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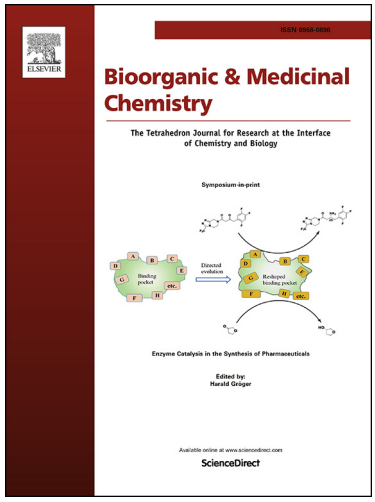

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Design, Synthesis, and Effects of Novel Phenylpyrimidines as Glucagon Receptor Antagonists

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Abstract

The hormone glucagon increases blood glucose levels through increasing hepatic glucose output. In diabetic patients, dysregulation of glucagon secretion contributes to hyperglycemia. Thus, the inhibition of glucagon receptor is one target for the treatment of hyperglycemia in type 2 diabetes. Here we designed and synthesized a series of small molecules based on phenylpyrimidine. Of these, the compound ***(R)*-7a** most significantly decreased the glucagon-induced cAMP production and glucagon-induced glucose production during *in vitro* and *in vivo* assays. In addition, ***(R)*-7a** showed good efficacy in glucagon

challenge tests and lowered blood glucose levels in diabetic *db/db* mice. Our results suggest that the compound ***(R)*-7a** could be a potential glucose-lowering agent for treating type 2 diabetes.

Keywords: Glucagon receptor antagonist, type 2 diabetes, phenylpyrimidine

1. Introduction

Glucagon is a peptide hormone that acts to increase blood glucose levels [1]. The secretion of glucagon from the alpha cells of the islets of Langerhans in the pancreas is increased during fasting and prevents hypoglycemia [2]. Glucagon increases glycogenolysis and gluconeogenesis and thereby promotes glucose production in the liver [3-5]. In type 2 diabetes, hyperglucagonemia is associated with hyperglycemia, and elevated glucagon levels exacerbate the hyperglycemic condition by increasing hepatic glucose production [3, 6]. Therefore, reduction of glucagon concentrations or inhibition of glucagon actions might be a logical therapeutic strategy for the treatment of diabetes.

Glucagon acts on target tissues via the glucagon receptor (GCGR), which is a member of the seven-transmembrane G-protein coupled receptor superfamily [2, 7]. Glucagon binding to the GCGR activates adenylyl cyclase and increases intracellular cyclic adenosine monophosphate (cAMP), resulting in the biological effects [8-11]. Inhibition of the GCGR by GCGR neutralizing antibodies, anti-sense oligonucleotides and/or peptide and small molecule GCGR antagonists have been shown to decrease hepatic glucose output and improve glucose tolerance in various diabetes models [12-16]. To date, various small molecule GCGR antagonists such as BAY 27-9955, MK-0893, PF-06291874, LY-2409021, and LGD-6972, etc. [17-20] have been developed and evaluated as therapeutic agents for diabetes (Fig. 1).

In this paper, we report a series of phenylpyrimidines as novel GCGR antagonists. We found that the compound named ***(R)*-7a** has therapeutic effects in a type 2 diabetic model.

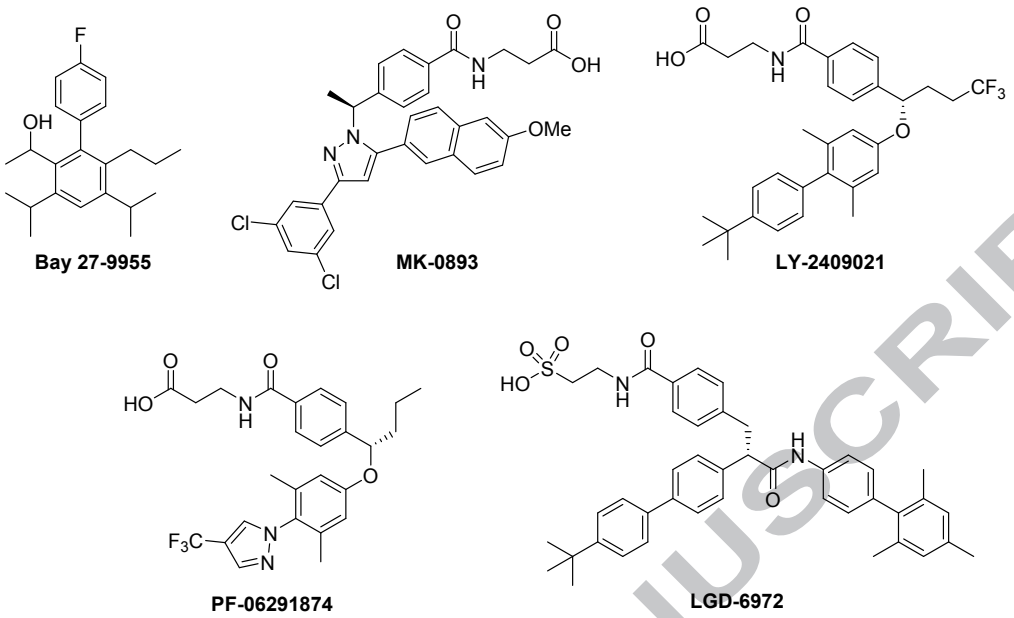


Fig. 1. Representative GCGR antagonists

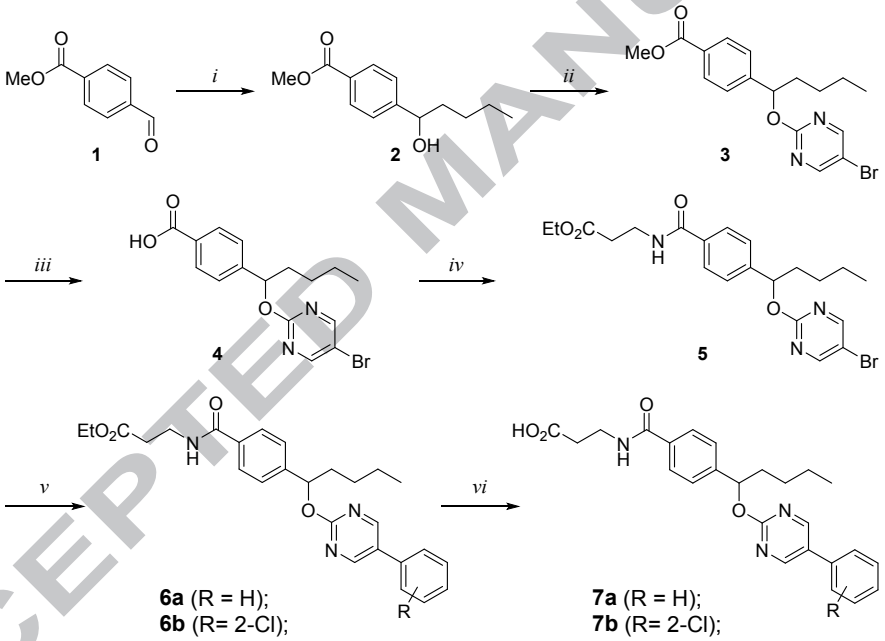
2. Results and discussion

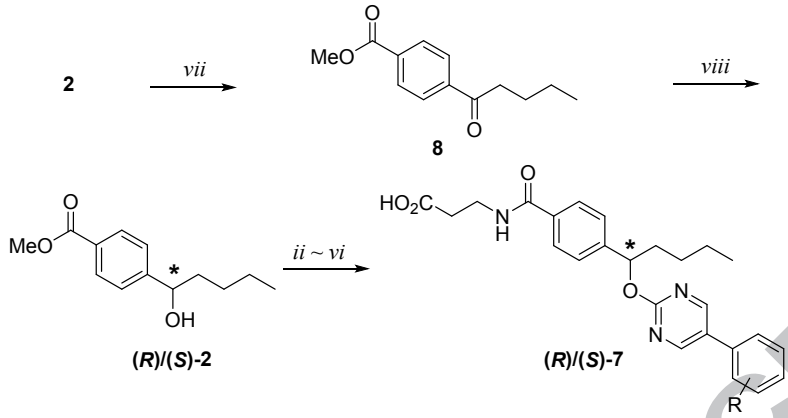
2.1. Chemistry

The bioisosteric replacement approach is an efficient way to find new lead compounds in drug discovery. In this approach, the benzene ring can be replaced with various five-membered or six-membered heteroaromatic cycles such as pyrrole, imidazole, oxazole, pyridine, or pyrazine. In this work, we designed pyrimidines derivatives based on LY-2409021. Pyrimidine ring as is considered and commonly adopted as one of bioisosteres of benzene ring in medicinal chemistry and might give benefits in terms of physicochemical properties and patent issue. Synthesis of phenylpyrimidines is depicted in **Scheme 1** (upper panel). Methyl terephthalaldehydate **(1)** was subjected to Grignard reaction to yield phenylpentyl alcohol **2**. 4-Bromopyrimidine was successfully introduced to the secondary alcohol by the Mitsunobu reaction to give the pyrimidine core **3** in 50% yield. Hydrolysis of the ester **3** under basic condition yielded benzoic acid **(4)**, which was converted to the amide **5** by coupling with *β*-alanine ethyl ester. The 4-bromopyrimidine **5** was transformed to

substituted phenylpyrimidine **6** through the Suzuki reaction with various substituted boronic acids. Finally, hydrolysis of the ester **6** delivered the desired carboxylic acids **(7)**.

