ACS Medicinal Chemistry Letters

Letter

Design and Synthesis of Novel, Selective GPR40 AgoPAMs

Christopher W. Plummer, Matthew J. Clements, Helen Chen, Murali Rajagopalan, Hubert Josien, William K Hagmann, Michael W Miller, Maria E. Trujillo, Melissa Kirkland, Daniel Kosinski, Joel Mane, Michele Pachanski, Boonlert Cheewatrakoolpong, Andrew F. Nolting, Robert K. Orr, Melodie Christensen, Louis-Charles Campeau, Michael J. Wright, Randal Bugianesi, Sarah B. Souza, Xiaoping Zhang, Jerry Di Salvo, Adam B. Weinglass, Richard Andre Tschirret-Guth, Ravi P Nargund, Andrew D. Howard, and Steven L. Colletti

ACS Med. Chem. Lett., **Just Accepted Manuscript** • DOI: 10.1021/acsmedchemlett.6b00443 • Publication Date (Web): 23 Jan 2017

ACS Publications

ACS Medicinal Chemistry Letters is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Design and Synthesis of Novel, Selective GPR40 AgoPAMs

Christopher W. Plummer[a],* Matthew J. Clements[a], Helen Chen[a], Murali Rajagopalan[a], Hubert Josien[a], William K. Hagmann[a], Michael Miller[a], Maria E. Trujillo[d], Melissa Kirkland[d], Daniel Kosinski[d], Joel Mane[d], Michele Pachanski[d], Boonlert Cheewatrakoolpong[d], Andrew F. Nolting[b], Robert Orr[b], Melodie Christensen[b], Louis-Charles Campeau[b], Michael J. Wright[e], Randal Bugianesi[e], Sarah Souza[e], Xiaoping Zhang[e], Jerry Di Salvo[e], Adam B. Weinglass[e], Richard Tschirret-Guth[c], Ravi Nargund[a], Andrew D. Howard[d], Steven L. Colletti[a]

[a] Departments of Discovery Chemistry, [b] Process Chemistry, [c] Drug Metabolism and Pharmacokinetics, [d] In Vivo Pharmacology, [e] In Vitro Pharmacology, Merck Research Laboratories, Kenilworth, NJ 07033, USA

KEYWORDS GPR40, FFA1, GPCR, diabetes, insulin secretogogue, agoPAM, chroman

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.

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-Squibb[11] 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**).

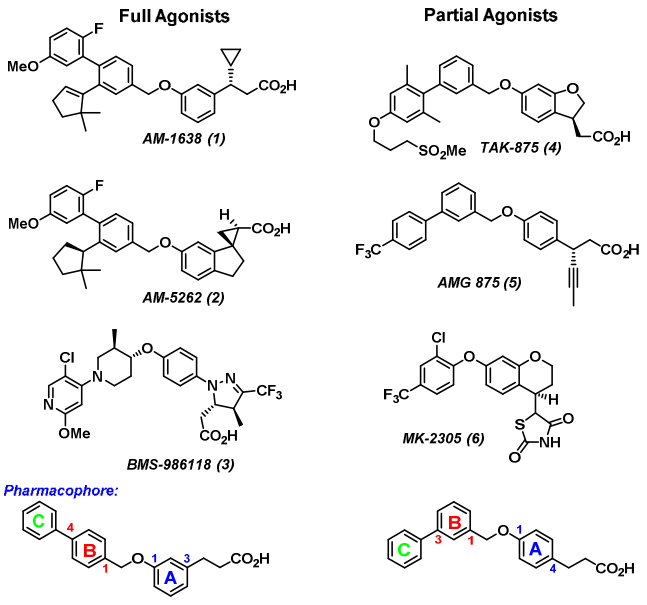


Figure 1. GPR40 "full agonists" and partial agonists.

