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Synthesis and Evaluation of 3-(4-(phenoxymethyl)phenyl)propanoic Acid and N-phenylbenzenesulfonamide Derivatives as FFA4 Agonists

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ABSTRACT

Free fatty acid receptor 4 (FFA4) has been recognized as an attractive target in metabolic diseases. To find potent and selective FFA4 agonist, 28 compounds of 3-(4-(phenoxymethyl)phenyl)propanoic acid and N-phenylbenzenesulfonamide derivatives were designed and synthesized, featuring O-C and SO2-N linkage. For the O-C linkage compounds, **1g** showed the most potent FFA4 agonistic activity with a pEC_{50} of 5.81 ± 0.04 and exhibited at least 64-fold selectivity against FFA1. For SO2-N linkage agonists, **2m** had a pEC_{50} of 5.66 ± 0.04 and displayed more than 46-fold selectivity against FFA1. Among these two series of compounds, **1g** was the most potent agonist at FFA4 and the best selectivity against FFA1, demonstrated by docking simulation. Moreover, **1g** showed receptor selectivity on other seven GPCRs. In anti-diabetic evaluation, **1g** dose-dependently reduced blood glucose, which was better than a clinical phase III drug TAK875. This study provides guidance for FFA4 ligand design and drug optimization.

Keywords: Free fatty acid receptor 4; GPR120; Agonist; Dynamic mass redistribution; Type 2 diabetes

Free fatty acid receptor 4 (FFA4, also known as GPR120) has been recognized as an attractive target for treatment of metabolic diseases, such as type 2 diabetes and obesity [1]. The receptor is activated by long chain fatty acids. Functionally, it is a member of lipid binding G-protein

coupled receptors (GPCRs) that include GPR40 (also known as FFA1), GPR41, GPR43 and GPR120 [2]. FFA4 agonist has been proved to improve insulin resistance in obese mice [3]. Besides, a report has found that a non-synonymous mutation of human FFA4 increased the risk of being obese in European people [4]. Moreover, it has been found that the ω-3 fatty acids activated ciliary FFA4 to regulate adipogenesis [5]. These results support a significant role of FFA4 receptor in metabolic diseases. Therefore, identification of selective FFA4 agonists is of great importance for investigating the biological functions of FFA4, and opening new opportunities for related disease treatment.

Since the endogenous ligands of FFA4 and FFA1 highly overlap, identification of agonists with high selectivity for FFA4 is a challenge for researchers. In 2008, Suzuki et al. developed the first carboxylic acid-containing FFA4-selective agonist **12** through modifying PPARγ agonists [6]. In 2012, TUG891 with phenylpropionic acid scaffold was disclosed as a potent and selective FFA4 agonist [7]. However, TUG891 exhibits limited selectivity for murine FFA4 against murine FFA1, limiting its use in studying specific pharmacologic functions on murine-derived cell lines that co-express both receptors [8]. Subsequently, a number of carboxylic acid-containing agonists were reported [9-11]. This indicated that carboxylic acid is important for the agonistic activity of FFA4. In 2010, a series of nonacidic benzosultams derivatives were identified as FFA4 agonists structurally different from other known FFA4 agonists [12]. Recently, Sparks et al. reported a series of nonacidic sulfonamide FFA4 agonists, like GSK137647A, with pEC_{50} value 6.3 and lack of activity on FFA1 [13]. Although a number of FFA4 agonists have been identified, there are a relatively few agonists with high activity available, and structural diversity is still scarce. Further research is still needed to develop potent, selective, and bioavailable FFA4 agonists.

Inspired by structures of known FFA4 agonists, they shared some commonalities, basically having two aromatic rings linked by C-O, C-N or SO2-N (**Fig. 1**) [7, 13-17]. The position of O in C-O linkage was located close to the benzene ring containing the -COOH group. The effect of the position change of C-O linkage to O-C linkage on agonistic activity at FFA4 is not reported. In this study, through a structure-activity relationship (SAR) study, a potent and selective O-C linkage FFA4 agonist (**1g**) with anti-diabetic activity was identified. Given that carboxylic acids (usually linked by C-O, C-N) and sulfonamides (usually linked by SO2-N) are mainly two categories FFA4 agonists, we also study a series of compounds with SO2-N linkage, and a potent SO2-N linked FFA4 agonist (**2m**) with excellent selectivity against FFA1 was developed.

