Discovery and optimization of *N*-(3-(1,3-dioxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-4-yloxy)phenyl)benzenesulfonamides as novel GPR119 agonists

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ABSTRACT

The discovery and optimization of novel *N*-(3-(1,3-dioxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-4-yloxy)phenyl)benzenesulfonamide GPR119 agonists is described. Modification of the pyridylphthalimide motif of the molecule with R^1 = –Me and R^2 = –^{i}Pr substituents, incorporated with a 6-fluoro substitution on the central phenyl ring offered a potent and metabolically stable tool compound **22**.

Type 2 diabetes is a metabolic disorder that afflicts over 250 million people worldwide.[1] Although a variety of treatment options exist, many patients are ultimately unable to achieve their target plasma glucose level. In addition, side effects, for example the hypoglycemia observed in patients treated with insulin or sulfonylurea drugs (agents which cause glucose-independent insulin secretion), remain a significant concern. New medications that increase insulin secretion in a glucose-dependent manner could potentially offer robust efficacy with limited hypoglycemia risk.

GPR119 is a G protein-coupled receptor (GPCR) expressed predominantly in the pancreatic islet β-cells and incretin-releasing intestinal cells.[2] GPR119 signals through the Gs class of G proteins. Accordingly GPR119 receptor activation stimulates adenylate cyclase activity and increases intracellular levels of cAMP. Physiologically, this result in glucose-dependent insulin secretion, increased plasma levels of the incretins GIP and GLP-1, and improved glucose homeostasis.[3] Phospholipids and lipid amides, including oleoyl-lysophosphatidylcholine and oleoylethanolamide (OEA) have been identified as endogenously-occurring ligands for GPR119.[3,4] In addition, several synthetic GPR119 agonists have been disclosed and many of them shown to improve in vivo glucose tolerance in a GPR119-specific manner.[4–6] Based on these findings, GPR119 has been pursued as a therapeutic target for treatment of type 2 diabetes.

We recently reported the discovery of compound **1** (Fig. 1), a potent (h-GPR119-cAMP EC_{50} = 0.024 μM),[7] and efficacious (85% maximal activity compared to **2**) GPR119 agonist with moderate in vivo clearance in rat (CL_{iv} = 1.8 L/h/kg).[8] One of the milestones in our early SAR toward **1** was the discovery of a potent transitional analogue **4** (0.031 μM, 97%). However, the conditions we initially designed for the synthesis of **4** resulted mainly in the corresponding pyridylphthalimide by-product **5** (32% yield), presumably after further cyclization of **4** (Scheme 1). Interestingly, when tested in the human GPR119 cAMP assay, compound **5** showed potency (0.045 μM) and efficacy (99%) equivalent to **4**.[9] Based on this finding, we set out to investigate this pyridylphthalimide sub-series.