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

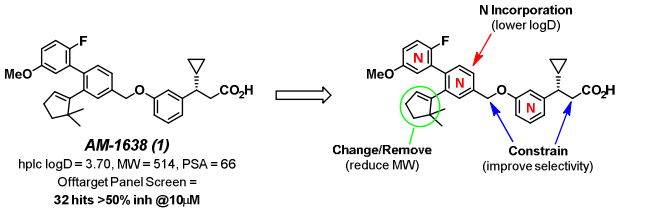


Figure 2. Medicinal chemistry tactics to identify GPR40 agoPAMs with improved ligand efficiency

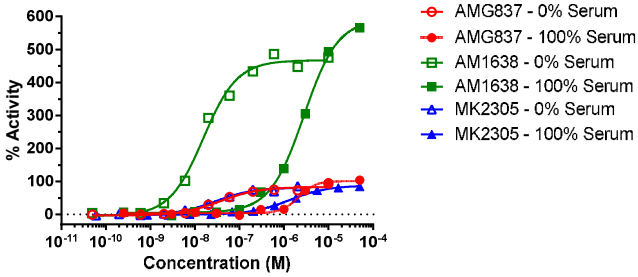


Figure 3. AgoPAMs deliver increased % activation in IP1 assay.

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 retainined, however the human serum-shifted IP1 potency was greatly diminished. Next, in an effort to install conformational constraint, we 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-flouro-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 agoPAMs[10] led to a marked improvement in potency and serum shift (**Table 2**, cpds **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 improvethe physicochemical profile, we examined smaller, heteroatom-containing substituents such as nitrile and and

Table 1. Initial Identification of Chroman agoPAMs

cpd	hIP1 EC50[a] 0% HS +/- SD (%act)	hIP1 EC50[a] +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 (2 isomers)	816 +/- 234 (377%)	3120 +/- 365 (139%)
13 (2 isomers)	1252 +/- 332 (159%)	>10k

[a] Mean of at least 2 runs.

triflouromethoxy analogs **22** and **23**. While these modifications improved physical properties, both resulted in a loss of potency as compared to compounds **14** and **15**.

Table 2. Exploration of B Ring SAR

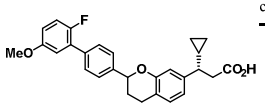
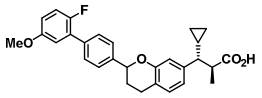
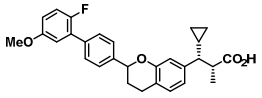
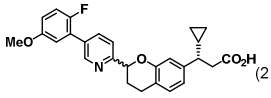
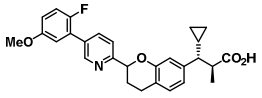
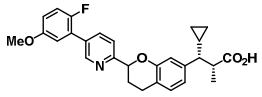
R	compound	hIP1 EC50[a] (nM) 0% HS +/- SD (%act)	hIP1 EC50[a] (nM) 100% HS +/- SD (%act)
	8	58 +/- 1.5 (388%)	139 +/- 2.6 (197%)
	9	90 +/- 8.4 (428%)	123 +/- 26 (197%)
	14	7.3 +/- 2.0 (512%)	14 +/- 6.0 (292%)
	15	7.8 +/- 2.7 (444%)	22 +/- 8.8 (347%)
	16	61 +/- 29 (465%)	1623 +/- 331 (238%)
	17	101 +/- 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%)

[a] Mean of at least 2 runs.

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. We postulated that vicinal stereocenters at the positions alpha and beta to the car-

boxylic 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 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.

