Design, Synthesis, and Evaluation of Novel and Selective G-protein Coupled Receptor 120 (GPR120) Spirocyclic Agonists

Jason M. Cox,^{*,†,‡,§} Hong D. Chu,^{†,‡} Mariappan V. Chelliah,^{†,‡,||} John S. Debenham,^{†,‡,||} Keith Eagen,^{†,‡,⊥} Ping Lan,^{†,‡} Matthew Lombardo,^{†,‡} Clare London,^{†,‡,‡} Michael A. Plotkin,^{†,‡,∇} Unmesh Shah,^{†,‡,○} Zhongxiang Sun,^{†,‡} Henry M. Vaccaro,^{†,‡,◆} Srikanth Venkatraman,^{†,‡} Takao Suzuki,[§] Nengxue Wang,[§] Eric R. Ashley,^{†,‡,||} Alejandro Crespo,^{†,‡} Maria Madeira,^{†,‡} Dennis H. Leung,^{†,‡,||} Candice Alleyne,^{†,‡} Aimie M. Ogawa,^{†,‡} Sarah Souza,^{†,‡} Brande Thomas-Fowlkes,^{†,‡} Jerry Di Salvo,^{†,‡} Adam Weinglass,^{†,‡} Melissa Kirkland,^{†,‡,□} Michele Pachanski,^{†,‡} Mary Ann Powles,^{†,‡} Effie Tozzo,^{†,‡,△} Taro E. Akiyama,^{†,‡} Feroze Ujjainwalla,^{†,‡} James R. Tata,^{†,‡} and Christopher J. Sinz^{†,‡}

[†]Merck & Co., Inc., Kenilworth, New Jersey 07033, United States

[‡]Merck & Co., Inc., Rahway, New Jersey 07065, United States

[§]WuXi AppTec, Shanghai, 200131, China

S Supporting Information

ABSTRACT: Type 2 diabetes mellitus (T2DM) is an ever increasing worldwide epidemic, and the identification of safe and effective insulin sensitizers, absent of weight gain, has been a long-standing goal of diabetes research. G-protein coupled receptor 120 (GPR120) has recently emerged as a potential therapeutic target for treating T2DM. Natural occurring, and more recently, synthetic agonists have been associated with insulin sensitizing, anti-inflammatory, and fat metabolism effects. Herein we describe the design, synthesis, and evaluation of a novel spirocyclic GPR120 agonist series, which culminated in the discovery of potent and selective agonist **14**. Furthermore, compound **14** was evaluated *in vivo* and demonstrated acute glucose lowering in an oral glucose tolerance test (oGTT), as well as improvements in homeostatic measurement assessment of insulin resistance (HOMA-IR; a surrogate marker for insulin sensitization) and an increase in glucose infusion rate (GIR) during a hyperinsulinemic euglycemic clamp in diet-induced obese (DIO) mice.

KEYWORDS: GPR120, FFAR4, insulin sensitization, type 2 diabetes, spirocyclic

Type 2 diabetes mellitus (T2DM) is an ever increasing epidemic that affects over 415 million people worldwide.¹

While current therapies such as metformin, sulfonylureas, glitazones, DPP-4 inhibitors, GLP-1 analogues, and SGLT2 inhibitors provide physicians many options for treating T2DM patients,^{2,3} eventually patients may become insulin resistant and must be treated with exogenous prandial and/or basal insulin.⁴ It has been a long-standing goal of diabetes research to identify safe and effective insulin sensitizers^{5,6} that do not have the weight gain side effect associated with the glitazones⁷ (peroxisome proliferator-activated receptor (PPAR) agonists).⁸

G-protein coupled receptor 120 (GPR120), encoded by the free fatty acid receptor 4 (FFAR4) gene, has gained attention in recent years as a potential target to treat T2DM.^{9,10} GPR120 is a member of the rhodopsin family of 7-transmembrane domain G-protein coupled receptors (GPCRs) and has been associated with insulin sensitizing, anti-inflammatory, and fat metabolism effects.¹¹ GPR120 is expressed primarily in the intestine, adipocytes, and pro-inflammatory macrophages and can be activated by long chain free fatty acids.¹² In mice, GPR120 is

preferentially expressed in pancreatic delta cells and regulates somatostatin secretion from islets.¹³

