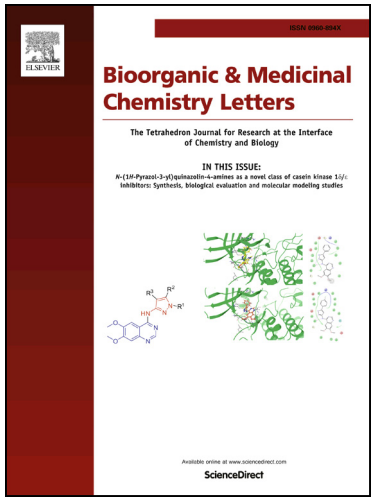

Optimization of a novel series of potent and orally bioavailable GPR119 agonists

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ABSTRACT

We describe the discovery and optimization of a novel series of furo[3,2-*d*]pyrimidines as G protein-coupled receptor 119 agonists. Agonistic activity of **4** (EC_{50} = 129 nM) was improved by replacing the intramolecular hydrogen bond between the fluorine atom and the aniline hydrogen in the head moiety with a covalent C-C bond to enhance conformational restriction, which consequently gave a lead compound **12** (EC_{50} = 53 nM). Optimized compound **26**, which was identified by the further optimization of **12**, exhibited potent activity (EC_{50} = 42 nM) with improved clearance in liver microsomes and induced a 33% reduction in blood glucose area under the curve at a dose of 10 mg/kg in an oral glucose tolerance test in C57BL/6N mice.

Diabetes mellitus (DM) is a chronic disease that eventually causes various complications, such as cardiovascular disorders, blindness, neuropathy, and renal failure, due to prolonged hyperglycemia caused by insulin resistance and/or insufficient insulin secretion.[1] More than 90% of diabetic patients are classified as having type 2 DM (T2DM). The number of patients with T2DM is expected to increase to 330 million by 2030.[2] Many different hypoglycemic agents, such as sulfonylureas, thiazolidinediones, glucagon-like peptide-1 (GLP-1) analogs, dipeptidyl peptidase-4 inhibitors, and sodium-glucose transporter-2 inhibitors, are used for the treatment of T2DM.[1,3] However, some patients fail to achieve the desired blood glucose levels despite using conventional hypoglycemics. Most of these drugs cause adverse effects such as hypoglycemia, weight gain, and loss of therapy responsiveness. Therefore, there are still significant unmet medical needs for treating T2DM.

G protein-coupled receptor 119 (GPR119) is predominantly expressed in pancreatic β-cells and intestinal L-cells.[4] The activation of GPR119 promotes insulin secretion from pancreatic β-cells and the release of GLP-1 from intestinal L-cells. The insulin-releasing effect is glucose-dependent; hence, the associated risk of hypoglycemia is expected to be low.[5] Besides the above, β-cell function preservation, which is assumed to be a critical target in current T2DM treatment,[6] as well as bodyweight reduction based on the secretion of GLP-1 are shown in animal models.[5b,7] These effects make GPR119 agonists promising drug targets for the treatment of T2DM. Indeed, many groups have investigated GPR119 agonists.[8] A general structure of GPR119 agonists consisting of head, linker, and tail moieties was proposed (Figure 1).[8,9] The head moiety has an aromatic ring substituted with electron-withdrawing groups such as a sulfonyl group and/or a fluorine atom, and the tail moiety has a piperidine group with a bulky alkyl carbamate or its bioisostere.

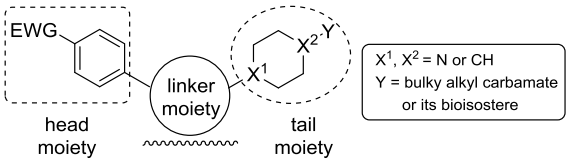

Figure 1. General structure of GPR119 agonists.

In this paper, we describe the synthesis and biological evaluation of a series of compounds with furo[3,2-*d*]pyrimidine as the linker and the optimization of the head and tail moieties. For the former optimization, molecular design based on conformational requirements was applied.