Table 3. α-Methyl and B-Ring Pyridyl

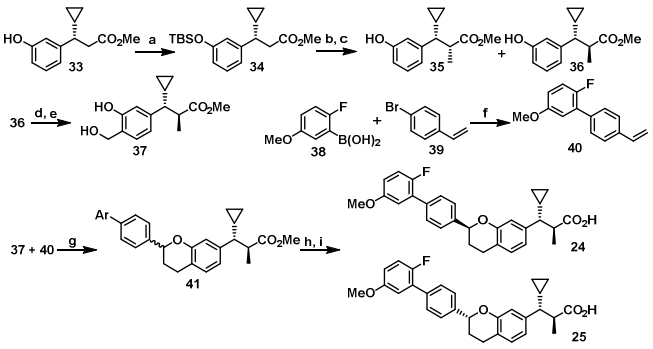
	compound	hIP1 EC50[a] (nM) 0% HS +/- SD (%act)	100% HS +/- SD (%act)
	10	36 +/- 22 (448%)	1690 +/- 467 (277%)
	11	18 +/- 11 (470%)	5010 +/- 688 (177%)
	24	1.1 +/- 0.4 (428%)	146 +/- 58 (383%)
	25	2.6 +/- 1.1 (420%)	127 +/- 66 (383%)
	26	56 +/- 39 (464%)	4010 +/- 2490 (232%)
	27	92 +/- 99 (460%)	3480 +/- 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%)

[a] **Mean of at least 2 runs.**

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 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 diasteromers, 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-flouro,4-methoxyphenyl boronic acid delivered biaryl styrene **40**. Heating of **37** and **40** under the conditions described by Chiba[15] 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 CO_2, 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]

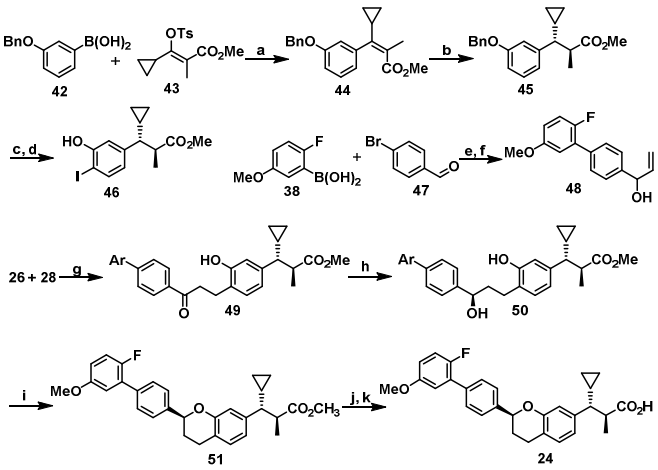
Scheme 1



Reagents 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, $MgCl_2$, TEA, MeCN, 74%; (e) $NaBH_4$, MeOH, 95%; (f) $Pd(PPh_3)_4$, K_2CO_3, dioxane, 93%; (g) Montmorillonite K10, $LiClO_4$, H_2O, $MeNO_2$, 36%; (h) LiOH, MeOH, H_2O, THF, 60 °C, 96% (i) SFC seperation – AD-H chiralpak, 60% IPA/CO_2 with 0.2% $HN(iPr)_2$ modifier

established both stereocenters as a single diastereomer in 98% ee. Ortho iodination with NIS delivered iodophenol **46**. Cross coupling of *p*-bromobenzaldehyde with 2-flouro-4-methoxyphenyl boronic acid followed by treatment with vinylmagnesium 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**.

Scheme 2



Reagents and conditions: (a) Cataxium-Pd precat, K_3PO_3, MeCN, 89%; (b) Ru-Josiphos, BF_4H-Et_2O, 500 atm H_2, 85°, MeOH, 86%, 98% ee; (c) Pd/Pt/C, H_2 gas, MeOH, 104%; (d) NIS, DCM, 91%; (e) $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, 98%; (f) vinylmagnesium bromide, THF, 67%; (g) tBuXPHOS Pd precat, $MeN(Cy)_2$, PhMe, 68%; (h) RuCl[(R,R)-TsDPEN(mesitylene)], TEA, Formic Acid,

MeCN, 100%, 92:8 dr; (i) PPh_3, DIAD, DCM, 83%; (j) LiOH, THF/MeOH/water, 97% (k) SFC separation - conditions

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

Table 4. Pharmacokinetic Profiles in Wistar Rats

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

[a] Aministered 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 analogs. Compounds **14**, **15**, **24**, **25**, **29**, and **30** were screened against a broad panel GPCR's, ion channels, transporters, and enzymes at 10 μM (**Table 5**). While compounds with higher logD exhibited 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 120[21]). None of these compounds displayed discernable agonism of GPR41, GPR43 or GPR120 up to 3 μM, 10 μM, and 8.3 μM, respectively.

