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Further optimization of sulfonamide analogs as EP1 receptor antagonists: Synthesis and evaluation of bioisosteres for the carboxylic acid group

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Abstract—4-{[2-[(2-Furylsulfonyl)(isobutyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoic acid analogs **2a** and **b** and a series of the acid analogs, in which the carboxylic acid residue of **2b** was replaced with various kinds of carboxylic acid bioisosteres, were synthesized and evaluated as EP1 receptor antagonists. Compound **2b** and its monocyclic acid analogs, in which the carboxylic acid residue of **2b** was replaced with monocyclic acid bioisosteres, were found to show potent EP1 receptor antagonist activity. Optimization of the linker Y between the phenyl moiety and the carboxylic acid residue of **2b** was also carried out (Table 5). Compounds **2b** and **16** and **17** possessing conformationally restricted linker Y were found to show the most optimized potency among the tested compounds. Cytochrome P450 inhibition of optimized compounds was also investigated. Details of the structure–activity relationship study are presented.

1. Introduction

Cyclooxygenases metabolize arachidonic acid to five primary prostanoids, PGE_2, PGF_2, PGI_2, TXA_2 (TX), and PGD_2. These lipid mediators interact with specific members of a family of distinct G-protein-coupled prostanoid receptors.[1] Coleman et al. proposed the existence of specific receptors for TX, PGI, PGE, PGF, and PGD, named TP, IP, EP, FP, and DP receptors, respectively.[2] They further classified the EP receptor into four subtypes (EP1, EP2, EP3, and EP4), all of which respond to PGE_2 in different ways. A number of specific ligands for these receptors and their therapeutic potential have already been described in the literature. Discovery of selective EP1 receptor antagonists would offer an opportunity to elucidate the role of this receptor in various pathological conditions such as hyperalgesia[3] and pollakisuria.[4]

In one of our previous papers,[5] we reported on the discovery of **1** as a new lead compound in the EP1 receptor antagonists. Compound **1** demonstrated remarkably weak antagonist activity (IC_{50}, 0.13 μM) for its strong receptor affinity (K_i, 0.0005 μM). In an effort to improve this weak antagonist activity, we incorporated bioisosteres into our further optimization process because this methodology has been frequently used for such a purpose in conventional medicinal chemistry. Accordingly, the phenylsulfonyl moiety and the carboxylic acid residue were replaced with a furan-2-sulfonyl moiety and acid residue, respectively (Fig. 1). We here report on further optimization efforts for the newly found EP1 receptor antagonist **1**.

2. Chemistry

The synthesis of the test compounds listed in Tables 1–5 is outlined in Schemes 1–3. Compounds **2b**, **4**, and **15–17** were synthesized as described in Schemes 1a and b. *O*-Alkylation of **19**[6] with methyl 4-(bromomethyl)

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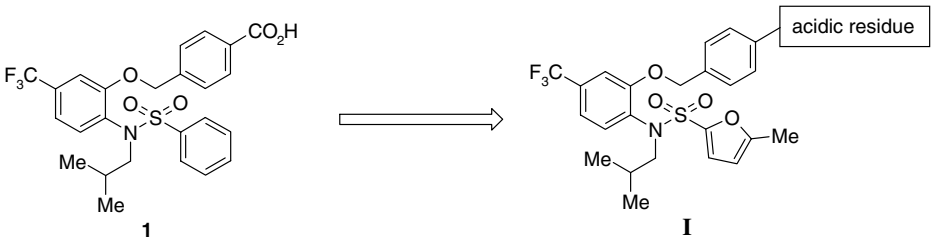
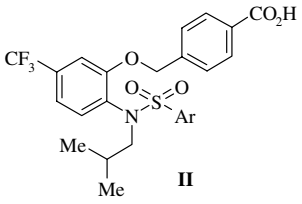
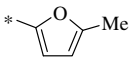


Figure 1. Transformation of a phenylsulfonyl aminobenzoic acid analog **1** to 5-methylfuran-2-sulfonyl aminobenzoic acid analogs **I**.

Table 1. Effect of transformation of the aryl moiety Ar on K_i values and antagonist activities



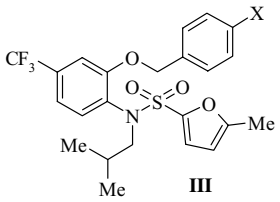
Compound	Ar	Binding K_i (μM)				Function IC_{50} (μM)
		EP1	EP2	EP3	EP4	EP1
1		0.00050	>10	0.41	>10	0.13
2a		0.00040	8.1	1.7	>10	0.17
2b		0.00020	>10	0.82	2.1	0.0056

benzoate in the presence of potassium carbonate yielded **20a**, reduction of which, with lithium borohydride, gave alcohol **21**. Oxidation of **21** with DMSO yielded an aldehyde **22**, C2 homologation of which, using malonic acid reaction followed by esterification, gave an α,β-unsaturated methyl ester **20b**.[7] Reduction of the nitro residue of **20a** and **b** yielded anilines **24a** and **b**, respectively. Hydrogenation of **24b** gave **24c**.[8] *N*-Sulfonylation of **24a–c** with 5-methylfuran-2-sulfonyl chloride **29**, which was prepared from **27** according to a previously reported method[9] (Scheme 1b), gave sulfonamides **25a–c**, respectively. *N*-Alkylation of **25a–c** with isobutyl iodide in the presence of potassium carbonate yielded **26a–c**, respectively. Alkaline hydrolysis of **26a** gave a carboxylic acid **2b**. Compound **2b** was converted to the corresponding acid chloride with thionyl chloride. Wittig reaction of the resulting acid chloride with methyl (triphenylphosphoranylidene) acetate, followed by heating, yielded **26d**.[10] Alkaline hydrolysis of **26d** gave the corresponding carboxylic acid **17**. Condensation of **2b** with methanesulfonamide in the presence of EDC yielded **4**. Alkaline hydrolysis of **26b** and **c** gave **16** and **15**, respectively.

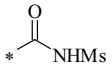
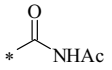
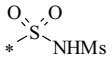
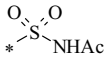
Synthesis of **3** and **8–11** is outlined in Scheme 2. Catalytic hydrogenation of a protected *O*-nitrophenol **30**, which was prepared by *O*-alkylation of **19** with methoxymethyl chloride, yielded **31**. *N*-Sulfonylation of **31** with 5-methylfuran-2-sulfonyl chloride gave **32**, *N*-alkylation of which with isobutyl iodide in the presence of potassium carbonate yielded **33**. Acidic deprotection of **33** gave **34**, *O*-alkylation of which with 4-(bromomethyl)benzonitrile, in the presence of potassium carbonate, produced the nitrile **3**. Reaction of the nitrile **3** with sodium azide, in the presence of triethylamine, resulted in the tetrazole **11**.[11] Reaction of the nitrile **3** with hydroxylamine, in the presence of triethylamine, produced the *N*-hydroxy amidine **35**. Reaction of **35** with thionyl chloride yielded 3*H*-1,2,3,5-oxathiadiazole 2-oxide **8**.[12] Reaction of **35** with 2-ethylhexyl chloroformate, followed by heating in xylene, gave oxadiazol-5-one **9**.[12] Reaction of **35** with thiocarbonyl diimidazole, followed by cyclization with boron trifluoride etherate, yielded thiadiazol-5-one **10**.[12]

Synthesis of **5–7**, **12–14**, and **18** is described in Scheme 3. Compounds **5–7** and **18** were prepared as outlined in Scheme 3a. Reaction of 4-bromomethylbenzoic acid (**36**) with thionyl chloride yielded the corresponding acid chloride, which was converted to the corresponding amide **40a** by the usual ammonolysis with aqueous ammonia. *O*-Alkylation of **34** (Scheme 2) with **40a** gave **41a**. *N*-Acylation of the amide function of **41a** yielded *N*-acetylcarboxyamide **5**. Ammonolysis of 4-bromomethyl benzenesulfonyl chloride (**37**) gave the sulfonamide **40b**. *O*-Alkylation of **34** (Scheme 2) with **40b**, in the presence of potassium carbonate, yielded **41b**. *N*-Methanesulfonylation of the primary sulfonamide residue of **41b** resulted in *N*-methanesulfonylsulfonamide **6**. *N*-Acetylation of the sulfonamide residue of **41b**

Table 2. Effect of transformation of the carboxylic acid moiety X on K_i values and antagonist activities

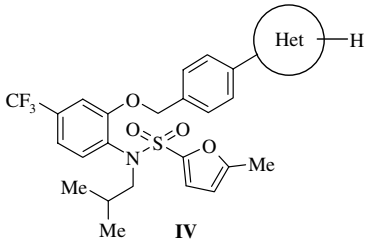


III

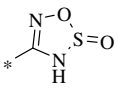
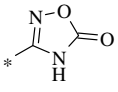
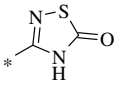
Compound	X	Binding K_i (μM)				Function IC_{50} (μM)
		EP1	EP2	EP3	EP4	EP1
2b		0.00020	>10	0.82	2.1	0.0056
3		0.30	>10	>10	>10	>10
4		0.0022	>10	0.61	>10	0.038
5		0.0073	>10	>10	>10	0.36
6		0.026	>10	0.61	>10	NT[a]
7		0.058	>10	>10	>10	0.83

[a] NT, not tested.

Table 3. Activity profiles of monocyclic acid analogs

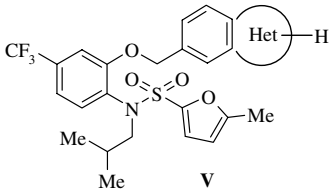


IV

Compound	Het—H	Binding K_i (μM)				Function IC_{50} (μM)
		EP1	EP2	EP3	EP4	EP1
8		0.0029	7.5	0.39	>10	0.0026
9		0.0031	4.5	0.48	>10	0.0016
10		0.0069	3.3	0.54	2.4	0.0035
11		0.0026	2.5	0.026	>10	0.00074

produced *N*-acetyl sulfonamide **7**. *O*-Alkylation of the phenol residue of **38** with methyl chloroacetate yielded **39**. Bromination reaction of benzyl alcohol **39** with phosphorus tribromide provided **40c**. *O*-Alkylation of **34** (Scheme 2) with **40c** yielded **41c**, alkaline hydrolysis of which resulted in the corresponding carboxylic acid **18**.

