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Synthesis and structure–activity relationship of 4-amino-2-phenylpyrimidine derivatives as a series of novel GPR119 agonists

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ABSTRACT

Through preparation and examination of a series of novel 4-amino-2-phenylpyrimidine derivatives as agonists for GPR119, we identified 2-(4-bromophenyl)-6-methyl-*N*-[2-(1-oxidopyridin-3-yl)ethyl]pyrimidin-4-amine (**9t**). Compound **9t** improved glucose tolerance in mice following oral administration and showed good pharmacokinetic profiles in rats.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disease developed due to either or both defects in insulin secretion from the pancreas and insulin sensitivity in the peripherals.[1] At present, several medications are on the market for use in treating T2DM patients, including agents which increase the amount of insulin secreted by the pancreas, agents which increase the insulin sensitivity of target organs, and agents which slow the absorption of glucose from the gastrointestinal (GI) tract. Among drugs which act on insulin secretion, sulfonylureas (SUs) fall into a class of insulin secretagogues which bind to an ATP-dependent K^+ channel on the cell membrane in pancreatic β cells. However, while SUs are indeed strongly effective in promoting insulin secretion, they tend to induce hypoglycemia due to excessive insulin production and release.[2] As such, incretin and incretin based therapies such as glucagon-like peptide-1 (GLP-1) mimetics and DPP-IV inhibitors have begun to garner considerable attention of late, as they can not only reduce the risk of hypoglycemia, due to their glucose-dependent insulin secretion (GDIS), but also upregulate insulin-gene transcription, promoting resistance to apoptosis and enhancing the survival of the β cell.[3]

The G-protein-coupled receptor 119 (GPR119), which is abundantly expressed in pancreatic β cells and the GI tract, was identified as the receptor for lysophospholipids and certain ethanolamide derivatives of long chain fatty acids, such as lysophosphatidylcholine and oleoylethanolamide.[4] Activation of GPR119 directly promotes GDIS through the upregulation of the intracellular cAMP, followed by a reduction in blood glucose level. Additionally, several GPR119 agonists have been reported to promote GLP-1 secretion from intestinal L-cells.[5] As such, it is suggested that GPR119 may present an attractive drug target for treating T2DM, and its agonists may therefore represent potential new insulin secretagogues free of the risk of causing hypoglycemia.

In recent years, a number of researches have investigated GPR119 agonists, with several compounds such as AR231453 (**1**; Fig. 1) and PSN632408 (**2**) reported to exert insulinotropic and antiobesity effects.[6] Further, several clinical trials of GPR119 agonists, including MBX-2982 (**3**) and GSK1292263 (**4**) are currently ongoing.[6]

From these facts, we have focused our attention to create novel GPR119 agonists as a new class of drugs for T2DM. With the purpose of finding out novel GPR119 agonists, high-throughput screening (HTS) to the Astellas chemical library was performed. Examination of agonistic activities toward GPR119 led to the identification of compound **9a**.[7] Compound **9a** showed moderate in vitro GPR119 agonistic activity. Additionally, this compound efficiently decreased the blood glucose levels without hypoglycemia in mice. Encouraged with these results and its preferable chemical and physicochemical property, such as low molecular weight and high solubility in water, compound **9a** was selected as a lead for further optimization.

Here, we describe the synthesis and structure–activity relationship (SAR) studies of 4-amino-2-phenylpyrimidine derivatives as novel GPR119 agonists.

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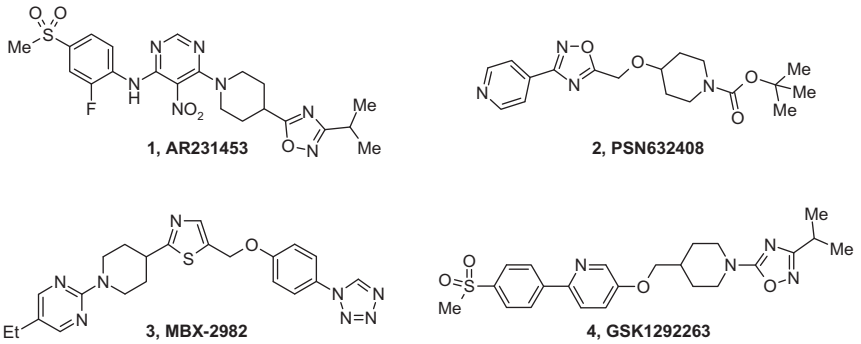
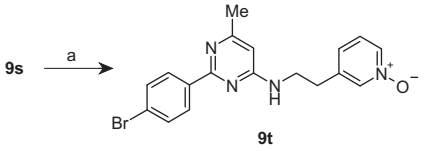


Figure 1. Structures of representative GPR119 agonists (AR231453 [**1**], PSN632408 [**2**], MBX-2982 [**3**] and GSK1292263 [**4**]).

2. Chemistry

Synthesis of this series of compounds started with corresponding benzonitrile **5a** or amidines **6b–f** (Scheme 1). Compound **5a** was first converted into amidine **6a** in two steps through the imidate intermediate. Amidines **6a–f** were then treated with the corresponding ketoesters or ethyl propiolate under basic conditions to obtain pyrimidones **7a–l**, which were treated with phosphorous oxychloride to afford 4-chloropyrimidines **8a–l**. These compounds 8a–**l** were then subjected to substitution with corresponding amines to obtain the desired 4-aminopyrimidine derivatives **9a–s**. Oxidation of compound **9s** with *m*-chloroperbenzoic acid (*m*-CPBA) ultimately afforded the *N*-oxide analog **9t** (Scheme 2).



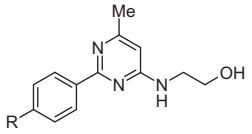
Scheme 2. Synthesis of compound **9t**. Reagents and conditions: (a) *m*-CPBA, $CHCl_3$, rt.

