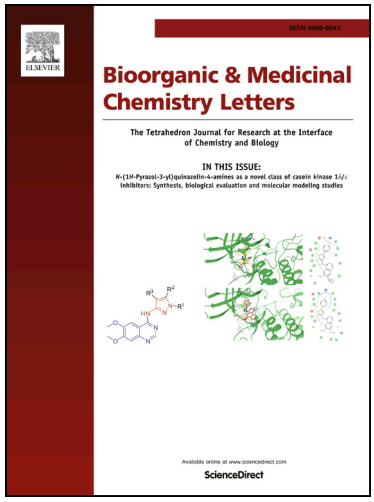

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Design, synthesis, and biological evaluation of aryl N-methoxyamide derivatives as GPR119 agonists

Yoon Kyung Jang[a,†], Kyu Myung Lee[a,†], Kwan-Young Jung[a], Seung Kyu Kang[a], Suvarna H. Pagire[a], Jun Mi Lee[a], Haushabhau S. Pagire[a], Kwang Rok Kim[a], Myung Ae Bae[a], Hohjai Lee[b,*], Sang Dal Rhee[a], Jin Hee Ahn[a,b,*]

[a]*Drug Discovery Division, Korea research Institute of Chemical Technology, Daejeon, 305-600, Republic of Korea*
[b]*Department of Chemistry, Gwangju Institute of Science and Technology, Gwangju 61005, Republic of Korea*

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ABSTRACT

A series of N-methoxyamide derivatives was identified and evaluated as GPR119 agonists. Several N-methoxyamides with thienopyrimidine and pyridine scaffolds showed potent GPR119 agonistic activities. Among them, compound **9c** displayed good in vitro activity and potency. Moreover, compound **9c** lowered glucose excursion in mice in an oral glucose tolerance test and increased GLP-1 secretion in intestinal cells.

The prevalence of type 2 diabetes mellitus (T2DM; non-insulin dependent diabetes) is increasing worldwide in all age groups. In order to deal with this situation several T2DM drugs have been developed in past few decades, which are included but not limited to, biguanides, sulfonylureas, thiazolidinediones, meglitinides, glucagon-like peptide 1 (GLP-1) analogs, DPP-4 inhibitors, and SGLT-2 inhibitors.[1-5] One of current focuses on diabetes drug discovery is to identify new agents that protect and preserve pancreatic β-cells.[6] G protein-coupled receptor 119 (GPR119) is activated by endogenous ligand, which in turn, induces glucose-stimulated insulin secretion (GSIS) in pancreatic beta cells and GLP-1 in intestine.[7] GLP-1 has β-cell protection and preservation potential through accumulating intracellular c AMP and enhancing adenylate cyclase activation. Moreover, it also has the ability to improve glucose homeostasis while concurrently slowing gastric emptying by reducing the food intake and promoting weight loss.[8-10] All of these characteristics make GPR119 a promising target for the treatment of T2DM.

According to recent studies, many GPR119 agonists have been reported,[7] and few GPR119 agonists have been entered into clinical trials but none have been approved up to date. In our recent work, we have also identified a series of thienopyrimidine derivatives.[10] Most GPR119 agonists display structural similarities, featuring a polar moiety (head group) such as methylsulfonyl or tetrazole groups[10-17] (Fig. 1).

Figure 1. Structures of GPR119 agonists: our previous compound (I) and clinical agonists with disclosed structure (II) GSK1292263, (III) APD668, (IV) APD597, (V) BMS-903452, and (VI) MBX-2982

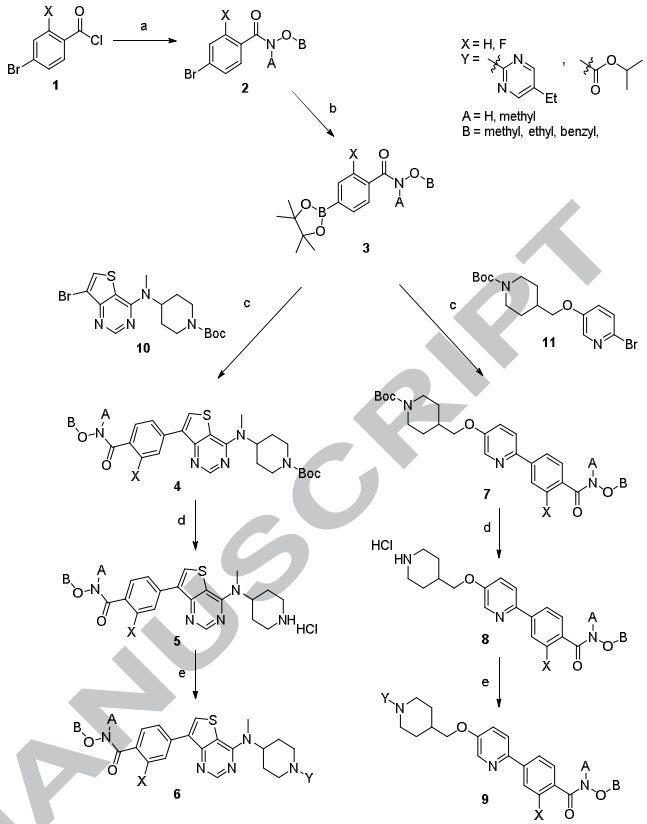
With the goal of identifying a novel chemotype, we replaced the polar head (methylsulfonyl or tetrazole) with diverse functional groups and identified N-alkoxyamide moiety as a methylsulfonyl or tetrazole surrogate. Thus, we report the synthesis and biological evaluation of new N-alkoxyamide GPR119 agonists.