During our efforts to discover small molecule GPR119 agonists, we first sought a novel linker moiety containing a bicyclic pyrimidine scaffold based on structures of reported compounds, for example, **1**, **2**, and **3** (Figure 2)[10-12] and found furo[3,2-*d*]pyrimidine as a promising structure. Furo[3,2-*d*]pyrimidine derivative **4** exhibited the most potent human GPR119 agonistic

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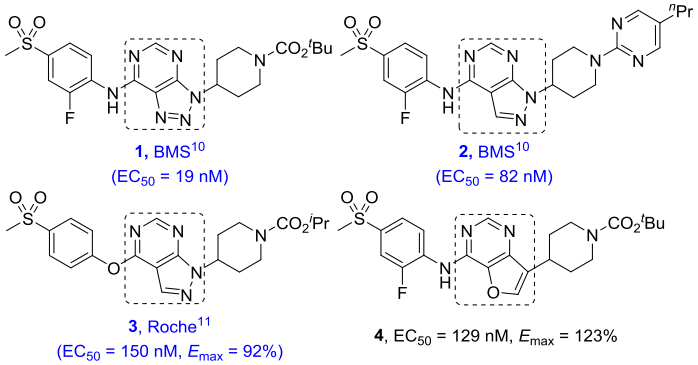
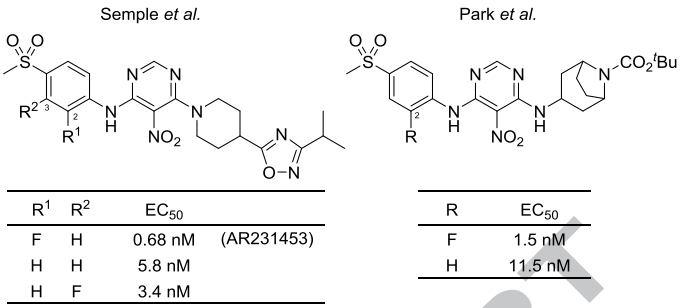


Figure 2. GPR119 agonists possessing bicyclic pyrimidines. Data in parentheses are cited from the literature.



R^1	R^2	EC_{50}	
F	H	0.68 nM	(AR231453)
H	H	5.8 nM	
H	F	3.4 nM	

R	EC_{50}
F	1.5 nM
H	11.5 nM

Figure 3. Importance of fluorine atom in 2-fluoro-4-(methylsulfonyl)aniline.

activity (EC_{50} = 129 nM, E_{max} = 123%) in our first group of GPR119 agonists[13] and showed 13% reduction in blood glucose area under the curve (AUC) at a dose of 30 mg/kg in an oral glucose tolerance test in C57BL/6N mice.

We next focused on the optimization of the head moiety and noticed the fluorine atom at the C2 position in 2-fluoro-4-(methylsulfonyl)aniline, which plays a pivotal role in enhancing potency against GPR119 (Figure 3). Semple *et al*. reported that AR231453 (R^1 = F, R^2 = H) exhibited approximately eight times more potent activity than the non-substituted compound (R^1, R^2 = H).[14] However, fluorine substitution at the C3 position (R^1 = H, R^2 = F) hardly led to an improvement of potency. Park's study also showed that the fluorinated compound at the C2 position (R = F) was superior in activity to the non-substituted derivative (R = H).[15]

We hypothesized that the fluorine atom at the C2 position induced conformational restriction by the intramolecular hydrogen bond between the fluorine atom and the aniline hydrogen atom[16] (Figure 4) because a number of studies have proposed that conformational rigidity contributes to high potency.[17] However, a fluorine atom is a poor hydrogen bond acceptor;[18] hence, we assumed that the cyclization by replacing the H-F hydrogen bond with a covalent C-C bond would enhance the rigidity to elevate the potency of **4**, and designed annulated anilines **5**.