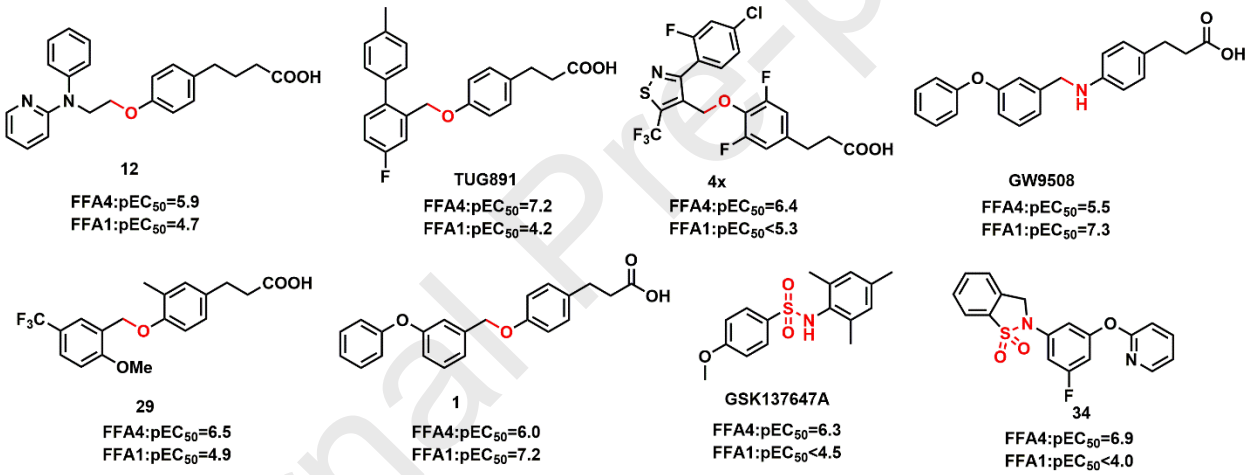
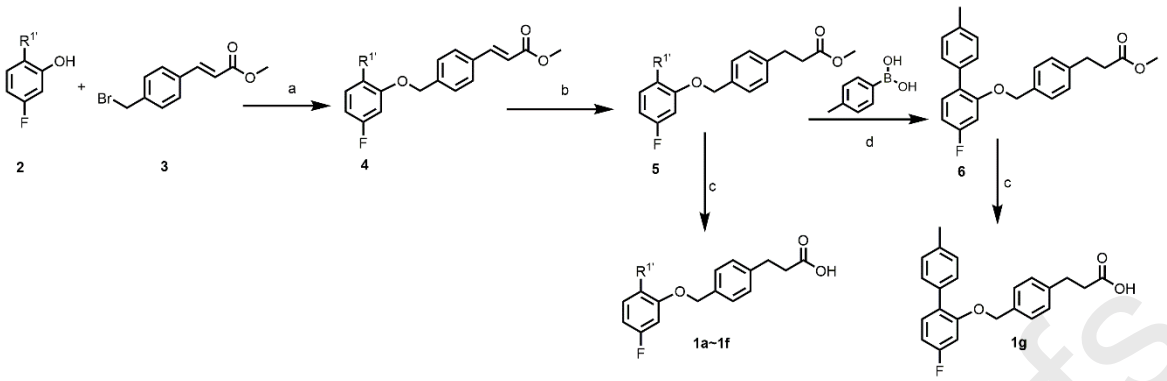


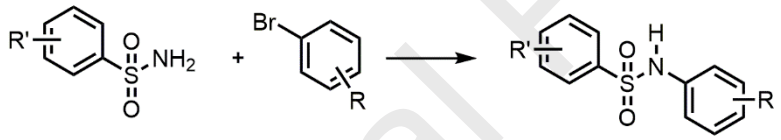
Fig. 1. Representative FFA4 agonist [6, 7, 13-17].

A series of O-C linkage compounds were synthesized. The general synthetic routes to prepare these compounds **1a** to **1g** are outlined in **Scheme 1**.

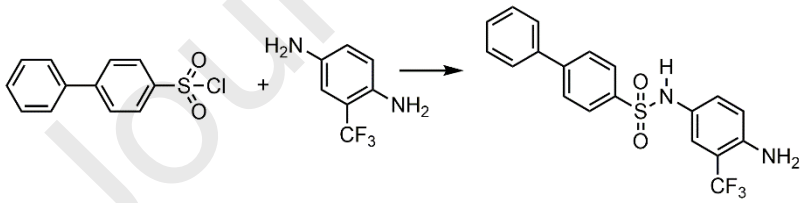


Scheme 1. General synthesis of the O-C linkage derivatives. Reagents and conditions: (a) K_2CO_3, RT, 84~95%; (b) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, 0 ℃, 24.5-98%; (c) NaOH or LiOH, RT, 27-93%; (d) $Pd(PPh_3)_4$, K_2CO_3, 75 ℃, 71%.

