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Discovery of heteroaryl sulfonamides as new EP1 receptor selective antagonists

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Abstract—4-({2-[Isobutyl(phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy}methyl)benzoic acid (**1**) is a functional PGE_2 antagonist selective for EP1 receptor subtype. Analogs of **1**, in which the phenyl-sulfonyl moiety has been replaced with more hydrophilic heteroarylsulfonyl moieties, exhibited more optimized antagonist activity, while some of them showed in vivo antagonist activity. Structure–activity relationship (SAR) studies are also presented.

1. Introduction

Prostanoid receptors, which are members of the G-protein coupled receptor superfamily, were classified into PGE, PGF, PGD, PGI, and TXA, named EP, FP, DP, IP, and TP receptors, respectively.[1] The EP receptor was further classified into four subtypes EP1-4 that each responds to the natural agonist PGE_2 in a different manner.[2] The molecular characterization of these receptors has resulted in renewed interest because selectivity of compounds on human prostanoid receptors can now be determined.

In our previous paper,[3] we reported the discovery of **1** (Fig. 1) as a highly selective EP1 receptor antagonist that contains a highly lipophilic benzenesulfonyl moiety. It should be noted that highly lipophilic compounds have been known to cause a problem regarding their in vivo efficacy, PK profiles, and safety.[4] In fact, **1** exhibited remarkably decreased antagonist activity for its strong receptor affinity. Thus, the high lipophilicity (clog*P* 6.91) of compound **1** should be lowered for it to be a drug candidate. We here report on highly potent EP1 receptor antagonists **2**–**4** as chemical leads for a drug candidate.

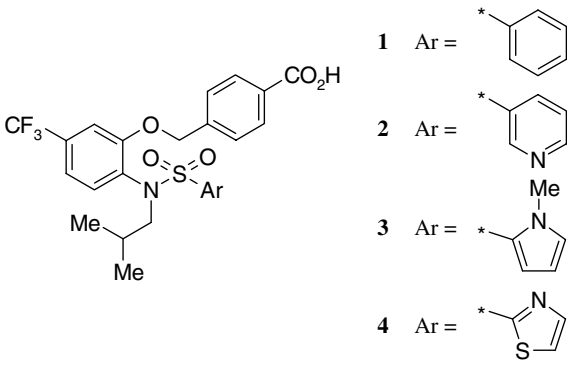

Figure 1. EP1 receptor selective antagonists.

2. Chemistry

All the compounds listed in Tables 1 and 2 were synthesized as outlined in Scheme 1. Oxidative hydroxylation of a commercially available 1-nitro-4-(trifluoromethyl)benzene **16** resulted in a nitrophenol **17**,[5] and O-alkylation with methyl 4-bromomethylbenzoate provided **18**. Hydrogenation of the nitrobenzene derivative **18** result-

Keywords: Prostaglandin; EP1 receptor; Antagonist; Sulfonamide.
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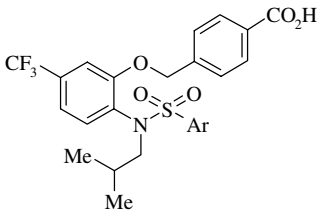
Table 1. Binding affinity and antagonist activity of **1**–**2** and **5**



	Ar	Binding K_i (μM)				IC_{50} (μM)[b]	clog *P*
		mEP1[a]	mEP2[a]	mEP3[a]	mEP4[a]	mEP1	
1		0.0005	>10	0.41	>10	0.13	6.91
5		0.0019	>10	0.64	>10	0.049	5.66
2		0.00029	>10	0.81	>10	0.0039	5.56

[a] mEP1–4: mouse EP1–4.
[b] IC_{50}: mEP1 receptor antagonist activity.

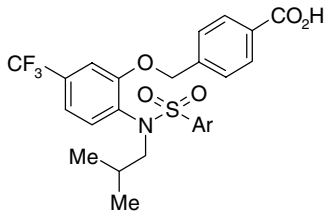
ed in the corresponding aniline **19**, which was used as a key intermediate. N-Sulfonylation of **19** with various kinds of sulfonyl chlorides[6] resulted in sulfonamides **20a**–**o**, N-alkylation of which resulted in **21a**–**o**, respectively. Alkaline hydrolysis of **21a**–**o** resulted in the corresponding carboxylic acids **1**–**15**, respectively. Structurally new heteroarylsulfonyl chlorides **23**, **26**, and **28** were prepared as outlined in Scheme 2. Successive treatment of 2-bromothiazole (**22**) with *n*-butyllithium and then sulfur dioxide, followed by the treatment with *N*-chlorosuccinimide, resulted in thiazole-2-sulfonyl chloride (**23**) (Scheme 2a).[7] N-Methylation of 4-iodopyrazole (**24**) produced **25**, which was converted to **26** according to essentially the same procedures as described above (Scheme 2b).[7] Oxidation of the mercapto group of 2-mercapto-5-methyl-1,3,4-thiadiazole (**27**) with chlorine resulted in the desired sulfonyl chloride **28** (Scheme 2c).[8]

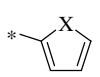
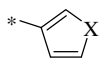
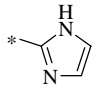
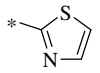
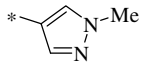
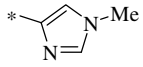
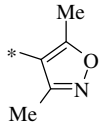
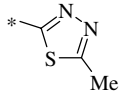
3. Results and discussion

The test compounds listed in Tables 1 and 2 were biologically evaluated for 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 mouse EP1 receptors expressed on CHO cells in the presence of 0.1% bovine serum albumin (BSA).

Focus was placed on the chemical modification of the benzenesulfonyl moiety of **1** with special focus on lowering its relatively high lipophilicity (clog *P* 6.91) for reasons described above. Replacement of the benzenesulfonyl moiety of **1** with more hydrophilic pyridine-2-sulfonyl and pyridine-3-sulfonyl moieties resulted in **5** (clog *P* 5.66) and **2** (clog *P* 5.56), respectively. As shown in Table 1, the pyridine-3-sulfonyl analog **2** showed a slightly more potent EP1 receptor affinity and a 33-fold more potent antagonist activity relative to the activity of **1**, while the pyridine-2-sulfonyl analog **5** showed a 3.8-fold less potent EP1 receptor affinity and a 2.7-fold more potent antagonist activity compared to the activity of **1**. These results strongly suggest that the lipophilic phenylsulfonyl moiety of **1** could be successfully replaced with more hydrophilic bioisosteres of a phenylsulfonyl moiety such as furansulfonyl, thiophenesulfonyl, and others. As illustrated in Table 2, all listed analogs **3**–**4** and **6**–**15** demonstrated lower clog *P* values than the chemical lead **1**. Replacement of the phenylsulfonyl moiety of **1** with a furan-2-sulfonyl moiety resulted in **6** with a retention of the potent EP1 receptor affinity and antagonist activity. The corresponding *N*-methylpyrrole-2-sulfonyl analog **3** showed a 2.4-fold less potent EP1 receptor affinity relative to **1**, while it showed a 59-fold more potent antagonist activity. Based on the successful result obtained with the transformation from **5** to **2**, compounds **7**–**10** were synthesized and evaluated. Unexpectedly, all of them showed a less potent EP1 receptor affinity relative to **1**. Compounds **7**–**8** and **10** exhibited a more potent antagonist activity relative to **1**, while **9** showed more than 10-fold increase in antagonist activity. Compounds **8** and **10** showed less potent EP1 receptor affinity than their corresponding 2-sulfonyl isomers **6** and **3**, respectively. The thiophene-3-sulfonyl analog **7** demonstrated a slightly less potent EP1 receptor affinity and antagonist activity relative to those of the corresponding furan-3-sulfonyl analog **8**. Especially the pyrrole-3-sulfonyl analog **9** was considerably less potent relative to **1** in both the EP1 receptor affinity and antagonist activity. N-Methylation of **9** resulted in **10** with a marked recovery of the antagonist activity.