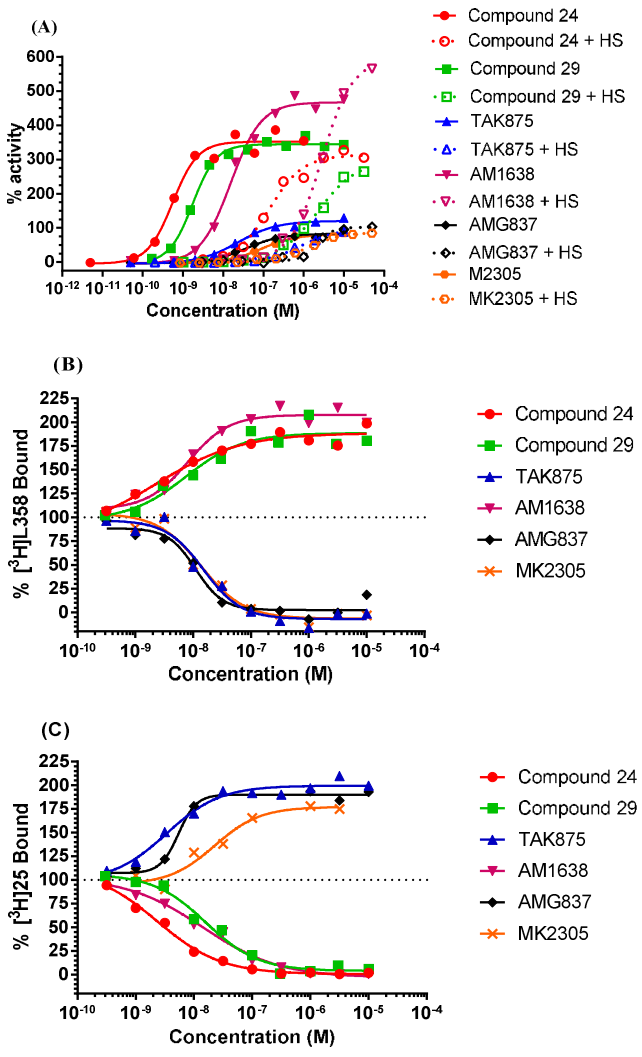
Table 5. Binding Activity Screen Against 40 Receptors

Cpd	# of hits >90% inh	>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

Detailed results of receptors and %inh are provided in Supporting Information

A more detailed in vitro characterization along the lines of Lin et al 2012[22] reveals that **24** and **29** demonstrate comparable efficacy to AM1638 in hGPR40/HEK293 cells (**Figure 4A**). To assure 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. [^{3}H]L358[6, 23], a thiazolidinedione allosteric partial agonist (see Supplementary Info for chemical structure), binding in a similar manner to AMG837[22] and TAK875[24]. 2. [^{3}H]**25**, a study compound utilized following binding studies demonstrating that GPR40 partial allosteric agonists and AgoPAM's demonstrated identical profiles with [^{3}H]AM1638 and [^{3}H]25 (data not shown). Like AM1638, **24** and **29** augment [^{3}H]L358, and displace, [^{3}H]**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 [^{3}H]**25** and displace the binding of [^{3}H]L358.

Figure 4. (A) IP1 Functional Assay [- or + human serum (HS)] (B) & (C) [^{3}H]L358 and [^{3}H]25 binding assays.