Synthesis of chiral compounds of selected phenylpyrimidines was carried out as shown in **Scheme 1** (lower panel). The alcohol intermediate **(2)** was oxidized to ketone **(8)** with pyridinium dichromate (PDC). Chiral alcohols were generated by asymmetric reduction of ketone with chiral CBS catalysts. *(S)*-Me-CBS catalyst yielded *(R)*-enantiomer of alcohol **(2)** and *(R)*-Me-CBS catalyst yielded the *(S)*-enantiomer. Synthesis of final chiral analogues **(7)** were completed following the procedure for racemate synthesis.





(*R*)-7a (R = H); **(*R*)-7f** (R = 4-*t*-Bu); **(*R*)-7g** (R = 3,5-Di-Cl)
(*S*)-7a (R = H); **(*S*)-7f** (R = 4-*t*-Bu); **(*S*)-7g** (R = 3,5-Di-Cl)

Scheme 1. Synthesis of phenylpyrimidines. *Reagents and conditions*: i. *n*-BuMgBr, dry THF, 0 °C, 60%; ii. 5-Bromo-2-hydroxypyrimidine, DIAD, PPh_3, THF, rt, 63%; iii. LiOH-H_2O, THF:H_2O (1.5:1), rt, 80%; iv. *β*-alanine ethyl ester hydrochloride, EDCI, HOBt, DIEA, DMF, 50 °C, 90%; v. substituted boronic acid, $NaHCO_3$, Pd(dppf)Cl_2, DMF, 90 °C, 38~86%; vi. LiOH-H_2O, THF:H_2O (1.5:1), rt, 30~99%. vii. PDC, MS4Å, DCM, rt, 59% viii. *(R)*-Me-CBS catalyst, BH_3-THF complex, dry THF, 0 °C, 78% for *(S)*-2; *(S)*-Me-CBS catalyst, BH_3-THF complex, dry THF, 0 °C, 73% for *(R)*-2

2.2. *In vitro* cytotoxicity studies

To examine whether the synthesized compounds have any cytotoxic effects on cells, we treated mouse primary hepatocytes with 20 μM of each compound for 24 h, and cell viability was measured by Cell Counting Kit-8 (CCK-8) assays. We found all compounds tested showed over 80% cell viability (Fig. 2A).

2.3. *Screening of synthesized compounds by in vitro functional antagonistic assay*

Glucagon promotes glycogenolysis and gluconeogenesis by mediated via GCGR in the liver to elevate blood glucose levels during the fasting state [2, 7]. GCGR acts primarily through the cAMP-protein kinase A (PKA) pathway [8-11]. Upon GCGR activation by glucagon, intracellular cAMP levels are increased by activation of adenylate cyclase, subsequently PKA

is activated. To evaluate the inhibitory effects of the compounds on GCGR signaling, we measured intracellular cAMP levels using the reporter cell line, cAMP Hunter™ CHO-K1 GCGR Gs cells. Glucagon treatment increased cAMP production and treatment with the synthesized compounds inhibited this glucagon-induced cAMP production. Most of the tested compounds showed over 60% inhibition at 10 μM (Fig. 2B). We evaluated the dose-dependent inhibitory effect of five compounds (**7a**, **7f, 7g**, **7i**, and **7j**) on glucagon-induced cAMP production in CHO-K1 GCGR Gs cells. The obtained IC_{50} values of each compound were 4.1 μM, 6.0 μM, 6.9 μM, 8.2 μM, and 17.7 μM for **7a**, **7f**, **7g**, **7i**, and **7j**, respectively (Fig. 2C).

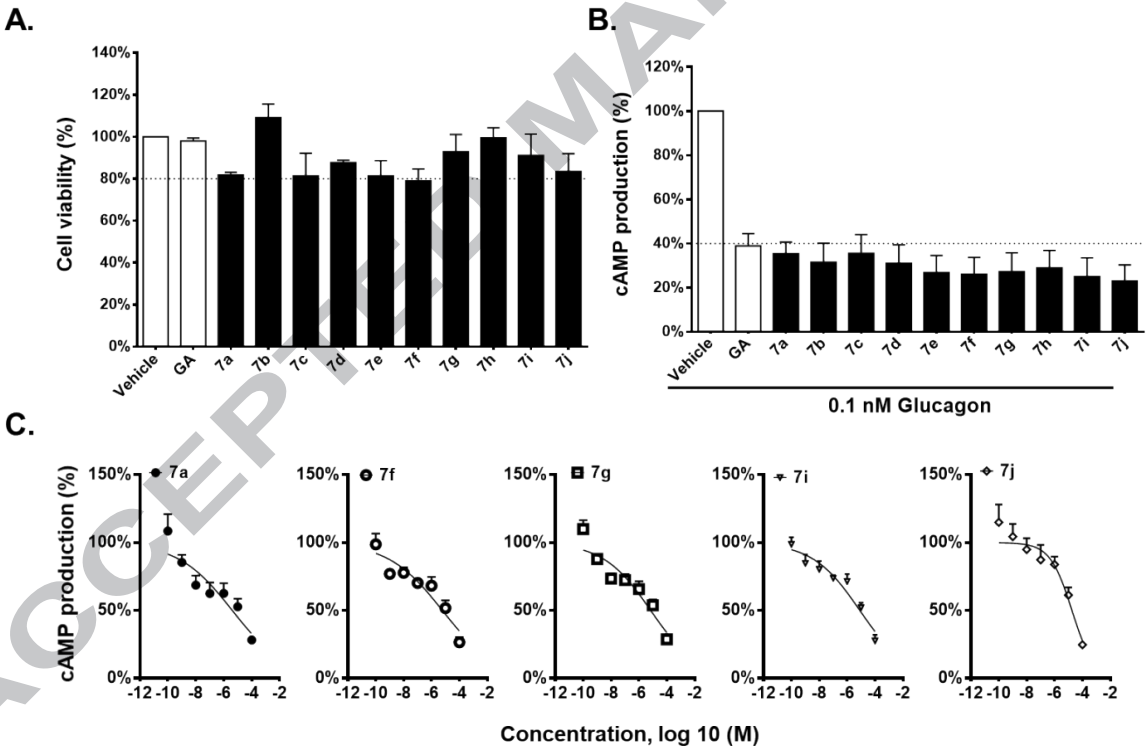


Fig. 2. Screening of phenylpyrimidine compounds by cytotoxicity assay and cAMP production assay.

A. Mouse primary hepatocytes were treated with 20 μM of the indicated compounds for 24 h and cell viability was determined by CCK-8 assay. B. cAMP production was measured after treatment of CHO-K1 GCGR Gs cells with 10 μM of the indicated compounds and 0.1 nM

glucagon. C. cAMP production was measured in CHO-K1 GCGR Gs cells after treatment with 0.0001, 0.001, 0.01, 0.1, 1, 10, or 100 μM of the indicated compounds and 0.1 nM glucagon. GA was used as a positive control for A (20 μM) and B (10 μM). Black bars in the graphs A and B are the selected compounds. Results are representative of 3 independent experiments. ** $p < 0.01$ vs. Vehicle, GA; GCGR antagonist I (Santa Cruz Biotechnology, sc-203972)

2.4. *Screening of synthesized compounds by glucagon-induced glucose production assay*

Activation of GCGR by glucagon promotes glucose production by inducing both glycogenolysis and gluconeogenesis in the liver [2, 7]. We examined the inhibitory efficacy of all compounds on glucagon-induced glucose production in mouse primary hepatocytes. Five compounds (**7a**, **7f, 7g**, **7i**, and **7j**) showed over 60% inhibition, and **7f** and **7g** were the most effective (Fig. 3A). According to the results shown in Fig. 2C and Fig. 3A, compounds **7a**, **7f**, and **7g** had lower IC_{50} values and better inhibitory effect on glucagon-induced glucose production than the other compounds and thus were selected for further study. To evaluate the dose-dependent effects of the compounds **7a**, **7f,** and **7g**, we assessed glucagon-induced glucose production in mouse primary hepatocytes. The compounds **7a**, **7f,** and **7g** showed dose-dependent inhibitory effects on glucagon-induced glucose production (Fig. 3B). Then we selected compounds **7a** and **7f** for pharmacokinetic analysis because they had the highest inhibitory effect on glucagon-induced glucose production at 10 μM.

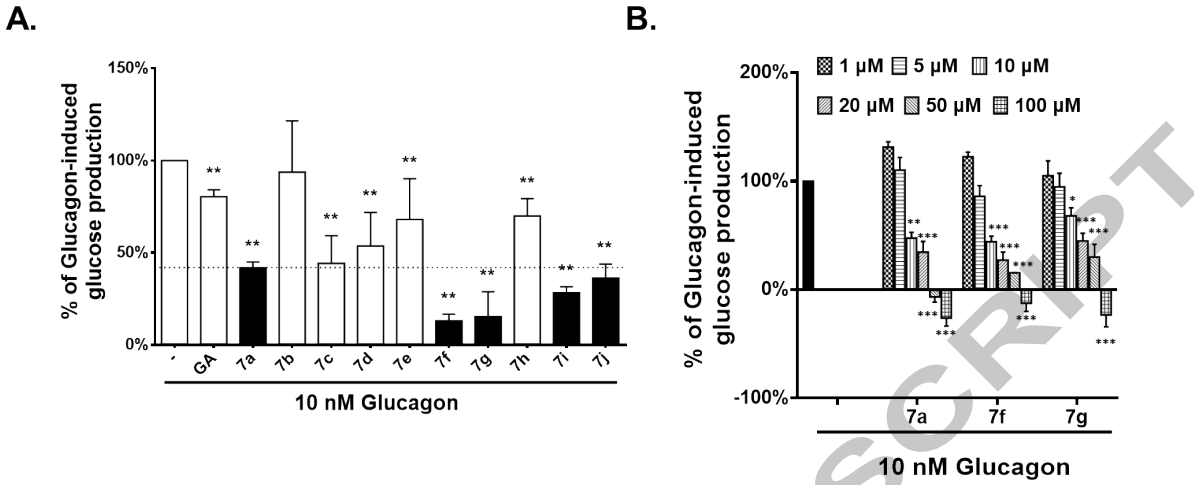


Fig. 3. Screening of phenylpyrimidine compounds by glucagon-induced glucose production assay.

