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Optimization of sulfonamide derivatives as highly selective EP1 receptor antagonists

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Abstract—A series of 4-[(2-{isobutyl[(5-methyl-2-furyl)sulfonyl]amino}phenoxy)methyl]benzoic acids and 4-({2-[isobutyl(1,3-thiazol-2-ylsulfonyl)amino]phenoxy}methyl)benzoic acids were synthesized and evaluated for their EP receptor affinities and EP1 receptor antagonist activities. Further structural optimization was carried out to reduce inhibitory activity against hepatic cytochrome P450 isozymes, which could represent a harmful potential drug interaction. Selected compounds were also evaluated for their binding affinities to hTP, hDP, mFP, and hIP, and for their hEP1 receptor antagonist activities. The results of structure–activity relationship studies are also presented.

1. Introduction

Coleman et al.[1] proposed the existence of specific receptors for thromboxane (TX), prostaglandin I (PGI), PGE, PGF, and PGD, which were named TP, IP, EP, FP, and DP, respectively. They further classified EP receptors into four subtypes, EP1–4, each of which responds to PGE_2 in different way. A number of specific ligands for these receptors have been reported in the literature.[2–5] In our previous papers,[6–8] we described the discovery of a highly selective EP1 receptor antagonist **1**. As shown in Table 1, **1** showed a significant in vivo antagonist activity with respect to the sulprostone-induced increase of intravesical pressure of bladder in rats, whereas the corresponding tetrazole analog **2**[8] showed increased activity as an EP1 antagonist in vivo in the same assay system. Analogs **1** and **2** were further evaluated for their ability to inhibit hepatic cytochrome P450 isozymes 1A2, 2C9, 2C19, 2D6, and 3A4, which are hepatic enzymes for drug metabolism. As shown in Table 2, the tetrazole analog, compound **2**, strongly inhibited 2C9, 2C19, and 3A4 at a concentration of 3 μM, whereas the corresponding carboxylic acid analog **1** did not.[8] Cytochrome P450 enzyme inhibition by drug candidates has been widely studied because of the potential for harmful drug interactions. For this reason, further optimization of acid analog **1**, which has less potent inhibitory activity against all the P450 isozymes, was carried out for identifying drug candidates. We here report on the discovery of highly selective EP1 receptor antagonists without inhibitory activity against cytochrome P450 isozymes at realistic concentrations.

2. Chemistry

Synthesis of test compounds is outlined in Schemes 1–4. Compounds **3**–**5** were synthesized as described in Scheme 1. Palladium-catalyzed carbonylation of triflates derived from phenols **19a** and **b** in the presence of methanol afforded methyl esters **20a** and **b**. Bromination of **20a** and **b** with *N*-bromosuccinimide in the presence of benzoyl perbromide provided **21a** and **b**, respectively. Lithium aluminum hydride (LAH) reduction of 4-bromo-2-methyl benzoic acid **22** gave an alcohol **23**.

Keywords: Prostaglandin; EP1 receptor; Antagonist; Sulfonamide.
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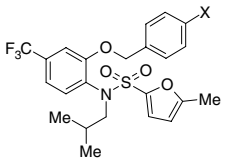
Table 1. Activity profiles of **1** and **2**



Compound	X	Binding K_i (μM)				IC_{50}[b] (μM)	In vivo EP1 function 1 mg/kg id (% inh)
		mEPl[a]	mEP2[a]	mEP3[a]	mEP4[a]	mEPl[a]	
1		0.00020	>10	0.82	0.21	0.020	37 ± 5
2		0.0026	2.5	0.026	>10	0.0089	74 ± 13

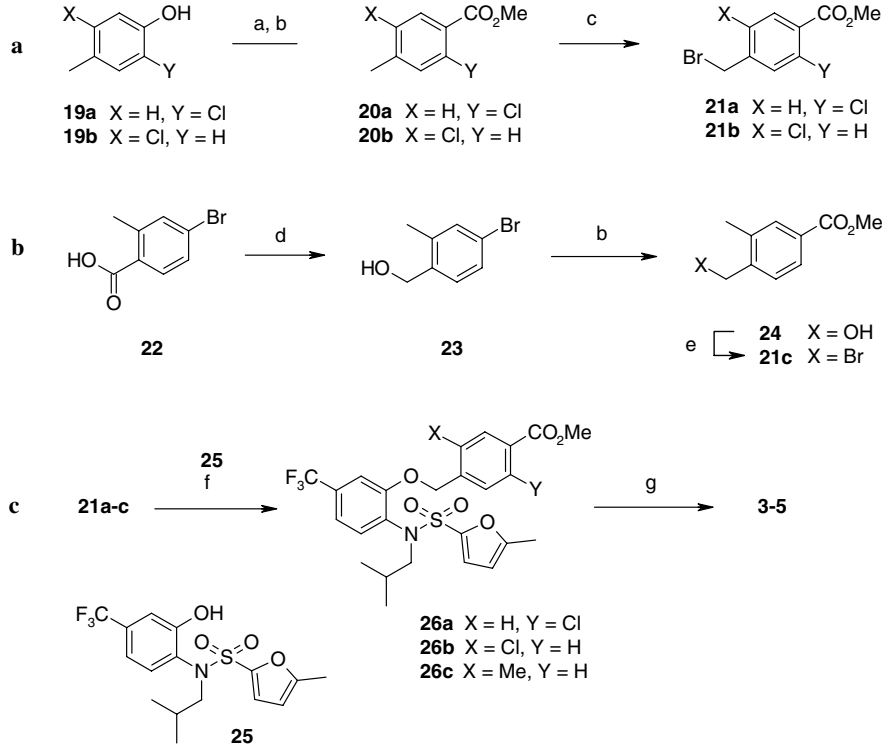
[a] mEPl-4, mouse EP1–4.
[b] IC_{50}, receptor antagonist activity.

