ACS Medicinal Chemistry Letters

Letter

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Discovery of DS-1558: A Potent and Orally Bioavailable GPR40 Agonist

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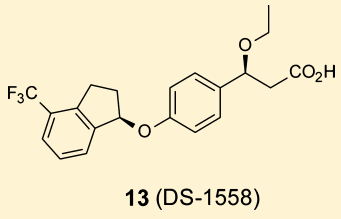
Supporting Information

ABSTRACT: GPR40 is a G protein-coupled receptor that is predominantly expressed in pancreatic β-cells. GPR40 agonists stimulate insulin secretion in the presence of high glucose concentration. On the basis of this mechanism, GPR40 agonists are possible novel insulin secretagogues with reduced or no risk of hypoglycemia. The improvement of *in vitro* activity and metabolic stability of compound **1** led to the discovery of **13**, (3*S*)-3-ethoxy-3-(4-{[(1*R*)-4-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-yl]oxy}phenyl)propanoic acid, as a potent and orally available GPR40 agonist. Compound **13** (DS-1558) was found to have potent glucose lowering effects during an oral glucose tolerance test in ZDF rats.



KEYWORDS: *GPR40, agonist, insulin secretagogue, diabetes, glucose lowering*

Type 2 diabetes is a metabolic disorder characterized by impaired glucose homeostasis caused by insufficient insulin secretion or insulin resistance. The number of diabetics has been increasing all over the world and has reached nearly 350 million.[1,2] Current common therapies include the use of insulin injections, sulfonylureas, metformin, and glinides.[3,4] Most of them are associated with problems such as weight gain, risk of hypoglycemia, and lack of sustained efficacy.[5−9] Lately, glucose-dependent insulin secretagogues, such as GPR119[10] and GPR142[11] agonists, have attracted attention as alternative treatments for diabetes. Among them, DPP-IV inhibitors enhancing the activity of GLP-1 have already been widely used. Most recently, SGLT2 inhibitors that inhibit the reuptake of urinal sugar have been developed as hypoglycemic agents with low risk of weight gain.

GPR40 is primarily expressed in pancreatic β-cells and activated by long-chain free fatty acids, resulting in enhancement of glucose-stimulated insulin secretion (GSIS) dependent on elevated glucose levels.[12−17] On the basis of this GSIS mechanism, GPR40 has also received considerable attention as a novel therapeutic target for type 2 diabetes because of its low risk of hypoglycemia.[18,19] Recently, several groups have reported GPR40 agonists that contain acidic moieties such as a carboxylic acid or thiazolidinedione (Figure 1).[20−28] We have also identified 3-ethoxypropanoic acid **1** as a promising lead compound (Figure 2).[29]

Herein we describe the lead optimization of **1** to discover (3*S*)-3-ethoxy-3-(4-{[(1*R*)-4-(trifluoromethyl)-2,3-dihydro-1*H*-inden-1-yl]oxy}phenyl)propanoic acid (**13**), a potent and orally available GPR40 agonist.

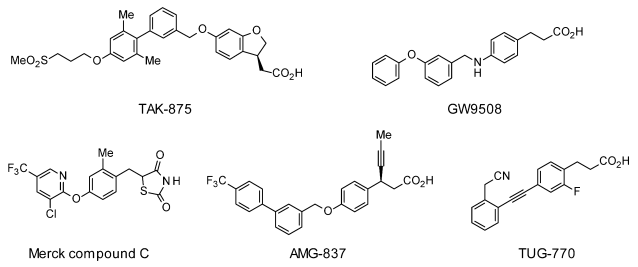


Figure 1. Reported GPR40 agonists.[20−28]

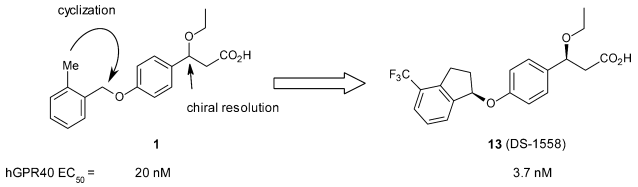


Figure 2. Optimization of lead compound **1**.

