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Discovery of the oxazabicyclo[3.3.1]nonane derivatives as potent and orally active GPR119 agonists

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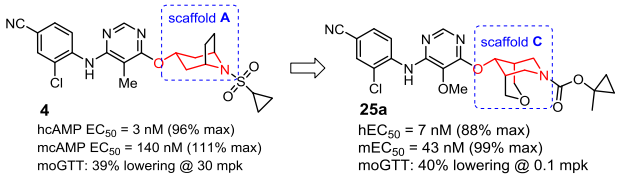
ABSTRACT

The design and synthesis of two conformationally restricted oxazabicyclo octane derivatives as GRP119 agonists is described. Derivatives of scaffold **C**, with syn configuration, have the best overall profiles with respect to solubility and in vivo efficacy. Compound **25a** was found to have extremely potent agonistic activity and was orally active in lowering blood glucose levels in a mouse oral glucose tolerance test at a dose of 0.1 mg/kg.



GPR119 is a G-protein-coupled receptor expressed in pancreatic β-cells and intestinal enteroendocrine cells. Since agonists of GPR119 stimulate both glucose-dependent insulin secretion and incretin release, GPR119 agonists have been under evaluation for their potential to promote anti-diabetic effects and control glucose homeostasis. Numerous Letters describing GPR119 agonists have been disclosed, and a number of compounds have been progressed into clinical trials.[1] Most of the reported GPR119 agonists share a common structural motif incorporating a piperidine with the piperidine nitrogen capped as a carbamate or by a heterocycle, and linked at the 4-position via a one atom spacer to an aryl group. Interestingly, several recent publications underscore the importance of conformational restriction of the piperidine portion in controlling human GPR119 pharmacology.[2,3]

We have recently reported our efforts to identify a series of GPR119 agonists with a bridged piperidine moiety (Fig. 1).[4,5] Bridged piperidines with both *anti* (**1**) and *syn* (**2**) configurations functioned as agonists with moderate efficacy at human GPR119 (hcAMP % max) and weak to moderate efficacy at mouse GPR119 (mcAMP % max). Capping of the more potent *syn* isomer **1** as a sulfonamide **3** provided increased mouse GPR119 agonist efficacy. Further optimization of the pyridinyl ring led to the discovery of sulfonamide **4**, a potent human GPR119 agonist. While **4** is a somewhat less potent agonist of mouse GPR119, its high % max made it suitable for evaluation in vivo in a mouse oral glucose tolerance test (oGTT). Compound **4** displayed significant activity in the mouse oGTT when administrated orally with a minimum effective dose of 10 mg/kg.[4,6] However, the compound suffered from poor aqueous solubility (0.17 μM, pH 7.4 buffer) which limited the exposure of the compound in exploratory safety studies and precluded it from further development. To address this issue we

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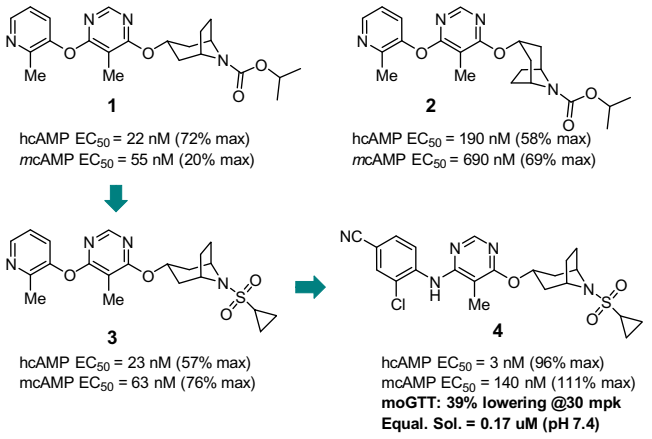


Figure 1. Initial optimization of bridged piperidine GPR119 agonists.

embarked on efforts to improve the solubility of compounds in this series which is the subject of this communication. Polar surface area (PSA), an indicator of hydrogen bonding capacity, plays an important role in the aqueous solubility.[7] Thus we explored introduction of an oxygen atom into the two-carbon-bridge (Fig. 2, scaffolds **B** and **C**) to increase the PSA of the molecules and provide a H-bond acceptor site for interaction with water, thereby improving solubility.

