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Synthesis and SAR studies of bicyclic amine series GPR119 agonists

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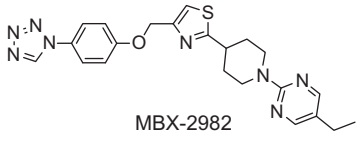
ABSTRACT

We disclosed a novel series of G-protein coupled receptor 119 (GPR119) agonists based on a bicyclic amine scaffold. Through the optimization of hit compound **1**, we discovered that the basic nitrogen atom of bicyclic amine played an important role in GPR119 agonist activity expression and that an indanone in various bicyclic rings was suitable in this series of compounds. The indanone derivative **2** showed the effect of plasma glucose control in oGTT and scGTT in the rodent model.

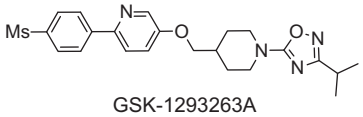
Type 2 diabetes mellitus (TDM) is a disease caused by a disorder of glucose metabolism that affects about 285 million patients worldwide. One of the causes of TDM is obesity, and an increase in physical activity and weight loss are usually recommended for TDM patients.[1] A number of diabetes therapeutic agents have been developed; however, most of the agents such as insulin, sulfonylureas, thiazolidinediones and so on, can control blood glucose levels, but cause body weight gain. On the other hand, dipeptidyl peptidase 4 inhibitors (DPP-4i) and glucagon like peptide-1 (GLP-1) mimetics, which have been marketed recently, are GLP-1-related drugs and can lower blood glucose by the stimulation of glucose-dependent insulin secretion.[2] In addition, DPP-4i has been shown to minimize body weight gain, while GLP-1 mimetics have been shown to delay gastric emptying, thereby decreasing appetite as well as body weight.

A GPR119 agonist, which will fall into the category of GLP-1 related drugs, promises to be a novel therapeutic approach to the treatment of TDM.[3] GPR119 is highly expressed only in pancreatic islets and various intestinal sub-regions in the human, rat, and mouse.[4,5] AR231453, a selective GPR119 agonist discovered at Arena Pharmaceuticals, Inc., increased cAMP and insulin release in HIT-T15 cells and also increased cAMP and GLP-1 release in GLUTag cells.[6] Therefore, the GPR119 agonist may not only provide improved glycemic control, but may also decrease body weight. Furthermore, the GPR119 agonist may provide greater benefits when used in combination with a DPP-4i.

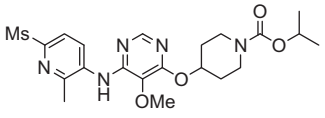
Several GPR119 agonists have advanced in clinical trials, such as MBX-2982, GSK-1293263A, PSN-821, APD597 (Fig. 1).[7] Recently, positive results of the phase 1 trials for MBX-2982 were reported from Metabolex, Inc.[8] In our study to develop GPR119 agonists, we found dihydrobenzothiophene **1** as a hit from an extensive



MBX-2982



GSK-1293263A



APD597

Figure 1. GPR119 agonists in clinical trial.

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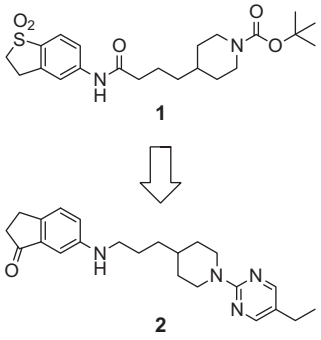
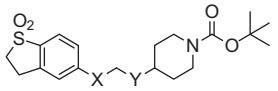


Figure 2. Design of bicyclic amine **2** analog from hit compound **1**.

screening of our internal compound library. Starting compound **1** has a characteristic structure with a linear methylene chain connecting the bicyclic ring and *N*-Boc piperidine. Such GPR119 agonists with linear linkers are poorly represented in the literature,[9] so we were interested in this structure and started this investigation. We report on a suitable tether length and bicyclic ring and show the importance of the basic nitrogen in this investigation. As a result, aminoindanone **2** as a potent GPR119 agonist was obtained by optimization of **1** (Fig. 2). In this Letter we report on the synthesis and SAR studies of a novel type GPR119 agonist and in vivo effects of the typical compound on plasma glucose control using rodent models.