The general synthesis of the SO2-N linkage agonists is shown in **Scheme 2**. The synthesis is very simple through one step reaction. Sulfonamide bond was formed by reaction of the phenyl sulfonamide and aryl bromides except compound **2g**. The synthetic routes to prepare compound **2g** are outlined in **Scheme 3**.



Scheme 2. General synthesis of the SO2-N linkage agonists. Reagents and conditions: K_2CO_3, CuI, DMEDA, 70 ℃.

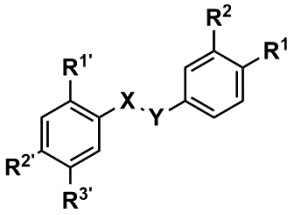


Scheme 3. Synthesis of the **2g**. Reagents and conditions: THF, RT, TEA, overnight.

Dynamic mass redistribution (DMR) assays afforded by label-free resonant waveguide grating (RWG) biosensors were used to profile compound activity at the CHO-K1-hFFA4 cell line. TUG891 was used as a positive control probe [18]. All compounds stimulated a dose-dependent

DMR in CHO-K1-hFFA4 cells, implying that these compounds acted as FFA4 agonists (**Table 1**). For the selective evaluation over FFA1 receptor, these compounds were tested for activation signals in CHO-K1-hFFA1 cells using DMR assays. Their potency on FFA1 and selectivity between FFA4 and FFA1 were shown in **Table 1**.

Table 1 Potency of compounds in human FFA4 and FFA1 using DMR assays



compound	R^1	R^2	$R^{1'}$	$R^{2'}$	$R^{3'}$	Human FFA4 pEC_{50} (efficacy)	Human FFA1 pEC_{50}	Selectivity
1a	CH2CH2COOH	H	CH3	H	F	5.28 ± 0.04 (84)	4.72 ± 0.03	4
1b	CH2CH2COOH	H	OCH3	H	F	5.02 ± 0.02 (80)	4.51 ± 0.17	4
1c	CH2CH2COOH	H	Br	H	F	5.24 ± 0.04 (82)	4.52 ± 0.04	5
1d	CH2CH2COOH	H	CN	H	F	5.22 ± 0.04 (86)	4.69 ± 0.05	3
1e	CH2CH2COOH	H	COOH	H	F	> 4	> 4	-
1f	CH2CH2COOH	H	COOCH3	H	F	5.01 ± 0.04 (54)	> 4	>10
1g	CH2CH2COOH	H	4-methylphenyl	H	F	5.81 ± 0.04 (78)	> 4	>64
2a	NH2	H	H	H	H	> 4	> 4	-
2b	NH2	NO2	H	H	H	4.75 ± 0.07 (24)	> 4	>5
2c	NH2	CH3	H	H	H	> 4	> 4	-
2d	NH2	F	H	H	H	4.20 ± 0.08 (58)	> 4	>1
2e	NH2	CF3	H	H	H	5.06 ± 0.06 (87)	> 4	>11
2f	NH2	CF3	H	OH	H	~ 4.30 (68)	> 4	>2
2g	NH2	CF3	H	ph	H	> 4	> 4	-
2h	NH2	CF3	H	NO2	H	4.89 ± 0.06 (54)	> 4	>8
2i	NH2	CF3	H	F	H	5.05 ± 0.03 (55)	> 4	>11
2j	NH2	CF3	H	Cl	H	5.31 ± 0.02 (95)	~ 4.25	~11
2k	NH2	CF3	H	Br	H	5.29 ± 0.03 (95)	4.54 ± 0.06	~6
2l	NH2	CF3	H	OCF3	H	~ 4.51 (99)	> 4	>3
2m	NH2	CF3	H	CH3	H	5.66 ± 0.04 (104)	> 4	>46

2n	NH2	CF3	H	CH2CH3	H	5.40 ± 0.14 (109)	> 4	>24
2o	NH2	CF3	H	OCH3	H	5.45 ± 0.05 (95)	> 4	>28
2p	NH2	CF3	H	C(CH3)3	H	~ 4.40 (84)	4.17 ± 0.05	~2
2q	NH2	CF3	NO2	H	H	4.66 ± 0.04 (73)	4.27 ± 0.17	3
2r	NH2	CF3	CH3	H	H	4.64 ± 0.06 (67)	4.54 ± 0.08	1
2s	NH2	CF3	F	F	H	4.66 ± 0.08 (56)	> 4	>5
2t	NH2	CF3	H	Br	CH3	5.34 ± 0.03 (85)	4.97 ± 0.08	2
2u	H	CF3	H	CH3	H	4.53 ± 0.09 (104)	4.31 ± 0.05	2
TUG891	CH2CH2COOH	H	4-methylphenyl	H	F	6.80 ± 0.03 (100)	4.47 ± 0.09	217

Compound **1a** ~ **1g** are O-C (X-Y) linkage compounds and **2a** ~ **2u** are SO2-NH (X-Y) linkage compounds. Selectivity equals EC_{50} (FFA1)/EC_{50} (FFA4).

