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Discovery and optimization of arylsulfonyl 3-(pyridin-2-yloxy) anilines as novel GPR119 agonists

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ABSTRACT

We describe the discovery of a series of arylsulfonyl 3-(pyridin-2-yloxy)anilines as GPR119 agonists derived from compound **1**. Replacement of the three methyl groups in **1** with metabolically stable moieties led to the identification of compound **34**, a potent and efficacious GPR119 agonist with improved pharmacokinetic (PK) properties.

Type 2 diabetes mellitus is a critical health care issue that affects more than 25 million people in the U.S. and 280 million worldwide.[1] Although many treatment options are available, especially during the early stages of the disease, many patients are still unable to achieve their target plasma glucose level. In addition, hypoglycemia remains a serious potential side effect of several anti-diabetic agents including insulin and the sulfonylureas, drugs which increase insulin secretion independent of the prevailing plasma glucose concentration. New oral agents that increase endogenous insulin secretion in a glucose-dependent manner have the potential to deliver robust efficacy with much lower risk of hypoglycemia.

GPR119 is a G protein-coupled receptor predominantly expressed in pancreatic islet β-cells and incretin releasing cells in the gastrointestinal tract. Phospholipids and lipid amides, such as oleoylethanolamide (OEA), have been identified as endogenously-occurring GPR119 agonists[2,3] and several reports have described synthetic agonists.[4–6] Activation of GPR119 results in elevation of intracellular cAMP both in a pancreatic β-cell line and in transfected cells. Physiologically, activation of GPR119 increases glucose-dependent insulin secretion from the pancreas and incretin secretion from the gut. Several synthetic GPR119 agonists have been evaluated in clinical studies, but it is still too early to know whether activation of this pathway will result in meaningful antidiabetic efficacy in humans. In this letter, we describe a medicinal chemistry study of a high-throughput screen (HTS) hit, compound **1**, which led to the identification of the arylsulfonyl 3-(pyridin-2-yloxy)aniline compound **34** as a potent and efficacious GPR119 agonist with improved PK properties.

Compound **1** was identified as a GPR119 agonist in a HTS of our compound library collection using a cAMP assay. The EC_{50} of **1** was 310 nM, with a maximal response (max %) of 105% compared to the previously reported compound **2** (Fig. 1).[7] Compound **1** had good selectivity against more than 19 related in-house targets. However, the compound was rapidly metabolized in both human and mouse liver microsomes (turnover = 72% and 100%, respectively, after 30 min incubation at 37 °C). Metabolite identification studies indicated that various oxidations occurred at the three methyl groups and also on the central electron-rich phenyl rings. We therefore aimed to improve the stability of the molecule by focusing on replacement of the methyl groups.

Our first step in the optimization was to determine the optimal substitution pattern for the middle aryl ring. The analogues with the *ortho*- (**3**) and *para*- (**4**) substitution pattern of the middle aryl ring (Fig. 2) exhibited no activity in the GPR119 cAMP assay. The results indicated that the 1,3-substitution is critical for the agonist activity, and therefore, the subsequent optimization used the *meta*-isomer as the core of the molecules.

To further investigate the relationship between **1** and **2** and to leverage the knowledge from the resulting inactivity of **3** and **4**, a

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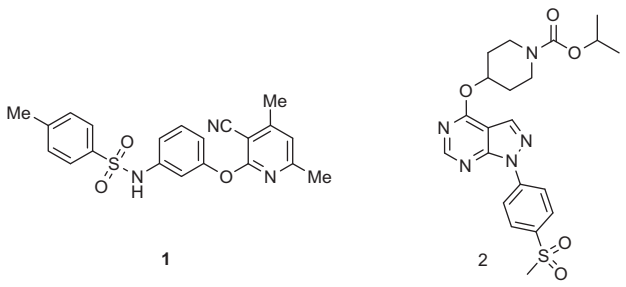


Figure 1. Structure of screening hit **1** and reference compound **2**.

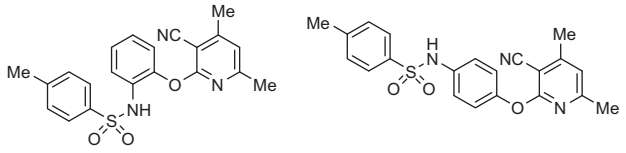


Figure 2. Structure of compounds **3** and **4**.