The synthesis of *syn* and *anti* 3-oxa-9-azabicyclo[3.3.1]nonan-7-ols **7** and **8** for scaffold **B** required development of a synthetic route to the common precursor 9-benzyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-one (**5**). This was achieved by the oxidation of tetrahydrofuran-3,4-diol and subsequent Robinson–Schopf reaction of the resulting dialdehyde with benzylamine and acetonedicarboxylic acid in aqueous medium (Scheme 1).[8] Removal of the *N*-benzyl group of **5** by catalytic hydrogenation followed by Boc protection afforded ketone **6**. Stereoselective reduction of the oxo function of **6** with sodium borohydride furnished *syn*-3-oxa-9-azabicyclo[3.3.1]nonan-7-ol (**7**). The *anti*-3-oxa-9-azabicyclo[3.3.1]nonan-7-ol (**8**) was obtained by a simple Mitsunobu inversion of **7**.

The starting material for scaffold **C**, 3-oxa-7-azabicyclo[3.3.1]nonan-9-ol was synthesized as a mixture of *syn* and *anti* isomers according to published procedures.[9] The final targets embodying scaffolds **B** and **C** were readily prepared by analogy to published procedures as outlined in Scheme 2.[10]

In order to evaluate both scaffolds **B** and **C**, close analogs of compound **4** were made. As shown in Figure 3, insertion of an oxygen atom into the bridge of compound **4** to afford compound **13** (hEC$_{50}$ = 268 nM) resulted in potency decrease of almost 90-fold. However, simply switching the capping group from sulfonamide to carbamate gave compound **14** of similar human GPR119 potency but significantly weaker functional activity at mouse GPR119. The corresponding *syn* isomer **15** was more potent than the corresponding *anti* isomer **14**. Although this compound was a partial agonist and not active in the mouse oGTT assay at 3 mg/kg p.o., compound **16**, which had a methanesulfonyl group on the phenyl ring in place of the cyano group of **15**, lowered blood

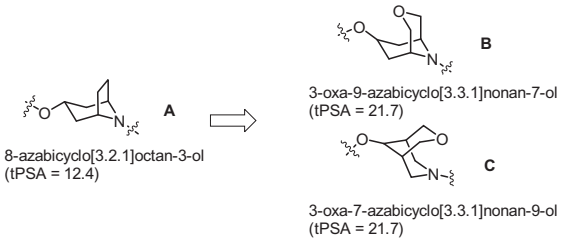
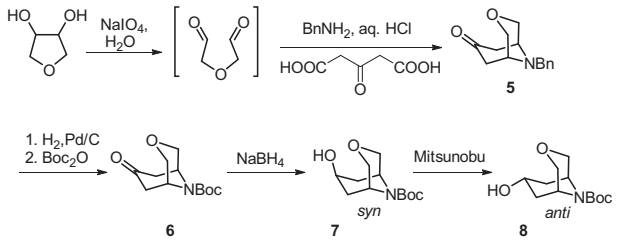
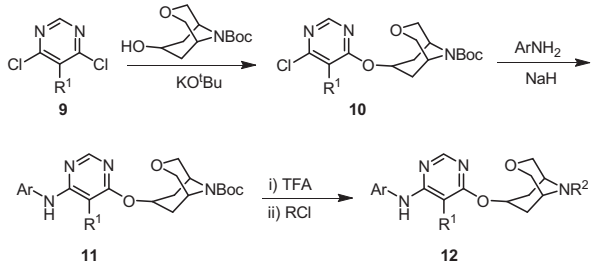


Figure 2. Bridged piperidines.



Scheme 1. Synthesis of 3-oxa-9-azabicyclo[3.3.1]nonan-7-ol.



Scheme 2. General synthesis of oxa-azabicyclo[3.3.1]nonane-derived GPR119 agonists.

