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

Agenda

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

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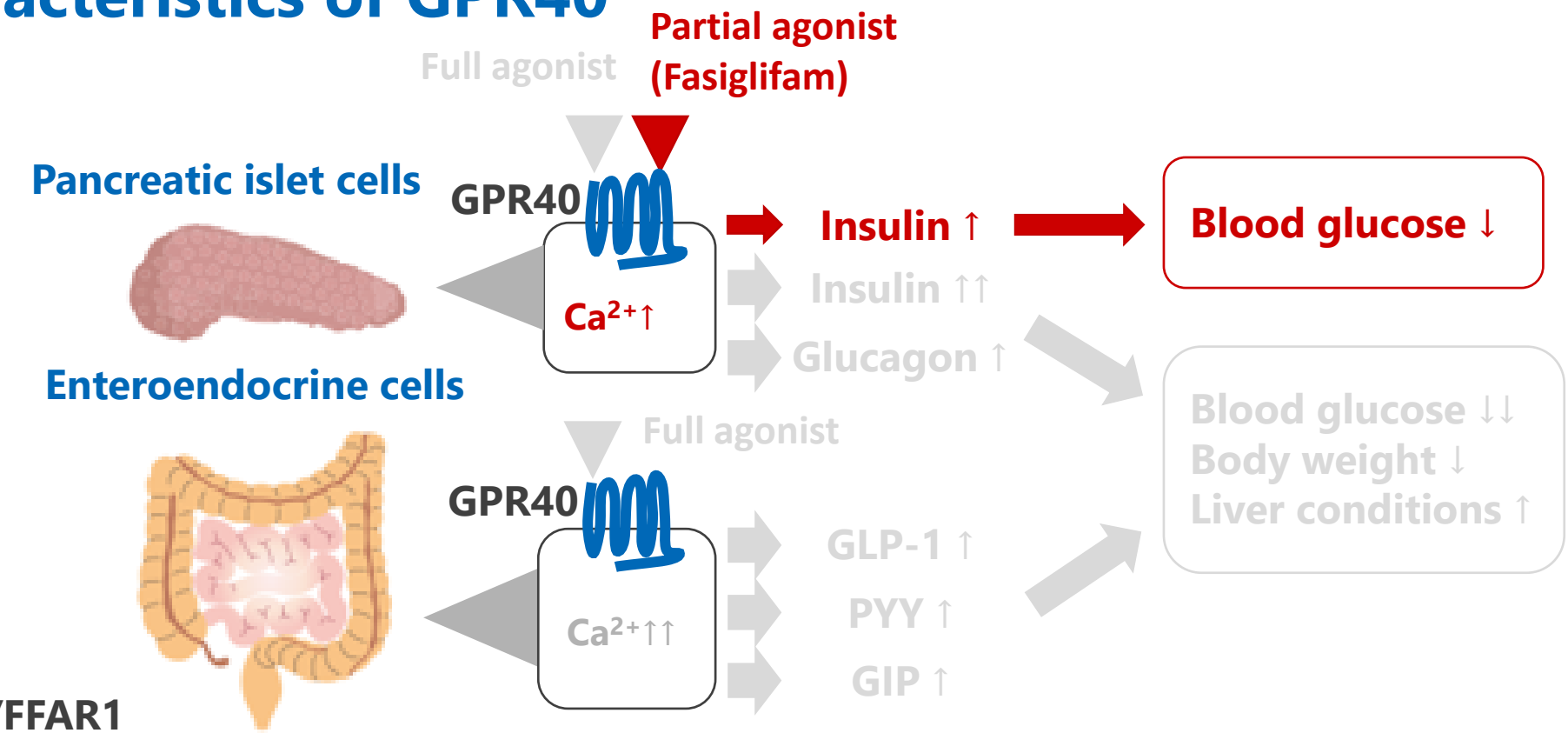
Characteristics of GPR40



- **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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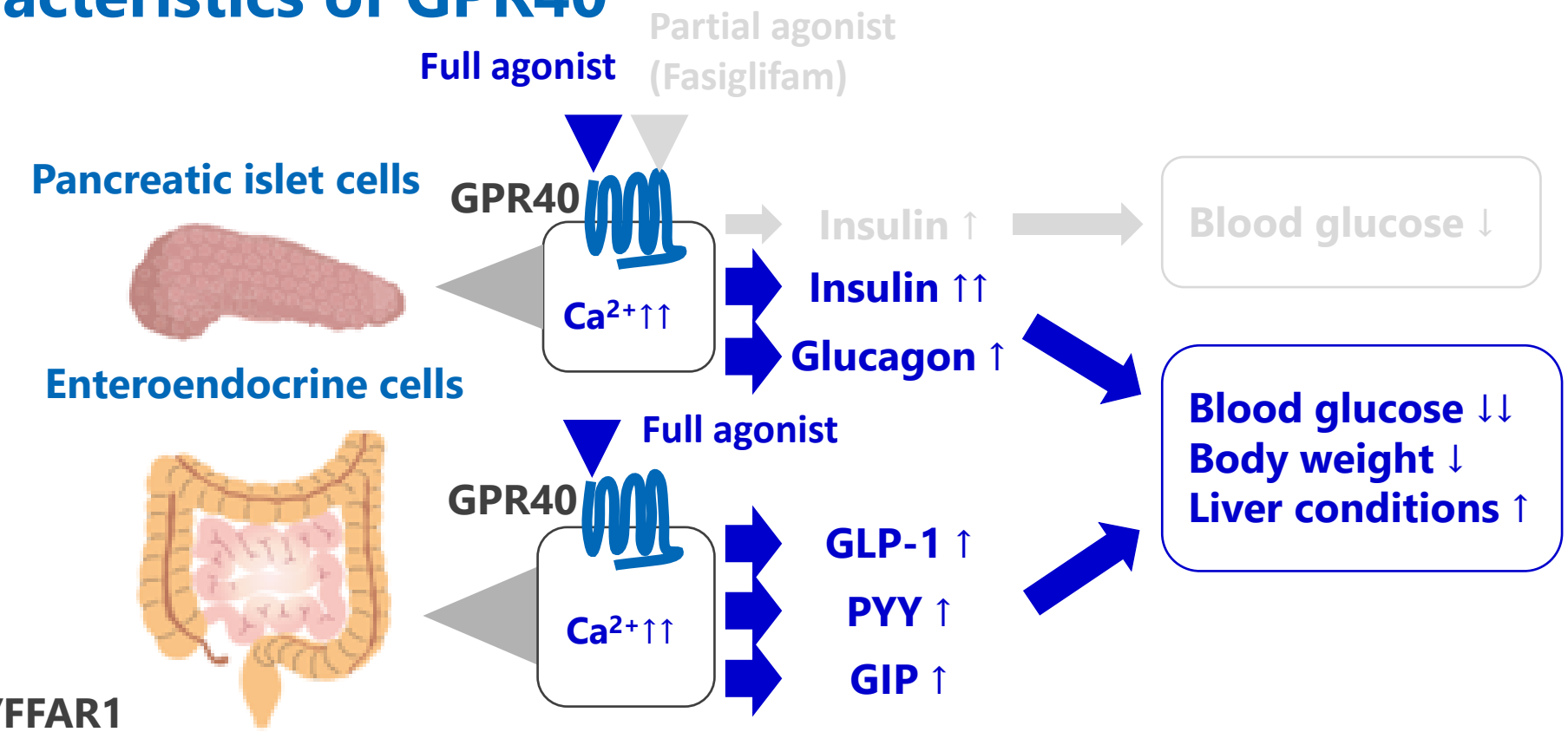

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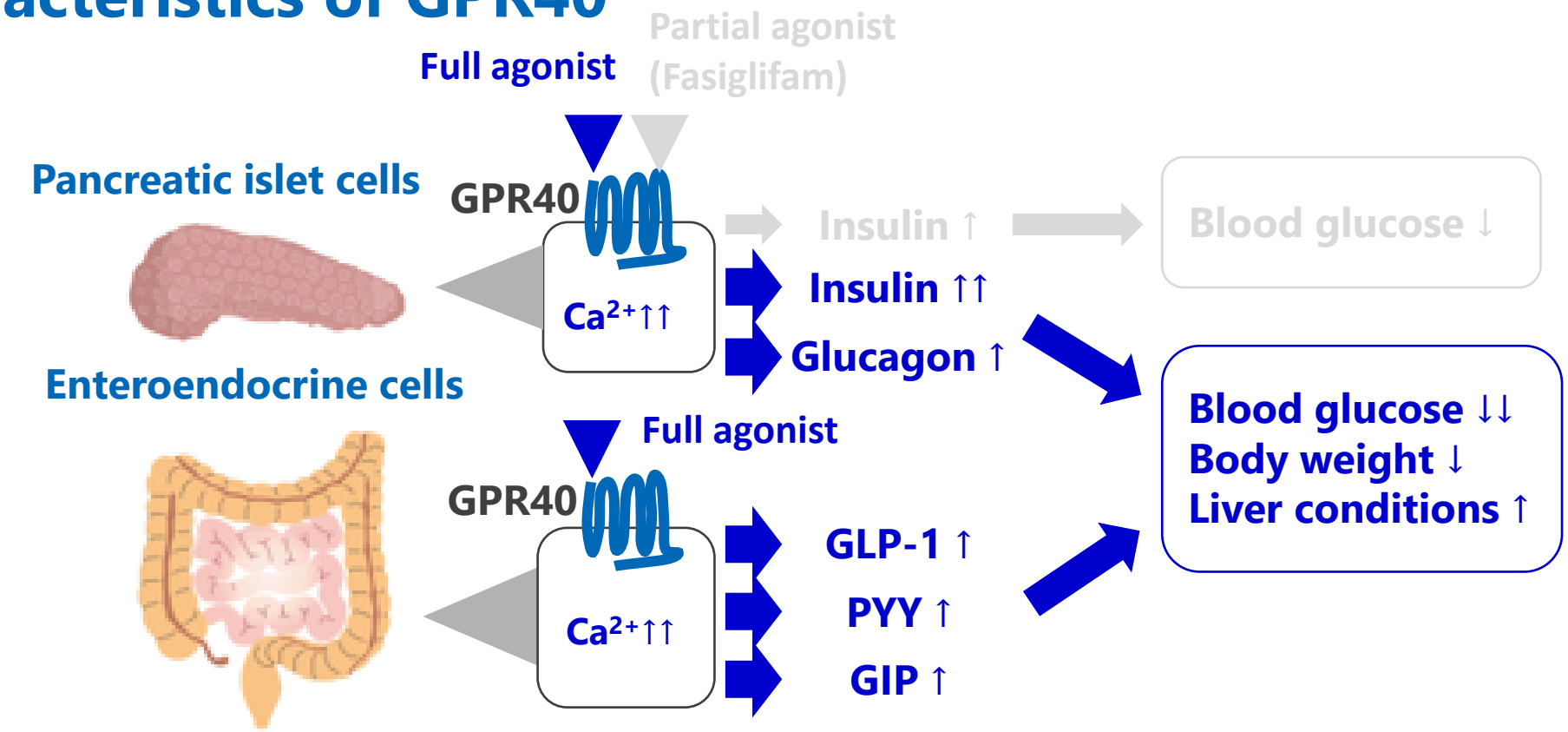