To investigate which structural features of the head moiety would be required for potent GPR119 agonistic activity, a series of compounds containing furo[3,2-*d*]pyrimidine as the linker were synthesized (Scheme 1).[19] *N*-Boc protection of **6** followed by mesylation with MsCl gave the corresponding mesylate, which was transformed with sodium cyanide into nitrile **7** in 77% yield based on **6**. Lithiation of **7** with lithium diisopropylamide (LDA) followed by formylation gave enolate **8** in 92% yield. Furan **9** was prepared by cyclization with diethyl chloromalonate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 50% yield, and the following condensation with formamidine acetate yielded furo[3,2-*d*]pyrimidine **10** in 56% yield. Activation of the hydroxy group of **10** was achieved with (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBop) to give intermediate **11** in 83% yield. Nucleophilic displacement reactions of **11** with the corresponding anilines and heterocyclic compounds[20] afforded **4** and **12–16**, respectively (13–91%).[21]

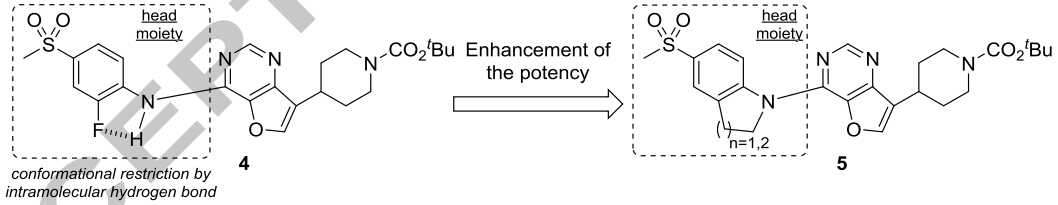
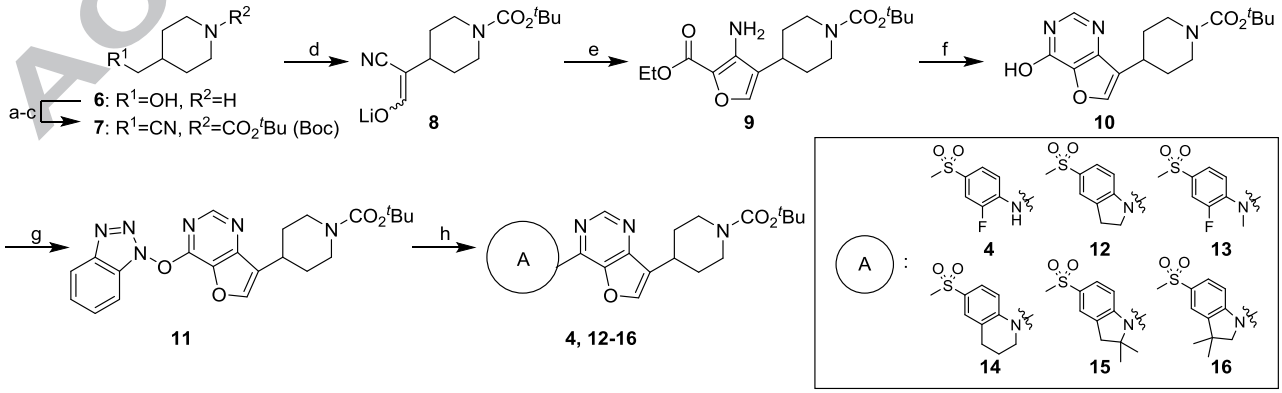
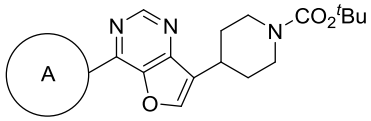


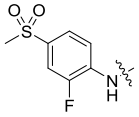
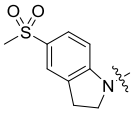
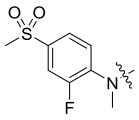
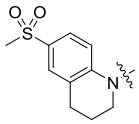
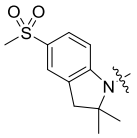
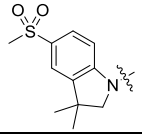
Figure 4. Design of annulated aniline **5** by fixing the conformation at the head moiety.



