Design and Synthesis of Novel, Selective GPR40 AgoPAMs

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S Supporting Information

ABSTRACT: GPR40 is a G-protein-coupled receptor expressed primarily in pancreatic islets and intestinal L-cells that has been a target of significant recent therapeutic interest for type II diabetes. Activation of GPR40 by partial agonists elicits insulin secretion only in the presence of elevated blood glucose levels, minimizing the risk of hypoglycemia. GPR40 agoPAMs have shown superior efficacy to partial agonists as assessed in a glucose tolerability test (GTT). Herein, we report the discovery and optimization of a series of potent, selective GPR40 agoPAMs. Compound 24 demonstrated sustained glucose lowering in a chronic study of Goto Kakizaki rats, showing no signs of tachyphylaxis for this mechanism.

KEYWORDS: GPR40, FFA1, GPCR, diabetes, insulin secretagogue, agoPAM, chroman

Type II diabetes is characterized by an inability to maintain glucose homeostasis due to insulin desensitization and insufficient insulin secretion.¹ GPR40 (FFAR1 or FFA1) is a G-protein-coupled receptor that is primarily expressed in pancreatic beta cells, intestinal enteroendocrine cells, and the brain.² When activated by its endogenous ligands (medium/long chain fatty acids), GPR40 elicits insulin secretion only in the presence of elevated glucose levels, making it a target of significant therapeutic interest due to a potentially reduced risk of hypoglycemia.³

Numerous groups have reported clinical candidates as novel insulin secretagogues via GPR40 agonism as a potential treatment for diabetes.^{4–7} To date, all GPR40 modulators that have been assessed in a clinical setting are partial agonists (Figure 1). Recently, researchers at Amgen^{8–10} and Bristol–Myers–Squibb¹¹ have reported several GPR40 agonists that operate as full agonists with positive allosteric modulation (effectively agoPAMs or ago-allosteric)^{12,13} on the endogenous ligands (e.g., DHA). GPR40 agoPAMs exhibit superior levels of receptor activation *in vitro* (so-called “full agonists”) and demonstrate superior *in vivo* efficacy versus the previously described partial agonists. In addition to stimulating insulin

secretion via pancreatic action, GPR40 agoPAMs have been reported to stimulate GLP-1 secretion in the gut, potentially accounting for the observed enhancement in efficacy.¹⁴

Given the promising level of glycemic control from the agoPAM mode of GPR40 activation, it became our objective to identify full agoPAM GPR40 modulators with clean off-target profiles in order to assess the risk of tachyphylaxis (desensitization) in a chronic setting. The medicinal chemistry strategy deployed in order to achieve this objective was to improve the off-target profiles through the design of conformationally constrained GPR40 agonists with acceptable physical properties (Figure 2).

Researchers at Amgen have shown that partial agonists and agoPAMs show differentiated levels of receptor activation in transiently transfected CHO cells expressing relatively low levels of hGPR40.¹⁰ The primary cell-based assay used for compound optimization measured inositol monophosphate (IP1) accumulation in HEK293 cells stably expressing human

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Figure 1. GPR40 “full agonists” and partial agonists.

Figure 2. Medicinal chemistry tactics to identify GPR40 agoPAMs with improved ligand efficiency.

GPR40 (hGPR40/HEK293). This cell line was designed to clearly differentiate the efficacy of partial agonists versus AgoPAMs and assess the impact of plasma proteins on potency in approaching 100% human serum (HS). Figure 3 shows that

Figure 3. AgoPAMs deliver increased % activation in IP1 assay.

while the partial agonist AMG837 delivers a standardized receptor activation of 100%, the full agoPAM AM1638 demonstrates approximately 400% activation. Moreover, the potencies of AMG837 and AM1638 are right shifted in the presence of HS.

