Discovery of an Isothiazole-Based Phenylpropanoic Acid GPR120 Agonist as a Development Candidate for Type 2 Diabetes

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S Supporting Information

hGPR120 (CaM): EC₅₀ = 42 nM
hGPR120 (β-Arrestin): EC₅₀ = 143 nM
mGPR120 (CaM): EC₅₀ = 77 nM
hGPR40 (CaM): EC₅₀ > 5 μM
C57BL/6 DIO mice OGTT: -137% delta AUC glucose at 60 mpk

ABSTRACT: We have discovered a novel series of isothiazole-based phenylpropanoic acids as GPR120 agonists. Extensive structure–activity relationship studies led to the discovery of a potent GPR120 agonist **4x**, which displayed good EC₅₀ values in both calcium and β-arrestin assays. It also presented good pharmaceutical properties and a favorable PK profile. Moreover, it demonstrated *in vivo* antidiabetic activity in C57BL/6 DIO mice. Studies in WT and knockout DIO mice showed that it improved glucose handling during an OGTT via GPR120. Overall, **4x** possessed promising antidiabetic effect and good safety profile to be a development candidate.

KEYWORDS: GPR120, phenylpropanoic acid, type 2 diabetes

GPR120 is a G_q-coupled GPCR activated by long-chain fatty acids (LCFAs). Functionally, it belongs to a family of lipid binding GPCRs that include GPR 40, 41, 43, and 120. Both GPR40 and GPR120 bind LCFAs although their sequence homology is only 10%.¹ At the amino acid level, GPCRs of the NPY and orexin family share the closest sequence homology with GPR120 with homologies ranging from 35%–42%.² However, none of these receptors have been shown to bind free fatty acids. The rat, mouse, bovine, and dog GPR120 receptors have been cloned and have ~86–91% homology with the human receptor.³ GPR120 is expressed in intestines, lung, adipose tissue, and pro-inflammatory macrophages. Upon stimulation by LCFAs, GPR120 can mediate GLP-1 secretion, insulin sensitization, anti-inflammation, and antiobesity effects.^{4–7} Therefore, GPR120 has emerged as an attractive target for the treatment of metabolic and inflammatory diseases such as obesity and type 2 diabetes.^{8,9}

There are a few reports of GPR120 agonists in the literature.^{10–19} Further research is still ongoing to discover potent, selective, and orally bioavailable small molecule GPR120 agonists. Ulven and co-workers reported a series of phenylpropanoic acid derivatives containing a biphenyl motif (compound I in Figure 1) as GPR120 agonists through exploring representative GPR40 ligands on GPR120.¹⁴ In collaboration with scientists at Metabolex, we explored a variety of five-membered heterocycle-containing phenylpropanoic

Figure 1. Isothiazole-based phenylpropanoic acids.

acids as GPR120 agonists.²⁰ Optimization of GPR120 potency, physical properties, pharmacokinetics, and *in vivo* efficacy profiles directed us to focus on the isothiazole series (II and III) for further investigation. Compound II is a moderately potent GPR120 agonist with an EC₅₀ value of 215 nM against human GPR120 (hGPR120). It displayed moderate metabolic stability (% remaining in liver microsomal preparations at 10 min: 86 (human), 73 (mouse), and 71 (rat)), which is not optimal for a lead compound. Therefore, improving metabolic stability, oral bioavailability, GPR120 potency, and *in vivo* efficacy became the principal goal during the lead optimization process. Herein, we describe the medicinal chemistry approach used to optimize

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Scheme 1. Synthesis of Isothiazoles 4^a

^aReagents and conditions: (1) chlorocarbonylsulfenyl chloride, K₂CO₃ reflux overnight in toluene, 75–92%; (2) R² ≡ CO₂Et, 1,3-di-Cl-benzene, 180 °C for 18 h, 80–88%; (3) DIBAL in toluene, –78 °C 1 h, 72–85%; (4) MsCl, TEA, 0 °C 1 h and then , K₂CO₃ in DMF rt to 80 °C for 4 h–overnight, 62–81%; (5) LiOH·H₂O, THF/MeOH/water (1:1:1), rt for 2 h–overnight, 85–98%.