Agonism of the related GPCR, GPR40 (FFAR1), has also gained attention in recent years as a potential treatment target for T2DM.^{14,15} Both GPR120 and GPR40 are activated by long chain fatty acids (LCFA), and in order to better understand the antidiabetic role of GPR120, identification of selective GPR120 agonists versus GPR40 agonists is essential. Recently, in collaboration with the Olefsky group, we published data regarding the insulin sensitizing and chronic anti-inflammatory effects of selective GPR120 spirocyclic agonist compound **A** (**14**).¹⁶ Herein we describe the design, synthesis, structure–activity relationship (SAR), *in vitro* selectivity, and expanded *in vivo* data for the spirocyclic series.

The inspiration for the spirocyclic series originated from early lead **1** (Figure 1). As we recently disclosed, **1** was derived from an ultra high-throughput screening (uHTS) hit, and we

Received: September 12, 2016

Accepted: November 17, 2016

Published: November 17, 2016

Figure 1. Alternate cyclization modes of early lead **1**.

utilized the common medicinal chemistry strategy of rigidifying through cyclization of compound **1**, via pathway “a” to form a novel benzofuran series represented by compound **2**.¹⁷ Both acyclic analogue **1** and cyclic analogue **2** had similar human (h) and mouse (m) IP1 and β -Arrestin2 (β -Arr2) GPR120 potency;¹⁸ however, cyclic analogue **2** lost selectivity versus GPR40 (Table 1). We envisioned using a similar rigidifying

Table 1. *In Vitro* Potency of Select GPR120 Agonists^a

entry	GPR120 EC ₅₀ (nM)				hGPR40 IP1 EC ₅₀ (nM)
	hIP1	mIP1	h β -Arr2	m β -Arr2	
1	94	16	1100	35	>10000
2	63	43	16	21	1829
3	300	89	1600	320	>10000
4	>10000	>10000	>10000	>10000	>10000
5	700	1490	NA	990	>10000

^aValues are the average of two experiments, each in 10-point titrations. All analogues tested were generally deemed to be full GPR120 agonists under assay conditions.

strategy, but in this case cyclizing via route “b” and changing the ether linkage to an amine, to provide piperidine **3** (Figure 1). While this change resulted in loss of potency on h/m IP1 and h/m β -Arrestin2 GPR120 assays for **3** (Table 1), it provided an initial baseline point suggesting that the alternate cyclization strategy was a reasonable approach to new analogue design.

The team was keenly interested in developing a viable novel series with which to build upon, and we felt it was important to diversify our structure class and explore broader chemical space. To this end, we made an initial ring switch of the A- and B-rings on piperidine **3**, to provide the trans-located piperidine **4** (Figure 2), which would also facilitate more rapid investigation of the C-ring SAR. Unfortunately, this change resulted in complete loss of GPR120 potency for **4** (Table 1).

We hypothesized that the piperidine B-ring was not the issue since the preceding molecule (**3**) also contained a piperidine-phenyl moiety, but that the phenyl A-ring was not allowing the carboxylic acid to adopt the appropriate conformation for potency. To test this hypothesis, we prepared the cyclohexyl carboxylic acid derivative **5** (Figure 2) as a mixture of *cis*- and *trans*-isomers. Gratifyingly, some of the potency lost during the A-/B-ring switch was recaptured by analogue **5** (Table 1), even as a mixture of isomers. To enhance the ability of the carboxylic acid to adopt the appropriate conformation for potency and inspired by structural minimization overlays with previous potent analogues (see Supporting Information), we envisioned adding a methylene spacer between the cyclohexyl A-ring and the carboxylic acid, as well as A-/B-ring spirocycle formation to generally maintain similar spacing of the acid moiety and the

Figure 2. Conceptual formation of the spirocyclic series.

aromatic C-ring. The aforementioned transformations resulted in the discovery of the novel GPR120 agonist spirocyclic series **6** (Figure 2, Table 2, and Table 3).¹⁹

The synthesis of the spirocyclic series commenced by ring annulation of aldehyde **7** with methyl vinyl ketone (MVK), in the presence of potassium hydroxide, to afford spirocycle **8** (Scheme 1). Key intermediate piperidine spirocycle **10** was prepared by Horner–Wadsworth–Emmons (HWE) reaction of ketone **8** with phosphonate **9**, followed by concomitant Cbz removal and olefin reduction with hydrogen, in the presence of Boc anhydride (to facilitate purification), and finally Boc removal with TFA. With piperidine spirocycle **10** in hand, we were poised to rapidly evaluate the C-ring SAR of the class by utilizing palladium N-arylation chemistry to provide final analogues **11** after saponification of the methyl ester with lithium hydroxide.