At first, for an investigation of a suitable tether, sulfone analogs having various tether lengths were synthesized from commercial 6-aminobenzothiophene **3** (Scheme 1). As for the synthesis of dihydrobenzothiophenes **5a–e,** 6-aminobenzothiophene **3** was coupled with appropriate carboxylic acids and then oxidized to **4a–e**. Reduction of amide **4a–e** with the borane–THF complex gave **5a–e** in good yield. Next, oxa-analog **5f** also commenced with **3**. Thus, ether **7** was synthesized by a Sandmeyer reaction of **3** according to the published procedure,[10] followed by a Mitsunobu etherification of 6-hydroxybenzothiophene **6**. The oxidation of **7** followed by hydrogenation led to the ether **5f**. The results of in vitro assays performed with compounds **5a–f** are shown in Table 1. The activity of these compounds was evaluated from EC_{50} values based on potency in the cAMP assay and the %max relative to human

Table 1
In vitro *h*GPR119 agonism data for sulfone analogs with different tethers

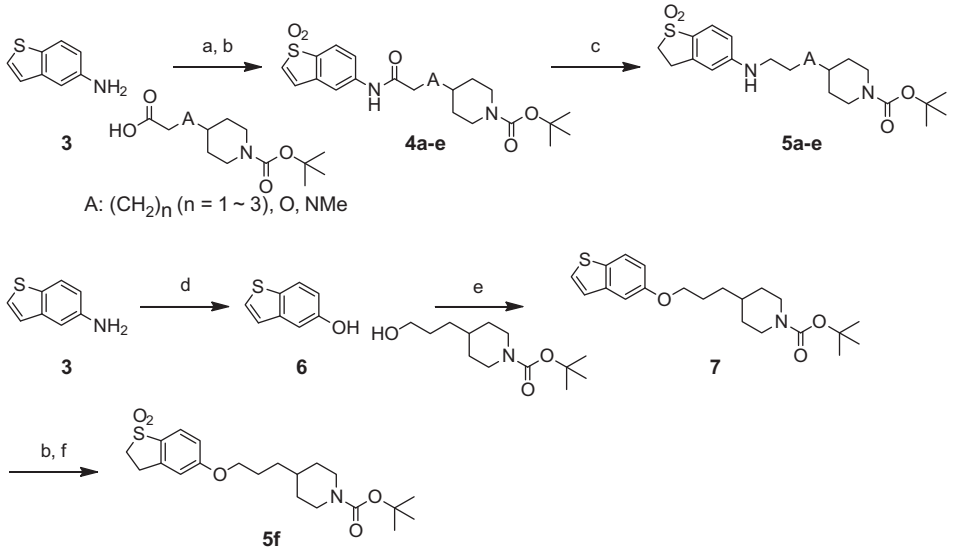


Compound	GRP119 agonist activity[a]			
	X	Y	Human (nM)	
			EC_{50}	E_{max}[d]
1	–NHCO–	$–(CH_2)_2–$	2610	56
5a	$–NHCH_2–$	$–(CH_2)_2–$	210	62
5b	$–NHCH_2–$	$–(CH_2)_3–$	145	65
5c	$–NHCH_2–$	$–CH_2–$	270	80
5d	$–NHCH_2–$	–O–	(33)[c]	33
5e	$–NHCH_2–$	–NMe–	(10)[b]	10
5f	$–OCH_2–$	$–CH_2–$	736	84

