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Identification of highly potent and orally available free fatty acid receptor 1 agonists bearing isoxazole scaffold

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ABSTRACT

The free fatty acid receptor 1 (FFA1) is being considered to be a novel anti-diabetic target based on its role in amplifying insulin secretion. We have previously identified several series of FFA1 agonists with different heterocyclic scaffolds. Herein, we describe the structural exploration of other heterocyclic scaffolds directed by drug-like physicochemical properties. Further structure-based design and chiral resolution provided the most potent compound **11** (EC_{50} = 7.9 nM), which exhibited improved lipophilicity ($LogD_{7.4}$: 1.93), ligand efficiency (LE = 0.32) and ligand lipophilicity efficiency (LLE = 6.2). Moreover, compound **11** revealed an even better pharmacokinetic property than that of TAK-875 in terms of plasma clearance, maximum concentration, and plasma exposure. Although robust agonistic activity and PK profiles for compound **11**, the glucose-lowering effects *in vivo* is not ideal, and the exact reason for *in vitro*/*in vivo* difference was worthy for further exploration.

1. Introduction

Type 2 diabetes mellitus (T2DM), a most common type of diabetes, is characterized by impaired insulin secretion and/or sensitization.[1,2] Various available oral insulin secretagogues, such as sulfonylureas, are widely used for the treatment of T2DM.[3] However, these available therapies are often related to side effect of hypoglycemia because insulin secretion induced by them are independent of glucose.[4] Thus, there are unmet needs for new oral insulin secretagogues without the risk of hypoglycemia.

The free fatty acid receptor 1 (FFA1, or GPR40), has emerged as an attractive target in the last decade for the treatment of T2DM.[5] FFA1 is predominantly expressed in the pancreatic β-cell and augments insulin secretion dependent on the levels of glucose, providing a huge advantage of reducing incidence rate of hypoglycemia.[6–8] Moreover, the limited tissue distribution of FFA1 suggests that less possibilities of adverse effects related to FFA1 in other tissues.[9]

As summarized in the most recent review,[10] many literatures have reported structurally diverse FFA1 agonists based on arylalkanoic acids (Fig. 1),[11–18] and the clinical trials were performed to evaluate the potential of TAK-875, LY2881835 and AMG-837 as anti-diabetic agents.[5,10] In addition, the chemical space of FFA1 agonists with different scaffolds has also been explored by our colleagues.[17–24] In particular, the common biphenyl scaffold has been systematically replaced by various heterocycles in our laboratory (eg., compounds **1** and **2** in Fig. 1) to reduce the lipophilicity, and the lipophilicity of candidate is usually related to a higher promiscuity, metabolic instability, and failure rates in research and development.[25–29] Herein, we describe our efforts toward discovering preferable heterocycle scaffold with better drug-like physicochemical properties directed by lipophilicity, ligand efficiency (LE) and ligand lipophilicity efficiency (LLE) (Fig. 2). These efforts ultimately led to the identification of compound **11**, a potent agonist with improved physicochemical properties and excellent pharmacokinetic (PK) profiles.

2. Results and discussion

2.1. Chemistry

The synthesis of heterocycle derivatives **3**–**5** and **8**–**11** is shown in Scheme 1. Compound **2** was synthesized *via* our previous published procedures.[18] The intermediates **3a** or **7a** were provided

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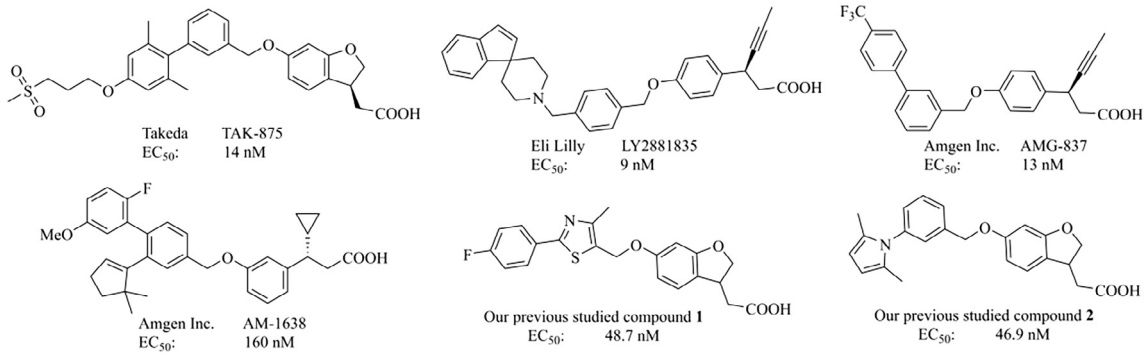


Fig. 1. Synthetic FFA1 agonists.