Although compound **1** showed a glucose lowering effect in rats after oral administration, its half-life was very short (Table 2). High *in vivo* clearance of **1** was probably due to metabolic oxidation at the benzyl position because we detected a glutathione (GSH) adduct of 2-methylbenzaldehyde, a putative metabolite of **1**, from a GSH trapping assay in human liver microsomes. Therefore, we designed the cyclized compounds

Received: September 26, 2014
Accepted: January 13, 2015
Published: January 13, 2015

ACS Publications © 2015 American Chemical Society

DOI: 10.1021/ml500391n
ACS Med. Chem. Lett. 2015, 6, 266−270

between the benzylic position and the ortho position of the phenyl ring to avoid benzyl oxidation (Figure 2).

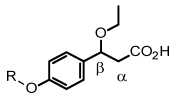
First we investigated the stereoconfiguration of the ethoxy moiety (Table 1). Chiral separation of the Cl-substituted derivative revealed that (*S*)-stereochemistry was preferred for GPR40 agonistic activity (**2**–**4**).

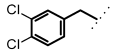
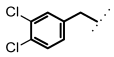
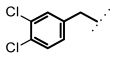
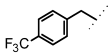
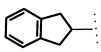
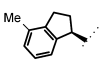
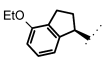
Next we synthesized cyclized derivatives with 5- or 6-membered rings. Among indane derivatives (**6**–**8**), compound **6** was the most potent agonist. Tetralin derivative **9** with the same stereochemistry at the benzyl position was weaker than **6**. Accordingly, we focused our investigation to the substituents on the indane ring. The methyl (**10**) and ethoxy (**11**) derivatives showed similar potency to compound **6**. The Cl (**12**) and CF_3 (**13**) substituents provided a significant leap in agonistic activity. We synthesized possible diastereomers (**14**–**16**) of **13** and confirmed that compound **13** was the most potent agonist. The stereoconfiguration at both indane and ethoxy moieties significantly impacted the GPR40 agonistic activity. Furthermore, compound **13** had no PPARγ agonistic activity up to 100 μM, whereas noncyclic compound **5** had partial PPARγ agonistic activity (EC_{50} = 10.4 μM, E_{max} =11.3% relative to rosiglitazone). This indicated that the fixed conformation improved the GPR40 selectivity over PPARγ. In addition, **13** had no activity for GPR120 and exhibited >100-fold selectivity over 68 other diverse receptors, ion channels, and transporters.[30] Thus, potent and selective GPR40 agonist **13**, named DS-1558, was selected for further investigations.

Compound **13** (DS-1558) was synthesized as shown in Scheme 1. This route was considered to be able to synthesize this compound on a large scale using mild reactions, which were arranged to suppress the production of diastereomers minimally. In actual fact, we obtained 80 g of **13** (DS-1558) starting from about 90 g of **17** with high optical purity (98% de).

Starting from a commercially available indanone **17**, chiral alcohol **18** was obtained by Ru-catalyzed asymmetric transfer hydrogenation with good enantioselectivity (99% ee).[31] A S_NAr reaction was used to obtain aryl ether **19**. After yielding benzoic acid **20** on hydrolysis in an alkali solution, β-ketoester **21** was synthesized by the condensation of magnesium methylmalonate with acid imidazolide preformed from **20** and CDI.[32] The chiral Ru-catalyst with opposite chirality was utilized again for

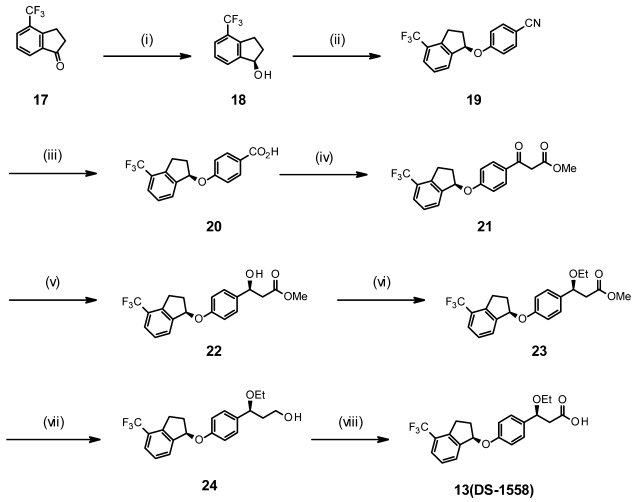
Table 1. Structures and *in Vitro* Activities of the Phenylpropanoic Acid Series



