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Article

Design and Identification of a GPR40 Full Agonist (SCO-267) Possessing a 2-Carbamoylphenyl Piperidine Moiety

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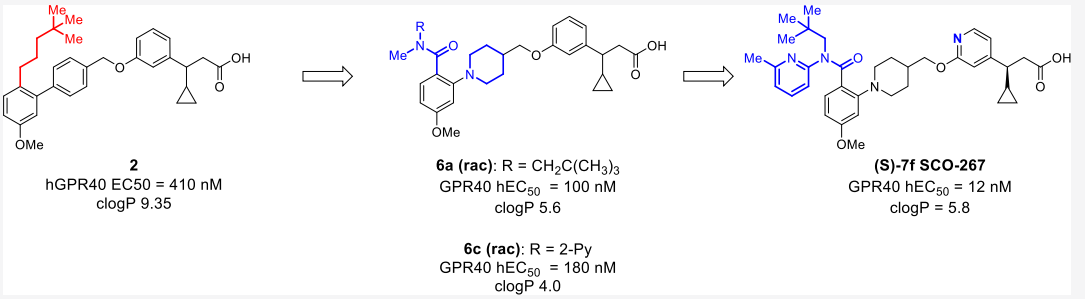

ABSTRACT: GPR40/FFAR1 is a G-protein-coupled receptor expressed in pancreatic β-cells and enteroendocrine cells. GPR40 activation stimulates secretions of insulin and incretin, both of which are the pivotal regulators of glycemic control. Therefore, a GPR40 agonist is an attractive target for the treatment of type 2 diabetes mellitus. Using the reported biaryl derivative **1**, we shifted the hydrophobic moiety to the terminal aryl ring and replaced the central aryl ring with piperidine, generating 2-(4,4-dimethylpentyl)phenyl piperidine **4a**, which had improved potency for GPR40 and high lipophilicity. We replaced the hydrophobic moiety with *N*-alkyl-*N*-aryl benzamides to lower the lipophilicity and restrict the *N*-alkyl moieties to the presumed lipophilic pocket using the intramolecular $\pi-\pi$ stacking of cis-preferential *N*-alkyl-*N*-aryl benzamide. Among these, orally available (3*S*)-3-cyclopropyl-3-(2-((1-(2-((2,2-dimethylpropyl)(6-methylpyridin-2-yl)carbamoyl)-5-methoxyphenyl)piperidin-4-yl)methoxy)pyridin-4-yl)propanoic acid (**SCO-267**) effectively stimulated insulin secretion and GLP-1 release and ameliorated glucose tolerance in diabetic rats via GPR40 full agonism.

INTRODUCTION

GPR40/FFAR1 is a class A G-protein-coupled receptor, which is highly expressed in pancreatic β-cells. The membrane protein GPR40 is activated by medium- and long-chain fatty acids, the endogenous ligands that stimulate insulin secretion by elevating cytosolic Ca^{2+} levels.[1−3] A variety of synthetic molecules have exhibited hypoglycemic properties in rodents as insulin secretagogues, thus offering an attractive target for the treatment of type 2 diabetes mellitus (T2DM).[4] The GPR40 partial agonist fasiglifam (TAK-875) significantly lowered glucose levels in T2DM patients, with a minimal risk of hypoglycemia, via glucose-stimulated insulin secretion (GSIS) mediated by GPR40 signaling.[5−8] Unlike the partial agonist TAK-875 (Figure 1), other types of synthetic GPR40 agonists, which are capable of acting as full agonists, have been reported.[9−16] A prior study using a Ca^{2+} mobilization assay in Chinese hamster ovary (CHO) cells, with relatively low expression levels of GPR40 (clone #2), revealed that partial and full agonists can be distinguished by measuring maximal

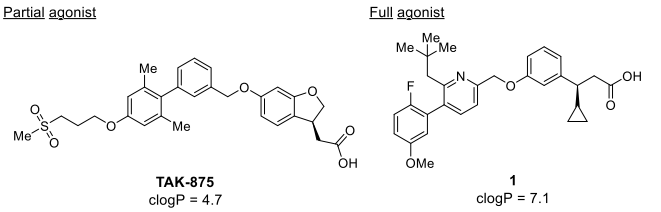

Figure 1. GPR40 partial and full agonists in Takeda.

Ca^{2+} response to test compounds. AM-1638, a GPR40 full agonist, had an EC_{50} value of 150 nM and an E_{max} value of

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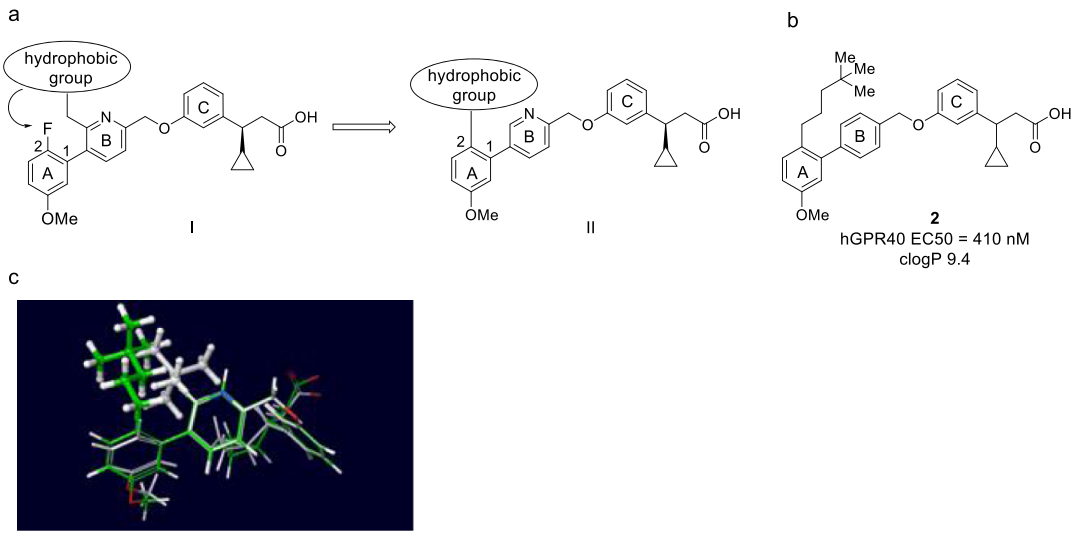
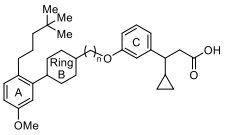


Figure 2. (a) Repositioning the hydrophobic group from the central aryl ring to the terminal aryl ring. (b) Structure of compound **2** possessing a hydrophobic group on the terminal aryl ring. (c) Flexible alignment of compounds **1** (gray) and **2** (green) using Maestro.



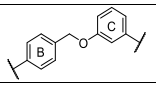
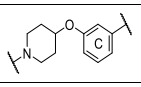
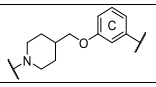
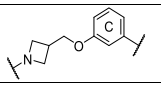
Linker				
Compound	**2**	**3**	**4a**	**5**
hEC_{50} (nM) [a]	410±7.7	22% at 10 μM [b]	11±4.6	250±77
E_{max} (%) [c]	105%	-	106%	102%

Figure 3. Replacement of the phenyl ring with saturated linkers. [a]Data are presented as mean values with standard deviation from more than two independent experiments in duplicate. [b]The value is from a single experiment in duplicate. [c]% Compared to the reference full agonist.

182% (% of γ-linolenic acid, an endogenous ligand). TAK-875 (a partial agonist) showed EC_{50} values of >1000 nM and E_{max} values of 22% (% of γ-linolenic acid).[17] Full agonists activate GPR40 expressed in the gastrointestinal tract and pancreatic β-cells to stimulate glucagon-like peptide-1 (GLP-1) secretion and insulin secretion simultaneously, providing a GLP-1-dependent anorectic effect and an additional mechanism to control GSIS.[18,19] Therefore, GPR40 full agonists may be an effective treatment for diabetes and obesity.

In an effort to discover full agonists of GPR40 as novel antidiabetic agents, we identified a β-cyclopropyl propionic acid derivative **1**.[20] Compound **1** exhibited moderate agonistic activity in CHO cells with a relatively low expression of GPR40 (clone #2) with an EC_{50} value of 150 nM and an E_{max} value of 88% (% of reference full agonist). As a result, we rearranged the hydrophobic moiety from the central ring to the terminal ring to access greater chemical space. We assumed that the fluorine-substituted position of compound I could easily access the presumed pocket that the neopentyl alkyl chain of compound **1** occupies (Figure 2a). Therefore, we incorporated an alkyl moiety to the ortho-position relative to the pyridine ring of compound II, which led to the identification of compound **2**, with an EC_{50} value of 410 nM and an E_{max} value of 105% (Figure 2b). The flexible alignment of the biaryl fragments of compounds **1** and **2** using Maestro[21] shown in Figure 2c may support this assumption.

We next attempted to replace the central benzene ring of **2** with a series of saturated linkers with the aim of breaking the aromaticity of compound **2**, which may allow us to identify compounds that better fit the spatial subtleties of the target protein and improve its overall physicochemical properties.[22] We designed 4-piperidine ether **3**, 4-methyl piperidine ether **4a**, and 3-methyl azetidine ether **5**, to keep the distance between ring A and C (Figure 3). The agonistic activity for each compound is depicted in Figure 3. 4-Piperidine ether **3** had poor agonistic activity as its conformation differed from that of biphenyl compound **2**, whereas 4-methyl piperidine ether **4a** and 3-methyl azetidine ether **5** showed potent agonistic properties, which implies that the saturated piperidine of compound **4a** may more effectively fit the spatial subtleties of GPR40 relative to the biaryl derivative **2**. To get a better understanding of compound **4a** binding, we performed a liquid chromatography−mass spectrometry (LC−MS)-based saturation binding assay. Saturation binding curves of allosteric partial agonists TAK-875 and AM-1638 were generated using an LC−MS-based saturation binding assay with the WT

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hGPR40-expressed VLP protein. The apparent K_d value of TAK-875 was 11.9 nM and AM-1638 was 5.0 nM.[23,24] Competitiveness of **4a** between TAK-875 and AM-1638 was also determined using the LC−MS-based competitive binding assay. As a result, AM-1638 competed with **4a** for binding to GPR40, whereas TAK-875 did not compete with **4a** (Figures 4

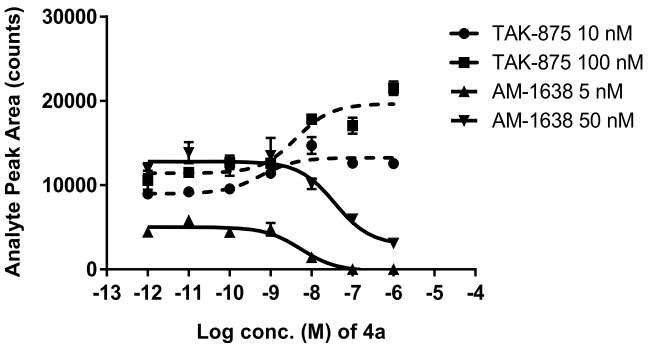
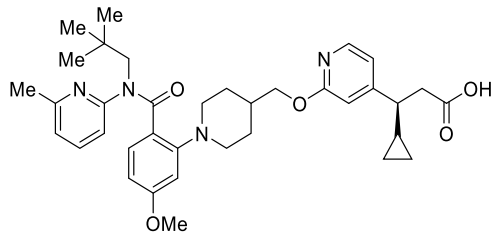


Figure 4. LC−MS-based competitive binding assay result of **4a** and two types of GPR40 agonists, TAK-875 and AM-1638. Two independent experiments in duplicate were performed. Data are shown separately in this figure and Figure S1.

and S1, Supporting Information). Furthermore, TAK-875 and **4a** showed potential to form a ternary complex with GPR40. Therefore, **4a** does not bind near the TAK-875 binding site. Based on the results obtained by in vitro characterization of the compounds, we embarked on a medicinal chemistry campaign starting with **4a** and a phenylpiperidine ring to discover potent derivatives to reveal the structure−activity relationship (SAR) of the substituents on ring A of **4a**. Herein, we report the design of a novel phenylpiperidine-bearing amide moiety on the benzene ring and the subsequent optimization studies that led to the identification of **SCO-267**, with high potency and significant glucose-lowering properties mediated by the full agonistic effects of GPR40 (Figure 5).



(S)-7f SCO-267
GPR40 hEC_{50} = 12 nM
clogP = 5.8
BA 16% (SD rat, 1 mg/kg)

Figure 5. Structural exploration of GPR40 full agonists.

CHEMISTRY

The derivatization on the β-position of phenyl propionates is depicted in Scheme 1 (**11a−b**, **14a−b**, **18**, and **22**). Aldehyde **8** was condensed with Meldrum's acid, followed by 1,4-addition with the cyclopropyl Grignard reagent to afford **10**. Conversion of alkyl Meldrum's acid derivative **10** was performed in dimethylformamide (DMF) and water, followed by esterification of the carboxylic acid under acidic conditions to afford **11a** as a methyl ester. The pyrolysis of **10** was also performed in ethanol to provide ethyl ester **11b**. 3-Alkoxy-substituted phenyl propionate **14** was furnished from the formation of β-hydroxyl esters **13** with lithium diisopropylamide and ethyl acetate. This was followed by silver carbonate-promoted alkylation and the removal of benzyl ether to afford two key building blocks **14a** and **14b**. Compound **18** was obtained from the coupling of the Grignard reagent with **15**. The resulting ketone **16** was converted to propionate **17** by the Horner−Wadsworth−Emmons (HWE) reaction, followed by reduction of the α,β-unsaturated ester. Deprotection of phenol of **17** afforded intermediate **18**. The Wittig reaction with oxetane **19**, followed by Rh-catalyzed 1,4-addition of 3-(benzyloxy)phenylboronic acid and the removal of benzyl ether, afforded 3,3-disubstituted derivative **22**.

The synthetic route for the modification of linker moieties is illustrated in Scheme 2. 2-Bromo-4-methoxybenzaldehyde **23** was subjected to Suzuki coupling conditions to introduce the aromatic fragment. The resulting ester **24** was converted to **25** by the Wittig reaction and reduction of olefin, followed by the reduction with $LiAlH_4$ to produce the key intermediate alcohol **26**. The alcohol **26** was condensed with phenol **11a** via the Mitsunobu reaction, followed by ester hydrolysis of the coupling product to produce the carboxylic acid **2**. N-substituted phenyl derivatives were prepared from 2-fluoro benzaldehyde by S_NAr, followed by the Wittig reaction, reduction, and condensation by the Mitsunobu reaction for **3** and **4a** or by alkylation with the corresponding mesylate for **5**. A similar reaction sequence to Scheme 2 delivered **4b−d** using Pd-catalyzed amination instead of S_NAr and **4e** (Scheme 3).

Several phenylpiperidine derivatives with diversified substituents were synthesized from a common precursor **30**. Protection of alcohol with TBSCl, followed by the addition of the Grignard reagent produced **43**. Chlorination of the alcohol of **43** with thionyl chloride and catalytic hydrogenation with palladium on carbon followed by deprotection of alcohol converted it to key intermediate alcohol **44**. Further conversion was performed on **44** through the sequential Mitsunobu reaction and ester hydrolysis to deliver the carboxylic acid **4f**. Compound **30** was also converted to intermediate **45** through the corresponding mesylate of **30** and the condensation with **11a**. The resulting aldehyde **45** was treated with *N*-methylisobutylamine and $NaBH(OAc)_3$, followed by ester hydrolysis to produce the carboxylic acid **4h** (Scheme 4). The synthetic route toward the derivative with a hydroxyl group on the terminal of the alkyl chain is depicted in Scheme 5. The Wittig reaction of **30**, followed by copper-catalyzed 1,4-reduction produced the ethyl ester **46**. The resulting ester **46** was converted to **47** by the addition of methyl magnesium chloride; the sequential protection of the two alcohols proceeded smoothly and regioselectivity through the initial treatment with TBSCl and imidazole, followed by Ac_2O and tetraethylammonium (TEA) to afford **49**. After the deprotection of **49** with tetrabutylammonium fluoride (TBAF), a condensation reaction with **11b** and hydrolysis yielded the carboxylic acid **4g**.

The amide analogues (**6a−6h**) were generated with benzylation of benzoic acid **51** under basic conditions, followed by the addition of 4-piperidinemethanol to afford **53**. The resulting **53** was converted to key intermediate benzyl carboxylic acid **55** by the Mitsunobu reaction and the removal of the benzyl protection of the ester (Scheme 6). Target compounds **6a−6h** were obtained by a condensation reaction

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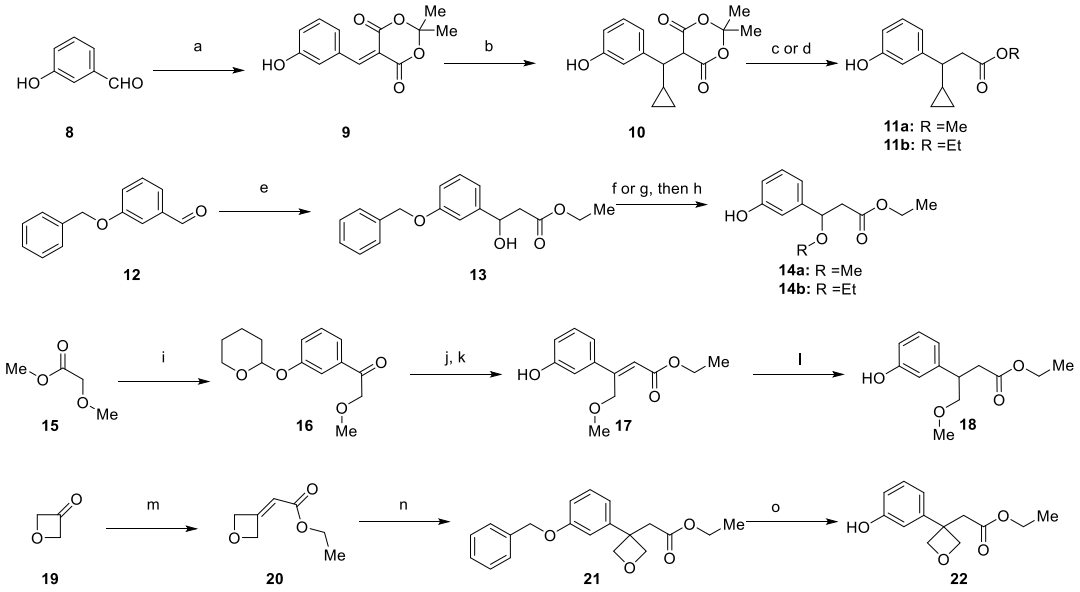
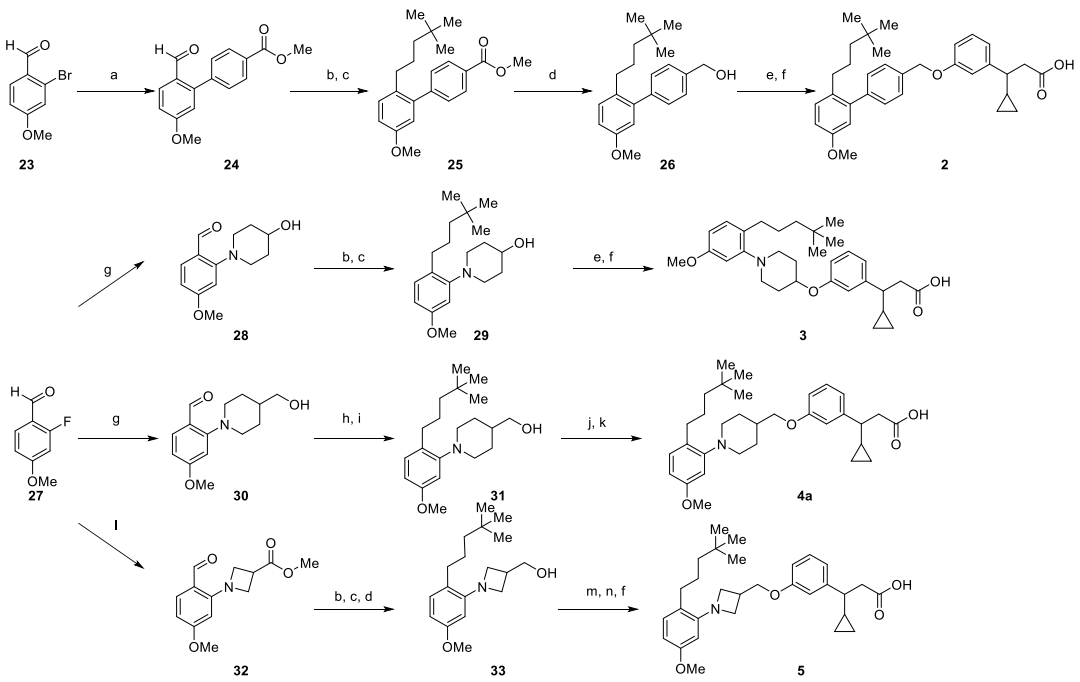
Scheme 1. Synthesis of 3-Substituted-3-(3-hydroxyphenyl)propionate[a]



[a]Reagents and conditions: (a) Meldrum's acid, water, r.t., 97%; (b) cyclopropylmagnesium bromide, THF, −10 °C to r.t., 93%; (c) (i) DMF, water, 90 °C, 92%; (ii) H_2SO_4 (cat), MeOH, 70 °C, 82% (for **11a**); (d) DMF, EtOH, 100 °C, 54% (for **11b**); (e) *n*-BuLi, diisopropylamine, THF, ethyl acetate, −78 °C; (f) iodomethane, silver carbonate, toluene, 100 °C, 69% (for **14a**); (g) iodoethane, silver carbonate, toluene, 100 °C, 44% (for **14b**); (h) H_2 (1 atm), 10% Pd on carbon, EtOH, r.t., 69−77%; (i) 2-(2-tetrahydro-2*H*-pyranoxy)phenylmagnesium bromide, THF, −78 °C; (j) 2-(diethoxyphosphoryl) acetate, NaH, THF, 0−50 °C; (k) zinc (powder), AcOH, 50 °C, 5% over 3 steps; (l) H_2 (1 atm), 10% Pd on carbon, EtOH, r.t., 97%; (m) (carbethoxymethylene)triphenylphosphorane, THF, 0 °C to r.t., 72%; (n) 3-(benzyloxy)phenylboronic acid, $Rh_2Cl_2(cod)_2$, KOH, dioxane, 100 °C, quant; (o) H_2 (1 atm), 10% Pd on carbon, EtOH, r.t., 87%.

Scheme 2. Synthesis of Derivatives with a Variety of Linkers[a]



[a]Reagents and conditions: (a) 4-(methoxycarbonyl)benzeneboronic acid, $Pd(PPh_3)_4$, 2 M Na_2CO_3 aq, DME, 130 °C, microwave, 99%; (b) (3,3-dimethylbutyl)triphenylphosphonium tosylate (for **25**, **29**, **33**), *t*-BuOK, THF, 50 °C; (c) 10% Pd on carbon, MeOH, H_2, r.t., 15−36% over 2 steps; (d) $LiAlH_4$, THF, 0 °C, 35−56%; (e) **11a**, DEAD, PPh_3, THF, r.t., 74%; (f) 1 M NaOH aq, MeOH, THF, r.t., 95% (g) 4-hydroxy piperidine (for **28**), 4-piperidinemethanol (for **30**), Cs_2CO_3, TBAI, DMF, 100−110 °C, 42−78%; (h) (3,3-dimethylbutyl)triphenylphosphonium bromide (for **31**), *n*-BuLi, THF, −78 °C, 53%, (i) 10% Pd on carbon, EtOH, H_2, r.t., 98% (j) **11b**, cyanomethylenetributylphosphorane, toluene, 100 °C; (k) 2 M NaOH, EtOH, THF, 80 °C, 82% over 2 steps; (l) (i) methyl azetidine-3-carboxylate hydrochloride, Cs_2CO_3, TBAI, DMSO, 120 °C; (ii) MeI, K_2CO_3, DMF, r.t., 41% over 2 steps; (m) mesyl chloride, TEA, THF, r.t.; (n) **11a**, K_2CO_3, DMF, 100 °C, 30%.

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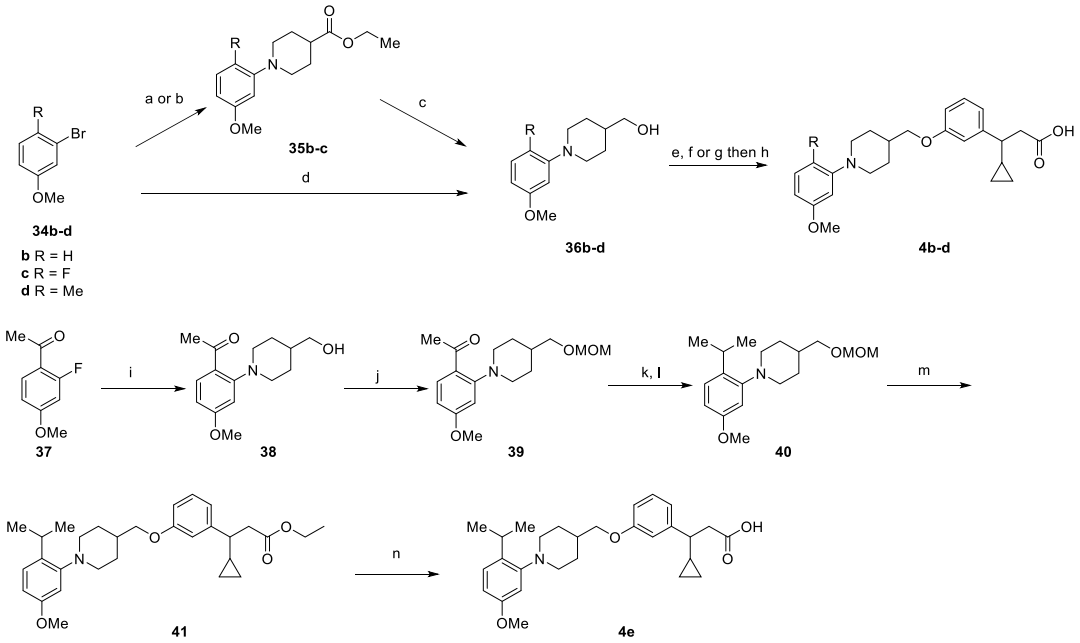
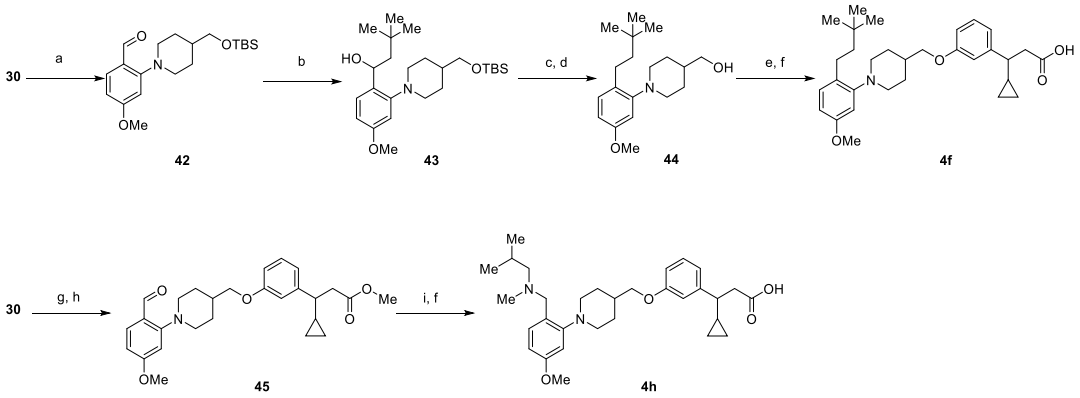
Scheme 3. Synthesis of Phenylpiperidine Derivatives with Small Substituents[a]



[a]Reagents and conditions: (a) ethyl isonipecotate, $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 100 °C, 67% (for **35b**); (b) ethyl isonipecotate, $Pd_2(dba)_3$, BINAP, NaO^{t}Bu, toluene, 100 °C, 79% (for **35c**); (c) $LiAlH_4$, THF, 0 °C; (d) 4-piperidinemethanol, $Pd_2(dba)_3$, BINAP, NaO^{t}Bu, toluene, 100 °C, 33% (for **36d**); (e) **11b**, DIAD, PPh_3, THF, r.t., 18% over 2 steps (for **4b**); (f) **11b**, ADDP, PBu_3, THF, 0 °C to r.t., 34% over 2 steps (for **4c**); (g) **11b**, cyanomethylenetributylphosphorane, toluene, 100 °C, quant (for **4d**); (h) 1 M NaOH aq, THF, MeOH or EtOH, r.t., 85−89%; (i) 4-piperidinemethanol, K_2CO_3, DMSO, 130 °C, 84%; (j) MOMCl, ^{i}Pr$_2$EtN, THF, r.t., quant; (k) *t*-BuOK, methyltriphenylphosphonium bromide, THF, 50 °C, 79%; (l) H_2 (1 atm), 10% Pd on carbon, EtOAc, r.t., 93%; (m) (i) HCl, MeOH, 60 °C; (ii) **11b**, cyanomethylenetributylphosphorane, toluene, 100 °C, 80% over 2 steps; (n) 1 M NaOH aq, THF, EtOH, 50 °C, 38%.