Table 4. Activity profiles of fused bicyclic acid analogs



V

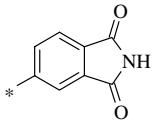
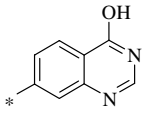
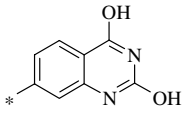
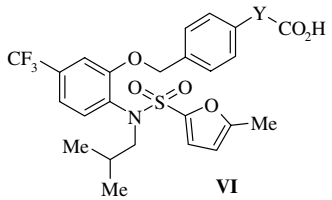
Compound		Binding K_i (μM)				Function IC_{50} (μM)
		EP1	EP2	EP3	EP4	EP1
12		0.0061	>10	>10	>10	0.68
13		0.0013	>10	>10	>10	0.19
14		0.0013	>10	>10	>10	0.56

Table 5. Effect of transformation of the linker Y on K_i values and antagonist activities



VI

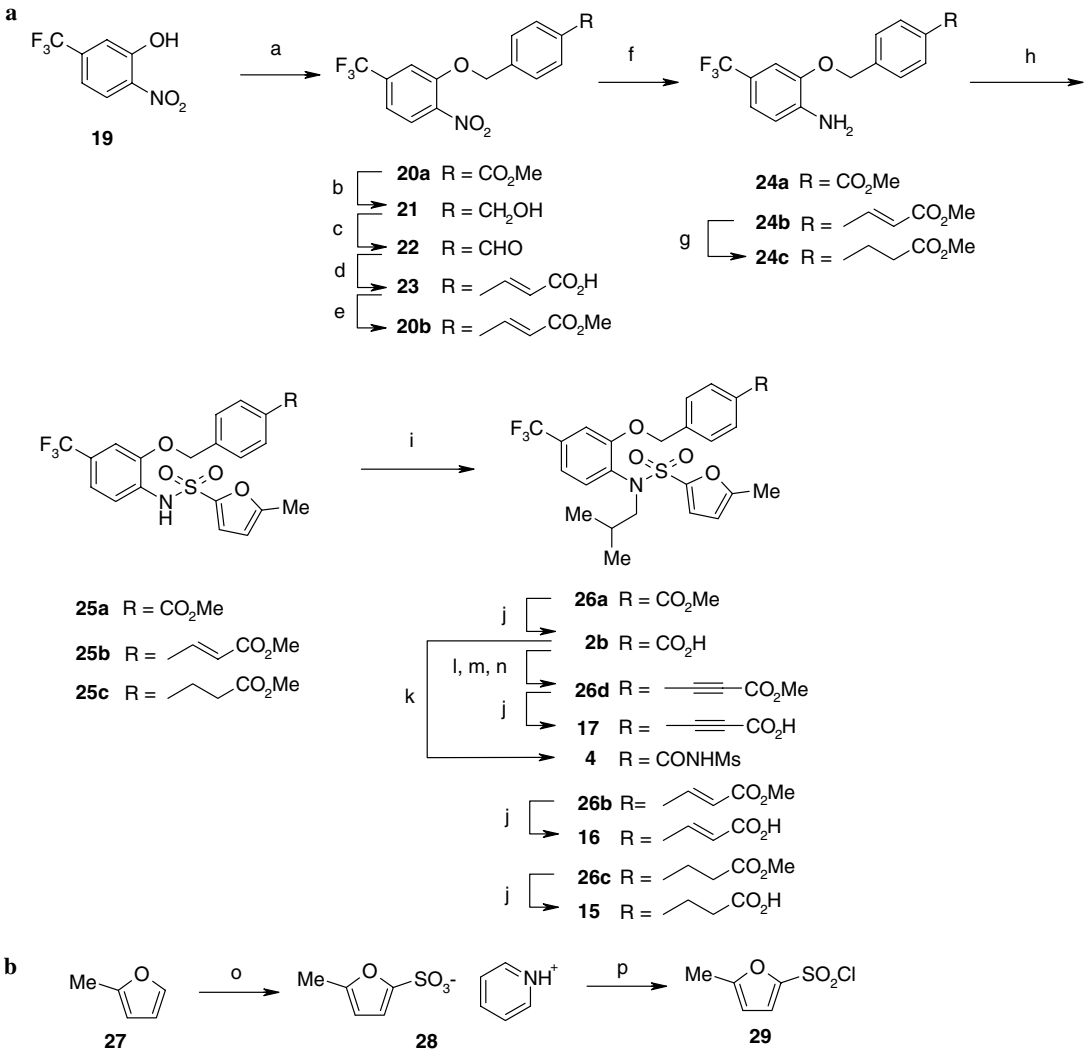
Compound	Y	Binding K_i (μM)				Function IC_{50} (μM)
		EP1	EP2	EP3	EP4	EP1
15		0.0034	3.0	1.1	2.9	0.17
16		0.0004	4.8	1.9	2.0	0.0053
17		0.0011	3.1	0.79	4.5	0.0058
18		0.00042	3.5	>10	>10	0.021

Compound **12** was prepared as shown in Scheme 3b. Bromination of **42** with *N*-bromosuccinimide yielded **43**. *O*-Alkylation of **34** (Scheme 2) with the bromide **43** produced **44**, alkaline hydrolysis of which yielded **45**. Heating of **45** in the presence of acetic anhydride, followed by ammonolysis and then heating in toluene, resulted in the phthalimide analog **12**.

Synthesis of **13** and **14** is described in Scheme 3c. Partial alkaline hydrolysis of **46** yielded **47**, reduction of which with diborane-dimethylsulfide complex produced **48**. *O*-Alkylation of **34** (Scheme 2) with **48**, using the Mitsunobu reaction, gave **49**. Reduction of **49** with iron powder, followed by alkaline hydrolysis, produced **51**. Cyclization of **51** with imidoformamide hydrochloride, with heating, resulted in 4-hydroxyquinazoline **13**.[13] Cyclization of **51** with urea, with heating, resulted in 2,4-dihydroxyquinzoline **14**.[14]

3. Results and discussion

The test compounds listed in Tables 1–5 were biologically evaluated for their inhibition of the specific binding of a radiolabeled ligand, [^{3}H]PGE_2, to membrane fractions prepared from cells stably expressing each mouse prostanoid receptor. The EP1 antagonist properties of these compounds were determined by a Ca^{2+} assay using



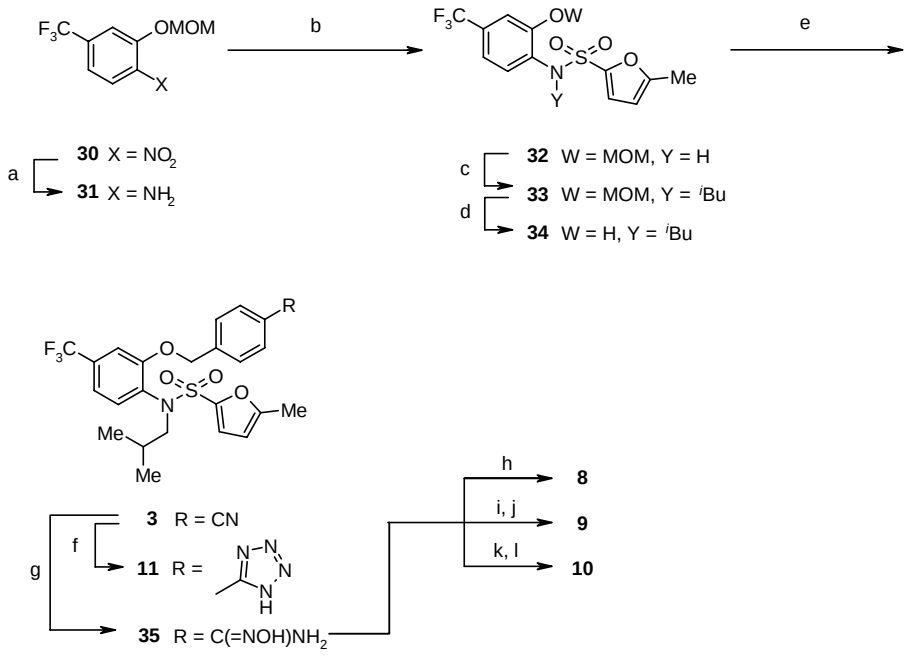
Scheme 1. Synthesis of **2b**, **4**, and **15–17**. Reagents and condition: (a) methyl 4-(bromomethyl)benzoate K_2CO_3, acetone; (b) $LiBH_4$, MeOH, Et_2O; (c) SO_3·Py, $^iPr_2NEt$, DMSO, EtOAc; (d) malonic acid, piperidine, pyridine; (e) MeI, K_2CO_3, DMF; (f) Fe, AcOH, H_2O; (g) $NaBH_4$, $NiCl_2$·$6H_2O$, EtOH, H_2O; (h) **29**, pyridine; (i) ^iBuI, K_2CO_3, DMF; (j) NaOH, MeOH, dioxane; (k) $MsNH_2$, EDC, DMAP, DMF; (l) $SOCl_2$, EtOAc; (m) Ph_3P = $CHCO_2Me$, Et_3N, toluene; (n) *o*-dichlorobenzene, heat; (o) SO_3·Py, CH_3CN; (p) $SOCl_2$, DMF.

mouse EP1 receptor expressed on CHO cells in the presence of 0.1% of bovine serum albumin.

Furan-2-sulfonyl analogs **2a**[15] and **b** were synthesized and evaluated (Table 1). Among these, 5-methylfuran-2-sulfonyl analog **2b** showed much stronger antagonist activity relative to the chemical lead **1**, while demethylated analog **2a** showed nearly the same potency as **1** in terms of both receptor affinity and antagonist activity. Based on these results, further optimization of 5-methylfuran-2-sulfonyl analogs, instead of the phenylsulfonyl and furan-2-sulfonyl analogs, was carried out as shown in Tables 2–5.

In proceeding the optimization process, focus was placed on the nitrile analog **3** (Table 2), in which a carboxylic acid residue was replaced by a nitrile residue. The marked reduction in the activity of this transformation strongly suggested a structural requirement for an acid residue at this position, which was supposed to correspond to the carboxylic acid residue of PGE_2. For this reason, synthesis and biological evaluation of the acid analogs listed in Tables 2–5 are of great interest to medicinal chemists.

The bioisostere is known as one of the useful transformations for improving the activity and/or pharmacokinetic profiles of chemical leads in medicinal chemistry.[16] In an effort to further optimize the acid residue of the chemical lead **2b**, the carboxylic acid was replaced by various bioisosteres, as illustrated in Tables 2–5. As shown in Table 2, replacement of the carboxylic acid of **2b** with an *N*-acylsulfonamide and an *N*-acylacetoamide (imide) yielded **4** and **5**, respectively. Compound **4** exhibited 11-fold less EP1 receptor affinity and 6.8-fold less antagonist activity relative to **2b**, while **5** exhibited less receptor affinity and antagonist activity. Replacement of the carboxylic acid residue of **2b** with a *N*-sulfonyl methanesulfonamide and a *N*-sulfonyl acetoamide yielded **6** and **7**, respectively, which showed less receptor affinity relative to **4** and **5**, respectively.



Scheme 2. Synthesis of **3** and **8–11**. Reagents and condition: (a) H_2, Pd–C, MeOH; (b) **29**, pyridine, CH_2Cl_2; (c) ^{i}BuI, K_2CO_3, DMF; (d) HCl, MeOH; (e) 4-(bromomethyl)benzonitrile, K_2CO_3, acetone; (f) NaN_3, $Et_3N{\cdot}HCl$, toluene; (g) $NH_2OH{\cdot}HCl$, Et_3N, EtOH; (h) $SOCl_2$, pyridine, THF; (i) 2-ethylhexyl chloroformate, pyridine; (j) xylene, heat; (k) thiocarbonyl diimidazole (TCDI), THF; (l) $BF_3{\cdot}OEt_2$, THF.