The key 4-chloro-pyrrolo[3,4-*c*]pyridine-1,3(2*H*)-dione intermediates **A** that were used to access most of the compounds discussed in this Letter were prepared according to the synthetic route illustrated in Scheme 2. Refluxing in the presence of piperidine an ethanol solution of commercially available 2-cyanoacetamide and ethyl β-keto-esters **A1** that contained desired $R^{1'}$s (–^{c}Pr or –Me) provided the ethyl 3-cyano-2-hydroxyisonicotinates **A2** in 35–59% yields. The resulting intermediates **A2**, after reaction with phenylphosphonic dichloride (150 °C, 25–45 min) followed by sulfuric acid (6.0 N) facilitated cyclization reaction, offered the corresponding bicyclic 4-chloro-pyrrolo[3,4-*c*]pyridine-1,3(2*H*)-diones **A4** in moderate yields (40–54%, two steps). The desired R^2 groups were finally introduced to provide **A** either through direct *N*-alkylation of **A4** with R^2I and cesium carbonate (R^2 = –Me, or –Et; 42–55%), via a Mitsunobu reaction (R^2 = –cyclopentyl, or
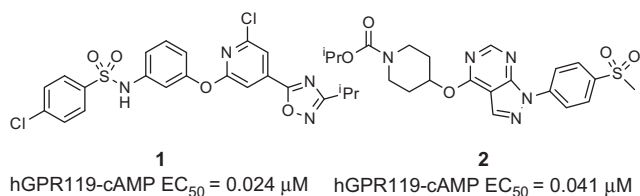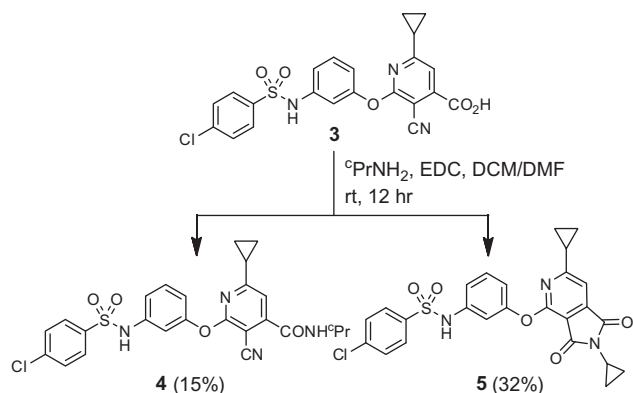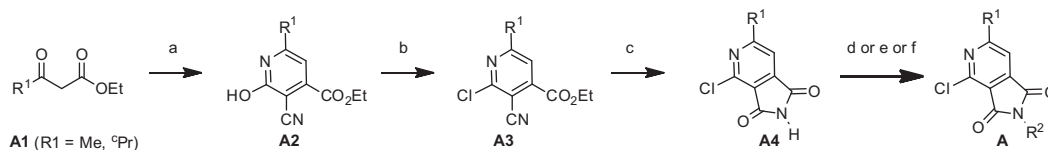
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Figure 1. Representative synthetic GPR119 agonists.

Scheme 1. Discovery of **5** from the synthesis of **4**.

–^{i}Pr; 31–51%), or utilizing a copper (II) acetate catalyzed coupling reaction with the relevant boronic acids R^{2}B(OH)$_2$ (R^2 = –^{c}Pr or – Ph; 11–68%).