Scheme 4. Synthesis of Phenylpiperidine Derivatives with Bulky Substituents[a]



[a]Reagents and conditions: (a) TBSCl, imidazole, DMF, 0 °C, 81%; (b) neopentylmagnesium chloride, THF, r.t., 73%; (c) $SOCl_2$, toluene, r.t., 95%; (d) H_2 (1 atm), 10% Pd on carbon, MeOH, r.t., 88%; (e) **11a**, ADDP, PBu_3, THF, 0 °C to r.t., 16%; (f) 1 M NaOH aq, THF, MeOH, r.t., 74−82%; (g) methane sulfonyl chloride, TEA, THF, r.t.; (h) **11a**, NaH, DMF, 100 °C, 64% over 2 steps; (i) *N*-methylisobutylamine, $NaBH(OAc)_3$, THF, r.t., 59%.

through 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo-[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) activation or acyl chlorination using chloro-*N*,*N*,2-trimethyl-1-propen-1-amine.

The convergent synthesis routes of **7a−d** with derivatization on the *β*-position to the propionic acid and **7e−f** with the replacement of the C-ring (Figure 3) with a pyridine ring are depicted in Schemes 7 and 8. **56** was obtained via the generation of acyl chloride, followed by S_NAr using 4-piperidinemethanol to afford **57**. The resulting **57** was converted to target **7a−d** by the Mitsunobu reaction and hydrolysis of the ester. For replacement of the C-ring, the reaction of cyclopropylmagnesium bromide with aldehydes **58a** and **58b** yielded alcohols **59a** and **59b**. The obtained alcohols were subjected to oxidation, followed by the HWE reaction and reduction of olefin using zinc to furnish **62a** and **62b**, which were treated with pyridinium hydrochloride to deliver the key intermediate **63a** and **63b**. The Mitsunobu reaction of phenol **63a** and **63b** with alcohol **57**, followed by ester hydrolysis yielded **7a−7f**. The chiral (***S***)-**7f** and (***R***)-**7f** were prepared by optical resolution using the chiral column. The configuration is discussed in Scheme 9 (vide infra).

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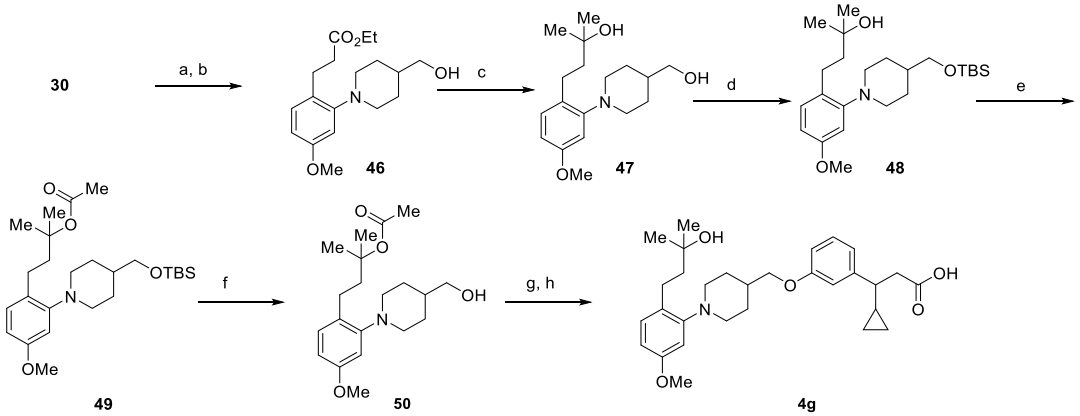
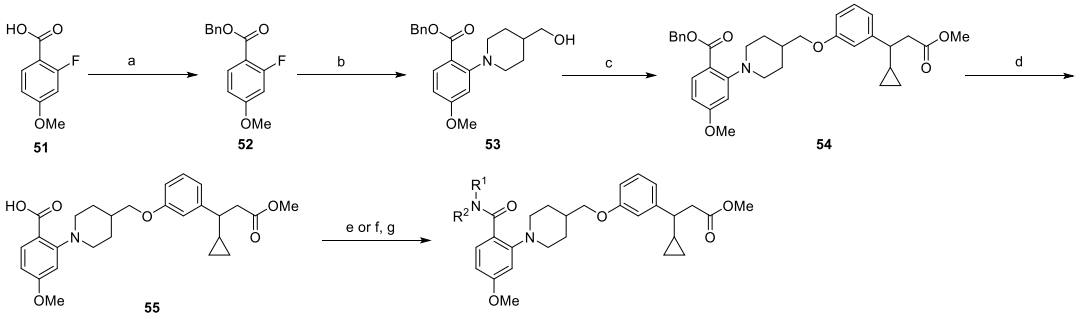
Scheme 5. Synthesis of a Phenylpiperidine Derivative with a Bulky Substituent[a]



[a]Reagents and conditions: (a) (carbethoxymethylene)triphenylphosphorane, toluene, r.t.; (b) CuCl, NaO^{t}Bu, BINAP, *t*-BuOH, PMHS, r.t., 24% over 2 steps; (c) methyl magnesium chloride, THF, 0 °C to r.t., 56%; (d) TBSCl, imidazole, DMF, 0 °C, 81%; (e) Ac_2O, TEA, DMAP, THF, 60 °C; (f) TBAF, THF, 60 °C, 76% over 2 steps; (g) **11b**, cyanomethylenetributylphosphorane, toluene, 100 °C, 76%; (h) 1 M NaOH aq, THF, MeOH, r.t., 85%.

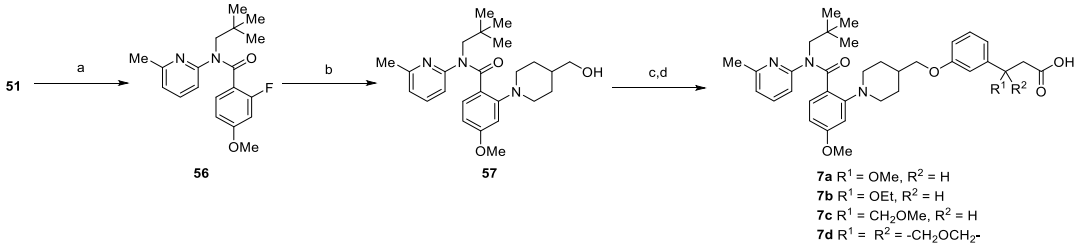
Scheme 6. Synthesis of Phenylpiperidine Derivatives with Amide Substituents[a]



6a R_1 = Me, R_2 = $CH_2C(CH_3)_3$
6b R_1 = Me, R_2 = Ph
6c R_1 = Me, R_2 = 2-Py
6d R_1 = ^{t}Bu, R_2 = 2-Py
6e R_1 = $CH_2C(CH_3)_3$, R_2 = 2-Py
6f R_1 = $CH_2C(CN)(CH_3)_2$, R_2 = 2-Py
6g R_1 = $CH_2C(OMe)(CH_3)_2$, R_2 = 2-Py
6h R_1 = $CH_2C(CH_3)_3$, R_2 = 6-Me-2-Py

[a]Reagents and conditions: (a) benzyl bromide, K_2CO_3, DMF, r.t., 95%; (b) 4-piperidinemethanol, Cs_2CO_3, TBAI, DMF, 100 °C, 59%; (c) **11b**, cyanomethylenetributylphosphorane, toluene, 100 °C, 90%; (d) H_2, 10% Pd on carbon, EtOH, THF using H-Cube, r.t., 93%; (e) R^1R^2NH, HATU, DIPEA, DMF, r.t., quant (for **6a**, **6c**) (f) R^1R^2NH, 1-chloro-*N*,*N*,2-trimethyl-1-propen-1-amine, Et_3N, toluene, 100 °C (for **6b**, **6d**−**6h**); (g) 1 M NaOH aq, THF, MeOH or EtOH, r.t., 53%-quant.

Scheme 7. Synthesis of 2-Carbamoylphenyl Piperidine with 3-Substituted-3-(pyridin-4-yl)propionic Acid[a]



7a R^1 = OMe, R^2 = H
7b R^1 = OEt, R^2 = H
7c R^1 = CH_2OMe, R^2 = H
7d R^1 = R^2 = $-CH_2OCH_2-$

[a]Reagents and conditions: (a) 6-methyl-*N*-neopentylpyridine-2-amine, oxalyl chloride, DMF, Et_3N, THF, r.t., 91%; (b) 4-piperidinemethanol, Cs_2CO_3, TBAI, DMF, 120 °C, 40%; (c) **11a** or **11b**, cyanomethylenetributylphosphorane, toluene, 100 °C; (d) 1 M NaOH aq, THF, MeOH, r.t., 55−83% over 2 steps.

RESULTS AND DISCUSSION

The newly synthesized compounds were initially evaluated for human GPR40 agonist activity with an increase in intracellular Ca^{2+} concentration in CHO cells expressing human GPR40 as an index. Compound **4a** exhibited potent agonistic activity in CHO cells with a relatively low expression of GPR40 (clone #2) and an EC_{50} value of 11 nM. However, compound **4a** exhibited cytotoxicity potential as evidenced by both decreased

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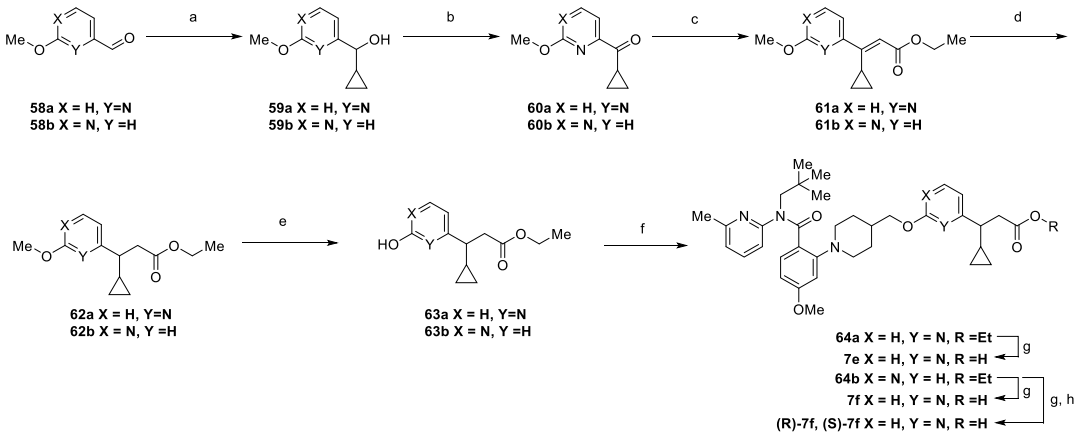
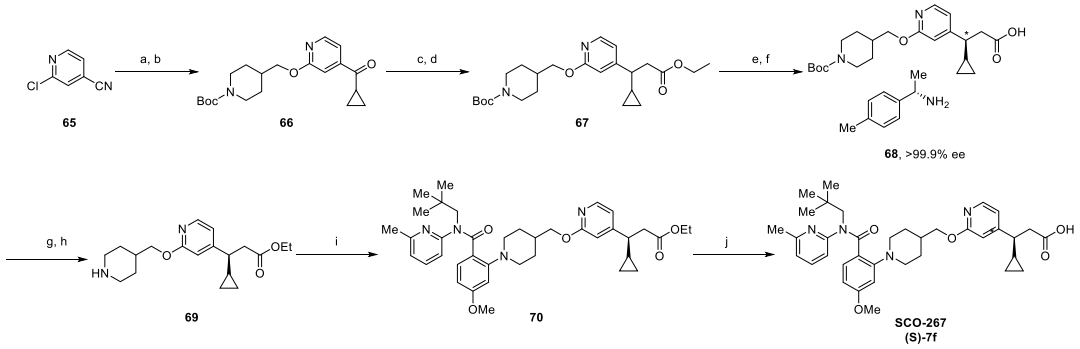
Scheme 8. Synthesis of 2-Carbamoylphenyl Piperidine with 3-Cyclopropyl-3-(pyridin-4-yl) Propionic Acid[a]



[a]Reagents and conditions: (a) cyclopropylmagnesium bromide, THF, 0 °C; (b) sulfur trioxide pyridine complex, TEA, DMSO, r.t.; (c) ethyl diethylphosphonoacetate, NaH, THF, 0 °C to r.t.; (d) zinc (powder), AcOH, r.t., 74% over 4 steps (for **62a**), 53% (for **62b**); (e) pyridinium hydrochloride, DMF, 120−130 °C, 71−92%; (f) **11a** or **11b**, cyanomethylenetributylphosphorane, toluene, 100 °C, 59−84%; (g) 1 M NaOH aq, THF, MeOH, r.t., 79−84%; (h) CHIRALPAK AD-H SFC separation, CO_2/2-propanol (3/2, v/v), 41%, >99.9% ee as the faster eluting compound (AD-H), 39%, 97% ee as the slower eluting compound (AD-H).

Scheme 9. Chiral Synthesis of Compound (*S*)-7f (SCO-267) via Diastereomeric Salt Formation[a]



[a]Reagents and conditions: (a) NaH, 1-Boc-4-piperidinemethanol, DMF, 0 °C, 74%; (b) cyclopropyl magnesium bromide, THF, 0 °C; (c) ethyl diethylphosphonoacetate, NaH, THF, 0 °C; (d) zinc (powder), AcOH, 90 °C; (e) 1 M NaOH aq, THF, EtOH, 0 °C; (f) (*S*)-4-methyl-methylbenzylamine, EtOH and then recrystallization twice; (g) 1 M HCl in EtOAc, 0 °C; (h) EtOH, H_2SO_4, 80 °C, (i) **56**, Cs_2CO_3, neat, 130 °C; (j) 1 M NaOH aq, THF, EtOH, 60 °C.

intracellular ATP content and Caspase induction activity, as shown in Table 1, because of its highly lipophilic properties, which may be reduced by a modification of the lipophilic group.[25] In an initial attempt to decrease the lipophilicity and improve the physicochemical properties of **4a**, we verified the tolerability of the substituent at the ortho-position relative to the piperidine nitrogen attachment. As shown in Table 1, the replacement of the long alkyl chain with a hydrogen resulted in a >250-fold decrease in GPR40 agonistic activity, despite the reduction in cytotoxicity potential (**4b**). Meanwhile, the introduction of a fluorine atom, methyl group, or iso-propyl group into **4b** resulted in tolerable potency (**4c**, **4d**, and **4e** vs **4b**). This result suggests that the lipophilic moiety in this position is essential for potent GPR40 agonistic activity. Further elongation of the alkyl group produced an analogue **4f** with a 3,3-dimethyl butyl moiety; there was a great impact on the GPR40 agonistic activity, similar to that seen in compound **4a**, suggesting that the lipophilic pocket may be located two or three carbons away from the A ring. Although the more lipophilic compounds increased the agonistic properties of GRP40, they were accompanied by an increase in cytotoxic potential. To reduce lipophilicity of compound **4f**, we replaced the terminal methyl moiety of **4f** with a hydroxyl group, leading to the mitigation of the cytotoxic potential and >10-fold reduction in agonistic activity (**4g**). In our search for acceptable polar functions, we briefly investigated the effects of introducing a heteroatom near the benzene ring on agonistic activity. We introduced a cationic amine moiety and a hydrophilic amide moiety. The amine derivative **4h** with the iso-butyl group exhibited a robust loss in agonistic activity compared to **4f**. In contrast, incorporation of an amide moiety resulted in only a threefold decline in the agonistic activity of **4f** with a robust reduction in cytotoxic potential (**6a**). Through this investigation, we found that the binding pocket encompassing the alkyl chain of **6a** favors hydrophobicity and the hydrophilic amide moiety is allowed near ring A of **6a**.

As a result of the retained agonistic activity of compound **6a** with less cytotoxic potential compared to that of alkyl derivatives (**4a** and **4f**), we obtained a new lead compound for further optimization. We replaced the *tert*-butyl group of compound **6a** with a small lipophilic and expandable benzene ring, which led to a similar agonistic activity. Consequently, the pyridine ring, characterized as a more polar substituent, retained the agonistic activity despite the reduction in

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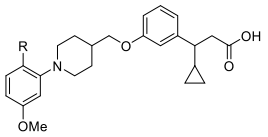
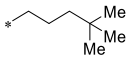
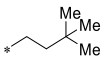
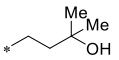
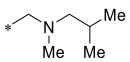
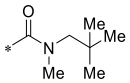
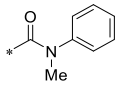
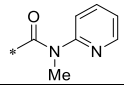
Table 1. Effect of Substituents on the Phenyl Group on GPR40 Agonistic Activity



Compound	R	hEC_{50} [a] (nM)	E_{max} [c]	clogP [d]	ATP [e]	Caspase [f]
4a		11±4.6	106%	8.4	0.1	26
4b		91% at 10 μM [b] 8% at 1 μM	-	5.0	92.0	-1.1
4c		670 [b]	114%	5.3	72.7	-1.7
4d		270 [b]	113%	5.5	67.4	8.3
4e		120±10	117%	6.4	0.1	43.4
4f		34 [b]	110%	7.9	0.1	67.3
4g		970±740	109%	5.2	76.6	0.1
4h		1000 [b]	110%	4.0	80.7	-1.1
6a		100±73	107%	5.6	82.2	6.6
6b		140±9.5	101%	5.5	79.3	2.8
6c		180±81	105%	4.0	83.6	-1.1

[a]Data are presented as means values with the standard deviation from more than two independent experiments in duplicate. [b]Values are from a single experiment in duplicate. [c]% Compared to the reference full agonist. [d]The clog *P* values were calculated using Daylight. [e]Intracellular ATP content (%) at 30 μM relative to the untreated control. Lowered ATP content relative to the untreated control (100%) indicates a decrease in cell viability. Data were obtained from a single experiment in triplicate. [f]Caspase-3/7 activity was measured using a Caspase-GloTM 3/7 assay kit (Promega) according to the manufacturer's instruction to confirm the scientific rigor of cytotoxicity in an orthogonal assay. Caspase-3/7 activity (%) at 30 μM relative to the response to the reference compound (staurosporine) was set to 100%. Data were obtained from a single experiment in triplicate.

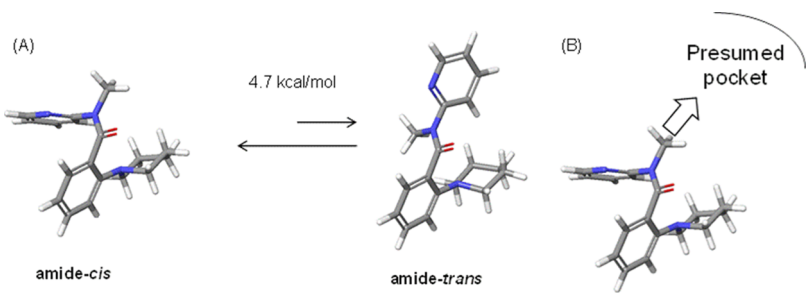


Figure 6. (A) Conformational preference of *N*-methylbenzanilide. (B) Elongation of the alkyl chain of *N*-methylbenzanilide toward the presumed lipophilic pocket that the *t*-butyl group of compound **4a** occupied.

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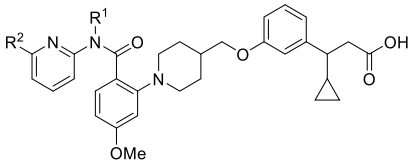
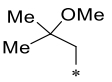
Table 2. Effect of Substituents on the Amide Group on GPR40 Agonistic Activity



Compound	R^1	R^2	hEC_{50} [a] (nM)	E_{max} [c]	clogP [d]
6d		H	29±20	107%	5.5
6e		H	26±6.3	110%	5.9
6f		H	160 [b]	108%	4.6
6g		H	100 [b]	105%	5.0
6h		Me	17±7.9	109%	6.4

[a]Data are presented as mean values with the standard deviation from more than two independent experiments in duplicate. [b]Values are from a single experiment in duplicate. [c]% Compared to the reference full agonist. [d]The clog *P* values were calculated using Daylight.

lipophilicity (clog *P* values of **6b** and **6c** are 5.5 and 4.0, respectively). Several studies have reported that the structures of the compounds containing the *N*-methyl-*N*-(2-phenyl) or *N*-methyl-*N*-(2-pyridyl) benzamide moiety place the aromatic rings in cis conformation to each other, and the methyl substituents on nitrogen were cis to the carbonyl group.[26−29] This implies that the methyl groups of compounds **6b** and **6c** are directed to and partially occupy the presumed lipophilic pocket because of the structural conformation of cis-preferential aromatic amides. Therefore, we hypothesized that incorporation of longer and bulky alkyl chains on the nitrogen group of the amide moiety instead of the methyl group could enhance the agonistic activity by effectively occupying the presumed lipophilic pocket (Figure 6).

As expected, the incorporation of iso-butyl dramatically impacted agonistic activity (**6c** vs **6d** in Table 2); moreover, further incorporation of the methyl group on the branched position of the iso-butyl group resulted in a slight enhancement of potency with good reproducibility (compound **6e**). However, the incorporation of polar substituents such as the cyano group and methoxy group negatively affected GPR40 potency (**6f** and **6g**). We verified that these SAR data are comparable with the results discussed in Table 1.

Based on the abovementioned findings, we have explored the optimal substituents on the pyridine ring. Introduction of a methyl group into the 6-position on the pyridine ring led to a discovery of **6h** with a good balance between agonistic activity and lipophilicity. From the lead identification study described thus far, (2,2-dimethylpropyl)(6-methylpyridin-2-yl)-carbamoylphenyl **6h** was identified as a potent GPR40 agonist possessing an amide moiety. We selected **6h** for further optimization to reduce lipophilicity (clog *P*: 6.4).

With (2,2-dimethylpropyl)(6-methylpyridin-2-yl)-carbamoylphenyl-based **6h**, we optimized the *β*-position of the propionic acid moiety and the C ring (Table 3). Replacement of the cyclopropyl group with a methoxy group reduced the lipophilicity of the molecule with a modest decline in agonistic activity. As with **7a**, other compounds such as ethoxy **7b**, methoxy methyl **7c**, and 3-oxetanyl **7d** derivatives were not in the desired potency range. This implies that cyclopropyl is an appropriate substituent in terms of potency. As for optimization of the C ring, we selected the 2-alkoxy substitution pattern on the pyridine ring because, as observed in our previous study, basic property is not tolerable around the C ring. As a result, in both 2-alkoxy patterns, 2,6-disubstituted pyridine derivative **7e** exhibited decreased agonistic activity with a lower clog *P* value compared to **6h**. Conversely, the 2,4-disubstituted pyridine derivative **7f** retained agonistic activity along with decreased lipophilicity. To obtain a better understanding of the difference, we calculated energy barriers for 2-alkoxy pyridine using Maestro, as illustrated in Figure 7. As for the 2,6-disubstituted pyridine derivative, **7e**-*anti* was found to be more stable than 7e-*syn*. However, the syn-form **7f**-*syn* is more stable than the **7f**-*anti*.[30] We assumed that the repulsion of lone pairs on the oxygen atom and the pyridine nitrogen could put the different spatial arrangement of whole structure conformation of **7f**-*syn*, which could be closer to the active conformer of **6h**, and this substitution pattern was deemed to be optimal in this series.

From an optimization study to enhance the potency of the lead compound **6a** discussed in Table 1, we successfully discovered **7f** as a racemate. To determine a eutomer conformation, we synthesized an enantiomer of **7f** via diastereomeric salt formation shown in Scheme 9. The synthesis was initiated from the alkoxylation of the 2-position

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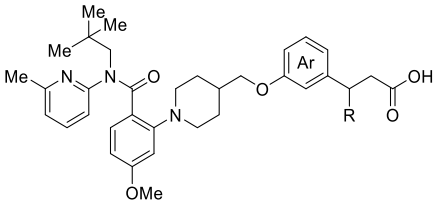
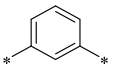
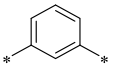
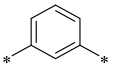
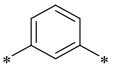
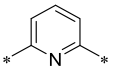
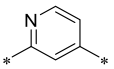
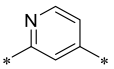
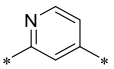
Table 3. Effect of Variation of β-Position and Polar Aromatic Ring of the Phenyl Propionic Acidic Moiety



Compound	Ar	R	hEC$_{50}$ [a] (nM)	E$_{max}$ [c]	clogP [d]
7a			62 [b]	109%	5.1
7b			74 [b]	104%	5.5
7c			120 [b]	104%	5.3
7d			840 [b]	115%	5.3
7e			39% at 10 μM [b]	-	5.8
7f			17±12	112%	5.8
SCO-267 (*S*)-7f			12±3.5	108%	5.8
(*R*)-7f			84±5.6	109%	5.8

[a]Data are presented as mean values with the standard deviation from more than two independent experiments in duplicate. [b]Values are from a single experiment in duplicate. [c]% Compared to the reference full agonist. [d]The clog *P* values were calculated using Daylight.

of 2-chloro-4-cyanopyridine (**65**) with sodium hydride, followed by the nucleophilic addition reaction with cyclopropylmagnesium bromide to produce heteroaryl alkyl ketone **66**. To prepare 3-cyclopropyl-propanoic acid **67**, the conventional HWE reaction of heteroaryl alkyl ketone **66** with ethyl diethylphosphonoacetate in the presence of sodium hydride gave the corresponding α,β-unsaturated ester, followed by reduction of olefin with the zinc metal under acidic conditions and hydrolysis of the ethyl ester. Diastereomeric salt formation of the corresponding carboxylic acid derivative with (*S*)-4-methyl-methylbenzylamine and recrystallization twice produced optically active **68** (>99.9% ee). The absolute configuration of **68** was determined by X-ray crystallographic analysis of the reference to the known configuration of (1*S*)-1-(4-methylphenyl)ethan-1-aminium. The chiral **68** was converted to compound **69** by a two-step sequence consisting of desalination and subsequent esterification. Compound **69** was converted to the key intermediate **70** through S_NAr substitution with **56**, which was then subjected to the final chiral product **7f** by a hydrolysis reaction. X-ray crystallographic analysis of the final chiral product **7f** provided further confirmation of the structure (Figure 8). We concluded (***S***)-**7f** (**SCO-267**) as a eutomer based on its agonistic activity with an EC$_{50}$ value of 12 nM. The *N*-(2,2-dimethylpropyl)-*N*-(2-pyridyl) amide moiety was in the geometrically cis conformation in the literature,[26−29] and the absolute configuration of compound **7f** was retained.

Based on these results, **SCO-267** was selected for further evaluation. **SCO-267** showed a good cytotoxicity profile (ATP: 92.1% at 30 μM) and did not display phospholipidosis potential in an in vitro assay and hERG inhibition potential in a patch clamp test (IC$_{50}$ > 10 μM). The oral bioavailability (*F*) of **SCO-267** in rats and mice was 16 and 26%, respectively (Table 4).

To evaluate their pharmacological effect on hormone secretion and glucose tolerance, **SCO-267** (0.1, 0.3, and 1 mg/kg) and sitagliptin (10 mg/kg) were orally dosed to male N-STZ-1.5 rats, a diabetic model displaying impairments in

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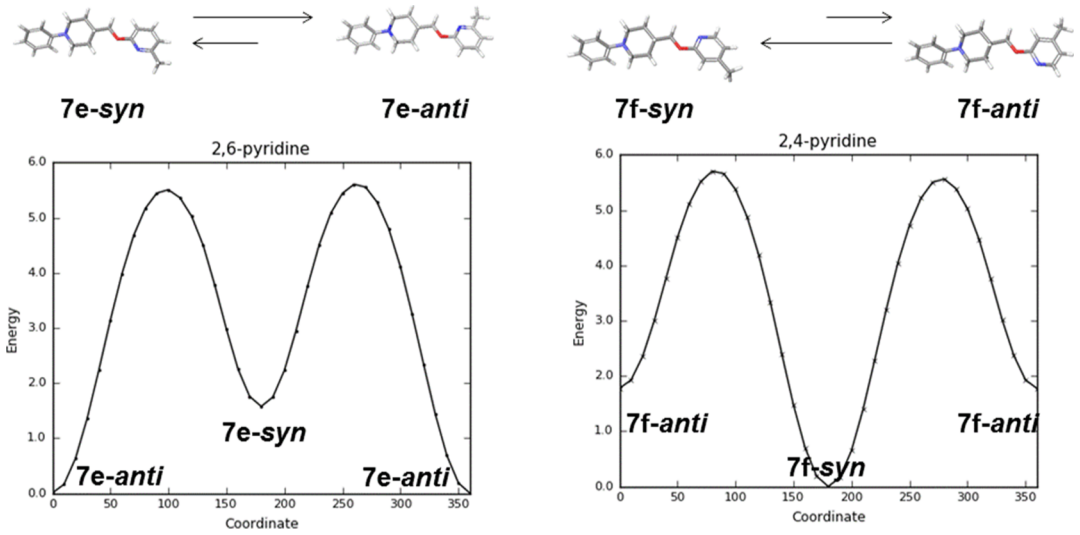

Figure 7. Conformational preference of the alkoxy moiety of 2,6-pyridine and 2,4-pyridine derivatives.

