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Design of potent and selective GPR119 agonists for type II diabetes

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ABSTRACT

Screening of the Merck sample collection identified compound **1** as a weakly potent GPR119 agonist (hEC_{50} = 3600 nM). Dual termini optimization of **1** led to compound **36** having improved potency, selectivity, and formulation profile, however, modest physical properties (PP) hindered its utility. Design of a new core containing a cyclopropyl restriction yielded further PP improvements and when combined with the termini SAR optimizations yielded a potent and highly selective agonist suitable for further preclinical development (**58**).

Agonism of the GPR119 receptor has recently emerged as a promising new approach for the treatment of type 2 diabetes mellitus.[1] GPR119 is a X-linked class A GPCR[2] whose expression in humans, mice and rats is highly restricted to pancreatic islets and specific intestinal regions.[3] GPR119 agonists have been implicated in the control of both incretin secretions (e.g., GLP-1)[1b,3b] and islet hormone release (i.e., insulin)[4] in mediating glucose homeostasis. Additionally, dosing of a synthetic GPR119 agonist has been reported to lower plasma glucose levels in an oral glucose tolerance test (OGTT) both preclinically[4] and clinically.[5]

The promise of GPR119 agonists to modulate glucose homeostasis through both an incretin-dependent (i.e., L-cell GLP-1 release) and an incretin-independent mechanism (i.e., beta cell insulin release) has attracted considerable attention as evidenced by many new patent filings[1] and presentations.[6] Recently, two detailed reports have appeared on the synthesis and characterization of synthetic GPR119 agonists.[7] Herein we report the synthesis, SAR optimization and in vivo effects on glucose plasma levels during an OGTT for a novel family of GPR119 agonists.

A new GPR119 agonist (**1**) was identified by screening the Merck sample collection (Table 1). This bis-piperidine class of agonists was characterized by poor PP (i.e., low aqueous solubility and high plasma protein binding), high mouse clearance, insufficient potency, and poor hERG selectivity. A key challenge for these agonists was optimizing the combination of solubility and selectivity while generating robust in vivo efficacy.

To develop agonists with a suitable profile, two SAR optimizations were simultaneously initiated. First, for the bis-piperidine core, the SAR of eastern and western amino moieties were investigated, focusing on identifying polar, solubilizing substituents. This initial strategy was to identify suitably polar and metabolically stable groups for either termini and thus improve both physical properties and hERG selectivity. A second focus, was modification of the agonist core to identify a new scaffold with an improved profile. Knowing that design of new cores would be more time intensive than termini optimization, we utilized molecular modeling and overlayed the core of **1** with another GPR119 agonist[7a] to aid design. The premise was that if the new core mapped similar space as the other agonists it would be possible to merge the information from these diverse exercises into a single, optimized molecule.

The synthesis of the bis-piperidine agonists has been previously reported with full experimental and spectral characterization.[8] The Boc containing bis-piperidines were synthesized by reaction of the commercially available Boc-amine with either: an appropriate aryl halide using the palladium catalyzed coupling protocol of Buchwald,[9] or S_NAr of a suitable heteroaryl halide at elevated temperatures to afford the desired analogs (**1**–**21**, Scheme 1). The Boc group was removed with TFA and the resulting amine further functionalized using the two methods described above to provide agonists **22**–**36** (Scheme 1).

To discover novel core scaffolds a series of racemic cyclopropanol intermediates was prepared (Scheme 2). The synthesis of all the cyclopropyl derivatives have been previously reported with full