Oral administration of **24** and **29** 1h 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** dosed at a maximally efficacious level. **24** was maximally

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

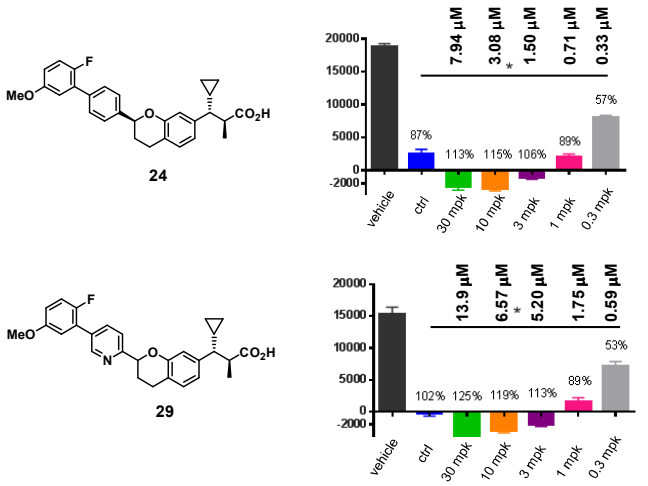


Figure 5. GK Rat oGTT titrations

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 versus knockout 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]

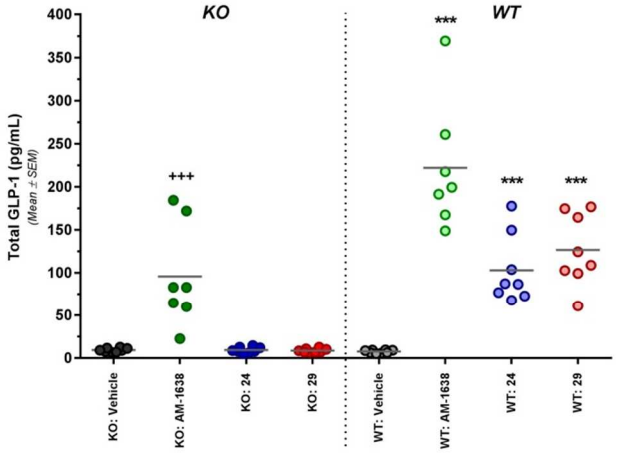


Figure 6. GLP-1 secretion for GPR40 KO versus WT mice

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-mouse study. In a chronic setting, compound **24** delivered sustained fasting plasma glucose lowering that was superior to

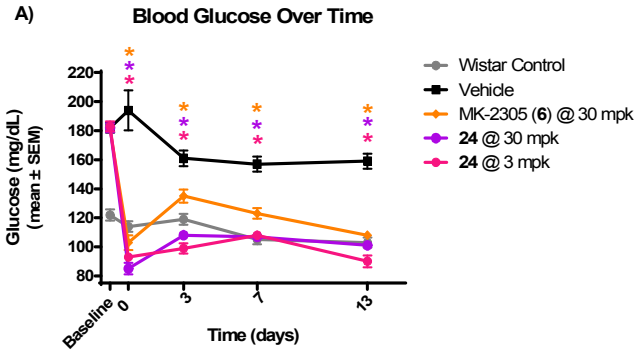


Figure 7. AgoPAM GK rat chronic study with **24**

the partial agonist control. These preclinical results suggest GPR40 agoPAMs may have the potential to affect a powerful new means of enhanced gylcemic control for diabetic patients.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data, and receptor screening data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* Email: christopher_plummer@merck.com

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

The authors would like to thank Leo Joyce for structural determination by VCD analysis.

ABBREVIATIONS

GPR40, g-protein-coupled receptor 40; FFAR1, free fatty acid receptor 1; agoPAM, ago-allosteric modulator; DHA, docosahexaenoic 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 flouride; 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.

REFERENCES

(1) Defronzo, R. A. From the triumvirate to the ominous octet: a new paradigm for the treatment of type II diabetes. *Diabetes* **2009**, *58*, 773-795.

(2) Itoh, Y.; Kawamata, Y.; Harada, M.; Kobayashi, M.; Fujii, R.; Fukusumi, S.; Ogi, K.; Hosoya, M.; Tanaka, Y.; Uejima, H.; Tanaka, H.; Maruyama, M.; Satah, R.; Okubo, S.; Kizawa, H.; Komatsu, H.; Matsumura, F.; Moguchi, Y.; Shinohara, T.; Hinuma, S.; Fujisawa, Y.; Fujino, M. Free fatty acids regulate insulin secretion from pancreatic β cells through GPR40. *Nature* **2003**, *422*, 173-176.