We initiated our investigation into the structure–activity relationship (SAR) of agoPAMs by examining the impact of removing the dimethylcyclopentenyl moiety of AM-1638 (1). Interestingly, the potency of 7 (Table 1) was retained; however, the human serum-shifted IP1 potency was greatly diminished. Next, in an effort to install conformational constraint, we

Table 1. Initial Identification of Chroman agoPAMs

cpd	hIP1 EC50 ^a	
	0% HS +/- SD (%act)	+100% HS +/- SD (%act)
1	130 +/- 63 (465%)	392 +/- 107 (209%)
7	79 +/- 15 (420%)	>10k
8	58 +/- 1.5 (388%)	139 +/- 2.6 (197%)
9	90 +/- 8.4 (428%)	123 +/- 26 (197%)
10	36 +/- 22 (447%)	1690 +/- 466 (277%)
11	18 +/- 11 (388%)	5010 +/- 688 (177%)
12	816 +/- 234 (377%)	3120 +/- 365 (139%)
13	1252 +/- 332 (159%)	>10k

^aMean of at least two runs.

cyclized the phenyl propionic acid headpiece onto the benzyl ether linker, making a chroman ring system (compounds 8 and 9, which are epimeric at the benzylic chroman position). This resulted in an improvement in the 100% HS IP1 potency. Removal of the dimethylcyclopentenyl moiety from this derivative resulted in compounds 10 and 11, which exhibited improved potency and physical properties (lower molecular weight and logD) relative to compounds 8 and 9 at the expense of decreased HS-shifted IP1 potency. In an effort to further benchmark the impact of substituents, the 2-fluoro-5-methoxy phenyl and cyclopropyl moieties were removed, resulting in compounds 12 and 13, respectively. Both modifications resulted in a significant loss of potency.

We next examined a variety of substituents at the meta position of the B ring. Incorporation of the methyl neopentoxy fragment known in previous GPR40 agoPAMs¹⁰ led to a marked improvement in potency and serum shift (Table 2, compounds 14 and 15, which are diastereomeric at the benzylic chroman position). Noting the high molecular weight and HPLC logD of these derivatives, we removed the *t*-butyl fragment to give compounds 16 and 17. This resulted in a loss of potency. Replacing the *t*-butyl group with a cyclopropyl group in 18, however, resulted in a log unit improvement in logD while retaining potency. In an effort to further improve the physicochemical profile, we examined smaller, heteroatom-containing substituents such as nitrile and trifluoromethoxy analogues 22 and 23. While these modifications improved physical properties, both resulted in a loss of potency as compared to compounds 14 and 15.

Returning to the notion of conformational constraint, we next examined the possibility of restricting the phenyl propionic acid headpiece to its active conformation by installing a methyl group alpha to the carboxylic acid (Table 3). We postulated that vicinal stereocenters at the positions alpha and beta to the carboxylic acid would restrict free rotation, potentially enhancing potency and selectivity. Incorporation of the *S*-configured methyl substituent (*trans* relative configuration) resulted in a remarkable improvement in potency over the des-methyl derivatives 10 and 11. The *R* diastereomer provided no improvement in potency. Finally, in an effort to further improve

Table 2. Exploration of B Ring SAR

		hPI1 EC50 ^a (nM)	
R	compound	0% HS +/- SD (%act)	100% HS +/- SD (%act)
	8	58 +/- 1.5 (388%)	139 +/- 2.6 (197%)
	9	90 +/- 8.4 (428%)	123 +/- 26 (197%)
	14	7.3 +/- 2.0 (512%)	14 +/- 6.0 (292%)
	15	7.8 +/- 2.7 (444%)	22 +/- 8.8 (347%)
	16	61 +/- 29 (465%)	1623 +/- 331 (238%)
	17	101 +/- 47 (450%)	4290 +/- 1370 (192%)
	18	5.2 +/- 0.4 (284%)	154 +/- 56 (225%)
	19	25 +/- 12 (365%)	762 +/- 573 (327%)
	20	23 +/- 4.5 (321%)	531 +/- 326 (219%)
	21	35 +/- 20 (323%)	1210 +/- 709 (221%)
	22 (2 isomers)	296 +/- 191 (391%)	5450 +/- 1080 (87%)
	23 (2 isomers)	29 +/- 17 (408%)	416 +/- 138 (207%)