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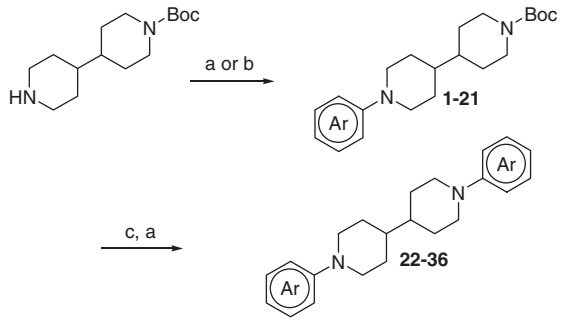
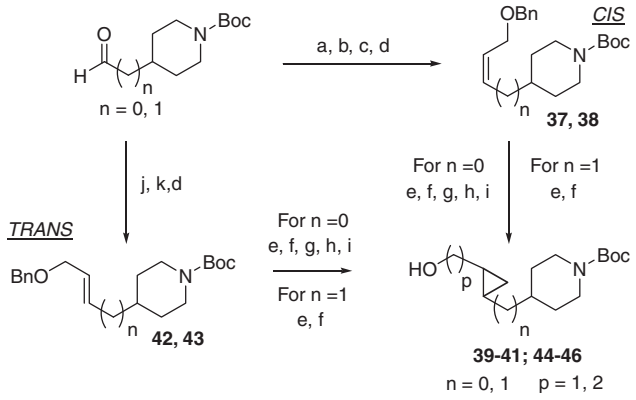


Scheme 1. Synthesis of various bis-piperidine agonists. Reagents and conditions: (a) Het-X, Cs_2CO_3 or DBU, 50–130 °C; (b) Ar-X, $Pd(OAc)_2$, Cs_2CO_3, toluene, 90 °C, PhDavePhos; (c) TFA (neat), rt.

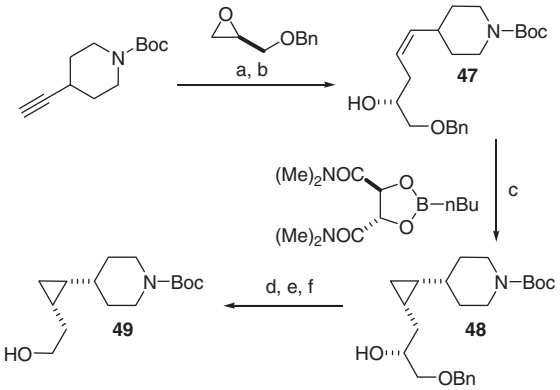


Scheme 2. Synthesis of various cyclopropanol core scaffolds. Reagents and conditions: (a) PPh_3, CBr_4; (b) *n*BuLi, $(CH_2O)_n$; (c) 5% Pd on $CaCO_3$ poisoned with Pb, quinoline, EtOAc, H_2; (d) BnBr, NaH, DMF; (e) Et_2Zn, $ClCH_2I$, DCE, −18 °C to −10 °C; (f) 20% $Pd(OH)_2$, H_2, 1:1 EtOAc/EtOH, 50 psi; (g) TPAP, NMO, DCM, rt; (h) *n*BuLi, Ph_3PCH_2I, THF, −78 °C; (i) (a) BH_3Me_2S, THF; (b) NaOH; (c) H_2O_2; (j) $P(O)(OEt)_2CH_2CO_2Me$, LiCl, DBU, rt; (k) DIBAL-H, DCM, −78 °C.

experimental and spectral characterization.[10] For the preparation of the *cis*-cyclopropanols, the aldehyde (n = 0, 1) was reacted with carbon tetrabromide and triphenyl phosphine and the resulting dibromo-olefin treated with *n*-butyl lithium to afford an alkyne. Reduction with Lindlar's catalyst gave the necessary *cis*-alkenes which were protected as the benzyl ethers (**37**, **38**; n = 0, 1). Cyclopropantion using a modification of the Charette cyclopropanation followed by hydrogenolysis gave the desired *cis*-cyclopropanols (**39**, **40**; n = 0, 1; p = 1) (Scheme 2).[10,11] Additionally, **39** (n = 0, p = 1) could be homologated by a sequence of TPAP oxidation, Wittig olefination, hydroboration and boronate oxidation to give the homologated *cis*-cyclopropanols (**41**; n = 0, p = 2).