The general synthetic procedure is outlined in Scheme 1. Commercially available 4-bromobenzoyl chloride **1** was coupled with *N*,*O*-dimethylhydroxylamine to yield **2**, which was borylated by cross-coupling with bis(pinacolato)diboron to pinacol ester **3**. Borylated compound **3** was coupled with thienopyrimidine **10** or pyridine derivative **11** to obtain products **4** and **7**. Boc groups of compounds **4** and **7** were deprotected by 4 M HCl to yield **5** and **8**, which were further substituted with 5-ethylpyrimidyl or isopropyl carboxylate moieties to obtain **6** and **9**.

The synthesized N-methoxyamide derivatives were evaluated for in vitro as GPR119 agonists (Tables 1-3) whereas GSK1292263 (II in Fig. 1) was used as the reference standard.

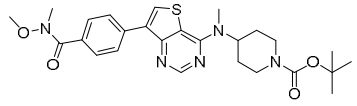
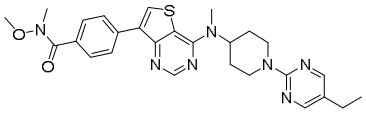
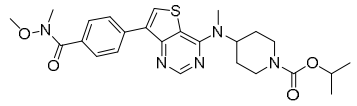
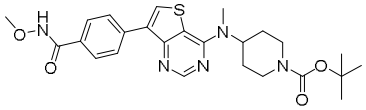
To identify novel sulfone or tetrazole surrogates, diverse functional groups including amide, N-sulfonyl amide, hydrazide, N-methoxy-N-methylamide, N-methoxyamide, N-ethoxyamide, N-benzyloxyamide, and 1,2-oxazinane were introduced on thienopyrimidine and pyridine backbones.

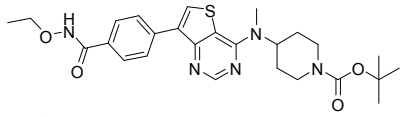
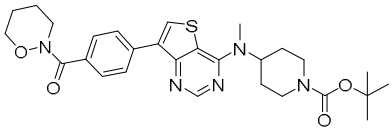
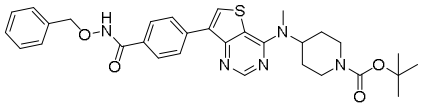
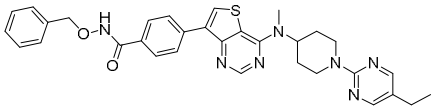
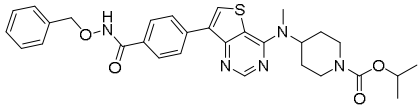
Thienopyrimidine (**10**) and pyridine (**11**) moieties are known linker groups in structures of GPR119 agonists.[10,11] Introduction of N-methoxy-N-methylamide as the polar head resulted in compound **4a**, showing potency (% activation relative to GSK1292263 (100%) at 1 μM) comparable to the reference compound (105 % activation at 1 μM) and good agonistic activity (EC_{50} 98 nM) (Table 1). In addition, compound **6b** showed moderate potency and good agonistic activity (EC_{50} 156 nM). These results indicated that N-methoxyamide could be a suitable methylsulfonyl/tetrazole surrogate. Next, N-methoxy-N-methylamide group was replaced with N-methoxyamide (**4b**), N-ethoxyamide (**4c**), N-benzyloxy amide (**4e** and **6c-d**) and 1,2-oxazinane (**4d**); however, these various derivatives showed reduced potency compared to compound **4a**.



Scheme 1. Reagents and conditions: (a) TEA, hydroxylamine, CH_2Cl_2 (>90%); (b) Bis(pinacolato)diboron, $PdCl_2$ (dppf) complex with CH_2Cl_2, potassium acetate, 1,4-dioxane, 80 °C (>90%); (c) $PdCl_2$ (dppf) complex with CH_2Cl_2, 3M Na_2CO_3, toluene, ethanol, reflux (68%); (d) 4M HCl in 1,4-dioxane; (e) 1) pyrimidine, 2-chloro-5-ethylpyrimidine, K_2CO_3, acetonitrile, 90 °C (>70%); 2) carbamate, isopropyl chloroformate, K_2CO_3, CH_2Cl_2, 45 °C (>70%).