Scheme 1. Synthesis of compounds **4** and **12–16**. Reagents and conditions: (a) Boc_2O, Na_2CO_3, THF, H_2O, rt, overnight; (b) MsCl, Et_3N, THF, 0 °C, 15 min; (c) NaCN, EtOH, H_2O, 80 °C, 24 h, 77% (3 steps); (d) (i) LDA, THF, −78 °C, 1 h; (ii) ethyl formate, −30 °C to rt, overnight, 92%; (e) (i) diethyl chloromalonate, DMF, rt, 24 h; (ii) DBU, EtOH, rt, 3 h, 50%; (f) formamidine acetate, EtOH, reflux, 2 days, 56%; (g) PyBop, DBU, THF, rt, 30 min, 83%; (h) anilines or heterocyclic compounds, NaH, DMF, 0 °C-100 °C, 13–91%.

Table 1 Effects of intramolecular hydrogen bond and structural requirements at head moiety.



Compound	A	hGPR119 agonistic activities	
		EC_{50} (nM)[a]	E_{max} (%)[b]
4		129	123
12		53	123
13		>1000	6
14		793	1
15		not active	-
16		not active	-

[a] Assay values are reported from a single determination performed in quadruplicate. See Ref. 22 for the assay protocol.

[b] E_{max} was defined as the percentage ratio between the maximum response for the test compound and the response for AR231453 at 100 nM.

Compounds **12–16** were evaluated (Table 1). As expected, annulated compound **12** containing the 5-(methylsulfonyl) indoline motif[23] was more potent (EC_{50} = 53 nM, E_{max} = 123%) than **4**. In contrast, *N*-methylated aniline **13** showed depletion of the agonistic activity. Along with these experimental findings, computational calculation using molecular dynamics software[24] suggested that C2-C1-N-R(C1′) of **4**, **12**, and **13** were arranged in periplanar/clinal, periplanar, and clinal conformations, respectively. The calculated results are shown in Figure 5. Estimated distribution of dihedral angles of C2-C1-N-R(C1′) of **4** (purple), **12** (red), and **13** (blue) were, −60° to +60°, −30° to +30°, and −180° to −30° (partially +30° to +180°), respectively, and these results suggested the principal conformation of each compound as mentioned above. Based on these results, we considered that the conformational restriction of C2-C1-N-R(C1′) in periplanar arrangement was a requisite for high agonistic activity. From this perspective, the six-membered ring system in **14** was expected to show activity comparable with that of the five-membered ring system in **12** because the computational calculation suggested that the C2-C1-N-C1′ of **14** (green in Figure 5) was also arranged in a periplanar conformation, as in **12** (red in Figure 5). However, contrary to expectations, tetrahydroquinoline derivative **14** did not show significant activity. A plausible explanation for this is that loss of planarity around the annulated part in the head moiety was caused by a half-chair conformation of the tetrahydroquinoline ring. In this series of compounds, dimethylindoline derivatives **15** and **16** also showed diminished activity. The loss of potency was probably caused by steric hindrance of the dimethyl groups on the indoline scaffold. We considered that planarity of the head moiety, not only the conformational restriction discussed above but also less steric bulkiness around the annulated part of the moiety, was a crucial structural requirement for a potent GPR119 agonist. Consequently, we selected 5-(methylsulfonyl)indoline as an optimal unit for the head moiety.

