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Article

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ABSTRACT

We initiated our structure-activity relationship (SAR) studies for selective ACC1 inhibitors from **1a** as a lead compound. SAR studies of bicyclic scaffolds revealed many potent and selective ACC1 inhibitors represented by **1f**, however most of them had physicochemical issues, particularly low aqueous solubility and potent CYP inhibition. To address these two issues and improve the drug-likeness of this chemical series, we converted the bicyclic scaffold into a monocyclic framework. Ultimately, this lead us to discover a novel monocyclic derivative **1q** as a selective ACC1 inhibitor, which showed highly potent and selective ACC1 inhibition as well as acceptable solubility and CYP inhibition profiles. Since compound **1q** displayed

favorable bioavailability in mouse cassette dosing testing, we conducted in vivo PD studies of this compound. Oral administration of **1q** significantly reduced the concentration of malonyl-CoA in HCT-116 xenograft tumors at doses of more than 30 mg/kg. Accordingly, our novel series of selective ACC1 inhibitors represents a set of useful orally-available research tools, as well as potential therapeutic agents for cancer and fatty acid related diseases.

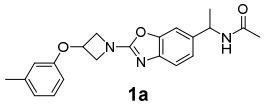
KEYWORDS: Acetyl-CoA carboxylase (ACC) 1 inhibitor, ^{14}C acetate uptake inhibition, solubility, CYP inhibition, Malonyl-CoA

INTRODUCTION

Since Otto Warburg's initial observations in the 1920s, it has been known that there are metabolic differences between rapidly-proliferating cancer cells and normal cells.[1] Recent research has demonstrated that these metabolic differences are actual drivers of tumor growth.[2,3] By modulating their metabolic processes, cancer cells are able to divert sugars, fats, and other energy sources away from energy production to satisfy the ever growing demands of uncontrolled proliferation. Drugs that intervene with the metabolism of cancer cells, redirecting them to the normal metabolic course, could present a completely new approach for treating cancer, either as monotherapy or in combination with other therapeutic approaches.[4-7]

Acetyl-CoA carboxylase (ACC) carboxylates acetyl-CoA to produce malonyl-CoA, representing the rate limiting step in fatty acid synthesis. Malonyl-CoA is an intermediate of de novo fatty acid synthesis, which acts as a substrate of fatty acid synthase (FAS) for acyl chain elongation. Furthermore, malonyl-CoA functions as an inhibitor of carnitine palmitoyltransferase 1 (CPT-1), regulating fatty acid beta-oxidation. Therefore, functional abnormalities of ACC are associated with blocking fatty acid synthesis, disturbing energy metabolism, and resulting in cell damage. Two ACC isoforms have been identified in mammals, ACC1 and ACC2. Recently, it has been reported that ACC1 is overexpressed in human cancer cells, such as colon, prostate, kidney, spleen, uterine cervix, uterus body, ovary, and small intestine cancer cells and is likely involved in tumor development and progression. Thus, ACC1 is a potential target for developing novel agents as cancer therapeutics.[8-15] However, selective ACC1 inhibitors have not been reported even though there are many reports for dual ACC1/2 inhibitors[16-24] and selective ACC2 inhibitors.[24-26] For evaluation of its potential in cancer therapy, a selective ACC1 inhibitor is required. Therefore, we initiated an investigation into the generation of potent and selective ACC1 inhibitors. As a starting point for these studies, we selected a unique 2-azetidyl-1,3-benzoxazole derivative **1a,** which had been found to show moderate ACC1 inhibitory potency with an IC_{50} value around 10 μM (48% inhibition at 10 μM) from our compound library, as a lead compound (Figure 1). We initiated

our research program around this compound in the belief that its novel structure could be used to selectively target ACC1, which has not been possible for known dual ACC1/2 and selective ACC2 inhibitors.



1a

hACC1: 48% inhibition @10 μM
hACC2: 22% inhibition @10 μM

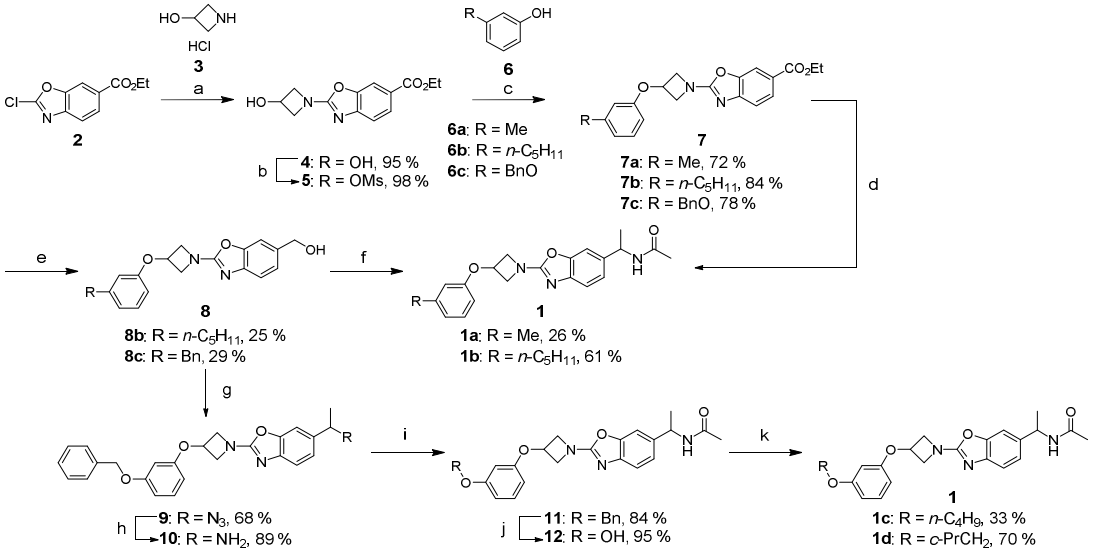
Figure 1. Lead compound for selective ACC1 inhibitors

CHEMISTRY

The preparations of 2-azetidyl-1,3-benzoxazole derivatives **1a**–**d** are shown in Scheme 1. Condensation of 2-chloro-1,3-benzoxazole **2** with 3-hydroxyazetidine hydrochloride (**3**) followed by methanesulfonylation afforded 2-azetidinyl-1,3-benzoxazole derivative **5**. Coupling of *m*-substituted phenol **6** with **5** yielded 2-(3-phenoxyazetidinyl)-1,3-benzoxazole analogue **7**. After conversion of the ester group of **7** into a 2-hydroxyethyl group by reduction of the ester group, Ru-catalyzed oxidation to form the aldehyde, followed by substitution with a methyl group, enabled synthesis of compounds **1a** and **1b** by the Ritter reaction using sulfuric acid in CH_3CN. Ru-catalyzed oxidation of **8**, substitution with a methyl group, and azidation with DPPA were carried out to produce the azide **9**. The acetamide analogue **11** was prepared

by Staudinger reaction of **9** and acetylation of the resulting amino group. After removing the benzyl group of **11** by hydrogenation, compounds **1c** and **1d** were synthesized by alkylation with the appropriate alkylbromide.

Scheme 1

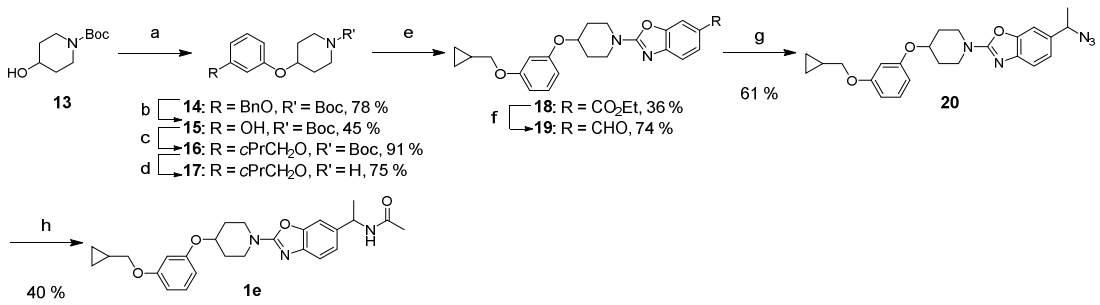


Reagents and conditions: a) **3**, DIPEA, rt, overnight, 95%; b) MsCl, Et_3N, THF, rt, overnight, 98%; c) **6**, Cs_2CO_3, DMF, 100 °C, 4 h – overnight, 72–78%; d) i) $LiAlH_4$, THF, 0 °C, 30 min; ii) TPAP, NMO, 4Å molecular sieves, CH_3CN, rt, 4 h; iii) MeMgBr, THF, 0 °C, 30 min; iv) H_2SO_4, CH_3CN, rt, 1 h, 26%; e) $LiAlH_4$, THF, 0 °C, 30 min, 25–29%; f) i) TPAP, NMO, 4Å molecular sieves, CH_3CN, rt, 4 h; ii) MeMgBr, THF, 0 °C, 30 min; iii) H_2SO_4, CH_3CN, rt, 1 h, 61%; g) i) TPAP, NMO, 4Å molecular sieves, CH_3CN, rt, 4 h; ii) MeMgBr, THF, 0 °C, 30 min; iii) DPPA, DBU, toluene, rt, 2 h, 68%; h) Ph_3P, water, THF, 60 °C, 2 h, 89%; i) Ac_2O, pyridine,

rt, 30 min, 84%; j) H_2 (1 atm), $Pd(OH)_2$, MeOH, THF, rt, overnight, 95 %; k) RBr, K_2CO_3, DMF, 80 °C, 2 h, 33–70%.

The preparation of **1e** is shown in Scheme 2. 4-Phenoxypiperidine **14** was synthesized from 4-hydroxypiperidine **13** by Mitsunobu reaction with phenol **6c**. After removal of the benzyl group of **14**, alkylation with a cyclopropylmethyl group, and removal of the Boc group, the resulting **17** was coupled with 2-chloro-1,3-benzoxazole **2** to afford 2-piperidinyl-1,3-benzoxazole derivative **18**. Stepwise conversion of the ester group of **18** into an azido group of **20** was carried out by reduction of the ester using $LiAlH_4$, Ru-catalyzed oxidation, substitution with MeMgBr, and azidation with DPPA. Finally, compound **1e** was synthesized from azide **20** by hydrogenation and acetylation of the resulting amino group.

Scheme 2

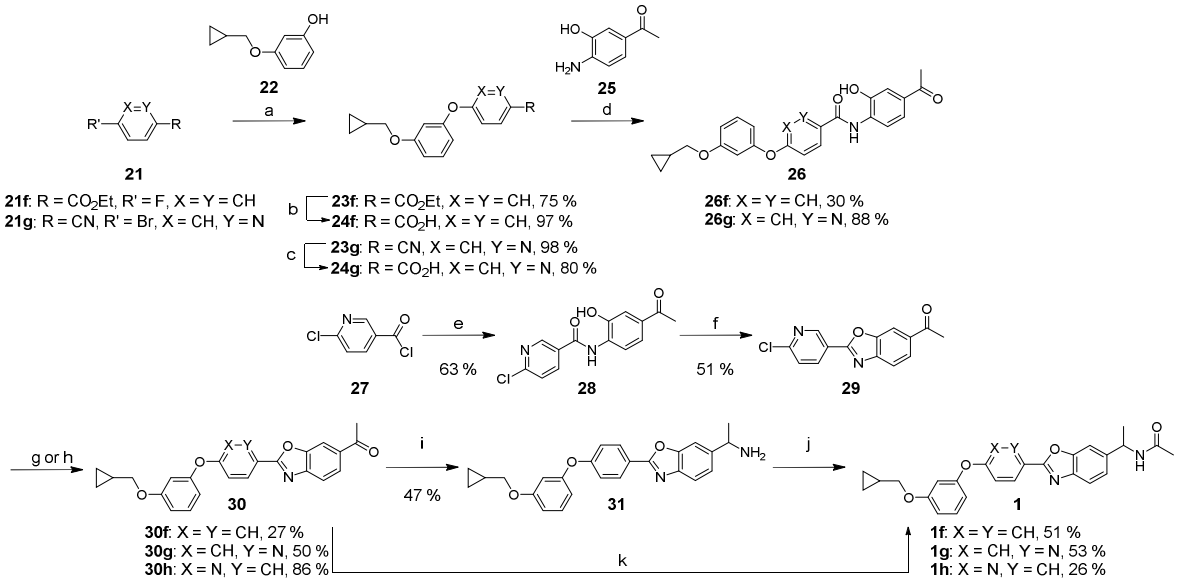


Reagents and conditions: a) **6c**, DIAD, Ph_3P, toluene, rt, overnight, 78%; b) H_2 (1 atm),

Pd/C, MeOH, rt, 2 h, 45%; c) *c*PrCH$_2$Br, K$_2$CO$_3$, DMF, 60 °C, overnight, 91%; d) 4 M HCl–AcOEt, rt, 4 h, 75%; e) **2**, DIPEA, DMF, rt, overnight, 36%; f) i) LiAlH$_4$, THF, 0 °C, 30 min; ii) TPAP, NMO, 4Å molecular sieves, CH$_3$CN, rt, 4 h, 74%; g) i) MeMgBr, THF, 0 °C, 1 h; ii) DPPA, DBU, toluene, rt, 4 h, 61%; h) i) H$_2$ (1 atm), Pd/C, THF, rt, 2 h; ii), Ac$_2$O, pyridine, rt, 2 h, 40%.

The preparation of **1f**–**h** is illustrated in Scheme 3. Coupling reaction of ethyl 4-fluorobenzoate (**21f**) or 5-bromo-2-cyanopyridine (**21g**) with phenol **22** yielded ethyl 4-phenoxybenzoate derivative **23f** or 5-phenoxy-2-cyanopyridine derivative **23g**, respectively. Hydrolysis of the ester or cyano group of **23** under basic conditions gave the corresponding acid **24**. Condensation reaction of **24** with aminophenol **25** gave the corresponding amide **26**. Cyclization of **26** under Mitsunobu reaction conditions afforded 2-phenyl-1,3-benzoxazole derivative **30f** and 2-pyridyl-1,3-benzoxazole derivative **30g**. Condensation reaction of **25** with 6-chloronicotinoyl chloride (**27**) gave the corresponding amide **28**. Mitsunobu cyclization of **28** gave 2-pyridyl-1,3-benzoxazole analogue **29**. Coupling reaction of **29** with phenol **22** gave the coupling product **30h**. Finally, reductive amination of **30f**–**h** followed by acetylation gave **1f**–**h**.

Scheme 3

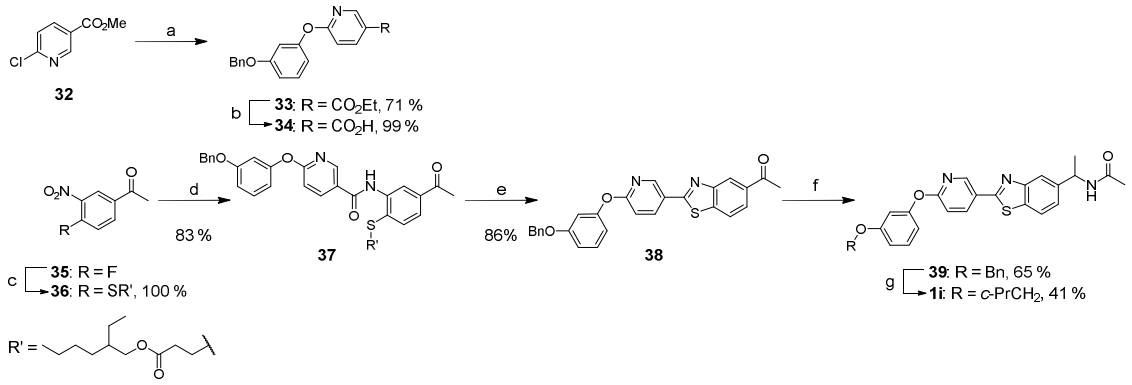


Reagents and conditions: a) **22**, Cs_2CO_3, DMF, 100 °C, overnight, 75–98%; b) 2 M NaOH, MeOH, THF, rt, 2 h, 97%; c) 2 M NaOH, EtOH, 80 °C, overnight, 80%; d) i) $(COCl)_2$, DMF, THF, rt, 1 h; ii) **25**, Et_3N, THF, rt, 1 h – overnight, 30–88%; e) **25**, Et_3N, THF, rt, overnight, 63%; f) DIAD, Ph_3P, THF, 60 °C, 2 h, 51%; g) **26**, DIAD, Ph_3P, THF, 60 °C, 1 h, 27–50%; h) **29**, **22**, Cs_2CO_3, DMF, 100 °C, 2 h, 86%; i) NH_4OAc, $NaBH_3CN$, MeOH, 60 °C, overnight, 47%; j) Ac_2O, pyridine, rt, 30 min, 51%; k) i) NH_4OAc, $NaBH_3CN$, MeOH, 60 °C, overnight; ii) Ac_2O, pyridine, rt, 30 min, 26–53%.

The preparation of **1i** is outlined in Scheme 4. Nicotinic acid derivative **34** was synthesized by the coupling of methyl 6-chloronicotinate (**32**) with phenol **6c** followed by hydrolysis.

Introduction of a thiol group into 4-fluoro-3-nitroacetophenone (**35**) under basic conditions gave thiol derivative **36**. After reduction of the nitro group into an amino group, condensation reaction with the acid chloride from **33** afforded benzothiazole precursor **37**. Treatment of **37** with NaOMe followed by TFA yielded benzothiazole derivative **38**. The synthesis of acetamide derivative **39** was carried out by reductive amination of the ketone of **38** using ammonium acetate followed by acetylation. Finally, removal of the benzyl group with TFA in thioanisole and alkylation with (bromomethyl)cyclopropane afforded **1i**.

Scheme 4

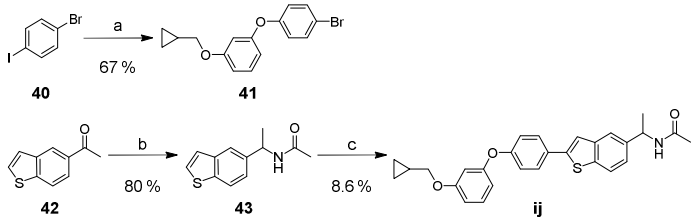


Reagents and conditions: a) **6c**, K_2CO_3, DMF, 100 °C, 5 h, 71%; b) 2M NaOH, THF, MeOH, rt, 2 h, 99%; c) 2-ethylhexyl beta-mercaptopropionate, K_2CO_3, DMF, rt, 2 h, 100%; d) i) Fe, NH_4Cl, EtOH, water, reflux, 30 min; ii) **34**, $SOCl_2$, THF, 60 °C, 30 min then Et_3N, THF, rt, 30 min, 83%; e) NaOMe, THF, rt, 30 min then TFA, THF 60 °C, 20 min, 86%; f) i) NH_4OAc, $NaBH_3CN$, THF, MeOH, reflux, 3 h; ii) Ac_2O, Et_3N, THF, rt, 1 h, 65%; g) i) TFA, thioanisole,

55 °C, 30 min; ii) *c*PrCH$_2$Br, K_2CO_3, DMF, 50 °C, overnight, 41%.

The preparation of **1j** is illustrated in Scheme 5. Cu-catalyzed coupling reaction of 4-bromoiodobenzene (**40**) with phenol **22** under microwave irradiation afforded 4-phenoxybromobenzene **41**. After reducing the ketone of 5-acetylbenzothiophene (**42**), the Ritter reaction was carried out to afford acetamide derivative **43**. Pd-catalyzed coupling reaction of **43** with bromobenzene **41** gave the desired benzo[*b*]thiophene analogue **1j**.