A. Mouse primary hepatocytes were treated with 20 μM of the indicated compounds in the presence of 10 nM glucagon and gluconeogenic substrates (2 mM sodium pyruvate and 20 mM sodium lactate). Glucose production was measured at 30 min after treatment with glucagon. B. Mouse primary hepatocytes were treated with 1, 5, 10, 20, 50, or 100 μM of the indicated compounds in the presence of 10 nM glucagon and gluconeogenic substrates (2 mM sodium pyruvate and 20 mM sodium lactate). Glucose production was measured by a glucose assay kit. As a positive control, mouse primary hepatocytes were treated with 20 μM of GA. Results are representative of 3 independent experiments. * $p < 0.05$, ** $p < 0.01$, or *** $p < 0.001$ vs. 10 nM Glucagon (black bar). GA; GCGR antagonist I (Santa Cruz Biotechnology, sc-203972).

2.5. The screening of enantiomers of compounds 7a and 7f

To define the importance of chirality of the selected compounds, we synthesized each enantiomer: ***(S)*-7a** (*(S)*-enantiomer of **7a**) and ***(R)*-7a** (*(R)*-enantiomer of **7a**), and ***(S)*-7f** (*(S)*-enantiomer of **7f**) and ***(R)*-7f** (*(R)*-enantiomer of **7f**). We evaluated the inhibitory effects of these four compounds on glucagon-induced glucose production in mouse primary

hepatocytes. As shown in Fig. 4A, each enantiomer of **7a**, ***(S)*-7a** and ***(R)*-7a,** significantly reduced glucagon-induced glucose production, and ***(R)*-7a** seemed to be significantly more potent than its racemates. However, neither ***(S)*-7f** nor ***(R)*-7f** showed better inhibitory effect on glucagon-induced glucose production than **7f**. To evaluate the cytotoxic effect of synthesized enantiomer compounds, we treated mouse primary hepatocytes with 20 μM of the compound for 24 h and cell viability was measured by CCK-8 assays. The compound ***(R)*-7a** did not show any toxicity and ***(S)*-7a** showed less cytotoxicity than ***(S)*-7f** and ***(R)*-7f** (Fig. 4B). Especially, the compound ***(S)*-7f** showed the strong cytotoxic effect in mouse primary hepatocyte. Therefore, we selected the compounds of **7a** enantiomer, ***(S)*-7a** and ***(R)*-7a**, to test *in vivo* efficacy. We then evaluated the dose-dependent inhibitory effect of **7a** enantiomer compounds on glucagon-induced cAMP production. The obtained IC_{50} values of ***(S)*-7a** and ***(R)*-7a** were 8.5 μM and 9.3 μM, respectively (Fig. 4C).

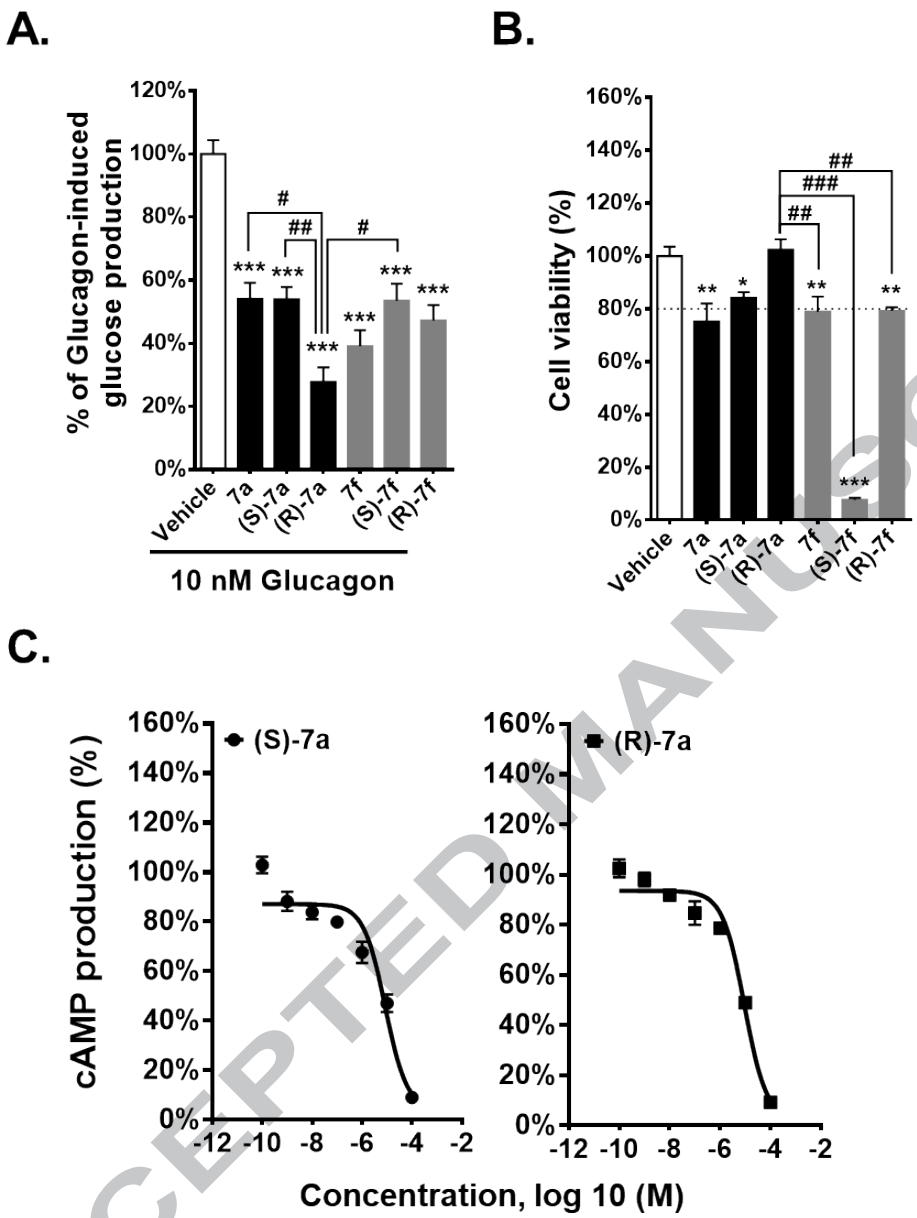


Fig. 4. Screening of enantiomers of **7a** and **7f** by cAMP production assay, cell cytotoxicity assay, and glucose production assay. A. Mouse primary hepatocytes were treated with 20 μM of the indicated compounds for 3 h in the presence of 10 nM glucagon and gluconeogenic substrates (2 mM sodium pyruvate and 20 mM sodium lactate). Glucose production was measured at 30 min after treatment with glucagon. B. Mouse primary hepatocytes were treated with 20 μM of the indicated compounds for 24 h, and cell viability was determined by CCK-8 assay. C. cAMP production was measured in CHO-K1 GCGR Gs cells after treatment

with 0.0001, 0.001, 0.01, 0.1, 1, 10, or 100 μM of the indicated compounds and 0.1 nM glucagon. Results are representative of 3 independent experiments. * $p < 0.05$, ** $p < 0.01$, or *** $p < 0.001$ vs. Vehicle, $^{\#}$ $p < 0.05$, $^{\#\#}$ $p < 0.01$ or $^{\#\#\#}$ $p < 0.001$

2.6. *In vivo* effect of the compounds *(S)*-7a and *(R)*-7a

To evaluate the blood glucose lowering effect of ***(S)*-7a** and ***(R)*-7a** compounds, diabetic *db/db* mice were given 50 mg/kg orally of ***(S)*-7a**, ***(R)*-7a**, or LY-2409021 once a day for 4 weeks. After 4 weeks of treatment, blood glucose levels were measured after 12 h fasting. Blood glucose levels were significantly decreased in the ***(R)*-7a**-treated group compared with the vehicle group. Blood glucose levels following the administration of ***(S)*-7a** were not statistically different from the vehicle-treated group, but showed a tendency for decrease blood glucose levels. (Fig. 5A). In fact, LY-2409021 treatment showed nearly no effect on severe hyperglycemic mice that had blood glucose levels of >450 mg/dL, whereas **(*S*)-** and **(*R*)-7a** showed glucose-lowering effects even in severe hyperglycemic mice in our study. Therefore, LY2409021 may be less effective than **(*S*)-** and **(*R*)-7a** in cases of severe hyperglycemia. In addition, we performed the glucagon challenge assay to confirm the inhibitory effect of ***(S)*-7a** and ***(R)*-7a** on glucagon-induced blood glucose elevation. As shown in Fig. 5B, treatment with ***(S)*-7a** or ***(R)*-7a** decreased glucagon-induced blood glucose in diabetic *db/db* mice given 15 μg/kg glucagon. This data indicated that ***(S)*-7a** and ***(R)*-7a** have the ability of GCGR antagonism in diabetic model.

