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2,5-Disubstituted pyridines as potent GPR119 agonists

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ABSTRACT

A series of 2-piperazinyl-5-alkoxypyridines were synthesized and screened against human GPR119 receptor. Through SAR analysis, compounds containing 2-alkylsulfonylpiperazinyl-5-alkoxypyridines were discovered and found to be potent agonists of the human GPR119 receptor.

GPR119 is a Family A, G protein-coupled receptor ($G\alpha_s$) predominantly expressed in pancreatic islets and gastrointestinal (GI) tract.[1–5] The tissue distribution suggests that GPR119 could be involved in the control of incretin and islet hormone release, and the regulation of glucose control. In fact, endogenous peptides and small molecule GPR119 agonists have both been shown to elicit insulinotropic effects in vitro.[5–7] It has also been reported that small molecule GPR119 agonists can promote incretin secretion contributing to lowering plasma glucose levels during an oral glucose tolerance test.[5–7] Furthermore, there is evidence to support the role of GPR119 agonists in slowing gastric emptying, reducing food intake and promoting weight loss, possibly through the actions of GLP-1 release, although it has been reported that not all GPR119 agonists demonstrate these effects.[5–7]

While the details of the mechanism of action of this receptor are not yet fully understood, GPR119 is nonetheless emerging as an attractive target for the treatment of diabetes. Likely reflecting the broad interest in modulating GPR119 receptor signaling for a therapeutic benefit, many synthetic GPR119 agonists have been reported in the past several years.[8–10] Two of the earlier GPR119 agonists with significant, published preclinical data are AR231453 (**1**) from Arena Pharmaceuticals and PSN632408 (**2**) from Prosidion Ltd. The field of GPR119 agonist research has progressed far enough for some companies to push compounds into the clinic. For example, Arena and partner Ortho-McNeil initiated the earliest FTIH studies with APD668 and have recently progressed APD597 into phase I clinical trials.[11] Prosidion and Metabolex have also announced clinical trials with GPR119 agonists with PSN821 and MBX-2982, respectively.[12,13] With early, positive reports on its clinical utility, the long-term efficacy and safety of this new class of therapeutic agents for the treatment of T2D will eventually dictate the future for GPR119 agonists.

We identified a series of dihydropyrrolopyrimidines (DHPP)[14] and biaryl compounds[15] as GPR119 agonists. Parallel to our efforts on the biaryl series, we began to explore 2-piperazinyl-5-alkoxypyridines, represented by generic structure **3**, with the hope of identifying a template with superior solubility, thus improving the overall pharmacokinetic properties over existing series. Coincidentally, a patent application from IRM LLC that claimed a series of GPR119 receptor agonists with similar or identical structures with our compounds was recently published.[16] Herein we report the synthesis and structure–activity relationships (SAR) of this novel series of compounds.

The synthesis of this series of compounds started from Boc-protected piperidinylalkyl alcohol **4** (Scheme 1). Mesylation of **4** with methanesulfonyl chloride in the presence of triethylamine provided intermediate **5**. Displacement of the mesylate with commercially available 2-bromo-5-hydroxypyridine (**6**) in the presence of a base provided key intermediate **7**. This two-step sequence was preferred over a one-step Mitsunobu reaction (DIAD, PPh_3, THF) due to purification issues.

In order to functionalize the 2-position of the pyridine ring of intermediate **7**, a set of substituted piperazines was required.