Scheme 5

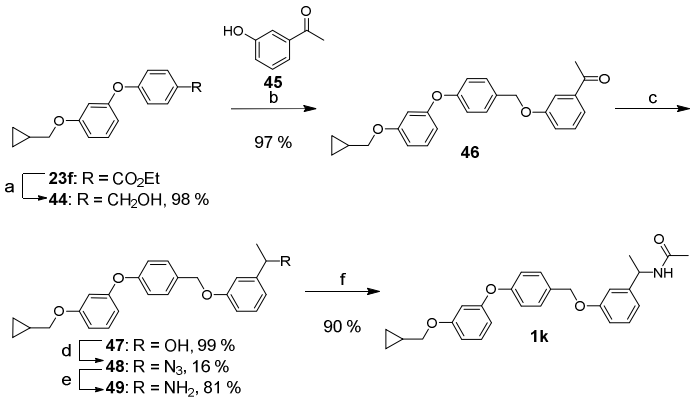


Reagents and conditions: a) **22**, CuI, dimethylaminoacetic acid hydrochloride, Cs_2CO_3, DME, 90 °C, overnight, 67%; b) i) $NaBH_4$, MeOH, rt, 1 h; ii) H_2SO_4, CH_3CN, rt, 1.5 h, 80%; c) **41**, $Pd(OAc)_2$, (*tert*-Bu)$_3$PBF$_4$, *tert*-BuOLi, DMA, 120 °C, overnight, 8.6%.

The preparation of **1k** is shown in Scheme 6. After reduction of the ester in **23f** to produce benzylalcohol **44**, benzylether derivative **46** was prepared by Mitsunobu reaction with

1-(3-hydroxyphenyl)ethanone (**45**). After reduction of the ketone of **46**, compound **1k** was prepared from alcohol **47** by azidation with DPPA, Staudinger reaction and acetylation.

Scheme 6

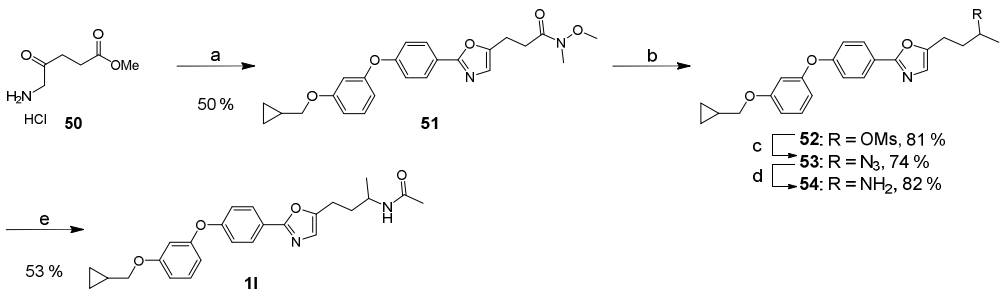


Reagents and conditions: a) $LiAlH_4$, THF, 0 °C, 30 min, 98%; b) **45**, Ph_3P, DIAD, THF, rt, 4h, 97%; c) $NaBH_4$, EtOH, THF, 0 °C, 30 min, 99 %; d) DPPA, DBU, toluene, rt, 2h, 16%; e) Ph_3P, THF, water, 60 °C, 1h, 81%; f) Ac_2O, pyridine, rt, 30 min, 90%.

The preparation of **1l** is displayed in Scheme 7. 2-Phenyl-1,3-oxazole derivative **51** was synthesized from amine **50** and benzoic acid **24f** by condensation reaction utilizing 2-chloro-1-methylpyridinium iodide, cyclization under Robinson–Gabriel cyclodehydration conditions using I_2 and Ph_3P, hydrolysis of the ester, and Weinreb amide formation. Weinreb amide **51** was converted to azide **53** in 4 steps by reaction with MeMgBr, reduction of the

ketone, methanesulfonylation, and substitution with an azido group. Finally, the desired acetamide derivative **1l** was prepared from azide **53** by Staudinger reaction and acetylation.

Scheme 7

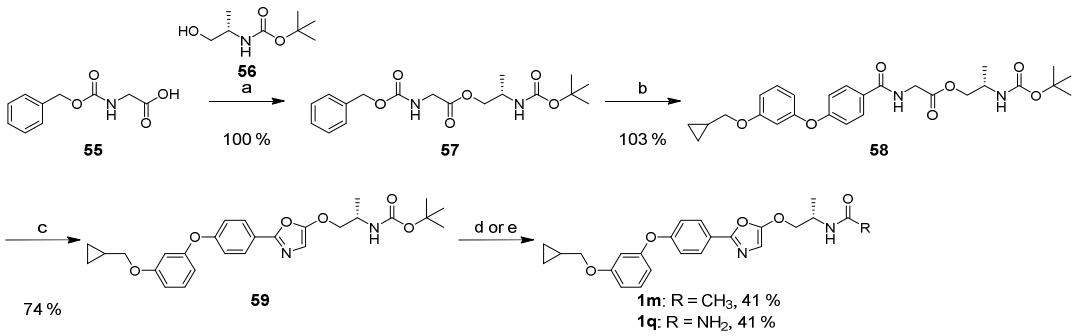


Reagents and conditions: a) i) **24f**, 2-chloro-1-methylpyridinium iodide, DIPEA, THF, 12 °C, 2 h; ii) I_2, Ph_3P, Et_3N, CH_2Cl_2, 12 °C, 1 h; iii) 1M NaOH, THF, MeOH, rt, overnight; iv) MeNH(OMe)·HCl, EDC·HCl, HOBt·H_2O, Et_3N, DMF, rt, overnight, 50%; b) i) MeMgBr, THF, 0 °C, 1 h; ii) $NaBH_4$, EtOH, 0 °C, 30 min, iii) MsCl, Et_3N, THF, rt, 1 h, 81%; c) NaN_3, DMF, 80 °C, 2 h, 74 %; d) Ph_3P, THF, water, 60 °C, 2 h, 82%; e) Ac_2O, pyridine, rt, 30 min, 53%.

2-Phenyl-1,3-oxazole derivatives **1m** and **1q** were prepared as shown in Scheme 8. Condensation of *N*-benzyloxycarbonylglycine (**55**) and *N*-Boc-(*S*)-alaninol (**56**) produced the corresponding ester **57**. After deprotection of the benzyloxycarbonyl group by hydrogenation, condensation with benzoic acid derivative **24f** was carried out to give cyclization precursor **58**.

Construction of the oxazole ring by Robinson–Gabriel cyclodehydration yielded **59**. Finally, the desired product **1m** was synthesized by removal of the Boc protecting group from **59** and acetylation. Ureido derivative **1q** was synthesized by formation of the 4-nitrophenyl carbamate followed by treatment with aqueous ammonia solution.

Scheme 8

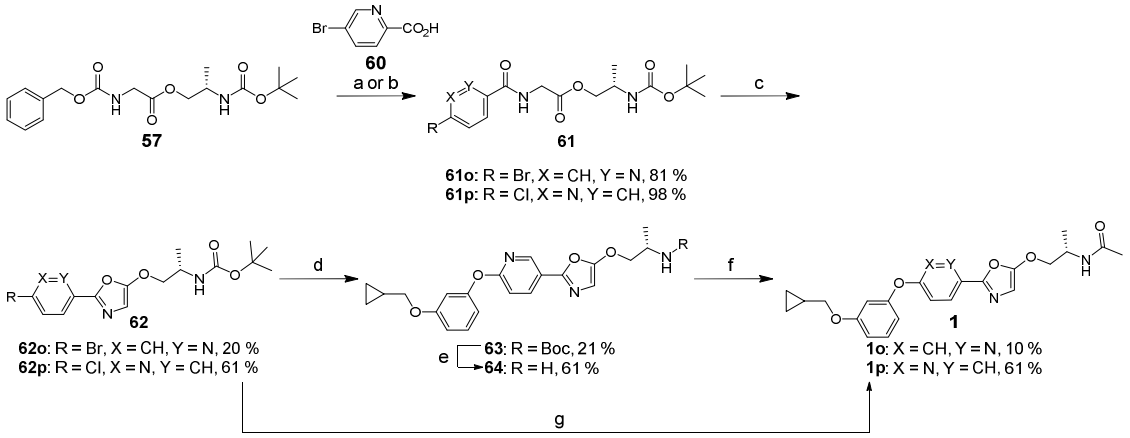


Reagents and conditions: a) **56**, EDC·HCl, DMAP, DMF, rt, overnight, 100%; b) i) H_2 (1 atm), Pd/C, THF, rt, 4 h; ii) **24f**, $(COCl)_2$, DMF, THF, rt, 1 h then Et_3N, THF rt, overnight, 103%; c) I_2, Ph_3P, Et_3N, CH_3CN, rt, overnight, 74%; d) i) TFA, toluene, rt, 30 min; ii) Ac_2O, pyridine, rt, 30 min, 41%; e) i) formic acid, 40 °C, 30 min, ii) 4-nitrophenyl chloroformate, Et_3N, THF, 0 °C, 1 h then 28% aq. NH_3, rt, 30 min, 41%.

The preparation of **1o** and **1p** is outlined in Scheme 9. The 2-pyridyl-1,3-oxazole analogue **62** was prepared by condensation with the deprotected amine from **57** followed by Robinson–

Gabriel cyclodehydration. After Cu-catalyzed coupling reaction between **62o** and phenol **22**, the desired product **1o** was produced by removal of the Boc protecting group and acetylation. After coupling reaction of **62p** with phenol **22** under basic conditions, the desired product **1p** was prepared by removal of the Boc protecting group and acetylation.

Scheme 9

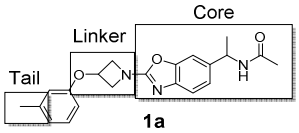


Reagents and conditions: a) i) H_2 (1 atm), Pd/C, THF, rt, 2 h; ii) **60**, $(COCl)_2$, DMF, THF, rt, 1 h then Et_3N, THF rt, 1 h, 81%; b) i) H_2 (1 atm), Pd/C, THF, rt, 2 h; ii) **27**, Et_3N THF rt, 1 h, 98%; c) I_2, Ph_3P, Et_3N, CH_3CN or CH_2Cl_2, rt, overnight, 20–61%; d) **22**, **62o**, Cs_2CO_3, DMF, 100 °C, 2 h, 21%; e) formic acid, 40 °C, 30 min, 61%; f) Ac_2O, pyridine, rt, 30 min, 61%; g) i) **22**, **62p**, CuI, picolinic acid, K_3PO_4, DMSO, 80–90 °C, 16 h; ii) formic acid 10–15 °C, 5 h; iii) Ac_2O, pyridine, 15–20 °C, 16 h, 10%.

RESULTS AND DISCUSSION

1. Investigation of bicyclic 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. In our initial SAR studies of selective ACC1 inhibitors, we paid particular attention to the novel *N*-(1-(1,3-benzoxazol-6-yl)ethyl)acetamide moiety of compound **1a** as the core scaffold (Fig. 2).



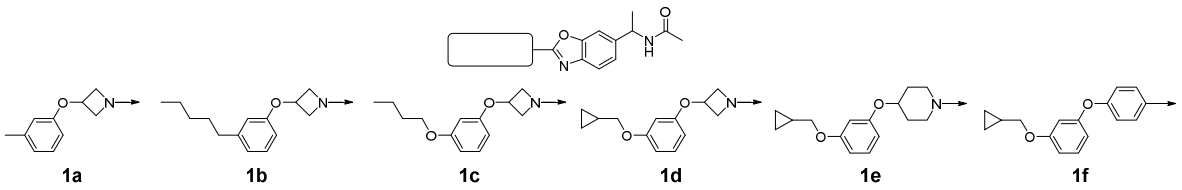
hACC1: 48% inhibition @10 μM
hACC2: 22% inhibition @10 μM

Figure 2. Synthetic strategies for initial SAR studies

First, we examined the effect of modifications around the tail region. Encouragingly, investigation of the alkyl chain in the tail region revealed that replacement with *n*-pentyl moiety could increase ACC1 inhibitory potency and provide good selectivity over ACC2 (compound **1b**: ACC1 IC_{50} = 220 nM, ACC2 IC_{50} >10000 nM). Furthermore, the improved enzymatic potency of compound **1b** translated into enhanced cellular potency (acetate uptake IC_{50} = 100

nM). Replacement of the alkyl tail of compound **1b** with an ether chain showed similar enzymatic activity (compound **1c**: ACC1 IC_{50} = 210 nM). Since ether **1c** displayed higher solubility (8.2 μg/mL at pH 6.8) than alkyl compound **1b** (0.44 μg/mL at pH 6.8), we conducted further modifications of the ether moiety for our SAR campaign in the tail region. Thus, introduction of a cyclopropylmethoxy group further improved ACC1 inhibitory potency along with good selectivity over ACC2 (compound **1d**: ACC1 IC_{50} = 23 nM, ACC2 IC_{50} = 5800 nM). This result indicated that the cyclopropylmethoxy group is important for ACC1 inhibitory potency. Next, we investigated modifications to the linker section and a series of cyclopropylmethyl ether derivatives were evaluated. Compound **1e**, possessing a 4-phenoxy piperidine moiety instead of the azetidine linker of **1d**, exhibited 10-fold lower ACC1 inhibitory potency. Notably, 2-(4-phenoxyphenyl)-1,3-benzoxazole derivative **1f** showed selective and highly potent ACC1 inhibition (ACC1 IC_{50} = 5.3 nM, ACC2 IC_{50} >10000 nM) along with high cellular potency (acetate uptake IC_{50} = 2.2 nM). Thus, the introduction of a phenyl ring at the 2-position of the 1,3-benzoxazole core was found to significantly improve enzymatic activity as well as cellular potency, indicating that 2-aryl-1,3-benzoxazle derivatives could be more potent and selective ACC1 inhibitors. Thus, we conducted further optimization by modification of the 2-arylbicyclic core.

Table 1. Effects of tail and linker modifications on biological activity[a]



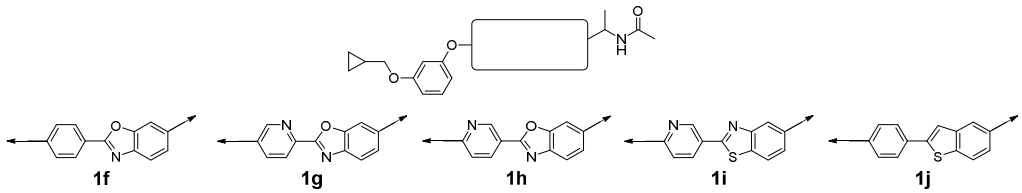
	IC_{50} (nM)[b]		
	hACC1	hACC2	Uptake[c]
1a	>10000 (48%)[d]	>10000 (22%)[d]	NT[e]
1b	220 (107–441)	>10000	100 (34.7–309.3)
1c	210 (81.1–532.9)	>10000	NT[e]
1d	23 (14.8–36.6)	5800 (3919–8631)	51 (79.0–152.6)
1e	230 (127.8–396.3)	>10000	400 (186.4–846.4)
1f	5.3 (4.7–5.9)	>10000	2.2 (1.6–3.0)

[a]IC_{50} values shown are the means of duplicate measurement. [b]IC_{50} values and 95%

confidence limits are calculated from the concentration-response curves generated by GraphPad Prism. [c]Acetate uptake inhibition in HCT-116 cells. [d]% inhibition at 10 μM. [e]Not tested.

For further SAR studies, we explored other core 2-arylbicyclic scaffolds to generate potent and selective ACC1 inhibitors. Introduction of a pyridine ring at the 1,3-benzoxazole 2-position produced 2-pyridyl-1,3-benzoxazoles **1g** and **1h**. These compounds showed potent and selective inhibition of ACC1 comparable to that of 2-phenyl-1,3-benzoxazole derivative **1f**. Remarkably, compound **1h** showed the most potent ACC1 inhibitory activity (IC_{50} = 1.8 nM) and cellular potency (IC_{50} = 0.76 nM) of the benzoxazole analogs. Additionally, these compounds exhibited improved solubility at pH 6.8 (**1g**: 5.8 μg/mL and **1h**: 1.6 μg/mL, respectively) compared with compound **1f** (<0.18 μg/mL) corresponding to their lower lipophilicity (**1g**: cLogP 4.44, **1h**: cLogP 4.23 and **1f**: cLogP 5.62, respectively), brought about by the introduction of a nitrogen atom. However, ACC1 selectivity over ACC2 for the 2-pyridyl derivatives decreased to 200-fold (**1g**) and 75-fold (**1h**) from that of **1f** (>1500-fold). For further investigation, analogues with other bicyclic core scaffolds were evaluated. They also displayed potent and selective ACC1 inhibition represented by compound **1i** and **1j** as shown in Table 2.

Table 2. In vitro activity, solubility, and CYP inhibition of inhibitors with modified bicyclic core scaffolds[a]



	IC_{50} (nM)[b]			Solubility	CYP inhibition[e]	
	hACC1	hACC2	Uptake[c]	(μg/mL)[d]	2C8 (%)	2C9 (%)
1f	5.3 (4.7–5.9)	>10000	2.2 (1.6–3.0)	<0.18	82.7	89.9
1g	7.1 (5.4–9.5)	1400 (274.8–7210)	9.9 (7.3–13.3)	5.8	81.4	90.6
1h	1.8 (1.5–2.1)	170 (80.6–355)	0.76 (0.4–1.5)	1.6	81.4	87.0
1i	7.4 (5.2–10.6)	>10000	14 (5.8–33.1)	<0.12	14.4	44.8
1j	26 (16.4–39.9)	>10000	11 (7.2–17.4)	<0.090	23.6	33.5

[a]IC_{50} values shown are the means of duplicate measurement. [b]IC_{50} values and 95% confidence limits are calculated from the concentration-response curves generated by GraphPad

Prism. [c]Acetate uptake inhibition in HCT-116 cells. [d]Solubility in pH6.8. [e]% inhibition at 10 μM.

Thus, by modification of the bicyclic scaffold, multiple potent ACC1-selective inhibitors were identified. While they generally showed potent and selective ACC1 inhibition as well as improved cellular potency compared to lead compound **1a**, they still bore some liabilities, such as poor solubility and potent CYP inhibition. Compound **1i** and **1j** showed lower levels of CYP inhibition than compound **1f**, however, possessed similarly low solubility. Other bicyclic derivatives we synthesized showed similar imbalances in potency, selectivity and physicochemical properties. According to these results, we concluded that it would be difficult to produce more potent and selective ACC1 inhibitors while maintaining favorable drug-like properties by the modification of these bicyclic derivatives. Therefore, we shifted our chemistry efforts to identify potent, selective, and more drug-like ACC1 inhibitors suitable for in vivo use.

2. Investigation of monocyclic derivatives

It is generally well known that reducing the number of aromatic rings in a compound is effective in ameliorating CYP inhibitory potency.[27] At the same time, increasing

conformational flexibility enhances the solubility of drug-like compounds.[28] Taken together, we thought to replace the bicyclic core structure with a monocycle, which we anticipated would minimize these issues simultaneously. Based on this consideration, we attempted the two approaches shown in Figure 3: removal of the oxazole ring to generate monocyclic benzyloxy derivative **1k** (approach A) and removal of a benzene ring to generate monocyclic oxazole derivative **1l** (approach B). Benzyloxy derivative **1k** showed moderate ACC1 inhibitory potency and >70-fold selectivity over ACC2 (ACC1 IC_{50}/ACC2 IC_{50} = 140 nM/>10000 nM). As expected, this compound demonstrated reduced CYP inhibitory activity, but with poor solubility (<0.23 μg/mL at pH 6.8) and weak cellular potency (IC_{50} >1000 nM). On the other hand, oxazole derivative **1l** exhibited slightly improved solubility (2.0 μg/mL at pH 6.8) and an lower CYP inhibitory activity. Importantly, this compound retained potent ACC1 inhibitory activity (IC_{50} = 4.9 nM) and cellular potency (IC_{50} = 8.6 nM). Accordingly, we chose to further explore approach B, with compound **1l** as our new lead compound for further optimization to identify a suitable in vivo tool compound with drug-like properties.

