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3-Substituted 3-(4-aryloxyaryl)-propanoic acids as GPR40 agonists

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ABSTRACT

The design, synthesis, and structure–activity relationship (SAR) for a series of β-substituted 3-(4-aryloxyaryl)propanoic acid GPR40 agonists is described. Systematic replacement of the pendant aryloxy group led to identification of potent GPR40 agonists. In order to identify candidates suitable for in vivo validation of the target, serum shifted potency and pharmacokinetic properties were determined for several compounds. Finally, further profiling of compound **7** is presented, including demonstration of enhanced glucose tolerance in an in vivo mouse model.

Type 2 diabetes is a growing public health epidemic. Given the worldwide spread of this debilitating condition, there is a continuing need for novel therapies. Recently, renewed focus has been placed on pancreatic islet-based insulin secretion as a novel mechanism for the treatment of type 2 diabetes. This approach has the potential for stabilization and restoration of β-cell function.[1] In this regard several orphan G-protein coupled receptors (GPCR's) have been identified that are preferentially expressed in the β-cells and are implicated in glucose stimulated insulin secretion (GSIS).[2] GPR40, which is a cell surface GPCR, is highly expressed in human (and rodent) islets as well as in insulin-secreting cell lines. Several naturally occurring medium to long-chain fatty acids (FA's)[3] as well as synthetic compounds, including members of the thiazolidinone class of PPARγ agonists[4] and other small molecule fatty acid mimetics,[5] have recently been identified as ligands for GPR40. The activation of the GPR40 receptor leads to inositol triphosphate (IP3) production, release of intracellular Ca^{+2} from the endoplasmic reticulum, and Ca^{+2} influx through membrane channels, collectively resulting in enhanced insulin secretion. Therefore, under hyperglycemic conditions, GPR40 agonists are capable of augmenting the release of insulin from islet cells. The specificity of this response is suggested by data showing that the inhibition of GPR40 by siRNA attenuates FA-induced amplification of GSIS.[6]

There are several potential advantages of GPR40 as a target for the treatment of type 2 diabetes. First, since GPR40 induced insulin secretion acts in a glucose dependent manner, there is little or no risk of hypoglycemia. Second, the limited tissue distribution of GPR40 (mainly in islets)[2] suggests that there may be less chance for side effects associated with GPR40 inhibition in other tissues. Third, GPR40 agonists that are active in islets may have the potential to restore or preserve islet function.[1b–d] This would be highly advantageous because long term diabetes therapy often leads to the gradual diminution of islet activity, so that after extended periods of treatment, it is often necessary for patients to receive daily insulin injections. By restoring or preserving islet cell function, GPR40 agonists may delay or prevent the loss of islet cell function in type 2 diabetic patients. Identification of a small molecule with sufficient pharmacokinetic and pharmacodynamic properties to effect islet GPR40 stimulation in vivo would allow for validation of this target in animal models, and potentially in the clinic. This

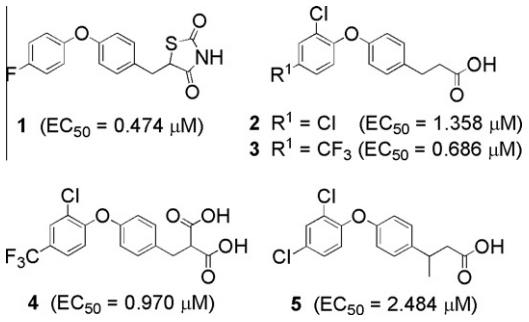

Figure 1. Small molecule GPR40 agonists (human GPR40 activity from FLIPR based functional assay).[9]

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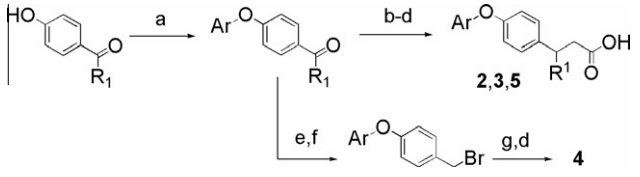
article describes the results of efforts to identify novel GPR40 agonists.

