**Introduction**

- Insulin and incretin hormones are the pivotal regulators for glycemic control (Nauck and Meier, 2018, Diabetes Obes Metab 20 Suppl 1-2).
- GPR40 full agonists can activate the enterosodentocrine system while stimulating insulin secretion (Jue 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.

**Lead Optimization**

- **Challenge of compound 3**
  - Highly lipophilic property
  - Introduction of a polar linker (X and/or Y) to decrease the lipophilicity and to improve the physicochemical property

**Effect of Substituent on the Benzene Ring A**

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

**Effect of Polar Aromatic Ring of Phenol Propanoic Acid Moiety**

- **Introduction of aromatic ring onto the amide nitrogen to extract the H-allyl moiety to the presuimded hydrophobic pocket**
  - Molecular design
  - Hypothesis
  - Incorporation of suitable lipophilic moiety onto the nitrogen group of the benzene moiety would enhance the agonistic activity

**Profiles of SCO-267**

- **GPR40 agonistic activity**
  - Human GPR40 EC50: 1.2 nM

- **Pharmacokinetic profiles in rat/mouse**
  - Good oral bioavailability

**New Lead Generation**

- **Challenges of compound (G)-1**
  - Aromaticity (negative impact on overall physicochemical properties etc.)
  - Insufficient agonistic activity

**Molecular design and hypothesis**

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

- The terminal aromatic ring (B) of (G)-1 would serve as just a linker to keep the positions and balance of terminal aromatic rings (A and C); therefore, it was replaced with a saturated ring system

- Full saturated position of the (B) would easily escape the presuimded hydrophobic pocket that the methoxyaryl chain of (B)-9 occupied

- **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**

**SCOHIA PHARMA, Inc.**

Contact information: https://www.scohia.com/en/contact_en/

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**References**


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**Graphs and Images**

- Graph A: Graphical representation of the compounds and their effects.
- Graph B: Graphical representation of the pharmacokinetic profiles.
- Image C: Image of the molecular structure.

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**Legend**

- SCO-267: The lead compound.
- GPR40: G-protein-coupled receptor.
- EC50: Effective concentration.
- hGPR40: Human GPR40.
- clogP: Logarithmic partition coefficient.
- hERG: Human ether-a-go-go related gene.

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**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 vivo/vivo Tox profiles**

- **SCO-267 stimulated insulin and GLP-1 secretion and ameliorated glucose tolerance in male N-STZ 1.5 rats**

- **A single dose of SCO-267 stimulated insulin secretion and GLP-1 release and ameliorated glucose tolerance in male 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, pharmacodynamics, and pharmacokinetic effect in healthy adults and people with impaired glucose tolerance is ongoing.

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**Authors**

- Seiji Miwatashi, Yasufumi Miyamoto, 2 Hideki Furukawa, Yasuhiro Hirata, Koji Watanabe, Yuko Hitomi, Yayo Yoshitomi, Junpei Aida, Nobuyuki Takakura, Kazuaki Takami, Yoko Kobayashi, Yoshihiro Hirozane, Teruki Hamada, Ryu Ito, Mitsuji Ookayama, Yasuke Morito, Masanori Watanabe, Tsuyoshi Maekawa