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Discovery of Chromane Propionic Acid Analogues as Selective Agonists of GPR120 with *in Vivo* Activity in Rodents

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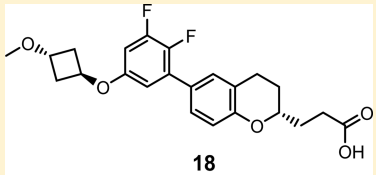
Supporting Information

ABSTRACT: GPR120 (FFAR4) is a fatty acid sensing G protein coupled receptor (GPCR) that has been identified as a target for possible treatment of type 2 diabetes. A selective activator of GPR120 containing a chromane scaffold has been designed, synthesized, and evaluated *in vivo*. Results of these efforts suggest that chromane propionic acid **18** is a suitable tool molecule for further animal studies. Compound **18** is selective over the closely related target GPR40 (FFAR1), has a clean off-target profile, demonstrates suitable pharmacokinetic properties, and has been evaluated in wild-type/knockout GPR120 mouse oGTT studies.

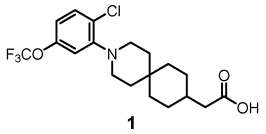


18

hGPR120 IP1 EC_{50} = 35 nM
hGPR120 β-Arr2 EC_{50} = 24 nM
hGPR40 IP1 EC_{50} = >10,000 nM

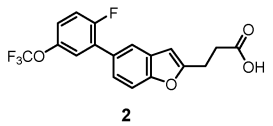
KEYWORDS: *GPR120, FFAR4, insulin sensitization, type 2 diabetes, chromane*

Type 2 diabetes mellitus (T2DM), a worldwide public health problem, is a metabolic disorder characterized by hyperglycemia, pancreatic β-cell impairment, impaired insulin secretion, and insulin resistance in various tissues, including skeletal muscle, adipose tissue, and liver.[1−3] Inflammation has been suggested to be a major contributor to this condition,[4] and chronic complications such as cardiovascular disease, retinopathy, neuropathy, and nephropathy can be encountered by those afflicted with this disease.[5]



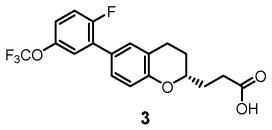
1

hGPR120 IP1 EC_{50} = 98 nM
hGPR120 β-Arr2 EC_{50} = 66 nM
hGPR40 IP1 EC_{50} = >10,000 nM



2

hGPR120 IP1 EC_{50} = 63 nM
hGPR120 β-Arr2 EC_{50} = 16 nM
hGPR40 IP1 EC_{50} = 1829 nM



3

hGPR120 IP1 EC_{50} = 170 nM
hGPR120 β-Arr2 EC_{50} = 17 nM
hGPR40 IP1 EC_{50} = 2100 nM

Figure 1. Comparison of core structures.

GPR120 (FFAR4) is a long-chain fatty acid sensing G protein-coupled receptor (GPCR) that is expressed in intestine, lung, macrophages, and adipose tissue.[6,7] Stimulation of this receptor by free fatty acids has been reported to promote secretion of glucagon-like peptide-1 (GLP-1).[8] Activation has also been demonstrated to display insulin sensitizing effects *in vivo*,[7] and as such GPR120 could be an attractive drug target.[9,10]

Due to the above considerations, a suitable agonist of GPR120 has been proposed to be desirable as a possible treatment for type 2 diabetes.[11−15] Due to the presence of multiple free fatty acid receptors that are able to be stimulated by structurally similar ligands and the manifestation of the complex pharmacology that can result,[16] we counterscreened against GPR40 (FFAR1) to identify compounds that are selective for activation of GPR120.[17,18] Herein is described our recent efforts to identify selective and potent agonists of GPR120 that have suitable pharmacokinetic profiles to support *in vivo* studies.