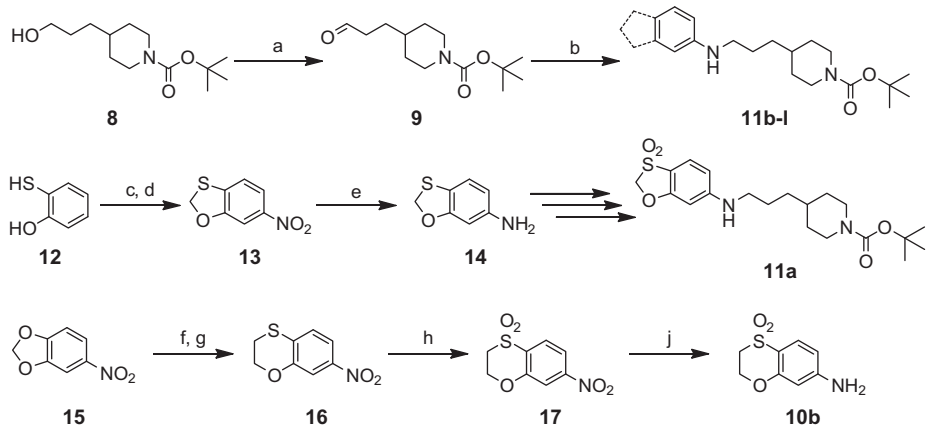
[a] Values are average of four experiments.
[b] Values in parenthesis indicate the agonist activity at 10 μM.
[c] Values in parenthesis indicate the agonist activity at 1 μM.
[d] E_{max} is %maximum, compared to the maximum response of AR231453.

GPR119 (*h*GPR119) agonist activity.[11] (%max of the test compounds was compared to the maximum response of AR231453.) More than a 10-fold increase in *h*GPR119 agonist activity was observed when the amide moiety in **1** was changed to aminomethylene (**1** vs **5a**). In addition, ether **5f** showed a threefold decrease in potency compared to the corresponding amine **5c**. These results indicated that the basic nitrogen atom in the tether plays an important role in GPR119 agonist activity in this series of compounds. In the case of constrained tethers exemplified by the Arena group, it is known that the oxygen atom is suitable as the connecting atom between the core ring system and *N*-Boc piperidine.[12] However, an oxygen atom (i.e., **5d**) did not work well in our case. We instead found that a tether length of three methylenes (i.e., **5c**) gave the best result with these three compounds. Consequently, the linear alkyl chain linker was optimal, and we infer that the lipophilicity of the tether also contributes to the high expression of GPR119 agonist activity.

Next we modified the bicyclic ring of **5c**. Basically, all compounds (except **11a)** were synthesized from the corresponding bicyclic amines and aldehyde **9** via reductive amination using $NaBH(OAc)_3$ (Scheme 2). Synthesis of amine **14** began with



Scheme 1. Synthesis of sulfone analogs. Reagents and conditions: (a) WSC, HOBt, DIPEA, DMF (>95%); (b) *m*-CPBA, DCM (60–85%); (c) BH_3–THF, THF (50–60%); (d) (i) $NaNO_2$, H_2SO_4, H_2O; (ii) H_2SO_4, H_2O (52%); (e) PPh_3, DEAD, DCM (90%); (f) Pd/C, H_2, EtOH (89%).

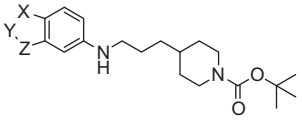


Scheme 2. Synthesis of amine analogs. Reagents and conditions: (a) Dess–Martin periodinane, DCM (92%); (b) **10b–l**, $NaBH(AcO)_3$, DCM (20–85%); (c) $BrCH_2Cl$, Cs_2CO_3, DMF (44%); (d) 40% HNO_3, AcOH (11%); (e) Fe, NH_4Cl, EtOH, H_2O (56%); (f) $HO(CH_2)_2SH$, DIPEA, NMP (26%); (g) PPh_3, DEAD, toluene (75%); (h) m-CPBA, DCM (99%); (j) Fe, AcOH, H_2O (99%).

