Bioorganic & Medicinal Chemistry 20 (2012) 3332–3358

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

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

Structure–activity relationships and key structural feature of pyridyloxybenzene-acylsulfonamides as new, potent, and selective peroxisome proliferator-activated receptor (PPAR) γ Agonists

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ARTICLE INFO

Article history:
Received 25 December 2011
Revised 13 March 2012
Accepted 14 March 2012
Available online 23 March 2012

Keywords:
PPARγ agonists
Diabetes mellitus
SBDD
Acylsulfonamide
Isosteric replacement

ABSTRACT

In our search for a novel class of non-TZD, non-carboxylic acid peroxisome proliferator-activated receptor (PPAR) γ agonists, we explored alternative lipophilic templates to replace benzylpyrazole core of the previously reported agonist **1**. Introduction of a pentylsulfonamide group into arylpropionic acids derived from previous in-house PPARγ ligands succeeded in the identification of 2-pyridyloxybenzene-acylsulfonamide **2** as a lead compound. Docking studies of compound **2** suggested that a substituent para to the central benzene ring should be incorporated to effectively fill the Y-shaped cavity of the PPARγ ligand-binding domain (LBD). This strategy led to significant improvement of PPARγ activity. Further optimization to balance in vitro activity and metabolic stability allowed the discovery of the potent, selective and orally efficacious PPARγ agonist **8f.** Structure-activity relationship study as well as detailed analysis of the binding mode of **8f** to the PPARγ-LBD revealed the essential structural features of this series of ligands.

1. Introduction

Type 2 diabetes mellitus (T2DM), which accounts for more than 90% of the diabetic patients, is a chronic multifactorial metabolic disease characterized by insulin resistance, hyperglycemia, and impaired insulin secretion. In the long term, metabolic perturbations, including compensatory hyperinsulinemia appear to contribute to the development of many other disorders such as dyslipidemia, hypertension, and coronary heart disease. The combination of these risk factors associated with a sedentary lifestyle and obesity significantly increases morbidity and mortality.[1] T2DM has rapidly reached epidemic proportions becoming a major public health issue worldwide, and this trend will continue to increase in the future reaching 380 million cases by the year 2025.[2]

In an era marked by the increasing prevalence of T2DM, one class of new therapeutic agents, thiazolidinediones (TZDs) represented by pioglitazone and rosiglitazone, has emerged as 'insulin sensitizers'. TZDs were originally identified and optimized through empirical in vivo screening in rodent diabetes models without knowledge of the target protein. In 1995, scientists from GlaxoSmithKline reported that TZDs are high affinity ligands for the nuclear receptor, peroxisome proliferator-activated receptor γ (PPARγ),[3] and these findings inspired extensive research in the area of antidiabetic drug discovery and development.[4–9] TZDs bind and activate PPARγ that functions as an essential transcriptional regulator of glucose and lipid homeostasis. Among the 3 PPAR subtypes, namely designated as PPARα, PPARγ, and PPARδ, PPARγ is the most extensively investigated. PPARγ is predominantly expressed in adipose tissue and regulates the expression of a constellation of genes closely related to adipocyte differentiation, glucose and lipid metabolism, insulin sensitivity, inflammatory responses, and cell proliferation.[3,10]

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http://dx.doi.org/10.1016/j.bmc.2012.03.036

To date, a majority of PPARγ ligands possessing a carboxylic acid or its heterocyclic bioisostere such as TZD, oxazolidinone, and tetrazole have been reported,[11] whereas acyclic isosteres have drawn little attention with only a few reports so far. In our search for a new class of non-TZD and non-carboxylic acid PPARγ agonists, we recently identified a series of potent, selective, and orally-active benzylpyrazole acylsulfonamides, represented by compound **1**, utilizing structure-based drug design (SBDD) (Fig. 1).[12] The co-crystal structure of **1** bound to the PPARγ-ligand-binding domain (LBD) revealed that the acylsulfonamide moiety interacts with Try327, His449 and/or Gln286 in the LBD and may contribute to high PPARγ selectivity over PPARα and δ. These findings encouraged us to investigate further acylsulfonamide-based PPARγ ligands.

Despite showing an attractive profile, the benzylpyrazole-acylsulfonamide **1** was found to have some disadvantages such as cytotoxicity, which is attributed to the high lipophilicity ($c\log P = 5.00$, $c\log D$ [pH 7.4] = 3.06).[13] To address the liability, we set out to identify an alternative and less hydrophobic template in place of benzylpyrazole moiety. The structure–activity relationship (SAR) of benzylpyrazole-acylsulfonamides indicates that an acylsulfonamide group connected via two carbon spacer is one of the key structural elements for PPARγ activity. Therefore, we focused on several arylpropionic acids derived from previously identified in-house PPARγ ligands. An attempt to incorporate a pentylsulfonamide group into the arylpropionic acids gave a successful result, leading to the identification of pyridyloxybenzene-acylsulfonamide **2** as a novel lead compound (Fig. 1). Indeed, the pyridyloxybenzene **2** ($c\log P = 4.59$, $c\log D$ [pH7.4] = 2.66)[13] is slightly less hydrophobic than the benzylpyrazole **1**. Overall, compound **2** was considered to be a promising starting point because of the moderate PPARγ potency as well as high subtype selectivity.

To support our optimization strategy, we performed a molecular docking study of **2** using the GOLD program (ver. 2.0, the Cambridge crystallographic date centre, UK). Compound **2** was docked to the 3-dimensional protein structure derived from the co-crystal structure of PPARγ-LBD with compound **1**[12] and the docking model was superposed with the complex of **1** (Fig. 2). Compound **2** was estimated to be bound to the PPARγ-LBD in a similar fashion to that of compound **1**. It can be seen that there is a space around the 4 position of the benzene ring of **2**, into which the isopropoxy group of **1** extends. Therefore, we reasoned that incorporation of a suitable substituent into this position could further improve the potency.

In this article, we wish to report the synthesis, SAR, in vitro and in vivo biological profiles of pyridyloxybenzene-acylsulfonamides. Furthermore, on the basis of X-ray co-crystallographic studies, the key pharmacophores and structural requirements for PPARγ binding are also discussed.

2. Chemistry

The pyridyloxybenzene-acylsulfonamides **2,8a–l,n,p,q** and -acylsulfamide **8r** possessing various alkoxy groups on the benzene ring and the terminal side chain were generally synthesized by the route outlined in Scheme 1. The 4-hydroxy group of commercially available dihydroxybenzaldehyde (**3**) was selectively protected as methoxymethyl (MOM) ether to give **4a**. Compound **4a** and commercially available **4b** were reacted with 2-chloropyridine to provide the pyridyloxybenzaldehydes **5a,b**, which were subjected to a Horner–Wadsworth–Emmons homologation to afford the cinnamate esters **6a–c**. Incorporation of various alkyl moieties into the 4-hydroxy group of the central benzene core of **6a,c** was carried out by deprotection of the MOM group, followed by O-alkylation or Mitsunobu reaction[14] with appropriate alcohols to yield **7d,e,g–m**. The double bond of **7e** was reduced by catalytic hydrogenation to produce **7f**. As for the preparation of **7a,c**, the double bond was hydrogenated prior to the MOM-deprotection and O-alkylation sequence. The esters **7a–m** were then converted to the target acylsulfonamides **2,8a–l,n,p,q** acylsulfamide **8r** by alkaline hydrolysis and subsequent condensation with various sulfonamides or sulfamide utilizing carbonyl diimidazole (CDI), water-soluble carbodiimide (WSC), or thionyl chloride as a coupling reagent. The 2-hydroxyethoxy and 3-oxobutoxy derivatives **8m,o** were lastly obtained by deprotection of triisopropyl (TIPS) group of **8l** or dioxolane of **8n** under standard conditions.

Modification of the 2-pyridyloxy group or linker moiety of **8f** was performed by the procedure shown in Scheme 2. Mitsunobu reaction of compound **3** with 2-methoxyethanol proceeded mainly at the 4-hydroxy group to furnish the desired regioisomer **9**. Conversion of **9** to the target compounds **13a–d,g** was achieved by the following 2 synthetic routes. The first is analogous to that described in Scheme 1. Installation of substituted pyridyl groups into **9** provided the pyridyloxybenzene congeners **11a,b**. Compound **11a** was then subjected to a Horner–Wadsworth–Emmons

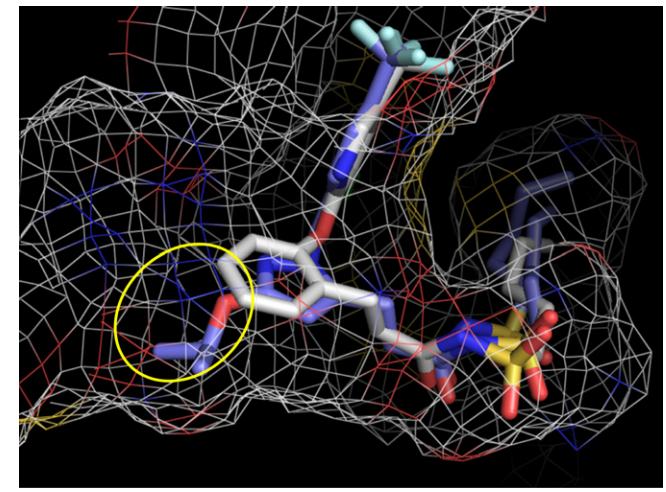
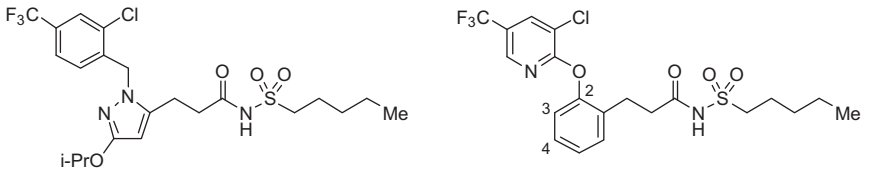
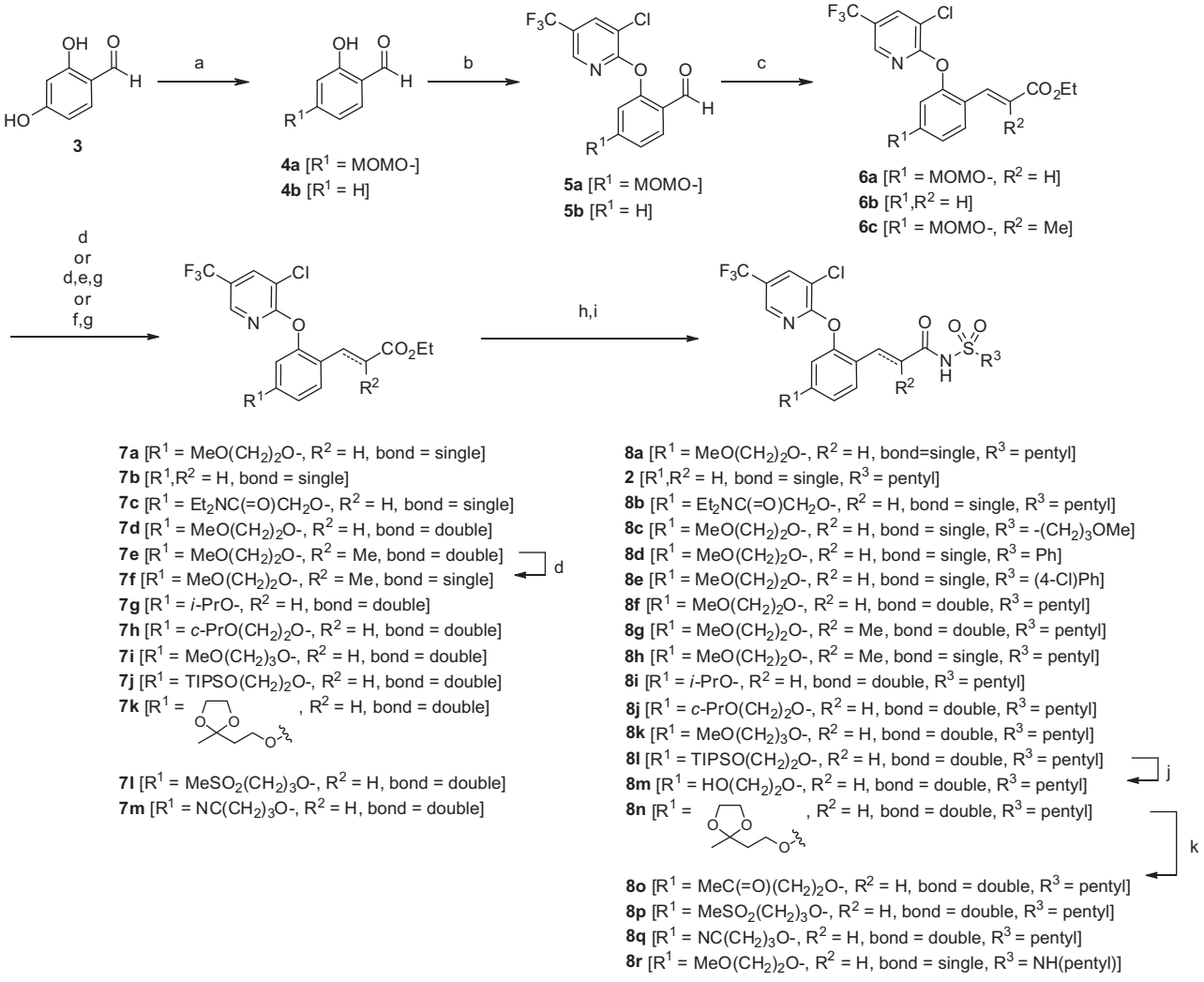


Figure 2. Superposition of the docking model of compound **2** (shown in white) bound to the PPARγ-LBD [PDB code: 1PRG] and the co-crystal structure of compound **1** (shown in blue). The binding space accommodating the isopropoxy group of **1** is marked by a yellow circle.



1: PPARγ/α/δ EC_{50} = 10 / >10000 / >10000 nM **2**: PPARγ/α/δ EC_{50} = 61 / >10000 / >10000 nM

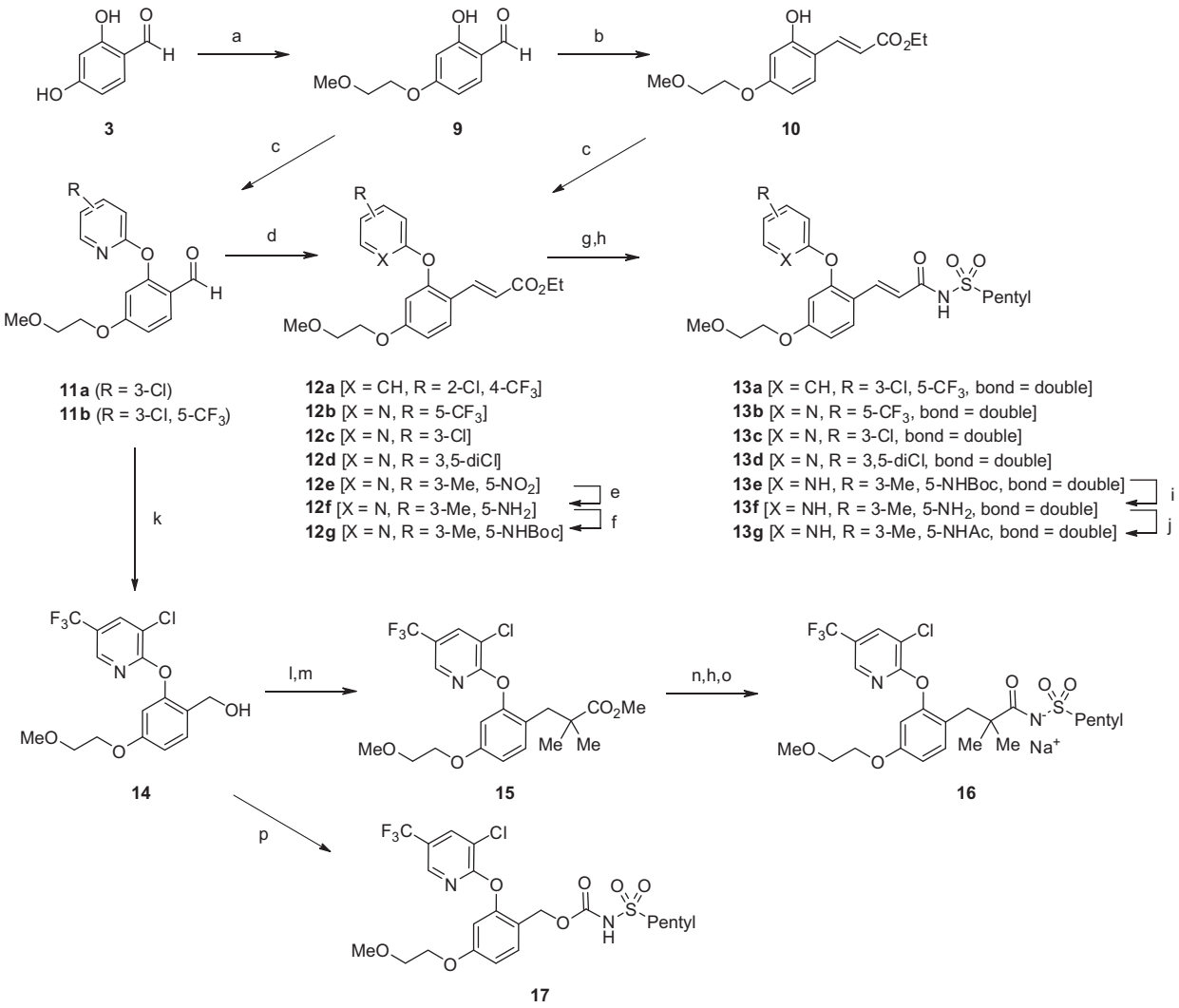
Figure 1. Benzylpyrazole- and pyridyloxybenzene-based acylsulfonamide PPARγ agonists **1** and **2**.



Scheme 1. Reagents and conditions: (a) MOMCl, K_2CO_3, acetone, rt; (b) 2,3-dichloro-5-(trifluoromethyl)pyridine, NaH, DMF, rt→50 °C; (c) $(EtO)_2P(=O)CHR^2CO_2Et$, NaH, THF, DMF, 0 °C→rt; (d) H_2, Pd/C, THF, rt; (e) conc. HCl, THF, 50 °C; (f) 1 M HCl, acetone, reflux; (g) alcohol, ADDP, tributylphosphine, THF, 50 °C, 12–95%, for **7a,d,e,h,j**; alkyl halide or alkyl tosylate, K_2CO_3, DMF, rt–80 °C, for **7c,g,i,k–m**; (h) 1 M NaOH, THF, EtOH, 50 °C; (i) CDI, THF, reflux, then sulfonamide, DBU, rt, for **2,8a–d,i**; sulfonamide or sulfamide, WSC-HCl, DMAP, with or without TEA, MeCN, for **8f–h,j–l,n,p–r;** $SOCl_2$, THF, 0 °C then 4-chlorobenzenesulfonamide, DIPEA, DMAP, THF, rt, for **8e**; (j) TBAF, THF, rt; (k) 1 M HCl, THF, 60 °C.

reaction to give compound **12c**. In the second route, a Wittig-elongation of **9** is performed prior to installation of aryl group. Treatment of **9** with carboethoxymethylenetriphenylphosphorane afforded 2-hydroxycinnamic acid ester **10**, which was converted to the aryloxybenzene derivatives **12a,b,d,e**. The nitro group of **12e** was reduced by zinc powder-acetic acid to furnish aniline **12f**, which was subsequently reacted with di-tert-butyl dicarbonate (Boc_2O) to yield Boc-protected aniline **12g**. Compounds **12a–d,g** were subjected to saponification and subsequent condensation with pentane-1-sulfonamide, using 2-methyl-6-nitrobenzoic anhydride (MNBA)[15] as a coupling agent in place of WSC-HCl, to generate **13a–e**. The Boc group of **13e** was removed by the treatment of hydrochloric acid in MeOH to furnish aniline **13f**, which was acetylated to yield acetanilide **13g**. In parallel, reduction of **11b** using sodium borohydride produced benzyl alcohol **14.** Acetylation of the alcohol of **14** followed by a Lewis acid-mediated S_N1 reaction of benzylic cation, generated from acetate ester of **14**, with silylketene acetal proceeded smoothly to give the β-phenylpivalic acid ester **15** in high yield.[16] Standard basic hydrolysis of the ester **15** accompanied cleavage of the C–O bond of the pyridyl ether to predominantly afford β-(2-hydroxylphenyl)pivalic acid. By contrast, acidic hydrolysis of **15** worked well, and the resulting carboxylic acid was subsequently coupled with pentane-1-sulfonamide to generate acylsulfonamide, which was treated with one equivalent of sodium hydroxide to afford the corresponding sodium salt **16**. Finally, benzyl alcohol **14** was coupled with pentane-1-sulfonamide using CDI to afford sulfonyl carbamate **17**.

Incorporation of the pyridyloxy group into the central benzene core at a later stage to prepare compounds **23a–d** possessing a single bond linker was performed as shown in Scheme 3. Selective and successive alkylation of the two hydroxyl groups of compound **3** produced 2-benzyloxybenzaldehydes **19a–c**, which were then subjected to a Horner–Wadsworth–Emmons reaction or aldol condensation with α-substituted acetate to give the cinnamic acid esters **20a–c**. Deprotection of the MOM group of **20c** and subsequent alkylation under Mitsunobu reaction conditions afforded **20e**. Saturation of the double bond and simultaneous removal of the benzyl group of **20a,b,e** were achieved by catalytic hydrogenation to provide the α-substituted propionic



Scheme 2. Reagents and conditions: (a) 2-methoxyethanol, DEAD, triphenylphosphine, THF, 0 °C→rt; (b) $Ph_3P{=}CHCO_2Et$, DCM, 0 °C→rt; (c) appropriately substituted 2-chloropyridine or 3-chloro-4-fluorobenzotrifluoride, K_2CO_3 or NaH DMF, 50–120 °C, for **11a,b,12a,b,d,e**; (d) $(EtO)_2P(=O)CH_2CO_2Et$, NaH, THF, 0 °C, for **12c**; (e) Zn, AcOH, H_2O, rt; (f) Boc_2O, THF, reflux; (g) 1 M NaOH, THF, EtOH, 50–60 °C; (h) pentane-1-sulfonamide, WSC-HCl or MNBA, DMAP, with or without TEA, MeCN or DMF, rt, for **13a–e**; CDI, THF, reflux, then pentane-1-sulfonamide, DBU, rt, for **16**; (i) 10% HCl in MeOH, 45 °C; (j) Ac_2O, DMAP, pyridine, rt; (k) $NaBH_4$, THF, MeOH, 0 °C; (l) Ac_2O, pyridine, rt; (m) 1-methoxy-2-methyl-1-(trimethylsiloxy)propene, $Mg(ClO_4)_2$, toluene, 50 °C; (n) conc. H_2SO_4, AcOH, THF, H_2O, 80 °C; (o) 1 M NaOH, MeOH; (p) CDI, DMF, 40 °C, then pentane-1-sulfonamide, DBU, DMAP, rt.

acid esters **21a–c**. Introduction of the pyridyl group into **21a–c** and final construction of acylsulfonamide or amide moiety afforded the target compounds **23a–d**.

Replacement of the vinylene linker of **8f** with cyclopropane was carried out by the procedure shown in Scheme 4. The MOM-protected cinnamic acid ester **24**, which was easily prepared from **10**, was subjected to a Corey-Chaykovsky cyclopropanation to successfully give **25** despite low yield.[17] The following conversion scheme was conducted by a similar procedure to that depicted in Scheme 3 to afford the desired compound **27**.

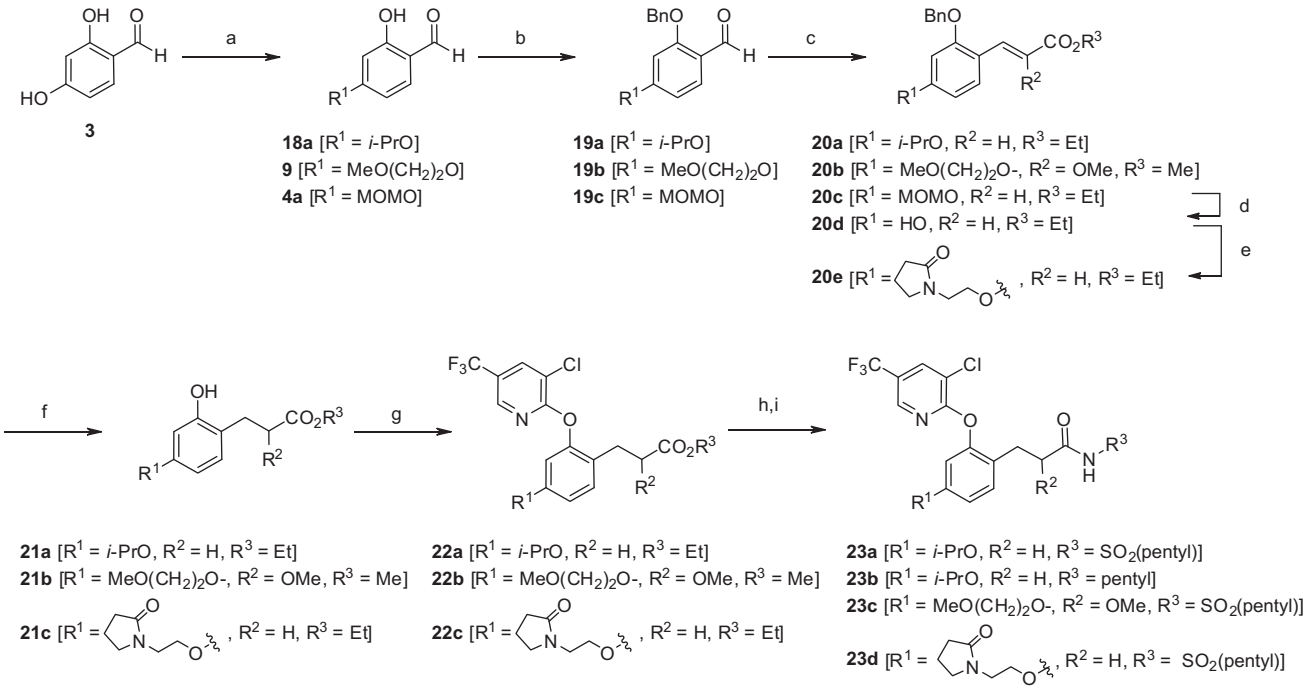
Replacement of the acylsulfonamide group of **8a** with various functional groups was carried out by the procedure shown in Scheme 5. The propionic acid ester **7b** was subjected to diisobutylaluminium hydride (DIBAL-H) reduction to provide propanol **28**. The alcohol of **28** was coupled with butylamine using CDI or with pentane-1-sulfonamide using triphosgene to afford carbamate **29a** and sulfonyl carbamate **29b**, respectively. On the other hand, the primary alcohol of **28** was converted to the corresponding amine under Gabriel method conditions and subsequent acylation with sulfonyl chloride or chloroformate to give sulfonamide **32a** and carbamate **32b**, respectively.