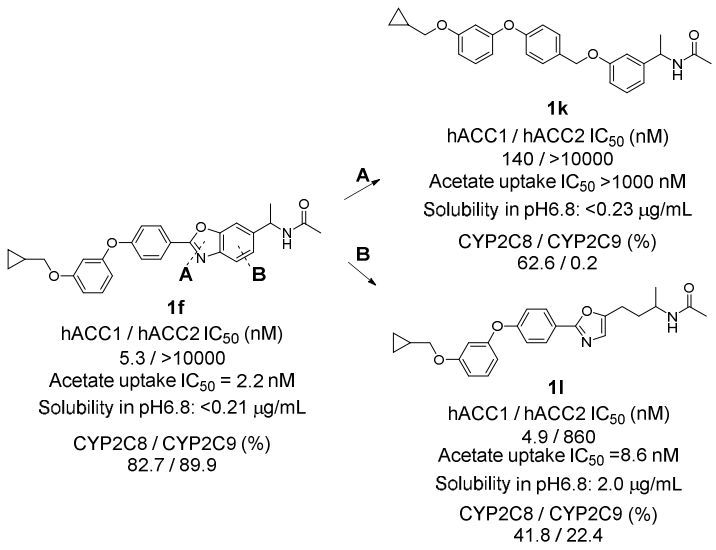
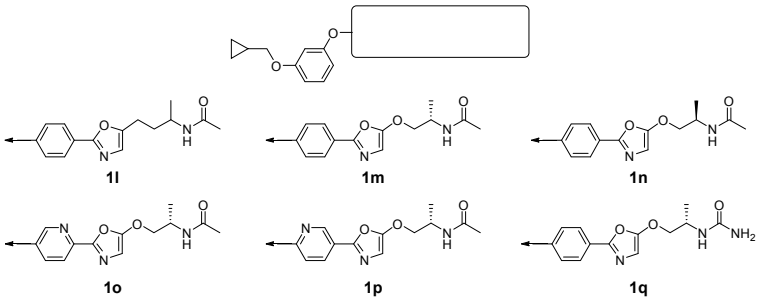


Figure 3. Synthetic strategies to improve CYP inhibition and solubility of ACC1 inhibitors

First, we examined the SAR of the linker between the acetamide moiety and the monocycle. Replacement of the alkyl linker of compound **1l** with a single enantiomer ether chain[21] produced highly potent ACC1 inhibitor **1m** (ACC1 IC_{50} = 0.96 nM). On the other hand, the *R*-isomer **1n** showed ca. 300-fold decrease in ACC1 inhibitory activity (ACC1 IC_{50} = 240 nM). Therefore, we focused on further derivative synthesis maintain the more potent *S*-isomer conformation in the linker region. Compound **1m** also showed potent cellular activity (ACC1 IC_{50} = 3.4 nM) and acceptable solubility (2.7 μg/mL at pH 6.8), along with increased ACC2 inhibitory potency (ACC2 IC_{50} = 95 nM). As part of our effort to further improve the solubility of these monocyclic oxazole derivatives, we investigated the effects of introducing a

nitrogen atom into compound **1m**, a modification that significantly affected the bicyclic derivatives described above. As a result, replacement of the 2-phenyl group of the 1,3-oxazole derivatives with a 2-pyridyl group produced improved solubility, as expected (**1o:** 19 μg/mL and **1p:** 9.4 μg/mL), while maintaining ACC1 inhibitory potency and selectivity over ACC2. Since increasing the solubility of **1o** and **1p** relative to **1m** would largely depend on lowering compound lipophilicity, we investigated replacement of the acetamide moiety with a ureido group. As a result, ureido derivative **1q** was prepared and shown to be a highly potent and selective ACC1 inhibitor (ACC1 IC_{50}/ACC2 IC_{50} = 0.58 nM/>10000 nM) with potent cellular activity (IC_{50} = 6.4 nM) and acceptable solubility (1.7 μg/mL at pH 6.8). Accordingly, the main effect of introducing the ureido moiety was in reducing ACC2 inhibitory potency. From our modifications of various monocyclic oxazole derivatives, overall we found compound **1q** to represent the most promising in vivo candidate with high potency and selectivity, as well as good physicochemical properties.

Table 3. In vitro biological activity and solubility of monocyclic oxazole derivatives[a]

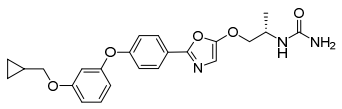


	IC_{50} (nM)[b]			Solubility	CYPinhibition[e]	
	hACC1	hACC2	Uptake[c]	(μg/mL)[d]	2C8 (%)	2C9 (%)
1l	4.9 (3.8–6.2)	860 (271.7–2744)	8.6 (7.1–10.5)	2.0	41.8	22.4
1m	0.96 (0.8–1.1)	95 (47.4–191.4)	3.4 (2.6–4.4)	2.7	13.5	19.6
1n	240 (163–365)	5700 (1068–30304)	710 (580–864)	NT[f]	NT[f]	NT[f]
1o	5.8 (4.3–7.9)	930 (517.3–1682)	51 (38.1–69.2)	19	4.7	2.4
1p	0.96 (0.9–1.0)	290 (139.9–598.4)	2.8 (2.2–3.6)	9.4	23.2	26.2
1q	0.58 (0.5–0.7)	>10000	6.4 (4.8–8.6)	1.7	23.5	14.8

[a]IC_{50} values shown are the means of duplicate measurement. [b]IC_{50} values and 95% confidence limits are calculated from the concentration-response curves generated by GraphPad Prism. [c]Acetate uptake inhibition in HCT-116 cells. [d]Solubility in pH6.8. [e]% inhibition at 10 μM. [f]Not tested.

3. In vivo evaluation of a selective ACC1 inhibitor

Through our SAR studies focused on the bicyclic and monocyclic analogues, highly potent and selective ACC1 inhibitor **1q** was identified. In order to evaluation this compound further, additional testing of its biological, ADMET, and PK properties was conducted. The overall profile of this compound is shown in Figure 4. Compound **1q** showed good metabolic stability in mouse liver microsomes, acceptable permeability, and no significant CYP inhibitory activities in our standard ADME and physicochemical profiling. Furthermore, pharmacokinetic (PK) studies in a mouse cassette dosing test (0.1 mg/kg, i.v. and 1 mg/kg, p.o.) exhibited excellent bioavailability, suggesting it could be used for in vivo evaluation. Based on the promising in vitro and in vivo profile of **1q**, we selected this compound for in vivo pharmacodynamics (PD) study to evaluate the potential of a selective ACC1 inhibitor in xenograft tumor models.



1q

hACC1 IC_{50} / hACC2 IC_{50} (nM)

0.58 / >10000

Acetate uptake IC_{50} = 6.4 nM

Solubility (μg/mL)	PAMPA (nm/sec)		Metabolic Stability (μL/min/mg)	
pH6.8	pH5.0	pH7.4	human	mouse
1.7	248	250	47	16

CYP inhibition at 10 μM (%)

2A1	2C8	2C9	2D6	3A4
-3.0	23.5	14.8	11.5	-54.5

mouse cassette dosing (1 mg/kg, po; 0.1 mg/kg, iv)

Cmax (ng/mL)	AUCpo (ng*h/mL)	MRTpo (h)	[a]F (%)
1936.6	13128.3	4.06	82.9

[a]F meens bioavailability.

Figure 4. Biological, ADMET, and PK profile of compound **1q**

In this preliminary PD study, malonyl-CoA concentration in tumors was measured as a direct PD marker. As a result, compound **1q** showed potent and sustained malonyl-CoA suppression at 16 h after single oral administration in HCT-116 xenograft mice at doses of more than 30 mg/kg.

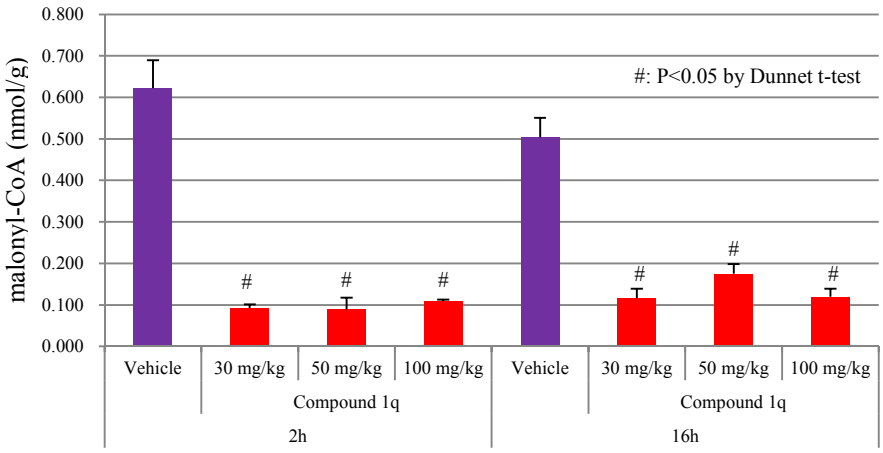


Figure 5. Effects of compound **1q** on malonyl-CoA concentration in HCT-116 xenograft tumors

CONCLUSIONS

We have described the identification of a novel series of potent and selective ACC1 inhibitors as a chemical probes for oncology research and potential use as anti-cancer agents. Our initial lead, 2-azetidyl-1,3-benzoxazole derivative **1a**, was optimized and converted to 2-phenyl-1,3-benzoxazole derivative **1f**. Compound **1f** showed >1800-fold more potent ACC1-selective inhibition than compound **1a** and potent cellular activity, although further testing suggested the need to improve the physicochemical and ADMET properties of **1f**, such as solubility and CYP inhibition. To address these needs, the bicyclic core was replaced with a monocyclic scaffold, which ultimately lead us to the discovery of ureido derivative **1q**, with an oxazole core scaffold. Compound **1q** showed an improved physicochemical and ADMET

profile, while maintaining potent and subtype-selective ACC1 inhibitory potency. Based on its promising PK profile and results from initial in vivo PD studies, compound **1q** was selected as an in vivo probe molecule and is undergoing further pharmacological evaluation to determine the therapeutic potential of selective ACC1 inhibition.

EXPERIMENTAL SECTION

General. The proton nuclear magnetic resonance (^{1}H NMR) spectra were measured on a Bruker Avance 300 (300 MHz), Bruker Avance 400 (400 MHz) or Varian 400 MHz spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane as the internal standard. All J values are given in hertz. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; br s, broad singlet. Analytical LC was performed on a Shimadzu LC-20AD separations module (L-column2 ODS (3.0 x50 mm I.D., CERI, Japan); 0.05% TFA in ultrapure water/acetonitrile gradient; UV detection 220 nm or 254 nm). MS spectra were recorded using a Shimadzu LCMS-2020 with electrospray ionization. High performance liquid chromatography (HPLC) was performed on Shimadzu LC-10A series. The purities of all the compounds tested in biological systems were assessed as being >95% using elemental analysis or analytical HPLC. Purity data were collected by HPLC with NQAD (nanoquality analyte detector) or Corona CAD (charged aerosol

detector). The column was an L-column 2 ODS (30 mm × 2.1 mm i.d., CERI) or a Capcell Pak C18AQ (50 mm × 3.0 mm i.d., Shiseido) with a temperature of 50 °C and a flow rate of 0.5 mL/min. Mobile phases A and B under a neutral conditions were a mixture of 50 mmol/L $AcONH_4$, water, and MeCN (1/8/1, v/v/v) and a mixture of 50 mmol/L $AcONH_4$ and MeCN (1/9, v/v), respectively. The ratio of mobile phase B was increased linearly from 5% to 95% over 3 min, 95% over the next 1 min. Melting points (mp) were determined on an OptiMelt MPA100 melting point apparatus and were uncorrected. Elemental analyses (C, H, N) were within ± 0.4% of theoretical values. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 F_{254}) and basic TLC plates (NH silica gel, Fuji Silysia Chemical Ltd.) were used. The products were purified on silica gel 60 (0.063-0.200, E. Merck), basic silica gel (Chromatorex NH, 100-200 mesh, Fuji Silysia Chemical Ltd.) or Purif-Pack (Si or NH, Shoko Scientific Co., Ltd.). Reagents and solvents were obtained from commercially sources and used without further purification.

***N*-(1-(2-(3-(3-methylphenoxy)azetidin-1-yl)-1,3-benzoxazol-6-yl)ethyl)acetamide (1a)**

Ethyl 2-(3-hydroxyazetidin-1-yl)-1,3-benzoxazole-6-carboxylate (4): A mixture of ethyl 2-chloro-1,3-benzoxazole-6-carboxylate (**2**) (17.5 g, 77.6 mmol), azetidin-3-ol hydrochloride (**3**)

(9.35 g, 85.3 mmol) and DIPEA (33.9 mL, 193.9 mmol) in DMF (175 mL) was stirred at room temperature overnight. Water was added and the mixture was stirred at room temperature for 30 min. The precipitate was collected by filtration and dried under reduced pressure to afford **4** (19.3 g, 95%) as an off-white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.32 (3H, t, J = 7.1 Hz), 3.92–4.05 (2H, m), 4.29 (2H, q, J = 7.1 Hz), 4.39–4.49 (2H, m), 4.58–4.73 (1H, m), 5.92 (1H, d, J = 6.6 Hz), 7.28–7.38 (1H, m), 7.79–7.86 (1H, m), 7.86–7.93 (1H, m). LCMS *m/z* calcd for $C_{13}H_{14}N_2O_4$: 262.10, found 262.9 [M+1].

Ethyl 2-(3-((methylsulfonyl)oxy)azetidin-1-yl)-1,3-benzoxazole-6-carboxylate (5): A mixture of **4** (20.7 g, 79.1 mmol), MsCl (9.18 mL, 118.6 mmol) and Et_3N (22 mL, 158.2 mmol) in THF (200 mL) was stirred at room temperature overnight. 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 triturated with IPE, filtered and dried under reduced pressure to afford **5** (26.3 g, 98 %) as a beige solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.32 (3H, t, J = 7.1 Hz), 3.31 (3H, s), 4.30 (2H, q, J = 7.1 Hz), 4.38 (2H, dd, J = 10.0, 3.3 Hz), 4.66 (2H, dd, J = 9.2, 7.0 Hz), 5.43–5.54 (1H, m), 7.41 (1H, d, J = 8.3 Hz), 7.86 (1H, dd, J = 8.2, 1.5 Hz), 7.94 (1H, d, J = 1.2 Hz). LCMS *m/z* calcd for $C_{14}H_{16}N_2O_6S$: 340.07, found 340.9 [M+1].

Ethyl 2-(3-(3-methylphenoxy)azetidin-1-yl)-1,3-benzoxazole-6-carboxylate (7a): A mixture of **5** (500 mg, 1.47 mmol), *m*-cresol (**6a**) (238 mg, 2.2 mmol) and Cs_2CO_3 (1.44 g, 4.41 mmol) in DMF (5 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 (NH silica gel, eluent: 5/95 to 25/75 AcOEt/hexane) to afford **7a** (372 mg, 72 %). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.32 (3H, t, J = 7.1 Hz), 2.29 (3H, s), 4.19–4.26 (2H, m), 4.30 (2H, q, J = 7.1 Hz), 4.68–4.78 (2H, m), 5.16–5.27 (1H, m), 6.63–6.74 (2H, m), 6.83 (1H, d, J = 7.6 Hz), 7.21 (1H, t, J = 7.8 Hz), 7.39 (1H, d, J = 8.2 Hz), 7.85 (1H, dd, J = 8.2, 1.6 Hz), 7.92 (1H, d, J = 1.1 Hz). LCMS *m/z* calcd for $C_{20}H_{20}N_2O_4$: 352.14, found 353.0 [M+1].

***N*-(1-(2-(3-(3-methylphenoxy)azetidin-1-yl)-1,3-benzoxazol-6-yl)ethyl)acetamide (1a):** To an ice cold stirred suspension of $LiAlH_4$ (80 mg, 2.11 mmol) in THF (5 mL) was added **7a** (372 mg, 1.06 mmol) in THF (5 mL). After stirring at 0 °C for 30 min, water (0.08 mL) was added followed by 1 M NaOH (0.08 mL). Water (0.24 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 the residue were added NMO (186 mg, 1.59 mmol), TPAP (37 mg,

0.11 mmol), 4Å molecular sieves (494 mg) and CH_3CN (5 mL). The mixture was stirred at room temperature for 4 h. The mixture was filtered and concentrated under reduced pressure. The residue was passed through a pad of silica gel (eluent: 1/1 AcOEt/hexane) and concentrated under reduced pressure. To the residue in THF (5 mL) was added MeMgBr (1.0 M THF solution, 2.12 mL, 2.12 mmol) at 0 °C. After stirring at 0 °C for 30 min, the mixture was extracted with AcOEt and sat. aq. NH_4Cl. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. To the residue in CH_3CN (5 mL) was added conc. H_2SO_4 (0.11 mL, 2.12 mmol) at 0 °C. After stirring at room temperature for 1h, the mixture was extracted with AcOEt and 1 M NaOH. 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 75/25 AcOEt/hexane) and crystallized from AcOEt and hexane to afford **1a** (100 mg, 26 %) as a white crystalline solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.34 (3H, d, J = 7.0 Hz), 1.83 (3H, s), 2.29 (3H, s), 4.15 (2H, dd, J = 9.3, 4.1 Hz), 4.60–4.71 (2H, m), 4.87–5.00 (1H, m), 5.12–5.25 (1H, m), 6.63–6.73 (2H, m), 6.82 (1H, d, J = 8.0 Hz), 7.12 (1H, dd, J = 8.2, 1.5 Hz), 7.16–7.28 (2H, m), 7.35 (1H, d, J = 1.5 Hz), 8.25 (1H, d, J = 8.1 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.56, 23.18, 23.33, 48.25, 58.85, 67.31, 107.30, 112.03, 115.79, 116.15, 122.39, 122.70, 130.00, 138.87, 139.92, 141.89, 149.36, 156.71, 163.08, 168.59. LCMS *m/z* calcd for $C_{21}H_{23}N_3O_3$: 365.17, found 366.0 [M+1]. Anal.

Calcd for $C_{21}H_{23}N_3O_3$: C, 69.02; H, 6.34; N, 11.50. Found: C, 68.86; H, 6.25; N, 11.34. Mp 174–176 °C.

***N*-(1-(2-(3-(3-pentylphenoxy)azetidin-1-yl)-1,3-benzoxazol-6-yl)ethyl)acetamide (1b)**

Ethyl 2-(3-(3-pentylphenoxy)azetidin-1-yl)-1,3-benzoxazole-6-carboxylate (7b): A mixture of 3-pentylphenol (**6b**) (334 mg, 2.03 mmol), **5** (692 mg, 2.03 mmol) and Cs_2CO_3 (994 mg, 3.05 mmol) in DMF (5 mL) was stirred at 100 °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 (silica gel, eluent: 5/95 to 25/75 AcOEt/hexane) to afford **7b** (700 mg, 84 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.87 (3H, t, J = 6.9 Hz), 1.21–1.40 (7H, m), 1.49–1.64 (2H, m), 2.52–2.60 (2H, m), 4.18–4.36 (4H, m), 4.73 (2H, dd, J = 9.4, 6.6 Hz), 5.14–5.29 (1H, m), 6.69 (2H, s), 6.79–6.89 (1H, m), 7.22 (1H, t, J = 7.8 Hz), 7.39 (1H, d, J = 8.2 Hz), 7.85 (1H, dd, J = 8.2, 1.6 Hz), 7.92 (1H, d, J = 1.1 Hz). LCMS *m/z* calcd for $C_{24}H_{28}N_2O_4$: 408.20, found 409.2 [M+1].