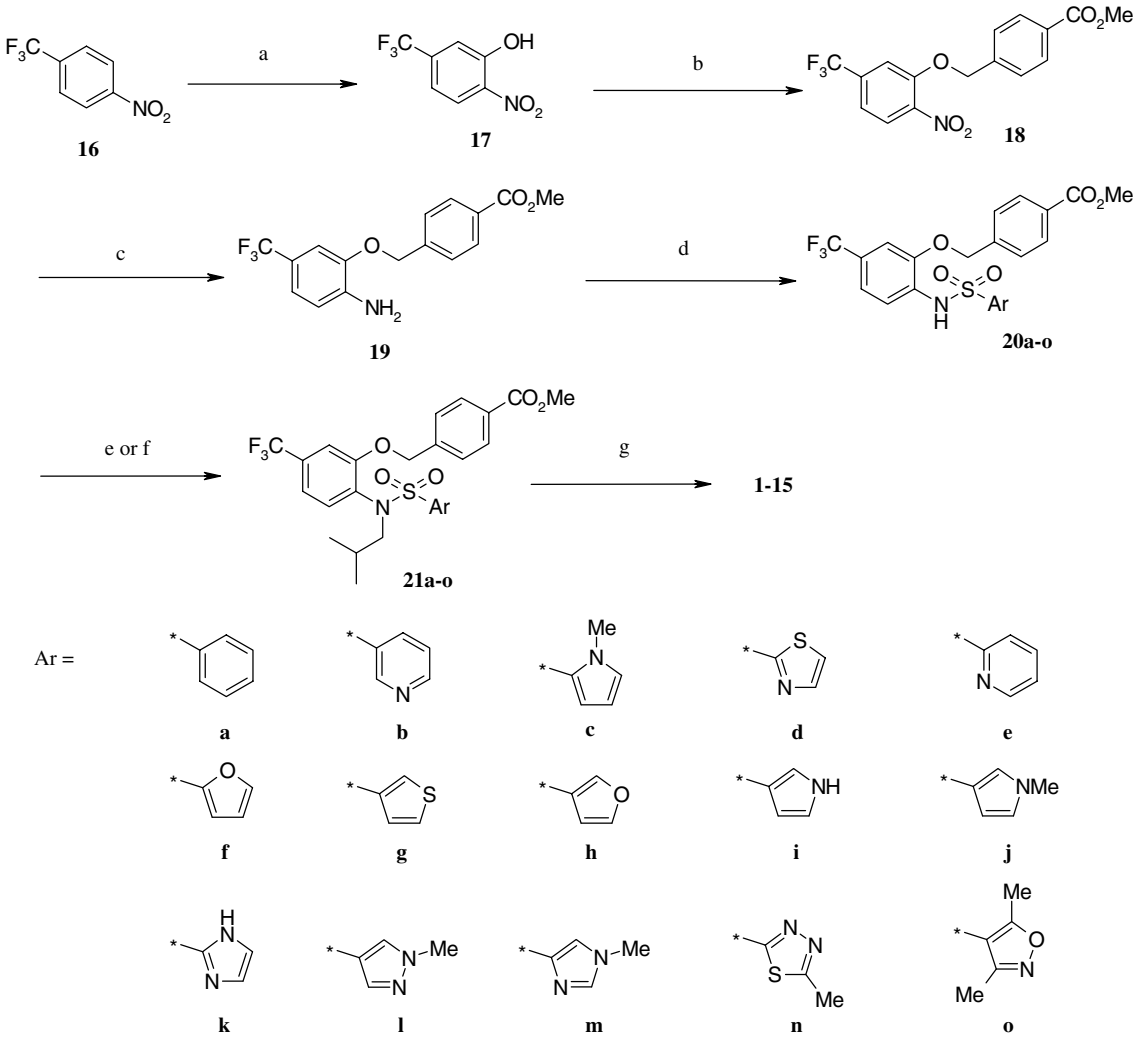
Table 2. Binding affinity and antagonist activity of **3**–**4** and **6**–**15**



	Ar	Binding K_i (μM)				IC_{50} (μM)	clog *P*
		mEP1	mEP2	mEP3	mEP4	mEP1	
6	 X = O	0.00040	8.1	1.7	>10	0.17	6.08
3	X = NMe	0.0012	>10	0.43	>10	0.0022	6.08
7		0.0026	5.7	0.48	>10	0.058	6.63
8	X = S	0.0016	5.8	0.46	>10	0.046	6.08
9	 X = O X = NH	0.0077	>10	0.86	NT[a]	1.6	5.91
10	X = NMe	0.0040	>10	0.57	>10	0.039	6.08
11		0.12	>10	>10	>10	>10	5.02
4		0.00060	>10	0.73	>10	0.0062	5.47
12		0.015	>10	>10	>10	0.27	5.19
13		0.044	>10	>10	>10	2.1	5.19
14		0.0037	>10	>10	>10	0.040	5.70
15		0.0027	>10	>10	>10	0.11	4.81

[a] NT: Not tested.

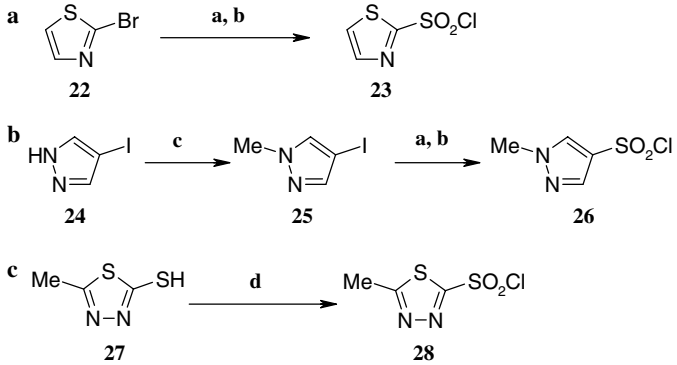
Furan analogs and *N*-methylpyrrole analogs had completely different SARs. For example, replacement of the furan-2-sulfonyl moiety of **6** with the furan-3-sulfonyl moiety resulted in **8** with a decreased EP1 receptor affinity and an increased antagonist activity, while the corresponding chemical modification of *N*-methylpyrrole analog **3** provided **10** with a decreased potency in both the EP1 receptor affinity and antagonist activity. Furthermore, the pyrrole-3-sulfonyl analog **9** showed a remarkable reduction in its antagonist activity and a slight reduction in its EP1 receptor affinity relative to that of the corresponding *N*-methylpyrrole analog **10**.



Scheme 1. Synthesis of **1**–**15**. Reagents: (a) BHP, ^{t}BuOK, NH_3; (b) methyl 4-bromomethyl benzoate, K_2CO_3, DMF; (c) Fe, AcOH, H_2O; (d) $ArSO_2Cl$, pyridine; (e) ^{i}BuI, K_2CO_3, DMA; (f) ^{i}BuOH, DEAD, PPh_3, THF; (g) NaOH, MeOH, THF.

Introduction of more than two heteroatoms into the five-membered aromatic ring resulted in **4** and **11**–**15** with lower c log *P* values compared to **3** and **6**–**10**. The imidazole-2-sulfonyl analog **11** showed a remarkable reduction in EP1 receptor affinity and antagonist activity relative to **1**, while the thiazole-2-sulfonyl analog **4** showed a retained EP1 receptor affinity and a 21-fold more potent antagonist activity relative to **1**.

Another imidazole analog, **13**, showed substantially lower activities than **1** although it showed a 2.7-fold more potent EP1 receptor affinity and a more potent



Scheme 2. Synthesis of heteroarylsulfonyl chloride **23**, **26** and **28**. Reagents: (a) ^{n}BuLi, THF, then SO_2; (b) NCS; (c) MeI, K_2CO_3, DMF; (d) Cl_2, AcOH.

antagonist activity than **11**. The *N*-Methylpyrazole-4-sulfonyl analog **12** also showed a remarkable reduction of EP1 receptor affinity and a slight reduction of antagonist activity relative to **1**. The 3,5-dimethyl isooxazole-4-sulfonyl analog **14** showed a 7.4-fold less potent EP1 receptor affinity and a 3.3-fold more potent antagonist activity relative to **1**. The 5-methyl-1,3,4-thiadiazole-2-sulfonyl analog **15** possessed the lowest clog*P* value among the tested compounds and showed a 5.4-fold less potent EP1 receptor affinity and a nearly equipotent antagonist activity relative to **1**.