Compd	R	Configuration of β-ethoxy moiety	GPR40 hEC_{50} (nM)[a]
1		*racemic*	20
2		*racemic*	6.2
3		 (*S*)-	3.9
4		 (*R*)-	360
5		(*S*)-	5.3
6		(*S*)-	31
7		(*S*)-	69
8		(*S*)-	83
9		(*S*)-	62
10		(*S*)-	29
11		(*S*)-	63
12		(*S*)-	5.0
13 (DS-1558)		(*S*)-	3.7
14		(*S*)-	19
15		(*R*)-	330
16		(*R*)-	2600

[a]A calcium flux assay in transfected-GPR40 CHO cells. Assay results are the average of triplicates. Standard deviation was ±20%.

Scheme 1[a]



[a]Reagents and conditions: (i) HCO_2H, NEt_3, RuCl[(*R*,*R*)-Tsdpen]-(mesitylene), r.t., 85%, 99% ee; (ii) 4-fluorobenzonitrile, NaH, THF/DMF, r.t., quant.; (iii) 5 N NaOH aq., 2-methoxyethanol, 120 °C, 84%; (iv) methyl potassium malonate, CDI, $MgCl_2$, NEt_3, THF/EtOAc, r.t. to 45 °C, 84%; (v) HCO_2H, NEt_3, RuCl[(*S*,*S*)-Tsdpen](mesitylene), 38 °C, 91%, 96% de; (vi) EtI, Ag_2O, toluene, 110 °C, 84%; (vii) $LiAlH_4$, THF, 0 °C, quant.; (viii) TEMPO, $NaClO_2$, NaClO, pH 6.86 phosphate buffer, acetonitrile, 0 to 10 °C, 85%, 98% de.

DOI: 10.1021/ml500391n
ACS Med. Chem. Lett. 2015, 6, 266–270

the asymmetric hydrogenation of β-ketoester to give β-hydroxyester **22** in a good diastereo ratio (96% de). The β-hydroxy group in **22** was alkylated in the neutral conditions of EtI and Ag_2O without the retro-aldol reaction. The ester group of **23** was reduced into primary alcohol and subsequently oxidized to carboxylic acid **13** (DS-1558) by TEMPO. This multistep procedure was adopted in order to avoid β-elimination.

The absolute stereochemistry of **13** (DS-1558) was determined by X-ray crystal structural analysis in the form with (*S*)-arginine and methanol solvate. On the basis of absolute configuration of the (*S*)-arginine, the absolute configurations of the ethoxy and the indane moieties were determined as (*S*) and (*R*), respectively (Figure 3).

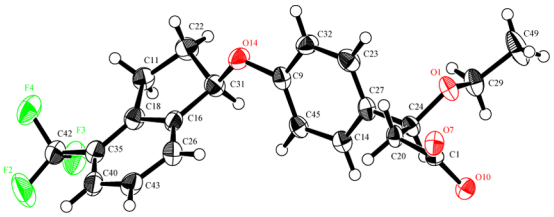


Figure 3. ORTEP representation of **13** (DS-1558).

Pharmacokinetic (PK) parameters were summarized in Table 2. Compound **13** (DS-1558) showed higher plasma exposure and longer half-life than compound **1** in rats. The improved PK profiles were also observed in monkeys and dogs. As we expected, the cyclization approach was efficient at improving the PK profiles.

Table 2. Comparison of Pharmacokinetic Properties of 1 and 13 (DS-1558) in Rats, Dogs, and Monkeys[a]

compd	**1**	**13** (DS-1558)		
species	rat	rat	dog	monkey
i.v.				
dose (mg/kg)	2	1	0.5	1
Cl (L/h/kg)	0.37	0.020	0.042	0.032
V_{dss} (L/kg)	0.16	0.19	0.23	0.62
$T_{1/2}$ (h)	0.37	6.0	4.0	17
p.o.				
dose (mg/kg)	3	1	1	1
C_{max} (μg/mL)	3.3	3.1	1.7	2.3
AUC (μg·h/mL)	5.3	40	14	30
F (%)	64	80	66	100

[a]The data is the mean value. The statistics are shown in the Supporting Information.