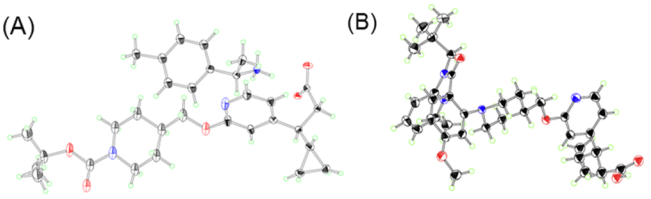

Figure 8. ORTEP diagram of (A) compound **68**, thermal ellipsoids are drawn at 30% probability. The minor disorder component is omitted for clarity, (B) **SCO-267**, thermal ellipsoids are drawn at 50% probability.

insulin secretion and action. A single dose of **SCO-267** stimulated insulin secretion and GLP-1 release and ameliorated glucose tolerance in male N-STZ-1.5 rats, whereas the GPR40 partial agonist TAK-875 provided almost no effect on GLP-1 secretion.[31] Sitagliptin elevated insulin secretion and ameliorated glucose tolerance. The efficacy of **SCO-267** on insulin secretion, GLP-1 release, and glucose tolerance was much better than that of sitagliptin. In addition, **SCO-267**-treated male N-STZ-1.5 rats showed better glucose tolerance than normal rats (Figure 9). These findings confirmed that our optimization strategy successfully produced a GPR40 full agonist that results in insulin and GLP-1 secretions. Consequently, these in vivo results suggest that our lead optimization strategy is an effective approach to discover novel GPR40 full agonists with enhanced glucose-lowering properties by incorporating an amide group as a linker in the left-hand side. We recently reported that 1 mg/kg **SCO-267** was more efficacious in ameliorating glucose tolerance than 10 mg/kg TAK-875 at the lower plasma exposure without a decrease in insulin secretion in a 2-week-dosing study of N-STZ-1.5 rats with diabetes (C_{max} and AUC_{0-24h} are as follows: 139 ng/mL vs 39.8 μg/mL and 626 ng·h/mL vs 255 μg·h/mL, respectively).[32] **SCO-267** was also efficacious in reducing body weight in a 2-week repeated-dosing study of diet-induced obese rats. These studies demonstrated the efficacy of **SCO-267** in ameliorating glycemic control and reducing body weight as a novel therapeutic drug for treating diabetes and obesity. Considering the effective exposure of 50 mg TAK-875 in patients (C_{max} = 5.3 μg/mL; AUC_{0-24h} = 100.3 μg·h/mL), the lower plasma exposure of **SCO-267** may be a safety advantage compared with exposure of TAK-875, which was terminated in phase 3 because of the unfavorable effects on the liver.[31] A phase I study of **SCO-267**, a first-in-class oral GPR40 full agonist, has been initiated in healthy adults and people with impaired glucose tolerance.

CONCLUSIONS

We identified a novel series of carbamoylphenyl piperidine derivatives as potent and orally bioavailable full agonists of GPR40. Starting with alkyl derivatives **4**, we explored an optimal linker of the hydrophobic group as a key pharmacophoric motif that showed a sufficient balance between potency and lipophilicity. Incorporation of a polar amide linker reduced the lipophilicity without a loss in agonistic activity. Consequently, *N*-methyl-*N*-(2-pyridyl) amide derivative **6c** was identified as an attractive lead compound with potent GPR40 agonistic activity and a chemically expandable motif. Subsequent optimization of substituents on the amide moiety was conducted to enhance agonistic activity by extension of the alkyl chain on the amide

Table 4. Pharmacokinetic Parameters of SCO-267 in Rats and Mice[a]

			intravenous (0.1 mg/kg)		oral (1 mg/kg)		
compound	species	F[b] (%)	CL_{total}[c] (mL/h/kg)	V_{ss}[d] (mL/kg)	C_{max}[e] (ng/mL)	AUC_{0-8h}[f] (ng·h/mL)	MRT[g] (h)
SCO-267	rats	16	1478	3094	19.9	126.6	4.1
	mice	26	2584	1349	33.2	98.7	2.3

[a]The pharmacokinetic parameters of **SCO-267** in 8 week-old male SD rats and 8 week-old male ICR mice after intravenous and oral administrations are summarized. [b]Bioavailability. [c]Total body clearance. [d]Volume of distribution at steady state. [e]Maximal plasma concentration. [f]Area under the plasma concentration−time curve (0−8 h). [g]Mean residence time. The parameters represent mean (n = 3 for each group).

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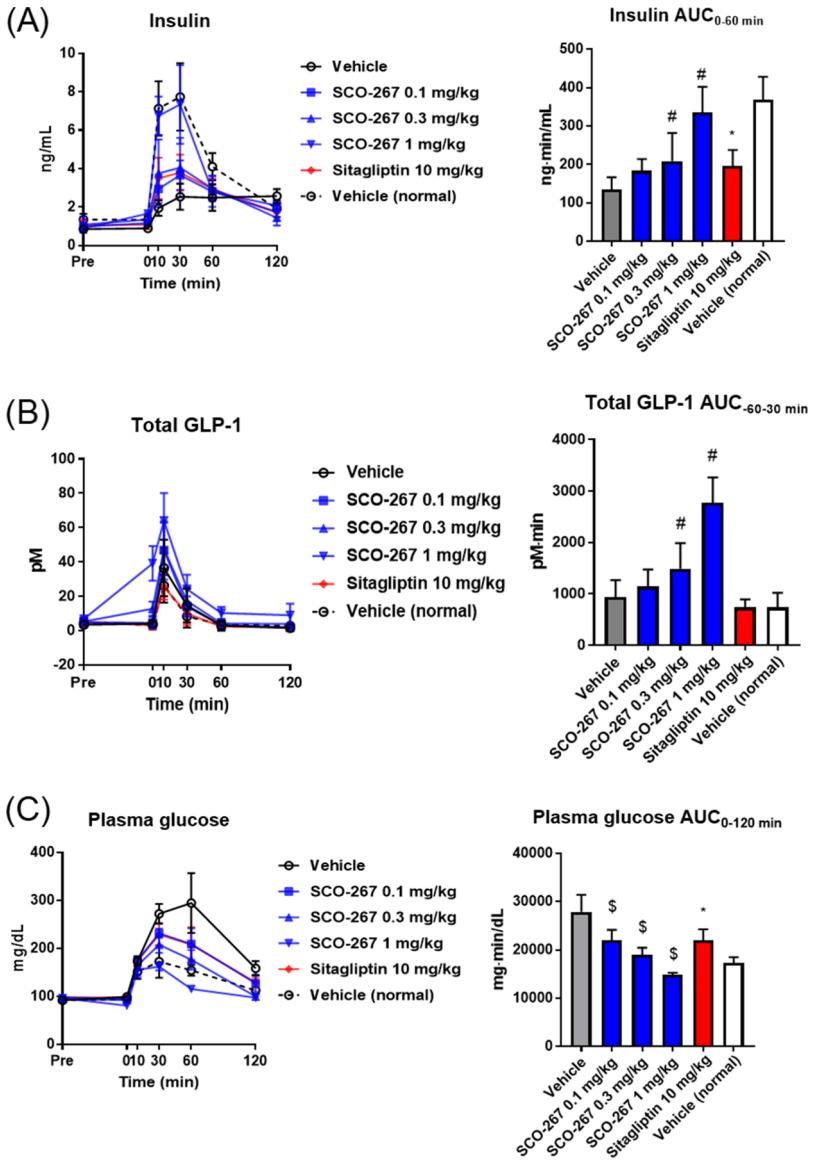

Figure 9. Effect of single administration of **SCO-267** and sitagliptin on hormone secretion and glucose tolerance in 26 week-old male diabetic N-STZ-1.5 rats. Plasma insulin (A), total GLP-1 (B), and glucose levels (C) in male N-STZ-1.5 rats. **SCO-267** elevated insulin levels, stimulated GLP-1 secretion, and ameliorated glucose tolerance. # 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).

moiety to the presumed lipophilic pocket, resulting in the identification of (3*S*)-3-cyclopropyl-3-(2-((1-(2-((2,2-dimethylpropyl)(6-methylpyridin-2-yl)carbamoyl)-5-methoxyphenyl)piperidin-4-yl)methoxy)pyridin-4-yl)-propanoic acid (**SCO-267**). **SCO-267** effectively stimulated insulin secretion and GLP-1 release and ameliorated glucose tolerance in male N-STZ-1.5 rats. These results indicate that our lead optimization strategy successfully produced potent, orally available, full agonists, and this series of GPR40 agonists may have potential in the treatment of diabetes and obesity.

■ EXPERIMENTAL SECTION

Chemistry General Method. Melting points were determined in open capillary tubes on a Büchi melting point apparatus B545 and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AVANCE III (300 MHz) or Bruker ADVANCE III plus (400 MHz) spectrometer. Chemical shifts for ^{1}H NMR are given in parts per million (ppm) downfield from tetramethylsilane (δ) as the internal standard in a deuterated solvent and coupling constants (J) are in hertz (Hz). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, dd = doublet of doublets, td = triplet of doublets, and bs = broad signal), and coupling constants. All solvents and reagents were obtained from commercial suppliers and used without further purification. Reaction progress was determined by thin layer chromatography (TLC) analysis on Merck silica gel plates $60F_{254}$. Silica gel column chromatography was performed on Purif-Pack (SI or NH, Shoko Scientific). Low-resolution mass spectra (MS) were acquired using an Agilent LC–MS system (Agilent1200SL/Agilent6130MS) or Shimadzu UFLC/MS (Prominence UFLC high pressure gradient system/LCMS-2020) operating in an electrospray ionization mode (ESI$^+$). The column used was an L-column 2 ODS (3.0 mm × 50 mm ID, 3 μm, CERI) with a temperature of 40 °C and a flow rate of 1.2 or 1.5 mL/min. Condition 1: mobile phases A and B under acidic conditions were 0.05% trifluoroacetic acid (TFA) in water and 0.05% TFA in MeCN, respectively. The ratio of mobile phase B was increased linearly from 5 to 90% over 0.9 min, 90% over

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the next 1.1 min. Condition 2: mobile phases A and B under neutral conditions were a mixture of 5 mM $AcONH_4$ and MeCN (9/1, v/v) and a mixture of 5 mM $AcONH_4$ and MeCN (1/9, v/v), respectively. The ratio of mobile phase B was increased linearly from 5 to 90% over 0.9 min, 90% over the next 1.1 min. Chemical intermediates were characterized by ^{1}H NMR or mass spectral data or both. Unless otherwise stated, the purities of the synthesized compounds for biological testing were >95% determined by elemental analyses within ±0.4% of the calculated values or analytical high-performance liquid chromatography (HPLC) or both (The purities of **7c** and **7d** were 92.6 and 92.7%, respectively). Analytical HPLC data were collected by HPLC with NQAD or Corona charged aerosol detector (CAD) or photodiode array detector. The column was a Capcell Pak C18AQ (50 mm × 3.0 mm ID, Shiseido, Japan) or L-column 2 ODS (30 mm × 2.0 mm ID, CERI, Japan) with a temperature of 50 °C and a flow rate of 0.5 mL/min. Mobile phases A and B were a mixture of 50 mM $AcONH_4$, water, and MeCN (1:8:1, v/v/v) and a mixture of 50 mM $AcONH_4$ and acetonitrile (1:9, v/v), respectively. The ratio of mobile phase B was increased linearly from 5 to 95% over 3 min, 95% over the next 1 min. Mobile phases A and B under acidic conditions were a mixture of 0.2% formic acid in 10 mM ammonium formate and 0.2% formic acid in MeCN, respectively. The ratio of mobile phase B was increased linearly from 14 to 86% over 3 min, 86% over the next 1 min. Preparative HPLC was performed on a Gilson Preparative HPLC system using a YMC-Actus Triart C18 column (150 mm × 20 mm ID, 5 μm, YMC). Condition 1: mobile phases A and B under acidic conditions were 0.1% TFA in water and 0.1% TFA in MeCN, respectively. Condition 2: mobile phases A and B under neutral conditions were 10 mM ammonium bicarbonate and MeCN, respectively. The ratio of mobile phase B was increased linearly in 5−10 min. All commercially available solvents and reagents were used without further purification. Yields were not optimized.

*3-Cyclopropyl-3-(3-((2′-(4,4-dimethylpentyl)-5′-methoxy-[1,1′-biphenyl]-4-yl)methoxy)phenyl)propanoic Acid (**2**).* To a solution of (2′-(4,4-dimethylpentyl)-5′-methoxy-[1,1′-biphenyl]-4-yl)methanol **26** (200 mg, 0.64 mmol), methyl 3-cyclopropyl-3-(3-hydroxyphenyl)-propanoate **11a** (155 mg, 0.70 mmol), and PPh_3 (504 mg, 1.92 mmol) in THF (dry) (5 mL) was added DEAD (0.873 mL, 1.92 mmol) under Ar and stirred for 30 min. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−25% EtOAc in hexane) to give methyl 3-cyclopropyl-3-(3-((2′-(4,4-dimethylpentyl)-5′-methoxy-[1,1′-biphenyl]-4-yl)methoxy)phenyl)propanoate (244 mg, 0.474 mmol, 74.1%) as a colorless oil. This product was subjected to a further step. A mixture of the obtained methyl ester (244 mg) and 1 M NaOH aq (2 mL) in MeOH and THF (1/1) was stirred at room temperature for 1 h. The mixture was neutralized with 1 N HCl and extracted with EtOAc three times. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−50% EtOAc in hexane) to give the title compound (226 mg, 96%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm −0.18 to −0.07 (1H, m), −0.05−0.13 (2H, m), 0.19−0.32 (1H, m), 0.51 (9H, s), 0.74−0.82 (3H, m), 1.03−1.13 (2H, m), 1.99−2.08 (1H, m), 2.21 (2H, br t, J = 7.7 Hz), 2.34−2.47 (2H, m), 3.50 (3H, s), 4.88 (2H, s), 6.46 (1H, d, J = 2.5 Hz), 6.58−6.67 (3H, m), 6.70 (1H, s), 6.93−7.01 (2H, m), 7.08 (2H, d, J = 7.9 Hz), 7.27 (2H, d, J = 7.8 Hz), 11.77 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 4.1, 5.3, 17.2, 26.6, 29.3, 30.2, 33.1, 41.3, 43.9, 46.8, 55.3, 69.9, 112.5, 113.2, 114.3, 115.2, 120.0, 127.3, 129.3, 129.4, 130.1, 132.6, 135.6, 141.8, 142.4, 145.6, 157.3, 158.9, 177.5. MS (ESI/APCI): m/z 499.2 [M − 1] $C_{33}H_{40}O_4$: 1.3 H_2O/C, 75.63; H, 8.19; N, 0.00. Found: C, 75.43; H, 8.40; N, 0.00. HPLC purity 98.8%.

*3-Cyclopropyl-3-(3-((1-(2-(4,4-dimethylpentyl)-5-methoxyphenyl)piperidin-4-yl)oxy)phenyl)propanoic Acid (**3**).* To a solution of 1-(2-(4,4-dimethylpentyl)-5-methoxyphenyl)piperidin-4-ol **29** (150 mg, 0.49 mmol) and TEA (0.103 mL, 0.74 mmol) in THF (dry) (20 mL) was added MsCl (0.046 mL, 0.59 mmol) and stirred at r.t. for 30 min. The mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a pale-yellow oil. The residue was mixed with sodium phenoxide, which was prepared by the addition of NaH (60% oil dispersion, 29.5 mg, 0.74 mmol) to the phenol **11a** (108 mg, 0.49 mmol) in DMF (20 mL). The mixture was stirred at 100 °C for 15 h. The mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−10% EtOAc in hexane) to give methyl 3-cyclopropyl-3-(3-((1-(2-(4,4-dimethylpentyl)-5-methoxyphenyl)piperidin-4-yl)oxy)phenyl)-propanoate as a pale-yellow oil (75 mg, 0.18 mmol, 30%). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 0.17 (1H, dt, J = 9.3, 4.6 Hz), 0.26 (1H, dq, J = 9.2, 4.7 Hz), 0.36−0.50 (1H, m), 0.51−0.65 (1H, m), 0.88 (9H, s), 0.93−1.11 (1H, m), 1.20−1.31 (4H, m), 1.55−1.65 (2H, m), 1.84−2.02 (2H, m), 2.06−2.18 (2H, m), 2.29−2.41 (1H, m), 2.49−2.59 (2H, m), 2.66−2.85 (2H, m), 3.03−3.18 (2H, m), 3.61 (3H, s), 3.79 (3H, s), 4.42 (1H, dt, J = 7.8, 3.9 Hz), 6.59 (1H, dd, J = 8.4, 2.6 Hz), 6.68 (1H, d, J = 2.6 Hz), 6.75−6.86 (3H, m), 7.11 (1H, d, J = 8.4 Hz), 7.17−7.25 (1H, m). MS (ESI/APCI): m/z 508.2 [M + H]$^+$. Compound **3** was prepared from the obtained methyl ester in a manner similar to that described for compound **2** [purification: column chromatography (silica gel, eluted with 0−50% EtOAc in hexane)]. Colorless oil. (54.0 mg, 0.109 mmol, 74%). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 0.09−0.18 (1H, m), 0.20−0.27 (1H, m), 0.28−0.36 (1H, m), 0.40−0.54 (1H, m), 0.86 (9H, s), 1.18−1.25 (2H, m), 1.44−1.60 (2H, m), 1.76 (2H, d, J = 8.8 Hz), 2.05 (2H, br s), 2.18−2.33 (1H, m), 2.56−2.70 (2H, m), 2.79 (2H, t, J = 9.3 Hz), 2.99 (2H, d, J = 11.4 Hz), 3.71 (3H, s), 4.51 (1H, br s), 6.59 (1H, dd, J = 8.3, 2.4 Hz), 6.64 (1H, d, J = 2.3 Hz), 6.76−6.83 (2H, m), 6.87 (1H, s), 7.08 (1H, d, J = 8.4 Hz), 7.18 (1H, t, J = 7.8 Hz), 12.02 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 4.1, 5.3, 17.2, 26.0, 29.4, 30.4, 31.2, 31.8, 41.4, 44.5, 46.8, 50.3, 55.2, 72.7, 106.9, 108.1, 113.7, 115.5, 119.8, 129.4, 130.0, 130.4, 145.7, 152.9, 157.5, 158.2, 178.0. MS (ESI/APCI): m/z 494.2 [M + H]$^+$. $C_{31}H_{43}NO_4$: 0.1 H_2O: C, 75.15; H, 8.79; N, 2.83. Found: C, 75.23; H, 8.73; N, 2.72. HPLC purity 99.5%.

*3-Cyclopropyl-3-(3-((1-(2-(4,4-dimethylpentyl)-5-methoxyphenyl)piperidin-4-yl)methoxy)phenyl)propanoic Acid (**4a**).* Cyanomethylenetri-*n*-butylphosphorane (9.85 mL, 37.56 mmol) was added to a solution of (1-(2-(4,4-dimethylpentyl)-5-methoxyphenyl)piperidin-4-yl)methanol **31** (6 g, 18.78 mmol) and ethyl 3-cyclopropyl-3-(3-hydroxyphenyl)propanoate **11b** (4.40 g, 18.78 mmol) in toluene (50 mL) at room temperature. The mixture was stirred at 100 °C under N_2 for 30 min. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−15% EtOAc in hexane) to give a pale-brown oil. The obtained oil was dissolved in EtOH (50 mL) and NaOH was added (50 mL, 50.00 mmol). The mixture was stirred at 50 °C for 2 h. The mixture was neutralized with 1 N HCl and extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−25% EtOAc in hexane) to give the title compound (7.80 g, 15.36 mmol, 82%) as a white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 0.12 (1H, dd, J = 9.0, 4.0 Hz), 0.19−0.27 (1H, m), 0.28−0.39 (1H, m), 0.41−0.56 (1H, m), 0.86 (9H, s), 0.93−1.07 (1H, m), 1.13−1.27 (2H, m), 1.36−1.61 (4H, m), 1.87 (3H, d, J = 10.2 Hz), 2.17−2.30 (1H, m), 2.47−2.53 (2H, m), 2.55−2.72 (4H, m), 3.00 (2H, d, J = 11.3 Hz), 3.70 (3H, s), 3.87 (2H, d, J = 5.4 Hz), 6.57 (1H, dd, J = 8.3, 2.4 Hz), 6.62 (1H, d, J = 2.4 Hz), 6.72−6.87 (3H, m), 7.07 (1H, d, J = 8.4 Hz), 7.18 (1H, t, J = 7.9 Hz), 11.98 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 4.1, 5.3, 17.2, 26.0, 29.5, 29.9, 30.4, 31.2, 36.0, 41.1, 44.5, 46.9, 53.0, 55.2, 72.6, 106.9, 107.7, 112.1, 113.8, 119.6, 129.4, 129.9, 130.4, 145.5, 153.4, 158.2, 159.2, 176.7. MS (ESI/APCI): m/z 508.4 [M + H]$^+$. $C_{32}H_{45}NO_4$: 0.1 H_2O: C, 75.43; H, 8.94; N, 2.75. Found: C, 75.68; H, 8.78; N, 2.56. HPLC purity 98.6%.

*3-Cyclopropyl-3-(3-((1-(2-(4,4-dimethylpentyl)-5-methoxyphenyl)azetidin-3-yl)methoxy)phenyl)propanoic Acid (**5**).*

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To a solution of (1-(2-(4,4-dimethylpentyl)-5-methoxyphenyl)-azetidin-3-yl)methanol **33** (100 mg, 0.34 mmol) and TEA (0.143 mL, 1.03 mmol) in THF (dry) (5 mL) was added MsCl (0.064 mL, 0.82 mmol) and stirred at r.t. for 30 min. The mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a pale-yellow oil. To a solution of methyl 3-cyclopropyl-3-(3-hydroxyphenyl)propanoate **11a** (151 mg, 0.69 mmol) in DMF (dry) (5 mL) were added K_2CO_3 (142 mg, 1.03 mmol) and the obtained mesylate. The mixture was stirred at 100 °C for 15 h. The mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−10% EtOAc in hexane) to give a mixture of methyl 3-cyclopropyl-3-(3-((1-(2-(4,4-dimethylpentyl)-5-methoxyphenyl)-azetidin-3-yl)methoxy)phenyl)propanoate (140 mg, 0.284 mmol, 83%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 0.15 (1H, dq, J = 9.6, 4.9 Hz), 0.26 (1H, dq, J = 9.4, 4.8 Hz), 0.36−0.50 (1H, m), 0.51−0.63 (1H, m), 0.87 (9H, s), 0.91−1.09 (1H, m), 1.25 (2H, q, J = 7.3 Hz), 1.45−1.61 (2H, m), 2.26−2.38 (1H, m), 2.38−2.50 (2H, m), 2.60−2.84 (2H, m), 2.95−3.17 (1H, m), 3.61 (3H, s), 3.72−3.81 (5H, m), 4.06 (2H, t, J = 7.3 Hz), 4.19 (2H, d, J = 6.9 Hz), 6.07 (1H, d, J = 2.3 Hz), 6.33 (1H, dd, J = 8.3, 2.3 Hz), 6.71−6.86 (3H, m), 6.96 (1H, d, J = 8.3 Hz), 7.22 (1H, t, J = 7.9 Hz). MS (ESI/APCI): m/z 494.16. $[M + H]^+$. HPLC 96.6% (LC−MS). Compound **5** was prepared from the obtained methyl ester in a manner similar to that described for compound **2** as a colorless oil (107 mg, 0.223 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 0.15 (1H, dq, J = 9.6, 4.9 Hz), 0.26 (1H, dq, J = 9.4, 4.8 Hz), 0.36−0.50 (1H, m), 0.51−0.63 (1H, m), 0.87 (9H, s), 0.91−1.09 (1H, m), 1.25 (2H, q, J = 7.3 Hz), 1.45−1.61 (2H, m), 2.26−2.38 (1H, m), 2.38−2.50 (2H, m), 2.60−2.84 (2H, m), 2.95−3.17 (1H, m), 3.61 (3H, s), 3.72−3.81 (5H, m), 4.06 (2H, t, J = 7.3 Hz), 4.19 (2H, d, J = 6.9 Hz), 6.07 (1H, d, J = 2.3 Hz), 6.33 (1H, dd, J = 8.3, 2.3 Hz), 6.71−6.86 (3H, m), 6.96 (1H, d, J = 8.3 Hz), 7.22 (1H, t, J = 7.9 Hz). MS (ESI/APCI): m/z 480.3 $C_{30}H_{41}NO_4$: 0.1 H_2O: C, 74.84; H, 8.63; N, 2.91. Found: C, 74.94; H,8.59; N,2.85. HPLC purity 99.6%.

*3-Cyclopropyl-3-(3-((1-(3-methoxyphenyl)piperidin-4-yl)-methoxy)phenyl)propanoic Acid (**4b**).* To a solution of (1-(3-methoxyphenyl)piperidin-4-yl)methanol **36b** (100 mg, 0.45 mmol), methyl 3-cyclopropyl-3-(3-hydroxyphenyl)propanoate (119 mg, 0.54 mmol), and PPh_3 (237 mg, 0.90 mmol) in THF (dry) (5.0 mL) was added diisopropyl azodicarboxylate (DIAD) (0.476 mL, 0.90 mmol) at room temperature. The mixture was stirred at room temperature for 20 h and evaporated. The residue was purified by column chromatography (silica gel, eluted with 5−15% EtOAc in hexane) to give methyl 3-cyclopropyl-3-(3-((1-(3-methoxyphenyl)piperidin-4-yl)methoxy)phenyl)propanoate (34.6 mg, 0.082 mmol, 18.1%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 0.09−0.20 (1H, m), 0.21−0.31 (1H, m), 0.37−0.49 (1H, m), 0.51−0.64 (1H, m), 0.94−1.10 (1H, m), 1.42−1.62 (2H, m), 1.87−2.03 (3H, m), 2.34 (1H, dt, J = 9.4, 7.6 Hz), 2.68−2.83 (4H, m), 3.61 (3H, s), 3.73 (2H, d, J = 12.5 Hz), 3.80 (3H, s), 3.83 (2H, d, J = 6.1 Hz), 6.40 (1H, dd, J = 8.0, 2.3 Hz), 6.50 (1H, t, J = 2.3 Hz), 6.58 (1H, dd, J = 8.1, 2.1 Hz), 6.71−6.86 (3H, m), 7.19 (2H, dt, J = 13.1, 8.0 Hz). MS (ESI/APCI): m/z 424.4 $[M + H]^+$. Compound **4b** was prepared from the obtained methyl ester in a manner similar to that described for compound **2** (purification: column chromatography (silica gel, eluted with 10−40% EtOAc in hexane)). Colorless oil. (29.9 mg, 0.073 mmol, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 0.11−0.23 (1H, m), 0.30 (1H, dq, J = 9.3, 4.7 Hz), 0.37−0.49 (1H, m), 0.52−0.65 (1H, m), 0.95−1.11 (1H, m), 1.52 (2H, qd, J = 12.5, 3.4 Hz), 1.86−2.01 (3H, m), 2.34 (1H, dt, J = 9.6, 7.5 Hz), 2.68−2.82 (4H, m), 3.72 (2H, d, J = 12.5 Hz), 3.79 (3H, s), 3.83 (2H, d, J = 6.1 Hz), 6.41 (1H, dd, J = 7.8, 2.1 Hz), 6.51 (1H, t, J = 2.3 Hz), 6.58 (1H, dd, J = 8.1, 2.1 Hz), 6.72−6.87 (3H, m), 7.12−7.25 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 4.1, 5.3, 17.2, 28.9, 36.1, 41.2, 46.9, 49.7, 55.2, 72.4, 103.1, 104.4, 109.5, 112.2, 113.9, 119.7, 129.4, 129.7, 145.6, 153.1, 159.1, 160.6, 177.1. MS (ESI/APCI): m/z 410.2 $[M + H]^+$. $C_{25}H_{31}NO_4$: 0.2 H_2O: C, 72.68; H, 7.66; N, 3.39. Found: C, 72.68; H, 7.39; N, 3.24. HPLC purity 100%.

*3-Cyclopropyl-3-(3-((1-(2-fluoro-5-methoxyphenyl)piperidin-4-yl)methoxy)phenyl)propanoic Acid (**4c**).* To a solution of (1-(2-fluoro-5-methoxyphenyl)piperidin-4-yl)methanol **36c** (353 mg, 1.48 mmol), methyl 3-cyclopropyl-3-(3-hydroxyphenyl)propanoate (357 mg, 1.62 mmol), and ADDP (558 mg, 2.21 mmol) in THF (dry) (20 mL) was added Bu_3P (0.587 mL, 2.21 mmol) at 0 °C. The mixture was stirred at room temperature for 6 h. The mixture was diluted with EtOAc and quenched with water at room temperature. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 1−15% EtOAc in hexane) to give methyl 3-cyclopropyl-3-(3-((1-(2-fluoro-5-methoxyphenyl)-piperidin-4-yl)methoxy)phenyl)propanoate (219 mg, 0.496 mmol, 33.6%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 0.09−0.21 (1H, m), 0.21−0.32 (1H, m), 0.36−0.50 (1H, m), 0.50−0.64 (1H, m), 0.93−1.11 (1H, m), 1.45−1.73 (2H, m), 1.96 (3H, d, J = 11.7 Hz), 2.34 (1H, dt, J = 9.8, 7.6 Hz), 2.61−2.83 (4H, m), 3.51 (2H, d, J = 12.1 Hz), 3.62 (3H, s), 3.77 (3H, s), 3.85 (2H, d, J = 5.7 Hz), 6.41 (1H, dt, J = 8.8, 3.2 Hz), 6.53 (1H, dd, J = 7.2, 3.0 Hz), 6.71−6.86 (3H, m), 6.93 (1H, dd, J = 12.3, 8.9 Hz), 7.21 (1H, t, J = 7.8 Hz). Compound **4c** was prepared from the obtained methyl ester in a manner similar to that described for compound **2** (purification: column chromatography (silica gel, eluted with 20−80% EtOAc in hexane)). White solid (166 mg, 0.389 mmol, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 0.11−0.24 (1H, m), 0.24−0.36 (1H, m), 0.38−0.51 (1H, m), 0.53−0.67 (1H, m), 1.04 (1H, ddt, J = 17.9, 8.0, 5.0, 5.0 Hz), 1.57−1.70 (2H, m), 1.84−2.03 (3H, m), 2.35 (1H, dt, J = 9.5, 7.8 Hz), 2.62−2.75 (2H, m), 2.79 (2H, dd, J = 7.4, 3.2 Hz), 3.51 (2H, d, J = 11.7 Hz), 3.77 (3H, s), 3.85 (2H, d, J = 6.1 Hz), 6.41 (1H, dt, J = 8.9, 3.1 Hz), 6.53 (1H, dd, J = 7.4, 2.8 Hz), 6.72−6.87 (3H, m), 6.88−6.98 (1H, m), 7.21 (1H, d, J = 8.3 Hz), 1 H was not found. ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 4.1, 5.3, 17.2, 29.3, 35.9, 41.2, 46.9, 50.9, 50.9, 55.7, 72.4, 105.1, 106.2, 112.2, 113.8, 116.0, 119.6, 129.4, 141.6, 145.5, 150.5, 156.0, 159.1, 177.3. MS (ESI/APCI): m/z 428.3. mp 150−152 °C. $C_{25}H_{30}FNO_4$: 0.1 H_2O: C, 69.94; H, 7.09; N, 3.26. Found: C, 70.09; H, 6.88; N, 3.21. HPLC purity 99.5%.