As shown in Scheme 3, another class of key building components for most of the compounds discussed in this Letter were the *N*-(3-hydroxyphenyl)-benzenesulfonamides **B1**. They were prepared in 25–87% yields by reaction of 4-chlorobenzenesulfonyl chloride with the corresponding 3-aminophenols of required substitution pattern (Z = –H, 2-F, 4-Me, 5-F, 6-F, or 6-Cl).[8] Intermediate **B1** (Z = H) was initially assembled through a potassium carbonate-mediated SN$_2$-Ar reaction with **A** (R$_1$ = R$_2$ = –^{c}Pr) to provide **5** (Table 1), and with **A4** (R$_1$ = –Me) to provide **8**, in 5% and 3% yield respectively. Compounds **17** and **18** (Table 3) were similarly assembled using the corresponding **B2** and **B3** intermediates made through procedures outlined in Scheme 3. Since this protocol was generally low yielding (3–12%), a 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed microwave assisted reaction (DMF, 130 °C) was developed which improved the reaction yields to 41–52% for the synthesis of compounds **5–7**, **9–13** (Table 1) and **20–24** (Table 4).[10] Compound **19** (Table 4) was made through direct N-methylation of **11** with MeI in 72% yield. The synthesis of **14–15** and **16** (Table 2) started with construction of the right hand side **C1** or **C2** components of the molecule. Subjecting 3-amino-thiophenols to conditions (K$_2$CO$_3$, THF, 60 °C) similar to, but milder than those described above provided **C1** in 99% (Z = –H) and 80% (Z = –Me) yields. Treating **C1** with 4-chlorobenzenesulfonyl chloride in pyridine gave **14** and **15** in 99% and 90% yields. The aminoaniline–pyridylphthalimide intermediate **C2** was
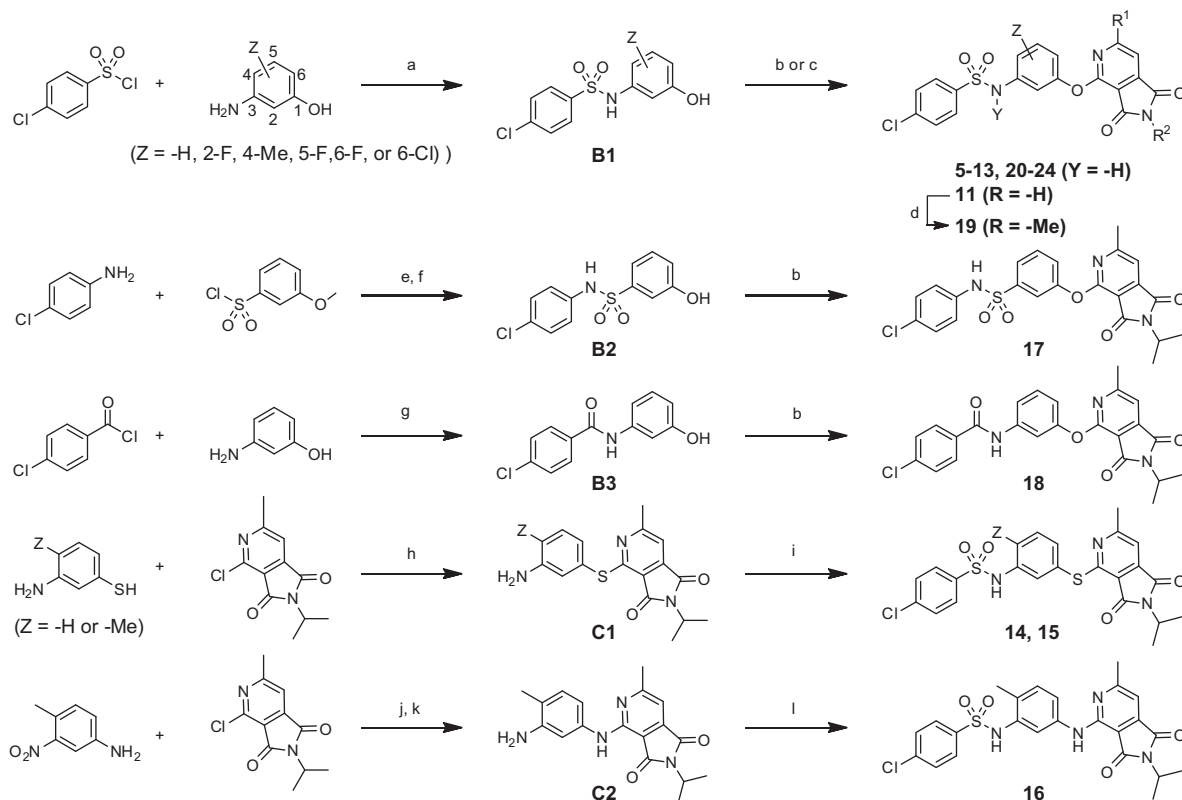
synthesized from 4-methyl-3-nitroaniline via Buchwald coupling with **A** (R^1 = –Me, R^2 = –^{i}Pr), followed by hydrogenation. Treating **C2** with 4-chlorobenzenesulfonyl chloride in pyridine completed the synthesis of **16** (Table 2) in 18% yield.

We first investigated the influence of the pyridylphthalimide R^1 and R^2 substituents on potency as summarized in Table 1. Starting with R^2 = –^{c}Pr as like in **5**, R^1 groups in a wide range of size and electronic properties were tested. Many of them were found to be well tolerated for this position, including –Cl and –OCF$_3$ (data not shown). From this exploration, the methoxy (**6**, 0.019 µM) and methyl (**7**, 0.015 µM) groups stood out as the most potent substituents. The methyl group was later selected over methoxy for R^1 for the subsequent SAR, primarily due to its potential for improved metabolic stability. The R^2 position was also quite sensitive toward substituent size. From compounds **7** to **11**, the EC$_{50}$ values were ranked in order of low to high potency as R^2 = –H > –Me > –^{c}Pr, –^{i}Pr > –Et, but larger substituents (e.g. **12** and **13**) led to significant loss of potency. The combination of R^1 = –Me and R^2 = –^{i}Pr, as shown in compound **11**, offered a twofold improvement in potency (EC$_{50}$ = 0.017 µM) compared to **5**. Compound **11** also demonstrated in vitro metabolic stability which, while poor (see below), was still slightly better than the more potent compound **7** and **10**. Therefore, the chemical feature of R^1 = –Me and R^2 = –^{i}Pr as in **11** was adopted for subsequent studies.