These compounds could be divided into two categories according to the X-Y linker. SAR study of the O-C linker compounds found that common small substitutions at the $R^{1'}$ position were unfavorable for agonistic activity as indicated by the pEC_{50} of **1a** ~ **1d** in **Table 1**. Therefore, strong hydrophilic and large lipophilic groups were tried such as COOH and 4-methylphenyl. Results showed that **1e** was little active (pEC_{50} > 4), while **1g** had the highest potency (pEC_{50} = 5.81 ± 0.04), and **1f** had a relatively low potency (pEC_{50} = 5.01 ± 0.04) (**Fig. 2a**), which revealed that a COOH (strong hydrophilic group) at $R^{1'}$ position was detrimental to the potency of compound and large lipophilic groups were beneficial. Compared with small lipophilic groups of -CH_3 (**1a**) or -OCH_3 (**1b**) at $R^{1'}$ position, large lipophilic groups, such as 4-methylphenyl (**1g**) was more effective. Replacement O-C linker with SO2-N developed a series of non-acidic agonists. Substitution in the R^2 position of the "right hand" benzene ring with a -CF_3 (**2e**) provided 7-fold and more than 22-fold increase in FFA4 potency compared with -F (**2d**) and -CH_3 (**2c**) group, respectively (**Fig. 2b**). When R^2 position was substituted with electron-donating group, the compounds were substantially free of FFA4 activity as indicated by compound **2c** (**Table 1**). It highlighted the importance of the electron-withdrawing group in the R^2 position. Next we maintained the -CF_3 in the R^2 position, and studied the SAR of the "left

hand" benzene ring in the $R^{2'}$ position. Changing the $R^{2'}$ position from -CH_3 (**2m**) to -OCF_3 (**2l**) resulted in approximately an order of magnitude loss in FFA4 potency (**Fig. 2c**). Changing of the $R^{2'}$ position from a -CH_3 to halogen (**2i**, **2j** and **2k**) resulted in a moderate loss of FFA4 potency. It suggested that the electron donating group in the $R^{2'}$ position was advantageous for the agonistic activity. However, substitution with -OH in the $R^{2'}$ demonstrated worse potency (**2f**), which may indicate that strong hydrophilic groups are unfavorable. Further studies showed that the large volume groups at the $R^{2'}$ were not conducive to the activity. As the benzene ring in the para-substitution completely abolished FFA4 activity (**2g**) and tertiary butyl substitution (**2p**) decreased FFA4 potency compared with -CH_2CH_3 group (**2n**) (**Fig. 2d**).

Then we continued to maintain CF_3 at R^2 position of SO2-N linker compounds, but replacement of $R^{2'}$ with H, and studied the SAR at $R^{1'}$ position. Results showed that substitution at $R^{1'}$ position (ortho-substitution) was not tolerated in contrast to para-substitution ($R^{2'}$ position), since it resulted in approximately an order of magnitude loss in FFA4 potency of **2r** compared with **2m**. Therefore, we have tried to construct ortho-para and meta-para disubstituted compounds. The results showed that the potency of FFA4 did not improve as indicated by the pEC_{50} of **2s** and **2t**. This indicated that the double substitution on the "left hand" benzene ring was not significant for the improvement of activity. At the same time, we examined the effect of NH_2 at the R^1 position. The results showed that when NH_2 at R^1 position was replaced by H, it was unfavorable for activity because the EC_{50} of **2u** is an order of magnitude larger than that of **2m**. In general, the SAR around the left benzene ring was not satisfactory and did not yield the active compound at the nanomolar level. But most of compounds showed pretty good selectivity to FFA4 against FFA1 (**Table 1**). Structure-activity results indicated that lipophilic electron donating groups at $R^{2'}$ position such as -CH_3 and -OCH_3 favored the selectivity to FFA4.

However, substitutions at the $R^{1'}$ or $R^{3'}$ were detrimental to the selectivity of SO2-N linker compounds. Among them, **2m** displayed the best FFA4 activity (pEC_{50} of 5.66 ± 0.04) and selectivity (> 46 more potent on FFA4 than FFA1).