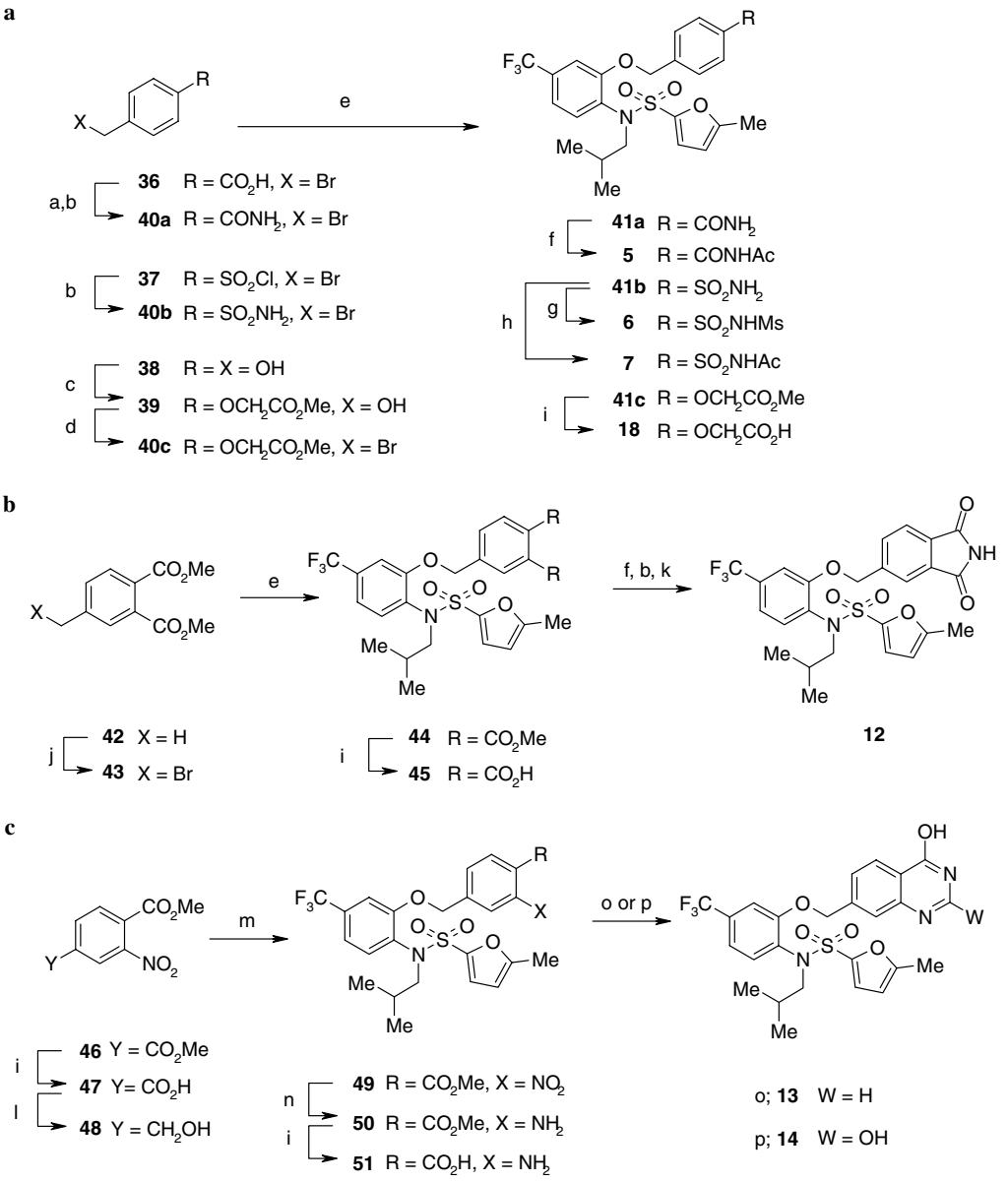
As illustrated in Table 3, monocyclic acid analogs were synthesized and evaluated.[12] 2-Oxido-3*H*-1,2,3,5-oxathiadiazol analog **8** showed 15-fold less potent EP1 receptor affinity relative to **2b**, while it showed 2.2-fold more potent antagonist activity. Oxadiazole-5-one analog **9** exhibited nearly equipotent receptor affinity and antagonist activity with **8**. A thiadiazole-5-one analog **10** showed 2.4-fold less potent EP1 receptor affinity and 1.3-fold less potent antagonist activity relative to **8**, while it also showed weak affinity for the EP4 receptor. A tetrazole analog **11** demonstrated the strongest antagonist activity among this series of analogs, although it showed nearly the same receptor affinity as **8–10**. Besides, **11** showed an increased affinity for EP3 receptor relative to **8–10**.

Activity profiles of fused bicyclic acid analogs are shown in Table 4. Analogs **12–14** showed weaker antagonist activity relative to the series of monocyclic acids **8–11**, although they showed equipotency in their EP1 receptor affinity and better subtype selectivity. Phthalimide analog **12** showed 31-fold less EP1 receptor affinity and 121-fold less potent antagonist activity relative to **2b**. 4-Hydroxyquinazoline analog **13** and 2,4-dihydroxyquinazoline analog **14** exhibited equipotency in their EP1 receptor affinity, while **13** showed 2.9-fold more potent antagonist activity than **14**.

Second, the effect of transformation of the linker Y (Table 5) between the carboxylic acid residue and the phenyl moiety on receptor affinity and antagonist activity was investigated. Replacement of the carboxylic acid residue of **2b** with a propionic acid residue yielded **15**, which showed 17-fold less potent EP1 receptor affinity and 30-fold less potent antagonist activity. Replacement of the carboxylic acid residue with a propenoic acid residue and a propynoic acid residue gave **16** and **17**, respectively, with 2-fold and 5.5-fold less potent EP1 receptor affinity, while both showed nearly the same antagonistic activity as **2b**. Oxyacetic acid analog **18** showed nearly the same EP1 receptor affinity as **16**, while it showed 4-fold less antagonist activity, which was weaker than its receptor affinity.

Based on the relatively stronger antagonist activity of **2b**, **16**, and **17**, conformational restriction of the acid residue was found to be one of the required partial structures for increased antagonist activity. Optimized compounds **2b**, **8–11**, and **16** and **17** were also evaluated for their inhibition of P450 enzymes, to predict their potential for drug–drug interactions.[17] As shown in Table 6, monocyclic acid analogs **8–11** exhibited relatively stronger inhibition. Tetrazole analog **11** demonstrated especially strong inhibitory activities against 2C9, 2C19, and 3A4. Propynoic acid analog **17** showed increased inhibitory activities against 2C9 and 3A4 compared with **2b**.

In summary, we synthesized and evaluated 5-methylfuran-2-sulfonyl analog **2b**, which exhibited much stronger antagonist activity than **1** and **2a**. Based on the data, the 5-methyl residue of **2b** was considered to play an important role in transmitting functional activity via the EP1 receptor. To improve antagonist activity, we also synthesized and evaluated acid analogs of **2b** by incorporating the concept of the bioisostere into further optimization. Among the tested compounds, monocyclic acid analogs **8–11** listed in Table 3 exhibited stronger EP1 receptor antagonist activity relative to **2b**, although all of them showed weaker receptor affinity. In



Scheme 3. Synthesis of **5–7**, **12–14**, and **18**. Reagents and conditions: (a) $SOCl_2$, EtOAc; (b) aqueous NH_3; (c) methyl chloroacetate, K_2CO_3, KI, acetone; (d) PBr_3, Et_2O; (e) **34**, K_2CO_3, DMF; (f) Ac_2O, heat; (g) MsCl, NaOH, THF; (h) Ac_2O, pyridine; (i) NaOH, dioxane; (j) NBS, $(BzO)_2$, CCl_4; (k) toluene, heat; (l) $BH_3{\cdot}SMe_2$, THF; (m) **34**, DEAD, PPh_3, THF; (n) Fe, AcOH, H_2O; (o) formamidine·HCl, heat; (p) urea, heat.

Table 6. Cytochrome P450 inhibitory activities of optimized analogs

Compound	P-450 inhibition (%, 3 μM)				
	1A2	2C9	2C19	2D6	3A4
2b	2.6	13.7	0.4	−5.1	11.7
8	22.2	8.5	32.7	2.0	67.6
9	10.2	32.6	28.9	4.4	32.2
10	5.9	−9.4	33.2	1.1	14.8
11	12.1	98.0	97.9	2.6	93.8
16	2.2	8.9	−3.8	−3.4	10.9
17	11.5	47.2	18.8	5.8	42.2

particular, tetrazole analog **11** showed the strongest antagonist activity among the tested compounds.

As a result, the carboxylic acid residue showed the most optimized receptor affinity as illustrated by the analogs **1**, **2a** and **b** (Table 1), while the monocyclic acid equivalents showed the most optimized antagonist activity as illustrated by the analogs **8–11** (Table 3). Based on the above-described results, the acidic equivalents of the analogs **4–7** (Table 2) were considered to show

decreased antagonist activities because of the more influence of bovine serum albumin (BSA)[18] relative to those of **8–11**. Fused bicyclic acid equivalents of the analogs **12–14** were also considered to show much more decreased antagonist activities for their relatively potent binding affinities because of the more influence of BSA such as a presumed increased protein binding.

The effect of transformation of the linker Y between the carboxylic acid residue and the phenyl moiety of **2b** was also investigated, and is illustrated in Table 5. Analogs **2b**, **16**, and **17**, possessing conformationally restricted carboxylic acid residues, tended to show stronger antagonist activity than analogs **15** and **18** which possess the more flexible carboxylic acid residues. Cytochrome P450 inhibition by the optimized compounds was also investigated. As a result, **2b** and **16** were found to possess the most desired in vitro profiles, based on their antagonist activity and P450 inhibition.

4. Experimental

4.1. General directions

Analytical samples were homogeneous as confirmed by TLC and afforded spectroscopic results consistent with the assigned structures. Proton nuclear magnetic resonance spectra (^{1}H NMR) were taken on a Varian Mercury 300 spectrometer or Varian GEMINI-200 or VXR-200s spectrometer using deuterated chloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-d_6) as the solvent. Fast atom bombardment mass spectra (FAB-MS, HRMS) and electron ionization (EI) were obtained on a JEOL JMS-DX303HF spectrometer. The matrix-assisted laser desorption ionization-time of flight high-resolution mass spectra (MALDI-TOF) were obtained on a PerSeptive voyager Elite spectrometer. Atmospheric pressure chemical ionization (APCI) was determined on a HTHACHI MI200H spectrometer. Infrared spectra (IR) were measured in a Perkin-Elmer FT-IR 1760X spectrometer. Melting points and results of elemental analyses uncorrected. Column chromatography was carried out on silica gel [Merck silica gel 60 (0.063–0.200 mm), Wako gel C200 or Fuji Silysia FL60D]. Thin-layer chromatography was performed on silica gel (Merck TLC or HPTLC plates, silica gel 60 F254). The following abbreviations for solvents and reagents are used; tetrahydrofuran (THF), diethyl ether (Et_2O), diisopropylether ($^iPr_2O$), dimethylsulfoxide (DMSO), ethyl acetate (EtOAc), dimethylformamide (DMF), dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), carbon tetrachloride (CCl_4), methanol (MeOH), ethanol (EtOH), isopropanol (^iPrOH), acetic acid (AcOH), hydrochloric acid (HCl), diisopropylethylamine ($^iPr_2NEt$), and triethylamine (TEA).

4.2. Methyl 4-{[2-nitro-5-(trifluoromethyl)phenoxy]methyl}benzoate (20a)

To a stirred suspension of **19**[6] (5 g, 24.1 mmol) and K_2CO_3 (6.7 g, 48.3 mmol) in acetone (30 mL) was added methyl 4-(bromomethyl)benzoate (6 g, 26.6 mmol) under argon atmosphere. The resulting mixture was stirred at 50 °C for 4 h, then quenched with water and extracted with EtOAc. The organic layer was washed with water, and brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was recrystallized from EtOH and hexane to yield **20a** (7.6 g, 89%). TLC $R_f = 0.38$ (EtOAc/hexane, 1:5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, $J = 6.3$ Hz, 2H), 7.95 (d, $J = 8.7$ Hz, 1H), 7.54 (d, $J = 6.3$ Hz, 2H), 7.40–7.25 (m, 2H), 5.33 (s, 2H), 3.94 (s, 3H).

4.3. Methyl 4-{[2-amino-5-(trifluoromethyl)phenoxy]methyl}benzoate (24a)

To a stirred solution of **20a** (7.6 g, 21.4 mmol) in AcOH (30 mL) and water (2 mL) was added iron (325 mesh, 6 g, 107 mmol) under argon atmosphere. After being stirred for 30 min at 50 °C, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo, diluted with aqueous $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was recrystallized from $^iPr_2O$ and hexane to yield **24a** (5.88 g, 85%). TLC $R_f = 0.50$ (EtOAc/hexane, 1:5); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.08 (d, $J = 8.4$ Hz, 2H), 7.51 (d, $J = 8.4$ Hz, 2H), 7.10 (d, $J = 8.0$ Hz, 1H), 7.04 (s, 1H), 6.75 (d, $J = 8.0$ Hz, 1H), 5.16 (s, 2H), 4.13 (br s, 2H), 3.94 (s, 3H).