As such, the antagonist activity does not always correlate with clog*P* values.[10] Nitrogen-containing heteroaromatic analogs **2**–**5** and **9**–**13** were predicted to posses a lower lipophilicity than furan analogs **6**, **8** and thiophene analog **7** based on their clog*P* values. Some of the nitrogen-containing heteroaromatic analogs **2**–**4** showed a marked increase in their antagonist activities relative to **1**, while furan and thiophene analogs **6**–**7** and **8** showed a retained or increased antagonist activity. Another nitrogen-containing heteroaromatic analog **9** resulted in the reduction of antagonist activity relative to **1**.

The in vivo EP1 receptor antagonist activity was evaluated using sulprostone,[9] which is known as an EP1 receptor agonist, and the selected compounds **2**–**4**, which were identified as potent in vitro receptor antagonists. Compounds **2**–**4** were tested for their ability to inhibit sulprostone-induced bladder contraction in rats.[11] As shown in Figure 2, all the tested compounds demonstrated an in vivo efficacy in a time dependent manner. Compounds **2** and **4** showed 46.6 ± 5.7% inhibition and 65.3 ± 4.3% inhibition, respectively, against sulprostone-induced bladder pressure 60 min after an intra-duodenal (id) dose of 3 mg/kg, while **3** showed the lowest potency while it exhibited the most potent in vitro antagonist activity among the tested compounds. This was probably due to its presumed poor PK profiles such as low oral absorption and metabolic instability.

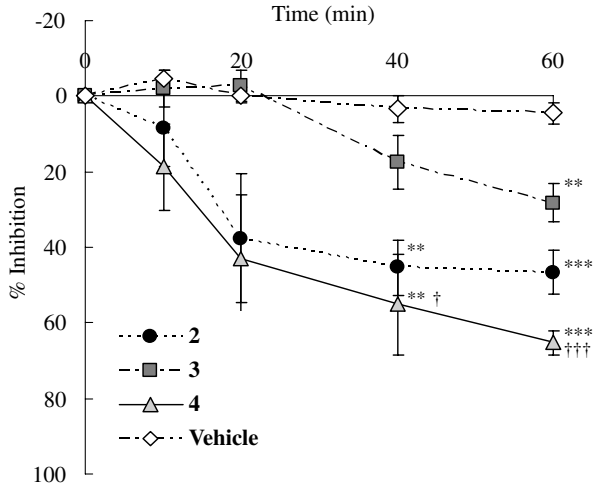


Figure 2. Inhibition percentage of **2**–**4** against sulprostone-induced bladder pressure at 3 mg/kg id. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ compared with the vehicle group value. $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$, $^{\dagger\dagger\dagger}P < 0.001$ compared with the value of compound **3**.

In summary, nitrogen-containing hetoro-aromatic sulfonyl moieties, such as pyridine-3-sulfonyl, *N*-methylpyrrole-2-sulfonyl and thiazole-2-sulfonyl, were identified as more hydrophilic substitutes for the phenylsulfonyl moiety. Compounds **1** and **6** exhibited similar potencies regarding receptor affinity and antagonist activity regardless of their clog*P* value.

Furan-2-sulfonyl analog **6** and unsubstituted pyrrole-3-sulfonyl analog **9** showed remarkably weak antagonist activity despite a strong receptor affinity. As illustrated in **1**, **6**, and **9**, the unsubstituted imidazole analog **11**, which exhibited relatively weak receptor affinity, also was estimated to show remarkably weak antagonist activity ($IC_{50} > 10$ μM) despite its EP1 receptor affinity.

Compounds **11**–**13** and **15** possessed relatively low clog*P* values and tended to show relatively weak antagonist activity regardless of their potent EP1 receptor affinity. Compounds **2**–**4**, which were selected based on their potent in vivo antagonist activity, were found to be effective in an animal model.

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 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 are 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 (*i*-Pr_2O), dimethylsulfoxide (DMSO), ethyl acetate (EtOAc), dimethylformamide (DMF), dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), methanol (MeOH), acetic acid (AcOH), hydrochloric acid (HCl), and triethylamine (TEA).

4.2. 2-Nitro-5-(trifluoromethyl)phenol (17)

This compound was prepared according to the method reported by Makosza et al.[5] To a stirred suspension of potassium *tert*-butoxide (44 g, 392 mmol) in liquid

ammonia (510 mL) were added a mixture of **16** (30 g, 157 mmol) and *tert*-butyl hydroperoxide (31.4 mL, 173 mmol of 5.5 M solution in decane) in THF (150 mL) at −78 °C and then the reaction mixture was wormed up to reflux temperature. After stirring for 30 min, the reaction mixture was quenched by the careful addition of NH_4Cl (25 g). Ammonia was removed by evaporation and the residue was acidified with 2 N HCl. The aqueous layer was extracted with Et_2O (2×) and the combined organic layers were washed with $Na_2S_2O_3$ aq. The organic layer was extracted with 1 N NaOH and then water. The combined aqueous layers were acidified with 2 N HCl and extracted with Et_2O. The combined organic layers were washed with water, brine, dried over $MgSO_4$, and evaporated. The resulting residue was purified by column chromatography on silica gel to yield **17** (25.4 g, 78%). TLC $R_f = 0.33$ (EtOAc/*n*-hexane, 1:10); ^1H NMR (200 MHz, $CDCl_3$) δ 10.61 (s, 1H), 8.25 (d, $J = 8.8$ Hz, 1H), 7.47 (m, 1H), 7.25 (m, 1H).

4.3. Methyl 4-{[2-nitro-5-(trifluoromethyl)phenoxy]methyl}benzoate (18)

To a stirred suspension of **17** (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 for 4 h at 50 °C, then quenched with water 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 EtOH and hexane to yield **18** (7.6 g, 89%). TLC $R_f = 0.38$ (EtOAc/hexane, 1:5); ^1H 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, 2 H), 7.40–7.25 (m, 2H), 5.33 (s, 2H), 3.94 (s, 3H).

4.4. Methyl 4-{[2-amino-5-(trifluoromethyl)phenoxy]methyl}benzoate (19)

To a stirred solution of **18** (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 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 $NaHCO_3$ aq, 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 *i*-Pr_2O and hexane to yield **19** (5.88 g, 85%). TLC $R_f = 0.50$ (EtOAc/Hex, 1:5); ^1H 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).

4.5. General procedure for the preparation of methyl 4-{[2-[(arylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate analogs (20a–o)

4.5.1. Methyl 4-{[2-[(phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (20a). To a stirred solution of **19** (664 mg, 2.04 mmol) and pyridine (0.5 mL, 6.18 mmol) in CH_2Cl_2 (6 mL), was added a solution of benzenesulfonyl chloride (0.287 mL, 2.25 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 4 h, quenched with water, and extracted with EtOAc (2×). The organic layer was washed with water, brine, dried over $MgSO_4$, and evaporated. The resulting residue was recrystallized from EtOAc to yield **20a** (821 mg, 86%). TLC $R_f = 0.76$ (EtOAc/benzene, 1:9); ^1H NMR (200 MHz, $CDCl_3$) δ 8.05 (d, $J = 8.2$ Hz, 2H), 7.77 (m, 2H), 7.69 (d, $J = 8.6$ Hz, 1H), 7.58 (m, 1H), 7.45 (m, 2H), 7.25 (m, 3H), 7.18 (m, 1H), 6.99 (m, 1H), 5.02 (s, 2H), 3.95 (s, 3H).

According to the same procedure as described above, **20b–o** were prepared from **19**.