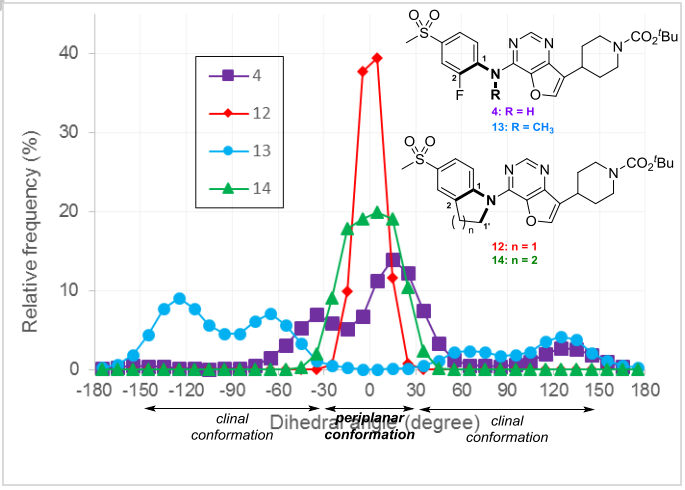
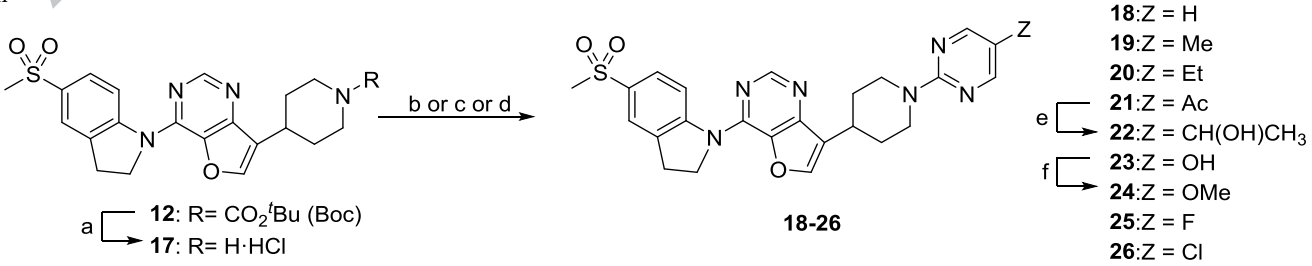
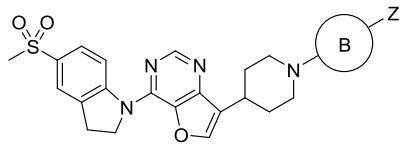


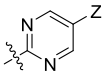
Figure 5. Distribution of dihedral angle at the head moiety.



Scheme 2. Synthesis of furo[3,2-*d*]pyrimidine derivatives **18**–**26**. Reagents and conditions: (a) 4N HCl in AcOEt, MeOH, $CHCl_3$, rt, 1.5 h, 73%; (b) for **18**, **20**, **21**, **25** and **26**: 2-chloropyrimidine derivatives, DIEA, DMF or IPA, rt to 100 °C, 15–98%; (c) for **19**: (i) 5-bromo-2-chloropyrimidine, DIEA, DMF, 100 °C,12 h, 84%; (ii) $MeB(OH)_2$, $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, Cs_2CO_3, THF, DMF, 100 °C, 12 h, 26%; (d) for **23**: (i) 2-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine, IPA, reflux, overnight; (ii) H_2O_2, THF, rt, overnight, 27% (2 steps); (e) $NaBH_4$, MeOH, CH_2Cl_2, 0 °C to rt, 0.5 h, 80%; (f) MeI, K_2CO_3, DMF, rt, 1 h, 16%.

Table 2 Optimizing study on the tail moiety.



Compound	B	Z	hGPR119 agonistic activities		$LMCl_{int}$[c]	
			EC_{50} (nM)[a]	E_{max} (%)[b]	human	mouse
12	-CO_2-	^{t}Bu	53	123	550	508
18		H	512	196	NT[d]	NT[d]
19		Me	252	159	349	145
20		Et	41	154	412	187
21		Ac	78	12	74	154
22			586	33	102	66
23		OH	391	145	132	107
24		OMe	310	186	255	189
25		F	201	229	257	154
26		Cl	42	117	113	108

[a] Assay values are reported from a single determination performed in quadruplicate. See ref. 22 for the assay protocol.

[b] E_{max} was defined as the percentage ratio between the maximum response for the test compound and the response for AR231453 at 100 nM.

[c] Liver microsome clearance (μl/min/mg/protein).

[d] Not tested.

We then focused on the optimization of the tail moiety. Although our pivotal compound **12** exerted potent in vitro agonistic activity, Boc group in the moiety was not suitable for oral administration because of its lability under acidic conditions. To circumvent this drawback, we focused on 5-substituted pyrimidines, which were recently reported as bioisosteres of carbamates.[25] 5-Substituted pyrimidine derivatives **18–26** were prepared as shown in Scheme 2. *N*-Boc deprotection of **12** under acidic conditions afforded hydrochloride salt **17** in 73% yield. Pyrimidine derivatives **18–26** were synthesized from hydrochloride salt **17** by a nucleophilic displacement reaction with the corresponding 2-halopyrimidines.

