

Discovery of SCO-267, a First-in-class GPR40 Full Agonist, as a Promising Candidate for the Treatment of Type 2 Diabetes Mellitus, Obesity, and NASH

*Naoyoshi Noguchi, Ph.D. on behalf of the GPR40 PJ Team
Research Division, Drug Discovery Chemistry Laboratory
SCOHIA PHARMA, Inc.*

EFMC-ISMC Virtual Event 2020

First Time Disclosures & Late Breaking News

📍 Online 📅 September 7-8, 2020



1. Introduction

2. Med. Chem. Campaign to Discover SCO-267

3. Pharmacological Efficacy of SCO-267

- Single Dosing and Repeated Dosing Effects in N-STZ-1.5 Rats (Diabetic Model)
- Repeated Dosing Effects in DIO-rats (Obese Model)
- Single Dosing and Repeated Dosing Effects in CDAHFD-fed Mice (NAFLD Model)

4. Summary

1. Introduction

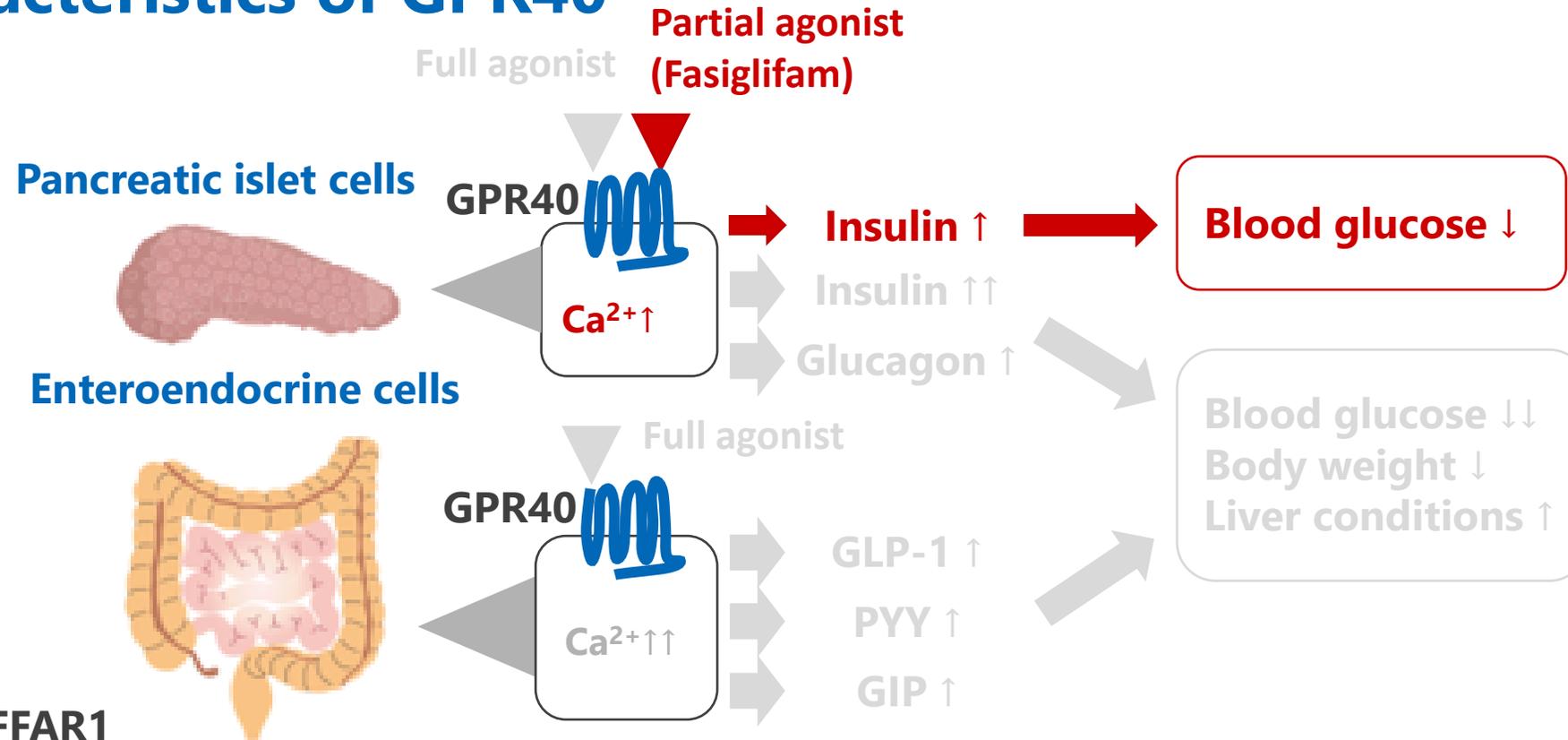
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Characteristics of GPR40



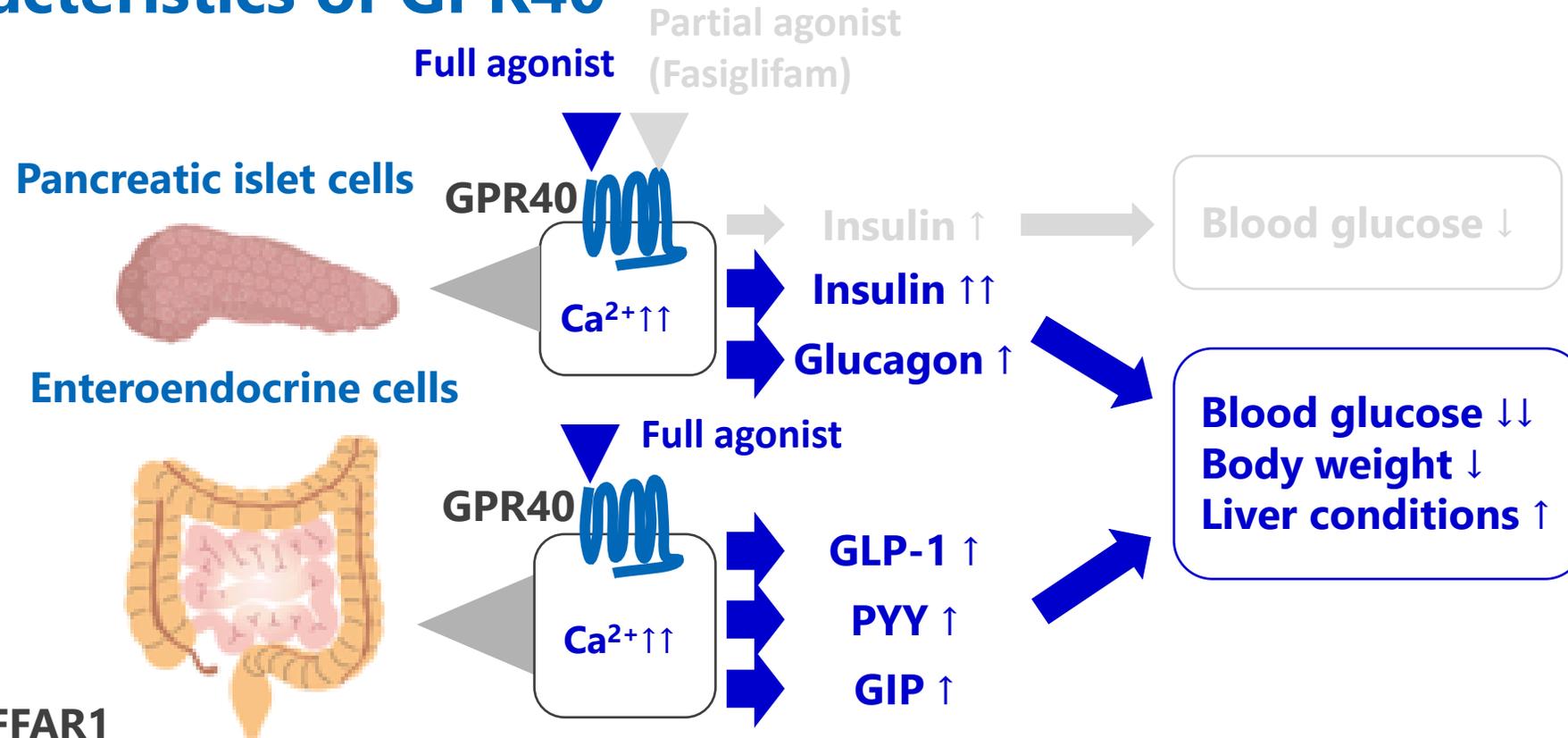
■ GPR40/FFAR1

- GPCR activated by endogenous ligands of medium-to-long chain fatty acids
- Expressed in pancreatic islet cells and enteroendocrine cells

■ Partial agonist - Fasiglifam

- Markedly improved glycemic control by increasing *insulin* secretion in patients with T2DM

