P151

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DESIGN AND IDENTIFICATION OF A GPR40 FULL AGONIST (SCO-267) POSSESSING A 2-CARBAMOYLPHENYL PIPERIDINE MOIETY FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

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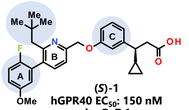
Introduction

- GPR40 is a G-protein-coupled receptor expressed in pancreatic islet cells and enteroendocrine cells, and its activation stimulates insulin and incretin secretion (Mancini and Poitout, 2013, *Trends Endocrinol Metab* 24:398-407.)
- Insulin and incretin hormones are the pivotal regulators for glycemic control (Nauck and Meier, 2018, *Diabetes Obes Metab* 20 Suppl 1:5-21.)
- GPR40 full agonists can activate the enteroendocrine system while stimulating insulin secretion (Luo et al., 2012, *PLoS One* 7:e46300.)
- As GPR40 partial agonists improve glycemic control in patients with diabetes (Kaku et al., 2016, *Diabetes Obes Metab* 18:925-929.), GPR40 full agonists are expected to provide superior efficacy and additional benefits in patients with metabolic diseases
- In this poster, we will describe the design, structure-activity relationships, and pharmacological effects of **SCO-267** as a potent and orally bioavailable GPR40 full agonist

New Lead Generation



(*S*)-1
hGPR40 EC_{50}: 150 nM
clogP: 7.1

Previously reported GPR40 full agonist (WO2013122029)

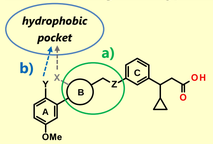
Challenges of compound (S)-1

- Aromaticity (negative impact on overall physicochemical properties etc.)
- Insufficient agonistic activity

Initial SAR

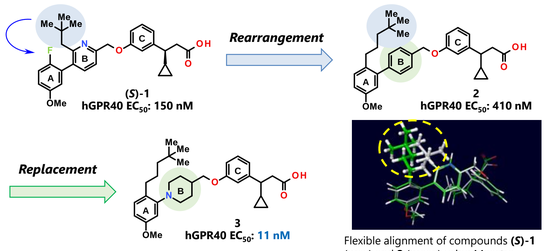
- The hydrophobic substituent and the terminal aromatic rings (A and C) are essential for potent agonistic activity

Molecular design and hypothesis



a. The central aromatic ring (B) of **(*S*)-1** would serve as just a linker to keep the position and distance of terminal aromatic rings (A and C), therefore, would be replaced with a saturated ring system

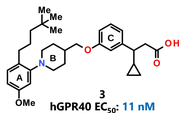
b. Fluorine-substituted position of **(*S*)-1** would easily access the presumed hydrophobic pocket that the neopentyl alkyl chain of **(*S*)-1** occupies



Flexible alignment of compounds **(*S*)-1** (gray) and **2** (green) using Maestro.

- **Rearrangement of the hydrophobic moiety on the central ring (B) to the terminal ring (A) retained agonistic activity**
- **4-Methyl piperidine ether 3 was identified as a new lead compound which showed potent agonistic activity**

Lead Optimization

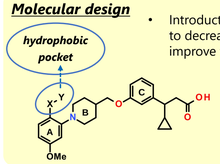


3
hGPR40 EC_{50}: 11 nM
clogP: 8.4
Cell viability ATP at 30 μM: 0.1%

Challenge of compound 3

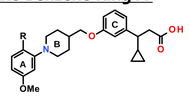
- Highly lipophilic property

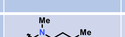
Molecular design



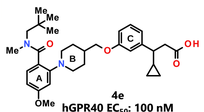
- Introduction of a polar linker (X and/or Y) to decrease the lipophilicity and to improve the physicochemical properties

Effect of Substituent on the Benzene Ring A



Compound	R	hEC_{50} nM	E_{max}	clogP	Cell viability ATP % at 30 μM
4a		190	108%	7.6	0.1
4b		97	112%	6.5	0.1
4c		1000	110%	4.0	80.7
4d		2200	96%	5.8	76.4
4e		100	107%	5.6	82.2

- **Introduction of amide moiety as a linker led to the improvement of druggability especially for lipophilicity and cell viability (set the target clogP value: <6.0)**

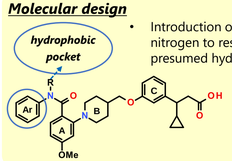


4e
hGPR40 EC_{50}: 100 nM
clogP: 5.6
Cell viability ATP at 30 μM: 82.2%

Challenge of compound 4e

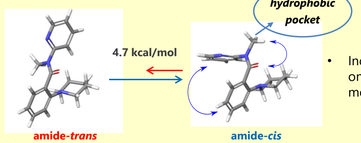
- Insufficient agonistic activity

Molecular design



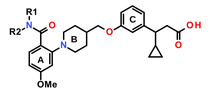
- Introduction of aromatic ring onto the amide nitrogen to restrict the *N*-alkyl moiety to the presumed hydrophobic pocket

Hypothesis



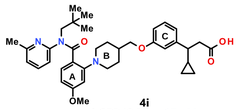
- Incorporation of suitable lipophilic moiety onto the nitrogen group of the benzanilide moiety would enhance the agonistic activity
- The structure of *N*-methylbenzanilide derivatives place the aromatic ring in *cis* conformation to each other, and the methyl substituent on nitrogen is *cis* to the carbonyl group

Effect of Substituents on the Amide Group



Compound	R^1	R^2	hEC_{50} nM	E_{max}	clogP
4f	Me		140	101%	5.5
4g	Me		180	105%	4.0
4h			26	110%	5.9
4i			17	109%	6.4