*3-Cyclopropyl-3-(3-((1-(5-methoxy-2-methylphenyl)piperidin-4-yl)methoxy)phenyl)propanoic Acid (**4d**).* Compound **4d** was prepared from (1-(5-methoxy-2-methylphenyl)piperidin-4-yl)-methanol **36d** in a manner similar to that described for compound **4a** (purification: column chromatography (silica gel, eluted with 15−40% EtOAc in hexane)). White solid (1.100 g, 2.60 mmol, 85%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.06−0.38 (3H, m), 0.43−0.56 (1H, m), 0.93−1.08 (1H, m), 1.36−1.57 (2H, m), 1.88 (3H, d, J = 9.7 Hz), 2.15 (3H, s), 2.19−2.32 (1H, m), 2.54−2.69 (4H, m), 3.09 (2H, d, J = 11.5 Hz), 3.70 (3H, s), 3.88 (2H, d, J = 5.9 Hz), 6.48−6.59 (2H, m), 6.72−6.88 (3H, m), 7.04 (1H, d, J = 8.3 Hz), 7.18 (1H, t, J = 7.9 Hz), 11.97 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 4.1, 5.3, 17.1, 17.2, 29.8, 36.0, 41.2, 46.9, 52.1, 55.3, 72.6, 106.1, 106.9, 112.2, 113.9, 119.6, 124.6, 129.4, 131.3, 145.5, 153.4, 158.4, 159.2, 176.9. MS (ESI/APCI): m/z 424.2 $[M + H]^+$. $C_{26}H_{33}NO_4$: 0.1 H_2O: C, 73.42; H, 7.87; N, 3.29. Found: C, 73.70; H, 7.63; N, 3.22. The corresponding intermediate ethyl 3-cyclopropyl-3-(3-((1-(5-methoxy-2-methylphenyl)piperidin-4-yl)methoxy)phenyl)propanoate (1380 mg, 3.06 mmol, 95%) was obtained as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.10−0.21 (1H, m), 0.27 (1H, dq, J = 9.3, 4.8 Hz), 0.37−0.48 (1H, m), 0.52−0.63 (1H, m), 0.93−1.09 (1H, m), 1.18 (3H, t, J = 7.1 Hz), 1.47−1.63 (2H, m), 1.87−2.00 (3H, m), 2.23 (3H, s), 2.35 (1H, dt, J = 9.7, 7.6 Hz), 2.59−2.76 (4H, m), 3.18 (2H, d, J = 11.9 Hz), 3.78 (3H, s), 3.86 (2H, d, J = 5.9 Hz), 4.02−4.11 (2H, m), 6.52 (1H, dd, J = 8.3, 2.6 Hz), 6.61 (1H, d, J = 2.5 Hz), 6.73−6.86 (3H, m), 7.07 (1H, d, J = 8.3 Hz), 7.18−7.24 (1H, m). MS (ESI/APCI): m/z 452.2 $[M + H]^+$. HPLC purity 99.7%.

*3-Cyclopropyl-3-(3-((1-(2-isopropyl-5-methoxyphenyl)piperidin-4-yl)methoxy)phenyl)propanoic Acid (**4e**).* A mixture of ethyl 3-cyclopropyl-3-(3-((1-(2-isopropyl-5-methoxyphenyl)piperidin-4-yl)-methoxy)phenyl)propanoate **41** (323.6 mg, 0.67 mmol) and 1 N NaOH (2.70 mL, 2.70 mmol) in THF (2.7 mL) and EtOH (2.7 mL)

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was stirred at 50 °C for 3 h. The mixture was neutralized with 1 N HCl and extracted with EtOAc twice. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 20−25% EtOAc in hexane) to give compound **4e** (114.5 mg, 0.254 mmol, 38%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.06−0.18 (1H, m), 0.18−0.39 (2H, m), 0.44−0.55 (1H, m), 0.93−1.06 (1H, m), 1.13 (6H, d, J = 6.9 Hz), 1.36−1.58 (2H, m), 1.87 (3H, d, J = 10.5 Hz), 2.18−2.31 (1H, m), 2.55−2.73 (4H, m), 2.97 (2H, d, J = 11.5 Hz), 3.23−3.38 (1H, m), 3.71 (3H, s), 3.88 (2H, d, J = 5.8 Hz), 6.59−6.67 (2H, m), 6.74−6.87 (3H, m), 7.11−7.23 (2H, m), 11.97 (1H, br s). ^{13}C NMR (101 MHz, DMSO-d_6): δ 3.9, 5.0, 17.4, 24.1, 25.7, 29.4, 35.3, 40.7, 46.4, 53.1, 54.9, 71.9, 106.4, 108.8, 111.8, 113.8, 119.5, 126.7, 129.1, 135.6, 146.1, 152.3, 157.7, 158.6, 173.0. MS (ESI/APCI): m/z 452.3 $[M + H]^+$. mp 112−114 °C. $C_{28}H_{37}NO_4$: 0.1 H_2O: C, 74.17; H, 8.27; N, 3.09. Found: C, 74.39; H, 8.00; N, 2.82. HPLC purity 99.8%.

*3-Cyclopropyl-3-(3-((1-(2-(3,3-dimethylbutyl)-5-methoxyphenyl)piperidin-4-yl)methoxy)phenyl)propanoic Acid (**4f**).* Compound **4f** was prepared from (1-(2-(3,3-dimethylbutyl)-5-methoxyphenyl)piperidin-4-yl)methanol **44** in a manner similar to that described for compound **4b** (purification: column chromatography (silica gel, eluted with 0−25% EtOAc in hexane)). White amorphous solid (62.0 mg, 0.126 mmol, 82%). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 0.12 (1H, d, J = 4.9 Hz), 0.20−0.37 (2H, m), 0.42−0.55 (1H, m), 0.95 (9H, s), 0.99 (1H, br s), 1.33−1.58 (4H, m), 1.87 (3H, d, J = 9.8 Hz), 2.17−2.30 (1H, m), 2.45−2.50 (2H, m), 2.56−2.73 (4H, m), 3.01 (2H, d, J = 12.0 Hz), 3.70 (3H, s), 3.87 (2H, d, J = 5.4 Hz), 6.50−6.65 (2H, m), 6.72−6.87 (3H, m), 7.05 (1H, d, J = 8.2 Hz), 7.18 (1H, t, J = 7.8 Hz), 11.97 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 4.1, 5.3, 17.2, 25.3, 29.4, 29.9, 30.6, 36.0, 41.1, 46.0, 46.9, 53.2, 55.2, 72.6, 106.9, 108.0, 112.2, 113.8, 119.6, 129.4, 130.2, 130.9, 145.5, 153.3, 158.2, 159.2, 176.7. MS (ESI/APCI): m/z 494.3. $C_{31}H_{43}NO_4$: 0.2 H_2O: C, 74.87; H, 8.80; N, 2.82. Found: C, 74.82; H, 8.80; N, 2.62. The corresponding intermediate methyl 3-cyclopropyl-3-(3-((1-(2-(3,3-dimethylbutyl)-5-methoxyphenyl)piperidin-4-yl)methoxy)phenyl)propanoate (78 mg, 0.154 mmol, 16.02%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 0.16 (1H, dq, J = 9.5, 5.0 Hz), 0.21−0.33 (1H, m), 0.36−0.49 (1H, m), 0.51−0.64 (1H, m), 0.97 (9H, s), 0.99−1.08 (1H, m), 1.46 (2H, dt, J = 8.4, 4.5 Hz), 1.50−1.62 (2H, m), 1.93 (3H, d, J = 10.2 Hz), 2.27−2.40 (1H, m), 2.49−2.60 (2H, m), 2.62−2.84 (4H, m), 3.12 (2H, d, J = 11.5 Hz), 3.62 (3H, s), 3.78 (3H, s), 3.85 (2H, d, J = 5.8 Hz), 6.58 (1H, dd, J = 8.3, 2.4 Hz), 6.66 (1H, d, J = 2.3 Hz), 6.72−6.85 (3H, m), 7.09 (1H, d, J = 8.3 Hz), 7.21 (1H, t, J = 7.8 Hz). MS (ESI/APCI): m/z 508.2 $[M + H]^+$. HPLC purity 100% (LC/MS).

*3-(3-((1-(2-(3-Acetoxy-3-methylbutyl)-5-methoxyphenyl)-piperidin-4-yl)methoxy)phenyl)-3-cyclopropylpropanoicacid (**4g**).* Compound **4g** was prepared from 4-(2-(4-(hydroxymethyl)-piperidin-1-yl)-4-methoxyphenyl)-2-methylbutan-2-yl acetate **50** in a manner similar to that described for compound **4a** (purification: column chromatography (silica gel, eluted with 0−50% EtOAc in hexane)). White amorphous solid (47.3 mg, 0.095 mmol, 85%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.04−0.18 (1H, m), 0.19−0.27 (1H, m), 0.28−0.38 (1H, m), 0.44−0.57 (1H, m), 0.95−1.06 (1H, m), 1.15 (6H, s), 1.48 (2H, d, J = 11.3 Hz), 1.56−1.66 (2H, m), 1.80−1.90 (2H, m), 2.18−2.30 (1H, m), 2.50−2.59 (3H, m), 2.59−2.73 (4H, m), 3.02 (2H, d, J = 10.5 Hz), 3.70 (3H, s), 3.87 (2H, d, J = 5.1 Hz), 4.16 (1H, br s), 6.51−6.63 (2H, m), 6.77 (1H, d, J = 7.7 Hz), 6.79−6.87 (2H, m), 7.05 (1H, d, J = 8.3 Hz), 7.14−7.23 (1H, m), 11.96 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 4.2, 5.3, 17.1, 25.1, 29.6, 29.6, 29.7, 36.0, 41.5, 45.1, 46.9, 53.5, 53.6, 55.3, 70.9, 72.3, 107.0, 108.8, 112.6, 113.7, 119.6, 129.4, 130.2, 130.7, 145.6, 152.7, 158.6, 159.2, 176.8. MS (ESI/APCI): m/z 496.3 $[M + H]^+$. $C_{30}H_{41}NO_5$: C, 72.70; H, 8.34; N, 2.83. Found: C, 72.75; H, 8.29; N, 2.75. HPLC purity 98.8%. The corresponding intermediate: ethyl 3-(3-((1-(2-(3-acetoxy-3-methylbutyl)-5-methoxyphenyl)piperidin-4-yl)methoxy)phenyl)-3-cyclopropylpropanoate (silica gel, eluted with 5−10% EtOAc in hexane). Colorless oil (289 mg, 0.511 mmol, 76%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.07−0.17 (1H, m), 0.18−0.27 (1H, m), 0.27−0.37 (1H, m), 0.44−0.57 (1H, m), 0.97−1.08 (1H, m), 1.08 (3H, t, J = 7.1 Hz), 1.45 (6H, s), 1.46−1.56 (2H, m), 1.81−1.91 (3H, m), 1.93 (3H, s), 1.93−2.01 (2H, m), 2.19−2.29 (1H, m), 2.52−2.58 (2H, m), 2.60−2.78 (4H, m), 3.00 (2H, d, J = 11.5 Hz), 3.70 (3H, s), 3.87 (2H, d, J = 4.9 Hz), 3.92−4.00 (2H, m), 6.59 (1H, d, J = 8.7 Hz), 6.63 (1H, s), 6.77 (1H, d, J = 7.9 Hz), 6.79−6.86 (2H, m), 7.05 (1H, d, J = 8.3 Hz), 7.18 (1H, t, J = 7.8 Hz).

*3-Cyclopropyl-3-(3-((1-(2-((isobutyl(methyl)amino)methyl)-5-methoxyphenyl)piperidin-4-yl)methoxy)phenyl)propanoic Acid (**4h**).* To a solution of methyl 3-cyclopropyl-3-(3-((1-(2-formyl-5-methoxyphenyl)piperidin-4-yl)methoxy)phenyl)propanoate **45** (200 mg, 0.44 mmol) and *N*,2-dimethylpropan-1-amine (77 mg, 0.89 mmol) in THF (dry) (5 mL) was added $NaBH(OAc)_3$ (188 mg, 0.89 mmol) and stirred at r.t. for 1 h. The mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0−20% EtOAc in hexane) to give methyl 3-cyclopropyl-3-(3-((1-(2-((isobutyl(methyl)amino)methyl)-5-methoxyphenyl)piperidin-4-yl)-methoxy)phenyl)propanoate (136 mg, 0.260 mmol, 59%) as a colorless oil that included Et ester. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 0.07−0.21 (1H, m), 0.26 (1H, dq, J = 9.2, 4.8 Hz), 0.35−0.50 (1H, m), 0.50−0.64 (1H, m), 0.88 (6H, d, J = 6.6 Hz), 0.94−1.13 (1H, m), 1.41−1.63 (2H, m), 1.72−1.86 (1H, m), 1.86−1.98 (3H, m), 2.07−2.20 (5H, m), 2.35 (1H, dt, J = 9.7, 7.6 Hz), 2.58−2.83 (4H, m), 3.28 (2H, d, J = 11.6 Hz), 3.42 (2H, s), 3.62 (3H, s), 3.80 (3H, s), 3.86 (2H, d, J = 6.0 Hz), 6.53−6.66 (2H, m), 6.72−6.85 (3H, m), 7.14−7.25 (1H, m), 7.36 (1H, d, J = 8.3 Hz) MS (ESI/APCI): m/z 523.6. Compound **4h** was prepared from the obtained methyl ester in a manner similar to that described for compound **4a** (purification: column chromatography (silica gel, eluted with 0−25% MeOH in EtOAc)). White amorphous solid (98 mg, 0.193 mmol, 74%). ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 0.05−0.18 (1H, m), 0.18−0.37 (2H, m), 0.41−0.56 (1H, m), 0.84 (6H, d, J = 6.6 Hz), 0.92−1.12 (1H, m), 1.35−1.58 (2H, m), 1.68−1.91 (4H, m), 1.99 (3H, s), 2.07 (2H, s), 2.16−2.30 (1H, m), 2.55−2.78 (4H, m), 3.23 (2H, d, J = 11.2 Hz), 3.37 (2H, s), 3.72 (3H, s), 3.88 (2H, d, J = 5.8 Hz), 6.59 (2H, dq, J = 4.5, 2.4 Hz), 6.73−6.87 (3H, m), 7.18 (1H, t, J = 7.8 Hz), 7.23−7.30 (1H, m), 11.99 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 4.1, 5.2, 17.6, 20.9, 25.2, 29.8, 36.0, 40.2, 43.2, 47.4, 53.3, 53.5, 55.0, 55.2, 63.6, 72.3, 107.0, 108.2, 111.9, 114.1, 120.0, 121.5, 129.0, 132.9, 147.2, 155.0, 159.0, 160.1, 177.2. MS (ESI/APCI): m/z 509.4 $[M + H]^+$. $C_{31}H_{44}N_2O_4$: 0.5 H_2O: C, 71.92; H, 8.76; N, 5.51. Found: C, 71.67; H, 8.92; N, 5.46. HPLC purity 99.8%.

*3-Cyclopropyl-3-(3-((1-(5-methoxy-2-(methyl(neopentyl)-carbamoyl)phenyl)piperidin-4-yl)methoxy)phenyl)propanoic Acid (**6a**).* To a solution of 2-(4-((3-(1-cyclopropyl-3-methoxy-3-oxopropyl)phenoxy)methyl)piperidin-1-yl)-4-methoxybenzoic acid **55** (414.4 mg, 0.89 mmol) in DMF (4.43 mL) were added HATU (506 mg, 1.33 mmol) and *N*,*N*-diisopropylethylamine (DIPEA) (0.232 mL, 1.33 mmol) at room temperature. The mixture was stirred at the same temperature for 1.5 h. The mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−30% EtOAc in hexane) to give methyl 3-cyclopropyl-3-(3-((1-(5-methoxy-2-(methyl(neopentyl)carbamoyl)phenyl)piperidin-4-yl)-methoxy)phenyl)propanoate (495 mg) as a yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.05−0.27 (2H, m), 0.27−0.39 (1H, m), 0.43−0.56 (1H, m), 0.69 (3H, s), 0.91−1.11 (7H, m), 1.22−1.51 (2H, m), 1.66−1.97 (3H, m), 2.18−2.33 (1H, m), 2.65−2.95 (6H, m), 3.02 (1H, s), 3.10−3.28 (2H, m), 3.32−3.46 (1H, m), 3.51 (3H, s), 3.72−3.79 (3H, m), 3.80−3.92 (2H, m), 6.51−6.67 (2H, m), 6.72−6.88 (3H, m), 6.96−7.12 (1H, m), 7.18 (1H, t, J = 7.9 Hz). The 1H peak was overlapped with the water peak. MS (ESI/APCI): m/z 551.5 $[M + H]^+$. Compound **6a** was prepared from the obtained methyl ester in a manner similar to that described for compound **4a**. White amorphous solid (471 mg, 0.878 mmol, 99%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.07−0.17 (1H, m), 0.19−0.37 (2H, m), 0.43−

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0.55 (1H, m), 0.69 (3H, s), 0.99 (7H, s), 1.25 (1H, br s), 1.29−1.51 (2H, m), 1.69−2.00 (3H, m), 2.17−2.31 (1H, m), 2.57−2.76 (2H, m), 2.77−2.97 (3H, m), 3.02 (1H, s), 3.10−3.25 (2H, m), 3.35−3.47 (1H, m), 3.73−3.79 (3H, m), 3.81−3.89 (2H, m), 6.47 (1H, d, J = 2.5 Hz), 6.51−6.66 (2H, m), 6.72−6.79 (1H, m), 6.79−6.86 (2H, m), 6.97−7.12 (1H, m), 7.18 (1H, t, J = 8.1 Hz), 11.97 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6): δ 3.9, 4.9, 17.4, 28.5, 29.0, 34.0, 35.2, 36.8, 40.7, 46.3, 50.0, 53.4, 55.0, 59.5, 71.7, 105.3, 107.3, 111.8, 113.6, 119.5, 125.6, 128.6, 129.1, 146.1, 150.8, 158.6, 160.1, 171.4, 173.0. Tautomer mixture. MS (ESI/APCI): m/z 537.3 $[M + H]^+$. $C_{32}H_{44}N_2O_5$: 0.1 H_2O: C, 71.37; H, 8.27; N, 5.20. Found: C, 71.16; H, 8.01; N, 5.15. HPLC purity 100%.

*3-Cyclopropyl-3-{3-[(1-{5-methoxy-2-[methyl(phenyl)-carbamoyl]phenyl}piperidin-4-yl)methoxy]phenyl}propanoic Acid (**6b**).* To a solution of compound **55** (100 mg, 0.21 mmol) in THF (2 mL) was added 1-chloro-*N*,*N*,2-trimethylprop-1-en-1-amine (0.041 mL, 0.31 mmol) at 0 °C. The mixture was stirred at room temperature under N_2 for 30 min. Then, *N*-methylaniline (44.5 mg, 0.42 mmol) and triethylamine (0.058 mL, 0.42 mmol) were added to the mixture at 0 °C. The mixture was stirred at room temperature under N_2 overnight. The mixture was quenched with water and extracted with EtOAc. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−30% EtOAc in hexane) to give ethyl 3-cyclopropyl-3-(3-((1-(5-methoxy-2-(methyl(phenyl)carbamoyl)phenyl)piperidin-4-yl)methoxy)phenyl)-propanoate (72.3 mg, 0.127 mmol, 61.0%) as (a) colorless oil. MS (ESI/APCI): m/z 571.4 $[M + H]^+$. Compound **6b** was prepared from the corresponding ethyl ester (72.3 mg, 0.127 mmol) in a manner similar to that described for compound **4a**. White amorphous solid (35 mg, 0.064 mmol, 51%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.07−0.17 (1H, m), 0.18−0.37 (2H, m), 0.43−0.54 (1H, m), 0.94−1.10 (1H, m), 1.45 (2H, br d, J = 10.8 Hz), 1.79 (3H, br d, J = 6.0 Hz), 2.17−2.31 (1H, m), 2.51−2.74 (4H, m), 3.69 (3H, br s), 3.89 (2H, br d, J = 5.4 Hz), 6.03−6.37 (1H, m), 6.55 (1H, br s), 6.74−6.87 (3H, m), 6.96−7.31 (7H, m), 11.98 (1H, br s). ^{13}C NMR (101 MHz, DMSO-d_6): δ 3.9, 4.9, 17.4, 28.7, 35.2, 40.7, 46.4, 55.0, 71.7, 104.4, 106.5, 111.9, 113.6, 119.5, 124.3, 125.5, 126.0, 127.8, 129.1, 130.2, 143.7, 146.1, 151.0, 158.6, 160.4, 170.1, 173.0. Two C peaks next to the nitrogen of the piperidine ring and a C peak of methyl on the amide were not detected. MS (ESI/APCI): m/z 543.4 $[M + H]^+$. $C_{33}H_{38}N_2O_5$: 0.4 H_2O: C, 72.08; H, 7.11; N, 5.09. Found: C, 71.92; H, 6.82; N, 5.20. HPLC purity 100%.

*3-Cyclopropyl-3-(3-((1-(5-methoxy-2-(methyl(pyridin-2-yl)-carbamoyl)phenyl)piperidin-4-yl)methoxy)phenyl)propanoic Acid (**6c**).* Compound **6c** was prepared from compound **55** (402.6 mg, 0.86 mmol) in a manner similar to that described for compound **6a**. White amorphous solid (330 mg, 0.607 mmol, 73%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.07−0.18 (1H, m), 0.18−0.37 (2H, m), 0.44−0.56 (1H, m), 0.91−1.09 (1H, m), 1.10−1.60 (2H, m), 1.70 (3H, d, J = 9.6 Hz), 2.18−2.32 (1H, m), 2.53−2.75 (4H, m), 3.42 (3H, s), 3.74 (3H, s), 3.80 (2H, d, J = 5.9 Hz), 6.30 (1H, d, J = 2.1 Hz), 6.61 (1H, dd, J = 8.5, 2.3 Hz), 6.75 (1H, dd, J = 7.8, 2.0 Hz), 6.79−6.94 (3H, m), 7.05 (1H, dd, J = 6.5, 4.9 Hz), 7.17 (1H, t, J = 8.0 Hz), 7.30 (1H, d, J = 8.4 Hz), 7.44−7.56 (1H, m), 8.38 (1H, dd, J = 4.8, 1.2 Hz), 12.00 (1H, br s). 2H were overlapped with the water peak. ^{13}C NMR (75 MHz, $CDCl_3$): δ 4.2, 5.3, 17.2, 28.8, 34.9, 35.8, 41.3, 46.9, 55.3, 72.4, 104.7, 106.3, 112.5, 113.7, 119.0, 119.6, 119.8, 123.1, 129.4, 131.6, 136.3, 145.6, 147.5, 151.6, 156.1, 159.1, 161.8, 171.6, 176.4. Two C peaks next to the nitrogen of the piperidine ring were not detected. MS (ESI/APCI): m/z 544.2 $[M + H]^+$. $C_{32}H_{37}N_3O_5$: 0.6 H_2O: C, 69.32; H, 6.94; N, 7.58. Found: C, 69.55; H, 6.69; N, 7.29. HPLC purity 99.3%. The corresponding intermediate: methyl 3-cyclopropyl-3-(3-((1-(5-methoxy-2-(methyl(pyridin-2-yl)carbamoyl)-phenyl)piperidin-4-yl)methoxy)phenyl)propanoate (purification: NH silica gel, eluted with 0−30% EtOAc in hexane). Colorless oil (311 mg, 0.558 mmol, 65%). ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 0.06−0.26 (2H, m), 0.26−0.38 (1H, m), 0.43−0.58 (1H, m), 0.93−1.11 (1H, m), 1.61−1.81 (3H, m), 2.18−2.30 (1H, m), 2.58 (2H, br s), 2.65−2.82 (3H, m), 3.42 (3H, s), 3.51 (3H, s), 3.69−3.87 (5H, m), 6.30 (1H, s), 6.61 (1H, dd, J = 8.5, 2.3 Hz), 6.72−6.95 (4H, m), 7.05 (1H, dd, J = 6.9, 5.1 Hz), 7.18 (1H, t, J = 8.0 Hz), 7.30 (1H, d, J = 8.4 Hz), 7.45−7.55 (1H, m), 8.38 (1H, d, J = 3.9 Hz). 3H were overlapped with the peak of DMSO. MS (ESI/APCI): m/z 558.5 $[M + H]^+$.

*3-Cyclopropyl-3-(3-((1-(2-(isobutyl(pyridin-2-yl)carbamoyl)-5-methoxyphenyl)piperidin-4-yl)methoxy)phenyl)propanoic Acid (**6d**).* Compound **6d** was prepared from compound **55** (100 mg, 0.21 mmol) in a manner similar to that described for compound **6b**. White amorphous solid (30.3 mg, 0.052 mmol, 60%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.06−0.39 (3H, m), 0.43−0.55 (1H, m), 0.81 (6H, br d, J = 6.6 Hz), 0.92−1.11 (1H, m), 1.11−1.59 (3H, m), 1.60−1.83 (4H, m), 2.20−2.29 (1H, m), 2.52−2.75 (4H, m), 3.11−3.30 (1H, m), 3.70 (3H, s), 3.83 (2H, br d, J = 5.9 Hz), 3.89−4.06 (2H, m), 6.17−6.29 (1H, m), 6.54 (1H, dd, J = 8.5, 2.3 Hz), 6.67−6.86 (4H, m), 7.02 (1H, dd, J = 6.9, 5.1 Hz), 7.14−7.24 (2H, m), 7.39−7.50 (1H, m), 8.36 (1H, dd, J = 4.8, 1.2 Hz), 12.00 (1H, br s). ^{13}C NMR (101 MHz, DMSO-d_6): δ 3.9, 4.9, 17.4, 20.0, 27.2, 28.2, 35.2, 40.7, 46.4, 52.7, 55.0, 71.8, 104.2, 106.4, 111.8, 113.6, 119.5, 120.1, 120.3, 123.5, 129.1, 131.1, 136.5, 146.1, 147.6, 151.0, 155.1, 158.6, 160.8, 170.2, 173.0. Two C peaks next to the nitrogen of the piperidine ring were not detected. MS (ESI/APCI): m/z 586.4 $(M + H)^+$. $C_{35}H_{43}N_3O_5$: 0.1 H_2O: C, 71.55; H, 7.41; N, 7.15. Found: C, 71.33; H, 7.21; N, 7.14. HPLC purity 98.4%. *The corresponding intermediate*: methyl 3-cyclopropyl-3-(3-((1-(2-(isobutyl(pyridin-2-yl)carbamoyl)-5-methoxyphenyl)piperidin-4-yl)methoxy)phenyl)-propanoic acid propanoate (purification: NH silica gel, eluted with 0−30% EtOAc in hexane). Colorless oil (75.1 mg, 0.122 mmol, 59%).

*3-Cyclopropyl-3-(3-((1-(5-methoxy-2-(neopentyl(pyridin-2-yl)-carbamoyl)phenyl)piperidin-4-yl)methoxy)phenyl)propanoic Acid (**6e**).* Compound **6e** was prepared from compound **55** (114 mg, 0.24 mmol) in a manner similar to that described for compound **6b**. White amorphous solid (129 mg, 0.215 mmol, 94%). ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 0.05−0.18 (1H, m), 0.18−0.39 (2H, m), 0.43−0.59 (1H, m), 0.77 (9H, s), 0.93−1.10 (1H, m), 1.20−1.39 (1H, m), 1.51 (1H, br s), 1.71 (3H, d, J = 11.6 Hz), 2.19−2.31 (1H, m), 2.31−2.47 (2H, m), 2.53−2.75 (4H, m), 3.69 (3H, s), 3.84 (2H, d, J = 5.9 Hz), 3.96−4.26 (2H, m), 6.22 (1H, d, J = 2.2 Hz), 6.52 (1H, dd, J = 8.4, 2.3 Hz), 6.70 (1H, d, J = 7.6 Hz), 6.75−6.89 (3H, m), 7.00 (1H, dd, J = 6.7, 4.9 Hz), 7.10−7.25 (2H, m), 7.36−7.46 (1H, m), 8.33 (1H, dd, J = 4.8, 1.2 Hz), 11.68−12.42 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 4.1, 5.3, 17.2, 28.4, 28.7, 34.2, 35.9, 41.2, 46.9, 49.8, 54.0, 55.2, 55.9, 72.5, 104.6, 106.1, 112.4, 113.8, 119.7, 120.0, 121.4, 124.2, 129.4, 131.6, 135.8, 145.6, 147.2, 151.3, 156.5, 159.2, 161.4, 171.7, 176.7. MS (ESI/APCI): m/z 600.3 $[M + H]^+$. $C_{36}H_{45}N_3O_5$: 0.1 H_2O: C, 71.88; H, 7.57; N, 6.99. Found: C, 72.12; H, 7.53; N, 6.74. HPLC purity 95.3%. *The corresponding intermediate*: ethyl 3-cyclopropyl-3-(3-((1-(5-methoxy-2-(neopentyl(pyridin-2-yl)-carbamoyl) phenyl)piperidin-4-yl)methoxy)phenyl)propanoate (purification: NH silica gel, eluted with 0−30% EtOAc in hexane). Colorless gum (143 mg, 0.228 mmol, 96%).

