ACS Medicinal Chemistry Letters

Letter

pubs.acs.org/acsmedchemlett

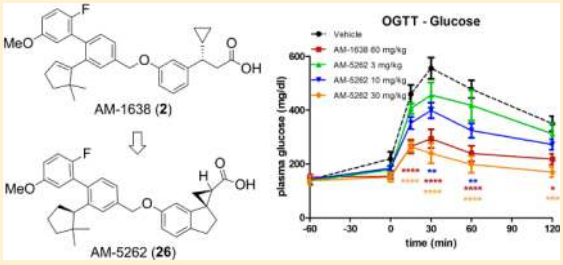
Discovery and Optimization of Potent GPR40 Full Agonists Containing Tricyclic Spirocycles

Yingcai Wang,* Jiwen (Jim) Liu, Paul J. Dransfield, Liusheng Zhu, Zhongyu Wang, Xiaohui Du, Xianyun Jiao, Yongli Su, An-rong Li, Sean P. Brown, Annie Kasparian, Marc Vimolratana, Ming Yu, Vatee Pattaropong, Jonathan B. Houze, Gayathri Swaminath, Thanhvien Tran, Khanh Nguyen, Qi Guo, Jane Zhang, Run Zhuang, Frank Li, Lynn Miao, Michael D. Bartberger, Tiffany L. Correll, David Chow, Simon Wong, Jian Luo, Daniel C.-H. Lin, and Julio C. Medina

Department of Therapeutic Discovery, Metabolic Disorders, Translational Sciences, Amgen Inc., 1120 Veterans Boulevard, South San Francisco, California 94080, United States and One Amgen Center Drive, Thousand Oaks, California 91320, United States

Supporting Information

ABSTRACT: GPR40 (FFAR1 or FFA1) is a target of high interest being pursued to treat type II diabetes due to its unique mechanism leading to little risk of hypoglycemia. We recently reported the discovery of AM-1638 (**2**), a potent full agonist of GPR40. In this report, we present the discovery of GPR40 full agonists containing conformationally constrained tricyclic spirocycles and their structure−activity relationships leading to more potent agonists such as AM-5262 (**26**) with improved rat PK profile and general selectivity profile. AM-5262 enhanced glucose stimulated insulin secretion (mouse and human islets) and improved glucose homeostasis in vivo (OGTT in HF/STZ mice) when compared to AM-1638.



KEYWORDS: *GPR40, full agonist, spirocycles, tricyclic, AM-5262, AM-1638, AMG 837, FFAR1, FFA1*

Type II diabetic patients lose their ability to maintain glucose homeostasis due to defects in both insulin secretion and action.[1] GPR40 (FFAR1 or FFA1) is a G-protein-coupled receptor, primarily expressed in pancreatic islet β-cells and intestinal enteroendocrine cells.[2] When activated by medium to long chain fatty acids, GPR40 elicits increased insulin secretion from islet β-cells only in the presence of elevated glucose levels.[3] This unique mechanism to treat type II diabetes potentially mitigates the risk of hypoglycemia seen with standard insulin secretagogues and has triggered significant efforts at identifying therapeutic agents utilizing this target.[4−21]

We previously described the discovery of a GPR40 partial agonist AMG 837 (**1**, Figure 1)[16] and a GPR40 full agonist AM-1638 (**2**).[21] AM-1638 showed greater antidiabetic efficacy in several rodent models[21,22] and provided compelling evidence that GPR40 full agonists can afford access to a powerful mechanism for maintaining glycemic control and great potential for the treatment of type II diabetic patients.

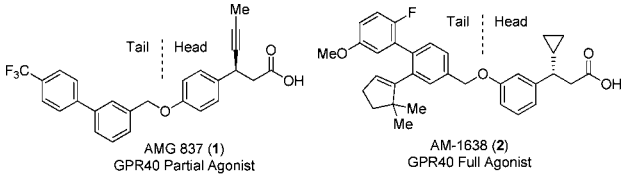


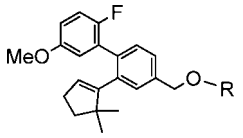
Figure 1. GPR40 partial agonist AMG 837 and full agonist AM-1638.

