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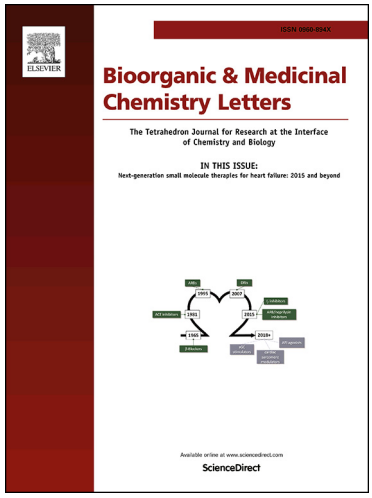

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Graphical Abstract

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Design, synthesis and biological evaluation of a series of novel GPR40 agonists containing nitrogen heterocyclic rings

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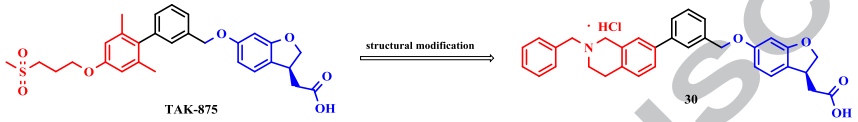

	EC_{50}(μM)	cLog P
30	0.8	1.30
TAK-875	5.1	2.60

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ABSTRACT

A novel series of GPR40 agonists is designed by introducing nitrogen-containing heterocyclic ring at the terminal phenyl ring of TAK-875 with the aim of decreasing its lipophilicity. Three different β-substituted phenylpropionic acids were investigated as the acidic components. A total of 34 compounds have been synthesized, among which, compound **30** exhibited comparable GPR40 agonistic activity *in vitro* with TAK-875 and relatively lower lipophilicity through calculation (**30**, EC_{50} = 1.2 μM, cLogP = 1.3; TAK-875: EC_{50} = 5.1 μM, cLogP = 3.4). Moreover, compound **30** was able to enhance the insulin secretion of primary islets isolated from normal ICR mice and showed no obvious inhibition against cytochromes P450 *in vitro*. *In vivo*, compound **30** exhibited efficacy in oral glucose tolerance test (oGTT) in normal ICR mice.

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G-protein coupled receptor 40 (GPR40), also known as a free fatty acid receptor, is dominantly expressed in pancreatic β cells and intestine K, L cells [1-2]. Besides, GPR40 is also reported to be expressed in brain, but its function is still unknown [3]. It is well documented that GPR40 agonist is able to decrease blood glucose level via stimulating the insulin secretion and take effect only when patients suffer from a high blood glucose level, which decreases the risk of hypoglycemia significantly [4,5]. Moreover, it is reported that GPR40 agonist is able to avoid weight gain effectively, which is a common side effect associated with clinic drugs used for treating type 2 diabetes [5]. Given the advantages mentioned above, GPR40 has become an excellent target for the treatment of type 2 diabetes. To date, multiple classes of GPR40 agonists, bearing a β-substituted phenyl propionic acid in common, have been explored [6-13] (Fig. 1).