We also explored modifications to the central –O– linker as highlighted in Table 2. We first replaced it with –S– as exemplified in **14** and **15**, but this change either showed no benefit or was detrimental to potency (0.019 and 0.224 µM, respectively). We then tested an –NH– substituent, as exemplified in **16**, but this was also detrimental to potency (0.382 µM). In addition, both the –S– and –NH– replacements reduced the efficacy by approximately 20%. Consequently, no further efforts were made in this area.

Pharmacokinetic studies of **11** suggested rapid metabolic decomposition of this compound in both rat liver microsomes (RLM) (CL$_{intrinsic}$ = 250 µl/min/mg)[11] and in vivo (rat IV CL = 4.8 L/ h/kg). Oxidative metabolism of the central phenyl ring was identified as the major route of metabolism for **11** in RLM. In order to improve the metabolic stability we reduced the electron density on the central phenyl ring, as illustrated by the examples shown in Table 3. In **17**, the connectivities of the sulfonamide moiety were reversed to reduce the electron density and therefore to lower the oxidative potential of the central phenyl ring. However, this compound displayed over 20-fold loss of potency (0.238 µM). In **18**, where a carboxylamide served as a sulfonamide surrogate, there was a noticeable improvement in RLM intrinsic clearance (40 µl/ min/mg). Unfortunately, compound **18** showed no activity in the functional assay (EC$_{50}$ >30 µM).

Given the modest improvement achieved from the efforts described above, and our knowledge from previous SAR[8] that the 4-Cl phenyl motif at the far left side is a well established chemical feature of this lead series, we decided to revisit the central phenyl ring with more delicate modifications (Table 4). To better manipulate the electron density around the central phenyl ring to increase its oxidative potential, methyl substitution was introduced at the sulfonamide nitrogen (**19**, Y = –Me, Z = –H) to disrupt the electron donating conjugation effect from the electron lone pair of the nitro-

Scheme 2. Synthesis of key pyridylphthalimide intermediate **A**. Reagents and conditions: (a) 2-cyanoacetamide, piperidine, EtOH, 80 °C, 35–59%; (b) PhP(O)Cl$_2$, 150 °C, 25–45 min, 55–76%; (c) H$_2$SO$_4$ (6.0 M), 80 °C, 4.0–8.0 h, 56–72%; (d) R^{2}Br, Cs$_2$CO$_3$, DMF, rt, 42–55%; (e) R^{2}OH, DEAD, Ph$_3$P, THF, 0 °C–rt, overnight, 31–51%; (f) R^{2}B(OH)$_2$, Cu(OAc)$_2$, 2,2′-dipyridine, Na$_2$CO$_3$, DMF, 70 °C, 1.5–4.0 h, 11–68%.

Scheme 3. Synthesis of compounds **5–24**. Reagents and conditions: (a) Py, dichloromethane, rt, overnight, 25–87%; (b) A, K_2CO_3, DMF, 60–80 °C, 7 h, 5–12%; (c) **A**, 1,4-diazabicyclo[2.2.2]octane, py, microwave, 130 °C, 1.0–4.0 h, 41–52%; (d) MeI, K_2CO_3, DMF, 0 °C–rt, 4 h, 72%; (e) Py, 0 °C–rt, overnight, 94%; (f) BBr_3, dichloromethane, −40 °C–rt, overnight, 81%; (g) DMAP, Et_3N, dichloromethane, 0 °C, 2 h, 77%; (h) K_2CO_3, THF, 60 °C, 1.5 h, 80–99%; (i) 4-Cl–$PhSO_2Cl$, py, rt, 4.0 h, 90–99%; (j) $Pd_2(dba)_3$ (0.2 equiv), 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (0.5 equiv), CsF (3.0 equiv), 76%; (k) H_2, Pd/C, EtOAc, 80%; (l) 4-Cl–$PhSO_2Cl$, py, rt, overnight, 18%.