^aMean of at least two runs.Table 3. α -Methyl and B-Ring Pyridyl

		hPI1 EC50 ^a (nM)	
compound		0% HS +/- SD (%act)	100% HS +/- SD (%act)
	10	36 +/- 22 (448%)	1690 +/- 467 (277%)
	11	18 +/- 11 (470%)	5010 +/- 688 (177%)
	24	1.1 +/- 0.4 (428%)	146 +/- 58 (383%)
	25	2.6 +/- 1.1 (420%)	127 +/- 66 (383%)
	26	56 +/- 39 (464%)	4010 +/- 2490 (232%)
	27	92 +/- 99 (460%)	3480 +/- 1240 (322%)
	28 (2 isomers)	16 +/- 5.1 (538%)	2530 +/- 684 (222%)
	29	1.7 +/- 1.1 (428%)	1380 +/- 636 (305%)
	30	3.1 +/- 1.5 (408%)	247 +/- 148 (335%)
	31	30 +/- 21 (330%)	>10k
	32	43 +/- 22 (376%)	4040 +/- 3090 (165%)

^aMean of at least two runs.

the physicochemical profile of our series, we replaced the B-ring phenyl with a pyridine ring. This resulted in compounds **29** and **30**, which were comparable in potency to phenyl derivatives **24** and **25**, although the impact of serum on potency was greater.

The preparation of biaryl chroman agoPAMs is exemplified by the synthesis of **24** (Scheme 1). α -Methylation of the TBS ether of **33**¹⁰ resulted in a ~2:1 (R/S) mixture of

Scheme 1^a

^aReagents and conditions: (a) TBSCl, imidazole, DMF, 98%; (b) LDA, MeI, THF; then KOtBu, HCl; (c) TBAF, THF, 70% over 3 steps, 3:1 dr **36/35**; (d) paraformaldehyde, MgCl₂, TEA, MeCN, 74%; (e) NaBH₄, MeOH, 95%; (f) Pd(PPh₃)₄, K₂CO₃, dioxane, 93%; (g) Montmorillonite K10, LiClO₄, H₂O, MeNO₂, 36%; (h) LiOH, MeOH, H₂O, THF, 60 °C, 96%; (i) SFC separation, AD-H chiralpak, 60% IPA/CO₂ with 0.2% HN(iPr)₂ modifier.

diastereomers. Epimerization of this mixture to deliver primarily the (S)-configured α -methyl diastereomer was affected via deprotonation with KOtBu followed by quenching with HCl to deliver a 1:3 mixture of diastereomers, favoring the desired (S) isomer. TBS deprotection with TBAF gave a separable mixture of phenol compounds **35** and **36**. The (S)-configured methyl diastereomer **36** was formylated and then reduced to give diol **37**. Suzuki coupling of *p*-bromostyrene and 2-fluoro-4-methoxyphenyl boronic acid delivered biaryl styrene **40**. Heating of **37** and **40** under the conditions described by Chiba¹⁵ resulted in a hetero Diels–Alder cycloaddition reaction to give chroman compound **41** as a 1:1 mixture of diastereomers at the newly formed benzylic stereocenter. Hydrolysis with LiOH followed by SFC separation (AD-H chiralpak, 60% IPA in CO₂, 0.2% DIPA) gave the final compounds **24** and **25**.

In order to support acute dose titrations and chronic *in vivo* studies, multigram quantities of **24** were needed and an improved synthesis was devised (Scheme 2). Suzuki cross coupling of vinyl tosylate **43**¹⁶ and 3-benzyloxyphenyl boronic acid gave cinnamate **44**. Asymmetric hydrogenation of the alkene in **44** at 500 psi with 2.5 mol % Ru-Josiphos^{17,18} established both stereocenters as a single diastereomer in 98% ee. *ortho*-Iodination with NIS delivered iodophenol **46**. Cross coupling of *p*-bromobenzaldehyde with 2-fluoro-4-methoxyphenyl boronic acid followed by treatment with vinyl-magnesium bromide gave allylic alcohol **48**. Iodophenol **46** and allylic alcohol **48** underwent Pd-mediated Heck coupling using *t*-butyl X-Phos and *N,N*-dicyclohexylmethylamine as base to give ketone **49**.¹⁹ Asymmetric reduction of the ketone in **49** using the Noyori protocol yielded benzylic alcohol **50** in 92:8 dr. Ring closure of diol **50** under Mitsunobu conditions afforded chroman **51** in high yield, notably without erosion in dr. Hydrolysis of the ester with aqueous LiOH followed by SFC purification to remove the minor chroman diastereomer delivered **24** in 36% overall yield from commercially available **42**.