3. Results and discussion

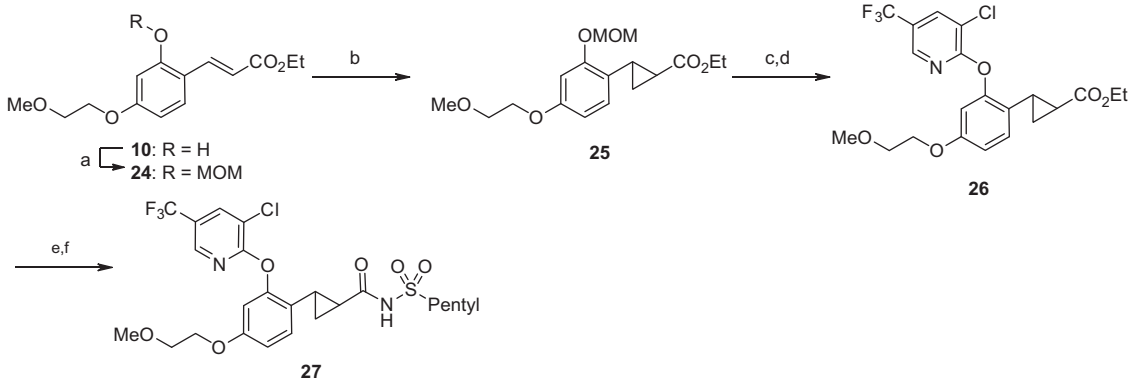
3.1. In vitro structure–activity relationships

The newly synthesized compounds in this study were evaluated for their ability to activate human PPAR subtypes γ, α, δ and their metabolic stability in human microsomes. Stably transfected CHO-K1 cells were used in PPARγ transactivation assay, and transiently transfected COS-1 cells were used in PPARα and δ transactivation assays. The results are summarized in Tables 1–6, where the activities are reported as half maximal effective concentration (EC_{50}) values. We used the agonists of PPARγ, α, and δ, (*R*)-5-(3-{4-[(2-furan-2-yl-5-methyl-1,3-oxazol-4-yl)-methoxy]-3-methoxy phenyl}propyl)-1,3-oxazolidine-2,4-dione,[18] ({3-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyl}sulfanyl)acetic acid,[19] and carbacyclin,[20] respectively as reference compounds. To assess metabolic stability, metabolic clearance was measured by the treatment of test compounds with human or rat liver microsomes (see Section 5).

Based on the above-mentioned docking study shown in Figure 2, we initially investigated incorporation of an alkoxy group into



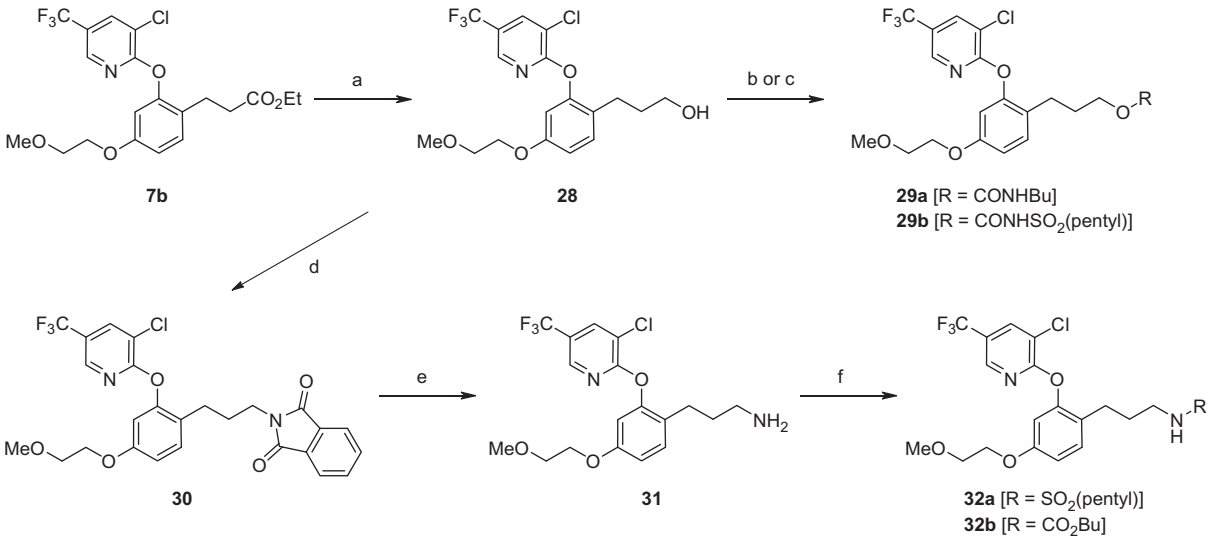
Scheme 3. Reagents and conditions: (a) 2-iodopropane, DIPEA, THF, rt, for **18a**; 2-methoxyethanol, DEAD, triphenylphosphine, THF, 0 °C→rt, for **9**; MOMCl, K_2CO_3, acetone, rt, for **4a**; (b) benzyl bromide, K_2CO_3, DMF, rt; (c) $(EtO)_2P(=O)CH_2CO_2Et$, NaH, THF, 0 °C, for **20a,c**; methyl methoxyacetate, KO*t*-Bu, THF, for **20b**; (d) conc. HCl, THF, 40 °C; (e) 1-(2-hydroxyethyl)-2-pyrrolidone, DEAD, TPP, THF, rt; (f) H_2, Pd/C, THF, EtOH, rt, 88%-quant., for **21a,c**; H_2, Pd/C, MeOH, rt, for **21b** (g) 2,3-dichloro-5-(trifluoromethyl)pyridine, NaH, DMF, 0 °C; (h) 1 M NaOH, THF, EtOH or MeOH, rt–50 °C; (i) CDI, THF, reflux, then pentane-1-sulfonamide, DBU, rt, for **23a,d**; $SOCl_2$, cat. DMF, THF, 0 °C then pentylamine, DIPEA, DMAP, THF, rt, for **23b;** pentane-1-sulfonamide, WSC-HCl, DMAP, MeCN, rt, for **23c**.



Scheme 4. Reagents and conditions: (a) MOM-Cl, K_2CO_3, MeCN, rt; (b) trimethylsulfoxonium iodide, NaH, DMSO, 0 °C→rt; (c) 1 M HCl, acetone, 50 °C; (d) 2,3-dichloro-5-(trifluoromethyl)pyridine, K_2CO_3, DMF, rt; (e) 1 M NaOH, THF, EtOH, rt; (f) pentane-1-sulfonamide, WSC-HCl, DMAP, MeCN.

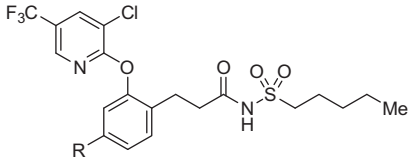
the 4-position of the central benzene ring of compound **2** and the results are shown in Table 1. The lead compound **2** lacking in a substituent at this position showed moderate PPARγ agonism with an EC_{50} value of 61 nM but suffered relatively high metabolic clearance. In the previous report, a good correlation among in vitro metabolic clearance, in vivo plasma exposure and in vivo antidiabetic efficacy was observed.[12] Therefore, we first aimed at improving PPARγ activity as well as metabolic clearance. According to the previous report, we set a goal of in vitro profiless to be EC_{50} <10 nM and metabolic clearance <50 μL/min/mg. As we had expected, incorporation of an alkoxy substituent (**8a,b,23a** and **23d**) into the 4-position significantly improved PPARγ activity compared with **2**. Isopropoxy analog **23a** was about 23-fold more potent than **2**; however, in terms of metabolic stability, introduction of the isopropoxy group produced little if any improvement. Thus, more polar alkoxy groups were briefly investigated. Ether (**8a**), amide (**8b** and **23d**) were well tolerated, exhibiting single-digit nanomolar potency, but the metabolic stability of these compounds was not improved.

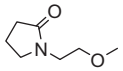
Next, modification of the terminal side chain on the sulfonyl group, maintaining the 2-methoxyethoxy group as the para substituent of the central benzene ring, was investigated and the representative results are shown in Table 2. In the previously-identified benzylpyrazole-acylsulfonamide series, the pentyl group was shown to be the optimal among linear alkyl groups. Thus, we examined substituents other than alkyl groups. Replacement of the 4th methylene carbon of the pentyl group of **8a** with an oxygen atom (**8c**) greatly enhanced metabolic stability while showing low double-digit nanomolar potency. However, the improvement in metabolic stability was not reflected in in vivo pharmacokinetic profile and efficacy of **8c** (data not shown). The reason for the discrepancy remains unclear. Substitution of the pentyl group of



Scheme 5. Reagents and conditions: (a) DIBAL-H, THF, 0 °C; (b) CDI, DMF, 60 °C, then butylamine, rt, for **29a**; (c) 1) triphosgene, pyridine, DCM, 0 °C; 2) pentane-1-sulfonamide, DIPEA, DMAP, THF, rt, for **29b**; (d) 1) MsCl, TEA, EtOAc, rt; 2) potassium phthalimide, DMF, 80 °C; (e) $H_2NNH_2 \cdot H_2O$, MeOH, 50 °C; (f) pentane-1-sulfonyl chloride or butyl chloroformate, pyridine, EtOAc, rt.

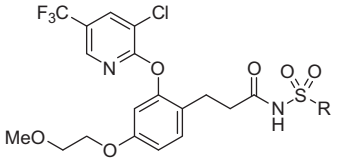
Table 1
In vitro transactivation activity and metabolic stability of compounds **2,8a,b,23a** and **23d**



Compound	R	PPARγ transactivation EC_{50}[a] (nM)	Metabolic clearance[b] h/r (μL/min/mg)
2	H	61	78/120
23a	*i*-PrO	2.6	57/94
8a	$MeO(CH_2)_2O$–	1.5	77/62
8b	$Et_2NC(=O)CH_2O$–	6.9	95/92
23d		3.4	78/104

[a] EC_{50} value means the effective concentration for 50% response of a given compound's intrinsic maximal response.
[b] Rate of metabolism in human or rat hepatic microsomes.

Table 2
In vitro transactivation activity and metabolic stability of compounds **8a,c–e**

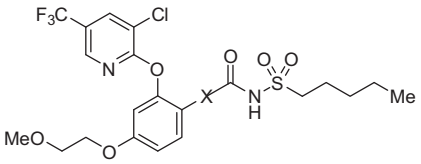


Compound	R	PPARγ transactivation EC_{50}[a] (nM)	Metabolic clearance[b] h/r (μL/min/mg)
8a	Pentyl	1.5	77/62
8c	$(CH_2)_3OMe$	11	7/11
8d	Ph	32	—[c]
8e	(4-Cl)Ph	8.6	67/71

[a,b] See the legends of Table 1.
[c] Not determined.

8a with a phenyl group reduced the potency by more than 20-fold (**8d**). The decrease in potency was regained by introduction of a para-chlorine atom onto the phenyl ring of **8d** (**8e**), but the metabolic stability of **8e** was comparable to that of **8a**. As in the case of the benzylpyrazole derivatives, the pentyl group proved to be optimal.

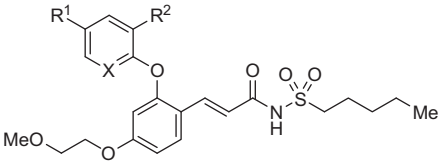
Table 3
In vitro transactivation activity and metabolic stability of compounds **8a,f–h,16,17,23b** and **27**



Compound	X	PPARγ transactivation EC_{50} (nM)[a]	Metabolic clearance[b] h/r (μL/min/mg)	Metobolic clearance in the absence of NADPh h/r[c] (% remaining)
8a		1.5	77/62	50.1/13.6
8f		15	9/6	94.8/87.3
8h		2.3	128/189	
16[d]		3.1	113/78	
27		5.5	40/26	73.8/81.7
8g		5.2	20/20	
23c		6.7	72/15	
17		10	23/31	

[a,b] See the legends of Table 1.
[c] Metabolic clearance is shown as the percent remaining of compounds after incubation in the absence of NADPH with human and rat hepatic microsomes at 37 °C for 2 h.
[d] Sodium-salt.

Table 4
In vitro transactivation activity and metabolic stability of compounds **8f** and **13a–d,f,g**

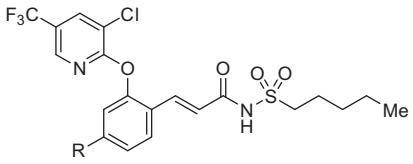


Compound	R^1	R^2	X	PPARγ transactivation EC_{50}[a] (nM)	Metabolic clearance h/r[b] (μL/min/mg)
8f	CF_3	Cl	N	15	9/6
13a	CF_3	Cl	CH	94	14/10
13b[d]	CF_3	H	N	>10,000	<1/<1
13c	H	Cl	N	>10,000	18/15
13d	Cl	Cl	N	190	9/9
13f[e]	NH_2	Me	N	>10,000	—[c]
13g	MeCONH	Me	N	>10,000	—[c]

[a,b] See the legends of Table 1.
[c] Not determined.
[d] Potassium salt.
[e] 2 HCl salt.

Subsequently, effects of modification of the linker between the central benzene ring and acylsulfonamide moiety on in vitro potency and metabolic stability were examined (Table 3). Desaturation of the ethylene linker (**8a**) significantly improved metabolic stability, but decreased potency by 10-fold (**8f**). A similar tendency was observed in the benzylpyrazole-based agonists. The high clearance of the ethylene linker analogue (**8a**) is considered to result from oxidative metabolism by CYP enzymes as well as non-oxidative metabolism, to which hydrolysis of the acylsulfonamide by esterases[21a] mainly contributes,. We hypothesized that compounds with the flexible ethylene linker tend to have multiple conformations by which they can adopt suitable conformation for metabolic enzymes. On the basis of the assumption, introduction of substituents into the α-carbon of the carbonyl group was investigated to block the hydrolysis and/or reduce the flexibility. As shown in Table 3, introduction of α-substituent were generally well tolerated. Compounds with α-methyl (**8h**), geminal dimethyl (**16**), and α-methoxy (**23c**) were almost as potent as the parent compound (**8a**), still maintaining single-digit nanomolar potency. Disappointingly, the modification tended to decrease metabolic stability. The result led us to design compounds with vinylene-related constrained linkers. The cyclopropane analogue **27** showed

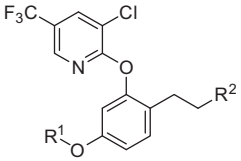
Table 5
In vitro transactivation activity and metabolic stability of compounds **8f,i–k,m,o–q**



Compound	R	PPARγ transactivation EC_{50}[a] (nM)	Metabolic clearance h/r[b] (μL/min/mg)
8f	$MeO(CH_2)_2$	15	9/6
8i	*i*-PrO	26	19/19
8j	*c*-Pr$O(CH_2)_2O$–	6.2	25/17
8k	$MeO(CH_2)_3O$–	7.4	16/15
8m	$HO(CH_2)_2O$–	80	<1/<1
8o	$MeC(=O)CH_2)_3O$–	59	30/19
8p	$MeSO_2(CH_2)_3O$–	320	6/<1
8q	$NC(CH_2)_3O$–	15	23/19

[a,b] See the legends of Table 1.

Table 6
In vitro transactivation activity and metabolic stability of compounds **8a,r,23a,b,29a,b** and **32a,b**



Compound	R^1	R^2	PPARγ transactivation EC_{50} (nM)[a]	Metabolic clearance h/r[b] (μL/min/mg)
23a	*i*-Pr	$CONHSO_2$(Pentyl)	2.6	57/94
23b	*i*-Pr	CONH(Pentyl)	290	—[c]
8a	$MeO(CH_2)_2$	$CONHSO_2$(Pentyl)	1.5	77/62
32a	$MeO(CH_2)_2$	CH_2NHSO_2(Pentyl)	32	210/204
32b	$MeO(CH_2)_2$	$CH_2NHCOOBu$	38	—[c]
29a	$MeO(CH_2)_2$	$CH_2NHCONHBu$	48	—[c]
29b	$MeO(CH_2)_2$	$CH_2OCONHSO_2$(Pentyl)	4.5	90/35
8r	$MeO(CH_2)_2$	$CONHSO_2NH$(Pentyl)	1.1	70/111

[a,b] See the legends of Table 1.
[c] Not determined.

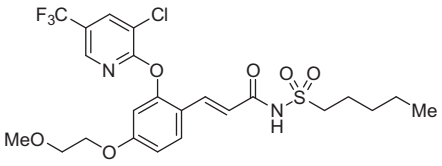
good potency but was less metabolically stable than the acryl amide **8f**. Introduction of α-methyl group into the acryl amide of **8f** gave a more potent agonist **8g** with acceptable metabolic stability. Considering the fact that compounds **8a,g,h** showed nanomolar potency, it is suggested that the linker of **8g** would be twisted in the active conformation similar to **8a,h** due to the steric repulsion between the α-methyl group and the ortho hydrogen of the central benzene ring. Replacement of a methylene group adjacent to the carbonyl group of **8a** with an oxygen atom (**17**) improved metabolic stability, but decreased potency by ca. 7-fold compared with **8a**. The increase in electron density on the carbonyl group may attenuate the susceptibility of the acylsulfonamide group by esterases. To estimate stability to non-oxidative metabolism metabolic clearance in the absence of NADPH with hepatic microsomes was also evaluated for the representative compounds **8a**,**f** and **27**. In accordance with the stability to oxidative metabolism (metabolic clearance shown in Table 3), the stability to non-oxidative metabolism is improved in the order of the rigidity and planarity. Indeed, compound **8f** with the vinylene linker is the most stable to both oxidative and non-oxidative metabolism, and is consistent with our hypothesis.

Based on the above-mentioned findings, effects of modification of the pyridyloxy group on activity and metabolic stability of compounds possessing the vinylene linker and pentylsulfonamide group were examined. As described in Table 4, the pyridine nitrogen as well as two substituents, the 3-chloro and 5-trifluoromethyl groups, on the pyridine ring were essential for potency. Replacement of the pyridine nitrogen of **8f** with a carbon atom resulted in about a 6-fold decrease in activity (**13a**) and concomitant increase in cytotoxicity (data not shown), presumably due to increased lipophilicity. Removal of the 3-chloro or 5-trifluoromethyl group of **8f** (**13b,c**) led to more than 600-fold decrease in potency. Substitution of a chlorine atom with the trifluoromethyl group of **8f** also decreased potency by more than 10-fold (**13d**), but the dichloro analog **13d** still exhibited low submicromolar activity. In contrast, incorporation of hydrophilic substituents such as an amino (**13f**) or acetylamino (**13g**) group was detrimental to in vitro potency. These results indicate that the 2-pyridyl group is preferable, and the lipophilic 3,5-substituents of the pyridine ring are indispensable for high potency.

Having identified the favorable moieties for balancing the potency and metabolic stability, the 4-alkoxy group on the benzene ring was re-investigated and the results are presented in Table 5. Isopropoxy analogue **8i** was essentially equipotent to **8f**, similarly to the ethylene linker derivatives (see Table 1). Replacement of the terminal methoxy group of **8f** with cyclopropoxy group (**8j**), or one carbon elongation of the alkylene spacer (**8k**) resulted in ca. 2-fold increase in potency. Furthermore, removal of the terminal methyl group of **8f** reduced the activity by 5-fold (**8m**). Replacement of the terminal methoxy group with an acetyl (**8o**) or methylsulfonylmethyl group (**8p**) reduced the potency by more than 4-fold, whereas the 3-cyanopropoxy analog **8q** was found to be equipotent to **8f**. These findings suggest that incorporation of long and bulky substituents into the terminus of the alkoxy moiety tends to have a deleterious effect on activity. Therefore, 2-methoxyethoxy group was the best-balanced in terms of potency and metabolic stability.

As mentioned above, a large variety of carboxylic acid-based ligands have been reported as non-TZD PPARγ ligands, while only a few acylsulfonamide-based ligands have been disclosed so far. Thus, for the purpose of better understanding a role of the acylsulfonamide as a pharmacophore, modification of the acylsulfonamide moiety, which is a characteristic structural feature in this series of PPARγ ligands, was carried out and the results are shown in Table 6. Removal of the sulfonyl group of **23a** led to **23b**, which exhibited over 100-fold decrease in potency relative to the parent acylsulfonamide. On the other hand, replacement of the carbonyl group of **8a** with a methylene group (**32a**) also reduced potency,

Table 7
In vitro and in vivo profiles of compound **8f**



PPARs EC_{50}[a] (nM)			PPARγ binding IC_{50}[b] (nM)	Metobolic clearance h/r[c] (μL/min/mg)	*c*log*P*[d]	*c*log*D*[d] (pH 7.4)
γ	α	δ				
15	>10,000	>10,000	330	9/6	4.04	2.05

Antidiabetic effects[e]		Pharmokinetics[h]	
PG ED_{25}[f] (mg/kg)	TG ED_{25}[g] (mg/kg)	C_{max}	AUC_{0-24} (ng h/mL)
0.17	0.20	946	15317

[a,c] See the legends of Table 1.
[b] IC_{50} value means the concentration of a given compound required for 50% inhibition of the specific binding of [^{3}H]-AD-5061 to human PPARγ.
[d] Calculated using ACD ver. 10.[13]
[e] Test compound was administered by oral gavage to male Wistar fatty rats for 7 days.
[f] Effective dose for 25% reduction of plasma glucose.
[g] Effective dose for 25% reduction of plasma triglyceride.
[h] Test compound was administered by oral gavage to male Wistar fatty rats.

but still maintained 10^{-8} M order transactivation. Based on these results, it clearly indicates that the sulfonyl group is more important than the carbonyl group in terms of PPARγ activity. Therefore, we conducted further modification of the sulfonamide group of **32a**. Carbamate **32b** showed comparable potency to **32a** and 'reverse' carbamate **29a** also essentially equipotent to **32a**. Taken together, it is suggested that the position of the hydrogen bonding acceptor (the sulfonyl or carbonyl groups at the 5th position from the central benzene ring, highlighted in red in Table 6) is more important than that of the imide NH group. Still, the acidity of the imide NH group could also contribute to high potency. In fact, sulfonylcarbamate **29b** designed by replacement of the butyl group of **29a** with pentylsulfonyl group exhibits nanomolar potency with moderate metabolic stability. It is noteworthy that the sulfonyl group as a hydrogen bonding acceptor is tolerated at the 7th position from the central benzene ring. Moreover, insertion of a NH group between the sulfonyl and pentyl groups of **8a** did not significantly affect either potency or metabolic stability (**8r**). From these results, it is suggested that the imide NH group contributes to adjusting overall lipophilicity, improving the metabolic stability. In fact, compounds **8a**,**29b** with acidic $CONHSO_2$ group (pK_a = 4.6),[21b] which can be deprotonated in physiological pH, showed better metabolic stability than sulfonamide **32a** (pK_a = 17.5).[22] Consequently, acylsulfamide **8r** displayed the highest activity in this class (EC_{50} = 1.1 nM); however, its metabolic stability was comparable to that of **8a**. Although we failed to identify a novel acidic moiety superior to the acylsulfonamide group, the acylsulfamide was found to be a reasonable alternative.

3.2. Further profiling including in vivo anti-diabetic effects

Further profiling of compound **8f**, which showed potent PPARγ activity with an EC_{50} value of 15 nM and good metabolic stability, was carried out. Compound **8f** was found to be a highly selective PPARγ agonist without showing significant PPARα,δ agonism up to 10 μM (Table 7). To assess whether **8f** is a bona fide PPARγ ligand, binding affinity to PPARγ was measured by scintillation proximity assay (SPA) using a radioligand [^{3}H]-AD-5061.[12] It is

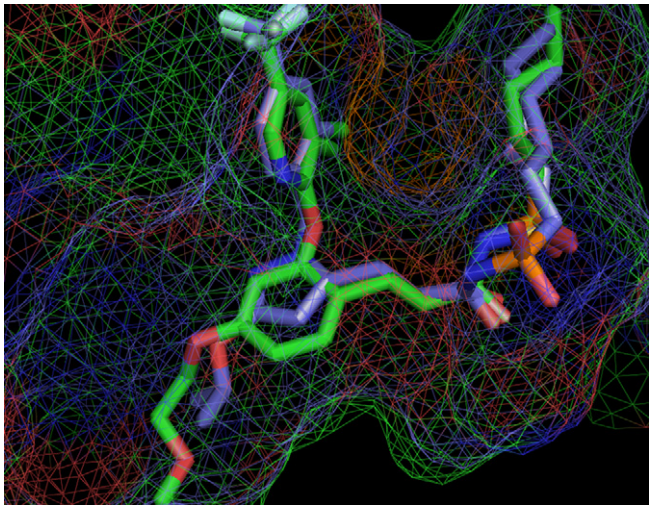


Figure 3. Superposition of the co-crystal structures of pyridyloxybenzene **8f** (shown in green) and benzylpyrazole **1** (shown in blue) bound to PPARγ-LBD.

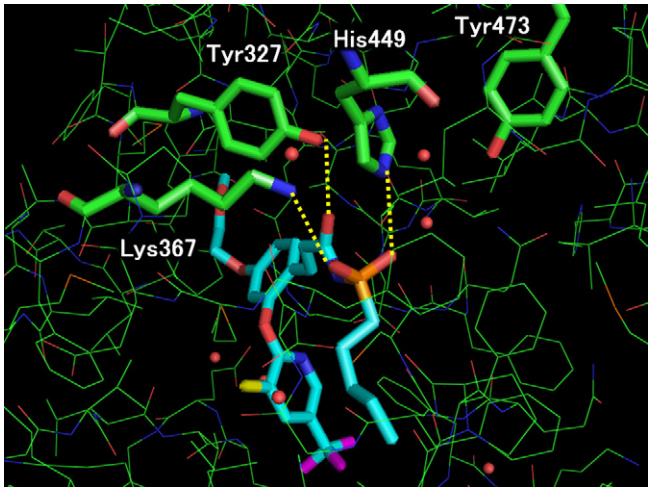


Figure 4. Co-crystal structure of **8f** (light blue) bound to the PPARγ-LBD. Residues His449, Tyr327, and Lys367 interacting with the acylsulfonamide group of **8f** are highlighted in green. Hydrogen bonds are shown as yellow dotted lines. Tyr473 is also shown for reference.