(3) Stoddart, L.A.; Smith, N.J.; Milligan, G. International union of pharmacology. LXXI. Free fatty acid receptors FFA1, -2, and -3: pharmacology and pathophysiological functions. *Pharmacol. Rev.* **2008**, *60*, 405-417.

(4) Negoro, N.; Sasaki, S.; Mikami, S.; Ito, M.; Suzuki, M.; Tsujihata, Y.; Ito, R,; Harada, A.; Takeuchi, K.; Suzuki, N.; Miyazaki, J.; Santou, T.; Odani, T.; Kanzaki, N.; Funami, M.; Tanaka, T.; Kogame, A.; Matsunaga, S.; Yasuma, T.; Momose, Y. Discovery of TAK-875: A potent, selective, and orally bioavailable GPR40 agonist. *ACS Med. Chem. Lett.* **2010**, *1*, 290-294.

(5) Christiansen, E.; Due-Hansen, M. E.; Urban, C.; Merten, N.; Pfleiderer, M.; Karlsen, K. K.; Rasmussen, S. S.; Steensgaard, M.; Hamacher, A.; Schmidt, J.; Drewke, C.; Petersen, R. K.; Kristiansen, K.; Ullrich, S.; Kostenis, E.; Kassak, M. U.; Ulven, T. Structure activity study of dihydrocinnamic acids and the discovery of the potent FFA1 (GPR40) agonist TUG-469. *ACS Med. Chem. Lett.* **2010**, *1*, 345-349.

(6) Houze, J. B.; Zhu, L.; Akerman, M.; Qiu, W.; Zhang, A. J.; Sharma, R.; Schmidt, M.; Wang, Y.; Liu, J.; Medina, J. C.; Regan, J. D.; Luo, J.; Tonn, G.; Zhang, J.; Lu, J. Y-L.; Chen, M.; Lopez, E.; Nguyen, K.; Yang, L.; Tang, L.; Tian, H.; Shuttleworth, S. J.; Lin, D. C-H. AMG-837: A potent, orally bioavailable GPR40 agonist. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1267-1270.

(7) Ge, Min; Yang, Lihu; Zhou, Changyou; Lin, Songnian; Tang, Haifeng; Cline, Eric Dean; Malkani, Sunita. Preparation of bicyclic compounds as antidiabetics. (2006) WO 2006083781 A1

(8) Brown, S. P.; Dransfield, P. J.; Vimolratana, M.; Jiao, X-Y.; Zhu, L.; Pattaropong, V.; Sun, Y.; Liu, J.; Luo, J.; Zhang, J.; Wong, S.; Zhuang, R.; Guo, Q.; Li, F.; Medina, J. C.; Swaminath, G.; Lin, D. C-H.; Houze, J. B. Discovery of AM-1638: A Potent and Orally Bioavailable GPR40/FFA1 Full Agonist. *ACS Med. Chem. Lett.* **2012**, 3, 726-730.

(9) Wang, Y.; Liu, J.; Dransfield, P. J.; Zhu, L.; Wang, Z.; Du, X.; Jiao, X.; Su, Y.; Li, A-R.; Brown, S. P.; Kasparian, A.; Vimolratana, M.; Yu, M.; Pattaropong, V.; Houze, J. B.; Swaminath, G.; Tran, T.; Nguyen, K.; Guo, Q.; Zhang, J.; Zhuang, R.; Li, F.; Miao, L.; Bartberger, M. D.; Correll, T. L.; Chow, D.; Wong, S.; Luo, J.; Lin, D. C-H.; Medina, J. C. Discovery and optimization of of potent GPR40 full agonists containing tricyclic spirocycles. *ACS Med. Chem. Lett.* **2013**, *4*, 551-555.

