Bioorg. Med. Chem. 35 (2021) 116056

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Design and synthesis of a monocyclic derivative as a selective ACC1 inhibitor by chemical modification of biphenyl ACC1/2 dual inhibitors

Ryo Mizojiri [*], Daisuke Tomita [1], Masako Sasaki, Yoshihiko Satoh [2], Yukiko Yamamoto, Hiroyuki Sumi [3], Hironobu Maezaki [4]

Research, Takeda Pharmaceutical Company Limited, 26-1, Muraoka-Higashi 2-chome, Fujisawa, Kanagawa 251-8555, Japan

ARTICLE INFO

Keywords:
Acetyl-CoA carboxylase (ACC) 1 inhibitor
Selectivity
^{14}C acetate uptake inhibition
Bioavailability
Malonyl-CoA

ABSTRACT

A structure–activity relationship (SAR) study towards novel ACC1-selective inhibitors was carried out by modifying the molecular length of the linker in biaryl derivative **1 g**, an ACC1/2 dual inhibitor. Ultimately, this leads us to discover novel phenoxybenzyloxy derivative **1i** as a potent ACC1-selective inhibitor. Further chemical modification of this scaffold to improve cellular potency as well as physicochemical and pharmacokinetic (PK) properties produced *N*-2-(pyridin-2-ylethyl)acetamide derivative **1n**, which showed highly potent ACC1-selective inhibition as well as sufficient PK profile for further in vivo evaluations. Oral administration of **1n** significantly reduced the concentration of malonyl-CoA in HCT-116 xenograft tumors at doses of 100 mg/kg. Accordingly, our novel series of potent ACC1-selective inhibitors represents a set of useful orally-available research tools, as well as potential therapeutic agents for cancer and fatty acid-related diseases.

1. Introduction

Acetyl-CoA carboxylase (ACC) catalyzes the rate-limiting step in de novo lipogenesis and plays an important role in the regulation of fatty acid metabolism.[1–5] Therefore, ACC inhibition provides a promising therapeutic potential in type 2 diabetes (T2DM), [6] obesity, [7] nonalcoholic fatty liver disease (NAFLD), [8–10] cancer [11–15] and immunology. [16,17] Two ACC isoforms have been identified in mammals, ACC1 and ACC2. Malonyl-CoA which is produced by ACC1 is an intermediate of de novo fatty acid synthesis, which acts as a substrate of fatty acid synthase (FAS) for acyl chain elongation. On the other hand, ACC2, a mitochondrial membrane-associated enzyme, generates malonyl-CoA primarily to inhibit carnitine palmitoyltransferase 1 (CPT-1) and regulate fatty acid transport into the mitochondria to enhance fatty acid oxidation (FAO). A number of mammalian ACC inhibitors have been reported as dual ACC1/2 inhibitors[18–30] or selective ACC2 inhibitors[28–33] for the treatment of fatty acid metabolism disorders, whereas selective ACC1 inhibitors have been rarely reported. Recently, we reported novel ACC1-selective inhibitors as in vivo probe molecules and demonstrated antitumor activity for cancer therapeutics. [34–36]

Among those reports, Haque et al. described the discovery of potent biphenyl-based ACC inhibitors.[27] In the report, it is interesting to note that compound **1b** possessing 4-propoxy tail unit showed potent dual ACC1/2 inhibitory activity, on the other hand, compound **1c** possessing 4-methoxyethyl tail unit demonstrated excellent ACC1-selective inhibition. These results indicate that oxygen atom in the tail unit would be effective to adjust selectivity for these molecules. Furthermore, the positional relationship of the oxygen in the tail unit to the acetamide moiety in the head part of the molecule, an essential moiety for potent ACCs inhibitory activity, could potentially give rise to a new series of selective ACC1 inhibitors. Therefore, we hypothesized that the insertion of an appropriate linker between biphenyl moieties of **1** would lead us to

Abbreviations: ATP, adenosine triphosphate; BSA, bovine serum albumin; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DIAD, diisopropyl azodicarboxylate; IPE, diisopropyl ether; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; DPPA, diphenylphosphoryl azide; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; HOBt, 1-hydroxybenzotriazole; MsCl, methanesulfonyl chloride; PBS, phosphate buffered saline; THF, tetrahydrofuran.

* Corresponding author.
E-mail address: ryo.mizojiri@takeda.com (R. Mizojiri).
[1] Otsuka Pharmaceutical Co., Ltd., Minato-ku, Tokyo 108-8242, Japan.
[2] Chordia Therapeutics Inc., Fujisawa-shi, Kanagawa 251-8585, Japan.
[3] Daiichi Sankyo Co., Ltd., Shinagawa-ku, Tokyo 140-0005, Japan.
[4] Axcelead Drug Discovery Partners Inc., Fujisawa-shi, Kanagawa 251-8585, Japan.

https://doi.org/10.1016/j.bmc.2021.116056
Received 8 December 2020; Received in revised form 28 January 2021; Accepted 30 January 2021
Available online 14 February 2021

discover a novel ACC1-selective inhibitor as shown in Figure 1.

Herein, we report the discovery of a novel series of selective ACC1 inhibitors using a different approach than we previously had reported,34 as well as the in vivo activity in xenograft tumors.

1.1. Chemistry

Preparation of biaryl compounds **1a**–**g** begins with the copper-catalyzed coupling reaction of 1-(4′-bromo-[1,1′-biphenyl]-4-yl)ethan-1-one (**2**) with corresponding phenols (**3**) to give phenyl ether derivatives (**4**). After conversion of ketones **4** into amines **6** by reduction to alcohol, then azidation with DPPA, followed by reduction of azide, compounds **1a**–**e** were synthesized by acetylation of the amino group in amines **6.** Lastly**,** alkylation of phenol moiety of **1e** yielded **1f** and **1 g** (Scheme 1).

Preparation of compound **1 h** is displayed in Scheme 2. Coupling reaction of 4-iodophenol (**7**) and 1-(4-fluorophenyl)ethan-1-one (**8**) followed by copper-catalyzed coupling reaction with phenol **10** gave 1,4-diphenoxyphenyl derivative **11**. Conversion of carbonyl group in **11** into amino group by reductive amination followed by acetylation produced compound **1 h**.

Preparation of compounds **1i**, **1j** and **1 l** is illustrated in Scheme 3. Acetylation of 4-(1-aminoethyl)phenol (**12**) gave acetamide **13**. Coupling reaction of phenol **10** with corresponding aryl and heteroaryl halides **14** produced biaryl ethers **15** which was subjected to reduction with $LiAlH_4$ or $NaBH_4$ to give benzyl alcohol derivatives **16**. Mitsunobu reaction of **16a** and **16c** with **13** yielded compounds **1i** and **1 l**, respectively. After methanesulfonylation of **16b**, compound **1j** was synthesized by the coupling reaction with **13**.

Preparation of compound **1 k** is shown in Scheme 4. Mitsunobu reaction of (5-bromopyridin-2-yl)methanol (**17**) with 1-(4-hydroxyphenyl)ethan-1-one (**18**) gave phenoxy derivative **19**. Copper-catalyzed coupling reaction of **19** with phenol **10** yielded **20**. Reduction of ketone **20** followed by azidation with DPPA produced azide **21**. Finally, hydrogenation of the azide followed by acetylation afforded **1 k**.

Preparation of compound **1 m** is explained in Scheme 5. Acetamide derivative **25** was synthesized via reduction of 2,6-difluoro-4-iodobenzaldehyde (**23**) with $NaBH_4$ followed by Mitsunobu reaction with phenol **13**. Copper-catalyzed coupling reaction of **25** with phenol **10** gave compound **1 m**.

Preparation of compounds **1n** and **1o** is shown in Scheme 6. Substitution reaction of **24** with fluoropyridines **26** gave benzyl ether derivative **27**. Copper-catalyzed coupling reaction of **27** with phenol **10** yielded **28**. Conversion of ester group in **28** into Weinreb amide via hydrolysis followed by amide formation produced **29**. Subsequent reaction with MeMgBr, followed by reductive amination and lastly acetylation gave compounds **1n** and **1o**.

Preparation of compound **1p** is described in Scheme 7. Copper-catalyzed coupling reaction of **24** with phenol **10** gave diphenyl ether derivative **30**. Substitution reaction of 3,6-dibromopyridazine (**31**) with **30** yielded bromopyridazine derivative **32**. Introduction of vinylether by Pd-catalyzed coupling reaction followed by hydrolysis under acidic condition introduced a ketone moiety. After reduction of ketone moiety in **33** into alcohol, azide derivative was synthesized via methansulfonylation followed by azidation with sodium azide. Finally, compound **1p** was synthesized via Staudinger reduction of azide group followed by acetylation.

Preparation of compound **1q** is illustrated in Scheme 8. Substitution reaction of 1-(5-chloropyrazin-2-yl)ethan-1-one (**36**) with **30** under microwave irradiation gave **37**. Conversion of ketone moiety in **37** into acetamide via reductive amination followed by acetylation yielded compound **1q**.

2. Results and discussion

1. Activity and selectivity for ACC1 inhibition of *N*-(1-phenylethyl) acetamide derivatives

Compounds prepared in this study were evaluated for their inhibitory activity against recombinant human ACC1 and ACC2 expressed in SF-9 cells. To measure the inhibition of de novo lipid synthesis in cells of our ACC1 inhibitors, we established a ^{14}C-acetate uptake assay in HCT-116 colon cancer cells. To begin our investigation, we assessed biphenyl ACC1 inhibitors **1a**–**c**, reported by Haque et al.,[27] using our enzyme assay condition (Table 1). Under our enzyme assay condition, reported compounds **1a**–**c** showed moderate ACC1 inhibitory potency (around 10 μM as IC_{50} value). Therefore, we tried to identify more potent ACCs inhibitor for our lead compound. During our chemical modification, replacement of tail unit at C4-position into C3-position dramatically improved ACC1 inhibitory potency (**1d**: hACC1 IC_{50} = 130 nM, hACC2 IC_{50} = 98 nM) compared to compound **1c**. After minor modification of tail unit at C3-position, compound **1 g** possessing 3-cyclopropylmethoxy group showed potent ACC1/2 dual inhibition (hACC1 IC_{50} = 60 nM, hACC2 IC_{50} = 150 nM). Accordingly, we initiated our synthetic strategy to insert appropriate linker between biphenyl moieties of this compound.

At the beginning of the investigation for a novel ACC1-selective inhibitor, our lead compound **1 g** showed potent ACC1 inhibitory potency

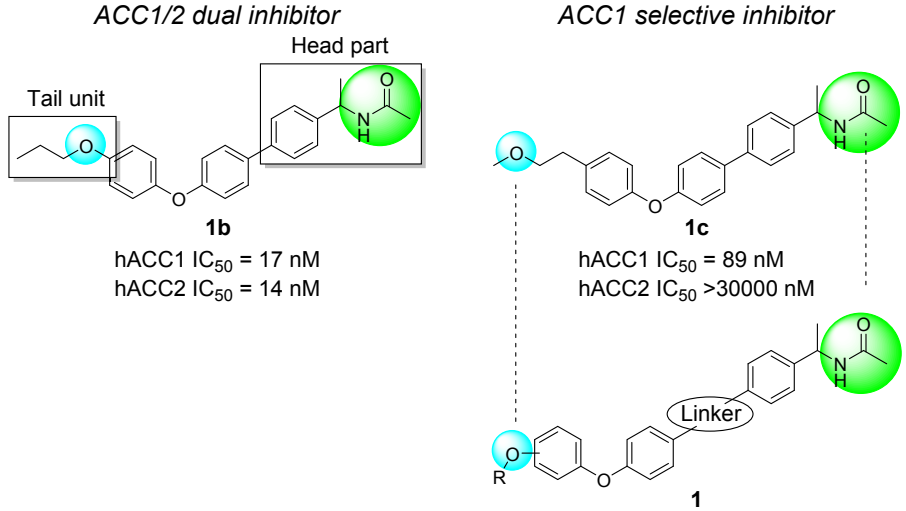
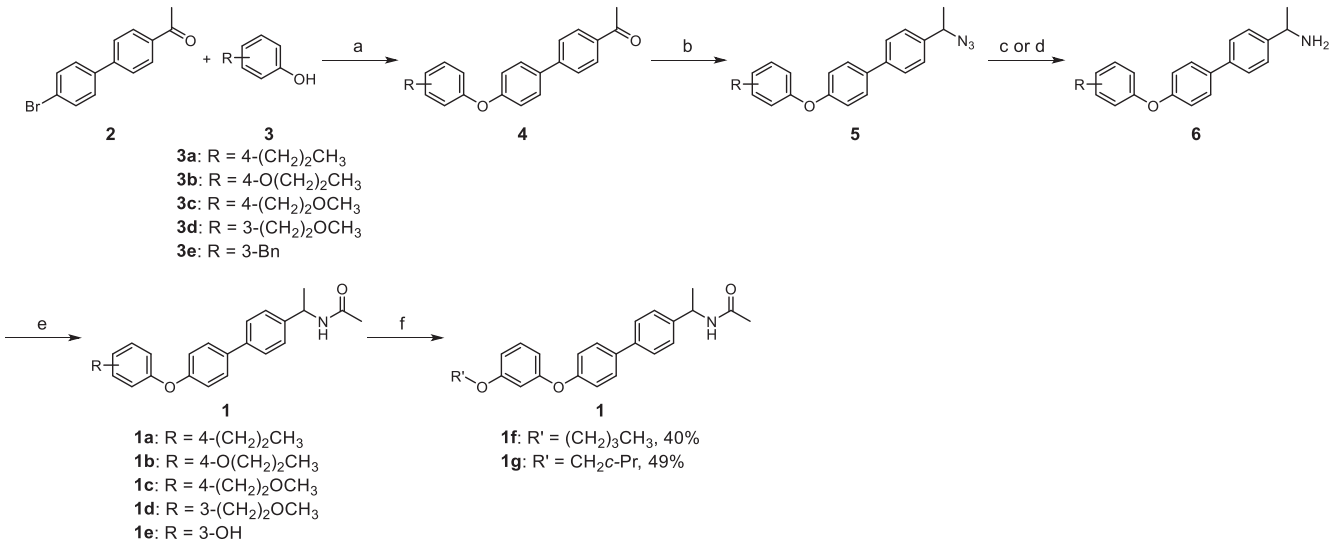
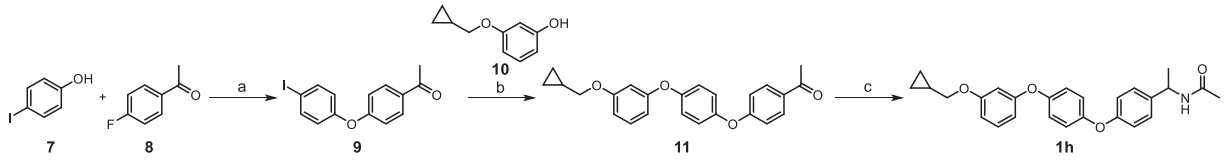


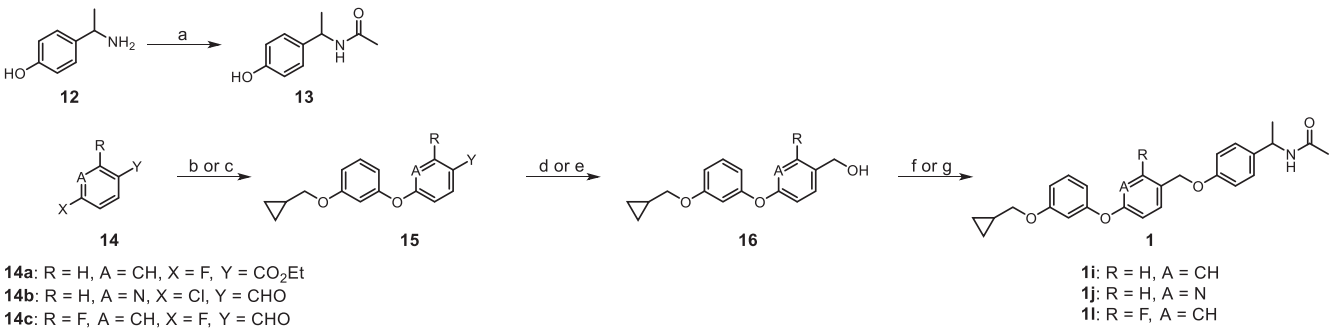
Fig. 1. Synthetic strategy for the generation of novel ACC1-selective inhibitors[a]. [a]Inhibitory activities refer the data in the literature.