4-hydroxybenzenethiol **12**. Compound **13** was prepared by cyclization of **12** with bromochloromethane, followed by the nitration with 40% HNO_3. Compound **14** was obtained after a reduction of the nitro group of **13** using iron and ammonium chloride. Synthesis of amine **10b** began with 4-methylenedioxynitrobenzene **15**. Thus, a nucleophilic substitution of **15** with 2-mercaptethanol and a subsequent cyclization via a Mitsunobu reaction, followed by oxidation of the sulfur atom with *m*-CPBA led to **17**, which was subjected to reduction to furnish amine **10b**. The other amines were purchased or synthesized according to published procedures.[13] The results of in vitro assays performed with compounds **11a–l** are shown in Table 2. The activities were evaluated in two species as expressed in hEC$_{50}$ and hE_{max} for human and mEC$_{50}$ and mE_{max} for mouse. At first, the expanded ring compounds **11b**, **11e,** and **11k** had reduced activities compared to the corresponding smaller ring size analogs **11a**, **11d,** and **11j**. Therefore, we focused on further modification of the bicyclic 5–6 ring systems. Isosteric replacement of the sulfone group of **5c** with a carbonyl group (**11d**) showed a threefold increase in potency, while sulfolactam and lactam (**11c** and **11g**) showed less potent GPR119 agonist activity. When the methylene in **11d** was replaced with an oxygen atom, a high EC$_{50}$ was observed in human and mouse. Next, we introduced electron withdrawing groups at the *meta*-position of the amino tether. In all cases (except **11h**), the activity was increased. Specifically, indanone **11i** improved potency of hEC$_{50}$ compared to **11d** and showed the highest activity among these compounds. As mentioned before, the basic nitrogen atom in the bicyclic core plays an important role in GPR119 agonist activity; therefore, we surmised that the increase in basicity of the amino group in **11i** might have partly contributed to the improved activity.

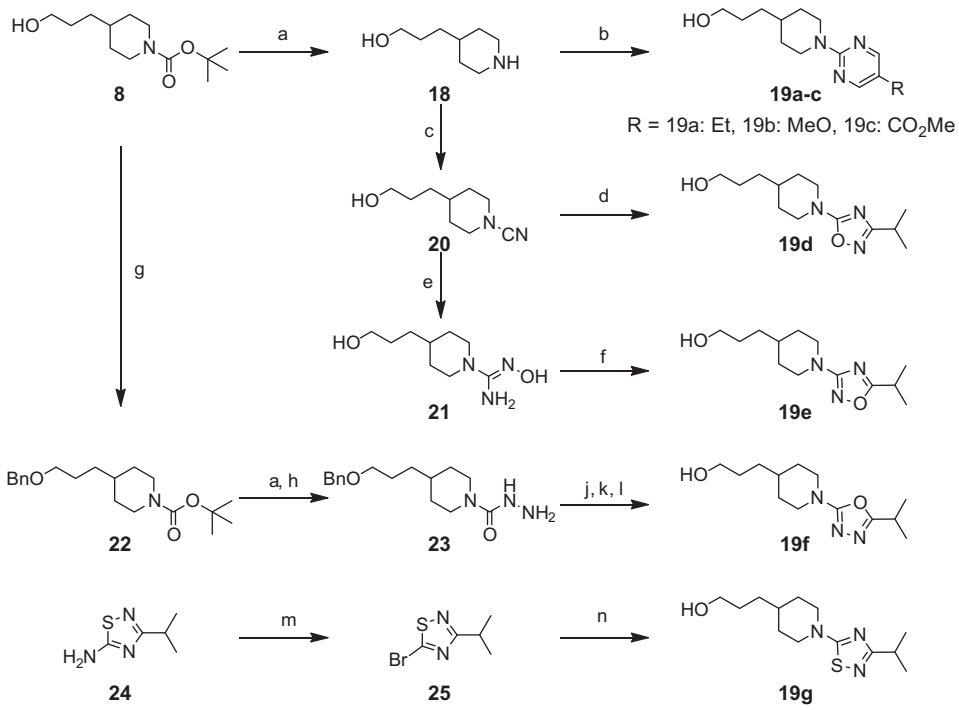
Finally, we replaced the Boc group in the highly potent compounds **11f** and **11i** with known carbamate isosteres, such as pyrimidine, oxadiazole, and thiadiazole.[9] The appropriate alcohols were synthesized from alcohol **8** (Scheme 3). Pyrimidine derivatives **19a–c** were prepared from the reaction of aminoalcohol **18** and 2-chloropyrimidine derivatives under basic conditions. The 1,2,4-oxadiazole **19d** was obtained by the conversion of nitrile **20**, which was prepared by the nitrilation of **18**, in good yield. Hydroxylguanidine **21**, prepared by guanidation of nitrile **20**, reacted with