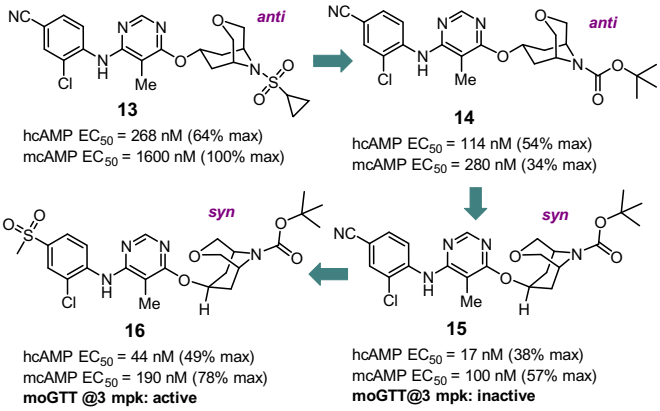


Figure 3. Initial SAR of scaffold **B**.

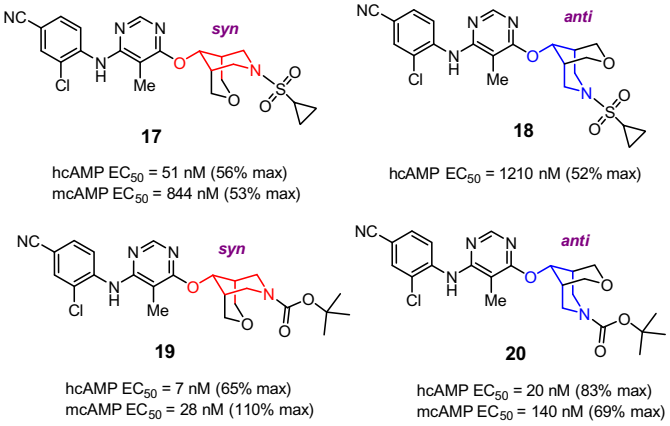


Figure 4. Initial SAR of scaffold **C**.[11]

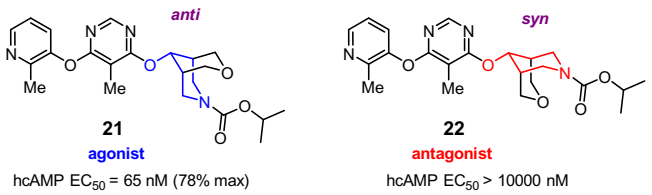


Figure 5. Conformation-based hypothesis by McClure and co-workers.[2a]

glucose levels significantly. Exploration of scaffold **C** (Fig. 4) revealed similar trends to those observed for scaffold **B**, with the *syn* isomers (**17** and **19**) being more potent than the *anti* isomers (**18** and **20**). Moreover, the carbamates (**19** and **20**) were generally more potent than the sulfonamides (**17** and **18**) and also tended to display greater agonist activity at human and mouse GPR119.

The agonist activity we have observed with scaffold **C** *syn* isomers **17** and **19** stands in contrast to results for similar analogs reported by McClure et al. (Fig. 5).[2a] They reported *anti* isomer **21** to be an agonist whereas its *syn* counterpart **22** was reported to be an antagonist devoid of intrinsic agonist activity at human GPR119. To rationalize this observation, McClure et al. invoked that the oxygen-containing bridge of *anti* isomer **21** locks the piperidine ring in the axial conformation that is required for agonist activity. On the other hand, the presence of the ether bridge in *syn* isomer **22** was proposed to lock the piperidine ring in the equatorial conformation, precluding access to the axial conformation required for agonist activity. Our observation that the *syn* isomers **17** and **19** show agonist activity at human GPR119 similar to that of the *anti* analogs **18** and **20** suggests that analysis of functional activity based solely on the relative position of the piperidine rings is insufficient, and that the nature of the piperidine capping group and/or the distal aryl group also influences functional GPR119 activity.