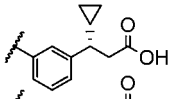
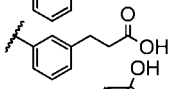
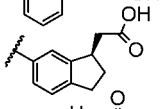
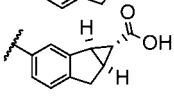
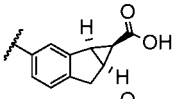
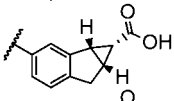
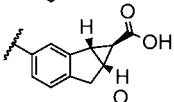
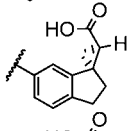
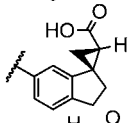
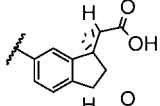
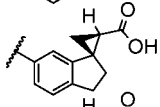
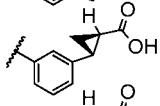
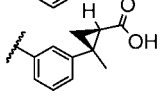
In this letter, we describe further optimization beyond AM-1638. We took on an approach to add conformational constraints, especially at the flexible phenylpropanoic acid region (subsequently referred to as the "head group", Figure 1).

Our efforts to define conformational constraints that maintain full agonist activity are shown in Table 1. Compared to phenylpropanoic acid (**3**), constraining the phenyl with a fused 5-membered ring (**4**) showed a modest improvement in potency. To further constrain the carboxylic acid, we explored fusing a cyclopropane to the cyclopentane ring of the 2,3-dihydro-1*H*-indene (**4**). Incorporation of cyclopropane through the fused connection (examples **5**−**8**) proved to be detrimental to potency, although **8** still retained full agonism. However, switching to a spiro-cyclopropane attached to the dihydroindene (examples **9**−**12**) resulted in increased potency (**12** vs **4**), while maintaining full agonism on GPR40. Note that only one of the four possible stereoisomers maintains both high potency and full efficacy on the target. To probe whether the tricyclic constraint was necessary, we eliminated the cyclopentane ring and made 2-phenylcyclopropanecarboxylic acids **13** and **14**. This change resulted in a 10-fold loss in potency and reduced efficacy.

Received: November 29, 2012
Accepted: May 7, 2013
Published: May 7, 2013

Table 1. Identification of Spirocyclic Head Groups



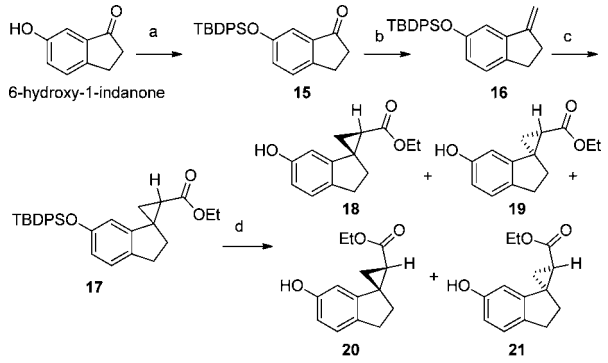
Compound	R	GPR40 Aequorin EC_{50} (± S.D.) (μM) [a]	GPR40 Aequorin E_{max} (± S.D.) (%) [a,b]
1	(see figure 1)	0.06 (±0.02)	20 (±5)
2		0.16 (±0.06)	100 (±4)
3		0.79 (±0.30)	126 (±8)
4		0.50	101
5		>30	15
6		>30	10
7		>30	17
8		1.42	99
9		3.78	27
10		>30	5
11		>30	12
12		0.18 (±0.004)	100 (±7)
13		1.38 (±0.06)	74 (±1)
14		2.13 (±0.13)	79 (±2)

[a]Mean of at least two runs. [b]% maximal efficacy compared to **2**.