(2-(3-(3-Pntylphenoxy)azetidin-1-yl)-1,3-benzoxazol-6-yl)methanol (8b): To an ice cold

stirred suspension of $LiAlH_4$ (65 mg, 1.71 mmol) in THF (7 mL) was added **7b** (700 mg, 1.71 mmol) in THF (7 mL). After stirring at 0 °C for 30 min, water (0.07 mL) was added followed by 1 M NaOH (0.07 mL). After stirring at 0 °C for 30 min, water (0.21 mL) was added. After stirring at room temperature for 30 min, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by column chromatography (NH silica gel, eluent: 5/95 to 50/50 AcOEt/hexane) to **8b** (157 mg, 25 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.80–0.93 (3H, m), 1.21–1.40 (4H, m), 1.47–1.63 (2H, m), 2.51–2.59 (2H, m), 4.16 (2H, dd, J = 9.8, 4.1 Hz), 4.52 (2H, d, J = 5.8 Hz), 4.67 (2H, dd, J = 9.8, 6.4 Hz), 5.13–5.26 (2H, m), 6.68 (2H, s), 6.83 (1H, d, J = 7.6 Hz), 7.14 (1H, d, J = 1.5 Hz), 7.17–7.29 (2H, m), 7.36 (1H, d, J = 0.8 Hz). LCMS *m/z* calcd for $C_{22}H_{26}N_2O_3$: 366.19, found 367.0 [M+1].

***N*-(1-(2-(3-(3-pentylphenoxy)azetidin-1-yl)-1,3-benzoxazol-6-yl)ethyl)acetamide (1b):** A mixture of **8b** (158 mg, 0.43 mmol), TPAP (15 mg, 0.04 mmol), NMO (75 mg, 0.64 mmol) and 4Å molecular sieves (200 mg) in DMF (5 mL) was stirred at room temperature for 2 h. The mixture was filtered and concentrated under reduced pressure. The residue was passed through a pad of silica gel (eluent: AcOEt) and concentrated under reduced pressure. To an ice cold stirred solution of the residue in THF (5 mL) was added MeMgBr (1.0 M THF solution,

0.86 mL, 0.86 mmol). After stirring at 0 °C for 1 h, the mixture was extracted with AcOEt and sat. aq. NH_4Cl. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. To an ice cold stirred solution of the residue in CH_3CN (3 mL) was added conc. H_2SO_4 (0.046 mL, 0.86 mmol). After stirring at room temperature for 2 h, the mixture was extracted with AcOEt and 1 M NaOH. 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 75/25 AcOEt/hexane) and crystallized from AcOEt and hexane to afford **1b** (110 mg, 61 %) as a white crystalline solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (3H, t, J = 6.9 Hz), 1.22–1.31 (4H, m), 1.34 (3H, d, J = 7.0 Hz), 1.48–1.64 (2H, m), 1.83 (3H, s), 2.52–2.59 (2H, m), 4.15 (2H, dd, J = 9.4, 4.0 Hz), 4.66 (2H, dd, J = 9.1, 6.5 Hz), 4.85–5.03 (1H, m), 5.11–5.26 (1H, m), 6.63–6.75 (2H, m), 6.78–6.89 (1H, m), 7.13 (1H, d, J = 1.3 Hz), 7.17–7.30 (2H, m), 7.35 (1H, d, J = 1.3 Hz), 8.25 (1H, d, J = 8.1 Hz). ^{13}H NMR (75 MHz, DMSO-d_6) δ 14.39, 22.42, 23.17, 23.32, 30.98, 31.36, 35.54, 48.24, 58.85, 67.32, 107.29, 112.11, 115.21, 116.14, 122.01, 122.38, 129.99, 138.87, 141.89, 144.90, 149.36, 156.70, 163.09, 168.59. LCMS *m/z* calcd for $C_{25}H_{31}N_3O_3$: 421.24, found 422.1 [M+1]. Anal. Calcd for $C_{25}H_{31}N_3O_3 \cdot 0.1H_2O$: C,70.93; H,7.43; N,9.93. Found: C,70.97; H,7.29; N,10.03. Mp 86–88 °C.

***N*-(1-(2-(3-(3-(Butyloxy)phenoxy)azetidin-1-yl)-1,3-benzoxazol-6-yl)ethyl)acetamide (1c)**

Ethyl 2-(3-(3-(benzyloxy)phenoxy)azetidin-1-yl)-1,3-benzoxazole-6-carboxylate (7c): A mixture of 3-(benzyloxy)phenol (**6c**) (9.71 g, 48.5 mmol), **5** (15 g, 44.1 mmol) and Cs_2CO_3 (28.7 g, 88.1 mmol) in DMF (150 mL) was stirred at 100 °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 MgSO4 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 **7c** (15.3 g, 78 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.32 (3H, t, J = 7.1 Hz), 4.18–4.25 (2H, m), 4.30 (2H, q, J = 7.1 Hz), 4.68–4.78 (2H, m), 5.10 (2H, s), 5.15–5.28 (1H, m), 6.44–6.50 (1H, m), 6.50–6.55 (1H, m), 6.64–6.71 (1H, m), 7.23 (1H, t, J = 8.2 Hz), 7.29–7.49 (6H, m), 7.85 (1H, d, J = 8.2 Hz), 7.92 (1H, d, J = 1.2 Hz). LCMS *m/z* calcd for $C_{26}H_{24}N_3O_5$: 444.17, found 445.0 [M+1].

(2-(3-(3-(Benzyloxy)phenoxy)azetidin-1-yl)-1,3-benzoxazol-6-yl)methanol (8c): To an ice cold stirred suspension of $LiAlH_4$ (1.96 g, 51.7 mmol) in THF (100 mL) was added **7c** (15.3 g, 34.5 mmol) in THF (100 mL) dropwise. After stirring at 0 °C for 30 min, water (2 mL) was added

followed by 1 M NaOH (2 mL). Water (6 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. The residue was purified by column chromatography (NH silica gel, eluent: 10/90 to 75/25 AcOEt/hexane) to afford **8c** (4 g, 29 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 4.15 (2H, dd, J = 9.6, 4.1 Hz), 4.52 (2H, d, J = 5.6 Hz), 4.66 (2H, dd, J = 9.3, 6.4 Hz), 5.10 (2H, s), 5.14–5.26 (2H, m), 6.43–6.49 (1H, m), 6.50–6.54 (1H, m), 6.63–6.71 (1H, m), 7.09–7.16 (1H, m), 7.21–7.29 (2H, m), 7.32–7.49 (6H, m). LCMS *m/z* calcd for $C_{24}H_{22}N_2O_4$: 402.16, found 403.0 [M+1].

6-(1-Azidoethyl)-2-(3-(3-(benzyloxy)phenoxy)azetidin-1-yl)-1,3-benzoxazole (9): A mixture of **8c** (4 g, 9.94 mmol), TPAP (0.18 g, 0.5 mmol), NMO (2.329 g, 19.9 mmol) and 4Å molecular sieves (8 g) in CH_3CN (80 mL) was stirred at room temperature for 4 h. The mixture was filtered and concentrated under reduced pressure. The residue was passed through a pad of silica gel (eluent: 1/1 AcOEt/hexane) and concentrated under reduced pressure. To an ice cold stirred solution of the residue in THF (40 mL) was added MeMgBr (1.0 M THF solution, 19.9 ml, 19.9 mmol). After stirring at 0 °C for 30 min, the mixture was extracted with AcOEt and sat. aq. NH_4Cl. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The mixture of the residue, DPPA (4.1 g, 14.9 mmol) and DBU (3 mL,

19.9 mmol) in toluene (40 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 **9** (3 g, 68 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.47 (3H, d, J = 6.8 Hz), 4.17 (2H, dd, J = 9.4, 4.0 Hz), 4.67 (2H, dd, J = 9.2, 6.6 Hz), 4.82–4.94 (1H, m), 5.10 (2H, s), 5.16–5.26 (1H, m), 6.43–6.49 (1H, m), 6.50–6.54 (1H, m), 6.64–6.71 (1H, m), 7.18–7.28 (2H, m), 7.30–7.48 (6H, m), 7.50 (1H, d, J = 1.5 Hz). LCMS *m/z* calcd for $C_{25}H_{23}N_5O_3$: 441.18, found 442.0 [M+1].

1-(2-(3-(3-(Benzyloxy)phenoxy)azetidin-1-yl)-1,3-benzoxazol-6-yl)ethanamine (10): A mixture of **9** (3 g, 6.8 mmol) and Ph_3P (3.56 g, 13.6 mmol) in THF (30 mL) and water (15 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 (NH silica gel, eluent: 10/90 to 100/0 AcOEt/hexane) to afford **10** (2.5 g, 89 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.24 (3H, d, J = 6.5 Hz), 1.77–1.92 (2H, m), 4.09–4.19 (2H, m), 4.58–4.71 (2H, m), 5.10 (2H, s), 5.15–5.26 (1H, m), 6.42–6.49 (1H, m), 6.50–6.55 (1H, m), 6.61–6.71 (1H, m), 7.18–7.28 (2H, m), 7.38–7.49 (5H, m), 7.50–7.67 (3H, m). LCMS *m/z* calcd

for $C_{25}H_{25}N_3O_3$: 415.19, found 416.0 [M+1]

***N*-(1-(2-(3-(3-(Benzyloxy)phenoxy)azetidin-1-yl)-1,3-benzoxazol-6-yl)ethyl)acetamide (11)**: A mixture of **10** (2.5 g, 6 mmol) and Ac_2O (2.84 mL, 30 mmol) in pyridine (15 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: 5/95 to 75/25 AcOEt/hexane) to afford **11** (2.3 g, 84 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.34 (3H, d, J = 7.0 Hz), 1.82 (3H, s), 4.08–4.19 (2H, m), 4.60–4.70 (2H, m), 4.88–5.01 (1H, m), 5.10 (2H, s), 5.16–5.27 (1H, m), 6.42–6.49 (1H, m), 6.50–6.54 (1H, m), 6.63–6.70 (1H, m), 7.07–7.15 (1H, m), 7.23–7.27 (1H, m), 7.38–7.50 (4H, m), 7.52–7.68 (3H, m), 8.25 (1H, d, J = 8.1 Hz). LCMS *m/z* calcd for $C_{27}H_{27}N_3O_4$: 457.20, found 458.0 [M+1].

***N*-(1-(2-(3-(3-Hydroxyphenoxy)azetidin-1-yl)-1,3-benzoxazol-6-yl)ethyl)acetamide (12)**: A mixture of **11** (2.3 g, 5 mmol) and 20% $Pd(OH)_2$ on carbon (50% wet, 0.353 g, 0.5 mmol) in THF (20 mL) and MeOH (20 mL) was stirred at room temperature overnight under H_2 atmosphere. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by column chromatography (NH silica gel, eluent: 10/90 to 100/0

AcOEt/hexane) to afford **12** (1.76 g, 95 %) as a white amorphous solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.34 (3H, d, J = 7.0 Hz), 1.83 (3H, s), 4.14 (2H, dd, J = 9.3, 4.0 Hz), 4.62 (2H, dd, J = 9.2, 6.5 Hz), 4.88–5.00 (1H, m), 5.08–5.21 (1H, m), 6.22–6.33 (2H, m), 6.37–6.47 (1H, m), 7.02–7.16 (2H, m), 7.25 (1H, d, J = 8.1 Hz), 7.36 (1H, d, J = 1.4 Hz), 8.25 (1H, d, J = 8.1 Hz), 9.46–9.59 (1H, m). LCMS *m/z* calcd for $C_{20}H_{21}N_3O_4$: 367.15, found 368.2 [M+1].

***N*-(1-(2-(3-(3-(Butyloxy)phenoxy)azetidin-1-yl)-1,3-benzoxazol-6-yl)ethyl)acetamide** (**1c**): A mixture of **12** (150 mg, 0.41 mmol), 1-bromobutane (0.1 mL, 0.93 mmol) and K_2CO_3 (120 mg, 0.87 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 **1c** (56.5 mg, 33 %) as a white crystalline solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.93 (3H, t, J = 7.3 Hz), 1.34 (3H, d, J = 6.9 Hz), 1.38–1.51 (2H, m), 1.60–1.75 (2H, m), 1.83 (3H, s), 3.95 (2H, t, J = 6.2 Hz), 4.15 (2H, d, J = 5.5 Hz), 4.65 (2H, t, J = 7.8 Hz), 4.89–5.03 (1H, m), 5.21 (1H, br s), 6.36–6.49 (2H, m), 6.58 (1H, d, J = 8.2

Hz), 7.12 (1H, d, *J* = 7.1 Hz), 7.16–7.29 (2H, m), 7.35 (1H, s), 8.26 (1H, d, *J* = 8.2 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.18, 19.23, 23.17, 23.33, 31.20, 48.24, 58.80, 67.45, 67.67, 101.86, 107.06, 107.30, 108.18, 116.15, 122.39, 130.78, 138.87, 141.88, 149.36, 157.87, 160.58, 163.07, 168.59. LCMS *m/z* calcd for $C_{24}H_{29}N_3O_4$: 423.22, found 424.2 [M+1]. Anal. Calcd for $C_{24}H_{29}N_3O_4 \cdot 0.1H_2O$: C,67.78; H,6.92; N,9.88. Found: C,67.67; H,6.74; N,9.92. Mp 116–118 °C.

_N_-(1-(2-(3-(3-(Cyclopropylmethoxy)phenoxy)azetidin-1-yl)-1,3-benzoxazol-6-yl)ethyl)acetamide (1d)

A mixture of **12** (150 mg, 0.41 mmol), (bromomethyl)cyclopropane (0.1 mL, 1.03 mmol) and K_2CO_3 (120 mg, 0.87 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 **1d** (121 mg, 70 %) as a white crystalline solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.25–0.35 (2H, m), 0.50–0.62 (2H, m), 1.14–1.28 (1H, m), 1.34 (3H, d, *J* = 7.0 Hz), 1.83 (3H, s), 3.79 (2H, d, *J* = 7.1 Hz), 4.09–4.19 (2H, m), 4.61–4.71 (2H,

m), 4.87–5.01 (1H, m), 5.15–5.27 (1H, m), 6.38–6.47 (2H, m), 6.53–6.60 (1H, m), 7.09–7.14 (1H, m), 7.16–7.28 (2H, m), 7.33–7.38 (1H, m), 8.26 (1H, d, J = 8.1 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.60, 10.59, 23.18, 23.33, 48.24, 58.50, 67.43, 72.58, 101.86, 107.16, 107.30, 108.10, 116.15, 122.39, 130.77, 138.87, 141.88, 149.36, 157.86, 160.52, 163.06, 168.59. LCMS *m/z* calcd for $C_{24}H_{27}N_3O_4$: 421.20, found 422.1 [M+1]. Anal. Calcd for $C_{24}H_{27}N_3O_4$: C,68.39; H,6.46; N,9.97. Found: C,68.31; H,6.41; N,9.86. Mp 135–136 °C.

***N*-(1-(2-(4-(3-(Cyclopropylmethoxy)phenoxy)piperidin-1-yl)-1,3-benzoxazol-6-yl)ethyl)acetamide (1e)**

***tert*-Butyl 4-(3-(benzyloxy)phenoxy)piperidine-1-carboxylate (14)**: A mixture of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (**13**) (2.21 g, 12 mmol), Ph_3P (3.14 g, 12 mmol), DIAD (1.9 M toluene solution, 5.83 mL, 12 mmol) and **6c** (2 g, 10 mmol) in THF (30 mL) was stirred at room temperature overnight. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 5/95 to 25/75 AcOEt/hexane) to afford **14** (2.98 g, 78 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.40 (9H, s), 1.44–1.55 (2H, m), 1.76–1.94 (2H, m), 3.01–3.26 (2H, m), 3.57–3.75 (2H, m), 4.43–4.62 (1H, m), 5.07 (2H, s), 6.49–6.65 (3H, m), 7.10–7.23 (1H,

m), 7.25–7.49 (5H, m). LCMS *m/z* calcd for $C_{23}H_{29}NO_4$: 383.21, found 284.2 [M+1−Boc].

***tert*-Butyl 4-(3-hydroxyphenoxy)piperidine-1-carboxylate (15)**: A mixture of **14** (3 g, 7.8 mmol) and 10% Pd on carbon (50% wet, 0.83 g, 0.78 mmol) in MeOH (100 mL) was stirred at room temperature for 2 h under H_2 atmosphere. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 10/90 to 50/50 AcOEt/hexane) to afford **15** (1.02 g, 45 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.40 (9H, s), 1.44–1.58 (2H, m), 1.79–1.93 (2H, m), 3.07–3.24 (2H, m), 3.54–3.74 (2H, m), 4.36–4.56 (1H, m), 6.26–6.50 (3H, m), 6.94–7.12 (1H, m), 9.34 (1H, s). LCMS *m/z* calcd for $C_{16}H_{23}NO_4$: 293.16, found 194.2 [M+1−Boc].

***tert*-Butyl 4-(3-(cyclopropylmethoxy)phenoxy)piperidine-1-carboxylate (16)**: A mixture of (bromomethyl)cyclopropane (0.5 mL, 5.1 mmol), **15** (1 g, 3.4 mmol) and K_2CO_3 (0.94 g, 6.82 mmol) in DMF (10 mL) was stirred at 60 °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: 5/95 to 25/75 AcOEt/hexane) to afford **16** (1.08 g, 91 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.22–0.36 (2H, m), 0.50–0.60 (2H, m), 1.18–1.25 (1H, m),

1.40 (9H, s), 1.43–1.59 (2H, m), 1.79–1.94 (2H, m), 3.07–3.26 (2H, m), 3.56–3.71 (2H, m), 3.77 (2H, d, J = 7.2 Hz), 4.40–4.63 (1H, m), 6.39–6.59 (3H, m), 7.04–7.22 (1H, m). LCMS *m/z* calcd for $C_{20}H_{29}NO_4$: 347.21, found 248.2 [M+1−Boc].

4-(3-(Cyclopropylmethoxy)phenoxy)piperidine hydrochloride (**17**): A mixture of **16** (1.08 g, 3.11 mmol) and 4 M HCl–AcOEt (7.77 mL, 31.1 mmol) in AcOEt (8 mL) was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure. The residue was treated with AcOEt, collected by filtration and dried under reduced pressure to afford **17** (0.66 g, 75 %) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.18–0.37 (2H, m), 0.49–0.64 (2H, m), 1.07–1.30 (1H, m), 1.69–1.90 (2H, m), 1.97–2.17 (2H, m), 2.95–3.13 (2H, m), 3.13–3.26 (2H, m), 3.78 (2H, d, J = 7.2 Hz), 4.46–4.69 (1H, m), 6.40–6.64 (3H, m), 7.16 (1H, t, J = 8.5 Hz), 8.75 (2H, br s). LCMS *m/z* calcd for $C_{15}H_{21}NO_2$: 247.16, found 248.2 [M+1].

Ethyl

2-(4-(3-(cyclopropylmethoxy)phenoxy)piperidin-1-yl)-1,3-benzoxazole-6-carboxylate (**18**): A mixture of **17** (755 mg, 2.66 mmol), DIPEA (0.93 mL, 5.32 mmol) and **2** (400 mg, 1.77 mmol) in DMF (4 mL) was stirred at room temperature overnight. 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: 10/90 to 50/50 AcOEt/hexane) to afford **18** (277 mg, 36 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.26–0.35 (2H, m), 0.51–0.62 (2H, m), 1.20–1.26 (1H, m), 1.32 (3H, t, J = 7.2 Hz), 1.62–1.82 (2H, m), 2.00–2.13 (2H, m), 3.54–3.70 (2H, m), 3.78 (2H, d, J = 7.2 Hz), 3.87–3.99 (2H, m), 4.30 (2H, q, J = 7.2 Hz), 4.61–4.76 (1H, m), 6.47–6.62 (3H, m), 7.17 (1H, t, J = 8.1 Hz), 7.33 (1H, d, J = 8.3 Hz), 7.83 (1H, dd, J = 8.3, 1.5 Hz), 7.89 (1H, d, J = 1.5 Hz). LCMS *m/z* calcd for $C_{25}H_{28}N_2O_5$: 436.20, found 437.2 [M+1].