Due to the nature of our synthesis, we were able to rapidly explore the C-ring SAR, as highlighted by select analogues in Table 2. The initial C-ring analogues prepared were based on our previous SAR knowledge from both the acyclic and cyclic analogues **1** and **2**, respectively. The first three analogues prepared in the spirocyclic series are listed in order of preparation, with the first (**12**) demonstrating modest GPR120 potency, the second (**13**) demonstrating improved GPR120 potency, and the third (**14**) demonstrating sub-100 nM GPR120 potency while maintaining hGPR40 selectivity. The sub-100 nM GPR120 potency for compound **14** was similar to benzofuran lead **2** at h/m IP1 and h/m β -Arrestin2 but proved to have superior GPR40 selectivity.

Changing the meta-substitution from $-\text{OCF}_3$ (**13**) to $-\text{CF}_3$ (**15**) resulted in approximately an order of magnitude loss in GPR120 potency and removing the meta-substitution as in entry **16** led to complete loss of GPR120 potency. Changing of the ortho-position from a halogen to $-\text{CN}$ (**17**) resulted in a moderate loss of GPR120 potency and reduced the GPR40 selectivity relative to previous analogues. Trisubstituted C-ring variants represented by analogues **18** and **19** led to variable GPR120 potencies; however, in all cases the potency was reduced relative to compound **14**. Analogues **20** and **21** are representative analogues with bis-meta-substitution and in general demonstrated worse potency when compared to **14**. In an effort to have greater effect on the physicochemical properties of the molecules, we replaced the *ortho*-halide as a pyridine, resulting in only a moderate loss of potency (analogue **22** versus analogue **15**). Unfortunately, other pyridine analogues resulted in significant loss of GPR120 potency for the series (data not shown). In general, the SAR around the C-ring was challenging and only limited modifications were

RN1CCCC2CCCC(C2)CC(=O)O

^aValues are the average of two experiments, each in 10-point titrations. All analogues tested were generally deemed to be full GPR120 agonists under assay conditions.

With the identification of the *ortho*-Cl, *meta*-OCF₃ substitution pattern for the C-ring, we next turned our attention toward modifying the spirocyclic core (Table 3). Substitution on the methylene spacer between the acid and the cyclohexyl ring resulted in significant loss of GPR120 potency, either as a methyl (23) or 2,3-cyclopropyl substitution (24). Introduction of a methyl group on the cyclohexyl ring also resulted in loss of GPR120 potency (compounds 25 and 26) relative to 14. Extending the carboxylic acid by one methylene (27) or reducing the acid of 14 to an alcohol (28), resulted in significant potency loss. In a similar vein as with the C-ring

GPR120 EC₅₀ (nM)

^aValues are the average of two experiments, each in 10-point titrations. All analogues tested were generally deemed to be full GPR120 agonists under assay conditions. In cases of possible stereoisomers, the isomers were separated and the data of the most potent is shown, but the stereochemistry was not determined.

SAR, introduction of heteroatom replacements for the cyclohexyl (pyran **29** or piperidine **30**) also resulted in substantial loss of GPR120 potency. The SAR observations within the spirocyclic core modifications reaffirmed the challenges we encountered with overall optimization of the series, resulting in no analogue having superior GPR120 potency and GPR40 selectivity when compared to spirocyclic lead **14**.

Often early leads have off target and pharmacokinetic (PK) issues, limiting their utility as tools to better understand biological processes; therefore, while investigating the SAR of the spirocyclic series, we began to profile compound **14** versus common counter screen assays. Ion channel activity for calcium ($\text{Ca}_v1.2 = 21 \mu\text{M}$),²⁰ potassium (IKr $> 60 \mu\text{M}$),²¹ sodium ($\text{Na}_v1.5 = 13 \mu\text{M}$),²² and cytochrome P-450 (CYP3A4, CYP2D6, CYP2C9 $> 48 \mu\text{M}$)²³ all offered acceptable values. Furthermore, **14** demonstrated minimal binding activity on PPAR α , δ , and γ ($>10 \mu\text{M}$; see [Supporting Information](#)).