A large scale synthetic route to prepare head groups shown in examples **9**−**12** was developed (Scheme 1). Commercially available 6-hydroxy-1-indanone (250 g) was protected with *tert*-butyldiphenylsilyl group, followed by a Wittig reaction to deliver the terminal olefin **16** in quantitative yields for both steps. Rhodium acetate catalyzed cyclopropanation with ethyl diazoacetate resulted in **17** in 80% yield. Deprotection followed by chiral separation delivered the head groups **18**−**21**.

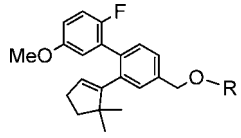
The relative configurations of the head groups shown in compounds **5**−**12** were assigned based on NMR studies.

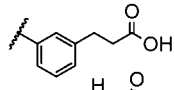
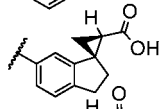
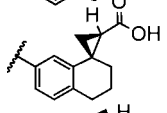
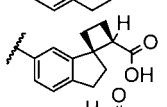
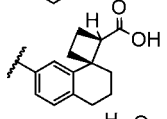
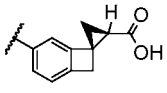
Scheme 1



[a]Reagents and conditions: (a) TBDPSCl, imidazole, DMF, 60 °C, 100%; (b) Ph_3PCH_3Br, *t*-BuOK, THF, 99%; (c) $Rh_2(OAc)_4$, $N_2CHCOOEt$, CH_2Cl_2, 45 °C, 80%; (d) TBAF, THF, 0 °C, 62% (total); chiral separation of four isomers: Chiracel AD-H column, 5% IPA/hexane.

Table 2. Optimization of Spirocyclic Ring Sizes



Compound	R	GPR40 Aequorin EC_{50} (± S.D.) (μM) [a]	GPR40 Aequorin E_{max} (± S.D.) (%) [a,b]
3		0.79 (±0.30)	126 (±8)
12		0.18 (±0.004)	100 (±7)
22		0.15 (±0.01)	98 (±1)
23		0.52 (±0)	92 (±3)
24		0.35 (±0.22)	83 (±4)
25		0.82 (±0.13)	96 (±1)

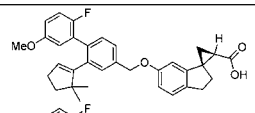
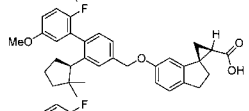
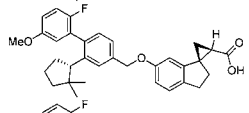
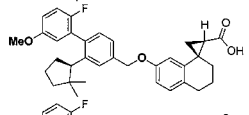
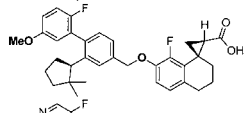
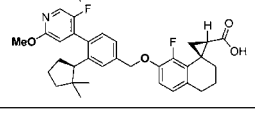
[a]Mean of at least two runs. [b]% maximal efficacy compared to **2**.

Absolute configurations were defined based on comparison of experimental and calculated vibrational circular dichroism (VCD)[23] spectra and optical rotations.[24] The configuration of head group **19** (in compound **11**, Table 1) was further verified by X-ray analysis of its brominated analogue.[25]

We then turned our attention to optimize the sizes of the spirocyclic rings (Table 2). Compared to the spiro[2,4]heptane in **12**, the spiro[2,5]octane in **22** showed equal potency and efficacy. Other variations on ring sizes (**23**−**25**) showed decreased potencies and thus indicated less optimal conformational restrictions than **12** and **22**; however, they were still equal to or better than the flexible phenylpropanoic acid **3**.