3. Results and discussion

We evaluated the agonistic activities of the synthesized compounds toward GPR119 via cAMP reporter assay using HEK293 cells transfected with human GPR119 and cAMP responsive element (pCRE)-Luciferase expression plasmids.[8] We successfully calculated the EC_{50} value of compound **9a** (2.5 μM) but ultimately deemed using EC_{50} values as the basis for the discussion about SARs too difficult, as high-level expression of GPR119 stimulated a significant increase in cAMP levels in transfected HEK293 cells.[9] Therefore, to discuss SARs in greater detail, we relatively evaluated the synthesized compounds by comparing EC and IA values of these compounds with those of lead compound **9a**. The EC value represents the concentration of the tested compounds in the cAMP reporter assay system at which those compounds were as effective as compound **9a** at 10 μM, while the IA values represents the relative activity (%) of the tested compounds compared to the efficacy of compound **9a** at 10 μM in the same assay system.[10,11]

The influence of the substituents at the 4-position in the phenyl moiety of compound **9a** on agonistic activity is shown in Table 1.

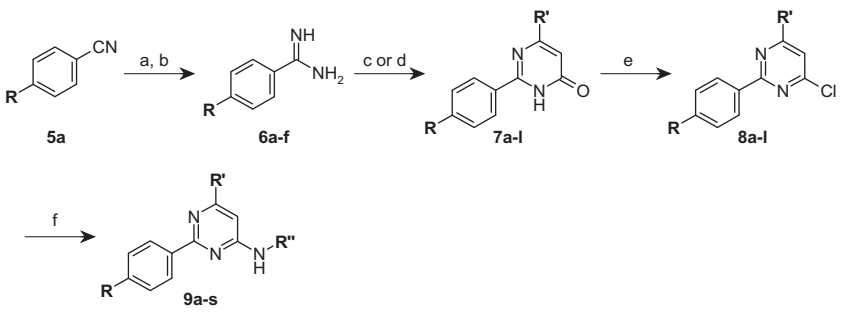
Table 1
In vitro SARs for analogs with substitution at 4-position of phenyl moiety



Compound	R-	GPR119/pCRE	
		EC (μM)[a]	IA (%)[b]
9a	Br-	10	100
9b	H-	NE[c]	ND[d]
9c	Cl-	12	48
9d	I-	19	66
9e	MeO-	NE[c]	ND[d]
9f	Me-	NE[c]	ND[d]

[a] Concentration of the tested compounds equipotent to the efficacy of **9a** at 10 μM in the human recombinant cell-based assay. See Section 5.
[b] Relative efficacy of tested compounds at 10 μM compared with efficacy of **9a** at 10 μM. See Section 5.
[c] Not effective at 10 μM.
[d] Not determined.

Removal of the bromo group (compound **9b**) reduced activity, indicating that the presence of the substituent at the 4-position of the



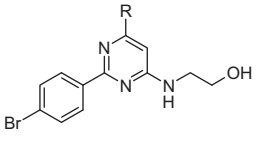
Scheme 1. Synthesis of 4-amino-2-phenylpyrimidine derivatives **9a–s**. Reagents and conditions: (a) HCl, EtOH, rt; (b) $(NH_4)_2CO_3$, EtOH, rt; (c) (R′≠H) R′$COCH_2CO_2$Me, NaOMe, MeOH, 60 °C; (d) (R′ = H) ethyl propiolate, KOH, EtOH, 80 °C, (e) $POCl_3$, 80 °C; (f) R″NH_2, DIPEA, MeCN, 70 °C.

phenyl moiety was essential for GPR119 agonistic activity. While replacement of the bromo group with other halogen groups (Cl; compound **9c** and I; compound **9d**) seemed to be tolerated, methoxy (compound **9e**) and methyl (compound **9f**) impaired activity. These results indicated that having a halogen group at the 4-position in the phenyl moiety was extremely important for maintaining agonistic activity in the compound.

We then examined the influence of substituents at the 6-position in the pyrimidine moiety (Table 2). As above, presence of a substituent at this position appeared to be crucial for the agonistic activity, as removal of the substituent at this position (compound **9g**) resulted in loss of activity. The ethyl derivative (**9h**) was found to be more potent than the parent compound **9a**, whereas the *n*-propyl and *iso*-propyl derivatives (**9i** and **9j**, respectively) were less active. Similarly, while replacement of the methyl group with a difluoromethyl group (compound **9k**) was tolerated, activity was decreased on replacement with a trifluoromethyl group (compound **9l**). From these findings, we speculated that while a small alkyl group would likely be favorable in terms of agonistic activity at the 6-position in the pyrimidine moiety, it would prove sterically bulky and might interfere with the compound binding to the receptor.

We then examined the influence of substituents to the amino group at the 4-position of the pyrimidine ring (Table 3). We concluded that hydrogen bonding between the amino group at the 4-position of the pyrimidine ring and GPR119 protein was important for agonistic activity of the compound, as the *N*-methylated analog (**9m**) showed no agonistic activity. While introduction of a methyl group onto the carbon atom next to the N–H group (compound **9n**) resulted in a reduction in agonistic activity, introduction next to the hydroxy group (compound **9o**) improved the agonistic activity by three-fold over compound **9a**. Further replacement of the hydroxy group itself with a methoxy group (compound **9p**) improved the agonistic activity by five-fold over compound **9a**. These results implied that the hydroxy group at the terminal position was not essential for GPR119 agonistic activity. A more than 10-fold increase in activity over compound **9a** was observed with the isobutylamino derivative (**9q**), indicating that substitution of a relatively lipophilic group at this region helped to improve GPR119 agonistic activity. Compounds equipped with a pyridyl group (**9r**, **9s**) showed improvement in vitro activity by approximately 10-fold over compound **9a**, and the *N*-oxide analog (**9t**) was found to be equipotent to the pyridyl derivative (**9s**). These results indicated that introduction of a heteroaryl group into this region was tolerated, and the basicity of the nitrogen atom in the pyridine ring was not essential for the agonistic activity.

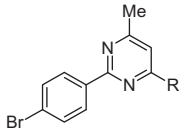
Table 2
In vitro SARs for analogs with replacement of the substituents at the 6-position of the pyrimidine ring

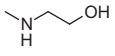
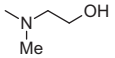
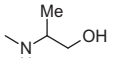
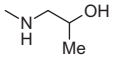
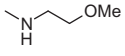
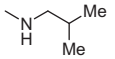
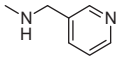
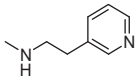
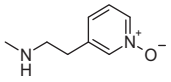


Compound	R-	GPR119/pCRE	
		EC (μM)[a]	IA (%)[b]
9a	Me-	10	100
9g	H-	NE[c]	ND[d]
9h	Et-	5.9	146
9i	*n*-Pr-	NE[c]	ND[d]
9j	*i*-Pr-	NE[c]	ND[d]
9k	F_2HC-	8.2	195
9l	F_3C-	NE[c]	ND[d]

[a–d] See the corresponding footnotes to Table 1.