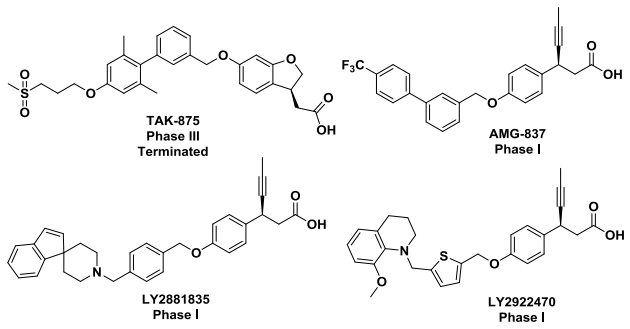


Fig 1. Representative GPR40 agonists

Although TAK-875 was terminated in phase III clinic trial, it is still an important lead compound for discovering novel GPR40 agonists. A great number of structural modifications based on TAK-875 have been carried out, and a common strategy was to introduce polar group into the structure of TAK-875 with the aim of decreasing its lipophilicity. A variety of heterocycles, such as thiazole, isoxazole and pyrrole, has been employed to replace the phenyl ring of biphenyl moiety in TAK-875 and achieved promising results [7-8, 14-16]. Inspired by these results, we envisioned to design a novel series of GRP40 agonists by introducing six-membered or five-membered nitrogen-containing heterocyclic rings into the structure of TAK-875. Theoretically, the introduction of nitrogen-containing heterocycles could decrease lipophilicity of these newly designed compounds. The N-H group of the heterocyclic rings could be further acylated or alkylated to give structurally diversified derivatives. In the meantime, the acidic component of TAK-875 could be replaced by other β-substituted phenylpropionic acids. The structural modification plan was depicted in Fig. 2.

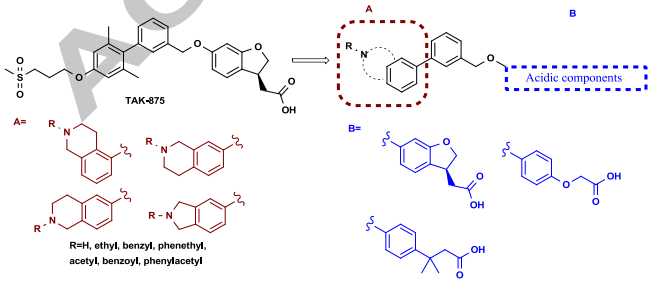
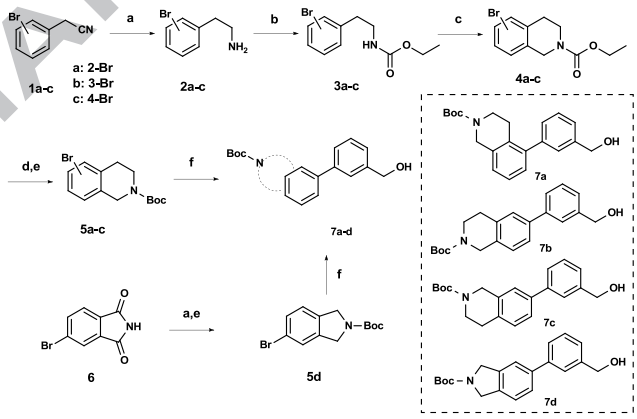


Fig 2. Design of novel GPR40 agonists

Totally, 34 compounds were synthesized with three different acidic heads and four different nitrogen-containing heterocyclic rings. Compound **30** was discovered as the promising lead compound for further investigation, as it exhibited comparable GPR40 agonistic activity (EC_{50} = 1.2 μM) and relatively lower lipophilicity (cLogP = 1.3) compared with TAK-875 (EC_{50} = 5.1 μM, cLogP = 3.4). It also showed no obvious inhibition against cytochrome P450 (CYP450). Besides, compound **30** was able to increase insulin secretion of primary islets isolated from normal ICR mice, and in oral glucose tolerance test (oGTT) in normal ICR mice, compound **30** also showed efficacy.