Table 1
Modification of R^1 and R^2 on the pyridylphthalimide motif

Compound	–R^1	–R^2	hGPR119-cAMP EC$_{50}$ (µM)/efficacy (%)[a,b,c]
5	–^{c}Pr	–^{c}Pr	0.045/99
6	–OMe	–^{c}Pr	0.019/97
7	–Me	–^{c}Pr	0.015/111
8	–Me	–H	0.121/109
9	–Me	–Me	0.023/122
10	–Me	–Et	0.011/120
11	–Me	–^{i}Pr	0.017/99
12	–Me	–Cyclopentyl	0.069/95
13	–Me	–Ph	0.299/102

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

gen. Unfortunately, compound **19** still demonstrated high in vitro clearance (CL$_{intrinsic}$ RLM >400 µl/min/mg). However, a methyl substitution at the 4-position of the phenyl ring achieved noticeable improvement in metabolic stability (**20**, Z = 4-Me, Y = –H; CL$_{intrinsic}$ RLM = 131 µl/min/mg). Compound **20** also well maintained the target activity (EC$_{50}$ = 0.009 µM). Other substituents (including -alkyl and –Cl) were subsequently explored for the 4-position, but loss of potency was observed (data not shown). A similar strategy was applied to the 6-position to weaken conjugation from the oxygen electron lone pair. Compound **21**, which featured a 6-Cl substitution, represented a breakthrough for metabolic stability, with an intrinsic RLM clearance of 29 µl/min/mg. The improvement in in vitro metabolic stability translated well into the in vivo rat IV clearance (CL$_{iv}$ = 0.22 L/h/kg). As a result, we subsequently investigated a large variety of 6-substituents, among which the 6-F analogue **22** showed a similar level of RLM stability (CL$_{intrinsic}$ = 84 µl/min/mg). In addition, the potency of **22** was restored back to 0.016 µM. With this finding, fluoro substitution was quickly screened for the rest positions around the phenyl ring (e.g., **23** and **24**),[12] but no further improvement in potency was noted.

Compound **22** was evaluated in in vitro and in vivo experiments. In addition to the good in vitro potency against
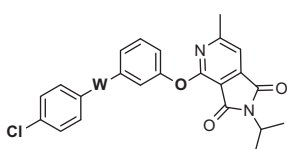
Table 2
Modification of the middle ether linker

Compound	X	–Z	hGPR119-cAMP EC$_{50}$ (µM)/efficacy (%)[a,b,c]
11	O	–H	0.013/99
14	S	–H	0.019/76
15	S	–Me	0.224/85
16	NH	–Me	0.382/81

[a] Values are means of two or more experiments.
[b] See Ref. 7 for assay protocol.
[c] Efficacy relative to compound **2**.
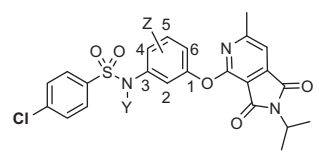
Table 3
Modification of the sulfonamide linkage

Compound	–W–	hGPR119-cAMP EC$_{50}$ (µM)/efficacy (%)[a,b]	Rat LM CL$_{intrinsic}$ (µl/min/mg)
11		0.013	250
17		0.238	ND[c]
18		>30	40

[a] Values are means of two or more experiments.
[b] See Ref. 7 for assay protocol.
[c] Data not determined.

Table 4
Central phenyl ring modification

Compound	–Y	–Z	h-GPR119-cAMP EC$_{50}$ (µM) [a,b]	Rat LM CL$_{intrinsic}$ (µl/min/mg)
11	–H	–H	0.013	250
19	–Me	–H	0.011	>400
20	–H	4-Me	0.009	131
21	–H	6-Cl	0.033	29
22	–H	6-F	0.016	84
23	–H	5-F	0.357	ND[c]
24	–H	2-F	0.493	ND[c]

[a] Values are means of two or more experiments.
[b] See Ref. 7 for assay protocol.
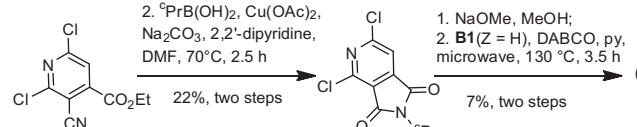[c] Data not determined.