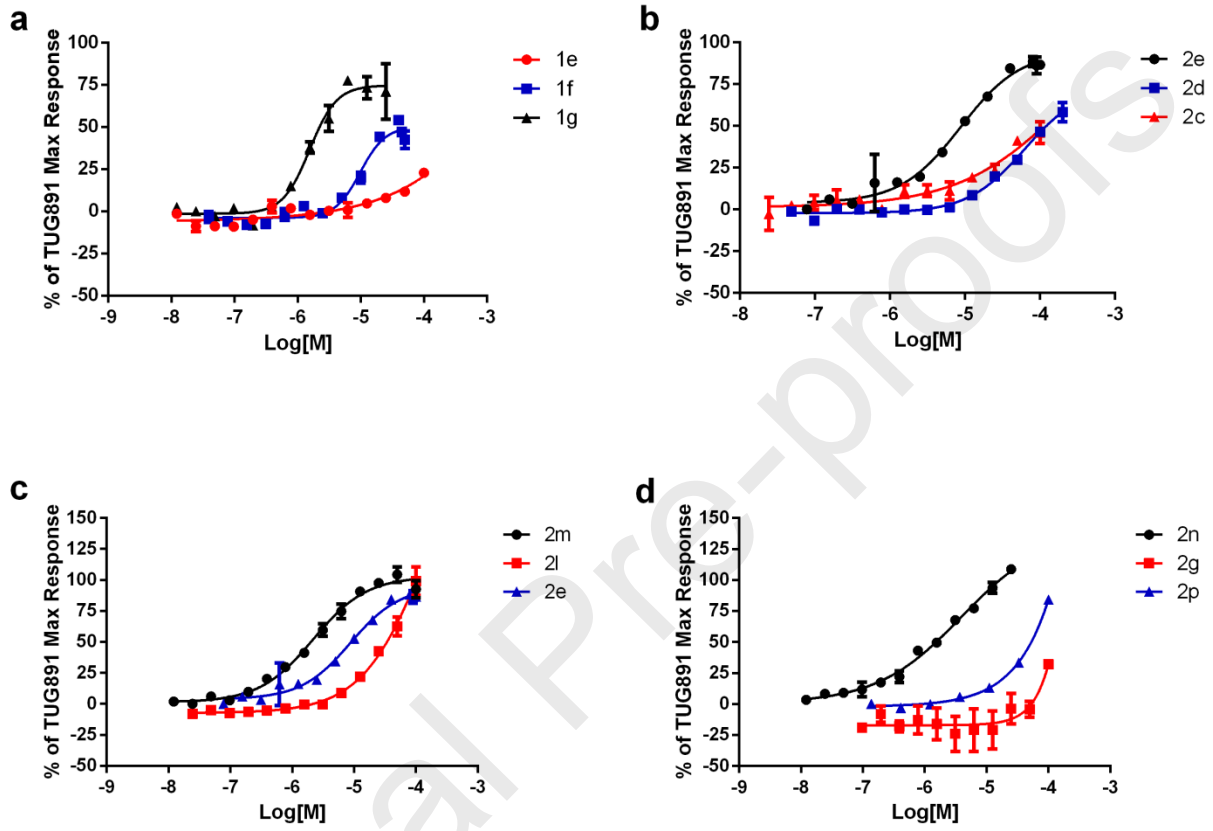


Fig. 2. Structure-activity relationship analysis of compounds. (a) The amplitudes of the DMR induced by compounds **1e**, **1f**, and **1g**. (b) The amplitudes of the DMR induced by compounds **2e**, **2d** and **2c**. (c) The amplitudes of the DMR induced by compounds **2m**, **2l** and **2e**. (d) The amplitudes of the DMR induced by compounds **2n**, **2g** and **2p**. The data represents mean ± s.d. from two independent assays, each with three replicates (n = 6).

Observing the three-dimensional (3D) structures of **1a**, **1b**, **1g** and the endogenous ligand α-linolenic acid (ALA) (**Fig. S1, Supplementary data**), it was found that when the $R^{1'}$ position was a large lipophilic group (**1g**), the 3D structure formed was the most similar to the 3D structure of ALA, which is like to the letter "L". It may be more beneficial for binding to the

FFA4 receptor. At the same time, we also found that the large lipophilic group at $R^{1'}$ position was beneficial to improve the selectivity over FFA1 as **1g** showed 64-fold more potent on FFA4 (**Table 1**). To further examine the agonistic activities of these O-C linker compounds, we conducted docking simulation in a FFA4 homology model. The homology model was built by multiple sequence alignment including five sequences. Firstly, a docking simulation of O-C linker compounds (except compound **1e** with $pEC_{50} > 4$), together with ALA, an endogenous ligand for FFA4, was performed using AutoDock Vina [19]. We calculated the affinity energy between the compounds and the FFA4 model. A plot of relative DMR EC_{50} activity versus calculated affinity energy (**Fig. 3**) showed a high correlation between the calculated affinity energy and DMR activities (R = 0.9289). The results showed that a docking simulation using the constructed FFA4 homology model could be useful in predicting the agonistic activity of O-C linker compounds.

