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# From partial to full agonism: Identification of a novel 2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole as a full agonist of the human GPR119 receptor

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ABSTRACT

A novel GPR119 agonist based on the 2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole scaffold was designed through lead optimization starting from pyrazole-based GPR119 agonist **1**. The design is centered on the conformational restriction of the core scaffold, while minimizing the change in spatial relationships of two key pharmacophoric elements (piperidine-carbamate and aryl sulfone).



GPR119 is a target of significant interest to the pharmaceutical industry for the treatment of diabetes based on a recent patent analysis of the therapeutic area.[1,2] Indeed, there has been a large increase in the number of composition of matter applications for GPR119 agonists over the past 5 years. Interest in targeting this class A G-protein coupled receptor (GPCR) stems from the potential for agonists to provide improved glucose control with a low risk of hypoglycemia.[3,4] In addition, recent data suggest that the preservation of beta cell function may also be possible through the activation of this receptor.[5,6] Oleoylethanolamide (OEA) has been reported to be the endogenous agonist for this receptor,[7] although a recent report shows that other endogenous lipids may act as agonists, including monoacylglycerols (MAG).[8] While OEA has helped define some of the potential benefits of GPR119 activation, studies in transgenic mice suggest that not all of these effects are GPR119 mediated.[9] Nevertheless, there are a number of small molecule agonists described that show antihyperglycemic effects in rodents.[10–21] Most of these compounds, like most small molecule GPR119 agonists reported show two key structural elements: (i) a piperidine-carbamate group or its isostere, and (ii) an aryl sulfone group or its isostere (Fig. 1).

Recently we disclosed the importance of the conformational disposition of the piperidine-carbamate for GPR119 activation.[22] As part of our systematic approach to this target we also evaluated conformational restriction of the core region of the molecule. The proving ground for this effort was in a series of pyrazole analogs exemplified by compound **1** (Fig. 2). Herein we describe the SAR of these pyrazole-based compounds and the identification of a novel GPR119 agonist centered on a rigid 2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole scaffold.

The pyrazole structure in **1** derives from our emphasis on identifying a polar core to provide flexibility in the balancing of pharmacology and ADME properties. While compound **1** shows modest potency with partial agonism in our cAMP assay,[23] by virtue of its relative polarity ($\mathrm{Log}D = 2.3$)[24] it shows reasonable human microsomal stability. In addition to addressing the deficiency in both $EC_{50}$ and intrinsic activity, our optimization effort focused on the embedment of the aniline structural motif to mitigate potential reactive metabolite formation and idiosyncratic toxicity risks.[25] Based on these objectives, the medicinal chemistry effort commenced with the structural modification of the piperidine-carbamate group and 2-fluoro-4-methylsulfonyl aniline group.

Analogs based on **1** were synthesized through the general sequence described in Scheme 1. Starting from the known intermediate **4**,[26] reductive amination with aromatic primary amines **2** and **3** afforded the corresponding secondary amine derivatives in good yields. Oxidation of the thioether group with *m*-CPBA, cleavage of the Boc group and subsequent reactions with the various chloroformates and heteroaromatic halides furnished analogs **5–8**.

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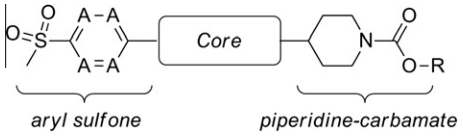
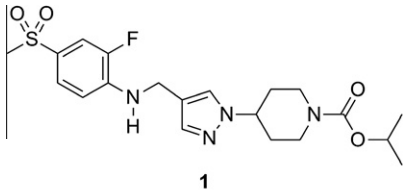


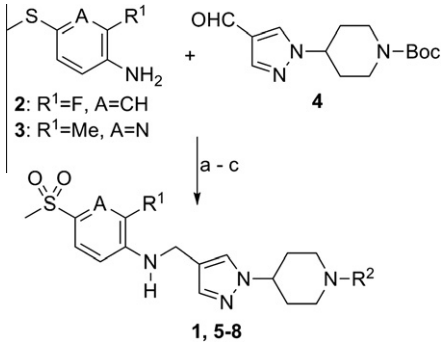

**Figure 1.** General structural features of GPR119 agonists.



**1**

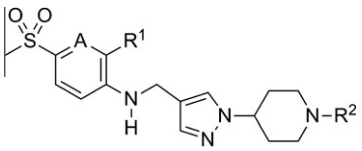
cAMP $EC_{50}$= 181 nM, 41% IA
CLint (HLM)= 9.7μL/min/mg
LogD= 2.3

**Figure 2.** In vitro profile of **1**.




**Scheme 1.** Synthesis of pyrazole-based GPR119 agonists. Reagents and conditions: (a) **2** or **3** (1 equiv), $NaBH(OAc)_3$ (2 equiv), AcOH (2.2 equiv), DCE, rt, 92% (from **2**), 71% (from **3**); (b) *m*-CPBA (2.5 equiv), DCM, rt, 85% (from **2**), 48% (from **3**); (c) HCl/MeOH or AcOEt, rt, followed by RCOCl (1 equiv), NMM/DCM or 2-chloro-5-ethylpyrimidine (1 equiv), DIPEA (4 equiv), DMSO, 120 °C, 31–62%.