Table 2
In vitro GPR119 agonism data for amines with different left rings



Compound	GRP119 agonist activity[a]						
	X	Y	Z	hEC$_{50}$ (nM)	hE_{max}	mEC$_{50}$ (nM)	mE_{max}
5c	$-SO_2-$	$-CH_2-$	$-CH_2-$	270	80	224	83
11a	$-SO_2-$	$-CH_2-$	–O–	254	93	266	105
11b	$-SO_2-$	$-(CH_2)_2-$	–O–	511	81	NT[b]	NT[b]
11c	$-SO_2-$	–NH–	–NH–	268	99	331	95
11d	–CO–	$-CH_2-$	$-CH_2-$	86	85	87	105
11e	–CO–	$-(CH_2)_2-$	$-(CH_2)_2-$	770	38	NT[b]	NT[b]
11f	–CO–	$-CH_2-$	–O–	52	94	66	108
11g	–CO–	–NH–	$-CH_2-$	550	91	515	102
11h	$-CH_2-$	$-CH_2-$	$-SO_2-$	1029	25	NT[b]	NT[b]
11i	$-CH_2-$	$-CH_2-$	–CO–	46	98	123	110
11j	–O–	$-CH_2-$	–CO–	88	95	262	116
11k	–O–	$-(CH_2)_2-$	–CO–	272	100	351	108
11l	$-CH_2-$	–NH–	–CO–	734	89	892	97

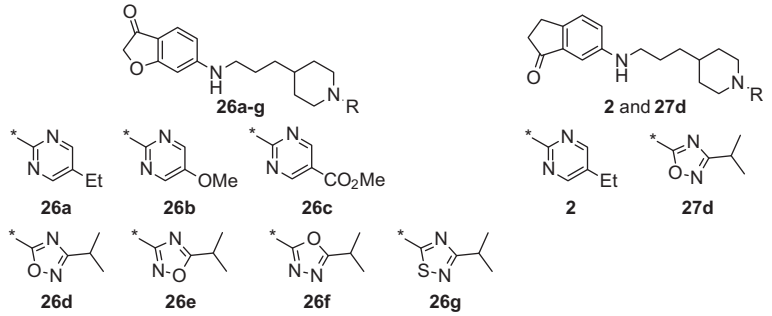
[a] Values are average of four experiments. hE_{max} and mE_{max} are %maximum, compared to the maximum response of AR231453.
[b] Not tested.