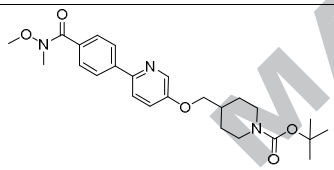
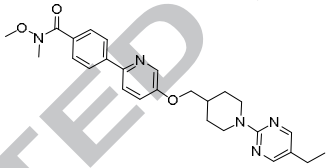
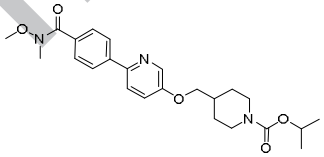
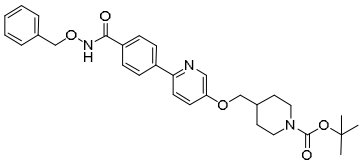
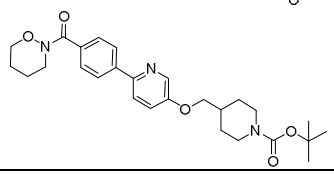
Table 1. GPR119 agonist activity of aryl N-alkoxyamide derivatives with thienopyrimidine scaffolds

Compound	Structure	% Activation at 1 μM[a]	Human GPR119 EC_{50} (nM)
4a KRI-62008		105	98
6a		80	ND[b]
6b		82	156
4b		82	ND[b]

4c		73	ND[b]
4d		66	ND[b]
4e		81	83
6c		41	ND[b]
6d		53	ND[b]

[a] Activation relative to GSK1292263.
[b] Not determined.

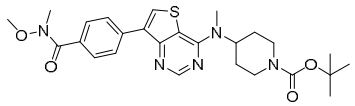
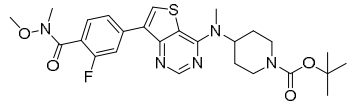
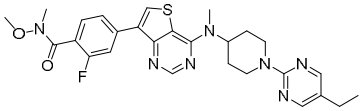
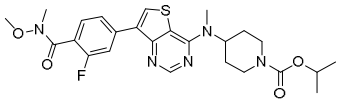
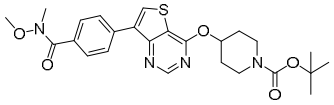
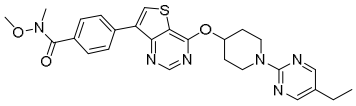
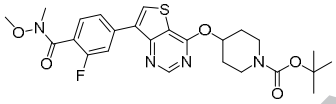
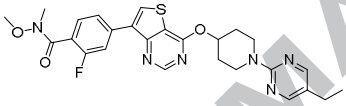
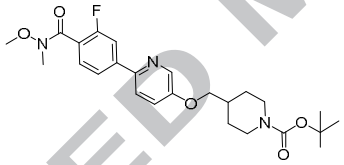
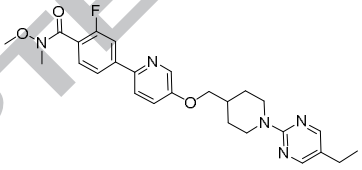
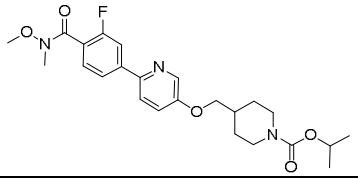
Table 2. GPR119 agonist activity of aryl N-alkoxyamide derivatives with pyridine scaffolds

Compound	Structure	% Activation at 1 μM[a]	Human GPR119 EC_{50} (nM)
7a		106	171
9a		95	319
9b		80	155
7b		69	ND[b]
7c		73	321

[a] Activation relative to GSK1292263.
[b] Not determined.

Table 3. GPR119 agonist activity of aryl N-alkoxyamide derivatives with thienopyrimidine and pyridine scaffolds

Compound	Structure	% Activation at 1 μM[a]	Human GPR119 EC_{50} (nM)

4a		105	98
4f		87	53
6e		81	ND[b]
6f		90	67
4g		100	64
6g		82	199
4h		88	57
6h		100	105
7d		114	73
9c		100	77
9d		96	92

[a] Activation relative to GSK1292263.
[b] Not determined.