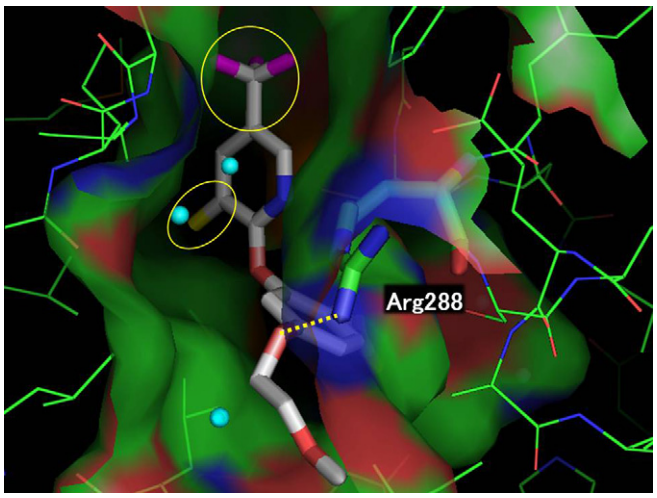


Figure 5. Co-crystal structure of **8f** (shown in white) bound to the PPARγ-LBD. Arg288 interacting with the 2-methoxyethoxy group of **8f** is highlighted in green, and the corresponding hydrogen bond is shown as a yellow dotted line. The lipophilic pockets accommodating the trifluoromethyl and chloro groups of **8f** are highlighted by yellow circles.

shown that compound **8f** proved to be a good PPARγ binder with an IC_{50} value of 330 nM. Additionally, **8f** did not show significant cytotoxicity up to 30 μM (data not shown) presumably due to a significant decrease in lipophilicity compared with benzylpyrazole **1** (*c*log*P* = 4.04, *c*log*D* [pH 7.4] = 2.05 for **8f** vs *c*log*P* = 5.00, clogP [pH7.4] = 3.06 for **1**). Next, antidiabetic effects of compound **8f** were investigated using a genetically obese rodent model of T2DM, Wistar fatty rats.[12] After once-daily oral dosing for 7 days, compound **8f** produced significant and dose-dependent reductions in plasma glucose level (PG, ED_{25} value: 0.17 mg/kg) and triglyceride level (TG, ED_{25} value: 0.20 mg/kg). In parallel, the pharmacokinetic (PK) profile of **8f** in Wistar fatty rats was determined following an oral dose of 0.18 mg/kg. As expected from its high stability to both oxidative and non-oxidative metabolism (see Table 3), the PK study revealed that **8f** shows sufficient plasma exposure (C_{max} = 946 ng/mL, AUC_{0-24h} = 15317 ng h/mL), which contributes to the potent in vivo efficacy.

3.3. X-ray co-crystallographic studies and computational analyses

In order to gain insight into molecular basis for the crucial interactions of this series of compounds with PPARγ-LBD, co-crystal structure of the protein in complex with compound **8f** was determined at 2.5 Å resolution. The superposition of the co-crystal structures of **8f** and the previously-identified benzylpyrazole **1** is shown in Figure 3. As we have expected, **8f** fully occupies all three arms of the Y-shaped pocket and adopts a closely similar binding mode to benzylpyrazole **1**.[12] It is consistent with the docking model shown in Figure 2 and the 3-chloro-5-trifluoromethylpyridyloxy and 2-chloro-4-trifluoromethylbenzyl groups are located at the essentially same position.

Although there is no interaction between **8f** and Tyr473, three hydrogen bonds between the acylsulfonamide moiety and particular amino acids of the TZD pocket are observed. As depicted in Figure 4, the three oxygen atoms of the acylsulfonamide form hydrogen bonds with amino acid residues adjacent to Tyr473: the carbonyl oxygen with Tyr327, one sulfonyl oxygen with Lys367, and the other sulfonyl oxygen with His449. On the other hand, the imide NH group does not form any hydrogen bonds with residues in the TZD pocket, which is consistent with the SAR shown in Table 6. The fact that both sulfonyl oxygens participate in the direct interaction could explain the importance of the sulfonyl group. Omission of the sulfonyl group of **23a** (**23b**) led to 100-fold decrease in activity, while replacement of the carbonyl group of **8a** with a methylene group (**32a**) gave about 12-fold drop (see Table 6). But it still remains unclear why carbamates **29a** and **32b** have comparable potency to sulfonamide **32a**.

Figure 5 illustrates the co-crystal structure of **8f** seen from a different direction to highlight additional interactions of **8f** with the LBD. The phenolic oxygen of the methoxyethoxy group of **8f** forms a direct hydrogen bond with Arg288, which is consistent with the SAR finding that the lead compound **2** without the 4-alkoxy group was less potent than the 4-alkoxy counterparts such as **8a** and **23a** (see Table 1). Moreover, there are two lipophilic pockets around the binding region that accommodates the 2-pyridyloxy group of **8f**. The 5-trifluoromethyl group on the pyridine ring binds to a comparatively large lipophilic pocket, while the chlorine atom at

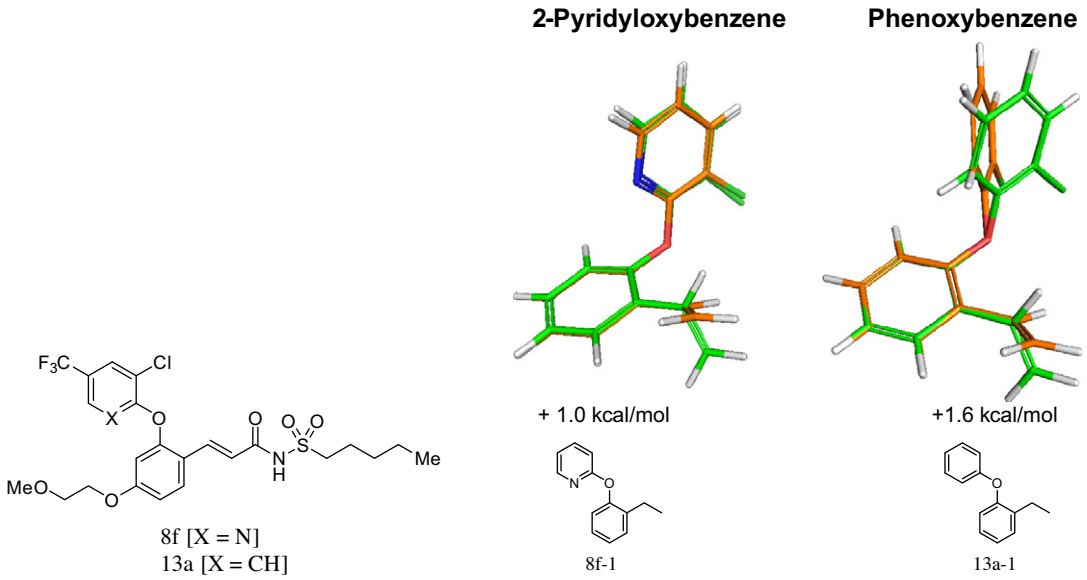


Figure 6. Superposition of the estimated global minimum conformations of simplified model compounds **8f–1**, **13a–1** (shown in orange) and binding conformations of the corresponding substructures of **8f** with PPARγ-LBD (shown in green). The putative binding conformation of **13a** was obtained by a docking study using the 3-dimesional LBD structure derived from the co-crystal structure of **8f**. Then **8f-1** and **13a-1**, partial structures of **8f** and **13a**, were energy-minimized by MMFF94s with the steepest descent minimum to a maximum gradient of 0.1 kcal/mol/Å separately without the protein. The energy differences between the two conformations of each compound are calculated.

3-position effectively occupies a small 'dimple'. The hydrophobic interactions unambiguously indicate the importance of these two substituents, leading to a plausible explanation of why removal of one of the two substituents dramatically decreased potency (see Table 4). In addition to the two lipophilic substituents, the pyridine nitrogen moderately increased the potency (**8f** vs **13a** in Table 4). But no interaction of the nitrogen with the protein was observed in the co-crystal structure of **8f**. To further clarify a role of the nitrogen atom, we conducted energy minimization around the rotatable bonds of simplified biaryl ether compounds of **8f-1** and **13a-1** using MMFF94s and compared with the corresponding binding conformations of 2-pyridyloxybenzene **8f** and phenoxybenzene **13a**. With regard to **13a**, the putative binding conformation was obtained by a docking study using the 3-dimesional LBD structure derived from the co-crystal structure of **8f**. As shown in Figure 6, the estimated global minimum conformation of pyridyloxybenzene **8f-1** is nearly identical with the actual binding conformation of the corresponding part seen in the co-crystal structure. In contrast, the lowest energy structure of phenoxybenzene **13a-1** is relatively different from the putative binding conformation of the corresponding part.[23]

Again, the results from the co-crystallographic studies and conformational calculation can help our understanding of several key structural requirements for affinity of these compounds. The molecular basis of the binding mode and the required structural features of **8f** described here offer a significant opportunity to search further for new PPARγ ligands.

4. Conclusion

We have carried out a medicinal chemistry study to explore a novel class of non-TZD and non-carboxylic acid-based PPARγ agonists starting from the benzylpyrazole agonist **1**. Replacement of the benzylpyrazole moiety of **1** with other templates derived from in-house carboxylic acid-based PPARγ ligands led to the identification of the pyridyloxybenzene-acylsulfonamides as new agonists. The SAR and computational analyses based on the X-ray co-crystallographic studies revealed the key structural features of this chemotype as a PPARγ ligand: the acylsulfonamide, chloro and trifluoromethyl groups on the pyridine ring, 4-methoxyethoxy side chain on the benzene ring, and vinylene linker are optimal for balancing the in vitro activity and metabolic stability.

Consequently, we have succeeded in discovering a new, potent, selective, and orally active PPARγ agonist, pyridyloxybenzene-acylsulfonamide **8f** with improved druglike properties. In fact, compound **8f** displayed potent and highly selective PPARγ agonism (EC_{50} = 15 nM) with good metabolic stability and no cytotoxicity up to 30 μM, presumably due to its decreased lipophilicity compared with the previous benzylpyrazole-acylsulfonamide **1**. Furthermore, oral administration of **8f** to Wistar fatty rats led to a robust and dose-dependent reduction in PG and TG levels (ED_{25} = 0.17, 0.25 mg/kg, respectively). The molecular basis of the binding mode and the required structural features of **8f** described here offer a significant opportunity to search further for new PPARγ ligands. A medicinal chemistry effort is in progress, and the results will be presented in due course.

5. Experimental section

5.1. Chemistry

5.1.1. General methods

Melting points (mp) were determined on a Büch melting point B-545 or a Yanagimoto micro melting point apparatus and were uncorrected. The proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AVANCE 300 (300 MHz) spectrometer or a Varian MERCURY plus 300 (300 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, doublets of doublet; br s, broad singlet. Elemental analyses (C, H, N) were within ±0.3% of theoretical values and were determined in Takeda Analytical Research Laboratories (Osaka, Japan). Liquid Chromatography-Mass Spectrometry (LC-MS) analysis was performed on a Shiseido CAPCELL PACK C-18 UG120 S-3 column in a Waters Alliance 2795 or an Agilent 1100 System equipped with a Waters 2487 absorbance detector and a Micromass ZQ2000 mass spectrometer, eluted with water containing 0.05% TFA with a linear gradient of 10% to 100% of MeCN containing 0.04% TFA. Mass spectra were recorded using electrospray ionization (ESI) in positive ion mode. Flash chromatography was performed with Merck silica gel 60 (0.063–0.200 mm) or Fuji Silysia Chemical Purif-Pack SI (60 μM) or Varian Bond Elut Si (40 μM). High-performance liquid chromatography (HPLC) was performed with Nomura Chemical Co., Ltd. Develosil ODS-UG10 using a Waters HPLC module equipped with a 2487 2-channel UV/VIS detector. Reaction progress was determined by thin layer chromatography (TLC) analysis on Merck silica gel 60 F_{254} plates. Visualization was with UV light (254 nm) or iodine. Yields are of purified compounds and were not optimized. Reagents and solvents were obtained from commercial sources and used without further purification. The following abbreviations are used: AcOH, acetic acid; Ac_2O, acetic anhydride; ADDP, 1,1′-(azodicarbonyl)dipiperidine; CDI, *N,N*-carbonyldiimidazole; DBU, 1,8-diazabicyclo[5.4.0]-7-undecene; DCM, dichloromethane; DEAD, diethyl azodicarboxylate; DIBAL-H, diisobutylaluminium hydride; DIPEA, diisopropylethylamine; DMA, *N,N*-dimethylacetamide; DMAP, 4-dimethylaminopyridine; DMF, *N,N*-dimethylformamide; DMSO, dimethylsulfoxide; EtOAc, ethyl acetate; EtOH, ethanol; Et_2O, diethyl ether; IPE, diisopropyl ether; MeCN, acetonitrile; MeOH, methanol; MNBA, 2-methyl-6-nitrobenzoic anhydride; MOMCl, methoxymethyl chloride; MsCl, methansulfonyl chloride; TBAF, tetrabutylammonium fluoride; TEA, triethylamine; TFA, trifluoroacetic acid; THF, tetrahydrofuran; WSC-HCl, water-soluble carbodiimide hydrochloride (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride).

5.1.1.1. 2-Hydroxy-4-methoxymethoxybenzaldehyde (4a). To a stirred solution of **3** (101 g, 0.730 mol) in acetone (2.0 L) was added K_2CO_3 (131 g, 0.948 mol), followed by MOMCl (66.0 mL, 0.877 mol) at room temperature, and the mixture was stirred at same temperature overnight. The reaction was quenched with water and extracted with EtOAc and the combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude solid, which was purified by silica gel chromatography (hexane-EtOAc, 4:1) to give a pale-orange solid. The solid was recrystallized from EtOAc/hexane to give **8** (127 g, 96%) as white crystals. Mp 55.5–55.7 °C. ^{1}H NMR ($CDCl_3$): δ 3.49 (s, 3H), 5.22 (s, 2H), 6.60 (d, *J* = 2.3 Hz, 1H), 6.65 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.34–7.51 (m, *J* = 8.7 Hz, 1H), 9.74 (s, 1H), 11.37 (s, 1H). Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.36; H, 5.50.

5.1.1.2. 2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)benzaldehyde (5a). To a stirred solution of **4a** (74.5 g, 410 mmol) in DMF (450 mL) was added NaH (60% dispersion in oil, 19.7 g, 491 mmol) at 0 °C and the mixture was stirred at the temperature for 30 min. Then 2,3-dichloro-5-(trifluoromethyl)pyridine (60.0 mL, 433 mmol) was added to the mixture, which was allowed to warm to room temperature, and stirred at room temperature for 1 h and at 50 °C for 1 h. The reaction was quenched with sat. NH_4Cl on ice-bath and extracted with EtOAc

and the combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual solid was purified by silica gel chromatography (hexane-EtOAc, 9:1 to 2:1) to give a pale-yellow solid, which was recrystallized from EtOAc/hexane to give **5a** (79.0 g, 53%) as white crystals. Mp 93.9–94.0 °C. ^{1}H NMR ($CDCl_3$): δ 3.50 (s, 3H), 5.25 (s, 2H), 6.91 (d, J = 2.3 Hz, 1H), 7.08 (dd, J = 8.7, 2.3 Hz, 1H), 7.92 (d, J = 8.7 Hz, 1H), 8.03 (d, J = 2.1 Hz, 1H), 8.24 (s, 1H), 9.99 (s, 1H). Anal. Calcd for $C_{15}H_{11}ClF_3NO_4$: C, 49.81; H, 3.07; N, 3.87. Found: C, 49.87; H, 3.01; N, 3.71.

5.1.1.3. 2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}benzaldehyde (5b). Compound **5b** (a brown oil) was prepared from **4b** and 2,3-dichloro-5-(trifluoromethyl)pyridine in quantitative yield following a similar procedure to provide **5a**. ^{1}H NMR ($CDCl_3$): δ 7.22–7.32 (m, 1H), 7.40–7.49 (m, 1H), 7.65–7.75 (m, 1H), 7.99 (dd, J = 7.7, 1.7 Hz, 1H), 8.04 (d, J = 2.3 Hz, 1H), 8.23 (dd, J = 2.3, 0.9 Hz, 1H), 10.17 (s, 1H).

5.1.1.4. Ethyl (2*E*)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]acrylate (6a). To an ice-cooled solution of ethyl diethylphosphonoacetate (2.76 g, 12.3 mmol) in THF (10 mL) was added NaH (60% dispersion in oil, 482 mg, 12.1 mmol) with stirring and after 30 min, **5a** (3.90 g, 10.8 mmol) in DMF (10 mL) was added to the mixture, which was allowed to warm to room temperature, and stirred for 30 min. The reaction was quenched with sat. NH_4Cl and extracted with EtOAc and the combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was purified by silica gel chromatography (hexane-EtOAc, 19:1 to 65:35) to give **6a** (4.66 g, quant.) as a pale-yellow solid. Recrystallization from EtOAc/hexane gave white crystals. Mp 73.5–74.5 °C. ^{1}H NMR ($CDCl_3$): δ 1.29 (t, J = 7.2 Hz, 3H), 3.48 (s, 3H), 4.20 (q, J = 7.0 Hz, 2H), 5.19 (s, 2H), 6.38 (d, J = 16.0 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 7.00 (dd, J = 8.7, 2.3 Hz, 1H), 7.64 (d, J = 8.9 Hz, 1H), 7.69 (d, J = 16.0 Hz, 1H), 8.01 (d, J = 1.7 Hz, 1H), 8.25 (dd, J = 2.2, 1.0 Hz, 1H). Anal. Calcd for $C_{19}H_{17}ClF_3NO_5$: C, 52.85; H, 3.97; N, 3.24. Found: C, 52.87; H, 3.89; N, 3.10.

5.1.1.5. Ethyl (2*E*)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)acrylate (6b). Compound **6b** (a pale-yellow oil) was prepared from **5b** in 84% yield following a similar procedure to provide **6a**. ^{1}H NMR ($CDCl_3$): δ (t, J = 7.2 Hz, 3H), 4.22 (q, J = 7.2 Hz, 2H), 6.49 (d, J = 16.2 Hz, 1H), 7.16 (dd, J = 8.1, 1.1 Hz, 1H), 7.28–7.36 (m, 1H), 7.42–7.50 (m, 1H), 7.71 (dd, J = 7.7, 1.7 Hz, 1H), 7.77 (d, J = 16.2 Hz, 1H), 8.01 (d, J = 1.9 Hz, 1H), 8.24 (dd, J = 2.1, 0.9 Hz, 1H).

5.1.1.6. Ethyl (2*E*)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]-2-methylacrylate (6c). Compound **6c** (a pale-yellow oil, E/Z = 1.0/0.15, determined by the integral value in ^{1}H NMR spectra at 6.92 ppm) was prepared from **5a** in quantitative yield following a similar procedure to provide **6a**. ^{1}H NMR ($CDCl_3$): δ 1.25 (t, J = 7.1 Hz, 3H), 2.01 (s, 3H), 3.50 (s, 3H), 4.17 (q, J = 7.0 Hz, 2H), 5.20 (s, 2H), 6.92 (d, J = 2.3 Hz, 1H), 7.01 (dd, J = 8.6, 2.2 Hz, 1H), 7.38 (d, J = 8.7 Hz, 1H), 7.49 (s, 1H), 7.96 (d, J = 1.3 Hz, 1H), 8.23 (s, 1H).

5.1.1.7. Ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(methoxymethoxy)phenyl]propanoate (33a). A stirred solution of **6a** (4.46 g, 10.3 mmol) in THF (50 mL) was hydrogenated under atmospheric pressure with 10% Pd/C (wet, 0.75 g, 0.34 mmol) at room temperature for 1 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give **33a** (4.49 g, quant.) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.21 (t, J = 7.1 Hz, 3H), 2.54–2.62 (m, 2H), 2.77 (t, J = 7.7 Hz, 2H), 3.47 (s, 3H), 4.09 (q, J = 7.1 Hz, 2H), 5.15 (s, 2H), 6.81 (d, J = 2.4 Hz, 1H), 6.93 (dd, J = 8.5, 2.4 Hz, 1H), 7.24 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 1.9 Hz, 1H), 8.26 (dd, J = 2.2, 1.0 Hz, 1H).

5.1.1.8. Ethyl 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)propanoate (33b). To a stirred solution of **33a** (27.5 g, 63.4 mmol) in THF (320 mL) was added conc. HCl (10.0 mL, 120 mmol) and the mixture was stirred at 50 °C for 45 min. After being cooled to room temperature, the reaction was quenched with 1 M NaOH (120 mL) and diluted with EtOAc and washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane-EtOAc, 19:1 to 4:1) to give **33b** (20.5 g, 83%) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.09–1.38 (m, 3H), 2.44–2.68 (m, 2H), 2.68–2.85 (m, 2H), 3.97–4.25 (m, 2H), 6.61 (d, J = 2.2 Hz, 1H), 6.65–6.77 (m, 1H), 7.18 (d, J = 8.1 Hz, 1H), 7.98 (d, J = 2.2 Hz, 1H), 8.26 (s, 1H).

5.1.1.9. Ethyl (2*E*)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)acrylate (33c). To a stirred solution of **6a** (52.9 g, 111 mmol) in acetone (500 mL) was added 1 M HCl (250 mL, 250 mmol) and the mixture was stirred under reflux for 5 h. After being cooled to room temperature, the reaction was neutralized with 1 M NaOH (250 mL, 250 mmol) and extracted with EtOAc and the combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual solid was purified by silica gel chromatography (hexane-EtOAc, 9:1 to 4:1) to give **33c** (44.5 g, quant.) as a white solid. Recrystallization from EtOAc/hexane gave white crystals. Mp 123.5–124.0 °C. ^{1}H NMR ($CDCl_3$): δ 1.28 (t, J = 7.2 Hz, 3H), 4.20 (q, J = 7.2 Hz, 2H), 5.46 (s, 1H), 6.36 (d, J = 16.0 Hz, 1H), 6.65 (d, J = 2.4 Hz, 1H), 6.79 (dd, J = 8.4, 2.4 Hz, 1H), 7.59 (d, J = 8.7 Hz, 1H), 7.70 (d, J = 16.0 Hz, 1H), 8.01 (d, J = 2.3 Hz, 1H), 8.26 (dd, J = 2.2, 1.0 Hz, 1H). Anal. Calcd for $C_{17}H_{13}ClF_3NO_4$: C, 52.66; H, 3.38; N, 3.61. Found: C, 52.74; H, 3.34; N, 3.46.

5.1.1.10. Ethyl (2*E*)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-hydroxyphenyl)-2-methyl acrylate (33d). Compound **33d** (colorless crystals) was prepared from **6c** in 84% yield following a similar procedure to provide **33c**. Mp 101.5–102.0 °C. ^{1}H NMR ($CDCl_3$): δ 1.26 (t, J = 7.2 Hz, 3H), 2.01 (d, J = 1.3 Hz, 3H), 4.17 (q, J = 7.2 Hz, 2H), 6.07 (s, 1H), 6.68 (d, J = 2.6 Hz, 1H), 6.77 (dd, J = 8.6, 2.5 Hz, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.50 (s, 1H), 7.98 (d, J = 1.9 Hz, 1H), 8.23 (d, J = 1.1 Hz, 1H). Anal. Calcd for $C_{18}H_{15}ClF_3NO_4$: C, 53.81; H, 3.76; N, 3.49. Found: C, 53.90; H, 3.74; N, 3.50.

5.1.1.11. Ethyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propanoate (7a). To a stirred solution of **33b** (9.90 g, 25.4 mmol), 2-methoxyethanol (2.50 mL, 31.7 mmol) and tributylphosphine (13.0 mL, 52.2 mmol) in THF was added potionwise ADDP (7.41 g, 29.4 mmol) at 50 °C, then the mixture was stirred for 5 min. The mixture was concentrated in vacuo, and the residue was washed with IPE and the filtrate was concentrated in vacuo. The crude oil was purified by silica gel chromatography (hexane-EtOAc, 19:1 to 4:1) to give **7a** (10.1 g, 89%) as a white solid. Recrystallization from EtOAc/hexane gave white needles. Mp 70.0–70.5 °C. ^{1}H NMR ($CDCl_3$): δ 1.21 (t, J = 7.2 Hz, 3H), 2.52–2.62 (m, 2H), 2.77 (t, J = 7.7 Hz, 2H), 3.43 (s, 3H), 3.73 (dd, J = 5.5, 4.0 Hz, 2H), 4.02–4.15 (m, 4H), 6.68 (d, J = 2.6 Hz, 1H), 6.82 (dd, J = 8.6, 2.5 Hz, 1H), 7.22 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 2.1 Hz, 1H), 8.26 (d, J = 0.9 Hz, 1H). Anal. Calcd for $C_{20}H_{21}ClF_3NO_5$: C, 53.64; H, 4.73; N, 3.13. Found: C, 53.64; H, 4.68; N, 2.95.

5.1.1.12. Ethyl 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(diethylamino)-2-oxoethoxy]phenyl}propanoate (7c). To a stirred solution of **33b** (0.68 g, 1.74 mmol) and K_2CO_3 (322 mg, 2.33 mmol) in DMF (15 mL) was added 2-chloro-*N*,*N*-diethylacetamide (0.31 g, 2.07 mmol) and the mixture was stirred at room temperature for 2 h, at 50 °C for 30 min, and at 80 °C for 1 h. Then, additional 2-chloro-*N*,*N*-diethylacetamide (0.30 g, 2.01 mmol) was added to the mixture, which was stirred at 80 °C for additional 30 min. After being cooled to room temperature, the reaction was acidified with 1 M HCl, and extracted with EtOAc, and the combined organic layer was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane-EtOAc, 9:1 to 1:2) to give crude **7c** (1.39 g, quant.) as a white solid. Recrystallization from EtOAc/hexane gave white needles. Mp 88.5–89.0 °C. ^{1}H NMR ($CDCl_3$): δ 1.13 (t, J = 7.2 Hz, 3H), 1.21 (td, J = 7.1, 1.8 Hz, 6H), 2.57 (t, J = 7.7 Hz, 2H), 2.76 (t, J = 7.6 Hz, 2H), 3.30–3.50 (m, 4H), 4.09 (q, J = 7.0 Hz, 2H), 4.64 (s, 2H), 6.73 (d, J = 2.6 Hz, 1H), 6.84 (dd, J = 8.4, 2.5 Hz, 1H), 7.24 (d, J = 9.0 Hz, 1H), 7.98 (d, J = 2.1 Hz, 1H), 8.23–8.32 (m, 1H). Anal. Calcd for $C_{23}H_{26}ClF_3N_2O_5$: C, 54.93; H, 5.21; N, 5.57. Found: C, 54.98; H, 5.11; N, 5.46.

5.1.1.13. Ethyl (2*E*)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylate (7d). Compound **7d** (white feather crystals) was prepared from **33c** and 2-methoxyethanol in 60% yield following the procedure to provide **7a**. Mp 78.2–78.5 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 1.28 (t, J = 7.1 Hz, 3H), 3.44 (s, 3H), 3.66–3.84 (m, 2H), 4.04–4.34 (m, 4H), 6.37 (d, J = 16.0 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.85–6.97 (m, 1H), 7.58–7.75 (m, 2H), 8.01 (d, J = 2.3 Hz, 1H), 8.24 (s, 1H). Anal. Calcd for $C_{20}H_{19}ClF_3NO_5$: C, 53.88; H, 4.30; N, 3.14. Found: C, 54.00; H, 4.30; N, 3.05.