4.5.2. Methyl 4-{[2-[(pyridin-3-ylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (20b). Yield 94%; TLC $R_f = 0.38$ (EtOAc/hexane, 1:1); ^1H NMR (300 MHz, $CDCl_3 + CD_3OD$) δ 8.96 (m, 1H), 8.76 (m, 1H), 8.10–8.00 (m, 3H), 7.69 (d, $J = 8.7$ Hz, 1H), 7.38 (m, 1H), 7.34–7.24 (m, 3H), 7.04 (br s, 1H), 5.02 (s, 2H), 3.96 (s, 3H).

4.5.3. Methyl 4-{[2-{[(1-methyl-1*H*-pyrrol-2-yl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoate (20c). Yield 82%; TLC $R_f = 0.34$ (EtOAc/hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 8.12–8.07 (m, 2H), 7.56 (d, $J = 8.1$ Hz, 1H), 7.40 (d, $J = 8.1$ Hz, 2H), 7.23–7.18 (m, 2H), 7.07 (m, 1H), 6.88 (dd, $J = 3.9$, 1.8 Hz, 1H), 6.73 (dd, $J = 2.4$, 1.8 Hz, 1H), 6.09 (dd, $J = 3.9$, 2.4 Hz, 1H), 5.13 (s, 2H), 3.95 (s, 3H), 3.69 (s, 3H).

4.5.4. Methyl 4-{[2-[(1,3-thiazol-2-ylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (20d). Yield 100%; TLC $R_f = 0.28$ (EtOAc/hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, $J = 3.0$ Hz, 1H), 7.98–7.92 (m, 3H), 7.59 (d, $J = 9.0$ Hz, 1H), 7.48 (d, $J = 8.0$ Hz, 2H), 7.36–7.31 (m, 2H), 5.17 (s, 2H), 3.85 (s, 3H).

4.5.5. Methyl 4-{[2-[(pyridin-2-ylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (20e). Yield 84%; TLC $R_f = 0.20$ (EtOAc/hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 8.64 (m, 1H) 8.08 (d, $J = 8.4$ Hz, 2H), 8.01 (d,$J = 7.8$ Hz, 1H), 7.88 (dt, $J = 7.8$ Hz, 1.8 Hz, 1H), 7.74 (d, $J = 8.1$ Hz, 1H), 7.61 (br s, 1H), 7.52–7.44 (m, 1H), 7.44 (d, $J = 8.4$ Hz, 2H), 7.18 (br d, $J = 8.7$ Hz, 1H), 7.01 (br s, 1H), 5.14 (s, 2H), 3.95 (s, 3H).

4.5.6. Methyl 4-{[2-[(2-furylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (20f). Yield 85%; TLC $R_f = 0.64$ (EtOAc/benzene, 1:9); ^1H NMR (200 MHz, $CDCl_3$) δ 8.11–8.07 (m, 2H), 7.50 (m, 1H), 7.50–7.35 (m, 4H), 7.25–7.20 (m, 1H), 7.10–7.06 (m, 2H), 6.84–6.46 (m, 1H), 5.15 (s, 2H), 3.95 (s, 3H).

4.5.7. Methyl 4-{[2-[(thien-3-ylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (20g). Yield 85%; TLC $R_f = 0.45$ (EtOAc/hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 8.10–8.05 (m, 2H), 7.93 (dd, $J = 3.0$, 1.5 Hz, 1H), 7.70 (d, $J = 7.8$ Hz, 1H), 7.35 (dd, $J = 5.4$, 3.0 Hz, 1H), 7.31 (d, $J = 7.8$ Hz, 2H), 7.24 (m,

1H), 7.20 (dd, J = 5.4, 1.5 Hz, 1H), 7.17 (s, 1H), 7.04 (d, J = 1.8 Hz, 1H), 5.8 (s, 2H), 3.95 (s, 3H).

4.5.8. Methyl 4-{[2-[(3-furylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (20h). Yield 77%; TLC R_f = 0.36 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11–8.07 (m, 2H), 7.89 (m, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.42 (dd, J = 2.1, 1.2 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.25 (m, 1H), 7.21 (s, 1H), 7.08 (d, J = 1.5 Hz, 1H), 6.48 (dd, J = 2.1, 0.6 Hz, 1H), 5.12 (s, 2H), 3.95 (s, 3H).

4.5.9. Methyl 4-{[2-[(1*H*-pyrrol-3-ylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (20i). Yield 98%; TLC R_f = 0.12 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (br s, 1H), 8.06 (d, J = 8.1 Hz, 2H), 7.69 (d, J = 8.1 Hz, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.29 (m, 1H), 7.21–7.19 (m, 2H), 7.02 (m, 1H), 6.77 (m, 1H), 6.41 (m, 1H), 5.11 (s, 2H), 3.95 (s, 3H).

4.5.10. Methyl 4-{[2-{[(1-methyl-1*H*-pyrrol-3-yl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoate (20j). Yield 91%; TLC R_f = 0.21 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09–8.05 (m, 2H), 7.65 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 8.1 Hz, 2H), 7.23–7.18 (m, 2H), 7.11 (dd, J = 2.4, 1.8 Hz, 1H), 7.03 (m, 1H), 6.56 (dd, J = 3.0, 2.4 Hz, 1H), 6.33 (dd, J = 3.0, 1.8 Hz, 1H), 5.12 (s, 2H), 3.95 (s, 3H), 3.62 (s, 3H).

4.5.11. Methyl 4-{[2-[(1*H*-imidazol-2-ylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (20k). Yield 81%; TLC R_f = 0.28 (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91(d, J = 8.1 Hz, 2H), 7.58–7.46 (m, 3H), 7.29–7.18 (m, 3H), 7.12–7.00 (m, 1H), 5.20 (s, 2H), 3.81 (s, 3H).

4.5.12. Methyl 4-{[2-{[(1-methyl-1*H*-pyrazol-4-yl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoate (20l). Yield 100%; TLC R_f = 0.15 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 8.4 Hz, 2H), 7.70 (s, 1H), 7.67 (s, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.25–7.18 (m, 3H), 7.07 (br s, 1H), 5.11 (s, 2H), 3.95 (s, 3H), 3.87 (s, 3H).

4.5.13. Methyl 4-{[2-{[(1-methyl-1*H*-imidazol-4-yl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoate (20m). Yield 98%; TLC R_f = 0.20 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 8.4 Hz, 2H), 7.63 (s, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.25–7.15 (m, 4H), 5.10 (s, 2H), 3.95 (s, 3H), 3.55 (s, 3H).

4.5.14. Methyl 4-{[2-{[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoate (20n). Yield 88%; TLC R_f = 0.24 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.30–7.22 (m, 2H), 7.11 (br s, 1H), 5.19 (s, 2H), 3.94 (s, 3H), 2.83 (s, 3H).

4.5.15. Methyl 4-{[2-{[(3,5-dimethylisoxazol-4-yl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoate (20o). Yield 95%; TLC R_f = 0.40 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.0 Hz, 1H), 7.13 (s, 1H), 5.07 (s, 2H), 3.96 (s, 3H), 2.40 (s, 3H), 2.14 (s, 3H).

4.6. The typical procedures for the preparation of alkylated sulfonamide derivatives 21a–o

4.6.1. Method A: Methyl 4-{[2-[isobutyl(phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]-methyl}benzoate (21a). To a stirred solution of **20a** (250 mg, 0.54 mmol) in DMF (3 mL) were added K_2CO_3 (178 mg, 1.28 mmol) and isobutyl iodide (0.15 mL, 1.28 mmol) under argon atmosphere. After being stirred overnight at 80 °C, 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 **21a** (280 mg, 100%). TLC R_f = 0.70 (EtOAc/benzene, 1:9); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.01 (d, J = 8.2 Hz, 2H), 7.70–7.60 (m, 2H), 7.50–7.20 (m, 5H), 7.17 (d, J = 8.2 Hz, 2H), 7.09 (d, J = 1.2 Hz, 1H), 4.90–4.70 (m, 2H), 3.95 (s, 3H), 3.50–3.40 (m, 2H), 1.70–1.50 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H) ; MS (APCI, Pos.) m/e 522 $(M+H)^+$.