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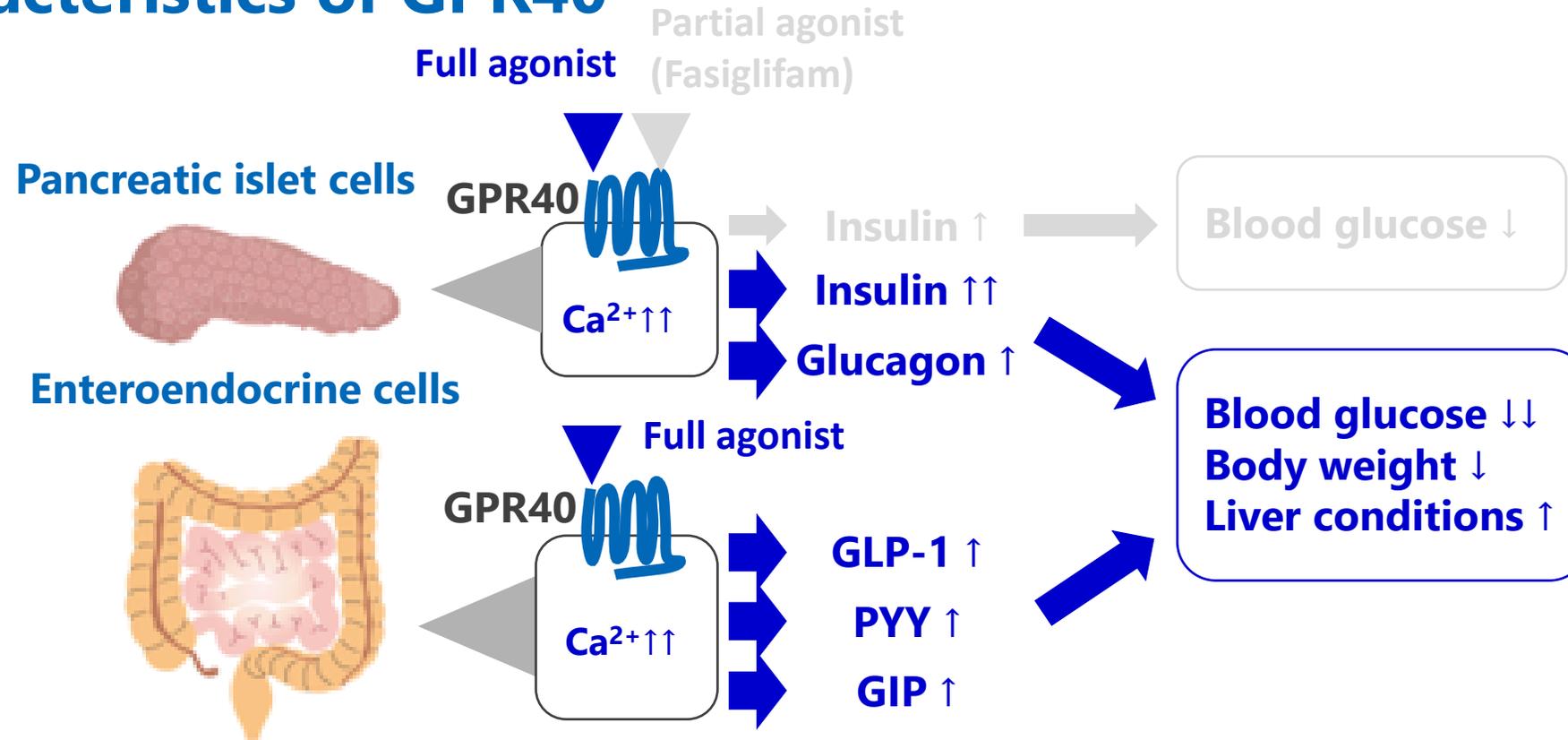
■ Partial agonist - Fasiglifam

- Markedly improved glycemic control by increasing *insulin* secretion in patients with T2DM

■ Full agonist

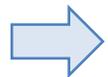
- Stimulates secretion of not only *insulin*, but also *GLP-1*, *GIP*, *PYY*, and *glucagon*

Characteristics of GPR40



■ Full agonist

- Stimulates secretion of not only *insulin*, but also *GLP-1*, *GIP*, *PYY*, and *glucagon*



GPR40 full agonist is expected to be a new drug option for the treatment of *diabetes*, *obesity*, and *NAFLD/NASH*

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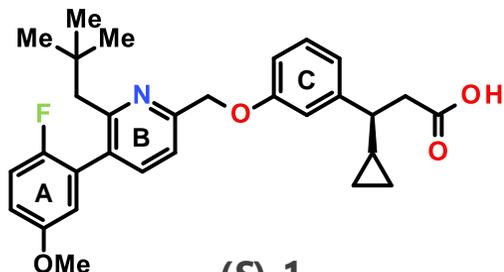
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Exploration of New Lead Compound



(S)-1

hGPR40 EC₅₀: 150 nM

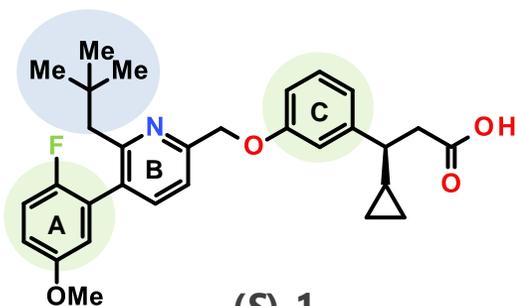
clogP: 7.1

Previously reported GPR40 full agonist
(WO2013122029)

Challenges of compound (S)-1

- Aromaticity (negative impact on overall physicochemical properties, DMPK profiles...)
- Insufficient agonistic activity

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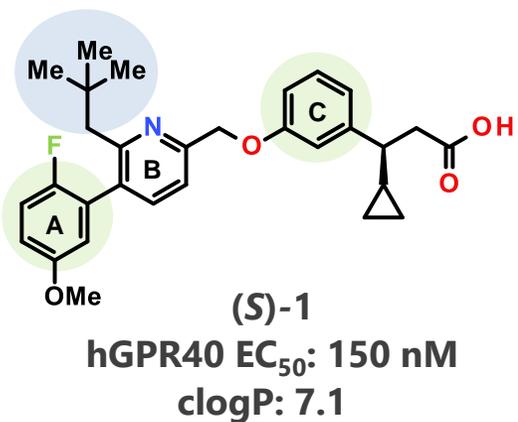
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Initial SAR

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

Exploration of New Lead Compound



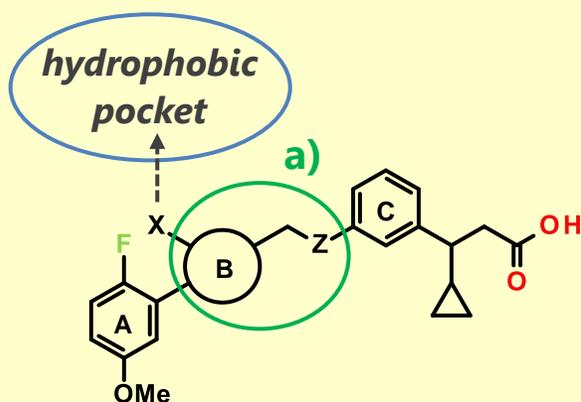
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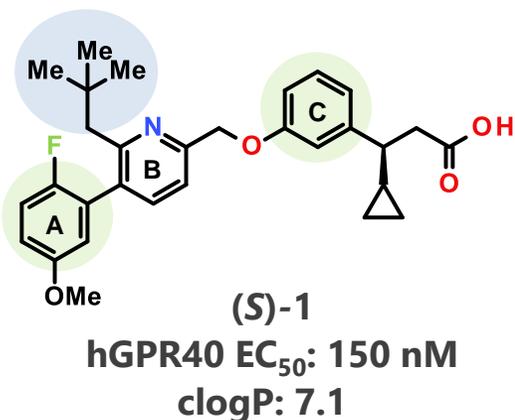
- The hydrophobic substituent and the terminal aromatic rings (A and C) are essential for potent agonistic activity

Molecular design and hypothesis



- a. The central aromatic ring (B) of compound (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

Exploration of New Lead Compound



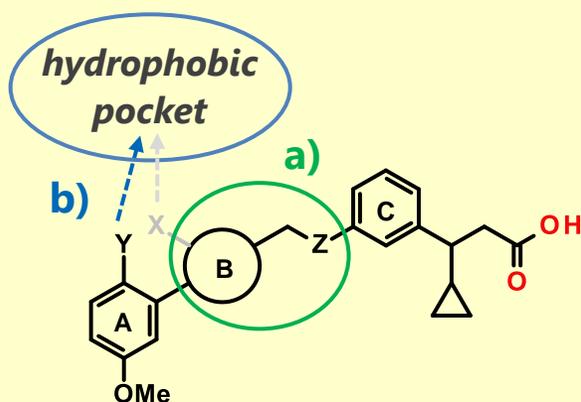
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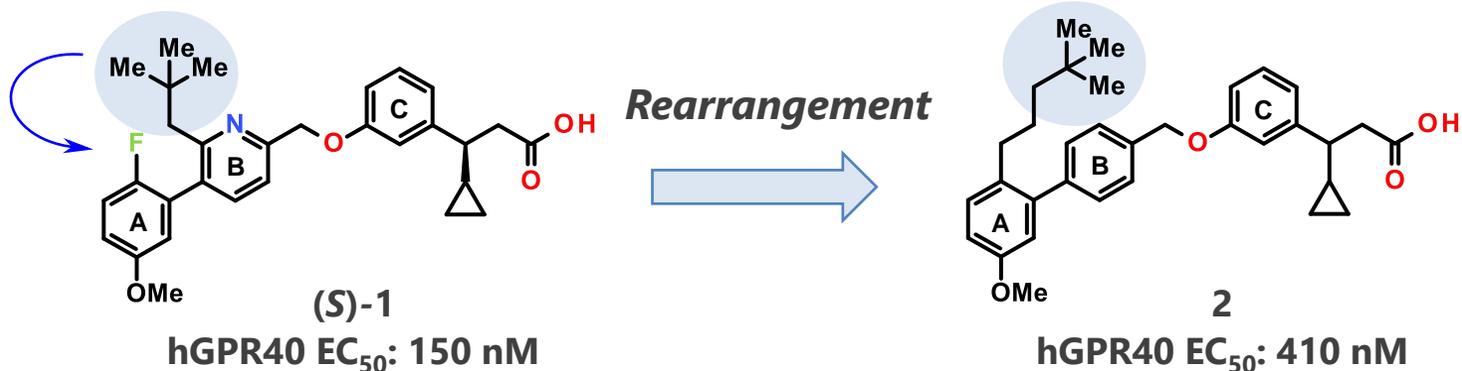