Scheme 2. Synthesis of Isothiazoles 9a and 9b^a

^aReagents and conditions: (1) propanedinitrile, piperidine in *n*-butanol, rt for 16 h, 56%; (2) S₂Cl₂, pyridine, 145 °C for 5 h, 57%; (3) H₂SO₄, 135 °C for 3 h followed by NaNO₂ in water, 0–50 °C for 0.5 h, 23%; (4) LAH in THF, 0 °C to rt for 12 h, 42%; (5) MsCl, TEA 0 °C for 1 h and then ethyl 3-(4-hydroxy-2,3-dimethylphenyl)propanoate, K₂CO₃ in DMF 25 °C for 4 h, 72%; (6) H₂ (1 atm), 5% Pd/C in EtOH, rt overnight, 36%; (7) LiOH·H₂O, THF/MeOH/water (1:1:1), rt for 2 h, 90–95%.

Scheme 3. Synthesis of Isothiazole 9c^a

^aReagents and conditions: (1) isopentyl nitrite, Br₂ in 3-methyl-1-nitrobutane 0 °C for 0.5 h, 85%; (2) H₂SO₄, 135 °C for 3 h followed by NaNO₂ in water, 0–50 °C for 0.5 h, 75%; (3) BH₃ in THF, 0 °C to rt for 12 h, 25%; (4) (4-chloro-phenyl)boronic acid, Pd(PPh₃)₄ (cat), K₃PO₄ in dioxane/water (1:1) 90 °C for 3 h, 78%; (5) ethyl 3-(4-hydroxy-2,3-dimethylphenyl)propanoate, *n*-Bu₃P, ADDP in toluene 80 °C for 4 h, 70%; (6) LiOH·H₂O, THF/MeOH/water (1:1:1), rt for 2 h, 88%.

this chemical scaffold to identify a development candidate for the treatment of type 2 diabetes.

The general synthetic routes to prepare isothiazoles 4a to 4y and 9a to 9c are outlined in Schemes 1–3 (see Supporting Information 2). Compounds were screened against human GPR120 transfected HEK293 cells in a calcium flux assay and counterscreened against a PathHunter CHO-K1 β-arrestin cell line expressing human GPR120 (see Supporting Information 3). We began our structure–activity relationship (SAR) studies by investigating the substitution pattern on the isothiazole core with particular attention to the R² substituent (Table 1). R¹ was chosen to be 4-Cl or 4-Et, and R³ was 2,3-dimethyl as these

were considered optimal substitutions from our earlier exploration of other five-membered heterocycle-containing phenylpropanoic acids. Introduction of a methyl group at the 5-position of the isothiazole ring (4b) improved hGPR120 potency ~2-fold compared to the unsubstituted analogue 4a (hGPR120 CaM EC₅₀ 106 nM vs 215 nM for 4b vs 4a). Addition of a larger group such as ethyl (4c) or isopropyl (4d) resulted in a significant loss of hGPR120 potency (EC₅₀, 680 nM or 1.64 μM, respectively), suggesting that steric bulk was not readily accommodated in this region of the molecule. Installation of a 5-trifluoromethyl group on the isothiazole ring had a beneficial effect on hGPR120 activity as indicated by

Table 1. SAR of the Isothiazole Core and the R² Substituent

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ID	R ¹		hGPR120 CaM ^a EC ₅₀ (nM)	hGPR120 β-arrestin ^b EC ₅₀ (nM)
4a	4-Cl		215	1,342
4b	4-Cl		106	128
4c	4-Et		680	nt ^c
4d	4-Et		1,640	nt
4e	4-Et		120	210
4f	4-Cl		155	141
4g	4-Et		332	nt
4h	4-Et		920	nt
9a	4-Et		191	nt
9b	4-Et		56	166
9c	4-Cl		94	105

^aThe calcium flux assay in human GPR120 transfected HEK293 cells ($n > 2$, average values, SEM $< \pm 25\%$). ^bThe β-arrestin assay in human GPR120 expressing PathHunter CHO-K1 cells ($n > 2$, average values, SEM $< \pm 25\%$). ^cnt: not tested.