4.6.2. Method B: Methyl 4-{[2-[isobutyl(pyridin-3-ylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (21b). To a stirred solution of **20b** (233 mg, 0.5 mmol), isobutylalcohol (0.093 mL, 1 mmol), and triphenylphosphine (262 mg, 1 mmol) in THF (2 mL) was added diethyl azodicarboxylate (0.49 mL, 1.25 mmol) at room temperature under argon atmosphere. After being stirred for 1 h, the reaction mixture was concentrated in vacuo and the resulting residue was purified by column chromatography on silica gel to yield **21b** (270 mg, 100%). TLC R_f = 0.63 (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (dd, J = 2.4, 0.9 Hz, 1H), 8.57 (dd, J = 4.8, 1.5 Hz, 1H), 8.03 (d, J = 8.4 Hz, 2H), 7.87 (m, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.31 (m, 1H), 7.20–7.10 (m, 4H), 5.03–4.60 (m, 2H), 3.95 (s, 3H), 3.50–3.30 (m, 2H), 1.65–1.50 (m, 1H), 1.00–0.85 (m, 6H).

4.6.3. Methyl 4-{[2-[isobutyl(1*H*-pyrrol-2-ylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (21c). (Method B) Yield 100%; TLC R_f = 0.59 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09–8.05 (m, 3H), 7.48 (d, J = 8.1 Hz, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.27 (br s, 1H), 7.12 (d, J = 1.5 Hz, 1H), 6.61 (dd, J = 4.2, 2.1 Hz, 1H), 6.53 (dd, J = 2.4, 2.1 Hz, 1H), 6.00 (dd, J = 4.2, 2.4 Hz, 1H), 4.97 (br s, 2H), 3.95 (s, 3H), 3.44 (d, J = 8.4 Hz, 2H), 3.39 (s, 3H), 0.88 (d, J = 6.6 Hz, 6H).

4.6.4. Methyl 4-{[2-[isobutyl(1,3-thiazol-2-ylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (21d). (Method A) Yield 69%; TLC R_f = 0.48 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 8.7 Hz, 2H), 7.72 (d, J = 3.0 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 3.0 Hz, 1H), 7.33 (d, J = 8.7 Hz, 2H), 7.27 (d, J = 8.4 Hz, 1H), 7.15 (s, 1H), 4.97 (br s, 2H), 3.95

(s, 3H), 3.64 (br d, J = 7.2 Hz, 2H), 1.73–1.50 (m, 1H), 0.93 (d, J = 6.6 Hz, 6H).

4.6.5. Methyl 4-{[2-[isobutyl(pyridin-2-ylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (21e). (Method B) Yield 92%; TLC R_f = 0.34 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (dt, J = 4.5, 1.5 Hz, 1H), 8.04 (d, J = 8.4 Hz, 2H), 7.76–7.66 (m, 2H), 7.52 (d, J = 8.4 Hz, 1H), 7.32–7.22 (m, 4H), 7.11 (br s, 1H), 4.91 (br s, 2H), 3.95 (s, 3H), 3.64 (br s, J = 7.2 Hz, 2H), 1.70–1.50 (m, 1H), 0.91 (d, J = 6.6 Hz, 6H).

4.6.6. Methyl 4-{[2-[(2-furylsulfonyl)(isobutyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (21f). (Method A) Yield 88%; TLC R_f = 0.40 (EtOAc/hexane, 1:3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.09–8.05 (m, 2H), 7.46–7.38 (m, 3H), 7.30–7.23 (m, 2H), 7.15 (dd, J = 2.0, 0.5 Hz, 1H), 6.81 (dd, J = 3.0, 0.5 Hz, 1H), 6.32 (dd, J = 3.0, 2.0 Hz, 1H), 5.04 (s, 2H), 3.94 (s, 3H), 3.50 (d, 2H), 1.90–1.70 (m, 1H), 0.89 (d, J = 6.5 Hz, 6H).

4.6.7. Methyl 4-{[2-[isobutyl(thien-3-ylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (21g). (Method A) Yield 97%; TLC R_f = 0.57 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, J = 6.6, 1.2 Hz, 2H), 7.72 (dd, J = 3.3, 1.2 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.31–7.25 (m, 3H), 7.17 (dd, J = 5.4, 3.3 Hz, 1H), 7.13 (d, J = 1.0 Hz, 1H), 7.08 (dd, J = 5.4, 1.2 Hz, 1H), 4.96 (s, 2H), 3.95 (s, 3H), 3.43 (d, J = 7.2 Hz, 2H), 1.60 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H).

4.6.8. Methyl 4-{[2-[(3-furylsulfonyl)(isobutyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (21h). (Method A) Yield 98%; TLC R_f = 0.53 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09–8.05 (m, 2H), 7.72 (dd, J = 1.8, 0.9 Hz, 1H), 7.44 (m, 1H), 7.38–7.34 (m, 2H), 7.29–7.24 (m, 2H), 7.16 (d, J = 1.5 Hz, 1H), 6.38 (dd, J = 1.8, 0.9 Hz, 1H), 5.04 (s, 2H), 3.94 (s, 3H), 3.42 (d, J = 7.5 Hz, 2H), 1.61 (m, 1H), 0.90 (d, J = 6.6 Hz, 6H).

4.6.9. Methyl 4-{[2-[isobutyl(1*H*-pyrrol-3-ylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (21i). (Method B) Yield 100%; TLC R_f = 0.25 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (br s, 1H), 8.04 (d, J = 8.1 Hz, 2H), 7.40–7.35 (m, 3H), 7.23 (dd, J = 8.1, 1.5 Hz, 1H), 7.14 (d, J = 1.5 Hz, 1H), 7.11 (m, 1H), 6.65 (m, 1H), 6.30 (m, 1H), 5.04 (s, 2H), 3.95 (s, 3H), 3.39 (d, J = 7.5 Hz, 2H), 1.58 (m, 1H), 0.88 (d, J = 6.6 Hz, 6H).

4.6.10. Methyl 4-{[2-{isobutyl[(1-methyl-1*H*-pyrrol-3-yl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoate (21j). (Method B) Yield 100%; TLC R_f = 0.29 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07–8.03 (m, 2H), 7.40 (d, J = 8.1 Hz, 1H), 7.38 (d, J = 8.1 Hz, 2H), 7.23 (m, 1H), 7.15 (d, J = 1.5 Hz, 1H), 6.93 (dd, J = 2.4, 1.8 Hz, 1H), 6.43 (dd, J = 2.7, 2.4 Hz, 1H), 6.18 (dd, J = 2.7, 1.8 Hz, 1H), 5.05 (s, 2H), 3.94 (s, 3H), 3.50 (s, 3H), 3.38 (d, J = 6.9 Hz, 2H), 1.59 (m, 1H), 0.88 (d, J = 6.6 Hz, 6H).

4.6.11. Methyl 4-{[2-[(1*H*-imidazol-2-ylsulfonyl)(isobutyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (21k). (Method B) Yield 100%; TLC R_f = 0.36 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.38 (s, 1H), 7.23 (d, J = 8.1 Hz, 1H), 7.15 (s, 1H), 7.10–6.90 (m, 1H), 6.53–6.30 (m, 2H), 5.06 (s, 2H), 3.94 (s, 3H), 3.59 (d, J = 7.5 Hz, 2H), 1.70–1.60 (m, 1H), 0.99 (d, J = 6.6 Hz, 6H).

4.6.12. Methyl 4-{[2-{isobutyl[(1-methyl-1*H*-pyrazol-4-yl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoate (21l). (Method A) Yield 100%; TLC R_f = 0.50 (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 2H), 7.55 (s, 1H), 7.50 (d, J = 0.6 Hz, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.30–7.26 (m, 1H), 7.17 (br d, J = 2.1 Hz, 1H), 5.03 (br s, 2H), 3.94 (s, 3H), 3.70 (s, 3H), 3.36 (dd, J = 13.5, 7.2 Hz, 2H), 1.65–1.55 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H).

4.6.13. Methyl 4-{[2-{isobutyl[(1-methyl-1*H*-imidazol-4-yl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoate (21m). (Method A) Yield 89%; TLC R_f = 0.57 (EtOAc/benzene, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.25–7.15 (m, 4H), 5.10 (s, 2H), 3.94 (s, 3H), 3.60–3.55 (m, 2H), 3.56 (s, 3H), 1.65–1.55 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H).