Table 3
In vitro SARs and in vivo antihyperglycemic effects and CYP1A2 inhibitory activities for analogs with replacement of the 4-(2-hydroxyethyl)amino moiety in compound **9a**



Compound	-R	GPR119/pCRE		OGTT (10 mg/kg po)[e]	CYP1A2
		EC (μM)[a]	IA (%)[b]	% Decrease	IC_{50} (μM)
9a		10	100	NE[c] (17 at 30 mg/kg p.o.)	0.66
9m		NE[c]	ND[d]	NT[f]	NT[f]
9n		13	82	NT[f]	NT[f]
9o		3.6	209	NT[f]	NT[f]
9p		1.8	209	13	<0.091
9q		0.91	322	24	<0.091
9r		1.3	294	NE[c]	<0.046
9s		0.73	772	17	<0.091
9t		1.2	325	38	0.97

[a–d] See the corresponding footnotes to Table 1.
[e] Antihyperglycemic effects of tested compounds in male ICR mice at 10 mg/kg po. See Section 5.
[f] Not tested.

The antihyperglycemic effects of **9a**, **9p**, **9q**, **9r**, **9s** and **9t** were evaluated via oral glucose tolerance test (OGTT) using male ICR mice (Table 3). Tested compounds were orally administered before glucose loading (2 g/kg po). Activity of tested compounds was then measured based on the blood glucose-lowering ratio (%) at 30 min after glucose loading in comparison with animals in the vehicle group. As mentioned above, compound **9a** demonstrated an antihyperglycemic effect at 30 mg/kg po. In contrast, compounds **9p**, **9q**, **9s**, and **9t** all demonstrated antihyperglycemic effects at 10 mg/kg po. In particular, compounds **9q** and **9t** were found to potently reduce the blood glucose level in OGTT.

We also evaluated CYP1A2 inhibitory activity of selected compounds, with results shown in Table 3. The parent compound **9a** inhibited CYP1A2 with an IC_{50} value in the sub-micro molar range, an observation we attributed to the either the low molecular weight or high lipophilicity of compound **9a**.[12] The methoxyethyl and the isobutyl derivatives (**9p** and **9q**, respectively) showed potent CYP1A2 inhibitory activity ($IC_{50} < 0.091$ μM for both), and even the pyridyl group compounds (**9r** or **9s**), which had higher molecular weights than compound **9a**, were equally as potent as **9p** and **9q** in CYP1A2 inhibition. In contrast, the *N*-oxide analog (**9t**) was found to be less potent than **9s**, suggesting that introduction of hydrophilic substituents lowers the CYP1A2 inhibitory activity of these compounds.

The pharmacokinetic profile of compound **9t** as evaluated in rats is described in Table 4. After intravenous administration

Table 4
Pharmacokinetic data for compound **9t** in rats

Route	Dose (mg/kg)	T_{max} (h)	$t_{1/2}$ (h)	V_{dss} (L/kg)	CL_{tot} (mL/min/kg)	Bioavailability (%)
iv	1		1.2	2.0	20.1	
po	3	0.25				56

(1 mg/kg), compound **9t** showed moderate total clearance (21.0 ml/min/kg), a steady-state volume of distribution (2.0 L/kg), and a half-life of 1.2 h. Compound **9t** was rapidly absorbed after oral dosing at 3 mg/kg and showed good bioavailability (56%), which was considered to contribute to its potent antihyperglycemic effect in vivo.

4. Conclusion

In our investigation of novel GPR119 agonists, we prepared and examined a series of novel 4-amino-2-phenylpyrimidine derivatives. We conducted an SAR study by modifying the lead compound **9a**, determining that halogen groups at the 4-position in the phenyl moiety and small alkyl groups at the 6-position in the pyrimidine moiety were extremely important for achieving GPR119 agonistic activity. In addition, we found that lipophilic substituents on the amino group at the 4-position of the pyrimidine ring were also capable of inducing potent activity. However, introduction of hydrophilic substituents into this region should be important for reducing their CYP1A2 inhibitory activity. Through our evaluation of the basic SARs of novel 4-amino-2-phenylpyrimidine derivatives as GPR119 agonists, we showed that 2-(4-bromophenyl)-6-methyl-*N*-[2-(1-oxidopyridin-3-yl)ethyl]pyrimidin-4-amine (**9t**) had potent GPR119 agonistic activity, good potency in vivo as assessed via OGTT, and a good PK profile. Further investigation will be carried out to improve the potency and PK profiles of this series of compounds.

5. Experimental

5.1. Chemistry

^{1}H NMR spectra were recorded on a JEOL JNM-EX400 spectrometer and were referenced to an internal standard, tetramethylsilane. The abbreviations used for the signal patterns are as follows: s, singlet; br, broad; d, doublet; t, triplet; q, quartet; dd, double doublet; m, multiplet. Mass spectra were recorded on a JEOL LX-2000 mass spectrometer. The elemental analyses were performed with a Yanako MT-5 microanalyzer (C, H, N) and a Yokogawa IC-7000S ion chromatographic analyzer (halogens). Where analyses are indicated by symbols, the analytical results are within ±0.4% of the theoretical values. Drying of organic solutions during workup was done over anhydrous $MgSO_4$. Column chromatography was performed with Wakogel C-200 or Merck silica gel 60.

5.1.1. 4-Bromobenzamidine hydrochloride (6a)

Hydrogen chloride gas was passed through a solution of 4-bromobenzonitrile (18.2 g) in chloroform (300 mL) and ethanol (100 mL) at −65 °C for 35 min. Then the solution was warmed up to room temperature, and stirred at room temperature overnight. The solution was evaporated in vacuo, and the resulting residue was dissolved in ethanol (400 mL). To the solution was added ammonium carbonate (48.0 g), and the reaction mixture was stirred at room temperature for 20 h. To the mixture was added water (300 mL), and ethanol was removed by concentration in vacuo. The resulting precipitate was collected by filtration, and washed with water, dried in vacuo to give **6a** (22.9 g, 97%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 2.55–4.60 (2H, br), 6.30–8.90 (6H, m); FAB-MS *m/z* 199, 201 [(M+H)$^+$].

