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Synthesis and biological evaluation of thienopyrimidine derivatives as GPR119 agonists

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ABSTRACT

A series of thienopyrimidine derivatives was synthesized and evaluated for their GPR119 agonistic ability. Several thienopyrimidine derivatives containing R^1 and R^2 substituents displayed potent GPR119 agonistic activity. Among them, compound **5d**, which is a prototype, showed good in vitro activity with an EC_{50} value of 3 nM and human and rat liver microsomal stability. Compound **5d** exhibited no CYP inhibition and induction, Herg binding, or mutagenic potential. Compound **5d** showed increase insulin secretion in beta TC-6 cell and lowered the glucose excursion in mice in an oral glucose-tolerance test.

Diabetes is a serious metabolic disorder that occurs when the pancreas does not produce enough insulin, or the body cannot effectively use existing insulin.[1] Hyperglycemia (high blood glucose) can lead to various health consequences such as kidney damage, heart disease, stroke, nerve damage and blindness. Type 2 diabetes mellitus (T2DM, or noninsulin dependent), is the most common form of diabetes caused by insulin resistance, and loss of pancreatic β-cell function and approximately 95% diabetic patients are suffering from type 2 diabetes. This health burden is growing at an alarming rate, and it is estimated that there are approximately 350 million diabetic people globally. The prevalence of the disease is expected to escalate to 439 million by 2030.[2–4] Although, a variety of treatments are available for T2DM, many patients are unable to achieve their target HbA1c level.[5] Considerable attention has been focused on overcoming this public health challenge worldwide. Hence, there is a strong need for novel approaches to achieve better glycemic control and normoglycemia. Strategies that promote significant glycemic control by limiting hypoglycemia and cardiovascular side effects by enhancing insulin secretion in a glucose dependent manner could offer robust treatment for T2DM.

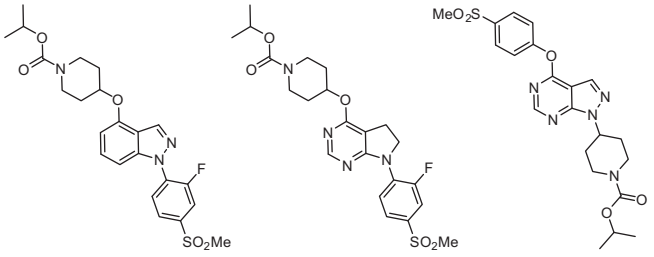

Figure 1. Representative bicyclic GPR119 agonists.

GPR119 is a member of the class A G protein-coupled receptor (GPCR) family, and it is highly expressed in pancreatic β-cells and intestinal endocrine cells.[6–8] Upon activation by its endogenous ligand, intracellular cAMP accumulates and adenylate cyclase activation enhances the effect of glucose-stimulated insulin secretion (GSIS) and GLP-1 release. Thus GPR119 represents a promising target for the treatment of type 2 diabetes and obesity owing to its ability to improve glucose homoeostasis while concurrently slowing gastric emptying, reducing food intake and promoting weight loss.[9,10]

Endogenous ligands for GPR-119 have been identified including lysophosphatidylcholine (LPC) and oleoylethanolamide (OEA).[9–11] Moreover, numerous small molecule GPR119 agonists have been

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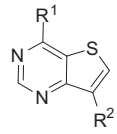
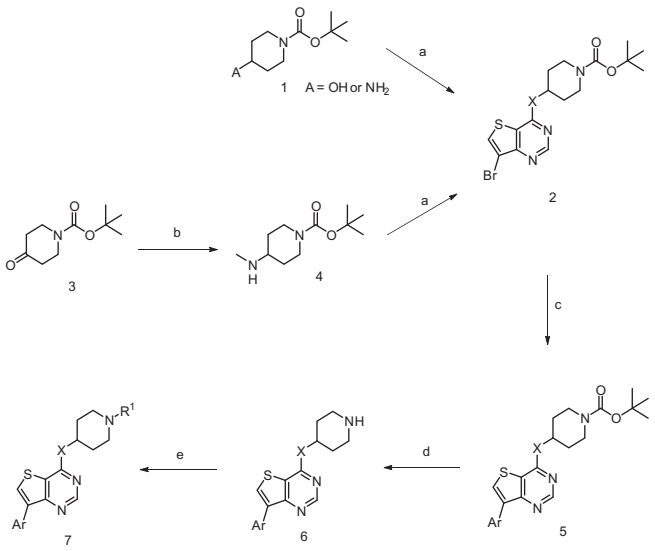


Figure 2. Structure of thienopyrimidine scaffold.