- The central aromatic ring (B) of compound (S)-1 would serve as just a linker to keep the position and distance of terminal aromatic rings (A and C), therefore, would be replaced with a saturated ring system
- Fluorine-substituted position of compound (S)-1 would easily access the presumed hydrophobic pocket that the neopentyl alkyl chain of compound (S)-1 occupies

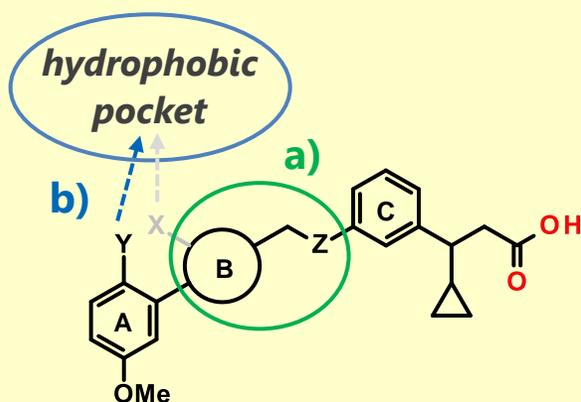


Flexible alignment of (S)-1 (gray) and designed compound (green) using Maestro.

Exploration of New Lead Compound



Molecular design and hypothesis



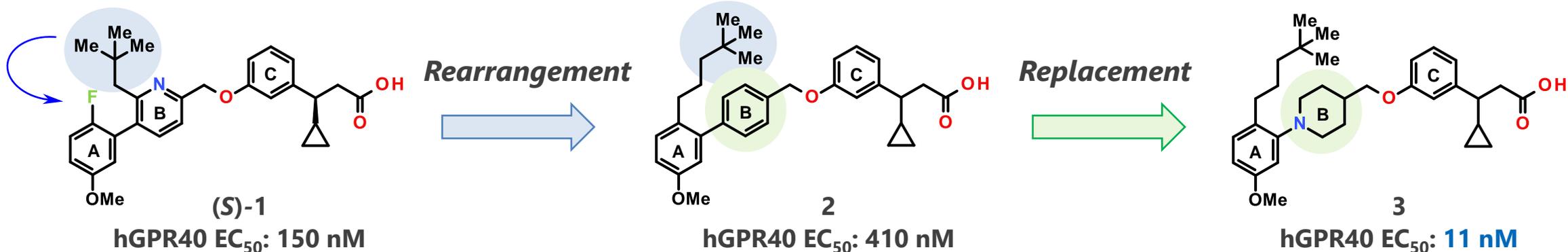
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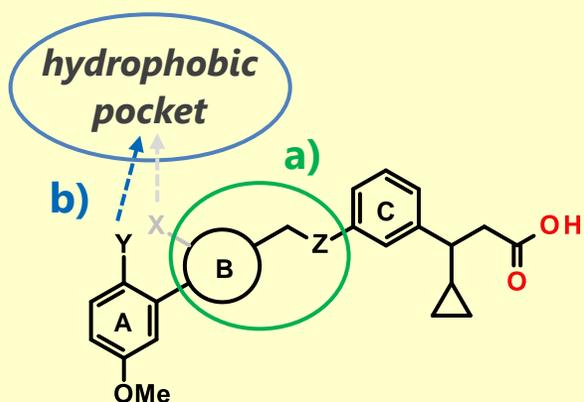
Flexible alignment of compounds **(S)-1** (gray) and **2** (green) using Maestro.

- **Rearrangement of the hydrophobic moiety on the central ring (B) to the terminal ring (A) retained agonistic activity**

Exploration of New Lead Compound



Molecular design and hypothesis



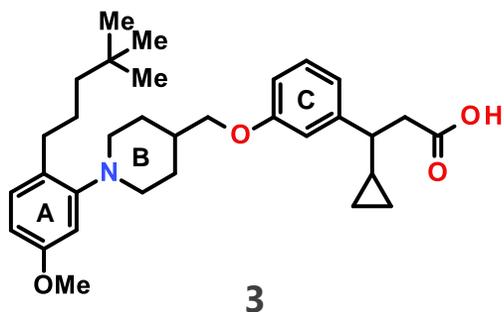
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Flexible alignment of compounds **(S)-1** (gray) and **2** (green) using Maestro.

- **4-Methyl piperidine ether 3** was identified as a new lead compound which showed **potent agonistic activity**

Effect of Substituent on the Benzene Ring A



hGPR40 EC₅₀: **11 nM**

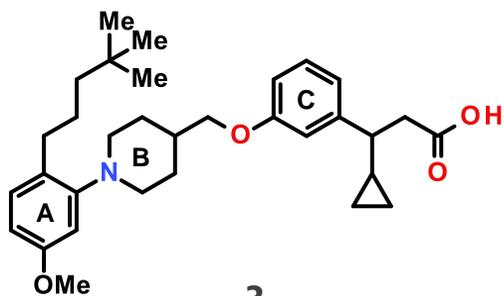
clogP: 8.4

Cell viability ATP at 30 μM: 0.1%

Challenge of compound 3

- Highly lipophilic property

Effect of Substituent on the Benzene Ring A



3

hGPR40 EC₅₀: 11 nM

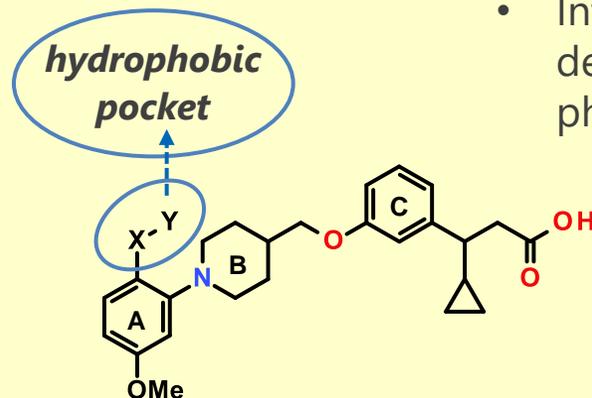
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Cell viability ATP at 30 μM: 0.1%

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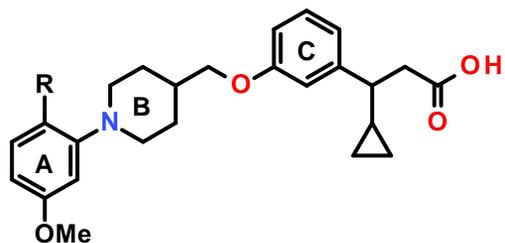
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Molecular design



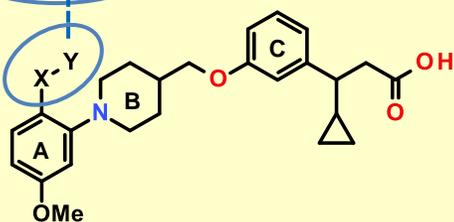
- Introduction of a polar linker (X and/or Y) to decrease the lipophilicity and to improve the physicochemical properties

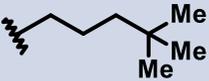
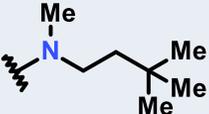
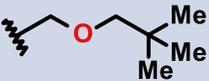
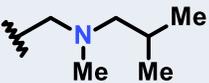
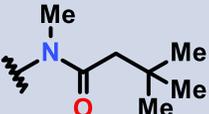
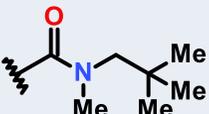
Effect of Substituent on the Benzene Ring A



Molecular design

hydrophobic pocket

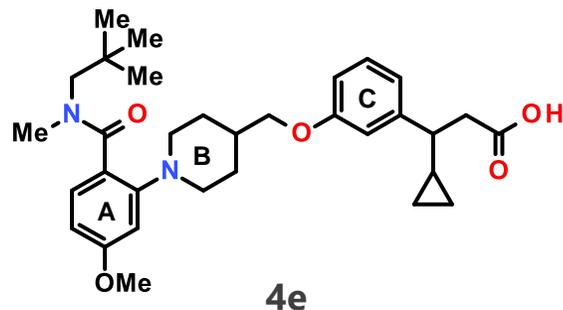


Compound	R	hEC ₅₀ nM	E _{max}	clogP	Cell viability ATP % at 30 μM
3		11	106%	8.4	0.1
4a		190	108%	7.6	0.1
4b		97	112%	6.5	0.1
4c		1000	110%	4.0	80.7
4d		2200	96%	5.8	76.4
4e		100	107%	5.6	82.2

- 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)