The other benzamidines (**6b–f**) were commercially available.

5.1.2. 2-(4-Bromophenyl)-6-methylpyrimidin-4-one (7a)

To a solution of 4-bromobenzamidine hydrochloride (**6a**, 12.7 g) in methanol (200 mL) was added sodium methoxide (2.9 g), and the mixture was stirred at room temperature for 10 min. To the mixture methyl acetoacetate (6.0 mL) and sodium methoxide (8.72 g) were added, and the reaction mixture was stirred at room temperature for 4 days. The reaction mixture was warmed up to 50 °C, and was stirred at the same temperature for 1 day. The reaction mixture was warmed up to 65 °C, and was stirred at the same temperature for 5 h. The mixture was cooled down to 5 °C, then 1 M hydrochloric acid (300 mL) was added to the mixture. The resulting precipitate was collected by filtration, washed with water, and dried in vacuo at 50 °C overnight to give **7a** (8.98 g, 63%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 2.29 (3H, s), 6.26 (1H, s), 7.73 (2H, d, J = 8.8 Hz), 8.07 (2H, d, J = 8.8 Hz), 12.00–13.00 (1H, br); FAB-MS *m/z* 265, 267 [(M+H)$^+$].

The following compounds (**7b–l**) were prepared by a procedure similar to that described for **7a**.

5.1.3. 6-Methyl-2-phenylpyrimidin-4-one (7b)

White solid (yield 34%); ^{1}H NMR (DMSO-d_6) δ 2.28 (3H, s), 6.21 (1H, s), 7.46–7.64 (3H, m), 8.00–8.20 (2H, m), 12.30–12.90 (1H, br); FAB-MS *m/z* 187 [(M+H)$^+$].

5.1.4. 2-(4-Chlorophenyl)-6-methylpyrimidin-4-one (7c)

White solid (yield 56%); ^{1}H NMR (DMSO-d_6) δ 2.29 (3H, s), 6.26 (1H, s), 7.59 (2H, d, J = 8.3 Hz), 8.05–8.25 (2H, m), 12.40–13.00 (1H, br); FAB-MS *m/z* 221 [(M+H)$^+$].

5.1.5. 2-(4-Iodophenyl)-6-methylpyrimidin-4-one (7d)

White solid (yield 50%); ^{1}H NMR ($CDCl_3$) δ 2.39 (3H, s), 6.30 (1H, s), 7.88 (2H, d, J = 8.6 Hz), 7.91 (2H, d, J = 8.6 Hz), 12.40–13.00 (1H, br); FAB-MS *m/z* 313 [(M+H)$^+$].

5.1.6. 2-(4-Methoxyphenyl)-6-methylpyrimidin-4-one (7e)

White solid (yield 22%); ^{1}H NMR ($CDCl_3$) δ 2.37 (3H, s), 3.89 (3H, s), 6.23 (1H, s), 7.03 (2H, d, J = 8.8 Hz), 8.06 (2H, d, J = 8.8 Hz); FAB-MS *m/z* 217 [(M+H)$^+$].

5.1.7. 6-Methyl-2-(4-methylphenyl)pyrimidin-4-one (7f)

White solid (yield 36%); ^{1}H NMR ($CDCl_3$) δ 2.38 (3H, s), 2.43 (3H, s), 6.26 (1H, s), 7.33 (2H, d, J = 8.1 Hz), 8.05 (2H, d, J = 8.1 Hz), 12.20–12.80 (1H, br); FAB-MS *m/z* 201 [(M+H)$^+$].

5.1.8. 2-(4-Bromophenyl)-6-ethylpyrimidin-4-one (7h)

White solid (yield 87%); ^{1}H NMR (DMSO-d_6) δ 1.20 (3H, t, J = 7.6 Hz), 2.56 (2H, q, J = 7.6 Hz), 6.23 (1H, s), 7.73 (2H, d, J = 8.3 Hz), 7.98–8.16 (2H, m), 12.20–13.00 (1H, br); FAB-MS *m/z* 279, 281 [(M+H)$^+$].

5.1.9. 2-(4-Bromophenyl)-6-difluoromethylpyrimidin-4-one (7i)

White solid (yield 90%); ^{1}H NMR (DMSO-d_6) δ 6.66 (1H, s), 6.82 (1H, t, J = 54.2 Hz), 7.77 (2H, d, J = 8.6 Hz), 8.09 (2H, d, J = 8.6 Hz), 12.80–13.50 (1H, br); FAB-MS *m/z* 301, 303 [(M+H)$^+$].

5.1.10. 2-(4-Bromophenyl)-6-trifluoromethylpyrimidin-4-one (7j)

White solid (yield 43%); ^{1}H NMR (DMSO-d_6) δ 6.91 (1H, s), 7.79 (2H, d, J = 8.8 Hz), 8.00–8.18 (2H, m), 13.00–13.70 (1H, br); FAB-MS *m/z* 319, 321 [(M+H)$^+$].

5.1.11. 2-(4-Bromophenyl)-6-propylpyrimidin-4-one (7k)

White solid (yield 80%); ^{1}H NMR (DMSO-d_6) δ 0.93 (3H, t, J = 7.3 Hz), 1.60–1.76 (2H, m), 2.45–2.60 (2H, m), 6.23 (1H, s), 7.73 (2H, d, J = 8.8 Hz), 8.00–8.17 (2H, m), 12.30–13.00 (1H, br); FAB-MS m/z 293, 295 [(M+H)$^+$].

5.1.12. 2-(4-Bromophenyl)-6-isopropylpyrimidin-4-one (7l)

Pale brown solid (yield 27%); ^{1}H NMR (DMSO-d_6) δ 1.21 (6H, d, J = 6.9 Hz), 2.70–2.90 (1H, m), 6.22 (1H, s), 7.74 (2H, d, J = 8.3 Hz), 7.98–8.20 (2H, m), 12.30–13.00 (1H, br); FAB-MS m/z 293, 295 [(M+H)$^+$].