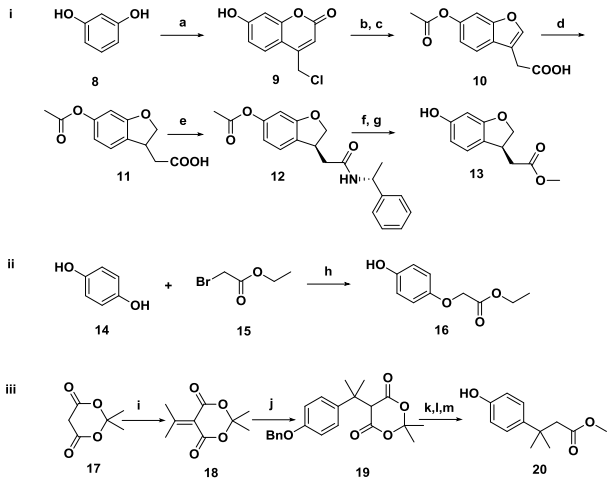
The nitrogen-containing heterocycles selected in this work involve 1,2,3,4-tetrahydroisoquinoline and isoindoline. The synthetic route of nitrogen-containing heterocycle components was shown in Scheme 1. The synthesis of compounds **7a-c** containing a tetrahydroisoquinoline moiety started from bromo substituted phenylacetonitrile. Reduction of bromo substituted phenylacetonitrile **1a-c** with BH_3 in THF gave compounds **2a-c**, which were then converted to compounds **3a-c** in the presence of ethyl chloroformate and triethylamine. Cyclization of compounds **3a-c** with paraformaldehyde in formic acid afforded the intermediates **4a-c**. Compounds **4a-c** were treated with potassium hydroxide, followed by protection of the amino group with $(Boc)_2O$ to form compounds **5a-c**. The coupling reaction of compounds **5a-c** with 3-(hydroxymethyl)phenylboronic acid catalyzed by $Pd(PPh_3)_4$ resulted in the formation of tetrahydroisoquinoline moieties **7a-c**. Compound **7d** bearing an isoindoline moiety was synthesized from 4-bromophthalimide **6** through reduction by BH_3 and then protection with $(Boc)_2O$. Compound **7d** was finally obtained through Suzuki crossing coupling reaction from compound **5d** and 3-(hydroxymethyl)phenylboronic acid.



Scheme 1. Synthesis of **7a-d**. Reagents and conditions: (a) BH_3·THF, THF, reflux, 80.0% - 85.2%; (b) ethyl chloroformate, TEA, DCM, 0 °C to r.t., 80.5% - 82.0%; (c) paraformaldehyde, HCOOH, reflux, 75.0% - 88.5%; (d) KOH, MeOH, reflux; (e) $(Boc)_2O$, DMAP, THF, r.t., 72.7% - 79.3% (for two steps); (f) 3-(hydroxymethyl)phenyl)boronic acid, $Pd(PPh_3)_4$, 2M Cs_2CO_3, DME, reflux, 81.8% - 87.2%.

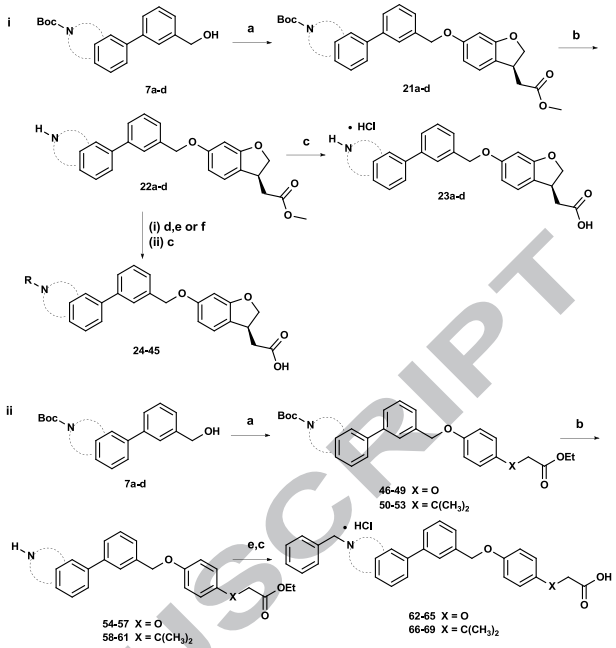
The synthesis of acidic components was described in Scheme 2. Three β-substituded phenylpropionic acids including (*S*)-2-(2,3-dihydrobenzofuran-3-yl)acetic acid, 2-phenoxyacetic acid and 3-methyl-3-phenylbutanoic acid, were prepared. (*S*)-methyl 2-(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate **13** was synthesized from resorcinol **8** via five steps. Treatment of resorcinol **8** with ethyl 4-chloroacetoacetate in the presence of H_2SO_4 generated compound **9** via Pechmann reaction. Treatment of compound **9** in potassium hydroxide solution, followed by esterification of -OH with acetic anhydride afforded compound **10**. Reduction of **10** under hydrogen atmosphere catalyzed by Pd/C gave key intermediate dihydrobenzofuran **11**. The reaction of the key intermediate **11** with (*R*)-(+)-α-phenylethylamine in the presence of EDCI, TEA and DMAP in DCM resulted in the formation of a pair of diastereoisomers. The desired diastereoisomer **12** was purified via recrystallization from mixed solvents of ethanol and acetone in 31.2% yield. Hydrolysis of compound **12** in the presence of potassium hydroxide and then esterification with methanol gave the final product (*S*)-methyl 2-