- **Full agonist**
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GPR40 full agonist is expected to be a new drug option for the treatment of *diabetes*, *obesity*, and *NAFLD/NASH*

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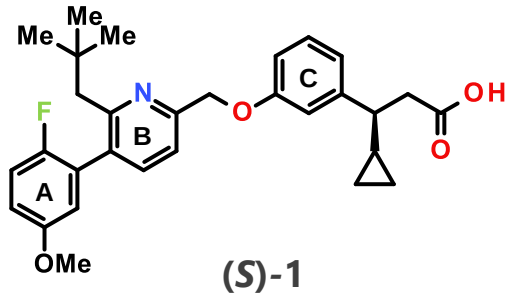
Exploration of New Lead Compound



(*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, DMPK profiles…)
- Insufficient agonistic activity

**All compounds are racemate unless otherwise noted*

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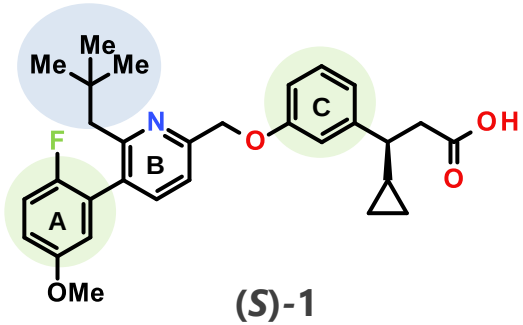

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- The hydrophobic substituent and the terminal aromatic rings (A and C) are essential for potent agonistic activity

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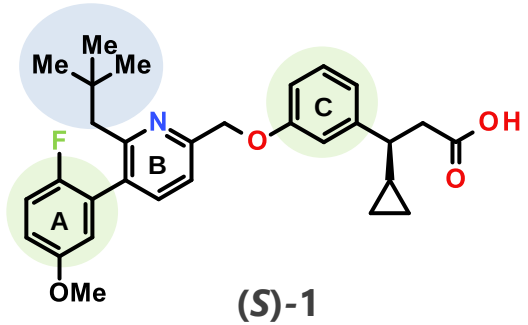

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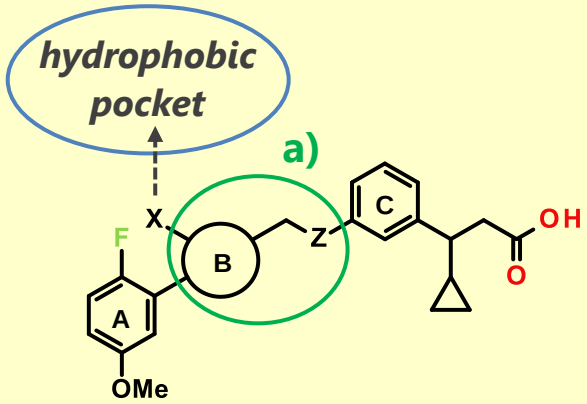
Molecular design and hypothesis



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

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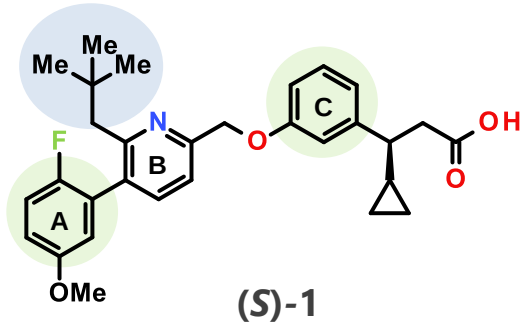

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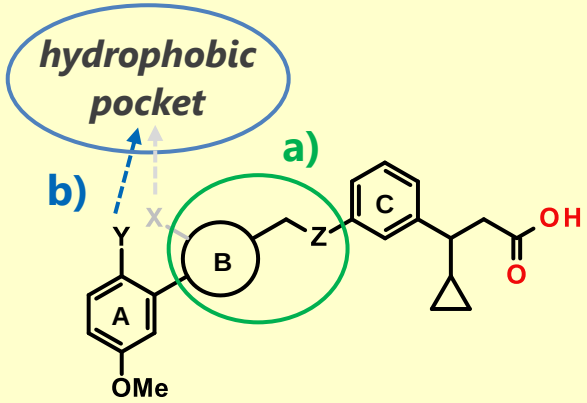

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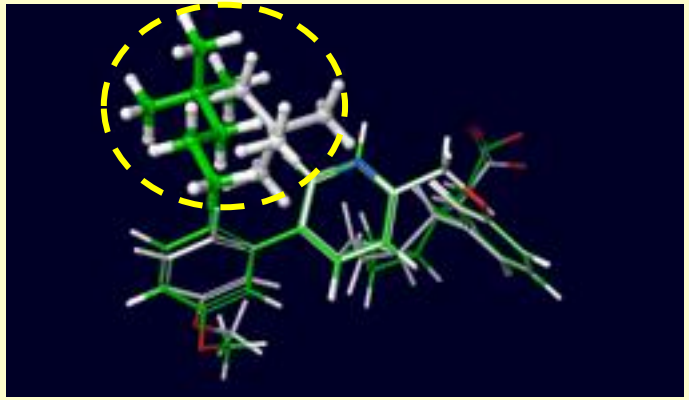

Flexible alignment of **(*S*)-1** (gray) and designed compound (green) using Maestro.

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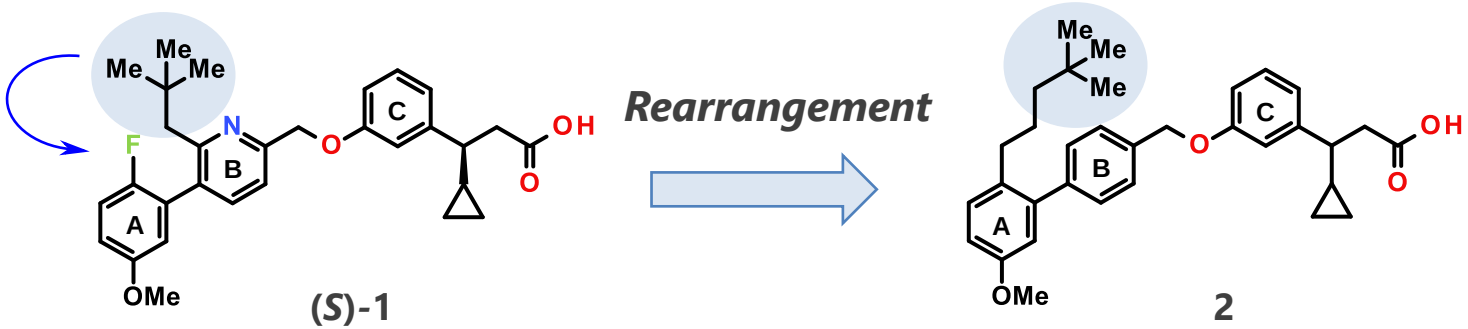
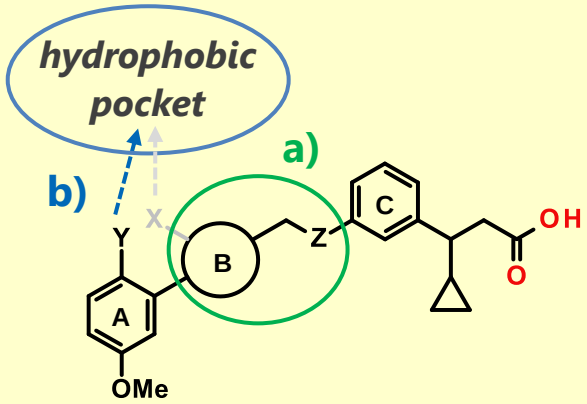
Exploration of New Lead Compound



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

2
hGPR40 EC_{50}: 410 nM

Molecular design and hypothesis



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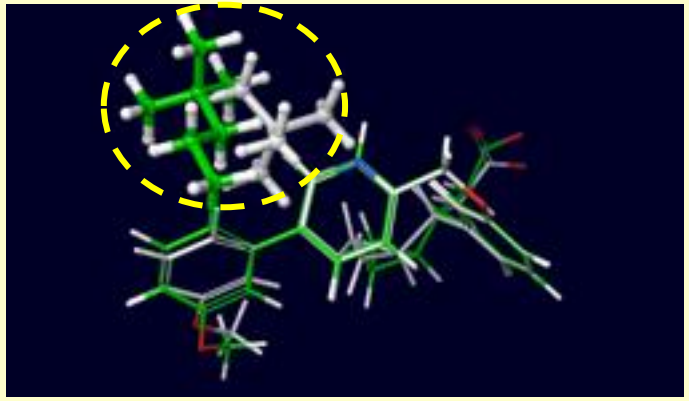

Flexible alignment of compounds **(*S*)-1** (gray) and **2** (green) using Maestro.