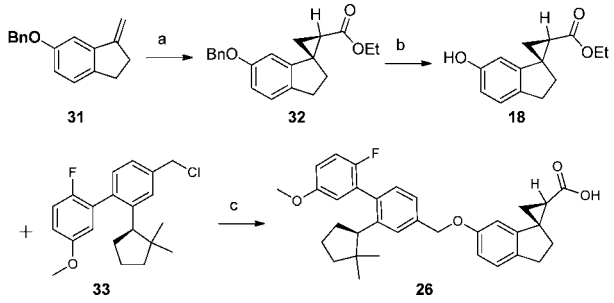
dx.doi.org/10.1021/ml300427u | ACS Med. Chem. Lett. 2013, 4, 551−555

Table 3. Combination of Best Head and Tail Groups

Compound	Structure	GPR40 Aequorin EC_{50} (± S.D.) (μM) [a]	GPR40 Aequorin E_{max} (± S.D.) (%) [a,b]
12		0.181 (±0.004)	100 (±7)
26 (AM-5262)		0.081 (±0.017)	101 (±1)
27		0.212 (±0.089)	104 (±2)
28		0.092 (±0.019)	101 (±1)
29		0.098 (±0.019)	90 (±2)
30		0.105 (±0.018)	90 (±2)

[a]Mean of at least two runs. [b]% maximal efficacy compared to **2**.

Scheme 2



[a]Reagents and conditions: (a) $[Ru(p\text{-cymene})Cl_2]_2$, 2,6-Bis[(4*S*)-(−)-isopropyl-2-oxazolin-2-yl]pyridine, N_2CHCO_2Et, THF, 60 °C, 94%, 90% *ee*; (b) Pd/C, H_2, EtOAc, 95%; (c) Cs_2CO_3, DMSO, 16 h; then added 2 N aqueous LiOH and MeOH, 50 °C, 15 h, 72%.

Table 4. Binding Activity Screen against 101 Receptors

compd	number of receptors that have >90% POC[a]	>80% POC[a]	>70% POC[a]
2	4	9	12
26	1	3	6
30	2	6	6

[a]Percent inhibition of control values or control specific binding.

Reduction of the cyclopentene in the tail region of **12** resulted in potency improvement for **26**, but not its diastereoisomer **27**, although both have full efficacy (Table 3). The spiro[2,5]octanes (**28**−**30**) again showed similar potency as spiro[2,4]heptane (**26**).

The preparation of these spirocyclic GPR40 full agonists is exemplified by the synthesis of **26** (Scheme 2). Asymmetric approaches to **18** were explored, and the chiral ruthenium bis(oxazolinyl) pyridine catalyst reported by Nishiyama[26] was found to be most effective to deliver the **18** precursor **32** in 94% yield with 90% *ee*. Coupling the head group **18** with tail group **33** was accomplished at room temperature with Cs_2CO_3 in DMSO, followed by hydrolysis with aqueous LiOH and MeOH to deliver **26** in one pot.

Highly conformationally constrained molecules, like **26** and **30**, were expected to improve off-target selectivity.[27] Both **26** and **30** showed better selectivity than **2** against a broad panel of 101 GPCRs, ion channels, transporters, and enzymes at 10 μM (Table 4, additional detail in Supporting Information).

Table 5. Improvement in Pharmacokinetic Properties

compd	species	Cl[a] (L/h/kg)	Vd_{ss}[a] (L/kg)	iv $t_{1/2}$[a] (h)	% F[b]
2	rat	0.91	1.1	1.8	15
	cyno[c]	0.81	2.0	2.1	71
26	rat	0.25	0.7	4.2	28
	cyno[c]	0.84	1.4	2.2	69
30	rat	0.17	0.8	4.1	61
	cyno[c]	0.11	0.4	3.7	44

[a]iv dose at 0.5 mg/kg. [b]Oral dose at 2 mg/kg. [c]Cynomolgus monkey.

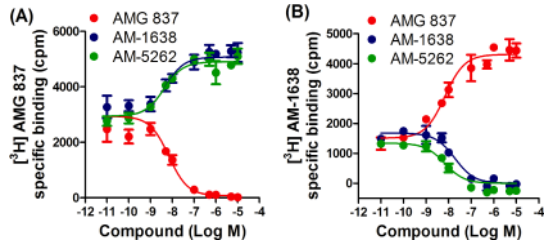


Figure 2. Binding of AM-5262 was examined in cross-interaction experiments with [3H] AMG 837 (A) and [3H] AM-1638 (B). Data are expressed as cpm specific binding and shown as means ± SEM of 2−3 independent experiments. The curves are fitted to an allosteric ternary complex model.