From these *in vivo* and *in vitro* data, we conclude that ***(R)*-7a** and ***(S)*-7a** were more effective than the other enantiomers. As ***(S)*-7a** has a slight toxicity to mouse primary hepatocytes, we recommend compound ***(R)*-7a** for further investigation.

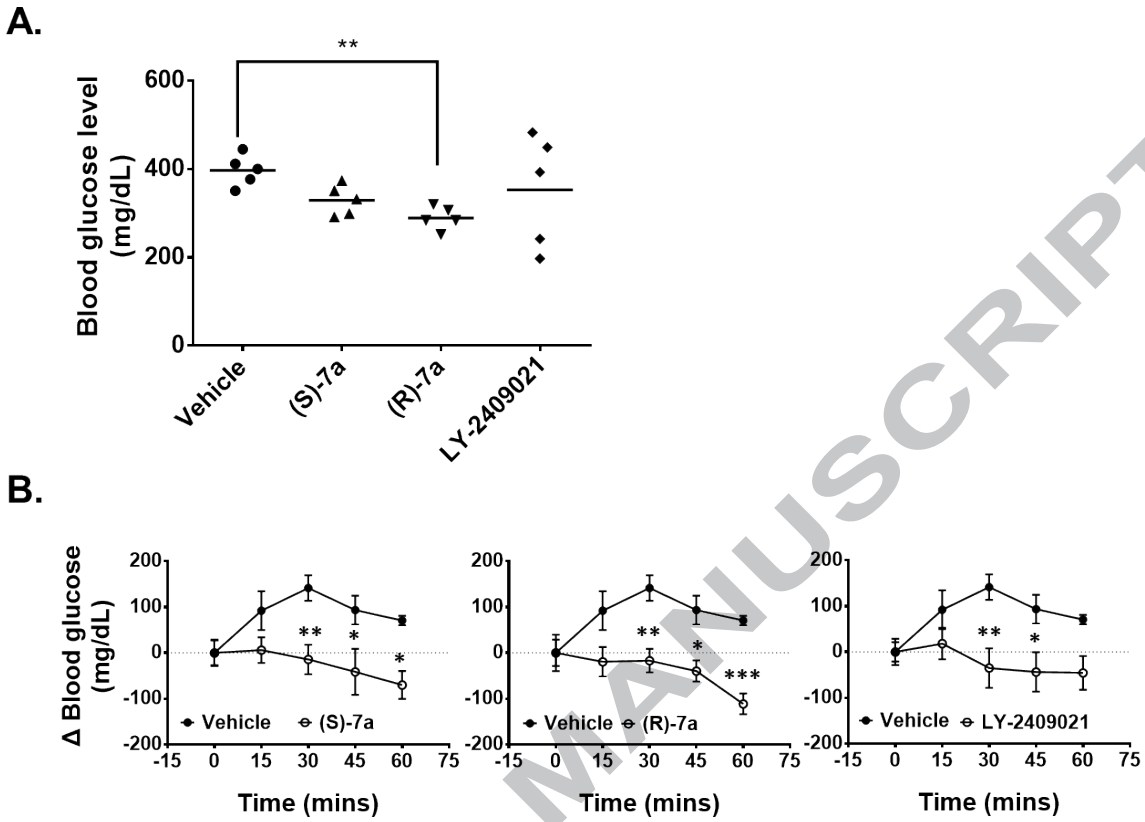


Fig. 5. Blood glucose lowering effect of ***(S)*-7a** and ***(R)*-7a** in *db/db* mice.

Diabetic *db/db* mice were orally administrated 50 mg/kg of ***(S)*-7a**, ***(R)*-7a**, or LY-2409021 once a day for 4 weeks. A. Fasting blood glucose levels were measured. (n=7/group) ** $p <$ 0.01 vs. Vehicle group B. Mice were fasted for 5 h and then 50 mg/kg of ***(S)*-7a**, ***(R)*-7a**, or LY-2409021 was orally gavaged. After 1 h, 15 μg/kg of glucagon was intraperitoneally injected. Blood glucose levels were measured 15, 30, 45 and 60 min after glucagon injection. (n=4-6/group) * $p < 0.05$, ** $p < 0.01$ or *** $p < 0.001$ vs. Vehicle group

3. Conclusion

A series of novel phenylpyrimidine derivatives were designed, synthesized, and evaluated as GCGR antagonists. Based on the inhibitory efficacy of glucagon-induced cAMP production in CHO-K1 GCGR Gs cells and glucagon-induced glucose production in mouse primary hepatocytes, we selected compounds **7a** and **7f** for further study. We next synthesized the two

enantiomers of **7a** and **7f,** and then selected ***(S)*-7a** and ***(R)*-7a** for *in vivo* study based on their superior inhibitory effects on glucagon-induced glucose production and cAMP production. In addition, The GCGR antagonist ***(R)*-7a** showed good efficacy of glucagon signaling blockage and blood glucose lowering effect in a diabetic animal model. Our results suggest that the compound ***(R)*-7a** could be a potential glucose-lowering agent for treating type 2 diabetes.

4. Experimental

4.1. Chemistry

The reaction solvents used for the synthesis were dried over appropriate drying agents or purchased as anhydrous grade or of reagent grade. The reactions were performed under N_2 atmosphere or at designated conditions. Purification of products was carried out using flash column chromatography with silica gel (40-63μm) purchased from ZEOprep or medium-performance liquid chromatography (Isolera™ by Biotage). Melting points were determined on Opti Melt-automated melting point system, Stanford Research Systems and were uncorrected. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker 600 (^{1}H NMR at 600 MHz and ^{13}C NMR at 150 MHz) spectrometer with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.5 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm, DMSO-d_6 at 39.5 ppm). Mass spectra were obtained using Waters 3100 Mass Detector spectrometer with electrospray ionization calibrated Waters Technologies, Accurate – Mass QTOF LCMS, 1200 series LC with dual spray ESI source. Optical rotation was determined on optical activity ltd AA-10R automatic polarimeter in DCM. Melting points were determined on Opti Melt-automated melting point system, Stanford Research Systems and were uncorrected.

Methyl 4-(1-hydroxypentyl)benzoate (2): A solution of methyl terephthalaldehydate (2.0 g, 12.2 mmol) in anhydrous THF (60 ml) was cooled to 0 °C while stirring under nitrogen. *n*-

BuMgBr (12.0 ml, 24.4 mmol) was added slowly over 5 min. The reaction was allowed to stir at 0 °C for 1 h, and then allowed to warm to rt. The reaction was monitored by TLC, and upon complete consumption of the aldehyde, the reaction was quenched carefully with 1N HCl. The reaction mixture was diluted with EtOAc (300 ml), the organic layer was washed with H_2O, brine and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the residue was purified by SiO_2 flash column chromatography to afford the desired product **2** (1.20 g, 60% yield) as a white solid. Mp: 32~34 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.97 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 4.69 (t, J = 6.6 Hz, 1H), 3.89 (s, 3H), 2.65 (s, 1H), 1.76 (m, 1H), 1.68 (m, 1H), 1.30 (m, 4H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 167.1, 150.3, 129.7, 129.0, 125.8, 74.1, 52.1, 38.8, 27.8, 22.6, 14.0; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{13}H_{19}O_3^+$ 223.1329, found 223.1325.

Methyl 4-(1-((5-bromopyrimidin-2-yl)oxy)pentyl)benzoate (3): To a solution of alcohol **2** (188 mg, 0.846 mmol), 5-bromo-2-hydroxypyrimidine (178 mg, 1.02 mmol) and PPh_3 (333 mg, 1.27 mmol) in anhydrous THF (4.5 ml) at rt was added DIAD (0.25 ml, 1.27 mmol) dropwise. The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with EtOAc (30 ml), the organic layer was washed with H_2O, brine and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the residue was purified by SiO_2 flash column chromatography to afford the desired product **3** (509 mg, 63% yield) as colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.45 (s, 2H), 7.99 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 7.8 Hz, 2H), 5.94 (q, J = 5.4, 7.8 Hz, 1H), 3.89 (s, 3H), 2.12-2.05 (m, 1H), 1.91-1.85 (m, 1H), 1.47-1.42 (m, 1H), 1.38-1.30 (m, 3H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 166.8, 163.3, 159.6, 146.4, 129.7, 129.5, 126.4, 111.9, 79.3, 52.1, 36.6, 27.6, 22.4, 13.9; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{17}H_{20}BrN_2O_3^+$ 379.0652, found 379.0648.

4-(1-((5-Bromopyrimidin-2-yl)oxy)pentyl)benzoic acid (4): To a solution of the methyl ester **3** (984 mg, 2.59 mmol) in THF/H_2O (1.5:1) (20 ml) was added LiOH-H_2O (218 mg, 5.19 mmol). The reaction mixture stirred at rt for overnight. After completion, the reaction mixture was diluted with H_2O (5 ml) and acidified to pH 2 with 1N HCl. The reaction mixture was diluted with EtOAc (50 ml), and the organic layer was washed with H_2O, brine and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the residue was purified by SiO_2 flash column chromatography to afford the desired product **4** (1.50 g, 80% yield) as a white solid. Mp: 110~112 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.47 (s, 2H), 8.07 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 5.96 (q, J = 6, 7.8 Hz, 1H), 2.13-2.07 (m, 1H), 1.93-1.87 (m, 1H), 1.49-1.43 (m, 1H), 1.39-1.32 (m, 3H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 171.6, 163.2, 159.6, 147.3, 130.4, 128.8, 126.5, 111.9, 79.3, 36.7, 27.6, 22.5, 13.9; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{16}H_{18}BrN_2O_3^+$ 365.0495, found 365.0486.