2-(4-(3-(Cyclopropylmethoxy)phenoxy)piperidin-1-yl)-1,3-benzoxazole-6-carbaldehyde (**19**): To ice cold stirred suspension of $LiAlH_4$ (24.1 mg, 0.64 mmol) in THF (3 mL) was added **18** (277 mg, 0.64 mmol) in THF (3 mL). After stirring at 0 °C for 30 min, water (25 µL) was added followed by 1 M NaOH (25 µL). After stirring at 0 °C for 30 min, water (75 µL) was added. After stirring at room temperature for 30 min, the mixture was filtered through a pad of Celite and concentrated under reduced pressure. A mixture of the residue, TPAP (22.5 mg, 0.06 mmol), NMO (112 mg, 0.96 mmol) and 4Å molecular sieves (415 mg) in CH_3CN (3 mL) was stirred at room temperature for 4 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 10/90 to 50/50

AcOEt/hexane) to afford **19** (185 mg, 74 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.25–0.35 (2H, m), 0.50–0.61 (2H, m), 1.20–1.28 (1H, m), 1.65–1.84 (2H, m), 2.01–2.14 (2H, m), 3.57–3.72 (2H, m), 3.78 (2H, d, J = 6.8 Hz), 3.89–4.01 (2H, m), 4.63–4.76 (1H, m), 6.46–6.62 (3H, m), 7.11–7.22 (1H, m), 7.42 (1H, d, J = 8.3 Hz), 7.74–7.81 (1H, m), 7.85 (1H, d, J = 1.1 Hz), 9.91 (1H, s). LCMS *m/z* calcd for $C_{23}H_{24}N_2O_4$: 392.17, found 393.2 [M+1].

6-(1-Azidoethyl)-2-(4-(3-(cyclopropylmethoxy)phenoxy)piperidin-1-yl)-1,3-benzoxazole (**20**): To an ice cold stirred solution of **19** (185 mg, 0.47 mmol) in THF (3 mL) was added MeMgBr (1.0 M THF solution, 0.94 mL, 0.94 mmol). After stirring at 0 °C for 1 h, the mixture was extracted with AcOEt and 1 M HCl. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. A mixture of the residue, DPPA (259 mg, 0.94 mmol) and DBU (0.21 mL, 1.41 mmol) in toluene (3 mL) was stirred at room temperature for 4 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: 10/90 to 50/50 AcOEt/hexane) to afford **20** (125 mg, 61 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.25–0.35 (2H, m), 0.50–0.62 (2H, m), 1.20–1.27 (1H, m),

1.47 (3H, d, J = 6.8 Hz), 1.63–1.80 (2H, m), 2.00–2.12 (2H, m), 3.48–3.63 (2H, m), 3.78 (2H, d, J = 6.8 Hz), 3.84–3.97 (2H, m), 4.61–4.74 (1H, m), 4.87 (1H, q, J = 6.9 Hz), 6.44–6.61 (3H, m), 7.11–7.23 (2H, m), 7.25–7.32 (1H, m), 7.47 (1H, s). LCMS *m/z* calcd for $C_{24}H_{27}N_5O_3$: 433.21, found 434.2 [M+1]

***N*-(1-(2-(4-(3-(Cyclopropylmethoxy)phenoxy)piperidin-1-yl)-1,3-benzoxazol-6-yl)ethyl)acetamide** (**1e**): A mixture of **20** (125 mg, 0.29 mmol) and 10% Pd on carbon (50% wet, 31 mg, 0.03 mmol) in THF (3 mL) was stirred at room temperature for 2 h under H_2 atmosphere. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. The mixture of the residue and Ac_2O (0.27 mL, 2.9 mmol) in pyridine (3 mL) was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 50/50 to 100/0 AcOEt/hexane) and crystallized from AcOEt and hexane to afford **1e** (51.8 mg, 40 %) as a white crystalline solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.24–0.35 (2H, m), 0.49–0.61 (2H, m), 1.17–1.27 (1H, m), 1.34 (3H, d, J = 7.2 Hz), 1.62–1.76 (2H, m), 1.82 (3H, s), 1.96–2.10 (2H, m), 3.45–3.61 (2H, m), 3.78 (2H, d, J = 7.2 Hz), 3.82–3.97 (2H, m), 4.57–4.77 (1H, m), 4.84–5.02 (1H, m), 6.40–6.61 (3H, m), 7.02–7.26 (3H, m), 7.29–7.37 (1H, m), 8.23 (1H, d, J = 8.3 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.57, 10.62, 23.19, 23.33, 43.18, 71.63, 72.48, 103.08, 107.08, 107.45, 108.52,

115.61, 122.29, 130.46, 138.26, 142.21, 148.89, 158.49, 160.47, 162.36, 168.57. LCMS *m/z* calcd for $C_{26}H_{31}N_3O_4$: 449.23, found 450.1 [M+1]. Anal. Calcd for $C_{26}H_{31}N_3O_4$: C,69.47; H,6.95; N,9.35. Found: C,69.29; H,7.02; N,9.25. Mp 139–141 °C.

***N*-(1-(2-(4-(3-(Cyclopropylmethoxy)phenoxy)phenyl)-1,3-benzoxazol-6-yl)ethyl)acetamide (1f)**

Ethyl 4-(3-(cyclopropylmethoxy)phenoxy)benzoate (23f): A mixture of **22** (5 g, 30.4 mmol), ethyl 4-fluorobenzoate (**21f**) (5 g, 29.7 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 **23f** (7.09 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+1].

4-(3-(Cyclopropylmethoxy)phenoxy)benzoic acid (24f): A mixture of **23f** (4.4 g, 14.1 mmol) and 2 M NaOH (20 mL, 40 mmol) in THF (20 mL) and MeOH (20 mL) was stirred at room temperature for 2 h. The mixture was acidified with 2 M HCl and extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure to afford **24f** (3.89 g, 97 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.25–0.36 (2H, m), 0.50–0.62 (2H, m), 1.12–1.27 (1H, m), 3.80 (2H, d, J = 7.0 Hz), 6.60–6.70 (2H, m), 6.75–6.85 (1H, m), 7.03 (2H, d, J = 8.7 Hz), 7.32 (1H, t, J = 8.0 Hz), 7.94 (2H, d, J = 8.8 Hz), 12.86 (1H, br s). LCMS *m/z* calcd for $C_{17}H_{16}O_4$: 284.10, found 285.1 [M+1].

***N*-(4-Acetyl-2-hydroxyphenyl)-4-(3-(cyclopropylmethoxy)phenoxy)benzamide (26f)**: To an ice cold stirred mixture of **24f** (3.89 g, 13.7 mmol) and DMF (0.1 mL, 1.29 mmol) in THF (40 mL) was added $(COCl)_2$ (2 mL, 22.9 mmol) dropwise. The mixture was stirred at room temperature for 1 h and concentrated under reduced pressure. To the residue were added THF (40 mL) followed by 1-(4-amino-3-hydroxyphenyl)ethanone (**25**) (2.5 g, 16.5 mmol) and Et_3N (6 mL, 43.1 mmol). The mixture was stirred at room temperature for 1 h. 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: 0/100 to 20/80 MeOH/AcOEt) to afford **26f** (1.7 g, 30 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.27–0.36 (2H, m), 0.51–0.62 (2H, m), 1.11–1.27 (1H, m), 2.53 (3H, s), 3.81 (2H, d, J = 7.1 Hz), 6.61–6.71 (2H, m), 6.75–6.84 (1H, m), 7.11 (2H, d, J = 8.8 Hz), 7.33 (1H, t, J = 8.1 Hz), 7.47 (1H, d, J = 1.8 Hz), 7.48–7.54 (1H, m), 7.95–8.07 (3H, m), 9.47 (1H, br s), 10.42 (1H, br s). LCMS *m/z* calcd for $C_{25}H_{23}NO_5$: 417.16, found 418.1 [M+1].

1-(2-(4-(3-(Cyclopropylmethoxy)phenoxy)phenyl)-1,3-benzoxazol-6-yl)ethanone (30f): To a stirred mixture of **26f** (1.7 g, 4.07 mmol) and Ph_3P (1.5 g, 5.72 mmol) in THF (15 mL) was added DIAD (1.9 M toluene solution, 3 mL, 5.7 mmol). The mixture was stirred at 60 °C for 1 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was triturated with EtOH to afford **30f** (0.447 g, 27 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.26–0.36 (2H, m), 0.51–0.62 (2H, m), 1.15–1.29 (1H, m), 2.67 (3H, s), 3.82 (2H, d, J = 7.0 Hz), 6.67–6.76 (2H, m), 6.83 (1H, d, J = 8.6 Hz), 7.20 (2H, d, J = 8.8 Hz), 7.36 (1H, t, J = 8.2 Hz), 7.85–7.93 (1H, m), 8.04 (1H, d, J = 8.2 Hz), 8.24 (2H, d, J = 8.9 Hz), 8.37 (1H, s). LCMS *m/z* calcd for $C_{25}H_{21}NO_4$: 399.15, found 400.1 [M+1].

1-(2-(4-(3-(Cyclopropylmethoxy)phenoxy)phenyl)-1,3-benzoxazol-6-yl)ethanamine (31): A mixture of **30f** (447 mg, 1.12 mmol), NH_4OAc (860 mg, 11.2 mmol) and $NaBH_3CN$ (700 mg,

11.1 mmol) in MeOH (20 mL) was stirred at 60 °C overnight. After cooling to room temperature, the mixture was evaporated to remove MeOH. The residue was extracted with AcOEt and sat. aq. $NaHCO_3$. 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 50/50 MeOH/AcOEt) to afford **31** (210 mg, 47 %).

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.25–0.38 (2H, m), 0.47–0.63 (2H, m), 1.18–1.26 (1H, m), 1.31 (3H, d, J = 6.6 Hz), 2.37 (2H, br s), 3.82 (2H, d, J = 7.1 Hz), 4.15 (1H, q, J = 6.4 Hz), 6.65–6.73 (2H, m), 6.78–6.84 (1H, m), 7.14–7.21 (2H, m), 7.34 (1H, t, J = 8.3 Hz), 7.40 (1H, dd, J = 8.3, 1.4 Hz), 7.68 (1H, d, J = 8.2 Hz), 7.77 (1H, d, J = 1.4 Hz), 8.14–8.23 (2H, m). LCMS *m/z* calcd for $C_{25}H_{24}N_2O_3$: 400.18, found 401.2 [M+1].

***N*-(1-(2-(4-(3-(Cyclopropylmethoxy)phenoxy)phenyl)-1,3-benzoxazol-6-yl)ethyl)acetamide (1f)**: A mixture of **31** (209 mg, 0.52 mmol) and Ac_2O (0.25 ml, 2.65 mmol) in pyridine (3 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) and crystallized from AcOEt and hexane to afford **1f** (118 mg, 51 %) as a white crystalline solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.26–0.37 (2H, m), 0.51–0.60 (2H, m), 1.12–1.28 (1H, m),

1.40 (3H, d, *J* = 7.0 Hz), 1.86 (3H, s), 3.82 (2H, d, *J* = 7.0 Hz), 5.04 (1H, quin, *J* = 7.1 Hz), 6.63–6.75 (2H, m), 6.77–6.87 (1H, m), 7.13–7.23 (2H, m), 7.31–7.41 (2H, m), 7.64–7.74 (2H, m), 8.14–8.23 (2H, m), 8.38 (1H, d, *J* = 7.8 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.57, 10.53, 23.17, 23.29, 48.46, 72.76, 106.80, 108.58, 111.46, 112.16, 118.72, 119.61, 121.58, 123.50, 129.81, 131.23, 140.78, 143.44, 150.78, 156.71, 160.55, 160.70, 162.49, 168.78. LCMS *m/z* calcd for $C_{27}H_{26}N_2O_4$: 442.19, found 443.2 [M+1]. Anal. Calcd for $C_{27}H_{26}N_2O_4$: C,73.28; H,5.92; N,6.33. Found: C,72.99; H,5.80; N,6.30. Mp 92–94 °C.

***N*-(1-(2-(5-(3-(Cyclopropylmethoxy)phenoxy)pyridin-2-yl)-1,3-benzoxazol-6-yl)ethyl)acetamide (1g)**

5-(3-(Cyclopropylmethoxy)phenoxy)pyridine-2-carbonitrile (**23g**): A mixture of **22** (12 g, 73.1 mmol), 5-bromopyridine-2-carbonitrile (**21g**) (14.7 g, 80.4 mmol) and Cs_2CO_3 (35.7 g, 110 mmol) in DMF (120 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 (NH silica gel, eluent: 5/95 to 50/50 AcOEt/hexane) to afford **23g** (19 g, 98 %) as a brown oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.25–0.35 (2H, m), 0.52–0.62 (2H, m), 1.19–1.27 (1H, m), 3.82 (2H, d, J = 7.0 Hz), 6.70–6.81 (2H, m), 6.86 (1H, ddd, J = 8.3, 2.4, 0.8 Hz), 7.37 (1H, t, J = 8.2 Hz), 7.49 (1H, dd, J = 8.6, 2.9 Hz), 8.02 (1H, dd, J = 8.7, 0.6 Hz), 8.52 (1H, dd, J = 2.9, 0.5 Hz). LCMS *m/z* calcd for $C_{16}H_{14}N_2O_2$: 266.11, found 267.8 [M+1].

5-(3-(Cyclopropylmethoxy)phenoxy)pyridine-2-carboxylic acid (**24g**): A mixture of **23g** (10 g, 37.6 mmol) and 2 M NaOH (94 mL, 188 mmol) in EtOH (100 mL) was stirred at 80 °C overnight. After cooling to room temperature, the mixture was acidified with 2 M HCl. The precipitated solid was collected by filtration and dried under reduced pressure to afford **24g** (8.58 g, 80 %) as a beige solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.22–0.37 (2H, m), 0.48–0.65 (2H, m), 1.10–1.30 (1H, m), 3.81 (2H, d, J = 7.1 Hz), 6.65–6.78 (2H, m), 6.79–6.87 (1H, m), 7.35 (1H, t, J = 8.2 Hz), 7.44 (1H, dd, J = 8.6, 2.9 Hz), 8.05 (1H, d, J = 8.5 Hz), 8.45 (1H, d, J = 2.5 Hz), 12.70–13.29 (1H, m). LCMS *m/z* calcd for $C_{16}H_{15}NO_4$: 285.10, found 285.9 [M+1].

***N*-(4-Acetyl-2-hydroxyphenyl)-5-(3-(cyclopropylmethoxy)phenoxy)pyridine-2-carboxamide (26g)**: To an ice cold stirred solution of **24g** (6 g, 21 mmol) and DMF (0.08 mL, 1.05 mmol) in THF (50 mL) was added $(COCl)_2$ (3.68 mL, 42.1 mmol). After stirring at room temperature for

1 h, the mixture was concentrated under reduced pressure. To the residue was added THF (50 mL), **25** (3.18 g, 21 mmol) and Et_3N (8.79 mL, 63.1 mmol) were added. The mixture was stirred at room temperature overnight. 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 triturated with EtOH to afford **26g** (7.76 g, 88 %) as a brown solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.26–0.36 (2H, m), 0.50–0.61 (2H, m), 1.16–1.28 (1H, m), 2.51 (3H, s), 3.82 (2H, d, J = 7.0 Hz), 6.70–6.80 (2H, m), 6.81–6.90 (1H, m), 7.36 (1H, t, J = 8.2 Hz), 7.45–7.51 (1H, m), 7.52–7.61 (2H, m), 8.20 (1H, d, J = 9.1 Hz), 8.48–8.56 (2H, m), 10.52 (1H, s), 10.76–10.97 (1H, m). LCMS *m/z* calcd for $C_{24}H_{22}N_2O_5$: 418.15, found 419.0 [M+1].

1-(2-(5-(3-(Cyclopropylmethoxy)phenoxy)pyridin-2-yl)-1,3-benzoxazol-6-yl)ethanone (**30g**): A mixture of **26g** (7.76 g, 18.5 mmol), Ph_3P (6.32 g, 24.1 mmol) and DIAD (1.9 M toluene solution, 11.7 mL, 24.1 mmol) in THF (50 mL) was stirred at 60 °C for 2 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was triturated with EtOH to afford **30g** (3.74 g, 50 %) as a brown solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.27–0.35 (2H, m), 0.52–0.61 (2H, m), 1.19–1.28 (1H, m), 2.69 (3H, s), 3.83 (2H, d, J = 7.0 Hz), 6.74–6.79 (1H, m), 6.81 (1H, t, J = 2.3 Hz), 6.83–6.89 (1H, m), 7.38 (1H, t, J = 8.2 Hz), 7.54–7.58 (1H, m), 7.92–7.98 (1H, m), 8.03–8.10 (1H, m), 8.39 (1H, d,

J = 8.7 Hz), 8.43 (1H, d, J = 1.0 Hz), 8.60 (1H, d, J = 2.5 Hz). LCMS *m/z* calcd for $C_{24}H_{20}N_2O_4$: 400.14, found 401.0 [M+1].

***N*-(1-(2-(5-(3-(Cyclopropylmethoxy)phenoxy)pyridin-2-yl)-1,3-benzoxazol-6-yl)ethyl)acetamide (1g)**: A mixture of **30g** (3.74 g, 9.34 mmol), NH_4OAc (7.2 g, 93.4 mmol) and $NaBH_3CN$ (2.93 g, 46.7 mmol) in MeOH (50 mL) was stirred at 60 °C overnight. After cooling to room temperature, the mixture was evaporated to a half volume. 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 mixture of the residue and Ac_2O (4.41 mL, 46.7 mmol) in pyridine (15 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: 5/95 to 75/25 AcOEt/hexane) and crystallized from AcOEt and hexane to afford **1g** (2.2 g, 53 %) as a white crystalline solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.26–0.35 (2H, m), 0.51–0.61 (2H, m), 1.13–1.29 (1H, m), 1.41 (3H, d, J = 7.0 Hz), 1.86 (3H, s), 3.83 (2H, d, J = 7.0 Hz), 5.06 (1H, quin, J = 7.2 Hz), 6.70–6.81 (2H, m), 6.84 (1H, dt, J = 8.3, 1.2 Hz), 7.32–7.43 (2H, m), 7.56 (1H, dd, J = 8.8, 2.8 Hz), 7.73 (1H, s), 7.77 (1H, d, J = 8.3 Hz), 8.32 (1H, d, J = 9.2 Hz), 8.41 (1H, d, J = 7.9 Hz), 8.56 (1H, d, J = 2.5 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.58, 10.52, 23.16, 23.27, 48.50, 72.84, 106.62,

108.88, 111.89, 111.93, 120.18, 123.79, 125.42, 125.81, 131.39, 140.16, 140.48, 141.19, 144.23, 151.04, 155.89, 156.35, 160.78, 161.54, 168.81. LCMS *m/z* calcd for $C_{26}H_{25}N_3O_4$: 443.18, found 444.0 [M+1]. Anal. Calcd for $C_{26}H_{25}N_3O_4$: C,70.41; H,5.68; N,9.47. Found: C,70.48; H,5.66; N,9.43. Mp 118–120 °C.