5.1.1.14. Ethyl (2*E*)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methylacrylate (7e). Compound **7e** (a colorless oil, E/Z = 1.00/0.13, determined by the integral value in ^{1}H NMR spectra at 6.78 ppm) was prepared from **33d** and 2-methoxyethanol in 95% yield following the procedure to provide **7a**. ^{1}H NMR ($CDCl_3$): δ1.23–1.29 (m, 3H), 2.02 (d, J = 1.5 Hz, 3H), 3.45 (s, 3H), 3.73–3.80 (m, 2H), 4.06–4.23 (m, 4H), 6.78 (d, J = 2.6 Hz, 1H), 6.91 (dd, J = 8.7, 2.4 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.50 (s, 1H), 7.96 (d, J = 2.1 Hz, 1H), 8.22 (d, J = 1.1 Hz, 1H).

5.1.1.15. Ethyl (2*E*)-3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)acrylate (7g). Compound **7g** (white feather crystals) was prepared from **33c** and 2-iodopropane in 96% yield following a similar procedure to provide **7c**. Mp 84.5–85.0 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 1.28 (t, J = 7.1 Hz, 3H), 1.35 (d, J = 6.0 Hz, 6H), 4.20 (q, J = 7.1 Hz, 2H), 4.44–4.64 (m, 1H), 6.35 (d, J = 16.0 Hz, 1H), 6.64 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 8.6, 2.5 Hz, 1H), 7.62 (d, J = 8.9 Hz, 1H), 7.69 (d, J = 16.0 Hz, 1H), 8.01 (d, J = 1.7 Hz, 1H), 8.25 (dd, J = 2.2, 1.0 Hz, 1H). Anal. Calcd for $C_{20}H_{19}ClF_3NO_4$: C, 55.89; H, 4.46; N, 3.26. Found: C, 55.87; H, 4.39; N, 3.31.

5.1.1.16. Ethyl (2*E*)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(cyclopropyloxy)ethoxy]-phenyl}acrylate (7h). Compound **7h** (white crystals) was prepared from **33c** and 2-cyclopropoxyethanol[24] in 72% yield following a similar procedure to provide **7a**. Mp 75.4–75.9 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 0.44–0.56 (m, 2H), 0.56–0.65 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 3.31–3.44 (m, 1H), 3.78–3.88 (m, 2H), 4.06–4.14 (m, 2H), 4.20 (q, J = 7.2 Hz, 2H), 6.36 (d, J = 16.2 Hz, 1H), 6.69 (d, J = 2.4 Hz, 1H), 6.88 (dd, J = 8.8, 2.4 Hz, 1H), 7.62 (d, J = 8.9 Hz, 1H), 7.69 (d, J = 16.0 Hz, 1H), 8.01 (d, J = 1.7 Hz, 1H), 8.24 (dd, J = 2.2, 1.0 Hz, 1H). Anal. Calcd for $C_{22}H_{21}ClF_3NO_5$: C, 56.00; H, 4.49; N, 2.97. Found: C, 56.02; H, 4.43; N, 2.97.

5.1.1.17. Ethyl (2*E*)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]acrylate (7i). Compound **7i** (white crystals) was prepared from **33c** and 1-bromo-3-methoxypropane in 70% yield following a similar procedure to provide **7c**. Mp 86.4–86.5 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 1.28 (t, J = 7.2 Hz, 3H), 1.91–2.12 (m, 2H), 3.34 (s, 3H), 3.53 (t, J = 6.1 Hz, 2H), 4.07 (t, J = 6.2 Hz, 2H), 4.20 (q, J = 7.2 Hz, 2H), 6.36 (d, J = 16.0 Hz, 1H), 6.68 (d, J = 2.6 Hz, 1H), 6.87 (dd, J = 8.7, 2.4 Hz, 1H), 7.63 (d, J = 8.9 Hz, 1H), 7.69 (d, J = 16.0 Hz, 1H), 8.01 (d, J = 2.3 Hz, 1H), 8.26 (d, J = 0.9 Hz, 1H). Anal. Calcd for $C_{21}H_{21}ClF_3NO_5$: C, 54.85; H, 4.60; N, 3.05. Found: C, 54.88; H, 4.47; N, 2.98.

5.1.1.18. 2-[(Triisopropylsilyl)oxy]ethanol. To a mixture of ethylene glycol (34 mL) and pyridine (34 mL) was added dropwise chloro(triisopropyl)silane (10.7 mL, 50 mmol) with stirring at room temperature over 20 min, then the mixture was stirred for 12 h. The mixture was diluted with water and extracted with EtOAc. The aqueous layer was washed with EtOAc. The combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane-EtOAc, 20:1 to 5:1) to give 2-[(triisopropylsilyl)oxy]ethanol (10.5 g, 96%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.99–1.17 (m, 2H), 2.17 (t, J = 6.22 Hz, 1H), 3.58–3.71 (m, 2H), 3.74–3.85 (m, 2H).

5.1.1.19. Ethyl (2*E*)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-{2-[(triisopropylsilyl)oxy]ethoxy}phenyl)acrylate (7j). Compound **7j** (a pale-yellow oil) was prepared from **33c** and 2-[(triisopropylsilyl)oxy]ethanol in 89% yield following a similar procedure to provide **7j**. ^{1}H NMR ($CDCl_3$): δ 0.97–1.15 (m, 21H), 1.28 (t, J = 7.06 Hz, 3H), 3.98–4.12 (m, 4H), 4.20 (q, J = 7.16 Hz, 2H), 6.36 (d, J = 16.20 Hz, 1H), 6.70 (d, J = 2.45 Hz, 1H), 6.89 (dd, J = 8.76, 2.54 Hz, 1H), 7.62 (d, J = 8.67 Hz, 1H), 7.68 (d, J = 16.20 Hz, 1H), 8.01 (d, J = 2.07 Hz, 1H), 8.25 (dd, J = 2.07, 0.94 Hz, 1H).

5.1.1.20. Ethyl (2*E*)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethoxy]phenyl}acrylate (7k). Compound **7k** (colorless crystals) was prepared from **33c** and 2-(2-bromoethyl)-2-methyl-1,3-dioxolane in 74% yield following a similar procedure to provide **7c**. Mp 167–168 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 1.28 (t, J = 7.1 Hz, 3H), 1.39 (s, 3H), 2.18 (t, J = 7.0 Hz, 2H), 3.88–4.02 (m, 4H), 4.11 (t, J = 7.0 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H), 6.36 (d, J = 16.0 Hz, 1H), 6.65–6.69 (m, 1H), 6.87 (dd, J = 8.8, 2.4 Hz, 1H), 7.59–7.73 (m, 2H), 8.01 (d, J = 1.9 Hz, 1H), 8.25 (dd, J = 2.1, 0.9 Hz, 1H). Anal. Calcd for $C_{23}H_{23}ClF_3NO_6$: C, 55.04; H, 4.62; N, 2.79. Found: C, 55.07; H, 4.67; N, 2.78.

5.1.1.21. Ethyl (2*E*)-3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(methylsulfonyl)propoxy]-phenyl}acrylate (7l). Compound **7l** (white crystals) was prepared from **33c** and 3-(methylsulfonyl)propyl 4-methylbenzenesulfonate[25] in 97% yield following a similar procedure to provide **7c**. Mp 190.6–191.0 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ1.29 (t, J = 7.2 Hz, 3H), 2.31–2.42 (m, 2H), 2.96 (s, 3H), 3.19–3.29 (m, 2H), 4.14 (t, J = 5.8 Hz, 2H), 4.20 (q, J = 7.2 Hz, 2H), 6.38 (d, J = 16.0 Hz, 1H), 6.68 (d, J = 2.4 Hz, 1H), 6.86 (dd, J = 8.7, 2.4 Hz, 1H), 7.62–7.73 (m, 2H), 8.02 (d, J = 1.9 Hz, 1H), 8.25 (dd, J = 2.1, 0.9 Hz, 1H). Anal. Calcd for $C_{21}H_{21}ClF_3NO_6S$: C, 49.66; H, 4.17; N, 2.76. Found: C, 49.55; H, 4.16; N, 2.66.

5.1.1.22. Ethyl (2*E*)-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-cyanopropoxy)phenyl]-acrylate (7m). Compound **7m** (colorless crystals) was prepared from **33c** and 4-bromobutyronitrile in 94% yield following a similar procedure to provide **7c**. Mp 106–107 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 1.29 (t, J = 7.1 Hz, 3H), 2.09–2.22 (m, 2H), 2.59 (t, J = 7.0 Hz, 2H), 4.10 (t, J = 5.7 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H), 6.38 (d, J = 16.0 Hz, 1H), 6.69 (d, J = 2.4 Hz, 1H), 6.87 (dd, J = 8.9, 2.4 Hz, 1H), 7.62–7.73 (2H, m), 8.02 (d, J = 2.1 Hz, 1H), 8.25 (dd, J = 2.1, 0.9 Hz, 1H). Anal. Calcd for $C_{21}H_{18}ClF_3N_2O_4$: C, 55.46; H, 3.99; N, 6.16. Found: C, 55.39; H, 3.94; N, 6.26.

5.1.1.23. 3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propanoic acid (34a). To a stirred solution of **7a** (5.21 g, 11.6 mmol) in THF (12 mL) and EtOH (12 mL) was added 1 M NaOH (25.0 mL, 25.0 mmol) and the mixture was stirred at 50 °C for 30 min. After being cooled to room temperature, the reaction was acidified with 1 M HCl (25.0 mL, 25.0 mmol), and extracted with EtOAc, and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a white solid, which was recrystallized from EtOAc/hexane to give **34a** (4.15 g, 85%) as white needles. Mp 116–117 °C. ^{1}H NMR ($CDCl_3$): δ 2.56–2.69 (m, 2H), 2.78 (t, J = 7.3 Hz, 2H), 3.43 (s, 3H), 3.73 (dd, J = 5.5, 4.0 Hz, 2H), 4.09 (dd, J = 5.5, 4.0 Hz, 2H), 6.68 (d, J = 2.4 Hz, 1H), 6.82 (dd, J = 8.5, 2.6 Hz, 1H), 7.22 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 2.1 Hz, 1H), 8.25 (dd, J = 2.2, 1.0 Hz, 1H). Anal. Calcd for $C_{18}H_{17}ClF_3NO_5$: C, 51.50; H, 4.08; N, 3.34. Found: C, 51.67; H, 4.02; N, 3.25.

5.1.1.24. 3-(2-{[3-Chloro-5-(trifluoromethyl)pyridin-2yl]oxy}-phenyl)propanoic acid (34b). A stirred solution of **6b** (6.13 g, 16.5 mmol) in THF (50 mL) was hydrogenated under atmospheric pressure with 10% Pd/C (wet, 3.46 g, 1.63 mmol) at room temperature for 2 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residual oil was purified by silica gel chromatography (hexane-EtOAc, 19:1 to 3:2) to give a mixture of ethyl 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)propanoate **(7b)** and ethyl 3-phenylpropanoate **(7b′)** (4.14 g, 67%, calculated as pure **7b**) as a yellow oil.

To a stirred solution of the mixture of **7b** and **7b′** (4.14 g, 11.1 mmol, calculated as pure **7b**) in THF (10 mL) and EtOH (10 mL) was added 1 M NaOH (25.0 mL, 25.0 mmol) and the mixture was stirred at 50 °C for 30 min. After being cooled to room temperature, the reaction was acidified with 1 M HCl (25.0 mL, 25.0 mmol), and diluted with toluene and concentrated in vacuo to remove THF and EtOH, The resultant solid was dissolved into EtOAc and water, and the separated organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude solid, which was recrystallized from EtOAc/hexane to give **34b** (2.71 g, 71%) as white feather crystals. Mp 99.5–100.0 °C. ^{1}H NMR ($CDCl_3$): δ 2.51–2.76 (m, 2H), 2.86 (t, J = 7.5 Hz, 2H), 7.10 (dd, J = 7.8, 1.4 Hz, 1H), 7.18–7.45 (m, 3H), 7.99 (d, J = 2.3 Hz, 1H), 8.25 (dd, J = 2.1, 0.9 Hz, 1H). Anal. Calcd for $C_{15}H_{11}ClF_3NO_3$: C, 52.11; H, 3.21; N, 4.05. Found: C, 52.16; H, 3.09; N, 4.17.

5.1.1.25. (2*E*)-3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]acrylic acid (34d). Compound **34d** (white feather crystals) was prepared from **7d** in 79% yield following a similar procedure to provide **34d**. Mp 156.5–157.5 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 3.44 (s, 3H), 3.72–3.77 (m, 2H), 4.14 (dd, J = 5.4, 3.9 Hz, 2H), 6.37 (d, J = 16.0 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.91 (dd, J = 8.8, 2.5 Hz, 1H), 7.64 (d, J = 8.9 Hz, 1H), 7.77 (d, J = 16.2 Hz, 1H), 8.02 (d, J = 1.9 Hz, 1H), 8.25 (dd, J = 2.1, 0.9 Hz, 1H). Anal. Calcd for $C_{18}H_{15}ClF_3NO_5$: C, 51.75; H, 3.62; N, 3.35. Found: C, 52.00; H, 3.69; N, 3.17.

5.1.1.26. (2*E*)-3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methylacrylic acid (34e). Compound **34e** (white needles) was prepared from **7e** in 79% yield following a similar procedure to provide **34a**. Mp 122.0–122.5 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 2.04 (d, J=1.3 Hz, 3H), 3.45 (s, 3H), 3.72–3.78 (m, 2H), 4.09–4.18 (m, 2H), 6.76 (d, J = 2.6 Hz, 1H), 6.91 (dd, J = 8.7, 2.4 Hz, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.64 (s, 1H), 7.97 (d, J = 2.1 Hz, 1H), 8.22 (d, J = 0.9 Hz, 1H). Anal. Calcd for $C_{19}H_{17}ClF_3NO_5$: C, 52.85; H, 3.97; N, 3.24. Found: C, 52.98; H, 4.03; N, 3.23.

5.1.1.27. 3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]-oxy}-4-(2-methoxyethoxy)phenyl]-2-methylpropanoic acid (34f). Compound **34f** (white crystals) was prepared from **7e** in 52% yield following the procedure to provide **34b**. Mp 129.5–131.0 °C. ^{1}H NMR ($CDCl_3$): δ 1.15 (d, J = 6.8 Hz, 3H), 2.53 (dd, J = 13.3, 7.4 Hz, 1H), 2.74–2.93 (m, 2H), 3.43 (s, 3H), 3.68–3.78 (m, 2H), 4.05–4.12 (m, 2H), 6.69 (d, J = 2.6 Hz, 1H), 6.81 (dd, J = 8.5, 2.6 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 2.1 Hz, 1H), 8.26 (d, J = 0.9 Hz, 1H). Anal. Calcd for $C_{19}H_{19}ClF_3NO_5$: C, 52.60; H, 4.41; N, 3.23. Found: C, 52.81; H, 4.52; N, 3.24.

5.1.1.28. (2*E*)-3-(2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)acrylic acid (34g). Compound **34g** (a white powder) was prepared from **7g** in 63% yield following a similar procedure to provide **34a**. Mp 138.0–139.5 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 1.35 (d, J = 6.0 Hz, 6H), 4.39–4.72 (m, 1H), 6.35 (d, J = 16.0 Hz, 1H), 6.64 (d, J = 2.4 Hz, 1H), 6.85 (dd, J = 8.9, 2.4 Hz, 1H), 7.63 (d, J = 8.9 Hz, 1H), 7.77 (d, J = 16.0 Hz, 1H), 8.01 (d, J = 2.1 Hz, 1H), 8.26 (d, J = 0.9 Hz, 1H). Anal. Calcd for $C_{18}H_{15}ClF_3NO_4$: C, 53.81; H, 3.76; N, 3.49. Found: C, 54.00; H, 3.81; N, 3.68.

5.1.1.29. (2*E*)-3-{2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(cyclopropyloxy)ethoxy]phenyl}acrylic acid (34h). Compound **34h** (white crystals) was prepared from **7h** and 2-(cyclopropyloxy)ethanol[24] in 97% yield following a similar procedure to provide **34a**. Mp 147–150 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 0.44–0.56 (m, 2H), 0.57–0.65 (m, 2H), 3.38 (tt, J = 6.0, 3.0 Hz, 1H), 3.85 (dd, J = 5.5, 4.1 Hz, 2H), 4.12 (dd, J = 5.5, 4.0 Hz, 2H), 6.37 (d, J = 16.2 Hz, 1H), 6.69 (d, J = 2.4 Hz, 1H), 6.90 (dd, J = 8.7, 2.4 Hz, 1H), 7.64 (d, J = 8.7 Hz, 1H), 7.77 (d, J = 16.0 Hz, 1H), 8.02 (d, J = 2.3 Hz, 1H), 8.25 (dd, J = 2.2, 1.0 Hz, 1H). Anal. Calcd for $C_{22}H_{17}ClF_3NO_5$: C, 54.13; H, 3.86; N, 3.16. Found: C, 54.25; H, 3.91; N, 2.94.

5.1.1.30. (2*E*)-3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]acrylic acid (34i). Compound **34i** (white crystals) was prepared from **7i** in 64% yield following a similar procedure to provide **34a**. Mp 131–133 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 2.05 (tt, J = 6.2 Hz, 2H), 3.34 (s, 3H), 3.54 (t, J = 6.0 Hz, 2H), 4.08 (t, J = 6.3 Hz, 2H), 6.36 (d, J = 16.0 Hz, 1H), 6.68 (d, J = 2.4 Hz, 1H), 6.88 (dd, J = 8.9, 2.4 Hz, 1H), 7.65 (d, J = 8.9 Hz, 1H), 7.76 (d, J = 16.2 Hz, 1H), 8.02 (d, J = 2.3 Hz, 1H), 8.26 (dd, J = 2.0, 0.8 Hz, 1H). Anal. Calcd for $C_{19}H_{17}ClF_3NO_5 \cdot 0.15$hexane: C, 53.75; H, 4.33; N, 3.15. Found: C, 53.45; H, 4.15; N, 2.87.

5.1.1.31. (2*E*)-3-(2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-{2-[(triisopropylsilyl)oxy]ethoxy}phenyl)acrylic acid (34j). Compound **34j** (a white solid) was prepared from **7j** in 85% yield following a similar procedure to provide **34a**. ^{1}H NMR ($CDCl_3$): δ 0.95–1.17 (m, 21H), 3.88–4.20 (m, 4H), 6.36 (d, J = 16.0 Hz, 2H), 6.70 (d, J = 2.5 Hz, 1H), 6.90 (dd, J = 8.7, 2.5 Hz, 1H), 7.64 (d, J = 16.0 Hz, 1H), 7.76 (d, J = 16.0 Hz, 1H), 8.02 (dd, J = 2.3 Hz, 1H), 8.25 (d, J = 2.3 Hz, 1H).

5.1.1.32. (2E)-3-{2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethoxy]phenyl}acrylic acid (34k). Compound **34k** (colorless crystals) was prepared from **7k** in 69% yield following a similar procedure to provide **34a**. Mp 144–146 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 1.39 (s, 3H), 2.18 (t, J = 7.1 Hz, 2H), 3.88–4.02 (m, 4H), 4.11 (t, J = 7.1 Hz, 4H), 6.36 (d, J = 16.0 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 6.84–6.92 (m, 1H), 7.64 (d, J = 8.9 Hz, 1H), 7.71–7.80 (m, 1H), 8.02 (d, J = 2.1 Hz, 1H), 8.23–8.28 (m, 1H). Anal. Calcd for $C_{21}H_{19}ClF_3NO_6$: C, 53.23; H, 4.04; N, 2.96. Found: C, 53.30; H, 4.15; N, 2.85.

5.1.1.33. (2*E*)-3-{2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(methylsulfonyl)propoxy]-phenyl}acrylic acid (34l). Compound **34l** (white crystals) was prepared from **7l** and 3-(methylsulfonyl)propyl tosylate[25] in 83% yield following a similar procedure to provide **34a**. Mp 202–203 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 2.08–2.19 (m, 2H), 3.01 (s, 3H), 3.21–3.29 (m, 2H), 4.12 (t, J = 6.1 Hz, 2H), 6.43 (d, J = 16.2 Hz, 1H), 6.93–7.00 (m, 2H), 7.44 (d, J = 16.0 Hz, 1H), 7.87 (d, J = 9.8 Hz, 1H), 8.51 (d, J = 1.1 Hz, 1H), 8.64 (d, J = 2.3 Hz, 1H). Anal. Calcd for $C_{19}H_{17}ClF_3NO_6S$: C, 47.56; H, 3.57; N, 2.92. Found: C, 47.33; H, 3.67; N, 2.91.

5.1.1.34. (2*E*)-3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-cyanopropoxy)phenyl]acrylic acid (34m). Compound **34m** (colorless crystals) was prepared from **7m** in 78% yield following a similar procedure to provide **34a**. Mp 183–185 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 2.10–2.22 (m, 2H), 2.59 (t, J = 7.0 Hz, 2H), 4.11 (t, J = 5.7 Hz, 2H), 6.38 (d, J = 16.0 Hz, 1H), 6.69 (d, J = 2.4 Hz, 1H), 6.88 (dd, J = 8.7, 2.4 Hz, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.77 (d, J = 16.0 Hz, 1H), 8.03 (d, J = 2.1 Hz, 1H), 8.26 (d, J = 1.1 Hz, 1H). Anal. Calcd for $C_{19}H_{14}ClF_3N_2O_4$: C, 53.47; H, 3.31; N, 6.56. Found: C, 53.51; H, 3.37; N, 6.54.

5.1.1.35. 3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-*N*-(pentylsulfonyl)propanamide (8a). To a stirred solution of **34a** (3.49 g, 8.31 mmol) in THF (40 mL) was added CDI (2.08 g, 12.8 mmol) and the mixture was stirred under reflux for 1 h. After being cooled to room temperature, was added pentane-1-sulfonamide (1.63 g, 10.8 mmol), followed by DBU (2.0 mL, 13.4 mmol) and the mixture was stirred at the same temperature overnight. The mixture was concentrated in vacuo and the residue was dissolved into EtOAc and the organic layer was washed with 1 M HCl, sat. $NaHCO_3$, water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane-EtOAc, 4:1 to 1:1) to give a white solid, which was recrystallized from EtOAc/hexane to give **8a** (1.62 g, 35%) as white feather crystals. Mp 140–142 °C. ^{1}H NMR ($CDCl_3$): δ 0.83–0.94 (m, 3H), 1.23–1.42 (m, 4H), 1.59–1.72 (m, 2H), 2.55 (t, J = 7.1 Hz, 2H), 2.95 (t, J = 7.1 Hz, 2H), 3.12–3.20 (m, 2H), 3.41 (s, 3H), 3.66–3.73 (m, 2H), 4.00–4.07 (m, 2H), 6.50 (d, J = 2.5 Hz, 1H), 6.77 (dd, J = 8.5, 2.5 Hz, 1H), 7.18 (d, J = 8.5 Hz, 1H), 8.06 (d, J = 2.2 Hz, 1H), 8.36 (d, J = 1.4 Hz, 1H), 8.99 (s, 1H). Anal. Calcd for $C_{23}H_{28}ClF_3N_2O_6S$: C, 49.95; H, 5.10; N, 5.07. Found: C, 50.02; H, 5.03; N, 5.04.

5.1.1.36. 3-(2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-phenyl)-*N*-(pentylsulfonyl)propanamide (2). Compound **2** (white crylstals) was prepared from **34b** and pentane-1-sulfonamide in 69% yield following a similar procedure to provide **8a**. Mp 97–100 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 0.84–0.97 (m, 3H), 1.22–1.42 (m, 4H), 1.52–1.69 (m, 2H), 2.60 (t, J = 7.3 Hz, 2H), 3.04 (t, J = 7.3 Hz, 2H), 3.09–3.18 (m, 2H), 6.88–6.99 (m, 1H), 7.13–7.41 (m, 3H), 8.09 (d, J = 2.3 Hz, 1H), 8.37 (dd, J = 2.2, 0.8 Hz, 1H), 8.99 (s, 1H). Anal. Calcd for $C_{20}H_{22}ClF_3N_2O_4S$: C, 50.16; H, 4.63; N, 5.85. Found: C, 50.10; H, 4.56; N, 5.92.

5.1.1.37. 3-{2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(diethylamino)-2-oxoethoxy]phenyl}-*N*-(pentylsulfonyl) propanamide (8b). To a stirred solution of **7c** (3.31 g, 6.58 mmol) in THF (15 mL) and EtOH (15 mL) was added 1 M NaOH (15.0 mL, 15.0 mmol) and the mixture was stirred at 50 °C for 1 h. After being cooled to room temperature, the reaction was acidified with 1 M HCl (15.0 mL, 15.0 mmol), and extracted with EtOAc, and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(diethylamino)-2-oxoethoxy]phenyl}-propanoic acid (**34c**, 2.91 g, 93%) as a pale-yellow solid. ^{1}H NMR ($CDCl_3$): δ 1.13 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H), 2.63 (t, J = 7.3 Hz, 2H), 2.78 (t, J = 7.5 Hz, 2H), 3.31–3.48 (m, 4H), 4.64 (s, 2H), 6.73 (d, J = 2.6 Hz, 1H), 6.84 (dd, J = 8.5, 2.4 Hz, 1H), 7.19–7.28 (m, 1H), 7.99 (d, J = 2.3 Hz, 1H), 8.25 (d, J = 1.3 Hz, 1H).

To a stirred solution of crude **34c** (2.23 g, 4.71 mmol) in THF (30 mL) was added CDI (1.17 g, 7.23 mmol) and the mixture was stirred at reflux for 1 h. After being cooled to room temperature, was added pentane-1-sulfonamide (1.07 g, 7.08 mmol) followed by DBU (1.0 mL, 6.96 mmol) to the mixture and the mixture was stirred at the same temperature overnight. The reaction was quenched with 1 M HCl and diluted with EtOAc and the organic layer was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual solid was purified by silica gel chromatography (hexane-EtOAc, 85:15 to 7:3) to give a pale-yellow solid, which was recrystallized from EtOAc/IPE to give **8b** (1.96 g, 69%) as a white powder. Mp 111–113 °C. ^{1}H NMR ($CDCl_3$): δ 0.85–0.94 (m, 3H), 1.12 (t, J = 7.2 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H), 1.24–1.46 (m, 4H), 1.60–1.87 (m, 2H), 2.54 (t, J = 7.3 Hz, 2H), 2.92 (t, J = 7.3 Hz, 2H), 3.15–3.25 (m, 2H), 3.29–3.46 (m, 4H), 4.63 (s, 2H), 6.59 (d, J = 2.4 Hz, 1H), 6.79 (dd, J = 8.5, 2.6 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 8.06 (d, J = 2.3 Hz, 1H), 8.33 (dd, J = 2.3, 0.9 Hz, 1H), 9.04 (s, 1H). Anal. Calcd for $C_{26}H_{33}ClF_3N_3O_6S$: C, 51.36; H, 5.47; N, 6.91. Found: C, 51.15; H, 5.45; N, 6.85.