*3-{3-[(1-{2-[(2-Cyano-2-methylpropyl)(pyridin-2-yl)carbamoyl]-5-methoxyphenyl}piperidin-4-yl)methoxy]phenyl}-3-cyclopropyl-propanoic Acid (**6f**).* Compound **6f** was prepared from compound **55** (100 mg, 0.21 mmol) in a manner similar to that described for compound **6b**. White amorphous solid (98 mg, 0.160 mmol, quant). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 0.09−0.18 (1H, m), 0.20−0.28 (1H, m), 0.29−0.37 (1H, m), 0.45−0.57 (1H, m), 0.92−1.06 (1H, m), 1.16−1.63 (4H, m), 1.29 (6H, br s), 1.64−1.87 (3H, m), 2.18−2.30 (1H, m), 2.51−2.74 (4H, m), 3.71 (3H, s), 3.84 (2H, d, J = 6.0 Hz), 4.18−4.63 (2H, m), 6.24 (1H, d, J = 1.9 Hz), 6.57 (1H, dd, J = 8.4, 2.3 Hz), 6.70 (1H, d, J = 6.0 Hz), 6.75−6.80 (1H, m), 6.81−6.86 (2H, m), 7.06 (1H, dd, J = 7.0, 5.2 Hz), 7.14−7.25 (2H, m), 7.44 (1H, t, J = 7.7 Hz), 8.37 (1H, d, J = 4.8 Hz), 11.99 (1H, br s). ^{13}C NMR (101 MHz, DMSO-d_6): δ 3.9, 5.0, 17.4, 24.7, 28.1, 33.2, 35.1, 40.7, 46.4, 51.5, 55.1, 71.8, 104.2, 106.6, 111.8, 113.6, 119.5, 120.8, 121.0, 122.8, 123.5, 129.1, 131.2, 136.5, 146.2, 147.4, 151.1, 154.2, 158.6, 161.1, 170.9, 173.1. Two C peaks next to the nitrogen of the piperidine ring were not detected. MS (ESI/APCI): m/z 611.2 $[M + H]^+$. $C_{36}H_{42}N_4O_5$: 0.4 H_2O: C, 69.97; H, 6.98; N, 9.07. Found:

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C, 69.78; H, 6.88; N, 9.02. HPLC purity 95.9%. *The corresponding intermediate*: ethyl 3-(3-((1-(2-((2-cyano-2-methylpropyl)(pyridin-2-yl)carbamoyl)-5-methoxyphenyl)piperidin-4-yl)methoxy)phenyl)-3-cyclopropylpropanoate (NH silica gel, eluted with 15−25% EtOAc in hexane). White amorphous solid (108.3 mg, 0.170 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 0.12−0.21 (1H, m), 0.23−0.32 (1H, m), 0.38−0.49 (1H, m), 0.53−0.64 (1H, m), 0.96−1.10 (1H, m), 1.19 (3H, t, J = 7.2 Hz), 1.39 (6H, br s), 1.38−1.68 (2H, m), 1.69−1.92 (3H, m), 2.30−2.39 (1H, m), 2.35−2.71 (3H, m), 2.67−2.80 (2H, m), 3.14−3.42 (1H, m), 3.78 (3H, s), 3.82 (2H, d, J = 6.3 Hz), 4.00−4.12 (2H, m), 4.33−4.86 (2H, m), 6.20 (1H, d, J = 2.1 Hz), 6.54 (2H, dd, J = 8.4, 2.3 Hz), 6.70−6.88 (3H, m), 6.90−7.01 (1H, m), 7.18−7.25 (2H, m), 7.37 (1H, d, J = 8.4 Hz), 8.40 (1H, d, J = 3.6 Hz).

*3-Cyclopropyl-3-{3-[(1-{5-methoxy-2-[(2-methoxy-2-methylpropyl)(pyridin-2-yl)carbamoyl]phenyl}piperidin-4-yl)-methoxy]phenyl}propanoic Acid (**6g**).* Compound **6g** was prepared from compound **55** (100 mg, 0.21 mmol) in a manner similar to that described for compound **6b**. White amorphous solid (77.9 mg, 0.127 mmol, 96%). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 0.08−0.16 (1H, m), 0.20−0.28 (1H, m), 0.29−0.39 (1H, m), 0.44−0.55 (1H, m), 0.93−1.19 (7H, m), 1.20−1.63 (2H, m), 1.66−1.87 (3H, m), 2.18−2.30 (1H, m), 2.40−2.72 (6H, m), 2.75 (3H, s), 3.68 (3H, s), 3.84 (2H, d, J = 5.9 Hz), 4.03−4.43 (2H, m), 6.24 (1H, s), 6.49 (1H, dd, J = 8.5, 2.2 Hz), 6.67 (1H, br s), 6.74−6.86 (3H, m), 6.95−7.03 (1H, m), 7.08 (1H, d, J = 8.5 Hz), 7.15−7.23 (1H, m), 7.31−7.45 (1H, m), 8.32 (1H, d, J = 4.8 Hz), 11.97 (1H, br s). ^{13}C NMR (101 MHz, DMSO-d_6): δ 3.9, 5.0, 17.4, 23.5, 28.3, 35.2, 40.7, 46.4, 48.5, 51.0, 55.0, 71.8, 75.9, 104.3, 106.4, 111.8, 113.7, 119.5, 120.3, 121.3, 123.9, 129.1, 130.7, 136.1, 146.1, 147.1, 151.1, 155.5, 158.6, 160.6, 170.5, 173.0. Two C peaks next to the nitrogen of the piperidine ring were not detected. MS (ESI/APCI): m/z 616.3 $[M + H]^+$. $C_{36}H_{45}N_3O_6$: 0.5 H_2O: C, 69.21; H, 7.42; N, 6.73. Found: C, 69.31; H, 7.33; N, 6.43. HPLC purity 97.0%. *The corresponding intermediate*: ethyl 3-cyclopropyl-3-(3-((1-(5-methoxy-2-((2-methoxy-2-methylpropyl)(pyridin-2-yl)carbamoyl)phenyl)piperidin-4-yl)methoxy)phenyl)propanoate (NH silica gel, eluted with 15−25% EtOAc in hexane). Colorless oil (85 mg, 0.132 mmol, 64%) ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 0.11−0.21 (1H, m), 0.24−0.35 (1H, m), 0.38−0.49 (1H, m), 0.52−0.64 (1H, m), 0.97−1.08 (1H, m), 1.12−1.23 (9H, m), 1.71−1.91 (3H, m), 2.27−2.79 (4H, m), 2.29−2.39 (1H, m), 2.73 (3H, tt, J = 14.6, 7.4 Hz), 2.83 (3H, s), 3.40 (1H, br s), 3.75 (3H, s), 3.83 (2H, d, J = 6.0 Hz), 3.98−4.12 (2H, m), 4.22−4.63 (2H, m), 6.20 (1H, s), 6.47 (1H, dd, J = 8.4, 2.3 Hz), 6.57 (1H, br s), 6.73−6.92 (4H, m), 7.21 (2H, t, J = 7.8 Hz), 7.24−7.32 (1H, m), 8.35 (1H, dd, J = 4.8, 1.2 Hz).

*3-Cyclopropyl-3-(3-((1-(5-methoxy-2-((6-methylpyridin-2-yl)-(neopentyl)carbamoyl)phenyl)piperidin-4-yl)methoxy)phenyl)-propanoic Acid (**6h**).* Compound **6h** was prepared from compound **55** (112.7 mg, 0.23 mmol) in a manner similar to that described for compound **6b**. White solid (27.5 mg, 0.045 mmol, 53%). ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 0.06−0.18 (1H, m), 0.18−0.38 (2H, m), 0.41−0.56 (1H, m), 0.77 (9H, s), 0.91−1.10 (1H, m), 1.42−1.82 (4H, m), 2.19−2.30 (1H, m), 2.36 (4H, s), 2.56−2.74 (3H, m), 3.69 (3H, s), 3.84 (2H, d, J = 5.9 Hz), 3.91−4.27 (2H, m), 6.22 (1H, s), 6.42−6.58 (2H, m), 6.73−6.89 (4H, m), 7.09−7.24 (2H, m), 7.28 (1H, t, J = 7.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 4.1, 5.3, 17.3, 24.3, 28.5, 28.8, 34.2, 36.0, 41.2, 46.9, 55.2, 72.6, 77.2, 104.6, 106.0, 112.2, 113.9, 118.0, 119.2, 119.6, 124.6, 129.4, 131.4, 136.0, 145.6, 151.3, 155.7, 156.0, 159.2, 161.2, 171.7, 176.4. Two C peaks next to the nitrogen of the piperidine ring were not detected. MS (ESI/APCI): m/z 614.4 $[M + H]^+$. $C_{37}H_{47}N_3O_5$: 0.1 H_2O: C, 72.19; H, 7.73; N, 6.83. Found: C, 72.03; H, 7.60; N, 6.73. HPLC purity 95.3%.

*3-Methoxy-3-(3-((1-(5-methoxy-2-((6-methylpyridin-2-yl)-(neopentyl)carbamoyl)phenyl)piperidin-4-yl)methoxy)phenyl)-propanoic Acid (**7a**).* To a solution of 2-(4-(hydroxymethyl)-piperidin-1-yl)-4-methoxy-*N*-(6-methylpyridin-2-yl)-*N*-neopentylbenzamide **57** (110.1 mg, 0.26 mmol) in toluene (2.59 mL) were added ethyl 3-(3-hydroxyphenyl)-3-methoxypropanoate (63.8 mg, 0.28 mmol) and cyanomethylenetri-*n*-butylphosphorane (136 μL, 0.52 mmol) at room temperature. The mixture was stirred at 100 °C under N_2 for 1 h. After cooling to room temperature, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 0−40% EtOAc in hexane) to give ethyl 3-methoxy-3-(3-((1-(5-methoxy-2-((6-methylpyridin-2-yl)(neopentyl)carbamoyl)phenyl)piperidin-4-yl)methoxy)phenyl)-propanoate as a pale-yellow gum. Compound **7a** was prepared from the obtained ethyl ester in a manner similar to that described for compound **4a** (purification: HPLC). White amorphous solid (98 mg, 0.193 mmol, 74%, 2 steps). ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 0.77 (9H, s), 1.57 (1H, br s), 1.65−1.84 (3H, m), 2.35 (3H, s), 2.53−2.69 (3H, m), 3.11 (3H, s), 3.24−3.29 (3H, m), 3.69 (3H, s), 3.86 (2H, d, J = 4.3 Hz), 3.96−4.26 (2H, m), 4.53 (1H, dd, J = 8.7, 4.9 Hz), 6.22 (1H, d, J = 2.2 Hz), 6.43−6.56 (2H, m), 6.82−6.94 (4H, m), 7.14 (1H, d, J = 8.4 Hz), 7.28 (2H, td, J = 7.8, 2.9 Hz), 12.20 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.3, 28.4, 28.8, 34.2, 35.9, 43.2, 50.0, 54.2, 55.2, 55.8, 56.9, 72.7, 79.8, 104.7, 106.1, 112.3, 114.3, 118.1, 118.8, 119.2, 124.6, 129.7, 131.4, 136.1, 141.8, 151.3, 155.7, 156.0, 159.5, 161.2, 171.7, 175.2. MS (ESI/APCI): m/z 604.4 $[M + H]^+$. $C_{35}H_{45}N_3O_6$: 0.4 H_2O: C, 68.81; H, 7.56; N, 6.88. Found: C, 68.65; H, 7.35; N, 6.88. HPLC purity 99.2%.

*3-Ethoxy-3-(3-((1-(5-methoxy-2-((6-methylpyridin-2-yl)-(neopentyl)carbamoyl)phenyl)piperidin-4-yl)methoxy)phenyl)-propanoic Acid (**7b**).* Compound **7b** was prepared from compound **57** (103.6 mg, 0.24 mmol) in a manner similar to that described for compound **7a**. White amorphous solid (100 mg, 0.162 mmol, 77%). ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 0.77 (9H, s), 1.07 (3H, t, J = 7.0 Hz), 1.24 (1H, s), 1.42−1.83 (4H, m), 2.36 (4H, s), 2.53−2.68 (3H, m), 3.22−3.38 (4H, m), 3.69 (3H, s), 3.79−3.93 (2H, m), 3.93−4.25 (2H, m), 4.64 (1H, dd, J = 8.6, 5.1 Hz), 6.22 (1H, d, J = 2.2 Hz), 6.42−6.56 (2H, m), 6.80−6.94 (4H, m), 7.14 (1H, d, J = 8.4 Hz), 7.22−7.32 (2H, m), 12.20 (1H, br s). ^{13}C NMR (101 MHz, DMSO-d_6): δ 15.1, 23.8, 28.2, 33.8, 35.2, 43.1, 49.3, 53.4, 55.0, 55.1, 63.5, 72.0, 77.6, 104.1, 106.3, 112.3, 113.6, 117.6, 118.5, 119.3, 124.2, 129.4, 130.9, 136.5, 143.2, 150.8, 155.1, 155.5, 158.8, 160.6, 170.7, 171.7. MS (ESI/APCI): m/z 618.3 $[M + H]^+$. $C_{36}H_{47}N_3O_6$: 0.4 H_2O: C, 69.18; H, 7.71; N, 6.72. Found: C, 69.42; H, 7.62; N, 6.44. HPLC purity 98.3%. *The corresponding intermediate*: ethyl 3-ethoxy-3-(3-((1-(5-methoxy-2-((6-methylpyridin-2-yl)(neopentyl)carbamoyl)-phenyl)piperidin-4-yl)methoxy)phenyl)propanoate (NH silica gel, eluted with 0−40% EtOAc in hexane). Pale-yellow gum (135.5 mg, 0.21 mmol). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 0.82 (9H, s), 1.16 (3H, t, J = 7.0 Hz), 1.21−1.31 (4H, m), 1.75 (3H, d, J = 11.2 Hz), 2.00 (1H, s), 2.35−2.71 (7H, m), 2.78 (1H, dd, J = 15.2, 9.3 Hz), 3.29−3.52 (3H, m), 3.76 (3H, s), 3.84 (2H, d, J = 6.1 Hz), 4.07−4.40 (4H, m), 4.72 (1H, dd, J = 9.2, 4.6 Hz), 6.20 (1H, d, J = 2.3 Hz), 6.34 (1H, br s), 6.49 (1H, dd, J = 8.5, 2.4 Hz), 6.70 (1H, d, J = 7.4 Hz), 6.80−6.89 (1H, m), 6.89−6.97 (2H, m), 7.09 (1H, t, J = 7.6 Hz), 7.21−7.35 (2H, m).

*4-Methoxy-3-(3-((1-(5-methoxy-2-((6-methylpyridin-2-yl)-(neopentyl)carbamoyl)phenyl)piperidin-4-yl)methoxy)phenyl)-butanoic Acid (**7c**).* Compound **7c** was prepared from compound **57** (195 mg, 0.46 mmol) in a manner similar to that described for compound **7a**. White amorphous solid (235 mg, 0.380 mmol, 83%). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 0.77 (9H, s), 0.86 (1H, t, J = 6.5 Hz), 1.12−1.31 (2H, m), 1.70 (2H, d, J = 11.3 Hz), 2.36 (3H, s), 2.58−2.72 (2H, m), 3.21 (3H, s), 3.23−3.30 (3H, m), 3.44 (2H, d, J = 6.8 Hz), 3.69 (3H, s), 3.83 (2H, d, J = 5.6 Hz), 4.03 (1H, d, J = 7.2 Hz), 4.16 (1H, br s), 6.22 (1H, br s), 6.47 (1H, br s), 6.52 (1H, d, J = 8.5 Hz), 6.72−6.92 (4H, m), 7.14 (1H, d, J = 8.4 Hz), 7.19 (1H, t, J = 7.8 Hz), 7.28 (1H, t, J = 7.8 Hz), 12.04 (1H, br s). ^{13}C NMR (101 MHz, DMSO-d_6): δ 13.9, 22.0, 23.9, 28.2, 30.9, 33.8, 35.2, 37.0, 41.5, 55.0, 58.0, 71.9, 75.8, 104.1, 106.3, 112.2, 114.1, 117.6, 119.3, 119.9, 124.2, 129.1, 130.9, 136.5, 143.6, 150.8, 155.1, 155.5, 158.6, 160.6, 170.6, 173.1. MS (ESI/APCI): m/z 618.3 $[M + H]^+$. $C_{36}H_{47}N_3O_6$: 0.4 H_2O: C, 69.18; H, 7.71; N, 6.72. Found: C, 69.30; H, 7.67; N, 6.42. HPLC purity 92.6%.

*2-(3-(3-((1-(5-Methoxy-2-((6-methylpyridin-2-yl)(neopentyl)-carbamoyl)phenyl)piperidin-4-yl)methoxy)phenyl)oxetan-3-yl)-acetic Acid (**7d**).* Compound **7d** was prepared from compound 57

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(144 mg, 0.34 mmol) in a manner similar to that described for compound **7a**. White amorphous solid (114 mg, 0.185 mmol, 55%). ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 0.77 (9H, s), 1.70 (3H, d, J = 11.5 Hz), 2.36 (3H, s), 3.30 (8H, br s), 3.05 (2H, s), 3.69 (3H, s), 3.85 (2H, d, J = 5.9 Hz), 4.68−4.81 (4H, m), 6.22 (1H, d, J = 2.0 Hz), 6.38−6.59 (2H, m), 6.76−6.89 (4H, m), 7.14 (1H, d, J = 8.4 Hz), 7.21−7.33 (2H, m), 12.14 (1H, br s). ^{13}C NMR (101 MHz, DMSO-d_6): δ 23.9, 28.2, 33.8, 35.2, 44.0, 44.7, 49.3, 53.3, 55.0, 55.1, 71.9, 81.0, 104.1, 106.3, 112.1, 112.6, 117.6, 118.4, 119.3, 124.2, 129.2, 130.9, 136.5, 146.0, 150.8, 155.0, 155.5, 158.6, 160.6, 170.6, 172.0. MS (ESI/APCI): m/z 616.3 $[M + H]^+$. $C_{36}H_{45}N_3O_6$: 0.4 H_2O: C, 69.41; H, 7.41; N, 6.75. Found: C, 69.29; H, 7.29; N, 6.52. HPLC purity 92.7%.

*3-Cyclopropyl-3-(6-((1-(5-methoxy-2-((6-methylpyridin-2-yl)-(neopentyl)carbamoyl)phenyl)piperidin-4-yl)methoxy)pyridin-2-yl)propanoic Acid (**7e**).* Compound **7e** was prepared from 2-(4-(hydroxymethyl)piperidin-1-yl)-4-methoxy-*N*-(6-methylpyridin-2-yl)-*N*-neopentylbenzamide **57** (100 mg, 0.43 mmol) in a manner similar to that described for compound **7a**. White solid (175 mg, 0.284 mmol, 79%). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 0.19−0.31 (2H, m), 0.33−0.41 (1H, m), 0.46−0.55 (1H, m), 0.76 (9H, s), 0.94−1.06 (1H, m), 1.08−1.31 (1H, m), 1.41−1.85 (4H, m), 2.27−2.44 (2H, m), 2.36 (3H, s), 2.44−2.63 (2H, m), 2.64 (1H, dd, J = 15.4, 5.5 Hz), 2.88 (1H, dd, J = 15.2, 9.0 Hz), 3.14−3.34 (1H, m), 3.69 (3H, s), 3.92−4.19 (2H, m), 4.16 (2H, d, J = 6.1 Hz), 6.21 (1H, br s), 6.44 (1H, br s), 6.52 (1H, d, J = 8.7 Hz), 6.62 (1H, d, J = 8.0 Hz), 6.80−6.93 (2H, m), 7.14 (1H, d, J = 8.4 Hz), 7.28 (1H, t, J = 7.3 Hz), 7.60 (1H, t, J = 7.8 Hz), 11.94 (1H, br s). ^{13}C NMR (101 MHz, DMSO-d_6): δ 4.0, 4.4, 16.6, 23.8, 28.2, 33.7, 35.0, 38.8, 47.2, 49.3, 53.4, 55.0, 69.4, 104.1, 106.3, 107.9, 115.0, 117.5, 119.3, 124.1, 130.9, 136.5, 139.2, 150.8, 155.1, 155.5, 160.6, 160.8, 162.6, 170.6, 173.3. MS (ESI/APCI): m/z 615.5 $[M + H]^+$. mp 139−141 °C. $C_{36}H_{46}N_4O_5$: 0.1 H_2O: C, 70.13; H, 7.55; N, 9.09. Found: C, 70.19; H, 7.37; N, 8.98. HPLC purity 99.8%. *The corresponding intermediate*: ethyl 3-cyclopropyl-3-(6-((1-(5-methoxy-2-((6-methylpyridin-2-yl)(neopentyl)carbamoyl) phenyl)piperidin-4-yl)methoxy)-pyridin-2-yl)propanoate (100 mg, 0.358 mmol, 84%). White amorphous solid (243 mg, 0.358 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.20−0.36 (2H, m), 0.38−0.51 (1H, m), 0.53−0.64 (1H, m), 0.82 (9H, s), 1.04−1.15 (1H, m), 1.19 (3H, t, J = 7.2 Hz), 1.22−1.34 (1H, m), 1.58−1.86 (4H, m), 2.04 (1H, s), 2.35−2.49 (2H, m), 2.44 (3H, s), 2.60 (2H, br s), 2.77 (1H, dd, J = 15.1, 6.1 Hz), 3.01 (1H, dd, J = 15.4, 8.3 Hz), 3.39 (1H, br s), 3.75 (3H, s), 3.97−4.41 (6H, m), 6.19 (1H, br s), 6.33 (1H, br s), 6.48 (1H, d, J = 8.8 Hz), 6.56 (1H, d, J = 8.2 Hz), 6.70 (1H, d, J = 7.2 Hz), 6.78 (1H, d, J = 7.2 Hz), 7.09 (1H, br s), 7.29 (1H, d, J = 8.4 Hz), 7.48 (1H, t, J = 7.7 Hz).

*3-Cyclopropyl-3-{2-[(1-{2-[(2,2-dimethylpropyl)(6-methylpyridin-2-yl)carbamoyl]-5-methoxyphenyl}piperidin-4-yl)methoxy]pyridin-4-yl}propanoic Acid (**7f**).* NaOH (20 mL, 20.00 mmol, 1 M) was added to a solution of ethyl 3-cyclopropyl-3-(2-((1-(5-methoxy-2-((6-methylpyridin-2-yl)(neopentyl)carbamoyl)phenyl)piperidin-4-yl)-methoxy)pyridin-4-yl)propanoate **64b** (1.95 g, 3.03 mmol) in THF (20 mL) and MeOH (10.00 mL) at room temperature. The mixture was stirred at 50 °C for 30 min. The mixture was neutralized with 1 N HCl at r.t. and extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, filtered through a silica gel pad, and concentrated in vacuo. The residue was crystallized from EtOAc (8 mL)/hexane (45 mL) to give the target compound as a white solid (washed with hex/AcOEt = 6:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 0.11−0.21 (1H, m), 0.22−0.40 (2H, m), 0.46−0.57 (1H, m), 0.77 (9H, s), 0.92−1.07 (1H, m), 1.08−1.32 (1H, m), 1.40−1.84 (4H, m), 2.18−2.28 (1H, m), 2.31−2.66 (3H, m), 2.36 (3H, s), 2.68 (2H, d, J = 7.2 Hz), 3.21−3.32 (1H, m), 3.69 (3H, s), 3.91−4.27 (4H, m), 6.21 (1H, s), 6.45 (1H, br s), 6.52 (1H, d, J = 8.8 Hz), 6.71 (1H, s), 6.85 (1H, d, J = 7.2 Hz), 6.91 (1H, d, J = 5.3 Hz), 7.14 (1H, d, J = 8.4 Hz), 7.28 (1H, t, J = 7.5 Hz), 8.04 (1H, d, J = 5.3 Hz), 12.08 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 4.2, 5.3, 16.6, 24.3, 28.4, 28.8, 34.1, 35.6, 40.2, 46.1, 55.2, 55.8, 70.6, 104.6, 106.0, 109.5, 116.1, 117.9, 119.1, 124.6, 131.3, 136.0, 146.7, 151.4, 155.7, 155.8, 156.1, 161.2, 164.4, 171.7, 175.7. Two C peaks next to the nitrogen of the piperidine ring were not detected. MS (ESI/APCI): m/z 615.3 $[M + H]^+$. Calcd for $C_{36}H_{46}N_4O_5$: C, 70.33; H, 7.54; N, 9.11. Found: C, 70.24; H, 7.48; N, 9.09. HPLC purity 97.6%.

*3-Cyclopropyl-3-{2-[(1-{2-[(2,2-dimethylpropyl)(6-methylpyridin-2-yl)carbamoyl]-5-methoxyphenyl}piperidin-4-yl)methoxy]pyridin-4-yl}propanoic Acid ((**S**)-**7f**, tR1).* The racemic **7f** (197.7 mg, 0.31 mmol) was purified by chiral HPLC. The desired fraction was concentrated in vacuo to give 3-cyclopropyl-3-(2-((1-(5-methoxy-2-((6-methylpyridin-2-yl)(neopentyl)carbamoyl)phenyl)piperidin-4-yl)methoxy)pyridin-4-yl)propanoic acid (78 mg, 0.127 mmol, 41%, >99.9% ee) as a white powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 0.18 (1H, dd, J = 7.9, 4.6 Hz), 0.22−0.42 (2H, m), 0.44−0.60 (1H, m), 0.77 (9H, s), 0.93−1.06 (1H, m), 1.23 (1H, br s), 1.42−1.90 (4H, m), 2.17−2.30 (2H, m), 2.36 (5H, s), 2.53−2.71 (3H, m), 3.69 (3H, s), 3.94−4.27 (4H, m), 6.21 (1H, d, J = 2.3 Hz), 6.39−6.57 (2H, m), 6.70 (1H, s), 6.84 (1H, d, J = 7.6 Hz), 6.91 (1H, dd, J = 5.3, 1.3 Hz), 7.14 (1H, d, J = 8.4 Hz), 7.28 (1H, t, J = 7.8 Hz), 8.04 (1H, d, J = 5.3 Hz), 12.09 (1H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 4.2, 5.3, 16.6, 24.3, 28.4, 28.7, 34.1, 35.6, 40.3, 46.1, 55.2, 55.8, 70.6, 104.6, 106.0, 109.5, 116.1, 118.0, 119.2, 124.6, 131.3, 136.0, 146.7, 151.4, 155.6, 155.8, 156.1, 161.2, 164.3, 171.8, 176.1. Two C peaks next to the nitrogen of the piperidine ring were not detected. MS (ESI/APCI): m/z 615.5$[M + H]^+$. mp 153−154 °C. Calcd for $C_{36}H_{46}N_4O_5$: C, 70.33; H, 7.54; N, 9.11. Found: C, 70.24; H, 7.48; N, 9.09. HPLC purity 100%. $[\alpha]_D^{20}$ +17.49 (c 1.0, MeOH).

*3-Cyclopropyl-3-{2-[(1-{2-[(2,2-dimethylpropyl)(6-methylpyridin-2-yl)carbamoyl]-5-methoxyphenyl}piperidin-4-yl)methoxy]pyridin-4-yl}propanoic Acid ((**R**)-**7f**, tR2).* Compound (**R**)-**7f** was prepared in a manner similar to that described for compound (**S**)-**7f**. The desired fraction was concentrated in vacuo to give 3-cyclopropyl-3-(2-((1-(5-methoxy-2-((6-methylpyridin-2-yl)(neopentyl)carbamoyl)phenyl)-piperidin-4-yl)methoxy)pyridin-4-yl)propanoic acid (73.6 mg, 0.120 mmol, 38.9%, 97% ee) as a powder. ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 0.10−0.22 (1H, m), 0.22−0.41 (2H, m), 0.45−0.58 (1H, m), 0.77 (9H, s), 0.91−1.09 (1H, m), 1.11−1.32 (1H, m), 1.42−1.86 (4H, m), 2.17−2.30 (2H, m), 2.36 (5H, s), 2.53−2.71 (3H, m), 3.69 (3H, s), 3.92−4.29 (4H, m), 6.21 (1H, d, J = 2.5 Hz), 6.40−6.55 (2H, m), 6.70 (1H, s), 6.84 (1H, d, J = 7.6 Hz), 6.91 (1H, dd, J = 5.3, 1.3 Hz), 7.14 (1H, d, J = 8.4 Hz), 7.28 (1H, t, J = 7.9 Hz), 8.04 (1H, d, J = 5.4 Hz), 12.09 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 4.2, 5.3, 16.6, 24.3, 28.4, 28.8, 34.1, 35.6, 40.2, 46.1, 55.2, 55.7, 70.6, 104.6, 106.0, 109.5, 116.1, 118.0, 119.1, 124.6, 131.3, 136.0, 146.7, 151.4, 155.7, 155.8, 156.1, 161.2, 164.4, 171.7, 175.7. Two C peaks next to the nitrogen of the piperidine ring were not detected. MS (ESI/APCI): m/z 615.5 $[M + H]^+$. Calcd for $C_{36}H_{46}N_4O_5$: C, 68.66; H, 7.52; N, 11.12. Found: C, 68.58; H, 7.47; N, 11.05. HPLC purity 99.5%.