4.4. Methyl 4-{[2-{[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoate (25a)

To a stirred solution of **24a** (1.05 g, 3.23 mmol) and pyridine (0.52 mL, 6.46 mmol) in CH_2Cl_2 (10 mL) was added **29** (874 mg, 4.84 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 9 h, quenched with water, and extracted with EtOAc (2×). The organic layers were washed with water, brine, dried over $MgSO_4$, and evaporated. The resulting residue was recrystallized from EtOH to yield **25a** (1.2 g, 80%). TLC $R_f = 0.33$ (EtOAc/hexane, 1:2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.09 (d, $J = 8.2$ Hz, 2H), 7.64 (d, $J = 8.4$ Hz, 1H), 7.42 (d, $J = 8.2$ Hz, 2H), 7.35 (s, 1H), 7.22 (m, 1H), 7.07 (m, 1H), 7.00 (d, $J = 3.4$ Hz, 1H), 6.06 (d, $J = 3.4$ Hz, 1H), 5.16 (s, 2H), 3.95 (s, 3H), 2.29 (s, 3H).

4.5. Methyl 4-{[2-{isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoate (26a)

To a stirred solution of **25a** (550 mg, 1.17 mmol) in DMF (2 mL) were added K_2CO_3 (484 mg, 3.51 mmol) and isobutyl iodide (0.20 mL, 1.76 mmol) under argon atmosphere. After being stirred at 80 °C overnight, the reaction mixture was poured into water and extracted with EtOAc (2×). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **26a** (577 mg, 94%). TLC $R_f = 0.45$ (EtOAc/hexane, 1:2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.06 (d, $J = 8.6$ Hz,

2H), 7.41 (d, J = 8.6 Hz, 2H), 7.50–7.40 (m, 1H), 7.22–7.30 (m, 1H), 7.16 (m, 1H), 6.74 (d, J = 3.6 Hz, 1H), 5.96 (m, 1H), 5.07 (s, 2H), 3.94 (s, 3H), 3.50 (d, J = 7.2 Hz, 2H), 2.14 (s, 3H), 1.72–1.62 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H).

4.6. 4-{[2-{Isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (2b)

To a stirred solution of **26a** (577 mg, 1.10 mmol) in MeOH (2 mL) and dioxane (2 mL) was added 2 M NaOH (2 mL) at room temperature. After being stirred overnight, the reaction mixture was acidified with 1 M HCl and extracted with EtOAc (2×). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was recrystallized from ^{i}PrOH and hexane to yield **2b** (495 mg, 88%). TLC R_f = 0.46 (MeOH/$CHCl_3$, 1:9); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.15 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 8.6 Hz, 2H), 7.41 (m, 1H), 7.29 (m, 1H), 7.18 (m, 1H), 6.76 (d, J = 3.4 Hz, 1H), 6.03–5.93 (m, 1H), 5.10 (s, 2H), 3.51 (d, J = 6.2 Hz, 2H), 2.16 (s, 3H), 1.64 (m, 1H), 0.90 (d, J = 6.8 Hz, 6H); IR (KBr) 2963, 1694, 1588, 1427, 1360, 1331, 1173, 1128, 1020 cm^{-1}; MS (APCI, Neg.) m/e 510 $(M-H)^-$; HRMS (Pos.) calcd for $C_{24}H_{25}F_3NO_6S$: 512.1355; found: 512.1349.

4.7. *N*-Isobutyl-5-methyl-*N*-[2-[(4-{[(methylsulfonyl)amino]carbonyl}benzyl)oxy]- 4-(trifluoromethyl)phenyl]furan-2-sulfonamide (4)

To a stirred solution of **2b** (130 mg, 0.25 mmol) in DMF (1 mL) were added methanesulfonamide (121 mg, 1.27 mmol), DMAP (37 mg, 0.31 mmol), and EDC (58 mg, 0.31 mmol) under argon atmosphere. After being stirred overnight, the reaction mixture was quenched with 0.5 M HCl and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **4** (38 mg, 25%). TLC R_f = 0.23 (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.13 (br s, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.46–7.43 (m, 2H), 7.38 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 3.3 Hz, 1H), 6.18 (dd, J = 3.3, 0.9 Hz, 1H), 5.22 (br s, 2H), 3.39 (d, J = 6.9 Hz, 2H), 3.35 (s, 3H), 2.15 (s, 3H), 1.51 (m, 1H), 7.82 (d, J = 6.9 Hz, 6H); IR (KBr) 3266, 2962, 2933, 2874, 1696, 1613, 1591, 1509, 1430, 1332, 1257, 1212, 1164, 1132, 1083, 1019, 972 cm^{-1}; MS (APCI, Pos.) m/e 611 $(M + Na)^+$, 589 $(M + H)^+$; HRMS (Pos.) calcd for $C_{25}H_{28}F_3N_2O_7S$: 589.1290; found: 589.1281.

4.8. (4-{[2-Nitro-5-(trifluoromethyl)phenoxy]methyl}phenyl)methanol (21)

To a stirred solution of **20a** (18.5 g, 52.1 mmol) in Et_2O (200 mL) and MeOH (3.2 mL) was added $LiBH_4$ (1.72 g, 78.2 mmol) under argon atmosphere. The reaction mixture was refluxed, stirred at 0 °C overnight, quenched with water, and extracted with EtOAc (2×). The combined organic layers were washed with water (2×), brine, dried over $MgSO_4$, and evaporated. The resulting residue was purified by column chromatography on silica gel to yield **21** (14.4 g, 85%). TLC R_f = 0.28 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 7.5 Hz, 1H), 7.47–7.31 (m, 6H), 5.28 (s, 2H), 4.27 (s, 2H), 1.69 (br s, 1H).

4.9. 4-{[2-Nitro-5-(trifluoromethyl)phenoxy]methyl}benzaldehyde (22)

To a stirred solution of **21** (13.9 g, 42.6 mmol), DMSO (93 mL) and ^{i}Pr$_2$NEt (44.5 mL, 256 mmol) in EtOAc (67 mL) was added SO_3·Py (20.3 g, 128 mmol) at room temperature. The reaction mixture was stirred for 30 min, quenched with water, and extracted with EtOAc (2×). The combined organic layers were washed with water (3×), brine, dried over $MgSO_4$, and evaporated to yield **22** (11.7 g, 81%). TLC R_f = 0.56 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.00–7.29 (m, 3H), 7.65 (d, J = 8.1 Hz, 2H), 7.40–7.36 (m, 2H), 5.36 (s, 2H).

4.10. (2*E*)-3-(4-{[2-Nitro-5-(trifluoromethyl)phenoxy]methyl}phenyl)acrylic acid (23)

A solution of **22** (11.3 g, 34.9 mmol), malonic acid (7.26 g, 69.8 mmol), and piperidine (6.9 mL, 69.8 mmol) in pyridine (70 mL) was stirred at 100 °C under argon atmosphere. After being stirred for 30 min, the reaction mixture was concentrated in vavuo, quenched with water, and extracted with EtOAc (2×). The combined organic layers were washed with 1 M HCl, water, brine, and dried over $MgSO_4$, and evaporated to afford a residue, which was recrystallized from EtOAc and hexane to yield **23** (11.6 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (m, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.77 (d, J = 15.6 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.40-7.30 (m, 1H), 6.48 (d, J = 15.6 Hz, 1H), 5.30 (s, 2H).

4.11. Methyl (2*E*)-3-(4-{[2-nitro-5-(trifluoromethyl)phenoxy]methyl}phenyl)acrylate (20b)

To a stirred solution of **23** (11.5 g, 31.4 mmol) and K_2CO_3 (6.6 g, 47.2 mmol) in DMF (125 mL) was added methyl iodide (2.9 mL, 47.2 mmol) under argon atmosphere. After being stirred for 1.5 h at 65 °C, the reaction mixture was quenched with water and extracted with EtOAc (2×). The combined organic layers were washed with water (3×), brine, dried over $MgSO_4$, and evaporated to yield **20b** (12.1 g, 100%). TLC R_f = 0.76 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 15.9 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.39–7.32 (m, 2H), 6.46 (d, J = 15.9 Hz, 1H), 5.29 (s, 2H), 3.82 (s, 3H).

4.12. Methyl (2*E*)-3-(4-{[2-amino-5-(trifluoromethyl)phenoxy]methyl}phenyl)acrylate (24b)

Compound **24b** was prepared from **20b** according to the same procedure as described for the preparation of **24a** from **20a**. Yield 91%; TLC R_f = 0.34 (EtOAc/hexane,

1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 15.9 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.09 (m, 1H), 7.04 (d, J = 1.2 Hz, 1H), 6.73 (dd, J = 8.1, 0.6 Hz, 1H), 6.47 (d, J = 15.9 Hz, 1H), 5.12 (s, 2H), 4.12 (br s, 2H), 3.88 (s, 3H).

4.13. Methyl (2*E*)-3-(4-{[2-{[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}phenyl)acrylate (25b)

Compound **25b** was prepared from **24b** according to the same procedure as described for the preparation of **25a** from **24a**. Yield 80%; TLC R_f = 0.59 (EtOAc/benzene, 1:9); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72 (d, J = 16.2 Hz, 1H), 7.67–7.53 (m, 3H), 7.44–7.32 (m, 3H), 7.22 (d, J = 7.6 Hz, 1H), 7.10 (m, 1H), 7.00 (d, J = 3.4 Hz, 1H), 6.48 (d, J = 16.2 Hz, 1H), 6.06 (d, J = 3.4 Hz, 1H), 5.11 (s, 2H), 3.83 (s, 3H), 2.28 (s, 3H).

4.14. Methyl (2*E*)-3-(4-{[2-{isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}phenyl)acrylate (26b)

Compound **26b** was prepared from **25b** according to the same procedure as described for the preparation of **26a** from **25a**. Yield 94%; TLC R_f = 0.44 (EtOAc/hexane, 1:3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70 (d, J = 16.0 Hz, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.45–7.15 (m, 3H), 7.37 (d, J = 8.2 Hz, 2H), 6.73 (d, J = 3.4 Hz, 1H), 6.47 (d, J = 16.0 Hz, 1H), 5.96 (dq, J = 3.4, 1.0 Hz, 1H), 5.03 (s, 2H), 3.82 (s, 3H), 3.51 (d, J = 7.2 Hz, 2H), 2.14 (s, 3H), 1.75–1.50 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H).

4.15. (2*E*)-3-(4-{[2-{Isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}phenyl)acrylic acid (16)

Compound **16** was prepared from **26b** according to the same procedure as described for the preparation of **2b** from **26a**. Yield 91%; TLC R_f = 0.51 (EtOAc/hexane/AcOH, 1:1:0.02); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.80 (d, J = 16.2 Hz, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.45–7.36 (m, 3H), 7.26 (dd, J = 8.2, 1.8 Hz, 1H), 7.18 (d, J = 1.8 Hz, 1H), 7.00–5.00 (br, 1H), 6.75 (d, J = 3.4 Hz, 1H), 6.49 (d, J = 16.2 Hz, 1H), 5.98 (dq, J = 3.4, 0.8 Hz, 1H), 5.05 (br s, 2H), 3.51 (d, J = 7.4 Hz, 2H), 2.16 (q, J = 0.8 Hz, 3H), 1.75–1.50 (m, 1H), 0.90 (d, J = 6.8 Hz, 6H); IR (KBr) 2967, 1683, 1630, 1510, 1424, 1380, 1331, 1219, 1127, 1086, 1066, 1041, 1019 cm^{-1}; MS (FAB, Pos.) *m/e* 538 $(M + H)^+$; Anal. Calcd for $C_{26}H_{26}F_3NO_6$ S: C, 58.09; H, 4.88; N, 2.61; S, 5.96. Found: C, 58.11; H, 4.77; N, 2.56; S, 6.20.