**Table 1**
SAR around **1**



| Compd | $R^1$ | A | $R^2$ | $EC_{50}$ ± SD[a] (nM) | IA ± SD[a] (%) | Log $D^{24}$ |
|---|---|---|---|---|---|---|
| 1 | F | CH | $CO_2$*i*Pr | 181 ± 76 | 41 ± 6 | 2.3 |
| 5 | Me | N | $CO_2$*i*Pr | >10000 | N.D.[b] | 1.6 |
| 6 | F | CH | $CO_2$*i*Bu | 240±82 | 24 ± 3 | 2.8 |
| 7 | F | CH | $CO_2$*c*Bu | 462±135 | 42 ± 9 | 2.5 |
| 8 | F | CH | 5-Et-2-Pyrimidyl | 47±27 | 43 ± 3 | 3.0 |

[a] Values are arithmetic means of at least three experiments. See Ref. 22 for details.
[b] N.D. = not determined.

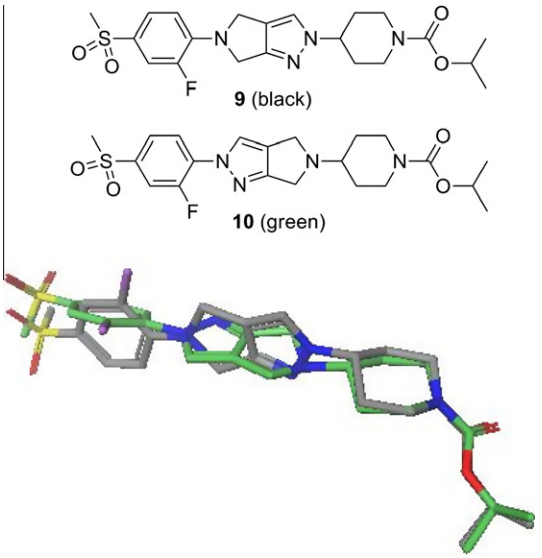



**Figure 3.** Superposition of **9** and **10**.

As shown in Table 1, changes made to the carbamate or aromatic sulfone had little impact on the intrinsic activity of these compounds. The attempt to replace the aniline motif in **1** with an aminopyridine derivative **5** led to a significant decrease in potency. Modifications to the carbamate group varied the potency with minimal impact on the intrinsic activity. The lowest $EC_{50}$ in this compound set was achieved when the *i*Pr carbamate group was replaced by 5-Et-2-pyrimidyl group (**8**), however, again no increase in intrinsic activity was achieved.

Based on the above results, we next turned our attention to the modification of the central core/spacer region. It was hypothesized that restriction of free rotation around the $–CH_2NH–$ bond might lead to potency gains and/or increases in intrinsic activity.

To this end, compound **9** possessing the 2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole scaffold was designed in order to highly constrain the positions available for the key pharmacophoric elements, as shown in Figure 3. Parallel to this effort, a 'flipped' version based on this bicyclic core was designed to embed the aniline structural motif from **9** (Fig. 3). This design was driven by the hypothesis that the core/spacer functions to position the two key pharmacophoric elements (piperidine-carbamate and aryl sulfone). Unsurprisingly, the superposition of **9** and **10** after global minimization[27] supported that the 2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole scaffold positions the two key pharmacophoric elements of **9** and **10** in similar space.

Analogs based on this hypothesis were prepared as outlined in Scheme 2. The synthesis of **10**, **13** and **14** started from the $S_NAr$ reaction of *N*-Boc 2,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazole, prepared from the commercially available dihydrochloride salt **11**, and 1,2-difluoro-4-(methylsulfonyl)benzene, to afford a ~1:1 mixture of *N*-1 and *N*-2 adducts. After silica gel column chromatography, the desired *N*-1 adduct **12** was obtained.[28] Boc cleavage, followed by reductive amination with various piperidone derivatives furnished analogs **10** and **13**. The corresponding *N*-oxide **14** was also synthesized by treating **13** with *m*-CPBA. Compound **9** was synthesized analogously through $S_NAr$ reaction of **11** with 1,2-difluoro-4-(methylsulfonyl)benzene and subsequent $S_N2$ reaction with isopropyl 4-(methylsulfonyloxy)piperidine-1-carboxylate.

The results obtained from these core modifications are summarized in Table 2. Conformationally restricted analog **9** showed comparable potency to the lead pyrazole **1** with similar intrinsic activity, suggesting that this mode of conformational restriction is sub-optimal to elicit a full agonist response. In contrast, a significant increase in intrinsic activity was achieved when the 'flipped' core C was examined, albeit with a decrease in potency