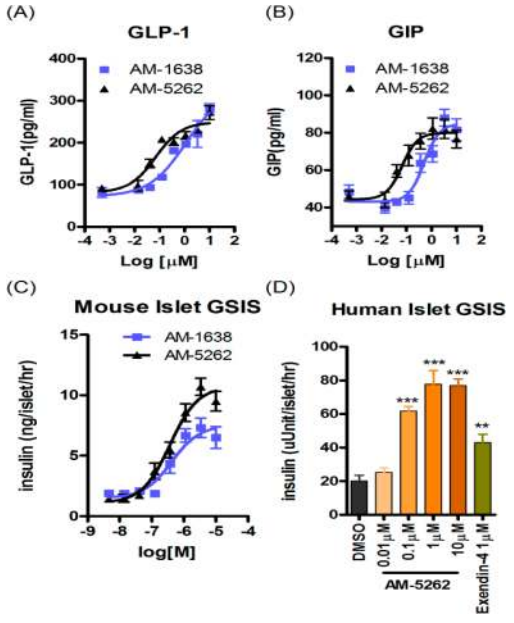


Figure 3. Characterization of AM-5262 activity in isolated primary cells. Stimulation of (A) GLP-1 and (B) GIP secretion by AM-1638 and AM-5262 from rat fetal intestinal cells. Potentiation of glucose-dependent insulin secretion from (C) mouse and (D) human islets in response to indicated treatments.

dx.doi.org/10.1021/ml300427u | *ACS Med. Chem. Lett.* 2013, 4, 551−555

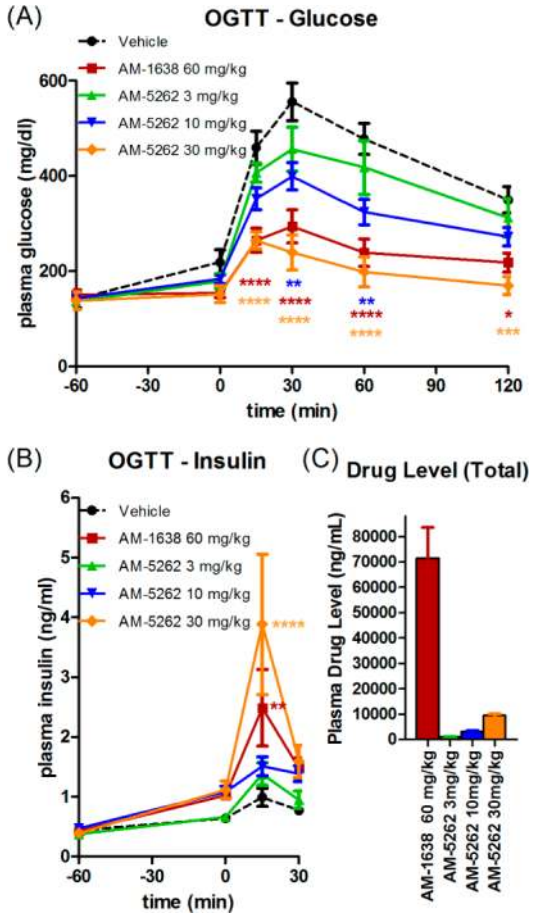


Figure 4. AM-5262 improves glucose metabolism in high-fat fed/STZ treated mice. (A) Glucose and (B) insulin levels during an OGTT in response to treatments indicated in the figure legends. Compounds were dosed orally at −60 min, and oral glucose was administered at 0 min. (C) Total (bound + free) drug levels in the plasma 1 h post-drug dose during the OGTT.

Compound **2** showed greater than 70% inhibition compared to controls for the adenosine A1 receptor, thyrotropin releasing hormone TRH1 receptor, the norepinephrine transporter, the cholecystokinin CCK2 receptor, the histamine H4 receptor, the dopamine D1 receptor, and the kappa opioid receptor; while **26** and **30** displayed less than 70% inhibition against these receptors.

