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Discovery of novel selective GPR120 agonists with potent anti-diabetic activity by hybrid design

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ABSTRACT

GPR120 is an attractive target for the treatment of type 2 diabetes. In this study, a series of biphenyl derivatives were designed, synthesized by hybrid design. The selected compound **6a** exhibited potent GPR120 agonist activity (EC_{50} = 93 nM) and high selectivity over GPR40. The results of oral glucose tolerance test (OGTT) demonstrated that **6a** exhibited significant glucose-lowering effect in glucose-loaded ICR male mice. Analysis of the structure–activity relationship is also presented. Compound **6a** deserves further biological evaluation and structural modifications.

G protein-coupled receptor 120 (GPR120), also known as free fatty acid receptor 4 (FFAR4), is a specific receptor for long-chain fatty acids (LCFA). It is highly expressed in intestine, macrophages and adipose tissue in both human and rodents.[1–4] It was reported that the activation of GPR120 by long-chain fatty acids or small molecule agonists could promote the secretion of GLP-1 and thus increase glucose-stimulated insulin secretion. GPR120 agonism could also increase insulin sensitivity and display anti-diabetic effect by repressing chronic macrophage-induced tissue inflammation in obesity.[1,2,5] Therefore, GPR120 is emerging as a potential target for the treatment of obesity, type 2 diabetes and other chronic low-grade inflammatory diseases.

The representative GPR120 agonists of are listed in Fig. 1. Availability of both potent and highly selective GPR120 agonists is quite challenging due to the fact that some GPR120 agonists are also GPR40 ligands, although the sequence homology between GPR120 and GPR40 is only 10%.[6] **GW9508** (**1**, Fig. 1) is a dual GPR40/GPR120 agonist that is more favorable for GPR40 activation.[7] **NCG21** (**2**, Fig. 1), obtained by modifying of a PPARγ ligand had only moderate potency for GPR120 activation and moderate selectivity for GPR120 over GPR40.[8] **TUG-891** (**3**, Fig. 1) with potent activity on GPR120 displayed a 1478 fold selectivity for GPR120 over GPR40.[9] Compound **4** was reported to be a nanomolar GPR120 agonist (EC_{50} = 35 nM) with high selectivity over GPR40.[10] Compound **5** was reported to have a moderate potency of GPR120 activation (EC_{50} = 0.2–2 μM),[11] and this series compounds containing the (2,6-difluorophenoxy)carboxylic acid group showed good GPR120 activity. Together, discovery of novel GPR120 agonists with both high potency and high selectivity is highly desirable. In this study, we employed a hybrid design based on **4** and **5** (Fig. 2) according to our speculation that the diflurobenzene moieties of **4** and **5** might be favorable for potent and selective activation of GPR120. Therefore, we designed and synthesized a series of biphenyl derivatives **6**. Among them, compound **6a** exhibited potent GPR120 agonist activity (EC_{50} = 93 nM) and high selectivity over GPR40. Analysis of structure-activity relationship of **6** was also performed.

The general synthetic route to the biphenyl derivatives is shown in Schemes 1, 2 and 3. (3-Methoxycyclobutoxy)benzene derivatives **7** were prepared from commercially available anti-3-(benzyloxy) cyclobutan-1-ol and 3, 4-difluorophenol over four steps (reduction, Mitsunobu reaction, debenzylation and methylation).[10] Borylation of **7** gave boronates **8** in the presence of iridium (I) catalyst. Phenols or thio-

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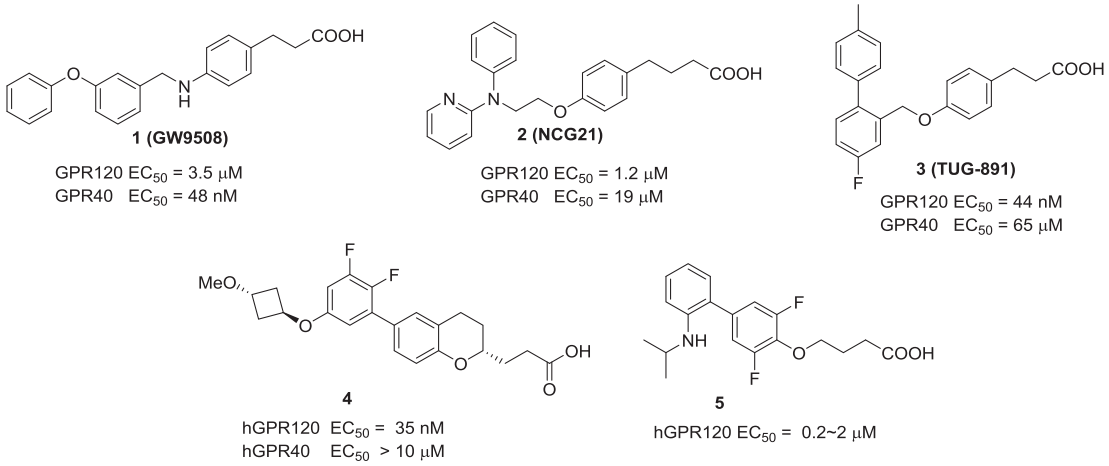

Figure 1. GPR120 agonists.