The compounds studied in Table 4 demonstrated acceptable exposure and half-life for further profiling in rodent models. While neopentox derivatives **14** and **15** have moderate clearance in rats, compounds **24** and **29** and their chroman stereoisomers showed improved clearance.

Scheme 2^a

^aReagents and conditions: (a) Catagium-Pd precatal, K₃PO₃, MeCN, 89%; (b) Ru-Josiphos, BF₃H-Et₂O, 500 atm H₂, 85°, MeOH, 86%, 98% ee; (c) Pd/Pt/C, H₂ gas, MeOH, 104%; (d) NIS, DCM, 91%; (e) Pd(PPh₃)₄, K₂CO₃, 1,4-dioxane, 98%; (f) vinylmagnesium bromide, THF, 67%; (g) *t*BuXPHOS Pd precatal, MeN(Cy)₂, PhMe, 68%; (h) RuCl[(*R,R*)-TsDPEN(mesitylene)], TEA, formic acid, MeCN, 100%, 92:8 dr; (i) PPh₃, DIAD, DCM, 83%; (j) LiOH, THF/MeOH/water, 97%; (k) SFC separation conditions.

Table 4. Pharmacokinetic Profiles in Wistar Rats^a

Cpd	Cl (mL/min/kg)	Vd _{ss} (L/kg)	T _{1/2} (h)	%F
14	8.2	2.6	6.1	24
15	6.6	1.1	2.9	63
24	3.1	0.41	3.5	50
25	3.0	0.39	2.4	77
29	1.1	0.35	6.2	50
30	1.9	0.56	4.4	48

^aAdministered at a dose of 1 mg/kg iv, 2 mg/kg po.

With leaner, more ligand efficient agonists in hand, we began to assess the selectivity of several analogues. Compounds 14, 15, 24, 25, 29, and 30 were screened against a broad panel of GPCRs, ion channels, transporters, and enzymes at 10 μM (Table 5). While compounds with higher logD exhibited

Table 5. Binding Activity Screen Against 40 Receptors^a

Cpd	>90% inh	# of hits	>70% inh	>50% inh	hplc LogD/MW/PSA
14	4	14	23	3.76/546/71	
15	3	9	23	3.81/546/71	
24	0	1	9	2.82/460/62	
25	0	2	8	2.81/460/62	
29	0	0	3	2.24/461/76	
30	0	0	5	2.26/461/76	

^aDetailed results of receptors and %inh are provided in the Supporting Information.

poorer selectivity (# of hits), the conformationally restricted compounds 29 and 30 showed improved selectivity, exhibiting an excellent correlation between the number of off-target hits and logD. We also examined the selectivity of these compounds for GPR40 versus other free fatty acid G-protein coupled receptors (41, 43,²⁰ and 120²¹). None of these compounds displayed discernible agonism of GPR41, GPR43, or GPR120 up to 3, 10, and 8.3 μM, respectively.

A more detailed in vitro characterization along the lines of Lin et al.²² reveals that 24 and 29 demonstrate comparable efficacy to AM1638 in hGPR40/HEK293 cells (Figure 4A). To

Figure 4. (A) IP1 functional assay [– or + human serum (HS)]. (B,C) [³H]L358 and [³H]25 binding assays.

ensure that 24 and 29 bind to hGPR40 in a similar manner to AM1638, competition binding experiments were performed in membranes from stably transfected CHO-K1 cells. Two different radioligands were used; 1. [³H]L358,^{6,23} a thiazolidinedione allosteric partial agonist (see Supplementary Info for chemical structure), binding in a similar manner to AMG837²² and TAK875.²⁴ 2. [³H]25, a study compound utilized following binding studies demonstrating that GPR40 partial allosteric agonists and AgoPAMs demonstrated identical profiles with [³H]AM1638 and [³H]25 (data not shown). Like AM1638, 24 and 29 augment [³H]L358 and displace [³H]25 binding (Figure 4B,C). These properties are consistent with an agoPAM binding mode and clearly contrast with those of AMG837, TAK875, MK-2305, and L358, which augment [³H]25 and displace the binding of [³H]L358.