EC₅₀ values of 120 and 155 nM for **4e** and **4f**, respectively, in the calcium flux assay. The improved potency of **4b**, **4e**, and **4f** was also evident in the β-arrestin assay with EC₅₀ values of 128, 210, and 141 nM, respectively. Unfortunately, the 5-methyl analogue **4b** displayed only modest metabolic stability (% remaining in liver microsomal preparations at 10 min: 74 (human), 35 (mouse), and 57 (rat)). In contrast, the 5-CF₃ analogue **4f** exhibited excellent metabolic stability (% remaining in liver microsomal preparations at 10 min: 104 (human), 127 (mouse), and 133 (rat)), which made it more attractive for further optimization. As expected, substitution of the 5-position of the isothiazole ring with a slightly bulkier group, such as pentylfluoroethyl (**4g**), was not well tolerated as indicated by >2-fold decrease in the EC₅₀. Introduction of a polar group also adversely affected hGPR120 potency as can be seen with 5-OMe substituted isothiazole **4h** (EC₅₀ value of 920 nM). Isomeric isothiazole cores were also examined as shown by **9a**, **9b**, and **9c** in Table 1. Compounds **9a** and **9c** maintained or improved hGPR120 potency compared to **4a** and **4f** with isomeric isothiazole template. Compound **9b** bearing a 3-Cl group on the isothiazole ring was the most potent analogue in Table 1, with an EC₅₀ value of 56 nM for hGPR120 in the calcium flux assay. Although **9b** showed good stability in mouse liver microsomes (102% remaining at 10 min), it was only moderately stable in human liver microsomes (76% remaining at 10 min).

Given the good hGPR120 potency and metabolic stability of **4f**, 5-CF₃ substituted isothiazole analogues were selected for further SAR studies of both the R¹ and R³ groups (Table 2). We first examined the effect of the R³ group on hGPR120 potency. Whereas monosubstitution with ethyl (**4i**) or CF₃ (**4j**) tended to reduce potency (EC₅₀ values of 202 and 236 nM for **4i** and **4j**, respectively), introduction of a 3-Br substituent, as in **4k**, enhanced potency by more than 4-fold (EC₅₀ of 31 nM), suggesting halogen substitution might favor stronger ligand–receptor binding. We then focused on fluoro-containing bis- (**4l–4n**), tri- (**4o**, **4p**), or tetra-substituted (**4q**) phenylpropanoic acids. In general, introduction of a fluoro substituent maintained or improved hGPR120 potency compared to the 2,3-dimethyl analogue **4f**. Bis-fluorination seemed to be most effective in boosting hGPR120 potency as evidenced by 3,5-di-F (**4m**) and 2,3-di-F (**4n**). Both compounds displayed EC₅₀ values <100 nM against hGPR120, which achieved our target potency level for pharmacokinetics and *in vivo* pharmacologic characterization. Next, we shifted our effort to optimization of the R¹ substituent. Compound **4r** with an unsubstituted phenyl group was ~3-fold less potent against hGRP120 than 4-Cl substituted analogue **4m**. A 4-ethyl group was well tolerated, as compound **4s** exhibited good hGPR120 potency. However, substitution with a 4-CF₃ group (**4t**) resulted in a 2-fold reduction of the EC₅₀ value in the calcium flux assay but equal potency in the β-arrestin assay (EC₅₀ 108 vs 51 nM). It is interesting to note that **4t** had slight bias toward the β-arrestin

Table 2. SAR of R¹ and R³ Groups on Phenylpropanoic Acids **4** (R² = CF₃)

ID	R ¹	R ³	hGPR120 CaM ^a EC ₅₀ (nM)	hGPR120 β-arrestin ^b EC ₅₀ (nM)
4i	4-Cl	3-Et	202	156
4j	4-Cl	2-CF ₃	236	421
4k	4-Cl	3-Br	31	83
4l	4-Cl	2-Me, 5-F	121	nt ^c
4m	4-Cl	3,5-di-F	51	62
4n	4-Cl	2,3-di-F	86	98
4o	4-Cl	2-Me, 3,5-di-F	99	71
4p	4-Cl	2,3,5-tri-F	104	112
4q	4-Cl	2,3,4,5-tetra-F	173	183
4r	4-H	3,5-di-F	160	132
4s	4-Et	3,5-di-F	34	98
4t	4-CF ₃	3,5-di-F	108	51
4u	4-OMe	3,5-di-F	75	91
4v	4-OCF ₃	3,5-di-F	314	99
4w	4-CN	3,5-di-F	672	332
4x	2-F, 4-Cl	3,5-di-F	42	143
4y	3-F, 4-Cl	3,5-di-F	25	86

^aThe calcium flux assay in human GPR120 transfected HEK293 cells ($n > 2$, average values, SEM $\pm$ 25%). ^bThe β-arrestin assay in human GPR120 expressing Path-Hunter CHO-K1 cells ($n > 2$, average values, SEM $\pm$ 25%). ^cnt: not tested.

signaling pathway, as the most potent compounds in this series consistently displayed equal or lower EC₅₀ values in the calcium flux assay. Incorporation of polar R¹ substituents was generally not well tolerated. Although the 4-OMe analogue **4u** displayed only a slight drop in hGPR120 potency, substitution with 4-OCF₃ (**4v**) or 4-CN (**4w**) resulted in a dramatic loss of hGPR120 potency (EC₅₀ 314 nM for **4v** and 672 nM for **4w**). Consistent with the lipophilic character of LCFAs, lipophilic R¹ groups were favored for high hGPR120 potency as evidenced by 2-F-4-Cl (**4x**) and 3-F-4-Cl (**4y**) substituted analogues. Both compounds were metabolically stable in liver microsomal preparations (87–100% remain at 10 min), providing excellent tools for pharmacokinetic assessment and *in vivo* pharmacological profiling.