5.1.1.38. 3-Methoxypropane-1-sulfonamide. To a solution of 1-bromo-3-methoxypropane (19.5 g, 0.127 mol) in DMF (200 mL) was added potassium thioacetate (15.2 g, 0.133 mol), and the mixture was stirred overnight at room temperature. Water was added to the reaction mixture, and the mixture was extracted with Et_2O. The organic layer was washed with water and saturated brine, dried over $MgSO_4$, filtrated and concentrated to give a yellow oil.

To a solution of the obtained oil in Et_2O (200 mL) was added 1 M NaOH (250 mL, 250 mmol) at 0 °C, and the mixture was stirred at the same temperature. After 1 h, 12 M NaOH (20 mL, 240 mmol) and MeOH (50 mL) were added, and the mixture was stirred at room temperature for 20 min. Conc. HCl (45 mL) was added to the reaction mixture, and the mixture was extracted with Et_2O. The organic layer was washed with water, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtrated and concentrated.

Into a solution of the obtained residue in acetic acid (200 mL) and water (200 mL) was carefully bubbled gaseous chlorine over 2 h to prevent the reaction temperature from rising to more than 15 °C. Gaseous nitrogen was bubbled at room temperature for 1 h, and the reaction mixture was added dropwise to an ice-cooled sat. $NaHCO_3$, and the mixture was extracted with Et_2O. The organic layer was washed with sat. $NaHCO_3$, 10% NaS_2O_3 and brine, dried over $MgSO_4$, filtrated and concentrated to give a pale-yellow oil.

A solution of the obtained oil in THF (10 mL) was added dropwise to a solution of 28% NH_3 (50 mL) and THF (50 mL) at 0 °C, and the mixture was subsequently stirred for 30 min. The reaction mixture was concentrated in vacuo and the concentrate was dissolved in EtOAc. The organic layer was washed with water and

brine, dried ($MgSO_4$), filtrated and concentrated to give an orange oil. The obtained oil was dissolved in a suspension of activated carbon in ethyl acetate, and the mixture was stirred at room temperature for 1 h. The mixture was filtrated and concentrated to give 3-methoxypropane-1-sulfonamide (0.88 g, 5%) as an orange solid. ^{1}H NMR ($CDCl_3$): δ 1.86–2.25 (m, 2H), 3.19–3.28 (m, 2H), 3.35 (s, 3H), 3.53 (t, J = 5.8 Hz, 2H), 4.71 (s, 2H).

5.1.1.39. 3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-*N*-[(3-methoxypropyl)sulfonyl]propanamide (8c). Compound **8c** (white feather crystals) was prepared from **34a** and 3-methoxypropane-1-sulfonamide in 50% yield following the procedure to provide **8a**. Mp 112–113 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 1.77–1.92 (m, 2H), 2.55 (t, J = 7.2 Hz, 2H), 2.97 (t, J = 7.2 Hz, 2H), 3.23–3.30 (m, 2H), 3.31 (s, 3H), 3.36–3.41 (m, 2H), 3.42 (s, 3H), 3.66–3.83 (m, 2H), 3.96–4.15 (m, 2H), 6.50 (d, J = 2.6 Hz, 1H), 6.78 (dd, J = 8.5, 2.4 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 8.08 (d, J = 2.3 Hz, 1H), 8.38 (dd, J = 2.3, 0.9 Hz, 1H), 9.04 (s, 1H). Anal. Calcd for $C_{22}H_{26}ClF_3N_2O_7S$: C, 47.61; H, 4.72; N, 5.05. Found: C, 47.64; H, 4.70; N, 4.97.

5.1.1.40. 3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-*N*-(phenylsulfonyl)propanamide (8d). Compound **8d** (white feather crystals) was prepared from **34a** and benzenesulfonamide in 51% yield following a similar procedure to provide **8d**. Mp 108–109 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 2.46 (t, J = 7.2 Hz, 2H), 2.85 (t, J = 7.1 Hz, 2H), 3.44 (s, 3H), 3.73 (dd, J = 5.4, 3.9 Hz, 2H), 4.04 (dd, J = 5.4, 3.7 Hz, 2H), 6.31–6.41 (m, 1H), 6.44 (d, J = 2.3 Hz, 1H), 6.77 (d, J = 8.5 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.57–7.68 (m, 1H), 7.81–7.87 (m, 2H), 8.09 (d, J = 2.3 Hz, 1H), 8.46 (d, J = 1.1 Hz, 1H), 9.42 (br s, 1H). Anal. Calcd for $C_{24}H_{22}ClF_3N_2O_6S$: C, 51.57; H, 3.97; N, 5.01. Found: C, 51.58; H, 3.85; N, 4.98.

5.1.1.41. *N*-[(4-Chlorophenyl)sulfonyl]-3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-propanamide (8e). To a stirred solution of **34a** (114 mg, 0.272 mmol) in THF (2 mL) was added thionyl chloride (50 μL, 0.695 mmol), followed by DMF (10 μL, 0.130 mmol) at 0 °C. After being stirred for 2 h at the same temperature, the mixture was concentrated in vacuo, and the residue was dissolved into THF (2 mL). To the solution was added 4-chlorobenzenesulfonamide (60.0 mg, 0.313 mmol), followed by DIPEA (50 μL, 0.292 mmol) and DMAP (39.0 mg, 0.320 mmol) at room temperature. After being stirred for 3 h, the reaction was quenched with sat. NH_4Cl and extracted with EtOAc and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual solid was purified by silica gel chromatography (hexane-EtOAc, 9:1 to 3:2) to give a white solid, which was recrystallized from EtOAc/hexane to give **8e** (88.0 mg, 54%) as white crystals. Mp 140.0–141.5 °C. ^{1}H NMR ($CDCl_3$): δ 2.47 (t, J = 7.1 Hz, 2H), 2.87 (t, J = 7.2 Hz, 2H), 3.45 (s, 3H), 3.71–3.76 (m, 2H), 3.99–4.11 (m, 2H), 6.17–6.52 (m, 2H), 6.75 (d, J = 8.7 Hz, 1H), 7.47 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H), 8.11 (s, 1H), 8.48 (s, 1H). Anal. Calcd for $C_{24}H_{21}Cl_2F_3N_2O_6S$: C, 48.58; H, 3.57; N, 4.72. Found: C, 48.33; H, 3.69; N, 4.55.

5.1.1.42. (2*E*)-3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-*N*-(pentylsulfonyl)acrylamide (8f). To a stirred solution of **34d** (1.00 g, 2.39 mmol), WSC-HCl (424 mg, 2.80 mmol) and DMAP (370 mg, 3.03 mmol) in MeCN was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (400 mg, 2.58 mmol) at 0 °C, and the mixture was allowed to warm to room temperature. After being stirred overnight at the same temperature, the reaction was quenched with 1 M HCl and extracted with EtOAc. The organic layer was washed with 1 M HCl, sat. $NaHCO_3$, water and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residual oil was purified by silica gel chromatography (hexane-EtOAc, 19:1 to 7:3) to give a white solid, which was recrystallized from EtOAc/hexane to give **8f** (763 mg, 58%) as white crystals. Mp 125.5–126.0 °C. ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.2 Hz, 3H), 1.24–1.48 (m, 4H), 1.75–1.90 (m, 2H), 3.44 (s, 3H), 3.45–3.52 (m, 2H), 3.66–3.84 (m, 2H), 4.02–4.30 (m, 2H), 6.37 (d, J = 15.8 Hz, 1H), 6.71 (d, J = 2.4 Hz, 1H), 6.91 (dd, J = 8.8, 2.4 Hz, 1H), 7.61 (d, J = 8.9 Hz, 1H), 7.73 (s, 1H), 7.79 (d, J = 15.8 Hz, 1H), 8.03 (d, J = 2.1 Hz, 1H), 8.25 (dd, J = 2.1, 0.9 Hz, 1H). Anal. Calcd for $C_{23}H_{26}ClF_3N_2O_6S$: C, 50.14; H, 4.76; N, 5.08. Found: C, 50.24; H, 4.86; N, 5.16.

5.1.1.43. (2*E*)-3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methyl-*N*-(pentylsulfonyl)acrylamide (8g). Compound **8g** (white crystals) was prepared from **34e** and pentane-1-sulfonamide in 54% yield following a similar procedure to provide **8f**. Mp 108–111 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 0.85–0.94 (m, 3H), 1.24–1.48 (m, 4H), 1.75–1.90 (m, 2H), 2.07 (d, J = 1.3 Hz, 3H), 3.45 (s, 3H), 3.45–3.52 (m, 2H), 3.70–3.81 (m, 2H), 4.09–4.24 (m, 2H), 6.78 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 8.7, 2.4 Hz, 1H), 7.30–7.43 (m, 2H), 7.87 (s, 1H), 8.00 (d, J = 1.9 Hz, 1H), 8.25 (dd, J = 2.1, 0.9 Hz, 1H). Anal. Calcd for $C_{24}H_{28}ClF_3N_2O_6S{\cdot}0.10$hexane: C, 51.51; H, 5.17; N, 4.88. Found: C, 51.64; H, 5.23; N, 4.84.

5.1.1.44. 3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methyl-*N*-(pentylsulfonyl)propanamide (8h). Compound **8h** (white crystals) was prepared from **34f** and pentane-1-sulfonamide in 57% yield following a similar procedure to provide **8f**. Mp 136.5–138.0 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 0.85–0.94 (m, 3H), 1.22 (d, J = 5.8 Hz, 3H), 1.25–1.40 (m, 4H), 1.48–1.72 (m, 2H), 2.54–2.66 (m, 2H), 2.86 (ddd, J = 13.8, 10.3, 5.5 Hz, 1H), 2.98–3.12 (m, 1H), 3.21 (ddd, J = 14.0, 10.4, 5.6 Hz, 1H), 3.41 (s, 3H), 3.61–3.77 (m, 2H), 3.97–4.07 (m, 2H), 6.43 (d, J = 2.4 Hz, 1H), 6.75 (dd, J = 8.4, 2.5 Hz, 1H), 7.14 (d, J = 8.5 Hz, 1H), 8.11 (d, J = 1.9 Hz, 1H), 8.42 (dd, J = 2.1, 0.9 Hz, 1H), 9.53 (s, 1H). Anal. Calcd for $C_{24}H_{30}ClF_3N_2O_6S$: C, 50.84; H, 5.33; N, 4.94. Found: C, 50.88; H, 5.26; N, 4.93.

5.1.1.45. (2*E*)-3-(2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-*N*-(pentylsulfonyl)acrylamide (8i). Compound **8i** (white fine needles) was prepared from **34g** and pentane-1-sulfonamide in 35% yield following a similar procedure to provide **8a**. Mp 142–144 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.1 Hz, 3H), 1.19–1.47 (m, 10H), 1.72–2.02 (m, 2H), 3.27–3.54 (m, 2H), 4.33–4.66 (m, 1H), 6.36 (d, J = 15.6 Hz, 1H), 6.64 (d, J = 2.4 Hz, 1H), 6.85 (dd, J = 8.9, 2.6 Hz, 1H), 7.59 (d, J = 8.9 Hz, 1H), 7.79 (d, J = 15.6 Hz, 1H), 8.03 (d, J = 2.3 Hz, 1H), 8.26 (s, 1H). Anal. Calcd for $C_{23}H_{26}ClF_3N_2O_5S$: C, 51.64; H, 4.90; N, 5.24. Found: C, 51.91; H, 4.99; N, 5.06.

5.1.1.46. (2*E*)-3-{2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(cyclopropyloxy)ethoxy]phenyl}-*N*-(pentylsulfonyl)acrylamide (8j). Compound **8j** (white crystals) was prepared from **34h** and pentane-1-sulfonamide in 42% yield following a similar procedure to provide **8f**. Mp 104.6–106.5 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 0.45–0.56 (m, 2H), 0.57–0.65 (m, 2H), 0.89 (t, J = 7.1 Hz, 3H), 1.21–1.47 (m, 4H), 1.83 (tt, J = 7.8, 7.2 Hz, 2H), 3.38 (tt, J = 5.9, 3.0 Hz, 1H), 3.43–3.51 (m, 2H), 3.85 (dd, J = 5.5, 4.0 Hz, 2H), 4.08–4.16 (m, 2H), 6.37 (d, J = 15.5 Hz, 1H), 6.69 (d, J = 2.7 Hz, 1H), 6.90 (dd, J = 8.9, 2.5 Hz, 1H), 7.60 (d, J = 9.1 Hz, 1H), 7.74 (s, 1H), 7.79 (d, J = 15.9 Hz, 1H), 8.03 (d, J = 2.3 Hz, 1H), 8.25 (dd, J = 2.1, 0.9 Hz, 1H). Anal. Calcd for $C_{25}H_{28}ClF_3N_2O_6S$: C, 52.04; H, 4.89; N, 4.85. Found: C, 51.96; H, 4.87; N, 4.84.

5.1.1.47. (2*E*)-3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-methoxypropoxy)phenyl]-*N*-(pentylsulfonyl)acrylamide (8k). Compound **8k** (white crystals) was prepared from **34i** and pentane-1-sulfonamide in 26% yield following a similar procedure to provide **8f**. Mp 116.5–118.0 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 0.82–0.94 (m, 3H), 1.25–1.48 (m, 4H), 1.76–1.92 (m, 2H), 2.05 (tt, J = 6.1 Hz, 2H), 3.34 (s, 3H), 3.43–3.50 (m, 2H), 3.54 (t, J = 6.0 Hz, 2H), 4.08 (t, J = 6.2 Hz, 2H), 6.37 (d, J = 15.6 Hz, 1H), 6.68 (d, J = 2.4 Hz, 1H), 6.89 (dd, J = 8.9, 2.5 Hz, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.73 (br s, 1H), 7.79 (d, J = 15.4 Hz, 1H), 8.04 (d, J = 2.1 Hz, 1H), 8.13–8.32 (m, 1H). Anal. Calcd for $C_{24}H_{28}ClF_3N_2O_6S$: C, 51.02; H, 5.00; N, 4.96. Found: C, 51.06; H, 5.01; N, 4.77.

5.1.1.48. (2*E*)-3-(2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-{2-[(triisopropylsilyl)oxy]ethoxy}phenyl)-*N*-(pentylsulfonyl)acrylamide (8l). Compound **8l** (a white powder) was prepared from **34j** and pentane-1-sulfonamide in 46% yield following a similar procedure to provide **8f**. Mp 106–108 °C (IPE/hexane). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.2 Hz, 3H), 0.98–1.17 (m, 21H), 1.21–1.49 (m, 4H), 1.70–1.92 (m, 2H), 3.35–3.56 (m, 2H), 3.91–4.19 (m, 4H), 6.37 (d, J = 15.8 Hz, 1H), 6.70 (d, J = 2.5 Hz, 1H), 6.90 (dd, J = 8.7, 2.5 Hz, 1H), 7.60 (d, J = 8.9 Hz, 1H), 7.72–7.83 (m, 2H), 8.03 (d, J = 2.1 Hz, 1H), 8.25 (dd, J = 2.0, 0.9 Hz, 1H). Anal. Calcd for $C_{31}H_{44}ClF_3N_2O_6SSi$: C, 53.71; H, 6.40; N, 4.04. Found: C, 53.65; H, 6.40; N, 4.07.

5.1.1.49. (2*E*)-3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-hydroxy-2-methylpropoxy)phenyl]-*N*-(pentylsulfonyl)acrylamide (8m). To a solution of **8l** (4.40 g, 6.35 mmol) in THF (6 mL) was added 1 M TBAF in THF (9.52 mL, 9.52 mmol) at room temperature, and the mixture was stirred at 50 °C for 30 min. The mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtrated and concentrated. The obtained residue was subjected to silica gel column chromatography (hexane-EtOAc, 20:1 to 4:1) and the obtained residue was recrystallized from IPE/hexane to give **8m** (1.03 g, 30%) as a white powder. Mp 112.5–112.8 °C. ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J = 7.2 Hz, 3H), 1.23–1.47 (m, 4H), 1.74–1.90 (m, 2H), 3.38–3.55 (m, 2H), 3.88–4.03 (m, 2H), 4.04–4.19 (m, 2H), 6.37 (d, J = 15.6 Hz, 1H), 6.71 (d, J = 2.5 Hz, 1H), 6.89 (dd, J = 8.9, 2.5 Hz, 1H), 7.60 (d, J = 8.9 Hz, 1H), 7.79 (d, J = 15.6 Hz, 1H), 8.03 (d, J = 2.1 Hz, 1H), 8.25 (d, J = 1.1 Hz, 1H). Anal. Calcd for $C_{22}H_{24}ClF_3N_2O_6S{\cdot}0.50H_2O$: C, 48.40; H, 4.62; N, 5.13. Found: C, 48.71; H, 4.78; N, 5.13.

5.1.1.50. (2*E*)-3-{2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-methyl-1,3-dioxolan-2-yl)ethoxy]phenyl}-*N*-(pentylsulfonyl)acrylamide (8n). Compound **8n** (colorless crystals) was prepared from **34k** in 52% yield following a similar procedure to provide **8f**. Mp 90–92 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 0.85–0.93 (m, 3H), 1.22–1.46 (m, 7H), 1.76–1.89 (m, 2H), 2.18 (t, J = 7.1 Hz, 2H), 3.42–3.51 (m, 2H), 3.91–4.00 (m, 4H), 4.12 (t, J = 7.1 Hz, 2H), 6.37 (d, J = 15.6 Hz, 1H), 6.67 (d, J = 2.5 Hz, 1H), 6.88 (dd, J = 8.9, 2.5 Hz, 1H), 7.60 (d, J = 8.9 Hz, 1H), 7.78 (d, J = 15.6 Hz, 1H), 8.03 (d, J = 2.3 Hz, 1H), 8.26 (d, J = 0.9 Hz, 1H). Anal. Calcd for $C_{26}H_{30}ClF_3N_2O_7S$: C, 51.44; H, 4.98; N, 4.61. Found: C, 51.54; H, 5.02; N, 4.41.

5.1.1.51. (2*E*)-3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-oxobutoxy)phenyl]-*N*-(pentylsulfonyl)acrylamide (8o). A mixture of **8n** (750 mg), 1 M HCl (5 mL), and THF (15 mL) was stirred at 60 °C for 1 h. After being cooled to room temperature, the mixture was concentrated under reduced pressure. Water was added to the obtained residue, and the mixture was extracted with EtOAc. The organic layer was washed with saturated brine, dried over $MgSO_4$, and concentrated. The obtained solid was recrystallized from EtOAc to give **8o** (418 mg, 60%) as colorless crystals. Mp 180–181 °C. ^{1}H NMR ($CDCl_3$): δ 0.85–0.94 (m, 3H), 1.20–1.47 (m, 4H), 1.75–1.90 (m, 2H), 2.24 (s, 3H), 2.93 (t, J = 6.2 Hz, 2H), 3.41–3.52 (m, 2H), 4.25 (t, J = 6.2 Hz, 2H), 6.38 (d, J = 15.6 Hz, 1H), 6.67 (d, J = 2.4 Hz, 1H), 6.87 (dd, J = 8.8, 2.4 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.79 (d, J = 15.6 Hz, 1H), 7.93 (br s, 1H), 8.03 (d, J = 2.1 Hz, 1H), 8.23–8.26 (m, 1H). Anal. Calcd for $C_{24}H_{26}ClF_3N_2O_6S$: C, 51.20; H, 4.65; N, 4.98. Found: C, 51.08; H, 4.60; N, 4.91.

5.1.1.52. (2*E*)-3-{2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[3-(methylsulfonyl)propoxy]phenyl}-*N*-(pentylsulfonyl)acrylamide (8p). Compound **8p** (white crystals) was prepared from **34l** and pentane-1-sulfonamide in 56% yield following a similar procedure to provide **8f**. Mp 194–196 °C (EtOH/H_2O). ^{1}H NMR (DMSO-d_6): δ 0.72–0.90 (m, 3H), 1.11–1.42 (m, 4H), 1.47–1.74 (m, 2H), 2.01–2.24 (m, 2H), 3.01 (s, 3H), 3.21–3.29 (m, 2H), 3.29–3.32 (m, 2H), 4.13 (t, J = 6.3 Hz, 2H), 6.56 (d, J = 15.8 Hz, 1H), 6.92–7.15 (m, 2H), 7.53 (d, J = 15.1 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 8.45–8.55 (m, 1H), 8.66 (d, J = 2.1 Hz, 1H), 11.78 (s, 1H). Anal. Calcd for $C_{24}H_{28}ClF_3N_2O_7S_2$: C, 47.02; H, 4.60; N, 4.57. Found: C, 47.18; H, 4.48; N, 4.43.

5.1.1.53. (2*E*)-3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(3-cyanopropoxy)phenyl]-*N*-(pentylsulfonyl)acrylamide (8q). Compound **8q** (colorless crystals) was prepared from **34m** in 26% yield following a similar procedure to provide **8f**. Mp 165–166 °C (EtOAc). ^{1}H NMR ($CDCl_3$): δ 0.83–0.94 (m, 3H), 1.21–1.47 (m, 4H), 1.75–1.90 (m, 2H), 2.09–2.22 (m, 2H), 2.59 (t, J = 7.0 Hz, 2H), 3.41–3.52 (m, 2H), 4.11 (t, J = 5.7 Hz, 2H), 6.38 (d, J = 15.8 Hz, 1H), 6.69 (d, J = 2.6 Hz, 1H), 6.88 (dd, J = 8.9, 2.6 Hz, 1H), 7.62 (d, J = 8.9 Hz, 1H), 7.79 (d, J = 15.8 Hz, 1H), 8.04 (d, J = 2.1 Hz, 1H), 8.25 (d, J = 1.1 Hz, 1H). Anal. Calcd for $C_{24}H_{25}ClF_3N_3O_5S$: C, 51.48; H, 4.50; N, 7.50. Found: C, 51.61; H, 4.55; N, 7.51.

5.1.1.54. Benzyl [(pentylamino)sulfonyl]carbamate (35)[26]. To a stirred solution of benzyl alcohol (3.06 g, 28.3 mmol) in DCM (150 mL) was added chlorosulfonyl isocyanate (2.55 mL, 29.3 mmol) at 0 °C and after 30 min, pyridine (8.00 mL, 99.1 mmol) was added. After being stirred at the same temperature for additional 1 h, pentylamine (16.0 mL, 138 mmol) was added to the mixture, which was allowed to warm to room temperature. After being stirred overnight, the reaction was quenched with 1 M HCl and diluted with EtOAc and the organic layer was washed with water, 1 M HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residual solid was recrystallized from EtOAc/hexane to give **35** (8,18 g, 96%) as white crystals. Mp 142.5–143.0 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ ppm 0.85–0.92 (m, 3H), 1.25–1.34 (m, 4H), 1.46–1.63 (m, 2H), 2.79–3.14 (m, 2H), 5.07 (s, 1H), 5.19 (s, 2H), 7.26 (s, 1H), 7.28–7.54 (m, 5H). Anal. Calcd for $C_{13}H_{20}N_2O_4S$: C, 51.98; H, 6.71; N, 9.33. Found: C, 52.16; H, 6.78; N, 9.46.

5.1.1.55. *N*-Pentylsulfamide (36). A stirred solution of **35** (5.83 g, 19.4 mmol) in THF (50 mL) and EtOH (50 mL) was hydrogenated under atmospheric pressure with 10% Pd/C (wet, 3.11 g, 2.92 mmol) at room temperature for 2 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residual solid was recrystallized from EtOAc/IPE to give **36** (3.15 mg, 98%) as white mica crystals. Mp 60–64 °C. ^{1}H NMR ($CDCl_3$): δ ppm 0.78–1.00 (m, 3H), 1.17–1.44 (m, 4H), 1.51–1.67 (m, 2H), 3.13 (t, J = 7.2 Hz, 1H), 4.52 (br s, 3H). Anal. Calcd for $C_5H_{14}N_2O_2S$: C, 36.12; H, 8.49; N, 16.85. Found: C, 36.04; H, 8.36; N, 16.93.

5.1.1.56. 3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-*N*-[(pentylamino)sulfonyl]propanamide (8r). Compound **8r** (white crystals) was prepared from **34d** and **36** in 13% yield following a similar procedure to provide **8f**. Mp 153.0–154.5 °C (EtOH/H_2O). ^{1}H NMR ($CDCl_3$): δ 0.85–0.93 (m, 3H), 1.20–1.37 (m, 4H), 1.47 (tt, *J* = 7.3, 7.2 Hz, 2H), 2.57 (t, *J* = 7.2 Hz, 2H), 2.71 (q, *J* = 6.8 Hz, 2H), 2.92 (t, *J* = 7.3 Hz, 2H), 3.42 (s, 3H), 3.68–3.74 (m, 2H), 4.03–4.08 (m, 2H), 4.99 (t, *J* = 6.3 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 6.78 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 2.3 Hz, 1H), 8.35 (dd, *J* = 2.0, 0.8 Hz, 1H), 8.76 (s, 1H). Anal. Calcd for $C_{23}H_{29}ClF_3N_3O_6S$: C, 48.63; H, 5.15; N, 7.40. Found: C, 48.66; H, 4.95; N, 7.30.

5.1.1.57. 2-Hydroxy-4-(2-methoxyethoxy)benzaldehyde (9). Compound **9** (white fine needles) was prepared from **3** in 35% yield following a similar procedure to provide **7a** using DEAD and triphenylphosphine instead of ADDP and tributylphosphine. Mp 64.5–65.5 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 3.45 (s, 3H), 3.70–3.82 (m, 2H), 4.10–4.32 (m, 2H), 6.44 (d, *J* = 2.3 Hz, 1H), 6.58 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 9.72 (s, 1H), 11.47 (s, 1H). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.23; H, 6.23.

5.1.1.58. Ethyl (2*E*)-3-[2-hydroxy-4-(2-methoxyethoxy)-phenyl]acrylate (10). To a stirred solution of **9** (14.6 g, 74.4 mmol) in DCM (60 mL) was added a solution of (carbethoxymethylene)triphenylphosphorane (28.6 g, 74.0 mmol) in DCM (100 mL) at 0 °C over 10 min, and the mixture was allowed to warm to room temperature. After being stirred at room temperature for 1 h, the reaction was quenched with AcOH (2 mL). The reaction mixture was concentrated under reduced pressure, and the residue was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The obtained residue was subjected to silica gel chromatography (hexane-EtOAc, 3:2) to give a white solid, which was recrystallized from EtOAc/hexane to give **10** (17.7 g, 89%) as colorless crystals. ^{1}H NMR ($CDCl_3$): δ 1.33 (t, *J* = 7.2 Hz, 3H), 3.47 (s, 3H), 3.76–3.80 (m, 2H), 4.10–4.14 (m, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 6.44–6.52 (m, 3H), 7.06 (s, 1H), 7.37 (d, *J* = 9.3 Hz, 1H), 7.92 (d, *J* = 16.2 Hz, 1H).