Scheme 3. Synthesis of alcohol analogs. Reagents and conditions: (a) HCl/dioxane, DCM (95%); (b) corresponding pyrimidines, DIPEA, *i*-PrOH (30–95%); (c) BrCN, $NaHCO_3$, DCM, H_2O (95%); (d) (i) hydroxyamidine, $ZnCl_2$, EtOAc, THF; (ii) EtOH, concd HCl (78%); (e) NH_2OH HCl, K_2CO_3, EtOH, H_2O (76%); (f) isobutyric acid, WSC, HOBt, DIPEA, DMF (50%); (g) BnBr, NaH, DMF (95%); (h) (i) *p*-nitrophenyl chloroformate, DIPEA, DCM (96%); (ii) NH_2NH_2, EtOH (45%); (j) isobutyric acid, TBTU, HOBt, DIPEA, DMF (66%); (k) CCl_4, Et_3N, PPh_3, DCM (63%); (l) Pd/C, H_2, EtOH (99%); (m) *tert*-butylnitrate, CuBr, Acetone (67%); (n) **18**, Et_3N, DCM (98%).

isobutyric acid, WSC and HOBt to yield the 1,2,4-oxadiazole **19e**. Synthesis of 1,3,4-oxadiazole **19f** began with preparation of benzyl ether **22**. The hydrazide **23** was synthesized by deprotection of the Boc group of ether **22**, followed by a hydrazidation of **22** through *p*-nitrophenyl carbamate. Acylation of **23** with isobutyric acid and then cyclization with CCl_4 and PPh_3, followed by deprotection of the benzyl group with catalytic hydrogenolysis led to **19f**. Thiadiazole **19g** was obtained from the reaction of aminoalcohol **18** and bromothiadiazole **25** prepared by a Sandmyer reaction of aminothiadiazole **24**.[14] The desired compounds **26a–g**, **2** and **27d** were

Table 3
In vitro GPR119 agonism data for the effect of isosteres of Boc group



Compound	GRP119 agonist activity[a]			
	hEC_{50} (nM)	hE_{max}	mEC_{50} (nM)	mE_{max}
11f	52	94	66	108
26a	117	115	159	98
26b	115	101	60	106
26c	149	85	139	67
26d	73	94	NT[b]	NT[b]
26e	161	91	NT[b]	NT[b]
26f	704	85	1015	88
26g	121	10	812	93
11i	46	98	123	110
2	51	113	167	110
27d	58	110	158	113

[a] Values are average of four experiments. hE_{max} and mE_{max} are %maximum, compared to the maximum response of AR231453.
[b] Not tested.