Head-to-head comparison of **4x** and **4y** indicated that both compounds had similar physical properties and PK profiles (Supporting Information 4). However, **4x** was slightly more potent against the mouse GPR120 receptor than **4y** (mGPR120 EC₅₀ 77 nM for **4x** and 102 nM for **4y** in the calcium flux assay), which made it the better tool compound for investigation in multiple mouse models. Furthermore, compound **4x** exhibited an EC₅₀ value $> 5 \mu\text{M}$ against hGPR40 compared to an EC₅₀ of $\sim 3 \mu\text{M}$ for **4y**. Hence, **4x** was selected as an advanced GPR120 agonist candidate for pharmacological characterization.

An oral glucose tolerance test (OGTT) was conducted to assess the *in vivo* antidiabetic properties of **4x** in C57BL/6 diet-induced obesity (DIO) mice (Figure 2, see Supporting Information 6). Compound **4x** was dosed orally at 0.1, 0.3, 1, and 3 mg/kg 30 min prior to an oral glucose challenge. This resulted in a dose-dependent lowering of plasma glucose levels

Glucose -30 to 90 Delta Glucose Curve

AUC -30 to 90 Delta

Figure 2. Compound **4x** reduces glucose excursion during OGTT in C57BL/6 DIO mice.

compared to vehicle. Specifically, compound **4x** at 1 and 3 mg/kg reduced plasma glucose levels with delta AUC (area under the curve) values of 61% and 83%, respectively ($p < 0.001$), after 120 min when compared with glucose alone. As positive control, saxagliptin at 1 mg/kg reduced plasma glucose level with a delta AUC value of 87% in the same study.

To confirm the effect on glucose handling was mediated via GPR120, compound **4x** was dosed daily at 60 mg/kg for 3 weeks to both wild type (WT) and GPR120-knockout mice on a 60% high-fat diet (HFD) (Figure 3, see Supporting Information 6). A glucose challenge 30 min after dosing of **4x** in WT mice led to markedly improved glucose tolerance. Specifically, **4x** significantly reduced plasma glucose levels with a ΔAUC value of -137% ($p < 0.001$) compared to the vehicle-treated wild-type mice, whereas **4x** at the same dose displayed no effect on glucose levels in GPR120 KO mice compared to the vehicle-treated GPR120 KO mice. We are investigating the mechanism of action by studying insulin sensitivity, energy expenditure, and lipid metabolism. The detailed pharmacology will be reported elsewhere.

Compound **4x** was a selective GPR120 agonist, showing no significant inhibitory activity at a concentration of $10 \mu\text{M}$ against a broad panel of receptors and ion channels (see

Figure 3. Compound 4x reduces glucose excursion via GPR120.

Supporting Information 5). It did not inhibit cytochrome P450 enzymes *in vitro* at concentrations up to 10 μ M, and it is a weak activator of PXR (25.4% @ 5 μ M). Compound 4x had an IC_{50} value >50 μ M in a hERG binding assay, and it demonstrated no significant hERG functional activity in a Patch Express study (hERG patch, inhibition % (background): 5.9 (4.0), 11.2 (6.4), 12.5 (9.6) @ 3, 10, and 30 μ M). Although 4x showed high plasma protein binding (99.87% in human, 99.81% in rat, and 99.68% in mouse), it was moderately soluble in PBS (kinetic solubility: 38.9 μ M) and possessed good permeability in the MDCK study (A to B, Papp: 17.5×10^{-6} cm/s; B to A/A to B: 1.05).

Compound 4x also exhibited a pharmacokinetic profile suitable for further development. It exhibited good oral bioavailability CD rats ($F\%$ = 57.2) when dosed at 10 mg/kg using 0.5% methocel as a vehicle ($t_{1/2}$ = 0.98 h, C_{max} = 3563 ng/mL, AUC_{last} = 4468 h·ng/mL). In DIO C57/Black mice, compound 4x had a C_{max} of 9268 ng/mL, AUC_{last} of 46822 h·ng/mL, and $t_{1/2}$ of 5.23 h when dosed at 20 mg/kg using 0.5% methocel as a vehicle. The adipose tissue/plasma concentration ratio was 0.08.