During the optimization of GPR120 agonists spiropiperidine **1** and benzofuran **2** (Figure 1), which were previously disclosed by our colleagues,[19−22] it was discovered that replacement of

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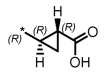
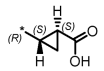
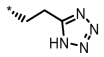
Table 1. SAR Overview of a Promising Series of Chromanes as GPR120 Agonists[a]

Compound		hGPR120 EC_{50} (nM) IP1	hGPR120 EC_{50} (nM) β-Arr2	hGPR40 IP1 EC_{50} (nM)
3		170	17	2100
4		180	42	>10,000
5		69	33	>10,000
6		320	130	>10,000
7		330 (17%)	890	>10,000

[a]Values are the average of at least two experiments, each in 10-point titrations. Unless noted, all analogues tested were generally deemed to be full GPR120 agonists under assay conditions.

the scaffold core with a chromane system, as in propionic acid **3**, resulted in maintained agonist activity on GPR120.[23]

We decided to optimize this chromane series and identify a selective agonist via an *in vitro* evaluation using IP1 and *β*-Arrestin2 (*β*-Arr2) assays to measure on target activation of human (h) GPR120 in conjunction with an IP1 assay to determine activation of hGPR40.

Toward this end, we explored the effects of modifying the propionic acid side chain via substitution on the carbon chain and replacement of the acid with various isosteres. Multiple examples were prepared and tested, but most exhibited a loss of activity. The most promising derivatives are summarized in Table 1.

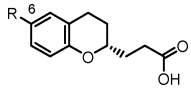
Both the *R* and *S* chromane enantiomers, **3** and **4**, respectively, were found to be agonists of GPR120, but we focused on the *R* chromane scaffold for the majority of structure−activity relationship (SAR) development due to its slightly better *in vitro* activity in multiple examples.

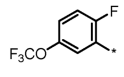
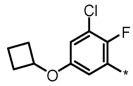
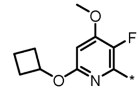
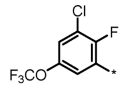
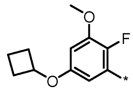
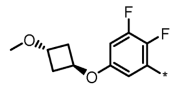
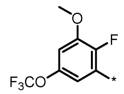
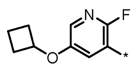
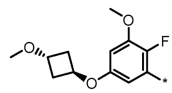
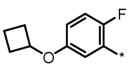
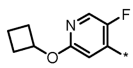
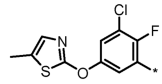
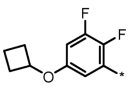
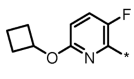
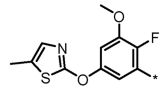
Most substitutions on the side chain were found to be detrimental to activity, but it was discovered that a cyclopropionic acid was tolerated and could improve selectivity over GPR40 as observed in chromane **5**. The stereochemical configuration of the cyclopropane was critical, as the (*R*,*R*,*R*)-isomer **5** displayed more potency than the (*R*,*S*,*S*)-cyclopropane diastereomer **6** for GPR120 activation.

The tetrazole functionality was identified as a possible carboxylic acid bioisostere, exemplified here by compound **7**. This modification was accompanied by an attenuation of potency, and the tetrazole **7** seemed to display partial agonist activity when compared to a standard GPR120 agonist under the conditions used in the hGPR120 IP1 assay (>50% activation is considered full).

Concurrent to the SAR exploration on the acid side chain, the aryl substitution at the chromane 6-position was also modified (Table 2). One observed trend was that appropriate substitution ortho to the fluorine resulted in an improvement of *in vitro* potency on GPR120. Furthermore, analogues containing a trifluoromethoxy group para to the fluorine were not as selective against GPR40 as analogues where the

Table 2. Chromane Biaryl SAR Optimization[a]



Compound		hGPR120 EC50 (nM) IP1	hGPR120 EC50 (nM) β-Arr2	hGPR40 IP1 EC_{50} (nM)	Compound		hGPR120 EC50 (nM) IP1	hGPR120 EC50 (nM) β-Arr2	hGPR40 IP1 EC_{50} (nM)	Compound		hGPR120 EC50 (nM) IP1	hGPR120 EC50 (nM) β-Arr2	hGPR40 IP1 EC_{50} (nM)
3		170	17	2100	**12**		40	8.3	>10k	**17**		15	6.2	>10k
8		72	17	2200	**13**		15	9	>10k	**18**		35	24	>10k
9		25	11	4400	**14**		79	140	>10k	**19**		14	5.0	>10k
10		28	10	3600	**15**		250	230	2000	**20**		14	5.6	>10k
11		21	13	>10k	**16**		30	21	>10k	**21**		37	13	>10k

[a]Values are the average of at least two experiments, each in 10-point titrations. Unless noted, all analogues tested were generally deemed to be full GPR120 agonists under assay conditions.