Since we had identified promising GPR119 agonist activity with analogs that incorporated each of the scaffolds **B** and **C**, both structural types were further investigated. To address concerns of susceptibility to acid cleavage and oxidative metabolism the *t*-butyl carbamate of **16** and **19** was replaced with the more stable methylcyclopropyl carbamate affording **23** and **24**. As shown in Figure 6, both **23** and **24** had improved solubilities validating our original design. In pH 7.4 buffer, the equilibrium solubilities of **23** and **24** were 3.4 and 6 μM, respectively, compared to 0.17 μM for compound **4**. In vitro activity trends with **23** and **24** were consistent with those observed for the corresponding t-butyl carbamates **16** and **19**. Scaffold **C** as in **24** conferred greater potency at human and mouse GPR119 relative to **23**, although agonist efficacy was similar between the two compounds. Both **23** and **24** showed robust glucose lowering activity in a mouse oGTT test at the oral dose of 3 mg/kg, with the significantly higher unbound plasma

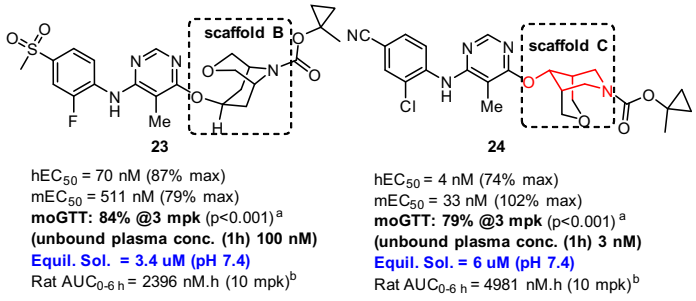
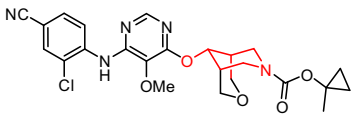
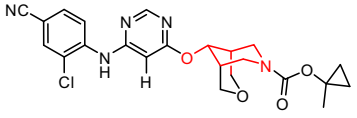
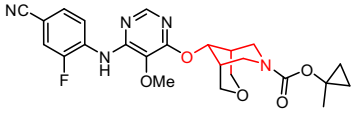
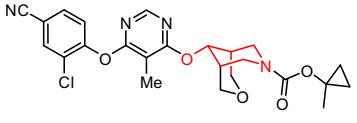


Figure 6. Profile of compounds **23** and **24**. [a]% glucose lowering relative to vehicle treated group. [b]plasma AUC_{0-6h} determined following oral administration of compound in 20% hydroxypropyl β-cyclodextrin vehicle. Plasma levels averaged from 2 rats following serial bleeding in Sprague–Dawley rats.

Table 1
SAR of scaffold **C**

Compound	*h*EC_{50} (nm) (% max)	*m*EC_{50} (nm) (% max)	*mo*GTT[a]@ 3 mpk (%)	Rat AUC_{0-6h} (nM h)[b]@10 mpk
 **25a**	7 (88)	43 (99)	78	8235
 **25b**	25(88)	254 (105)	78	1189
 **25c**	5 (99)	47 (116)	78	1425
 **25d**	16 (78)	128 (143)	75	1490

[a] % glucose lowering relative to vehicle treated group.[6]
[b] Plasma AUC_{0-6h} determined following oral administration of compound in 20% hydroxypropyl β-cyclodextrin vehicle. Plasma levels averaged from 2 rats following serial bleeding in Sprague–Dawley rats.