*All compounds are racemate unless otherwise noted

Effect of Substituents on the Amide Group



hGPR40 EC₅₀: 100 nM

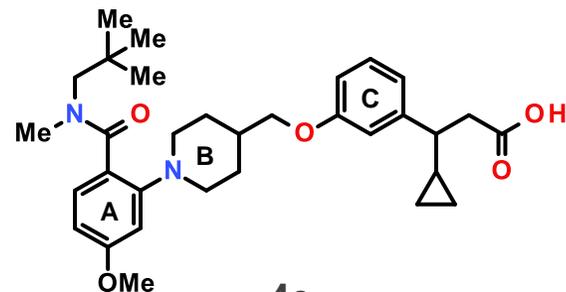
clogP: 5.6

Cell viability ATP at 30 μM: 82.2%

Challenge of compound 4e

- Insufficient agonistic activity

Effect of Substituents on the Amide Group



4e

hGPR40 EC₅₀: 100 nM

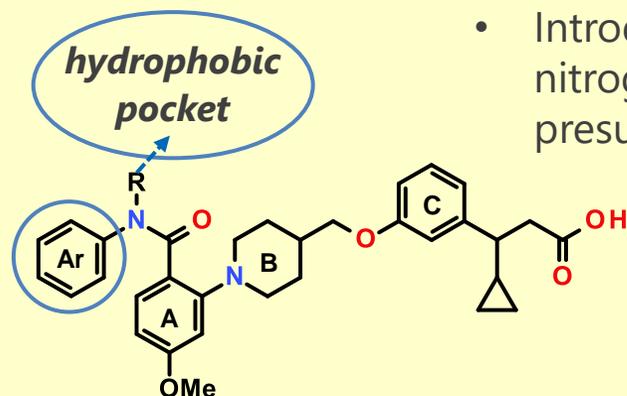
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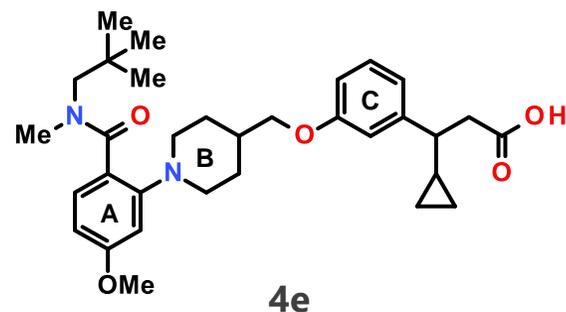
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Molecular design



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

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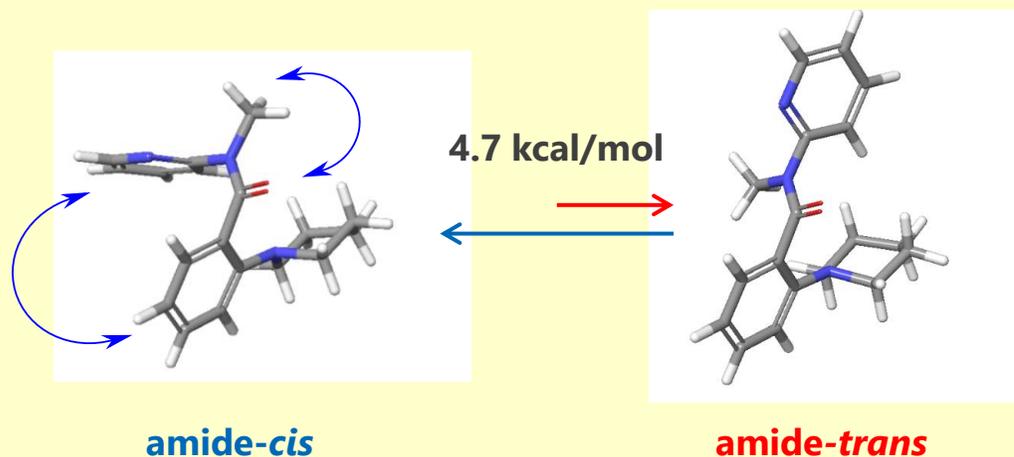
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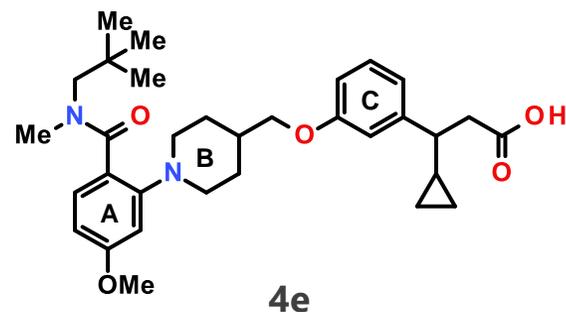
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Conformational preference of *N*-methylbenzanilide



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



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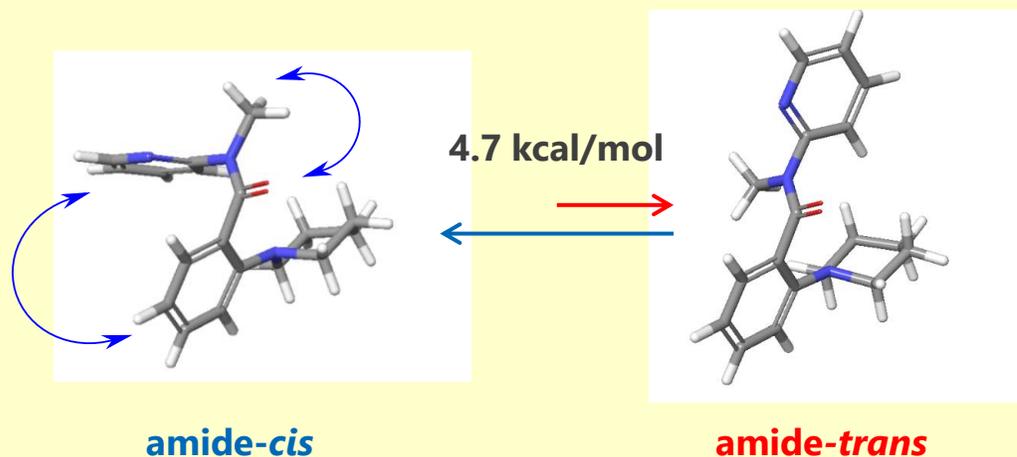
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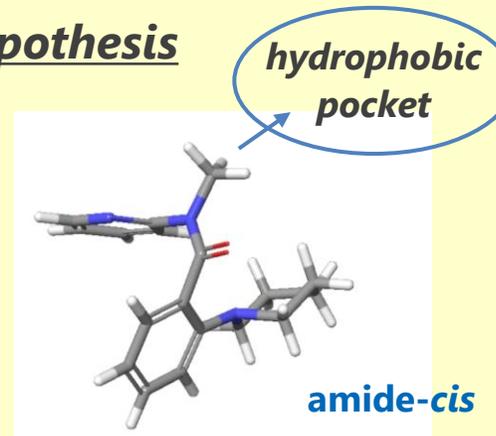
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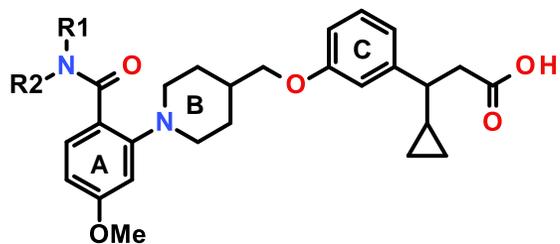


Hypothesis



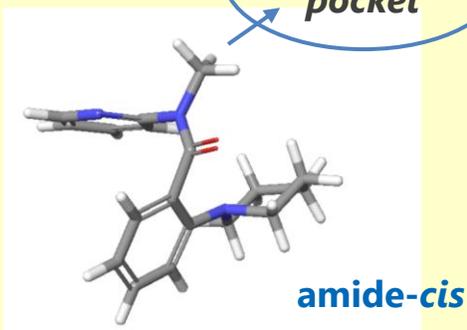
Incorporation of suitable lipophilic moiety onto the nitrogen group of the benzanilide moiety would enhance the agonistic activity

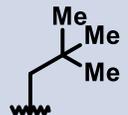
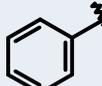
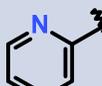
Effect of Substituents on the Amide Group



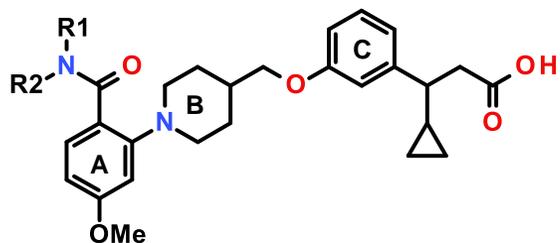
Hypothesis

hydrophobic pocket



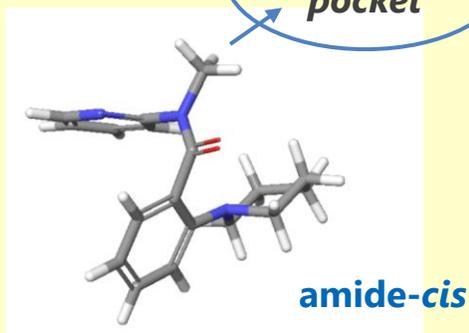
Compound	R ¹	R ²	hEC ₅₀ nM	E _{max}	clogP
4e		Me	100	107%	5.6
4f	Me		140	101%	5.5
4g	Me		180	105%	4.0

Effect of Substituents on the Amide Group

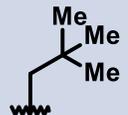
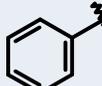
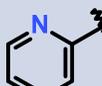
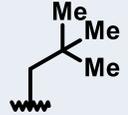
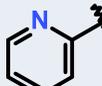


Hypothesis

hydrophobic pocket

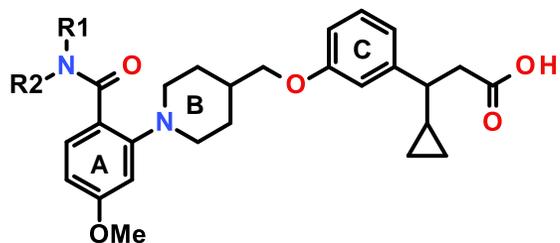


amide-cis

Compound	R ¹	R ²	hEC ₅₀ nM	E _{max}	clogP
4e		Me	100	107%	5.6
4f	Me		140	101%	5.5
4g	Me		180	105%	4.0
4h			26	110%	5.9