***N*-(1-(2-(6-(3-(Cyclopropylmethoxy)phenoxy)pyridin-3-yl)-1,3-benzoxazol-6-yl)ethyl)acetamide (1h)**

***N*-(4-acetyl-2-hydroxyphenyl)-6-chloronicotinamide (28)**: To an ice cold stirred solution of **25** (2.9 g, 19.2 mmol) and Et_3N (4.02 mL, 28.8 mmol) in THF (40 mL) was added 6-chloronicotinoyl chloride (**27**) (3.38 g, 19.2 mmol). After stirring at room temperature overnight, 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 triturated with EtOH. The precipitated solid was collected by filtration and dried under reduced pressure to afford **28** (3.5 g, 63 %) as a brown solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.53 (3H, s), 7.43–7.55 (2H, m), 7.70 (1H, dd, J = 8.4, 0.5 Hz), 7.94 (1H, d, J = 8.2 Hz), 8.35 (1H, dd, J = 8.3, 2.5 Hz), 8.94 (1H, d, J = 2.0 Hz), 9.92–10.33 (2H, m). LCMS *m/z* calcd for $C_{14}H_{11}N_2O_3Cl$: 290.05, found 290.8 [M+1].

1-(2-(6-Chloropyridin-3-yl)-1,3-benzoxazol-6-yl)ethanone (**29**): A mixture of **28** (3.5 g, 12 mmol), Ph_3P (4.74 g, 18.1 mmol) and DIAD (1.9 M toluene solution, 8.8 mL, 18.1 mmol) in THF (40 mL) was stirred at 60 °C for 2 h. After cooling to room temperature, the mixture was evaporated. The residue was triturated with EtOH. The precipitated solid was collected by filtration and dried under reduced pressure to afford **29** (1.68 g, 51 %) as a brown solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.69 (3H, s), 7.78–7.87 (1H, m), 7.99 (1H, s), 8.03–8.13 (1H, m), 8.40–8.45 (1H, m), 8.61 (1H, dd, J = 8.4, 2.5 Hz), 9.14–9.31 (1H, m). LCMS *m/z* calcd for $C_{14}H_9N_2O_2Cl$: 272.04, found 272.8 [M+1].

1-(2-(6-(3-(Cyclopropylmethoxy)phenoxy)pyridin-3-yl)-1,3-benzoxazol-6-yl)ethanone (**30h**): A mixture of **22** (1.21 g, 7.4 mmol), **29** (1.68 g, 6.16 mmol) and Cs_2CO_3 (4.01 g, 12.3 mmol) in DMF (15 mL) was stirred at 100 °C for 2 h. After cooling to room temperature, water was added to the mixture. After stirring at room temperature for 30 min, the precipitated solid was collected by filtration and dried under reduced pressure to afford **30h** (2.11 g, 86 %) as a brown solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.26–0.36 (2H, m), 0.51–0.61 (2H, m), 1.13–1.28 (1H, m), 2.68 (3H, s), 3.83 (2H, d, J = 7.0 Hz), 6.75–6.89 (3H, m), 7.25 (1H, d, J = 9.2 Hz), 7.35 (1H, t, J =

8.2 Hz), 7.89–7.94 (1H, m), 8.05 (1H, dd, *J* = 8.4, 1.6 Hz), 8.40 (1H, d, *J* = 1.2 Hz), 8.59 (1H, dd, *J* = 8.7, 2.5 Hz), 8.99 (1H, d, *J* = 2.0 Hz). LCMS *m/z* calcd for $C_{24}H_{20}N_2O_4$: 400.14, found 401.0 [M+1].

***N*-(1-(2-(6-(3-(cyclopropylmethoxy)phenoxy)pyridin-3-yl)-1,3-benzoxazol-6-yl)ethyl)aceta mide** (**1h**): A mixture of **30h** (2.11 g, 5.27 mmol), NH_4OAc (4.06 g, 52.7 mmol) and $NaBH_3CN$ (0.993 g, 15.8 mmol) in MeOH (20 mL) was stirred at 60 °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 mixture of the residue and Ac_2O (2.49 mL, 26.4 mmol) in pyridine (10 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) and crystallized from AcOEt and hexane to afford **1h** (600 mg, 26 %) as a white crystalline solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.28–0.36 (2H, m), 0.53–0.61 (2H, m), 1.19–1.27 (1H, m), 1.40 (3H, d, *J* = 7.0 Hz), 1.86 (3H, s), 3.82 (2H, d, *J* = 7.0 Hz), 5.01–5.09 (1H, m), 6.74–6.81 (2H, m), 6.82–6.88 (1H, m), 7.22 (1H, d, *J* = 9.2 Hz), 7.31–7.39 (2H, m), 7.69–7.71 (1H, m), 7.74 (1H, d, *J* = 8.3 Hz), 8.39 (1H, d, *J* = 7.6 Hz), 8.54 (1H, dd, *J* = 8.7, 2.5 Hz), 8.94 (1H, d, *J* = 2.4 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.58, 10.55, 23.16, 23.29, 48.46, 72.77, 108.42, 108.65, 112.00,

112.29, 113.85, 118.81, 119.76, 123.69, 130.75, 139.21, 140.49, 143.84, 147.34, 150.73, 154.67, 160.38, 160.79, 165.44, 168.80. LCMS *m/z* calcd for $C_{26}H_{25}N_3O_4$: 443.18, found 444.1 [M+1]. Anal. Calcd for $C_{26}H_{25}N_3O_4 \cdot H_2O$: C,69.01; H,5.79; N,9.29. Found: C,69.55; H,5.70; N,9.17. Mp. 121–122 °C.

***N*-(1-(2-(6-(3-(Cyclopropylmethoxy)phenoxy)pyridin-3-yl)-1,3-benzothiazol-5-yl)ethyl)acetamide (1i)**

Methyl 6-(3-(benzyloxy)phenoxy)nicotinate (33): K_2CO_3 (3.22 g, 23.3mmol) was added to a solution of **6c** (2.45 g, 12.2 mmol) and methyl 6-chloronicotinate (**32**) (2 g, 11.66 mmol) in DMF (50 mL) at room temperature. The mixture was stirred at 100 °C for 5 h. After cooling, the mixture was quenched with water and extracted with AcOEt. The organic layer was separated, washed with water and 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 30/70 AcOEt/hexane) to give **33** (2.78 g, 71 %) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 3.86 (3H, s), 5.10 (2H, s), 6.70–6.81 (1H, m), 6.82–6.99 (2H, m), 7.10 (1H, d, *J* = 8.7 Hz), 7.20–7.59 (6H, m), 8.30 (1H, dd, *J* = 8.7, 2.5 Hz), 8.59–8.80 (1H, m). LCMS *m/z* calcd for $C_{20}H_{17}NO_4$: 335.12, found 335.9 [M+1].

6-(3-(Benzyloxy)phenoxy)nicotinic acid (34): To a solution of **33** (2 g, 6 mmol) in THF (20 mL) and MeOH (20 mL) was added 2 M NaOH solution (5.96 mL, 11.9 mmol) at room temperature. The mixture was stirred at room temperature for 2 h. The mixture was acidified with 2 M HCl. The resultant precipitate solid was collected by filtration, and washed with water to give **34** (1.9 g, 99 %) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 5.10 (2H, s), 6.76 (1H, dd, J = 7.9, 1.8 Hz), 6.82–6.98 (2H, m), 7.08 (1H, d, J = 8.6 Hz), 7.26–7.55 (6H, m), 8.28 (1H, dd, J = 8.6, 2.5 Hz), 8.68 (1H, d, J = 2.1 Hz), 13.21 (1H, br s). LCMS *m/z* calcd for $C_{19}H_{15}NO_4$: 321.1, found 321.9 [M+1].

2-Ethylhexyl 3-((4-acetyl-2-nitrophenyl)sulfanyl)propanoate (36): K_2CO_3 (2.83 g, 20.5 mmol) was added to a solution of 2-ethylhexyl beta-mercaptopropionate (3.1 mL, 13.7 mmol) and 1-(4-fluoro-3-nitrophenyl)ethanone (**35**) (2.5 g, 13.7 mmol) in DMF (30 mL) at room temperature. The mixture was stirred at room temperature for 2 h. The mixture was diluted with water and extracted with AcOEt. The organic layer was separated, washed with water and 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 20/80 AcOEt/hexane) to give **36** (5.2 g, 100 %) as a yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.69–0.91 (6H, m), 1.07–1.36 (8H, m), 1.39–1.67 (1H, m), 2.64 (3H, s), 2.77 (2H, t, J = 6.8 Hz), 3.37 (2H, t, J = 6.8 Hz), 3.97 (2H, d, J = 5.8 Hz), 7.81 (1H, d, J = 8.6 Hz), 8.20 (1H, dd, J = 8.6, 2.0 Hz), 8.64 (1H, d, J = 2.0 Hz). LCMS *m/z* calcd for $C_{19}H_{27}NO_5S$: 381.16, found 404.0 [M+1+Na].

2-Ethylhexyl 3-((4-acetyl-2-(((6-(3-(benzyloxy)phenoxy)pyridin-3-yl)carbonyl)amino)phenyl)sulfanyl)propanoate (**37**): Iron (0.586 g, 10.5 mmol) was added to a solution of **36** (1 g, 2.62 mmol) in EtOH (25 mL) at room temperature. The mixture was stirred at 100 °C. To the solution was added freshly prepared solution of ammonium chloride (1.54 g, 28.8 mmol) in water (25 mL). The mixture was stirred for 30 min under reflux conditions. The mixture was allowed to room temperature and insoluble materials were removed by filtration through a pad of Celite. The filtrate was concentrated under reduced pressure. The residue was suspended in sat. aq. $NaHCO_3$ and extracted with AcOEt. The organic layer was separated, washed with water and sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure to afford the corresponding crude amine. To a mixture of $SOCl_2$ (0.955 mL, 13.1 mmol) and **34** (0.9 g, 2.8 mmol) in THF (10 mL) was added 3 drops of DMF at room temperature. The mixture was stirred at 60 °C for 30 min. After cooling, the mixture was concentrated under reduced pressure. The residue was dissolved

in THF (10 mL). To the solution was added Et_3N (0.73 mL, 5.23 mmol) and the above amine. The mixture was stirred at room temperature for 30 min. The mixture was quenched with sat. aq. $NaHCO_3$ and extracted with AcOEt. The organic layer was separated, washed with water and 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 50/50 AcOEt/hexane) to give **37** (1.42 g, 83 %) as a light brown oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.56–0.94 (6H, m), 1.06–1.30 (8H, m), 1.36–1.64 (1H, m), 2.57 (3H, s), 2.62–2.72 (2H, m), 3.23 (2H, t, J = 6.8 Hz), 3.92 (2H, d, J = 4.9 Hz), 5.11 (2H, s), 6.69–6.81 (1H, m), 6.83–6.89 (1H, m), 6.89–6.98 (1H, m), 7.15 (1H, d, J = 8.9 Hz), 7.25–7.50 (6H, m), 7.58 (1H, d, J = 8.3 Hz), 7.80–7.97 (2H, m), 8.21–8.49 (1H, m), 8.75 (1H, d, J = 2.2 Hz), 10.17 (1H, s). LCMS *m/z* calcd for $C_{38}H_{42}N_2O_6S$: 654.28, found 655.2 [M+1].

1-(2-(6-(3-(Benzyloxy)phenoxy)pyridin-3-yl)-1,3-benzothiazol-5-yl)ethanone (**38**): To a mixture of **37** (1.15 g, 1.76 mmol) in THF (15 mL) was added NaOMe (28% MeOH solution, 0.75 mL, 3.51 mmol) at room temperature. After being stirred at room temperature for 30 min, TFA (2.03 mL, 26.3 mmol) was added to the reaction mixture at 0 °C. Then the mixture was stirred at 60 °C for 20 min. After cooling, The mixture was quenched with sat. aq. $NaHCO_3$ at 0 °C and extracted with AcOEt. The organic layer was separated, washed with water, sat. aq. NaCl, and

passed through a pad of silica gel (eluent: 50/50 AcOEt/hexane). The filtrate was concentrated under reduced pressure and the residue was triturated with IPE/hexane (50/50) (10 mL) to give **38** (0.68g, 86 %) as a pale yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 2.71 (3H, s), 5.12 (2H, s), 6.76–6.85 (1H, m), 6.87–7.00 (2H, m), 7.14–7.26 (1H, m), 7.29–7.56 (6H, m), 8.01 (1H, dd, J = 8.5, 1.7 Hz), 8.31 (1H, d, J = 8.5 Hz), 8.53 (1H, dd, J = 8.7, 2.5 Hz), 8.65 (1H, d, J = 1.2 Hz), 8.80–9.00 (1H, m). LCMS *m/z* calcd for $C_{27}H_{20}N_2O_3S$: 452.53, found 453.0 [M+1].

***N*-(1-(2-(6-(3-(Benzyloxy)phenoxy)pyridin-3-yl)-1,3-benzothiazol-5-yl)ethyl)acetamide** (**39**): To a mixture of NH_4OAc (3.07 g, 39.8 mmol) and **38** (600 mg, 1.33 mmol) in MeOH (10 mL) and THF (10 mL) was added $NaBH_3CN$ (170 mg, 2.71 mmol) at room temperature. The mixture was heated a reflux for 3 h. After cooling, the mixture was quenched with sat. aq. $NaHCO_3$ and extracted with AcOEt. The organic layer was separated, washed with water and sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. To the residue and Et_3N (0.55 mL, 4 mmol) in THF (10 mL) was added Ac_2O (0.25 mL, 2.65 mmol) at room temperature. The mixture was stirred at room temperature for 1 h. The mixture was quenched with sat. aq. $NaHCO_3$ and extracted with AcOEt. The organic layer was separated, washed with water and 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 80/20 AcOEt/hexane) to give **39** (425 mg, 65 %) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.41 (3H, d, J = 7.0 Hz), 1.87 (3H, s), 4.97–5.09 (1H, m), 5.12 (2H, s), 6.73–6.85 (1H, m), 6.86–6.99 (2H, m), 7.20 (1H, d, J = 8.7 Hz), 7.29–7.53 (7H, m), 7.98 (1H, d, J = 1.5 Hz), 8.09 (1H, d, J = 8.3 Hz), 8.33–8.45 (1H, m), 8.49 (1H, dd, J = 8.7, 2.5 Hz), 8.86 (1H, d, J = 2.0 Hz). LCMS *m/z* calcd for $C_{29}H_{25}N_3O_3S$: 495.16, found 496.1 [M+1].

***N*-(1-(2-(6-(3-(Cyclopropylmethoxy)phenoxy)pyridin-3-yl)-1,3-benzothiazol-5-yl)ethyl)acetamide** (**1i**): A mixture of thioanisole (0.24 mL, 2.02 mmol) and **39** (100 mg, 0.2 mmol) in TFA (2 mL, 26 mmol) was stirred 55 °C for 30 min. After cooling, the mixture was concentrated under reduced pressure. The residue was dissolved in DMF (3 mL). To the solution were added K_2CO_3 (167 mg, 1.21 mmol) and (bromomethyl)cyclopropane (0.039 mL, 0.4 mmol). The mixture was stirred at 50 °C overnight. After cooling, the mixture was quenched with sat. aq. $NaHCO_3$ and extracted with AcOEt. The organic layer was separated, washed with water and sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (NH silica gel, AcOEt/hexane = 30/70 to 100/0) and crystallized from AcOEt and hexane to give **1i** (38.4 mg, 41 %) as white crystalline solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.21–0.40 (2H, m), 0.46–0.67 (2H, m), 1.07–1.32 (1H, m),

1.41 (3H, d, *J* = 7.0 Hz), 1.87 (3H, s), 3.82 (2H, d, *J* = 7.0 Hz), 4.87–5.19 (1H, m), 6.70–6.93 (3H, m), 7.19 (1H, d, *J* = 8.6 Hz), 7.34 (1H, t, *J* = 8.1 Hz), 7.42 (1H, dd, *J* = 8.4, 1.6 Hz), 7.98 (1H, s), 8.08 (1H, d, *J* = 8.3 Hz), 8.41 (1H, d, *J* = 8.0 Hz), 8.49 (1H, dd, *J* = 8.7, 2.5 Hz), 8.86 (1H, d, *J* = 2.5 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.58, 10.56, 23.18, 23.22, 48.25, 72.77, 108.35, 111.90, 112.32, 113.78, 120.18, 122.54, 124.73, 125.17, 130.72, 132.92, 139.11, 144.68, 146.91, 154.07, 154.82, 160.36, 164.83, 165.20, 168.81. LCMS *m/z* calcd for $C_{26}H_{25}N_3O_3S$: 459.16, found 460.0 [M+1]. Anal. Calcd for $C_{26}H_{25}N_3O_3S$: C,67.95; H,5.48; N,9.14. Mp. 175-177 °C.

***N*-(1-(2-(4-(3-(Cyclopropylmethoxy)phenoxy)phenyl)-1-benzothiophen-5-yl)ethyl)acetamide (1j)**

1-(4-Bromophenoxy)-3-(cyclopropylmethoxy)benzene (**41**): A mixture of **22** (3 g, 18.3 mmol), 4-bromoiodobenzene (**40**) (5.69 g, 20.1mmol), CuI (0.348 g, 1.83 mmol), dimethylaminoacetic acid hydrochloride (0.765 g, 5.48 mmol), Cs_2CO_3 (8.93 g, 27.4 mmol) and DME (45 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 (eluent: 50/50 AcOEt/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 afford **41** (3.92 g, 67 %) as a colorless oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.26–0.34 (2H, m), 0.51–0.60 (2H, m), 1.11–1.27 (1H, m), 3.79 (2H, d, J = 7.2 Hz), 6.52–6.61 (2H, m), 6.73 (1H, dd, J = 8.1, 2.1 Hz), 6.93–7.01 (2H, m), 7.28 (1H, t, J = 8.1 Hz), 7.51–7.59 (2H, m). LCMS *m/z* calcd for $C_{16}H_{15}O_2Br$: 318.03, found 318.8 [M+1]

***N*-(1-(1-Benzothiophen-5-yl)ethyl)acetamide** (**43**): To a solution of 1-(1-benzothiophen-5-yl)ethanone (**42**) (530 mg, 3.01 mmol) in MeOH (10 mL) was added $NaBH_4$ (114 mg, 3.01 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. The mixture was poured into water and extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. To a solution of the residue in CH_3CN (10 mL) was added dropwise H_2SO_4 (0.299 mL, 5.61 mmol) at room temperature. The mixture was stirred at room temperature for 1.5 h. The mixture was poured into sat. aq. $NaHCO_3$ and extracted with AcOEt. 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: 50/50 to 100/0 AcOEt/hexane) to afford **43** (493 mg, 80 %) as a white powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.39 (3H, d, J = 7.1 Hz), 1.84 (3H, s), 4.95–5.08 (1H, m), 7.32 (1H, dd, J = 8.4, 1.7 Hz), 7.43 (1H, dd, J = 5.4, 0.6 Hz), 7.75 (1H, d, J = 5.4 Hz), 7.77–7.80 (1H, m), 7.93 (1H, d, J = 8.3 Hz), 8.34 (1H, d, J = 7.8 Hz). LCMS *m/z* calcd for $C_{12}H_{13}NOS$: 219.07, found 220.1 [M+1].