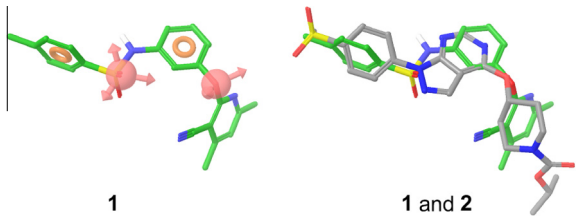
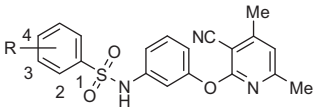


Figure 3. Modeling structure of compounds **1** and **2**.

pharmacophore model was generated for compound **1**.[8] The resulting model is shown on the left in Figure 3 and illustrates a low energy conformation with four features of interest, two acceptors and two aromatic rings. Illustrated to the right is the alignment of a low energy conformation of compound **2** to compound **1** based on the pharmacophore. The alignment shows overlap between the central aryl ring of **1** and the bicyclic core of **2** and also shows alignment between the phenyl rings on the left hand side of the molecules. There is also overlay with the ether acceptors from both compounds and the sulfonamide oxygen atoms of **1** with a nitrogen atom from the bicyclic core of **2**. However, with this alignment there is no significant overlap with the right hand side of the compounds. This was improved with subsequent optimization.

Table 1
SAR of the sulfonyl phenyl ring

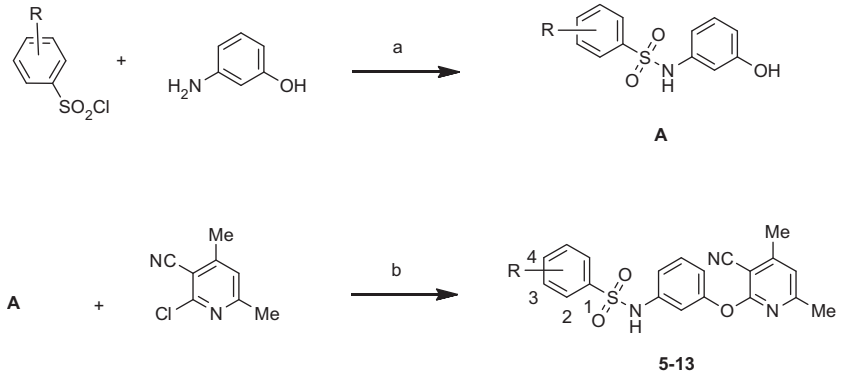


Compounds	R	h-GPR119cAMP EC_{50} (μM) / efficacy[a,b,c] (%)
1	4-Me	0.31/105
5	4-H	8.4/112
6	4-Et	0.66/85
7	4-^{i}Pr	0.81/26
8	**4-Cl**	**0.27/118**
9	4-F	0.38/105
10	4-CN	0.96/110
11	4-NO_2	1.60/91
12	4-OCF_3	0.38/46
13	4-OMe	0.44/111

[a] Values are means of two or more experiments.
[b] See Ref. 7 for assay protocol.
[c] Efficacy relative to compound **2**.

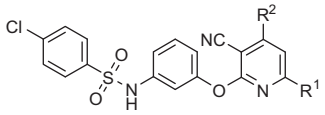
We then focused on the replacement of the methyl group on the sulfonyl phenyl ring. Thus, the *para*-position methyl group on this phenyl ring was systematically replaced with various alkyl, alkoxyl, halo and electron-withdrawing groups such as NO_2 and CN. The analogues were synthesized according to the chemistry as illustrated in Scheme 1. The *N*-(3-hydroxyphenyl)-benzene-sulfonamides, the intermediates **A**, were obtained by reaction of the corresponding substituted benzenesulfonyl chloride with 3-aminophenol in presence of pyridine. Subsequent treatment of 2-chloronicotinonitrile with intermediates **A** offered the corresponding products **5**–**13** in 35–70% yields. The assay results indicated that the *para*-substitution was the key pharmacophore required for the activity (Table 1). Removing the methyl group led to compound **5** (R = H), which displayed very weak potency. Increasing the size of the alkyl groups (R = 4-Et, 4-^{i}Pr) slightly decreased the potency. Chlorine (Cl) and small alkoxyl groups could be added while maintaining potency. Moving the methyl or Cl group from *para*- to other positions on the phenyl ring (*m*- and *o*-) did not improve the potency (data not shown). Overall, the modifications in this phenyl ring did not significantly improve the potency. However, the addition of Cl in compound **8** was tolerated and in subsequent experiments shown to marginally improve human liver microsome stability (HLM turnover = 66% vs 72% for **1**). Therefore further optimization was conducted using 4-chloro substituted phenyl group as left hand side.