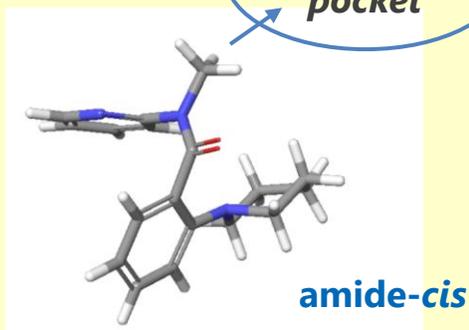
- Incorporation of aromatic ring and suitable lipophilic moiety dramatically impacted agonistic activity

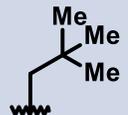
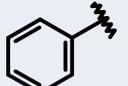
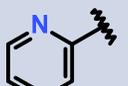
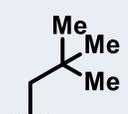
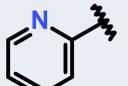
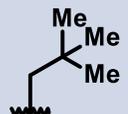
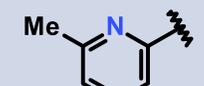
Effect of Substituents on the Amide Group



Hypothesis

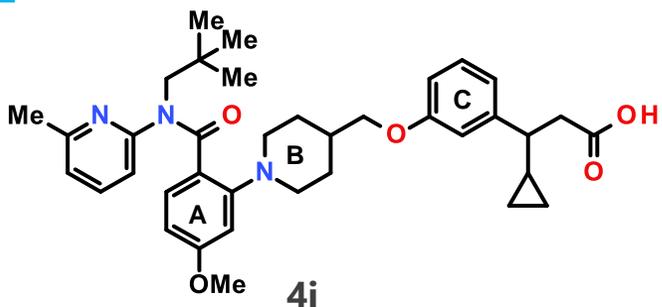
hydrophobic pocket



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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

Effect of Polar Aromatic Ring of Phenyl Propanoic Acid Moiety



4i

hGPR40 EC₅₀: 17 nM

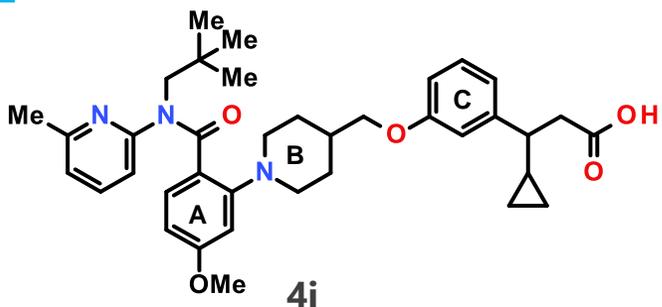
clogP: 6.4

Cell viability ATP at 30 μM: 5.0%

Challenge of compound 4i

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

Effect of Polar Aromatic Ring of Phenyl Propanoic Acid Moiety



4i

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clogP: 6.4

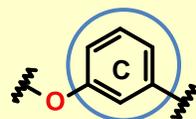
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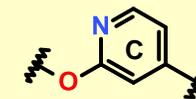
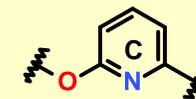
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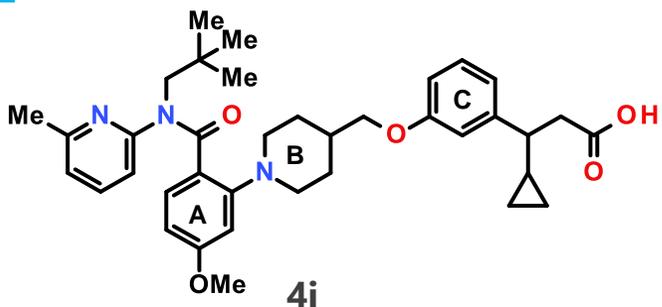
- Replacement of the benzene ring (C) with a 2-alkoxy pyridine ring to reduce the lipophilicity



Basic property is NOT tolerable for agonistic activity



Effect of Polar Aromatic Ring of Phenyl Propanoic Acid Moiety



4i

hGPR40 EC₅₀: **17 nM**

clogP: 6.4

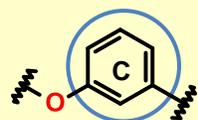
Cell viability ATP at 30 μM: 5.0%

Challenge of compound 4i

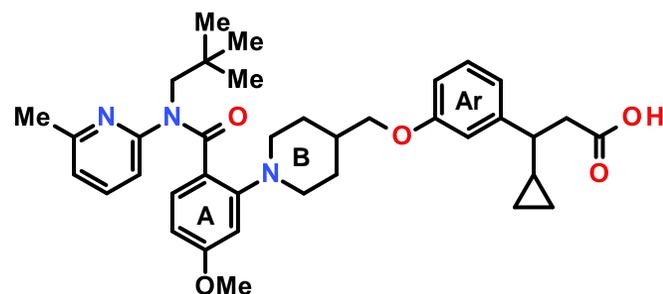
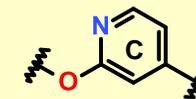
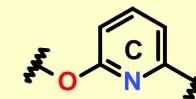
- Slightly high lipophilicity (Target clogP value: <6.0)

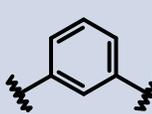
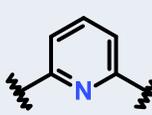
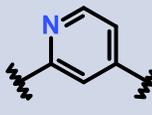
Molecular design

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



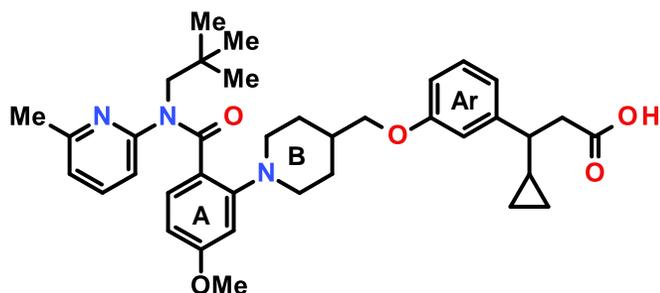
Basic property is NOT tolerable for agonistic activity

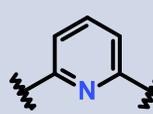
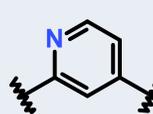


Compound	Ar	hEC ₅₀ nM	E _{max}	clogP
4i		17	109%	6.4
5a		39% at 10 μM	-	5.8
5b		17	112%	5.8

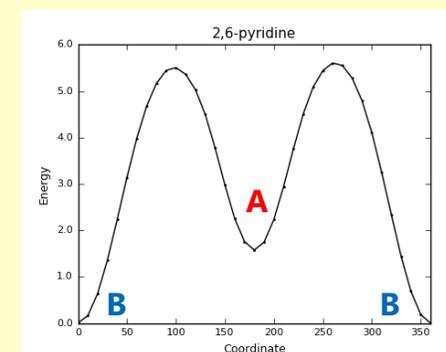
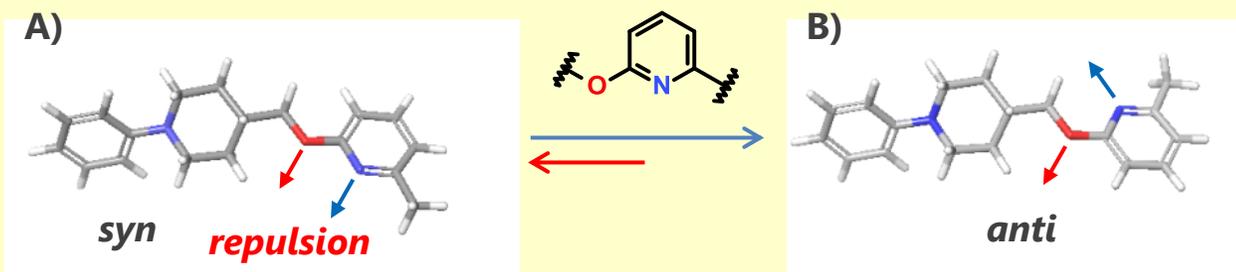
■ 2,4-Disubstituted pyridine derivative 5b retained agonistic activity with decreased lipophilicity

Effect of Polar Aromatic Ring of Phenyl Propanoic Acid Moiety

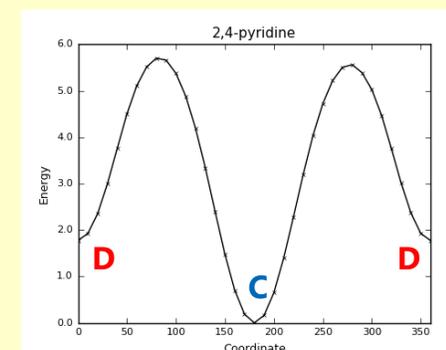
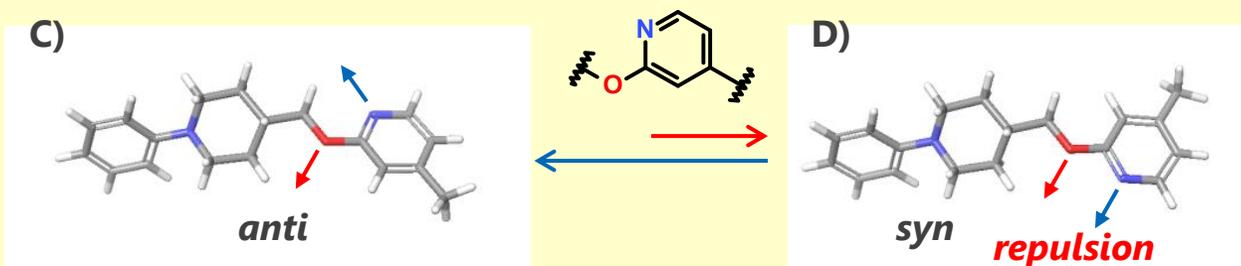