5.1.1.59. 2-[(3-Chloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)benzaldehyde (11a). Compound **11a** (colorless crystals) was prepared from **9** in 49% yield following a similar procedure to provide **5a**. ^{1}H NMR ($CDCl_3$): δ 3.43 (s, 3H), 3.73–3.77 (m, 2H), 4.15–4.19 (m, 2H), 6.72 (d, *J* = 2.3 Hz, 1H), 6.90 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.03 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.81 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 8.02 (dd, *J* = 4.9, 1.7 Hz, 1H), 10.11 (s, 1H).

5.1.1.60. 2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzaldehyde (11b). Compound **11b** (white prisms) was prepared from **9** and 2,3-dichloro-5-(trifluoromethyl)pyridine in 60% yield following a similar procedure to provide **5a**. Mp 80.5–81.0 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 3.45 (s, 3H), 3.66–3.84 (m, 2H), 4.10–4.34 (m, 2H), 6.77 (d, *J* = 2.3 Hz, 1H), 6.97 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.91 (d, *J* = 8.9 Hz, 1H), 8.03 (d, *J* = 2.3 Hz, 1H), 8.23 (d, *J* = 1.1 Hz, 1H), 9.98 (s, 1H). *Anal.* Calcd for $C_{16}H_{13}NO_4ClF_3$: C, 51.15; H, 3.49; N, 3.73. Found: C, 51.18; H, 3.48; N, 3.64.

5.1.1.61. Ethyl (2*E*)-3-{2-[2-chloro-4-(trifluoromethyl)phenoxy]-4-(2-methoxyethoxy)phenyl}acrylate (12a). Compound **12a** (colorless crystals) was prepared from **10** and 3-chloro-4-fluorobenzotrifluoride in 88% yield following a similar procedure to provide **5a**. ^{1}H NMR ($CDCl_3$): δ 1.30 (t, *J* = 7.2 Hz, 3H), 3.41 (s, 3H), 3.69–3.72 (m, 2H), 4.05–4.09 (m, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 6.36 (d, *J* = 2.4 Hz, 1H), 6.43 (d, *J* = 16.2 Hz, 1H), 6.77 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.75 (s, 1H), 7.85 (d, *J* = 16.2 Hz, 1H).

5.1.1.62. Ethyl (2*E*)-3-[4-(2-methoxyethoxy)-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl]acrylate (12b). Compound **12b** (a colorless oil) was prepared from **10** in 88% yield following a similar procedure to provide **5a**. ^{1}H NMR ($CDCl_3$): δ 1.27 (t, *J* = 7.2 Hz, 3H), 3.43 (s, 3H), 3.71–3.76 (m, 2H), 4.08–4.14 (m, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 6.35 (d, *J* = 16.2 Hz, 1H), 6.67 (d, *J* = 2.6 Hz, 1H), 6.88 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.72 (d, *J* = 16.2 Hz, 1H), 7.93 (dd, *J* = 8.7, 2.6 Hz, 1H), 8.42 (s, 1H).

5.1.1.63. Ethyl (2*E*)-3-{2-[(3-chloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl}acrylate (12c). Compound **12c** (colorless crystals) was prepared from **11a** in 96% yield following a similar procedure to provide **6a**. ^{1}H NMR ($CDCl_3$): δ 1.28 (t, *J* = 7.2 Hz, 3H), 3.42 (s, 3H), 3.71–3.75 (m, 2H), 4.09–4.13 (m, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 6.38 (d, *J* = 16.0 Hz, 1H), 6.67 (d, *J* = 2.6 Hz, 1H), 6.84 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.99 (dd, *J* = 7.7, 4.9 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.73–7.84 (m, 2H), 8.01 (dd, *J* = 4.9, 1.7 Hz, 1H).

5.1.1.64. Ethyl (2*E*)-3-[2-[(3,5-dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]acrylate (12d). Compound **12d** (colorless crystals) was prepared from **10** in 72% yield following a similar procedure to provide **5a**. Mp 70.7–71.3 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 1.29 (t, *J* = 7.2 Hz, 3H), 3.43 (s, 3H), 3.71–3.76 (m, 2H), 4.10–4.14 (m, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 6.36 (d, *J* = 16.1 Hz, 1H), 6.66 (d, *J* = 2.7 Hz, 1H), 6.85 (dd, *J* = 8.4, 2.7 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 16.1 Hz, 1H), 7.80 (s, 1H), 7.94 (s, 1H). Anal. Calcd for $C_{19}H_{19}Cl_2NO_5$: C, 55.35; H, 4.65; N, 3.40. Found: C, 55.44; H, 4.83; N, 3.30.

5.1.1.65. Ethyl (2*E*)-3-{4-(2-methoxyethoxy)-2-[(3-methyl-5-nitropyridin-2-yl)oxy]phenyl}acrylate (16e). Compound **12e** (pale-yellow crystals) was prepared from **10** and 2-chloro-5-nitro-3-picoline in 98% yield following a similar procedure to provide **5a**. ^{1}H NMR ($CDCl_3$): δ 1.27 (t, *J* = 7.1 Hz, 3H), 2.52 (s, 3H), 3.44 (s, 3H), 3.73–3.76 (m, 2H), 4.12–4.15 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 6.32 (d, *J* = 16.2 Hz, 1H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.90 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 16.2 Hz, 1H), 8.35 (d, *J* = 1.8 Hz, 1H), 8.81 (d, *J* = 1.8 Hz, 1H).

5.1.1.66. Ethyl (2*E*)-3-{2-[(5-amino-3-methylpyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl}acrylate (12f). To a suspension of H_2O (5 mL) and zinc powder (379 mg, 5.80 mmol) was added a solution of **12e** (455 mg, 1.13 mmol) in AcOH (5 mL), and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, the obtained residue was basified with 8 M NaOH, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The obtained residue was subjected to silica gel column chromatography (hexane-EtOAc, 1:1) to give **12f** (307 mg, 73%) as brown crystals. ^{1}H NMR ($CDCl_3$): δ 1.30 (t, *J* = 7.2 Hz, 3H), 2.23 (s, 3H), 3.41 (s, 3H), 3.51 (s, 2H), 3.67–3.71 (m, 2H), 4.03–4.07 (m, 2H), 4.21 (q, *J* = 7.2 Hz, 2H), 6.38 (s, 1H), 6.41 (d, *J* = 15.9 Hz, 1H), 6.67 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 7.52–7.55 (m, 2H), 7.93 (d, *J* = 15.9 Hz, 1H).

5.1.1.67. Ethyl (2*E*)-3-[2-({5-[(tert-butoxycarbonyl)amino]-3-methylpyridin-2-yl}oxy)-4-(2-methoxyethoxy)phenyl]acrylate (12g). To a solution of **12f** (300 mg, 0.806 mmol) in THF (10 mL) was added di-*tert*-butyl dicarbonate (880 mg, 4.03 mmol), and the mixture was stirred at 60 °C for 11 h. The reaction mixture

was concentrated under reduced pressure, the obtained residue was subjected to silica gel column chromatography, (hexane-EtOAc, 2:1) to give **12g** (351 mg, 92%) as colorless crystals. ^{1}H NMR ($CDCl_3$): δ 1.29 (t, J = 7.2 Hz, 3H), 1.52 (s, 9H), 2.35 (s, 3H), 3.41 (s, 3H), 3.69–3.72 (m, 2H), 4.05–4.08 (m, 2H), 4.20 (q, J = 7.2 Hz, 2H), 6.36 (d, J = 15.9 Hz, 1H), 6.34–6.40 (m,1H), 6.49 (d, J = 2.7 Hz, 1H), 6.74 (dd, J = 8.7, 2.7 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.78–7.79 (m, 1H), 7.85 (d, J = 15.9 Hz, 1H), 7.93 (s, 1H).

5.1.1.68. (2*E*)-3-[2-[2-Chloro-4-(trifluoromethyl)phenoxy]-4-(2-methoxyethoxy)phenyl]acrylic acid (37a). Compound **37a** (colorless crystals) was prepared from **12a** in 97% yield following a similar procedure to provide **7a**. Mp 165.6–166.0 °C (EtOAc/hexane). ^{1}H NMR (DMSO-d_6): δ 3.27 (s, 3H), 3.60–3.64 (m, 2H), 4.10–4.14 (m, 2H), 6.47 (d, J = 16.2 Hz, 1H), 6.64 (d, J = 2.4 Hz, 1H), 6.94 (dd, J = 8.7, 2.4 Hz, 1H), 7.05 (d, J = 8.7 Hz, 1H), 7.59 (d, J = 16.2 Hz, 1H), 7.69 (d, J = 8.7 Hz, 1H), 7.89 (d, J = 8.7 Hz, 1H), 8.07 (s, 1H), 12.34 (s, 1H). Anal. Calcd for $C_{19}H_{16}ClF_3O_5$: C, 54.75; H, 3.87. Found: C, 54.80; H, 3.79.

5.1.1.69. (2*E*)-3-(4-(2-Methoxyethoxy)-2-{[5-(trifluoromethyl)-pyridin-2-yl]oxy}phenyl)acrylic acid (37b). Compound **37b** (colorless crystals) was prepared from **12b** in 96% yield following a similar procedure to provide **7a**. Mp 179.5–179.8 °C (EtOH/hexane). ^{1}H NMR (DMSO-d_6): δ 3.29 (s, 3H), 3.60–3.66 (m, 2H), 4.10–4.16 (m, 2H), 6.41 (d, J = 15.9 Hz, 1H), 6.86 (d, J = 2.7 Hz, 1H), 6.94 (dd, J = 8.7, 2.7 Hz, 1H), 7.34 (d, J = 8.7 Hz, 1H), 7.49 (d, J = 15.9 Hz, 1H), 7.86 (d, J = 8.7 Hz, 1H), 8.27 (dd, J = 8.7, 2.7 Hz, 1H), 8.57 (s, 1H), 12.26 (s, 1H). Anal. Calcd for $C_{18}H_{16}F_3NO_5$: C, 56.40; H, 4.21; N, 3.65. Found: C, 56.49; H, 4.17; N, 3.65.

5.1.1.70. (2*E*)-3-[2-[(3-Chloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]acrylic acid (37c). Compound **37c** (colorless crystals) was prepared from **12c** in 97% yield following a similar procedure to provide **7a**. Mp 150.5–150.9 °C (EtOH/hexane). ^{1}H NMR (DMSO-d_6): δ 3.28 (s, 3H), 3.61–3.66 (m, 2H), 4.09–4.16 (m, 2H), 6.41 (d, J = 16.2 Hz, 1H), 6.80 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 8.9, 2.4 Hz, 1H), 7.20 (dd, J = 7.8, 4.8 Hz, 1H), 7.48 (d, J = 16.2 Hz, 1H), 7.83 (d, J = 8.9 Hz, 1H), 8.06 (dd, J = 4.8, 1.6 Hz, 1H), 8.10 (dd, J = 7.8, 1.6 Hz, 1H), 12.29 (s, 1H). Anal. Calcd for $C_{17}H_{16}ClNO_5$: C, 58.38; H, 4.61; N, 4.00. Found: C, 58.32; H, 4.46; N, 3.91.

5.1.1.71. (2*E*)-3-[2-[(3,5-Dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]acrylic acid (37d). Compound **37d** (colorless crystals) was prepared from **12d** in 92% yield following a similar procedure to provide **7a**. Mp 182.3–184.0 °C (THF/hexane). ^{1}H NMR (DMSO-d_6): δ 3.28 (s, 3H), 3.61–3.65 (m, 2H), 4.10–4.14 (m, 2H), 6.42 (d, J = 16.2 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 8.7, 2.4 Hz, 1H), 7.47 (d, J = 16.2 Hz, 1H), 7.83 (d, J = 8.7 Hz, 1H), 8.16 (d, J = 2.1 Hz, 1H), 8.41 (d, J = 2.1 Hz, 1H), 12.31 (s, 1H). Anal. Calcd for $C_{17}H_{15}Cl_2NO_5$: C, 53.14; H, 3.94; N, 3.65. Found: C, 53.24; H, 3.96; N, 3.48.

5.1.1.72. (2*E*)-3-[2-({5-[(tert-Butoxycarbonyl)amino]-3-methyl-pyridin-2-yl}oxy)-4-(2-methoxyethoxy)phenyl]acrylic acid (37e). Compound **37e** (colorless crystals) was prepared from **12g** in 99% yield following a similar procedure to provide **7a**. Mp 159.0–160.0 °C (EtOH/hexane). ^{1}H NMR (DMSO-d_6): δ 1.46 (s, 9H), 2.29 (s, 3H), 3.27 (s, 3H), 3.59–3.64 (m, 2H), 4.05–4.11 (m, 2H), 6.39 (d, J = 16.1 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H), 6.82 (dd, J = 8.7, 2.4 Hz, 1H), 7.59 (d, J = 16.1 Hz, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.87 (s, 1H), 7.95 (d, J = 2.4 Hz, 1H), 9.43 (s, 1H), 12.21 (s, 1H). Anal. Calcd for $C_{23}H_{28}N_2O_7$: C, 62.15; H, 6.35; N, 6.30. Found: C, 61.97; H, 6.26; N, 6.19.

5.1.1.73. (2*E*)-3-[2-[2-Chloro-4-(trifluoromethyl)phenoxy]-4-(2-methoxyethoxy)phenyl]-*N*-(pentylsulfonyl)acrylamide (13a). Compound **13a** (colorless crystals) was prepared from **37a** and pentane-1-sulfonamide in 30% yield following a similar procedure to provide **8f**. Mp 134.1–135.1 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.1 Hz, 3H), 1.30–1.45 (m, 4H), 1.77–1.90 (m, 2H), 3.41 (s, 3H), 3.42–3.52 (m, 2H), 3.69–3.74 (m, 2H), 4.05–4.12 (m, 2H), 6.33 (s, 1H), 6.49 (d, J = 15.7 Hz, 1H), 6.74–6.79 (m, 1H), 7.02 (d, J = 8.7 Hz, 1H), 7.51 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.72 (s, 1H), 7.77 (s, 1H), 7.92 (d, J = 15.7 Hz, 1H). Anal. Calcd for $C_{24}H_{27}ClF_3NO_6S$: C, 52.41; H, 4.95; N, 2.55. Found: C, 52.34; H, 4.82; N, 2.41.

5.1.1.74. Potassium [(2*E*)-3-(4-(2-methoxyethoxy)-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)acryl](pentylsulfonyl)azanide (13b). (2*E*)-3-(4-(2-methoxyethoxy)-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)-*N*-(pentylsulfonyl)acrylamide (a colorless amorphous solid) was prepared from **37b** and pentane-1-sulfonamide in 91% yield following a similar procedure to provide **13c** (described below). ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J = 7.0 Hz, 3H), 1.25–1.46 (m, 4H), 1.74–1.89 (m, 2H), 3.43 (s, 3H), 3.43–3.45 (m, 2H), 3.71–3.79 (m, 2H), 4.10–4.16 (m, 2H), 6.38 (d, J = 15.6 Hz, 1H), 6.68 (d, J = 2.4 Hz, 1H), 6.88 (dd, J = 8.7, 2.4 Hz, 1H), 7.09 (d, J = 8.7 Hz, 1H), 7.59 (d, J = 8.7 Hz, 1H), 7.81 (d, J = 15.6 Hz, 1H), 7.95 (dd, J = 8.7, 2.4 Hz, 1H), 8.15 (s, 1H), 8.42 (s, 1H). Anal. Calcd for $C_{23}H_{27}F_3N_2O_6S$: C, 53.48; H, 5.27; N, 5.42. Found: C, 53.27; H, 5.30; N, 5.34.

To a solution of (2*E*)-3-(4-(2-methoxyethoxy)-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}phenyl)-*N*-(pentylsulfonyl)acrylamide (259 mg, 0.501 mmol) in MeOH (4 mL) was added a solution of $KHCO_3$ (50 mg, 0.499 mmol) in H_2O (0.5 mL), and the mixture was stirred at room temperature for 90 min. The reaction mixture was concentrated under reduced pressure, and the obtained crude product were recrystallized from EtOH/hexane to give **13b** (254 mg, 91%) as colorless crystals. Mp 153.0–155.2 °C. ^{1}H NMR (DMSO-d_6): δ 0.77–0.84 (m, 3H), 1.16–1.29 (m, 4H), 1.40–1.56 (m, 2H), 2.86–2.94 (m, 2H), 3.29 (s, 3H), 3.60–3.66 (m, 2H), 4.07–4.12 (m, 2H), 6.31 (d, J = 15.9 Hz, 1H), 6.77 (d, J = 2.3 Hz, 1H), 6.89 (dd, J = 8.7, 2.3 Hz, 1H), 7.17 (d, J = 15.9 Hz, 1H), 7.27 (d, J = 8.7 Hz, 1H), 7.69 (d, J = 8.7 Hz, 1H), 8.24 (dd, J = 8.7, 2.7 Hz, 1H), 8.55 (s, 1H). Anal. Calcd for $C_{23}H_{26}F_3KN_2O_6S{\cdot}0.5H_2O$: C, 49.01; H, 4.83; N, 4.97. Found: C, 49.27; H, 4.79; N, 4.96.

5.1.1.75. (2*E*)-3-[2-[(3-Chloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]-*N*-(pentylsulfonyl)acryl-amide (13c). To a stirred mixture of **37c** (427 mg, 1.22 mmol), pentane-1-sulfonamide (193 mg, 1.28 mmol), MNBA[15] (506 mg, 1.47 mmol) and DMAP (151 mg, 1.24 mmol) in acetonitrile (10 mL) was added TEA (385 mg, 3.80 mmol) at room temperature, and the mixture was stirred at room temperature for 96 h. The reaction mixture was concentrated, sat. NH_4Cl was added to the residue, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained residue was subjected to silica gel chromatography (hexane-EtOAc, 1:1) to give a white solid, which was recrystallized from EtOAc/hexane to give **13c** (523 mg, 88%) as colorless crystals. Mp 134.7–136.6 °C. ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.0 Hz, 3H), 1.26–1.45 (m, 4H), 1.76–1.88 (m, 2H), 3.42 (s, 3H), 3.42–3.50 (m, 2H), 3.71–3.76 (m, 2H), 4.09–4.14 (m, 2H), 6.40 (d, J = 15.9 Hz, 1H), 6.66 (d, J = 2.5 Hz, 1H), 6.84 (dd, J = 8.7, 2.5 Hz, 1H), 7.03 (dd, J = 7.6, 4.9 Hz, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.75–7.88 (m, 3H), 8.03 (dd, J = 4.9, 1.5 Hz, 1H). Anal. Calcd for $C_{22}H_{27}ClN_2O_6S$: C, 54.71; H, 5.63; N, 5.80. Found: C, 54.72; H, 5.63; N, 5.81.

5.1.1.76. (2*E*)-3-[2-[(3,5-Dichloropyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]-*N*-(pentylsulfonyl)acrylamide (13d). Compound **13d** (colorless crystals) was prepared from **37d** and pentane-1-sulfonamide in 43% yield following a similar procedure to provide **8f**. Mp 119.0–120.3 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 0.89 (t, J = 7.2 Hz, 3H), 1.25–1.45 (m, 4H), 1.78–1.88 (m, 2H), 3.43 (s, 3H), 3.44–3.50 (m, 2H), 3.73–3.77 (m, 2H), 4.10–4.15 (m, 2H), 6.37 (d, J = 15.6 Hz, 1H), 6.65 (d, J = 2.4 Hz, 1H), 6.86 (dd, J = 8.7, 2.4 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.65 (s, 1H), 7.79–7.84 (m, 2H), 7.96 (d, J = 2.4 Hz, 1H). Anal. Calcd for $C_{22}H_{26}Cl_2N_2O_6S$: C, 51.07; H, 5.06; N, 5.41. Found: C, 51.02; H, 5.01; N, 5.29.

5.1.1.77. tert-Butyl [6-(5-(2-methoxyethoxy)-2-{(2*E*)-3-oxo-3-[(pentylsulfonyl)amino]prop-1-en-1-yl}phenoxy)-5-methylpyridin-3-yl]carbamate (13e). Compound **13e** (colorless crystals) was prepared from **37e** and pentane-1-sulfonamide in 86% yield following a similar procedure to provide **13c**. Mp 149.5–150.2 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J = 7.0 Hz, 3H), 1.28–1.47 (m, 4H), 1.53 (s, 9H), 1.75–1.86 (m, 2H), 2.24 (s, 3H), 3.36–3.45 (m, 5H), 3.67–3.72 (m, 2H), 4.03–4.08 (m, 2H), 6.39 (s, 1H), 6.42 (d, J = 15.9 Hz, 1H), 6.49–6.51 (m, 1H), 6.72 (dd, J = 8.7, 2.5 Hz, 1H), 7.46 (d, J = 8.7 Hz, 1H), 7.82–7.88 (m, 3H), 8.71 (br s, 1H). Anal. Calcd for $C_{28}H_{39}N_3O_8S$: C, 58.21; H, 6.80; N, 7.27. Found: C, 58.30; H, 7.03; N, 6.87.

5.1.1.78. (2*E*)-3-[2-[(5-Amino-3-methylpyridin-2-yl)oxy]-4-(2-methoxyethoxy)phenyl]-*N*-(pentylsulfonyl)acrylamide dihydrochloride (13f). To a solution of **13e** (327 mg, 0.566 mmol) in MeOH (3 mL) was added 10% HCl in MeOH solution (3 mL), and the mixture was stirred at room temperature for 14 h and further at 45 °C for 3 h. The reaction mixture was concentrated under reduced pressure, and the obtained crude crystals were recrystallized from MeOH/IPE to give **13f** (207 mg, 66%) as colorless crystals. Mp 206.0–207.2 °C. ^{1}H NMR (DMSO-d_6): δ 0.80–0.85 (m, 3H), 1.14–1.29 (m, 4H), 1.30–1.49 (m, 2H), 2.39 (s, 3H), 3.09–3.27 (m, 4H), 3.30 (s, 3H), 3.65–3.67 (m, 2H), 4.13–4.16 (m, 2H), 6.21–6.24 (m, 1H), 6.96 (dd, J = 8.7, 2.4 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.66–7.67 (m, 2H), 11.93 (s, 1H). Anal. Calcd for $C_{23}H_{33}Cl_2N_3O_6S$: C, 50.18; H, 6.04; N, 7.63. Found: C, 50.07; H, 5.98; N, 7.60.

5.1.1.79. (2*E*)-3-[2-{[5-(Acetylamino)-3-methylpyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-*N*-(pentylsulfonyl)acrylamide (13g). To a solution of **13f** (321 mg, 0.606 mmol) in pyridine (5 mL) were added Ac_2O (445 mg, 4.36 mmol) and DMAP (145 mg, 1.19 mmol), and the mixture was stirred at room temperature for 7 h. The reaction mixture was concentrated, sat. NH_4Cl was added to the residue, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The obtained residue was subjected to silica gel column chromatography (EtOAc). The crude crystals were recrystallized from EtOAc/hexane to give **13g** (150 mg, 49%) as colorless crystals. Mp 187.9–188.2 °C. ^{1}H NMR ($CDCl_3$): δ 0.87 (t, J = 7.1 Hz, 3H), 1.22–1.40 (m, 4H), 1.70–1.84 (m, 2H), 2.05–2.18 (m, 6H), 3.30–3.44 (m, 5H), 3.66–3.75 (m, 2H), 4.04–4.09 (m, 2H), 6.23–6.70 (m, 3H), 7.42 (d, J = 8.7 Hz, 1H), 7.70–8.10 (m, 3H), 9.61 (br s, 1H). Anal. Calcd for $C_{25}H_{33}N_3O_7S$: C, 57.79; H, 6.40; N, 8.09. Found: C, 57.66; H, 6.43; N, 8.11.

5.1.1.80. [2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]methanol (14). To a stirred solution of **11b** (9.86 g, 26.2 mmol) in THF (40 mL) and MeOH (30 mL) was added $NaBH_4$ (2.60 g, 169 mmol) at 0 °C and the mixture was stirred the same temperature for 10 min. The reaction was quenched with 1 M HCl at 0 °C and diluted with EtOAc and the organic layer was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residual oil was purified by basic silica gel chromatography (hexane-EtOAc, 85:15 to 65:35) to give **14** (10.1 g, quant.) as a white solid. The solid was recrystallized from EtOAc/hexane to give white feathered crystals. Mp 85.0–85.5 °C. ^{1}H NMR ($CDCl_3$): δ 1.88 (t, J = 6.2 Hz, 1H), 3.44 (s, 3H), 3.69–3.83 (m, 2H), 4.02–4.17 (m, 2H), 4.54 (d, J = 6.2 Hz, 2H), 6.71 (d, J = 2.6 Hz, 1H), 6.89 (dd, J = 8.5, 2.6 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 1.9 Hz, 1H), 8.25 (dd, J = 2.1, 0.9 Hz, 1H). Anal. Calcd for $C_{16}H_{15}NO_4ClF_3$: C, 50.87; H, 4.00; N, 3.71. Found: C, 50.82; H, 3.95; N, 3.52.

5.1.1.81. 2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl acetate (38). To a solution of **14** (11.5 g, 30.4 mmol) in pyridine (25 mL) was added Ac_2O (25 mL), and the mixture was stirred at room temperature for 1 h. The reaction was quenched with sat. $NaHCO_3$, and the mixture was extracted with EtOAc. The organic layer was washed with 1 M HCl, sat. $NaHCO_3$, and brine, dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The obtained residue was subjected to silica gel column chromatography (hexane-EtOAc, 100:0 to 3:2) give **14** (8.80 g, 76%) as a white solid. Recrystallization from EtOAc/hexane gave white crystals. Mp 52.5–53.0 °C. ^{1}H NMR ($CDCl_3$): δ 1.90 (s, 3H), 3.44 (s, 3H), 3.65–3.78 (m, 2H), 4.05–4.17 (m, 2H), 5.00 (s, 2H), 6.75 (d, J = 2.4 Hz, 1H), 6.88 (dd, J = 8.5, 2.4 Hz, 1H), 7.40 (d, J = 8.7 Hz, 1H), 7.99 (d, J = 1.9 Hz, 1H), 8.26 (dd, J = 2.2, 1.0 Hz, 1H). Anal. Calcd for $C_{18}H_{17}ClF_3NO_5$: C, 51.50; H, 4.08; N, 3.34. Found: C, 51.33; H, 3.92; N, 3.33.