Similarly the *trans*-cyclopropanols were obtained via an analogous sequence. The aldehyde (n = 0, 1) was transformed under Horner–Emmons olefination to provide the *trans* olefin. The ester was reduced with DIBAL-H and the resulting alcohol protected as the benzyl ether (**42**, **43**; n = 0, 1). Cyclopropanation and benzyl deprotection proceeded as described for the *cis* route to give the desired *trans*-cyclopropanols (**44**, **45**; n = 0, 1; p = 1) (Scheme 2). Additionally the *trans*-cyclopropanol **44** (n = 0, p = 1) could be homologated as described above to give the extended *trans*-cyclopropanol (**46**, n = 0, p = 2).

Cyclopropane scaffold **49** was of particular interest and to obtain large quantities of this chiral intermediate we developed a large scale double, diastereoselective protocol[10] based on Charette's enantioselective cyclopropanation reaction[11] (Scheme 3). The starting alkyne was reacted with the (*R*)-glycidyl epoxide to provide the (*R*)-glycidyl **47**. Reduction with Lindlar's catalyst and

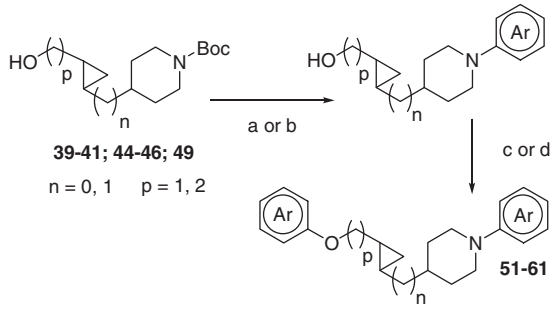


Scheme 3. Chiral cyclopropanol scaffold synthesis. Reagents and conditions: (a) *n*BuLi, $BF_3{\cdot}Et_2O$, epoxide; (b) 5% Pd on $CaCO_3$ poisoned with Pb, quinoline, EtOAc, H_2; (c) Et_2Zn, CH_2I_2, dioxaborolane, DCM, Et_2O (1 equiv), −20 °C to −0 °C; (d) 20% $Pd(OH)_2$, H_2, 1:1 EtOAc/EtOH, 50 psi; (e) $NaIO_4$, DCM, water, 0 °C; (f) $NaBH_4$, EtOH, rt.

cyclopropanation using the (*S*, *S*) dioxaborolane as a chiral auxiliary afforded the chiral diastereomeric cyclopropanation products **48** (93:7 dr).[10] Subsequent debenzylation with palladium hydroxide, periodate oxidation of the diol and reduction of the resulting aldehyde furnished the desired chiral cyclopropane. A final chiral chromatographic separation gave the desired *cis*-cyclopropanol **49** in >99:1 er. In contrast, not using the chiral ligand or not incorporating the chiral alcohol gave much lower enantioselection (83:17 dr and 78:22 er, respectively).

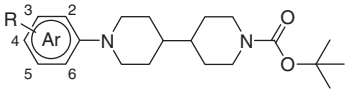
The final cyclopropane agonists were synthesized in a route analogous to the bis-piperidines (Scheme 4). The Boc groups (**39**–**41**, **44**–**46**, **49**) were removed with TFA and coupling with an appropriate heterocyclic-halide provided the desired aryl intermediates. Mistunobu reaction of the alcohol gave agonists **51**–**57** and **59**. Alternatively, deprotonation of the alcohol with sodium hydride and reaction with a heteroaryl-halide gave compounds **58**, **60**, **61**. In some cases the racemic compounds were resolved using chiral chromatography (**54**, **55**) or the single enantiomers were prepared directly (**58**–**61**) from **49** (Scheme 4).