Ethyl 3-(4-(1-((5-bromopyrimidin-2-yl)oxy)pentyl)benzamido)propanoate (5): To a solution of benzoic acid **5** (674 mg, 1.85 mmol), β-alanine ethyl ester hydrochloride (567 mg, 3.69 mmol), HOBt (565 mg, 3.69 mmol) and EDCI (708 mg, 3.69 mmol) in anhydrous DMF (9 ml) was added DIEA (0.90 ml, 5.54 mmol). The reaction was stirred at 50 °C for 1 h. After cooling, the reaction mixture was diluted with EtOAc (300 ml), and the organic layer was washed with H_2O, brine and dried over $MgSO_4$. The solution was filtered and the solvent was removed under reduced pressure. The residue was purified by SiO_2 flash column chromatography to afford the desired product **5** (774 mg, 90% yield) as colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.44 (s, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 6.82 (t, J = 5.4 Hz, 1H), 5.91 (q, J = 5.4, 7.8 Hz, 1H), 4.16 (q, J = 7.2, 14.4 Hz, 2H), 3.71 (q, J = 6, 12 Hz, 2H), 2.62 (t, J = 6 Hz, 2H), 2.11-2.05 (m, 1H), 1.90-1.84 (m, 1H), 1.46-1.41 (m, 1H), 1.37-1.32 (m, 3H), 1.27 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR

(150 MHz, $CDCl_3$) δ (ppm): 172.9, 166.9, 163.3, 159.6, 144.8, 133.8, 127.0, 126.7, 111.9, 79.3, 60.8, 36.6, 35.3, 33.9, 27.6, 22.4, 12.2, 13.9; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{21}H_{27}BrN_3O_4^+$ 464.1179, found 464.1172.

General procedure for the synthesis of 6 (Synthesis of **6a);** To a solution of bromopyrimidine **5** (70 mg, 0.152 mmol), substitute boronic acid (20.0 mg, 0.172 mmol) and $NaHCO_3$ (38 mg, 0.450 mmol) were dissolved in anhydrous DMF (0.8 ml). The mixture was purged with nitrogen for 5 min, $Pd(dppf)Cl_2$-CH_2Cl_2 complex (37 mg, 0.051 mmol) was added and the mixture was stirred at 90 °C for 6 h ~ 12 h. The mixture was partitioned between EtOAc (30 ml) and water, and the aqueous layer was extracted with EtOAc (30 ml). The combined organic layer was washed with H_2O, brine and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the residue was purified by SiO_2 flash column chromatography to afford the desired product **6a** (35.0 mg, 50% yield) as colorless oil. ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.63 (s, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.47-7.44 (m, 3H), 7.40-7.37 (m, 1H), 6.81 (t, J = 6 Hz, 1H), 6.04 (q, J = 6, 7.8 Hz, 1H), 4.16 (q, J = 7.2, 14.4 Hz, 2H), 3.71 (q, J = 6, 12 Hz, 2H), 2.62 (t, J = 6 Hz, 2H), 2.15-2.08 (m, 1H), 1.93-1.87 (m, 1H), 1.51-1.45 (m, 1H), 1.39-1.34 (m, 3H), 1.26 (t, J = 6.6 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 172.9, 167.1, 164.1, 157.3, 145.5, 134.4, 133.6, 129.2, 128.4, 128.2, 127.0, 126.7, 126.5, 78.6, 60.8, 36.8, 36.5, 35.3, 33.9, 31.4, 27.7, 22.5, 14.2, 14.0; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{27}H_{32}N_3O_4^+$ 462.2387, found 462.2369.

Ethyl 3-(4-(1-((5-(2-chlorophenyl)pyrimidin-2-yl)oxy)pentyl)benzamido)propanoate (6b); Colorless oil; Yield 66%; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.64 (s, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.49-7.46 (m, 3H), 7.35-7.32 (m, 1H), 7.26 (m, 1H), 6.82 (t, J = 6 Hz, 1H), 6.06 (q, J = 5.4, 7.8 Hz, 1H), 4.16 (q, J = 7.2, 14.4 Hz, 2H), 3.71 (q, J = 6, 12 Hz, 2H), 2.62 (t, J = 6 Hz, 2H), 2.15-2.08 (m, 1H), 1.94-1.88 (m, 1H), 1.51-1.45 (m,

1H), 1.40-1.33 (m, 3H), 1.27 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 172.9, 167.1, 163.9, 162.5, 159.2, 145.3, 133.6, 133.5, 132.8, 130.9, 130.3, 129.7, 127.3, 127.0, 126.8, 126.7, 78.7, 60.8, 36.8, 36.5, 35.3, 33.9, 31.4, 27.7, 22.5, 14.2, 14.0; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{27}H_{31}ClN_3O_4^+$ 496.1998, found 496.1994.

Ethyl 3-(4-(1-((5-(3-chlorophenyl)pyrimidin-2-yl)oxy)pentyl)benzamido)propanoate (6c); Colorless oil; Yield 55%; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.61 (s, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.45 (t, J = 1.8 Hz, 1H), 7.40-7.33 (m, 3H), 6.81 (t, J = 6 Hz, 1H), 6.04 (q, J = 6, 7.8 Hz, 1H), 4.16 (q, J = 7.2, 14.4 Hz, 2H), 3.71 (q, J = 6, 11.4 Hz, 2H), 2.62 (t, J = 6 Hz, 2H), 2.15-2.09 (m, 1H), 1.93-1.87 (m, 1H), 1.51-1.46 (m, 1H), 1.40-1.32 (m, 3H), 1.28-1.25 (m, 3H), 0.89 (t, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 172.9, 167.0, 164.4, 157.3, 145.3, 136.2, 135.2, 133.7, 130.5, 128.2, 127.2, 127.0, 126.7, 126.6, 124.6, 78.8, 60.8, 60.4, 36.8, 35.3, 33.9, 27.7, 22.5, 21.1, 14.2, 14.0; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{27}H_{31}ClN_3O_4^+$ 496.1998, found 496.1994.

Ethyl 3-(4-(1-((5-(4-chlorophenyl)pyrimidin-2-yl)oxy)pentyl)benzamido)propanoate (6d); Colorless oil; Yield 78%; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.60 (s, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.40 (q, J = 9, 19.2 Hz, 4H), 6.92 (t, J = 5.4 Hz, 1H), 6.04 (t, J = 6 Hz, 1H), 4.15 (q, J = 7.2, 14.4 Hz, 2H), 3.70 (q, J = 6, 12 Hz, 2H), 6.22 (t, J = 6 Hz, 2H), 2.14-2.08 (m, 1H), 1.93-1.87 (m, 1H), 1.50-1.46 (m, 1H), 1.38-1.37 (m, 3H), 1.26 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 172.9, 167.1, 164.2, 157.2, 145.3, 134.4, 133.6, 132.8, 129.5, 127.7, 127.3, 127.1, 126.7, 78.8, 60.8, 36.8, 35.3, 33.9, 27.7, 22.5, 14.2, 14.0; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{27}H_{31}ClN_3O_4^+$ 496.1998, found 496.1994.

Ethyl 3-(4-(1-((5-(4-trifluoromethylphenyl)pyrimidin-2-yl)oxy)pentyl)benzamido)propanoate (6e); Colorless oil; Yield 53%; ^{1}H NMR (600 MHz,

$CDCl_3$) δ (ppm): 8.67 (s, 2H), 7.72 (t, J = 8.4 Hz, 4H), 7.58 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 7.8 Hz, 2H), 6.81 (t, J = 6 Hz, 1H), 6.05 (q, J = 6, 7.8 Hz, 1H), 4.16 (q, J = 7.2, 14.4 Hz, 2H), 3.71 (q, J = 6, 12 Hz, 2H), 2.62 (t, J = 6 Hz, 2H), 2.16-2.10 (m, 1H), 1.93-1.88 (m, 1H), 1.51-1.45 (m, 1H), 1.40-1.34 (m, 3H), 1.26 (t, J = 14.4 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 173.0, 167.0, 164.6, 157.5, 145.2, 133.7, 127.7, 126.8, 126.7, 126.2, 78.9, 60.8, 53.4, 36.8, 35.3, 33.9, 27.7, 22.5, 14.2, 14.0; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{28}H_{31}F_3N_3O_4^+$ 530.2261, found 530.2257.

Ethyl 3-(4-(1-((5-(4-(*tert*-butyl)phenyl)pyrimidin-2-yl)oxy)pentyl)benzamido)propanoate (6f); Colorless oil; Yield 86%; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.62 (s, 2H), 7.73-7.70 (m, 2H), 7.52 (d, J = 8.4 Hz, 1H), 7.48-7.45 (m, 2H), 7.41-7.39 (m, 1H), 6.81 (t, J = 6 Hz, 1H), 6.04 (q, J = 6, 7.8 Hz, 1H), 4.18-4.14 (m, 2H), 3.71 (q, J = 6, 12 Hz, 2H), 2.62 (t, J = 6 Hz, 2H), 2.15-2.07 (m, 1H), 1.94-1.85 (m, 1H), 1.50-1.41 (m, 1H), 1.34 (s, 8H) 1.29-1.25 (m, 4H), 0.88 (q, J = 6.6, 13.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 172.9, 167.1, 164.0, 159.6, 157.2, 145.5, 144.8, 133.6, 128.3, 127.1, 127.0, 126.7, 126.2, 79.3, 78.5, 60.8, 60.4, 53.4, 36.9, 36.6, 35.3, 34.6, 33.9, 31.3, 27.6, 22.5, 21.1, 14.2, 14.0; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{31}H_{40}N_3O_4^+$ 518.3013, found 518.3005.