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

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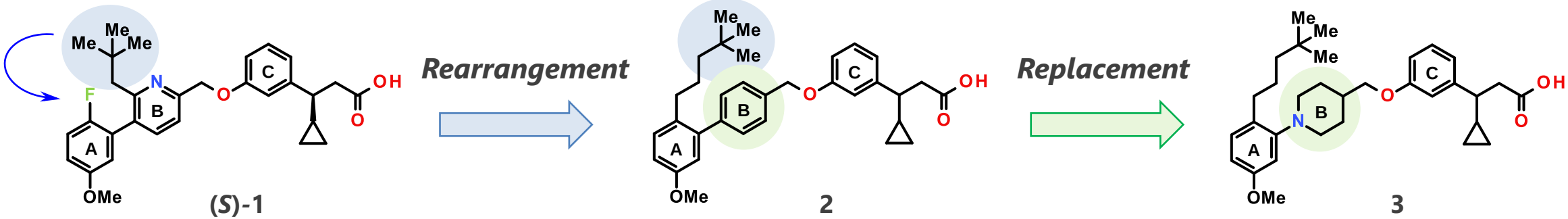
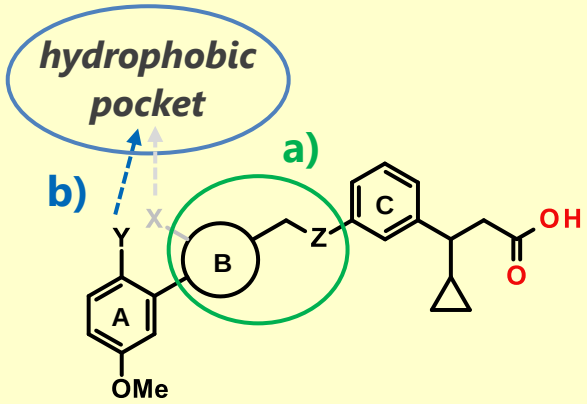


(*S*)-1
hGPR40 EC_{50}: 150 nM

2
hGPR40 EC_{50}: 410 nM

3
hGPR40 EC_{50}: **11 nM**

Molecular design and hypothesis



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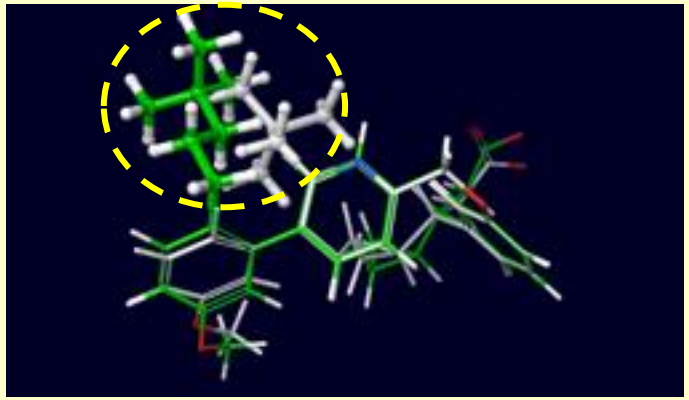

Flexible alignment of compounds **(*S*)-1** (gray) and **2** (green) using Maestro.

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

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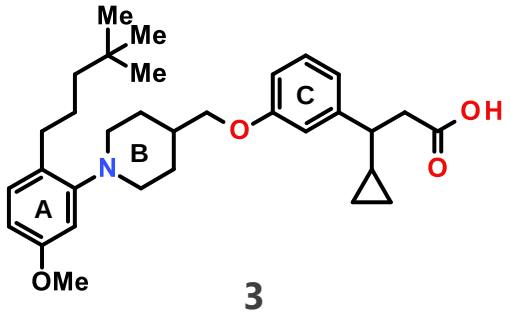
Effect of Substituent on the Benzene Ring A



3

hGPR40 EC_{50}: 11 nM

clogP: 8.4

Cell viability ATP at 30 μM: 0.1%

Challenge of compound 3

- Highly lipophilic property

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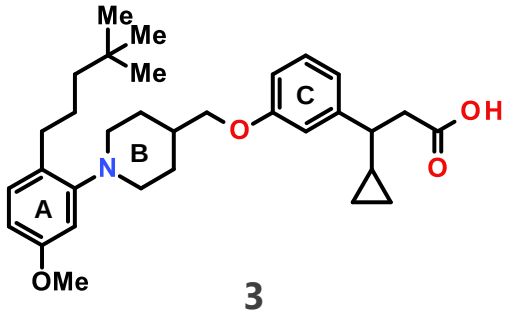

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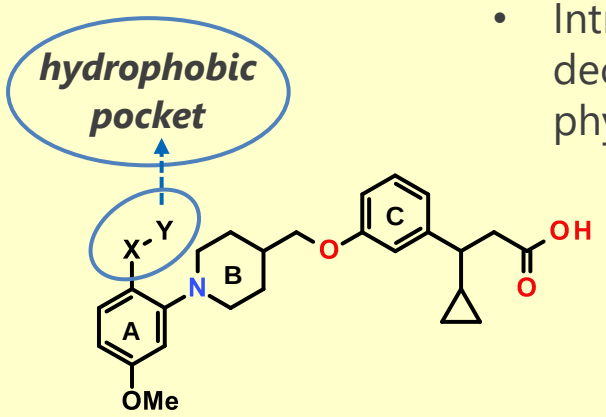

- Introduction of a polar linker (X and/or Y) to decrease the lipophilicity and to improve the physicochemical properties

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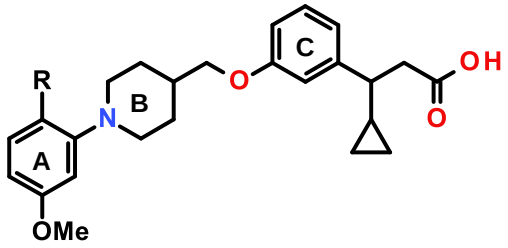

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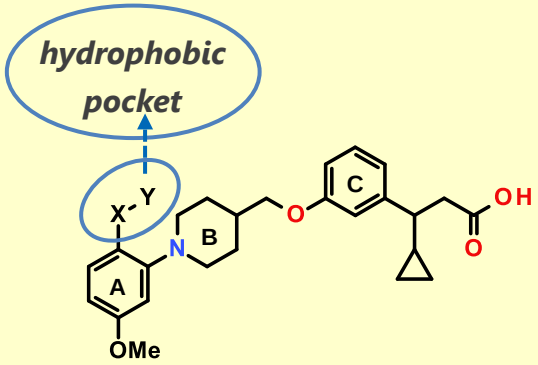
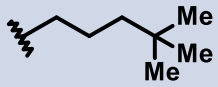
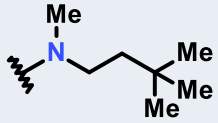
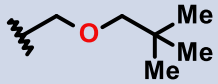
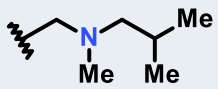
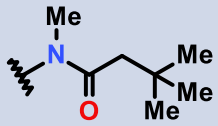
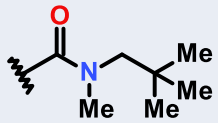


Compound	R	hEC_{50} nM	E_{max}	clogP	Cell viability ATP % at 30 μM
3		11	106%	8.4	0.1
4a		190	108%	7.6	0.1
4b		97	112%	6.5	0.1
4c		1000	110%	4.0	80.7
4d		2200	96%	5.8	76.4
4e		100	107%	5.6	82.2

- **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)**

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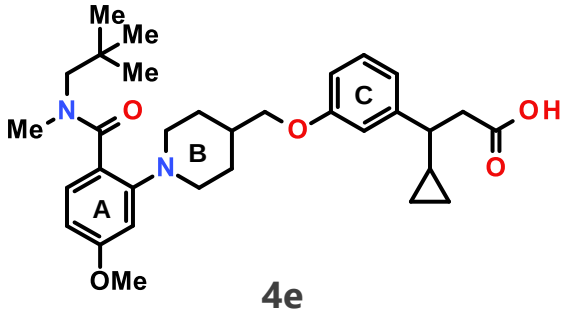
Effect of Substituents on the Amide Group