***N*-(1-(2-(4-(3-(Cyclopropylmethoxy)phenoxy)phenyl)-1-benzothiophen-5-yl)ethyl)acetamide** (**1j**): A mixture of **43** (200 mg, 0.91 mmol), **41** (582 mg, 1.82 mmol), $Pd(OAc)_2$ (102 mg, 0.46 mmol), Tri(*tert*-butyl)phosphoniumtetrafluoroborate (265 mg, 0.91 mmol), *tert*-BuOLi (365 mg, 4.56 mmol) and DMA (10 mL) was stirred at 120 °C overnight under N_2 atmosphere. The reaction mixture was diluted with water and AcOEt. The insoluble material was removed by filtration through a pad of Celite. The filtrate was extracted with AcOEt. The organic layer was washed with water and sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 50/50 to 100/0 AcOEt/hexane), by column chromatography (NH silica gel, eluent: 50/50 to 100/0 AcOEt/hexane) and by preparative HPLC (eluted with aqueous acetonitrile containing 0.1% TFA). The resulting product was partitioned between AcOEt and sat. aq. $NaHCO_3$ The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was crystallized from IPE to give **1j** (36 mg, 8.6 %) as a colorless powder.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.27–0.35 (2H, m), 0.51–0.60 (2H, m), 1.12–1.28 (1H, m), 1.40 (3H, d, J = 7.0 Hz), 1.85 (3H, s), 3.80 (2H, d, J = 7.0 Hz), 4.94–5.07 (1H, m), 6.58–6.66 (2H, m), 6.75 (1H, ddd, J = 8.3, 2.2, 0.8 Hz), 7.07–7.14 (2H, m), 7.26–7.34 (2H, m), 7.70–7.75 (1H, m), 7.75–7.82 (3H, m), 7.89 (1H, d, J = 8.3 Hz), 8.36 (1H, d, J = 7.9 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.57, 10.54, 23.10, 23.19, 48.29, 72.70, 105.97, 110.62, 111.28, 119.56, 119.97, 121.13, 122.70, 123.68, 128.24, 129.30, 131.06, 137.23, 141.07, 142.28, 143.45, 157.42, 157.75, 160.60, 168.69. LCMS *m/z* calcd for $C_{28}H_{27}NO_3S$: 457.17, found 458.0 [M+1]. Anal. Calcd for $C_{28}H_{27}NO_3S$: C,73.49; H,5.95; N,3.06. Found: C,73.45; H,5.96; N,3.06. Mp. 115–117 °C.

_N_-(1-(3-((4-(3-(Cyclopropylmethoxy)phenoxy)benzyl)oxy)phenyl)ethyl)acetamide (1k)

(4-(3-(Cyclopropylmethoxy)phenoxy)phenyl)methanol (44): To an ice cold mixture of $LiAlH_4$ (0.13 g, 3.43 mmol) in THF (10 mL) was added **23f** (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 M 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 **44** (0.85 g, 98 %) as a colorless oil.

^{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+1−OH].

1-(3-((4-(3-(Cyclopropylmethoxy)phenoxy)benzyl)oxy)phenyl)ethanone (46): To a stirred mixture of **44** (0.86 g, 3.18 mmol), 1-(3-hydroxyphenyl)ethanone (**45**) (0.5 g, 3.67 mmol) and Ph_3P (1 g, 3.81 mmol) in THF (10 mL) was added DIAD (1.9 M toluene solution, 2 mL, 3.8 mmol) dropwise. After stirring at room temperature for 4 h, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (NH silica gel, eluent: 10/90 to 50/50 AcOEt/hexane) to afford **46** (1.2 g, 97 %) as a colorless oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.30 (2H, d, *J* = 4.9 Hz), 0.48–0.63 (2H, m), 1.24–1.29 (1H, m), 2.57 (3H, s), 3.78 (2H, d, *J* = 7.0 Hz), 5.15 (2H, s), 6.50–6.60 (2H, m), 6.67–6.76 (1H, m), 7.04 (2H, d, *J* = 8.5 Hz), 7.19–7.33 (2H, m), 7.38–7.66 (5H, m). LCMS *m/z* calcd for $C_{25}H_{24}O_4$: 388.17, found 389.2 [M+1].

1-(3-((4-(3-(Cyclopropylmethoxy)phenoxy)benzyl)oxy)phenyl)ethanol (47): To an ice cold stirred mixture of **46** (1.2 g, 3.09 mmol) in THF (5 mL) and EtOH (5 mL) was added $NaBH_4$ (0.12 g, 3.17 mmol) portionwise. After stirring at 0 °C for 30 min, the mixture was extracted with

AcOEt and 1 M HCl. 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 **47** (1.2 g, 99 %) as a colorless oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.23–0.37 (2H, m), 0.47–0.63 (2H, m), 1.02–1.14 (1H, m), 1.30 (3H, d, J = 6.4 Hz), 3.78 (2H, d, J = 7.0 Hz), 4.78 (1H, td, J = 13.1, 6.4 Hz), 5.05 (2H, s), 5.12 (1H, d, J = 4.3 Hz), 6.48–6.57 (2H, m), 6.65–6.76 (1H, m), 6.81–6.96 (2H, m), 6.97–7.08 (3H, m), 7.17–7.30 (2H, m), 7.47 (2H, d, J = 8.6 Hz). LCMS *m/z* calcd for $C_{25}H_{26}O_4$: 390.18, found 373.2 [M+1−OH].

1-(1-Azidoethyl)-3-((4-(3-(cyclopropylmethoxy)phenoxy)benzyl)oxy)benzene (48): A mixture of **47** (1.2 g, 3.07 mmol), DPPA (1 mL, 4.65 mmol) and DBU (1 mL, 6.63 mmol) in toluene (10 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 **48** (0.21 g, 16 %) as a colorless oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.23–0.37 (2H, m), 0.47–0.61 (2H, m), 1.18–1.28 (1H, m), 3.78 (2H, d, J = 7.0 Hz), 4.80 (1H, q, J = 6.7 Hz), 5.09 (2H, s), 6.47–6.59 (2H, m), 6.66–6.77 (1H, m), 6.90–7.09 (5H, m), 7.21–7.38 (2H, m), 7.48 (2H, d, J = 8.6 Hz). LCMS *m/z* calcd for

$C_{25}H_{25}N_3O_3$: 415.19, found 388.2 [M+1−N_2].

1-(3-((4-(3-(Cyclopropylmethoxy)phenoxy)benzyl)oxy)phenyl)ethanamine (49): A mixture of **48** (0.21 g, 0.51 mmol) and Ph_3P (0.25 g, 0.95 mmol) in THF (4 mL) and water (2 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 50/50 MeOH/AcOEt) to afford **49** (0.16 g, 81 %) as a colorless oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.26–0.35 (2H, m), 0.50–0.60 (2H, m), 1.14–1.20 (1H, m), 1.24 (3H, d, J = 6.6 Hz), 2.79 (2H, br s), 3.78 (2H, d, J = 7.0 Hz), 3.97 (1H, q, J = 6.6 Hz), 5.05 (2H, s), 6.49–6.58 (2H, m), 6.66–6.75 (1H, m), 6.84 (1H, dd, J = 7.8, 2.1 Hz), 6.94 (1H, d, J = 7.6 Hz), 7.00–7.08 (3H, m), 7.24 (2H, dt, J = 14.4, 8.0 Hz), 7.47 (2H, d, J = 8.6 Hz). LCMS *m/z* calcd for $C_{25}H_{27}NO_3$: 389.20, found 390.2 [M+1].

***N*-(1-(3-((4-(3-(Cyclopropylmethoxy)phenoxy)benzyl)oxy)phenyl)ethyl)acetamide (1k):** A mixture of **49** (160 mg, 0.41 mmol) and Ac_2O (0.2 mL, 2.12 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 100/0

AcOEt/hexane) to afford **1k** (160 mg, 90 %) as a colorless oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.25–0.34 (2H, m), 0.51–0.60 (2H, m), 1.17–1.23 (1H, m), 1.31 (3H, d, J = 7.0 Hz), 1.83 (3H, s), 3.79 (2H, d, J = 7.0 Hz), 4.87 (1H, quin, J = 7.3 Hz), 5.05 (2H, s), 6.50–6.59 (2H, m), 6.71 (1H, ddd, J = 8.3, 2.2, 1.0 Hz), 6.83–6.91 (2H, m), 6.94 (1H, d, J = 1.9 Hz), 6.99–7.07 (2H, m), 7.24 (2H, dt, J = 10.5, 8.1 Hz), 7.47 (2H, d, J = 8.6 Hz), 8.24 (1H, d, J = 8.2 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.55, 10.54, 23.08, 23.16, 48.16, 69.16, 72.65, 105.65, 110.19, 112.97, 113.18, 118.91, 119.10, 129.75, 130.21, 130.96, 132.66, 147.05, 156.65, 158.21, 158.85, 160.55, 168.65. LCMS *m/z* calcd for $C_{27}H_{29}NO_4$: 431.21, found 432.2 [M+1].

***N*-(4-(2-(4-(3-(Cyclopropylmethoxy)phenoxy)phenyl)-1,3-oxazol-5-yl)butan-2-yl)acetamide (1l)**

3-(2-(4-(3-(Cyclopropylmethoxy)phenoxy)phenyl)-1,3-oxazol-5-yl)-*N*-methoxy-*N*-methylpropanamide (51): To a stirred suspension of methyl 5-amino-4-oxopentanoate hydrochloride (**50**) (11.9 g) and **24f** (18.5 g, 65.1 mmol) in THF (300 mL) was added DIPEA (30.4 g, 264 mmol), followed by addition of 2-chloro-1-methylpyridinium iodide (31.7 g, 132 mmol) at 12 °C. After addition, the mixture was stirred at 12 °C for 2 h. The mixture was partitioned between water and AcOEt. The organic layer was separated and the aqueous layer

was extracted with AcOEt. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. To a stirred solution of I_2 (32 g, 126 mmol) in CH_2Cl_2 (300 mL) was added Ph_3P (36 g, 137.4 mmol) at 12 °C. The solution was stirred at 12 °C for 10 min. Then Et_3N (28 g, 277 mmol) was added at 12 °C. To the mixture was added dropwise a solution of the above residue in CH_2Cl_2 (100 mL). After addition, the mixture was stirred at 12 °C for 1 h. The mixture was poured into ice water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 3/97 to 17/83 AcOEt/petroleum ether) to give crude product (2 g). The mixture of impure residue (2 g) and 1 M NaOH (20 mL, 20 mmol) in THF (10 mL) and MeOH (10 mL) was stirred at room temperature overnight. The mixture was acidified with 1 M HCl and extracted with AcOEt. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The mixture of the residue, *N*,*O*-dimethylhydroxylamine hydrochloride (0.72 g, 7.38 mmol), EDC·HCl (1.42 g, 7.38 mmol), HOBt·H_2O (1.13 g, 7.38 mmol) and Et_3N (1.03 mL, 7.38 mmol) in DMF (10 mL) was stirred at room temperature overnight. 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 50/50

AcOEt/hexane) to afford **51** (0.784 g, 50 %) as a pale yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.26–0.34 (2H, m), 0.51–0.61 (2H, m), 1.18–1.25 (1H, m), 2.76–2.84 (2H, m), 2.92–3.01 (2H, m), 3.11 (3H, s), 3.67 (3H, s), 3.80 (2H, d, J = 7.0 Hz), 6.58–6.67 (2H, m), 6.73–6.81 (1H, m), 6.98 (1H, s), 7.10 (2H, d, J = 8.9 Hz), 7.31 (1H, t, J = 8.3 Hz), 7.93 (2H, d, J = 8.9 Hz). LCMS *m/z* calcd for $C_{24}H_{26}N_2O_5$: 422.18, found 423.1 [M+1].

4-(2-(4-(3-(Cyclopropylmethoxy)phenoxy)phenyl)-1,3-oxazol-5-yl)butan-2-yl methanesulfonate (52): To an ice cold stirred mixture of **52** (784 mg, 1.86 mmol) in THF (10 mL) was added MeMgBr (1.0 M THF solution, 3.71 mL, 3.71 mmol). After stirring at 0 °C for 1 h, the mixture was extracted with AcOEt and sat. aq. NH_4Cl. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. To the residue in EtOH (10 mL) was added $NaBH_4$ (0.141 g, 3.72 mmol) at 0 °C. After stirring at 0 °C for 30 min, the mixture was extracted with AcOEt and 1 M HCl. The organic layer was washed with sat. aq. NaCl e, dried over $MgSO_4$ and concentrated under reduced pressure. The mixture of the residue, MsCl (0.432 mL, 5.58 mmol) and Et_3N (0.778 mL, 5.58 mmol) in THF (10 mL) was stirred at room temperature for 1 h. 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 75/25 AcOEt/hexane)

to afford **52** (686 mg, 81 %) as a colorless oil.

^{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), 1.40 (3H, d, J = 6.2 Hz), 1.99–2.06 (2H, m), 2.76–2.91 (2H, m), 3.31 (3H, s), 3.80 (2H, d, J = 7.1 Hz), 4.75–4.89 (1H, m), 6.59–6.66 (2H, m), 6.73–6.80 (1H, m), 7.03 (1H, s), 7.10 (2H, d, J = 8.9 Hz), 7.28 (1H, s), 7.92–7.97 (2H, m). LCMS *m/z* calcd for $C_{24}H_{27}NO_6S$: 457.16, found 458.0 [M+1].

5-(3-Azidobutyl)-2-(4-(3-(cyclopropylmethoxy)phenoxy)phenyl)-1,3-oxazole (53): A mixture of **52** (686 mg, 1.5 mmol) and NaN_3 (195 mg, 3 mmol) in DMF (10 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 (silica gel, eluent: 5/95 to 25/75 AcOEt/hexane) to afford **53** (450 mg, 74 %) as a colorless oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.26–0.34 (2H, m), 0.50–0.59 (2H, m), 1.20–1.24 (1H, m), 1.27 (3H, d, J = 6.5 Hz), 1.70–1.91 (2H, m), 2.76–2.85 (2H, m), 3.59–3.74 (1H, m), 3.80 (2H, d, J = 7.0 Hz), 6.58–6.67 (2H, m), 6.73–6.80 (1H, m), 7.03 (1H, s), 7.10 (2H, d, J = 8.9 Hz), 7.31 (1H, t, J = 8.3 Hz), 7.93 (2H, d, J = 8.9 Hz). LCMS *m/z* calcd for $C_{23}H_{24}N_4O_3$: 404.18, found 405.1 [M+1].

4-(2-(4-(3-(Cyclopropylmethoxy)phenoxy)phenyl)-1,3-oxazol-5-yl)butan-2-amine (54): A mixture of **53** (450 mg, 1.11 mmol) and Ph_3P (584 mg, 2.23 mmol) in THF (8 mL) and water (4 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 (NH silica gel, eluent: 10/90 to 100/0 AcOEt/hexane) to afford **54** (346 mg, 82 %) as a pale yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.26–0.34 (2H, m), 0.50–0.60 (2H, m), 1.01 (3H, d, J = 6.3 Hz), 1.11–1.27 (1H, m), 1.42–1.71 (4H, m), 2.65–2.86 (3H, m), 3.80 (2H, d, J = 7.0 Hz), 6.59–6.67 (2H, m), 6.73–6.80 (1H, m), 6.97 (1H, s), 7.10 (2H, d, J = 4.8 Hz), 7.31 (1H, t, J = 8.3 Hz), 7.92 (2H, d, J = 4.7 Hz). LCMS *m/z* calcd for $C_{23}H_{26}N_2O_3$: 378.19, found 379.1 [M+1].

***N*-(4-(2-(4-(3-(Cyclopropylmethoxy)phenoxy)phenyl)-1,3-oxazol-5-yl)butan-2-yl)acetamide (1l)**: A mixture of **54** (346 mg, 0.91 mmol) and Ac_2O (0.431 mL, 4.57 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: 5/95 to 75/25 AcOEt/hexane) and crystallized from AcOEt and hexane to afford **1l** (204 mg, 53 %) as a white crystalline solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.26–0.35 (2H, m), 0.50–0.60 (2H, m), 1.07 (3H, d, J = 6.6 Hz), 1.13–1.26 (1H, m), 1.67–1.77 (2H, m), 1.79 (3H, s), 2.64–2.76 (2H, m), 3.75–3.88 (3H, m, J = 7.0 Hz), 6.59–6.67 (2H, m), 6.72–6.81 (1H, m), 6.98 (1H, s), 7.10 (2H, d, J = 8.8 Hz), 7.25–7.36 (1H, m), 7.74 (1H, d, J = 8.3 Hz), 7.92 (2H, d, J = 8.8 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.56, 10.53, 21.08, 22.44, 23.24, 34.33, 44.11, 72.71, 106.35, 111.02, 111.70, 118.95, 122.78, 124.10, 128.03, 131.13, 153.00, 157.22, 158.88, 159.74, 160.63, 168.91. LCMS *m/z* calcd for $C_{25}H_{28}N_2O_4$: 420.20, found 421.0 [M+1]. Anal. Calcd for $C_{25}H_{28}N_2O_4$: C,71.41; H,6.71; N,6.66. Found: C,71.37; H,6.67; N,6.68. Mp. 79–81 °C.

_N_-((2_S_)-1-((2-(4-(3-(cyclopropylmethoxy)phenoxy)phenyl)-1,3-oxazol-5-yl)oxy)propan-2-yl)acetamide (1m)

(2*S*)-2-((*tert*-Butoxycarbonyl)amino)propyl *N*-((benzyloxy)carbonyl)glycinate (57): A mixture of *N*-((benzyloxy)carbonyl)glycine (**55**) (7.16 g, 34.2 mmol), *tert*-butyl ((2*S*)-1-hydroxypropan-2-yl)carbamate (**56**) (5 g, 28.5 mmol), EDC·HCl (8.21 g, 42.8 mmol) and DMAP (0.349 g, 2.85 mmol) in DMF (70 mL) was stirred at room temperature overnight. 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 50/50 AcOEt/hexane) to afford **57** (10.5 g, 100 %) as a pale yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.01 (3H, d, J = 6.7 Hz), 1.38 (9H, s), 3.62–3.74 (1H, m), 3.77 (2H, d, J = 6.0 Hz), 3.85–3.99 (2H, m), 5.04 (2H, s), 6.80 (1H, d, J = 5.6 Hz), 7.23–7.43 (5H, m), 7.68 (1H, t, J = 6.0 Hz). LCMS *m/z* calcd for $C_{18}H_{26}N_2O_6$: 366.18, found 266.9 [M+1−Boc].

(2*S*)-2-((tert-Butoxycarbonyl)amino)propyl *N*-(4-(3-(cyclopropylmethoxy)phenoxy)benzoyl)glycinate (58): A mixture of **57** (10.5 g, 28.5 mmol) and 10% Pd on carbon (50% wet, 1.52 g, 1.43 mmol) in THF (200 mL) was stirred at room temperature for 4 h under H_2 atmosphere. The mixture was filtered through a pad of Celite and concentrated under reduced pressure to afford corresponding amine. To an ice cold stirred mixture of **24f** (9.73 g, 34.2 mmol) and DMF (0.221 mL, 2.85 mmol) in THF (100 mL) was added $(COCl)_2$ (4.99 mL, 57.1 mmol) dropwise. The mixture was stirred at room temperature for 1 h and concentrated under reduced pressure. The residue was dissolved in THF (100 mL) and the above amine followed by Et_3N (7.95 mL, 57.1 mmol) were added to the mixture. The reaction mixture was stirred at room temperature overnight. 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 50/50 AcOEt/hexane) to afford **58** (14.6 g, 103 %) as a pale yellow oil, with concomitant AcOEt.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.25–0.34 (2H, m), 0.51–0.60 (2H, m), 1.02 (3H, d, J = 6.8 Hz), 1.19–1.27 (1H, m), 1.38 (9H, s), 3.65–3.76 (1H, m), 3.80 (2H, d, J = 7.0 Hz), 3.86–4.03 (4H, m), 6.58–6.67 (2H, m), 6.73–6.84 (2H, m), 7.05 (2H, d, J = 8.8 Hz), 7.31 (1H, t, J = 8.2 Hz), 7.89 (2H, d, J = 8.9 Hz), 8.87 (1H, t, J = 5.9 Hz). LCMS *m/z* calcd for $C_{27}H_{34}N_2O_7$: 498.24, found 399.0 [M+1−Boc].