4.6.14. Methyl 4-{[2-{isobutyl[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}-benzoate (21n). (Method A) Yield 76%; TLC R_f = 0.84 (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.32–7.26 (m, 1H), 7.20 (br s, 1H), 5.05 (br s, 2H), 3.94 (s, 3H), 3.64 (d, J = 6.6 Hz, 2H), 2.65 (s, 3H), 1.76–1.66 (m, 1H), 0.94 (d, J = 6.6 Hz, 6H).

4.6.15. Methyl 4-{[2-[(3,5-dimethylisoxazol-4-ylsulfonyl)(isobutyl)amino]-5-(trifluoromethyl)phenoxy]methyl}-benzoate (21o). (Method A) Yield 100%; TLC R_f = 0.50 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.1 Hz, 1H), 7.40–7.26 (m, 3H), 7.15 (s, 1H), 4.98 (br s, 1H), 4.79 (br s, 1H), 3.96 (s, 3H), 3.63–3.50 (m, 1H), 3.45–3.30 (m, 2H), 2.09 (s, 3H), 2.08 (s, 3H), 1.65–1.55 (m, 1H), 0.97 (br s, 3H), 0.90 (br s, 3H).

4.7. General procedure for the preparation of 4-{[2-[(2-arylsulfonyl)(isobutyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoic acids (1–15)

4.7.1. 4-{[2-[Isobutyl(phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (1). To a stirred solution of **21a** (280 mg, 0.54 mmol) in MeOH (6 mL) and THF (6 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 EtOAc and hexane to yield **1** (220 mg, 80%). TLC

R_f = 0.53 (MeOH/$CHCl_3$, 1/9); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 2H), 7.70–7.60 (m, 2H), 7.50–7.20 (m, 7H), 7.11 (d, J = 1.6 Hz, 1H), 5.00–4.80 (m, 2H), 3.44 (d, J = 7.4 Hz, 2H), 1.70–1.50 (m, 1H), 0.90 (d, J = 6.4 Hz, 6H); IR (KBr) 2963, 1694, 1614, 1510, 1448, 1427, 1331, 1289, 1257, 1213, 1169, 1127, 1086, 1019 cm^{-1}; MS (FAB, Pos.) *m/e* 508 $(M+H)^+$; Anal. Calcd for $C_{25}H_{24}F_3NO_5S$: C, 59.16; H, 4.77; N, 2.76; S, 6.32. Found: C, 59.50; H, 4.73; N, 2.75; S, 6.54.

According to the same procedure as described above, **2**–**15** were prepared from **21b**–**o**, respectively.

4.7.2. 4-{[2-[Isobutyl(pyridin-3-ylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}-benzoic acid (2). Yield 69%; TLC R_f = 0.27 (MeOH/$CHCl_3$, 1:9); ^{1}H NMR (300 MHz, CD_3OD) δ 8.63 (m, 1H), 8.53 (dd, J = 5.1, 1.8 Hz, 1H), 7.99–7.94 (m, 3H), 7.56 (d, J = 7.5 Hz, 1H), 7.40–7.29 (m, 3H), 7.23 (d, J = 8.4 Hz, 2H), 5.10–4.80 (m, 2H), 3.58–3.40 (m, 2H), 1.61 (m, 1H), 0.92 (br d, J = 6.0 Hz, 6H); IR (KBr) 3441, 2924, 1705, 1615, 1587, 1511, 1417, 1362, 1333, 1277, 1171, 1124 cm^{-1}; MS (APCI, Neg.) *m/e* 507 $(M-H)^-$; Anal. Calcd for $C_{24}H_{23}F_3N_2O_5S$: C, 56.69; H, 4.56; N, 5.51; S, 6.31. Found: C, 56.87; H, 4.54; N, 5.55; S, 6.22.

4.7.3. 4-{[2-[Isobutyl(1*H*-pyrrol-2-ylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (3). Yield 58%; TLC R_f = 0.45 (MeOH/$CHCl_3$, 1:5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15–8.10 (m, 2H), 7.47 (dd, J = 8.1, 0.9 Hz, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.27 (m, 1H), 7.13 (d, J = 1.5 Hz, 1H), 6.63 (dd, J = 4.2, 2.1 Hz, 1H), 6.55 (dd, J = 2.4, 2.1 Hz, 1H), 6.02 (dd, J = 4.2, 2.4 Hz, 1H), 5.01 (br s, 2H), 3.44 (d, J = 7.5 Hz, 2H), 3.41 (s, 3H), 1.59 (m, 1H), 0.89 (d, J = 6.6 Hz, 6H); IR (KBr) 2961, 1694, 1615, 1511, 1429, 1332, 1295, 1170, 1122, 1086, 1019 cm^{-1}; MS (FAB, Pos.) *m/e* 511 $(M+H)^+$; Anal. Calcd for $C_{24}H_{25}F_3N_2O_5S$: C, 56.46; H, 4.94; N, 5.49; S, 6.28. Found: C, 56.49; H, 4.99; N, 5.32; S, 6.43.

4.7.4. 4-{[2-[Isobutyl(1,3-thiazol-2-ylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (4). Yield 87%; TLC R_f = 0.60 (EtOAc); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.03 (d, J = 3.0 Hz, 1H), 7.95 (d, J = 8.1 Hz, 2H), 7.90 (d, J = 3.0 Hz, 1H), 7.50–7.45 (m, 2H), 7.45–7.35 (m, 3H), 5.11 (br s, 2H), 3.49 (d, J = 7.2 Hz, 2H), 1.60–1.45 (m, 1H), 0.83 (d, J = 6.6 Hz, 6H); IR (KBr) 3413, 3084, 2967, 2872, 1687, 1615, 1579, 1512, 1430, 1360, 1333, 1296, 1174, 1126 cm^{-1}; MS (APCI, Neg.) *m/e* 513 $(M-H)^-$; Anal. Calcd for $C_{22}H_{21}F_3N_2O_5S_2$: C, 51.36; H, 4.11; N, 5.44; S, 12.46. Found: C, 51.63; H, 4.08; N, 5.51; S, 12.17.

4.7.5. 4-{[2-[Isobutyl(pyridin-2-ylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (5). Yield 87%; TLC R_f = 0.29 (MeOH/$CHCl_3$, 1:9); ^{1}H NMR (300 MHz, CD_3OD) δ 8.39 (br d, J = 4.5 Hz, 1H), 8.00 (d, J = 8.1 Hz, 2H), 7.83 (dt, J = 7.8, 1.8 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.40–7.35 (m, 1H), 7.34–7.26 (m, 4H), 5.00–4.90 (m, 2H), 3.61 (br d, J = 6.9 Hz, 2H), 1.68–1.54 (m, 1H), 0.91 (d, J = 6.6 Hz, 6H); IR (KBr) 3452, 1697, 1613, 1579, 1509, 1428, 1332, 1173, 1127 cm^{-1}; MS (APCI, Neg.) *m/e* 507 $(M-H)^-$; HRMS (Pos.) calcd for $C_{24}H_{24}F_3N_2O_5S$: 509.1358. Found: 509.1355.

4.7.6. 4-{[2-[(2-Furylsulfonyl)(isobutyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (6). Yield 89%; TLC R_f = 0.20 (EtOAc/hexane, 1:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.18–8.14 (m, 2H), 7.48–7.40 (m, 2H), 7.30–7.26 (m, 3H), 7.16 (dd, J = 2.0, 1.0 Hz, 1H), 6.84 (dd, J = 3.5, 1.0 Hz, 1H), 6.35 (dd, J = 3.5, 2.0 Hz, 1H), 5.07 (s, 2H), 3.54 (d, J = 7.0 Hz, 2H), 1.64 (sept, J = 7.0 Hz, 1H), 0.90 (d, J = 7.0 Hz, 6H); IR (KBr) 2971, 1687, 1511, 1434, 1332, 1124, 1018 cm^{-1}; MS (FAB, Pos.) *m/e* 498 $(M+H)^+$; Anal. Calcd for $C_{23}H_{22}F_3NO_6S$: C, 55.53; H, 4.46; N, 2.82; S, 6.45. Found: C, 55.82; H, 4.66; N, 2.83; S, 6.64.