In light of the minimal off-target activity, we continued to profile spirocycle **14** by conducting rat, mouse, dog, and Rhesus monkey PK studies ([Table 4](#)). The clearance and volume of

Table 4. PK Profile of Compound **14**^a

property	rat	mouse	dog	Rhesus
AUC iv ($\mu\text{M}\cdot\text{h}$)	17.5	14.6	4.6	8.7
Clp (mL/min/kg)	2.3	8.4	9.8	2.7
Vd _{ss} (L/kg)	0.4	8.9	6.7	1.7
t _{1/2} (h)	1.4	18.1	11	9.1
MRT (h)	3.0	26.5	10.5	10.1
F _{oral} (%)	95	100	100	77
PPB (% bound)	99.87	99.79	99.85	99.72
Unbound Cl (Clp/f _{umb} ^b)	1769	4000	6533	964

^aClp, plasma clearance; t_{1/2}, terminal half-life; MRT, mean residence time; F_{oral}, oral bioavailability; AUC, area under the plasma concentration vs time curve following iv dosing; Vd_{ss}, volume of distribution at steady state; PPB, plasma protein binding. ^bf_{umb} = (100 – (%PPB))/100.

distribution at steady state resulted in a 1.4 h half-life and 3.0 h mean residence time for the rat, while resulting in longer half-life and MRT in the mouse, dog, and Rhesus. The oral bioavailability across species was high ($>77\%$), but so too was the unbound clearance (>964). Unfortunately, all attempts to reduce clearance by introduction of more polar groups or additional substitutions, resulted in significant loss of potency on the GPR120 receptor (*vide supra*). At this time it became clear that **14** was the lead compound in the spirocyclic series since the overall PK profile allowed for evaluation in more advanced preclinical *in vivo* studies.

Spirocyclic lead **14** was assessed for its ability to improve glucose tolerance in lean mice ([Figure 3](#)). A dose titration, in an oral glucose tolerance test (oGTT),²⁴ was conducted with three doses of **14** (10, 30, 100 mpk), utilizing compound **2** (30 mpk) as a positive control and vehicle controls with and without a dextrose challenge. Compounds **2** and **14** were orally administered 1 h prior to dextrose challenge and **14** dose-dependently reduced blood glucose, with the 100 mpk dose demonstrating comparable reduction to **2** at 30 mpk. As previously disclosed, both **14**¹⁶ and **2**¹⁷ demonstrated on-target effects in wild-type/GPR120 knock out acute mouse oGTT studies.

With a superior *in vitro* GPR40 selectivity profile of spirocyclic lead **14** versus **2**, we further evaluated **14** for its ability to improve insulin sensitivity following five week dosing in insulin-resistant diet-induced obese (DIO) mice using pioglitazone (PPAR α and γ active) as a positive control ([Figure 4](#)). While only modest, nonstatistically significant reductions in glucose were observed for **14** and pioglitazone ([Figure 4A](#)), both showed statistically significant

Figure 3. Mouse oral glucose tolerance test (oGTT) dose titration of compound **14** in comparison to GPR120 positive control compound **2**. (A) Blood glucose (mg/dL) over time (minutes). (B) Net blood glucose area under the curve (AUC). Vehicle (veh); dextrose (dex) challenge; Tx = vehicle and compound administration. * $P < 0.05$ compared to vehicle, ** $P < 0.001$ compared to vehicle; two-way ANOVA. Data are represented as mean $\pm$ SEM.

reductions in insulin levels on days 14 and 28 of the study ([Figure 4B](#)). Furthermore, compound **14** demonstrated statistically significant reduction in homeostatic model assessment of insulin resistance (HOMA-IR),²⁵ a surrogate marker for insulin resistance, at days 14 and 28 ([Figure 4C](#)).