Scheme 1. Reagents and conditions: a) *N*, *N*-dimethylglycine hydrochloride, CuI, Cs_2CO_3, DMF, 140 °C, overnight, 17–52%; b) i) $NaBH_4$, THF, MeOH, 0 °C, 1 h; ii) DPPA, DBU, toluene, rt, 2 h, 46–100%; c) for **1a**–**1c** and **1e**: H_2 (1 atm), Pd/C, THF, rt, 2 h; d) for **1d**: Ph_3P, THF, water, 60 °C, 1 h, 62%; e) Ac_2O, pyridine, rt, 30 min, 5–98%; f) R'Br, K_2CO_3, DMF, 80 °C, 2 h, 40–49%.



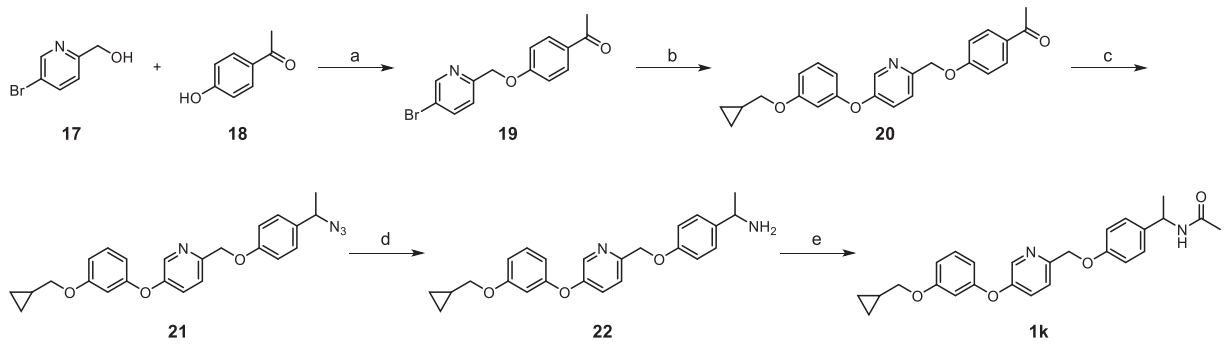
Scheme 2. Reagents and conditions: a) K_2CO_3, DMF, 50 °C, overnight, 69%; b) 3-(cyclopropylmethoxy)phenol (**10**), *N*,*N*-Dimethylglycine hydrochloride, CuI, Cs_2CO_3, DMF, 90 °C, overnight, 56%; c) i) NH_4OAc, $NaBH_3CN$, MeOH, 60 °C, overnight; ii) Ac_2O, Et_3N, THF, rt, 3 h, 68%.



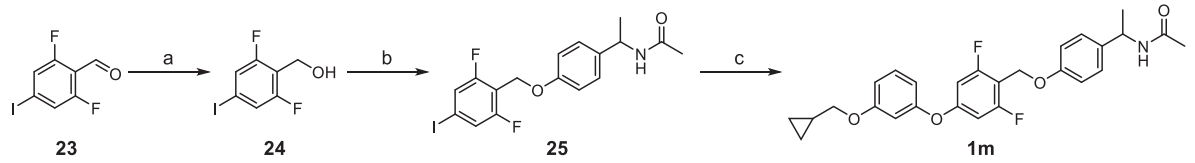
Scheme 3. Reagents and conditions: a) Ac_2O, THF, rt, 2 h, 61%; b) for **15a** and **15c**: **10**, Cs_2CO_3, DMF, 60–100 °C, 3 h to overnight, 60%; c) for **15b**: **10**, K_2CO_3, DMF, 60 °C, 2 h, 53%; d) for **16a**: $LiAlH_4$, THF, 0 °C, 30 min, 98%; e) for **16b** and **16c**: $NaBH_4$, MeOH, 0 °C, 2 h, 30%; f) for **1i** and **1 l**: **13**, tributylphosphine, 1,1′-(azodicarbonyl)-dipiperidine, toluene, rt, overnight, 30–39%, g) for **1j**: MsCl, Et_3N, THF, 0 °C, 4 h; ii) **13**, K_2CO_3, DMF, 50 °C, overnight, 15%.

(ACC1 IC_{50} = 60 nM), however, its selectivity over ACC2 was not enough (ca. 2.5 fold) for our research of ACC1-selective inhibitors. To adjust the positional relationship of acetamide moiety in the head part and ether group in the tail unit, insertion of oxygen atom between biphenyl moiety was attempted and compound **1 h** possessing 1,4-quinone moiety in the linker section was produced as a potent ACC1/2 dual inhibitor (hACC1 IC_{50} = 39 nM, hACC2 IC_{50} = 20 nM). This result indicated that the position of both the head and tail units may not be optimal for ACC1-selective inhibition. Therefore, we continued our investigation for an alternative linker. Interestingly enough, this led us to identify a novel 4-phenoxybenzyloxy derivative **1i**, which showed potent ACC1-selective inhibition with excellent selectivity over ACC2 (hACC1 IC_{50} = 220 nM, hACC2 IC_{50} > 10000 nM). Accordingly, we found that the positional relationship between the acetamide moiety and the ether group of compound **1i** was essential for highly potent ACC1-selective inhibition (Fig. 2).

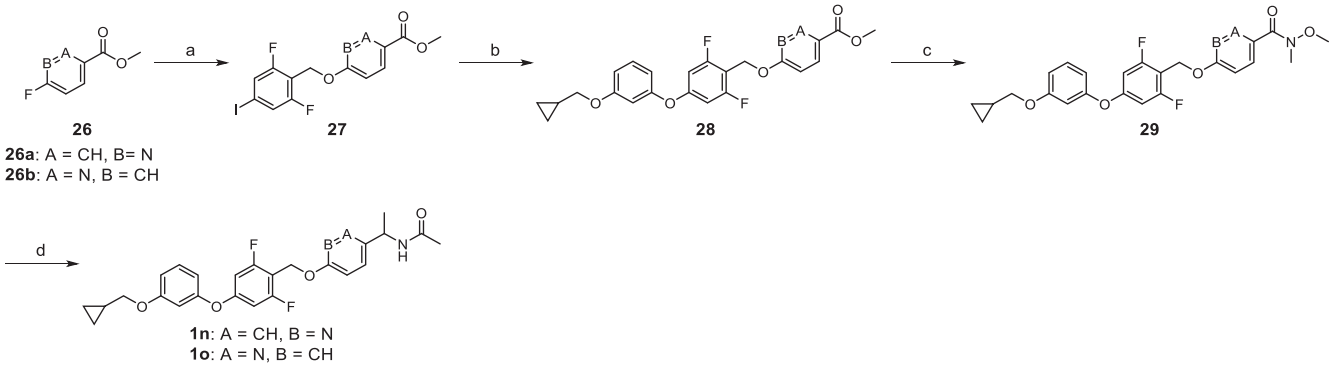
Next, we conducted modification of our novel 4-phenoxybenzyloxy derivative as a selective ACC1 inhibitor to identify in vivo probe molecule (Table 2). Compound **1i** showed potent ACC1-selective inhibition, however its cellular potency of Acetate uptake inhibition in HCT-116 cells was not sufficient for further in vitro and in vivo evaluations. In order to improve the cellular potency, we first investigated chemical modification of the middle aromatic ring (Ring A, highlighted in yellow) to improve ACC1 inhibitory activity. The replacement of the phenyl ring for a pyridine ring decreased ACC1 inhibitory potency as well as cellular activity (**1j**: hACC1 IC_{50} = 1200 nM, Acetate uptake IC_{50} > 1000 nM; **1 k**: hACC1 IC_{50} = 790 nM, Acetate uptake IC_{50} = 900 nM) compared to compound **1i** (hACC1 IC_{50} = 220 nM, Acetate uptake IC_{50} 420 nM). Further investigation by introducing heteroaryl ring instead of phenyl moiety was not effective in enhancing ACC1 inhibitory potency.



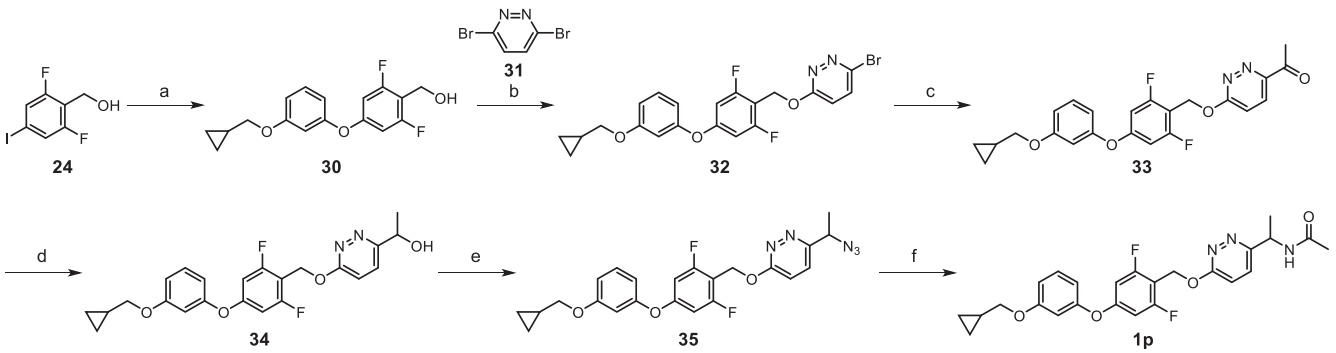
Scheme 4. Reagents and conditions: a) DIAD, Ph_3P, THF, rt, overnight, 88%; b) **10**, picolinic acid, CuI, K_3PO_4, DMSO, 90 °C, 4 h, 55%; c) i) $NaBH_4$, EtOH, THF, rt, 4 h; ii) DPPA, DBU, toluene, rt, 2 h, 88%; d) Ph_3P, water , THF, 60 °C, 1 h, 79%; e) Ac_2O, pyridine, rt, 30 min, 76%.



Scheme 5. Reagents and conditions: a) $NaBH_4$, EtOH, 0 °C, 1 h, 98%; b) **13**, DIAD, Ph_3P, THF, 12 °C, 4 h, 76%; c) **10**, picolinic acid, CuI, K_3PO_4, DMSO, 90 °C, overnight, 38%.

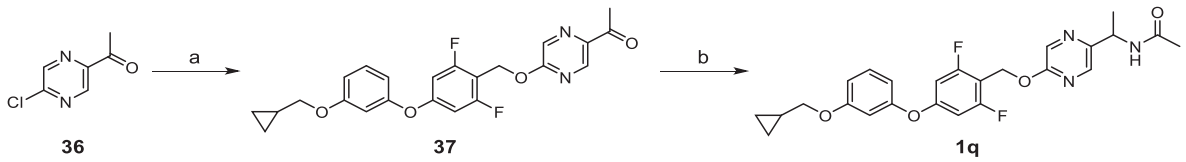


Scheme 6. Reagents and conditions: a) **24**, NaH, DMF, 30 °C, 2 h, 36–53%; b) **10**, picolinic acid, CuI, K_3PO_4, DMSO, 90 °C, 12–24 h, 63%; c) i) $LiOH{\cdot}H_2O$, THF, MeOH, water, 26–32 °C, 3–12 h; ii) N.O-dimethlyhydroxylamine hydrochloride, EDCI, HOBt, Et_3N, DMF, 30 °C, 3 h, 83%; d) i) MeMgBr, THF, 0 °C, 1 h; ii) NH_4OAc, $NaBH_3CN$, MeOH, reflux, 12 h; iii) Ac_2O, MeOH, 30 °C, 1–2 h, 9–45%.



Scheme 7. Reagents and conditions: a) **10**, picolinic acid, CuI, K_3PO_4, DMSO, 90 °C, 15 h, 54%; b) 3,6-dibromopyridazine (**31**), NaH, THF, 18 °C, 4 h, 75%; c) i) tributyl(1-ethoxyvinyl)tin, $Pd(Ph_3P)_2Cl_2$, DMF, 80 °C, 15 h; ii) aqueous HCl, acetone, 20 °C, 1 h, 57%; d) $NaBH_4$, MeOH, 20 °C, 0.5 h, 93%; e) i) MsCl, Et_3N, CH_2Cl_2, 20 °C, 1 h; ii) NaN_3, DMF, 60 °C, 2 h, 77%; f) i) Ph_3P, THF, water, reflux, 15 h; ii) Ac_2O, MeOH, 20 °C, 1 h, 52%.

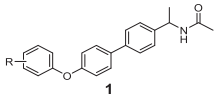
Therefore, we then investigated the substituent on Ring A as a tight SAR space. According to our continuous research, only small lipophilic substituent (e.g. fluorine atom) was acceptable for ACC1 inhibition. In compound **1 l**, the introduction of fluorine atom at *C*2-position of phenyl ring showed potent ACC1 inhibitory activity with excellent selectivity over ACC2 and improved cellular potency (hACC1 $IC_{50} = 69$ nM, hACC2 $IC_{50} > 10000$ nM, Acetate uptake $IC_{50} = 63$ nM). Furthermore, substitution of fluorine atoms at *C*2 and C6-position on the middle aromatic



Scheme 8. Reagents and conditions: a) **30**, 1-(5-chloropyrazin-2-yl)ethan-1-one (**36**), NaH, THF, 135 °C, 1 h, MW, 24%; b) i) NH_4OAc, $NaBH_3CN$, MeOH, 65 °C, overnight; ii) Ac_2O, THF, rt, 1 h, 53%.

Table 1

Initial SAR studies of biphenyl derivatives [a]



Compound	R	IC_{50} (nM) ACC1	ACC2
1a	4-$(CH_2)_2CH_3$	38%[b]	11%[b]
1b	4-$O(CH_2)_2CH_3$	50%[b]	51%[b]
1c	4-$(CH_2)_2OCH_3$	49%[b]	6%[b]
1d	3-$(CH_2)_2OCH_3$	130 (92–191)	98 (53–181)
1f	3-$O(CH_2)_3CH_3$	120 (88–165)	210 (129–337)
1 g	3-OCH_2cPr	60 (35–101)	150 (111–212)

[a] IC_{50} is presented as the mean of duplicate experiments along with 95% confidence intervals (95%CI) in parentheses. [b]Inhibitory potency was shown as a % inhibition at 10 μM.

ring led us to identify highly potent ACC1-selective inhibitor **1 m** which also exhibited improved cellular potency (hACC1 IC_{50} = 15 nM, hACC2 IC_{50} > 10000 nM, Acetate uptake IC_{50} = 9.7 nM).Table 3.

According to our investigation of Ring A, 4-phenoxy-2,6-difluorobenzyl derivative **1 m** was identified as a highly potent ACC1-selective inhibitor. Further physicochemical profiling revealed that **1 m** possessed low solubility due to its high lipophilicity (cLog P = 6.22, Solubility: <0.21 mg/mL). Therefore, we next conducted modification of phenyl ring in the head part (Ring B) to reduce its lipophilicity. Replacement of the phenyl ring into a pyridine moiety reduced lipophilicity as expected (**1n** and **1o**: cLog P = 5.23). Among these, compound **1n** showed highly potent ACC1-selective inhibition (hACC1 IC_{50} = 17 nM, hACC2 IC_{50} > 10000 nM, Acetate uptake IC_{50} = 24 nM) comparable to **1 m** (hACC1 IC_{50} = 15 nM, hACC2 IC_{50} > 10000 nM, Acetate uptake IC_{50} = 9.7 nM). Further introduction of nitrogen atom to reduce lipophilicity gave pyridazine derivative **1p** (cLog P = 4.26) and pyrazine derivative **1q** (cLog P = 4.40) which showed acceptable ACC1 inhibitory potency, however both compounds showed decreased cellular activity compared to compound **1n** in return for the reduction of lipophilicity. Accordingly, compound **1 m** and **1n** were identified as a highly potent ACC1-selective inhibitors possessing excellent cellular activity.