5.1.13. 2-(4-Bromophenyl)-pyrimidin-4-one (7g)

4-Bromobenzamidine hydrochloride (**6a**, 707 mg) was treated with 5 M aqueous sodium hydroxide (8 mL), and extracted with chloroform. The organic layer was dried, filtered and evaporated to give colorless solid (472 mg). To the solution of the obtained solid in ethanol (5 mL) was added ethyl propiolate (0.27 mL) and the mixture was warmed up to 60 °C, then potassium hydroxide (175 mg) in ethanol (4 mL) was added dropwise over 15 min. The mixture was warmed up to 80 °C and stirred for 6 h, then cooled down to room temperature. To the mixture was added 1 M hydrochloric acid (10 mL), and the precipitate was collected by filtration, washed with water, dried in vacuo at 50 °C overnight to give **7g** (267 mg, 35%) as a pale brown solid: ^{1}H NMR (DMSO-d_6) δ 6.25–6.50 (1H, m), 7.74 (2H, d, J = 8.3 Hz), 7.95–8.25 (3H, m), 12.50–13.20 (1H, br); FAB-MS m/z 251, 253 [(M+H)$^+$].

5.1.14. 2-(4-Bromophenyl)-4-chloro-6-methylpyrimidine (8a)

2-(4-Bromophenyl)-6-methylpyrimidin-4-one (**7a**, 8.80 g) in phosphorus oxychloride (80 mL) was stirred at 80 °C for 2 h. The mixture was cooled down to room temperature, and evaporated in vacuo. To the resulting residue was added 1 M aqueous sodium hydroxide (150 mL), and the resulting precipitate was collected by filtration, washed with water, dried in vacuo at 50 °C to give **8a** (10.13 g, 108%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 2.56 (3H, s), 7.58 (1H, s), 7.75 (2H, d, J = 8.8 Hz), 8.27 (2H, d, J = 8.8 Hz); FAB-MS m/z 283, 285 [(M+H)$^+$].

The following compounds (**8b–l**) were prepared by a procedure similar to that described for **8a**.

5.1.15. 4-Chloro-6-methyl-2-phenylpyrimidine (8b)

White solid (yield 101%); ^{1}H NMR ($CDCl_3$) δ 2.58 (3H, s), 7.10 (1H, s), 7.43–7.55 (3H, m), 8.40–8.49 (2H, m); FAB-MS m/z 205 [(M+H)$^+$].

5.1.16. 4-Chloro-2-(4-chlorophenyl)-6-methylpyrimidine (8c)

White solid (yield 105%); ^{1}H NMR ($CDCl_3$) δ 2.57 (3H, s), 7.11 (1H, s), 7.44 (2H, d, J = 8.8 Hz), 8.40 (2H, d, J = 8.8 Hz); FAB-MS m/z 239 [(M+H)$^+$].

5.1.17. 4-Chloro-2-(4-iodophenyl)-6-methylpyrimidine (8d)

White solid (yield 59%); ^{1}H NMR ($CDCl_3$) δ 2.57 (3H, s), 7.11 (1H, s), 7.82 (2H, d, J = 8.3 Hz), 8.17 (2H, d, J = 8.3 Hz); FAB-MS m/z 331 [(M+H)$^+$].

5.1.18. 4-Chloro-2-(4-methoxyphenyl)-6-methylpyrimidine (8e)

White solid (yield 108%); ^{1}H NMR ($CDCl_3$) δ 3.00 (3H, s), 3.93 (3H, s), 7.09 (2H, d, J = 8.8 Hz), 7.29 (1H, s), 8.70 (2H, d, J = 8.8 Hz); FAB-MS m/z 235 [(M+H)$^+$].

5.1.19. 4-Chloro-6-methyl-2-(4-methylphenyl)pyrimidine (8f)

White solid (yield 96%); ^{1}H NMR ($CDCl_3$) δ 2.42 (3H, s), 2.56 (3H, s), 7.07(1H, s), 7.28 (2H, d, J = 8.1 Hz), 8.33 (2H, d, J = 8.1 Hz); FAB-MS m/z 219 [(M+H)$^+$].

5.1.20. 2-(4-Bromophenyl)-4-chloropyrimidine (8g)

Yellow solid (yield 99%); ^{1}H NMR (DMSO-d_6) δ 7.69 (1H, d, J = 5.4 Hz), 7.77 (2H, d, J = 8.6 Hz), 8.28 (2H, d, J = 8.6 Hz), 8.90 (1H, d, J = 5.4 Hz); FAB-MS m/z 269, 271 [(M+H)$^+$].

5.1.21. 2-(4-Bromophenyl)-4-chloro-6-ethylpyrimidine (8h)

White solid (yield 93%); ^{1}H NMR (DMSO-d_6) δ 1.30 (3H, t, J = 7.6 Hz), 2.84 (2H, q, J = 7.6 Hz), 7.58 (1H, s), 7.75 (2H, d, J = 8.6 Hz), 8.29 (2H, d, J = 8.6 Hz); FAB-MS m/z 297, 299 [(M+H)$^+$].

5.1.22. 2-(4-Bromophenyl)-4-chloro-6-difluoromethylpyrimidine (8i)

Brown solid (yield 96%); ^{1}H NMR (DMSO-d_6) δ 7.08 (1H, t, J = 53.7 Hz), 7.80 (2H, d, J = 8.8 Hz), 7.97 (1H, s), 8.29 (2H, d, J = 8.8 Hz); FAB-MS m/z 319, 321 [(M+H)$^+$].

5.1.23. 2-(4-Bromophenyl)-4-chloro-6-trifluoromethylpyrimidine (8j)

Brown solid (yield 93%); ^{1}H NMR (DMSO-d_6) δ 7.81 (2H, d, J = 8.3 Hz), 8.25–8.32 (3H, m); FAB-MS m/z 337, 339 [(M+H)$^+$].

5.1.24. 2-(4-Bromophenyl)-4-chloro-6-propylpyrimidine (8k)

Pale brown solid (yield 102%); ^{1}H NMR (DMSO-d_6) δ 0.95 (3H, t, J = 7.5 Hz), 1.70–1.85 (2H, m), 2.79 (2H, t, J = 7.5 Hz), 7.58 (1H, s), 7.75 (2H, d, J = 8.6 Hz), 8.28 (2H, d, J = 8.6 Hz); FAB-MS m/z 311, 313 [(M+H)$^+$].