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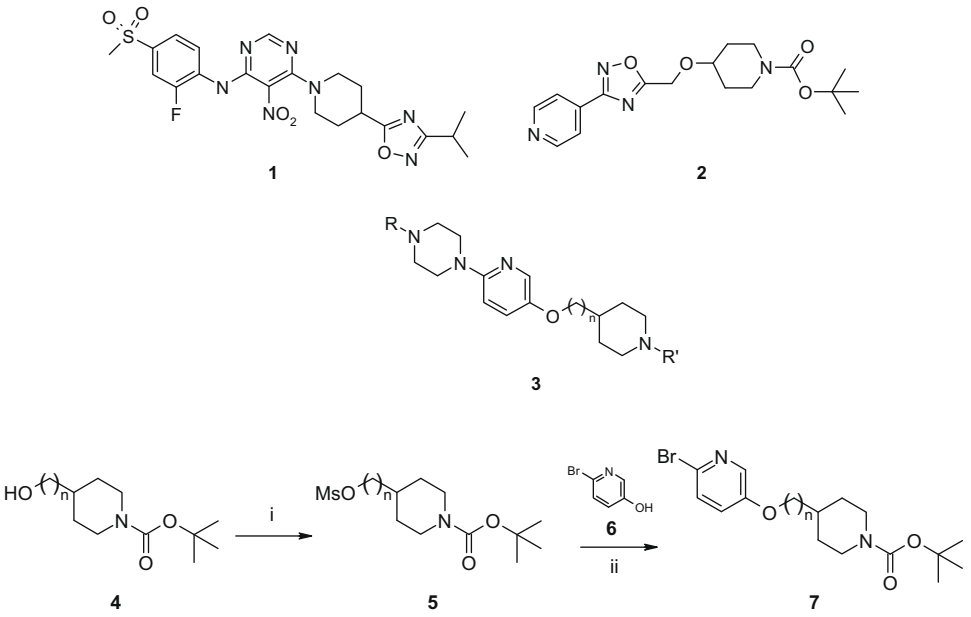
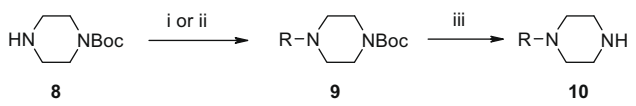


Scheme 1. Synthesis of intermediate **7** (n = 0–2). Reagents: (i) MsCl, Et_3N, DCM; (ii) **6**, K_2CO_3, DMF.



Scheme 2. General synthetic process for substituted piperazine **10**. Reagents: (i) alkyl halides, K_2CO_3, DMF; (ii) acyl or sulfonyl chloride, Et_3N, DCM; (iii) 4 M HCl in 1,4-dioxane or TFA, DCM.

These substituted piperazines were generally synthesized in a two-step process (Scheme 2). The first step involved reacting *N*-Boc-protected piperazine **8** with commercially available alkyl halides and acyl or sulfonyl chlorides under basic conditions to afford intermediate **9**. Acid treatment of compound **9** with either hydrogen chloride or TFA, followed by washing with sodium bicarbonate solution, provided substituted piperazine **10**.

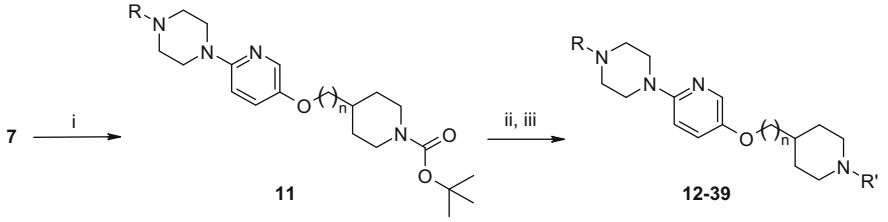
Preparation of the final compounds was accomplished by palladium catalyzed amination of pyridine **7** with mono-substituted piperazine **10** to provide analog **11**. Removal of the Boc group in **11** with acids (Scheme 3), followed by further derivatization of the piperidine with acyl chloride provided the desired final compounds **12–39**.

A variety of functional groups were introduced on the piperazine. However, only alkylsulfonamide derivatives consistently gave good potency (Table 1). Other functional groups, such as urea **12**, amide **13** and acetamide **14**, all showed poor GPR119 agonism with EC_{50} >10 μM. Compared to acetamide **14**, 2-furanylamide **15** showed improvement in potency. Arylsulfonamide derivatives **24–25** as well as *N*-alkylsulfamides **26–27** also showed lower potency compared to alkylsulfonamides. The data in Table 1 indicated the trend of descending potency was in the order of: cyclohexylmethyl (**23**) > *n*-butyl (**20**) > cyclohexyl (**22**) > *n*-propyl (**19**) ≈ *iso*-propyl (**18**) > ethyl (**17**). Generally speaking, non-polar alkylsulfonamide end groups conferred better GPR119 agonism.