(6-hydroxy-2,3-dihydrobenzofuran-3-yl)acetate **13**. Ethyl 2-(4-hydroxyphenoxy)acetate **16** was prepared from hydroquinone **14** and ethyl bromoacetate **15** through alkylation. The synthesis of the third acidic component **20** started from isopropylidene malonate **17**. Condensation of isopropylidene malonate **17** with acetone furnished compound **18**, which subsequently underwent Michael addition reaction to generate compound **19**. Treatment of **19** with hydrochloric acid in DMF triggered hydrolyzation and decarboxylation, followed by debenzylation and esterification to give the target compound **20**.



Scheme 2. Synthesis of the acidic components **13**, **16** and **20**. Reagents and conditions: (a) ethyl 4-chloroacetoacetate, H_2SO_4, 0 °C to r.t., 80.4%; (b) KOH, reflux; (c) Ac_2O, 0 °C to r.t., 89.1% (for two steps); (d) Pd/C, H_2, 30psi, MeOH, r.t., 79.7%; (e) (*R*)-(+)-α- phenylethylamine, EDCI, DMAP, TEA, DCM, r.t., 31.2%; (f) 8M KOH, MeOH, reflux; (g) $SOCl_2$, MeOH, 0 °C, 56.0% (for two steps). (h) EtONa, EtOH, r.t., 56.5%; (i) Acetone, AcOH, morpholine, r.t., 75.6%; (j) Mg, 1-benzyloxy-4-iodobenzene, THF, reflux to 0 °C, 65.9%; (k) 8M HCl, DMF, reflux; (l) Pd/C, H_2, 30 psi, MeOH, r.t.; (m) $SOCl_2$, MeOH, 0 °C, 68.9% (for three steps).

With the nitrogen-containing heterocycle components and the acidic components in hand, the final products were synthesized according to the procedure as depicted in Scheme 3. Reaction of **7a-d** with various β-substituded phenylpropionic acid (**13**, **16** and **20**), followed by deprotection by TFA, smoothly provided the corresponding intermediates **22a-d**, **54-61**, respectively. Hydrolysis of **22a-d** resulted in the formation of products **23a-d**. Alternatively, compounds **22a-d** were reacted with alkyl halides or acyl halides, which were then hydrolyzed with sodium hydroxide to yield target products **24-45**. The synthesis of compounds **62-69** was realized according to the method established above.

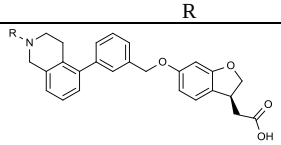
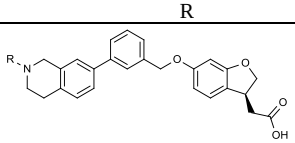


Scheme 3. Synthesis of final products. Reagents and conditions: (a) **13**, **16** or **20**, ADDP, tributylphosphane, toluene, r.t., 78.2% - 93.0%; (b) TFA, DCM, r.t., 72.5% - 91.6%; (c) NaOH, MeOH, r.t.; (d) acetaldehyde, $NaCNBH_3$, AcOH, THF, 0 °C; (e) alkyl halide, K_2CO_3, KI, DMF, 100 °C; (f) acyl chloride, TEA, DCM, 0 °C to r.t..

All compounds were initially evaluated for their GPR40 agonistic activity by detecting luciferase activity in HEK293E cells expressed hGPR40 at a concentration of 10 μM [17]. TAK-875 was employed as the positive compound. The results are summarized in Table 1.