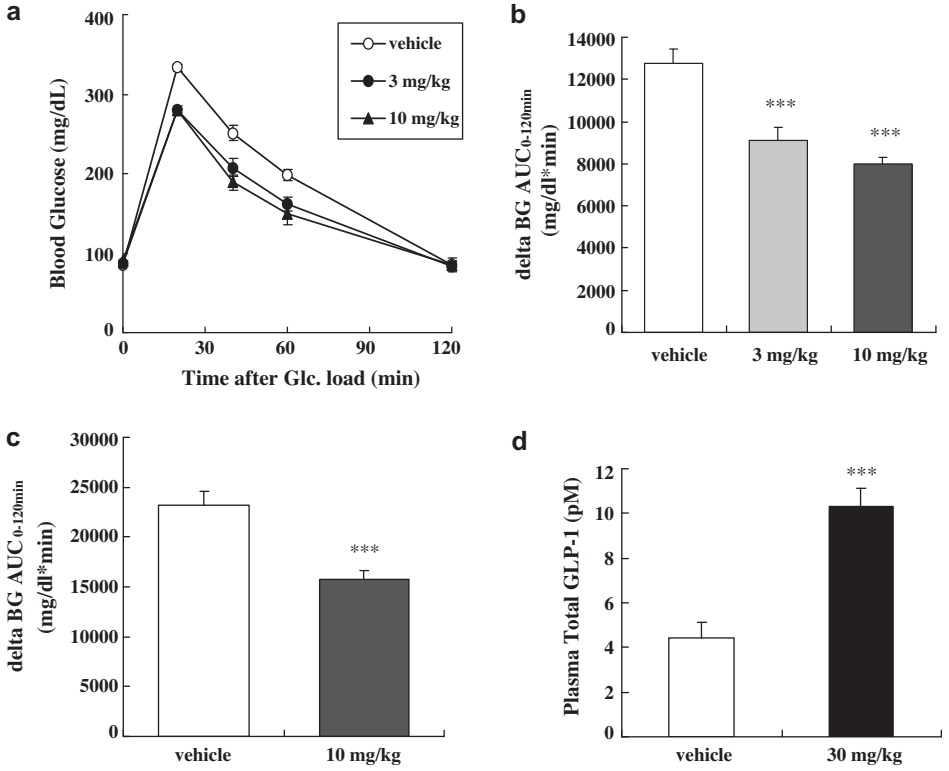


Figure 3. Effect of compound **2** on glucose tolerance test and GLP-1 secretion in C57BL/6J mice. (a) The effect on blood glucose (BG) levels during an oGTT. The incremental area under the curve $(AUC)_{0-120\ min}$ of BG levels in (b) oGTT or (c) scGTT. (d) Plasma total GLP-1 level at 30 min after treatment. Data are presented mean ± SE. ***p <0.001 versus vehicle group.

synthesized from the appropriate alcohols **19a–g** according to the reaction sequences described in Scheme 2.

The replacement of the Boc group in the pyrimidine derivatives in the **11f** series **26a–c** showed a slightly reduced potency of $h\mathrm{EC}_{50}$ compared to **11f**, but the hE_{max} of these compounds improved as their lipophilicity log$P$[15] increased (Table 3). In particular, **26a** showed a high hE_{max} and agonist activity equal to **11f** at 100 nM. The 1,2,4-oxadiazole derivative **26d** retained agonist activity but the other isomers **26e** and **26f** showed less potency. Thiadiazole derivative **26g**, which is the thia-analog of **26d**, was less potent. Within the **11i** series, the agonist activity of **2** and **27d** were equal to that of **11i**. In addition, **2** and **27d** showed a high E_{max} in both human and mouse, and equipotent activity in the mouse at 100 nM in response to **11f** and **26b** which showed the highest mE_{max} in this series of compounds. As a result, 5-ethylpyrimidine and 3-isopropyl-1,2,4-oxadiazole worked as good isosteres of the Boc group in our GPR119 agonist, and **2** and **27d** showed a high $h\mathrm{EC}_{50}$ and a high hE_{max} and mE_{max}. It is also noteworthy that the species difference between human and mouse in the agonist activity was somewhat smaller than that observed in reported GPR119 agonists.[12,16] We speculate that our GPR119 agonists have flexible linear tethers, whereby they can easily adopt suitable conformations to the active sites of both GPR119.

With these encouraging results in hand, we next conducted preliminary oral glucose tolerance test (oGTT) using 30 mg/kg each of the potent compounds such as **2**, **11f**, **11i**, **11j**, **26b** and **27d** to evaluate their in vivo potencies (data not shown). Unfortunately, only compounds **2** and **27d** showed significant reduction in glucose excursion and thereby were assessed in pharmacokinetic experiments, Compound **2** showed higher exposure and good bioavailability compared to **27d** (data not shown); therefore, compound **2** was selected for further evaluation of in vivo efficacy. As shown in Figure 3, compound **2** showed a dose-dependent lowering of the blood glucose excursion in an oGTT in the C57BL/6j mouse.[17] The excursion of the AUC from 0 to 120 min was 29% and 38% at 3 and 10 mpk, respectively. Moreover, compound **2** significantly lowered the blood glucose excursion in a subcutaneous glucose tolerance test (scGTT) and reduced the glucose excursion of the AUC with 32% inhibition.[17] Subcutaneous administration of glucose caused an increase of blood glucose but did not cause GLP-1 secretion from the GI tract by glucose stimulation. Therefore, the glucose-lowering potential of compound **2** was independent of GLP-1 secretion. Furthermore, compound **2** showed a significant increase of GLP-1 secretion (over twofold) by measuring the total plasma GLP-1 concentration after oral administration of compound **2** without glucose loading.[18] Very recently, it was reported that MBX-2982 alone also stimulated GLP-1 secretion prior to a glucose load, and moreover it significantly increased GLP-1 secretion after glucose loading compared to no glucose loading.[19] Compound **2** produced almost equal GLP-1 secretion compared to that reported for MBX-2982, and we supposed that compound **2** had sufficiently high potential to cause GLP-1 secretion; in addition stronger stimulation of GLP-1 secretion by compound **2** is expected with glucose loading.