After identification of **1** as a weakly potent GPR119 agonist the termini optimization of the bis-piperidine core began with the SAR of the western aryl (Table 1). Compound efficacy was evaluated for the human and mouse receptors in vitro using a GPR119 HTRF cAMP activation assay.[8,10] Removal of the pyridyl nitrogen gave the phenyl analog **2**, which formed a platform for rapid investigation. A methyl group was substituted around the phenyl ring (**3**–**5**). Substitution at the *meta* (**4**) and *para* (**5**) positions improved potency, while *ortho* (**3**) substitution reduced activity. In general, for the agonists described herein, *ortho* substitution was poorly



Scheme 4. Synthesis of various cyclopropane agonists. Reagents and conditions: (a) TFA (neat), rt; (b) Het-X, Cs_2CO_3, NMP; (c) DBAD, (polymer)-Ph_3P, DCM, THF; (d) (i) NaH, 0 °C, (ii) Het-X, rt.

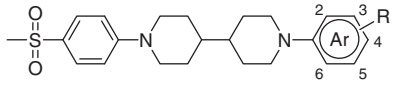
Table 1
Bis-piperidine SAR: western aryl optimization[a,b]



Compd	Ar	R	hGPR119 EC_{50} (nM)	mGPR119 EC_{50} (nM)
1	3-Pyridyl	H	3.6 K	NA
2	Ph	H	1.4 K	NA
3	Ph	2-Me	NA	NA
4	Ph	3-Me	514	NA
5	Ph	4-Me	338	1.9 K
6	Ph	4-SO_2Me	22	36
7	Ph	3-SO_2Me	1.9 K	NA
8	Ph	4-SOMe	11	132
9	Ph	4-C(O)Me	25	341
10	Ph	4-SMe	600	513
11	Ph	4-C(O)NH_2	76	165
12	Ph	3-C(O)NH_2	NA	NA
13	2-Pyridyl	H	831	2.5 K
14	2,4-Pyrimidyl	H	116	379
15	2,6-Pyrimidyl	H	526	523
16	2,5-Pyrazinyl	H	103	142
17	2,4-Pyrimidyl	3-CN	6	11
18	2,4-Pyrimidyl	5-CN	6	31
19	2,4-Pyrimidyl	3-CN, 5-Me	1	2
20	2,4-Pyrimidyl	3-Me, 5-CN	2	2
21	2,4-Pyridyl	3-Me, 5-CN	15	119

[a] Values are means of at least two independent titrations.
[b] NA = not active, <10% activation at 10 μM.

Table 2
Bis-piperidine SAR: eastern aryl optimization[a,b]



Compd	Ar	R	hGPR119 EC_{50} (nM)	mGPR119 EC_{50} (nM)
22	2-Pyridyl	H	39	682
23	2,5-Pyrazinyl	H	201	239
24	2,6-Pyrimidyl	H	98	887
25	2,6-Pyrimidyl	4-Me	57	45
26	2,6-Pyrimidyl	3-Me	NA	NA
27	2-Pyridyl	4-Cl	48	131
28	2-Pyridyl	4-F	19	206
29	2-Pyridyl	4-Me	18	73
30	2-Pyridyl	4-CN	62	41
31	2-Pyridyl	4-CF_3	13	8
32	2,6-Pyrimidyl	4-Cl	5	8

[a] Values are means of at least two independent titrations.
[b] NA = not active, <10% activation at 10 μM.

tolerated generally producing inactive compounds; with the exception being small groups (i.e., fluorine or nitrogen lone pair). Indications from competitors patents[1b] led to preparation of a series of methyl sulfones. *para*-Substitution (**6**) was preferred, however *meta* substitution (**7**) greatly reduced activity. While **6** had improved in vitro potency by >163-fold, the utility of this compound was limited due to poor solubility in dosing vehicles and PK (Table 3). To better understand the improvement in potency, a series of related analogs were prepared **8**–**10**. Sulfoxide **8**, and ketone **9** were roughly equipotent to **6**, while sulfide **10** lost >27-fold in potency suggesting that a key contact is formed by an oxygen lone pair in the *para* position promoting agonism. Interestingly, while the primary *para* amide **11** was a potent agonist, the *meta* amide **12** was inactive further supporting the model that a lone pair at this position is a key feature to potentiate agonism.

