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Structure-based design of free fatty acid receptor 1 agonists bearing non-biphenyl scaffold

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ABSTRACT

The free fatty acid receptor 1 (FFA1) enhances the glucose-stimulated insulin secretion without the risk of hypoglycemia. However, most of FFA1 agonists have a common biphenyl moiety, leading to a relative deprivation in structure types. Herein, we describe the exploration of non-biphenyl scaffold based on the co-crystal structure of FFA1 to increase additional interactions with the lateral residues, which led to the identification of lead compounds **3** and **9**. In induced-fit docking study, compound **3** forms an edge-on interaction with Trp150 by slightly rotating the indole ring of Trp150, and compound **9** has additional hydrogen bond and δ-π interactions with Leu135, which demonstrated the feasibility of our design strategy. Moreover, lead compounds **3** and **9** revealed improved polar surface area compared to GW9508, and have considerable hypoglycemic effects in mice. This structure-based study might inspire us to design more promising FFA1 agonists by increasing additional interactions with the residues outside of binding pocket.

1. Introduction

Type 2 diabetes mellitus (T2DM), a worldwide metabolic disease, characterized by impaired glucose homeostasis due to insulin deficiency and/or desensitization [1,2]. There are many pharmacotherapies developed for the treatment of T2DM, but most of drugs are often related to the side effects such as hypoglycemia, gastrointestinal discomfort and body weight gain [3–6]. Therefore, a novel agent with improved safety and efficacy is still an unmet need for T2DM [7,8]. The long-chain free fatty acid receptor 1 (FFA1, previously known as GPR40), a new antidiabetic target in pancreatic β-cells, enhances the glucose-stimulated insulin secretion without the risk of hypoglycemia [9–12]. Hence, the FFA1 agonists might provide enormous advantage for the treatment of T2DM by decreasing the risk of hypoglycemia.

Recently, a lot of synthetic FFA1 agonists containing acidic moieties have been reported (Fig. 1) [13–21]. Notably, most of FFA1 agonists usually have the common biphenyl scaffold, which resulted in a relative deprivation in structure types of agonists [22,23]. To enlarge the chemical space of FFA1 agonists, different structure scaffolds were introduced in our previous studies [24–32]. Currently, Srivastava et al. reported the co-crystal structure of FFA1 bound with TAK-875 (Fig. 2) [33]. Interestingly, the 1,3-dimethyl-5-(3-(methylsulphonyl)propoxy) benzene group of TAK-875 (left-hand of diphenyl scaffold) was exposed to the outside of receptor without direct interaction with FFA1. Therefore, we hypotheses the optimization of terminal benzene ring will further increase the interactions with the lateral residues such as Leu135, Val81 or Pro80.

Herein, GW9508 (Fig. 1) was selected as lead compound due to its high-activity and unique non-biphenyl scaffold. However, the phenylpropanoic acid of GW9508 was susceptibility to β-oxidation, so the (2,3-dihydro-1-benzofuran-3-yl)acetic acid moiety of TAK-875 was introduced in this study (Fig. 3). Moreover, the function of FFA1 expressed in brain is unclear [10], and FFA1 agonist with low polar surface area (tPSA) exhibited obvious central nervous system (CNS) exposure [34]. Thus, the improvement of tPSA values is also an important design strategy to obtain drug-like lead compounds in this research. After exploration of series of non-biphenyl scaffolds, the potent lead compounds and their binding mode were identified.

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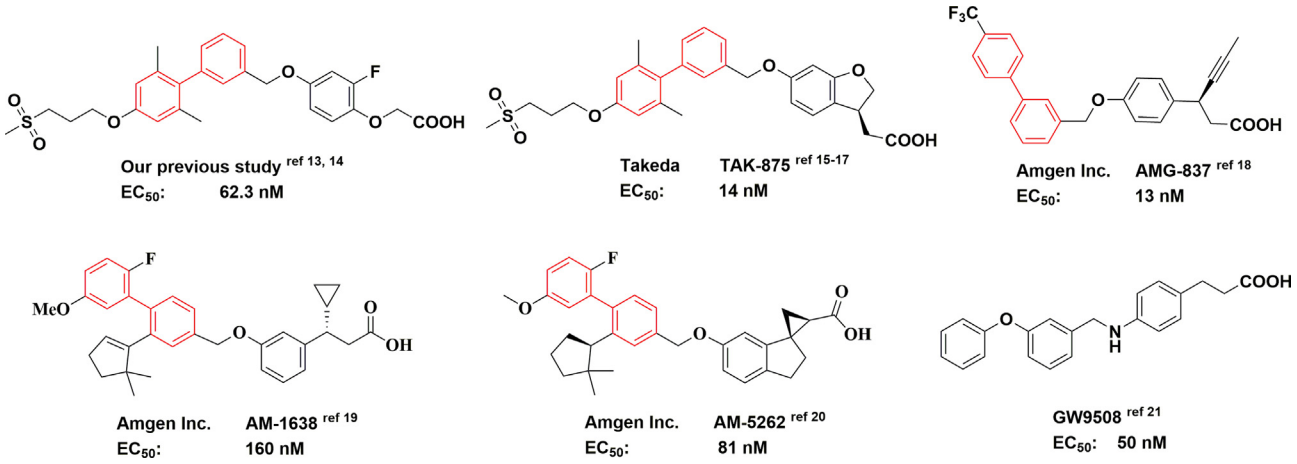

Fig. 1. Synthetic FFA1 agonists.