One of the relatively potent compounds in Table 1 is carbamate **19**. Efforts to find the optimal fragments on the substituted piperidine were focused on the replacement of the carbamate with amides and ureas. However, switching from isopropyl carbamate (Table 2) to isopropyl urea **28** lowered potency by about threefold (from EC_{50} = 0.3 μM to 1.0 μM). The *iso*-butyl amide compound **29** also showed lower potency compared to compound **19**. Attempts to improve potency of the urea derivatives by introducing bulkier functional groups gave mixed results. In the case of compounds **30** and **36**, the potency was increased to sub-micromolar range, while compounds **32** and **35** significantly lost potency with EC_{50} >10 μM. Data in Table 2 also clearly showed amide derivatives, such as **29**, **31** and **33–34**, were weaker GPR119 receptor agonists.

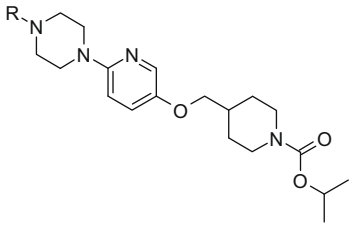
In order to determine the optimal distance between the pyridine ring and piperidine ring, the linker length was adjusted by changing the number of methylene units (n = 0–2). As shown in the table (Table 3), the linker length only had a modest effect on GPR119 activity. Compound **37** (n = 0), where the oxygen was directly connected to the piperidine ring, had the lowest potency. However, compounds with linker lengths of 1 and 2 methylenes showed comparable potency.

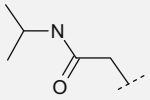
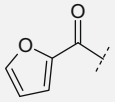
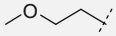
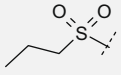
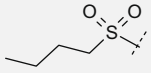
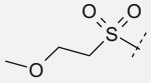
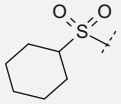
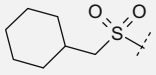
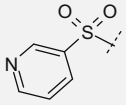
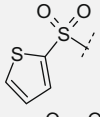
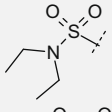
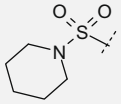
The pharmacokinetic profile of compound **19** was evaluated in mouse (Table 4). The data showed compound **19** had low to medium plasma clearance (CL = 15.7 mL/min/kg), short plasma half-life



Scheme 3. General procedure for the synthesis of the 2,5-disubstituted pyridines **12**–**39**. Reagents: (i) **10**, Pd(*t*-$Bu_3P)_2$, *t*-BuONa, toluene; (ii) 4 M HCl in 1,4-dioxane or TFA, DCM; (iii) R′COCl, Et_3N, DCM.

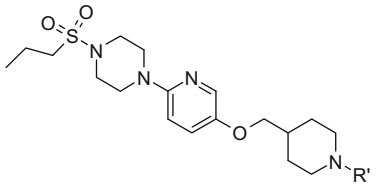
Table 1
In vitro human GPR119 agonism[a] data for analogs with different R groups

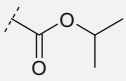
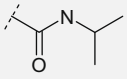
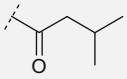
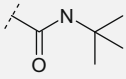
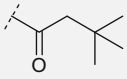
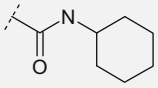
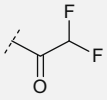
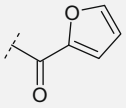
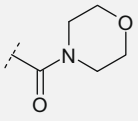
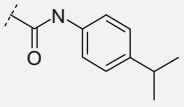


Compd	R	Human EC_{50} (μM)	M.R. (%)[b]
12		>10	23
13		>10	11
14		>10	<10
15		1.9	112
16		2.6	28
17		1.3	167
18		0.3	171
19		0.3	153
20		0.1	164
21		0.3	178
22		0.2	165
23		0.09	136
24		2.0	100
25		1.8	69
26		1.2	125
27		1.0	118

[a] CHO:CRE reporter assay, see Ref. 17.
[b] Percent of GPR119 receptor maximum response, see Ref. 18.

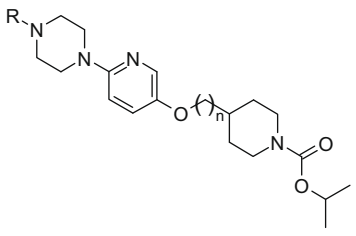
Table 2
In vitro human GPR119 agonism[a] data for analogs with different R′ groups



Compd	R′	Human EC_{50} (μM)	M.R. [b] (%)
19		0.3	153
28		1.0	45
29		1.6	186
30		0.8	75
31		2.8	175
32		>10	16
33		2.1	97
34		2.0	112
35		>10	41
36		0.9	67

[a] CHO:CRE reporter assay, see Ref. 17.
[b] Percent of GPR119 receptor maximum response, see Ref. 18.