Table 3
Mouse pharmacokinetic parameters for GPR1119 agonists[a]

Compd	Cl (ml/min/kg)	Vd_{ss} (L/kg)	$t_{1/2}$ (h)	AUC_n (μM h kg/mg)
6	120	6.9	0.6	0.09
27	2	2.3	13.5	19.3

[a] 2/10 mpk iv/po.

Next, a series of aromatic heterocycles was investigated, which in principle, would improve both physical properties and potency by appropriate display of a nitrogen lone pair. Introduction of nitrogen at the 2-position (**13**) was tolerated and equipotent with phenyl **2** thus a series of related heterocycles were prepared which displayed a second lone pair at the 2, 3, and 4-positions (**14**–**16**). As the previous analysis indicated, positioning a lone pair in either the *meta* or *para* position gave a >10-fold increase in potency (**14**, **16**) without increasing molecular weight. A variety of substituted heterocycles were surveyed, focusing on substituents with the potential to be metabolically, non-displaceable (e.g., cyano and methyl). Addition of a nitrile at either the 3- or 5-position (**17**, **18**) greatly improved potency (>20-fold). Gratifyingly, addition of a second methyl substituent (**19**, **20**) was additive and further increased potency to provide single digit nanomolar agonists. Other substituted heterocycles were investigated (e.g., **21**), however, these analogs were all less potent than the corresponding pyrimidines, especially on the GPR119 mouse receptor.

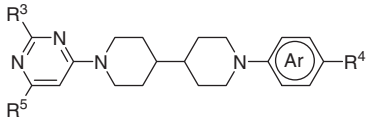
SAR optimization of the eastern group focused on PK improvement. It was postulated that the Boc group was a key driver of the poor PK observed (Tables 3 and 6) and replacement with a metabolically stable heterocyclic isostere would improve the profile. A series of heterocycles were surveyed, and pyridines, pyrazines, and pyrimidines were all well tolerated **22**–**24**. In general, for the eastern aryl, substitution was allowed at the 2, 4, and 6-positions, while substitution at the 3- or 5-positions greatly decreased potency. For example, 4-methyl substitution (**25**) yields a potent agonist (hEC_{50} = 57 nM), while 3-substitution is completely inactive (**26**).

A substituent survey was conducted for a series of 4-substituted pyridines, with a bias towards metabolically robust groups (**27**–**31**). It was observed that methyl, chloro, fluoro, cyano and CF_3 were acceptable (Table 2). A potent 4-chloro analog **27** (hEC_{50} = 48 nM) was identified and profiled in mouse PK to test this replacement strategy. Comparison of the pyridyl replacement **27** to the Boc parent **6** demonstrates that replacement of the Boc with a heterocyclic bioisostere greatly improves the PK profile (Table 3). Notably, plasma clearance decreased from 120 (ml/min/kg) for **6** to 2 (ml/min/kg) for agonist **27**. From this basis set, the best substituents were added onto other allowed heteroaryls to identify other preferred replacements, that is, 4-chloro pyrimidine (e.g., **32**), and 4-methyl pyrimidine/pyrazine (Table 4).

With optimized eastern and western subunits identified, a matrix exercise was initiated to determine the optimal combination of groups for both termini (Table 4). Compounds were profiled for their GPR119 potency, hERG selectivity, and efficacy in OGTT.[13] The four optimized compounds are shown in Table 4 (**33**–**36**). As predicted, all the agonists possess good to excellent potency, however, the key issue was insufficient hERG selectivity. Compounds **33** and **34** were disqualified from further profiling due to unacceptable hERG activity (**33**, **34**). Surprisingly, while **35** and **36** are pyrimidine regioisomers, **35** had no in vivo efficacy at 30 mpk. Ultimately, **36** was identified as having the best overall profile from the bis-piperidines possessing the desired combination of in vitro potency, OGTT efficacy, and physical properties suitable for high level dosing (i.e., 750 mpk) and advanced in vivo profiling.