As shown in [Figure 4D](#), selective GPR120 agonist **14** demonstrated a statistically significant increase in the glucose infusion rate (GIR), which was similar to the known insulin sensitizer pioglitazone, during the hyperinsulinemic euglycemic clamp. These results are indicative of an insulin sensitizing effect of **14**, consistent with previous reports.¹⁶ Notably, after 5 weeks of treatment, no body weight changes were observed for **14**, which is in contrast to the body weight increase for pioglitazone (see [Supporting Information](#)) and body weight decrease observed with a recently described benzosultam GPR120 agonist.²⁶

Interest in GPR120 has increased in recent years as a potential type 2 diabetes mellitus target, in particular for its potential role in insulin sensitization. Through systematic modification of an internal hit, we identified a spirocyclic lead series that resulted in the discovery of lead compound **14**. Analogue **14** had suitable off-target (including high selectivity versus GPR40 and PPARs) and PK profiles to further evaluate the physiological effects of GPR120 agonism. Lead **14** dose-dependently increased glucose excursion (oGTT) and upon five week administration, reduced insulin levels, decreased HOMA-IR, and increased GIR during a hyperinsulinemic euglycemic DIO mouse clamp. The disclosure of further efforts on GPR120 agonism will be forthcoming.

Figure 4. Five week diet induced obese (DIO) mouse study with compound 14 and pioglitazone. (A) Glucose changes over time. (B) Insulin changes over time. (C) Homeostatic model assessment of insulin resistance (HOMA-IR) changes over time; $\text{HOMA-IR} = \text{glucose (mM)} \times \text{insulin (}\mu\text{U/mL)} / 22.5$. (D) Glucose infusion rate (GIR) change during hyperinsulinemic euglycemic clamp. For (B–D), $*P < 0.05$ compared to vehicle; one-way ANOVA for (B) and (C); two-way ANOVA for (D). Data are represented as mean $\pm$ SEM.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmchemlett.6b00360.

Experimental procedures and analytical data for the synthesis of all compounds; GPR120 and GPR40 *in vitro* assay procedures; PK protocol; oGTT (including 2.5 h

PK) and five week DIO clamp study protocols, including body weight changes (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*Phone: 908-740-0425. E-mail: jason_cox@merck.com.

ORCID

Jason M. Cox: 0000-0002-6247-9155

John S. Debenham: 0000-0002-9327-2835

Eric R. Ashley: 0000-0002-0513-3342

Present Addresses

^{||}(M.C.) FDA, 10903 New Hampshire Ave., Silver Spring, MD 20993, USA.

[⊥](K.E.) Leidos, 356 Ninth Ave., Suite 106, Picatinny Arsenal, NJ 07806, USA.

[#](C.L.) Dotmatics, 800 W. Cummings Park, Suite 2950, Woburn, MA 01801, USA.

[▽](M.A.P.) Merck and Co., Inc., West Point, PA 19486, USA.

[○](U.S.) Jones Day, 250 Vesey Street, New York, NY 10281, USA.

[◆](H.M.V.) Retired.

[¶](D.L.) Genentech, 1 DNA Way, South San Francisco, CA 94080, USA.

[□](M.K.) Charles River Laboratories, 334 South St., Shrewsbury, MA 01545, USA.

[△](E.T.) Mitobridge Inc., 1030 Massachusetts Ave., Suite 200, Cambridge, MA 02138, USA.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors would like to acknowledge Junling Gao and Mengfen (Melissa) Lin for analytical and WuXi AppTec for synthetic chemistry support.

■ ABBREVIATIONS

T2DM, type 2 diabetes mellitus; DPP-4, dipeptidyl peptidase IV; GLP-1, glucagon like peptide 1; SGLT2, sodium glucose cotransporter 2; GPR120, G-protein coupled receptor 120; FFA4, free fatty acid receptor 4; GPCR, G-protein coupled receptor; GPR40, G-protein coupled receptor 40; FFAR1, free fatty acid receptor 1; LCFA, long-chain fatty acid; uHTS, ultra high-throughput screen; IP1, D-myo-inositol-1-phosphate; oGTT, oral glucose tolerance test; DIO, diet induced obese; GIR, glucose infusion rate; HOMA-IR, homeostatic model assessment for insulin resistance