5.1.25. 2-(4-Bromophenyl)-4-chloro-6-isopropylpyrimidine (8l)

Brown solid (yield 118%); ^{1}H NMR (DMSO-d_6) δ 1.30 (6H, d, J = 6.8 Hz), 3.02–3.16 (1H, m), 7.59 (1H, s), 7.76 (2H, d, J = 8.8 Hz), 8.29 (2H, d, J = 8.8 Hz); FAB-MS m/z 311, 313 [(M+H)$^+$].

5.1.26. 2-{[2-(4-Bromophenyl)-6-methylpyrimidin-4-yl]amino}ethanol (9a)

To a solution of 2-(4-bromophenyl)-4-chloro-6-methylpyrimidine (**8a**, 2.27 g) in acetonitrile (20 mL) was added ethanolamine (2.0 mL), and the mixture was stirred at 70 °C for 14 h. To the reaction mixture was added additional ethanolamine (4.0 mL) and the mixture was stirred at 85 °C for 6.5 h. The reaction mixture was cooled down to room temperature, and evaporated in vacuo. To the resulting residue was added 1 M aqueous sodium hydroxide (40 mL), and extracted with ethyl acetate. The organic layer was dried, and the desiccant was removed by filtration, and then the solvent was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography (chloroform-methanol) to obtain **9a** (2.03 g, 82%) as a white amorphous solid: ^{1}H NMR (DMSO-d_6) δ 2.28 (3H, s), 3.34–3.64 (4H, m), 4.74 (1H, t, J = 5.4 Hz), 6.31 (1H, s), 7.15–7.45 (1H, br), 7.65 (2H, d, J = 8.8 Hz), 8.25 (2H, d, J = 8.8 Hz); FAB-MS m/z 308, 310 [(M+H)$^+$]. Anal. ($C_{13}H_{14}N_3OBr$): C, H, N, Br.

The following compounds (**9b–s**) were prepared by a procedure similar to that described for **9a**.

5.1.27. 2-{[6-Methyl-2-phenylpyrimidin-4-yl]amino}ethanol (9b)

White solid (yield 89%); ^{1}H NMR ($CDCl_3$) δ 2.40 (3H, s), 3.47–3.53 (2H, m), 3.83 (2H, t, J = 4.9 Hz), 5.22 (1H, s), 6.12 (1H, s), 7.41–7.47 (3H, m), 8.29–8.34 (2H, m); FAB-MS m/z 230 [(M+H)$^+$]. Anal. ($C_{13}H_{15}N_3O$): C, H, N.

5.1.28. 2-{[2-(4-Chlorophenyl)-6-methylpyrimidin-4-yl]amino}ethanol hydrobromide (9c)

White solid (yield 84%); ^{1}H NMR (DMSO-d_6) δ 2.44 (3H, s), 2.80–4.50 (4H, m), 6.59 (1H, s), 7.74 (2H, d, J = 8.3 Hz), 8.21 (2H, d, J = 8.3 Hz), 9.00–9.70 (1H, br), 13.00–14.00 (1H, br); FAB-MS m/z 264 [(M+H)$^+$]. Anal. ($C_{13}H_{14}N_3OCl{\cdot}HBr{\cdot}H_2O$): C, H, N, Cl, Br.

5.1.29. 2-{[2-(4-Iodophenyl)-6-methylpyrimidin-4-yl]amino}ethanol oxalate (9d)

White solid (yield 84%); ^{1}H NMR (DMSO-d_6) δ 2.29 (3H, s), 3.20–3.70 (4H, m), 6.33 (1H, s), 7.10–7.70 (1H, br), 7.84 (2H, d, J = 8.3 Hz), 8.08 (2H, d, J = 8.3 Hz); FAB-MS m/z 356 [(M+H)$^+$]. Anal. ($C_{13}H_{14}N_3OI{\cdot}C_2H_2O_4{\cdot}0.25H_2O$): C, H, N, I.

5.1.30. 2-{[2-(4-Methoxyphenyl)-6-methylpyrimidin-4-yl]amino}ethanol (9e)

White solid (yield 68%); ^{1}H NMR ($CDCl_3$) δ 2.39 (3H, s), 3.60–3.64 (2H, m), 3.84 (2H, t, J = 4.9 Hz), 3.85 (3H, s), 5.14 (1H, s), 6.09 (1H, s), 6.93–6.97 (2H, m), 8.27–8.30 (2H, m); FAB-MS m/z 260 [(M+H)$^+$]. Anal. ($C_{14}H_{17}N_3O_2$): C, H, N.

5.1.31. 2-{[6-Methyl-2-(4-methylphenyl)pyrimidin-4-yl]amino}ethanol (9f)

White solid (yield 82%); ^{1}H NMR ($CDCl_3$) δ 2.37 (3H, s), 2.38 (3H, s), 3.50–3.55 (2H, m), 3.79 (2H, t, J = 4.9 Hz), 5.27 (1H, s), 6.06 (1H, s), 7.23 (2H, d, J = 7.8 Hz), 8.19 (2H, d, J = 7.8 Hz); FAB-MS m/z 244 [(M+H)$^+$]. Anal. ($C_{14}H_{17}N_3O$): C, H, N.

5.1.32. 2-{[2-(4-Bromophenyl)pyrimidin-4-yl]amino}ethanol oxalate (9g)

Pale yellow solid (yield 58%); ^{1}H NMR (DMSO-d_6) δ 3.30–3.70 (4H, m), 6.49 (1H, d, J = 5.8 Hz), 7.55–7.70 (1H, br), 7.67 (2H, d, J = 8.8 Hz), 8.80–8.20 (1H, m), 8.24 (2H, d, J = 8.8 Hz); FAB-MS m/z 294, 296 [(M+H)$^+$]. Anal. ($C_{12}H_{12}N_3OBr{\cdot}C_2H_2O_4{\cdot}0.25H_2O$): C, H, N, Br.