5.1.1.82. Methyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2,2-dimethylpropanoate (15). To a solution of **38** (1.80 g, 4.29 mmol) in toluene (20 mL) were added 1-methoxy-2-methyl-1-(trimethylsiloxy)propene (3.50 mL, 17.2 mmol) and $MgClO_4$ (1.44 g, 6.45 mmol), and the mixture was stirred at 50 °C for 3 h. Water was added to the reaction mixture, and the mixture was diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The obtained residue was subjected to silica gel column chromatography (hexane-EtOAc, 100:0 to 7:3) to give **15** (1.78 g, 90%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.17 (s, 6H), 2.73 (s, 2H), 3.43 (s, 3H), 3.66 (s, 3H), 3.73 (dd, J = 5.5, 4.0 Hz, 2H), 4.08 (dd, J = 5.5, 4.0 Hz, 2H), 6.66 (d, J = 2.4 Hz, 1H), 6.80 (dd, J = 8.6, 2.5 Hz, 1H), 7.15–7.24 (m, 1H), 7.98 (d, J = 2.1 Hz, 1H), 8.25 (dd, J = 2.3, 0.9 Hz, 1H).

5.1.1.83. 3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2,2-dimethylpropanoic acid (39). To a solution of **15** (1.75 g, 3.79 mmol) in THF (4 mL) was added conc. H_2SO_4-AcOH-H_2O (1:6:6, 8 mL), and the mixture was stirred at 80 °C for 24 h. After being allowed to cool to room temperature, the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The obtained residue was subjected to silica gel column chromatography (hexane-EtOAc, 9:1 to 1:1) to give **39** (1.36 g, 80%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.20 (s, 6H), 2.77 (s, 2H), 3.43 (s, 3H), 3.73 (dd, J = 5.0, 3.9 Hz, 2H), 4.04–4.12 (m, 2H), 6.67 (d, J = 1.9 Hz, 1H), 6.81 (dd, J = 8.6, 1.6 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 7.98 (s, 1H), 8.25 (d, J = 0.9 Hz, 1H).

5.1.1.84. Sodium {3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2,2-dimethylpropanoyl}(pentylsulfonyl)azanide (16). 3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2,2-dimethyl-*N*-(pentylsulfonyl)propanamide (a colorless oil) was prepared from **39** and pentane-1-sulfonamide in 96% yield following a

similar procedure to provide **7a**. ^{1}H NMR ($CDCl_3$): δ 0.82–0.95 (m, 3H), 1.25 (s, 6H), 1.28–1.48 (m, 4H), 1.75 (tt, J = 7.6, 7.6 Hz, 2H), 2.76 (s, 2H), 3.34–3.42 (m, 2H), 3.43 (s, 3H), 3.73 (dd, J = 5.4, 3.9 Hz, 2H), 4.09 (dd, J = 5.5, 4.0 Hz, 2H), 6.68 (d, J = 2.4 Hz, 1H), 6.82 (dd, J = 8.7, 2.6 Hz, 1H), 7.20 (d, J = 8.7 Hz, 1H), 7.82 (br s, 1H), 8.01 (d, J = 2.3 Hz, 1H), 8.28 (dd, J = 2.1, 0.9 Hz, 1H).

To a solution of 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2,2-dimethyl-*N*-(pentylsulfonyl)propanamide (1.23 g, 2.12 mmmol) in MeOH (2 mL) was added 1 M NaOH (2.12 mL, 2.12 mmol) at room temperature for 2 h, and the reaction mixture was concentrated under reduced pressure. The obtained residue was washed with cold MeOH to give **16** (982 mg, 77%) as white crystals. Mp 190.5–191.0 °C. ^{1}H NMR (DMSO-d_6): δ 0.76–0.86 (m, 3H), 0.90 (s, 6H), 1.07–1.32 (m, 4H), 1.37–1.61 (m, 2H), 2.55 (s, 2H), 2.78–2.95 (m, 2H), 3.29 (s, 3H), 3.55–3.68 (m, 2H), 3.94–4.11 (m, 2H), 6.66–6.78 (m, 2H), 7.27–7.36 (m, 1H), 8.49 (dd, J = 2.3, 0.9 Hz, 1H), 8.53 (d, J = 1.9 Hz, 1H). Anal. Calcd for $C_{25}H_{31}ClF_3N_2NaO_6S$: C, 49.79; H, 5.18; N, 4.65. Found: C, 49.74; H, 5.12; N, 4.55.

5.1.1.85. 2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)benzyl (pentylsulfonyl)carbamate (17). To a stirred solution of **14** (473 mg, 1.25 mmol) in DMF (5 mL) was added CDI (295 mg, 1.82 mmol) and the mixture was stirred at room temperature for 1 h and at 40 °C for 30 min, then pentane-1-sulfonamide (289 mg, 1.91 mmol) and DBU (0.30 mL, 2.09 mmol) were successively added to the mixture, which was stirred at the same temperature overnight. DMAP (215 mg, 1.76 mmol) was added to the mixture, and after 1 h, the reaction was quenched with 1 M HCl and extracted with EtOAc. The combined organic layer was washed with 1 M HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residual oil was purified by silica gel chromatography twice (hexane-EtOAc, 9:1 to 65:35, then hexane-EtOAc, 7:1 to 4:1) to give a white solid, which was recrystallized from EtOAc/hexane to give **17** (373 mg, 54%) as white crystals. Mp 130–132 °C. ^{1}H NMR ($CDCl_3$): δ 0.83–0.94 (m, 3H), 1.19–1.49 (m, 4H), 1.70–1.88 (m, 2H), 3.27–3.41 (m, 2H), 3.44 (s, 3H), 3.69–3.78 (m, 2H), 4.04–4.14 (m, 2H), 5.13 (s, 2H), 6.75 (d, J = 2.4 Hz, 1H), 6.88 (dd, J = 8.6, 2.5 Hz, 1H), 6.94 (s, 1H), 7.42 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 1.9 Hz, 1H), 8.26 (dd, J = 2.2, 1.0 Hz, 1H). *Anal.* Calcd for $C_{22}H_{26}ClF_3N_2O_7S$: C, 47.61; H, 4.72; N, 5.05. Found: C, 47.56; H, 4.77; N, 4.90.

5.1.1.86. 2-Hydroxy-4-isopropoxybenzaldehyde (18a). A mixture of **3** (100 g, 0.724 mol) and DIPEA (127 mL, 0.730 mol) in THF (350 mL) was added 2-iodomethame (72.9 mL, 0.730 mol) with stirring at room temperature, then stirred for 3 h. To this mixture was added 2-iodomethane (20 mL, 0.20 mol), and the mixture waas stirred under reflux for 12 h. The mixture was diluted with water, extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, then concentrated in vacuo. The residue was purified by silica gel chromatography (hexane-EtOAc, 20:1 to 10:1) to give **18a** (30.9 g, 24%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.37 (d, J = 6.0 Hz, 6H), 4.48–4.72 (m, 1H), 6.40 (d, J = 2.5 Hz, 1H), 6.49 (dd, J = 8.8, 2.2 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 9.69 (s, 1H), 11.47 (s, 1H).

5.1.1.87. 2-Benzyloxy-4-isopropoxybenzaldehyde (19a). Compound **19a** (a pale-yellow oil) was prepared from **18a** and benzyl bromide in 91% yield following a similar procedure to provide **7c**. ^{1}H NMR ($CDCl_3$): δ 1.35 (d, J = 6.2 Hz, 6H), 4.49–4.71 (m, 1H), 5.15 (s, 2H), 6.49 (d, J = 2.1 Hz, 1H), 6.54 (dd, J = 8.7, 1.9 Hz, 1H), 7.31–7.50 (m, 5H), 7.82 (d, J = 8.7 Hz, 1H), 10.37 (d, J = 0.8 Hz, 1H).

5.1.1.88. 2-(Benzyloxy)-4-(2-methoxyethoxy)benzaldehyde (19b). Compound **19b** (white crystals) was prepared from **9** and benzyl bromide in 79% yield following a similar procedure to provide **7c**. Mp 67.5–68.0 °C. ^{1}H NMR ($CDCl_3$): δ 3.45 (s, 3H), 3.67–3.88 (m, 2H), 4.08–4.20 (m, 2H), 5.15 (s, 2H), 6.50–6.69 (m, 2H), 7.31–7.52 (m, 5H), 7.83 (d, J = 9.2 Hz, 1H), 10.38 (s, 1H). *Anal.* Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.15; H, 6.26.

5.1.1.89. 2-Benzyloxy-4-methoxymethoxybenzaldehyde (19c). Compound **19c** (a colorless oil) was prepared from **4b** and benzyl bromide in 72% yield following a similar procedure to provide **7c**. ^{1}H NMR ($CDCl_3$): δ 3.47 (s, 3H), 5.16 (s, 2H), 5.20 (s, 2H), 6.58–6.76 (m, 2H), 7.30–7.48 (m, 5H), 7.82 (d, J = 9.1 Hz, 1H), 10.40 (s, 1H).

5.1.1.90. Ethyl (2*E*)-3-(2-benzyloxy-4-isopropoxyphenyl)acrylate (20a). Compound **20a** (a colorless oil) was prepared from **19a** in 97% yield following the procedure to provide **6a**. ^{1}H NMR ($CDCl_3$): δ 1.31 (t, J = 7.1 Hz, 3H), 1.31 (d, J = 6.0 Hz, 6H), 4.23 (q, J = 7.2 Hz, 2H), 4.44–4.63 (m, 1H), 5.13 (s, 2H), 6.42 (d, J = 16.2 Hz, 1H), 6.46–6.52 (m, 2H), 7.29–7.50 (m, 6H), 7.99 (d, J = 16.2 Hz, 1H).

5.1.1.91. Ethyl (2*E*)-3-(2-benzyloxy-4-methoxymethoxyphenyl)acrylate (20c). Compound **20c** (a yellow oil) was prepared from **19c** in 96% yield following a similar procedure to provide **6a**. ^{1}H NMR ($CDCl_3$): δ 1.32 (t, J = 7.2 Hz, 3H), 3.46 (s, 3H), 4.23 (q, J = 7.2 Hz, 2H), 5.14 (s, 2H), 5.16 (s, 2H), 6.44 (d, J = 16.2 Hz, 1H), 6.65–6.69 (m, 2H), 7.28–7.49 (m, 6H), 8.00 (d, J = 16.2 Hz, 1H).

5.1.1.92. Ethyl (2*E*)-3-(2-benzyloxy-4-hydroxyphenyl)acrylate (20d). Compound **20d** (colorless prisms) was prepared from **20c** in 78% yield following a similar procedure to provide **33b**. Mp 131–133 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 1.32 (t, J = 7.2 Hz, 3H), 4.23 (q, J = 7.2 Hz, 2H), 5.12 (s, 2H), 5.25 (s, 1H), 6.36–6.53 (m, 3H), 7.29–7.51 (m, 6H), 8.00 (d, J = 16.2 Hz, 1H). *Anal.* Calcd For $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.24; H, 5.94.

5.1.1.93. Ethyl (2*E*)-3-{2-(benzyloxy)-4-[2-(2-oxopyrrolidin-1-yl)ethoxy]phenyl}acrylate (20e). To a stirred solution of **20d** (2.01 g, 6.74 mmol) in THF (100 mL) was added 1-(2-hydroxyethyl)-2-pyrrolidone (0.80 mL, 7.12 mmol), followed by triphenylphosphine (2.65 g, 10.1 mmol) and DEAD (2.2 M in toluene, 5.50 mL, 12.1 mmol) at 0 °C and the mixture was allowed to warm to room temperature. After being stirred for 3 h, the mixture was concentrated in vacuo, and the residual oil was purified by silica gel chromatography (hexane-EtOAc, 3:1 to EtOAc to EtOAc-MeOH, 9:1) to give **20e** (4.01 g, quant.) as a white solid. Recrystallization from EtOAc/hexane gave white crystals. Mp 94–97 °C. ^{1}H NMR ($CDCl_3$): δ 1.32 (t, J = 7.2 Hz, 3H), 1.84–2.12 (m, 2H), 2.39 (t, J = 8.1 Hz, 2H), 3.47–3.57 (m, 2H), 3.66 (t, J = 5.2 Hz, 2H), 4.10 (t, J = 5.2 Hz, 2H), 4.23 (q, J = 7.2 Hz, 2H), 5.14 (s, 2H), 6.43 (d, J = 16.2 Hz, 1H), 6.47–6.52 (m, 2H), 7.29–7.54 (m, 6H), 7.99 (d, J = 16.2 Hz, 1H). *Anal.* Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.22; H, 6.61; N, 3.28.

5.1.1.94. Ethyl 3-(2-hydroxy-4-isopropoxyphenyl)propanoate (21a). A stirred solution of **20a** (172 g, 0.505 mol) in THF (250 mL) and EtOH (250 mL) was hydrogenated under atmospheric pressure with 10% Pd/C (wet, 30.0 g, 14.1 mmol) at room temperature for 40 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residual oil was passed through silica gel to give **20a** (112 g, 88%) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.24 (t, J = 7.2 Hz, 3H), 1.31 (d, J = 6.0 Hz, 6H), 2.59–

2.72 (m, 2H), 2.75–2.88 (m, 2H), 4.15 (q, J = 7.2 Hz, 2H), 4.37–4.57 (m, 1H), 6.38–6.45 (m, 1H), 6.44–6.48 (m, 1H), 6.94 (d, J = 8.3 Hz, 1H), 7.42 (s, 1H).

5.1.1.95. Methyl 3-[2-hydroxy-4-(2-methoxyethoxy)phenyl]-2-methoxypropanoate (21b). To a solution of **19b** (11.9 g, 41.6 mmol) in THF (80 mL) were added methyl methoxyacetate (6.16 g, 59.2 mmol) and KO*t*-Bu (6.81 g, 60.7 mmol), and the mixture was stirred at room temperature for 5 h. The reaction was quenched with 1 M HCl, and the mixture was diluted with EtOAc. The organic layer was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The obtained residue was subjected to silica gel column chromatography (hexane-EtOAc, 100:1 to 2:3) to give a yellow oil (**20b**).

To a solution of **20b** in MeOH (100 mL) was added 10% Pd/C (wet, 5.01 g, 2.35 mmol), and the mixture was stirred under hydrogen atmosphere at room temperature for 5 h. The reaction mixture was filtrated, and the filtrate was concentrated under reduced pressure. The obtained residue was subjected to silica gel column chromatography (hexane-EtOAc, 19:1 to 55:45) to give **21b** (3.45 g, 29%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.91–3.11 (m, 2H), 3.44 (s, 3H), 3.49 (s, 3H), 3.70–3.77 (m, 5H), 4.01–4.12 (m, 3H), 6.43 (dd, J = 8.3, 2.6 Hz, 1H), 6.51 (d, J = 2.6 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 7.69 (s, 1H).

5.1.1.96. Ethyl 3-{2-hydroxy-4-[2-(2-oxopyrrolidin-1-yl)ethoxy]phenyl}propanoate (21c). Compound **21c** (a white powder) was prepared from **20e** in quantitative yield following a similar procedure to provide **21a**. Mp 112–115 °C (EtOAc/IPE). ^{1}H NMR ($CDCl_3$): δ 1.24 (t, J = 7.2 Hz, 3H), 1.94–2.08 (m, 2H), 2.38 (t, J = 8.1 Hz, 2H), 2.61–2.74 (m, 2H), 2.78–2.93 (m, 2H), 3.57 (t, J = 7.1 Hz, 2H), 3.65 (t, J = 5.1 Hz, 2H), 4.06 (t, J = 5.1 Hz, 2H), 4.14 (q, J = 7.2 Hz, 2H), 6.40 (dd, J = 8.3, 2.6 Hz, 1H), 6.46 (d, J = 2.4 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 7.74 (s, 1H). *Anal.* Calcd for $C_{23}H_{28}ClF_3N_2O_6S$ 0.25H_2O: C, 62.66; H, 7.27; N, 4.30. Found: C, 62.45; H, 7.12; N, 4.25.

5.1.1.97. Ethyl 3-(2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propanoate (22a). Compound **22a** (a pale-yellow oil) was prepared from **21a** and 2,3-dichloro-5-(trifluoromethyl)pyridine in 88% yield following a similar procedure to provide **5a**. ^{1}H NMR ($CDCl_3$): δ 1.21 (t, J = 7.2 Hz, 3H), 1.32 (d, J = 6.0 Hz, 6H), 2.50–2.62 (m, 2H), 2.68–2.84 (m, 2H), 4.09 (q, J = 7.1 Hz, 2H), 4.38–4.58 (m, 1H), 6.63 (d, J = 2.6 Hz, 1H), 6.76 (dd, J = 8.5, 2.6 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 1.7 Hz, 1H), 8.27 (dd, J = 2.3, 0.9 Hz, 1H).

5.1.1.98. Methyl 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methoxypropanoate (22b). Compound **22b** (a yellow oil) was prepared from **21b** and 2,3-dichloro-5-(trifluoromethyl)pyridine in 75% yield following a similar procedure to provide **5a**. ^{1}H NMR ($CDCl_3$): δ 1.21 (t, J = 7.2 Hz, 3H), 1.32 (d, J = 6.0 Hz, 6H), 2.50–2.62 (m, 2H), 2.68–2.84 (m, 2H), 4.09 (q, J = 7.1 Hz, 2H), 4.38–4.58 (m, 1H), 6.63 (d, J = 2.6 Hz, 1H), 6.76 (dd, J = 8.5, 2.6 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 1.7 Hz, 1H), 8.27 (dd, J = 2.3, 0.9 Hz, 1H).

5.1.1.99. 3-(2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)propanoic acid (40a). Compound **40a** (a white powder) was prepared from **21a** in quantitative yield following a similar procedure to provide **34a**. Mp 107.0–107.5 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 1.32 (d, J = 6.2 Hz, 6H), 2.55–2.70 (m, 2H), 2.70–2.85 (m, 2H), 4.36–4.61 (m, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.77 (dd, J = 8.5, 2.4 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 2.1 Hz, 1H), 8.26 (dd, J = 2.1, 0.9 Hz, 1H). *Anal.* Calcd for $C_{18}H_{17}NO_4ClF_3$: C, 53.54; H, 4.24; N, 3.47. Found: C, 53.61; H, 4.16; N, 3.43.

5.1.1.100. 3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methoxypropanoic acid (40b). Compound **40b** (white crystals) was prepared from **25b** in 54% yield following a similar procedure to provide **34a**. Mp 93–96 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 2.81–2.92 (m, 1H), 3.00–3.10 (m, 1H), 3.28 (s, 3H), 3.42–3.45 (m, 3H), 3.70–3.76 (m, 2H), 4.00 (dd, J = 7.8, 4.6 Hz, 1H), 4.07–4.12 (m, 2H), 6.69 (d, J = 2.6 Hz, 1H), 6.83 (dd, J = 8.6, 2.5 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 1.9 Hz, 1H), 8.26 (dd, J = 2.1, 0.9 Hz, 1H). *Anal.* Calcd for $C_{19}H_{19}NO_6ClF_3$: C, 50.73; H, 4.26; N, 3.11. Found: C, 50.90; H, 4.37; N, 3.19.

5.1.1.101. 3-{2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-oxopyrrolidin-1-yl)ethoxy]phenyl}propanoic acid (40c). To a stirred solution of **21c** (2.90 g, 6.74 mmol) was added NaH (60% dispersion in oil, 464 mg, 11.6 mmol) at 0 °C and after 30 min, 2,3-dichloro-5-(trifluoromethyl)pyridine (1.50 mL, 10.8 mmol) was added to the mixture, which was allowed to warm to room temperature. After being stirred for 1 h, the reaction was quenched with sat. NH_4Cl and extracted with EtOAc and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residual oil was purified by silica gel chromatography (hexane-EtOAc, 1:1 to EtOAc) to give crude ethyl 3-{2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-oxopyrrolidin-1-yl)-ethoxy]-phenyl}propanoate **(22c)** (3.17 g) as an orange oil.

To a stirred solution of **22c** (3.17 g) in THF (15 mL) and EtOH (15 mL) was added 1 M NaOH (16.0 mL, 16.0 mmol) and the mixture was stirred at room temperature for 12 h, and additional 1 M NaOH (15.0 mL, 15.0 mmol) was added and after 1 h, 1 M NaOH (10.0 mL, 10.0 mmol) was added and the mixture was stirred for 1 h. The reaction was acidified with 1 M HCl (41.0 mL, 41.0 mmol), and concentrated in vacuo, and the residue was dissolved into EtOAc, and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual solid was purified by silica gel chromatography (hexane-EtOAc, 3:1 to EtOAc to EtOAc-MeOH, 9:1) to give **40c** (0.85 g, 27%) as a white solid. Recrystallization from EtOAc/hexane gave a white powder. Mp 145.0–145.5 °C. ^{1}H NMR ($CDCl_3$): δ 1.90–2.11 (m, 2H), 2.38 (t, J = 8.1 Hz, 2H), 2.63 (t, J = 7.4 Hz, 2H), 2.78 (t, J = 7.3 Hz, 2H), 3.48–3.62 (m, 2H), 3.66 (t, J = 5.1 Hz, 2H), 4.07 (t, J = 5.1 Hz, 2H), 6.64 (d, J = 2.4 Hz, 1H), 6.77 (dd, J = 8.5, 2.6 Hz, 1H), 7.12–7.27 (m, 1H), 7.99 (d, J = 1.9 Hz, 1H), 8.26 (dd, J = 2.2, 1.0 Hz, 1H). *Anal.* Calcd for $C_{21}H_{20}ClF_3N_2O_5$: C, 53.34; H, 4.26; N, 5.92. Found: C, 53.45; H, 4.32; N, 5.80.

5.1.1.102. 3-(2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-5-(pentylsulfonyl)propanamide (23a). Compound **23a** (white crystals) was prepared from **40a** and pentane-1-sulfonamide in 50% yield following a similar procedure to provide **8a**. Mp 94–95 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 0.85–0.94 (m, 3H), 1.24–1.41 (m, 10H), 1.60–1.73 (m, 2H), 2.55 (t, J = 7.2 Hz, 2H), 2.96 (t, J = 7.1 Hz, 2H), 3.12–3.20 (m, 2H), 4.36–4.55 (m, 1H), 6.45 (d, J = 2.4 Hz, 1H), 6.74 (dd, J = 8.4, 2.5 Hz, 1H), 7.17 (d, J = 8.5 Hz, 1H), 8.08 (d, J = 2.1 Hz, 1H), 8.33–8.43 (m, 1H). *Anal.* Calcd for $C_{23}H_{28}N_2O_5SClF_3$: C, 51.44; H, 5.26; N, 5.22. Found: C, 51.36; H, 5.21; N, 5.21.

5.1.1.103. 3-(2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-isopropoxyphenyl)-*N*-pentylpropanamide (23b). To a stirred solution of **40a** (315 mg, 0.776 mmol) in THF (10 mL) was added $SOCl_2$ (0.1 mL, 1.39 mmol), followed by DMF (10 μL, 0.130 mmol) at 0 °C. After being stirred for 2 h at the same

temperature, the mixture was concentrated in vacuo and the residue was dissolved into THF (2 mL). To the solution was added pentylamine (0.20 mL, 1.72 mmol), followed by pyridine (0.50 mL, 6.19 mmol) and DMAP (12.1 mg, 0.124 mmol) at room temperature, and the mixture was stirred for 2 h. The reaction was quenched with 1 M HCl and diluted with EtOAc and the organic layer was washed sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual solid was recrystallized from EtOAc/hexane to give **23b** (166 mg, 45%) as white crystals. Mp 106–107.5 °C. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, J = 7.1 Hz, 3H), 1.11–1.48 (m, 12H), 2.39 (t, J = 7.5 Hz, 2H), 2.80 (t, J = 7.4 Hz, 2H), 3.02–3.18 (m, 2H), 4.38–4.63 (m, 1H), 5.42 (s, 1H), 6.59 (d, J = 2.6 Hz, 1H), 6.75 (dd, J = 8.5, 2.6 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 1.7 Hz, 1H), 8.26 (dd, J = 2.2, 1.0 Hz, 1H). *Anal.* Calcd for $C_{23}H_{28}ClF_3N_2O_3$: C, 58.41; H, 5.97; N, 5.92. Found: C, 58.25; H, 5.99; N, 5.94.

5.1.1.104. 3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-2-methoxy-*N*-(pentylsulfonyl)propanamide (23c). Compound **23c** (white crystals) was prepared from **40b** and pentane-1-sulfonamide in 23% yield following a similar procedure to provide **8f**. Mp 76.0–78.0 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 0.86–0.95 (m, 3H), 1.23–1.49 (m, 4H), 1.64–1.85 (m, 2H), 2.87 (dd, J = 14.4, 7.1 Hz, 1H), 3.08–3.37 (m, 6H), 3.43 (s, 3H), 3.66–3.76 (m, 2H), 3.95 (dd, J = 7.1, 4.1 Hz, 1H), 4.03–4.15 (m, 2H), 6.65 (d, J = 2.4 Hz, 1H), 6.81 (dd, J = 8.5, 2.6 Hz, 1H), 7.21 (d, J = 8.7 Hz, 1H), 8.02 (d, J = 1.9 Hz, 1H), 8.29 (dd, J = 2.2, 1.0 Hz, 1H), 8.86 (s, 1H). *Anal.* Calcd for $C_{24}H_{30}ClF_3N_2O_7S$: C, 49.44; H, 5.19; N, 4.80. Found: C, 49.51; H, 5.08; N, 4.86.

5.1.1.105. 3-{2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-[2-(2-oxopyrrolidin-1-yl)ethoxy]phenyl}-*N*-(pentylsulfonyl)propanamide (23d). Compound **23d** (a white powder) was prepared from **40c** and pentane-1-sulfonamide in 74% yield following a similar procedure to provide **8a**. Mp 123–126 °C (EtOAc/IPE). ^{1}H NMR ($CDCl_3$): δ 0.86–0.93 (m, 3H), 1.20–1.47 (m, 4H), 1.59–1.78 (m, 2H), 1.93–2.18 (m, 2H), 2.38 (t, J = 8.1 Hz, 2H), 2.56 (t, J = 7.2 Hz, 2H), 2.94 (t, J = 7.2 Hz, 2H), 3.14–3.27 (m, 2H), 3.54 (t, J = 7.1 Hz, 2H), 3.64 (t, J = 5.1 Hz, 2H), 4.04 (t, J = 5.2 Hz, 2H), 6.49 (d, J = 2.6 Hz, 1H), 6.75 (dd, J = 8.5, 2.6 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 8.08 (d, J = 1.7 Hz, 1H), 8.35 (dd, J = 2.3, 0.9 Hz, 1H), 9.02 (s, 1H). *Anal.* Calcd for $C_{26}H_{31}ClF_3N_3O_6S$: C, 51.53; H, 5.16; N, 6.93. Found: C, 51.27; H, 5.06; N, 6.89.

5.1.1.106. Ethyl (2*E*)-3-[4-(2-methoxyethoxy)-2-(methoxymethoxy)phenyl]acrylate (24). To a stirred solution of **10** (7.40 g, 27.8 mmol) and K_2CO_3 (7.40 g, 53.5 mmol) in MeCN (150 mL) was added MOMCl (2.40 mL, 31.6 mmol) at room temperature, and the mixture was stirred for 2 h. Water was added to the mixture and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give **24** (9.01 g, quant.) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.33 (t, J = 7.2 Hz, 3H), 3.45 (s, 3H), 3.49 (s, 3H), 3.72–3.78 (m, 2H), 4.10–4.17 (m, 2H), 4.25 (q, J = 7.2 Hz, 2H), 5.23 (s, 2H), 6.40 (d, J = 16.2 Hz, 1H), 6.58 (dd, J = 8.6, 2.4 Hz, 1H), 6.77 (d, J = 2.4 Hz, 1H), 7.46 (d, J = 8.7 Hz, 1H), 7.95 (d, J = 16.2 Hz, 1H).