In conclusion, we have discovered an isothiazole-based phenylpropanoic acid derivative 4x as a potent GPR120 agonist through extensive SAR studies on the core isothiazole ring, the phenylpropanoic acid moiety and the distal phenyl ring. Compound 4x dose-dependently lowered plasma glucose levels during an OGTT in C57BL/6 DIO mice. The effect on glucose excursion was confirmed to be mediated by GPR120 as it was not observed in GPR120 knockout mice. Compound 4x also exhibited good pharmaceutical properties, excellent oral bioavailability, and a clean safety profile, making it an attractive development candidate.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmmedchemlett.7b00233.

Experimental procedures and characterization for the synthesis of 4a–y and 9a–c as well as *in vitro* and *in vivo* biological protocols (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Hirasawa, A.; Tsumaya, K.; Awaji, T.; Katsuma, S.; Adachi, T.; Yamada, M.; Sugimoto, Y.; Miyazaki, S.; Tsujimoto, G. Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. *Nat. Med.* **2005**, *11*, 90.
- (2) Tikhonova, I. G. Application of GPCR Structures for Modelling of Free Fatty Acid Receptors. In *Handbook of Experimental Pharmacology*; Free Fatty Acid Receptors; Milligan, G., Ikue, K., Eds.; Springer International Publishing: 2017; Vol. 236, pp 57–77.
- (3) Moore, K.; Zhang, Q.; Murgolo, N.; Hosted, T.; Duffy, R. Cloning and characterization of the rat free fatty acid receptor GPR120: *in vivo* effect of the natural ligand on GLP-1 secretion and proliferation of pancreatic beta cells. *Comp. Comp. Biochem. Physiol., Part B: Biochem. Mol. Biol.* **2009**, *154*, 419.
- (4) Vangaveti, V.; Shashidhar, V.; Jarrod, G.; Baune, B. T.; Kennedy, R. L. Free fatty acid receptors: emerging targets for treatment of diabetes and its complications. *Ther. Adv. Endocrinol. Metab.* **2010**, *1*, 165.
- (5) Oh, D. Y.; Talukdar, S.; Bae, E. J.; Imamura, T.; Morinaga, H.; Fan, W. Q.; Li, P. 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.
- (6) Suckow, A. T.; Polidori, D.; Yan, W.; Chon, S.; Ma, J.; Leonard, J.; Briscoe, C. P. Alteration of the glucagon axis in GPR120 (FFAR4) knockout mice: a role for GPR120 in glucagon secretion. *J. Biol. Chem.* **2014**, *289*, 15751.
- (7) Lombardo, Y. B.; Chicco, A. G. Effects of dietary polyunsaturated n-3 fatty acids on dyslipidemia and insulin resistance in rodents and humans. *J. Nutr. Biochem.* **2006**, *17*, 1.