Next we turned our attention to the metabolic stability issue of the two methyl groups on the pyridine by replacing them with



Scheme 1. Synthesis of compounds **5**–**13**. Reagents and conditions: (a) pyridine, rt, overnight, 25-80%; (b) DMF, 100 °C, overnight, 35-70%.

Table 2
SAR of the pyridine ring



Compounds	R^1	R^2	h-GPR119cAMP EC_{50} (μM) / efficacy[a,b,c] (%)
8	Me	Me	0.27/118
14	Me	H	1.71/125
15	CF_3	H	2.12/102
16	^{c}Pr	CF_3	2.06/103
17	**Me**	**CO_2Et**	**0.013/105**
18	^{c}Pr	CO_2Et	0.13/115
19	^{t}Bu	CO_2Et	4.0/101
20	Me	CO_2H	2.74/130
21	^{c}Pr	CON(H)^{c}Pr	0.031/97
22	Me	CON(H)^{t}Bu	0.35/108
23	Me	$CONMe_2$	2.95/121
24	Me	$CONEt_2$	0.61/122

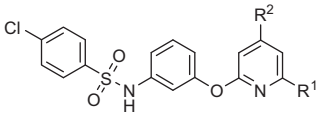
[a] Values are means of two or more experiments.
[b] See Ref. 7 for assay protocol.
[c] Efficacy relative to compound **2**.

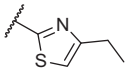
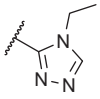
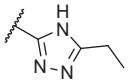
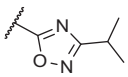
more metabolically stable groups while maintaining or improving the potency (Table 2). The compounds with other alkyl and hydrogen group were tolerated but only with decreased potency. For example, compound **14** with R^2 = H showed a sixfold decrease in potency as compared with the parent methyl compound **8**. As expected, replacing the methyl groups with metabolically stable groups helped the compounds to further improve stability. As an example, compound **16**, with R^1 = *c*-Pr and R^2 = CF_3, increased stability significantly and its microsomal turnover in HLM was 13%. In rats, the clearance of this compound was 0.19 L/h/kg (0.5 mg/kg, iv administration). This result demonstrated that the stability issue could be addressed by modification of these methyl groups. However, the potency for this compound declined eight-fold compared to compound **8** which limited its further utility.

Additional optimization around the pyridine moiety led to improvements of potency by introducing an ester group at R^2, Table 2. Compound **17** significantly improved the potency and was the first compound that achieved an EC_{50} in the double-digit nM range in the cAMP assay (EC_{50} = 13 nM). Similar results were also observed with other ester compounds. The potency improvement seemed to result from the direct interaction of the ester group with the target, as the acid derivative, **20**, was not able to maintain the activity. Smaller groups at R^1 gave improved potency, as shown by compounds **17**–**19** (Table 2). Next, considering the potential metabolic liability of the ester group, we replaced the ester with isosteric groups such as amides and heterocycles.[9] As shown in Table 2, the amides of primary amines (**21** and **22**) were more potent than the amides of secondary amines (**23** and **24**).