Compound	Ar	hEC ₅₀ nM	E _{max}	clogP
5a		39% at 10 μM	-	5.8
5b		17	112%	5.8

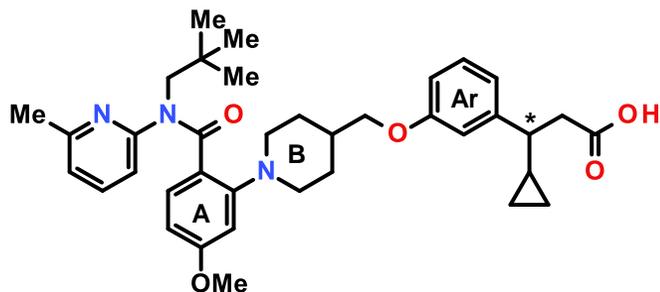
2,6-disubstituted pyridine (5a): presumed active conformer A is less stable than B

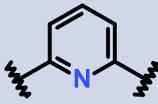
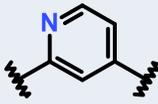
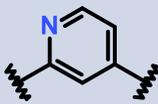
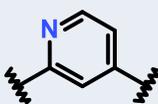


2,4-disubstituted pyridine (5b): presumed active conformer C is more stable than D



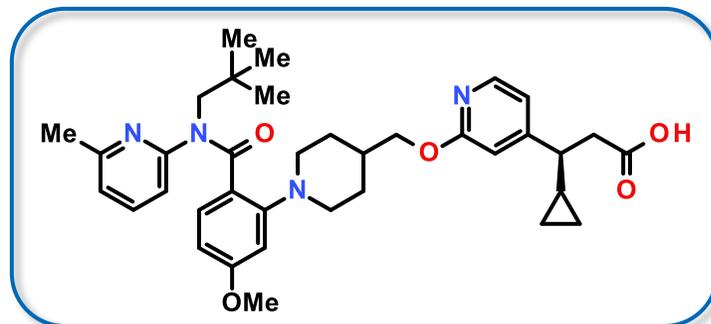
Effect of Polar Aromatic Ring of Phenyl Propanoic Acid Moiety



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
(R)-5b		84	109%	5.8

- (S)-5b was identified as an eutomer based on its agonistic activity
- (S)-5b (SCO-267) was selected for further evaluation

Profiles of SCO-267



■ GPR40 agonistic activity

human GPR40 EC₅₀: 12 nM

■ Pharmacokinetic profiles in rat/mouse

Good oral bioavailability

Compound	Species	F (%)	Intravenous (0.1 mg/kg)		Oral (1 mg/kg)		
			CL _{total} (mL/h/kg)	V _{ss} (mL/kg)	C _{max} (ng/mL)	AUC _{0-8h} (ng·h/mL)	MRT (h)
SCO-267	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

1. Introduction

2. Med. Chem. Campaign to Discover SCO-267

3. Pharmacological Efficacy of SCO-267

- Single Dosing and Repeated Dosing Effects in N-STZ-1.5 Rats (Diabetic Model)
- Repeated Dosing Effects in DIO-rats (Obese Model)
- Single Dosing and Repeated Dosing Effects in CDAHFD-fed Mice (NAFLD Model)

4. Summary

Single Dosing Effects in N-STZ-1.5 Rats (Diabetic Model)

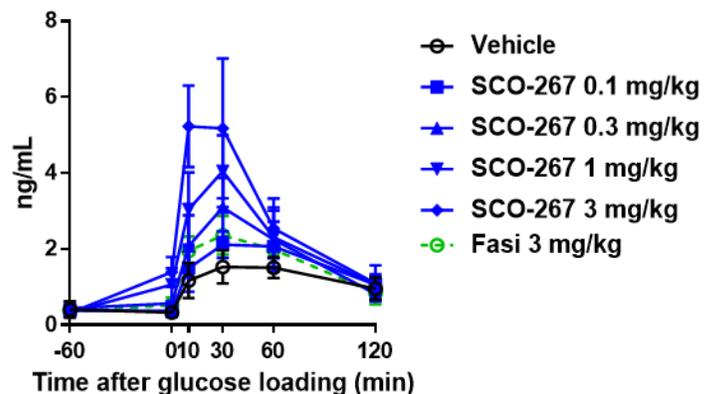
Male N-STZ-1.5 rats
(25-week-old)
Fasted

• Vehicle (*p.o.*) • SCO-267 (*p.o.*) • Fasiglifam (*p.o.*)

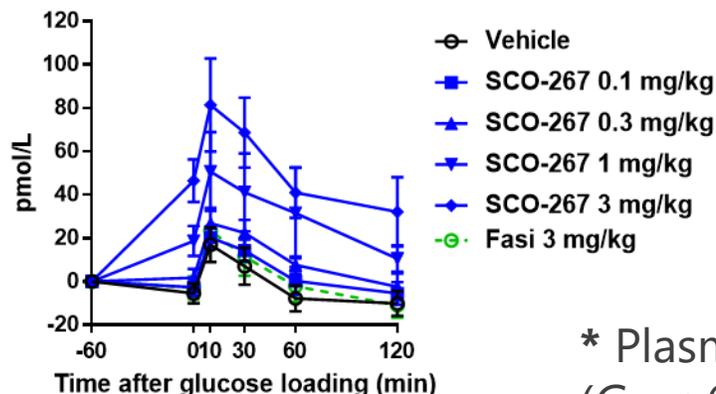
Single oral dosing → OGTT (1.5 g/kg) 1 h after drug dosing

* $P < 0.025$ and # $P < 0.025$ vs. vehicle by one-tailed Williams' test and one-tailed Shirley-Williams test, respectively. Values are presented as mean \pm S.D. ($n = 6$). Fasi, fasiglifam.

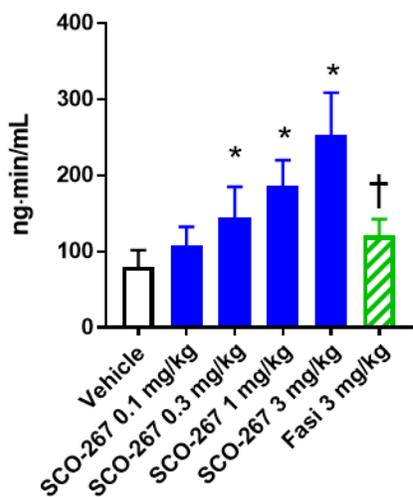
Plasma insulin



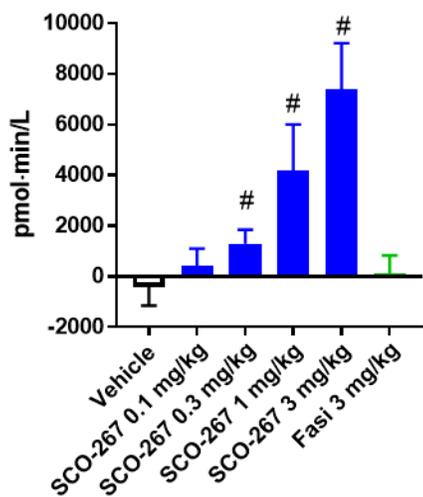
Plasma GLP-1 change



Plasma insulin AUC_{0-60min}



Plasma GLP-1 change AUC_{-60-120 min}



* Plasma concentration of 3 mg/kg fasiglifam (C_{max} : 6170 ng/ml) in N-STZ-1.5 rats is similar levels with clinically effective exposure of 50 mg fasiglifam (C_{max} : 5300 ng/ml) in T2DM patients

■ **Single dosing of SCO-267 increased insulin and GLP-1 in N-STZ-1.5 rats in a dose-dependent manner**

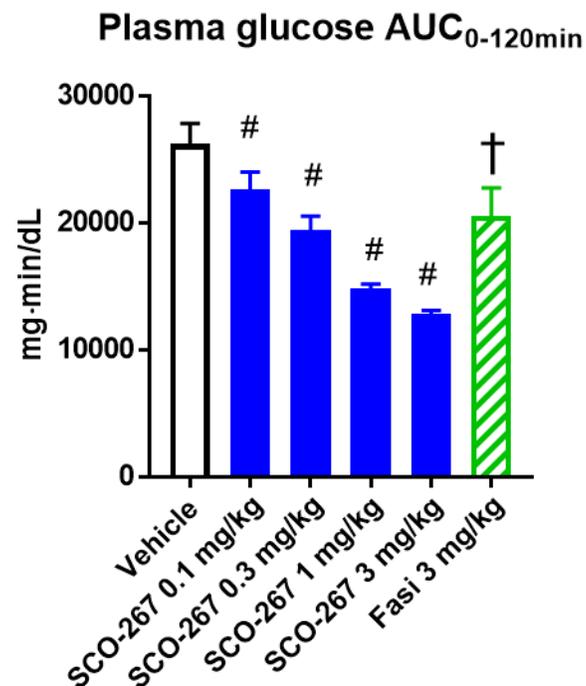
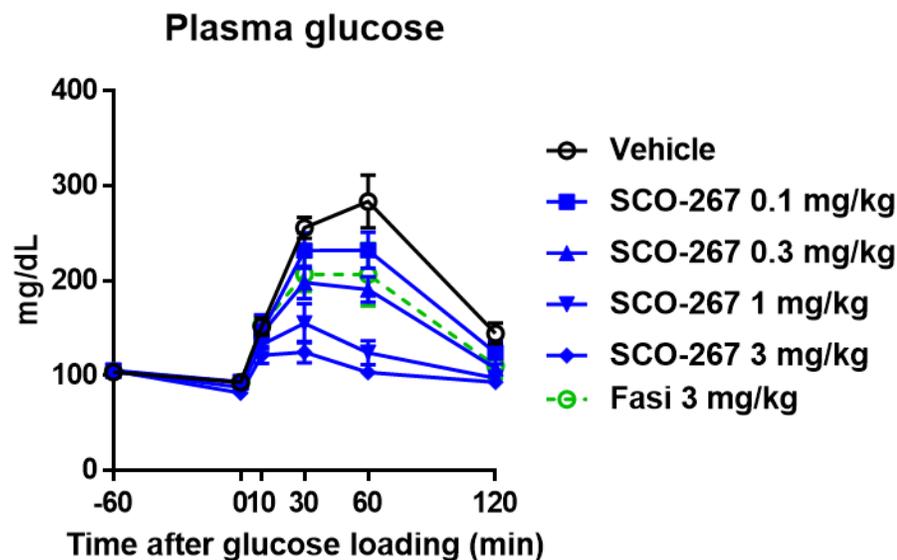
Single Dosing Effects in N-STZ-1.5 Rats (Diabetic Model)