3. In vivo evaluation of an ACC1-selective inhibitor

Physicochemical and PK profiles for compounds **1 m** and **1n** are displayed in Table 4. Both compounds showed excellent ACC1-selective inhibition as well as potent cellular activity. On the other hand, they still had insufficient solubility due to high lipophilicity. Further investigation for their ADMET profiles revealed that both compounds demonstrated sufficient properties such as permeability, metabolic stability in liver microsomes. In terms of CYP inhibition potential, they showed acceptable properties for CYP2C8 and CYP2C9, which were challenges with bicyclic ACC1-selective inhibitors.[34] Furthermore, they possessed good bioavailability in mouse cassette PK study. In comparison between the two compounds, **1n** showed improved solubility under acidic conditions and a better PK profile than **1 m**, hence as a promising probe molecule for further in vivo evaluations.

Based on the promising in vitro and in vivo profile of **1n**, we selected this compound for in vivo PD study to evaluate the potential of an ACC1 inhibitor in xenograft tumor models. In this PD study, malonyl-CoA concentration in tumors was measured as a direct PD marker. As a result, compound **1n** showed potent malonyl-CoA suppression at 2 h after single oral administration in HCT-116 xenograft mice at 100 mg/kg, and its reduction by compound **1n** was sustained up to 16 h after the administration (Fig. 3).

4. Conclusions

We have investigated a new approach to discover a novel series of 4-phenoxybenzyloxy derivatives as chemical probes of selective ACC1 inhibitors from biaryl ACC1/2 dual inhibitors by the modification of the linker section. In the beginning of our research, we found compound **1i** showed potent ACC1 inhibitory activity with excellent selectivity over ACC2. After chemical modification of the middle section (Ring A) of the molecule, compound **1 m** showed highly potent ACC1-selective inhibition as well as excellent cellular activity (Acetate uptake: IC_{50} = 9.7 nM), however this compound possessed low solubility due to high lipophilicity. Further optimization of the head part (Ring B) produced *N*-2-(pyridin-2-ylethyl)acetamide derivative **1n**, which showed highly potent ACC1-selective inhibition as well as sufficient PK profile for further in vivo evaluations. Based on the promising PK profile and results from in vivo PD study, **1n** is considered to be useful in vivo probe molecule for basic pharmacology research into ACC1 function.

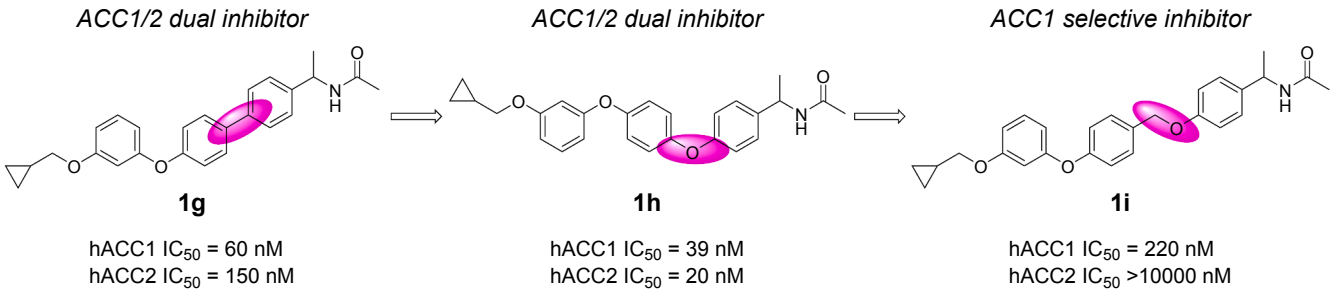
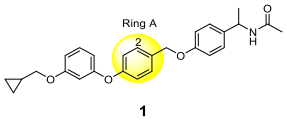
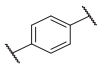
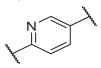
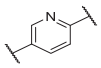
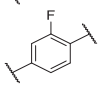
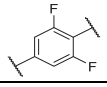


Fig. 2. Initial SAR studies of the linker part for ACC1 inhibitors.

Table 2
Optimization for Ring A of 4-phenoxybenzyloxy derivatives [a]



1

Compound		IC_{50} (nM) ACC1	ACC2	Acetate[b]
1i		220 (109–428)	>10000	420 (223–797)
1j		790 (342–1819)	>10000	900 (398–2037)
1 k		1200 (750–1764)	>10000	>1000
1 l		69 (37–128)	>10000	63 (35–114)
1 *m*		15 (9.0–27)	>10000	9.7 (7.3–13)

[a] IC_{50} is presented as the mean of duplicate experiments along with 95% confidence intervals (95%CI) in parentheses.
[b] Acetate uptake inhibition in HCT-116 cells.

5. Experimental section

5.1. General

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker AVANCE-300 (300 MHz) and Bruker AVANCE-400 (400 MHz) instruments in $CDCl_3$, CD_3OD or DMSO-d_6 solution. Chemical shifts are given in parts per million (ppm) with tetramethylsilane as an internal standard. Abbreviations are used as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, brs = broad singlet. Coupling constants (*J* values) are given in hertz (Hz). Melting points (mp) were determined on an Opti-Melt MPA100 melting point apparatus and were uncorrected. Elemental analyses were carried out by Sumika Chemical Analysis Service, Ltd. and were within 0.4% of the theoretical values. Low-resolution mass spectra (MS) were acquired using a Shimadzu UFLC/MS (Prominence UFLC high pressure gradient system/LCMS-2020) operating in an electron spray ionization mode (ESI +). The column used was an L-column 2 ODS (3.0 × 50 mm I.D., 3 μm, CERI, Japan) 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 an acidic condition were 0.05% TFA in water and 0.05% TFA in CH_3CN, 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. The ratio of mobile phase B was increased linearly from 5% to 90% over 0.9 min, 90% over the next 1.1 min. The purities of all compounds tested in biological systems were assessed as being > 95% using elemental analysis or LCMS. Reagents and solvents were obtained from commercial sources and used without further purification. Reaction progress was determined by thin layer chromatography (TLC) analysis on Merck Kieselgel 60 F254 plates or Fuji Silysia NH plates. Chromatographic purification was carried out on silica gel columns ((Inject column and Universal column, YAMAZEN Co.) or on Purif-Pack (Si or NH, Shoko Scientific Co., Ltd.)). All commercially available solvents and reagents were used without further purification. Starting materials (**2**, **3**, **7**, **8**, **10**, **12**, **14**, **17**, **18**, **23**, **26**, **31** and **36**) were purchased from commercial companies, and used as such. Yields were not optimized.

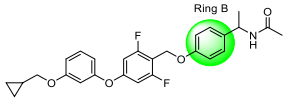
5.1.1. General procedure for the preparation of compound 1a–c, e

1-[4′-(4-propylphenoxy)[1,1′-biphenyl]-4-yl]ethan-1-one (4a): A mixture of 4-propylphenol (**2a**) (0.52 g, 3.8 mmol), 1-(4′-bromo[1,1′-*biphenyl*]-4-yl)ethan-1-one (**3**) (1 g, 3.6 mmol), *N*,*N*-dimethylglycine hydrochloride (0.051 g, 0.36 mmol), CuI (0.012 mL, 0.36 mmol) and Cs_2CO_3 (1.8 g, 5.5 mmol) in DMF (10 mL) was stirred at 140 °C overnight. After cooling to room temperature, the mixture was extracted with AcOEt and water. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and pass through a pad of NH silica gel (eluted with AcOEt). After concentration, the residue was crystallized from EtOH to afford **4a** (0.28 g, 24%) as a beige solid.

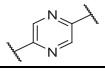
^{1}H NMR (300 MHz, DMSO-d_6) δ 0.91 (3H, t, J = 7.3 Hz), 1.47–1.68 (2H, m), 2.53–2.65 (5H, m), 6.92–7.12 (4H, m), 7.24 (2H, d, J = 8.5 Hz), 7.69–7.90 (4H, m), 8.02 (2H, d, J = 8.5 Hz). LCMS *m/z* calcd for $C_{23}H_{22}O_2$: 330.16, found 331.1 [M + H] + .

1-[4′-(4-Propoxyphenoxy)[1,1′-biphenyl]-4-yl]ethan-1-one (4b): Product was prepared according to the general procedure from 0.58 g of 4-propoxyphenol (**3b**) and obtained (0.65 g, 52%) as a white solid.

Table 3
Optimization for Ring B of 4-phenoxy-2,6-difluorobenzyloxy derivatives.[a]



1

Compound		IC_{50} (nM) ACC1	ACC2	Acetate[b]	cLogP	Solubility[c] (mg/mL)
1m		15 (9.0–27)	>10000	9.7 (7.3–13)	6.22	<0.21
1n		17 (10–28)	>10000	24 (18–30)	5.23	<0.23
1o		38 (24–59)	>10000	70 (41–120)	5.23	1.5
1p		31 (20–49)	>10000	110 (88–131)	4.26	2.3
1q		89 (49–162)	>10000	180 (99–310)	4.40	0.46

[a] IC_{50} is presented as the mean of duplicate experiments along with 95% confidence intervals (95%CI) in parentheses.
[b] Acetate uptake inhibition in HCT-116 cells.
[c] Solubility in pH 6.8.

Table 4
Physicochemical and PK profiles of benzyloxy derivatives.[a]

Compound		**1 m**		**1n**	
IC_{50} (nM)		15	>10000	17	>10000
ACC1	ACC2	(9.0–27)		(10–28)	
Acetate uptake IC_{50} (nM)[b]		9.7 (7.3–13)		24 (18–30)	
cLogP	LogD	6.22	5.01	5.23	4.82
Solubility[c] (mg/mL)		<0.23	<0.21	0.96	<0.23
pH1.2	pH6.8				
PAMPA (nm/*sec*)		111	346	683	662
pH7.4	pH5.0				
Metabolic Stability (μL/min/mg)		30	36	12	17
human	mouse				
CYP inhibition (%)		31.4	−22.7	32.0	−13.8
2C8	2C9				
Mouse Cassette PK[d]		1584.1	31.1	5346.0	70.5
AUC[e] (ng•h/mL)	*F*[f] (%)				

Reagents and conditions: a) *N*, *N*-dimethylglycine hydrochloride, CuI, Cs_2CO_3, DMF, 140 °C, overnight, 17–52%; b) i) $NaBH_4$, THF, MeOH, 0 °C, 1 h; ii) DPPA, DBU, toluene, rt, 2 h, 46–100%; c) for **1a**–**1c** and **1e**: H_2 (1 atm), Pd/C, THF, rt, 2 h; d) for **1d**: Ph_3P, THF, water, 60 °C, 1 h, 62%; e) Ac_2O, pyridine, rt, 30 min, 5–98%; f) R'Br, K_2CO_3, DMF, 80 °C, 2

[a] IC_{50} is presented as the mean of duplicate experiments along with 95% confidence intervals (95%CI) in parentheses. [b]Acetate uptake inhibition in HCT-116 cells. [c]Solubility in pH 6.8. [d]Male ICR mice (n = 3). Dose: i.v. at 0.1 mg/kg; p.o. at 1 mg/kg. [e]Area under the curve from 0 to 8 h. [f]Bioavailability.

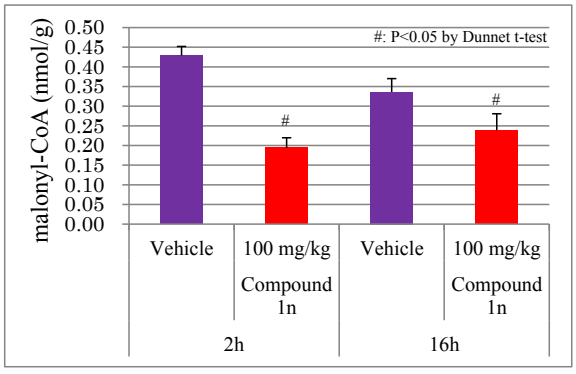


Fig. 3. Effects of compound **1n** on malonyl-CoA concentration in HCT-116 xenograft tumors. h, 40–49%.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.99 (3H, t, J = 7.4 Hz), 1.60–1.82 (2H, m), 2.60 (3H, s), 3.86–3.99 (2H, m), 6.90–7.10 (6H, m), 7.69–7.85 (4H, m), 8.00 (2H, s). LCMS *m/z* calcd for $C_{23}H_{22}O_3$: 346.16, found 347.1 [M + H] + .

1-{4′-[4-(2-Methoxyethyl)phenoxy] [1,1′-biphenyl] -4-yl} ethan-1-one (**4c**): Product was prepared according to the general procedure from 0.58 g of 4-(2-methoxyethyl)phenol (**3c**) and obtained (0.29 g, 23%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.60 (3H, s), 2.73–2.86 (2H, m), 3.26 (3H, s), 3.46–3.57 (2H, m), 6.92–7.13 (4H, m), 7.28 (2H, d, J = 8.6 Hz), 7.78 (4H, dd, J = 10.7, 8.6 Hz), 8.03 (2H, d, J = 8.5 Hz). LCMS *m/z* calcd for $C_{23}H_{22}O_3$: 346.16, found 347.1 [M + H] + .

1-{4′-[3-(2-Methoxyethyl)phenoxy] [1,1′-biphenyl] -4-yl} ethan-1-one (**4d**): Product was prepared according to the general procedure from 1 g of 3-(2-methoxyethyl)phenol (**3d**) and obtained (0.9 g, 40%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.61 (3H, s), 2.82 (2H, t, J = 6.8 Hz), 3.33 (3H, s), 3.54 (2H, t, J = 6.8 Hz), 6.91 (1H, dd, J = 7.7, 2.1 Hz), 6.99 (1H, s), 7.03–7.15 (3H, m), 7.27–7.39 (1H, m), 7.80 (4H, dd, J = 9.6, 8.8 Hz), 8.03 (2H, d, J = 8.5 Hz). LCMS *m/z* calcd for $C_{23}H_{22}O_3$: 346.16, found 347.1 [M + H] + .

1-{4′-[3-(Benzyloxy)phenoxy] [1,1′-biphenyl] -4-yl}ethan-1-one (**4e**): Product was prepared according to the general procedure from 1 g of 3-(benzyloxy)phenol (**3e**) and obtained (0.32 g, 17%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.61 (3H, s), 5.11 (2H, s), 6.60–6.68 (1H, m), 6.74 (1H, t, J = 2.3 Hz), 6.80–6.89 (1H, m), 7.12 (2H, d, J = 8.7 Hz), 7.28–7.46 (6H, m), 7.80 (4H, dd, J = 11.9, 8.6 Hz), 8.03 (2H, d, J = 8.5 Hz). LCMS *m/z* calcd for $C_{27}H_{22}O_3$: 394.16, found 395.1 [M + H] + .