4.16. Methyl 3-(4-{[2-amino-5-(trifluoromethyl)phenoxy]methyl}phenyl)propanoate (24c)

To a stirred solution of **24b** (500 mg, 1.43 mmol) in EtOH (2 mL) and THF (2 mL) were added $NiCl_2{\cdot}6H_2O$ (34 mg, 0.14 mmol) and $NaBH_4$ (59 mg, 1.57 mmol) under argon atmosphere. The reaction mixture was stirred for 1 h at room temperature, quenched with water, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **24c** (370 mg, 74%). TLC R_f = 0.39 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 7.11–7.04 (m, 2H), 6.73 (d, J = 8.1 Hz, 1H), 5.06 (s, 2H), 4.09 (br, 2H), 3.68 (s, 3H), 2.98 (t, J = 7.8 Hz, 2H), 2.65 (t, J = 7.8 Hz, 2H); MS (APCI, Pos.) *m/e* 354 $(M + H)^+$.

4.17. Methyl 3-(4-{[2-{[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}phenyl)propanoate (25c)

Compound **25c** was prepared from **24c** according to the same procedure as described for the preparation of **25a** from **24a**. Yield 100%; TLC R_f = 0.33 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 8.7 Hz, 1H), 7.34 (s, 1H), 7.32–7.16 (m, 5H), 7.09 (d, J = 1.8 Hz, 1H), 6.98 (d, J = 2.7 Hz, 1H), 6.05 (dq, J = 3.3, 0.9 Hz, 1H), 5.03 (s, 2H), 3.68 (s, 3H), 2.99 (t, J = 7.2 Hz, 2H), 2.66 (t, J = 7.2 Hz, 2H), 2.28 (d, J = 0.9 Hz, 3H); MS (APCI, Pos.) *m/e* 498 $(M + H)^+$.

4.18. Methyl 3-(4-{[2-{isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}phenyl)propanoate (26c)

Compound **26c** was prepared from **25c** according to the same procedure as described for the preparation of **26a** from **25a**. Yield 70%; TLC R_f = 0.55 (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, J = 8.1, 0.6 Hz, 1H), 7.30–7.15 (m, 6H), 6.69 (dd, J = 3.3, 0.3 Hz, 1H), 5.94 (dq, J = 3.6, 1.2 Hz, 1H), 4.95 (br s, 2H), 3.68 (s, 3H), 3.52 (d, J = 7.5 Hz, 2H), 2.97 (t, J = 7.5 Hz, 2H), 2.65 (t, J = 7.5 Hz, 2H), 2.10 (d, J = 0.3 Hz, 3H), 1.62 (sept, J = 6.9 Hz, 1H), 0.90 (d, J = 6.9 Hz, 6H); MS (APCI, Pos.) *m/e* 554 $(M + H)^+$.

4.19. 3-(4-{[2-{Isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}phenyl)propanoic acid (15)

Compound **15** was prepared from **26c** according to the same procedure as described for the preparation of **2** from **26a**. Yield 98%; TLC R_f = 0.39 (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, J = 8.1, 1.8 Hz, 1H), 7.27–7.22 (m, 5H), 7.16 (d, J = 1.8 Hz, 1H), 6.69 (d, J = 3.3 Hz, 1H), 5.94 (dd, J = 3.3, 1.2 Hz, 1H), 4.95 (s, 2H), 3.51 (d, J = 6.9 Hz, 2H), 2.99 (t, J = 7.5 Hz, 2H), 2.71 (t, J = 7.5 Hz, 2H), 2.10 (s, 3H), 1.60 (sept, J = 6.9 Hz, 1H), 0.89 (d, J = 6.9 Hz, 6H); IR (neat) 2979, 1712, 1611, 1590, 1513, 1427, 1330, 1129, 1038, 903, 698 cm^{-1}; MS (APCI, Neg.) *m/e* 538 $(M–H)^-$; HRMS (Pos.) calcd for $C_{26}H_{29}F_3NO_6$ S: 540.1668; found: 540.1684.

4.20. Methyl 3-(4-{[2-[[(5-methyl-2-furyl)sulfonyl](isobutyl)amino]-5-(trifluoromethyl)phenoxy]methyl}phenyl)prop-2-ynoate (26d)

To a stirred solution of **2b** (250 mg, 0.49 mmol) in EtOAc (4 mL) was added $SOCl_2$ (0.071 mL, 0.98 mmol)

under argon atmosphere. After being stirred for 1.5 h at 80 °C, the reaction mixture was concentrated in vacuo. To the resulting residue were added toluene (4 mL), methyl (triphenylphosphoranylidene)acetate (167 mg, 0.50 mmol), and Et_3N (0.07 mL, 0.50 mmol) under argon atmosphere. After being stirred for 3 h at 125 °C, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. A solution of the resulting residue in *o*-dichlorobenzene (2 mL) was stirred at 200 °C for 3.5 h and then concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **26d** (170 mg, 63%). TLC $R_f = 0.52$ (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, $J = 8.4$ Hz, 2H), 7.40 (d, $J = 8.1$ Hz, 1H), 7.31 (d, $J = 8.4$ Hz, 2H), 7.27 (m, 1H), 7.15 (d, $J = 1.5$ Hz, 1H), 6.74 (d, $J = 3.3$ Hz, 1H), 5.98 (dd, $J = 3.3$, 0.9 Hz, 1H), 5.09 (br s, 2H), 3.86 (s, 3H), 3.49 (d, $J = 6.9$ Hz, 2H), 2.16 (s, 3H), 1.60 (sept, $J = 6.9$ Hz, 1H), 0.88 (d, $J = 6.9$ Hz, 6H).

4.21. 3-(4-{[2-{Isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}phenyl)prop-2-ynoic acid (17)

Compound **17** was prepared from **26c** according to the same procedure as described for the preparation of **2b** from **26a**. Yield 91%; TLC $R_f = 0.24$ (MeOH/$CHCl_3$, 1:4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, $J = 8.1$ Hz, 2H), 7.43–7.37 (m, 3H), 7.27 (m, 1H), 7.16 (d, $J = 1.5$ Hz, 1H), 6.76 (d, $J = 3.3$ Hz, 1H), 5.99 (dd, $J = 3.3$, 0.9 Hz, 1H), 5.06 (br s, 2H), 3.48 (d, $J = 6.9$ Hz, 2H), 2.18 (s, 3H), 1.63 (sep, $J = 6.9$ Hz, 1H), 0.88 (d, $J = 6.9$ Hz, 6H); IR (KBr) 3437, 3085, 2967, 2582, 2227, 2202, 1679, 1513, 1427, 1358, 1331, 1212, 1127, 909 cm^{-1}; MS (FAB, Pos.) *m/e* 558 $(M + Na)^+$, 536 $(M + H)^+$; Anal. Calcd for $C_{26}H_{24}F_3NO_6$ S: C, 58.31; H, 4.52; N, 2.62; S, 5.99. Found: C, 58.51; H, 4.53; N, 2.60; S, 5.96.

4.22. Pyridinium 5-methylfuran-2-sulfonate (28)

To a stirred solution of **27** (46 g, 560 mmol) in CH_3CN (60 mL) was added SO_3·Py (116 g, 728 mmol). After being stirred at 40 °C for 23 h under argon atmosphere, the reaction mixture was diluted with EtOAc (120 mL) and stirred for 2 h at 5 °C. The resulting precipitates were collected by filtration to yield **28** (126 g, 93%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.95 (dd, $J = 6.3$, 1.5 Hz, 2H), 8.61 (tt, $J = 8.1$, 1.5 Hz, 1H), 8.08 (dd, $J = 8.1$, 6.3 Hz, 2H), 6.27 (d, $J = 3.0$ Hz, 1H), 5.98–5.94 (m, 1H), 2.24 (d, $J = 0.6$ Hz, 3H).

4.23. 5-Methylfuran-2-sulfonyl chloride (29)

To a stirred suspension of **28** (102 g, 420 mmol) in DME (300 mL) were added oxalyl chloride (55 mL, 631 mmol) and then DMF (33 mL) at 0 °C under argon atmosphere. After being stirred for 3 h at room temperature, the reaction mixture was quenched with ice-water and extracted with toluene. The organic layer was washed with aqueous $NaHCO_3$, water, and brine, dried over $MgSO_4$, and evaporated to yield **29** (31 g, 41%), which was used for the next step without further purification. TLC $R_f = 0.32$ (EtOAc/hexane, 1:2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.23-7.21 (m, 1H), 6.27–6.25 (m, 1H), 2.47 (s, 3H).

4.24. 2-(Methoxymethoxy)-4-(trifluoromethyl)aniline (31)

A suspension of **30** (2.32 g, 9.24 mmol) and 10% Pd–C (232 mg) in MeOH (10 mL) was stirred for 1 h under hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **31** (1.88 g, 88%). TLC $R_f = 0.49$ (EtOAc/hexane, 1:2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.24 (m, 1H), 7.10 (m, 1H), 6.73 (m, 1H), 5.22 (s, 2H), 3.51 (s, 3H).

4.25. *N*-[2-(Methoxymethoxy)-4-(trifluoromethyl)phenyl]-5-methylfuran-2-sulfonamide (32)

To a stirred solution of **31** (1.88 g, 8.50 mmol) and pyridine (1.7 mL, 20.4 mmol) in CH_2Cl_2 (10 mL) was added **29** (1.84 g, 10.2 mmol) at 0 °C under argon atmosphere. After being stirred for 6 h at room temperature, the reaction mixture was quenched with water and extracted with EtOAc (2×). The combined organic layers were washed with 0.5 M HCl, water, and brine, dried over $MgSO_4$, and concentrated in vacuo to yield **32** (2.86 g, 92%). TLC $R_f = 0.51$ (EtOAc/hexane, 1:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.61 (d, $J = 8.4$ Hz, 1H), 7.43 (br s, 1H), 7.32 (d, $J = 1.8$ Hz, 1H), 7.24 (dd, $J = 8.4$, 1.8 Hz, 1H), 7.02 (d, $J = 3.4$ Hz, 1H), 6.07 (d, $J = 3.4$ Hz, 1H), 5.21 (s, 2H), 3.47 (s, 3H), 2.31 (s, 3H).

4.26. *N*-Isobutyl-*N*-[2-(methoxymethoxy)-4-(trifluoromethyl)phenyl]-5-methylfuran-2- sulfonamide (33)

Compound **33** was prepared from **32** according to the same procedure as described for the preparation of **26a** from **25a**. Yield 63%; TLC $R_f = 0.63$ (EtOAc/hexane, 1:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, $J = 1.8$ Hz, 1H), 7.34 (d, $J = 8.4$ Hz, 1H), 7.28–7.22 (m, 1H), 6.76 (d, $J = 3.6$ Hz, 1H), 6.08 (d, $J = 3.6$ Hz, 1H), 5.03 (br s, 2H), 3.48 (q, $J = 7.5$ Hz, 2H), 3.44 (s, 3H), 2.39 (s, 3H), 1.70–1.50 (m, 1H), 0.91 (d, $J = 6.9$ Hz, 6H).

4.27. *N*-[2-Hydroxy-4-(trifluoromethyl)phenyl]-*N*-isobutyl-5-methylfuran-2-sulfonamide (34)

To a stirred solution of **33** (2.08 g, 4.94 mmol) in MeOH (10 mL) was added 4 M HCl in dioxane (4 mL) at room temperature. After being stirred for 6 h, the reaction mixture was quenched with aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with water (2×), brine, dried over $MgSO_4$ and concentrated in vacuo to yield **34** (1.75 g, 94%). TLC $R_f = 0.27$ (EtOAc/Hex, 1:3); ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.31 (d, $J = 8.7$ Hz, 1H), 7.14 (d, $J = 6.6$ Hz, 2H), 6.89 (d, $J = 3.3$ Hz, 1H), 6.29 (d, $J = 3.3$ Hz, 1H), 3.39 (d, $J = 7.5$ Hz, 2H), 2.35 (s, 3H), 1.50 (qn, $J = 6.9$ Hz, 1H), 0.85 (d, $J = 6.9$ Hz, 6H).