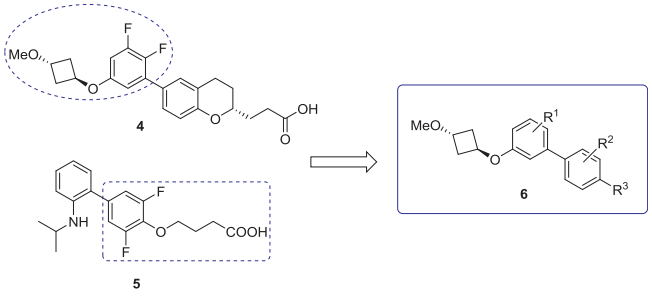

Figure 2. Compound design based on the fragment combination strategy.

phenes **9** were reacted with bromoalkylcarboxylic acid methyl ester or ethyl ester in the presence of Cs_2CO_3 to give esters **10**. Reaction of boronates **8** with aryl bromides **10** under Suzuki coupling condition afforded esters **11.** Esters **11** were hydrolyzed to form carboxylic acids **6a**-**6b**, **6d**-**6g** and **6j**-**6m**. Ester **11f** (R^1 = 2, 3-di-F, R^2 = 3, 5-di-F, Y = S) was oxidized with mCPBA and followed by hydrolysis to afford carboxylic acid **6g**. Reaction of **6a** with methanesulfinamide or benzenesulfonamide in the presence of DMAP and EDCI in DCM gave *N*-sulfonylamides **6n** or **6o**. Treatment of **6a** with thionyl chloride followed reaction with N-(2-hydroxyethyl) acetamide afforded ester **6p** (Scheme 1). In the similar pattern, carboxylic acids **6c**, **6h** and **6i** were prepared (Scheme 2). Ester **10a** reacted with boronate **15**, then followed by hydrolysis to afford **6q**. Ester **10a** reacted with boronate **16** under Suzuki coupling condition get phenol **17**, phenol **17** reacted with different alcohol under Mitsunobu reaction condition, then followed by hydrolysis to afford **6r** and **6s**.

The GPR120 agonist activity of the compounds was evaluated by the calcium flux assay.[12] The results are shown in Table 1. We found that compound **6a** exhibited good potent GPR120 agonist activity (EC_{50} = 93 nM) and high selectivity over GPR40 in this assay. To get GPR120 agonists with more GPR120 potency and high GPR120/GPR40 selectivity, the structure-activity relationship of compounds **6a** is summarized as below.

Firstly, the impact on activity and selectivity was made by replacing the 2, 3-di-F substitution of ring A with 2,3-OCH_2O- (**6b**) and 2-NO_2 (**6c**) substitutions, and replacing the 3, 5-di-F substitution of ring B with 3,5-di-OMe (**6d**) and 3,5-di-Me (**6e**) substitutions. Compound **6b** kept moderate activity (EC_{50} = 220 nM) and good selectivity over GPR40. The EC_{50} value of nitro substitued phenyl **6c** was about 1.478 μM. The 3,5-di-Me substitution on the ring B (**6e)** resulted in a loss of GPR120 potency (EC_{50} = 847 nM), though kept a moderate selectivity. Even 3,5-di-OMe **6d** abolished GPR120 activity (Table 1). We speculated that this result may be explained by electronic or steric effects.

Secondly, we examined the SAR profile of phenoxybutanoic acid side chain (Table 2). Replacement of the oxygen atom with sulphur atom led to compound **6f** with a moderate activity (EC_{50} = 347 nM) and a good selectivity. Compound **6g** with a sulfonyl group to replace the oxygen atom completely lost GPR120 agonist activity. Then the acid chain was modified by shortening and lengthening to afford compounds **6h** and **6j-m**. The shortening of the chain resulted in loss of activity (**6h**). Lengthening the carbon chain to five carbons led to a moderate activity (**6j**, EC_{50} = 186 nM) and a good selectivity over GPR40, while **6k** with a six-carbon chain displayed decreased activity and selectivity. Further extension of the carbon chain (**6l**, **6m**) resulted in sharp decrease in both potency and selectivity, favoring GPR40 agonism over GPR120 agonism. Introduction of di-α-methyl group on the phenoxybutanoic acid side chain (**6i**) was not beneficial for improving the activity and selectivity. Replacement of the acid group by *N*-sulfonylamide group (**6n**, **6o**) completely abolished GPR120 agonism activity, indicating that the acid 'bullet' was crucial for the GPR120 agonism activity. A probable explanation is that the carboxylic acid group could interact with the key amino acid residue of GPR120 to form a critical hydrogen bond.[13–15] Attempt to explore the necessary of the methoxycyclobutoxy group of **6a** for GPR120 potency, we replaced the methoxycyclobutoxy group with a simple methoxy group (**6q**). To our delight, compound **6q** (EC_{50} = 69 nM) exhibited better GPR120 potency than **6a,** but displayed low selectivity. Then we replaced the methoxycyclobutoxy group with 4-methoxytetrahydro-2H-pyran group (**6r**) and 3-(methoxymethyl)-2-methyl-1,1′-biphenyl group (**6s**), we found both of compound **6r** and **6s** displayed weak activity (Table 3). It seems that the methoxycyclobutoxy group is necessary for maintaining the GPR120 agonist activity and selectivity over GPR40. To explore more potent GPR120 agonist with high selectivity over GPR40, further

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