4-(1-Azidoethyl)-4′-(4-propylphenoxy)-1,1′-biphenyl (**5a**): To an ice cold stirred solution of **4a** (284 mg, 0.86 mmol) in THF (5 mL) and MeOH (2 mL) was added $NaBH_4$ (33 mg, 0.86 mmol). After stirring at 0 °C for 1 h, the mixture was extracted with AcOEt and 1 N HCl. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure to afford the alcohol. A mixture of the alcohol, DPPA (473 mg, 1.7 mmol) and DBU (0.26 mL, 1.7 mmol) in toluene (5 mL) was stirred at room temperature for 2 h. The mixture was extracted with toluene and water. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 5/95 to 25/75 AcOEt/hexane) to afford **5a** (190 mg, 62%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.90 (3H, t, J = 7.3 Hz), 1.49 (3H, d, J = 6.8 Hz), 1.54–1.67 (2H, m), 2.53–2.61 (2H, m), 4.80–4.96 (1H, m), 6.93–7.10 (4H, m), 7.23 (2H, d, J = 8.5 Hz), 7.46 (2H, d, J = 8.2 Hz), 7.61–7.74 (4H, m).

4-(1-Azidoethyl)-4′-(4-propoxyphenoxy)-1,1′-biphenyl (**5b**): Product was prepared according to the general procedure from 651 mg of **4b** and obtained (321 mg, 46%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.99 (3H, t, J = 7.4 Hz), 1.49 (3H, d, J = 6.8 Hz), 1.63–1.84 (2H, m, J = 7.3 Hz), 3.92 (2H, t, J = 6.5 Hz), 4.72–5.02 (1H, m), 6.86–7.11 (6H, m), 7.45 (2H, d, J = 8.2 Hz), 7.65 (4H, d, J = 8.4 Hz).

4-(1-Azidoethyl)-4′-[4-(2-methoxyethyl)phenoxy] -1,1′-biphenyl (**5c**): Product was prepared according to the general procedure from 292 mg of **4c** and obtained (200 mg, 64%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.49 (3H, d, J = 6.8 Hz), 2.81 (2H, t, J = 6.8 Hz), 3.25 (3H, s), 3.54 (2H, t, J = 6.8 Hz), 4.88 (1H, d, J = 6.7 Hz), 6.94–7.10 (4H, m), 7.27 (2H, d, J = 8.3 Hz), 7.46 (2H, d, J = 8.0 Hz), 7.67 (4H, dd, J = 8.3, 4.7 Hz).

4-(1-Azidoethyl)-4′-[3-(2-methoxyethyl)phenoxy] -1,1′-biphenyl (**5d**): Product was prepared according to the general procedure from 0.9 g of **4d** and obtained (0.97 g, 100%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.49 (3H, d, J = 6.9 Hz), 2.81 (2H, t, J = 6.8 Hz), 3.23 (3H, s), 3.46–3.60 (2H, m), 4.89 (1H, q, J = 6.8 Hz), 6.84–6.94 (1H, m), 6.98 (1H, d, J = 2.1 Hz), 7.02–7.11 (3H, m), 7.28–7.32 (1H, m), 7.47–7.51 (4H, m), 7.69–7.73 (2H, m).

4-(1-Azidoethyl)-4′-[3-(benzyloxy)phenoxy] -1,1′-biphenyl (**5e**): Product was prepared according to the general procedure from 310 mg of **4e** and obtained (266 mg, 80%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.49 (3H, d, J = 6.8 Hz), 4.89 (1H, q, J = 6.8 Hz), 5.10 (2H, s), 6.62 (1H, ddd, J = 8.1, 2.3, 0.8 Hz), 6.72 (1H, t, J = 2.3 Hz), 6.83 (1H, ddd, J = 8.3, 2.4, 0.8 Hz), 7.05–7.13 (2H, m), 7.26–7.52 (8H, m), 7.65–7.74 (4H, m).

***N*-{1-[4′-(4-Propylphenoxy) [1,1′-biphenyl] -4-yl] ethyl}acetamide** (**1a**): A mixture of **5a** (190 mg, 0.53 mmol) and 10% Pd on carbon (50% wet, 57 mg, 0.05 mmol) in THF (5 mL) was stirred at room temperature for 2 h under H_2 atmosphere (1 atm). The mixture was filtered through a pad of Celite and concentrated under reduced pressure to afford the amine. A mixture of amine and Ac_2O (0.5 mL, 5.3 mmol) in pyridine (2 mL) was stirred at room temperature for 30 min. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (NH silica gel, eluent: 10/90 to 10/0 AcOEt/hexane) and crystallized from AcOEt and hexane to afford **1a** (31 mg, 16%) as a white crystal.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.90 (3H, t, J = 7.3 Hz), 1.36 (3H, d, J = 7.0 Hz), 1.53–1.69 (2H, m), 1.85 (3H, s), 2.52–2.59 (2H, m), 4.80–5.02 (1H, m), 6.90–7.09 (4H, m), 7.22 (2H, d, J = 8.6 Hz), 7.36 (2H, d, J = 8.2 Hz), 7.50–7.69 (4H, m), 8.29 (1H, d, J = 8.1 Hz). ^{13}C

NMR (75 MHz, DMSO-d_6) δ 14.08, 22.86, 23.14, 24.64, 36.97, 47.95, 118.91 (2C), 119.37 (2C), 126.77 (2C), 127.03 (2C), 128.57 (2C), 130.29 (2C), 135.37, 138.01, 138.38, 144.20, 154.74, 157.20, 168.68. LCMS *m/z* calcd for $C_{25}H_{27}NO_2$: 373.20, found 374.2 [M + H] + .

***N*-{1-[4′-(4-Propoxyphenoxy)[1,1′-biphenyl]-4-yl]ethyl}acetamide (1b)**: Product was prepared according to the general procedure from 321 mg of **5b** and obtained (115 mg, 34%) as a white crystal.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.98 (3H, t, J = 7.4 Hz), 1.35 (3H, d, J = 7.0 Hz), 1.62–1.78 (2H, m), 1.84 (3H, s), 3.92 (2H, t, J = 6.5 Hz), 4.83–5.01 (1H, m), 6.89–7.08 (6H, m), 7.35 (2H, d, J = 8.2 Hz), 7.58 (4H, dd, J = 15.7, 8.5 Hz), 8.21–8.37 (1H, m). ^{13}C NMR (75 MHz, DMSO-d_6) δ 10.89, 22.54, 22.86, 23.14, 47.95, 69.80, 116.14 (2C), 118.02 (2C), 121.32 (2C), 126.73 (2C), 127.01 (2C), 128.49 (2C), 134.88, 138.41, 144.13, 149.61, 155.67, 158.10, 168.68. LCMS *m/z* calcd for $C_{25}H_{27}NO_3$: 389.50, found 390.2 [M + H] + .

***N*-(1-{4′-[4-(2-Methoxyethyl)phenoxy][1,1′-biphenyl]-4-yl}ethyl)acetamide (1c)**: Product was prepared according to the general procedure from 200 mg of **5c** and obtained (11 mg, 5%) as a white crystalline solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.36 (3H, d, J = 7.0 Hz), 1.84 (3H, s), 2.74–2.85 (2H, m), 3.25 (3H, s), 3.54 (2H, t, J = 6.8 Hz), 4.84–5.02 (1H, m), 6.91–7.10 (4H, m), 7.23–7.31 (2H, m), 7.32–7.39 (2H, m), 7.52–7.71 (4H, m), 8.19–8.39 (1H, m). LCMS *m/z* calcd for $C_{25}H_{27}NO_3$: 389.50, found 390.2 [M + H] + .

***N*-{1-[4′-(3-Hydroxyphenoxy)[1,1′-biphenyl]-4-yl]ethyl}acetamide (1e)**: Product was prepared according to the general procedure from 266 mg of **5e** and obtained (150 mg, 68%) as a white crystal.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.36 (3H, d, J = 7.0 Hz), 1.85 (3H, s), 4.93 (1H, quin, J = 7.2 Hz), 6.38–6.43 (1H, m), 6.47 (1H, dd, J = 8.1, 1.6 Hz), 6.55 (1H, dd, J = 8.1, 1.5 Hz), 7.08 (2H, d, J = 8.7 Hz), 7.17 (1H, t, J = 8.1 Hz), 7.37 (2H, d, J = 8.3 Hz), 7.58 (2H, d, J = 8.2 Hz), 7.65 (2H, d, J = 8.7 Hz), 8.32 (1H, d, J = 8.0 Hz), 9.63 (1H, s). LCMS *m/z* calcd for $C_{22}H_{21}NO_3$: 347.15, found 348.1 [M + H] + .

5.1.2. N-(1-{4′-[3-(2-Methoxyethyl)phenoxy][1,1′-biphenyl]-4-yl}ethyl)acetamide (1d)

1-{4′-[3-(2-Methoxyethyl)phenoxy][1,1′-biphenyl]-4-yl}ethan-1-amine (6d): A mixture of **5d** (970 mg, 2.6 mmol) and Ph_3P (1.4 g, 5.3 mmol) in THF (6 mL) and water (3 mL) was stirred at 60 °C for 1 h. After cooling to room temperature, the mixture was extracted with AcOEt and water. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 0/100 to 75/25 MeOH/AcOEt) to afford **6d** (561 mg, 62%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.27 (3H, d, J = 6.6 Hz), 1.90–2.00 (2H, m), 2.81 (2H, t, J = 6.8 Hz), 3.23 (3H, s), 3.53 (2H, t, J = 6.8 Hz), 3.97–4.07 (1H, m), 6.87 (1H, ddd, J = 8.1, 2.5, 0.8 Hz), 6.96 (1H, t, J = 1.9 Hz), 7.01–7.09 (3H, m), 7.27–7.35 (1H, m), 7.40–7.47 (2H, m), 7.53–7.60 (2H, m), 7.62–7.69 (2H, m). LCMS *m/z* calcd for $C_{23}H_{25}NO_2$: 347.45, found 331.2 [M + H–NH_3] + .

***N*-{1-{4′-[3-(2-Methoxyethyl)phenoxy][1,1′-biphenyl]-4-yl}ethyl)acetamide (1d)**: A mixture of **6d** (561 mg, 1.6 mmol) and Ac_2O (0.75 mL, 8.0 mmol) in pyridine (4 mL) was stirred at room temperature for 30 min. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (NH silica gel, eluent: 10/90 to 100/0 AcOEt/hexane) to afford **1d** (616 mg, 98%) as a white amorphous.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.36 (3H, d, J = 7.0 Hz), 1.85 (3H, s), 2.81 (2H, t, J = 6.7 Hz), 3.23 (3H, s), 3.53 (2H, t, J = 6.8 Hz), 4.93 (1H, quin, J = 7.1 Hz), 6.88 (1H, dd, J = 8.1, 1.7 Hz), 6.97 (1H, s), 7.01–7.10 (3H, m), 7.27–7.41 (3H, m), 7.58 (2H, d, J = 8.3 Hz), 7.65 (2H, d, J = 8.7 Hz), 8.31 (1H, d, J = 8.0 Hz). LCMS *m/z* calcd for $C_{25}H_{27}NO_3$: 389.50, found 390.1 [M + H] + . Anal Calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.85; H, 6.82; N, 3.55.

***N*-{1-[4′-(3-Butoxyphenoxy)[1,1′-biphenyl]-4-yl]ethyl}acetamide (1f)**: A mixture of **1e** (75 mg, 0.22 mmol), 1-bromobutane (0.05 mL, 0.47 mmol) and K_2CO_3 (60 mg, 0.43 mmol) in DMF (2 mL) was stirred at 80 °C for 2 h. After cooling to room temperature, the mixture was extracted with AcOEt and water. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (NH silica gel, eluent: 10/90 to 100/0 AcOEt/hexane) and crystallized from AcOEt and hexane to afford **1f** (35 mg, 40%) as a white crystalline solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.92 (3H, t, J = 7.4 Hz), 1.36 (3H, d, J = 7.0 Hz), 1.39–1.47 (2H, m), 1.62–1.72 (2H, m), 1.85 (3H, s), 3.95 (2H, t, J = 6.4 Hz), 4.87–4.99 (1H, m), 6.55–6.63 (2H, m), 6.73 (1H, d, J = 8.8 Hz), 7.09 (2H, d, J = 8.7 Hz), 7.28 (1H, t, J = 8.2 Hz), 7.37 (2H, d, J = 8.3 Hz), 7.59 (2H, d, J = 8.2 Hz), 7.66 (2H, d, J = 8.8 Hz), 8.31 (1H, d, J = 7.6 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.14, 19.18, 22.86, 23.15, 31.14, 47.95, 67.79, 105.47, 110.01, 110.99, 119.57 (2C), 126.76 (2C), 127.03 (2C), 128.60 (2C), 131.04, 135.69, 138.24, 144.28, 156.49, 158.10, 160.56, 168.69. LCMS *m/z* calcd for $C_{26}H_{29}NO_3$: 403.21, found 404.1 [M + H] + . Anal. Calcd for $C_{26}H_{29}NO_3$: C, 77.39; H, 7.24; N, 3.47. Found: C, 77.09; H, 7.05; N, 3.24. Mp 108–110 °C.

***N*-(1-{4′-[3-(Cyclopropylmethoxy)phenoxy][1,1′-biphenyl]-4-yl}ethyl)acetamide (1 g)**: Product was prepared according to the general procedure of **1f** from 75 mg of **1e** and obtained (42 mg, 49%) as a white crystalline solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.26–0.35 (2H, m), 0.50–0.59 (2H, m), 1.12–1.27 (1H, m), 1.36 (3H, d, J = 7.0 Hz), 1.85 (3H, s), 3.80 (2H, d, J = 7.0 Hz), 4.93 (1H, t, J = 7.5 Hz), 6.55–6.63 (2H, m), 6.68–6.76 (1H, m), 7.08 (2H, d, J = 8.7 Hz), 7.28 (1H, t, J = 8.3 Hz), 7.37 (2H, d, J = 8.2 Hz), 7.59 (2H, d, J = 8.2 Hz), 7.66 (2H, d, J = 8.8 Hz), 8.31 (1H, d, J = 8.2 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.54 (2C), 10.53, 22.85, 23.15, 47.96, 72.67, 105.78, 110.23, 111.07, 119.46 (2C), 126.82 (2C), 127.04 (2C), 128.60 (2C), 130.97, 135.78, 138.33, 144.27, 156.54, 158.14, 160.57, 168.69. LCMS *m/z* calcd for $C_{26}H_{27}NO_3$: 401.20, found 402.2 [M + H] + . Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.90; H, 6.53; N, 3.19. Mp 122–124 °C

5.1.3. N-[1-(4-{4-[3-(Cyclopropylmethoxy)phenoxy]phenoxy}phenyl)ethyl]acetamide (1 h)

1-[4-(4-Iodophenoxy)phenyl]ethan-1-one (9): A mixture of 4-iodophenol (**7**) (1.7 g, 7.6 mmol), 1-(4-fluorophenyl)ethan-1-one (**8**) (1 g, 7.2 mmol) and K_2CO_3 (1.2 g, 8.7 mmol) in DMF (6 mL) was stirred at 50 °C overnight. The mixture was diluted with AcOEt and toluene, washed with 0.1 N HCl aq., sat. aq. NaCl and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 5/95 to 50/50 AcOEt/Hexane) to give **9** (1.7 g, 69%) as a yellow amorphous powder.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.58 (3H, s), 6.79–6.87 (2H, m), 6.97–7.03 (2H, m), 7.66–7.71 (2H, m), 7.93–7.98 (2H, m). LCMS *m/z* calcd for $C_{14}H_{11}IO_2$: 337.98, found 338.8 [M + H] + .

1-(4-{4-[3-(Cyclopropylmethoxy)phenoxy]phenoxy}phenyl)ethan-1-one (11): A mixture of 3-(cyclopropylmethoxy)phenol (**10**) (80 mg, 0.49 mmol), CuI (25.3 mg, 0.13 mmol), dimethylaminoacetic acid hydrochloride (56 mg, 0.4 mmol), Cs_2CO_3 (217 mg, 0.67 mmol) and DME (1 mL) was stirred at 90 °C overnight. The reaction mixture was diluted with AcOEt, filtered through a pad of Celite and washed with AcOEt. The filtrate was concentrated under reduced pressure. The residue was diluted with toluene and AcOEt, filtered through a pad of silica gel and washed with 50% AcOEt in hexane. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 0/100 to 20/80 AcOEt/hexane) to give **11** (93 mg, 56%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.22–0.42 (2H, m), 0.48–0.72 (2H, m), 1.22–1.30 (1H, m), 2.58 (3H, s), 3.78 (2H, d, J = 7.0 Hz), 6.42–6.72 (3H, m), 6.90–7.10 (6H, m), 7.18–7.25 (1H, m), 7.90–7.99 (2H, m).