***tert*-Butyl ((2*S*)-1-((2-(4-(3-(cyclopropylmethoxy)phenoxy)phenyl)-1,3-oxazol-5-yl)oxy)propan-2-yl)carbamate (59)**: To an ice cold stirred mixture of Ph_3P (15.4 g, 58.6 mmol) in CH_3CN (100 mL) was added I_2 (14.9 g, 58.6 mmol) followed by Et_3N (16.3 mL, 117 mmol) dropwise. After stirring at 0 °C for 10 min, **58** (14.6 g, 29.3 mmol) in CH_3CN (50 mL) was added. The reaction mixture was stirred at room temperature overnight and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 5/95 to 50/50 AcOEt/hexane) to afford **59** (10.4 g, 74 %) as a pale yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.26–0.34 (2H, m), 0.51–0.60 (2H, m), 1.11 (3H, d, J = 6.8 Hz), 1.19–1.26 (1H, m), 1.38 (9H, s), 3.80 (2H, d, J = 7.0 Hz), 3.83–3.92 (1H, m), 3.98–4.02 (2H,

m), 6.44 (1H, s), 6.58–6.65 (2H, m), 6.72–6.80 (1H, m), 6.98 (1H, d, *J* = 8.0 Hz), 7.08 (2H, d, *J* = 8.9 Hz), 7.30 (1H, t, *J* = 8.3 Hz), 7.83 (2H, d, *J* = 9.0 Hz). LCMS *m/z* calcd for $C_{27}H_{32}N_2O_6$: 480.23, found 481.1 [M+1].

***N*-((2*S*)-1-((2-(4-(3-(cyclopropylmethoxy)phenoxy)phenyl)-1,3-oxazol-5-yl)oxy)propan-2-yl)acetamide (1m)**: A mixture of **59** (10.4 g, 21.6 mmol) and TFA (16.7 mL, 216 mmol) in toluene (50 mL) was stirred at room temperature for 30 min. The mixture was concentrated under reduced pressure. To the residue was added toluene and the solvent evaporated under reduce pressure (repeated twice). The residue was dissolved in pyridine (50 mL) and Ac_2O (6.13 mL, 64.9 mmol) was added. After stirring at room temperature for 30 min, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (NH silica gel, eluent: 5/95 to 75/25 AcOEt/hexane) and crystallized from AcOEt and hexane to afford **1m** (3.72 g, 41 %) as a white crystalline solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.25–0.35 (2H, m), 0.50–0.59 (2H, m), 1.15 (3H, d, *J* = 6.7 Hz), 1.17–1.27 (1H, m), 1.81 (3H, s), 3.80 (2H, d, *J* = 7.0 Hz), 3.98–4.06 (2H, m), 4.07–4.22 (1H, m), 6.45 (1H, s), 6.57–6.67 (2H, m), 6.73–6.80 (1H, m), 7.08 (2H, d, *J* = 8.8 Hz), 7.31 (1H, t, *J* = 8.2 Hz), 7.83 (2H, d, *J* = 8.9 Hz), 7.99 (1H, d, *J* = 7.6 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.56, 10.53, 17.21, 23.13, 44.00, 72.71, 74.64, 100.95, 106.37, 110.98, 111.71, 118.96, 122.59, 127.31,

131.21, 151.50, 157.24, 158.59, 160.02, 160.63, 169.36. LCMS *m/z* calcd for $C_{24}H_{26}N_2O_5$: 422.18, found 423.0 [M+1]. Anal. Calcd for $C_{24}H_{26}N_2O_5$: C,68.23; H,6.20; N,6.63. Found: C,68.16; H,6.17; N,6.66. Mp. 94–95 °C. $[\alpha]^{25}_D$ −48.9° (c 0.988, MeOH).

***N*-((2*S*)-1-((2-(5-(3-(Cyclopropylmethoxy)phenoxy)pyridin-2-yl)-1,3-oxazol-5-yl)oxy)propan-2-yl)acetamide (1o)**

(2*S*)-2-((*tert*-Butoxycarbonyl)amino)propyl *N*-((5-bromopyridin-2-yl)carbonyl)glycinate (61o): A mixture of **57** (7.16 g, 19.5 mmol) and 10% Pd on carbon (50% wet, 1 g, 0.94 mmol) in THF (100 mL) was stirred at room temperature for 2 h under H_2 atmosphere. The mixture was filtered through a pad of Celite and concentrated under reduced pressure to afford the corresponding amine. To an ice cold stirred mixture of 5-bromopicolinic acid (**60**) (4 g, 19.8 mmol) and DMF (0.15 mL, 1.94 mmol) in THF (50 mL) was added $(COCl)_2$ (3 mL, 34.3 mmol) dropwise. After stirring at room temperature for 1 h, the mixture was concentrated under reduced pressure to the corresponding acid chloride. To the above amine was added a mixture of the acid chloride in THF (50 mL) followed by Et_3N (6 mL, 43.1 mmol). The mixture was stirred at room temperature for 1 h. 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 triturated with EtOH to afford **61o** (6.56 g, 81 %) as a pale yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.02 (3H, d, J = 6.7 Hz), 1.38 (9H, s), 3.71 (1H, br s), 3.86–3.99 (2H, m), 4.05 (2H, d, J = 5.9 Hz), 6.81 (1H, d, J = 7.7 Hz), 7.97 (1H, d, J = 8.3 Hz), 8.28 (1H, d, J = 8.4 Hz), 8.82 (1H, s), 9.13 (1H, br s). LCMS *m/z* calcd for $C_{16}H_{22}N_3O_5Br$: 415.07, found 316.0 [M+1−Boc].

***tert*-Butyl ((2*S*)-1-((2-(5-bromopyridin-2-yl)-1,3-oxazol-5-yl)oxy)propan-2-yl)carbamate (62o)**: To a solution of I_2 (5.12 g, 20.2 mmol) and Ph_3P (5.29 g, 20.2 mmol) in CH_2Cl_2 (150 mL) was added Et_3N (4.08 g, 40.4 mmol) at 10–15 °C under N_2 atmosphere and stirred at this temperature for 30 min. And then a solution of **61o** (4.2 g, 10.1 mmol) in CH_2Cl_2 (150 mL) was added into the above solution. The reaction mixture was stirred at 10–15 °C for 16 h. The reaction mixture was diluted with CH_2Cl_2, washed with sat. aq. $NaHCO_3$, sat. aq. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 30/70 AcOEt/petroleum ether) and then, was further purified by prep-HPLC (0.1% TFA as additive) to afford **62o** (800 mg, 20%) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.12 (3H, d, J = 6.8 Hz), 1.37 (9H, s), 3.85–3.95 (1H, m), 4.05 (2H, d, J = 5.6 Hz), 6.61 (1H, s), 7.01 (1H, d, J = 8.0 Hz), 7.90 (1H, d, J = 8.4 Hz), 8.18

(1H, dd, *J* = 8.4, 2.4 Hz), 8.76 (1H, d, *J* = 2.0 Hz). LCMS *m/z* calcd for $C_{16}H_{20}N_3O_4Br$: 399.06, found 400.0 [M+1].

***N*-((2*S*)-1-((2-(5-(3-(Cyclopropylmethoxy)phenoxy)pyridin-2-yl)-1,3-oxazol-5-yl)oxy)propan-2-yl)acetamide (1o)**: A mixture of **62o** (374 mg, 0.939 mmol), **22** (170 mg, 1.03 mmol), K_3PO_4 (399 mg, 1.88 mmol), CuI (17.89 mg, 0.093 mmol) and picolinic acid (23 mg, 0.19 mmol) in DMSO (5 mL) was stirred at 80–90 °C under N_2 atmosphere for 16 h. The mixture was cooled to 10–15 °C, quenched with water and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent: 33/67 AcOEt/petroleum ether). A mixture of the residue in formic acid (5 mL) was stirred at 10–15 °C under N_2 atmosphere for 5 h. Most of the formic acid was removed by N_2 gas and the remaining residue was dissolved in water (10 mL) and dried by lyophilization. To a solution of the crude solid in pyridine (5 mL) was added Ac_2O (52 mg, 0.51 mmol) at 0 °C dropwise and the resulting mixture was stirred at 15–20 °C for 16 h. The solution was concentrated under reduced pressure. The residue was purified by prep-HPLC (neutral condition), dried by lyophilization to give **1o** (38 mg, 10 %) as an off-white amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.30–0.40 (2H, m), 0.60–0.70 (2H, m), 1.20–1.30 (1H, m),

1.33 (3H, d, *J* = 6.8 Hz), 2.00 (3H, s), 3.78 (1H, d, *J* = 6.8 Hz), 4.12 (1H, dd, *J* = 9.2, 3.2 Hz), 4.18 (1H, dd, *J* = 9.2, 3.6 Hz), 4.35–4.45 (1H, m), 5.73 (1H, d, *J* = 8.0 Hz), 6.29 (1H, s), 6.60–6.65 (2H, m), 6.70–6.75 (1H, m), 7.25–7.29 (2H, m), 7.35 (1H, dd, *J* = 8.8, 2.8 Hz), 7.96 (1H, d, *J* = 8.8 Hz), 8.44 (1H, d, *J* = 2.4 Hz). LCMS *m/z* calcd for $C_{23}H_{25}N_3O_5$: 423.18, found 424.1 [M+1].

_N_-((2_S_)-1-((2-(6-(3-(cyclopropylmethoxy)phenoxy)pyridin-3-yl)-1,3-oxazol-5-yl)oxy)propan-2-yl)acetamide (1p)

(2*S*)-2-((*tert*-Butoxycarbonyl)amino)propyl *N*-((6-chloropyridin-3-yl)carbonyl)glycinate (61p): A mixture of **57** (7.01 g, 19.1 mmol) and 10% Pd on carbon (50% wet, 1 g, 0.94 mmol) in THF (100 mL) was stirred at room temperature for 2 h under H_2 atmosphere. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. To the residue was added THF (50 mL) followed by **27** (3.4 g, 19.3 mmol) and Et_3N (6 mL, 43.1 mmol). The mixture was stirred at room temperature for 1 h. 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: 10/90 to 75/25 AcOEt/hexane) to afford **61p** (7 g, 98 %) as a pale yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.02 (3H, d, J = 6.8 Hz), 1.38 (9H, s), 3.72 (1H, br s), 3.87–4.01 (2H, m), 4.04 (2H, d, J = 5.3 Hz), 6.81 (1H, d, J = 7.1 Hz), 7.68 (1H, d, J = 8.2 Hz), 8.25 (1H, dd, J = 8.4, 2.3 Hz), 8.85 (1H, d, J = 1.9 Hz), 9.18–9.31 (1H, m). LCMS *m/z* calcd for $C_{16}H_{22}N_3O_5Cl$: 371.12, found 272.2 [M+1−Boc].

***tert*-Butyl ((2*S*)-1-((2-(6-chloropyridin-3-yl)-1,3-oxazol-5-yl)oxy)propan-2-yl)carbamate (62p)**: To a stirred solution of I_2 (10 g, 39.4 mmol) in CH_3CN (200 mL) was added Ph_3P (10 g, 38.1 mmol). After stirring at room temperature for 30 min, Et_3N (10 mL, 71.8 mmol) was added dropwise maintaining around room temperature. After stirring at room temperature for 10 min, **61p** (7 g, 18.8 mmol) in CH_3CN (50 mL) was added. The reaction mixture was stirred at room temperature overnight. The mixture was concentrated under reduced pressure. The residue was extracted with AcOEt and sat. aq. $Na_2S_2O_3$. 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 50/50 AcOEt/hexane) and then purified by column chromatography (silica gel, eluent: 10/90 to 50/50 AcOEt/hexane) to afford **62p** (4.08 g, 61 %) as a pale yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.12 (3H, d, J = 6.4 Hz), 1.37 (9H, br s), 3.87 (1H, br s), 4.06 (2H, d, J = 5.3 Hz), 6.59 (1H, s), 7.00 (1H, d, J = 6.1 Hz), 7.65 (1H, d, J = 8.2 Hz), 8.22 (1H,

d, J = 7.0 Hz), 8.84 (1H, br s). LCMS *m/z* calcd for $C_{16}H_{20}N_3O_4Cl$: 353.11, found 298.0 [M+1−*t*Bu].

***tert*-Butyl ((2*S*)-1-((2-(6-(3-(cyclopropylmethoxy)phenoxy)pyridin-3-yl)-1,3-oxazol-5-yl)oxy)propan-2-yl)carbamate (63)**: A mixture of **62p** (2.2 g, 6.22 mmol), **22** (1 g, 6.09 mmol) and Cs_2CO_3 (3 g, 9.21 mmol) in DMF (20 mL) was stirred at 100 °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: 10/90 to 50/50 AcOEt/hexane) to afford **63** (0.61 g, 21 %) as a light brown solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.27–0.35 (2H, m), 0.50–0.64 (2H, m), 1.11 (3H, d, J = 6.7 Hz), 1.20–1.28 (1H, m), 1.37 (9H, s), 3.81 (2H, d, J = 7.0 Hz), 3.87 (1H, d, J = 6.9 Hz), 4.03–4.08 (2H, m), 6.49 (1H, s), 6.66–6.76 (2H, m), 6.81 (1H, dd, J = 8.3, 1.4 Hz), 6.99 (1H, d, J = 7.3 Hz), 7.10 (1H, d, J = 8.7 Hz), 7.31 (1H, t, J = 8.2 Hz), 8.22 (1H, dd, J = 8.7, 2.5 Hz), 8.59 (1H, d, J = 1.8 Hz). LCMS *m/z* calcd for $C_{26}H_{31}N_3O_6$: 481.22, found 482.2 [M+1].

(2*S*)-1-((2-(5-(3-(cyclopropylmethoxy)phenoxy)pyridin-3-yl)-1,3-oxazol-5-yl)oxy)propan-2

-amine (64): A mixture of **63** (609 mg, 1.26 mmol) in formic acid (4 mL) was stirred at 40 °C for 30 min. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was extracted with AcOEt and sat. aq. $NaHCO_3$. 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) to afford **64** (293 mg, 61 %) as a pale yellow oil.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.27–0.37 (2H, m), 0.51–0.62 (2H, m), 1.05 (3H, d, J = 6.5 Hz), 1.19–1.28 (1H, m), 1.66 (2H, br s), 3.08–3.23 (1H, m), 3.81 (2H, d, J = 7.0 Hz), 3.85–3.96 (2H, m), 6.48 (1H, s), 6.68–6.76 (2H, m), 6.81 (1H, dd, J = 8.3, 1.4 Hz), 7.10 (1H, d, J = 8.7 Hz), 7.32 (1H, t, J = 8.1 Hz), 8.22 (1H, dd, J = 8.6, 2.5 Hz), 8.59 (1H, d, J = 1.9 Hz). LCMS *m/z* calcd for $C_{21}H_{23}N_3O_4$: 381.17, found 382.1 [M+1].

***N*-((2*S*)-1-((2-(6-(3-(Cyclopropylmethoxy)phenoxy)pyridin-3-yl)-1,3-oxazol-5-yl)oxy)propan-2-yl)acetamide (1p)**: A mixture of **64** (297 mg, 0.78 mmol) and Ac_2O (0.35 mL, 3.71 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 100/0 AcOEt/hexane) and crystallized from AcOEt and hexane to afford **1p** (200 mg, 61 %) as a white crystalline solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.25–0.39 (2H, m), 0.56 (2H, q, J = 5.8 Hz), 1.15 (3H, d, J = 6.6 Hz), 1.22 (1H, d, J = 7.6 Hz), 1.81 (3H, s), 3.81 (2H, d, J = 7.0 Hz), 4.02–4.23 (3H, m), 6.50 (1H, s), 6.68–6.77 (2H, m), 6.81 (1H, d, J = 8.5 Hz), 7.10 (1H, d, J = 8.6 Hz), 7.32 (1H, t, J = 8.0 Hz), 8.00 (1H, d, J = 7.4 Hz), 8.23 (1H, dd, J = 8.6, 2.4 Hz), 8.59 (1H, d, J = 2.1 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.57, 10.54, 17.19, 23.13, 44.00, 72.73, 74.72, 101.05, 108.26, 111.72, 112.15, 113.69, 119.47, 130.68, 137.11, 144.76, 149.58, 154.93, 160.28, 160.33, 164.04, 169.37. LCMS *m/z* calcd for $C_{23}H_{25}N_3O_5$: 423.18, found 424.2 [M+1]. Anal. Calcd for $C_{23}H_{25}N_3O_5 \cdot 0.56H_2O$: C, 63.72; H, 6.07; N, 9.69. Found: C, 63.71; H, 5.80; N, 9.71. Mp 112–114 °C. $[\alpha]^{25}_D$ −49.9° (c 0.8995, MeOH).

1-((2*S*)-1-((2-(4-(3-(Cyclopropylmethoxy)phenoxy)phenyl)-1,3-oxazol-5-yl)oxy)propan-2-yl)urea (1q)

A mixture of **59** (28 g, 58.3 mmol) in formic acid (150 mL) was stirred at 40 °C for 30 min. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was extracted with AcOEt and sat. aq. $NaHCO_3$. The organic layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in THF (200 mL). To the mixture were added Et_3N (13 mL, 93.3 mmol) and 4-nitrophenyl chloroformate (15 g, 74.4 mmol). After stirring at 0 °C for 1 h, 28% aq. NH_3 (50 mL) was added.

After stirring at room temperature for 30 min, the mixture was extracted with AcOEt. 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 **1q** (10 g, 41 %) as a white crystalline solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 0.24–0.37 (2H, m), 0.50–0.59 (2H, m), 1.14 (3H, d, J = 6.7 Hz), 1.18 (1H, d, J = 5.8 Hz), 3.80 (2H, d, J = 7.0 Hz), 3.90–4.10 (3H, m), 5.49 (2H, s), 6.10 (1H, d, J = 7.6 Hz), 6.45 (1H, s), 6.56–6.67 (2H, m), 6.72–6.81 (1H, m), 7.01–7.11 (2H, m), 7.31 (1H, t, J = 8.3 Hz), 7.79–7.88 (2H, m). ^{13}C NMR (75 MHz, DMSO-d_6) δ 3.56, 10.53, 17.96, 44.44, 72.71, 75.46, 100.84, 106.38, 110.98, 111.72, 118.95, 122.61, 127.31, 131.12, 151.45, 157.24, 150.50, 160.63. LCMS *m/z* calcd for $C_{23}H_{25}N_3O_5$: 423.18, found 446.1 [M+1+Na]. Anal. Calcd for $C_{23}H_{25}N_3O_5$: C, 65.24; H, 5.95; N, 9.92. Found: C, 65.15; H, 5.87; N, 9.89. Mp 115–117 °C. $[\alpha]^{25}_D$ −25.3° (c 0.7995, MeOH).

ACC enzyme assay

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.

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 ºC. 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 ºC. 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 compound **1f** 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).

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 (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 **1q**. 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 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 $852.0 \rightarrow 808.0$ for malonyl-CoA and m/z $855.0 \rightarrow 810.0$ 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.

ASSOCIATE CONTENT

Supporting Information

The supporting Information is available free of charge on the ACS Publications website.

Molecular formula strings (CSV)

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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., M. A., D. T., H. B., N. N., and H. M. contributed design and synthesis of compounds; M. S., H. S., Y. S., Y. Y., Y. S., and T. M. contributed in vitro and in vivo study.

Notes

The authors declare no competing financial interest.

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ABBREVIATION USED

adenosine triphosphate, ATP; bovine serum albumin, BSA; 1,8-diazabicyclo[5.4.0]undec-7-ene, DBU; diisobutylaluminium hydride, DIBAL-H; diisopropyl azodicarboxylate, DIAD; *N*,*N*-diisopropylethylamine, DIPEA; 1,2-dimethoxyethane, DME; *N*,*N*-dimethyl-4-aminopyridine, DMAP; *N*,*N*-dimethylformamide, DMF; dimethylsulfoxide, DMSO; diphenylphosphoryl azide, DPPA; 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, EDC; 1-hydroxybenzotriazole, HOBt; 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid, HEPES; lithium hexamethyldisilazide, LiHMDS; methanesulfonyl chloride, MsCl; *N*-methylmorpholine *N*-oxide, NMO; phosphate buffered saline, PBS; tetrahydrofuran, THF; tetrapropylammonium perruthenate, TPAP; trifluoroacetic acid, TFA; trifluoroacetic anhydride, TFAA.

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