4.7.7. 4-{[2-[Isobutyl(thien-3-ylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (7). Yield 75%; TLC R_f = 0.36 (MeOH/$CHCl_3$, 1:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14–8.10 (m, 2H), 7.74 (dd, J = 3.3, 1.5 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 8.1 Hz, 2H), 7.27 (m, 1H), 7.20 (dd, J = 4.8, 3.0 Hz, 1H), 7.15 (d, J = 1.2 Hz, 1H), 7.10 (dd, J = 4.8, 1.5 Hz, 1H), 4.99 (s, 2H), 3.45 (d, J = 6.9 Hz, 2H), 1.61 (m, 1H), 0.90 (d, J = 6.9 Hz, 6H); IR (KBr) 2963, 1693, 1511, 1421, 1332, 1210, 1159, 1128, 1017 cm^{-1}; MS (APCI, Neg.) *m/e* 496 $(M-H)^-$; Anal. Calcd for $C_{23}H_{22}F_3NO_5S_2$: C, 53.79; H, 4.32; N, 2.73; S, 12.49. Found: C, 53.86; H, 4.23; N, 2.69; S, 12.60.

4.7.8. 4-{[2-[(3-Furylsulfonyl)(isobutyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (8). Yield 88%; TLC R_f = 0.37 (MeOH/$CHCl_3$, 1:10); ^{1}H NMR (300 MHz, CDCl3) δ 8.16–8.11 (m, 2H), 7.74 (dd, J = 1.8, 0.6 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 7.8 Hz, 2H), 7.28 (dd, J = 1.8, 1.8 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 1.5 Hz, 1H), 6.40 (dd, J = 1.8, 0.6 Hz, 1H), 5.07 (s, 2H), 3.43 (d, J = 7.5 Hz, 2H), 1.62 (m, 1H), 0.90 (d, J = 6.6 Hz, 6H); IR (KBr) 2961, 1693, 1510, 1431, 1333, 1130, 1081, 1015 cm^{-1}; MS (APCI, Neg.) *m/e* 512 $(M-H)^-$; Anal. Calcd for $C_{23}H_{22}F_3NO_6S$: C, 55.53; H, 4.46; N, 2.82; S, 6.45. Found: C, 55.55; H, 4.50; N, 2.72; S, 6.37.

4.7.9. 4-{[2-[Isobutyl(1*H*-pyrrol-3-ylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (9). Yield 65%; TLC R_f = 0.45 (MeOH/$CHCl_3$, 1:5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (br s, 1H), 8.12 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 7.8 Hz, 1H), 7.24 (m, 1H), 7.16 (d, J = 1.2 Hz, 1H), 7.14 (m, 1H), 6.68 (m, 1H), 6.33 (m, 1H), 5.08 (s, 2H), 3.40 (d, J = 7.5 Hz, 2H), 1.60 (m, 1H), 0.88 (d, J = 6.6 Hz, 6H); IR (KBr) 3348, 2961, 1697, 1511, 1429, 1333, 1173, 1132, 1083, 1043 cm^{-1}; MS (FAB, Pos.) *m/e* 497 $(M+H)^+$; Anal. Calcd for $C_{23}H_{23}F_3N_2O_5S$: C, 55.64; H, 4.67; N, 5.64; S, 6.46. Found: C, 55.55; H, 4.75; N, 5.47; S, 6.58.

4.7.10. 4-{[2-{Isobutyl[(1-methyl-1*H*-pyrrol-3-yl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]-methyl}benzoic acid (10). Yield 73%; TLC R_f = 0.46 (MeOH/$CHCl_3$, 1:5);

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.1 Hz, 1H), 7.24 (d, J = 8.1 Hz, 1H), 7.17 (s, 1H), 6.95 (dd, J = 2.1, 1.8 Hz, 1H), 6.45 (dd, J = 3.0, 2.4 Hz, 1H), 6.20 (m, 1H), 5.09 (s, 2H), 3.53 (s, 3H), 3.38 (d, J = 7.5 Hz, 2H), 1.60 (m, 1H), 0.88 (d, J = 6.6 Hz, 6H); IR (KBr) 2958, 1688, 1615, 1511, 1427, 1338, 1151, 1120, 1080, 1051 cm^{-1}; MS (FAB, Pos.) *m/e* 511 $(M+H)^+$; Anal. Calcd for $C_{24}H_{25}F_3N_2O_5S$: C, 56.46; H, 4.94; N, 5.49; S, 6.28. Found: C, 56.36; H, 4.85; N, 5.38; S, 6.42.

4.7.11. 4-{[2-[(1*H*-Imidazol-2-ylsulfonyl)(isobutyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (11). Yield 35%; TLC R_f = 0.25 (MeOH/$CHCl_3$, 1:5); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90 (d, J = 8.4 Hz, 2H), 7.45–7.27 (m, 5H), 7.26–6.97 (m, 2H), 5.21–5.09 (m, 2H), 3.38 (d, J = 7.5 Hz, 2H), 1.52–1.38 (m, 1H), 0.75 (d, J = 6.3 Hz, 6H); IR (KBr) 2958, 1688, 1615, 1511, 1427, 1338, 1151, 1120, 1080, 1051 cm^{-1}; MS (FAB, Pos.) *m/e* 498 $(M+H)^+$; Anal. Calcd for $C_{22}H_{22}F_3N_3O_5S$: C, 53.11; H, 4.46; N, 8.45; S, 6.45. Found: C, 52.95; H, 4.47; N, 8.19; S, 6.60.

4.7.12. 4-{[2-{Isobutyl[(1-methyl-1*H*-pyrazol-4-yl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (12). Yield 78%; TLC R_f = 0.50 (EtOAc); ^{1}H NMR (300 MHz, CD_3OD) δ 8.04 (d, J = 8.7 Hz, 2H), 7.92 (s, 1H), 7.50–7.40 (m, 2H), 7.42–7.36 (m, 3H), 7.32 (br d, J = 7.8 Hz, 1H), 5.10 (br s, 2H), 3.68 (s, 3H), 3.42 (d, J = 7.5 Hz, 2H), 1.65–1.55 (m, 1H), 0.90 (d, J = 6.6 Hz, 6H); IR (KBr) 3444, 3131, 2966, 1692, 1650, 1614, 1578, 1511, 1432, 1415, 1388, 1332, 1294, 1174, 1152, 1123 cm^{-1}; MS (APCI, Neg.) *m/e* 510 $(M-H)^-$; Anal. Calcd for $C_{23}H_{24}F_3N_3O_5S$: C, 54.01; H, 4.73; N, 8.21; S, 6.27. Found: C, 54.17; H, 4.96; N, 8.01; S, 5.99.

4.7.13. 4-{[2-{Isobutyl[(1-methyl-1*H*-imidazol-4-yl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (13). Yield 63%; TLC R_f = 0.42 (MeOH/$CHCl_3$, 1:5); ^{1}H NMR (300 MHz, CD_3OD) δ 8.04 (d, J = 8.1 Hz, 2H), 7.50–7.40 (m, 5H), 7.36 (s, 1H), 7.29 (d, J = 8.4 Hz, 1H), 5.11 (br s, 2H), 3.54–3.52 (m, 5H), 1.70–1.55 (m, 1H), 0.90 (d, J = 6.9 Hz, 6H); IR (KBr) 3445, 2959, 1703, 1613, 1534, 1509, 1469, 1432, 1358, 1332, 1256, 1217, 1160, 1128 cm^{-1}; MS (APCI, Neg.) *m/e* 510 $(M-H)^-$; Anal. Calcd for $C_{23}H_{24}F_3N_3O_5S$: C, 54.01; H, 4.73; N, 8.21; S, 6.27. Found: C, 53.93; H, 4.67; N, 8.06; S, 6.42.