4.28. *N*-[2-[(4-Cyanobenzyl)oxy]-4-(trifluoromethyl)phenyl]-*N*-isobutyl-5-methylfuran-2-sulfonamide (3)

A solution of **34** (800 mg, 2.12 mmol), 4-(bromomethyl)benzonitrile (424 mg, 2.12 mmol), and K_2CO_3 (293 mg, 2.12 mmol) in DMF (8 mL) was stirred at 65 °C under argon atmosphere. After being stirred for 40 min, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **3** (777 mg, 74%). TLC $R_f = 0.84$ (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.27 (dd, $J = 7.8$, 1.5 Hz, 1H), 7.17 (d, $J = 1.5$ Hz, 1H), 6.79 (d, $J = 3.3$ Hz, 1H), 6.02 (dd, $J = 3.3$, 0.9 Hz, 1H), 5.13 (s, 2H), 3.46 (d, $J = 6.9$ Hz, 2H), 2.23 (s, 3H), 1.61 (m, 1H), 0.87 (d, $J = 6.9$ Hz, 6H); IR (KBr) 3450, 2962, 1700, 1593, 1569, 1429, 1332, 1182, 1128, 1019 cm^{-1}; MS (FAB, Pos.) *m/e* 670 $(M + H)^+$; Anal. Calcd for $C_{24}H_{23}F_3N_2O_4S$: C, 58.53; H, 4.71; N, 5.69; S, 6.51. Found: C, 58.36; H, 4.76; N, 5.59; S, 6.79.

4.29. *N*-Isobutyl-5-methyl-*N*-[2-{[4-(1*H*-tetraazol-5-yl)benzyl]oxy} -4-(trifluoromethyl)phenyl]furan-2-sulfonamide (11)

A solution of **3** (230 mg, 0.47 mmol), sodium azide (40 mg, 0.61 mmol), and $Et_3N{\cdot}HCl$ (84 mg, 0.61 mmol) in toluene (2 mL) was stirred at 120 °C under reflux condition. After being stirred overnight, the reaction mixture was quenched with 0.5 N HCl, extracted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **11** (49 mg, 20%). TLC $R_f = 0.38$ (MeOH/$CHCl_3$, 1:4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.36 (d, $J = 8.4$ Hz, 1H), 7.26 (m, 1H), 7.20 (s, 1H), 6.78 (d, $J = 3.3$ Hz, 1H), 6.02 (d, $J = 3.3$ Hz, 1H), 5.11 (br, 2H), 3.49 (d, $J = 6.3$ Hz, 2H), 2.21 (s, 3H), 1.63 (m, 1H), 0.88 (d, $J = 6.3$ Hz, 6H); IR (KBr) 2962, 1592, 1510, 1428, 1332, 1256, 1212, 1173, 1128, 1084, 1064, 1022, 912 cm^{-1}; MS (FAB, Pos.) *m/e* 536 $(M + H)^+$; HRMS (Pos.) calcd for $C_{24}H_{25}F_3N_5O_4S$: 536.1579; found: 536.1582.

4.30. *N*′-Hydroxy-4-{[2-{isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzenecarboximidamide (35)

A solution of **3** (547 mg, 1.11 mmol), $NH_2OH{\cdot}HCl$ (155 mg, 2.22 mmol), and Et_3N (0.31 mL, 2.22 mmol) in EtOH (6 mL) was stirred at 78 °C under argon atmosphere. After being stirred for 2.5 h, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated in vacuo to yield **35** (584 mg, quant). TLC $R_f = 0.53$ (EtOAc/hexane, 1:1).

4.31. *N*-Isobutyl-5-methyl-*N*-[2-{[4-(2-oxido-3*H*-1,2,3,5-oxathiadiazol-4-yl)benzyl]oxy}-4-(trifluoromethyl)phenyl]furan-2-sulfonamide (8)

To a stirred solution of **35** (150 mg, 0.29 mmol) and pyridine (0.047 mL, 0.58 mmol) in THF (6 mL) was added $SOCl_2$ (0.022 mL, 0.29 mmol) at 0 °C under argon atmosphere. After being stirred for 30 min, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **8** (83 mg, 51%). TLC $R_f = 0.56$ (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.18 (br s, 1H), 7.86 (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.50 (s, 1H), 7.44 (d, $J = 8.4$ Hz, 1H), 7.38 (d, $J = 8.4$ Hz, 1H), 6.91 (d, $J = 3.3$ Hz, 1H), 6.18 (dd, $J = 3.3$, 1.2 Hz, 1H), 5.24 (br, 2H), 3.39 (d, $J = 6.6$ Hz, 2H), 2.15 (s, 3H), 1.52 (sep, $J = 6.6$ Hz, 1H), 0.82 (d, $J = 6.6$ Hz, 6H); IR (KBr) 3252, 2961, 2930, 2873, 1613, 1592, 1508, 1332, 1211, 1173, 1130, 1020 cm^{-1}; MS (FAB, Pos.) *m/e* 572 $(M + H)^+$; HRMS (Pos.) calcd for $C_{24}H_{25}F_3N_3O_6S_2$: 572.1137; found: 572.1116.

4.32. *N*-Isobutyl-5-methyl-*N*-[2-{[4-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)benzyl]oxy}-4-(trifluoromethyl)phenyl]furan-2-sulfonamide (9)

To a stirred solution of **35** (200 mg, 0.38 mmol) and pyridine (0.034 mL, 0.42 mmol) in DMF (1 mL) was added 2-ethylhexyl chloroformate (0.075 mL, 0.38 mmol) at 0 °C under argon atmosphere. After being stirred for 30 min, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. To a stirred solution of the resulting residue in xylene (3 mL) was stirred at 140 °C for 2 h, the reaction mixture was concentrated and purified by column chromatography on silica gel to yield **9** (77 mg, 36%). TLC $R_f = 0.50$ (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.95 (br s, 1H), 7.82 (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.50 (s, 1H), 7.44 (d, $J = 8.4$ Hz, 1H) 7.38 (d, $J = 8.4$ Hz, 1H), 6.90 (d, $J = 3.3$ Hz, 1H), 6.18 (dd, $J = 3.3$, 1.2 Hz, 1H), 5.23 (br, 2H), 3.39 (d, $J = 6.6$ Hz, 2H), 2.15 (s, 3H), 1.51 (sept, $J = 6.6$ Hz, 1H), 0.81 (d, $J = 6.6$ Hz, 6H); IR (KBr) 3490, 3138, 2957, 2930, 2871, 1766, 1508, 1428, 1369, 1328, 1255, 1214, 1173, 1136, 1020, 910 cm^{-1}; MS (FAB, Pos.) *m/e* 552 $(M + H)^+$; HRMS (Pos.) calcd for $C_{25}H_{25}F_3N_3O_6S$: 552.1416; found: 552.1403.

4.33. *N*-Isobutyl-5-methyl-*N*-[2-{[4-(5-oxo-4,5-dihydro-1,2,4-thiadiazol-3-yl)benzyl]oxy}-4-(trifluoromethyl)phenyl]furan-2-sulfonamide (10)

To a stirred solution of **35** (400 mg, 0.78 mmol) and DBU (432 mg, 3.13 mmol) in CH_3CN (7 mL) was added TCDI (233 mg, 1.17 mmol) under argon atmosphere. After being stirred for 1 h, the reaction mixture was quenched with 1 M HCl and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. To the

stirred solution of the resulting residue in THF (5 mL) was added $BF_3{\cdot}OEt_2$ (0.51 mL, 3.91 mmol) under argon atmosphere. After being stirred for 1 h, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with 1 M HCl, water, and brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **10** (49 mg, 20%). TLC $R_f = 0.74$ (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.38 (br s, 1H), 7.95 (d, $J = 8.1$ Hz, 2H), 7.50 (s, 1H), 7.48 (d, $J = 8.1$ Hz, 2H), 7.44 (d, $J = 8.1$ Hz, 1H), 7.38 (d, $J = 8.1$ Hz, 1H), 6.90 (d, $J = 3.3$ Hz, 1H), 6.18 (d, $J = 3.3$ Hz, 1H), 5.21 (br, 2H), 3.39 (d, $J = 6.9$ Hz, 2H), 2.15 (s, 3H), 1.51 (sept, $J = 6.9$ Hz, 1H), 0.81 (d, $J = 6.9$ Hz, 6H); IR (KBr) 3423, 3271, 2973, 2930, 2875, 1712, 1687, 1413, 1360, 1258, 1165, 1117, 1016, 911 cm^{-1}; MS (FAB, Pos.) *m/e* 568 $(M + H)^+$; HRMS (Pos.) calcd for $C_{25}H_{25}F_3N_3O_5S_2$: 568.1188; found: 568.1168.

4.34. 4-(Bromomethyl)benzamide (40a)

To a stirred solution of **36** (2.15 g, 10.0 mmol) in EtOAc (40 mL) was added $SOCl_2$ (1.1 mL, 15.0 mmol). After being stirred overnight at 75 °C, the reaction mixture was concentrated in vacuo and the resulting residue was dissolved with CH_2Cl_2 (40 mL). To this stirred solution was added 28% NH_3 (1.2 mL, 20.0 mmol) at 0 °C under argon. After being stirred for 10 min, the reaction mixture was quenched with water and filtered through a pad of Celite. The filtrate was extracted with EtOAc and the organic layer was washed with 1 M HCl, water, and brine, dried over Na_2SO_4, and concentrated in vacuo to yield **40a** (1.39 g, 65%). TLC $R_f = 0.44$ (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.97 (br s, 1H), 7.83 (d, $J = 8.4$ Hz, 2H), 7.49 (d, $J = 8.4$ Hz, 2H), 7.38 (br s, 1H), 4.73 (s, 2H); MS (APCI, Neg.) *m/e* 214 and 212 $(M–H)^-$.

4.35. 4-{[2-{Isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzamide (41a)

A stirred solution of **34** (150 mg, 0.40 mmol), **40a** (88 mg, 0.40 mmol) and K_2CO_3 (57 mg, 0.40 mmol), in DMF (2 mL) was stirred at 70 °C under argon atmosphere. After being stirred for 1.5 h, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **41a** (179 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, $J = 8.1$ Hz, 2H), 7.46 (d, $J = 8.1$ Hz, 2H), 7.39 (d, $J = 8.1$ Hz, 1H), 7.26 (dd, $J = 8.1$, 1.8 Hz, 1H), 7.17 (d, $J = 1.8$ Hz, 1H), 6.76 (d, $J = 3.3$ Hz, 1H), 6.17 (br, 1H), 5.99 (dd, $J = 3.3$, 0.6 Hz, 1H), 5.75 (br, 1H), 5.09 (br s, 2H), 3.49 (d, $J = 6.9$ Hz, 2H), 2.18 (s, 3H), 1.63 (m, 1H), 0.88 (d, $J = 6.9$ Hz, 6H).