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

• Vehicle (p.o.) • SCO-267 (p.o.) • Fasi (p.o.)

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

* $P < 0.025$ and # $P < 0.025$ vs. vehicle by one-tailed Williams' test and one-tailed Shirley-Williams test, respectively. Values are presented as mean \pm S.D. ($n = 6$). Fasi, faspiglifam.



■ **0.3 mg/kg SCO-267 (C_{max} : 22.7 ng/ml) had a glucose-lowering efficacy comparable to that of 3 mg/kg faspiglifam (C_{max} : 6170 ng/ml)**

Repeated Dosing Effects in N-STZ-1.5 Rats (Diabetic Model)

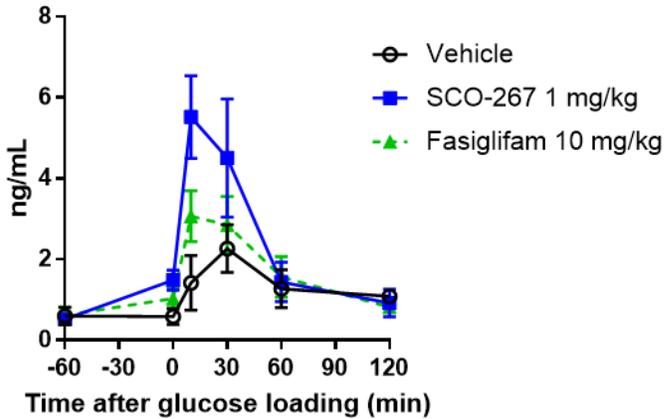
Male N-STZ-1.5 rats
(27-week-old)

• Vehicle (p.o.) • SCO-267 (p.o.) • Fasiglifam (p.o.)

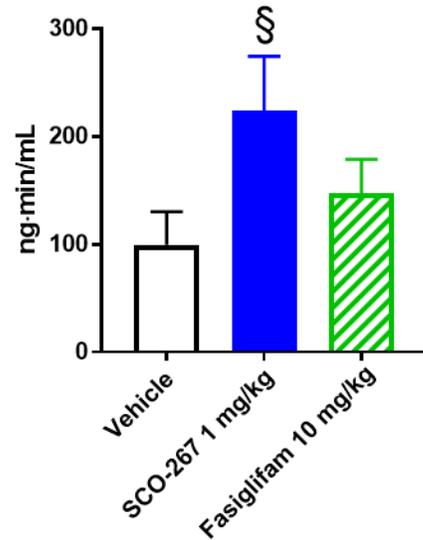
Once daily dosing for 2 weeks → OGTT (1.5 g/kg) 1 h
after drug dosing

§ and ¶ < 0.05 vs vehicle by Dunnett's test and Steel test, respectively.
Values are presented as mean ± SD (n=6).

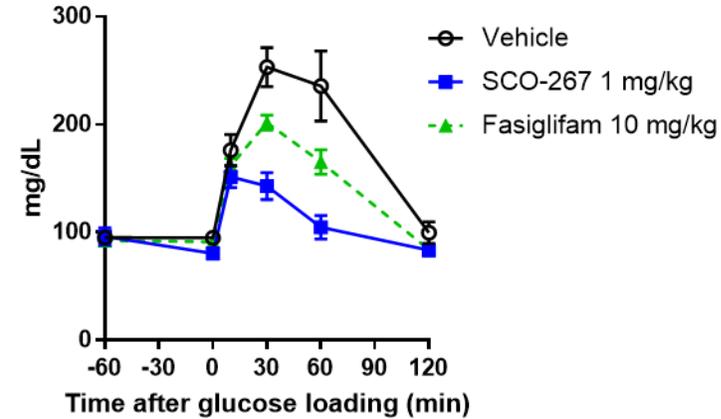
Plasma insulin



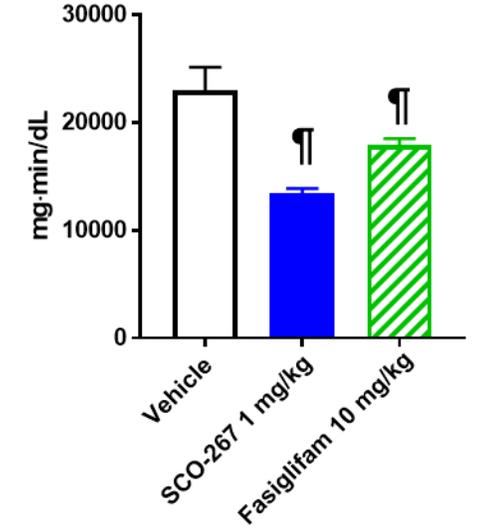
Plasma insulin AUC_{0-60min}



Plasma glucose



Plasma glucose AUC_{0-120min}



- 2 weeks of repeated dosing of SCO-267 resulted in sustained glucose lowering, and the efficacy was much better than that of fasiglifam
- 1 mg/kg (3-fold higher dose of MED) SCO-267 did not induce desensitization in N-STZ-1.5 Rats

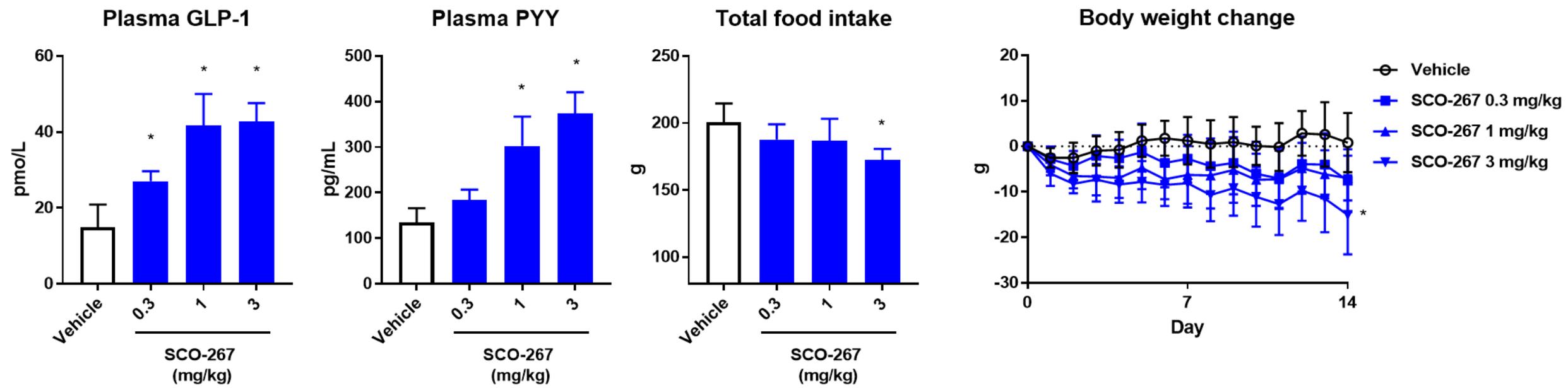
Repeated Dosing Effects in DIO-rats (Obese Model)

Male F344 rats (49-week-old)
 High fat diet (M12451M)
 Baseline BW: 487 g

· Vehicle (p.o.) · SCO-267 (p.o.)

Once daily dosing for 2 weeks → measure GLP-1 and PYY
 16 h after the 15th dosing

* $P < 0.025$ vs. vehicle by one-tailed Williams' test.
 Values are presented as mean \pm S.D. ($n = 6$).