In summary, we have shown the SAR for a new series of GPR119 agonists and synthesized some GPR119 agonists having high potency. This series of agonists has a bicyclic amine structure, and the basic nitrogen atom of the amine played an important role in the production of the agonist activity. We also found that a carbonyl group on the bicyclic core ring was a better pharmacophore than a sulfonyl group. Above all, high potency of the indanone derivatives was observed; the in vivo effect of compound **2** in mice was characterized. The evolution of this series of compounds will be reported as results become available.

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11. Cell-based cAMP functional assay: Cellular cAMP was measured using HTRF cAMP HiRange reagent (CISBIO, Cedex, France). CHO-K1 cells expressing *h*GPR119 receptors were obtained from Applied Cell Sciences and were grown in flasks containing F-12 medium supplemented with 10% FBS, 1% non essential amino acids (NEAA), 20 mM HEPES, 50 units/ml penicillin, 50 μl/ml streptomycin, and 400 μg/ml geneticin. CHO-K1 cells expressing *m*GPR119 receptors were prepared in house and were grown in flasks containing F-12 medium supplemented with 10% FBS, 1% non essential amino acids (NEAA), 20 mM HEPES, 50 units/ml penicillin, 50 μl/ml streptomycin, and 400 μg/ml geneticin. For the *h*GPR119 or *m*GPR119 functional assay, cells expressing *h*GPR119 or *m*GPR119 were harvested, resuspended in incubation buffer (F-12 medium, 20 mM HEPES, 1 mM IBMX), and dispensed into 384-well plates at a density of 1.5×10^4 cells/well in the presence or absence of test compounds. Cells were incubated at 37 °C for 30 min, and the cAMP-d2-conjugated antibody and the anti-cAMP-cryptase-conjugated antibody were added to the plate. After incubation for 60 min at room temperature, measurements were made using a HTRF® (TR-FRET) Microplate Reader ARTEMIS (Furuno Electric Co., Ltd, Tokyo, Japan). Data analysis was performed based on the ratio of fluorescence intensity of each well at 620 and 665 nm. The sigmoidal dose–response equation was used to determine EC_{50} and E_{max} values. These values represent the relative efficacy that was defined as the ratio of the response of test compound to the maximum response of AR231453 (7.4 nM for $h EC_{50}$ and 20 nM for $m EC_{50}$).
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17. oGTT and scGTT: Male 8-week-old C57BL/6J (Charles River Japan) were fasted overnight and then received orally administrated vehicle (20% HPβCD) or compound **2** at 3 or 10 mg/kg ($n = 8$). After 30 min, glucose was given orally or subcutaneously at 2 g/kg, and blood samples were collected from tail veins at 0, 20, 40, 60 and 120 min. Blood glucose level was measured using Glutest Pro R (Sanwa Kagaku Kenkyusyo).
18. GLP-1 secretion: Male 10-week-old C57BL/6J were fasted for 5 h and received orally administered vehicle (5% DMSO, 0.1% Tween 80 and 0.5% methylcellulose) or compound **2** at 30 mg/kg ($n = 10$). Plasma total GLP-1 (both intact GLP-1 (7–36) amide and its primary metabolite) levels at 30 min after the administration were measured by ELISA using anti-GLP-1 monoclonal antibodies.
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