(10) Du, X.; Dransfield, P. J.; Lin, D. C-H.; Wong, S.; Wang, Y.; Wang, Z.; Kohn, T.; Yu, M.; Brown, S. P.; Vimolratana, M.; Zhu, L.; Li, A-R.; Su, Y.; Jiao, X.; Liu, J.; Swaminath, G.; Tran, T.; Luo, J.; Zhuang, R.; Zhang, J.; Guo, Q.; Li, F.; Connors, R.; Medina, J. C.; Houze, J. B. Improving the pharmacokinetics of GPR40/FFA1 full agonists. *ACS Med. Chem. Lett.* **2014**, *5*, 384-389.

(11) Bruce A Ellsworth, Jun Shi, Elizabeth A Jurica, Laura L Nielsen, Ximao Wu, Andres H Hernandez, Zhenghua Wang, Zhengxiang Gu, Kristin N Williams, Bin Chen, Emily C Cherney, Xiang-Yang Ye, Ying Wang, Min Zhou, Gary Cao, Chunshan Xie, Jason J Wilkes, Heng Liu, Lori K Kunselman, Arun Kumar Gupta, Ramya Jayarama, Thangeswaran Ramar, J. Prasada Rao, Bradley A Zinker, Qin Sun, Elizabeth A Dierks, Kimberly A Foster, Tao Wang, Mary Ellen Cvijic, Jean M Whaley, Jeffrey A Robl, William R Ewing. Discovery of BMS-986118, a dual MOA GPR40 agonist that produces glucose-dependent insulin and GLP-1 secretion. *248th ACS National Meeting*, San Francisco, CA, United States, August 10-14, **2014**.

(12) for a review of GPCR allostery, see: Wooten, D.; Christopoulos, A.; Sexton, P. M. Emerging paradigms in GPCR allostery: implications for drug discovery. *Nat. Rev. Drug Dis.* **2013**, *12*(8), 630-644.

(13) for precedent of agoPAMs applied to other GPCRs, see: Noetzel, M. J.; Rook, J. M.; Vinson, P. N.; Cho, H. P.; Days, E.; Zhou, Y.; Rodriguez, A. L.; Lavreysen, H.; Stauffer, S. R.; Niswender, C. M.; Xiang, Z.; Daniels, J. S.; Jones, C. K.; Lindsley, C. W.; Weaver, C. D.; Conn, P. J. Functional impact of allosteric agonist activity of selective positive allosteric modulators of metabotropic glutamate receptor subtype 5 in regulating central nervous system function. *Molecular Pharmacology* **2012**, *81*(2), 120-133.

(14) Edfalk, S.; Steneberg, P.; Edlund, H. GPR40 is expressed in enteroendocrine cells and mediates free fatty acid stimulation of incretin secretion. Diabetes 2008, *57*, 2280-2287.

(15) Chiba, K.; Hirano, T.; Kitano, Y.; Tada, M. Montmorillonite-mediated hetero-Diels-Alder reaction of alkenes and o-quinone methanes generated in situ by dehydration of o-hydroxybenzyl alcohols. *Chem. Commun.* **1999**, *8*, 691-692.

(16) See Supplementary Info the preparation of intermediate **43**

(17) Dobbs, D. A.; Vanhessche, K. P. M.; Brazi, E.; Rautenstrauch, V.; Lenoir, J.-V.; Genêt J.-P.; Wiles, J. Industrial synthesis of (+)-cis-methyl dihydrojasmonate by enantioselective catalytic hydrogenation; identification of the precatalyst [Ru((-)-Me-DuPhos)(H)-(η^6-1,3,5-cyclooctatriene)](BF4). *Angew. Chem. Int. Ed.* **2000**, *39* (11), 1992-1995.