While **36** possessed an acceptable profile for early development, the PP were insufficient to provide a formulation usable for later

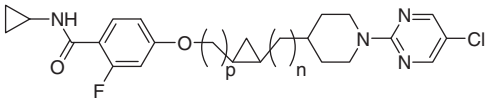
Table 4
Optimized agonists combining east and west aryls



Compd	R^3, R^5	Het	R^4	hGPR119 EC_{50} (nM)[a]	mGPR119 EC_{50} (nM)[a]	hERG IC_{50} (nM)[a]	OGTT[b] Dose (mpk)	OGTT[b] % glu. Corr.[c]
33	3-CN, 5-Me	2,6-Pyrimidyl	Cl	2	11	277	30	37*
34	3-Me, 5-CN	2,6-Pyrimidyl	Me	8	10	1.8 K	30	46*
35	3-Me, 5-CN	2,5-Pyrazinyl	Me	30	82	5.4 K	30	7
36	3-CN, 5-Me	2,5-Pyrazinyl	Me	19	24	10.6 K	1, 3, 10, 30	7, 26*, 30*, 35*

[a] Values are means of at least two independent titrations.
[b] HFF mice (3 weeks on diet) were po dosed qd and the glucose AUC monitored.[13]
[c] *P* values of ⩽0.05 indicated by *.

Table 5
Core SAR: scaffold optimization[a]



Compd	*n*, *p*	Stereo[b]	hGPR119 EC_{50} (nM)	mGPR119 EC_{50} (nM)	hERG IC_{50} (nM)
50[c]	–$(CH)_3$–	NA	0.2	0.8	>30 K
51	0, 1	*cis*	38	9	1.5 K
52	0, 1	*trans*	20	23	1.9 K
53	0, 2	*cis*	0.3	0.4	>30 K
54	0, 2	*trans* (+)	14	5	>30 K
55	0, 2	*trans* (−)	3	2	2.6 K
56	1, 1	*cis*	18	36	1.2 K
57	1, 1	*trans*	9	18	>30 K

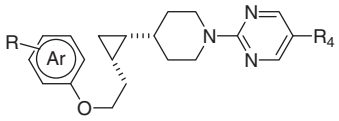
[a] Values are means of at least two independent titrations.
[b] All compounds are racemic except where noted.
[c] Acyclic lead with no cyclopropyl restriction in the methylene chain. Prepared from commercially available SM.

stage testing, thus a new core with improved PP was required. There was a correlation between poor formulatability of certain bis-piperidine analogs and high crystallinity of those solids. It was postulated that a new core with increased flexibility and/or less symmetry would improve PP. The initial design was simple opening of a piperidine ring to form the corresponding acyclic 4 atom chain (with an oxygen for nitrogen replacement) **50**. While this agonist had the desired combination of potency and PP, shortly after being identified a competitors patent[14] appeared necessitating further core development.

Next, a cyclopropane restriction was incorporated into the chain and both the (*rac*)-*cis* (**51**) and (*rac*)-*trans* (**52**) isomers were prepared. While both potency and selectivity were decreased, the restricted analogs remained active providing an avenue for further design. Addition of a second methylene gave the homologated *cis*- (**53**) and *trans*-cyclopropanes (**54**, **55**). The two *trans*-enantiomers were separated, however both these analogs suffered from either loss of potency (**54**) or poor selectivity (**55**) (Table 5). Interestingly, the *cis*-cyclopropane scaffold is highly optimized for GPR119 agonism (**53**), possessing picomolar activity and excellent hERG selectivity. It was determined that most of the potency resided in only one enantiomer, and the absolute configuration for the more potent antipode is shown **60**.[12] For example, **61** is >250-fold more potent (GPR119 hEC_{50}) than the less active isomer (Table 6). Additionally, the corresponding *cis* and *trans*-cyclopropyl regioisomers were prepared (**56**, **57**; $n = 1$, $p = 1$), however these cores had insufficient potency and selectivity (Table 5).

