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Design, synthesis and structure–activity relationship studies of novel phenoxyacetamide-based free fatty acid receptor 1 agonists for the treatment of type 2 diabetes

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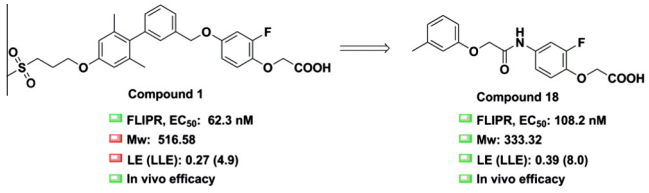
ABSTRACT



The free fatty acid receptor 1 (FFA1) has attracted extensive attention as a novel antidiabetic target in the last decade. Several FFA1 agonists reported in the literature have been suffered from relatively high molecular weight and lipophilicity. We have previously reported the FFA1 agonist **1**. Based on the common amide structural characteristic of SAR1 and NIH screened compound, we here describe the continued structure–activity exploration to decrease the molecular weight and lipophilicity of the compound **1** series by converting various amide linkers. All of these efforts lead to the discovery of the preferable lead compound **18**, a compound with considerable agonistic activity, high LE and LLE values, lower lipophilicity than previously reported agonists, and appreciable efficacy on glucose tolerance in both normal and type 2 diabetic mice.

1. Introduction

The increasing and alarming prevalence of type 2 diabetes mellitus (T2DM) along with the undesirable side effects (such as body weight gain, gastric symptoms, risk of hypoglycemia, etc.) associated with many oral antidiabetic agents has promoted a great development in evaluating novel targets to achieve preferable hypoglycemic drugs.[1–4] The free fatty acid receptor 1 (FFA1, also known as GPR40), the prominent ones of novel antidiabetic targets in the last decade, play a key role in amplifying glucose-stimulated insulin secretion (GSIS) on pancreatic β-cells but does not affect insulin secretion at low blood glucose levels.[5–8] Therefore, this particular mechanism of FFA1 provides the tremendous potential for boosting insulin levels without the risk of hypoglycemia.

Recently, a number of synthetic FFA1 agonists contained acidic moieties have been reported in the literature (Fig. 1),[9–17] and the compounds TAK-875, AMG-837 and LY2881835 were in clinical trials for treatment of T2DM. However, many of these agonists have relatively high molecular weight and lipophilicity (red mark in Fig. 1), which most likely associated with poor water-solubility, high promiscuity, strong metabolic toxicity, and correlated with a high risk of attrition in clinical trials.[18–22] Studies have suggested

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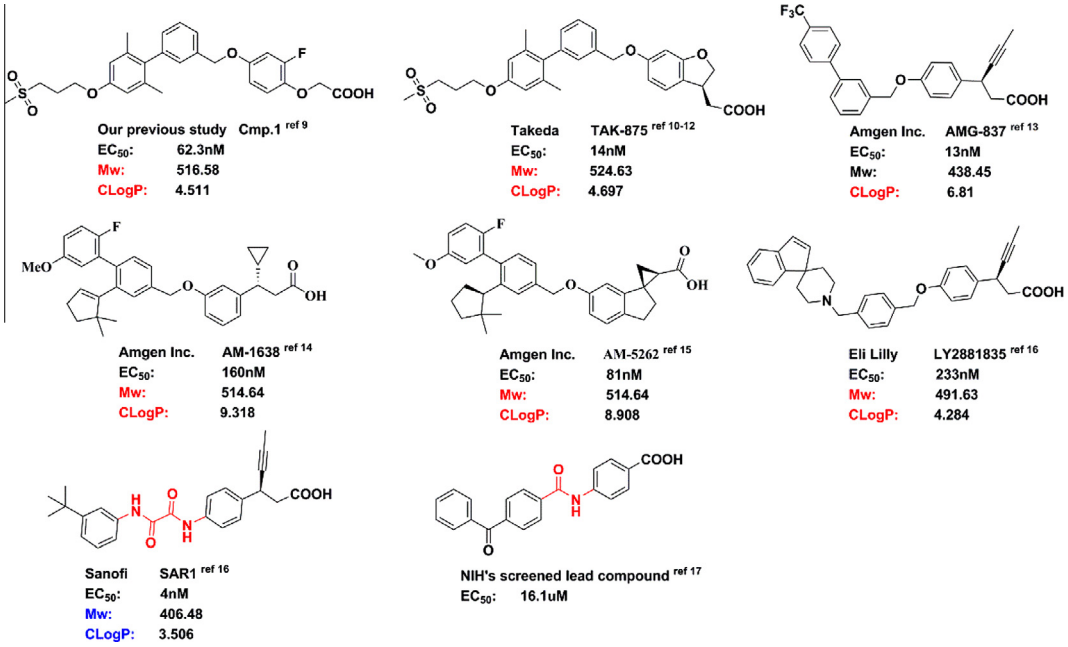

