]. There are a lot of anti-diabetic drugs for the treatment of T2DM, while many of them are related to problems including the risk of hypoglycemia, gained body weight, and lack of persistent efficacy [6]. Hence, there is an unmet clinical need for therapeutics with improved safety and efficacy [7–9].

The long-chain free fatty acid receptor 1 (FFA1), also known as G protein-coupled receptor 40 (GPR40), is mainly located in pancreatic β-cells, which enhanced insulin secretion in a glucose-dependent manner [10–13]. The activation of FFA1 in pancreatic β-cells improves the activity of phospholipase C, generating the inositol triphosphate. Then, the increased Ca^{2+} levels was derived from endoplasmic reticulum, leading to an enhanced insulin secretion in a glucose-dependent manner [14,15]. Currently, the pathway of FFA1–PLC/PKC–TRPC3 was identified as a cooperator of K_{ATP} channel in the secretion of insulin [16].

Recently, a lot of FFA1 agonists bearing carboxylic acid moiety have been reported (Fig. 1) [17–26]. Notably, there are several candidates have progressed in clinical trials [27,28]. So far, series of FFA1 agonists with different scaffolds have been explored in our laboratory [26,29–35]. Among these study, we independently identified compound **1** (Fig. 1) by comprehensively exploring eleven heteroaromatic scaffolds [26]. Interestingly, the methyl group at thiazole of compound **1** occupied a small hydrophobic subpocket (Fig. 2A), which had no hydrophobic interactions with TAK-875, the foreground candidate once in Phase III clinical trials. However, the small hydrophobic subpocket was still not fully occupied by the small methyl group (the red circle in Fig. 2B). To better fit this small hydrophobic subpocket, a series of hydrophobic substituents were incorporated in this study to replace the small methyl group at thiazole ring. Moreover, the drug-like concepts of ligand efficiency (LE) [36] and lipophilicity ($LogD_{7.4}$), as well as ligand lipophilicity efficiency (LLE) [37] have been introduced to avoid oversized molecular and lipophilicity, which is usually related to high promiscuity, metabolic instability, and a higher attrition in drug development [38–42]. After exploration of structure-activity relationship and application of docking model, the potent agonist **6** and its binding mode were identified. In pharmacological study,

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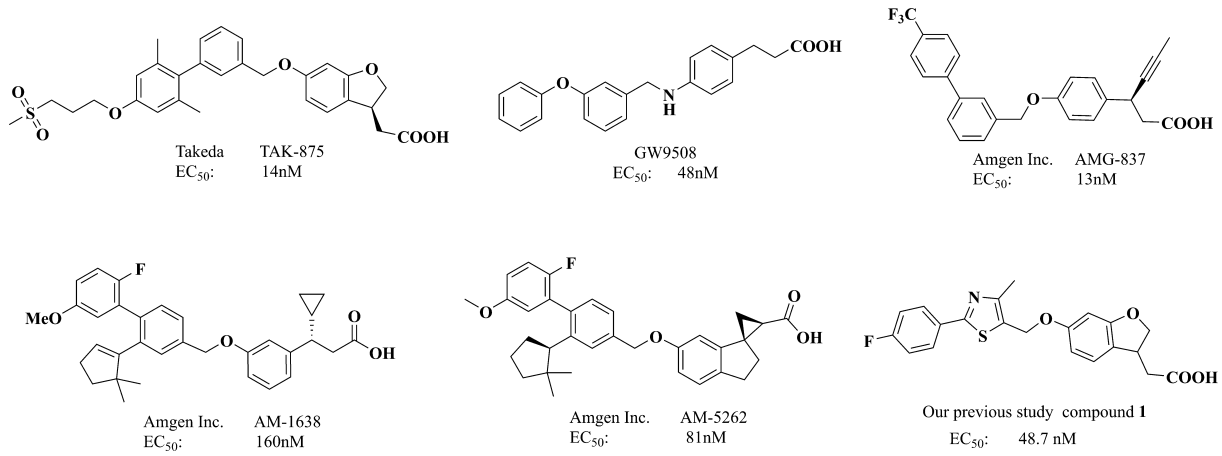

Fig. 1. Examples of small molecule FFA1 agonists.