Based on data shown in Table 1, thienopyrimidine scaffold was replaced with pyridine (**11**), and the activity data summarized in **Table 2**. As shown in Table 2, most of the pyridine compounds showed similar potency and activity to thienopyrimidine analogs. Compounds **7a**, **9a**, and **9b** showed good to moderate potency and moderate agonistic activity (EC_{50} 150-350 nM). Meanwhile, compounds **7b** and **7c** substituted with benzyloxyamide and 1,2-oxazinane showed reduced potency, similar to their thienopyrimidine analogs.

We considered that N-methoxy-N-methylamide was the most appropriate functional group from the activity data as shown in Table 1, 2. Therefore, herein supposed to need to modify other parts by fixing N-methoxy-N-methylamide part. As shown in Table 3, 2-fluoro aryl substituents increased the agonistic activity of thienopyrimidine compounds. Compounds **4f**, and **6f** showed good in vitro activities with an EC_{50} of 53 and 67 nM, compared to **4a**, and **6b**. Compounds **4g**, **4h**, **6g**, and **6h** in which methylamino group of the thienopyrimidine scaffold was replaced with oxygen showed moderately improved potency and agonistic activity compared to methylamine analogs **4a**, **6a**, **4f**, and **6e**. Additionally, pyridine compounds **7d**, **9c**, and **9d** showed potential for further evaluation with significantly improved

agonistic activity (up to 5-fold) and potency relative to compounds **7a**, **9a**, and **9b** which lack of fluorine.

From in vitro data, we chose four representative compounds (**6f**, **6h**, **9c** and **9d**) and performed in vivo oral glucose tolerance tests (OGTT) (data not shown). Among them, compound **9c** showed good glucose lowering efficacy, therefore it was selected as a prototype compound. As shown in Fig 2, compound **9c** significantly reduced plasma glucose levels (determined using AUC) in OGTT at doses of 30 and 50 mg/kg.

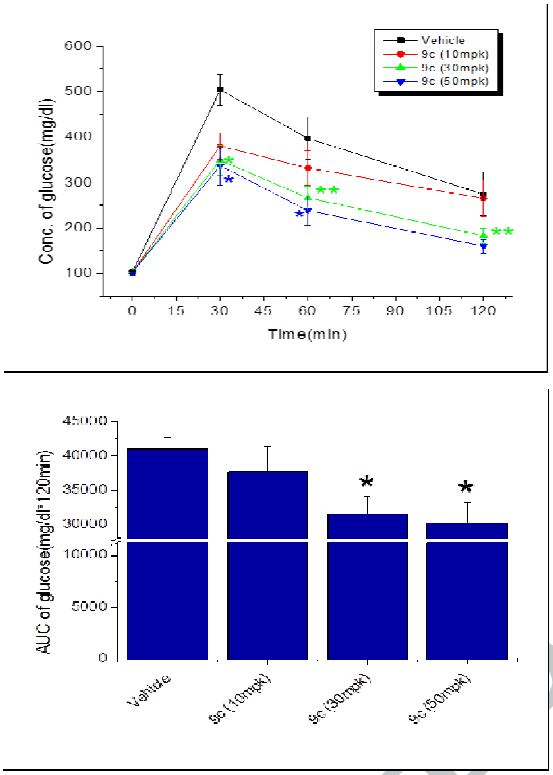


Figure 2. In vivo oral glucose tolerance tests of compound **9c** in normal mice. Data are expressed as means ± SEM for n = 7 mice/group. *P < 0.05, **P < 0.01

Differentiated NCI-H716 cells, which express high levels of GLP-1 represent a useful cellular model for regulation of GLP-1 secretion in humans.[19] Compound **9c** (at 100 nM) significantly stimulated GLP-1 secretion in NCI-H716 cells.

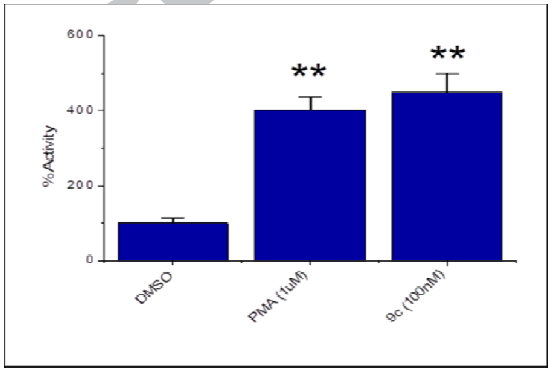


Figure 3. Effects of compound **9c** on GLP-1 release in NCI-H716 cells. **P < 0.01

In conclusion, we identified N-methoxy-N-methylamide as a novel methanesulfonyl/tetrazole surrogate in structures of GPR119 agonists. Several compounds showed good agonistic activity (EC_{50} < 100 nM) and potency. Among them, compound **9c** showed good in vitro activity, in vivo efficacy (OGTT) as well as GLP-1 secretion in intestinal cells.

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† These authors contributed equally to this work.

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Supplementary Material

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