4e

hGPR40 EC_{50}: 100 nM

clogP: 5.6

Cell viability ATP at 30 μM: 82.2%

Challenge of compound 4e

- Insufficient agonistic activity

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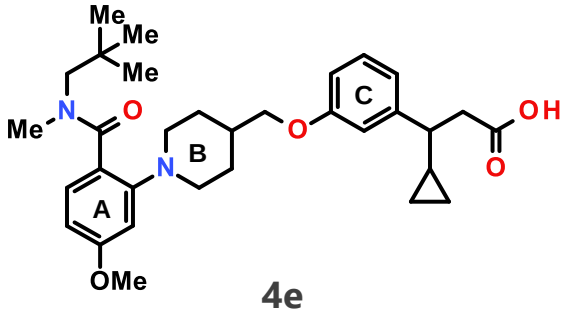

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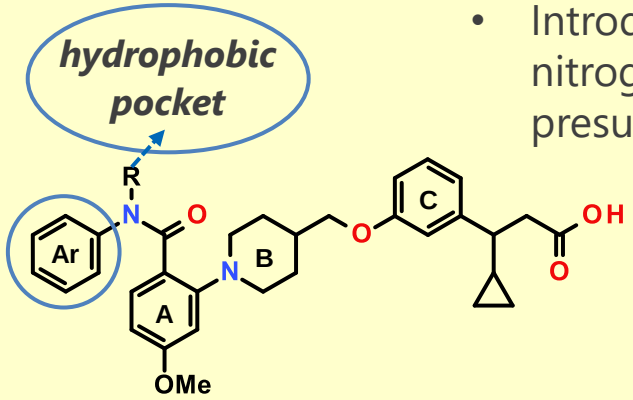

- Introduction of aromatic ring onto the amide nitrogen to restrict the *N*-alkyl moiety to the presumed hydrophobic pocket

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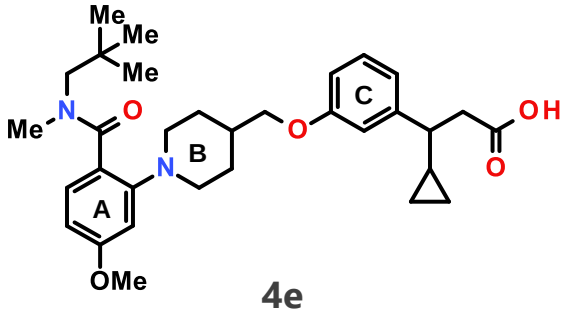

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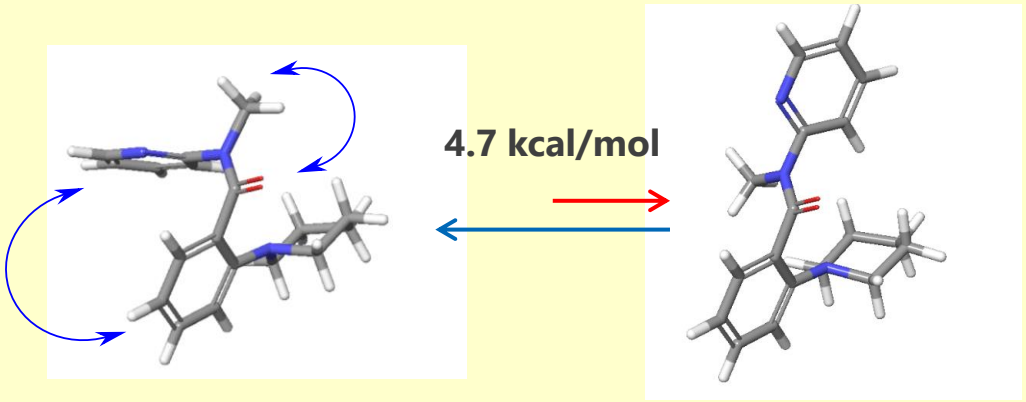
Conformational preference of N-methylbenzanilide



amide-*cis*

amide-*trans*

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

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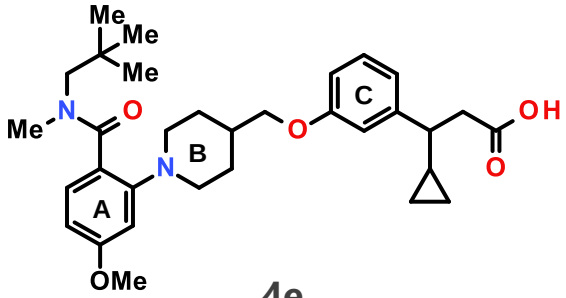

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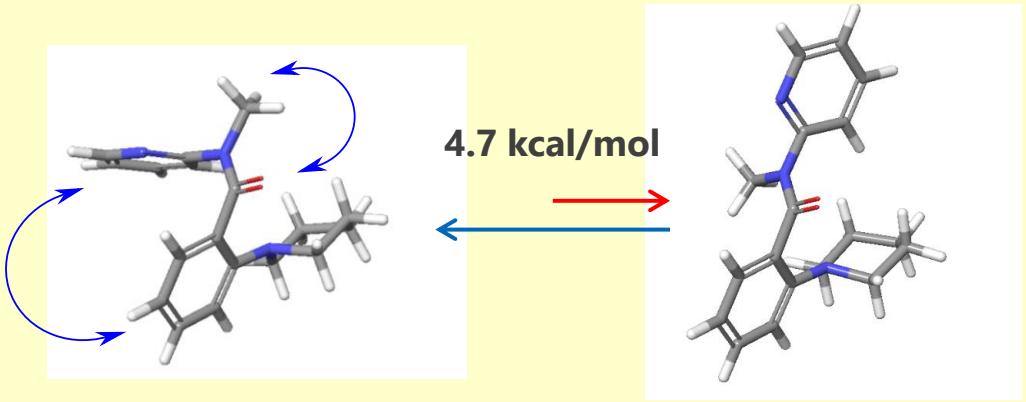
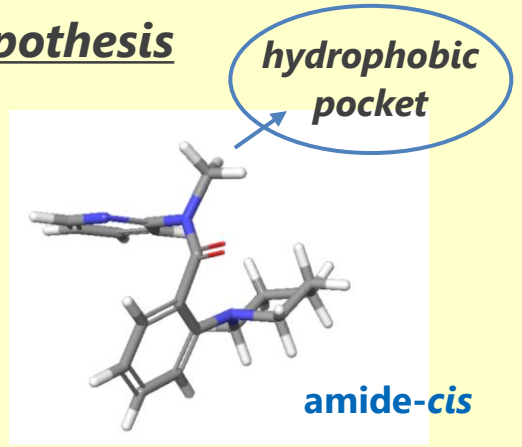


amide-*cis*

amide-*trans*

Hypothesis



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

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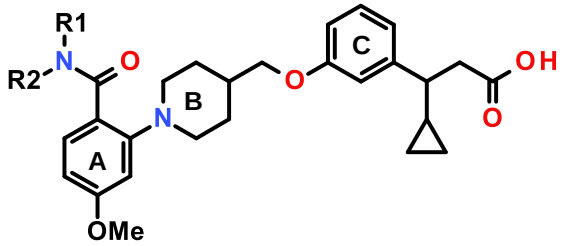

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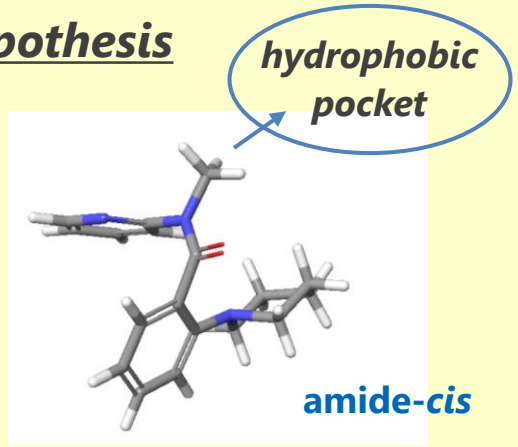
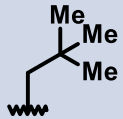
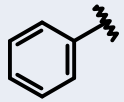
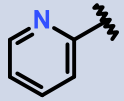
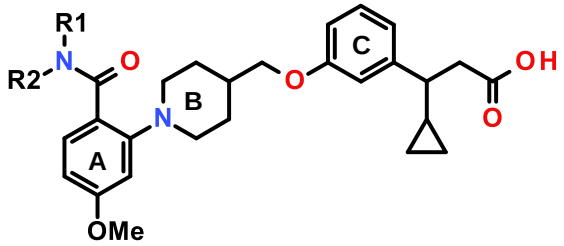


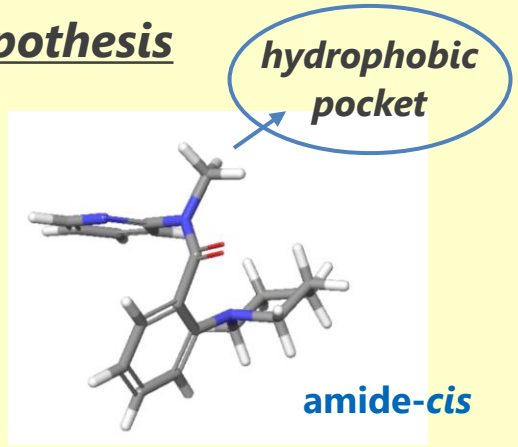
Compound	R^1	R^2	hEC_{50} nM	E_{max}	clogP
4e		Me	100	107%	5.6
4f	Me		140	101%	5.5
4g	Me		180	105%	4.0