*5-(3-Hydroxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**9**).* To a solution of 3-hydroxybenzaldehyde **8** (20 g, 163.77 mmol) in water (600 mL) was added 2,2-dimethyl-1,3-dioxane-4,6-dione (23.60 g, 163.77 mmol) at room temperature. The mixture was stirred at room temperature for 24 h. After evaporation and addition of water, the mixture was extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$, and concentrated in vacuo to give the title compound (39.2 g, 158 mmol, 97%) as a pale-yellow solid. This product was used without further purification. ^{1}H NMR (300 MHz, CDCl3): δ 1.81 (6H, s), 5.36 (1H, s), 7.00−7.15 (1H, m), 7.29−7.41 (1H, m), 7.43−7.52 (1H, m), 7.73−7.80 (1H, m), 8.36 (1H, s). MS (ESI/APCI): m/z not detected. HPLC 97.6% (LC−MS).

*5-(Cyclopropyl(3-hydroxyphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**10**).* To a solution of compound **9** (26.1 g, 105.1 mmol) in THF (dry) (780 mL) was added cyclopropylmagnesium bromide (900 mL, 630 mmol) at −10−0 °C. The mixture was stirred at room temperature for 1.5 h. After addition of 1 N HCl aq (1050 mL), EtOAc (270 mL) was added. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−50% EtOAc in hexane) to give the title compound (28.5 g, 98 mmol, 93%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_s$): δ 0.16−

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0.28 (1H, m), 0.32−0.46 (1H, m), 0.58−0.79 (2H, m), 1.32 (3H, s), 1.68 (3H, s), 1.85−2.04 (1H, m), 2.80−2.89 (1H, m), 3.86 (1H, d, J = 3.0 Hz), 5.14 (1H, br s), 6.75 (1H, d, J = 0.8 Hz), 6.84−6.94 (2H, m), 7.10−7.22 (1H, m). MS (ESI/APCI): m/z 291.1 $[M + H]^+$. HPLC 95.6% (LC−MS).

*Methyl 3-Cyclopropyl-3-(3-hydroxyphenyl)propanoate (**11a**).* H_2SO_4 (2.56 mL, 48.02 mmol) was added to a solution of 3-cyclopropyl-3-(3-hydroxyphenyl)propanoic acid (99 g, 480.03 mmol) in MeOH (990 mL) at room temperature. The mixture was stirred at 64 °C for 2 h. The mixture was quenched with water and NaCl at room temperature and extracted with EtOAc. The organic layer was separated, washed with sat. $NaHCO_3$ aq and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 25% EtOAc in hexane) to give methyl 3-cyclopropyl-3-(3-hydroxyphenyl)propanoate (84 g, 381 mmol, 79%) as a pale-yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.04−0.14 (1H, m), 0.14−0.23 (1H, m), 0.27−0.37 (1H, m), 0.44−0.53 (1H, m), 0.92−1.04 (1H, m), 2.13−2.23 (1H, m), 2.60−2.76 (2H, m), 3.51 (3H, s), 6.58 (1H, d, J = 8.0 Hz), 6.63 (1H, s), 6.66 (1H, d, J = 7.7 Hz), 7.06 (1H, t, J = 7.7 Hz), 9.24 (1H, s).

*Ethyl 3-Cyclopropyl-3-(3-hydroxyphenyl)propanoate (**11b**).* A solution of compound **10** (62.34 g, 214.74 mmol) in EtOH (63 mL) and DMF (126 mL) was stirred at 100 °C for 7 h. The resulting mixture was concentrated in vacuo and diluted with ethyl acetate. The mixture was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to yield a brown oil. The oil was purified by column chromatography (silica gel, eluted with 10−25% EtOAc in hexane) to give the title compound (27.0 g, 115 mmol, 54%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.14 (1H, dq, J = 9.5, 4.9 Hz), 0.26 (1H, dq, J = 9.4, 4.8 Hz), 0.37−0.47 (1H, m), 0.52−0.61 (1H, m), 0.94−1.05 (1H, m), 1.17 (3H, t, J = 7.2 Hz), 1.67 (1H, s), 2.26−2.36 (1H, m), 2.59−2.79 (2H, m), 3.99−4.10 (2H, m), 5.22 (1H, s), 6.68 (1H, dd, J = 8.0, 1.6 Hz), 6.71 (1H, s), 6.79 (1H, d, J = 7.5 Hz), 7.16 (1H, t, J = 7.8 Hz).

*Ethyl 3-(3-(Benzyloxy)phenyl)-3-hydroxypropanoate (**13**).* To a solution of diisopropylamine (4.32 g, 42.7 mmol) in THF (dry) (100 mL) was added butyllithium (12.07 mL, 19.32 mmol) dropwise at −78 °C and stirred for 15 min. To the mixture was added ethyl acetate (3.44 g, 39.1 mmol) and stirred for 1 h and then 3-(benzyloxy)benzaldehyde **12** (4.1 g, 19.32 mmol) was added. The mixture was stirred for 1h and quenched with sat. NH_4Cl aq and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−25% EtOAc in hexane) to give the title compound (5.05 g, 16.81 mmol, 87%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.27 (3H, t, J = 7.2 Hz), 2.63−2.81 (2H, m), 3.24 (1H, d, J = 3.4 Hz), 4.19 (2H, q, J = 7.2 Hz), 5.07 (2H, s), 5.11 (1H, dt, J = 8.0, 3.8 Hz), 6.90 (1H, dd, J = 8.2, 1.8 Hz), 6.96 (1H, d, J = 7.5 Hz), 7.05 (1H, s), 7.22−7.49 (6H, m). MS (ESI/APCI): m/z 299.1 $[M - H]^-$. HPLC 95.9% (LC−MS).

*Ethyl 3-(3-Hydroxyphenyl)-3-methoxypropanoate (**14a**).* A mixture of compound **13** (2.5 g, 8.32 mmol), iodomethane (4.73 g, 33.29 mmol), and silver(I) oxide (3.86 g, 16.65 mmol) in toluene (50 mL) was stirred at 100 °C under N_2 for 15 h. The insoluble material was removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−10% EtOAc in hexane) to give the corresponding methyl ether (1.810 g, 5.76 mmol, 69%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.18−1.27 (3H, m), 2.56 (1H, dd, J = 15.3, 4.6 Hz), 2.77 (1H, dd, J = 15.3, 9.2 Hz), 3.22 (3H, s), 4.09−4.25 (2H, m), 4.61 (1H, dd, J = 9.2, 4.6 Hz), 5.07 (2H, s), 6.86−6.95 (2H, m), 6.95−7.01 (1H, m), 7.18−7.49 (6H, m). MS (ESI/APCI): m/z not detected. A mixture of the obtained compound and 10% Pd−C (150 mg, 1.41 mmol) in EtOH (10 mL) and THF (10 mL) was hydrogenated under balloon pressure at room temperature overnight. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to give the title compound (0.900 g, 4.01 mmol, 69%) as a colorless oil. This product was used without further purification. ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 1.10−1.17 (3H, m), 2.53−2.71 (2H, m), 3.09 (3H, s), 3.98−4.09 (2H, m), 4.46 (1H, dd, J = 8.7, 5.2 Hz), 6.63−6.77 (3H, m), 7.14 (1H, td, J = 7.5, 0.8 Hz), 9.40 (1H, s). MS (ESI/APCI) not detected. HPLC 94.9% (LC−MS).

*Ethyl 3-Ethoxy-3-(3-hydroxyphenyl)propanoate (**14b**).* Compound **14b** was prepared from compound **13** (2.5 g, 8.32 mmol) and iodoethane (5.19 g, 33.29 mmol) in a manner similar to that described for compound **14a**. Colorless oil (0.660 g, 2.77 mmol, 77%). ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 1.05 (3H, t, J = 7.0 Hz), 1.10−1.19 (3H, m), 2.53−2.68 (2H, m), 3.19−3.34 (2H, m), 3.95−4.13 (2H, m), 4.57 (1H, dd, J = 8.5, 5.5 Hz), 6.62−6.76 (3H, m), 7.08−7.17 (1H, m), 9.38 (1H, s). MS (ESI/APCI) not detected. HPLC 95.5% (LC−MS).

*2-Methoxy-1-(3-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-ethanone (**16**).* To a solution of methyl 2-methoxyacetate **15** (3.79 g, 36.36 mmol) in THF (dry) (50 mL) was added (3-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)magnesium bromide (80 mL, 40.00 mmol) dropwise at −78 °C and stirred for 1 h. To the mixture was added methyl 2-methoxyacetate (3.79 g, 36.36 mmol) and stirred at r.t. for 3 h. The mixture was poured into water and insoluble materials were removed by filtration and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give the title compound (9.00 g, 36.0 mmol, 99%) as a brown oil. This product was used without further purification.

*(Z)-Ethyl 3-(3-Hydroxyphenyl)-4-methoxybut-2-enoate (**17**).* To a suspension of NaH (2.88 g, 71.92 mmol) in THF (100 mL) was added ethyl 2-(diethoxyphosphoryl)acetate (16.12 g, 71.92 mmol) at 0 °C and stirred for 30 min. To the mixture was added compound **16** (9 g, 35.96 mmol) and stirred at 50 °C for 15 h. The reaction mixture was quenched with sat. NH_4Cl aq and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give (*Z*)-ethyl 4-methoxy-3-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)but-2-enoate (11.00 g, 34.3 mmol) as a brown oil. The obtained product was dissolved in AcOH (50 mL). Zinc (22.45 g, 343.34 mmol) was added portionwise thereto at room temperature. The mixture was stirred at 50 °C for 3 h. The reaction mixture was filtered through Celite pad, and the filtrate was concentrated in vacuo. The residue was dissolved in 1 N HCl and washed with EtOAc. The aqueous layer was basified with $NaHCO_3$ and extracted with AcOEt, washed with sat. $NaHCO_3$ aq and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−25% EtOAc in hexane) to give the title compound (0.390 g, 1.651 mmol, 4.8%, over 3 steps) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.20 (3H, t, J = 7.2 Hz), 3.49 (2H, s), 3.72 (3H, s), 4.12 (2H, q, J = 7.1 Hz), 5.02 (1H, br s), 6.52 (1H, s), 6.66 (1H, dd, J = 8.0, 2.0 Hz), 6.75 (1H, t, J = 1.9 Hz), 6.84 (1H, d, J = 7.7 Hz), 7.14 (1H, t, J = 7.9 Hz). MS (ESI/APCI): m/z not detected. HPLC 93.1% (LC−MS).

*Ethyl 3-(3-Hydroxyphenyl)-4-methoxybutanoate (**18**).* A mixture of compound **17** (390 mg, 1.65 mmol) and 10% Pd−C (50 mg, 0.47 mmol) in EtOH (5 mL) was hydrogenated under balloon pressure at room temperature overnight. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to give the title compound (380 mg, 1.595 mmol, 97%) as a colorless oil. This product was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.17 (3H, t, J = 7.1 Hz), 2.51−2.63 (1H, m), 2.71−2.86 (1H, m), 3.32 (3H, s), 3.34−3.59 (3H, m), 4.00−4.11 (2H, m), 4.93 (1H, br s), 6.62−6.73 (2H, m), 6.75−6.83 (1H, m), 7.10−7.23 (1H, m). MS (ESI/APCI): m/z 237.1 $[M-H]^-$

*Ethyl 2-(Oxetan-3-ylidene)acetate (**20**).* (Carbethoxymethylene)-triphenylphosphorane (3.83 g, 11.00 mmol) was added to a solution of oxetan-3-one **19** (0.721 g, 10 mmol) in THF (dry) (20 mL) at 0 °C. The mixture was stirred at room temperature under N_2 overnight. To the reaction mixture were added silica gel and hexane, and the precipitate was removed by filtration. The filtrate was concentrated in vacuo to give the title compound (1.09 g, 7.21 mmol, 72%) as a colorless oil. This product was subjected to the next reaction without

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further purification. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.19 (3H, t, J = 7.0 Hz), 4.08 (2H, q, J = 7.2 Hz), 5.20−5.28 (2H, m), 5.33−5.41 (2H, m), 5.75 (1H, quin, J = 2.4 Hz).

*Ethyl 2-(3-(3-(Benzyloxy)phenyl)oxetan-3-yl)acetate (**21**).* To a solution of chloro(1,5-cyclooctadiene)rhodium(I), dimer (73.5 mg, 0.15 mmol) in dioxane (5 mL) was added KOH (3.73 mL, 5.59 mmol), and the yellow solution was stirred for 15 min. Then, a mixture of (3-(benzyloxy)phenyl)boronic acid (1701 mg, 7.46 mmol) and compound **20** (530 mg, 3.73 mmol) in dioxane (5 mL) was slowly added, and the color of the solution turned to orange. After the mixture was stirred for 30 min at room temperature, the reaction was quenched by the addition of brine (40 mL). The aqueous phase was extracted two times with AcOEt. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, eluted with 0−25% EtOAc in hexane) to give the title compound (1.3 g) as a slightly yellow oil. This product was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.13 (3H, t, J = 7.2 Hz), 3.09 (2H, s), 3.97−4.05 (2H, m), 4.81−4.87 (2H, m), 4.99 (2H, d, J = 6.3 Hz), 5.05 (2H, s), 6.72−6.77 (1H, m), 6.78−6.81 (1H, m), 6.86 (1H, ddd, J = 8.3, 2.5, 0.7 Hz), 7.22−7.28 (1H, m), 7.29−7.47 (5H, m).

*Ethyl 2-(3-(3-Hydroxyphenyl)oxetan-3-yl)acetate (**22**).* Compound **22** was prepared from compound **21** (1.3 g, 3.98 mmol) in a manner similar to that described for compound **14a**. Colorless oil (0.818 g, 3.46 mmol, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 1.13 (3H, t, J = 7.1 Hz), 3.10 (2H, s), 4.02 (2H, q, J = 7.2 Hz), 4.86 (2H, d, J = 6.3 Hz), 5.00 (2H, d, J = 6.2 Hz), 5.42 (1H, s), 6.63−6.70 (2H, m), 6.72 (1H, d, J = 2.1 Hz), 7.20 (1H, t, J = 7.9 Hz).

*Methyl 2′-Formyl-5′-methoxy-[1,1′-biphenyl]-4-carboxylate (**24**).* A mixture of 2-bromo-4-methoxybenzaldehyde **23** (1 g, 4.65 mmol), (4-(methoxycarbonyl)phenyl)boronic acid (1.26 g, 6.98 mmol), $Pd(Ph_3P)_4$ (0.269 g, 0.23 mmol), and 2 M Na_2CO_3 (4.65 mL, 9.30 mmol) in dimethyl ether (DME) (13 mL) was heated at 130 °C for 1 h under microwave irradiation under N_2. The mixture was poured into water, and the aqueous phase was extracted with EtOAc twice. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 3−20% EtOAc in hexane) to give the title compound(1.25 g, 4.62 mmol, 99%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (3H, s), 3.97 (3H, s), 6.87 (1H, d, J = 2.5 Hz), 7.04 (1H, ddd, J = 8.8, 2.5, 0.8 Hz), 7.43−7.51 (2H, m), 8.04 (1H, d, J = 8.8 Hz), 8.10−8.17 (2H, m), 9.81 (1H, d, J = 0.8 Hz). MS (ESI/APCI): m/z 271.1 $[M + H]^+$. HPLC 95.8% (LC−MS).

*Methyl 2′-(4,4-Dimethylpentyl)-5′-methoxy-[1,1′-biphenyl]-4-carboxylate (**25**).* To a solution of (3,3-dimethylbutyl)-triphenylphosphate(III), MsOH (16.41 g, 37.00 mmol) in THF (dry) (100 mL) was added potassium 2-methyl-propan-2-olate (8.30 g, 74.00 mmol) and stirred for 30 min. To the reaction mixture was added compound **24** (2 g, 7.40 mmol) and stirred at 50 °C for 10 min. The mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−10% EtOAc in hexane) to give the corresponding olefin (5.5 g) as a colorless oil. MS (ESI/APCI): m/z 339.2 $[M + H]^+$. The title compound was reduced in a manner similar to that described for compound **18**. Colorless oil (2.200 g, 6.46 mmol, 40%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.67−0.76 (9H, m), 0.91−1.02 (2H, m), 1.20−1.30 (2H, m), 1.57 (3H, s), 2.43 (2H, t, J = 7.7 Hz), 3.75 (3H, s), 6.66−6.74 (1H, m), 6.91 (1H, dd, J = 8.5, 2.8 Hz), 7.24 (1H, d, J = 8.5 Hz), 7.41−7.50 (2H, m), 7.90−8.03 (2H, m).

*(2′-(4,4-Dimethylpentyl)-5′-methoxy-[1,1′-biphenyl]-4-yl)-methanol (**26**).* To a solution of compound **25** (2.2 g, 6.46 mmol) in THF (20 mL) was added $LiAlH_4$ (0.270 g, 7.11 mmol) portionwise at 0 °C and stirred for 30 min. To the reaction mixture were added H_2O (0.33 mL), 15% NaOH (0.33 mL), and H_2O (0.99 mL) and stirred for 1 h. The insoluble material was removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−15% EtOAc in hexane) to give the title compound (1.13 g, 3.62 mmol, 56%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.75 (9H, s), 0.93−1.03 (2H, m), 1.25−1.36 (2H, m), 2.43 (2H, t, J = 7.7 Hz), 3.74 (3H, s), 4.54 (2H, d, J = 5.6 Hz), 5.19 (1H, t, J = 5.7 Hz), 6.67 (1H, d, J = 2.6 Hz), 6.86 (1H, dd, J = 8.5, 2.6 Hz), 7.17−7.28 (3H, m), 7.36 (2H, d, J = 7.8 Hz). MS (ESI/APCI): m/z 295.2. HPLC 99.2% (LC−MS).

*2-(4-Hydroxypiperidin-1-yl)-4-methoxybenzaldehyde (**28**).* A mixture of 2-fluoro-4-methoxybenzaldehyde **27** (9.83 g, 63.8 mmol), piperidin-4-ol (4.3 g, 42.5 mmol), Cs_2CO_3 (27.7 g, 85.0 mmol), and tetrabutylammonium iodide (TBAI) (1.57 g, 4.25 mmol) in DMF (dry) (100 mL) was stirred at 110 °C for 15 h. The mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−50% EtOAc in hexane) to give the title compound Cs_2CO_3 (4.24 g, 18.02 mmol, 42%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55 (1H, d, J = 4.1 Hz), 1.69−1.86 (2H, m), 2.01−2.11 (2H, m), 2.85−3.01 (2H, m), 3.21−3.41 (2H, m), 3.86 (3H, s), 3.91 (1H, td, J = 8.1, 4.2 Hz), 6.56 (1H, d, J = 2.3 Hz), 6.62 (1H, dd, J = 8.6, 2.1 Hz), 7.79 (1H, d, J = 8.7 Hz), 10.13 (1H, s).

*1-(2-(4,4-Dimethylpentyl)-5-methoxyphenyl)piperidin-4-ol (**29**).* Compound **29** was prepared from compound **28** in a manner similar to that described for compound **25**. Colorless oil (220 mg, 0.720 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 0.87 (9H, s), 1.19−1.31 (2H, m), 1.47−1.62 (2H, m), 1.65−1.81 (2H, m), 2.00 (2H, d, J = 9.7 Hz), 2.53 (2H, t, J = 7.9 Hz), 2.64−2.77 (2H, m), 2.99−3.14 (2H, m), 3.78 (3H, s), 3.79−3.88 (1H, m), 6.58 (1H, dd, J = 8.3, 2.4 Hz), 6.64 (1H, d, J = 2.5 Hz), 7.10 (1H, d, J = 8.3 Hz).

*2-(4-(Hydroxymethyl)piperidin-1-yl)-4-methoxybenzaldehyde (**30**).* Compound **30** was prepared from **27** in a manner similar to that described for compound **28**. Light-yellow oil (12.6 g, 50.4 mmol, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (1H, t, J = 5.5 Hz), 1.42−1.56 (2H, m), 1.58−1.75 (1H, m), 1.87 (2H, dd, J = 12.5, 1.8 Hz), 2.79−2.90 (3H, m), 3.36 (2H, d, J = 12.4 Hz), 3.59 (2H, t, J = 5.8 Hz), 3.86 (3H, s), 6.50−6.64 (2H, m), 7.79 (1H, d, J = 8.6 Hz), 10.12 (1H, d, J = 0.6 Hz). MS (ESI/APCI): m/z 250.1 $[M + H]^+$. HPLC 95.3% (LC−MS).

*(1-(2-(4,4-Dimethylpentyl)-5-methoxyphenyl)piperidin-4-yl)-methanol (**31**).* A mixture of diisopropylamine (74.08 g, 173.49 mmol) in dried THF (500 mL) was cooled to −78 °C. Then, to the mixture was dropwise added *n*-BuLi (130.1 mL, 2.5 N, 325.30 mmol) at −78 °C. The mixture was stirred at −78 °C for 30 min. Then, to the mixture was dropwise added a solution of **30** (27 g, 108.43 mmol) in THF (100 mL) at −78 °C and the mixture was stirred at −78 °C for 1 h. The reaction mixture was slowly poured into ice water (500 mL) and extracted with ethyl acetate (1000 mL). The organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo, and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, from 20/1 to 5/1) to give the olefin product (18.5 g, yield: 53%) as an off-white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.94−0.96 (9H, m), 1.42−1.48 (2H, m), 1.62−1.69 (1H, m), 1.84 (2H, d, J = 10.5 Hz), 2.11−2.26 (2H, m), 2.61−2.65 (2H, m), 3.32−3.38 (2H, m), 3.59−3.62 (2H, m), 3.79 (3H, s), 5.68−6.12 (1H, m), 6.49−6.58 (3H, m), 7.18−7.38 (1H, m). An OH peak was not observed. MS (ESI/APCI): m/z 318.3 $[M + H]^+$. The solution of the obtained product (22.2 g, 69.9 mmol) and Pd−C (1 g, 0.94 mmol) in EtOH (200 mL) was stirred at r.t. for 21.5 h under a H_2 atmosphere. The reaction mixture was filtered with Celite and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−70% EtOAc in hexane) to give the title compound (21.90 g, 68.5 mmol, 98%) as a pale-yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.76−0.91 (9H, m), 1.10−1.61 (7H, m), 1.74 (2H, d, J = 10.1 Hz), 2.38−2.68 (4H, m), 2.95 (2H, d, J = 11.8 Hz), 3.23−3.39 (2H, m), 3.70 (3H, s), 4.45 (1H, t, J = 5.3 Hz), 6.48−6.66 (2H, m), 7.05 (1H, d, J = 8.3 Hz). MS (ESI/APCI): m/z 320.2 $[M + H]^+$. HPLC 94.1% (LC−MS).

*Methyl 1-(2-Formyl-5-methoxyphenyl)azetidine-3-carboxylate (**32**).* The title compound was prepared from compound **27** (1.65 g, 10.7 mmol) and methyl azetidine-3-carboxylate hydrochloride

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(1.48 g, 9.76 mmol) in DMSO (30 mL) in a manner similar to that described for compound **28**. Yellow oil (1.00 g, 4.02 mmol, 41%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.53−3.64 (1H, m), 3.75 (3H, s), 3.85 (3H, s), 4.13−4.19 (2H, m), 4.28−4.36 (2H, m), 5.94 (1H, d, J = 2.3 Hz), 6.44 (1H, dd, J = 8.8, 2.3 Hz), 7.62 (1H, d, J = 8.8 Hz), 9.80 (1H, s). MS (ESI/APCI): m/z 250.1 $[M + H]^+$. HPLC 100% (LC−MS).

*(1-(2-(4,4-Dimethylpentyl)-5-methoxyphenyl)azetidin-3-yl)-methanol (**33**).* Compound **33** was prepared from compound **32** (300 mg, 1.20 mmol) in a manner similar to that described for compound **24** and **25** (purification: silica gel, eluted with 0−30% EtOAc in hexane). Colorless oil (18.3 mg, 0.063 mmol, 5% over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (9H, s), 1.20−1.27 (2H, m), 1.46−1.59 (2H, m), 1.63 (1H, t, J = 4.9 Hz), 2.39−2.47 (2H, m), 2.70−2.84 (1H, m), 3.68 (2H, dd, J = 7.2, 4.8 Hz), 3.77 (3H, s), 3.86−3.92 (2H, m), 3.98 (2H, t, J = 7.5 Hz), 6.06 (1H, d, J = 2.5 Hz), 6.33 (1H, dd, J = 8.3, 2.5 Hz), 6.96 (1H, d, J = 8.3 Hz). MS (ESI/APCI): m/z 292.2 $[M + H]^+$. HPLC 100% (LC−MS).

*Ethyl 1-(3-Methoxyphenyl)piperidine-4-carboxylate (**35b**).* To a mixture of ethyl isonipecotate (0.978 mL, 6.36 mmol), *m*-bromoanisole (**34b**, 0.797 mL, 6.36 mmol), BINAP (0.436 g, 0.70 mmol), and Cs_2CO_3 (6.22 g, 19.08 mmol) was added $Pd(OAc)_2$ (0.143 g, 0.64 mmol). The mixture was stirred at 100 °C for 24 h. The mixture was quenched with water and extracted with EtOAc. The organic layer was separated, washed with water and brine successively, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−30% EtOAc in hexane) to give the title compound (1.33 g, 5.05 mmol, 79%) as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (3H, t, J = 7.1 Hz), 1.75−1.95 (2H, m), 1.95−2.07 (2H, m), 2.34−2.49 (1H, m), 2.72−2.86 (2H, m), 3.64 (2H, dt, J = 12.7, 3.3 Hz), 3.79 (3H, s), 4.15 (2H, q, J = 7.2 Hz), 6.35−6.45 (1H, m), 6.47 (1H, t, J = 2.3 Hz), 6.55 (1H, dd, J = 8.0, 2.0 Hz), 7.16 (1H, t, J = 8.2 Hz). MS (ESI/APCI): m/z 264.2 $[M + H]^+$. HPLC 95.3% (LC−MS).

*Ethyl 1-(2-Fluoro-5-methoxyphenyl)piperidine-4-carboxylate (**35c**).* Compound **35c** was prepared from compound **34c** (1.0 g, 4.88 mmol) and ethyl piperidine-4-carboxylate (1.15 g, 7.32 mmol) in a manner similar to that described for compound **35c**. Pale-yellow oil (916 mg, 3.26 mmol, 67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (3H, t, J = 7.2 Hz), 1.86−2.08 (4H, m), 2.35−2.49 (1H, m), 2.72 (2H, td, J = 11.4, 3.0 Hz), 3.43 (2H, dt, J = 11.9, 3.1 Hz), 3.76 (3H, s), 4.16 (2H, q, J = 7.1 Hz), 6.40 (1H, dt, J = 8.7, 3.2 Hz), 6.49 (1H, dd, J = 7.2, 3.0 Hz), 6.92 (1H, dd, J = 12.1, 8.7 Hz). HPLC 96.6% (LC−MS).

*(1-(3-Methoxyphenyl)piperidin-4-yl)methanol (**36b**).* Compound **36b** was prepared from compound **35b** (325 mg, 1.23 mmol) in a manner similar to that described for compound **26**. Colorless oil (306 mg, 1.383 mmol, quant). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (1H, t, J = 1.0 Hz), 1.23−1.47 (2H, m), 1.61−1.74 (1H, m), 1.85 (2H, dt, J = 6.9, 3.2 Hz), 2.72 (2H, td, J = 12.3, 2.7 Hz), 3.55 (2H, t, J = 6.1 Hz), 3.66−3.76 (2H, m), 3.79 (3H, s), 6.39 (1H, dd, J = 7.6, 2.3 Hz), 6.49 (1H, t, J = 2.5 Hz), 6.56 (1H, dd, J = 8.0, 1.9 Hz), 7.16 (1H, t, J = 8.1 Hz).

*(1-(2-Fluoro-5-methoxyphenyl)piperidin-4-yl)methanol (**36c**).* Compound **36c** was prepared from compound **35c** (400 mg) in a manner similar to that described for compound **26** (purification: column chromatography (silica gel, eluted with 20−60% EtOAc in hexane)). Colorless oil (354 mg, 1.479 mmol, quant). This product was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (1H, t, J = 5.5 Hz), 1.39−1.54 (2H, m), 1.58−1.75 (1H, m), 1.85 (2H, dd, J = 12.7, 1.7 Hz), 2.65 (2H, td, J = 11.8, 2.1 Hz), 3.48 (2H, d, J = 12.1 Hz), 3.56 (2H, t, J = 5.9 Hz), 3.77 (3H, s), 6.40 (1H, dt, J = 8.8, 3.2 Hz), 6.51 (1H, dd, J = 7.2, 3.0 Hz), 6.92 (1H, dd, J = 12.3, 8.9 Hz).

*(1-(5-Methoxy-2-methylphenyl)piperidin-4-yl)methanol (**36d**).* Compound **36d** was prepared from compound **34d** (2 g, 9.95 mmol) and piperidin-4-ylmethanol (3.44 g, 29.8 mmol) in a manner similar to that described for compound **34c**. Pale-brown oil (0.760 g, 3.23 mmol, 33%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29−1.39 (1H, m), 1.45 (2H, td, J = 12.1, 3.8 Hz), 1.57−1.73 (1H, m), 1.82 (2H, dd, J = 12.3, 2.0 Hz), 2.21 (3H, s), 2.61 (2H, td, J = 11.7, 2.3 Hz), 3.11−3.22 (2H, m), 3.57 (2H, d, J = 1.9 Hz), 3.78 (3H, s), 6.51 (1H, dd, J = 8.2, 2.6 Hz), 6.59 (1H, d, J = 2.5 Hz), 7.06 (1H, dd, J = 8.3, 0.4 Hz).