Following directed screening of the Merck compound collection, thiazolidinedione **1** was identified as a modestly potent GPR40 agonist (Fig. 1). Extensive modifications were carried out in the thiazolidinedione series which led to potent compounds,[7] although off target ion channel activity plagued some members of this class. A full account of this research will be presented elsewhere. Replacement of the thiazolidinedione functionality led to dihydrocinnamic acid derivatives typified by **2** and **3**, as well as the malonic acid **4**. These carboxylic acids possess modest GPR40 agonist activity, however, carboxylic acids of this type failed to provide activity in our in vivo models. We speculated that these types of fatty acid mimetics may undergo extensive protein binding in vivo, leading to low free fractions and subsequent lack of efficacy. Addition of a methyl substituent at the β-carbon (**5**) led to about a two-fold loss in potency, however, further exploration of this position led to significant potency enhancement.[8] This letter describes the synthesis and biological activity of a series of β-substituted propionic acids with improved potency.

A general synthesis of the carboxylic acids **2**–**5** is shown in Scheme 1. Initially, the *p*-substituted phenols were coupled to the appropriate aryl fluorides. For the synthesis of dihydrocinnamic acids **2** and **3**, and the β-methyl dihydrocinnamic acid **5**, Wittig homologation was followed by catalytic reduction of the resulting olefins and finally ester hydrolysis. For the synthesis of malonic acid **4**, the 4-aryloxyaryl aldehyde intermediate was reduced to the alcohol and subsequently converted to the primary bromide. The resulting bromide was used in the alkylation of diethyl malonate, followed again by ester hydrolysis to provide **4**.

The synthesis of a series of β-(2-propynyl)dihydrocinnamic acids **6**–**19** is shown in Scheme 2. Condensation of the appropriate anisaldehyde with 2,2-dimethyl-1,3-dioxane-4,6-dione was followed by conjugate addition of propynyl magnesium bromide. Heating of the resulting product in the appropriate alcohol solvent led to decarboxylation and concomitant transesterification. Hydrolysis of the aryl methoxy group provided the phenols, which were coupled using one of two methods to provide diversity at the R^3 position (Scheme 2). A range of biaryl ethers (**6**–**15**, **19**; Table 1) were formed through nucleophilic aromatic substitution of the corresponding aryl halides. Alternatively, Mitsunobu coupling with the corresponding alkyl alcohols provided **16**–**18**. In both cases, hydrolysis of the esters completed the desired β-(2-propynyl)dihydrocinnamic acids.

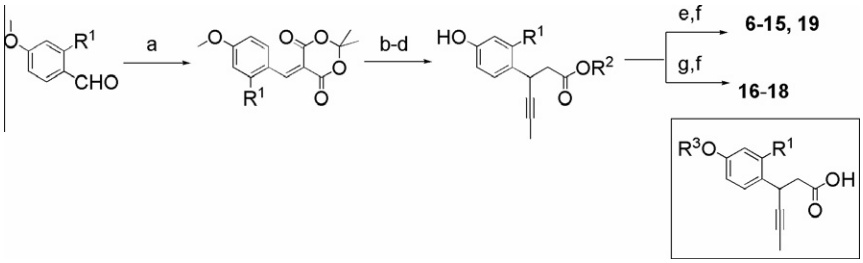


Scheme 1. Synthesis of dihydrocinnamic acids: R^1 = H or Me, Ar = 2,4-di-ClPh or 2-Cl,4-CF_3Ph. Reagents and conditions: (a) Ar-F, $CsCO_3$, 80 °C, DMF (61–79%); (b) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, 0 °C; (c) Pd/C, H_2, EtOAc; (57–72%, two steps) (d) LiOH, MeOH/H_2O (83–97%); (e) $LiBH_4$, THF, 0 °C; (f) CBr_4, PPh_3, imidazole, CH_2Cl_2 (48% two steps); (g) $(EtO_2C)_2CH_2$, NaH, DMF (51%).

Cis- and *trans*- cyclopropyl hexynoic acids **20** and **21** were prepared as shown in Scheme 3. Addition of propynyl magnesium bromide to the biaryl ether ketone prepared as described in Scheme 1, followed by elimination with catalytic *p*-toluene sulfonic acid furnished the eneyne. This unstable intermediate was immediately subjected to cyclopropanation using ethyl diazoacetate under copper catalysis.[10] Chromatographic separation of the *cis* and *trans* diastereomers, followed by hydrolysis of the esters provided the desired targets.[11]

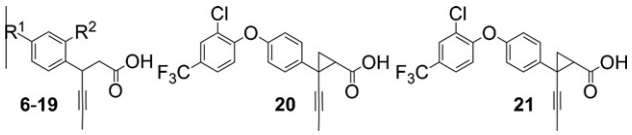
The synthesis of compounds **22**–**25**, in which the carboxylic acid has been replaced by an oxazolidinedione, is depicted in Scheme 4. Condensation of 4-hydroxybenzaldehyde with 2,2-dimethyl-1,3-dioxane-4,6-dione was followed by conjugate addition of propynyl magnesium bromide. Thermal hydrolysis of the dimethylacetal with concomitant decarboxylation was followed by methyl ester formation and bezyl protection of the phenol to complete the oxazolidinedione precursor. This transformation was accomplished through α-oxygenation utilizing the Davis oxaziridine, conversion of the ester to the primary amide, and finally cyclization. Hydrolysis of the benzyl ether revealed the phenol, which was coupled to appropriate aryl fluoride to provide **23** as a 2:1 mixture of *trans*:*cis* diastereomers. Careful chromatographic separation provided **24** and **25** as pure diastereomers.