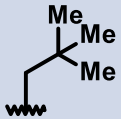
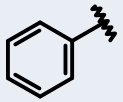
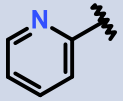
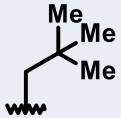
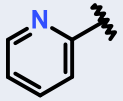
*All compounds are racemate unless otherwise noted

Effect of Substituents on the Amide Group



Hypothesis

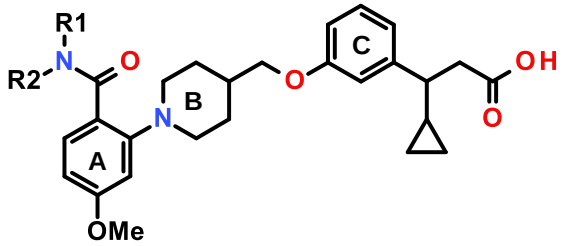


Compound	R^1	R^2	hEC_{50} nM	E_{max}	clogP
4e		Me	100	107%	5.6
4f	Me		140	101%	5.5
4g	Me		180	105%	4.0
4h			26	110%	5.9

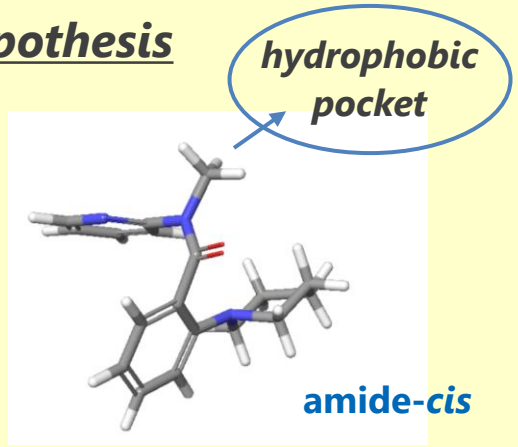
- **Incorporation of aromatic ring and suitable lipophilic moiety dramatically impacted agonistic activity**

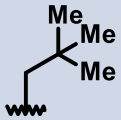
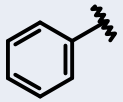
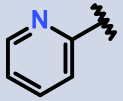
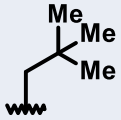
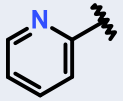
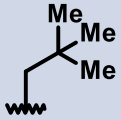
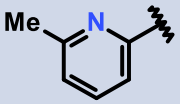
**All compounds are racemate unless otherwise noted*

Effect of Substituents on the Amide Group



Hypothesis

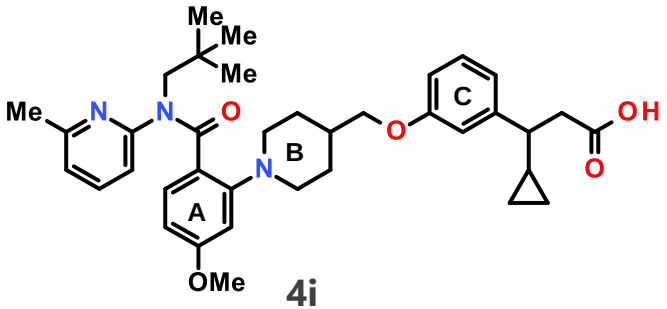


Compound	R^1	R^2	hEC_{50} nM	E_{max}	clogP
4e		Me	100	107%	5.6
4f	Me		140	101%	5.5
4g	Me		180	105%	4.0
4h			26	110%	5.9
4i			17	109%	6.4

- 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

*All compounds are racemate unless otherwise noted

Effect of Polar Aromatic Ring of Phenyl Propanoic Acid Moiety



4i

hGPR40 EC_{50}: 17 nM

clogP: 6.4

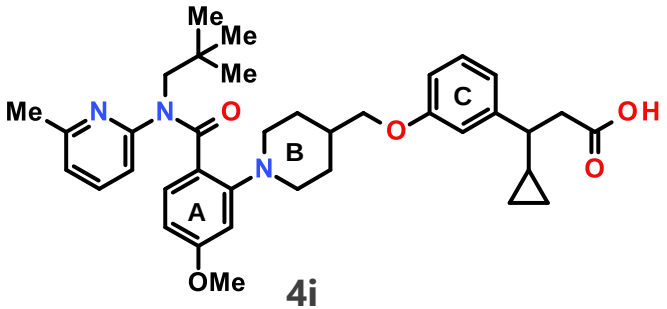
Cell viability ATP at 30 μM: 5.0%

Challenge of compound 4i

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

**All compounds are racemate unless otherwise noted*

Effect of Polar Aromatic Ring of Phenyl Propanoic Acid Moiety



4i

hGPR40 EC_{50}: 17 nM

clogP: 6.4

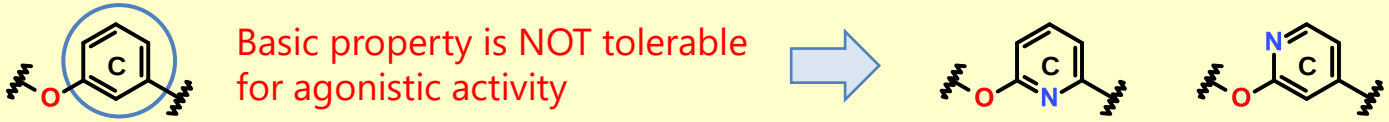
Cell viability ATP at 30 μM: 5.0%

Challenge of compound 4i

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

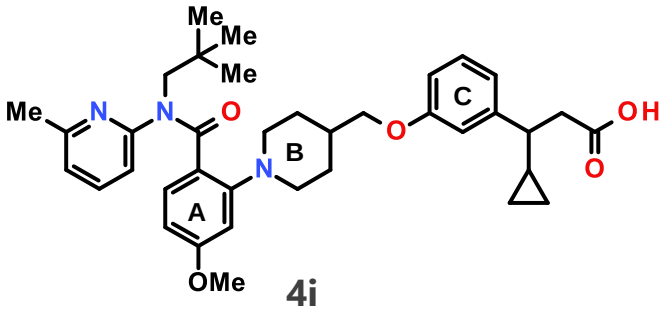
Molecular design

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



*All compounds are racemate unless otherwise noted

Effect of Polar Aromatic Ring of Phenyl Propanoic Acid Moiety



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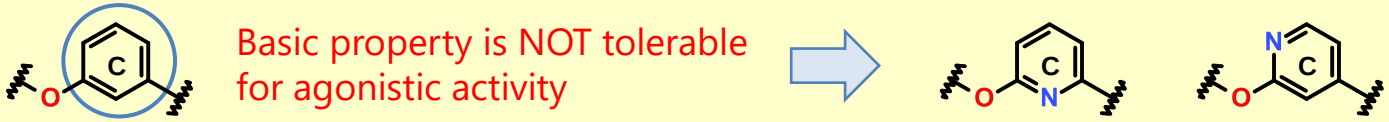
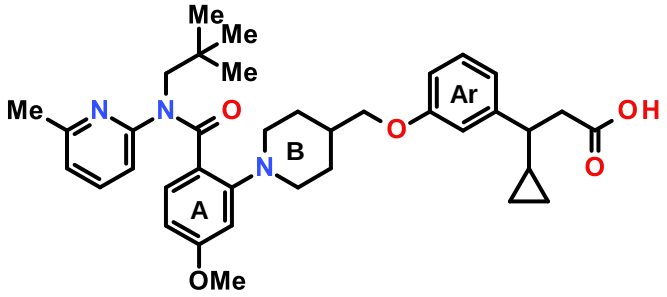
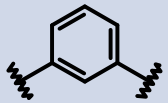
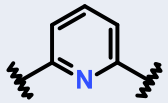
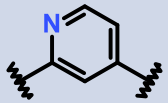


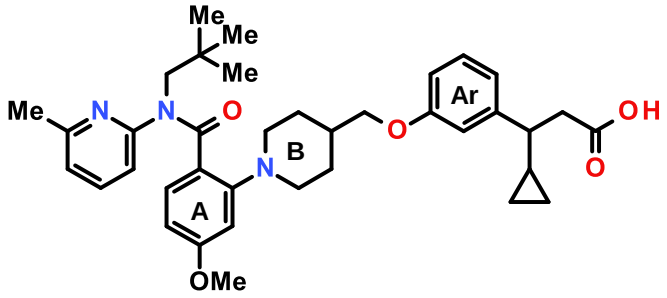


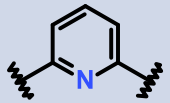
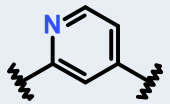
Compound	Ar	hEC_{50} nM	E_{max}	clogP
4i		17	109%	6.4
5a		39% at 10 μM	-	5.8
5b		17	112%	5.8

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

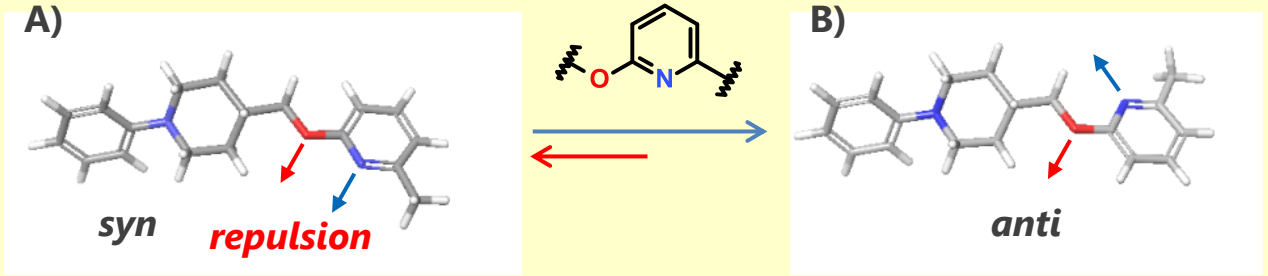
**All compounds are racemate unless otherwise noted*