The GPR40-mediated effects of **13** (DS-1558) on glucose-stimulated insulin secretion were confirmed in isolated islets from GPR40 KO and wild-type mice. Improvement of glucose tolerance and insulin secretion were also recognized during the *in vivo* studies of these mice and ZF rats.[33] Furthermore, we evaluated *in vivo* efficacy of this compound by an oral glucose tolerance test (OGTT) in Zucker diabetic fatty (ZDF) rats, which exhibit obesity with diabetes and are widely used for therapeutic research on type 2 diabetes. The compound was orally administrated 30 min prior to a glucose challenge (2 g/kg). Even at the minimum dosing, 0.03 mg/kg, the **13** (DS-1558) treatment markedly reduced the glucose excursion compared to the control (Figure 4A). The glucose-lowering

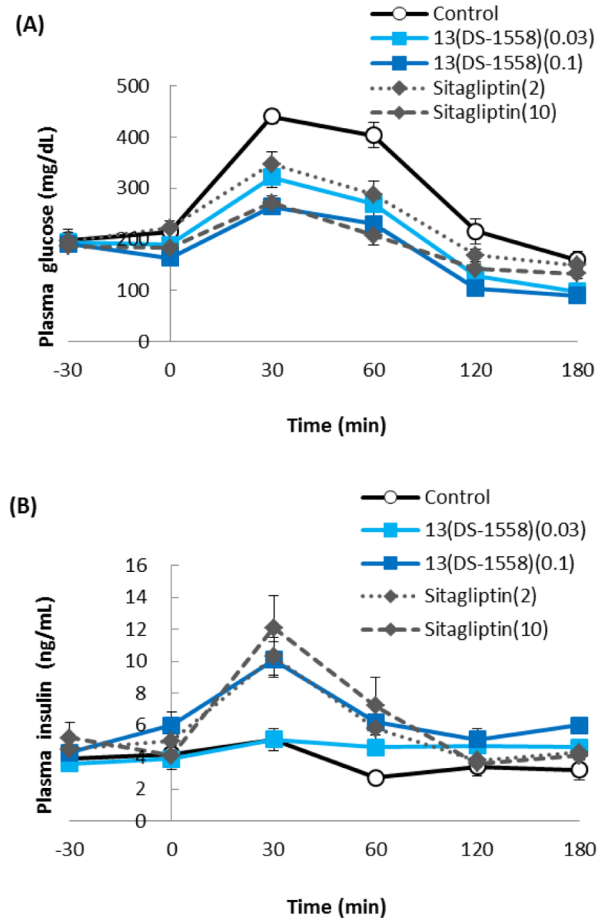


Figure 4. Effects of **13** (DS-1558) during an OGTT in male ZDF rats. Time-dependent changes of plasma glucose (A) and plasma insulin (B). The results are represented as the mean ± standard error (n = 6, 9-weeks old).

potency of **13** (DS-1558) at 0.1 mg/kg was similar to that of sitagliptin at 10 mg/kg. Simultaneously, the augmentation of plasma insulin levels by **13** (DS-1558) at 0.1 mg/kg and sitagliptin at 10 mg/kg was observed (Figure 4B).

In conclusion, we have shown the lead optimization of 3-ethoxypropanoic acid **1** to identify the promising compound **13** (DS-1558). The cyclization of benzyl carbon improved not only the half-life but also GPR40 selectivity. We developed the chiral synthesis of **13** (DS-1558) on a large scale with Ru-catalyzed asymmetric transfer hydrogenation as a key reaction. The potent *in vivo* glucose lowering effect of **13** (DS-1558) was demonstrated in ZDF rats, type 2 diabetic model rats. Further details of **13** (DS-1558) will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

DOI: 10.1021/ml500391n
ACS Med. Chem. Lett. 2015, 6, 266−270

■ ABBREVIATIONS

CDI, 1,1′-carbonyldiimidazole; TEMPO, 2,2,6,6-tetramethylpiperidine *N*-oxyl; PPAR, peroxisome proliferator-activated receptor

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