- **Incorporation of aromatic ring and suitable lipophilic moiety dramatically impacted agonistic activity**
- **Introduction of a *"magic methyl"* group onto the pyridine ring led to a discovery of 4i with a good balance between agonistic activity and lipophilicity**



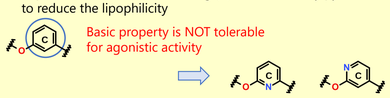
4i
hGPR40 EC_{50}: 17 nM
clogP: 6.4
Cell viability ATP at 30 μM: 5.0%

Challenge of compound 4i

- Slightly high lipophilicity (Target clogP value: <6.0)

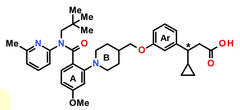
Molecular design

- Replacement of the benzene ring (C) with a 2-alkoxy pyridine ring to reduce the lipophilicity



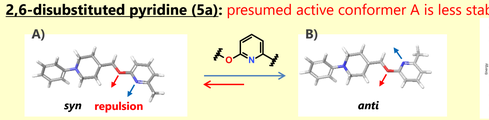
Basic property is NOT tolerable for agonistic activity

Effect of Polar Aromatic Ring of Phenyl Propanoic Acid Moiety

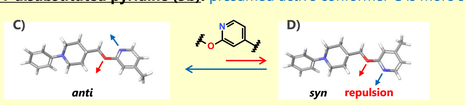


Compound	Ar	hEC_{50} nM	E_{max}	clogP
5a		39% at 10 μM	-	5.8
5b		17	112%	5.8
(*S*)-5b SCO-267		12	108%	5.8

2,6-disubstituted pyridine (5a): presumed active conformer A is less stable than B

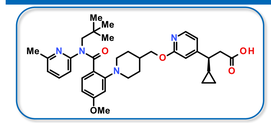


2,4-disubstituted pyridine (5b): presumed active conformer C is more stable than D



- **2,4-Disubstituted pyridine derivative 5b retained agonistic activity with decreased lipophilicity**
- **(*S*)-5b (SCO-267) was identified as an eutomer based on its agonistic activity**

Profiles of SCO-267



- **GPR40 agonistic activity**

human GPR40 EC_{50}: 12 nM

- **Pharmacokinetic profiles in rat/mouse**

Good oral bioavailability

Species	F (%)	Intravenous (0.1 mg/kg)		Oral (1 mg/kg)		
		CL_{total} (mL/h/kg)	Vss (mL/kg)	Cmax (ng/mL)	AUC_{0-8h} (ng·h/mL)	MRT (h)
rat	16	1478	3094	19.9	126.6	4.1
mouse	26	2584	1349	33.2	98.7	2.3

- **In vitro Tox assessment**

Good cell viability profile (ATP: 92.1% at 30 μM), No risk of hERG inhibition and Ames test

- **In vivo Tox assessment**

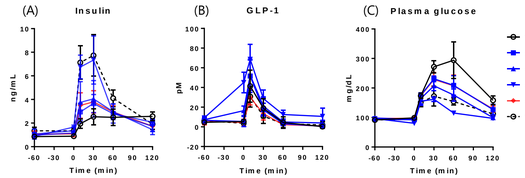
Wide safety margin (633- (male) to 776- (female) and 471- (male) to 421- (female) fold in the rat and dog 4-week studies, respectively), No concerns in the safety pharmacology studies

OGTT in N-STZ-1.5 Rats

Male N-STZ-1.5 rats (26-week-old) Fasted

・Vehicle (*p.o.*) ・**SCO-267** (*p.o.*) ・**Sitagliptin** (*p.o.*)

Single oral dosing→OGTT (1.5 g/kg) 1 h after drug dosing



Effect of single administration of SCO-267 and sitagliptin on hormone secretion and glucose tolerance in 26 weeks old male diabetic N-STZ-1.5 rats. Plasma insulin (A), total GLP-1 (B), and glucose levels (C) in male N-STZ-1.5 rats. # and $p<0.025 vs. vehicle-treated male N-STZ-1.5 rats by one-tailed Williams' test and Shirley-Williams test, respectively. *p<0.05 vs. vehicle-treated male N-STZ-1.5 rats by Student's *t*-test. Values are means ± S.D. (n = 6 for each group)

- **A single dose of SCO-267 stimulated insulin secretion and GLP-1 release and ameliorated glucose tolerance in male N-STZ-1.5 rats**

Summary

- New lead compound **3** was discovered by rearrangement of the lipophilic moiety onto the terminal aromatic ring (A) and replacement of central aromatic ring (B) with piperidine linker
- Introduction of amide linker, then incorporation of aromatic ring and suitable lipophilic moiety onto the amide nitrogen showed good balance between agonistic activity and lipophilicity
- Further optimization of terminal ring (C) to reduce the lipophilicity led to the identification of **SCO-267**, which exhibited potent GPR40 full agonistic activity, good oral bioavailability, and favorable in vitro/in vivo Tox profiles
- **SCO-267** stimulated insulin and GLP-1 secretion and effectively improved glycemic control in N-STZ-1.5 rats

Conclusion

- A first-in-class GPR40 full agonist **SCO-267** is expected to be an attractive drug for the treatment of type 2 diabetes mellitus
- Ph1 clinical study to evaluate safety, pharmacokinetics, and pharmacodynamic effect in healthy adults and people with impaired glucose tolerance is ongoing

Reference: *J. Med. Chem.* **2020**, *in press*

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