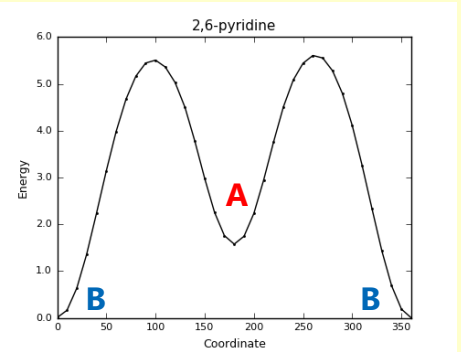
Effect of Polar Aromatic Ring of Phenyl Propanoic Acid Moiety



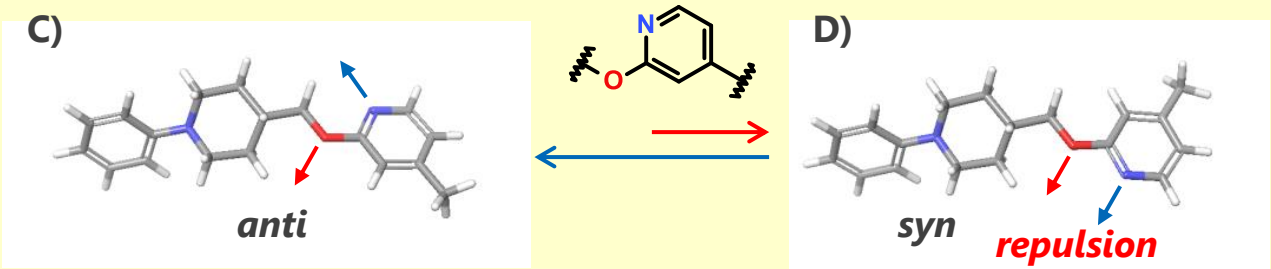
Compound	Ar	hEC_{50} nM	E_{max}	clogP
5a		39% at 10 μM	-	5.8
5b		17	112%	5.8

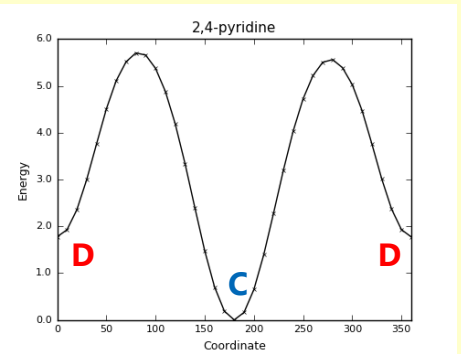
2,6-disubstituted pyridine (5a): presumed active conformer A is less stable than B





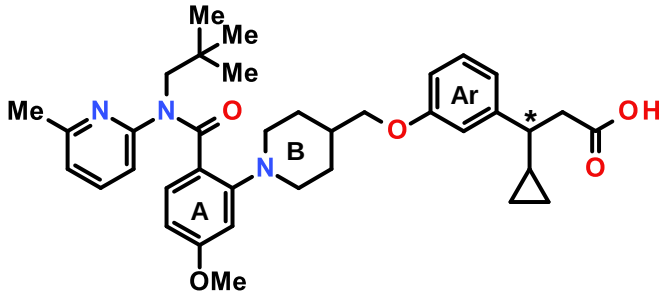
2,4-disubstituted pyridine (5b): presumed active conformer C is more stable than D

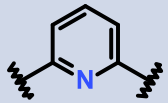
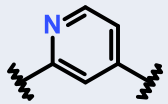
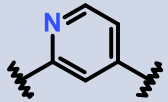
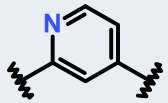




*All compounds are racemate unless otherwise noted

Effect of Polar Aromatic Ring of Phenyl Propanoic Acid Moiety

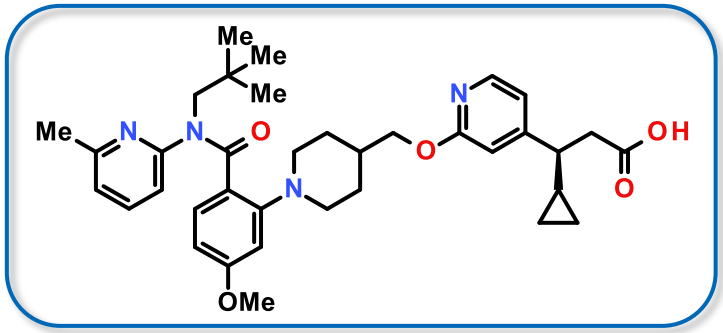


Compound	Ar	hEC_{50} nM	E_{max}	clogP
5a		39% at 10 μM	-	5.8
5b		17	112%	5.8
(*S*)-5b SCO-267		12	108%	5.8
(*R*)-5b		84	109%	5.8

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

*All compounds are racemate unless otherwise noted

Profiles of SCO-267



GPR40 agonistic activity

human GPR40 EC_{50}: 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)	Vss (mL/kg)	Cmax (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

Agenda

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)

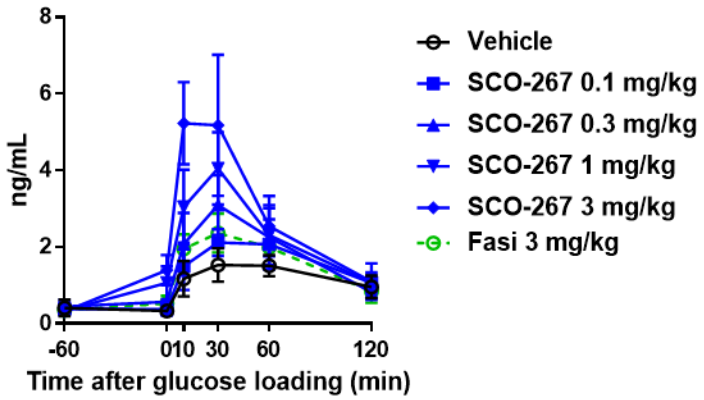
Male N-STZ-1.5 rats (25-week-old) Fasted

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

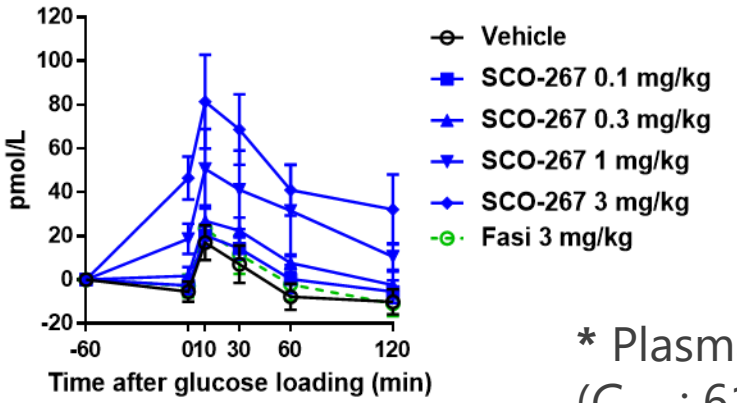
Single oral dosing→OGTT (1.5 g/kg) 1 h after drug dosing

*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 ± S.D. (n = 6).
Fasi, fasiglifam.

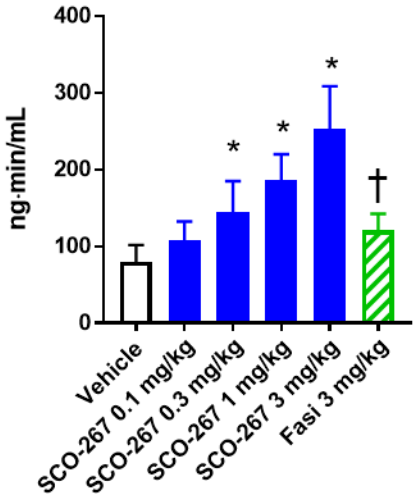
Plasma insulin



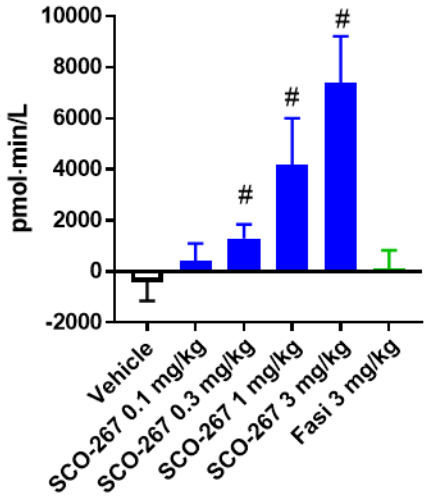
Plasma GLP-1 change



Plasma insulin $AUC_{0\text{-}60min}$



Plasma GLP-1 change $AUC_{-60\text{-}120\ min}$



* 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**

J Pharmacol Exp Ther. 2019;370(2):172-181.