Ethyl 3-(4-(1-((5-(3,4-dichlorophenyl)pyrimidin-2-yl)oxy)pentyl)benzamido)propanoate (6g); Colorless oil; Yield 79%; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.59 (s, 2H), 7.72 (t, J = 7.8 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 1H), 7.38 (t, J = 1.8 Hz, 1H), 7.34 (d, J = 1.8 Hz, 1H), 6.81 (bs, 1H) 6.04 (q, J = 6, 7.8 Hz, 1H), 4.18-4.14 (m, 2H), 3.71 (q, J = 6, 11.4 Hz, 2H), 2.62 (t, J = 6 Hz, 2H), 2.15-2.06 (m, 1H), 1.93-1.85 (m, 1H), 1.50-1.41 (m, 1H), 1.40-1.32 (m, 3H), 1.28-1.25 (m, 4H), 0.90-0.86 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 173.0, 167.0, 159.6, 157.3, 145.1, 137.4, 135.9, 133.8, 128.1, 127.1, 126.7, 124.9, 79.0, 60.8, 60.4, 53.4, 36.7, 36.6, 35.3, 33.9, 27.6, 22.5, 14.2, 13.9; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{27}H_{30}Cl_2N_3O_4^+$ 530.1608, found 530.1606.

Ethyl 3-(4-(1-((5-(2-fluoro-4-(trifluoromethyl)phenyl)pyrimidin-2-yl)oxy)pentyl)benzamido)propan-oate (6h); Colorless oil; Yield 55%; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.63 (s, 1H), 8.44 (s, 1H), 7.74-7.70 (m, 2H), 7.65-7.63 (m, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.30 (t, J = 9 Hz, 1H), 6.81 (d, J = 5.4 Hz, 1H), 6.05 (q, J = 5.4, 7.8 Hz, 1H), 5.91 (q, J = 5.4 Hz, 7.8 Hz, 1H), 4.18-4.14 (m, 2H), 3.71 (q, J = 6, 12 Hz, 2H), 2.62 (t, J = 6 Hz, 2H), 2.17-2.06 (m, 1H), 1.94-1.84 (m, 1H), 1.51-1.40 (m, 1H), 1.39-1.32 (m, 3H), 1.28-1.32 (m, 3H), 0.91-0.86 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 172.9, 166.9, 159.6, 127.0, 126.7, 79.3, 60.8, 36.7, 35.3, 33.9, 27.6, 22.4, 14.2, 13.9; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{28}H_{30}F_4N_3O_4^+$ 548.2167, found 548.2161.

Ethyl 3-(4-(1-((5-(4-phenoxyphenyl)pyrimidin-2-yl)oxy)pentyl)benzamido)propanoate (6i); Colorless oil; Yield 38%; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.60 (s, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.42-7.40 (m, 2H), 7.38-7.35 (m, 2H), 7.15-7.13 (m, 1H), 7.08-7.04 (m, 3H), 6.80 (t, J = 6 Hz, 1H), 6.04 (q, J = 6, 7.8 Hz, 1H), 4.16 (J = 7.2, 13.8 Hz, 2H), 3.71 (q, J = 6, 12 Hz, 2H), 2.62 (t, J = 5.4 Hz, 2H), 2.14-2.08 (m, 1H), 1.93-1.87 (m, 1H), 1.51-1.47 (m, 1H), 1.38-1.34 (m, 3H), 1.28-1.25 (m, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 172.9, 167.0, 163.9, 157.7, 157.0, 156.6, 145.5, 133.6, 129.9, 127.9, 127.0, 126.6, 123.8, 119.3, 78.6, 60.8, 53.4, 36.8, 35.3, 33.9, 27.7, 22.5, 14.2, 14.0; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{33}H_{36}N_3O_5^+$ 554.2649, found 554.2647.

Ethyl 3-(4-(1-((5-(4-ethylphenyl)pyrimidin-2-yl)oxy)pentyl)benzamido)propanoate (6j); Colorless oil; Yield 78%; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.61 (s, 1H), 8.44 (s, 1H), 7.72 (t, J = 8.4 Hz, 2H), 7.52 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 6.81 (t, J = 5.4 Hz, 1H), 6.05-5.90 (m, 1H), 4.18-4.14 (m, 2H), 3.71 (q, J = 6, 11.4 Hz, 2H), 2.68 (q, J = 7.8, 15.6 Hz, 1H), 2.62 (t, J = 5.4 Hz, 2H), 2.14-2.06 (m, 1H), 1.93-1.84 (m, 1H), 1.51-1.41 (m, 1H), 1.38-1.32 (m, 3H), 1.28, 1.25 (m, 5H), 0.88 (q, J = 6.6, 13.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 172.9, 167.1, 163.9, 163.3,

159.6, 157.1, 145.5, 144.9, 144.5, 133.8, 133.6, 131.7, 128.8, 128.4, 127.0, 126.6, 111.9, 79.3, 78.5, 60.8, 53.4, 36.9, 36.6, 35.3, 33.9, 28.5, 27.7, 27.6, 22.5, 15.5, 14.2, 13.9; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{29}H_{36}N_3O_4^+$ 490.2700, found 490.2704.

General procedure for the synthesis of 7 (Synthesis of **7a);** To a solution of the ethyl ester **6** (34.0 mg, 0.071 mmol) in THF/H_2O (1.5:1) (0.60 ml) was added LiOH-H_2O (6.00 mg, 0.152 mmol). The reaction mixture stirred at rt for 5 h ~ 10 h. After completion, the reaction mixture was diluted with H_2O (3 ml) and acidified pH 2 with 1N HCl. The reaction mixture was diluted with EtOAc (30 ml), the organic layer was washed with H_2O, brine and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the residue was purified by SiO_2 flash column chromatography to afford the desired product **7a** (11.0 mg, 36% yield) as Caramel. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.63 (s, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.44 (m, 4H), 7.40-7.37 (m, 1H), 6.91, (t, J = 6 Hz, 1H), 6.04 (q, J = 5.4, 7.2 Hz, 1H), 3.71 (q, J = 6, 11.4 Hz, 2H), 2.69 (t, J = 6 Hz, 2H), 2.12-2.06 (m, 1H), 1.91-1.85 (m, 1H), 1.48-1.43 (m, 1H), 1.38-1.31 (m, 3H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 176.1, 167.5, 163.9, 157.3, 145.5, 134.2, 133.4, 129.3, 128.5, 128.2, 127.1, 126.7, 126.5, 78.7, 36.8, 35.3, 33.7, 27.6, 22.5, 14.0; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{25}H_{28}N_3O_4^+$ 434.2074, found 434.2069.

3-(4-(1-((5-(2-Chlorophenyl)pyrimidin-2-yl)oxy)pentyl)benzamido)propanoic acid (7b); Caramel; Yield 30%; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.54 (s, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.49-7.46 (m, 1H), 7.34-7.31 (m, 2H), 7.26-7.24 (m, 1H), 6.92 (t, J = 6Hz, 1H), 6.06 (q, J = 6, 7.8 Hz, 1H), 3.72 (q, J = 6, 11.4 Hz, 2H), 2.70 (t, J = 5.4 Hz, 2H), 2.13-2.07 (m, 1H), 1.92-1.86 (m, 1H), 1.49-1.43 (m, 1H), 1.38-1.33 (m, 3H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 176.2, 167.5, 163.8, 159.2, 145.4, 133.4, 133.3, 132.8, 131.0, 130.3, 129.8, 127.4, 127.1, 126.9, 126.7, 78.7, 36.7, 35.3, 33.7, 27.6,

22.5, 14.0; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{25}H_{27}ClN_3O_4^+$ 468.1685, found 468.1677.

3-(4-(1-((5-(3-Chlorophenyl)pyrimidin-2-yl)oxy)pentyl)benzamido)propanoic acid (7c); White solid, Mp: 108~110 °C; Yield 78%; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.61 (s, 2H), 7.72 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.3 Hz, 2H), 7.43 (m, 1H), 7.39-7.32 (m, 3H), 6.99 (t, J = 5.9 Hz, 1H), 6.04 (q, J = 6, 7.8 Hz, 1H), 3.70 (q, J = 5.8, 11.5 Hz, 2H), 2.69 (t, J = 5.4 Hz, 2H), 2.12-2.06 (m, 1H), 1.91-1.85 (m, 1H), 1.47-1.42 (m, 1H), 1.38-1.33 (m, 3H), 0.87 (t, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 176.2, 167.5, 164.2, 159.6, 157.3, 145.3, 136.0, 135.2, 133.4, 130.5, 128.3, 127.2, 127.2, 126.7, 126.6, 124.6, 78.9, 36.7, 35.3, 33.7, 27.6, 22.5, 14.0; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{25}H_{27}ClN_3O_4^+$ 468.1685, found 468.1677.

3-(4-(1-((5-(4-Chlorophenyl)pyrimidin-2-yl)oxy)pentyl)benzamido)propanoic acid (7d); White solid, Mp: 143~145 °C; Yield 52%; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.61 (s, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 7.8 Hz, 2H), 7.42-7.37 (m, 4H), 6.97, (t, J = 6 Hz, 1H), 6.03 (q, J = 6, 7.8 Hz, 1H), 3.71 (q, J = 6, 11.4 Hz, 2H), 2.69 (t, J = 6 Hz, 2H), 2.12-2.06 (m, 1H), 1.91-1.85 (m, 1H), 1.48-1.42 (m,1H), 1.38-1.31 (m, 3H), 0.87 (t, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 176.3, 171.3, 167.5, 164.0, 159.6, 157.1, 145.4, 134.6, 133.4, 132.6, 129.5, 127.7, 127.4, 127.1, 126.7, 78.8, 60.5, 36.7, 35.3, 33.7, 27.6, 22.5, 21.1, 14.2, 14.0; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{25}H_{27}ClN_3O_4^+$ 468.1685, found 468.1677.