Compound **2** has medium clearance in both rats (Cl = 0.91 L/h/kg) and cynomolgus monkeys (cyno, Cl = 0.81 L/h/kg). Table 5 showed that **26** improved clearance in rat (0.25 L/h/kg) and that **30** improved clearance by 5−7-fold in both rat and cyno.

Binding data obtained from reciprocal competition experiments demonstrated that similarly to AM-1638 (**2**), AM-5262 (**26**) exhibits positive cooperativity and occupies a different binding site from AMG 837 (Figure 2).[28] Conversely, experiments with radiolabeled AM-1638 clearly showed that AM-5262 binds at the same site as AM-1638, further providing evidence of allosteric behavior with AMG 837.

GPR40 full agonists stimulate incretin and insulin secretion in vitro and in vivo.[22] The activity of AM-5262 was compared head-to-head with AM-1638 in isolated primary cells from rodents and humans. AM-5262 stimulated GLP-1 and GIP secretion from rat intestinal cells, and the potency of AM-5262 was 2−5-fold greater than AM-1638 (Figure 3A,B). AM-5262 potentiated glucose stimulated insulin secretion from both mouse (Figure 3C) and human islets (Figure 3D), and the activity was greater than that of exendin-4 in human islets.

When compared for their ability to improve glycemic control in HF/STZ type II diabetic mice,[22] AM-5262 showed similar efficacy at 30 mg/kg dose compared to AM-1638 at 60 mg/kg during an oral glucose tolerance test (OGTT, Figure 4A). AM-1638 displays maximal efficacy at 60 mg/kg in this model. Glucose AUC improved ∼48% in response to 30 mg/kg AM-5262, and this was associated with an increase in insulin secretion (Figure 4B). Total plasma levels of drugs were measured one hour post-dose (Figure 4C). Total drug plasma levels were 6−7-fold lower for AM-5262 at 30 mg/kg compared to AM-1638 at 60 mg/kg, suggesting that AM-5262 displays greater potency in vivo.

In conclusion, we have described the discovery and SAR of potent GPR40 full agonists with highly conformationally constrained tricyclic head groups. These compounds demonstrated improved rat PK and off-target selectivity profiles compared to their unconstrained parent compounds. AM-5262 (**26**) binds to the same ligand site on GPR40 as AM-1638 and has enhanced glucose stimulated insulin secretion (mouse and human islets) and improved glucose homeostasis in vivo (OGTT in HF/STZ mice).

■ 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

*(Y.W.) E-mail: yingcaiw@amgen.com.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Defronzo, R. A. From the triumvirate to the ominous octet: A new paradigm for the treatment of type 2 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.; Satoh, R.; Okubo, S.; Kizawa, H.; Komatsu, H.; Matsumura, F.; Noguchi, 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) For a review, see: Medina, J. C.; Houze, J. B. GPR40 (FFAR1) modulators. *Annu. Rep. Med. Chem.* **2008**, *43*, 75−85.

(5) For a review on patents, see: Bharate, S. B.; Nemmani, K. V.; Vishwakarma, R. A. Progress in the discovery and development of small-molecule modulators of G-protein-coupled receptor 40 (GPR40/FFA1/FFAR1): An emerging target for type 2 diabetes. *Expert Opin. Ther. Pat.* **2009**, *19*, 237−264.

(6) Garrido, D. M.; Corbett, D. F.; Dwornik, K. A.; Goetz, A. S.; Littleton, T. R.; McKeown, S. C.; Mills, W. Y.; Smalley, T. L.; Briscoe, C. P.; Peat, A. J. Synthesis and activity of small molecule GPR40 agonists. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1840−1845.

(7) McKeown, S. C.; Corbett, D. F.; Goetz, A. S.; Littleton, T. R.; Bigham, E.; Briscoe, C. P.; Peat, A. J.; Watson, S. P.; Hickey, D. M. B.