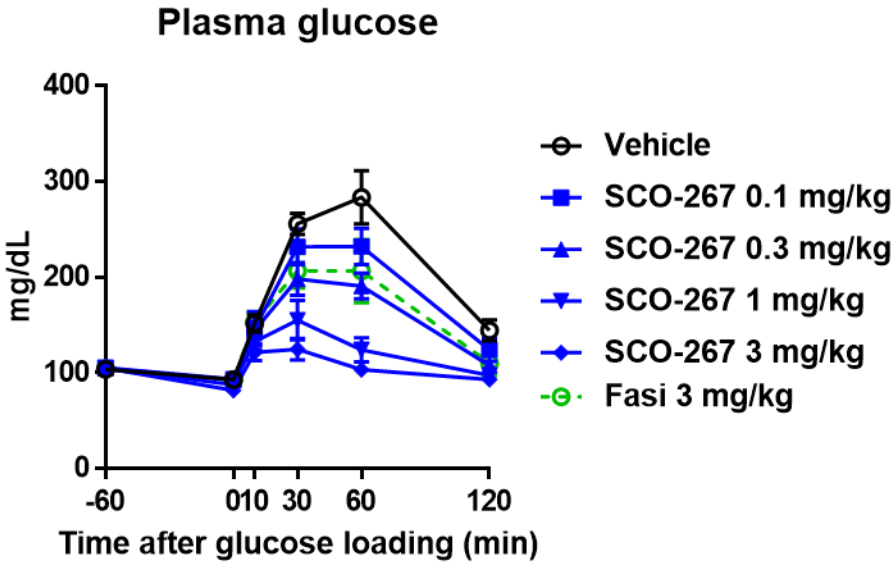
Single Dosing Effects in N-STZ-1.5 Rats (Diabetic Model)

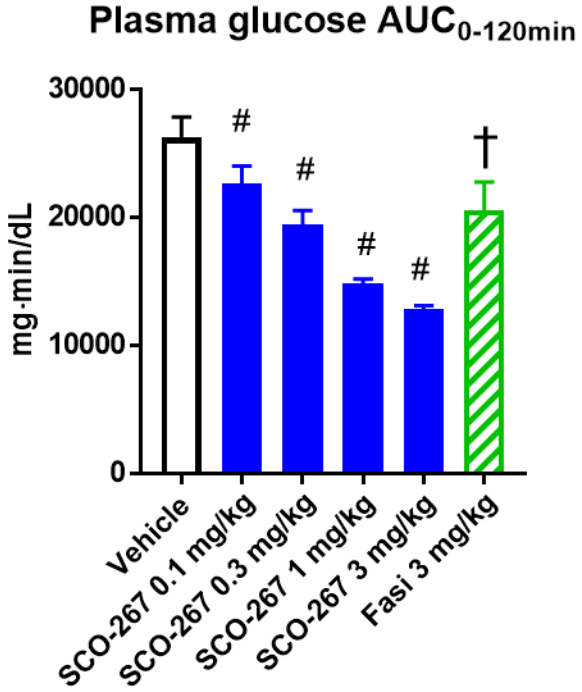
Male N-STZ-1.5 rats
(25-week-old)
Fasted

· 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 ± S.D. (n = 6).
Fasi, fasiglifam.





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

J Pharmacol Exp Ther. 2019;370(2):172-181.

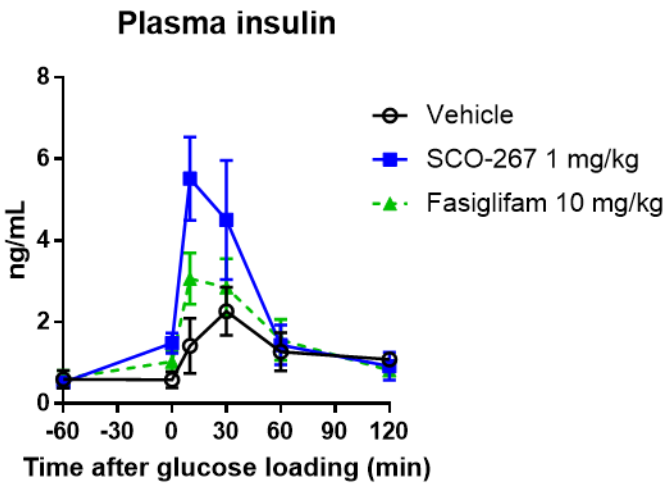
Repeated Dosing Effects in N-STZ-1.5 Rats (Diabetic Model)

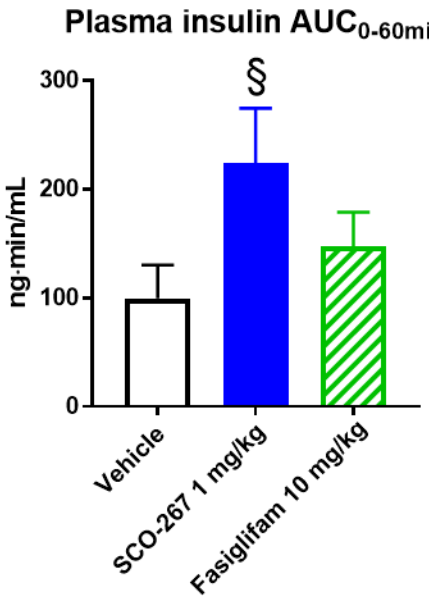
Male N-STZ-1.5 rats (27-week-old)

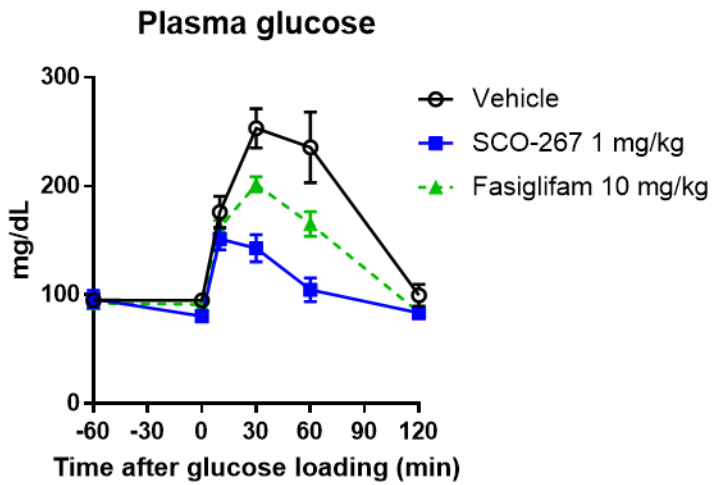
· Vehicle (*p.o.*) · SCO-267 (*p.o.*) · Fasiglifam (*p.o.*)

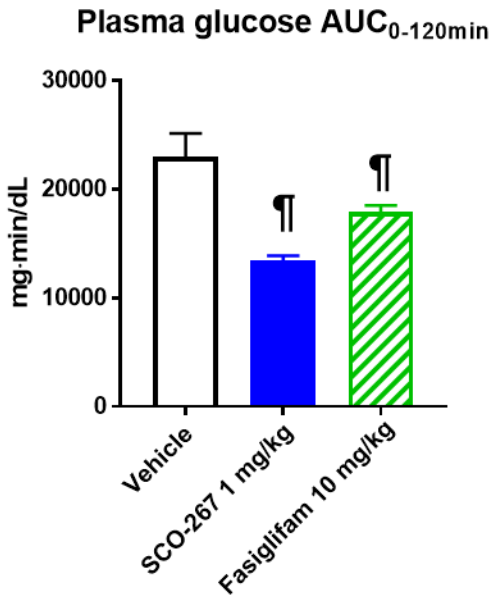
Once daily dosing for 2 weeks→OGTT (1.5 g/kg) 1 h after drug dosing

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









- 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

J Pharmacol Exp Ther. 2019;370(2):172-181.

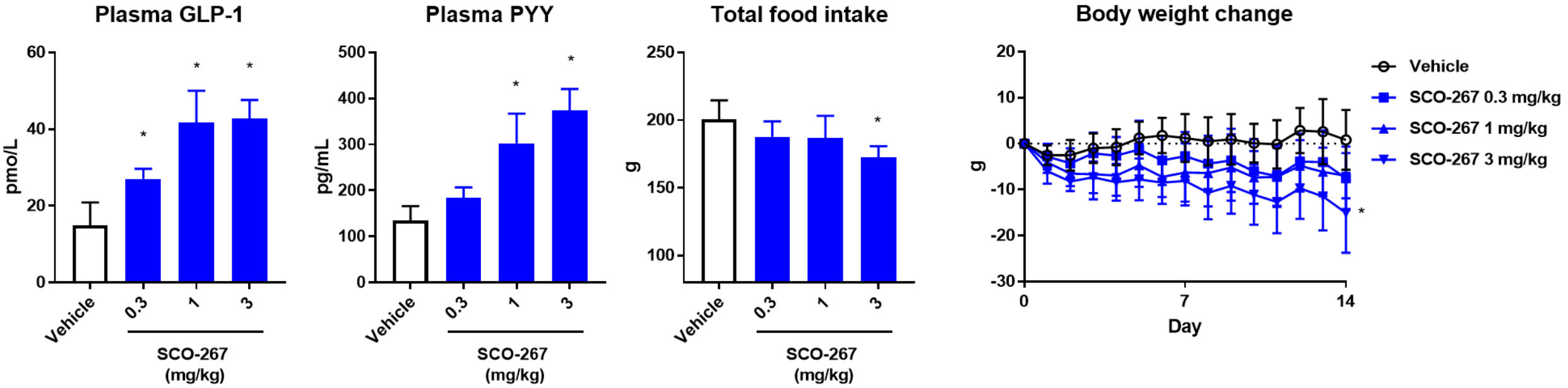
Repeated Dosing Effects in DIO-rats (Obese Model)

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 ± 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

J Pharmacol Exp Ther. 2019;370(2):172-181.