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Table 3. Rat IV Pharmacokinetic Data of Selected Chromane Derived GPR120 Agonists[a]

Compound	Cl_p	$t_{1/2}$	Vd_{ss}	PPB	Cl_{int}
3	9.5	1.3	0.64	99.84	10500
11	5.4	1.3	0.45	99.93	8700
16	9.1	0.74	0.23	99.77	4500
18	1.3	2.1	0.24	99.76	560
19	3.4	2.4	0.49	99.68	760
20	1.6	0.93	0.14	99.97	6200
21	1.6	1.2	0.15	99.93	3600

[a]Cl_p, plasma clearance (mL/min/kg); $t_{1/2}$, terminal half-life (h); Vd_{ss}, volume of distribution at steady state (L/kg); PPB, plasma protein binding (% bound extrapolated from 10% plasma); Cl_{int}, intrinsic clearance (mL/min/kg). IV cassette dosing (DMSO/PEG400/H_2O = 20/60/20; 0.1 mg/kg).

substituent was replaced with a cyclobutoxy group. Replacement of the phenyl ring with a series of pyridine analogues was evaluated, and the 6-cyclobutoxy-3-fluoropyridin-2-yl derivative **16** displayed better potency on GPR120 than fluoro pyridines **14** or **15**. Similar to the SAR observed when employing a phenyl ring, substitution ortho to the fluorine in the methoxy pyridine analogue **17** improved potency on GPR120.

Further exploration of substitution on the cyclobutyl ring revealed that *trans*-methoxy substitution at the 3-position was tolerated in analogues **18** and **19**. Aryl groups could also be used to replace the cyclobutyl ring with retention of potency, exemplified here by the methyl thiazoles **20** and **21**.

Upon identification of these potent and selective compounds, promising derivatives were studied to determine their pharmacokinetic (PK) profiles in rats via IV dosing (Table 3). Oral bioavailability was >70% for compounds throughout this series (*vide infra*, Table 7), so optimization of rat half-life through lowering intrinsic clearance was a main factor that guided SAR development and tool compound selection. All compounds were >99% bound to plasma proteins. Analysis of intrinsic clearance (Cl_{int}) for this series suggested that chromanes **18** and **19** may be good choices as potential tool compound candidates due to their comparatively low Cl_{int} and longer half-lives in rats. Consequently, these compounds were selected for further *in vivo* evaluation.

Promising propionic acid replacements were next evaluated in combination with the optimized aryl groups from Table 2. SAR trends were maintained in the case of the cyclopropane containing analogues (Table 4); substitution ortho to the fluorine improved activity, and *trans*-methoxy substitution was tolerated.

Congeners combining the best aryl groups and a replacement of the carboxylic acid with the tetrazole moiety were also synthesized and evaluated (Table 5). In the case of the tetrazole series, methoxy substituion ortho to the fluorine provided a more marked improvement in potency on GPR120 than did the difluoro substitution. The analogues with weaker potency seemed to display partial activity on hGPR120 under the conditions of the IP1 assay. This partial activity was not observed in the *β*-Arr2 assay, however, and upon identifying analogues with improved potency this partial behavior returned to full agonism. Importantly, compound **26**, which displayed similar potency and full agonist activity in a mouse GPR120 IP1 assay (results not shown), demonstrated *in vivo* efficacy in a mouse oral glucose tolerance test (oGTT) (Figure 2). These results suggest that exploration of the tetrazole series or other

Table 4. Cyclopropionic Acid Analogues[a]

Compound	hGPR120 EC_{50} (nM) IP1	hGPR120 EC_{50} (nM) β-Arr2	hGPR40 IP1 EC_{50} (nM)
5	69	33	>10k
22	25	8.0	>10k
23	18	7.8	>10k
24	45	17	>10k
25	55	78	>10k

[a]Values are the average of at least two experiments, each in 10-point titrations. Unless noted, all analogues tested were generally deemed to be full GPR120 agonists under assay conditions.