4.36. *N*-Acetyl-4-{[2-{isobutyl](5-methyl-2-furyl)sulfonyl]amino}-5- (trifluoromethyl)phenoxy]methyl}benzamide (5)

A solution of **41a** (179 mg, 0.35 mmol) in acetic anhydride (2 mL) was stirred at 140 °C under argon atmosphere. After being stirred for 3 h, the reaction mixture was concentrated in vacuo, quenched with aqueous $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **5** (50 mg, 26%). TLC $R_f = 0.61$ (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (br s, 1H), 7.87 (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.36 (d, $J = 7.8$ Hz, 1H), 7.26 (m, 1H), 7.16 (d, $J = 1.5$ Hz, 1H), 6.78 (d, $J = 3.3$ Hz, 1H), 6.01 (dd, $J = 3.3$, 1.2 Hz, 1H), 5.13 (br, 2H), 3.48 (d, $J = 6.9$ Hz, 2H), 2.63 (s, 3H), 2.22 (s, 3H), 1.59 (sept, $J = 6.9$ Hz, 1H), 0.88 (d, $J = 6.9$ Hz, 6H); IR (KBr) 3423, 3271, 2973, 2930, 2875, 1712, 1687, 1413, 1360, 1258, 1165, 1117, 1016, 911 cm^{-1}; MS (FAB, Pos.) *m/e* 553 $(M + H)^+$; HRMS (Pos.) calcd for $C_{26}H_{28}F_3N_2O_6S$: 553.1620; found: 553.1611.

4.37. 4-(Bromomethyl)benzenesulfonamide (40b)

To a stirred solution of **37** (3.0 g, 11.1 mmol) in THF (40 mL) was added 28% NH_3 (2.8 mL) at 0 °C. After being stirred for 1 h, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated to yield **40b** (2.39 g, 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, $J = 8.4$ Hz, 2H), 7.62 (d, $J = 8.4$ Hz, 2H), 7.37 (br s, 2H), 4.75 (s, 2H).

4.38. 4-{[2-{Isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzenesulfonamide (41b)

Compound **41b** was prepared from **34** and **40b** according to the same procedure as described for the preparation of **41a** from **34** and **40a**. Yield 69%; TLC $R_f = 0.27$ (EtOAc/hexane, 2:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, $J = 8.7$ Hz, 2H), 7.57 (d, $J = 8.7$ Hz, 2H), 7.37 (m, 1H), 7.26 (m, 1H), 7.18 (m, 1H), 6.78 (m, 1H), 6.03 (m, 1H), 5.14 (s, 2H), 4.90 (m, 2H), 3.47 (d, $J = 7.2$ Hz, 2H), 2.23 (s, 3H), 1.62 (m, 1H), 0.87 (d, $J = 6.6$ Hz, 6H).

4.39. *N*-Isobutyl-5-methyl-*N*-[2-[(4-{[(methylsulfonyl)amino]sulfonyl}benzyl)oxy]-4- (trifluoromethyl)phenyl]furan-2-sulfonamide (6)

To a stirred solution of **41b** (365 mg, 0.67 mmol) in THF (5 mL) were added 1 M NaOH (2.68 mL, 2.68 mmol) and methanesulfonyl chloride (0.124 mL, 1.6 mmol) at room temperature under argon atmosphere. After being stirred for 1 h, the reaction mixture was quenched with 2 M HCl and extracted with EtOAc. The organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **6** (374 mg, 90%). TLC $R_f = 0.33$ (MeOH/$CHCl_3$, 1:4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, $J = 8.7$ Hz, 2H), 7.45 (d, $J = 8.7$ Hz, 2H), 7.27 (m, 1H), 7.20 (m, 1H), 7.11 (m, 1H), 6.69 (d, $J = 3.3$ Hz, 1H), 5.94 (m, 1H), 5.10–4.88 (br, 2H), 3.37 (d, $J = 7.5$ Hz, 2H), 2.67 (s, 3H), 2.19 (s, 3H), 1.51 (m, 1H), 0.76 (d, $J = 6.9$ Hz, 6H); IR (KBr) 3545, 1509, 1431, 1353, 1333, 1281, 1257, 1125, 1088,

1061 cm^{-1}; MS (FAB, Pos.) *m/e* 647 $(M + Na)^+$, 625 $(M + H)^+$; HRMS (Pos.) calcd for $C_{24}H_{27}F_3N_2O_8S_3Na$: 647.0779; found: 647.0764.

4.40. *N*-[2-({4-[(Acetylamino)sulfonyl]benzyl}oxy)-4-(trifluoromethyl)phenyl]-*N*-isobutyl-5-methylfuran-2-sulfonamide (7)

To a stirred solution of **41b** (190 mg, 0.35 mmol) in pyridine (1.5 mL) was added acetic anhydride (0.040 mL, 0.42 mmol) at room temperature under argon atmosphere. After being stirred for 1 h at 70 °C, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **7** (124 mg, 65%). TLC $R_f = 0.63$ (MeOH/$CHCl_3$, 1:4); ^1H NMR (300 MHz, DMSO-d_6) δ 12.11 (s, 1H), 7.92 (d, $J = 8.1$ Hz, 2H), 7.56 (d, $J = 8.1$ Hz, 2H), 7.51 (d, $J = 1.5$ Hz, 1H), 7.47 (d, $J = 8.1$ Hz, 1H), 7.39 (dd, $J = 8.1$, 1.5 Hz, 1H), 6.88 (d, $J = 3.3$ Hz, 1H), 6.10 (dd, $J = 3.3$, 0.9 Hz, 1H), 5.24 (br s, 2H), 3.42 (d, $J = 7.2$ Hz, 2H), 2.03 (s, 3H), 1.93 (s, 3H), 1.54 (m, 1H), 0.82 (d, $J = 7.2$ Hz, 6H); IR (KBr) 3447, 3255, 2963, 2874, 1726, 1592, 1508, 1430, 1332, 1213, 1165, 1129, 1020 cm^{-1}; MS (APCI, Neg.) *m/e* 587 $(M–H)^-$; HRMS (Pos.) calcd for $C_{25}H_{28}F_3N_2O_7S_2$: 589.1290; found: 589.1281.

4.41. Methyl [4-(hydroxymethyl)phenoxy]acetate (39)

To a stirred solution of **38** (2.48 g, 20 mmol) and methyl chloroacetate (2.60 g, 24 mmol) in acetone (40 mL) were added K_2CO_3 (5.53 g, 40 mmol) and KI (332 mg, 2.0 eq). After being stirred for 4.5 h at 65 °C, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **39** (2.0 g, 51%). TLC $R_f = 0.46$ (MeOH/$CHCl_3$, 1:4); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, $J = 8.7$ Hz, 2H), 6.90 (d, $J = 8.7$ Hz, 2H), 4.64 (s, 2H), 4.63 (s, 2H), 3.81 (s, 3H).

4.42. Methyl [4-(bromomethyl)phenoxy]acetate (40c)

To a stirred solution of **39** (435 mg, 2.22 mmol) in CH_2Cl_2 (2 mL) was added a solution of PBr_3 (0.24 mL, 2.66 mmol) in Et_2O (2 mL). After being stirred for 30 min, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated in vacuo to yield **40c** (523 mg, 91%). TLC $R_f = 0.66$ (EtOAc/hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, $J = 8.7$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 4.64 (s, 2H), 4.49 (s, 2H), 3.81 (s, 3H).

4.43. Methyl (4-{[2-{Isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}phenoxy)acetate (41c)

Compound **41c** was prepared from **34** and **40c** according to the same procedure as described for the preparation of **41a** from **34** and **40a**. Yield 90%; TLC $R_f = 0.40$ (EtOAc/hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, $J = 7.8$ Hz, 1H), 7.30–7.15 (m, 4H), 6.91 (d, $J = 9.0$ Hz, 2H), 6.70 (d, $J = 3.3$ Hz, 1H), 6.00–5.95 (m, 1H), 4.93 (s, 2H), 4.66 (s, 2H), 3.82 (s, 3H), 3.49 (d, $J = 6.9$ Hz, 2H), 2.15 (s, 3H), 1.70–1.50 (m, 1H), 0.88 (d, $J = 6.6$ Hz, 6H).

4.44. (4-{[2-{Isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}phenoxy)acetic acid (18)

Compound **18** was prepared from **41c** according to the same procedure as described for the preparation of **2b** from **26a**. Yield 93%; TLC $R_f = 0.28$ (MeOH/$CHCl_3$, 1:9); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, $J = 8.1$ Hz, 1H), 7.35–7.15 (m, 4H), 6.94 (d, $J = 8.7$ Hz, 2H), 6.71 (d, $J = 3.3$ Hz, 1H), 6.00–5.95 (m, 1H), 4.94 (br, 2H), 4.71 (s, 2H), 3.48 (d, $J = 6.9$ Hz, 2H), 2.16 (s, 3H), 1.70–1.50 (m, 1H), 0.88 (d, $J = 6.6$ Hz, 6H); IR (KBr) 3448, 2961, 2930, 2874, 1740, 1613, 1591, 1515, 1429, 1358, 1332, 1212, 1177, 1127, 1082, 1012, 909 cm^{-1}; MS (MALDI, Pos.) *m/e* 580 $(M + K)^+$, 564 $(M + Na)^+$; HRMS (Pos.) calcd for $C_{25}H_{27}F_3NO_7S$: 542.1460; found: 542.1455.

4.45. Dimethyl 4-(bromomethyl)phthalate (43)

To a stirred solution of **42** (10.4 g, 50 mmol) in CCl_4 (40 mL) were added *N*-bromo succinimide (8.90 g, 50 mmol) and dibenzoyl peroxide (847 mg, 3.5 mmol). After being stirred for 1 h at 76 °C under argon atmosphere, the reaction mixture was concentrated in vacuo, diluted with EtOAc, and filtered through a pad of Celite. The filtrate was purified by column chromatography on silica gel to yield **43** (9.0 g, 63%). TLC $R_f = 0.30$ (EtOAc/hexane, 1:4); ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, $J = 1.8$ Hz, 1H), 7.73 (d, $J = 7.8$ Hz, 1H), 7.52 (dd, $J = 7.8$, 1.8 Hz, 1H), 4.48 (s, 2H), 3.92 (s, 3H), 3.91 (s, 3H).

4.46. Dimethyl 4-{[2-{isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}phthalate (44)

Compound **44** was prepared from **34** and **43** according to the same procedure as described for the preparation of **41a** from **34** and **40a**. Yield 80%; TLC $R_f = 0.31$ (EtOAc/hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, $J = 7.8$ Hz, 1H), 7.71 (d, $J = 1.2$ Hz, 1H), 7.56 (m, 1H), 7.42 (dd, $J = 7.8$, 0.6 Hz, 1H), 7.28 (m, 1H), 6.73 (d, $J = 3.3$ Hz, 1H), 5.96 (dd, $J = 3.3$, 0.9 Hz, 1H), 5.06 (br s, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 3.58 (d, $J = 6.6$ Hz, 2H), 2.14 (s, 3H), 1.63 (m, 1H), 0.89 (d, $J = 6.6$ Hz, 6H); MS (APCI, Pos.) *m/e* 552 $(M + H)^+$.

4.47. 4-{[2-{Isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}phthalic acid (45)

Compound **45** was prepared from **44** according to the same procedure as described for the preparation of **2b** from **26a**. Yield 99%; TLC $R_f = 0.25$ (MeOH/$CHCl_3$/

AcOH, 2:20:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 7.8 Hz, 1H), 7.87 (s, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.32–7.13 (m, 1H), 7.19 (s, 1H), 6.77 (d, J = 3.3 Hz, 1H), 5.97 (dd, J = 3.3, 1.2 Hz, 1H), 5.12 (br, 2H), 3.48 (d, J = 6.9 Hz, 2H), 2.16 (s, 3H), 1.67 (m, 1H), 0.90 (d, J = 6.6 Hz, 6H); MS (APCI, Pos.) m/e 556 $(M + H)^+$.