As can be seen from Table 1, the substituents on the nitrogen atom had a remarkable influence on the GPR40 agonistic activity. Compounds **23a-d** without any substituents on N atom did not show any activity on GPR40 cell. Compounds **24**, **29** and **35** bearing an ethyl group on the N atom only exhibited slight agonistic activities on GPR40. In contrast, introduction of benzyl group led to a dramatic increase of GPR40 agonistic activity *in vitro*. The activities of compounds **25** and **41** were approximately 90% of that of TAK-875, while compounds **30** and **36** exhibited better activities than TAK-875. Compounds (**28**, **33**, **39** and **44**) possessing a benzoyl group showed moderate activity on GPR40. Increasing the distance between the distal phenyl and N atom as exemplified in compounds **26**, **31**, **37** and **42** resulted in a loss of GPR40 agonistic activity. The position of the six-membered nitrogen-containing heterocycles had little if any effect on the GPR40 agonistic activity, but generally the activity of 1,2,3,4-tetrahydroisoquinoline derivatives was superior to that of isoindoline derivatives. Replacing the acidic component with phenoxyacetic acid and 3-methyl-3-phenyl-butanoic acid led to a reduced GPR40 activity, except compound **66**, which maintained comparable activity with TAK-875. The result was outlined in Table 2.

Table 1. *In vitro* GPR40 agonistic activity of compounds **23a-d** and **24-45**

Compd.	R	Act%	Compd.	R	Act%
					
23a[a]	R=H	n/a	**23c**[a]	R=H	n/a
24[a]	R=Ethyl	7.8	**35**[a]	R=Ethyl	n/a
25[a]	R=Benzyl	89.4	**36**[a]	R=Benzyl	107.7
26[a]	R=Phenethyl	54.8	**37**[a]	R=Phenethyl	n/a
27	R=Acetyl	43.6	**38**	R=Acetyl	n/a

28	R=Benzoyl	84.2	**39**	R=Benzoyl	46.0
			40	R=Phenylacetyl	20.4
23b[a]	R=H	n/a	**23d**[a]	R=H	n/a
29[a]	R=Ethyl	n/a	**41**[a]	R=Benzyl	89.8
30[a]	R=Benzyl	136.3	**42**[a]	R=Phenethyl	77.0
31[a]	R=Phenethyl	85.0	**43**	R=Acetyl	36.8
32	R=Acetyl	5.0	**44**	R=Benzoyl	60.8
33	R=Benzoyl	39.8	**45**	R=Phenylacetyl	34.8
34	R=Phenylacetyl	31.6	**TAK-875**		100

[a] Compounds was prepared as hydrochloride.

Table 2. *In vitro* GPR40 agonistic activity of compounds **62-69**

Compd.	X	Act%	Compd.	X	Act%
62	O	28.8	**64**	O	4.6
66	$C(CH_3)_2$	90.0	**68**	$C(CH_3)_2$	22.8
63	O	17.8	**65**	O	18.9
67	$C(CH_3)_2$	58.6	**69**	$C(CH_3)_2$	23.8
TAK-875		100			

As listed in Table 1 and Table 2, several compounds exhibited excellent GPR40 agonistic activity at a concentration of 10 μM, which was similar to or even better than the positive compound TAK-875. To further investigate the activity of these compounds, EC_{50} was evaluated and listed in Table 3. All tested compounds exhibited comparable activity with TAK-875. The highest activity was observed with compounds **30**, **36** and **66** with the EC_{50} value of 1.2 μM, 0.8 μM and 0.8 μM, respectively.

The cLogP values of these compounds were also calculated using Molinspiration cheminformatics, which was used to predict their lipophilicity premilinarily (Table 3) [18]. The result demonstrated that cLogP values of these compounds were generally lower than TAK-875, which suggested this novel series of GPR40 agonists could show a relatively low lipophilicity compared with TAK-875.