Oral administration of 24 and 29 1 h before oral dextrose challenge in a rodent oGTT (oral glucose tolerability test)^{25,26} significantly reduced blood glucose levels compared to vehicle (Figure 5). The efficacy of both agoPAMs examined in this study was superior to the partial agonist positive control 6

Figure 5. GK Rat oGTT titrations.

dosed at a maximally efficacious level. Compound 24 was maximally efficacious at 10 mpk with a total drug plasma level of 3.1 μ M. Compound 29 was dosed up to 30 mpk, which corresponded to a drug plasma level of 13.9 μ M and resulted in 125% reduction in glucose AUC.

GPR40 agoPAMs have been previously reported to stimulate GLP-1 secretion.¹⁴ To demonstrate that the enhanced GLP-1 secretion observed with GPR40 agoPAMs was entirely on-target, total GLP-1 (ng/mL) was measured in wild type (WT) versus knockout (KO) GPR40 mice. Figure 6 shows that no off-target incretin effects were observed in this study for compounds 24 and 29, while AM-1638 did exhibit off-target GLP-1 elevation.²⁷

Figure 6. GLP-1 secretion for GPR40 KO versus WT mice.

In order to assess the duration of effect on fasting plasma glucose, 24 was dosed at 3 and 30 mg/kg in Goto Kakizaki rats for 14 days. AgoPAM 24 demonstrated excellent efficacy with respect to fasting plasma glucose lowering (as compared to the partial agonist control MK-2305 (6)) with no indication of tachyphylaxis or desensitization (Figure 7).

In conclusion, here we report on the identification of a novel, selective, and highly efficacious series of GPR40 agoPAMs through the incorporation of conformational constraint and careful modulation of physicochemical properties. These compounds induce GLP-1 secretion through a GPR40-mediated mechanism, as demonstrated in a GPR40 KO/WT

Figure 7. AgoPAM GK rat chronic study with 24.

mouse study. In a chronic setting, compound 24 delivered sustained fasting plasma glucose lowering that was superior to the partial agonist control. These preclinical results suggest GPR40 agoPAMs may have the potential to affect a powerful new means of enhanced glycemic control for diabetic patients.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmmedchemlett.6b00443.

Experimental procedures, analytical data, and receptor screening data (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

GPR40, g-protein-coupled receptor 40; FFAR1, free fatty acid receptor 1; agoPAM, ago-allosteric modulator; DHA, docosa-hexaenoic acid; GLP-1, glucagon-like peptide 1; CHO, Chinese hamster ovarian (cell line); HEK293, human embryonic kidney (cell line); HPLC, high performance liquid chromatography; TBS, *t*-butyl dimethylsilyl; TBAF, tetra-*n*-butylammonium fluoride; LDA, lithium diisopropylamide; THF, tetrahydrofuran; SFC, supercritical fluid chromatography; NIS, *N*-iodosuccinimide; DCM, dichloromethane; DIAD, diisopropylazodicarboxylate; WT/KO, wild-type/knockout; mpk, milligrams per kilogram; dr, diastereomeric ratio; HS, human serum

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(25) See [Supporting Information](#) for oGTT study protocol.

(26) See [Supporting Information](#) for potency (nM) and efficacy (% act) of key GPR40 agonists against the human, mouse, and rat receptors.

(27) The authors note that results previously reported by researchers at Amgen (Luo et al, Plos One 2012, e46300) indicate no off target GLP-1 effects associated with AM1638 in a similar GPR40 WT/KO mouse experiment. We propose that differences in GLP-1 sampling times (30 min in the Amgen study and 1 h for the study reported herein) is one possible explanation for this discrepancy. Further, it is notable that the GLP-1 secretion induced by AM1638 is greater than one might predict on the basis of GPR40 target engagement alone compared to other compounds in this class (based on measured potency and exposure), potentially indicating additive, non-GPR40-mediated GLP-1 elevation may be operative.