Scheme 1. Reagents and conditions: (a) 6-Bromo-4-chlorothieno[3,2-*d*]pyrimidine, A = OH, NaH, THF room temperature, 12 h; A = NH_2, DMSO, room temperature, 12 h; (b) 40% methylamine in methanol, $NaBH(OAc)_3$, 1,2-dichloroethane, room temperature, 12 h; (c) $Pd(PPh_3)_4$, Na_2CO_3, arylboronic acid, 1,4-dioxane, 110 °C, 24 h; (d) 4 M HCl in dioxane, room temperature, 2 h; (e) carbamate, alkylchloroformate, triethylamine, CH_2Cl_2, room temperature, 1 h; amide: acylhalide, triethylamine, CH_2Cl_2, DMF, room temperature, 12 h; pyrimidine; 2-chloro-5-ethylpyrimidine, triethylamine, DMF, 130 °C, 3 h.

identified in recent years. Among them, structurally rigid bicyclic compounds were identified as promising scaffolds. These bicyclic analogues exhibited potent GPR119 agonistic activity, efficacy and PK profiles (Fig. 1).[12–16]

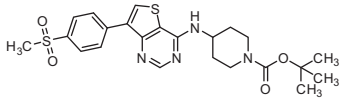
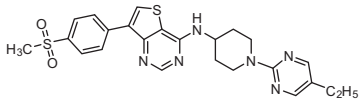
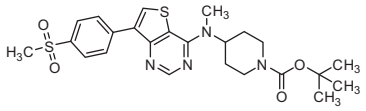
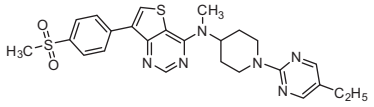
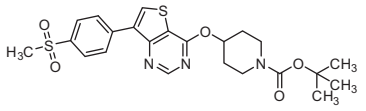
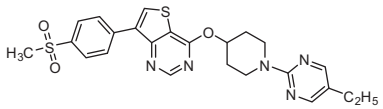
This prompted us to look for an alternate bicyclic scaffold, as a result, we identified the thienopyrimidine scaffold.[17] In this present work we wish to report the synthesis and biological evaluation of thienopyrimidine derivatives as GPR119 agonists (Fig. 2).

The general method for compound synthesis is outlined in Scheme 1. As shown in Scheme 1, commercially available Boc protected piperidine derivative **1** was coupled with 6-bromo-4-chlorothieno[3,2-*d*]pyrimidine to yield coupled product **2**, which was treated with diverse aryl boronic acids by Suzuki coupling in the presence of palladium catalyst afforded compound **5** with good yield. Meanwhile, Boc-protected piperidinone **3** was converted to 4-methylaminopiperidine derivative **4** via reductive amination, and it was then coupled with 6-bromo-4-chlorothieno[3,2-*d*]pyrimidine, followed by Suzuki reaction to yield compound **5**. Deprotection of compound **5** with 4 M HCl afforded compound **6**, which was derivatized by diverse electrophiles to give the final thienopyrimide derivative **7**.

Thus synthesized thienopyrimidine derivatives were evaluated in vitro for GPR119 agonistic activity, and the results are summarized in Tables 1–3. First, we fixed the 4-methylsulfonylphenyl substituent at the R^2 position on the thienopyrimidine ring, and derivatized at the R^1 position. As shown in Table 1, **5a** and **7a** showed weak agonistic activities; however, the introduction of a Boc-protected *N*-methylpiperidine to thienopyrimidine **5b** exhibited good in vitro activity with an EC_{50} value of 39 nM. Also, pyrimidine substituted *N*-methylpiperidine derivative **7b** displayed moderate potency (EC_{50} = 1200 nM). 4-Oxypiperidine derivatives **5c** and **7c** also activated GPR119 with EC_{50} values of 100 nM and 240 nM, respectively.

Based on the data shown in Table 1, we further derivatized the R^1 position with an *N*-methylaminopiperidine group. As shown in

Table 1
In vitro GPR119 agonist activity of thienopyrimidine derivatives

Compound	Structure	% Activation at 1 μM[a]	Human EC_{50} (nM)
5a		49	ND[b]
7a		49	ND
5b		76	39
7b		67	1200
5c		64	100
7c		75	240

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