Table 3 EC_{50} and cLogP values of representative compounds

Compd.	EC_{50} (μM)	cLogP
25	5.4	1.3
28	2.2	3.2
30	1.2	1.3
31	4.0	1.5
36	0.8	1.3
41	3.0	1.1
66	0.8	4.4
TAK-875	5.1	3.4

The direct effect of stimulating insulin secretion of compounds **30** and **36** was evaluated on primary islets isolated from normal ICR mice at a concentration of 10 μM [19]. The result indicated that compounds **30** and **36** could increase insulin secretion in a high concentration of glucose (16.8 mM) (Table 4 and Figure 3).

Table 4 The effect of stimulating insulin secretion of compounds **30** and **36**

Compd.	Insulin (ng/mL/protein)
DMSO (G-2.8 mM)	0.1±0.2***
DMSO (G-16.8 mM)	1.8±0.6
TAK-875	2.1±0.1
30	2.9±0.8*
36	2.8±0.7*

*P<0.05; ***P<0.001, versus DMSO (G-16.8 mM)

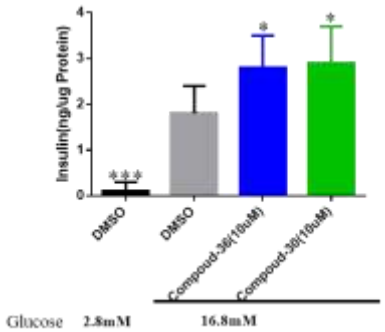


Fig 3. Glucose-stimulated insulin secretion in primary islets isolated from ICR mice in the presence of glucose (2.8 mM and 16.8 mM, respectively) and testing compounds as indicated. The insulin concentraion was quantified by ELISA and was presented as a ratio to the total protein concentration of islets. Data are presented as mean ± SD (n = 5), *P<0.05, versus DMSO (2.8 mM glucose).

The cytochrome P450 inhibition of compounds **30** and **36** was then tested at a concentration of 5 μM (Table 5). The results showed that compounds **30** and **36** exhibited no significant inhibition against CYP2D6, CYP2C9, CYP3A4 and CYP1A2.

Table 5 CYP450 inhibitory activity (%) of compounds **30**, **36** and TAK-875

CYP	**30**	**36**	**TAK-875**

2D6	23.60	39.47	23.22
2C9	16.25	3.94	21.02
3A4	30.69	27.62	33.96
1A2	20.92	25.73	28.00

Furthermore, we evaluated the efficacy of compounds **30** and **36** *in vivo* by oral glucose tolerance test (oGTT) in normal ICR mice [20]. Compound **30** effectively reduced the area under the curve of blood glucose (AUC low 13.8%, P<0.01) after oral glucose administration at 50 mg/kg, however **36** did not have an obvious effect on the blood glucose compared with control group (Table 6 and Figure 4).

Table 6 The oGTT of compounds **30** and **36**

Group	dose (mg/kg)	blood glucose (mg/dL)				AUC (mg*h/dL)
		0 min	30 min	60 min	120 min	
Control		67.0±13.4	227.6±18.7	175.8±25.0	53.7±9.9	290.0±23.5
TAK-875	50	58.1±9.2	155.2±19.4***	120.0±21.2***	49.0±7.4	206.6±22.8***
30	50	60.3±12.6	196.2±27.9**	150.2±26.3*	49.9±8.2	250.8±32.2**
36	50	61.2±13.0	214.1±39.9	172.7±34.3	58.0±9.4	280.9±46.7