*1-(2-(4-(Hydroxymethyl)piperidin-1-yl)-4-methoxyphenyl)-ethanone (**38**).* Compound **38** was prepared from compound **37** (5.01 g, 29.77 mmol) in a manner similar to that described for compound **28**. Yellow solid (6.59 g, 25.0 mmol, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33−1.54 (3H, m), 1.57−1.71 (1H, m), 1.79−1.89 (2H, m), 2.62 (3H, s), 2.73 (2H, ddd, J = 12.0, 2.3 Hz), 3.22−3.31 (2H, m), 3.58 (2H, dd, J = 5.7 Hz), 3.83 (3H, s), 6.50−6.58 (2H, m), 7.48−7.53 (1H, m). MS (ESI/APCI): m/z 264.1 $[M + H]^+$. HPLC 100% (LC−MS).

*1-(4-Methoxy-2-(4-((methoxymethoxy)methyl)piperidin-1-yl)-phenyl)ethanone (**39**).* To a solution of compound **38** (6.59 g, 25.0 mmol) and *N*,*N*′-diisopropylethylamine (17.4 mL, 100.11 mmol) in THF (60 mL) was added chloromethyl methyl ether (5.70 mL, 75.1 mmol) at room temperature. The mixture was stirred at the same temperature overnight. The mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 5−30% EtOAc in hexane) to give the title compound (8.08 g, 26.3 mmol, quant.) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40−1.54 (2H, m), 1.64−1.90 (3H, m), 2.63 (3H, s), 2.73 (2H, ddd, J = 12.1, 2.4 Hz), 3.21−3.30 (2H, m), 3.37 (3H, s), 3.44 (2H, d, J = 6.3 Hz), 3.83 (3H, s), 4.63 (2H, s), 6.50−6.58 (2H, m), 7.50 (1H, d, J = 8.6 Hz). MS (ESI/APCI): m/z 308.1 $[M + H]^+$. HPLC 100% (LC−MS).

*1-(2-Isopropyl-5-methoxyphenyl)-4-((methoxymethoxy)methyl)-piperidine (**40**).* Compound **40** was prepared from compound **39** (353 mg, 1.15 mmol) in a manner similar to that described for compound **25**. Colorless oil (259 mg, 0.841 mmol, 93%). This product was used without further purification. MS (ESI/APCI): m/z 308.2 $[M + H]^+$. HPLC 92.2% (LC−MS).

*Ethyl 3-Cyclopropyl-3-(3-((1-(2-isopropyl-5-methoxyphenyl)-piperidin-4-yl)methoxy)phenyl)propanoate (**41**).* HCl (0.701 mL, 8.41 mmol) was added to a solution of compound **40** (259 mg, 0.84 mmol) in MeOH (3 mL) at room temperature. The mixture was stirred at 60 °C for 1 h. The mixture was neutralized with sat. $NaHCO_3$ aq at r.t. and extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue and compound **11b** (256 mg, 1.09 mmol) were dissolved in toluene (3 mL). To the solution was added 2-(tributylphosphoranylidene)acetonitrile (0.441 mL, 1.68 mmol) at r.t.. The mixture was stirred at 100 °C under N_2 for 2 h. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 2−5% EtOAc in hexane) to give the title compound (324 mg, 0.675 mmol, 80%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.10−0.21 (1H, m), 0.28 (1H, dq, J = 9.3, 4.7 Hz), 0.37−0.49 (1H, m), 0.52−0.63 (1H, m), 0.95−1.10 (1H, m), 1.14−1.21 (9H, m), 1.46−1.65 (2H, m), 1.85−1.99 (3H, m), 2.35 (1H, dt, J = 9.6, 7.6 Hz), 2.63−2.81 (4H, m), 3.07 (2H, d, J = 11.6 Hz), 3.29−3.46 (1H, m), 3.78 (3H, s), 3.86 (2H, d, J = 5.9 Hz), 4.00−4.11 (2H, m), 6.59−6.70 (2H, m), 6.74−6.85 (3H, m), 7.13−7.25 (2H, m). MS (ESI/APCI): m/z 480.3 $[M + H]^+$. HPLC 90.4% (LC−MS).

*2-(4-(((tert-Butyldimethylsilyl)oxy)methyl)piperidin-1-yl)-4-methoxybenzaldehyde (**42**).* To a solution of compound **30** (11.1 g, 44.52 mmol) in DMF (25 mL) were added 1*H*-imidazole (6.06 g, 89.05 mmol) and *tert*-butylchlorodimethylsilane (7.38 g, 48.98 mmol). The reaction mixture was stirred at r.t for 2 h, cooled to r.t., quenched with sat. aqueous NH_4Cl (20 mL), and extracted with EtOAc (50 mL). The combined organic layers were washed with brine (3 × 20 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 90−10% EtOAc in hexane) to give the title compound (12.5 g, 34.4 mmol, 77%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.00 (5H, s), 0.03 (1H, s), 0.84−0.86 (9H, m), 1.31−1.47 (2H, m), 1.52−1.65 (1H, m), 1.72−1.82 (2H, m), 2.77 (2H, td, J = 11.9, 2.2 Hz), 3.27 (2H, br d, J = 12.3 Hz), 3.46 (2H, d, J = 6.2 Hz), 3.79 (3H, s),

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6.48 (1H, d, J = 2.3 Hz), 6.53 (1H, dd, J = 8.6, 2.4 Hz), 7.72 (1H, d, J = 8.7 Hz), 9.99−10.09 (1H, m).

*1-(2-(4-(((tert-Butyldimethylsilyl)oxy)methyl)piperidin-1-yl)-4-methoxyphenyl)-3,3-dimethylbutan-1-ol (**43**).* To a solution of compound **42** (1.55 g, 4.26 mmol) in THF (dry) (10 mL) was added neopentylmagnesium chloride (5.12 mL, 5.12 mmol) and stirred at r.t. for 5 min. The mixture was poured into sat. NH_4Cl aq and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−10% EtOAc in hexane) to give the title compound (1.360 g, 3.12 mmol, 73.2%) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.00 (6H, s), 0.85 (9H, s), 0.93 (9H, br s), 1.26−1.42 (2H, m), 1.49 (1H, dd, J = 14.2, 2.8 Hz), 1.66 (1H, dd, J = 14.2, 9.3 Hz), 1.77 (2H, d, J = 12.4 Hz), 2.54−2.78 (2H, m), 2.98 (1H, d, J = 11.2 Hz), 3.08 (1H, d, J = 11.2 Hz), 3.45 (2H, d, J = 6.3 Hz), 3.72 (3H, s), 4.91 (1H, d, J = 3.8 Hz), 5.31 (1H, br s), 6.61 (1H, dd, J = 8.4, 2.5 Hz), 6.70 (1H, d, J = 2.5 Hz), 7.03 (1H, d, J = 8.4 Hz). MS (ESI/APCI): m/z 436.2. HPLC 93.5% (LC−MS).

*(1-(2-(3,3-Dimethylbutyl)-5-methoxyphenyl)piperidin-4-yl)-methanol (**44**).* A mixture of compound **43** (500 mg, 1.15 mmol) and $SOCl_2$ (0.168 mL, 2.30 mmol) in toluene (5 mL) was stirred at r.t. for 2 h. The mixture was neutralized with sat. $NaHCO_3$ aq at 0 °C and extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. A mixture of the residue (330 mg) and 10% Pd−C (50 mg, 0.05 mmol) in MeOH (10 mL) was hydrogenated under balloon pressure at room temperature for 15 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−25% EtOAc in hexane) to give (293 mg, 0.959 mmol, 88%) a colorless oil. ^{1}H NMR (400 MHz, CDCl3): δ 0.96 (9H, s), 1.33−1.49 (4H, m), 1.59−1.69 (1H, m), 1.82 (2H, d, J = 11.3 Hz), 2.49−2.57 (2H, m), 2.60−2.68 (2H, m), 3.09 (2H, d, J = 11.7 Hz), 3.57 (2H, br s), 3.77 (3H, s), 6.57 (1H, dd, J = 8.3, 2.6 Hz), 6.64 (1H, d, J = 2.5 Hz), 7.08 (1H, d, J = 8.3 Hz). MS (ESI/APCI): m/z 306.4. HPLC 98.7% (LC−MS).

*Methyl 3-Cyclopropyl-3-(3-((1-(2-formyl-5-methoxyphenyl)-piperidin-4-yl)methoxy)phenyl)propanoate (**45**).* To a solution of compound **30** (5.7 g, 22.86 mmol) and TEA (4.78 mL, 34.30 mmol) in THF (dry) (50 mL) was added MsCl (2.124 mL, 27.44 mmol) and stirred at r.t. for 30 min. The mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a pale-yellow oil. To a solution of the obtained **11a** (5.04 g, 22.86 mmol) in DMF (dry) (50 mL) were added NaH (0.914 g, 22.86 mmol) and the obtained methanesulfonate. The mixture was stirred at 100 °C for 1 h. The mixture was poured into water and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−20% EtOAc in hexane) to give the title compound (6.60 g, 14.62 mmol, 64%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.09−0.20 (1H, m), 0.20−0.31 (1H, m), 0.37−0.49 (1H, m), 0.52−0.63 (1H, m), 0.94−1.08 (1H, m), 1.60−1.73 (1H, m), 1.98 (2H, br d, J = 10.5 Hz), 2.26−2.40 (1H, m), 2.65−2.82 (2H, m), 2.89 (1H, br t, J = 11.4 Hz), 3.38 (1H, br d, J = 11.7 Hz), 3.56−3.65 (3H, m), 3.83−3.88 (3H, m), 6.55−6.63 (1H, m), 6.66−6.88 (3H, m), 7.13−7.26 (2H, m), 7.80 (1H, d, J = 8.7 Hz), 10.14 (1H, s). MS (ESI/APCI): m/z 452.5 $[M + H]^+$.

*Ethyl 3-(2-(4-(Hydroxymethyl)piperidin-1-yl)-4-methoxyphenyl)-propanoate (**46**).* (Carbethoxymethylene)triphenyl phosphorane (22.68 g, 65.12 mmol) was added to a solution of compound **30** (10.82 g, 43.41 mmol) in toluene (80 mL) at room temperature. The mixture was refluxed under N_2 for 2 h. The reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 35−45% EtOAc in hexane) to give (*E*)-ethyl 3-(2-(4-(hydroxymethyl)piperidin-1-yl)-4-methoxyphenyl)acrylate (13.73 g, 43.0 mmol, 99%) as a pale-yellow oil containing triphenylphosphine oxide. This product was subjected to the next reaction without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.25 (3H, t, J = 7.1 Hz), 1.28−1.41 (2H, m), 1.50 (1H, br s), 1.68−1.83 (2H, m), 2.59−2.70 (2H, m), 3.08 (2H, d, J = 11.8 Hz), 3.32−3.37 (2H, m), 3.78 (3H, s), 4.16 (2H, q, J = 7.2 Hz), 4.51 (1H, t, J = 5.3 Hz), 6.40 (1H, d, J = 16.1 Hz), 6.58−6.67 (2H, m), 7.49−7.69 (1H, m), 7.83 (1H, d, J = 16.2 Hz). A mixture of copper(I) chloride (0.426 g, 4.30 mmol), sodium 2-methylpropan-2-olate (0.413 g, 4.30 mmol), and 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (2.68 g, 4.30 mmol) in toluene (100 mL) was stirred at r.t. for 5 min. To the reaction mixture were added sequentially PMHS (5.20 mL, 86.00 mmol), the obtained compound (13.73 g, 43 mmol), and 2-methylpropan-2-ol (20.27 mL, 215.00 mmol) at r.t.. The mixture was stirred at room temperature under Ar for 30 min. The mixture was quenched with EtOH and sat. NH_4Cl aq at room temperature and extracted with EtOAc. The organic layer was separated, washed with sat. NH_4Cl aq and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluted with 35−45% EtOAc in hexane and then silica gel, eluted with 25−35% EtOAc in hexane) to give the title compound (3.31 g, 10.29 mmol, over 24%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.12−1.18 (3H, m), 1.21−1.35 (2H, m), 1.47 (1H, br s), 1.74 (2H, d, J = 11.4 Hz), 2.53−2.64 (4H, m), 2.73−2.83 (2H, m), 2.96 (2H, d, J = 11.5 Hz), 3.25−3.36 (2H, m), 3.70 (3H, s), 3.98−4.08 (2H, m), 4.47 (1H, t, J = 5.2 Hz), 6.57 (1H, dd, J = 8.3, 2.2 Hz), 6.62 (1H, d, J = 2.1 Hz), 7.06 (1H, d, J = 8.4 Hz).

*4-(2-(4-(Hydroxymethyl)piperidin-1-yl)-4-methoxyphenyl)-2-methylbutan-2-ol (**47**).* Methylmagnesium chloride in THF (5.54 mL, 16.61 mmol) was added to a solution of compound **46** (890 mg, 2.77 mmol) in THF (dry) (20 mL) at 0 °C. The mixture was stirred at room temperature under N_2 for 20 min. The mixture was quenched with sat. NH_4Cl aq at room temperature and extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 50−60% EtOAc in hexane) to give the title compound (476 mg, 1.547 mmol, 56%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.14 (6H, s), 1.21−1.35 (2H, m), 1.47 (1H, br s), 1.54−1.62 (2H, m), 1.74 (2H, d, J = 11.9 Hz), 2.50−2.61 (4H, m), 2.97 (2H, d, J = 11.3 Hz), 3.27−3.31 (2H, m), 3.69 (3H, s), 4.17 (1H, s), 4.46 (1H, t, J = 5.2 Hz), 6.51−6.61 (2H, m), 7.04 (1H, d, J = 8.2 Hz).

*4-(2-(4-(((tert-Butyldimethylsilyl)oxy)methyl)piperidin-1-yl)-4-methoxyphenyl)-2-methylbutan-2-ol (**48**).* The title compound **48** was obtained from compound **47** (336 mg, 1.09 mmol) in a manner similar to that described for compound **42**. Colorless oil (372 mg, 0.883 mmol, 81%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.04 (6H, s), 0.88 (9H, s), 1.13 (6H, s), 1.28−1.43 (2H, m), 1.46−1.63 (3H, m), 1.71 (2H, d, J = 11.4 Hz), 2.49−2.63 (4H, m), 2.97 (2H, d, J = 11.3 Hz), 3.50 (2H, d, J = 5.9 Hz), 3.69 (3H, s), 4.14 (1H, s), 6.50−6.63 (2H, m), 7.04 (1H, d, J = 8.0 Hz).

*4-(2-(4-(Hydroxymethyl)piperidin-1-yl)-4-methoxyphenyl)-2-methylbutan-2-yl Acetate (**50**).* Ac_2O (0.167 mL, 1.77 mmol) was added to a solution of compound **48** (372 mg, 0.88 mmol), DMAP (216 mg, 1.77 mmol), and TEA (0.369 mL, 2.65 mmol) in THF (dry) (3 mL) at room temperature. The mixture was stirred at 60 °C for 3 h. The mixture was quenched with water at room temperature and extracted with EtOAc. The organic layer was separated, washed with 1 N HCl aq, sat. $NaHCO_3$ aq, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was dissolved in THF (3 mL). To the mixture was added TBAF (2.65 mL, 2.65 mmol). The mixture was stirred at 60 °C for 10 min. The mixture was quenched with water at room temperature and extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 30−40% EtOAc in hexane) to give the title compound (236 mg, 0.674 mmol, 76%) as (a) colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.22−1.35 (2H, m), 1.37−1.55 (1H, m), 1.44 (6H, s), 1.75 (2H, d, J = 11.5 Hz), 1.89−1.97 (2H, m), 1.93 (3H, s), 2.46−2.64 (4H, m), 2.95 (2H, d, J = 11.0 Hz), 3.22−3.35 (2H, m), 3.70 (3H, s), 4.45 (1H, t, J = 4.6 Hz), 6.45−6.68 (2H, m), 7.04 (1H, d, J = 8.2 Hz).

*Benzyl 2-Fluoro-4-methoxybenzoate (**52**).* To a solution of 2-fluoro-4-methoxybenzoic acid **51** (15.46 g, 90.87 mmol) in DMF

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(363 mL) were added K_2CO_3 (18.84 g, 136.30 mmol) and benzyl bromide (11.9 mL, 100.0 mmol) at room temperature. The mixture was stirred at the same temperature under N_2 for 8 h. The mixture was quenched with iced water at 0 °C and extracted with EtOAc. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−20% EtOAc in hexane) to give the title compound (22.5 g, 86 mmol, 95%) as a colorless oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.85 (3H, s), 5.32 (2H, s), 6.84−7.00 (2H, m), 7.31−7.49 (5H, m), 7.88 (1H, t, J = 8.7 Hz). MS (ESI/APCI): m/z 261.2.

*Benzyl 2-(4-(Hydroxymethyl)piperidin-1-yl)-4-methoxybenzoate (**53**).* Compound **53** was prepared from compound **52** (1.02 g, 3.91 mmol) in a manner similar to that described for compound **28**. Pale-yellow oil (813 mg, 2.29 mmol, 59%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.11−1.28 (2H, m), 1.33−1.52 (1H, m), 1.64 (2H, d, J = 10.3 Hz), 2.56−2.70 (2H, m), 3.17−3.28 (4H, m), 3.78 (3H, s), 4.43 (1H, t, J = 5.3 Hz), 5.25 (2H, s), 6.49−6.58 (2H, m), 7.29−7.48 (5H, m), 7.63−7.70 (1H, m).

*Benzyl 2-(4-((3-(1-Cyclopropyl-3-ethoxy-3-oxopropyl)phenoxy)-methyl)piperidin-1-yl)-4-methoxybenzoate (**54**).* The title compound **54** was obtained from compound **53** (3.01 g, 8.47 mmol) and compound **11a** (1.98 g, 8.47 mmol) in a manner similar to that described for compound **4a**. Colorless gum (4.36 g, 7.63 mmol, 90%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.07−0.18 (1H, m), 0.18−0.28 (1H, m), 0.28−0.40 (1H, m), 0.44−0.56 (1H, m), 0.96−1.12 (4H, m), 1.27−1.46 (2H, m), 1.67−1.90 (3H, m), 2.19−2.32 (1H, m), 2.61−2.79 (4H, m), 3.20−3.29 (2H, m), 3.74−3.84 (5H, m), 3.89−4.00 (2H, m), 5.26 (2H, s), 6.52−6.59 (2H, m), 6.75 (1H, dd, J = 8.2, 1.6 Hz), 6.79−6.86 (2H, m), 7.19 (1H, t, J = 8.0 Hz), 7.27−7.42 (3H, m), 7.42−7.49 (2H, m), 7.69 (1H, d, J = 8.9 Hz).

*2-(4-((3-(1-Cyclopropyl-3-ethoxy-3-oxopropyl)phenoxy)methyl)-piperidin-1-yl)-4-methoxybenzoic Acid (**55**).* A solution of compound **54** (4.36 g, 7.63 mmol) in EtOH (102 mL) and THF (50.8 mL) was deprotected using H-Cube (70 mm 10% Pd/C, r.t., flow: 1.0 mL/min, reaction time: 5 h). The mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−100% EtOAc in hexane) to give (3.41 g, 7.08 mmol, 93%) a white amorphous solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.07−0.17 (1H, m), 0.17−0.27 (1H, m), 0.27−0.39 (1H, m), 0.45−0.56 (1H, m), 0.97−1.13 (4H, m), 1.43−1.62 (2H, m), 2.01 (3H, d, J = 14.0 Hz), 2.19−2.31 (1H, m), 2.63−2.80 (2H, m), 3.04−3.18 (4H, m), 3.85 (3H, s), 3.89−4.03 (4H, m), 6.76−6.89 (3H, m), 6.99 (1H, dd, J = 8.8, 2.5 Hz), 7.19 (1H, t, J = 7.8 Hz), 7.26 (1H, d, J = 2.4 Hz), 7.98 (1H, d, J = 8.8 Hz). MS (ESI/APCI): m/z 482.4 $[M + H]^+$. HPLC 96.8% (LC−MS).

*2-Fluoro-4-methoxy-N-(6-methylpyridin-2-yl)-N-neopentylbenzamide (**56**).* Oxalyl dichloride (8.10 mL, 92.6 mmol) was added to a solution of compound **51** (14.3 g, 84.1 mmol) and 5 drops of DMF in THF (150 mL) at room temperature. The mixture was stirred at room temperature under N_2 for 10 min. The mixture was concentrated in vacuo. To a THF (150 mL) solution of 6-methyl-*N*-neopentylpyridin-2-amine (7.5 g, 42.07 mmol) and triethylamine (17.59 mL, 126.21 mmol) was added dropwise THF solution (15 mL) of the acid chloride at 0 °C. The mixture was stirred at room temperature under N_2 overnight. The mixture was quenched with water at room temperature and extracted with EtOAc. The organic layer was separated, washed with water, 1 N NaOH aq, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was filtered through NH silica gel (eluted with 5−15% EtOAc in hexane), and the residue was solidified. The solid was washed with cold hexane to give the title compound (12.7 g, 38.4 mmol, 91%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (9H, s), 2.47 (3H, s), 3.73 (3H, s), 4.13 (2H, s), 6.39 (1H, d, J = 11.5 Hz), 6.53 (1H, d, J = 8.4 Hz), 6.60 (1H, d, J = 7.9 Hz), 6.84 (1H, d, J = 7.5 Hz), 7.14 (1H, t, J = 8.3 Hz), 7.24−7.32 (1H, m).

*2-(4-(Hydroxymethyl)piperidin-1-yl)-4-methoxy-N-(6-methylpyridin-2-yl)-N-neopentylbenzamide (**57**).* Compound 57 was prepared from compound **56** (1.5 g, 4.54 mmol) in a manner similar to that described for compound **28** (purification: column chromatography (NH silica gel, eluted with 0−50% EtOAc in hexane) crystallization: EtOAc/hexane). White powder (0.773 g, 1.817 mmol, 40%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.81 (9H, s), 1.14 (1H, d, J = 4.8 Hz), 1.24−1.35 (1H, m), 1.43−1.53 (2H, m), 1.56−1.70 (2H, m), 2.35−2.48 (4H, m), 2.48−2.66 (2H, m), 3.38 (1H, br s), 3.47−3.60 (2H, m), 3.75 (3H, s), 4.09−4.23 (1H, m), 4.27 (1H, br s), 6.18 (1H, d, J = 2.1 Hz), 6.32 (1H, br s), 6.48 (1H, dd, J = 8.4, 2.4 Hz), 6.70 (1H, d, J = 7.3 Hz), 7.08 (1H, t, J = 7.5 Hz), 7.29 (1H, d, J = 8.5 Hz).

*Cyclopropyl(6-methoxypyridin-2-yl)methanol (**59a**).* The title compound was obtained from cyclopropyl magnesium bromide THF solution derived from cyclopropyl bromide (3.50 mL, 43.75 mmol) and **58a** (1.75 mL, 14.6 mmol) in a manner similar to that described for compound **43**. Pale-brown oil. This product was subjected to the next reaction without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.25−0.49 (4H, m), 1.02−1.23 (1H, m), 3.83 (3H, s), 3.99−4.08 (1H, m), 5.19 (1H, d, J = 4.9 Hz), 6.65 (1H, d, J = 8.2 Hz), 7.04 (1H, d, J = 7.3 Hz), 7.66 (1H, dd, J = 8.1, 7.5 Hz).

*Cyclopropyl(2-methoxypyridin-4-yl)methanol (**59b**).* Compound **59b** was prepared from compound **58b** (4.33 g) in a manner similar to that described for compound **59a**. Brown oil (5.30 g). This compound was used for the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.34−0.50 (4H, m), 0.90−1.04 (1H, m), 3.83 (3H, s), 3.95 (1H, dd, J = 7.2, 4.6 Hz), 5.35 (1H, d, J = 4.6 Hz), 6.77 (1H, s), 6.99 (1H, d, J = 5.3 Hz), 8.07 (1H, d, J = 5.3 Hz).

*Cyclopropyl(6-methoxypyridin-2-yl)methanone (**60a**).* Py·SO_3 (9.28 g, 58.3 mmol) was added to a solution of compound **59a** (2.29 mL, 14.6 mmol) and TEA (16.3 mL, 116.6 mmol) in DMSO (80 mL) at room temperature. The mixture was stirred at room temperature for 5 min. The mixture was quenched with water at room temperature and extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to give a brown oil. This product was subjected to the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02−1.12 (2H, m), 1.18−1.30 (2H, m), 3.40−3.55 (1H, m), 4.04 (3H, s), 6.94 (1H, d, J = 8.0 Hz), 7.61−7.66 (1H, m), 7.67−7.75 (1H, m).

*Cyclopropyl(2-methoxypyridin-4-yl)methanone (**60b**).* Compound **60b** was prepared from compound **59b** (5.30 g) in a manner similar to that described for compound **60a**. Brown oil. This compound was used for the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.00−1.19 (4H, m), 2.82−2.95 (1H, m), 3.92 (3H, s), 7.34 (1H, s), 7.45 (1H, d, J = 5.3 Hz), 8.37 (1H, d, J = 5.3 Hz).

*Ethyl 3-Cyclopropyl-3-(6-methoxypyridin-2-yl)acrylate (**61a**).* Triethyl phosphonoacetate (7.23 mL, 36.5 mmol) was added to a suspension of NaH (1.28 g, 32.1 mmol) in THF (80 mL) at 0 °C. The mixture was stirred at room temperature under N_2 for 5 min. To the solution was added compound **60a** (2.27 mL, 14.6 mmol) at r.t.. The mixture was refluxed under N_2 overnight. The mixture was quenched with water at room temperature and extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to give the title compound as brown oil. This product was subjected to the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.65−0.75 (2H, m), 0.78−0.91 (2H, m), 1.22−1.29 (3H, m), 1.73−1.90 (1H, m), 3.91 (3H, s), 4.08−4.27 (2H, m), 5.89 (1H, s), 6.64−6.69 (1H, m), 6.80 (1H, d, J = 7.0 Hz), 7.50−7.57 (1H, m).

*Ethyl 3-Cyclopropyl-3-(2-methoxypyridin-4-yl)acrylate (**61b**).* Compound **61b** was prepared from compound **60b** (4.42 g) in a manner similar to that described for compound **61a**. This compound was used for the next step without further purification.

*Ethyl 3-Cyclopropyl-3-(6-methoxypyridin-2-yl)propanoate (**62a**).* Zinc (9.53 g, 145.80 mmol) was added to a solution of compound **61a** (3.61 g, 14.6 mmol) in AcOH (50 mL) at room temperature. The mixture was stirred at room temperature for 20 min. The reaction mixture was filtered, and the filtrate was concentrated in vacuo (azeotropy with PhMe). The residue was purified by column chromatography (silica gel, eluted with 0−5% EtOAc in hexane) to give (2.68 g, 10.75 mmol, 74% over 4 steps) a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.18−0.34 (2H, m), 0.39−0.50 (1H, m),

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0.52−0.64 (1H, m), 1.01−1.13 (1H, m), 1.18 (3H, t, J = 7.2 Hz), 2.34−2.49 (1H, m), 2.77 (1H, dd, J = 15.3, 6.0 Hz), 3.02 (1H, dd, J = 15.2, 8.5 Hz), 3.90 (3H, s), 3.98−4.17 (2H, m), 6.56 (1H, d, J = 8.3 Hz), 6.79 (1H, d, J = 7.3 Hz), 7.47 (1H, t, J = 7.7 Hz).

*Ethyl 3-Cyclopropyl-3-(2-methoxypyridin-4-yl)propanoate (**62b**).* Compound **62b** was prepared from compound **61b** in a manner similar to that described for compound **62a**. Pale-yellow oil (4.17 g, 53% over 4 steps). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.09−0.20 (1H, m), 0.20−0.29 (1H, m), 0.29−0.38 (1H, m), 0.44−0.57 (1H, m), 0.94−1.05 (1H, m), 1.08 (3H, t, J = 7.1 Hz), 2.19−2.30 (1H, m), 2.75 (2H, d, J = 7.5 Hz), 3.82 (3H, s), 3.90−402 (2H, m), 6.71 (1H, s), 6.92 (1H, d, J = 5.1 Hz), 8.05 (1H, d, J = 5.1 Hz).

*Ethyl 3-Cyclopropyl-3-(6-hydroxypyridin-2-yl)propanoate (**63a**).* Pyridine hydrochloride (12.4 g, 107.5 mmol) was added to a solution of compound **62a** (2.68 g, 10.75 mmol) in DMF (5 mL) at room temperature. The mixture was stirred at 120 °C under N_2 for 30 min. The reaction mixture was diluted with THF at r.t.. The resulting precipitate was removed by filtration through Celite, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 3−8% MeOH in EtOAc) to give pale-yellow oil. The residue was solidified and washed with i-Pr_2O to give the title compound (1.79 g, 7.61 mmol, 71%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.14−0.23 (1H, m), 0.24−0.32 (1H, m), 0.32−0.40 (1H, m), 0.45−0.55 (1H, m), 0.97−1.07 (1H, m), 1.09 (3H, t, J = 7.1 Hz), 2.11−2.25 (1H, m), 2.69−2.78 (1H, m), 2.79−2.89 (1H, m), 3.90−4.05 (2H, m), 5.95−6.09 (1H, m), 6.14 (1H, d, J = 8.4 Hz), 7.33 (1H, t, J = 7.6 Hz), 11.51 (1H, br s).

*Ethyl 3-Cyclopropyl-3-(2-hydroxypyridin-4-yl)propanoate (**63b**).* Compound **63b** was prepared from compound **62b** (4.17 g) in a manner similar to that described for compound **63a**. Yellow oil (3.61 g). ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.10−0.28 (2H, m), 0.29−0.43 (1H, m), 0.43−0.58 (1H, m), 0.86−1.03 (1H, m), 1.11 (3H, t, J = 7.1 Hz), 2.07 (1H, dt, J = 9.7, 7.6 Hz), 2.68 (2H, d, J−7.5 Hz), 3.91−4.07 (2H, m), 6.19 (1H, s), 6.20−6.25 (1H, m), 7.30 (1H, d, J = 6.7 Hz), 11.48 (1H, br s).