Although **20** exerted higher activity (EC_{50} = 41 nM, E_{max} = 154%, Table 2) than **12**, the metabolic instability of **20** assessed by clearances in both human and mouse liver microsomes was increased (412 and 187 μl/min/mg/protein in human and mouse, respectively). Because plausible metabolites of **20** (**21** and **22**) were less potent, these compounds as well as **20** could not be regarded as candidates for further evaluation. The unpromising potency of **23** and **24** also suggested intolerance for the introduction of a hydrophilic group at the 5-position. To fulfill both requirements, namely, potency and metabolic stability, substitution with a halogen atom at this position was examined. Although 5-fluoropyrimidine **25** exhibited moderate EC_{50} (201 nM), 5-chloropyrimidine **26** showed potent GPR119 agonistic activity (EC_{50} = 42 nM, E_{max} = 117%). Moreover, compound **26** showed improved human and mouse liver microsome clearances (113 and 108 μl/min/mg/protein). We assumed that the improvement in metabolic stability by the replacement of the ethyl group by a chlorine atom was mainly caused by the removal of the carbon atom adjacent to the aromatic ring, which is generally susceptible to oxidative metabolism.[26] Consequently, compound **26** was selected and evaluated further as the most promising GPR119 agonist in the optimization in vitro.[27]

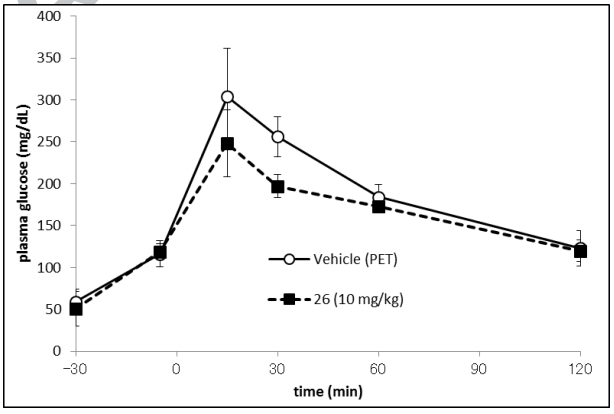
The pharmacokinetic properties of **26** are shown in Table 3. Compound **26** possessed a good pharmacokinetic profile in mice, and lowered the blood glucose excursion at a dose of 10 mg/kg in an oral glucose tolerance test in C57BL/6N mice (Figure 6). The reduction of blood glucose AUC was 33%, which was 20% higher than the results obtained upon 30 mg/kg administration of lead compound **4**.

Table 3. Pharmacokinetic parameters of **26** in mice.[a]

CLp_{iv} (ml/min/kg)	Vss_{iv} (L/kg)	$t_{1/2\,iv}$ (h)	$C_{max\,po}$ (ng/ml)	AUC_{po} (ng h/ml)	BA[b] (%)
6.5	2.3	5.1	2015	9386	37

[a] **26** was dosed at 0.5 mg/kg (iv) and 10 mg/kg (po) in vehicle of PET (80% PEG400, 10% ethanol, 10% Tween80™).

[b] Bioavailability.



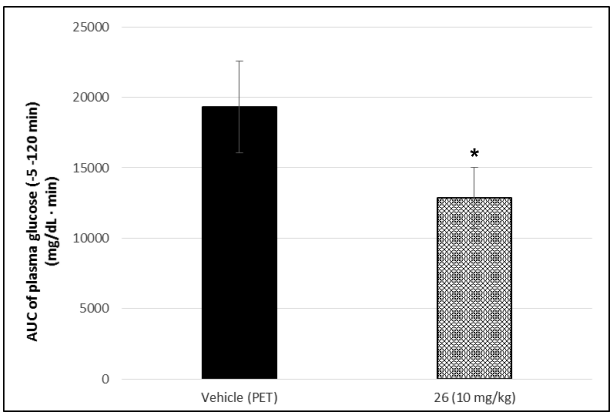


Figure 6. Effect of **26** (10 mg/kg) on glucose excursion in an oral glucose tolerance test in C57BL/N mice. **26** was administered in PET 25 min prior to glucose loading at 3 g/kg. Glucose levels were monitored for 120 min. * indicates a *p* value of <0.01.