Table 5. Tetrazole Analogues[a]

Compound	hGPR120 EC_{50} (nM) IP1	hGPR120 EC_{50} (nM) β-Arr2	hGPR40 IP1 EC_{50} (nM)
7	330 (17%)	890	>10k
26	220 (44%)	84	>10k
27	240 (24%)	170	>10k
28	130 (45%)	150	>10k
29	53	43	>10k
30	51	32	>10k

[a]Values are the average of at least two experiments, each in 10-point titrations. Unless noted, all analogues tested were generally deemed to be full GPR120 agonists under assay conditions.

carboxylic acid bioisosteres could potentially be an area for future investigation.

We evaluated compounds **18**, **24**, and **26** *in vivo* using the mouse oral glucose tolerance test (oGTT).[24] Figure 2 summarizes the results of compounds **18** (3, 10, 30 mg/kg) in a dose titration and single dose evaluation of **24** (30 mg/kg) and

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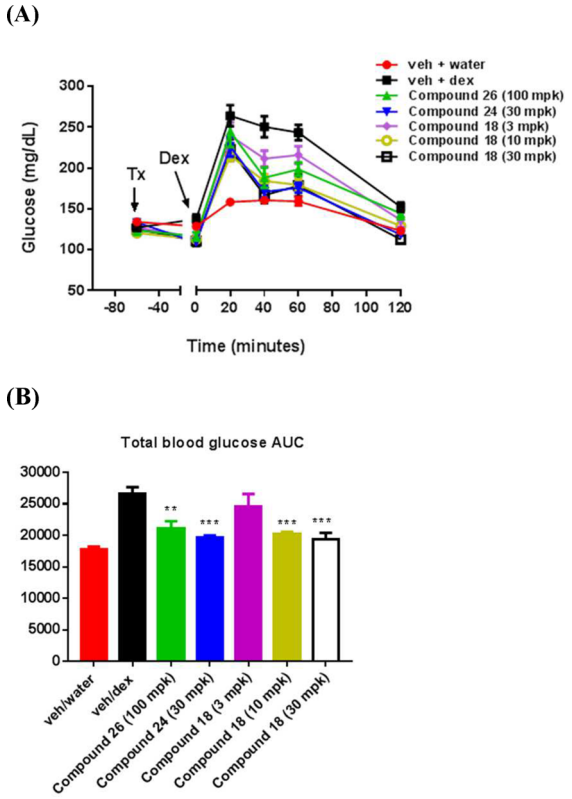

Figure 2. Glucose lowering effects as measured by mouse oGTT. The following doses were used, resulting in the corresponding plasma concentrations (C_p) at 3 h: **18**, 3 mg/kg [n = 3, 0.75 μM (s = 0.04 μM)]; 10 mg/kg [n = 3, 1.17 μM (s = 0.13 μM)]; 30 mg/kg [n = 3, 3.12 μM (s = 1.02 μM); **24**, 30 mg/kg [n = 3, 37.4 μM (s = 3.43 μM)]; **26**, 100 mg/kg [n = 3, 40.6 μM (s = 16.4 μM)]. (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; mpk = mg/kg. $^{**}P < 0.01$ compared to vehicle, $^{***}P < 0.0001$ compared to vehicle; two-way ANOVA.

26 (100 mg/kg). All three compounds showed reduction of blood glucose, demonstrating that propionic acid replacements such as the cyclopropionic acid and the tetrazole are capable of exhibiting *in vivo* glucose lowering activity. Furthermore, compound **18** showed a dose-dependent glucose reduction with a plateau of efficacy observed at 10 mg/kg thus defining the minimum dose that afforded maximal efficacy (MED_{max}) in this model.