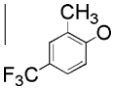
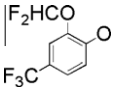
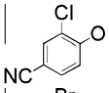
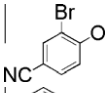
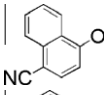
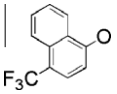
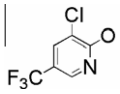
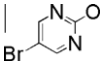
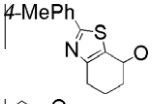
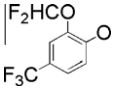
The GPR40 activities of selected 4-aryloxyaryl and 4-alkyloxyaryl (3-phenyl)hexynoic acids are shown in Table 1. In general compounds displayed similar levels of agonist activity across species when mouse and human GPR40 was compared, and observed IC_{50}'s in the human GPR40 binding assay in most cases paralleled the agonist EC_{50}'s. As previously mentioned, β-methylation of **2** to provide **5**, resulted in a slight loss in GPR40 activity, however incorporation of the 2-propynyl substituent (**6**) resulted in a significant potency increase. Alternative aryl substitutions led to compounds with similar potency levels, including the larger 4-cyanonaphthyloxy group (**10**). Replacement of the cyano substituent in **10** with the trifluoromethyl group (**11**) resulted in a surprising loss in potency. In an effort to increase the polarity of aryl substituent, a series of heteroaryl subunits were examined (**12**–**15**). Most of these heterocycles resulted in a loss of GPR40 agonist activity with the notable exception of the pyridyl substituent in **12**. Carbocycles were also tolerated, resulting in potent GPR40 agonists **16**–**18**. SAR in related series revealed the central phenyl ring was less tolerant of substitution, however, the fluoro substituted **19** proved to be a potent GPR40 agonist. Finally, disubstituted cyclopropyl carboxylic acids have previously been reported as potent GPR40 agonists. Unfortunately, no synergistic effect was observed



Scheme 2. Synthesis of hexynoic acids: R^1 = H or F, R^2 = Me or Et, for R^3 see Table 1 below, X = F, Cl, or Br. Reagents and conditions: (a) 2,2-dimethyl-1,3-dioxane-4,6-dione, H_2O (78–99%); (b) $CH_3CHCMgBr$, THF, 0 °C; (c) R^2OH, reflux; (d) BBr_3, CH_2Cl_2, −78 °C → rt (11–62%, three steps); (e) Ar-X, $CsCO_3$, 80 °C, DMF (25–78%); (f) LiOH, THF, water, 0 °C (19–83%); (g) DIAD, PPh_3, THF (17–75%).

Table 1
GPR40 agonist activities for compounds **4**–**20**[a]

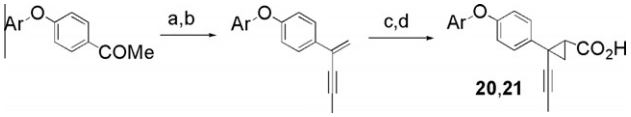


Compd #	R^1	R^2	hGPR40[b] EC_{50} (nM)	mGPR40[c] EC_{50} (nM)	hSpa[d] IC_{50} (nM)
5	—	—	2484	Na	Na
6		H	94	127	40
7		H	71	77	12
8		H	42	48	23
9		H	85	88	36
10		H	53	93	13
11		H	1401	1248	211
12		H	108	95	30
13		H	1568	1484	433
14		H	1578	985	2487
15		H	394	149	342
16[e]		H	31	47	42
17[f]		H	51	100	23
18		H	114	124	312
19		F	113	104	49
20	—	—	2820	871	3435
21	—	—	24,490	>40,000	>10,000

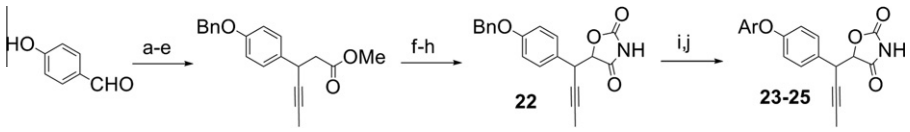
[a] All compounds racemic unless otherwise noted.
[b] Human GPR40 activity from FLIPR based functional assay.[9]
[c] Mouse GPR40 activity from FLIPR based functional assay.[9]
[d] Human GPR40 activity from SPA based binding assay.[12]
[e] R stereochemistry at bezyl alcohol, mixture of diastereomers.
[f] Racemic, mixture of diastereomers.[13]

when this functionality was combined with our pharmacophore to provide the trisubstituted cyclopropyl acids.