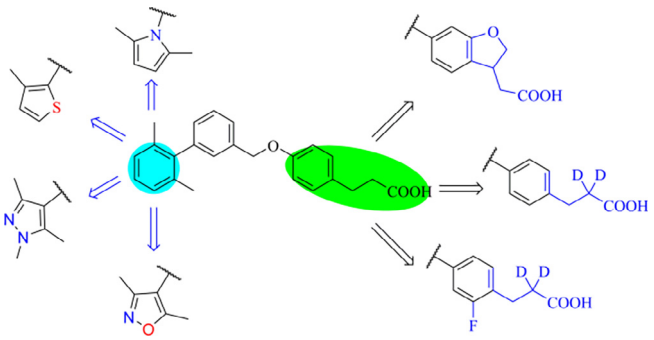


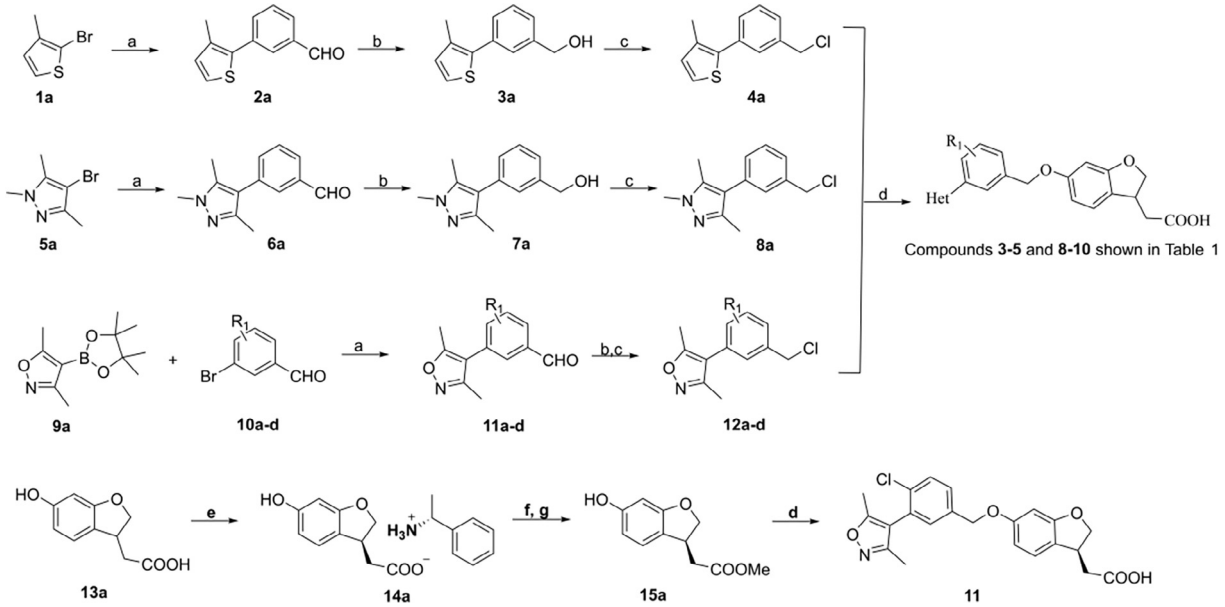
Fig. 2. Design strategy of FFA1 agonists bearing various heterocycles.

by reduction of intermediates **2a** or **6a**, which were prepared from Suzuki-Miyaura cross-coupling of 3-formylphenylboronic acid with commercially available aryl bromide **1a** or **5a** in the presence of $Pd(PPh_3)_4$. The intermediates **3a** or **7a** were treated with thionyl chloride catalyzed by DMF to afford chlorine intermediates **4a** or **8a**. The isoxazole intermediates **12a–d** were synthesized by palladium-catalyzed Suzuki coupling between commercially available isoxazole borate **9a** and appropriate bromobenzene **10a–d**, followed by reduction and chlorination. The dihydrobenzofuran **13a** was prepared *via* previous reported procedures.[11] Williamson ether synthesis of intermediates **4a**, **8a** or **12a–d** with **13a**, followed by basic hydrolysis with lithium hydrate, afforded the desired heterocycle derivatives **3**–**5** and **8**–**10**. A new and simple chiral resolution was developed to convert the racemate **13a** to optically pure **15a** by using R-phenethylamine. Further condensation of intermediate **12b** with **15a**, followed by hydrolysis, furnished the target compound **11**.

The deuterated compounds **6** and **7** were synthesized according to the route summarized in Scheme 2. The key intermediates **17a** and **17b** were afforded by Knoevenagel reaction with Meldrum's acid and 4-hydroxybenzaldehyde **16a–b**, followed by treating with $NaBH_4$. The intermediates **17a** and **17b** were further converted to deuterated **18a** and **18b** by decarboxylation with D_2O and then esterification. Compounds **6** and **7** were synthesized from deuterated intermediates **18a–b** and **12a** by condensation followed by basic hydrolysis.

2.2. FFA1 agonistic activity and structure-based optimization

To counteract the negative factors associated with high lipophilicity, the LE, LLE, and $LogD_{7.4}$ were monitored to screen



Scheme 1. Synthesis of target compounds **3**–**5** and **8**–**11**. Reagents and conditions: (a) $Pd(PPh_3)_4$, Na_2CO_3, toluene, ethanol, H_2O, 80 °C, 12 h; (b) $NaBH_4$, CH_3OH, THF, 0 °C, 1 h; (c) $SOCl_2$, CH_2Cl_2, DMF, 40 °C, 4 h; (d) **12b** or **13a**, K_2CO_3, KI, acetone, reflux, 12 h; and then $LiOH{\cdot}H_2O$, THF/MeOH/H_2O, rt, 4 h; (e) R-Phenethylamine, acetone, reflux; (f) 1 M HCl; (g) H_2SO_4, MeOH, reflux.