4.7.14. 4-{[2-{Isobutyl[(5-methyl-1,3,4-thiadiazol-2-yl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (14). Yield 70%; TLC R_f = 0.35 (MeOH/$CHCl_3$, 1:9); ^{1}H NMR (300 MHz, CD_3OD) δ 8.03 (d, J = 7.8 Hz, 2H), 7.59 (d, J = 8.1 Hz, 1H), 7.43 (br s, 1H), 7.40–7.34 (m, 3H), 5.20–4.95 (m, 2H), 3.65–3.58 (m, 2H), 2.59 (s, 3H), 1.78–1.60 (m, 1H), 0.95 (d, J = 6.6 Hz, 6H); IR (KBr) 3445, 1694, 1511, 1415, 1370, 1331, 1174, 1125 cm^{-1}; MS (APCI, Neg.) *m/e* 528 $(M-H)^-$; Anal. Calcd for $C_{24}H_{25}F_3N_2O_6S$: C, 54.75; H, 4.79; N, 5.32; S, 6.09. Found: C, 54.92; H, 4.76; N, 5.21; S, 6.18.

4.7.15. 4-{[2-[(3,5-Dimethylisoxazol-4-ylsulfonyl)(isobutyl)amino]-5-(trifluoromethyl)phenoxy]-methyl}benzoic acid (15). Yield 78%; TLC R_f = 0.30 (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.96 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 8.1 Hz, 1H), 7.51 (s, 1H), 7.43–7.38 (m, 3H), 5.30–5.18 (br s, 1H), 5.05–4.90 (br s, 1H), 3.48–3.35 (m, 2H), 2.13 (s, 3H), 1.81 (s, 3H), 1.60–1.43 (m, 1H), 0.95–0.78 (m, 6H); IR (KBr) 2967, 2873, 1691, 1613, 1591, 1508, 1421, 1332, 1289, 1181, 1119 cm^{-1}; MS (MALDI, Pos) *m/e* 549 $(M+Na)^+$, 527 $(M+H)^+$; Anal. Calcd for $C_{22}H_{22}F_3N_3O_5S_2$: C, 49.90; H, 4.19; N, 7.93; S, 12.11. Found: C, 50.07; H, 4.21; N, 7.66; S, 11.77.

4.7.16. 1,3-Thiazole-2-sulfonyl chloride (23). To a stirred solution of **22** (5.0 g, 30.5 mmol) in Et_2O (100 mL) was added *n*-butyl lithium (30.5 mmol) below −60 °C under argon atmosphere. After being stirred for 1 h, sulfur dioxide gas was bubbled into the reaction mixture for 5 min. After being stirred at room temperature, the reaction mixture was concentrated in vacuo. The resulting residue was suspended with CH_2Cl_2 (200 mL) under argon atmosphere. To a stirred suspension was added *N*-chlorosuccinimide (4.48 g, 33.6 mmol). After being stirred for 1.5 h, the reaction mixture was filtered through a pad of Celite, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **23** (4.6 g, 82%). TLC R_f = 0.75 (EtOAc/hexane, 1:4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 3.0 Hz, 1H), 7.88 (d, J = 3.0 Hz, 1H).

4.8. 4-Iodo-1-methyl-1*H*-pyrazole (25)

To a stirred solution of **24** (5.0 g, 25.8 mmol) in DMF (50 mL) were added K_2CO_3 (4.26 g, 30.9 mmol) and iodomethane (1.76 mL, 28.4 mmol) at room temperature under argon atmosphere. After being stirred for 1 h, the reaction mixture was diluted with EtOAc, filtered through a pad of Celite and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **25** (2.6 g, 49%). TLC R_f = 0.41 (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.40 (s, 1H), 3.92 (s, 3H).

4.9. 1-Methyl-1*H*-pyrazole-4-sulfonyl chloride (26)

To a stirred solution of **25** (2.6 g, 12.5 mmol) in Et_2O (125 mmol) was added *n*-butyl lithium (13.1 mol) dropwise below −60 °C under argon atmosphere. After being stirred for 1 h, the reaction mixture was charged with sulfur dioxide until the internal temperature rise up to −45 °C. After being stirred for 15 min, the reaction mixture was warmed up to room temperature. After stirring for 1 h, the reaction mixture was concentrated in vacuo to yield a white powder. To a stirred suspension of the powder in CH_2Cl_2 (125 mL) was added *N*-chlorosuccinimide (1.67 g, 12.5 mmol). After being stirred for 3 h, the suspension was filtered through a pad of Celite and concentrated in vacuo to yield **26** (2.5 g, 100%). TLC R_f = 0.36 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.97 (s, 1H), 4.01 (s, 3H).

4.10. 5-Methyl-1,3,4-thiadiazole-2-sulfonyl chloride (28)

Chlorine gas was bubbled into 33% aqueous AcOH (35 mL) for 15 min below 5 °C. To a stirred solution of chlorine in aqueous AcOH, which was prepared as described above, was added a suspension of **27** (850 mg, 6.4 mmol) below 5 °C. After being stirred for 1 h at 0 °C, the reaction mixture was extracted with Et_2O. The organic layer was washed with water, $NaHCO_3$ aq, brine, dried over Na_2SO_4, and concentrated in vacuo to yield **28** (590 mg, 46%), which was used for the next reaction without further purification.

4.11. Calculation of clog *P*

Calculated log *P* values (clog *P*) were calculated using PCmodels software version 4.8.3 by DAYLIGHT Chemical Information Systems Inc (http://www.daylight.com).

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 [^{3}H]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:

$$K_i = IC_{50}/(1 + [L]/K_d),$$

where [L] is the concentration of radiolabeled ligand; K_d is the 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 mEP1 receptor, 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's α-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 probenecid) was discarded. After the addition of assay buffer (Hanks' balanced salt solution (HBSS) containing 0.1% (w/v) BSA, 2 μM indomethacin, 2.5 mM probenecid and 10 mM 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 were 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 was 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.

5.3. Inhibitory effect of selected compounds on the sulprostone-induced increase of intravesical bladder pressure in rats

Female rats (Wistar) were anesthetized by urethane and both ureters were ligated and cut off at the kidney side. The urinary bladder was incised at the top and a catheter was inserted. The other end of the catheter was connected to the pressure transducer and the infusion pump. The repeated micturition reflex that was induced by a continuous infusion of citrate buffer (pH 3.5) into the bladder was recorded. An increase of micturition pressure was elicited by a subcutaneous injection of diclofenac (5 mg/kg) and sulprostone (300 μg/kg). The inhibitory effect of the test compound on this increase of intravesical pressure was measured for 10, 20, 40, and 60 min after intra-duodenal administration (2 mL/kg). Statistical data analysis was performed with SAS System Release 8.2 (SAS Institute Japan Ltd., Tokyo, Japan) for Tukey's test. Differences with P values < 0.05 were considered significant.

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10. We have to keep the following points in our mind: (1) lipophilicity has been considered to be one of the factors which influences, the potency of protein binding; (2) clog*P* value has been used as a rough approximation of lipophilicity because isomerism (ex: **6** & **8**; **3** & **10**; **12** & **13**) and/or steric factors such as conformation are not always included in the calculation of clog*P* values. Medicinal chemists have used clog*P* as an index of lipophilicity instead of the experimental log*P* value for the convenience. It can be useful within a relatively small structural change as illustrated in the structural change from **1** to **2**–**4**. For such a reason, clog*P* cannot always explain all the disparity between receptor affinity and antagonist activity in vitro. But it is still useful to explain SAR within a small structural change in a series of homogeneous basic structures. On the basis of the above-described reason, it is difficult to explain the correlation between the activities and lipophilicity of all the listed compounds. Besides, our purpose is to create a new 'drug-like' chemical lead for a drug candidate in this paper. To avoid such a problem as described in Section 1, we worked on the synthetic strategy to lower clog*P* value. The clog*P* values are listed in the Tables mainly to show that our molecular design was carried out in a desired direction.
11. Good animal model for in vivo experiment is available in rat while mouse receptors for in vitro experiment are available. High homology at gene level between the two species has been known (96%). [1b]