■ REFERENCES

- (1) *IDF Diabetes Atlas*, 7th ed.; International Diabetes Federation: Brussels, Belgium, 2016. <http://www.diabetesatlas.org>.
- (2) George, C. M.; Bruijn, L. L.; Will, K.; Howard-Thompson, A. Management of Blood Glucose with Noninsulin Therapies in Type 2 Diabetes. *Am. Fam. Physician.* **2015**, *92*, 27–34.
- (3) DeFronzo, R. A.; Triplitt, C. L.; Abdul-Ghani, M.; Cersosimo, E. Novel Agents for the Treatment of Type 2 Diabetes. *Diabetes Spectrum* **2014**, *27*, 100–112.
- (4) Wallia, A.; Molitch, M. E. Insulin Therapy for Type 2 Diabetes Mellitus. *JAMA* **2014**, *311*, 2315–2325.
- (5) Larson, C. J. The Persistent Need for Insulin Sensitizers and other Disease-Modifying Anti-Diabetic Drugs. *Expert Rev. Endocrinol. Metab.* **2014**, *9*, 1–3.

- (6) Carpino, P. A.; Hepworth, D. Beyond PPARs and Metformin: New Insulin Sensitizers for the Treatment of Type 2 Diabetes. *Annu. Rep. Med. Chem.* **2012**, *47*, 177–192.
- (7) McCulloch, D. K. *Thiazolidinediones in the Treatment of Diabetes Mellitus*, 2015. <http://www.uptodate.com/contents/thiazolidinediones-in-the-treatment-of-diabetes-mellitus>.
- (8) Grygiel-Górniak, B. Peroxisome Proliferator-Activated Receptors and Their Ligands: Nutritional and Clinical Implications – a Review. *Nutr. J.* **2014**, *13*, 1–10.
- (9) Milligan, G.; Shimpukade, B.; Ulven, T.; Hudson, B. D. Complex Pharmacology of Free Fatty Acid Receptors. *Chem. Rev.* **2016**, DOI: 10.1021/acs.chemrev.6b00056.
- (10) Liu, H.-D.; Wang, W.; Xu, Z.; Liu, C.; He, D.; Du, L.; Li, M.; Yu, X.; Sun, J. FFA4 Receptor (GPR120): A Hot Target for the Development of Anti-Diabetic Therapies. *Eur. J. Pharmacol.* **2015**, *763*, 160–168.
- (11) Oh, D. Y.; Talukdar, S.; Bae, E. J.; Morinaga, H.; Fan, W.; Li, P.; Lu, W. J.; Watkins, S. M.; Olefsky, J. M. GPR120 is an Omega-3 Fatty Acid Receptor Mediating Potent Anti-Inflammatory and Insulin Sensitizing Effects. *Cell* **2010**, *142*, 687–698.
- (12) Miyauchi, S.; Hirasawa, A.; Ichimura, A.; Hara, T.; Tsujimoto, G. New Frontiers in Gut Nutrient Sensor Research: Free Fatty Acid Sensing in the Gastrointestinal Tract. *J. Pharmacol. Sci.* **2010**, *112*, 19–24.
- (13) Stone, V. M.; Dhayal, S.; Brocklehurst, K. J.; Lenaghan, C.; Winzell, M. S.; Hammar, M.; Xu, X.; Smith, D. M.; Morgan, N. G. GPR120 (FFAR4) is Preferentially Expressed in Pancreatic Delta Cells and Regulates Somatostatin Secretion from Murine Islets of Langerhans. *Diabetologia* **2014**, *57*, 1182–1191.
- (14) Sekiguchi, H.; Kasubuchi, M.; Hasegawa, S.; Pelisch, N.; Kimura, I.; Ichimura, A. A Novel Antidiabetic Therapy: Free Fatty Acid Receptors as Potential Drug Target. *Curr. Diabetes Rev.* **2015**, *11*, 107–115.
- (15) Mancini, A. D.; Poutout, V. GPR40 Agonists for the Treatment of Type 2 Diabetes: Life after ‘TAKing’ a Hit. *Diabetes, Obes. Metab.* **2015**, *17*, 622–629.
- (16) Oh, D. Y.; Walenta, E.; Akiyama, T. E.; Sagakos, W. S.; Lackey, D.; Pessentheiner, A. D.; Sasik, R.; Hah, N.; Chi, T. J.; Cox, J. M.; Powels, M. A.; Di Salvo, J.; Sinz, C.; Watkins, S. M.; Armando, A. M.; Chung, H.; Evans, R. M.; Quehenberger, O.; McNelis, J.; Bogner-Strauss, J. G.; Olefsky, J. M. A Gpr120-Selective Agonist Improves Insulin Resistance and Chronic Inflammation in Obese Mice. *Nat. Med.* **2014**, *20*, 942–949.