3-(4-(1-((5-(4-Trifluoromethylphenyl)pyrimidin-2-yl)oxy)pentyl)benzamido)propanoic acid (7e); White solid, Mp: 143~145 °C; Yield 80%; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.67 (s, 2H), 7.72 (dd, J = 8.4, 11.6 Hz, 4H), 7.58 (d, J = 8.1 Hz, 2H), 7.51 (d, J = 8.2 Hz, 2H), 6.93 (t, J = 5.9 Hz, 1H), 6.05 (q, J = 6, 7.8 Hz, 1H), 3.72 (q, J = 5.4, 11.4 Hz, 2H), 2.70 (t, J = 5.4 Hz, 2H), 2.14-2.07 (m, 1H), 1.94-1.87 (m, 1H), 1.49-1.43 (m, 1H), 1.39-1.31 (m,

3H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 176.5, 171.4, 167.6, 164.4, 163.9, 159.6, 157.4, 145.3, 137.8, 133.4, 130.5, 130.3, 127.2, 126.8, 126.7, 126.3, 124.8, 123.0, 79.0, 60.5, 36.6, 35.3, 33.7, 27.6, 22.4, 21.1, 14.2, 14.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calculated for $C_{26}H_{27}F_3N_3O_4^+$ 502.1948, found 502.1943.

3-(4-(1-((5-(4-(*tert*-Butyl)phenyl)pyrimidin-2-yl)oxy)pentyl)benzamido)propanoic acid (7f); White solid, Mp: 143~145 °C; Yield 70%; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.62 (s, 2H), 7.73 (d, J = 7.8 Hz, 2H), 7.49 (d, J = 7.8 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.02 (bs, 1H), 6.03 (q, J = 5.4, 7.2 Hz, 1H), 3.68 (d, J = 4.3 Hz, 2H), 2.65 (bs, 2H), 2.10-2.07 (m, 1H), 1.89-1.85 (m, 1H), 1.43 (m, 1H), 1.33 (s, 9H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 167.5, 163.8, 157.1, 151.4, 145.5, 133.3, 131.3, 128.4, 127.2, 126.7, 126.2, 78.6, 60.5, 50.8, 36.8, 35.4, 34.6, 34.0, 31.3, 27.6, 22.5, 21.1, 14.2, 14.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calculated for $C_{29}H_{36}N_3O_4^+$ 490.2700, found 490.2685.

3-(4-(1-((5-(3,4-Dichlorophenyl)pyrimidin-2-yl)oxy)pentyl)benzamido)propanoic acid (7g); White solid, Mp: 143~145 °C; Yield 97%; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.59 (s, 2H), 7.72 (d, J = 7.8 Hz, 2H), 7.48 (d, J = 7.8 Hz, 2H), 7.36 (s, 1H), 7.32 (d, J = 1.8 Hz, 2H), 7.00 (bs, 1H), 6.03 (q, J = 6, 7.8 Hz, 1H), 3.67 (bs, 2H), 2.65 (bs, 2H), 2.12-2.08 (m, 1H), 1.90-1.85 (m, 1H), 1.47-1.41 (m, 1H), 1.38-1.30 (m, 3H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 167.48, 164.5, 157.3, 145.1, 137.2, 135.9, 133.4, 128.2, 127.2, 126.7, 126.1, 124.9, 79.1, 53.4, 50.8, 36.6, 35.4, 33.9, 27.6, 22.5, 14.2, 14.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calculated for $C_{25}H_{28}Cl_2N_3O_4^+$ 502.1295, found 502.1288.

3-(4-(1-((5-(2-Fluoro-4-(trifluoromethyl)phenyl)pyrimidin-2-yl)oxy)pentyl)benzamido)propanoic acid (7h); White solid, Mp: 185~186 °C; Yield 99%; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.64 (d, J = 1.2 Hz, 2H), 7.74-7.70 (m, 2H), 7.65-7.62 (m, 2H), 7.51 (d, J = 12 Hz, 2H), 7.29 (t, J = 12 Hz, 1H), 6.90 (t, J = 6 Hz, 1H), 6.06 (q, J = 6 Hz, 1H), 3.71 (q, J = 6, 12 Hz, 2H), 2.69 (t, J = 6 Hz, 2H), 2.14-2.05 (m, 1H), 1.93-1.87 (m,

1H), 1.48-1.42 (m, 1H), 1.38-1.32 (m, 3H), 0.89-0.85 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 176.3, 167.5, 164.3, 160.5, 159.6, 158.8, 145.2, 144.9, 133.5, 127.5, 127.2, 126.7, 123.2, 122.2, 117.2, 117.0, 111.9, 79.0, 36.6, 35.3, 33.7, 27.6, 22.4, 14.0; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{26}H_{26}F_4N_3O_4^+$ 520.1854, found 520.1857.

3-(4-(1-((5-(4-Phenoxyphenyl)pyrimidin-2-yl)oxy)pentyl)benzamido)propanoic acid (7i); White solid, Mp : 85 °C; Yield 79%; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.61 (s, 2H), 7.72 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.40-7.38 (m, 2H), 7.37-7.34 (m, 2H), 7.15-7.12 (m, 1H), 7.07-7.02 (m, 4H), 6.94 (t, J = 5.9 Hz, 1H), 6.03 (q, J = 5.8, 7.6 Hz, 1H), 3.71 (q, J = 5.9, 11.7 Hz, 2H), 2.69 (t, J = 5.8 Hz, 2H), 2.11-2.05 (m, 1H), 1.91-1.85 (m, 1H), 1.48-1.40 (m, 1H), 1.37-1.31 (m, 3H), 0.87 (t, J = 7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 176.2, 167.5, 163.7, 157.8, 157.0, 156.6, 145.5, 133.4, 129.9, 128.9, 128.0, 127.9, 127.1, 126.7, 123.8, 119.3, 119.2, 78.7, 36.7, 35.3, 33.8, 27.6, 22.5, 14.0; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{31}H_{32}N_3O_5^+$ 526.2336, found 526.2334.

3-(4-(1-((5-(4-Ethylphenyl)pyrimidin-2-yl)oxy)pentyl)benzamido)propanoic acid (7j); White solid, Mp : 173~175 °C; Yield 81%; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.61 (s, 2H), 7.72 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 7.8 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.90 (bs, 1H), 6.03 (q, J = 5.8, 7.7 Hz, 1H), 3.70 (q, J = 6, 12 Hz, 2H), 2.70-2.66 (m, 4H), 2.12-2.05 (m, 1H), 1.91-1.85 (m, 1H), 1.49-1.44 (m, 1H), 1.38-1.31 (m, 3H), 1.25 (t, J = 7.8 Hz, 5H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 167.4, 163.8, 157.1, 145.5, 144.5, 133.4, 131.6, 128.8, 128.4, 127.1, 126.7, 126.4, 78.6, 36.8, 35.3, 29.7, 28.5, 27.6, 22.5, 15.5, 14.0: HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{27}H_{32}N_3O_4^+$ 462.2387, found 462.2369.

Methyl 4-pentanoylbenzoate (8): Alcohol **2** (1.60 g, 7.22 mmol) was dissolved in dry DCM (36 ml) and 4Å MS (500 mg) and PDC (4.00 g, 10.8 mmol) were added. After 1 day of stirring at rt, the precipitates were filtered off through a celite pad, and the filtrate was

concentrated. The residue was subjected to column chromatography to afford the desired product **8** (936 mg, 59% yield) as white solid. Mp: 40~43 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.10 (d, J = 12.6 Hz, 2H), 7.98 (d, J = 12.6 Hz, 2H), 3.93 (s, 3H), 2.97 (t, J = 10.8 Hz, 2H), 1.45-1.67 (m, 2H), 1.42-1.37 (m, 2H), 0.94 (t, J = 10.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 200.0, 166.3, 140.3, 133.7, 129.8, 127.9, 52.5, 38.7, 26.3, 22.4, 13.9; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calculated for $C_{13}H_{17}O_3^+$ 221.1172, found 221.1168.

Synthesis of (R)-2 : A solution of BH_3-THF complex (1M solution in THF, 2 ml, 2.04 mmol) was diluted with anhydrous THF (4 ml) and *(S)*-Me-CBS catalyst (38 mg, 0.14 mmol) was added at -40 °C. After 20 min of stirring at -40 °C, a solution of ketone **8** (300 mg, 1.36 mmol) in anhydrous THF (3 ml) was added dropwise and the mixture was stirred at -40 °C for 3 h. MeOH (5 ml) was added and the mixture was diluted with EtOAc (100 ml). The mixture washed with 1N HCl and brine successively, and the organic layer was dried over $MgSO_4$, purification of column chromatography to afford the desired product ***(R)*-2** (226 mg, 75 % yield) as colorless oil. All spectral data of ***(R)*-2** were identical to its racemate **2**. $[\alpha]_D$ +5.5 (c = 0.0055 in CH_2Cl_2). The optical rotation of ***(S)*-2** was $[\alpha]_D$ -9.7 (c = 0.0010 in CH_2Cl_2).