In a further set of wild-type/GPR120 knockout mouse oGTT experiments, compounds **18** and **19** both displayed glucose lowering at the superpharmacologic dose of 150 mg/kg in wild-type mice (Figure 3). Meanwhile, no efficacy was observed in the GPR120 knockout mice, suggesting that glucose lowering observed at very high doses is still linked to GPR120 activation. The *in vitro* profile of compounds **18** and **19** on mouse (m) GPR120 and mGPR40 was similar to that observed for the human receptor (Table 6).

Compound **18** was evaluated for potency in common off-target *in vitro* assays. Ion channel activity was determined to be minimal (IC_{50}s at $Ca_v1.2$ = 28 μM,[25] IKr > 60 μM,[26] $Na_v1.5$ = 27 μM[27]), and the cytochrome P-450 inhibition was also negligible (CYP3A4, CYP2D6, CYP2C9 IC_{50s} > 50 μM).[28] Additionally, compound **18** was characterized in a general broad panel screen of enzyme, ion channel, and GPCR assays

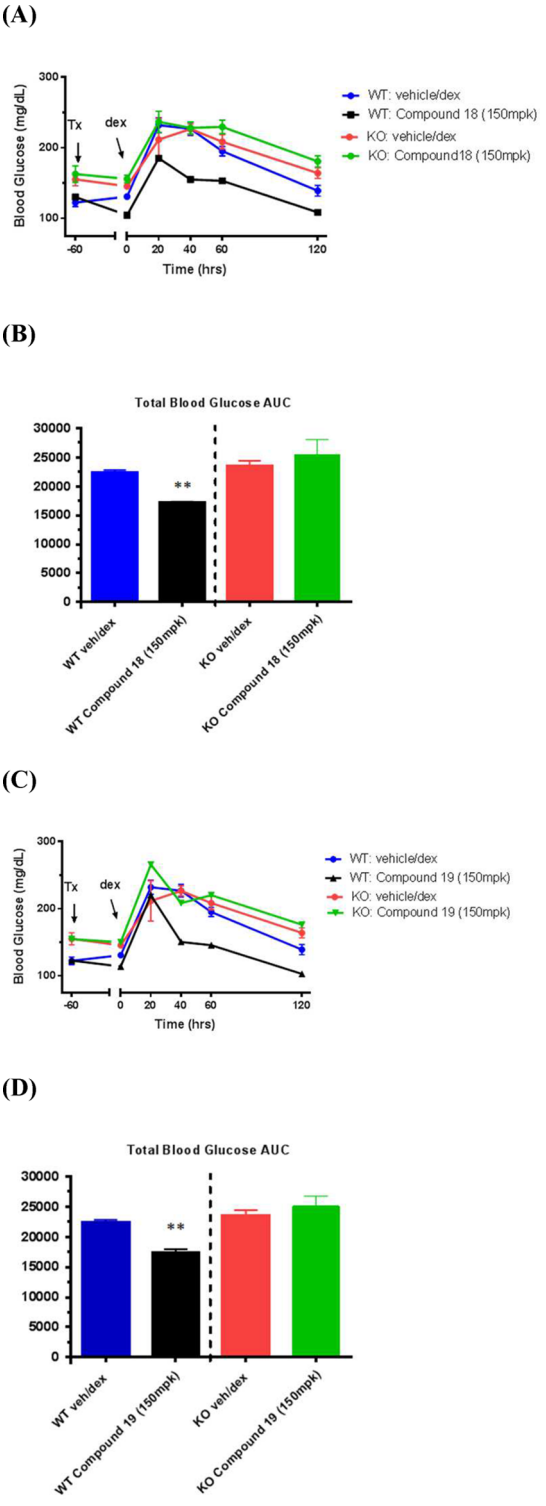

Figure 3. (A,B) Mouse oGTT of compound **18** in wild-type [150 mg/kg; n = 4, 3 h C_p= 43.9 μM (s = 15.8 μM)] and GPR120 knockout [150 mg/kg; n = 4, 3 h C_p = 53.4 μM (s = 14.0 μM)] mice. (C,D) Mouse oGTT of compound **19** in wild-type [150 mg/kg; n = 4, 3 h C_p = 33.5 μM (s = 21.0 μM)] and GPR120 knockout [150 mg/kg; n = 4, 3 h C_p = 27.6 μM (s = 6.03 μM)] mice. (A,C) Blood glucose (mg/dl) over time (minutes). (B,D) Net blood glucose area under the curve (AUC). Vehicle (veh); dextrose (dex) challenge; Tx = vehicle and compound administration; mpk = mg/kg. $^{**}P < 0.01$ compared to vehicle, two-way ANOVA.

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Table 6. Mouse *in Vitro* Data for Compounds 18 and 19[a]

Compound	mGPR120 EC_{50} (nM) IP1	mGPR120 EC_{50} (nM) β-Arr2	mGPR40 IP1 EC_{50} (nM)
18	6.4	6.8	>10k
19	5.6	4.6	>10k

[a]Values are the average of at least two experiments, each in 10-point titrations. Unless noted, all analogues tested were generally deemed to be full GPR120 agonists under assay conditions.

Table 7. Pharmacokinetic Profile of Compound 18 Across Multiple Species[a]

property	rat	mouse	Rhesus
AUC_{IV} (μM·h)	35.9	8.1	57.8
Cl_p (mL/min/kg)	1.1	9.9	0.33
Vd_{ss} (L/kg)	0.3	1.4	0.27
$t_{1/2}$ (h)	4.6	3.0	9.8
MRT (h)	4.6	2.4	13.5
F_{oral} (%)	93	76	82
PPB (% bound)	99.76	99.67	99.78
Cl_{int} (mL/min/kg)	470	3400	150