- (17) Lombardo, M.; Bender, K.; London, C.; Kirkland, M.; Mane, J.; Pachanski, M.; Geissler, W.; Cummings, J.; Habulihaz, B.; Akiyama, T. E.; Di Salvo, J.; Madeira, M.; Pols, J.; Powles, M. A.; Finley, M. F.; Johnson, E.; Roussel, T.; Uebele, V. N.; Crespo, A.; Leung, D.; Alleyne, C.; Trusca, D.; Lei, Y.; Howard, A. D.; Ujjainwalla, F.; Tata, J. R.; Sinz, C. J. Discovery of Benzofuran Propanoic Acid GPR120 Agonists: from uHTS Hit to Mechanism-Based Pharmacodynamic Effects. *Bioorg. Med. Chem. Lett.* **2016**, DOI: 10.1016/j.bmcl.2016.10.054.
- (18) Due to the complex pharmacology of GPR120 and to gain a better understanding of compound activities, both IP1 and β -Arrestin2 assays were used. See ref 9 for more detail on GPCR pharmacology.
- (19) Chelliah, M.; Chu, H. D.; Cox, J. M.; Debenham, J. S.; Eagen, K.; Lan, P.; London, C.; Plotkin, M. A.; Shah, U.; Sun, Z.; Vaccaro, H. M.; Venkatraman, S. Substituted Spiropiperidiny Compounds Useful as GPR120 Agonists. PCT Int. Appl. WO2014059232 A1.
- (20) Schoemaker, H.; Hicks, P. E.; Langer, S. Z. Calcium Channel Receptor Binding Studies for Diltiazem and its Major Metabolites: Functional Correlation to Inhibition of Portal Vein Myogenic Activity. *J. Cardiovasc. Pharmacol.* **1987**, *9*, 173–180.
- (21) Friesen, R. W.; Ducharme, Y.; Ball, R. G.; Blouin, M.; Boulet, L.; Cote, B.; Frenette, R.; Girard, M.; Guay, D.; Huang, Z.; Jones, T. R.; Laliberte, F.; Lynch, J. J.; Mancini, J.; Martins, E.; Masson, P.; Muise, E.; Pon, D. J.; Siegel, P. K. S.; Styhler, A.; Tsou, N. N.; Turner, M. J.; Young, R. N.; Girard, Y. Optimization of a Tertiary Alcohol Series of Phosphodiesterase-4 (PDE4) Inhibitors: Structure-Activity Relationship Related to PDE4 Inhibition and Human Ether-a-go-go Related Gene Potassium Channel Binding Affinity. *J. Med. Chem.* **2003**, *46*, 2413–2426.
- (22) Catterall, W. A. From Ionic Currents to Molecular Mechanisms: The Structure and Function of Voltage-Gated Sodium Channels. *Neuron* **2000**, *26*, 13–25.
- (23) Rendic, S. Summary of Information on Human CYP Enzymes: Human P450 Metabolism Data. *Drug Metab. Rev.* **2002**, *34*, 83–448.
- (24) Andrikopoulos, S.; Blair, A. R.; Deluca, N.; Fam, B. C.; Proietto, J. Evaluating the glucose tolerance test in mice. *Am. J. Physiol. Endocrinol. Metab.* **2008**, *295*, E1323–E1332.
- (25) Mathews, D. R.; Hosker, J. P.; Rudenski, A. S.; Naylor, B. A.; Treacher, D. F.; Tuner, R. C. Homeostasis Model Assessment: Insulin Resistance and β -cell Function from Fasting Plasma Glucose and Insulin Concentrations in Man. *Diabetologia* **1985**, *28*, 412–419.
- (26) Azevedo, C. M. G.; Watterson, K. R.; Wargent, E. T.; Hansen, S. V. F.; Hudson, B. D.; Kepczynska, M. A.; Dunlop, J.; Shimpukade, B.; Christiansen, E.; Milligan, G.; Stocker, C. J.; Ulven, T. Non-Acidic Free Fatty Acid Receptor 4 Agonists with Antidiabetic Activity. *J. Med. Chem.* **2016**, *59*, 8868.