*Ethyl 3-Cyclopropyl-3-(2-((1-(5-methoxy-2-((6-methylpyridin-2-yl)(neopentyl)carbamoyl)phenyl)piperidin-4-yl)methoxy)pyridin-4-yl)propanoate (**64b**).* Compound **64b** was prepared from compound **57** (221.5 mg, 0.52 mmol) and **61b** (135 mg, 0.57 mmol) in a manner similar to that described for compound **54** (purification: column chromatography (silica gel, eluted with 0−40% EtOAc in hexane)). Colorless gum (198 mg, 0.308 mmol, 59%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.11−0.22 (1H, m), 0.30 (1H, dq, J = 9.5, 4.7 Hz), 0.41−0.53 (1H, m), 0.54−0.67 (1H, m), 0.82 (9H, s), 0.90−1.07 (1H, m), 1.14−1.43 (4H, m), 1.60−1.89 (4H, m), 2.25−2.37 (1H, m), 2.44 (4H, s), 2.48−2.83 (4H, m), 3.39 (1H, br s), 3.75 (3H, s), 3.99−4.40 (6H, m), 6.19 (1H, d, J = 2.0 Hz), 6.35 (1H, br s), 6.48 (1H, dd, J = 8.5, 2.4 Hz), 6.63 (1H, d, J = 0.7 Hz), 6.69 (1H, d, J = 7.5 Hz), 6.76 (1H, dd, J = 5.3, 1.4 Hz), 7.08 (1H, t, J = 7.6 Hz), 7.29 (1H, d, J = 8.4 Hz), 8.07 (1H, d, J = 5.3 Hz).

*tert-Butyl 4-(((4-(Cyclopropanecarbonyl)pyridin-2-yl)oxy)-methyl)piperidine-1-carboxylate (**66**).* To a solution of compound **65** (2000 g, 9.29 mol) in DMF (6 L) was added NaH (440 g, 11.0 mol) at 0 °C. After being stirred at 0 °C for 40 min, a solution of *N*-Boc-4-hydroxymethylpiperidine (1250 g, 9.00 mol) in DMF (3 L) was added to the reaction mixture. The mixture was stirred at 0 °C for 2 h. The mixture was diluted with EtOAc and water, and the mixture was extracted with EtOAc. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a white powder. The powder was collected by filtration, washed with PE, and dried to give *tert*-butyl 4-{[(4-cyanopyridin-2-yl)oxy]-methyl}piperidine-1-carboxylate (2100 g) as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (2H, qd, J = 12.3, 4.5 Hz), 1.46 (9H, s), 1.79 (2H, d, J = 12.6 Hz), 1.85−2.09 (1H, m), 2.74 (2H, t, J = 12.1 Hz), 4.13 (2H, br s), 4.19 (2H, d, J = 6.3 Hz), 6.98 (1H, t, J = 1.2 Hz), 7.06 (1H, dd, J = 5.1, 1.2 Hz), 8.28 (1H, dd, J = 5.1, 0.8 Hz). A solution of the obtained product (2100 g, 6.616 mol) in THF (15 L) was added dropwise to cyclopropylmagnesium bromide (1 M in THF, 13.3 L, 13.3 mol) at room temperature. The mixture was stirred at the same temperature for 2 h. The resulting mixture was slowly quenched with 1 N aq HCl below 10 °C and extracted with EtOAc at this temperature. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo to give the title compound (2250 g) as a brown oil which was used for the next reaction without further purifications.

*tert-Butyl 4-({[4-(1-Cyclopropyl-3-ethoxy-3-oxopropyl)pyridin-2-yl]oxy}methyl)piperidine-1-carboxylate (**67**).* To a suspension of NaH (499.4 g, 12.49 mol) in THF (10 L) was added ethyl 2-(diethoxyphosphoryl)acetate (2785 g, 12.49 mmol) at 0 °C and stirred for 30 min. To the mixture was added a solution of compound **66** (2250 g, 6.243 mol) in THF (10 L) and stirred at 80 °C for 3 h. The reaction mixture was poured into sat. NH_4Cl aq (10 L), and the mixture was extracted with EtOAc. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give *tert*-butyl 4-[({4-[(1*E*)-1-cyclopropyl-3-ethoxy-3-oxoprop-1-en-1-yl]pyridin-2-yl}oxy)methyl]piperidine-1-carboxylate (2450 g) as a brown oil which was used for the next reaction without further purifications. Zinc (2215 g, 34.15 mol) was added portionwise to a solution of the obtained product (2450 g, 5.691 mol) in AcOH (10 L) at room temperature. The mixture was stirred at room temperature for 2 h. The reaction mixture was filtered through Celite pad, and the filtrate was concentrated in vacuo. The residue was basified with $NaHCO_3$and extracted with EtOAc. The organic layer was separated, washed with sat. $NaHCO_3$ aq and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 0−25% EtOAc in hexane) to give the title compound (1750 g, 71%) as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.17 (1H, dt, J = 9.6, 4.8 Hz), 0.28 (1H, dt, J = 9.6, 4.8 Hz), 0.39−0.52 (1H, m), 0.54−0.66 (1H, m), 0.94−1.08 (1H, m), 1.15−1.22 (3H, m), 1.27−1.35 (2H, m), 1.46 (9H, s), 1.81 (2H, d, J = 12.0 Hz), 1.88−2.01 (1H, m), 2.30 (1H, dt, J = 9.6, 7.5 Hz), 2.58−2.84 (4H, m), 4.02−4.10 (2H, m), 4.10−4.23 (4H, m), 6.58−6.62 (1H, m), 6.76 (1H, dd, J = 5.4, 1.5 Hz), 7.86−8.16 (1H, m).

*(3*S*)-3-(2-{[1-(tert-Butoxycarbonyl)piperidin-4-yl]methoxy}-pyridin-4-yl)-3-cyclopropylpropanoic Acid-(1*S*)-1-(4-Methylphenyl)ethan-1-amine (1/1) (**68**).* To a solution of compound **67** (1750 g, 4.045 mol) in MeOH (6 L) was added 4 N NaOH (4.045 L, 16.18 mmol) at room temperature. After stirring at ambient temperature for 2 h, TLC showed that the reaction was completed. The mixture was concentrated in vacuo to remove MeOH. The residue was dissolved into H_2O and extracted with Et_2O. The aqueous phase was acidified with 1 N HCl to pH = 4−5. The solid was collected by filtration, washed with PE, and dried in vacuo to give the corresponding carboxylic acid (1510 g, 92%) as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.12−0.20 (1H, m), 0.30−0.34 (1H, m), 0.41−0.51 (1H, m), 0.56−0.65 (1H, m), 0.95−1.01 (1H, m), 1.18−1.32 (2H, m), 1.46 (9H, s), 1.77−1.82 (2H, m), 1.91−1.98 (1H, m), 2.28 (1H, dd, J = 17.1, 7.5 Hz), 2.69−2.84 (4H, m), 4.10−4.13 (4H, m), 6.60 (1H, 2), 6.75 (1H, dd, J = 5.4, 1.2 Hz), 8.03 (1H, d, J = 5.4 Hz). MS (ESI/APCI): m/z 405 $[M + H]^+$. To a solution of 3-(2-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)methoxy)pyridin-4-yl)-3-cyclopropylpropanoic acid (870 g, 2150.80 mmol) in EtOH (5.4 L) was added EtOAc (10.80 L) solution of (*S*)-1-(*p*-tolyl)ethanamine (291 g, 2150.80 mmol) at room temperature. The mixture was stirred at room temperature under a dry atmosphere ($CaCl_2$ tube) for 16.5 h. The resulting white precipitate was collected by filtration and washed with AcOEt/EtOH (2:1, 2.4 L). The precipitate was dried in vacuo to give the title compound (477 g, 884 mmol, 41%) as a white crude solid. The obtained product (237 g, 439.13 mmol) was dissolved in EtOH (3.1 L) at 70 °C. To the solution was added dropwise heptane (4.7 L) at 60−50 °C. After addition of a small amount of the seed crystal, the mixture was stirred at 50 °C for 1.5 h, then r.t. for 12 h, and then cooled with a water bath for 1 h. The resulting white solid was collected, washed with EtOH/heptane (1:2), and dried in vacuo to give the crude material (182.3 g, 338 mmol) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.41−0.54 (1H, m), 0.87−1.21 (4H, m), 1.25 (3H, d, J = 6.7 Hz), 1.39 (9H, s), 1.72 (2H, d, J = 11.2 Hz), 1.81−1.98 (1H, m), 2.15−2.30 (4H, m), 2.58 (2H, d, J = 7.5 Hz),

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2.72 (1H, br s), 3.88−4.11 (5H, m), 6.67 (1H, s), 6.88 (1H, dd, J = 5.3, 1.2 Hz), 7.11 (2H, d, J = 7.8 Hz), 7.25 (2H, d, J = 8.1 Hz), 8.00 (1H, d, J = 5.3 Hz). MS (ESI/APCI): m/z 405.3 $[M + H]^+$. 99.3% ee (HPLC on CHIRALPAK IC 4.6 mm ID × 150 mmL), mobile phase: H_2O/MeCN/TFA = 700/300/1, flow rate = 1 mL/min, 30 °C, UV detection: 254 nm.

*Ethyl (3S)-3-Cyclopropyl-3-{2-[(piperidin-4-yl)methoxy]pyridin-4-yl}propanoate (**69**).* HCl aq (460 mL, 460 mmol, 1 N) was added to a suspension of (*S*)-1-(*p*-tolyl)ethanamine 3-(2-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)methoxy)pyridin-4-yl)-3-cyclopropylpropanoate 68 (46 g, 86 mmol) in EtOAc (750 mL) at 0 °C. The mixture was stirred at 0 °C for 5 min. The mixture was extracted with EtOAc/THF (1:1, 200 mL, three times). The organic layer was separated, washed with brine (200 mL), dried over $MgSO_4$, and concentrated in vacuo to give a white solid. The white solid was washed with i-Pr_2O to give 3-(2-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)methoxy)pyridin-4-yl)-3-cyclopropylpropanoic acid (35 g, 83 mmol, 97%) as a white solid (containing 4 wt % of (*S*)-1-(*p*-tolyl)ethanamine). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.10−0.20 (1H, m), 0.22−0.39 (2H, m), 0.44−0.58 (1H, m), 0.90−1.05 (1H, m), 1.06−1.21 (2H, m), 1.40 (9H, s), 1.72 (2H, d, J = 13.8 Hz), 1.82−1.99 (1H, m), 2.15−2.27 (1H, m), 2.60−2.83 (2H, m), 2.68 (2H, d, J = 7.2 Hz), 3.97 (2H, d, J = 11.5 Hz), 4.08 (2H, d, J = 6.5 Hz), 6.69 (1H, s), 6.90 (1H, d, J = 5.4 Hz), 8.02 (1H, d, J = 5.3 Hz), 12.04 (1H, br s). H_2SO_4 (4.8 mL, 91 mmol) was added to a solution of 3-(2-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)methoxy)pyridin-4-yl)-3-cyclopropylpropanoic acid (15 g, 36 mmol) in EtOH (360 mL) at room temperature. The mixture was stirred at 80 °C for 1 h. The reaction mixture was concentrated in vacuo. The residue was diluted with AcOEt/THF (150/150 mL). To the suspension was added 2 N NaOH aq (73 mL, 150 mmol) at 0 °C. The mixture was extracted with EtOAc/THF (50/50 mL) with NaCl. The organic layer was separated, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo to give the title compound (14 g, 37 mmol, 101%, 86 wt %, mixture with PhMe used for azeotropy) as colorless oil. This product was subjected to the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.07−0.20 (1H, m), 0.24−0.35 (1H, m), 0.38−0.51 (1H, m), 0.55−0.66 (1H, m), 0.86−1.05 (1H, m), 1.18 (3H, t, J = 7.2 Hz), 1.26−1.45 (2H, m), 1.85 (2H, d, J = 13.4 Hz), 1.89−2.03 (1H, m), 2.24−2.33 (1H, m), 2.61−2.79 (4H, m), 3.17 (2H, d, J = 12.3 Hz), 3.99−4.13 (2H, m), 4.12 (2H, d, J = 6.5 Hz), 6.61 (1H, s), 6.75 (1H, d, J = 5.3 Hz), 8.05 (1H, d, J = 5.3 Hz).

*Ethyl (3S)-3-Cyclopropyl-3-{2-[(1-{2-[(2,2-dimethylpropyl)(6-methylpyridin-2-yl)carbamoyl]-5-methoxyphenyl}piperidin-4-yl)-methoxy]pyridin-4-yl}propanoate (**70**).* A mixture of 2-fluoro-4-methoxy-*N*-(6-methylpyridin-2-yl)-*N*-neopentylbenzamide **56** (12 g, 36 mmol), ethyl 3-cyclopropyl-3-(2-(piperidin-4-ylmethoxy)pyridin-4-yl)propanoate **69** (14 g, 37 mmol, 86 wt %), and cesium carbonate (18 g, 54 mmol) was stirred at 130 °C under N_2 for 19 h (200 mL flask, neat). After dilution with PhMe, the mixture was filtered through Celite pad. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, eluted with 5−15% EtOAc in hexane twice) to give the desired product as a mixture with **4**. The mixture was dissolved in AcOEt and extracted with 2 N HCl aq, and the aqueous layer was basified with 2 N NaOH aq and sat. $NaHCO_3$ aq. The aqueous layer was extracted with AcOEt, washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo to give the title compound (17 g, 25 mmol, 69%) as a pale-orange amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.11−0.24 (1H, m), 0.25−0.36 (1H, m), 0.39−0.54 (1H, m), 0.55−0.66 (1H, m), 0.82 (9H, s), 0.93−1.06 (1H, m), 1.19 (3H, t, J = 7.2 Hz), 1.52−1.89 (5H, m), 2.25−2.35 (1H, m), 2.40−2.86 (5H, m), 2.44 (3H, s), 3.40 (1H, br s), 3.75 (3H, s), 3.98−4.38 (6H, m), 6.19 (1H, br s), 6.33 (1H, br s), 6.48 (1H, d, J = 8.3 Hz), 6.63 (1H, s), 6.69 (1H, d, J = 7.5 Hz), 6.76 (1H, d, J = 5.3 Hz), 7.08 (1H, br s), 7.29 (1H, d, J = 8.4 Hz), 8.07 (1H, d, J = 5.1 Hz).

*(3S)-3-Cyclopropyl-3-{2-[(1-{2-[(2,2-dimethylpropyl)(6-methylpyridin-2-yl)carbamoyl]-5-methoxyphenyl}piperidin-4-yl)-methoxy]pyridin-4-yl}propanoic Acid (**(S)-7f, SCO-267**).* NaOH aq (170 mL, 170 mmol, 1 N) was added to a solution of ethyl 3-cyclopropyl-3-(2-((1-(5-methoxy-2-((6-methylpyridin-2-yl)-(neopentyl)carbamoyl)phenyl)piperidin-4-yl)methoxy)pyridin-4-yl)-propanoate (**5**, 17 g, 25 mmol) in THF (170 mL) and MeOH (85 mL) at room temperature. The mixture was stirred at 60 °C under N_2 for 30 min. The mixture was quenched with 1 N HCl aq (170 mL) at room temperature (water bath) and extracted with EtOAc (150 mL × 2). The organic layer was separated, washed with brine (150 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was solidified and dissolved in isopropylacetate (110 mL) at 60 °C. To the solution was added heptane (120 mL) dropwise at 60 °C and stirred at 30 min. Additional heptane (65 mL) was added at the same temperature and then stirred at 60 °C for 30 min and room temperature for 1 h. The solid was collected and washed with heptane/isopropylacetate (3:1) to give 3-cyclopropyl-3-(2-((1-(5-methoxy-2-((6-methylpyridin-2-yl)(neopentyl)carbamoyl)phenyl)-piperidin-4-yl)methoxy)pyridin-4-yl)propanoic acid (13 g, 22 mmol, 87%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.10−0.22 (1H, m), 0.23−0.39 (2H, m), 0.45−0.56 (1H, m), 0.77 (9H, s), 0.93−1.05 (1H, m), 1.10−1.30 (1H, m), 1.45−1.60 (1H, m), 1.61−1.86 (3H, m), 2.18−2.28 (1H, m), 2.30−2.66 (4H, m), 2.36 (3H, s), 2.68 (2H, d, J = 7.4 Hz), 3.69 (3H, s), 3.93−4.27 (4H, m), 6.21 (1H, br s), 6.45 (1H, br s), 6.52 (1H, d, J = 8.4 Hz), 6.71 (1H, s), 6.85 (1H, d, J = 7.5 Hz), 6.91 (1H, d, J = 5.1 Hz), 7.14 (1H, d, J = 8.4 Hz), 7.28 (1H, t, J = 7.7 Hz), 8.04 (1H, d, J = 5.3 Hz), 12.09 (1H, br s). MS m/z 615.5 $(M + H)^+$. $C_{36}H_{46}N_4O_5$: C, 70.33; H, 7.54; N, 9.11. Found: C, 70.24; H, 7.48; N, 9.09.

Crystallography Methods. All measurements were performed on a Rigaku R-AXIS RAPID-191R diffractometer using multilayer mirror monochromated Cu Kα radiation. The structure was solved by direct methods with SHELXS-97[33] and was refined using full-matrix least-squares on F2 with SHELXL-97. All non-H atoms were refined with anisotropic displacement parameters.

CCDC1978712 for **SCO-267** and CCDC 1978713 for compound 68 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/structures.

*Crystal Data for **SCO-267**.* (CCDC 1978712): $C_{36}H_{46}N_4O_5$, MW = 614.78; crystal size, 0.10 × 0.07 × 0.04 mm; colorless, needle; monoclinic, space group $P1$, a = 10.3497 (2) Å, b = 13.5736 (3) Å, c = 14.4222 (3) Å, α = 103.627 (2)°, β = 107.2110 (8)°, γ = 109.413(2)°, V = 1695.28(8) Å^3, Z = 2, dx = 1.204 g/cm^3, T = 100 K, μ = 0.647 mm^{-1}, λ = 1.54184 Å, R_1 = 0.0415, wR_2 = 0.1118, S = 1.039, Flack parameter[30] = 0.04(9).

*Crystal Data for Compound **68**.* (CCDC 1978713): $C_{22}H_{31}N_2O_5^-\cdot C_9H_{14}N^+$, MW = 539.71; crystal size, 0.19 × 0.05 × 0.05 mm; colorless, needle; monoclinic, space group $P2_1$, a = 13.1146(3) Å, b = 6.3865(2) Å, c = 17.9946(4) Å, $\alpha = \gamma$ = 90°, β = 94.942(7)°, V = 1501.56(5) Å^3, Z = 2, dx = 1.194 g/cm^3, T = 100 K, μ = 0.648 mm^{-1}, λ = 1.54187 Å, R_1 = 0.0924, wR_2 = 0.2416, S = 1.064, Flack parameter[34] = 0.2(5). The absolute configuration was determined using the reference to the known configuration of the (1*S*)-1-(4-methylphenyl)ethan-1-aminium.

Cell Lines. To establish CHO cells (dhfr-) stably expressing hFFAR1, CHO/dhfr- (ATCC catalog # CRL-9096) cells were transfected with hFFAR1-pAKKO-111H using Lipofectamine 2000 (Thermo Fisher Scientific). After transfection, a limiting dilution was performed, and clone cells were selected with a selective medium, nucleotide-free α-minimum essential medium (Thermo Fisher Scientific) supplemented with 10% dialyzed fetal bovine serum (Thermo Fisher Scientific), 100 IU/mL penicillin, and 100 mg/mL streptomycin (Thermo Fisher Scientific). The expression level of human hFFAR1 mRNA was confirmed by TaqMan PCR (Thermo Fisher Scientific), the intracellular calcium mobilization activity of γ-linolenic acid as an hFFAR1 ligand was confirmed using a fluorometric imaging plate reader (FLIPR) system (Molecular Devices), and clones of hFFAR1-expressing CHO cells, including clone #2 herein, were selected.

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In Vitro Ca^{2+} Mobilization Assay. CHO cells stably expressing human GPR40 (clones #2) were cultured with minimum essential medium-α (Nikken Bio Medical Laboratory) containing 10% dialyzed fetal bovine serum (Gemini Bio-Products), 10 mmol/L *N*-(2-hydroxyethyl)piperazine-*N*′-ethanesulfonic acid (HEPES) (Thermo Fisher Scientific), and 1× penicillin/streptomycin (Thermo Fisher Scientific) in 5% CO_2 at 37 °C. Cells were seeded at 1×10^4 cells/well in a 384-well black/clear plate and then incubated overnight. After removing the medium, cells were incubated with 30 μL of loading buffer Hanks' balanced salt solution (Thermo Fisher Scientific) containing 20 mmol/L HEPES (Thermo Fisher Scientific), 0.1% fatty acid-free bovine serum albumin (Sigma), 2.5 mmol/L Probenecid (Dojindo), and 2.5 μL of calcium probe (Dojindo) for 60 min in 5% CO_2 at 37 °C. Test compounds at indicated concentrations (10^{-10}, 10^{-9}, 10^{-8}, 10^{-7}, 10^{-6}, and 10^{-5} mol/L) were added to the cells, and the increase in the intracellular Ca^{2+} concentration was monitored using an FLIPR tetra system (Molecular Devices) for 150 s. Regarding determination of the agonist activity rate, the Ca^{2+} influx of no compound was set as 0% of agonist activity and the Ca^{2+} influx of (*S*)-3-cyclopropyl-3-(3-((2-((*R*)-2,2-dimethylcyclopentyl)-2′-fluoro-5′-methoxy-[1,1′-biphenyl]-4-yl)methoxy)-2-fluorophenyl)-propanoic acid[14] was set as 100% of agonist activity. The agonist activity rate (% of control) of test compounds was calculated as $(C_{\text{sample}} - C_{0\%\text{ of agonist activity}})/(C_{100\%\text{ of agonist activity}} - C_{0\%\text{ of agonist activity}}) \times 100$ where *C* indicates Ca^{2+} influx values. Data were expressed as % of control. Data of **2**, **4a**, **4e**, **4g**, **5**, **6a**, **6b**, **6c**, **6d**, **6e**, **6h**, **7f**, (***S***)**-7f**, and (***R***)**-7f** were obtained from more than two experiments in duplicate. Data of **3**, **4b**, **4c**, **4d**, **4f**, **4h**, **6f**, **6g**, **7a**, **7b**, **7c**, **7d**, and **7e** were obtained from a single experiment in duplicate. Furthermore, the agonist activity of test compounds for hGPR40 was shown as the EC_{50} value from the dose−response curve. Their EC_{50} values and standard deviation were calculated using Prism 6 software (GraphPad Software).

Cytotoxicity Test. HepG2 cells were cultured at 37 °C, 5% CO_2 in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, 50 IU/mL penicillin, and 50 μg/mL streptomycin. Cells were seeded at 2×10^4 cells/well in a 96-well white plate (Corning) and cultured with test compounds or DMSO control in DMEM supplemented with 0.5% fetal bovine serum, 2 mM L-glutamine, 1 mM sodium pyruvate, 50 IU/mL penicillin, and 50 μg/mL streptomycin for 1 day. The intracellular ATP content was measured using ATPlite-M (PerkinElmer) according to the manufacturer's instruction. ATP content was calculated as follows: ATP content (% of control) = (RLU of compound/RLU of 1% DMSO) × 100. Data were obtained from a single experiment in triplicate. Caspase-3/7 activity was measured using a Caspase-GloTM 3/7 assay kit (Promega) according to the manufacturer's instruction. Caspase-3/7 activity was calculated as follows: Caspase-3/7 activity (%) = (RLU of compound − RLU of 1% DMSO)/(RLU of 30 μM staurosporine − RLU of 1% DMSO) × 100. Data were obtained from a single experiment in triplicate.

Pharmacokinetic Analysis in Rat and Mouse Cassette Dosing Studies. Three male SD rats (8 weeks old) and three male ICR mice (8 weeks old) were used in the pharmacokinetic study. Test compounds were administered to nonfasted rats and mice as a cassette dosing study, which is a technique for evaluation of the pharmacokinetic profile by simultaneous administration of multiple compounds to a single animal. After oral and intravenous administration, blood samples were collected and centrifuged to obtain the plasma fraction. The plasma samples were deproteinized with acetonitrile containing an internal standard. After centrifugation, the supernatant was diluted with 10 mmol/L ammonium acetate and centrifuged again. The compound concentrations in the supernatant were measured by high-performance LC−tandem MS. The area under the plasma concentration−time curve (AUC) and the area under the first moment of plasma concentration−time curve (AUMC) were calculated using a linear trapezoidal method. The mean residence time (MRT) was derived from the AUMC divided by the AUC. The total body clearance (CL_{total}) was determined as the quotient of the dose divided by the AUC after intravenous administration, and the steady-state distribution volume (V_{ss}) was determined as the product of the CL_{total} multiplied by the MRT after intravenous administration. The maximum plasma concentration ($C_{\max}$) was recorded from the experimental data after oral administration. The bioavailability (*F*) was determined as the quotient of dose-normalized AUC at oral administration divided by that at intravenous administration.

LC−MS-Based Binding Assay. To get a better understanding of compound **4a** binding to GPR40, we performed an LC−MS-based binding assay.[23] GPR40 protein samples were diluted to 3 μg/mL in the binding assay buffer [50 mM Tris-HCl (pH 7.5), 5 mM $MgCl_2$, 5 mM ethylenediaminetetraacetic acid (EDTA), and 0.005% Tween 20] and dispensed in a 96-well plate (Corning). Compound **4a** was added at 10^{-6} to 10^{-12} M of the final concentration. In turn, TAK-875 and AMG-1638 were added at the final concentration of their K_d and 10 times of K_d at room temperature for 2 h. The K_d value of TAK-875 to GPR40 was 11.9 nM and that of AMG-1638 was 5.0 nM to be evaluated by the LC−MS-based binding assay.[23,24] After the incubation, free compounds which were not bound to GPR40 was separated by 96-well plate-based size exclusion chromatography.[35] Subsequently, 70% acetonitrile and 0.2% formic acid were added to each well to dissociate the compound bound to GPR40. The samples were subjected to to LC−MS analysis, and the peak area of TAK-875 and AMG-1638 was quantified. Sigmoidal dose response curves were calculated using Prism 5.03 software (GraphPad Software). Two independent experiments in duplicate were performed. Data are shown separately in Figures 4 and S1.

N-STZ-1.5 Rat Study. The care of the animals and use of the experimental protocols in the current studies were approved by the Institutional Animal Care and Use Committee (IACUC) in a Shonan Health Innovation Park accredited by the American Association for Accreditation of Laboratory Animal Care (AAALAC). All rats were housed in a room with controlled temperature (23 °C), lighting (lights remained on between 7:00 am and 7:00 pm), and humidity (55%) and were allowed free access to standard chow diet (CE-2, CLEA, Japan Inc.) and water. Male N-STZ-1.5 Wistar Kyoto rats (N-STZ-1.5 rats), which are diabetic, were developed via subcutaneous administration of 120 mg/kg streptozotocin (STZ) to Wistar Kyoto rats (Rabics, Ltd. Kanagawa, Japan) at 1.5 days after birth. N-STZ rats display impairments in insulin secretion and action which resemble those observed in human patients with diabetes. To evaluate the efficacy of single dosing, 26 week-old male N-STZ-1.5 rats and normal male rats (Wistar Kyoto rats) were fasted (12 h) and fasting glucose levels were determined. Rats were randomized into groups ($n = 6$ for each group) based on glycosylated hemoglobin levels, body weight, and fasting glucose levels. After 15 h fasting, the vehicle (0.5% methylcellulose solution) and the test materials (**SCO-267**, 0.3−1 mg/kg; Sitagliptin phosphate 10 mg/kg [Cayman]) were orally administered. Glucose solution (1.5 g/kg) was orally loaded 60 min after the vehicle and the test material dosing (total 16 h fasting). Blood samples were collected before the glucose load (time 0) and 10, 30, 60, and 120 min after the glucose load, and plasma glucose was determined using an autoanalyzer 7180 (Hitachi). Plasma insulin was determined using an ELISA kit (M1101, Takara), and plasma total GLP-1 was determined using an ELISA kit (EZGLP1T-36K, Merck).

Statistical Analysis. Statistical significance was first analyzed using Bartlett's test for homogeneity of variances, followed by the Williams' test ($P > 0.05$) and Shirley−Williams test ($P \leq 0.05$) for dose-dependent studies. Alternatively, statistical significance was analyzed using the *F* test for homogeneity of variances, followed by Student's *t*-test ($P > 0.2$) or the Aspin−Welch test ($P \leq 0.2$). The Williams' and Shirley−Williams tests were conducted using a one-tailed significance level of 2.5% (0.025). Other tests were conducted using a two-tailed significance level of 5% (0.05). All data are presented as mean ± standard deviation (S.D.).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jmedchem.0c00843.

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Analytical RP-HPLC traces and another competitive binding assay result of **4a** (PDF)

Molecular formula strings with human GPR40 EC_{50} data and E_{max} (%) (CSV)

Accession Codes

Atomic coordinates and structure factors for the crystal structures of **SCO-267** and compounds **68** are deposited in The Cambridge Crystallographic Data Centre with the deposition number 1978712 and 1978713, respectively. Authors will release the atomic coordinates and experimental data upon article publication.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

GPR40, G protein-coupled receptor 40; T2DM, type 2 diabetes mellitus; FFA, free fatty acid; GSIS, glucose-stimulated insulin secretion; FLIPR, fluorometric imaging plate reader; TBAF, tetrabutylammonium fluoride; CHO, Chinese hamster ovary; PG, plasma glucose; OGTT, oral glucose tolerance test

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