5.1.1.107. Ethyl 2-[4-(2-methoxyethoxy)-2-(methoxymethoxy)phenyl]cyclopropanecarboxylate (25). To a stirred suspension of trimethylsulfoxonium iodide (9.17 g, 41.7 mmol) in DMSO (50 mL) was added NaH (60% dispersion in oil, 1.67 g, 41.8 mmol) at 0 °C and the mixture was stirred at room temperature for 1 h. Then a solution of **24** (9.01 g, 29.0 mmol) in DMSO (75 mL) was added to the mixture dropwise over 20 min, which was stirred at room temperature for 2 days. The reaction was quenched with sat. NH_4Cl on ice-bath and extracted with EtOAc/hexane (1:1) and the combined organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was purified by silica gel chromatography (hexane-EtOAc, 100:0 to 3:2) to give **25** (0.85 g, 9%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.22–1.29 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.51 (ddd, J = 9.3, 5.0, 4.3 Hz, 1H), 1.76 (ddd, J = 8.2, 5.1, 4.4 Hz, 1H), 2.63 (ddd, J = 9.2, 6.8, 4.3 Hz, 1H), 3.44 (s, 3H), 3.47 (s, 3H), 3.66–3.76 (m, 2H), 4.04–4.10 (m, 2H), 4.13–4.21 (m, 2H), 5.14–5.21 (m, 2H), 6.48 (dd, J = 8.5, 2.4 Hz, 1H), 6.71 (d, J = 2.4 Hz, 1H), 6.82 (d, J = 8.5 Hz, 1H).

5.1.1.108. Ethyl 2-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]cyclopropanecarboxylate (26). To a stirred solution of **25** (0.85 g, 2.62 mmol) in acetone (10 mL) was added 1 M HCl (5 mL) and the mixture was stirred at 50 °C for 6 h. After being cooled to room temperature, 1 M NaOH (5 mL) was added to the mixture and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give ethyl 2-[2-hydroxy-4-(2-methoxyethoxy)phenyl]cyclopropanecarboxylate (0.80 g) as a brown oil.

To a stirred solution of the obtained ethyl 2-[2-hydroxy-4-(2-methoxyethoxy)phenyl]cyclopropanecarboxylate (0.80 g) and K_2CO_3 (724 mg, 5.23 mmol) in DMF was added 2,3-dichloro-5-(trifluoromethyl)pyridine (726 μL, 5.21 mmol) and the mixture was stirred at room temperature overnight. The reaction was quenched with 1 M HCl and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was purified by silica gel chromatography (hexane-EtOAc, 65:35) to give **26** (488 mg, 41%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.17 (t, J = 7.2 Hz, 3H), 1.20–1.32 (m, 1H), 1.38 (ddd, J = 9.2, 4.8, 4.7 Hz, 1H), 1.62 (ddd, J = 8.1, 5.1, 4.8 Hz, 1H), 2.33 (ddd, J = 9.1, 6.7, 4.3 Hz, 1H), 3.44 (s, 3H), 3.70–3.76 (m, 2H), 3.87–4.00 (m, 2H), 4.07–4.13 (m, 2H), 6.72 (d, J = 2.4 Hz, 1H), 6.82 (dd, J = 8.6, 2.5 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 1.7 Hz, 1H), 8.25 (dd, J = 2.2, 1.0 Hz, 1H).

5.1.1.109. 2-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]cyclopropanecarboxylic acid (41). Compound **41** (white crystals) was prepared from **26** in 99% yield following a similar procedure to provide **34a**. Mp 121.0–121.5 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 1.36 (ddd, J = 8.3, 6.9, 4.7 Hz, 1H), 1.44 (ddd, J = 9.3, 4.8 Hz, 1H), 1.62 (ddd, J = 8.1, 5.1, 4.7 Hz, 1H), 2.39 (ddd, J = 9.1, 6.9, 4.5 Hz, 1H), 3.44 (s, 3H), 3.65–3.79 (m, 2H), 3.96–4.14 (m, 2H), 6.74 (d, J = 2.4 Hz, 1H), 6.82 (dd, J = 8.6, 2.5 Hz, 1H), 7.04 (d, J = 8.7 Hz, 1H), 7.94 (d, J = 1.9 Hz, 1H), 8.25 (dd, J = 2.2, 1.0 Hz, 1H). *Anal.* Calcd for $C_{19}H_{17}ClF_3NO_5$: C, 52.85; H, 3.97; N, 3.24. Found: C, 52.87; H, 4.02; N, 3.17.

5.1.1.110. 2-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-*N*-(pentylsulfonyl)cyclopropanecarboxamide (27). Compound **27** (white crystals) was prepared from **41** and pentane-1-sulfonamide in 67% yield following a similar procedure to provide **8f**. Mp 184.0–184.5 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 0.83–0.94 (m, 3H), 1.22–1.48 (m, 6H), 1.57–1.63 (m, 1H), 1.78 (tt, J = 7.6, 7.6 Hz, 2H), 2.25–2.58 (m, 1H), 3.21–3.39 (m, 2H), 3.43 (s, 3H), 3.62–3.80 (m, 2H), 3.96–4.19 (m, 2H), 6.69 (d, J = 2.4 Hz, 1H), 6.82 (dd, J = 8.6, 2.5 Hz, 1H), 7.05 (d, J = 8.7 Hz, 1H), 8.01 (d, J = 2.1 Hz, 1H), 8.26 (dd, J = 2.1, 0.9 Hz, 1H). *Anal.* Calcd for $C_{24}H_{28}ClF_3N_2O_6S$: C, 51.02; H, 5.00; N, 4.96. Found: C, 51.02; H, 5.04; N, 4.94.

5.1.1.111. 3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-ol (28). To a stirred solution of **7b** (12.1 g, 26.9 mmol) in THF (60 mL) was added DIBAL-H (1.5 M in toluene, 65.0 mL, 97.5 mmol) dropwise at 0 °C and the mixture was stirred at the same temperature for 10 min. The reaction was quenched with sat. NH_4Cl (5.40 mL) dropwise on ice-bath and the mixture was allowed to warm to at room temperature with stirring. After being stirred for 1 h, the precipitates were filtered off and the filtrate was concentrated under reduced pressure to give **28** (7.69 g, 70%) as a white powder. Recrystallization from EtOAc/hexane gave white crystals. Mp 74.5–75.5 °C (EtOAc/hexane). ^{1}H NMR (CDCl3): δ 1.37 (s, 1H), 1.77–1.89 (m, 2H), 2.54 (t, J = 7.5 Hz, 2H), 3.44 (s, 3H), 3.60 (q, J = 6.1 Hz, 2H), 3.68–3.78 (m, 2H), 4.05–4.12 (m, 2H), 6.67 (d, J = 2.6 Hz, 1H), 6.84 (dd, J = 8.5, 2.4 Hz, 1H), 7.22 (d, J = 8.7 Hz, 1H), 7.98 (d, J = 2.3 Hz, 1H), 8.26 (d, J = 1.1 Hz, 1H). *Anal.* Calcd for $C_{18}H_{19}ClF_3NO_4$: C, 53.28; H, 4.72; N, 3.45. Found: C, 53.21; H, 4.74; N, 3.25.

5.1.1.112. 3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl butylcarbamate (29a). To a stirred solution of **28** (0.30 g, 0.740 mmol) in DMF (7 mL) was added CDI (0.18 g, 1.11 mmol) and the mixture was stirred at 60 °C. After being stirred for 1 h, butylamine (0.22 mL, 2.23 mmol) was added to the mixture, and after 6 h, the reaction was quenched with water and extracted with EtOAc and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residual oil was purified by silica gel chromatography (hexane-EtOAc, 9:1 to 7:3) to give a crude solid, which was recrystallized from IPE/hexane to give **29a** (297 mg, 80%) as a white powder. Mp 91.7–91.8 °C. ^{1}H NMR ($CDCl_3$): δ 0.92 (t, J = 7.4 Hz, 3H), 1.31–1.46 (m, 4H), 1.80–1.95 (m, 2H), 2.50 (t, J = 7.1 Hz, 2H), 3.09–3.20 (m, 2H), 3.44 (s, 3H), 3.72–3.75 (m, 2H), 4.00 (t, J = 6.5 Hz, 2H), 4.07–4.10 (m, 2H), 4.54 (s, 1H), 6.68 (d, J = 3.6 Hz, 1H), 6.82 (dd, J = 8.4, 2.4 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 2.4 Hz, 1H), 8.25 (dd, J = 2.0, 1.1 Hz, 1H). *Anal.* Calcd for $C_{23}H_{28}ClF_3N_2O_5$: C, 54.71; H, 5.59; N, 5.55. Found: C, 54.74; H, 5.44; N, 5.54.

5.1.1.113. 3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl (pentylsulfonyl)carbamate (29b). To a stirred solution of triphosgene (67.9 mg, 0.229 mmol) in DCM (5 mL) was added **28** (205 mg, 0.504 mmol), followed by pyridine (0.10 mL, 1.24 mmol) at 0 °C. After completion of the addition, the mixture was concentrated in vacuo, and the residue was dissolved into THF (10 mL). To the THF solution were added successively pentane-1-sulfonamide (125 mg, 0.827 mmol), DIPEA (0.40 mL, 2.34 mmol) and DMAP (61.5 mg, 0.503 mmol), and the mixture was stirred at room temperature for 10 min. The reaction was quenched with 1 M HCl and diluted with EtOAc and the saparated organic layer was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residual oil was purified by silica gel chromatography twice (hexane-EtOAc, 19:1 to 1:1, then hexane-EtOAc, 9:1 to 1:1) to give a white solid, which was recrystallized from EtOAc/hexane to give **29b** (34.9 mg, 12%) as white crystals. Mp 97.5–99.0 °C. ^{1}H NMR (CDCl3): δ 0.91 (t, J = 7.1 Hz, 3H), 1.24–1.47 (m, 4H), 1.72–2.07 (m, 4H), 2.57 (t, J = 7.3 Hz, 2H), 3.27–3.39 (m, 2H), 3.43 (s, 3H), 3.70–3.75 (m, 2H), 4.05–4.12 (m, 2H), 4.16 (t, J = 6.3 Hz, 2H), 6.68 (d, J = 2.4 Hz, 1H), 6.82 (dd, J = 8.5, 2.6 Hz, 1H), 7.18 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 2.1 Hz, 1H), 8.28 (d, J = 0.9 Hz, 1H). *Anal.* Calcd for $C_{24}H_{30}ClF_3N_2O_7S$: C, 49.44; H, 5.19; N, 4.80. Found: C, 49.55; H, 5.21; N, 4.60.

5.1.1.114. 2-{3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}-1H-isoindole-1,3(2*H*)-dione (30). To a stirred solution of **28** (4.94 g, 12.2 mmol) in EtOAc (100 mL) was added TEA (3.50 mL, 25.1 mmol), followed by MsCl (1.40 mL, 18.1 mmol) at room temperature and the mixture was stirred at the same temperature for 1 h. The reaction was quenched with 1 M HCl and diluted with EtOAc and the separated organic layer was washed with sat. $NaHCO_3$, and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give crude 3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl methanesulfonate (6.15 g) as a pale-yellow oil.

To a stirred solution of crude intermediate (6.15 g) in DMF (50 mL) was added potassium phthalimide (2.46 g, 13.3 mmol) and the mixture was stirred at 80 °C for 3 h. After being cooled to room temperature, the reaction was quenched with water and extracted with EtOAc and the organic layer was washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual solid was washed with IPE to give **30** (6.39 g, 98%) as a white solid. Recrystallization from EtOAc/hexane gave white crystals. Mp 101–103 °C. ^{1}H NMR ($CDCl_3$): δ 1.82–1.99 (m, 2H), 2.39–2.53 (m, 2H), 3.43 (s, 3H), 3.63–3.77 (m, 4H), 4.02–4.11 (m, 2H), 6.67 (d, J = 2.6 Hz, 1H), 6.82 (dd, J = 8.4, 2.5 Hz, 1H), 7.23 (d, J = 8.7 Hz, 1H), 7.67–7.73 (m, 2H), 7.76–7.83 (m, 2H), 7.86 (d, J = 2.1 Hz, 1H), 8.22 (d, J = 1.1 Hz, 1H). *Anal.* Calcd for $C_{26}H_{22}ClF_3N_2O_5$: C, 58.38; H, 4.15; N, 5.24. Found: C, 58.38; H, 4.22; N, 5.13.

5.1.1.115. 3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propan-1-amine (31). To a stirred solution of **30** (6.12 g, 11.4 mmol) in MeOH (100 mL) was added hydrazine hydrate (4.02 g, 80.3 mmol) and the mixture was stirred at 50 °C for 2 h. The mixture was concentrated in vacuo, and the residue was washed with Et_2O and the filtrates were evaporated. The residue was washed with Et_2O and the filtrates were concentrated in vacuo. The oil was dissolved into EtOAc and the organic layer was washed sat. $NaHCO_3$-brine (1:1) and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to give **31** (2.51 g, 54%) as a dark-brown oil. ^{1}H NMR ($CDCl_3$): δ 1.51–1.95 (m, 4H), 2.40–2.55 (m, 2H), 2.68 (t, J = 7.0 Hz, 2H), 3.44 (s, 3H), 3.65–3.80 (m, 2H), 4.09 (d, 2H), 6.67 (d, J = 2.4 Hz, 1H), 6.83 (dd, J = 8.4, 2.5 Hz, 1H), 7.21 (d, J = 8.7 Hz, 1H), 7.98 (d, J = 2.1 Hz, 1H), 8.26 (d, J = 0.9 Hz, 1H).

5.1.1.116. *N*-{3-[2-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]propyl}-pentane-1-sulfonamide (32a). To a stirred solution of **31** (1.01 g, 2.49 mmol) in pyridine (2.5 mL) and EtOAc (10 mL) was added pentane-1-sulfonyl chloride (0.50 g, 2.93 mmol) at room temperature, and the mixture was stirred at the same temperature for 1.5 h. The reaction was quenched with sat. NH_4Cl and diluted with EtOAc and the organic layer was washed with 1 M HCl, sat. $NaHCO_3$, water and brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residual oil was purified by silica gel chromatography (hexane-EtOAc, 19:1 to 3:2) to give a white solid, which was recrystallized from EtOAc/hexane to give **32a** (198 mg, 15%) as white crystals. Mp 87–90 °C. ^{1}H NMR ($CDCl_3$): δ 0.90 (t, J = 6.9 Hz, 3H), 1.21–1.41 (m, 4H), 1.64–1.93 (m, 4H), 2.53 (t, J = 7.4 Hz, 2H), 2.85–2.99 (m, 2H), 3.06 (t, J = 6.6 Hz, 2H), 3.43 (s, 3H), 3.65–3.81 (m, 2H), 4.03–4.11 (m, 2H), 4.13–4.25 (m, 1H), 6.66 (d, J = 2.5 Hz, 1H), 6.84 (dd, J = 8.5, 2.7 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 1.9 Hz, 1H), 8.18–8.28 (m, 1H). *Anal.* Calcd for $C_{23}H_{30}ClF_3N_2O_5S$: C, 51.25; H, 5.61; N, 5.20. Found: C, 51.37; H, 5.82; N, 5.02.

5.1.1.117. Butyl {3-[2-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-4-(2-methoxyethoxy)phenyl]-propyl}carbamate (32b). Compound **32b** (white crystals) was prepared from **31** and butyl chloroformate in 3% yield following a similar procedure to provide **32a**. Mp 91.5–92.0 °C (EtOAc/hexane). ^{1}H NMR ($CDCl_3$): δ 0.92 (t, J = 7.3 Hz, 3H), 1.27–1.44 (m, 2H), 1.50–1.62 (m, 2H), 1.70–1.83 (m, 2H), 2.48 (t, J = 7.5 Hz, 2H), 3.09–3.18 (m, 2H), 3.43 (s, 3H), 3.62–3.76 (m, 2H), 4.01 (t, J = 6.5 Hz, 2H), 4.04–4.20 (m, 2H), 4.69 (s, 1H), 6.67 (d, J = 2.4 Hz, 1H), 6.83 (dd, J = 8.5, 2.6 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 1.9 Hz, 1H), 8.26 (d, J = 1.1 Hz, 1H). Anal. Calcd for $C_{23}H_{28}ClF_3N_2O_5$: C, 54.71; H, 5.59; N, 5.55. Found: C, 54.62; H, 5.44; N, 5.35.

5.2. Biology

5.2.1. Metabolic stability assay

Human or rat hepatic microsomes were purchased from Xenotech, LLC (Lenexa, KS). An incubation mixture with a final volume of 0.1 mL consisted of microsomal protein in 50 mmol/L phosphate buffer (pH 7.4) and 1 μmol/L test compound. The concentration of hepatic microsomal protein was 0.2 mg/mL. An NADPH-generating system containing 50 mmol/L $MgCl_2$, 50 mmol/L glucose-6-phosphate, 5 mmol/L beta-NADP$^+$ and 15 unit/mL glucose-6-phosphate dehydrogenase was prepared and added to the incubation mixture with a 10% volume of the reaction mixture. After the addition of the NADPH-generating system, the mixture was incubated at 37 °C for 0 and 20 min. The reaction was terminated by the addition of equivalent volume of MeCN to that of the reaction mixture. All incubations were made in duplicate. The amounts of test compound in the reaction mixtures were measured by HPLC analysis which was performed by Nemoto Science Co., Ltd (Tokyo, Japan). Metabolic stability was assessed as disappearance rate of the parent compound. Disappearance rate is represented as a percentage of the amount of the parent compound in the reaction mixture for 20 min relative to that in the reaction mixture for 0 min taken as 100%.

5.2.2. Pharmacokinetic analyses in Wistar fatty rats

The test compound was administered to nonfasted rats. After oral and intravenous administration, blood samples were collected. The blood samples were centrifuged to obtain the plasma fraction. The plasma samples were deproteinized with MeCN containing an internal standard. After centrifugation, the supernatant was diluted and centrifuged again. The compound concentrations in the supernatant were measured by LC/MS/MS.

5.2.3. Establishment of a stable transformed cell expressing human PPARγ1, human RXRα, and PPAR responsive luciferase reporter gene

The full length human PPARγ1, full length human RXRα, and PPAR responsive luciferase reporter gene were stably expressed in CHO-K1 cells. Transfection of mammalian expression plasmid, pVGRXR2-hPPARγ-zeo, and reporter plasmid, pGL3-(PPREx4)-Tk-neo, into the cells was performed by electroporation using a Gene Pulser (Bio-Rad, Japan). G418 (Life Technologies Inc., U.S.A.) and Zeocin (Invitrogen, U.S.A.) resistant clones were selected and examined for their ability to introduce liciferase expression in the presence of pioglitazone. Finally, we selected the clone, PPARγ:RXRα:4ERPP/CHO-K1 No.10, which expressed high levels of luciferase activity by pioglitazone.

5.2.4. Transactivation assay of hPPARγ1

PPARγ:RXRα:PPRE×4/CHO-K1 cells were used for transactivation assays of hPPARγ1. These cells were seeded into an OPAQUE PLATE (white 96 well half area plate, COSTAR, U.S.A.) at the density of 1×10^4 cells/well, and cultured in 5% CO_2 at 37 °C overnight. After washing the OPAQUE PLATE with PBS, 45 μL of HAM F12 medium containing 0.1% fatty acid free-BSA and 5 μL of test compounds were added to the plate, which was then cultured in 5% CO_2 at 37 °C for 1 day. After removing the medium, 20 μL of PICAGENE-LT7.5 (Wako Pure Chemical Ind., Ltd., Japan), which was diluted to half with HANK'S BALANCED SALT SOLUTION, was added to each well. After stirring, luciferase activities were determined in microplate-based luminescence reader (Perkinnelmer, U.S.A.).

5.2.5. Transient co-transfection assay of hPPARα and hPPARδ

COS-1 cells were seeded at 5×10^6 cells in 150 cm^2 tissue culture flask, and cultured in 5% CO_2 at 37 °C overnight. Transfections were performed with LipofectAMINE (Life Technologies, Inc., U.S.A.) according to the instructions of manufacturer. Briefly, the transfection mixture contained 125 μL of LipofectAMINE, 100 μL of plus reagent, 2.5 μg of each expression plasmid pMCMVneo-hPPARα (pMCMVneo-hPPARδ) and pMCMVneo-hRXRα, 5 μg of reporter plasmid pGL3-PPRE×4-tk-luc-neo, and 5 μg of pRL-tk (Promega, U.S.A.). Cells were incubated in 25 mL of transfection mixture for 3 h in 5% CO_2 at 37 °C. After adding 25 mL of DMEM medium (Life Technologies, Inc., U.S.A.) containing 0.1% fatty acid free-BSA, the cells were then incubated for 1 day in 5% CO_2 at 37 °C. After transfection, cells were detached by treating with trypsin-EDTA (Life Technologies INC., U.S.A.) centrifuged and then suspended in DMEM medium containing 0.1% fatty acid free-BSA. The suspended cells were added into an OPAQUE PLATE (white 96 well half area plate, COSTAR, U.S.A.) at the density of 5×10^3 cells/well in 45 μL of DMEM medium containing 0.1% fatty acid free-BSA and 5 μL of test compounds and then cultured in 5% CO_2 at 37 °C for 2 days. After removing the medium, 20 μL of PICAGENE-LT7.5 (Wako Pure Chemical Ind., Ltd., Japan), which was diluted to half with HANK'S BALANCED SALT SOLUTION, was added to each well. After stirring, luciferase activities were determined in microplate-based luminescence reader (Perkinnelmer, U.S.A.).

5.2.6. Evaluation of plasma glucose- and triglyceride-lowering activities in Wistar fatty rats

Male Wistar fatty rats were obtained from Takeda Rabics (Japan) and were used in these experiments. Throughout the study, they were housed in metal cages and fed a commercial diet CE-2 (Clea, Japan) and water *ad libitum*. At the beginning of experiment, blood samples were withdrawn from tail vein with heparin as anticoagulant, and initial body weight was measured. Plasma samples were obtained from blood samples by centrifugation. Plasma levels of glucose and triglyceride were measured enzymatically using Autoanalyzer 7080 (Hitachi, Japan). Rats were divided based on body weight, plasma glucose and triglyceride (n = 5/group). Wistar fatty rats were orally administered test compounds suspended in 0.5% methylcellurose solution once daily for 7 days. The next day of final administration, blood samples were withdrawn from tail vein, and body weight was measured. After obtaining of plasma samples by centrifugation of blood samples, we measured plasma glucose and triglyceride. The change (%) from the initial levels of plasma glucose and triglyceride after 7-day treatment was calculated in each group. The degree of the lowering effect in each group was estimated from the relative ratio of the change (%) in each group to the change in the control group. Then, the ED_{25} for the glucose- and triglyceride-lowering effects of test compounds were calculated from the dose-response curves of the relative ratios generated by logistic regression using the PCP systems.

5.3. Docking study

The atomic coordinates of the crystal structures (1FM6 and 1PRG) were obtained from the web site of RCSB protein data bank (http://www.rcsb.org/pdb/home/home.do). Both protein structures

Table 8
X-ray data collection and refinement statistics

	8f
Crystal	
Space group	$P2_12_12_1$
Unit cell dimensions	a = 58.8 Å
	b = 62.3 Å
	c = 157.6 Å
Molecules/asymmetric unit	2
Data collection	
Resolution [Å] (outer shell)	50–2.43 (2.52–2.43)
Observations (unique)	125131 (22489)
Redundancy	5.6
Completeness overall (outer shell)	99.7 (99.4)%
I/δ (I) overall (outer shell)	20.4 (3.3)
R_{symm} overall (outer shell)	0.082 (0.524)
Refinement	
Resolution [Å]	20–2.5
Reflections used	19584
R-factor	0.196
R_{free}	0.269
RMS bonds [Å]	0.009
RMS angles [°]	1.11
Average B-value [Å^2]	37.0

were added hydrogens and then only hydrogens were energetically optimized in MOE (ver. 2000.02, Chemical Computing Group Inc, Canada.). Each compound was docked into the PPARγ-LBD using the GOLD program (ver. 2.0, the Cambridge crystallographic data centre, UK) with the default parameter set. After some manual adjustment to remove large steric hindrances, docking poses showing high score (Gold score) were subjected to energy minimization using MMFF94s force field in MOE. During the energy minimization procedure firstly whole protein structure was fixed and secondly that within 3.5 Å from the each ligand was relaxed.

5.4. X-ray co-crystallography study

5.4.1. Protein expression and purification

The ligand binding domain (LBD) of human PPARγ (NM_005037; aa 202–475) was cloned into pET28a vector (Novagen) and expressed as an *N*-terminal 6xHis fusion protein in E. coli. Fusion protein was purified by Ni affinity chromatography (Probond, Invitrogen) at pH 7.9, followed by anion exchange (Q Sepharose FF, GE Healthcare) and size exclusion chromatography (Superdex S200, GE Healthcare). Before crystallization, the protein solution was concentrated to 16 mg/ml by centrifugal ultrafiltration.

5.4.2. Crystallization and data collection

Crystals of the PPARγ-LBD **8f** complex were obtained by pre-incubating a 15 mg/ml protein preparation with 2.0 mM **8f**, and were grown at 20 °C by sitting-drop vapor diffusion using Nanovolume Crystallization techniques with 50 nL of protein solution and 50 nL of reservoir containing 20% polyethylene glycol 3000, 0.1 M TRIS, pH 7.0 and 0.2 M calcium acetate.

Single crystals were harvested in reservoir solutions supplemented with 25% ethylene glycol as cryoprotectant and flash-frozen by direct immersion in liquid nitrogen. X-ray diffraction data were collected at the Advanced Light Source in Berkeley, California at Beam Line 5.0.3 equipped with an ADSC Quantum 4r CCD detector. The diffraction intensities were integrated and scaled using the HKL2000 program suite.[27] Data collection statistics are presented in Table 8.

5.4.3. Structure determination and refinement

The **8f** complex structure was determined by molecular replacement using MolRep[28] and 2PRG[29] as the search model. The initial solutions were refined with REFMAC,[30] and the models were visually inspected and manually built and rebuilt using the XtalView/Xfit program suite.[31] The crystallographic refinement statistics are presented in Table 8.

Acknowledgment

We would like to thank Robert Wynands for his help in preparing the manuscript and the staff of the Advanced Light Source, which is supported by the Director, Office of Science, Office of Basic Energy Science of the U.S. Department of Energy under Contract No. DE-AC02–05CH11231. We would also like to thank Shinkichi Suzuki for supporting the optimization study by conducting high-throughput organic synthesis.

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