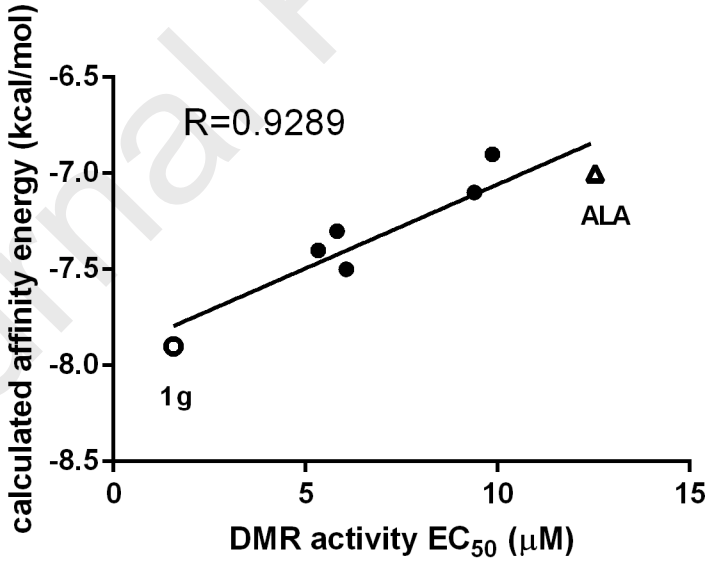


Fig. 3. Structure-activity relationships of FFA4 ligands. The relative DMR activity (x-axis) versus the calculated affinity energy of interaction based on modeling (y-axis) was plotted.

An inspection of the stimulated FFA4/ALA complex showed that there were two hydrogen bonds and one salt bridge between the carboxylate of ALA and the guanidine of Arg 24 (**Fig. 4a**). For FFA4/**1g** complex (**Fig. 4b**), there were one hydrogen bond and one salt bridge between the carboxylate of compound **1g** and the guanidine of Arg 24. Moreover, there were one π-cation interaction between the benzene ring of compound **1g** and guanidine of Arg 22. However, for complex FFA4/**1a** and FFA4/**1b**, results showed that there were two hydrogen bonds and one salt bridge between the carboxylate of both compounds and guanidine of Arg 22 (**Fig. 4c** and **Fig. 4d**). Additionally, a π-π interaction formed between the benzene ring of both compounds and benzene ring of Phe216. The calculation results in this study suggested that the substituent on the $R^{1'}$ with large lipophilic group (compound **1g**) might alter the conformation of the compound in the ligand binding domain, which affected the interaction between its carboxylate and the guanidine of Arg 24 or Arg 22. The large lipophilic group on the $R^{1'}$ position may bring the carboxylate closer to Arg 24 and make the interaction stronger with the guanidine of Arg 24 via salt bridge and hydrogen bond, which might induce a more potent activation of FFA4. Therefore, SAR study, 3D structure analysis and docking simulation suggested that **1g** was the most potent ligand with agonistic activity among O-C linker compounds. We were gratified to find that both types of modifications led to analogues with FFA4 potency. In particular, **1g** exhibited the best agonistic activity among these compounds (pEC_{50} of 5.81 ± 0.04). Moreover, it had superior selectivity for FFA4 over FFA1 (**Fig. S2, Supplementary data**).

