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Original article

Design, synthesis and evaluation of potent G-protein coupled receptor 40 agonists

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ABSTRACT

GPR40 has emerged as an attractive drug target for the treatment of type 2 diabetes due to its role in the enhancement of insulin secretion with glucose dependency. With the aim to improve the metabolic and safety profiles, a series of novel phenylpropionic acid derivatives were synthesized. Extensive structural optimization led to identification of compounds **22g** and **23e** as potent GPR40 agonists with moderate liver microsomal stability. All the discovery supported further exploration surrounding this scaffold.

1. Introduction

The prevalence of type 2 diabetes (T2DM) is now a serious global health burden. The total number of people suffering from diabetes is expected to grow from 171 million in 2000 to 366 million by 2030 [1]. Despite some medications are available for treatment of T2DM, current therapy is often associated with weight gain and hypoglycemia (sulfonylureas), also with other adverse effects such as gastrointestinal discomfort or edema [2]. Therefore, there still remains a significant unmet need for new effective, oral anti-diabetic agents that improve glycemic control while maintaining an excellent safety profile.

The G protein-coupled receptor 40 (GPR40, also known as FFA1) primarily expressed in pancreatic β-cells and enteroendocrine cells of the small intestine [3]. When activated by medium to long chain fatty acids, GPR40 elicits enhanced insulin secretion only in the presence of elevated glucose but does not affect insulin secretion at low glucose levels [4,5]. This alluring mechanism to treat type 2 diabetes presents that small molecule agonists of GPR40 may serve as novel insulin secretagogues with little or no risk of hypoglycemia. In recent years, a number of potent GPR40 agonists have been reported and some of them have progressed to clinical trials, exemplified by TAK-875, AMG-837 and LY2881835 (Fig. 1) [6]. Unfortunately, these compounds have been terminated due to safety concerns [6]. By analyzing their structures, we find that there is a common structural moiety of benzyloxy fragment in these compounds. This may cause poor oral pharmacokinetic profiles (PK) and potential safety concern due to benzaldehyde moiety resulted from metabolic oxidation at the benzyl position [7]. Therefore, as an effort to identify novel GPR40 agonists with improved PK and safety profiles, we designed a series of new linkers between the left phenyl (B ring) and phenylpropanoic acid to avoid benzyl oxidation. This paper described the synthesis and biological evaluation of a series of novel phenylpropanoic acid derivatives as potential GPR40 agonists (Fig. 2).

2. Experimental

The synthetic routes of compounds **7** and **13** are outlined in Scheme 1. Condensation of compounds **4a** and **b** with propargyl bromide in the presence of potassium carbonate as a base afforded **5a** and **b**. Compounds **6** and **10** were obtained by Sonogashira cross-coupling reaction of **5a** and **b** and appropriate aromatic bromides [8]. Deprotection of **10** in THF with tetrabutylammonium fluoride and further esterification with triflic anhydride gave **11**. Suzuki-Miyaura cross-coupling of **11** with 3-methoxybenzeneboronic acid provided **12**. Basic hydrolysis of intermediates **6** and **12** afforded the corresponding carboxylic acids **7** and **13**, respectively.

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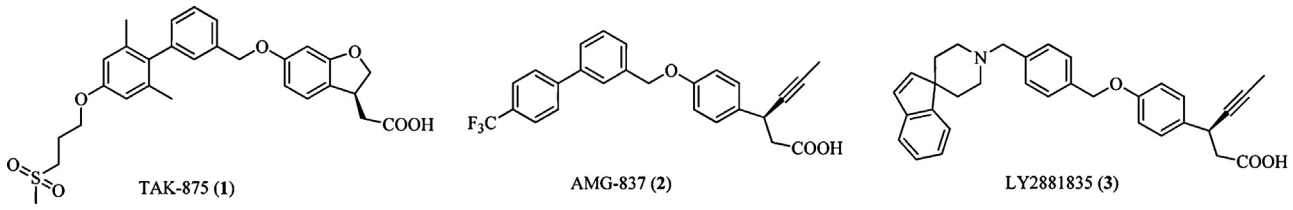


Fig. 1. Structures of representative GPR40 agonists.