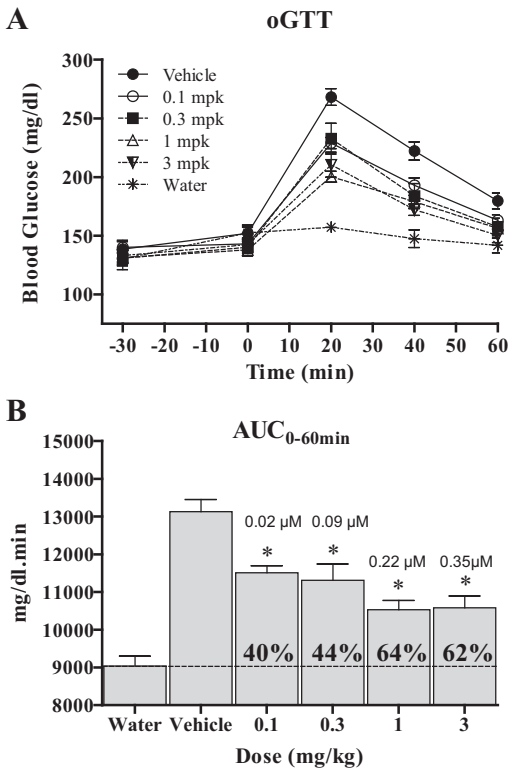


Figure 7. oGTT PK/PD response of orally administered compound **25a** in lean mice (10% NMP, 5% cremophor, and 20% HPβCD vehicle).

exposure of **23** likely compensating for it weaker potency at mouse GPR119 relative to **24**. Compounds **23** and **24** were also evaluated in an oral rat pharmacokinetic assay and both compounds showed high, sustained plasma exposures.

Having identified highly potent GPR119 agonistic activity having scaffold **C** of **24**, we shifted our focus to modifications elsewhere in these molecules. Several examples are highlighted in Table 1 and encompassed the substituent at the 5-position of the pyrimidine core (**25a** and **25b**), the halogen substituent on the phenyl ring (**25c**), and the linker between the phenyl and pyrimidine rings (**25d**). These compounds retained potent human GPR119 EC_{50} values while maintaining a consistent trend of being an order of magnitude less potent at mouse GPR119. In general, these compounds also had strong agonist properties as reflected by the high % max values for human and mouse GPR119. The compounds uniformly displayed excellent in vivo activity in the mouse oGTT assay when orally administered at a dose of 3 mg/kg. In a pharmacokinetic and pharmacodynamic dose–response study in lean mice (Fig. 7),[12] compound **25a** orally administered across the dose range 0.1–3 mg/kg elicited a dose dependent lowering of blood glucose excursion (as represented by the glucose AUC excursion from 0 to 60 min) with statistically significant lowering observed at all doses. The total plasma concentrations of **25a** increased in a less than dose proportional across the dose range. Additionally, **25a** maintained improved solubility with measured solubility 30 μM in pH 7.4 buffer.

In summary, we prepared and profiled a series of GPR119 agonists that incorporated two distinct conformationally restricted oxazabicyclic scaffolds: 3-oxa-9-azabicyclo[3.3.1]nonan-7-ol (scaffold **B**) and 3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (scaffold **C**), with a goal of improving the solubility over an initial lead **4**. From this work, we have discovered a potent and orally active GPR119 agonist **25a**, incorporating scaffold C, which lowered blood glucose significantly in the mouse oGTT assay at low oral doses and plasma levels. Our subsequent efforts that led to the identification of a highly effective molecule in the 3-oxa-7-azabicyclo[3.3.1]nonan-9-ol series will be detailed elsewhere.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.09.047.

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5. Detail information of cAMP assay is available in the Supporting information.
6. Compounds were initially screened in vivo using an acute oral glucose tolerance test (oGTT) in male C57B1/6NCrl mice (6–8 week old). Test compound or vehicle was orally administered to overnight-fasted animals at 3 mg/kg. Glucose was administered to the animals 30 min post-dosing (3 g/kg p.o.) and blood glucose levels were measured using a hand-held glucometer (Bayer Breeze 2) prior to compound or vehicle dosing, prior to glucose administration, and 20 min after glucose administration. The glucose level of mice dosed with test compound was expressed as a percentage of the glucose level in vehicle treated mice (defined as 100%).
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11. NMR studies of **19** and **20** are available in the Supporting information.
12. oGTT dose response studies were conducted in a similar manner as acute oGTT with the following modifications. A vehicle-treated group challenged with water rather than glucose was included in the study. Blood glucose was measured prior to compound or vehicle dosing, prior to glucose or water administration, and 20, 40, and 60 min after glucose or water administration. The glucose area under the curve (AUC) from 0 to 60 min was calculated and compared to the vehicle treated group.