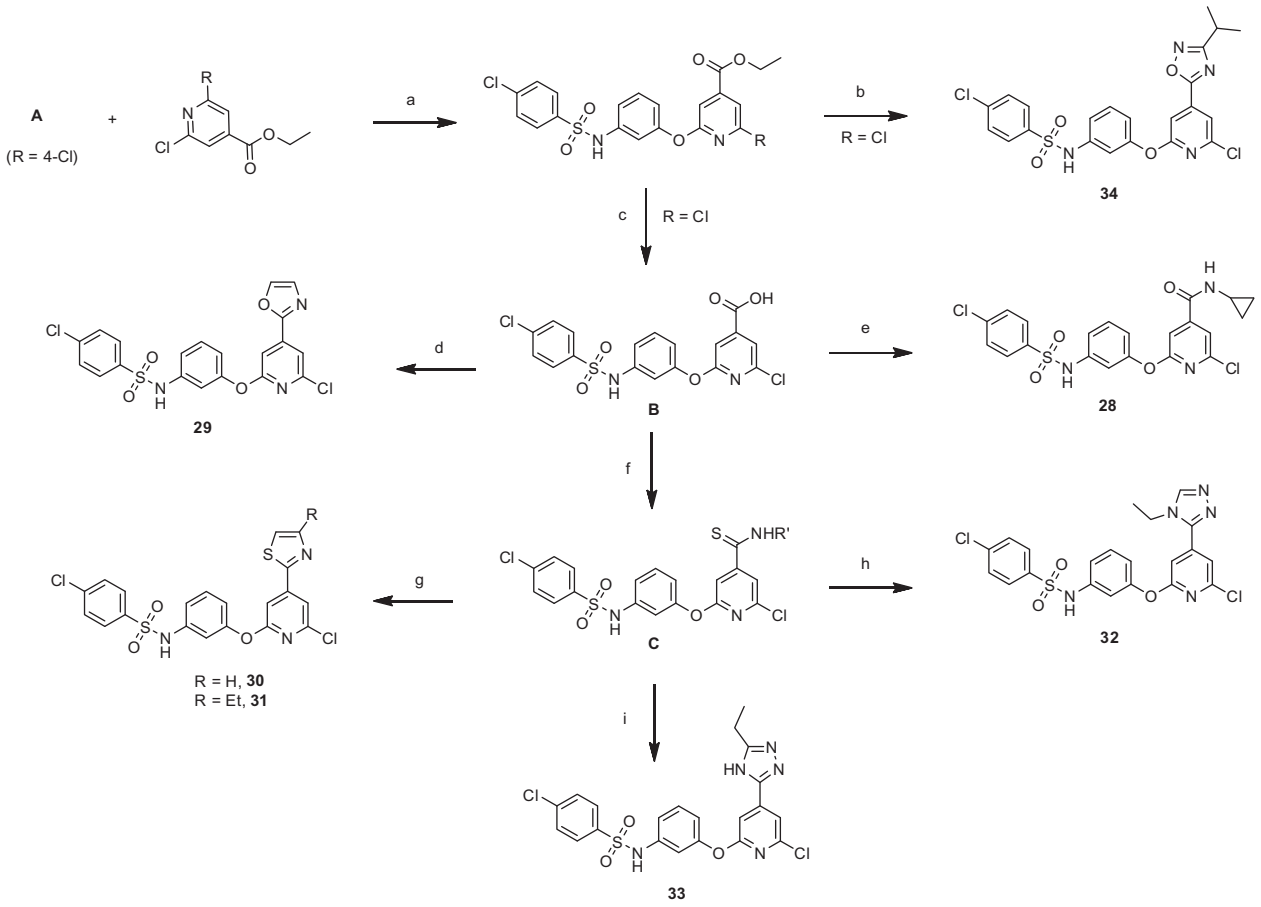
Our next goal was to further simplify the molecular structure by removing the cyano group.[10] Compared with **17**, compound **25** showed slightly decreased potency; however, replacing the methyl group with chlorine (compound **26**) retained the potency of **17** (Table 3). Converting the ester into an amide in this series did not improve the potency (**28**, Table 3). However, replacing the ester group with 5-membered heterocycles resulted in a compound with balanced potency and pharmacokinetic profile. The heterocycles **29** to **34** were synthesized according to the procedures outlined in Scheme 2. Treatment of acid chloride with 1H-1,2,3-triazole in tetramethylenesulfone under heating condition offered oxazole **29**.[11] The carbothioamides **C** were prepared from the acid **B** through

Table 3
SAR of the pyridine ring



Compounds	R^1	R^2	h-GPR119cAMP EC_{50} (μM) / efficacy[a,b,c] (%)
25	Me	CO_2Et	0.05/80
26	**Cl**	**CO_2Et**	**0.016/92**
27	H	CO_2Et	0.16/78
28	Cl	CON(H)^{c}Pr	0.45/99
29	Cl		0.091/94
30	Cl		0.068/88
31	Cl		0.089/80
32	Cl		0.30/98
33	Cl		1.06/87
34	**Cl**		**0.024/85**

[a] Values are means of two or more experiments.
[b] See Ref. 7 for assay protocol.
[c] Efficacy relative to compound **2**.



