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Letter

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

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Cardiovascular and Metabolic Research, Janssen Research & Development, LLC, Welsh & McKean Roads, Box 776, Spring House, PA 19477

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ABSTRACT: We have discovered a novel series of isothiazole-based phenylpropanoic acids as GPR120 agonists. Extensive SAR 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 knock-out 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.

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%. 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-inflammatory and anti-obesity 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 5membered heterocycle-containing phenylpropanoic acids as GPR120 agonists.²⁰ Optimization of GPR120 potency, physical properties, pharmacokinetic 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), 74 (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 goals during the lead optimization process. Herein we describe the medicinal chemistry approach

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



Figure 1. Isothiazole-based phenylpropanoic acids

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 ß-arrestin cell line expressing human GPR120 (see supporting information 3). We began our SAR studies by investigating the substitution pattern on the isothiazole core with particular attention to the R^2 substituent (Table 1). R^1 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 5-membered heterocycle-containing phenylpropanoic acids. Introduction of a methyl group at the 5-postion 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 EC₅₀ values of 120 nM 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 nM, 210 nM and 141 nM, respectively. Unfortunately, the 5-methyl analogue 4b displayed only modest metabolic stability

Scheme 1. Synthesis of isothiazoles 4



Reagents and conditions: 1) chlorocarbonylsulfenyl chloride, K_2CO_3 reflux overnight in toluene, 75-92%; 2) h, 80~88%; 3) DIBAL in toluene, $-78^{\circ}C$ 1 h, 72~85%; 4) MsCl, TEA, 0°C 1h and then $62\sim81\%$; 5) LiOH.H₂O, THF/MeOH/water (1:1:1), r,t for 2 h-overnight, 85~98%

Scheme 2. Synthesis of isothiazoles 9a and 9b



Reagents and conditions: 1) propanedinitrile, piperidine in n-butanol, r.t. 16 h, 56%; 2) S_2Cl_2 , pyridine, 145°C for 5h, 57%; 3) H_2SO_4 , 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 r.t for 12 h, 42%; 5) MsCl, TEA 0°C 1h and then ethyl 3-(4-hydroxy-2,3-dimethylphenyl)propanoate, K_2CO_3 in DMF 25°C for 4 h, 72%; 6) H_2 (1 atm), 5% Pd/C in EtOH, r.t. overnight, 36%;7) LiOH.H₂O, THF/MeOH/water (1:1:1), r,t for 2 h, 90~95%

Scheme 3. Synthesis of isothiazole 9c



Reagents and conditions: 1) isopentyl nitrite, Br_2 in 3-methyl-1-nitrobutane 0°C for 0.5 h, 85%; 2) H_2SO_4 , 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 r.t 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), r.t. for 2 h, 88%

(% remaining in liver microsomal preparations at 10 min: 74 (human), 35 (mouse) and 57 (rat)). In contrast, the 5-CF₃ analog **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 analog 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% re- mainin

maining at 10 min).

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



ID	\mathbf{R}^1	A B B R ²	hGPR120 CaM ^a EC ₅₀ (nM)	hGPR120 β-arrestin ^b EC ₅₀ (nM)
4a	4-Cl	N-S	215	1,342
4b	4-Cl		106	128
4c	4-Et		680	nt ^c
4d	4-Et	N S	1,640	nt
4e	4-Et		120	210
4f	4-Cl		155	141
4g	4-Et		332	nt
4h	4-Et	N S OMe	920	nt
9a	4-Et	S-N-N-N	191	nt
9b	4-Et	S N CI	56	166
9c	4-Cl	S N⇒ CF3	94	105

^a The calcium flux assay in human GPR120 transfected HEK293 cells; ^b The β-arrestin assay in human GPR120 expressing PathHunter CHO-K1 cells; ^{a,b} (n>2, average values, SEM< \pm 25%); ^c nt: not tested

Given the good hGPR120 potency and metabolic stability of 4f, 5-CF₃ substituted isothiazole analogues were selected for further SAR studies of both the R^1 and R^3 groups (Table 2). We first examined the effect of the R³ group on hGPR120 potency. Whereas mono-substitution 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 substitutent, 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- (41-4n), tri- (40, 4p) or tetra-(4q) substituted phenylpropanoic acids. In general, introduction of a fluoro substituent maintained or improved hGPR120 potency compared to the 2,3-dimethyl analog 4f. Bis-fluorination seemed to be most effective in boosting hGPR120 potency as evidenced by 3,5di-F (4m) and 2.3-di-F (4n). Both compounds displayed EC_{50} 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 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 analog 4u displayed only a slightly 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

Table 2. SAR of R^{1} and R^{3} Groups on Phenylpropanoic Acids 4 ($R^{2} = CF_{3}$)



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
41	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
40	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
4 w	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

^a The calcium flux assay in human GPR120 transfected HEK293 cells; ^b The β -arrestin assay in human GPR120 expressing Path-Hunter CHO-K1 cells; ^{a,b} (n>2, average values, SEM<±25%); ^cnt: not tested

Figure 2. 4x Reduces Glucose Excursion During OGTT in C57BL/6 DIO Mice

Glucose -30 to 90 Delta Glucose Curve





stable in liver microsomal preparations (87~>100% remain at 10 min), providing excellent tools for pharmacokinetic assessment and *in vivo* pharmacological profiling.

AUC -30 to 90 Delta

Figure 3. 4x Reduces Glucose Excursion Via GPR120



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 μ M against hGPR40 compared to an EC₅₀ of ~ 3 μ 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 dietinduced obesity (DIO) mice (Figure 2, see supporting information 6). Compound 4x was dosed orally at 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg and 3 mg/kg 30 min prior to an oral glucose challenge. This resulted in a dose-dependent lowering of plasma glucose levels compared to vehicle. Specifically, compound 4x at 1 mg/kg 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 three 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 delta AUC 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 μ M against a broad panel of receptors and ion channels (see 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 IC₅₀ 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, 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 x 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. 4x also exhibited good pharmaceutical properties, excellent oral bioavailability, and a clean safety profile, making it an attractive development candidate.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization for the synthesis of **4a-y** and **9a-c** as well as *in vitro* and *in vivo* biological protocols are available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Tel: 215-628-7877. Fax: 215-540-4612. E-mail: xzhang5@its.jnj.com

Notes

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The authors declare no competing financial interest.

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