***N*-[1-(4-{4-[3-(Cyclopropylmethoxy)phenoxy]phenoxy}phenyl)ethyl]acetamide (1 h)**: $NaBH_3CN$ (39 mg, 0.62 mmol) was added to a solution of ammonium acetate (329 mg, 4.3 mmol) and **11** (80 mg, 0.21 mmol) in MeOH (5 mL) at room temperature. The mixture

was stirred at 60 °C overnight. After cooling, the mixture was concentrated under reduced pressure and diluted with sat. aq. $NaHCO_3$ and AcOEt. The mixture was extracted with AcOEt. The organic layer was separated, washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure to give the amine. A mixture of the amine, Et_3N (0.15 mL, 1.1 mmol) and Ac_2O (0.059 mL, 0.6 mmol) in THF (1 mL) was stirred at room temperature for 3 h. The mixture was quenched with water at 0 °C and extracted with AcOEt. The organic layer was separated, washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 0/100 to 100/0 AcOEt/hexane) to give **1 h** (60 mg, 68%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.27–0.38 (2H, m), 0.60–0.70 (2H, m), 1.21–1.31 (1H, m), 1.49 (3H, d, J = 7.0 Hz), 1.99 (3H, s), 3.77 (2H, d, J = 6.8 Hz), 5.02–5.19 (1H, m), 5.55–5.67 (1H, m), 6.51–6.66 (3H, m), 6.94–7.05 (6H, m), 7.21 (1H, t, J = 8.1 Hz), 7.27–7.31 (2H, m). LCMS *m/z* calcd for $C_{26}H_{27}NO_4$: 179.09, found 201.9 [M + H + Na]+.

5.1.4. N-{1-[4-({4-[3-(Cyclopropylmethoxy)phenoxy]phenyl}methoxy) phenyl]ethyl}acetamide (1i)

***N*-[1-(4-Hydroxyphenyl)ethyl] acetamide (13)**: A mixture of 4-(1-aminoethyl)phenol (**12**) (3 g, 22 mmol) and Ac_2O (2.1 mL, 22 mmol) in THF (20 mL) was stirred at room temperature for 2 h. The mixture was quenched with sat. aq. NH_4Cl at room temperature and extracted with AcOEt. The organic layer was separated, washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 0/100 to 100/0 AcOEt/hexane and 0/100 to 30/70 MeOH/AcOEt) to give **13** (2.4 g, 61%) as a white solid.

^{1}H NMR (300 MHz, CD_3OD) δ 1.39 (3H, d, J = 7.0 Hz), 1.93 (3H, s), 4.89–4.97 (1H, m), 6.73 (2H, d, J = 8.5 Hz), 7.13 (2H, d, J = 8.7 Hz). LCMS *m/z* calcd for $C_{10}H_{13}NO_2$: 179.22, found 440.0 [M + H + Na]+.

Ethyl 4-[3-(cyclopropylmethoxy)phenoxy] benzoate (15a): A mixture of **10** (5 g, 31 mmol), ethyl 4-fluorobenzoate (**14a**) (5 g, 30 mmol) and Cs_2CO_3 (15 g, 46 mmol) in DMF (50 mL) was stirred at 100 °C overnight. After cooling to room temperature, the mixture was extracted with AcOEt and water. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 0/100 to 10/90 AcOEt/hexane) to afford **15a** (7.1 g, 75%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.26–0.34 (2H, m), 0.50–0.60 (2H, m), 1.19–1.25 (1H, m), 1.31 (3H, t, J = 7.1 Hz), 3.80 (2H, d, J = 7.0 Hz), 4.29 (2H, q, J = 7.1 Hz), 6.60–6.70 (2H, m), 6.80 (1H, ddd, J = 8.3, 2.3, 0.9 Hz), 7.01–7.13 (2H, m), 7.33 (1H, t, J = 8.3 Hz), 7.91–8.01 (2H, m). LCMS *m/z* calcd for $C_{19}H_{20}O_4$: 312.14, found 313.1 [M + H] + .

{4-[3-(Cyclopropylmethoxy)phenoxy] phenyl}methanol (16a): To an ice cold mixture of $LiAlH_4$ (0.13 g, 3.4 mmol) in THF (10 mL) was added **15a** (1 g, 3.2 mmol) in THF (5 mL) dropwise. After stirring at 0 °C for 30 min, water (0.13 mL) was added slowly followed by 1 N NaOH (0.13 mL). Water (0.39 mL) was added and the mixture was stirred at room temperature for 30 min. The mixture was filtered through a pad of Celite and concentrated under reduced pressure to afford **16a** (0.85 g, 98%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.21–0.38 (2H, m), 0.47–0.65 (2H, m), 1.17–1.24 (1H, m), 3.77 (2H, d, J = 7.0 Hz), 4.47 (2H, d, J = 5.7 Hz), 5.16 (1H, t, J = 5.7 Hz), 6.45–6.54 (2H, m), 6.61–6.75 (1H, m), 6.89–7.04 (2H, m), 7.17–7.28 (1H, m), 7.33 (2H, d, J = 8.7 Hz). LCMS *m/z* calcd for $C_{17}H_{18}O_3$: 270.13, found 253.1 [M + H–H_2O]+.

***N*-{1-[4-({4-[3-(Cyclopropylmethoxy)phenoxy] phenyl} methoxy)phenyl] ethyl}acetamide (1i)**: **16a** (200 mg, 0.74 mmol) and **13** (146 mg, 0.81 mmol) were dissolved in toluene (4 mL). To the mixture were added tributylphosphine (0.3 mL, 1.2 mmol) followed by 1,1′-(azodicarbonyl)-dipiperidine (303 mg, 1.2 mmol) at room temperature. The mixture was stirred at room temperature overnight. To the solution was added AcOEt/hexane (1/2) (20 mL) and white precipitate was filtered off and washed with 33% AcOEt/hexane. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 10/90 to 100/0 AcOEt/Hexane) and crystallized from IPE and hexane to give **1i** (125 mg, 40%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.27–0.40 (2H, m), 0.62–0.70 (2H, m), 1.22–1.32 (1H, m), 1.50 (3H, d, J = 6.9 Hz), 1.99 (3H, s), 3.78 (2H, d, J = 6.9 Hz), 5.03 (2H, s), 5.06–5.18 (1H, m), 5.56–5.70 (1H, m), 6.54–6.71 (3H, m), 6.93–7.00 (2H, m), 7.02–7.07 (2H, m), 7.19–7.31 (3H, m), 7.40 (2H, d, J = 8.6 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.53 (2C), 10.52, 22.92, 23.15, 47.54, 69.21, 72.64, 105.66, 110.17, 110.94, 114.93 (2C), 119.09 (2C), 127.61 (2C), 130.02 (2C), 130.94, 132.74, 137.49, 156.60, 157.53, 158.20, 160.55, 168.51. LCMS *m/z* calcd for $C_{27}H_{29}NO_4$: 431.21, found 432.1 [M + H] + .

5.1.5. N-{1-[4-({6-[3-(Cyclopropylmethoxy)phenoxy]pyridin-3-yl} methoxy)phenyl]ethyl}acetamide (1j)

6-[3-(Cyclopropylmethoxy)phenoxy] pyridine-3-carbaldehyde (15b): A mixture of **10** (1 g, 6.1 mmol), 6-chloropyridine-3-carbaldehyde (**14b**) (0.86 g, 6.1 mmol) and K_2CO_3 (1.7 g, 12.2 mmol) in DMF (20 mL) was stirred at 60 °C for 2 h. After cooling to room temperature, the mixture was extracted with AcOEt and water. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 5/95 to 25/75 AcOEt/hexane) to afford **15b** (875 mg, 53%).

LCMS *m/z* calcd for $C_{16}H_{15}NO_3$: 269.11, found 269.9 [M + H] + .

{6-[3-(Cyclopropylmethoxy)phenoxy] pyridin-3-yl}methanol (16b): To a solution of **15b** (875 mg, 3.3 mmol) in MeOH (10 mL) was added $NaBH_4$ (123 mg, 3.3 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h. The mixture was quenched with water at 0 °C and extracted with AcOEt/THF. The organic layer was separated, washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 10/90 to 100/0 AcOEt/hexane) to give **16b** (264 mg, 30%).

LCMS *m/z* calcd for $C_{16}H_{17}NO_3$: 271.12, found 271.9 [M + H] + .

***N*-{1-[4-({6-[3-(Cyclopropylmethoxy)phenoxy] pyridin-3-yl} methoxy)phenyl] ethyl}acetamide (1j)**: To a solution of **16b** (130 mg, 0.48 mmol) and Et_3N (0.16 mL, 1.2 mmol) in THF (4 mL) was added MsCl (0.045 mL, 0.57 mmol) at 0 °C. The mixture was stirred at 0 °C for 4 h. The mixture was quenched with water at 0 °C and extracted with AcOEt. The organic layer was separated, washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure to afford the metanesulfonate. A mixture of the methanesulfonate, **13** (103 mg, 0.58 mmol) and K_2CO_3 (100 mg, 0.72 mmol) in DMF (7 mL) was stirred at 50 °C overnight. The mixture was quenched with water at room temperature and extracted with AcOEt. The organic layer was separated, washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 10/90 to 100/0 AcOEt/hexane) to give **1j** (32 mg, 15%) as a light brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.22–0.32 (2H, m), 0.50–0.61 (2H, m), 1.13–1.24 (1H, m), 1.39 (3H, d, J = 7.0 Hz), 1.90 (3H, s), 3.71 (2H, d, J = 7.0 Hz), 4.92 (2H, s), 4.96–5.08 (1H, m), 5.64 (1H, d, J = 7.7 Hz), 6.58–6.72 (3H, m), 6.82–6.90 (3H, m), 7.16–7.23 (3H, m), 7.69 (1H, dd, J = 8.4, 2.5 Hz), 8.16 (1H, d, J = 2.1 Hz). LCMS *m/z* calcd for $C_{26}H_{28}N_2O_4$: 432.20, found 433.1 [M + H] + .

5.1.6. N-{1-[4-({4-[3-(Cyclopropylmethoxy)phenoxy]-2-fluorophenyl} methoxy)phenyl]ethyl}acetamide (1 l)

4-[3-(Cyclopropylmethoxy)phenoxy] -2-fluorobenzaldehyde (15c): A mixture of **10** (849 mg, 5.2 mmol), 2,4-difluorobenzaldehyde (**14c**) (700 mg, 4.9 mmol) and Cs_2CO_3 (1.6 g, 4.9 mmol) in DMF (10 mL) was stirred at 60 °C for 3 h. The mixture was quenched with water at 0 °C and extracted with AcOEt. The organic layer was separated, washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica

gel, eluent: 0/100 to 50/50 AcOEt/hexane) to give **15c** (852 mg, 60%).

LCMS *m/z* calcd for $C_{17}H_{15}FO_3$: 286.10, found 286.9 [M + H] + .

***N*-{1-[4-({4-[3-(Cyclopropylmethoxy)phenoxy]-2-fluorophenyl}methoxy)phenyl]ethyl}acetamide (1 l)**: **15c** (300 mg, 1.1 mmol) were dissolved in MeOH (5 mL). $NaBH_4$ (119 mg, 3.1 mmol) was added to the mixture at 0 °C. The mixture was stirred at 0 °C for 3 h. The mixture was quenched with water at 0 °C and extracted with AcOEt. The organic layer was separated, washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure to afford the alcohol. The alcohol and **13** (282 mg, 1.6 mmol) were dissolved in toluene (8 mL). To the mixture was added tributylphosphine (0.393 mL, 1.6 mmol) followed by 1,1′-(azodicarbonyl)-dipiperidine (397 mg, 1.6 mmol) at room temperature. The mixture was stirred at room temperature overnight. To the solution was added 33% AcOEt/hexane and white precipitate was filtered off and washed with 33% AcOEt/hexane. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 10/90 to 100/0 AcOEt/hexane) and by preparative HPLC. The residue was crystallized from IPE and hexane to give **1 l** (142 mg, 30%) as a white crystalline solid.

^{1}H NMR (300 MHz, CD_3OD) δ 0.28–0.37 (2H, m), 0.54–0.64 (2H, m), 1.14–1.28 (1H, m), 1.41 (3H, d, J = 7.0 Hz), 1.94 (3H, s), 3.79 (2H, d, J = 6.8 Hz), 4.91–5.01 (1H, m), 5.06 (2H, s), 6.55–6.62 (2H, m), 6.68–6.83 (3H, m), 6.91–6.99 (2H, m), 7.19–7.32 (3H, m), 7.41–7.50 (1H, m), 8.36 (1H, d, J = 7.9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.54 (2C), 10.51, 22.94, 23.15, 47.54, 63.70 (d, J = 2.25 Hz), 72.72, 106.26 (d, J = 24 Hz), 106.30, 111.10, 111.58, 114.40, 114.86 (2C), 119.07 (d, J = 15 Hz), 127.63 (2C), 131.12, 132.38, 137.72, 157.17, 157.39, 158.65 (d, J = 11.25 Hz), 160.62, 161.44 (d, J = 246 Hz), 168.51. LCMS *m/z* calcd for $C_{27}H_{28}FNO_4$: 449.20, found 450.1 [M + H] + . Anal. Calcd for $C_{27}H_{28}FNO_4$: C,72.14; H,6.28; N,3.12. Found: C,71.90; H,6.30; N,3.10.

5.1.7. N-{1-[4-({5-[3-(Cyclopropylmethoxy)phenoxy]pyridin-2-yl}methoxy)phenyl]ethyl}acetamide (1 k)

1-{4-[(5-Bromopyridin-2-yl)methoxy]phenyl}ethan-1-one (19): A mixture of (5-bromopyridin-2-yl)methanol (**17**) (1 g, 5.3 mmol), 1-(4-hydroxyphenyl)ethan-1-one (**18**) (0.7 g, 5.1 mmol), DIAD (40% in toluene, 3 mL, 5.7 mmol) and Ph_3P (1.5 g, 5.7 mmol) in THF (15 mL) was stirred at room temperature overnight. The mixture was concentrated under reduced pressure and the residue was triturated with EtOH to afford **19** (1.4 g, 88%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.51 (3H, s), 5.27 (2H, s), 7.08–7.17 (2H, m), 7.51 (1H, d, J = 8.2 Hz), 7.94 (2H, d, J = 9.0 Hz), 8.11 (1H, dd, J = 8.4, 2.4 Hz), 8.73 (1H, d, J = 2.0 Hz). LCMS *m/z* calcd for $C_{14}H_{11}BrNO_2$: 307.00, found 308.0 [M + H] + .

1-[4-({5-[3-(Cyclopropylmethoxy)phenoxy]pyridin-2-yl}methoxy)phenyl]ethan-1-one (20): A mixture of **19** (1.4 g, 4.7 mmol), **10** (0.8 g, 4.9 mmol), picolinic acid (0.12 g, 0.97 mmol), CuI (0.09 g, 0.47 mmol) and K_3PO_4 (1.5 g, 7.1 mmol) in DMSO (15 mL) was stirred at 90 °C for 4 h. After cooling to room temperature, the mixture was extracted with AcOEt and water. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (NH silica gel, eluent: 5/95 to 25/75 AcOEt/hexane) to afford **20** (1 g, 55%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.26–0.34 (2H, m), 0.50–0.60 (2H, m), 1.19–1.25 (1H, m), 2.52 (3H, s), 3.80 (2H, d, J = 7.0 Hz), 5.26 (2H, s), 6.60 (1H, dt, J = 8.1, 1.2 Hz), 6.64 (1H, t, J = 2.3 Hz), 6.73–6.79 (1H, m), 7.11–7.17 (2H, m), 7.30 (1H, t, J = 8.2 Hz), 7.44–7.52 (1H, m), 7.53–7.59 (1H, m), 7.89–7.99 (2H, m), 8.38 (1H, d, J = 2.2 Hz). LCMS *m/z* calcd for $C_{24}H_{23}NO_4$: 389.16, found 390.3 [M + H] + .