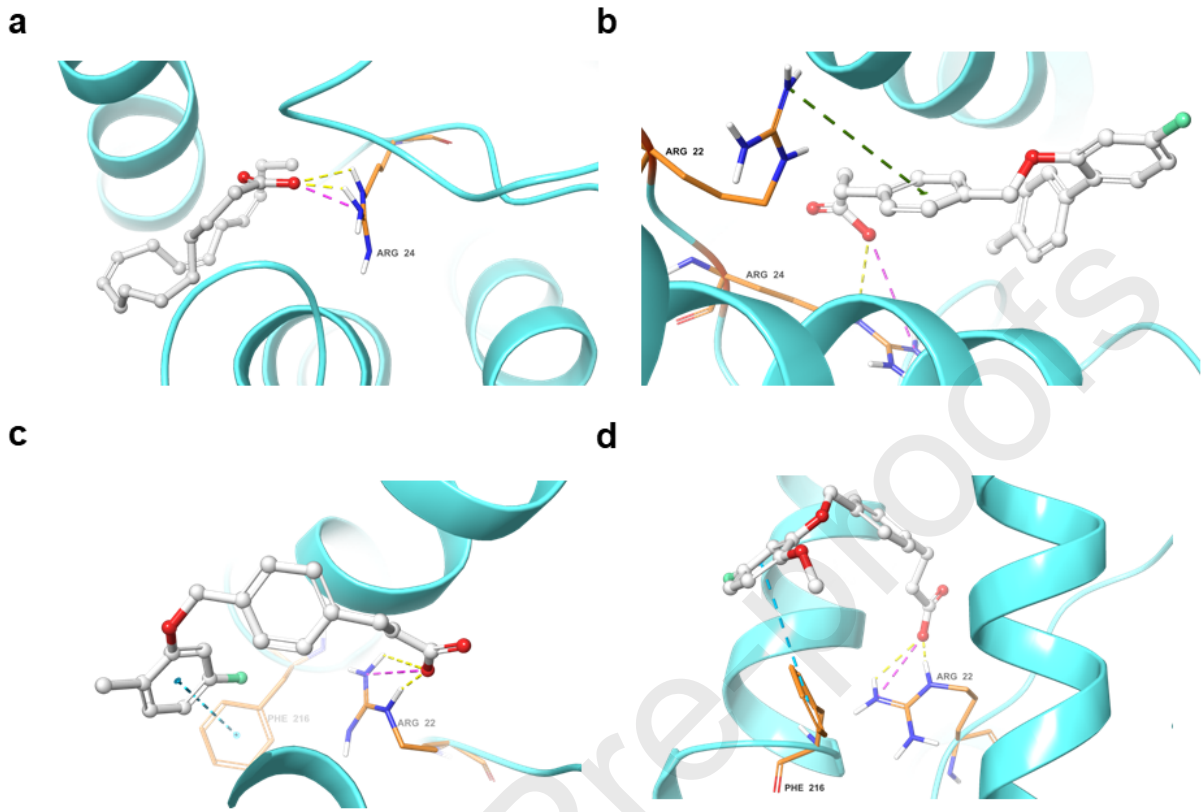


Fig. 4. FFA4 homology model (PDB code: 1u19, 4zj8, 3odu, 4lde and 5gli) docked with (a) ALA (b) **1g** (c) **1a** and (d) **1b**. The yellow dashed lines indicate hydrogen bonds between the compounds and the Arg 22 or Arg 24. The pink dashed lines indicate salt bridge between the compounds and Arg 22 or Arg 24. The blue dashed lines indicate π-π between the compounds and Phe 216. The green dashed lines indicate π-cation between the compounds and Arg 22.

Receptor selectivity was conducted among seven different targets including muscarinic receptor (M1), opioid receptor (μOPR), histamine receptor (H2), adrenergic receptor (β2), endothelin receptor (ETA and ETB) and orphan receptor (GPR35) by DMR desensitization assays using corresponding probes. The results showed that **1g** was almost unable to reduce the response of the corresponding probe at these seven receptors (**Fig. 5**), which suggested that **1g** was selective for FFA4, showing at least 20-fold selectivity against the seven GPCRs (estimating

at 50% desensitization concentration of **1g** at these 7 receptors). Consequently, it was selected for further *in vivo* evaluation.