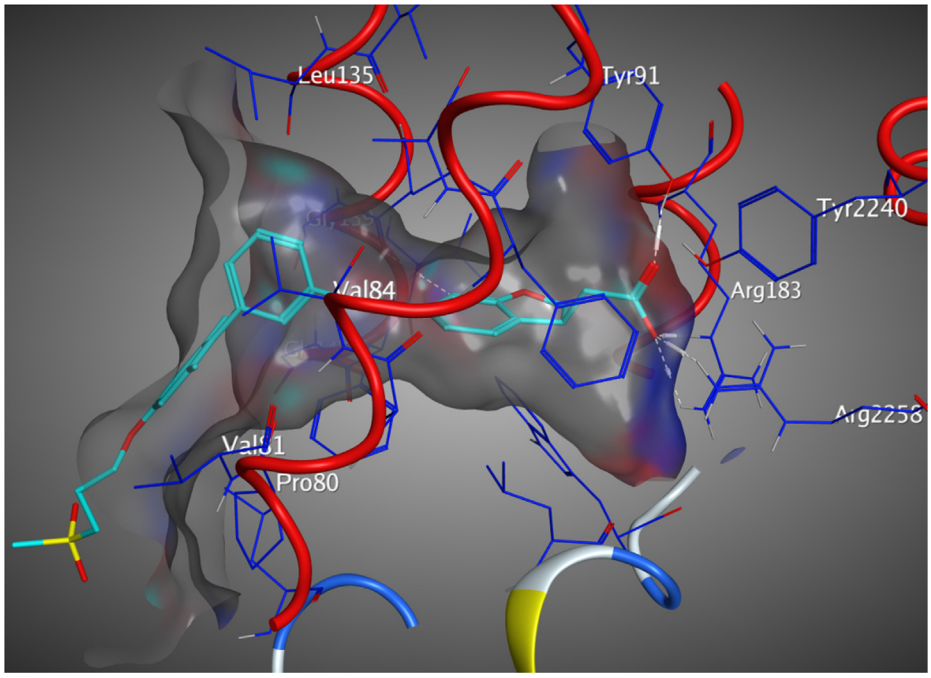

Fig. 2. The co-crystal structure of FFA1 with TAK-875 (PDB code: 4PHU). The key residues are labeled in white, and hydrogen bonds are represented by white dashed lines.

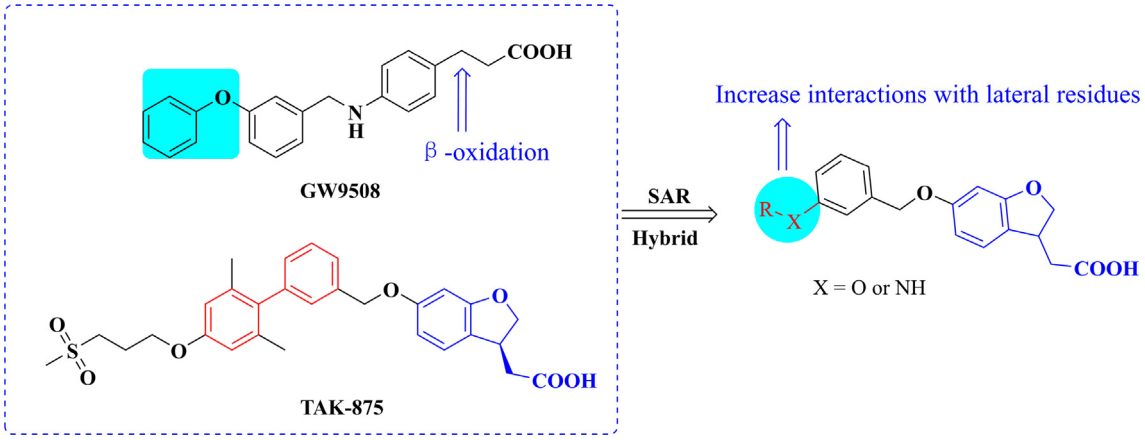

Fig. 3. Hybrid strategy of GW9508 and TAK-875.