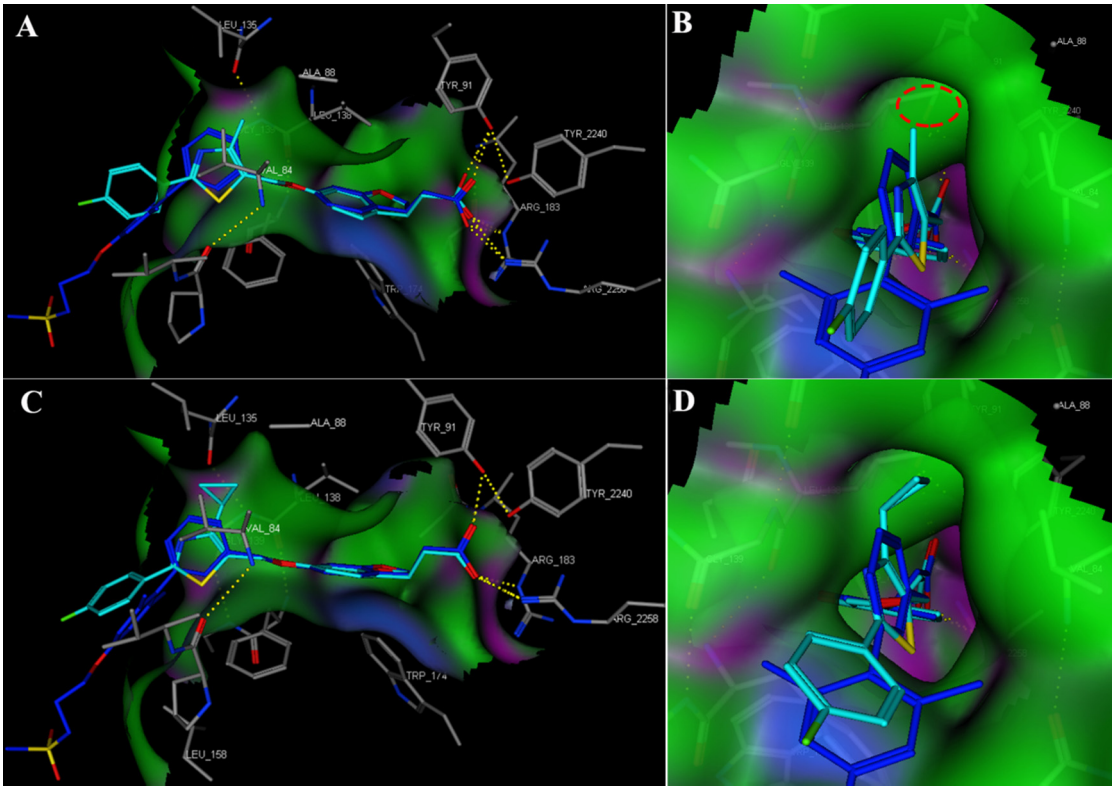

Fig. 2. The frontal view (A) and side-view (B) in docking model of compound 1 (silvery) in crystal structure of hFFA1. The frontal view (C) and side-view (D) in docking model of compound 6 (silvery) in crystal structure of hFFA1. Key residues are labeled in white, TAK-875 is represented by blue, and hydrogen bonding interactions are represented by yellow dashed lines, the unoccupied subpocket is highlighted by a red circle.

compound **6** revealed a stronger glucose-lowering effect than compound **1**.

2. Results and discussion

2.1. Chemistry

The synthetic routes of compounds **2**–**7** are summarized in Scheme 1. The selective α-halogenation of various β-keto-esters **1a-f** was performed by a previous reported method with NBS in DMSO [43]. The obtained intermediates **2a-f** were treated with 4-fluorothiobenzamide to afford thiazole esters **3a-f** [44]. Subsequently, the intermediates **3a-f** underwent reduction with $NaBH_4$ in methanol [45], which were then treated with thionyl chloride to deliver intermediates **4a-f**. The synthesis of intermediate **7a** began with commercially available resorcinol **5a**, followed by Pechmann reaction to provide intermediate **6a**. Treatment of intermediate **6a** with a sodium hydroxide aqueous solution triggered the intramolecular ring-opening and recyclization, followed by esterification to obtain the intermediate **7a**. The catalytic hydrogenation of **7a** under hydrogen atmosphere furnished the dihydrobenzofuran **8a** [17], which was further condensed with **4a-e** by Williamson ether synthesis, followed by basic hydrolysis, afforded the desired target compounds **2**–**7**.