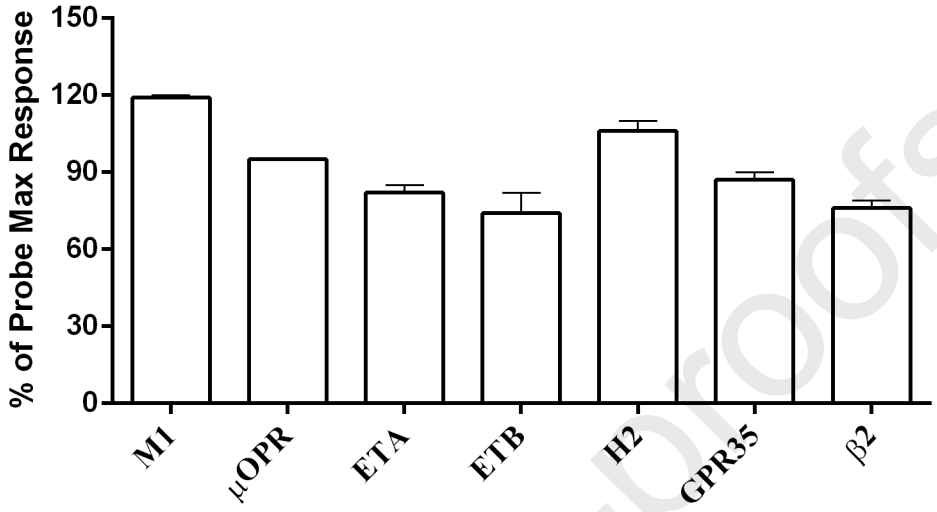


Fig. 5. 1g to desensitize the probes of corresponding receptors. For M1, μOPR, ETA, ETB and H2, the concentration of **1g** was at 20 μM. For GPR35 and β2, the concentration of **1g** was at 40 μM.

Given the promising *in vitro* profiles, **1g** was assessed the in vivo anti-diabetic properties using oral glucose tolerance test (OGTT) in db/db mice. The db/db mice were intraperitoneally administered compound solution once before being dosed with glucose (1 g/kg body weight, po). It showed a dose response for lowering plasma glucose in OGTT (**Fig. 6**). Compound **1g** at 10 mg/kg and 20 mg/kg dose-dependently reduced plasma glucose levels with AUC (area under the curve) values of 43.7% and 68.8%, respectively. As a positive control, TAK875, this had entered clinical phase III, reduced plasma glucose levels with an AUC value of 21.4% at 10 mg/kg in the same study. This indicates that **1g** has a stronger glucose lowering effect than TAK875 at the same dose. **1g** displayed the most pronounced effect on blood glucose lowering in 1 h post stimulation.

As a whole, **1g** exhibited anti-diabetic activity in oral glucose tolerance test. These results provide guidance for drug design for the treatment of FFA4 related disorders.

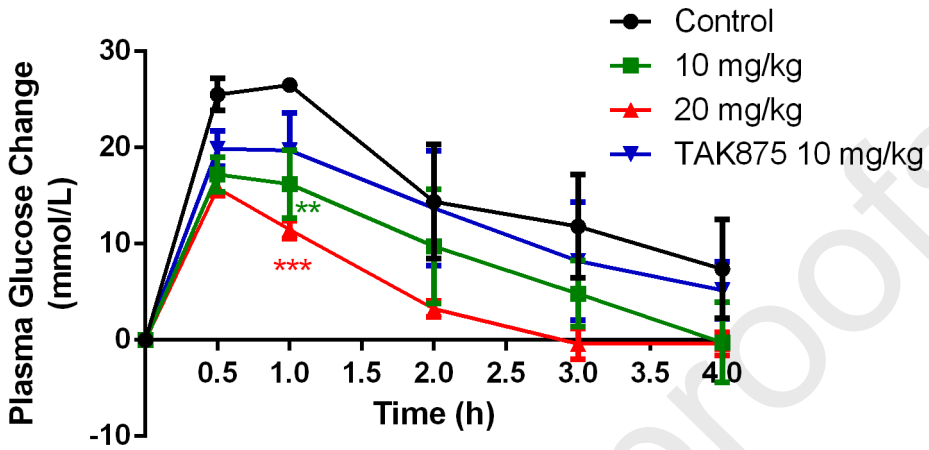


Fig. 6. Glucose lowering effects as measured by OGTT. Time-dependent changes of plasma glucose levels. (n = 3 mice per group; **p ≤ 0.01, ***p ≤ 0.001, two-way ANOVA with Bonferroni posttests). The db/db mice were intraperitoneally administered compound solution once before being dosed with glucose (1 g/kg body weight, po).

In the study, the optimization of a series twenty-eight of O-C and SO2-N linkage FFA4 agonists and their SAR were investigated. Selected compound from the O-C linkage series displayed the most potent FFA4 agonistic activity with a pEC_{50} of 5.81 ± 0.04, possessed at least 64-fold selectivity against FFA1, and also displayed significant anti-diabetic activity in db/db mice. Docking simulation was applied to study the interaction of O-C linkage compound, and it might be useful in predicting the agonistic activity. Besides, most SO2-N linkage agonists displayed good selectivity to FFA4 against FFA1. **2m** showed the most potent FFA4 activity with a pEC_{50} of 5.66 ± 0.04, exhibited more than 46-fold selectivity against FFA1. The results may offer new future directions for researchers pursuing FFA4 agonists.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data, experiment details and NMR and HRMS spectra associated with this article can be found, in the online version.

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