n = 10, *P<0.05; **P<0.01; ***P<0.001 versus control group

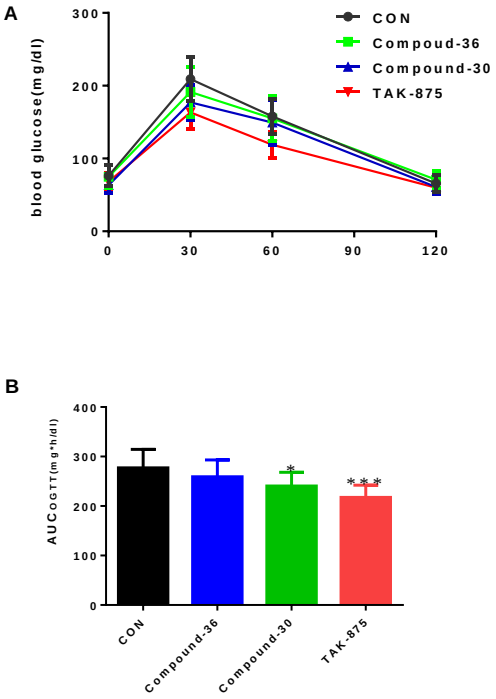


Fig 4. Blood glucose curves (A) and AUC (B) of oGTT in ICR mice. To perform oGTT, 12h-fasted mice were orally administered with compound **30**, **36** and TAK-875 (at the indicated doses) 1 hour prior to oral glucose load (2 g/kg). Blood glucose levels were determined at 0 min and 30, 60, 120 minutes after glucose load. Data are presented as mean ± SD (n = 10), *P<0.05, ***P<0.001, versus control.

To further understand the interaction of this series of GPR40 agonists with GPR40, the molecular simulation between compound **30** and GPR40 protein (the complex structure of GPR40 was obtained from the Protein Data Bank, PDB code: 4PHU) was conducted using CDocker protocol with default settings in Discovery Studio 2017 software package (BIOVIA, San Diego: Dassault Systemes). The molecular simulation result indicated compound **30** bound to GPR40 predominantly through a strong hydrogen bond between the carboxyl group with ARG183 and two salt bridges with ARG183 and ARG 2258. Besides, benzene rings were interacted with a number of amino acid residues via Pi-Pi interaction (-CDocker interaction energy = 37.76 kcal/mol, Figure 5).

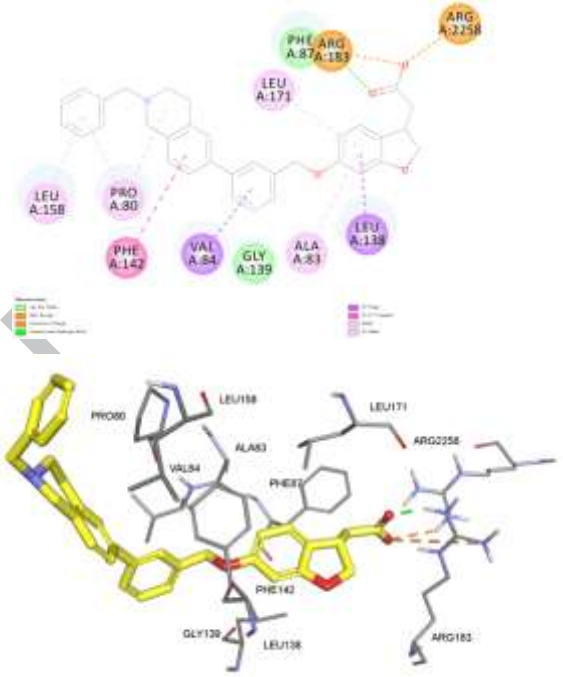


Fig 5. Molecular simulation of compound **30** and GPR40

In conclusion, a novel series of GPR40 agonists containing nitrogen heterocyclic rings derived from TAK-875 were designed and synthesized. The structural activity relationship studies indicated that the substituents on the nitrogen atom had a remarkable effect on the GPR40 agonistic activity. Compounds bearing benzyl group on N atom exhibited excellent activity. Among all compounds, compound **30** showed excellent GPR40 agonistic activity *in vitro*. It was able to increase insulin secretion and did not have obvious inhibition on cytochrome P450 *in vitro*. Premilinary study indicated that compound **30** could regulate blood glucose level of normal ICR mice effectively. Moreover, the cLogP value of compound **30** was lower than that of TAK-875. Further investigation of compound **30** is still in progress in our laboratory and the result will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary datd associated with this article can be found, in the online version, at http://dx.doi.org/

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Highlights

- A series of novel GPR 40 agonists was prepared.
- The compounds feature the nitrogen-containing heterocycles.
- Compound 30 exhibited efficacy both in vitro and in vivo.