Scheme 2. Synthesis of compounds **29**–**34**. Reagents and conditions: (a) Cs_2CO_3, DMSO, 80 °C, overnight, 32%; (b) NaH, *N*′-hydroxyisobutyrimidamide, THF, reflux, overnight, 21%. (c) LiOH, THF–MeOH, rt, 5 h, 92%; (d) (i) cat. DMF, oxalyl chloride, THF, rt, 0.5 h; (ii) 1H-1,2,3-triazole, K_2CO_3, tetramethylenesulfone, 140 °C, overnight; (e) (i) cat. DMF, oxalyl chloride, THF, rt, 0.5 h; (ii) cyclopropanamine, triethyl amine, 80%. (f) R′ = H, (i) cat. DMF, oxalyl chloride, THF, rt, 0.5 h; (ii) NH_4OH; 97% (iii) Lawesson's reagent, THF, reflux, 2 h; 58%; R′ = Et, (i) cat. DMF, oxalyl chloride, THF, rt, 0.5 h; (ii) $EtNH_2$; 91% (iii) Lawesson's reagent, THF, reflux, 2 h; 68%; (g) R = H, bromoacetaldehyde dimethyl acetal, DMF, rt 2 h; 21%; R = Et, 1-bromo-2-butanone, EtOH, 90 °C, 3 h; 36%; (h) formic acid hydrazide, $Hg(OAc)_2$, 1,4-dioxane, reflux, overnight; (i) propionohydrazide, $Hg(OAc)_2$, 1,4-dioxane, reflux, 45 min, 5%.

the formation of the amides and subsequent treatment with the Lawesson's reagent. The thiazoles **30** and **31** were obtained from the reaction of these thioamides **C** with α-bromo substituted aldehyde or ketone. The triazole compounds **32** and **33** were synthesized by reaction of the corresponding thioamides with hydrazides in presence of $Hg(OAc)_2$ in dioxane. Reaction of ester with *N*′-hydroxyisobutyrimidamide in presence of NaH under THF reflux condition gave oxadiazole compound **34**. As indicated in Table 3, most of the heterocycles were tolerated well. The isopropyl-1,2,4-oxadiazol-5-ylpyridine compound **34** was the most potent heterocycle analogue that achieved the similar potency as the esters compounds **17** and **26**. In addition, the pharmacokinetic properties of this compound were evaluated; this compound displayed a moderate clearance of 1.8 L/h/kg in rat.

In summary, we have explored a GPR119 agonist screening hit to improve its stability and potency, which led to the discovery of compound **34**, a 24 nM agonist with an improved pharmacokinetic profile. The metabolic instability of the hit was resolved by replacing methyl groups with appropriate metabolically stable substitutions. The potency was dramatically improved by introducing ester and its isosteres. Subsequent replacement of the ester with small heterocycles led to the discovery of an oxadiazole compound with well-balanced potency and PK properties.

Acknowledgments

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References and notes

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7. *cAMP assay for GPR119:* HEK 293 cells stably expressing GPR119 were plated into 96-well plates at a density of 5000 cells per well in 80 μL DMEM containing 0.5% FBS and 1% Pen/Strep/L-glutamine. Cells were then incubated overnight at 37 °C. GPR119 agonists were dissolved and serially diluted in DMSO, and then further diluted 1:10 in PBS; 20 μL of this final mixture was added to the cells for 30 min at 37 °C. The media was then aspirated and cAMP levels were measured using a DiscoverX cAMP kit following the manufacturer's protocol. Plates were read for 30 s on PerkinElmer ViewLux Microplate Imager. All compounds are referenced to a small molecule GPR119 agonist, compound **2**, for evaluation of intrinsic efficacy (% max response).
8. Maestro v9.3, Phase v3.4. Schrodinger, LLC; New York, NY. Pharmacophores and alignments were generated with Phase using conformers created with ConfGen. Resulting hyphotheses consisting of all combinations of all possible features were scored, ranked and inspected visually and a high-scoring 4-point pharmacophore was chosen for the reference alignment.
9. Alignment of these compounds with the pharmacophore developed from compound **1** and reference compound **2** shows a good overlay of the extended acceptor feature between the carbonyl from the esters and amides, an acceptor atom in the heterocycles and the carbonyl of the carbamate from **2** and contributes to the improved potency of these analogs over **1**.
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