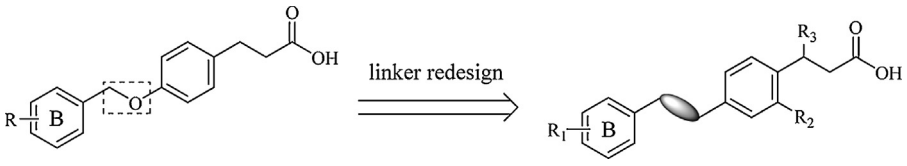
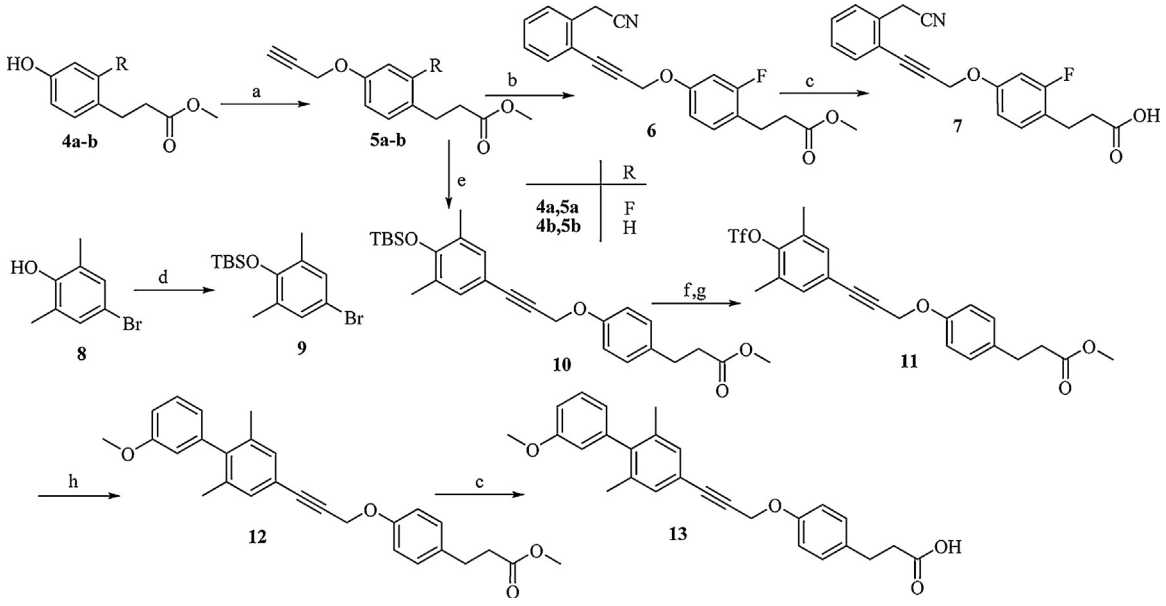


Fig. 2. Design of phenylpropanoic acid derivatives with new linker.



Scheme 1. Synthesis of compounds **7** and **13**. Reagents and conditions: (a) K_2CO_3, DMF, propargyl bromide, 80 °C, 88%–91%; (b) **5a** and 2-bromophenylacetonitrile, Na_2PdCl_4, CuI, H_2O, TMEDA, 2-(di-*tert*-butylphosphino)-1-phenylindole, 80 °C, 62%; (c) 1 mol/L LiOH aq., MeOH, r.t., 82%–87%; (d) TBSCl, TEA, THF, r.t., 92%; (e) **5b** and **9**, Na_2PdCl_4, CuI, H_2O, TMEDA, 2-(Di-*tert*-butylphosphino)-1-phenylindole, 80 °C, 76%; (f) TBAF, THF, r.t., 94%; (g) triflic anhydride; pyridine, DCM, 92%; (h) 3-methoxybenzeneboronic acid, 2 mol/L Na_2CO_3, LiCl, $Pd(PPh_3)_4$, 85 °C, 75%.

Compounds **16**, **22a–g** and **23a–e** were synthesized according to Scheme 2. The preparation of compound **16** began with the conversion of compound **14** to **15**, which was followed by Sonogashira coupling with **25** and basic hydrolysis. Compounds **17a–c** were protected by benzyl bromide and then coupled with pinacolborane to give boronic esters **19a–c**. Suzuki coupling of **19a–c** with appropriate aromatic bromides provided **20a–f**. Compounds **21a–f** were yielded by deprotection of intermediates **20a–f** and then alkylation of the phenols. Sonogashira coupling of **21a–f** with group **24** or **25**, and followed by final basic hydrolysis resulted in **22a–g**. Compounds **23a–e** were synthesized from the intermediate **21f** and **26a–e** [9] according to the synthesis procedures of **22a–g**.

3. Results and discussion

Agonist activities of the synthesized compounds were measured with Calcium flux assay in GPR40-transfected HEK293 cells [10]. As a starting modification effort, we exchanged benzyloxy moiety with propinyloxy group to avoid benzyl oxidation. First we investigated the effect of different connection position of propinyloxy with two phenyl rings (A ring and B ring) on the GRP40 agonistic activity (Table 1). Docosa-hexaenoic acid (DHA), the endogenous ligand for GPR40, was selected as positive control. The results indicated that compounds with linker L2 showed more potent GPR40 agonistic activity than those with linker L1 (compound **7** *vs.* **16**; **13** *vs.* **22a**). Accordingly, we chose compound **22a** as a new lead compound for further chemical optimization and focused our investigation to the substituents on the phenyl ring and β-position to the carboxylic function (Table 2). The CF_3 (**22b**) substituent provided a significant decrease in agonistic activity. When introduced the same tail as seen in compound TAK-875, the derivative (**22c**) showed slightly weaker potency than compound **22a**. So we kept the methoxy group as the favorable substituent at the 5″-position of C ring. Then a fluoro group was introduced into the 2-position of the A ring, which increased the activity significantly (**22d**). We next turned our attention to optimize the biphenyl group. About 2-fold increase in potency was observed