In order to examine the role of the carboxylic acid in potential plasma protein binding interactions, we also prepared a set of oxazolidinediones (OZD's, **22**–**25**; Table 2). This heterocycle has previously been shown to act as a carboxylic acid surrogate due the similar pK_a of the NH. The benzyloxy OZD (**22**) was

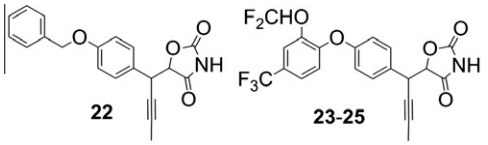


Scheme 3. Synthesis of cyclopropyl hexynoic acids: Ar = 2-Cl,4-CF_3Ph. Reagents and conditions: (a) $CH_3CHCMgBr$, THF, 0 °C; (b) $MePhSO_3H$, CH_2Cl_2, rt (51%, two steps) (c) $Cu(OTf)_2$, N_2CCO_2Et, (+)-2,2′-isopropylidenebis[(4R)-4-phenyl-2-oxazoline], CH_2Cl_2, 0 °C; (d) LiOH, THF, water, 0 °C (23–25%, two steps).



Scheme 4. Synthesis of oxazolidinediones: Ar = 2-OCF_2H,4-CF_3Ph. Reagents and conditions: (a) 2,2-dimethyl-1,3-dioxane-4,6-dione, H_2O; (b) $CH_3CHCMgBr$, THF, 0 °C (84%, two steps); (c) 3-pentanone, H_2O, reflux; (d) SO_2Cl, MeOH, 0 °C; (e) BnBr, NaH, DMF, 0 °C → rt (56%, three steps); (f) (i) KHMDS, THF, −78 °C; (ii) $PhSO_2$(N–O–CH)Ph, −78 °C → rt; (g) NH_3, MeOH, rt; (h) CDI, CH_2Cl_2, rt (15%, three steps); (i) BBr_3, CH_2Cl_2, −78 °C → 0 °C; (j) Ar-F, $CsCO_3$, 80 °C, DMF (43%, two steps).

Table 2
GPR40 agonist activities for compounds **22**–**25**[a]



Compd #	Stereochem.	hGPR40[b] EC_{50} (nM)	mGPR40[c] EC_{50} (nM)	h Spa[d] IC_{50} (nM)
22	*cis*/*trans* mix	954	3707	4399
23	*cis*/*trans* mix	124	266	19
24	*Trans*	7581	7058	2414
25	*Cis*	130	136	151

[a] All compounds racemic.
[b] Human GPR40 activity from FLIPR based functional assay.[9]
[c] Mouse GPR40 activity from FLIPR based functional assay.[9]
[d] Human GPR40 activity from SPA based binding assay.[12]

Table 3
GPR40 activity for selected compounds in the presence of serum

Compd #	hGPR40[a] EC_{50} (nM)	hIP3 + 10% HS EC_{50} (nM)	hIP3 + 0.4% MSA EC_{50} (nM)
7	71	436	455
8	42	519	597
10	53	172	247
12	108	409	NA
19	113	306	349
23	124	224	249

[a] Human GPR40 activity from FLIPR based functional assay.[9]

shown to be a modest GPR40 agonist with respect to both human and mouse receptors. Conversion of the benzyl group to one of the preferred biaryl ethers from our carboxylic acid SAR (**23**) led to a compound with comparable potency to the corresponding carboxylic acid. Separation of the diastereomers revealed that the majority of the GPR40 activity resulted from the *cis* diastereomer.

In order to assess the potential effect of plasma protein in vivo, an assay was developed which measured IP3 production from human cells in the presence of either human serum (10%), or rat serum albumin (0.4%).[14] Table 3 summarizes the serum shifted potencies of selected GPR40 agonists in this assay. In this assay, the relative polarity of the aryl group had little effect on the serum shifted potency, however, fluorination of the central ring slightly reduced the serum shift (**7** vs **19**). In agreement with our earlier prediction, conversion of the carboxylic acid to the OZD does appear to reduce the serum shift (**7** vs **23**).