Figure 1. Selected examples of synthetic GPR40 agonists. *c*log*P* values are calculated with ChemDraw Ultra 12.0 using the '*c*log*P*' option.

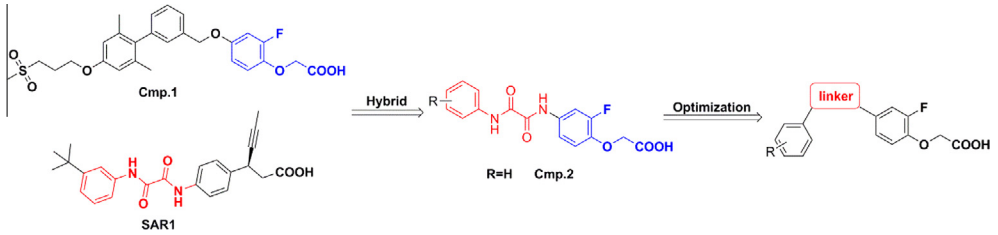

Figure 2. Our strategy to decrease the molecular weight and lipophilicity of compound **1**.

that *c*log*P* values should not exceed 4–5,[18,23] and concepts such as ligand efficiency (LE) and ligand lipophilicity efficiency (LLE) have been recommended to direct the optimization process.[24,25] Inspired by the relatively low molecular weight and lipophilicity of SAR1, we first designed and synthesized compound **2**, which was a hybrid structure containing both the oxalamide moiety of SAR1 and phenoxyacetic acid structure of our previously reported compound **1** (Fig. 2). However, the compound **2** and its analogs appeared to diminish the in vitro agonistic activity, indicating that the interaction mode of compound **2** series was different from SAR1. Subsequently, a series of amide linkers were designed based on the common amide structural characteristic of SAR1 and NIH screened compound. Among them, the most potent amide linker phenoxyacetamide was selected to systematically explore the SAR, which lead to the identification of lead compound **18**, a compound with considerable agonistic activity, high LE and LLE values, lower lipophilicity than previously reported agonists, and appreciable antihyperglycemic effect in both normal and type 2 diabetic mice.

2. Results and discussion

2.1. Chemistry

The synthetic routes of target compounds **2**–**36** are summarized in Scheme 1. The key intermediate **3a** was prepared by the reduction of nitrobenzene **2a**, which was derived from the substitution of commercially available phenol **1a** with methyl chloroacetate in the presence of K_2CO_3. The intermediate **3a** was treated with various substituted anilines and oxalyl chloride, followed by basic hydrolysis, afforded the desired carboxylic acids **2**–**7**. Acylation of the intermediate **3a** with corresponding acyl chloride, formed from commercially available carboxylic acid **4a** or **4b** with oxalyl chloride catalyzed by DMF catalyze, generated the desired esters, which were isolated pure from ethanol. Hydrolysis of esters with lithium hydroxide provided the designed compounds **8** and **9** in high yield. Mono-acylation of the cyclopropane-1,1-dicarboxylic acid with aniline to afford compound **6a**, which was subsequently converted to compounds **10** by acylation with intermediate **3a** and esterolysis. The desired compound **12** was obtained from aniline and compound **3a** in the presence of triphosgene and Et_3N, followed by hydrolysis. The target compounds **11** and **13**–**36** were synthesized from the starting material various substituted phenoxyacetic acid according to the method for the synthesis of compound **8**.

2.2. FFA1 agonistic activity and SAR study

Inspired by the low molecular weight and lipophilicity of SAR1, we first designed and synthesized compound **2**, a hybrid structure containing both the oxalamide moiety of SAR1 and phenoxyacetic acid structure of compound **1**. The compound **2**, however, appeared to diminish the FFA1 agonistic activity compared with the parent compound **1** (Table 1). The introduction of various substituents in compound **2** to give compounds **3**–**7** did not appear to