2-{[4-(1-Azidoethyl)phenoxy]methyl}-5-[3-(cyclopropylmethoxy)phenoxy]pyridine (21): To an ice cold mixture of **20** (1 g, 2.6 mmol) in EtOH (5 mL) and THF (5 mL) was added $NaBH_4$ (0.1 g, 2.6 mmol). After stirring at room temperature for 4 h, the mixture was acidified with 1 N HCl and extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. To the residue was added toluene (10 mL). To the mixture were added DPPA (1.5 g, 5.5 mmol) and DBU (0.8 mL, 5.3 mmol). After stirring at room temperature for 2 h, the mixture was extracted with toluene and water. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 5/95 to 25/75 AcOEt/hexane) to afford **21** (0.94 g, 88%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.22–0.39 (2H, m), 0.49–0.62 (2H, m), 1.20–1.27 (1H, m), 1.43 (3H, d, J = 6.8 Hz), 3.80 (2H, d, J = 7.0 Hz), 4.77 (1H, q, J = 6.8 Hz), 5.17 (2H, s), 6.55–6.67 (2H, m), 6.72–6.80 (1H, m), 7.01–7.11 (2H, m), 7.29 (2H, s), 7.48 (2H, dd, J = 8.0, 2.0 Hz), 7.52–7.59 (1H, m), 8.37 (1H, d, J = 2.4 Hz). LCMS *m/z* calcd for $C_{24}H_{24}N_4O_3$: 416.18, found 417.2 [M + H] + .

1-[4-({5-[3-(Cyclopropylmethoxy)phenoxy]pyridin-2-yl}methoxy)phenyl]ethan-1-amine (22): A mixture of **21** (937 mg, 2.3 mmol) and Ph_3P (1.2 g, 4.6 mmol) in THF (6 mL) and water (3 mL) was stirred at 60 °C for 1 h. After cooling to room temperature, the mixture was extracted with AcOEt and water. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 0/100 to 100/0 MeOH/AcOEt) to afford **22** (693 mg, 79%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.26–0.34 (2H, m), 0.52–0.60 (2H, m), 1.13–1.15 (1H, m), 1.21 (3H, d, J = 4.8 Hz), 1.82 (2H, brs), 3.80 (2H, d, J = 7.0 Hz), 3.93 (1H, q, J = 6.5 Hz), 5.13 (2H, s), 6.55–6.66 (2H, m), 6.72–6.79 (1H, m), 6.90–6.98 (2H, m), 7.24–7.33 (3H, m), 7.43–7.49 (1H, m), 7.50–7.56 (1H, m), 8.37 (1H, d, J = 2.2 Hz). LCMS *m/z* calcd for $C_{24}H_{26}N_2O_3$: 390.19, found 391.1 [M + H] + .

***N*-{1-[4-({5-[3-(Cyclopropylmethoxy)phenoxy]pyridin-2-yl}methoxy)phenyl]ethyl}acetamide (1 k)**: A mixture of **22** (693 mg, 1.8 mmol) and Ac_2O (0.75 mL, 8.0 mmol) in pyridine (4 mL) was stirred at room temperature for 30 min. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (NH silica gel, eluent: 10/90 to 100/0 AcOEt/hexane) to afford **1 k** (585 mg, 76%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.26–0.34 (2H, m), 0.50–0.60 (2H, m), 1.17–1.24 (1H, m), 1.30 (3H, d, J = 7.0 Hz), 1.81 (3H, s), 3.80 (2H, d, J = 7.0 Hz), 4.85 (1H, quin, J = 7.1 Hz), 5.13 (2H, s), 6.56–6.66 (2H, m), 6.75 (1H, dd, J = 8.3, 1.7 Hz), 6.96 (2H, d, J = 8.7 Hz), 7.22 (2H, d, J = 8.6 Hz), 7.29 (1H, t, J = 8.2 Hz), 7.43–7.49 (1H, m), 7.50–7.55 (1H, m), 8.20 (1H, d, J = 8.1 Hz), 8.36 (1H, d, J = 2.2 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.55 (2C), 10.54, 22.94, 23.15, 47.54, 66.86, 72.69, 108.03, 111.29, 111.73, 113.48, 114.98 (2C), 127.62 (2C), 128.33, 130.57, 137.70, 140.66, 147.56, 155.42, 157.31, 160.29, 163.25, 168.53. LCMS *m/z* calcd for $C_{26}H_{28}N_2O_4$: 432.20, found 433.4 [M + H] + .

5.1.8. N-{1-[4-({4-[3-(Cyclopropylmethoxy)phenoxy]-2,6-difluorophenyl}methoxy)phenyl]ethyl}acetamide (1 m)

(2,6-Difluoro-4-iodophenyl)methanol (24): To an ice cold stirred mixture of 2,6-difluoro-4-iodobenzaldehyde (**23**) (6.6 g, 25 mmol) in EtOH (60 mL) was added $NaBH_4$ (1 g, 26 mmol). After stirring at 0 °C for 1 h, the mixture was acidified with 1 N HCl and concentrated under reduced pressure. The residue was extracted with AcOEt and water. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure to afford **24** (6.5 g, 98%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 4.44 (2H, d, J = 5.7 Hz), 5.28 (1H, t, J = 5.7 Hz), 7.50–7.58 (2H, m). LCMS *m/z* calcd for $C_7H_5F_2IO$: 269.94, found 253.0 [M + H–H_2O]+.

***N*-(1-{4-[(2,6-Difluoro-4-iodophenyl)methoxy]phenyl}ethyl)acetamide (25)**: To a mixture of **24** (4.7 g, 17 mmol), **13** (3.1 g, 17 mmol) and Ph_3P (5 g, 19 mmol) in THF (80 mL) was added DIAD (3.84 g, 19.0 mmol) dropwise, and the mixture was stirred at 12 °C for 4 h under N_2 atmosphere. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The

residue was purified by column chromatography (silica gel, eluent: AcOEt) and by prep-HPLC (0.1% NH_4HCO_3 as additive) to afford **25** (6 g, 76%) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, d, J = 6.8 Hz), 1.81 (3H, s), 4.80–4.90 (1H, m), 5.03 (2H, s), 6.95 (2H, d, J = 8.8 Hz), 7.22 (2H, d, J = 8.4 Hz), 7.65 (2H, d, J = 6.8 Hz), 8.21 (1H, d, J = 8.4 Hz). LCMS *m/z* calcd for $C_{17}H_{16}F_2INO_2$: 431.02, found 431.8 [M + H] + .

***N*-{1-[4-({4-[3-(Cyclopropylmethoxy)phenoxy]-2,6-difluorophenyl}methoxy)phenyl]ethyl}acetamide (1 m)**: A mixture of **10** (318 mg, 1.9 mmol), **25** (700 mg, 1.6 mmol), CuI (75 mg, 0.39 mmol), picolinic acid (160 mg, 1.3 mmol) and K_3PO_4 (690 mg, 3.3 mmol) in DMSO (5 mL) was stirred at 90 °C overnight. After cooling to room temperature, the mixture was extracted with AcOEt and water. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (NH silica gel, eluent: 10/90 to 100/0 AcOEt/hexane) to afford **1 m** (292 mg, 38%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.27–0.35 (2H, m), 0.51–0.60 (2H, m), 1.13–1.26 (1H, m), 1.30 (3H, d, J = 7.0 Hz), 1.82 (3H, s), 3.82 (2H, d, J = 7.1 Hz), 4.85 (1H, quin, J = 7.2 Hz), 5.02 (2H, s), 6.65–6.73 (2H, m), 6.76–6.85 (3H, m), 6.94–6.99 (2H, m), 7.23 (2H, d, J = 8.7 Hz), 7.34 (1H, t, J = 8.2 Hz), 8.20 (1H, d, J = 8.1 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.53 (2C), 10.49, 22.92, 23.14, 47.55, 57.92 (d, J = 9.75 Hz), 72.80, 101.87, 102.26, 106.86, 107.40 (t, J = 20.25 Hz), 111.96, 112.14, 114.81 (2C), 127.66 (2C), 131.28, 137.96, 156.13, 157.31, 159.78 (t, J = 14.25 Hz), 160.57, 160.71, 163.94 (d, J = 11.25 Hz), 168.54. LCMS *m/z* calcd for $C_{27}H_{27}F_2NO_4$: 467.19, found 468.1 [M + H] + .

5.1.9. N-{1-[6-({4-[3-(Cyclopropylmethoxy)phenoxy]-2,6-difluorophenyl}methoxy)pyridin-3-yl]ethyl}acetamide (1n)

Methyl 6-[(2,6-difluoro-4-iodophenyl)methoxy]pyridine-3-carboxylate (27a): To a solution of **24** (2 g, 7.4 mmol) in THF (20 mL) was added NaH (60% in mineral oil, 296 mg, 7.4 mmol) portionwise at 30 °C and the mixture was stirred at 30 °C for 0.5 h. To the mixture was added methyl 6-fluoropyridine-3-carboxylate (**26a**) (1.4 g, 8.9 mmol) and the mixture was stirred at 30 °C for 2 h. The mixture was diluted with water and extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 7/93 AcOEt/Petroleum ether) to afford a crude off-white solid. The solid was triturated with AcOEt/Petroleum ether (2/1) to afford **24** (1.1 g, 36%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (3H, s), 5.45 (2H, s), 6.76 (1H, d, J = 8.4 Hz), 7.32 (2H, d, J = 6.4 Hz), 8.16 (1H, dd, J = 8.8, 2.4 Hz), 8.85 (1H, d, J = 2.4 Hz). LCMS *m/z* calcd for $C_{14}H_{10}F_2INO_3$: 404.97, found 405.9 [M + H] + .

Methyl 6-({4-[3-(cyclopropylmethoxy)phenoxy]-2,6-difluorophenyl}methoxy)pyridine-3-carboxylate (28a): To a solution of **27a** (870 mg, 2.2 mmol) in DMSO (15 mL) were added 10 (423 mg, 2.6 mmol), K_3PO_4 (912 mg, 4.3 mmol), CuI (99 mg, 0.52 mmol) and picolinic acid (127 mg, 1 mmol) at 30 °C and the mixture was stirred at 90 °C under N_2 atmosphere for 24 h. The mixture was cooled to room temperature and diluted with water. The mixture was extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 7/93 AcOEt/Petroleum ether) to afford **28a** (600 mg, 63%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.25–0.40 (2H, m), 0.55–0.73 (2H, m), 1.15–1.35 (1H, m), 3.78 (2H, d, J = 7.2 Hz), 3.91 (3H, s), 5.43 (2H, s), 6.50–6.70 (4H, m), 6.71–6.80 (2H, m), 7.28 (1H, t, J = 8.0 Hz), 8.16 (1H, dd, J = 8.8, 2.4 Hz), 8.86 (1H, d, J = 2.0 Hz). LCMS *m/z* calcd for $C_{24}H_{21}F_2NO_5$: 441.14, found 442.1 [M + H] + .

6-({4-[3-(Cyclopropylmethoxy)phenoxy]-2,6-difluorophenyl}methoxy)-*N*-methoxy-*N*-methylpyridine-3-carboxamide (29a): To a solution of **28a** (600 mg, 1.4 mmol) in THF (6 mL) and MeOH (6 mL) were added $LiOH·H_2O$ (100 mg, 4.2 mmol) and water (6 mL) at 30 °C. The mixture was stirred at 26–32 °C for 12 h. After removal of MeOH under reduced pressure, the mixture was diluted with water (30 mL). The mixture was acidified with 1 N HCl, and was then extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated under reduced pressure to afford the carboxylic acid. To a solution of the carboxylic acid in DMF (10 mL) were added *N*,*O*-dimethylhydroxylamine hydrochloride (191 mg, 2.6 mmol), HOBt (437 mg, 3.2 mmol), EDCI (621 mg, 3.2 mmol) and Et_3N (663 mg, 6.6 mmol) at 30 °C, and the mixture was stirred at 30 °C for 3 h. The mixture was diluted with water and extracted with AcOEt. The combined organic layers were washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 33/67 AcOEt/Petroleum ether) to afford **29a** (530 mg, 83%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.25–0.40 (2H, m), 0.55–0.73 (2H, m), 1.15–1.35 (1H, m), 3.38 (3H, s), 3.59 (3H, s), 3.78 (2H, d, J = 6.8 Hz), 5.42 (2H, s), 6.55 (2H, d, J = 8.8 Hz), 6.57–6.70 (2H, m), 6.71–6.80 (2H, m), 7.20–7.35 (1H, m), 8.00 (1H, dd, J = 8.8, 2.4 Hz), 8.66 (1H, d, J = 2.0 Hz). LCMS *m/z* calcd for $C_{25}H_{24}F_2N_2O_5$: 470.47, found 471.0 [M + H] + .

***N*-{1-[6-({4-[3-(Cyclopropylmethoxy)phenoxy]-2,6-difluorophenyl}methoxy)pyridin-3-yl]ethyl}acetamide (1n)**: To a solution of **29a** (530 mg, 1.1 mmol) in THF (10 mL) was added MeMgBr (3 M Et_2O solution, 2.7 mL, 8.1 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. The mixture was quenched with sat. aq. NH_4Cl and the mixture was extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure to afford the ketone. To a solution of the ketone in MeOH (15 mL) were added NH_4OAc (500 mg, 6.5 mmol) and $NaBH_3CN$ (82 mg, 1.3 mmol) at 30 °C and the mixture was stirred at reflux for 12 h to afford the amine. To the reaction mixture of the amine was added Ac_2O (204 mg, 2 mmol) at 30 °C and continued to stir at 30 °C for 2 h. The mixture was concentrated under reduced pressure. The residue was diluted with water and the mixture was extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by prep-HPLC (0.1% $NH_3·H_2O$ as additive) to afford **1n** (137 mg, 45%) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.22–0.45 (2H, m), 0.47–0.60 (2H, m), 1.10–1.30 (1H, m), 1.33 (3H, d, J = 6.8 Hz), 1.82 (3H, s), 3.81 (2H, d, J = 7.2 Hz), 4.80–4.95 (1H, m), 5.28 (2H, s), 6.62–6.74 (2H, m), 6.75–6.85 (4H, m), 7.33 (1H, t, J = 8.4 Hz), 7.64 (1H, dd, J = 8.4, 2.4 Hz), 8.10 (1H, d, J = 2.0 Hz), 8.31 (1H, d, J = 7.6 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.53 (2C), 10.48, 22.47, 23.07, 45.71, 55.24, 72.78, 101.86, 102.25, 106.81, 107.67 (t, J = 19.5 Hz), 110.69, 111.90, 112.10, 131.26, 134.11, 137.98, 144.78, 156.19, 159.62 (t, J = 14.25 Hz), 160.64, 160.70, 162.01, 164.01 (d, J = 10.5 Hz), 168.78. LCMS *m/z* calcd for $C_{26}H_{26}F_2N_2O_4$: 468.19, found 469.0 [M + H] + .