- (8) Oh, D. Y.; Walenta, E.; Akiyama, T. E.; Lagakos, W. S.; Lackey, D.; Pessentheiner, A. R.; 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.
- (9) Ichimura, A.; Hirasawa, A.; Poulain-Godefroy, O.; Bonnefond, A.; Hara, T.; Yengo, L.; Kimura, I.; Leloire, A.; Liu, N.; Iida, K.; Choquet, H.; Besnard, P.; Lecoeur, C.; Vivequin, S.; Ayukawa, K.; Takeuchi, M.; Ozawa, K.; Tauber, M.; Maffei, C.; Morandi, A.; Buzzetti, R.; Elliott, P.; Pouta, A.; Jarvelin, M. R.; Körner, A.; Kiess, W.; Pigeire, M.; Caiazzo, R.; Van Hul, W.; Van Gaal, L.; Horber, F.; Balkau, B.; Lévy-Marchal, C.; Rouskas, K.; Kouvatsi, A.; Hebebrand, J.; Hinney, A.; Scherag, A.; Pattou, F.; Meyre, D.; Koshimizu, T. A.; Wolowczuk, I.; Tsujimoto, G.; Froguel, P. Dysfunction of lipid sensor GPR120 leads to obesity in both mouse and human. *Nature* **2012**, *483*, 350.
- (10) Suzuki, T.; Igari, S. I.; Hirasawa, A.; Hata, M.; Ishiguro, M.; Fujieda, H.; Itoh, Y.; Hirano, T.; Nakagawa, H.; Ogura, M.; Makishima, M.; Tsujimoto, G.; Miyata, N. Identification of G protein-coupled receptor 120-selective agonists derived from PPAR γ agonists. *J. Med. Chem.* **2008**, *51*, 7640.
- (11) Hara, T.; Hirasawa, A.; Sun, Q.; Sadakane, K.; Itsubo, C.; Iga, T.; Adachi, T.; Koshimizu, T.; Hashimoto, T.; Asakawa, Y.; Tsujimoto, G. Novel selective ligands for free fatty acid receptors GPR120 and GPR40. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2009**, *380*, 247.
- (12) Sun, Q.; Hirasawa, A.; Hara, T.; Kimura, I.; Adachi, T.; Awaji, T.; Ishiguro, M.; Suzuki, T.; Miyata, N.; Tsujimoto, G. Structure-activity relationships of GPR120 agonists based on a docking simulation. *Mol. Pharmacol.* **2010**, *78*, 804.
- (13) Sparks, S. M.; Chen, G.; Collins, J. L.; Danger, D.; Dock, S. T.; Jayawickreme, C.; Jenkinson, S.; Laudeman, C. M.; Leesnitzer, A.; Liang, X.; Maloney, P.; McCoy, D. C.; Moncol, D.; Rash, V.; Rimele, T.; Vulimiri, P.; Way, J. M.; Ross, S. Identification of diarylsulfonamides as agonists of the free fatty acid receptor 4 (FFA4/GPR120). *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3100.
- (14) 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.
- (15) Hudson, B. D.; Shimpukade, B.; Mackenzie, A. E.; Butcher, A. J.; Pediani, J. D.; Christiansen, E.; Heathcote, H.; Tobin, A. B.; Ulven, T.; Milligan, G. The Pharmacology of TUG-891, a potent and selective agonist of the free fatty acid receptor 4 (FFA4/GPR120), demonstrates both potential opportunity and possible challenges to therapeutic agonism. *Mol. Pharmacol.* **2013**, *84*, 710.
- (16) Azevedo, C. M. G.; Watterson, K. R.; Wargent, E. T.; Hansen, S. V. F.; Hudson, B. D.; Kępczyńska, 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.
- (17) Adams, G. L.; Velazquez, F.; Jayne, C.; Shah, U.; Miao, S.; Ashley, E. R.; Madeira, M.; Akiyama, T. E.; Di Salvo, J.; Suzuki, T.; Wang, N.; Truong, Q.; Gilbert, E.; Zhou, D.; Verras, A.; Kirkland, M.; Pachanski, M.; Powles, M.; Yin, W.; Ujjainwalla, F.; Venkatraman, S.; Edmondson, S. D. Discovery of chromane propionic acid analogues as selective agonists of GPR120 with in vivo activity in rodents. *ACS Med. Chem. Lett.* **2017**, *8*, 96.
- (18) Cox, J. M.; Chu, H. D.; Chelliah, M. V.; Debenham, J. S.; Eagen, K.; Lan, P.; Lombardo, M.; London, C.; Plotkin, M. A.; Shah, U.; Sun, Z.; Vaccaro, H. M.; Venkatraman, S.; Suzuki, T.; Wang, N.; Ashley, E. R.; Crespo, A.; Madeira, M.; Leung, D. H.; Alleyne, C.; Ogawa, A. M.; Souza, S.; Thomas-Fowlkes, B.; Di Salvo, J.; Weinglass, A.; Kirkland, M.; Pachanski, M.; Powles, M.; Tozzo, E.; Akiyama, T. E.; Ujjainwalla, F.; Tata, J. R.; Sinz, C. J. Design, synthesis, and evaluation of novel and selective G-protein coupled r120 (GPR120) spirocyclic agonists. *ACS Med. Chem. Lett.* **2017**, *8*, 49.
- (19) 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.; 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**, *26*, 5724.
- (20) Zhang, X.; Cai, C.; Winters, M.; Wells, M.; Wall, M.; Lanter, J.; Sui, Z.; Ma, J.; Novack, A.; Nashashibi, I.; Wang, Y.; Yan, W.; Suckow, A.; Hua, H.; Bell, A.; Haug, P.; Clapper, W.; Jenkinson, C.; Gunnet, J.; Leonard, J.; Murray, W. V. Design, Synthesis and SAR of a Novel Series of Heterocyclic Phenylpropanoic Acids as GPR120 Agonists. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 3272.