Solid phase synthesis and SAR of small molecule agonists for the GPR40 receptor. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1584−1589.
(8) Song, F.; Lu, S.; Gunnet, J.; Xu, J. Z.; Wines, P.; Proost, J.; Liang, Y.; Baumann, C.; Lenhard, J.; Murray, W. V.; Demarest, K. T.; Kuo, G.-H. Synthesis and biological evaluation of 3-aryl-3-(4-phenoxy)-propionic acid as a novel series of G protein-coupled receptor 40 agonists. *J. Med. Chem.* **2007**, *50*, 2807−2817.
(9) Christiansen, E.; Urban, C.; Merten, N.; Liebscher, K.; Karlsen, K. K.; Hamacher, A.; Spinrath, A.; Bond, A. D.; Drewke, C.; Ullrich, S.; Kassack, M. U.; Kostenis, E.; Ulven, T. Discovery of potent and selective agonists for the free fatty acid receptor 1 (FFA1/GPR40), a potential target for the treatment of type II diabetes. *J. Med. Chem.* **2008**, *51*, 7061−7064.
(10) Zhou, C. Y.; Tang, C.; Chang, E.; Ge, M.; Lin, S. N.; Cline, E.; Tan, C. P.; Feng, Y.; Zhou, Y. P.; Eiermann, G. J.; Petrov, A.; Salituro, G.; Meinke, P.; Mosley, R.; Akiyama, T. E.; Einstein, M.; Kumar, S.; Berger, J.; Howard, A. D.; Thornberry, N.; Mills, S. G.; Yang, L. H. Discovery of 5-aryloxy-2,4-thiazolidinediones as potent GPR40 agonists. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1298−1301.
(11) 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.
(12) 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.; Kassack, M. U.; Ulven, T. Structure−activity study of dihydrocinnamic acids and discovery of the potent FFA1 (GPR40) agonist TUG-469. *ACS Med. Chem. Lett.* **2010**, *1*, 345−349.
(13) Sasaki, S.; Kitamura, S.; Negoro, N.; Suzuki, M.; Tsujihata, Y.; Suzuki, N.; Santou, T.; Kanzaki, N.; Harada, M.; Tanaka, Y.; Kobayashi, M.; Tada, N.; Funami, M.; Tanaka, T.; Yamamoto, Y.; Fukatsu, K.; Yasuma, T.; Momose, Y. Design, synthesis, and biological activity of potent and orally available G protein-coupled receptor 40 agonists. *J. Med. Chem.* **2011**, *54*, 1365−1378.
(14) Walsh, S. P.; Severino, A.; Zhou, C. Y.; He, J. F.; Liang, G. B.; Tan, C. P.; Cao, J.; Eiermann, G. J.; Xu, L.; Salituro, G.; Howard, A. D.; Mills, S. G.; Yang, L. H. 3-Substituted 3-(4-aryloxyaryl)-propanoic acids as GPR40 agonists. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3390−3394.
(15) Christiansen, E.; Urban, C.; Grundmann, M.; Due-Hansen, M. E.; Hagesaether, E.; Schmidt, J.; Pardo, L.; Ullrich, S.; Kostenis, E.; Kassack, M. U.; Ulven, T. Identification of a potent and selective free fatty acid receptor 1 (FFA1/GPR40) agonist with favorable physicochemical and in vitro ADME properties. *J. Med. Chem.* **2011**, *54*, 6691−6703.
(16) Houze, J. B.; Zhu, L.; Sun, Y.; Akerman, M.; Qiu, W.; Zhang, A. J.; Sharma, R.; Schmitt, M.; Wang, Y.; Liu, J.; Liu, J.; Medina, J. C.; Reagan, 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.
(17) Negoro, N.; Sasaki, S.; Ito, M.; Kitamura, S.; Tsujihata, Y.; Ito, R.; Suzuki, M.; Takeuchi, K.; Suzuki, N.; Miyazaki, J.; Santou, T.; Odani, T.; Kanzaki, N.; Funami, M.; Tanaka, T.; Yasuma, T.; Momose, Y. Identification of fused-ring alkanoic acids with improved pharmacokinetic profiles that act as G protein-coupled receptor 40/free fatty acid recptor 1 agonists. *J. Med. Chem.* **2012**, *55*, 1538−1552.