[a]AUC_{iv}, area under the plasma concentration vs time curve following IV dosing; Cl_p, plasma clearance; Vd_{ss}, volume of distribution at steady state; $t_{1/2}$, terminal half-life; MRT, mean residence time; F_{oral}, oral bioavailability; PPB, plasma protein binding; Cl_{int}, intrinsic clearance. IV dosing in DMSO/PEG400/H_2O = 20/60/20 (rat 1 mg/kg, mouse 2 mg/kg, Rhesus 0.5 mpk). PO dosing via suspension in methylcellulose 0.5% (rat 2 mg/kg, mouse 30 mg/kg, Rhesus 1 mpk).

and displayed minimal activity, including at PPAR *alpha*, *delta*, and *gamma* (>10 μM).

The pharmacokinetic profile of compound **18** was evaluated in multiple species, including rat in a higher dose study, and determined to be suitable for further *in vivo* evaluation in various PD models (Table 7). High oral bioavailabilities were observed as well as relatively long half-lives in these species. The pharmacokinetic profile in Rhesus was particularly encouraging, as it suggests that this series could be optimized toward efficient oral dosing in primates.

In summary, the optimization of a potent and selective series of chromane derived GPR120 agonists was described. Selected compounds from the series exhibit pharmacokinetic properties in the rat that supported their use as *in vivo* tools. Three compounds demonstrated glucose lowering in mouse oGTT studies, including cyclopropionic acid **24** and tetrazole **26**, which may offer new future directions for teams pursuing GPR120 agonists. Finally, two compounds (**18** and **19**) demonstrated mechanism-based glucose lowering even at supra-pharmacologic exposures in mice, suggesting that these compounds will be good tools for further *in vivo* studies, which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.6b00394.

Experimental procedures and analytical data for the synthesis of all compounds; GPR120 and GPR40 *in vitro* assay procedures; PK protocol; oGTT protocols (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

FFAR1, free fatty acid receptor 1; FFAR4, free fatty acid receptor 4; T2DM, type 2 diabetes mellitus; GLP-1, glucagon like peptide 1; GPR120, G-protein coupled receptor 120; GPCR, G-protein coupled receptor; GPR40, G-protein coupled receptor 40; IP1, D-myo-inositol-1-phosphate; oGTT, oral glucose tolerance test

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