- Plasma GLP-1 and PYY levels remained high 16 h after the final dose of SCO-267
- These hormones contributed to the food intake reduction and body weight loss
- Efficacy on body weight control was durable

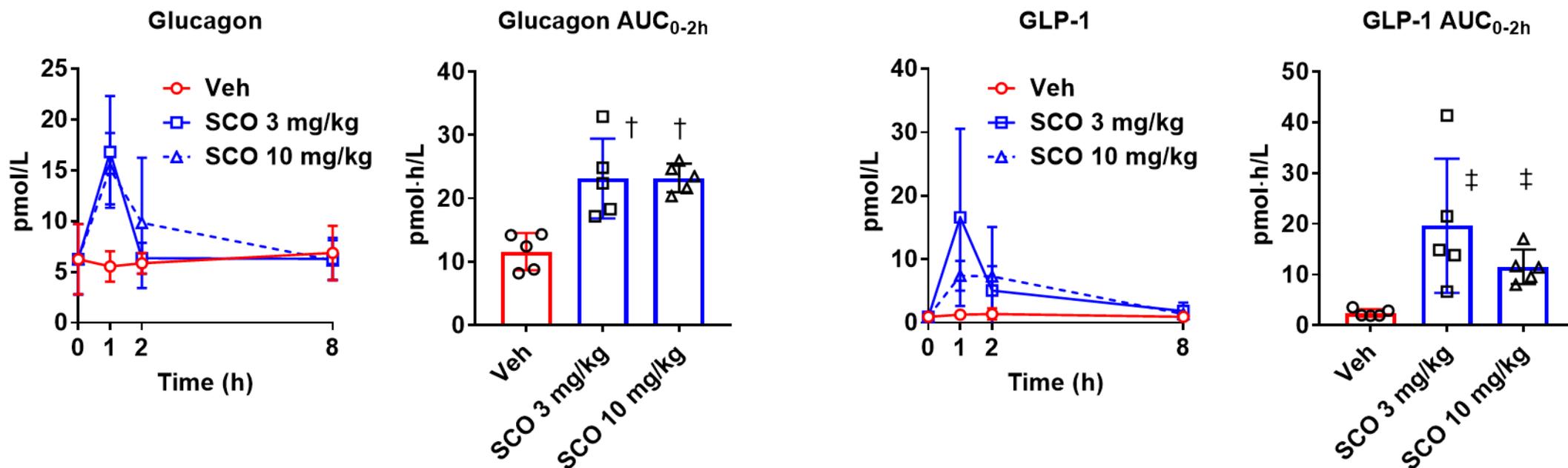
Single Effects in CDAHFD-fed Mice (NAFLD Model)

Male CDAHFD-fed mice
(12-week-old)
Non-fasting

• Vehicle (*p.o.*) • SCO-267 (*p.o.*)

Single oral dosing

Values are presented as mean \pm S.D. (n = 8).
†P<0.025 vs. vehicle by one-tailed Williams' test.
‡P<0.025 vs. vehicle by one-tailed Shirley-Williams test.



■ SCO-267 stimulated glucagon and GLP-1 secretion in a mouse model of NAFLD

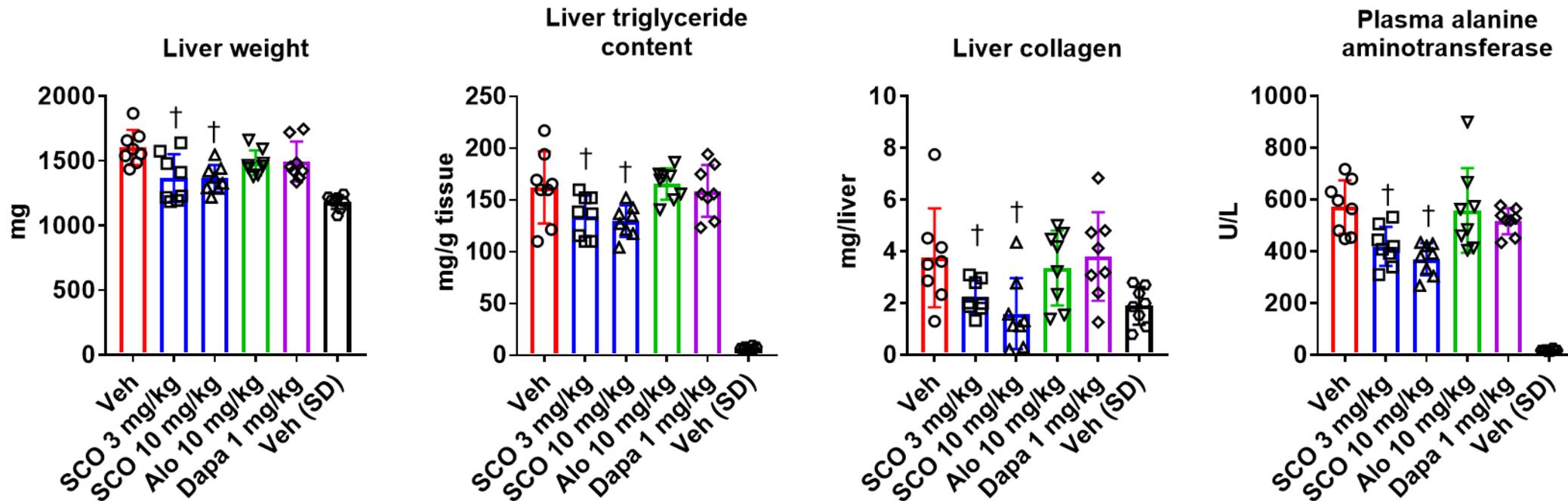
Repeated Dosing Effects in CDAHFD-fed Mice (NAFLD Model)

Male CDAHFD-fed mice
(11-week-old)
Non-fasting

- Vehicle (*p.o.*) • SCO-267 (*p.o.* BID)
- Alogliptin (*p.o.* BID) • Dapagliflozin (*p.o.* BID)

Repeated administration for 4 weeks

Values are presented as mean \pm S.D. (n = 8).
†P<0.025 vs. vehicle by one-tailed Williams' test.
Alo, alogliptin benzoate; Dapa, dapagliflozin.



- SCO-267 decreased liver weight, liver triglyceride content, liver collagen levels, and plasma ALT levels in CDAHFD-fed mice, a non-diabetic animal model of NAFLD.
- These effects were induced without any effects on glucose levels or body weight

1. Introduction

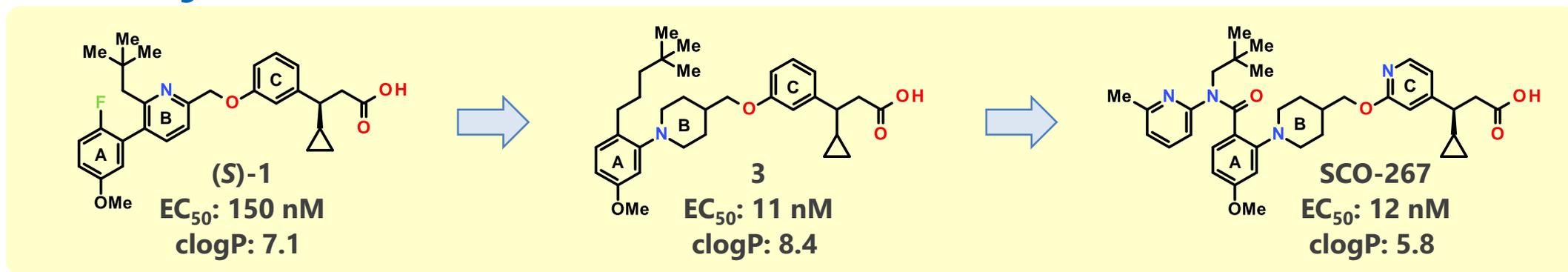
2. Med. Chem. Campaign to Discover SCO-267

3. Pharmacological Efficacy of SCO-267

- Single Dosing and Repeated Dosing Effects in N-STZ-1.5 Rats (Diabetic Model)
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- Single Dosing and Repeated Dosing Effects in CDAHFD-fed Mice (NAFLD Model)

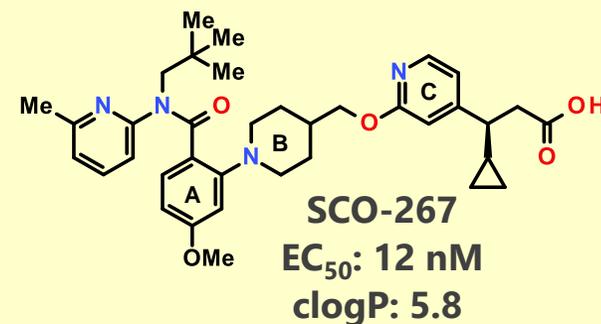
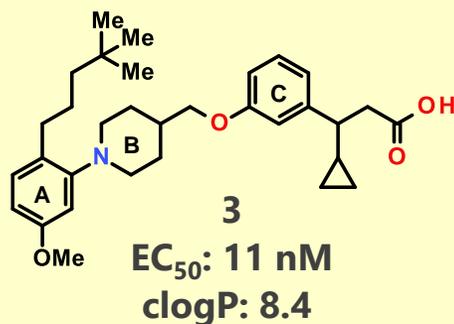
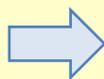
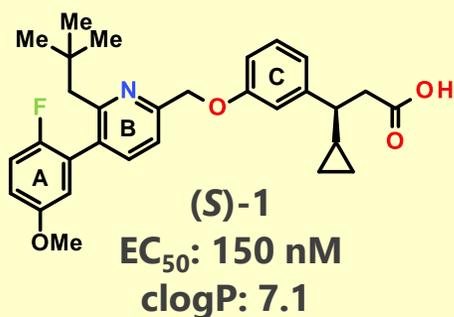
4. Summary

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**
- **SCO-267** exhibited potent GPR40 full agonistic activity, good oral bioavailability, and favorable in vitro/in vivo Tox profiles
- **SCO-267** effectively improved glycemic control in N-STZ-1.5 rats (*diabetic model*), decreased body weight in DIO-rats (*obese model*), and improved liver parameters in CDAHFD-fed mice (*NAFLD model*)

Summary



- *Ph1 clinical study to evaluate safety, pharmacokinetics, and pharmacodynamic effect in healthy adults and people with impaired glucose tolerance is ongoing.*

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■ Analytical

Motoo Iida

■ Toxicol

Yoshimasa Ishimura

Thank you for your attention!

&

QA session

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