Table 3
In vitro human GPR119 agonism[a] data for analogs with different linker lengths



Compd	R	*n*	Human EC_{50}(μM)	M.R. [b] (%)
37	$EtSO_2$	0	2.1	93
17	$EtSO_2$	1	1.3	167
38	$EtSO_2$	2	1.2	69
19	*n*-$PrSO_2$	1	0.3	153
39	*n*-$PrSO_2$	2	0.7	95

[a] CHO:CRE reporter assay, see Ref. 17.
[b] Percent of GPR119 receptor maximum response, see Ref. 18.

Table 4
In vivo DMPK properties in mouse for compound **19**

Compd	Route	Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC_{0-24} (ng h/mL)	CL (ng/min/kg)	VD_{SS} (L/kg)
19	IV	3	3077	0.75	0.62	3132	15.7	0.76
	PO	30	2996	0.25	0.40	2352		

($T_{1/2}$ = 0.40 h) and high artificial membrane permeability (470 nm/s). The measured fasted simulated intestinal fluid (FaSSIF at pH 6.5) solubility of compound **19** (3.41 μg/mL) was comparable to those of our corresponding biaryl compounds, which were also poorly soluble. The low to medium clearance combined with high permeability suggests low solubility be the culprit for low systemic exposure (AUC_{0-24} = 2353 ng h/mL) and bioavailability ($F \sim 8\%$) for this compound.

In summary, we have synthesized a series of piperazinylpyridine derivatives as GPR119 receptor agonists. Compounds with

alkylsulfonamide and isopropylcarbamate end groups showed potent GPR119 receptor activity. However, the pharmacokinetic profiles of compounds screened in this series, exemplified by compound **19**, were not optimal. Compound **19** possessed relatively low exposure (AUC_{0-24}) and a short half-life. Further efforts are being focused on designing compounds with better pharmacokinetic profiles as GPR119 agonists for the treatment of type 2 diabetes.

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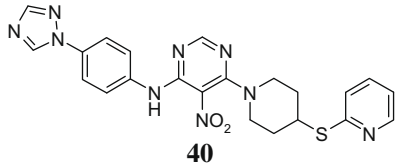
17. The assay consists of CHO-K1 6CRE-luciferase cells that stably express human GPR119 receptor plated at 15,000 cells/well in Dulbecco's Modified Eagle Medium: Nutrient Mixture F12 (DMEM/F12), 5% fetal bovine serum (FBS), 2 mM L-glutamine in black 384-well assay plates. On the following day, the media is removed by aspiration and replaced with 20 μL of DMEM/F12, 2 mM L-glutamine (no FBS) utilizing a Matrix Multidrop. Test compounds (20 μL) are then pipetted into the assay plate using a Packard Minitrak. The plates are then incubated for 5 h at 37 °C. Under subdued light conditions, 15 μL of a 1:1 solution containing SteadyLite™ and Dulbecco's Phosphate Buffered Saline with 1 mM $CaCl_2$ and 1 mM $MgCl_2$ is added to the plates using a Matrix Multidrop. Plates are then sealed with self-adhesive clear plate seals and the amount of luciferase generated is quantified in a Wallac Viewlux™. Compounds are also tested in the same manner against cells without the GPR119 receptor so as to check for false positives.
18. All compounds are referenced to a small molecule GPR119 agonist for evaluation of intrinsic efficacy (%max response) since this reporter assay is not sensitive enough to demonstrate robust activity of putative endogenous ligands (OEA, LPC, etc.). Our experience with the ~3000 compounds made for the program is that compounds with ~80–200%max response are likely full agonists. Compounds with consistent levels of receptor activation below 80% may be partial agonists. The degree of variability in the assay accounts for the large range considered as full agonists. The structure of our standard compound **40**, with an EC_{50} = 0.2 μM (max response = 100%), is shown below. This compound is reported[19] to have an EC_{50} = 0.13 μM in a cAMP assay.



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