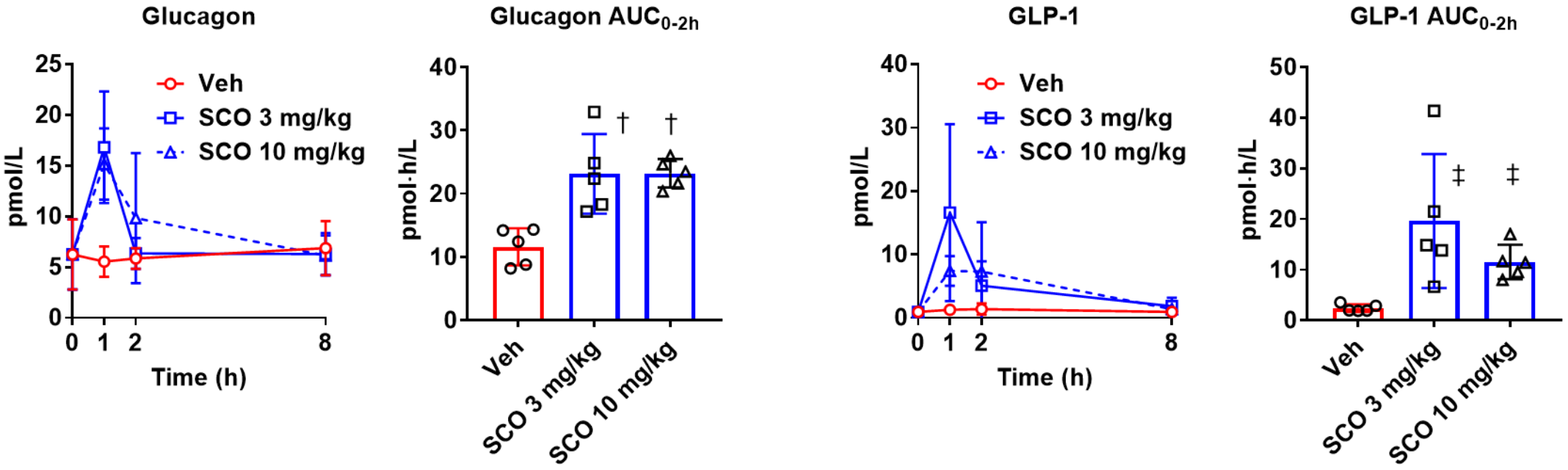
Single Effects in CDAHFD-fed Mice (NAFLD Model)

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

・Vehicle (*p.o.*) ・SCO-267 (*p.o.*)

Single oral dosing

Values are presented as mean ± 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

J Pharmacol Exp Ther. 2020 *in press*

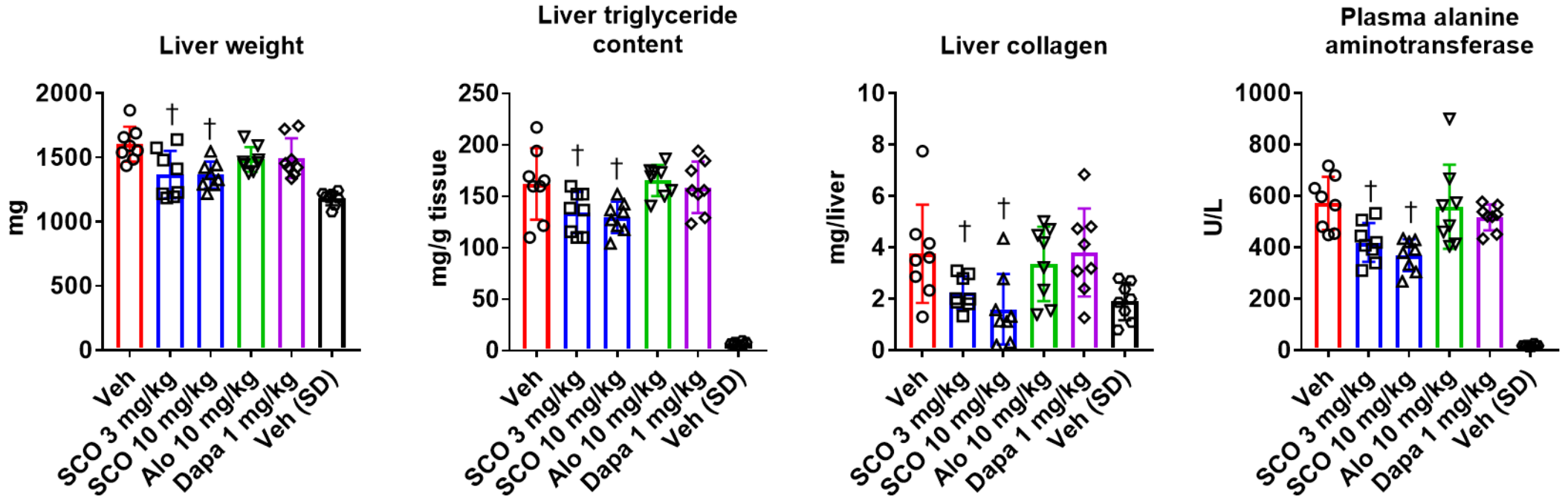
Repeated Dosing Effects in CDAHFD-fed Mice (NAFLD Model)

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 ± 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

J Pharmacol Exp Ther. 2020 *in press*

Agenda

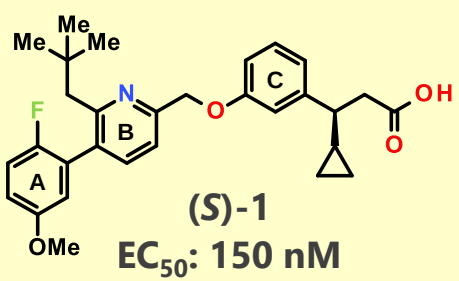
1. Introduction

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

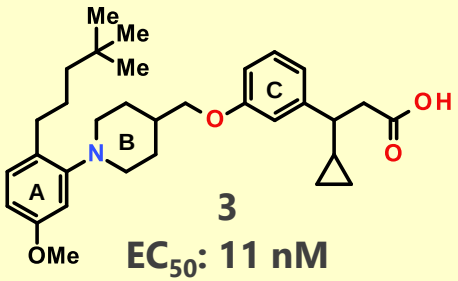
3. Pharmacological Efficacy of SCO-267
   - Single Dosing and Repeated Dosing Effects in N-STZ-1.5 Rats (Diabetic Model)
   - Repeated Dosing Effects in DIO-rats (Obese Model)
   - Single Dosing and Repeated Dosing Effects in CDAHFD-fed Mice (NAFLD Model)

4. Summary

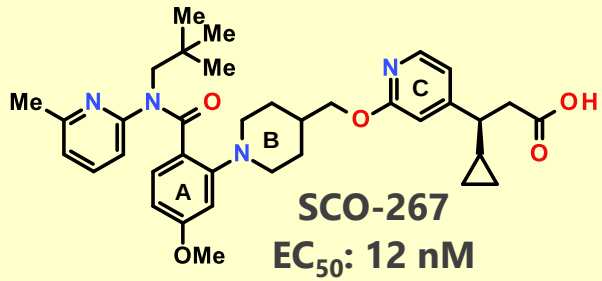
Summary



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



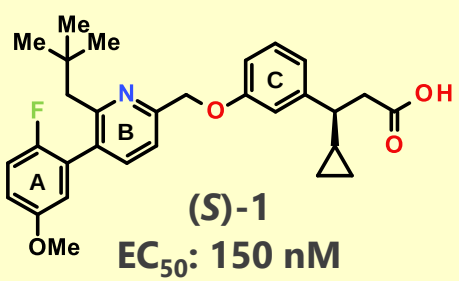
3
EC_{50}: 11 nM
clogP: 8.4



SCO-267
EC_{50}: 12 nM
clogP: 5.8

- 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



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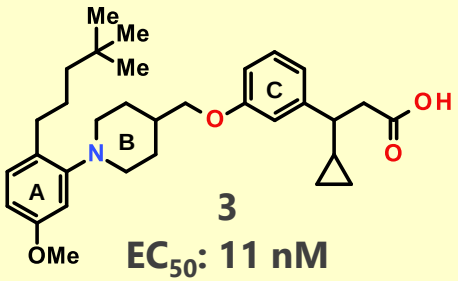

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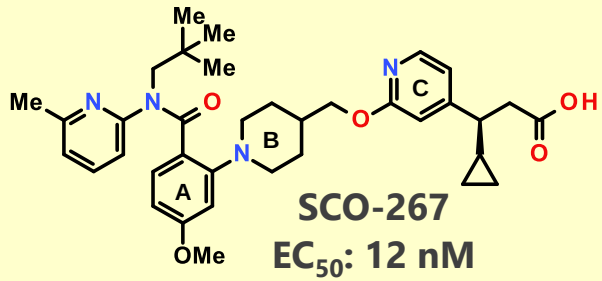

SCO-267
EC_{50}: 12 nM
clogP: 5.8

- ***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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Motoo Iida

Toxicol

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Thank you for your attention!
&
QA session

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