Bioorganic & Medicinal Chemistry Letters 24 (2014) 156–160

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

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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ARTICLE INFO

Article history:
Received 26 October 2013
Revised 17 November 2013
Accepted 20 November 2013
Available online 1 December 2013

Keywords:
GPR119
Agonist
Type 2 diabetes

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**.

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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 oleoyllysophosphatidylcholine 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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http://dx.doi.org/10.1016/j.bmcl.2013.11.053

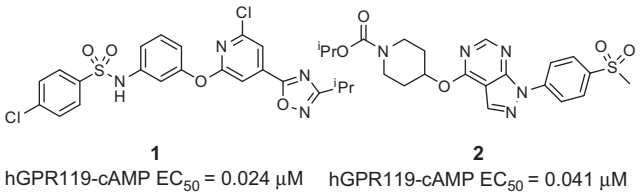
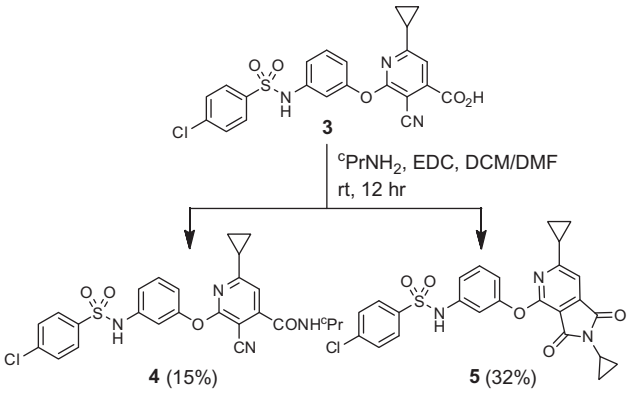


Figure 1. Representative synthetic GPR119 agonists.



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 relavent boronic acids $R^2B(OH)_2$ (R^2 = –^{c}Pr or –Ph; 11–68%).

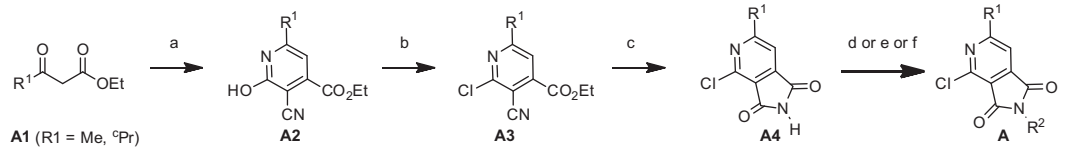
As shown in Scheme 3, another class of key building components for most of the compounds discussed in this Letter were the *N*-(3-hydroxyphenyl)-benzenesulfonamides **B1**. They were prepared in 25–87% yields by reaction of 4-chlorobenzenesulfonyl chloride with the corresponding 3-aminophenols of required 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-aminothiophenols to conditions (K_2CO_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_2SO_4 (6.0 M), 80 °C, 4.0–8.0 h, 56–72%; (d) R^2Br, Cs_2CO_3, DMF, rt , 42–55%; (e) R^2OH, DEAD, Ph_3P, THF, 0 °C–rt, overnight, 31–51%; (f) $R^2B(OH)_2$, $Cu(OAc)_2$, 2,2′-dipyridine, Na_2CO_3, DMF, 70 °C, 1.5–4.0 h, 11–68%.

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