5.1.10. N-{1-[5-({4-[3-(Cyclopropylmethoxy)phenoxy]-2,6-difluorophenyl}methoxy)pyridin-2-yl]ethyl}acetamide (1o)

Methyl 5-[(2,6-difluoro-4-iodophenyl)methoxy]pyridine-2-carboxylate (27b): To a solution of **24** (3 g, 11 mmol) in THF (30 mL) was added NaH (60% in mineral oil, 444 mg, 11 mmol) portionwise at 30 °C and the mixture was stirred at 30 °C for 0.5 h. To the mixture was added methyl 5-[(2,6-difluoro-4-iodophenyl)methoxy]pyridine-2-carboxylate (**26b**) (2.1 g, 13 mmol) and the mixture was stirred at 30 °C for 2 h. The mixture was diluted with water and extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 33/67 AcOEt/Petroleum ether) to afford **27b** (2.4 g, 53%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (3H, s), 5.17 (2H, s), 7.30–7.45 (3H, m), 8.12 (1H, d, J = 8.8 Hz), 8.43 (1H, d, J = 2.8 Hz). LCMS *m/z* calcd for $C_{14}H_{10}F_2INO_3$: 404.97, found 405.9 [M + H] + .

***N*-{1-[5-({4-[3-(Cyclopropylmethoxy)phenoxy]-2,6-difluorophenyl}methoxy)pyridin-2-yl]ethyl}acetamide (1o)**: To a solution of compound **27b** (1.0 g, 2.5 mmol) in DMSO (20 mL) was added compound **2a** (485 mg, 3 mmol), K_3PO_4 (1.1 g, 5 mmol), CuI (113 mg, 0.6 mmol) and picolinic acid (146 mg, 1.2 mmol) at 30 °C and the mixture was stirred at 100 °C for 12 h. The mixture was cooled to room temperature and diluted with water. The mixture was extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 33/67 AcOEt/Petroleum ether) to afford the ester. To a solution of the eater in THF (6 mL) and MeOH (6 mL) were added $LiOH{\cdot}H_2O$ (200 mg, 8.3 mmol) and water (6 mL) at 30 °C. The mixture was stirred at 30 °C for 2 h. The mixture was concentrated under reduced pressure. The residue was diluted with water and the mixture was acidified with 1 N aqueous HCl and extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated under reduced pressure to afford the carboxylic acid. To a solution of the carboxylic acid in DMF (10 mL) were added *N*,*O*-dimethylhydroxylamine hydrochloride (250 mg, 3.4 mmol), HOBt (568 mg, 4.2 mmol), EDCI (807 mg, 4.2 mmol) and Et_3N (850 mg, 8.4 mmol) at 30 °C and the mixture was stirred at 30 °C for 3 h. The mixture was diluted with water and extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 33/67 AcOEt/Petroleum ether) to afford the Weinreb amide. To a solution of the Weinreb amide in THF (10 mL) was added MeMgBr (3 M Et_2O solution, 2.7 mL, 8.1 mmol) dropwise at 0 °C and the mixture was stirred at 0 °C for 1 h. The mixture was quenched with sat. aq. NH_4Cl and extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated under reduced pressure to afford the ketone. To a solution of the ketone in MeOH (15 mL) were added NH_4OAc (550 mg, 7.1 mmol) and $NaBH_3CN$ (90 mg, 1.4 mmol) at 30 °C and the mixture was stirred at reflux for 12 h to afford the amine. To the reaction mixture of the amine was added Ac_2O (204 mg, 2 mmol) at 30 °C and the mixture was stirred at 30 °C for 1 h. The mixture was concentrated under reduced pressure. The residue was diluted with water and extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by prep-HPLC (0.1% $NH_3{\cdot}H_2O$ as additive) to afford **1o** (69 mg, 9%) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.20–0.36 (2H, m), 0.45–0.60 (2H, m), 1.10–1.30 (1H, m), 1.32 (3H, d, J = 6.8 Hz), 1.84 (3H, s), 3.80 (2H, d, J = 6.8 Hz), 4.80–4.99 (1H, m), 5.11 (2H, s), 6.65–6.71 (2H, m), 6.72–6.89 (3H, m), 7.25–7.40 (2H, m), 7.49 (1H, dd, J = 8.4, 2.8 Hz), 8.27 (1H, d, J = 2.8 Hz), 8.32 (1H, d, J = 8.0 Hz). LCMS *m/z* calcd for $C_{26}H_{26}F_2N_2O_4$: 468.19, found 469.0 [M + H] + .

5.1.11. N-{1-[6-({4-[3-(Ccyclopropylmethoxy)phenoxy]-2,6-difluorophenyl}methoxy)pyridazin-3-yl]ethyl}acetamide (1p)

{4-[3-(Cyclopropylmethoxy)phenoxy]-2,6-difluorophenyl}methanol (30): A mixture of **24** (6 g, 22 mmol), **10** (3.7 g, 22 mmol), CuI (423 mg, 2.2 mmol), picolinic acid (546 mg, 4.4 mmol) and K_3PO_4 (9.4 g, 44 mmol) in DMSO (60 mL) was stirred at 90 °C for 15 h under N_2 atmosphere. The reaction mixture was poured into water and the mixture was extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 9/91 AcOEt/Petroleum ether) to afford **30** (3.7 g, 54%) as a yellow oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.25–0.35 (2H, m), 0.50–0.60 (2H, m), 1.15–1.25 (1H, m), 3.80 (2H, d, J = 6.8 Hz), 4.44 (2H, d, J = 5.6 Hz), 5.20 (1H, t, J = 5.6 Hz), 6.60–6.68 (2H, m), 6.71 (2H, d, J = 8.8 Hz), 6.80 (1H, d, J = 7.6 Hz), 7.32 (1H, t, J = 8.0 Hz).

3-Bromo-6-({4-[3-(cyclopropylmethoxy)phenoxy]-2,6-difluorophenyl}methoxy)pyridazine (32): A mixture of **30** (500 mg, 1.6 mmol) in THF (10 mL) was added NaH (60% in mineral oil, 65 mg, 1.6 mmol) and the mixture was stirred at 15 °C for 30 min. To the mixture was added 3,6-dibromopyridazine (**31**) (388 mg, 1.6 mmol), and the mixture was stirred at 18 °C for 4 h. The reaction mixture was poured into water and the mixture was extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 9/91 AcOEt/Petroleum ether) to afford **32** (570 mg, 75%) as a colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.25–0.35 (2H, m), 0.50–0.60 (2H, m), 1.15–1.25 (1H, m), 3.81 (2H, d, J = 7.2 Hz), 5.47 (2H, s), 6.65–6.73 (2H, m), 6.75–6.85 (3H, m), 7.28 (1H, d, J = 9.2 Hz), 7.34 (1H, t, J = 8.0 Hz), 7.91 (1H, d, J = 9.2 Hz). LCMS *m/z* calcd for $C_{21}H_{17}BrF_2N_2O_3$: 462.04, found 462.9 [M + H] + .

1-[6-({4-[3-(Cyclopropylmethoxy)phenoxy]-2,6-difluorophenyl}methoxy)pyridazin-3-yl]ethan-1-one (33): A mixture of **32** (570 mg, 1.2 mmol), tributyl(1-ethoxyvinyl)tin (535 mg, 1.5 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) in DMF (15 mL) was stirred at 80 °C for 15 h under N_2 atmosphere. To the mixture was added sat. aq. KF (40 mL) and the mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into water and the mixture was extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude yellow solid. The solid was dissolved in a mixture of 1 N HCl (20 mL) and acetone (20 mL), and the mixture was stirred at 20 °C for 1 h. The mixture was neutralized with sat. aq. $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 5/95 AcOEt/Petroleum ether) to afford **33** (300 mg, 57%) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.25–0.35 (2H, m), 0.50–0.60 (2H, m), 1.15–1.25 (1H, m), 2.72 (3H, s), 3.81 (2H, d, J = 6.8 Hz), 5.63 (2H, s), 6.65–6.73 (2H, m), 6.75–6.85 (3H, m), 7.30–7.41 (2H, m), 8.05 (1H, d, J = 8.8 Hz). LCMS *m/z* calcd for $C_{23}H_{20}F_2N_2O_4$: 426.14, found 427.1 [M + H] + .

1-[6-({4-[3-(Cyclopropylmethoxy)phenoxy]-2,6-difluorophenyl}methoxy)pyridazin-3-yl]ethan-1-ol (34): To a mixture of **33** (300 mg, 0.7 mmol) in MeOH (10 mL) was added $NaBH_4$ (53 mg, 1.4 mmol), and the mixture was stirred at 20 °C for 0.5 h. The reaction mixture was poured into water and the mixture was extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure to **34** (280 mg, 93%) as a colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.25–0.35 (2H, m), 0.50–0.60 (2H, m), 1.15–1.25 (1H, m), 1.40 (3H, d, J = 6.8 Hz), 3.82 (2H, d, J = 7.2 Hz), 4.85–4.95 (1H, m), 5.48 (2H, s), 5.55 (1H, d, J = 4.8 Hz), 6.65–6.73 (2H, m), 6.75–6.88 (3H, m), 7.24 (1H, d, J = 9.2 Hz), 7.34 (1H, t, J = 8.0 Hz), 7.70 (1H, d, J = 8.8 Hz). LCMS *m/z* calcd for $C_{23}H_{22}F_2N_2O_4$: 428.15, found 429.0 [M + H] + .

3-(1-Azidoethyl)-6-({4-[3-(cyclopropylmethoxy)phenoxy]-2,6-difluorophenyl}methoxy)pyridazine (35): To a mixture of **34** (280 mg, 0.65 mmol) and Et_3N (198 mg, 2 mmol) in CH_2Cl_2 (10 mL) was added MsCl (150 mg, 1.3 mmol) at 0 °C, and the mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure to afford the mesylate. To a mixture of the mesylate in DMF (10 mL) was added NaN_3 (213 mg, 3.3 mmol), and the mixture was stirred at 60 °C for 2 h. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 33/67 AcOEt/Petroleum ether) to afford **35** (230 mg, 77%) as a colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.25–0.35 (2H, m), 0.50–0.60 (2H, m), 1.15–1.25 (1H, m), 1.57 (3H, d, J = 6.8 Hz), 3.81 (2H, d, J = 7.2 Hz), 4.94–5.00 (1H, m), 5.51 (2H, s), 6.65–6.73 (2H, m), 6.78–6.88 (3H, m),

7.30–7.29 (2H, m), 7.74 (1H, d, J = 9.2 Hz). LCMS m/z calcd for $C_{23}H_{21}F_2N_5O_3$: 453.16, found 454.0 [M + H] + .

***N*-{1-[6-({4-[3-(Cyclopropylmethoxy)phenoxy]-2,6-difluorophenyl}methoxy)pyridazin-3-yl]ethyl}acetamide (1p)**: A mixture of **35** (230 mg, 0.51 mmol) and Ph_3P (200 mg, 0.76 mmol) in THF (10 mL) and water (1 mL) was refluxed for 15 h. To the reaction mixture was added Ac_2O (104 mg, 1 mmol), and the mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by prep-HPLC (0.1% NH_4HCO_3 as additive) to afford **1p** (123 mg, 52%) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 0.25–0.35 (2H, m), 0.50–0.60 (2H, m), 1.15–1.25 (1H, m), 1.41 (3H, d, J = 7.2 Hz), 1.85 (3H, s), 3.81 (2H, d, J = 6.8 Hz), 5.02–5.11 (1H, m), 5.48 (2H, s), 6.65–6.73 (2H, m), 6.75–6.86 (3H, m), 7.21 (1H, d, J = 9.2 Hz), 7.34 (1H, t, J = 8.0 Hz), 7.56 (1H, d, J = 8.8 Hz), 8.42 (1H, d, J = 8.0 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.53 (2C), 10.48, 21.07, 23.00, 48.50, 56.55, 72.79, 101.89, 102.27, 106.85, 107.13 (t, J = 20.25 Hz), 111.95, 112.14, 118.06, 128.96, 131.29, 156.13, 159.89 (t, J = 15 Hz), 160.71, 160.82, 161.13, 163.86, 164.04 (d, J = 10.5 Hz), 169.23. LCMS m/z calcd for $C_{25}H_{25}F_2N_3O_4$: 469.18, found 470.0 [M + H] + .

5.1.12. *N*-{1-[5-({4-[3-(Cyclopropylmethoxy)phenoxy]-2,6-difluorophenyl}methoxy)pyrazin-2-yl]ethyl}acetamide (1q)

1-[5-({4-[3-(Cyclopropylmethoxy)phenoxy]-2,6-difluorophenyl}methoxy)pyrazin-2-yl]ethan-1-one (37): A mixture of **30** (60 mg, 0.2 mmol), 1-(5-chloropyrazin-2-yl)ethan-1-one (**36**) (34 mg, 0.22 mmol) and NaH (60% in mineral oil, 12 mg, 0.29 mmol) in THF (1 mL) was stirred at room temperature for 10 min. The mixture was heated to 135 °C for 1 h under microwave irradiation. The mixture was quenched with water at 0 °C and extracted with AcOEt. The organic layer was separated, washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by prep-HPLC (0.1% TFA additive) to afford **37** (20 mg, 24%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.31–0.42 (2H, m), 0.61–0.70 (2H, m), 1.22–1.30 (1H, m), 2.66 (3H, s), 3.79 (2H, d, J = 7.0 Hz), 5.47 (2H, s), 6.53–6.68 (4H, m), 6.76 (1H, ddd, J = 8.3, 2.4, 0.8 Hz), 7.27–7.34 (1H, m), 8.18–8.23 (1H, m), 8.81–8.88 (1H, m). LCMS m/z calcd for $C_{23}H_{20}F_2N_2O_4$: 426.14, found 427.2 [M + H] + .

***N*-{1-[5-({4-[3-(Cyclopropylmethoxy)phenoxy]-2,6-difluorophenyl}methoxy)pyrazin-2-yl]ethyl}acetamide (1q)**: A mixture of **37** (12 mg, 0.03 mmol), $NaBH_3CN$ (3.5 mg, 0.06 mmol) and NH_4OAc (11 mg, 0.14 mmol) in MeOH (1 mL) was stirred at 65 °C overnight. The mixture was quenched with water at room temperature and extracted with AcOEt. The organic layer was separated, washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure to afford the amine. To a mixture of the amine in THF (1 mL) was added Ac_2O (0.008 mL, 0.08 mmol) at room temperature. The mixture was stirred at room temperature for 1 h. The mixture was quenched with water at room temperature and extracted with AcOEt. The organic layer was separated, washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by prep-HPLC (0.1% TFA additive) to afford **1q** (7 mg, 53%) as white amorphous powder.

^{1}H NMR (300 MHz, CD_3OD) δ 0.30–0.40 (2H, m), 0.56–0.67 (2H, m), 1.18–1.26 (1H, m), 1.47 (3H, d, J = 7.2 Hz), 1.97 (3H, s), 3.81 (2H, d, J = 6.8 Hz), 5.02–5.11 (1H, m), 5.40 (2H, s), 6.53–6.68 (4H, m), 6.77–6.85 (1H, m), 7.24–7.36 (1H, m), 8.14 (2H, s). LCMS m/z calcd for $C_{25}H_{25}F_2N_3O_4$: 469.18, found 470.0 [M + H] + .