A second matrix optimization was conducted combining this newly identified scaffold and the best eastern/western termini from the prior SAR. Compounds were selected based on hGPR119 in vitro potency, hERG selectivity, PP (quantified by measured solubility in PEG400) and efficacy in OGTT. The four best analogs identified are shown in Table 6. All compounds **58**–**61** possessed excellent in vitro potency (Table 6) and mouse PK.[15] hERG selectivity was identified as a key issue, thus compounds were profiled in a patch clamp hERG assay and determined to have acceptable (**61**) to excellent selectivities (**58**–**60**). For the western SAR, three new groups were developed as extensions of the prior SAR, and included in the matrix (**58**–**60**). It was determined that 2-pyridyl analogs were equipotent with phenyl, and these pyridyl analogs had improved log *D*'s (e.g., **58** and **60**) and improved solubilities (Table 6). Additionally, the potent cyclopropyl amide SAR (Table 5) was optimized by bioisosteric replacement of the amide with stable, five-membered heterocycles. While a variety of heterocycles was explored (e.g., pyrazole, triazoles, tetrazoles, and oxadiazoles), the 1,2,3-triazoles were ultimately identified as superior (**59**, **60**).

Table 6
Optimized cyclopropyl agonists combining the east and west aryl SAR



Compd	Ar	R	R_4	hGPR119 EC_{50} (nM)[a]	mGPR119 EC_{50} (nM)[a]	hERG(patchclamp) IC_{50} (nM)	Solubility[c] PEG400 (mg/ml)	OGTT[b] MEDmax (mpk)
58	2-Pyridyl	4-SO_2Me	Cl	4	4	19 K	7.1	1–3
59	Ph	4-(1,2,3-triazolyl)	Cl	4	6	19 K	5.0	10
60	2-Pyridyl	4-(1,2,3-triazolyl)	Cl	2	4	44 K	11.4	1–3
61	2,6-Pyrimidyl	3-Me, 5-CN	Me	2	2	4 K	24.8	0.01–0.03

[a] Values are means of at least two independent titrations.
[b] HFF mice (3 weeks on diet) were po dosed qd and glucose AUC monitored. MEDmax is the minimal dose for maximal efficacy.[13]
[c] Equilibrium values reported after comparison at 3 and 7 days.

Notably, these agonists (**58**–**61**) possessed good in vitro potencies, however, it was their physical properties, selectivity and efficacy in OGTT that differentiated these agonists (Table 6). Solubilities ranged from modest (**59**) to excellent (**61**). Each compound **58**–**61** was titrated in OGTT and the MEDmax (minimal efficacious dose for maximal efficacy) determined.

While the in vitro potencies were uniformly excellent (GPR119 hEC_{50} from 2 to 4 nM) the in vivo efficacy of these agents differed dramatically (MEDmax from 10 to 0.01 mpk). It is interesting to compare the correlation of compound solubility in PEG400 and the MEDmax. Notably, increased solubility correlates with an impressive increase in OGTT efficacy. Based on the combination of superior solubility and in vivo potency, **61** was selected for advanced profiling. Unfortunately, **61** was ultimately disqualified due to unacceptable QTc prolongation in the CV dog. With this QTc issue identified **58** was selected for further testing. Compound **58** combines excellent off-target selectivity (i.e., counterscreening against a panel of 175 receptors identified only two weak, micromolar hits) with good in vivo efficacy, and was shown to have no effects in the CV dog. This systematic combination of eastern, western and core SAR investigations lead to a series of agonists that successfully combine excellent in vivo potency, selectivity, and PP, and ultimately identified **58** as a candidate suitable for further preclinical investigation.

In summary, a new series of GPR119 agonists is presented. Synthetic methodology was described for the chiral synthesis of the key chiral cyclopropane scaffold. Information from the systematic SAR optimization of both terminal ends was successfully merged onto new agonist scaffolds. These combined optimizations lead to the identification of highly potent and selective agonists which successfully combine excellent in vivo potency, selectivity, and physical properties.

Acknowledgment

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