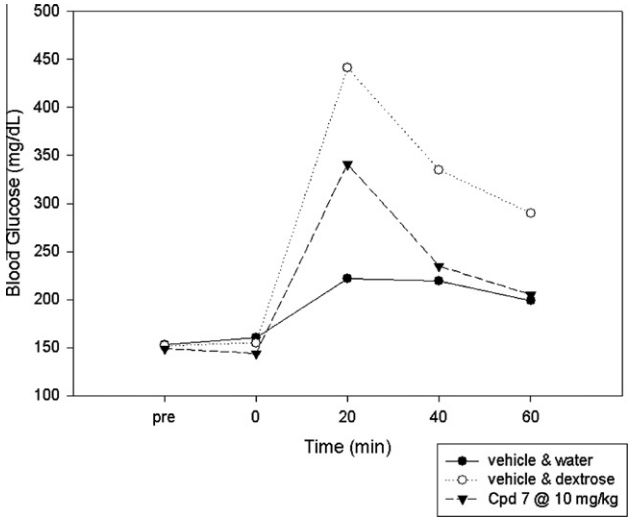


Figure 2. Lean mouse ipGTT results.

From the above set, two compounds were selected for pharmacokinetic profiling in mouse (Table 4). These compounds are characterized by low clearance and volume of distribution, consistent with high plasma protein binding, as well as long half-life and good oral bioavailability.

Table 4
Pharmacokinetic properties of selected GPR40 agonists[a]

Compd #	Clp (mL/min/kg)	V_d (L/kg)	$t_{1/2}$ (h)	PO AUCN (μM·h·kg/mg)	*F* (%)	C_{max} (μM)	T_{max} (h)
7	0.49	0.31	7.8	83.8	112	12	4.0
25	0.85	0.47	7.0	42.6	93	5.5	4.7

[a] Dose.

Table 5
Off targets activity of selected GPR40 agonists

Compd #	CYP2C9 IC_{50} (μM)	CYP2D6 IC_{50} (μM)	CYP3A4 IC_{50} (μM)	hERG IC_{50} (μM)	CAV 1.2 IC_{50} (μM)
7	>50	>50	>50	>60	>30
19	28.0	>50	>50	25.0	25.6
25	2.4	>50	>50	3.4	5.1

Compound **7** was selected for further profiling in vivo (Fig. 2). Oral administration of **7** in normal lean mice one hour prior to dextrose challenge in an intraperitoneal glucose tolerance test (IPGTT)[15] significantly reduced blood glucose excursion (66% inhibition of AUC_{Glu}, p <0.004) at a dose of 10 mpk.

Finally, the carboxylic acid **7** as well as the related fluoro substituted carboxylic acid **19** and OZD **25** were profiled in a series of off target assays (Table 5). For all three compounds, P450 inhibition was found to be minimal, with **25** demonstrating <5 μM inhibition of the CYP2C9 isoform. Consistent with previous results, the two carboxylic acids showed minimal ion channel activity against the hERG and CAV 1.2 channels, although the OZD **25** displayed modest activity.

In conclusion, a series of β-substituted 3-(4-aryloxyaryl)propanoic acids were prepared and their activities as GPR40 agonists were evaluated. The OZD group was found to be a suitable acid surrogate, which reduced the serum shifted EC_{50} in vitro, but also led to modest ion channel activity. Following SAR optimization, compound **7** was selected for in vivo evaluation, where it demonstrated the potential of this class of small molecule GPR40 agonists as glucose lowering agents.

Acknowledgment

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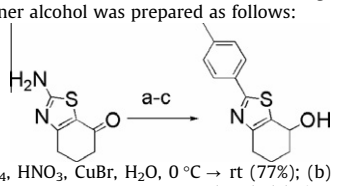
12. SPA binding assay was carried out using receptor isolated from CHO cells overexpressing human GPR40. All reported values are means of ⩾3 experiments, with standard deviations <75% of the average.
13. The coupling partner alcohol was prepared as follows:



(a) $NaNO_2$, H_3PO_4, HNO_3, CuBr, H_2O, 0 °C → rt (77%); (b) 4-$CH_3C_6H_4B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME, EtOH, 140 °C, MW (68%); (c) $LiBH_4$, THF, 0 °C (72%).
14. IP3 assay protocol is described in Ref. 7b.
15. For a full account of the experimental protocol used in the IPGTT assay see Ref. 7b.