(18) Christensen, Melodie; Nolting, Andrew; Shevlin, Michael; Weisel, Mark; Maligres, Peter E.; Lee, Joshua; Orr, Robert K.; Plummer, Christopher W.; Tudge, Matthew T.; Campeau, Louis-Charles; Ruck, Rebecca. Enantioselective Synthesis of α-Methyl-β-cyclopropyldihydrocinnamates. *J. Org. Chem*. **2016**, *81* (3), 824-830

(19) Robert K. Orr, Louis-Charles Campeau, Harry R. Chobanian, Jamie M. McCabe Dunn, Barbara Pio, Christopher W. Plummer, Andrew Nolting, Rebecca T. Ruck. A Modular Synthesis of 2-Alkyl- and 2-Arylchromans via a Three Step Sequence. *Synthesis* **2016**, 48, A-J (ASAP).

(20) Ulven, T. Short-chain free fatty acid receptors FFA2/GPR43 and FFA3/GPR41 as new potential therapeutic targets. *Front. Endocrinol*. **2012**, *3*, 1−9.

(21) Shimpukade, B.; Hudson, B. D.; Hovgaard, C. K.; Milligan, G.; Ulven, T. Discovery of a potent and selective GPR120 agonist. *J. Med. Chem*. **2012**, *55*, 4511-4515

(22) Lin, D.C.-H.; Guo, Q.; Luo, J.; Zhang, J.; Nguyen, K.; Tran, T.; Dransfield, P.J.; Brown, S. P.; Houze, J. B.; Vimolratana, M.; Jiao, X. Y.; Wang, Y.; Birdsall, N. J.; Swaminath, G. Identification and pharmacological characterization of multiple allosteric binding sites on the FFA1 receptor. *Molecular Pharmacology* **2012**, *82*(5) 843

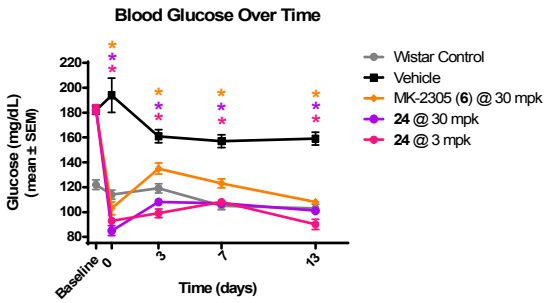
(23) Hauge, M.; Vestmar, M. A.; Husted, A.S.; Ekberg, J.P.; Wright, M.J.; Di Salvo, J.; Weinglass, A.B.; Engelstoft, M.S.; Madsen, A.N.; Lückmann, M.; Miller, M.W.; Trujillo, M.E.; Frimurer, T.M.; Holst, B.; Howard A. D.; Schwartz, T. W.; GPR40 (FFAR1)-Combined Gs and Gq signaling *in vitro* is associated with robust incretin secretagogue action *ex vivo* and *in vivo*, *Molecular Metabolism* **2015**, 4(1): 3-14; see Supplementary Info for the structure of L358.

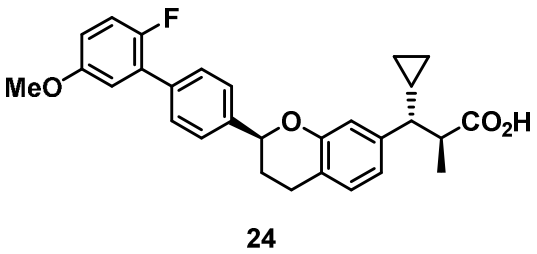
(24) Yabuki, C.; Komatsu, H.; Tsujihata, Y.; Maeda, R.; Ito, R.; Matsuda-Nagasumi, K.; Sakuma, K.; Miyawaki, K.; Kikuchi, N.; Takeuchi, K.; Habata, Y.; Mori, M.; A novel antidiabetic drug, fasiglifam/TAK875, acts as an Ago-allosteric modulator of FFAR1, *PLOS ONE* **2013**, 8(10): 1-10.

(25) See Supplementary Info for oGTT study protocol

(26) See Supplemmentary Info 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 minutes in the Amgen study and 1 hour 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.





24

Insert Table of Contents artwork here