(18) Mikami, S.; Kitamura, S.; Negoro, N.; Sasaki, S.; Suzuki, M.; Tsujihata, Y.; Miyazaki, T.; Ito, R.; Suzuki, N.; Miyazaki, J.; Santou, T.; Kanzaki, N.; Funami, M.; Tanaka, T.; Yasuma, T.; Momose, Y. Discovery of phenylpropanoic acid derivatives containing polar functionalities as potent and orally bioavailable G protein coupled receptor 40 agonists for the treatment of type 2 diabetes. *J. Med. Chem.* **2012**, *55*, 3756−3776.
(19) Negoro, N.; Sasaki, S.; Mikami, S.; Ito, M.; Tsujihata, Y.; Ito, R.; Suzuki, M.; Takeuchi, K.; Suzuki, N.; Miyazaki, J.; Santou, T.; Odani, T.; Kanzaki, N.; Funami, M.; Morohashi, A.; Nonaka, M.; Matsunaga, S.; Yasuma, T.; Momose, Y. Optimization of (2,3-dihydro-1-benzofuran-3-yl)acetic acids: discovery of a non-free fatty acid-like, highly bioavailable G protein-coupled receptor 40/free fatty acid receptor 1 agonist as a glucose-dependent insulinotropic agent. *J. Med. Chem.* **2012**, *55*, 3960−3974.
(20) Christiansen, E.; Due-Hansen, M. E.; Urban, C.; Grundmann, M.; Schröder, R.; Hudson, B. D.; Milligan, G.; Cawthorne, M. A.; Kostenis, E.; Kassack, M. U.; Ulven, T. Free fatty acid receptor 1 (FFA1/GPR40) agonists: mesylpropoxy appendage lowers lipophilicity and improves ADME properties. *J. Med. Chem.* **2012**, *55*, 6624−6628.
(21) Brown, S. P.; Dransfield, P. J.; Vimolratana, M.; Jiao, X.; 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.
(22) Luo, J.; Swaminath, G.; Brown, S. P.; Zhang, J.; Guo, Q.; Chen, M.; Nguyen, K.; Tran, T.; Miao, L.; Dransfield, P. J.; Vimolratana, M.; Houze, J. B.; Wong, S.; Toteva, M.; Shan, B.; Li, F.; Zhuang, R.; Lin, D. C.-H. A potent class of GPR40 full agonists engages the enteroinsular axis to promote glucose control in rodents. *PLoS One* **2012**, *7*, e46300.
(23) Stephens, P. J.; Devlin, F. J.; Pan, J.-J. The determination of the absolute configurations of chiral molecules using vibrational circular dichroism (VCD) spectroscopy. *Chirality* **2008**, *20*, 643−663.
(24) Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J.; Rosini, C. Determination of absolute configuration using optical rotation calculated using density functional theory. *Org. Lett.* **2002**, *4*, 4595−4598.
(25) X-ray data was collected by Frederick J. Hollander and Antonio DiPasquale at UC Berkeley and submitted to the Cambridge Structural Database (www.ccdc.cam.ac.uk): CCDC 903315.
(26) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S. B.; Itoh, K. New chiral ruthenium bis(oxazolinyl)pyridine catalyst. Efficient asymmetric cyclopropanation of olefins with diazoacetates. *J. Am. Chem. Soc.* **1994**, *116*, 2223−2224.
(27) Mann, A. Conformational Restriction and/or Steric Hindrance in Medicinal Chemistry. In *The Practice of Medicinal Chemistry*, 2nd ed.; Wermuth, C. G., Ed.; Academic Press: London, U.K., 1996; pp 233−250.
(28) 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. *Mol. Pharmacol.* **2012**, *82*, 843−859.