5.2. ACC enzyme assay

SF-9 cells were infected with the baculovirus containing human or mouse ACC and cultured at 27 °C for 3 days. Harvested cells were homogenized in buffer A (50 mM HEPES (pH7.5), 300 mM NaCl, 25 mM sodium glycerophosphate, 1 mM sodium orthovanadate, 10% glycerol, complete protease inhibitor), and subjected to ultracentrifuge at 185700xg for 50 min at 4 °C. ACC protein with 6xHis-tag at the *N*-terminal was purified from the supernatant using Ni-NTA Super Flow Gel (QIAGEN). Eluted protein was dialyzed against buffer B (50 mM HEPES (pH7.5), 300 mM NaCl, 10 mM $MgCl_2$, 10 mM tripotassium citrate, 2 mM dithiothreitol) and concentrated using Amicon Ultra (Merck). Compounds were dissolved in DMSO and then diluted with an enzyme reaction buffer (50 mM HEPES (pH 7.5), 10 mM $MgCl_2$, 10 mM tripottasium citrate, 2 mM dithiothreitol, 0.001% fatty acid-free BSA). Recombinant human ACC1 or ACC2 was diluted with the enzyme reaction buffer to a concentration of 0.2 μg/mL. A 5 μL aliquot of compound solution was added to each well of a 384-well assay plate, and 5 μL of the enzyme mixture was added to each well. The mixture was incubated at room temperature for 60 min. Then, a substrate solution (50 mM $KHCO_3$, 200 μM ATP, 200 μM acetyl-CoA, 5 μL) was added to each well, and the mixture was reacted at room temperature for 30 min. The reaction was stopped by adding a 40 μL of stop solution (1.3% formic acid, 0.2 μM malonyl-$^{13}C_3$-CoA) to each of the obtained reaction mixtures. The production of malonyl-CoA was detected by RapidFire-Mass spectrometry and corrected by malonyl-$^{13}C_3$-CoA. IC_{50} values were calculated by XLfit from the data expressed as inhibition (%) using fit Model 204 (4 Parameter Logistic Model). The response of vehicle control was set as 0% inhibition and the response without enzyme was set as 100% inhibition.

5.3. Acetate uptake assay

HCT-116 cells (ATCC) were plated in a 96-well cell culture plate at 50,000 cells/well and incubated overnight in RPMI medium, supplemented with 10% fetal bovine serum, penicillin (10,000 unit/mL), and streptomycin (10,000 μg/mL), under 5% CO_2 at 37 °C. The cells were washed twice with 100 μL PBS and incubated with 90 μL of test compounds in assay medium (RPMI and 0.1% fatty acid-free BSA) for 60 min. Then, 0.1 μCi/well of [^{14}C]acetic acid was added to the well and incubated for 2 h at 37 °C. Cells were washed twice with 100 μL of PBS to remove the radioactive medium, and 60 μL of Microscint20 was added. The radioactivity in each well was measured by Topcount (PerkinElmer). The well containing 100 nM reference compound (compound **1f** in ref. 34) was used as a 100% inhibition control. The well containing DMSO was used as a 0% inhibition control. IC_{50} values were calculated by XLfit from the data expressed as inhibition (%) using fit Model 204 (4 Parameter Logistic Model).

5.4. In vivo PD study

All experimental procedures were approved by the Institutional Animal Care and Use Committee of Takeda Pharmaceutical Company Ltd., which is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. Athymic nude mice (female BALB/cA Jcl-nu/nu) and HCT-116 human colorectal carcinoma cell line were purchased from CLEA (Tokyo, Japan) and ATCC (American Type Culture Collection), respectively. Mice (6 weeks old) received s.c. injections into the hind flank with 100 μL cultured HCT-116 cancer cell suspension in Hanks' balanced salt solution (Invitrogen) with Matrigel (BD Cat.356237). After the tumor xenografts were established, the animals were randomly grouped by using tumor volume. Tumor volumes were assessed by measurement of two dimensions with vernier calipers and were calculated as length × width^2 × 1/2. The mice with s.c. HCT-116 xenografts were orally given the vehicle (0.5% methyl cellulose, Wako) or compound **1n** at 100 mg/kg. Whole blood and tumor tissue samples were collected after 2 and 16 h treatment. The blood was centrifuged to collect plasma, and tumor tissues were snap frozen for measurement of malonyl-CoA. Concentration of malonyl-CoA in tumor was measured by reverse-phase liquid chromatography-tandem mass spectrometry (RPLC-MS/MS). The frozen samples were pulverized under liquid nitrogen. The powdered tissue was mixed with [$^{13}C_3$]-

malonyl-CoA, and then homogenized with 6% aqueous perchloric acid. After centrifugation, the supernatants were applied onto an Oasis HLB cartridge (Waters, Milford, MA) for solid-phase extraction. The sample-loaded cartridges were washed with water and then eluted with acetonitrile/water/dibutylammonium acetate (500:500:1, v/v/v). The eluted samples were centrifuged, and the supernatants were used for RPLC-MS/MS. For the liquid chromatography separation, the samples were injected to a Capcell PAK C18 AQ (Shiseido, Tokyo, Japan) with column temperature at 40 °C. Chromatographic separation was performed by gradient elution of two mobile phases: mobile phase A consisted of 5 mmol/L ammonium acetate/dibutylammonium acetate (100:1, v/v, pH 9.0), and mobile phase B consisted of acetonitrile. Malonyl-CoA and [$^{13}C_3$]-malonyl-CoA were detected using a mass spectrometer by multiple reaction monitoring (MRM) with transitions of *m/z* 852.0 → 808.0 for malonyl-CoA and *m/z* 855.0 → 810.0 for [$^{13}C_3$]–malonyl-CoA, respectively. The malonyl-CoA concentration was determined using a calibration curve, which was calculated by the responses of given concentrations of standard reagents normalized by the response of [$^{13}C_3$]–malonyl-CoA as an internal standard.

5.5. Statistical analysis

Data were represented as mean ± standard deviation (SD). Statistical differences between the control and the treated groups were analyzed by Dunnett's test, and a value of $P < 0.05$ was considered significant.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. R. M., D. T., and H. M. contributed design and synthesis of compounds; M. S., Y. S., Y. Y., and H. S. contributed in vitro and in vivo study.

Declaration of Competing Interest

The authors declare no competing financial interest.

Acknowledgements

We sincerely appreciate Drs. Hiroshi Miyake, Takahito Hara, Tomoyasu Ishikawa, Yuichi Hikichi, for intellectual support during this work. We also appreciate Drs. Yasuhiro Imaeda and HugoKaHo Fong, for helpful suggestions during the preparation of this manuscript. We would like to express our appreciation to Moriteru Asano, Hiroshi Banno, Noriyuki Nii and Krista E. Gipson for derivative synthesis; Takeo Moriya and Yoshinori Satomi for evaluating in vivo PD test; Kazunobu Aoyama and Naomi Kamiguchi for supporting in PK studies; Yoshitaka Inui for helping in drug safety; Youko Ishihara for contributing formulation analyses.

References

1 Kim C-W, Addy C, Kusunoki J, et al. *Acetyl CoA Carboxylase Inhibition Reduces Hepatic Steatosis but Elevates Plasma Triglycerides in Mice and Humans: a Bedside to Bench Investigation Cell Metab.* 2017;26:394–406.
2 Wakil SJ, Abu-Elheiga LA. Fatty Acid Metabolism: Target for Metabolic Syndrome. *J Lipid Res.* 2009:S138–S143.
3 Brownsey RW, Boone AN, Elliott JE, Kulpa JE, Lee WM. Regulation of Acetyl-CoA Carboxylase. *Biochem Soc. Trans.* 2006;34:223–227.
4 Tong L, Acetyl-Coenzyme A. Carboxylase: Crucial Metabolic Enzyme and Attractive Target for Drug Discovery. *Cell Mol. Life Sci.* 2005;62:1784–1803.
5 Kim K-H. Regulation of Mammalian Acetyl-Coenzyme A Carboxylase Annu. *Rev. Nutl.* 1997;17:77–99.
6 Cantley J, Davenport A, Vetterli L, Nemes NJ, Whitworth PT, Boslem E. Distruption of Beta Cell Acetly-CoA Carboxylase-1 in Mice Impairs Insulin Secretion and Beta Cell Mass. *Diabetologia.* 2019;62:99–111.
7 Waldrop GL, Stephens JN. Targeting Acetyl-CoA Carboxylase for Anti-obesity Therapy. *Curr Med Chem. Immunol. Endocr. Metab. Agents.* 2003;3:229–234.
8 Gao YS, Qian MY, Wei QQ, et al. WZ66, a Novel Acetyl-CoA Carboxylase Inhibitor: Alleviates Nonalcoholic Steatohepatitis (NASH) in Mice. *Acta Pharmacol Sin.* 2020;41:336–347.
9 Lu Y, Su X, Zhao M, et al. Comparative RNA-sequencing Profiled the Differential Gene Expression of Liver in Response to Acetyl-CoA Carboxylase Inhibitor GS-0976 in a Mouse Model of NASH. *PeerJ.* 2019;7. e8155.
10 Postic C, Girard J. Contribution of De Novo Fatty Acid Synthesis to Hepatic Steatosis and Insulin Resistance: Lessons from Genetically Engineered Mice. *J. Clin. Invest.* 2008;118:829–838.
11 Petrova E, Scholz A, Paul J, et al. Acetyl-CoA Carboxylase Inhibitors Attenuate WNT and Hedgehog Signaling and Suppress Pancreatic Tumor Growth. *Oncotarget.* 2016;8:48660–48670.
12 Svensson RU, Parker SJ, Eichner LJ, et al. Inhibition of Acetyl-CoA Carboxylase Suppresses Fatty Acid Synthesis and Tumor Growth of Non-small-cell Lung Cancer in Preclinical Models. *Nat Med.* 2016;22:1108–1119.
13 Wang C, Ma J, Zhang N, Yang Q, Jin Y, Wang Y. The Acetyl-CoA Carboxylase Enzyme: a Target for Cancer Therapy? *Expert Rev Anticancer Ther.* 2015;15:667–676.
14 Wang C, Rajput S, Watabe K, Liao DF, Cao D. *Acetyl-CoA Carboxylase-a as a Novel Target for Cancer Therapy Front Biosci.* 2010;1:515–526.
15 Beckers A, Organe S, Timmermans L, et al. *Chemical Inhibition of Acetyl-CoA Carboxylase Induces Growth Arrest and Cytotoxicity Selectively in Cancer Cells Cancer Res.* 2007;67:8180–8187.
16 Wang, X.; Zhou, y.; Tang, D. ; Zhu, Z. ; Li, Y. ACC1 (Acetyl Coenzyme A Carboxylase 1) is a Potential Immune Modulatory Target of Cerebral Ischemic Stroke 2019, 50, 1869–1878.
17 Lee JE, Walsh MC, Hoehn KL, James DE, Wherry EJ, Choi Y. Regulation of Fatty Acid Metabolism, Acetyl CoA Carboxylase 1 (ACC1) Control T Cell Immunity. *J. Immunol.* 2014;192:3190–3199.
18 Wei Q, Mei L, Yang Y, et al. Design, Synthesis and Biological Evaluation of Novel Spiro-pentacylamides as Acetyl-CoA Carboxylase Inhibitors. *Bioorg Med Chem.* 2018;26:3866–3874.
19 Harriman G, Greenwood J, Bhat S, et al. Acetyl-CoA Carboxylase Inhibition by ND-630 reduces Hepatic Steatosis, Improves Insulin Sensitivity, and Modulates Dyslipidemia in Rats. *PNAS.* 2016;113:E1796–E1805.
20 Kung DW, Griffith DA, Esler WP, et al. Discovery of Spirocyclic-diamine Inhibitors of Mammalian Acetyl CoA-carboxylase. *Bioorg Med. Chem. Lett.* 2015;25:5352–5356.
21 Griffith DA, Kung DW, Esler WP, et al. Decreasing the Rate of Metabolic Ketone Reduction in the Discovery of a Clinical Acetyl-CoA Carboxylase Inhibitor for the Treatment of Diabetes. *J Med Chem.* 2014;57:10512–10526.
22 Kamata M, Yamashita T, Kina A, et al. Symmetrical Approach of Spiro-pyrazolidinediones as Acetyl-CoA Carboxylase Inhibitors. *Bioorg Med. Chem. Lett.* 2012;22:4769–4772.
23 Kamata M, Yamashita T, Kina A, et al. Design, Synthesis, and Structure-activity Relationships of Novel Spiro-piperidines as Acetyl-CoA Carboxylase Inhibitors. *Bioorg Med. Chem. Lett.* 2012;22:3643–3647.
24 Chonan T, Wakasugi D, Yamamoto D, et al. Discovery of Novel (4-Piperidinyl)-piperazines as Potent and Orally Active Acetyl-CoA Carboxylase 1/2 Non-selective Inhibitors: F-Boc and triF-Boc Groups are Acid-stable Bioisosteres for the Boc Group. *Bioorg Med Chem.* 2011;19:1580–1593.
25 Keil S, Müller M, Zoller G, et al. Identification and Synthesis of Novel Inhibitors of Acetyl-CoA Carboxylase with In Vitro and In Vivo Efficacy on Fat Oxidation. *J Med Chem.* 2010;53:8679–8687.
26 Corbett, J. W.; Freeman-Cook, K. D.; Elliott, R.; Vajdos, F,; Rajamohan, F.; Kohls, D.; Marr, E.; Zhang, H.; Tong, L.; Tu, M.; Murdande, S.; Doran, S. D.; Houser, J. A.; Song, W.; Jones, C. J.; Coffey, S. B.; Buzon, L.; Minich, M. L.; Dirico, K. J.; Tapley, S.; McPherson, R. K.; Sugarman, E.; Harwood, H.J. Jr.; Esler, W. Discovery of Small Molecule Isozyme Non-specific Inhibitors of Mammalian Acetyl-CoA Carboxylase 1 and 2 Bioorg. Med. Chem. Lett. 2010, 20, 2383–2388.
27 Haque TS, Liang N, Golla R, et al. Potent Biphenyl- and 3-Phenyl Pyridine-based Inhibitors of Acetyl-CoA Carboxylase. *Bioorg Med. Chem. Lett.* 2009;19:5872–5876.
28 Wu X, Huang T. Recent Development in Acetyl-CoA Carboxylase Inhibitors and Their Potential as Novel Drugs. *Future Med Chem.* 2020;12:533–561.
29 Chen L, Duan Y, Wei H, et al. Acetyl-CoA Carboxylase (ACC) as a Therapeutic Target for Metabolic Syndrome and Recent Developments in ACC1/2 inhibitors. *Expert Opin Investig Drugs.* 2019;28:917–930.
30 Corbett JW. Review of Recent Acetyl-CoA Carboxylase Inhibitor Patents: Mid-2007 – 2008. *Expert Opin Ther Patents.* 2009;19:943–956.
31 Nishiura Y, Matsumura A, Kobayashi N, et al. Discovery of a Novel Olefin Derivative as a Highly Potent and Selective Acetyl-CoA Carboxylase 2 Inhibitor with in Vivo Efficacy. *Bioorg Med Chem Lett.* 2018;28:2498–2503.
32 Gu YG, Weitzberg M, Clark RF, et al. N-{3-[2-(4-alkoxyphenoxy)thiazol-5-yl]-1-methylprop-2-ynyl}carboxy Derivatives as Acetyl-coA Carboxylase Inhibitors-Improvement of Cardiovascular and Neurological Liabilities via Structural Modifications. *J Med Chem.* 2007;50:1078–1082.
33 Gu YG, Weitzberg M, Clark R, et al. Synthesis and Structure-activity Relationships of N-{3-[2-(4-Alkoxyphenoxy)thiazol-5-yl]-1-methylprop-2-ynyl}carboxy Derivatives as Selective Acetyl-CoA Carboxylase 2 Inhibitors. *J Med Chem.* 2006;49:3770–3773.
34 Mizojiri R, Asano M, Tomita D, et al. Discovery of Novel Selective Acetyl-CoA Carboxylase (ACC) 1 Inhibitors. *J Med Chem.* 2018;61:1098–1117.
35 Mizojiri R, Nii N, Asano M, et al. Design and Synthesis of a Novel 1*H*-Pyrrolo[3.2-*b*] pyridine-3-carboxamide as an Orally Available ACC1 Inhibitor. *Bioorg Med Chem.* 2019;27:2521–2530.
36 Mizojiri R, Asano M, Sasaki M, et al. The Identification and Pharmacological Evaluation of Potent, Selective and Orally Available ACC1 inhibitor. *Bioorg Med. Chem. Lett.* 2019;29, 126749.