human GPR119, compound **22** exhibited an EC$_{50}$ of 0.073 µM in the cynomolgus monkey GPR119 cAMP assay with full efficacy (102%). The intrinsic clearance of **22** in human liver microsomes was 29 µl/min/mg, which corresponded with 88% of compound recovered intact after incubation at 1.0 µM for 30 min at 37 °C. Compound **22** showed a reasonable PK profile in rats, with CL = 0.7l L/h/kg, $t_{1/2}$ = 1.5 h, and V_{dss} = 1.5 L/kg following a 0.5 mg/kg IV dose, and 95% bioavailability following a 2.0 mg/kg PO dose. In cynomolgus monkeys, the IV clearance was 0.45 L/h/kg[13] and the oral bioavailability was 29%.[14] Compound **22** did not show noticeable hPXR activation or cytochrome P450 inhibition. It was also free from hERG liability (IC$_{50}$ >30 µM, patch-clamp assay) and did not bind to BSEP. Unfortunately, compound **22** demonstrated high plasma protein binding (>99%) in both human and cynomolgus monkey and poor activity on rodent GPR119.[15] These parameters precluded evaluation of its anti-diabetic efficacy in vivo.

In summary, novel *N*-(3-(1,3-dioxo-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridin-4-yloxy)phenyl)benzenesulfonamide GPR119 agonists were discovered. Optimization of the pyridylphthalimide portion of the molecule with R^1 = –Me, R^2 = –^{i}Pr substituents improved the GPR119 activity from 0.045 to 0.017 µM. Substitution of the middle phenyl ring with a 6-fluoro group significantly

improved the metabolic stability of the compound. Pharmacokinetic and selectivity properties of **22** were excellent, but its plasma protein binding remained high and the rodent potency was suboptimal.