In summary, we conducted optimization of the lead compound **4** and obtained **26** as a drug candidate of a GPR119 agonist for further evaluations. We noticed the pivotal role of the fluorine atom in 2-fluoro-4-(methylsulfonyl)aniline at the head moiety of **4,** based on the analysis that the intramolecular hydrogen bond between the fluorine atom and the aniline hydrogen was associated with the restriction of conformation, and found 5-(methylsulfonyl)indoline as an optimal unit for the moiety. We considered that planarity of the head moiety, involving not only the conformational restriction but also less steric bulkiness around the annulated part of the moiety, was a crucial structural requirement for a potent GPR119 agonist. The optimized compound **26** showed potent GPR119 agonistic activity (EC_{50} = 42 nM, E_{max} = 117%) with improved liver microsome clearance, and exerted 33% reduction in blood glucose AUC at a dose of 10 mg/kg in an oral glucose tolerance test in C57BL/6N mice. Follow-up studies and their results will be reported in due course.

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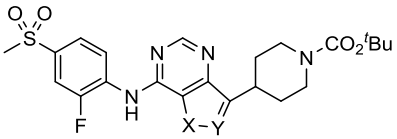

X	Y	hGPR119 agonistic activities	
		EC_{50} (nM)	E_{max} (%)
S	C	79	82
NH	C	>1000	9
NMe	C	>1000	3
O	N	353	137

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20. Please see Supporting Information section for synthetic schemes associated with the analogs.
21. Yields of the final step depend on the reactivity of the substrates. For example, compound **15** was obtained in low yield (13%) probably due to the steric hindrance of the dimethyl group.
22. The assay consists of CHO-K1 CRE-luciferase cells that stably express human GPR119 receptor plated at 20,000 cells/well in 80 μL of Ham's F12 Nutrient Mixture and 0.1% fetal bovine serum in white 96-well assay plates. On the following day, 20 μl of test compounds are pipetted into the assay plates. The plates are then incubated for 4 h at 37 °C. According to the Bright-Glo™ Luciferase Assay System (Promega), the amount of luciferase generated is quantified in a Centro LB960. Compounds are also tested in the same manner against cells without the GPR119 receptor so as to check for false positives. Reliability of the data was confirmed by visual inspection of the viability of cells during the assay.
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24. Molecular dynamics simulations were performed with the gromacs 5.1.1 package employing General AMBER Force Field and periodic boundary conditions in saline solution at 310K.
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26. Metabolic stability predictions were performed with StarDrop (Optibrium. StarDrop. www.optibrium.com/stardrop). The calculation suggested that the ethyl group of compound **20** was easily metabolized by cytochrome P450.
27. The cytotoxicity of compound **26** against CHO-K1 cells was assessed by Cell Counting Kit-8 (Dojindo Laboratories, Kumamoto, Japan). The IC_{50} value was >10 μM.

Graphical Abstract

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Optimization of a novel series of potent and orally bioavailable GPR119 agonists

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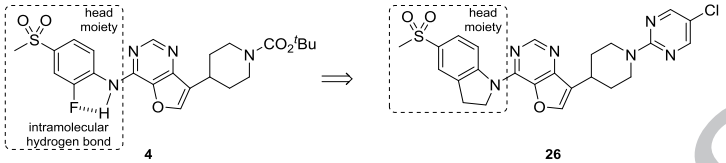
Tomoaki Koshizawa*, Toshiharu Morimoto, Gen Watanabe, Toshiaki Watanabe, Nao Yamasaki, Yoshikazu Sawada, Tomoaki Fukuda, Ayumu Okuda, Kimiyuki Shibuya and Tadaaki Ohgiya



4
hGPR119 EC_{50} = 129 nM
mOGTT; 13% lowering at 30 mg/kg

26
hGPR119 EC_{50} = 42 nM
mOGTT; 33% lowering at 10 mg/kg