4.2. Cell culture

The cAMP Hunter™ CHO-K1 GCGR Gs cell line (CHO-K1 GCGR Gs cells) expressing the human GCGR was purchased from DiscoveRx (Fremont, USA). Cells were maintained in CHO-K1 medium (DiscoverX, Fremont, USA). Primary mouse hepatocytes were grown in HepatoZYME (GibcoBL, Grand Island, NY, USA) with 10% fetal bovine serum (FBS; GibcoBL, Grand Island, NY, USA) and 1% antibiotics (100 unit/ml penicillin and 100 μg/ml streptomycin; GibcoBL, Grand Island, NY, USA). Cells were maintained at subconfluent conditions in a humidified incubator at 37 °C with ambient oxygen and 5% CO_2.

4.3. Isolation of mouse primary hepatocyte

Isolation of hepatocytes was performed as previously described [21]. Briefly, 10 week-old male C57BL/6N mice were anesthetized using 150 µl of ketamine per mouse. The liver was perfused through the portal vein using perfusion buffer I for 10 minutes and then perfusion buffer II for 5 minutes. The liver was removed and dissected into cold high glucose DMEM to separate the hepatic cells. Cells were centrifuged at 50 g for 5 min at 4°C, washed using cold high glucose DMEM, and then centrifuged at 50 g for 5 min at 4°C. Hepatocytes were isolated by Percoll gradient centrifugation (250 g for 5 min without break at 4 °C). Isolated hepatocytes were maintained in HepatoZYME (GibcoBL, Grand Island, NY, USA) with 10% FBS and 1% antibiotics.

4.4. In vitro cytotoxicity assay

The cytotoxicity of GCGR antagonist candidates was determined by Cell Counting Kit-8 (CCK-8) assay (Dojindo, Japan). In brief, mouse primary hepatocytes were seeded at 1 × 104 cells/well in 96-well plates and treated with various concentrations of GCGR antagonist candidates in Cell plating reagent (DiscoverX, Fremont, USA) for 24 h. After one day of treatment, the CCK-8 solution was added and cells were incubated at 37 °C for 2 h. Then the absorbance was recorded at 450 nm using a microplate reader (VersaMax, Molecular Devices). Three independent experiments were performed in triplicate.

4.5. Measurement of cAMP production

CHO-K1 GCGR Gs cells were maintained in CHO-K1 medium (DiscoverX, Fremont, USA). Briefly, 1 × 10^4 cells/well were seeded in 96-well plates. The next day, cells were treated with GCGR antagonist candidates in PBS for 15 min at 37°C and 5% CO_2. After incubation, 0.1 nM glucagon and 10 µM forskolin were added, and the cells were incubated for a further 30 min at 37 °C and 5% CO_2. cAMP was measured using the HitHunter® cAMP Assay for Small Molecules Kit (DiscoveRx, Fremont, USA) according to manufacturer's

instructions. Luminescence was measured using Victor 3 (Perkin Elmer, Waltham, MA, USA).

4.6. Measurement of glucose production in mouse primary hepatocytes

Mouse primary hepatocytes were seeded at 2.5×10^5 cells/well in 12-well plates. After 24 h, cells were washed twice in a pre-warmed glucose-free DMEM medium and incubated for another 3 h in glucose-free DMEM. Cells were treated with various concentrations of GCGR antagonist candidates, gluconeogenic substrates (20 mM sodium lactate and 2 mM sodium pyruvate), and 10 nM glucagon. After 30 min, glucose in the media was quantified using a glucose assay kit (Sigma-Aldrich, St. Louis, MO, USA) and normalized to cellular protein concentrations [21]. Five independent experiments were performed in triplicate.

4.7. Antihyperglycemic effects in db/db mice

Six-week old male *db/db* mice were purchased from Korea Research Institute of Bioscience and Biotechnology (KRIBB; Daejeon, Korea) and maintained under specific pathogen-free conditions in a temperature-controlled room in a 12 h light/dark cycle with ad libitum access to food and water at the Animal Care Center, Lee Gil Ya Cancer and Diabetes Institute, Gachon University of Medicine and Science, South Korea. Diabetic mice (blood glucose levels over 400 mg/dL) were used for the experiments. Fifty mg/kg of ***(R)*-7a**, ***(S)*-7a**, or LY-2409021 (dissolved in 9% cremophore with 10% DMSO in sterilized water) was given orally by intubation once a day for 4 weeks. Fasting blood glucose levels were checked at 4 weeks after administration of ***(R)*-7a**, ***(S)*-7a**, or LY-2409021 after 12 h fasting with a glucose analyzer (Onetouch® Ultra, Lifescan, Johnson & Johnson, Milpitas, CA, USA). All animal experiments were approved by the Institutional Animal Care and Use Committee of the Lee Gil Ya Cancer and Diabetes Institute (LCDI-2015-0006).

4.8. Glucagon challenge assay

Diabetic *db*/*db* mice were orally administered with 50 mg/kg of ***(R)*-7a**, ***(S)*-7a**, or LY-2409021 (dissolved in 9% cremophore with 10% DMSO in sterilized water) by intubation once a day for 4 weeks. At 4 weeks after drug administration, mice were fasted for 5 h and then 50 mg/kg of ***(R)*-7a**, ***(S)*-7a** or LY-2409021 was orally gavaged. After 1 h, glucagon was injected intraperitoneally at a dose of 15 μg/kg, and then blood glucose levels were measured at 15, 30, 45 and 60 min after glucagon injection.

4.9. Statistical analysis

All data were expressed as means ± SE. Multiple group comparisons were performed by analysis of variance (ANOVA) followed by Fisher's protected Least Significant Difference test at * $p < 0.05$, ** $p < 0.01$ or *** $p < 0.001$ using the Graph Pad Prism software. The IC_{50} values were determined for test compounds of three independent determinations and calculated using Graph Pad prism software.

5. Author contributions

Kyoung Mee Lee, Dongyun Shin and Hee-Sook Jun conceived and designed the experiments. Eun-Young Park, Hojung Choi, and Chang-Yong Lee performed the experiments and analyzed data. Especially, Chang-Young Lee prepared all compounds. Hojung Choi, Eun-Young Park, Kyoung Mee Lee, Dongyun Shin and Hee-Sook Jun conducted the data analyses. Hojung Choi, Chang-Yong Lee, Dongyun Shin and Hee-Sook Jun summarized the work and wrote the manuscript.

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7. Conflicts of Interest

There are no competing financial, professional or personal interests that might have influenced the presentation of the work described in this manuscript.

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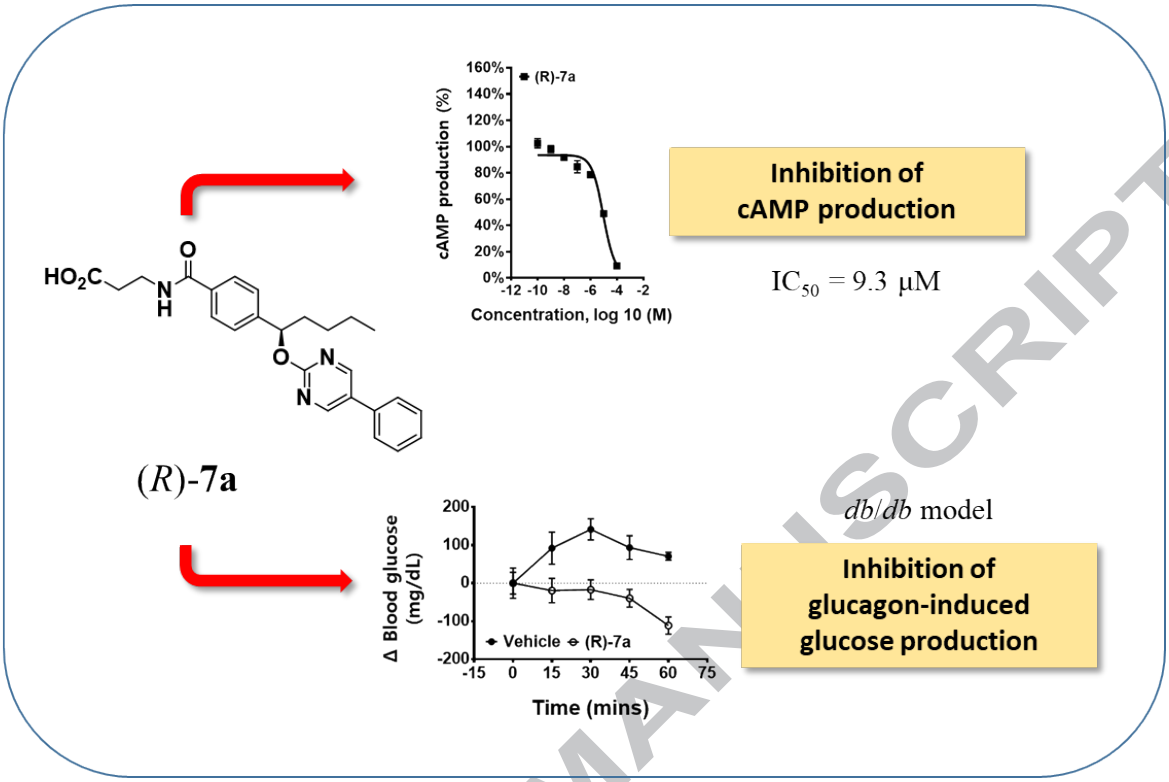
Graphic abstract



Highlights

- Design and synthesis of novel GCGR antagonists as pyrimidine derivatives.
- The compound of ***(R)*-7a** decreased the glucagon-induced cAMP production.
- The compound of ***(R)*-7a** decreased the glucagon-induced glucose production.
- The compound of ***(R)*-7a** decreased the glucagon-induced glucose excursion *in vivo*.
- The compound of ***(R)*-7a** lowering fasting blood glucose levels in *db*/*db* mice.