References and notes

1. (a) Centers for Disease Control and Prevention *National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States, 2007*; US Department of Health and Human Services, Centers for Disease Control and Prevention: Atlanta, GA, 2008; (b) Wild, S.; Roglic, G.; Green, A.; Sicree, R.; King, H. *Diabetes Care* **2004**, *27*, 1047; (c) National Diabetes Statistics, **2011**, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institutes of Health (NIH).; (d) Koopman, R. J.; Mainous, A. G. I. I. I.; Diaz, V. A.; Geeseey, M. E. *Ann. Fam. Med.* **2005**, *3*, 60.
2. Fredrikson, R.; Hoglund, P.; Gloriam, D. E. I.; Lagerstrom, M. C.; Schioth, H. B. *FEBS Lett.* **2003**, *554*, 381.
3. (a) Soga, T.; Ohishi, T.; Matsui, T.; Saito, T.; Matsumoto, M.; Takasaki, J.; Matsumoto, S.; Kamohara, M.; Hiyama, H.; Yoshida, S.; Momose, K.; Ueda, Y.; Matsushime, H.; Kobori, M.; Furuichi, K. *Biochem. Biophys. Res. Commun.* **2005**, *326*, 744; (b) Drucker, D. J. *Cell Metab.* **2006**, *3*, 153.
4. (a) Jones, R. M.; Leonard, J. N. *Annu. Rep. Med. Chem.* **2009**, *44*, 149; (b) Jones, R. M.; Leonard, J. N.; Buzard, D. J.; Lehmann, J. *Expert Opin. Ther. Pat.* **2009**, *19*, 1339; (c) Shah, U. *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 519; (d) Fyfe, M. C. T.; McCormack, J. G.; Overton, H. A.; Procter, M. J.; Reynet, C. *Expert Opin. Drug Discovery* **2008**, *3*, 403; (e) Jones, R. M. *Abstracts of Papers*, 239th ACS National Meeting, San Francisco, CA, 2010; Abstract MEDI-316.; (f) Peckham, G. E. *Abstracts of Papers*, 240th ACS National Meeting, Boston, MA, United States, 2010; Abstract MEDI-199.; (g) Wu, Y.; Kuntz, J. D.; Carpenter, A. *Abstracts of Papers*, 240th ACS National Meeting, Boston, MA, 2010; MEDI-203.
5. (a) Semple, G.; Fioravanti, B.; Pereira, G.; Calderon, I.; Uy, J.; Choi, K.; Xiong, Y.; Ren, A.; Morgan, M.; Dave, V.; Thomsen, W.; Unett, D. J.; Xing, C.; Bossie, S.; Carroll, C.; Chu, Z.; Grottick, A. J.; Hauser, E. K.; Leonard, J.; Jones, R. M. *J. Med. Chem.* **2008**, *51*, 5172; (b) Wu, Y.; Kuntz, J. D.; Carpenter, A. J.; Fang, J.; Sauls, H. R.; Gomez, D. J.; Ammala, C.; Xu, Y.; Hart, S.; Tadepalli, S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2577; (c) McClure, K. F.; Darout, E.; Guimaraes, C. R. W.; DeNinno, M. P.; Mascitti, V.; Munchhof, M. J.; Robinson, R. P.; Kohrt, J.; Harris, A. R.; Moore, D. E.; Li, B.; Samp, L.; Lefker, B. A.; Futatsugi, K.; Kung, D.; Bonin, P. D.; Cornelius, P.; Wang, R. D.; Salter, E.; Hornby, S.; Kalgutkar, A. S.; Chen, Y. *J. Med. Chem.* **2011**, *54*, 1948; (d) Semple, G.; Ren, A.; Fioravanti, B.; Pereira, G.; Calderon, l.; Choi, K.; Xiong, Y.; Shin, Y. J.; Gharbaoui, T.; Sage, C. R.; Morgan, M.; Xing, C.; Chu, Z. L.; Leonard, J. N.; Grottick, A. J.; Al-Shamma, H.; Liang, Y.; Demarest, K. T.; Jones, R. M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3134; (e) Szewczyk, J. W.; Acton, J.; Adams, A. D.; Chicchi, G.; Freeman, S.; Howard, A. D.; Huang, Y.; Li, C.; Meinke, P. T.; Mosely, R.; Murphy, E.; Samuel, R.; Santini, C.; Yang, M.; Zhang, Y.; Zhao, K.; Wood, H. B. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2665; (f) Xia, Y.; Chackalamannil, S.; Greenlee, W. J.; Jayne, C.; Neustadt, B.; Stamford, A.; Vaccaro, H.; Xu, X.; Baker, H.; O'Neill, K.; Woods, M.; Hawes, B.; Kowalski, T. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3290; (g) Mascitti, V.; Stevens, B. D.; Choi, C.; McClure, K. F.; Guimarães, C. R. W.; Farley, K. A.; Munchhof, M. J.; Robinson, R. P.; Futatsugi, K.; Lavergne, S. Y.; Lefker, B. A.; Cornelius, P.; Bonin, P. D.; Kalgutkar, A. S.; Sharma, R.; Chen, Y. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1306.
6. Chu, Z.-L.; Jones, R. M.; He, H. M.; Carroll, C.; Gutierrez, V.; Lucman, A.; Moloney, M.; Gao, H.; Mondala, H.; Bagnol, D.; Unett, D.; Liang, Y.; Demarest, K.; Semple, G.; Behan, D. P.; Leonard, J. *Endocrinology* **2007**, *148*, 2601.
7. Protocol for the GPR119 cAMP assay used for this program at Amgen: 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 (percentage of its maximal response).
8. Zhang, J.; Li, A.-R.; Yu, M.; Wang, Y.; Zhu, J.; Kayser, F.; Medina, J. C.; Siegler, K.; Conn, M.; Shan, B.; Grillo, M. P.; Eksterowicz, J.; Coward, P.; Liu, J. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3609.
9. Compound **5** was also found to be stable in liver microsomes (LM) (percentage turnover: 19% in human and 37% in rat). The intrinsic in vitro LM clearance of **5** was 27 and 63 µl/min/mg in human and rat, respectively.
10. Compound **6** was synthesized according to the following procedure:

11. The percentage of compound **11** remained intact after incubation in rat liver microsomes (RLM) at 1.0 µM for 30 min at 37 °C was 15%.

12. The 4-F substitution was also attempted at the central phenyl ring, but in a slightly different structure setting which did not allow for direct comparison with Table 4. This modification resulted in significant loss of potency.
13. Drug administered iv at 0.5 mg/kg; $t_{1/2}$ = 5.6 h, V_{dss} = 1.1 L/kg.
14. Drug administered po at 2.0 mg/kg.
15. Compound **22** was less potent in rodents than in human with a GPR119-cAMP EC_{50} of 1.97 and 2.05 μM in mouse and rat, respectively. Low rodent potency was a common observation made on this lead series.