4.48. *N*-[2-[(1,3-dioxo-2,3-dihydro-1*H*-isoindol-5-yl)methoxy]-4-(trifluoromethyl)phenyl]-*N*-isobutyl-5-methylfuran-2-sulfonamide (12)

A solution of **45** (480 mg, 0.86 mmol) in Ac_2O (10 mL) was stirred at 140 °C under argon atmosphere. After being stirred for 30 min, the reaction mixture was concentrated and diluted with THF (10 mL). To this stirred solution was added 28% NH_3 (1 mL) at 0 °C under argon atmosphere. After being stirred for 1 h, the reaction mixture was quenched with 1 N HCl and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. A solution of the resulting residue in toluene (10 mL) was stirred at 125 °C for 3 h, the reaction mixture was concentrated and purified by column chromatography on silica gel to yield **12** (65 mg, 13%). TLC R_f = 0.39 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 8.4 Hz, 1H), 7.88–7.83 (m, 2H), 7.65 (br s, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.32–7.25 (m, 1H), 7.19 (d, J = 1.8 Hz, 1H), 6.82 (d, J = 3.3 Hz, 1H), 6.04 (dd, J = 3.3, 0.9 Hz, 1H), 5.20 (s, 2H), 3.46 (d, J = 7.5 Hz, 2H), 2.24 (s, 3H), 1.63 (m, 1H), 0.88 (d, J = 6.6 Hz, 6H); IR (KBr) 3297, 1776, 1724, 1510, 1427, 1360, 1332, 1213, 1175, 1136, 1043, 860 cm^{-1}; MS (APCI, Pos.) m/e 537 $(M + H)^+$; HRMS (Pos.) calcd for $C_{25}H_{24}F_3N_2O_6S$: 537.1307; found: 537.1301.

4.49. 4-(Methoxycarbonyl)-3-nitrobenzoic acid (47)

To a stirred solution of **46** (10.1 g, 42.1 mmol) in MeOH (350 mL) was added 2 M NaOH (21 mL, 42.0 mmol). After being stirred for 1 day at room temperature, the reaction mixture was quenched with 2 M HCl and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was washed with hexane to yield **47** (6.22 g, 66%). TLC R_f = 0.42 ($MeOH/CHCl_3$, 1:4); ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.92 (br s, 1H), 8.45 (d, J = 1.5 Hz, 1H), 8.32 (dd, J = 8.0, 1.5 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 3.87 (s, 3H).

4.50. Methyl 4-(hydroxymethyl)-2-nitrobenzoate (48)

To a stirred solution of **47** (2.0 g, 8.88 mmol) in THF (20 mL) was added 2 M solution of $BH_3{\cdot}SMe_2$ in THF (4.5 mL, 9.0 mmol) under argon atmosphere. After being stirred for 3 days at room temperature, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **48** (1.94 g, 100%). TLC R_f = 0.43 ($MeOH/CHCl_3$, 1:9); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.94 (d, J = 1.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.75 (dd, J = 8.0, 1.0 Hz, 1H), 5.61 (t, J = 6.0 Hz, 1H), 4.64 (d, J = 6.0 Hz, 2H), 3.83 (s, 3H).

4.51. Methyl 4-{[2-{isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5- (trifluoromethyl)phenoxy]methyl}-2-nitrobenzoate (49)

To a stirred solution of **34** (520 mg, 1.38 mmol), **48** (580 mg, 2.75 mmol), and PPh_3 (725 mg, 2.76 mmol) in THF (10 mL) was added 40% solution of DEAD in toluene (1.25 mL, 2.76 mmol) at room temperature under argon atmosphere. After being stirred for 3 h, the reaction mixture was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **49** (625 mg, 80%). TLC R_f = 0.42 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.51 (s, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 3.0 Hz, 1H), 6.10 (d, J = 3.0 Hz, 1H), 5.32 (br s, 2H), 3.86 (s, 3H), 3.39 (d, J = 7.0 Hz, 2H), 2.11 (s, 3H), 1.67–1.47 (m, 1H), 0.83 (d, J = 7.0 Hz, 6H).

4.52. Methyl 2-amino-4-{[2-{isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoate (50)

To a stirred solution of **49** (509 mg, 0.89 mmol) in AcOH (5 mL) and water (0.5 mL) was added iron (325 mesh, 250 mg, 4.46 mmol) under argon atmosphere. After being stirred for 3 h at 50 °C, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo, diluted with aqueous $NaHCO_3$, and extracted with EtOAc. The organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **50** (376 mg, 78%). TLC R_f = 0.64 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.68 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.44 (s, 1H), 7.36 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 3.0 Hz, 1H), 6.71 (s, 2H), 6.67 (s, 1H), 6.48 (d, J = 8.0 Hz, 1H), 6.16 (d, J = 3.0 Hz, 1H), 5.00 (br s, 2H), 3.78 (s, 3H), 3.42 (d, J = 7.0 Hz, 2H), 2.14 (s, 3H), 1.60–1.40 (m, 1H), 0.83 (d, J = 7.0 Hz, 6H).

4.53. 2-Amino-4-{[2-{isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (51)

Compound **51** was prepared from **49** according to the same procedure as described for the preparation of **2b** from **26a**. Yield 80%; TLC R_f = 0.55 ($MeOH/CHCl_3$, 1:9); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.50–8.00 (br s, 2H), 7.67 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.44 (s, 1H), 7.36 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 3.0 Hz, 1H), 6.63 (s, 1H), 6.45 (d, J = 8.0 Hz, 1H), 6.17 (d, J = 3.0 Hz, 1H), 4.98 (br s, 2H), 3.42 (d, J = 7.0 Hz, 2H), 2.15 (s, 3H), 1.51 (sept, J = 7.0 Hz, 1H), 0.83 (d, J = 7.0 Hz, 6H); MS (APCI, Neg.) m/e 525 $(M–H)^-$.

4.54. *N*-[2-[(4-Hydroxyquinazolin-7-yl)methoxy]-4-(trifluoromethyl)phenyl]- *N*-isobutyl-5-methylfuran-2-sulfonamide (13)

A mixture of **51** (100 mg, 0.18 mmol) in formamidine hydrochloride (290 mg, 3.62 mmol) was stirred at 210 °C. After being stirred for 1 h, the reaction mixture was cooled to room temperature, quenched with water, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **13** (82 mg, 80%). TLC $R_f = 0.57$ ($MeOH/CHCl_3$, 1:9); ^1H NMR (300 MHz, DMSO-d_6) δ 12.27 (br s, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 8.11 (s, 1H), 7.66 (s, 1H), 7.52 (s, 1H), 7.46 (d, $J = 8.0$ Hz, 1H), 7.46 (d, $J = 8.0$ Hz, 1H), 7.39 (d, $J = 8.0$ Hz, 1H), 6.88 (d, $J = 3.0$ Hz, 1H), 6.12 (d, $J = 3.0$ Hz, 1H), 5.31 (br s, 2H), 3.43 (d, $J = 7.0$ Hz, 2H), 2.08 (s, 3H), 1.63–1.43 (m, 1H), 0.83 (d, $J = 7.0$ Hz, 6H); IR (KBr) 3443, 1690, 1621, 1426, 1333, 1175, 1135 cm^{-1}; MS (APCI, Pos.) *m/e* 536 $(M + H)^+$; Anal. Calcd for $C_{25}H_{24}F_3N_3O_5S$: C, 56.07; H, 4.52; N, 7.85; S, 5.99. Found: C, 55.89; H, 4.77; N, 7.92; S, 6.16.

4.55. *N*-[2-[(2,4-Dihydroxyquinazolin-7-yl)methoxy]-4-(trifluoromethyl)phenyl]- *N*-isobutyl-5-methylfuran-2-sulfonamide (14)

A mixture of **51** (88 mg, 0.16 mmol) and urea (100 mg, 1.67 mmol) was stirred at 200 °C. After being stirred for 1 h, the reaction mixture was cooled to room temperature, quenched with water, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **14** (80 mg, 87%). TLC $R_f = 0.55$ ($MeOH/CHCl_3$, 1:9); ^1H NMR (300 MHz, DMSO-d_6) δ 11.32 (br s, 2H), 7.88 (d, $J = 8.0$ Hz, 1H), 7.51 (s, 1H), 7.48 (d, $J = 8.0$ Hz, 1H), 7.39 (d, $J = 8.0$ Hz, 1H), 7.11 (d, $J = 8.0$ Hz, 1H), 7.06 (s, 1H), 6.88 (d, $J = 3.0$ Hz, 1H), 6.08 (d, $J = 3.0$ Hz, 1H), 5.19 (br s, 2H), 3.45 (br s, 2H), 2.04 (s, 3H), 1.66–1.46 (m, 1H), 0.85 (d, $J = 7.0$ Hz, 6H); IR (KBr) 3461, 3061, 2962, 1718, 1633, 1428, 1360, 1332, 1174, 1135 cm^{-1}; MS (APCI, Pos.) *m/e* 552 $(M + H)^+$; Anal. Calcd for $C_{25}H_{24}F_3N_3O_6S$: C, 54.44; H, 4.39; N, 7.62; S, 5.81. Found: C, 54.41; H, 4.68; N, 7.68; S, 5.93.

5. Biological assay method

5.1. Prostanoid mEP1-4 receptor binding assay

Competitive binding studies were conducted using radiolabeled ligands and membrane fractions prepared from Chinese hamster ovary (CHO) cells stably expressing the prostanoid receptors mEP1-4.

Membranes from CHO cells expressing prostanoid receptors were incubated with radioligand (2.5 nM $[^3H]PGE_2$) and test compounds at various concentrations in assay buffer (10 mM KH_2PO_4-KOH buffer containing 1 mM EDTA and 0.1 mM NaCl, pH 6.0). Incubation was carried out at 25 °C for 60 min except for mEP1 that was incubated for 20 min. Incubation was terminated by filtration through a Whatman GF/B filter. The filter was subsequently washed with ice-cold buffer (10 mM KH_2PO_4-KOH buffer containing 0.1 mM NaCl, pH 6.0), and the radioactivity on the filter was measured in 6 mL of liquid scintillation (ACSII) mixture with a liquid scintillation counter. Nonspecific binding was achieved by adding excess amounts of unlabeled PGE_2 in assay buffer. The concentration of the test compounds required for the inhibition of specific binding in the vehicle group by 50% (IC_{50} value) was estimated from the regression curve. The K_i value (M) was calculated according to the following equation.

$$K_i = IC_{50}/(l + [L]/K_d)$$

[L]: Concentration of radiolabeled ligand; K_d; Dissociation constant of radiolabeled ligand for the prostanoid receptors.

5.2. Measurement of the mEP1 receptor antagonist activity

To confirm that test compounds antagonized the mEP1 receptor and estimate potencies of antagonism for the mEP1receptor, a functional assay was performed by measuring PGE_2-stimulated changes in intracellular Ca^{2+} as an indicator of receptor function. The cells expressing mEP1 receptor were seeded at 1×10^4 cells/well in 96-well plates and cultured for 2 days with 10% FBS (fetal bovine serum)/minimum essential medium Eagle alpha modification (αMEM) in an incubator (37 °C, 5% CO_2). The cells in each well were rinsed with phosphate buffer (PBS(−)), and load buffer was added. After incubation for 1 h, the load buffer (10% FBS/αMEM containing 5 μM of Fura 2/AM, 20 μM of indomethacin, and 2.5 mM of probenecid) was discarded. After the addition of assay buffer (Hanks' balanced salt solution (HBSS) containing 0.1% (w/v) BSA, 2 μM of indomethacin, 2.5 mM of probenecid, and 10 mM of Hepes-NaOH) to each well, the cells were incubated in the dark at room temperature for 1 h. After the addition of a solution containing test compound (10 μl) and PGE_2 (10 μl), which was prepared with an assay buffer, intracellular calcium concentration was measured with a Fluorescence drug screening system (FDSS-4000, Hamamatsu Photonics). The fluorescence intensities emitted at 500 nm by an excitation wavelength of 340 and 380 nm were measured. The percent inhibition on the increase of the intracellular Ca^{2+} concentration induced by PGE_2 (100 nM) was calculated relative to the maximum Ca^{2+} concentration that occurred in the absence of the test compound (100%) to estimate the IC_{50} value.

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