5.1.33. 2-{[2-(4-Bromophenyl)-6-ethylpyrimidin-4-yl]amino}ethanol (9h)

Pale brown solid (yield 94%); ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, t, J = 7.5 Hz), 2.55 (2H, q, J = 7.5 Hz), 3.44–3.52 (2H, m), 3.54–3.60 (2H, m), 4.75 (1H, t, J = 5.4 Hz), 6.31 (1H, s), 7.25–7.40 (1H, br), 7.65 (2H, d, J = 8.6 Hz), 8.26 (2H, d, J = 8.6 Hz); FAB-MS m/z 322, 324 [(M+H)$^+$]. Anal. ($C_{14}H_{16}N_3OBr$): C, H, N, Br.

5.1.34. 2-{[2-(4-Bromophenyl)-6-difluoromethylpyrimidin-4-yl]amino}ethanol oxalate (9i)

White solid (yield 34%); ^{1}H NMR (DMSO-d_6) δ 2.80–4.00 (5H, m), 6.71 (1H, s), 6.79 (1H, t, J = 54.7 Hz), 7.70 (2H, d, J = 8.3 Hz), 7.97 (1H, s), 8.26 (2H, d, J = 8.3 Hz); FAB-MS m/z 344, 346 [(M+H)$^+$]. Anal. ($C_{13}H_{12}N_3OBrF_2{\cdot}C_2H_2O_4$): C, H, N, Br, F.

5.1.35. 2-{[2-(4-Bromophenyl)-6-trifluoromethylpyrimidin-4-yl]amino}ethanol (9j)

Pale brown solid (yield 93%); ^{1}H NMR (DMSO-d_6) δ 3.50–3.68 (4H, m), 4.84 (1H, t, J = 5.2 Hz), 6.89 (1H, s), 7.71 (2H, d, J = 8.6 Hz), 8.14–8.23 (1H, m), 8.26 (2H, d, J = 8.6 Hz); FAB-MS m/z 362, 364 [(M+H)$^+$]. Anal. ($C_{13}H_{11}N_3OBrF_3$): C, H, N, Br, F.

5.1.36. 2-{[2-(4-Bromophenyl)-6-propylpyrimidin-4-yl]amino}ethanol oxalate (9k)

White solid (yield 62%); ^{1}H NMR (DMSO-d_6) δ 0.93 (3H, t, J = 7.4 Hz), 1.60–1.80 (2H, m), 3.20–3.80 (4H, m), 6.32 (1H, s), 7.30–7.60 (1H, br), 7.67 (2H, d, J = 8.3 Hz), 8.24 (2H, d, J = 8.3 Hz); FAB-MS m/z 336, 338 [(M+H)$^+$]. Anal. ($C_{15}H_{18}N_3OBr{\cdot}C_2H_2O_4$): C, H, N, Br.

5.1.37. 2-{[2-(4-Bromophenyl)-6-isopropylpyrimidin-4-yl]amino}ethanol oxalate (9l)

White solid (yield 36%); ^{1}H NMR (DMSO-d_6) δ 1.22 (6H, d, J = 6.8 Hz), 2.70–2.90 (1H, m), 3.00–3.90 (4H, m), 6.32 (1H, s), 7.30–7.60 (1H, br), 7.67 (2H, d, J = 8.3 Hz), 7.97 (1H, s), 8.26 (2H, d, J = 8.3 Hz); FAB-MS m/z 336, 338 [(M+H)$^+$]. Anal. ($C_{15}H_{18}N_3OBr{\cdot}C_2H_2O_4{\cdot}0.25H_2O$): C, H, N, Br.

5.1.38. 2-{[2-(4-Bromophenyl)-6-methylpyrimidin-4-yl](methyl)amino}ethanol hydrochloride (9m)

White solid (yield 12%); ^{1}H NMR (DMSO-d_6) δ 2.48 (3H, s), 3.20–3.40 (3H, m), 3.60–4.00 (4H, m), 6.75–7.15 (1H, br), 7.85 (2H, d, J = 8.4 Hz), 8.19 (2H, d, J = 8.4 Hz); FAB-MS m/z 322, 324 [(M+H)$^+$]. Anal. ($C_{14}H_{16}N_3OBr{\cdot}HCl{\cdot}0.3H_2O$): C, H, N, Br, Cl.

5.1.39. 2-{[2-(4-Bromophenyl)-6-methylpyrimidin-4-yl]amino}propan-1-ol oxalate (9n)

White solid (yield 22%); ^{1}H NMR (DMSO-d_6) δ 1.16 (3H, d, J = 6.8 Hz), 2.29 (3H, s), 3.38 (1H, dd, J = 5.9, 10.8 Hz), 3.50 (1H, dd, J = 5.4, 10.8 Hz), 3.80–4.50 (2H, m), 6.31 (1H, s), 7.29 (1H, s), 7.67 (2H, d, J = 8.7 Hz), 8.23 (2H, d, J = 8.7 Hz); FAB-MS m/z 322, 324 [(M+H)$^+$]. Anal. ($C_{14}H_{16}N_3OBr{\cdot}C_2H_2O_4$): C, H, N, Br.

5.1.40. 1-{[2-(4-Bromophenyl)-6-methylpyrimidin-4-yl]amino}propan-2-ol oxalate (9o)

White solid (yield 34%); ^{1}H NMR (DMSO-d_6) δ 1.11 (3H, d, J = 6.3 Hz), 2.29 (3H, s), 2.80–3.70 (2H, m), 3.83 (1H, q, J = 6.0 Hz), 6.36 (1H, s), 7.20–7.60 (1H, br), 7.67 (2H, d, J = 8.8 Hz), 8.24 (2H, d, J = 8.8 Hz); FAB-MS m/z 322, 324 [(M+H)$^+$]. Anal. ($C_{14}H_{16}N_3OBr{\cdot}$–$C_2H_2O_4$): C, H, N, Br.

5.1.41. 2-(4-Bromophenyl)-*N*-(2-methoxyethyl)-6-methylpyrimidin-4-amine oxalate (9p)

White solid (yield 17%); ^{1}H NMR (DMSO-d_6) δ 2.30 (3H, s), 3.29 (3H, s), 3.51 (2H, t, J = 4.9 Hz), 3.53–3.80 (2H, m), 6.35 (1H, s), 7.40–7.70 (1H, br), 7.68 (2H, d, J = 8.3 Hz), 8.24 (2H, d, J = 8.3 Hz); FAB-MS m/z 322, 324 [(M+H)$^+$]. Anal. ($C_{14}H_{16}N_3OBr{\cdot}$–$C_2H_2O_4{\cdot}0.75H_2O$): C, H, N, Br.

5.1.42. 2-(4-Bromophenyl)-*N*-isobutyl-6-methylpyrimidin-4-amine oxalate (9q)

White solid (yield 57%); ^{1}H NMR (DMSO-d_6) δ 0.93 (6H, d, J = 6.3 Hz), 1.80–2.00 (1H, m), 2.28 (3H, s), 2.70–4.50 (2H, m), 6.31 (1H, s), 7.40–7.60 (1H, br), 7.67 (2H, d, J = 8.3 Hz), 8.23 (2H, d, J = 8.3 Hz); FAB-MS m/z 320, 322 [(M+H)$^+$]. Anal. ($C_{15}H_{18}N_3Br{\cdot}C_2H_2O_4$): C, H, N, Br.

5.1.43. 2-(4-Bromophenyl)-6-methyl-*N*-(pyridin-3-ylmethyl)pyrimidin-4-amine oxalate (9r)

White solid (yield 64%); ^{1}H NMR (DMSO-d_6) δ 2.30 (3H, s), 4.50–4.80 (2H, m), 6.36 (1H, s), 7.36 (1H, dd, J = 4.8, 7.9 Hz), 7.64 (2H, d, J = 8.3 Hz), 7.77 (1H, d, J = 7.9 Hz), 7.95–8.01 (1H, m), 8.23 (2H, d, J = 8.3 Hz), 8.45 (1H, d, J = 3.6 Hz), 8.62 (1H, s); FAB-MS m/z 355, 357 [(M+H)$^+$]. Anal. ($C_{17}H_{15}N_3Br{\cdot}2C_2H_2O_4{\cdot}H_2O$): C, H, N, Br.

5.1.44. 2-(4-Bromophenyl)-6-methyl-*N*-[2-(pyridin-3-yl)ethyl]pyrimidin-4-amine oxalate (9s)

Pale brown crystal (yield 62%); ^{1}H NMR (DMSO-d_6) δ 2.29 (3H, s), 2.93 (2H, t, J = 6.8 Hz), 3.50–4.00 (2H, m), 6.30 (1H, s), 7.35 (1H, dd, J = 4.7, 7.8 Hz), 7.59 (1H, s), 7.68 (2H, d, J = 8.3 Hz), 7.74 (1H, d, J = 7.8 Hz), 8.24 (2H, d, J = 8.3 Hz), 8.43 (1H, d, J = 4.7 Hz), 8.50 (1H, s); FAB-MS m/z 369, 371 [(M+H)$^+$]. Anal. ($C_{18}H_{17}N_4Br{\cdot}2C_2H_2O_4{\cdot}0.25H_2O$): C, H, N, Br.

5.1.45. 2-(4-Bromophenyl)-6-methyl-*N*-[2-(1-oxidopyridin-3-yl)ethyl]pyrimidin-4-amine oxalate (9t)

To a solution of 2-(4-bromophenyl)-6-methyl-*N*-[2-(pyridin-3-yl)ethyl]pyrimidin-4-amine (**9s**, 1.40 g) in chloroform (20 mL) was added *m*-CPBA (1.40 g), and the mixture was stirred at room temperature for 23 h. To the reaction mixture was added additional *m*-CPBA (0.20 g) and the mixture was stirred at room temperature for 13 h. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate (40 mL), and extracted with chloroform. The organic layer was dried, and the desiccant was re-

moved by filtration, and then the solvent was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography (chloroform-methanol) to obtain a yellow oil. Obtained oil was dissolved with ethanol and acetonitrile, and oxalic acid (257 mg) was added to the solution. The resulting precipitate was recrystallized from ethanol and acetonitrile to obtained compound **9t** (760 mg, 39%) as a colorless crystal: ^{1}H NMR (DMSO-d_6) δ 2.29 (3H, s), 2.87 (2H, t, J = 6.9 Hz), 3.40–3.90 (2H, m), 6.29 (1H, s), 7.26 (1H, d, J = 7.8 Hz), 7.33 (1H, dd, J = 6.4, 7.8 Hz), 7.50–7.63 (1H, br), 7.59 (1H, s), 7.67 (2H, d, J = 8.6 Hz), 8.07 (1H, d, J = 6.4 Hz), 8.19 (1H, s), 8.23 (2H, d, J = 8.6 Hz); FAB-MS m/z 385, 387 [$(M+H)^+$]. Anal. ($C_{18}H_{17}N_4Br\cdot1.5C_2H_2O_4$): C, H, N, Br.

5.2. Human GPR119 cAMP reporter assay

Human GPR119 agonist activity was evaluated in HEK293 cells stably expressing human GPR119 and pCRE-Luc. HEK293-hGPR119 cells were seeded in 96-well plates at 2.5 × 104 cells/well, incubated overnight at 37 °C in 5% CO_2, and then exposed to the test compound dissolved in DMSO at concentrations ranging from 0.01 to 10 μM. After 6 h incubation, cells were harvested using 0.2% Triton X-100 in phosphate-buffered saline (pH 7.4). Luciferase activity was measured using a model ML-3000 Luminometer (Dynex Tech, VA, USA). Three replicates for each concentration were performed.

5.3. Oral glucose tolerance test (OGTT)

Eight-week-old male ICR mice were fasted overnight and then orally administered 0.5% methyl-cellulose (vehicle) or 10 mg/kg test compounds. After 10 min, glucose was given orally at a dose of 2 g/kg/10 mL, and blood sample were collected from tail veins after 30 min. Blood glucose levels were determined using the Glucose CII test (Wako, Osaka, Japan).

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11. The EC and IA values we used in this paper are relative values with reference to the lead compound **9a**, and the IA values don't represent the maximal response of each compound. In addition, it was found to be difficult to evaluate the maximal response of each compound in our assay system. On the other hand, we found that the agonistic activity of **9a** at 10 μM could induce the sufficient insulin secretion in vivo. Therefore, we have decided to discuss the SARs by the comparison of the EC values only.
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