Table 2. Cytochrome P450 inhibition of **1** and **2**

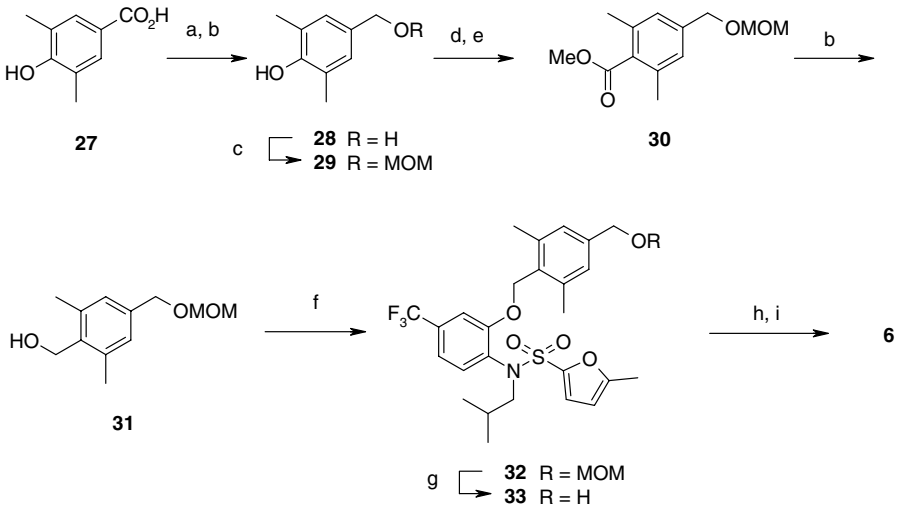
Compound	P450 % inhibition (3 μM)				
	1A2	2C9	2C19	2D6	3A4
1	2.6	14	0.40	−5.1	12
2	12	98	98	2.6	94

Palladium-catalyzed carbonylation of **23** in the presence of methanol provided a methyl benzoate **24**, bromination of which afforded a benzylbromide **21c**. Alkylation of a phenol intermediate **25**[8] with benzyl halides **21a–c** in the presence of potassium carbonate afforded **26a–c**, respectively. Alkaline hydrolysis of methyl esters **26a–c** gave **3–5**, respectively.

Synthesis of **6** is described in Scheme 2. Esterification of the benzoic acid **27** with diazomethane followed by LAH reduction gave a benzyl alcohol **28**, protection of which as a MOM ether afforded **29**. Trifluoromethanesulfonylation of **29** followed by palladium-catalyzed carbonylation in the presence of methanol provided **30**, LAH reduction of which afforded a benzyl alcohol **31**. O-Alkylation of the phenol residue of **25** using the Mitsunobu reaction gave **32**, acidic deprotection of which gave **33**. Oxidation of **33** with pyridinium-sulfur trioxide



Scheme 1. Synthesis of **3–5**. Reagents: (a) Tf_2O, pyridine, CH_2Cl_2; (b) CO, Et_3N, $Pd(OAc)_2$, dppf, DMSO, MeOH; (c) benzoyl perbromide, NBS, CCl_4; (d) $LiAlH_4$, THF; (e) PBr_3, MTBE; (f) pyridine, CH_2Cl_2; (g) NaOH, MeOH, dioxane.



Scheme 2. Synthesis of **6**. Reagents: (a) CH_2N_2, THF; (b) $LiAlH_4$, THF; (c) MOMCl, $^iPr_2NEt$, CH_2Cl_2; (d) Tf_2O, pyridine, CH_2Cl_2; (e) CO, Et_3N, $Pd(OAc)_2$, dppf, DMSO, MeOH; (f) **25**, DEAD, PPh_3, THF; (g) HCl, dioxane, H_2O; (h) SO_3·Pyr, DMSO, Et_3N, EtOAc; (i) $NaClO_2$, isobutene, NaH_2PO_4, ^{t}BuOH, H_2O.

and then further oxidation with sodium hypochlorite afforded a carboxylic acid **6**.

Synthesis of **7**–**10**, **12**,–**13** and **15**–**18** is described in Scheme 3a. O-Alkylation of nitrophenols **34a**–**d** with appropriate halides afforded benzyl phenyl ethers **35a**–**f**, respectively. Reduction of the nitro residue of **35a**–**f** produced their corresponding anilines **36a**–**f**, N-sulfonylation of which with appropriate sulfonyl chloride[7] gave sulfonamides **37a**–**j**, respectively. N-Alkylation of sulfonamides **37a**–**j** with isobutyl iodide afforded **38a**–**j**, respectively. Alkaline hydrolysis of **38a**–**j** produced **7**–**10**, **12**–**13**, and **15**–**18**, respectively.

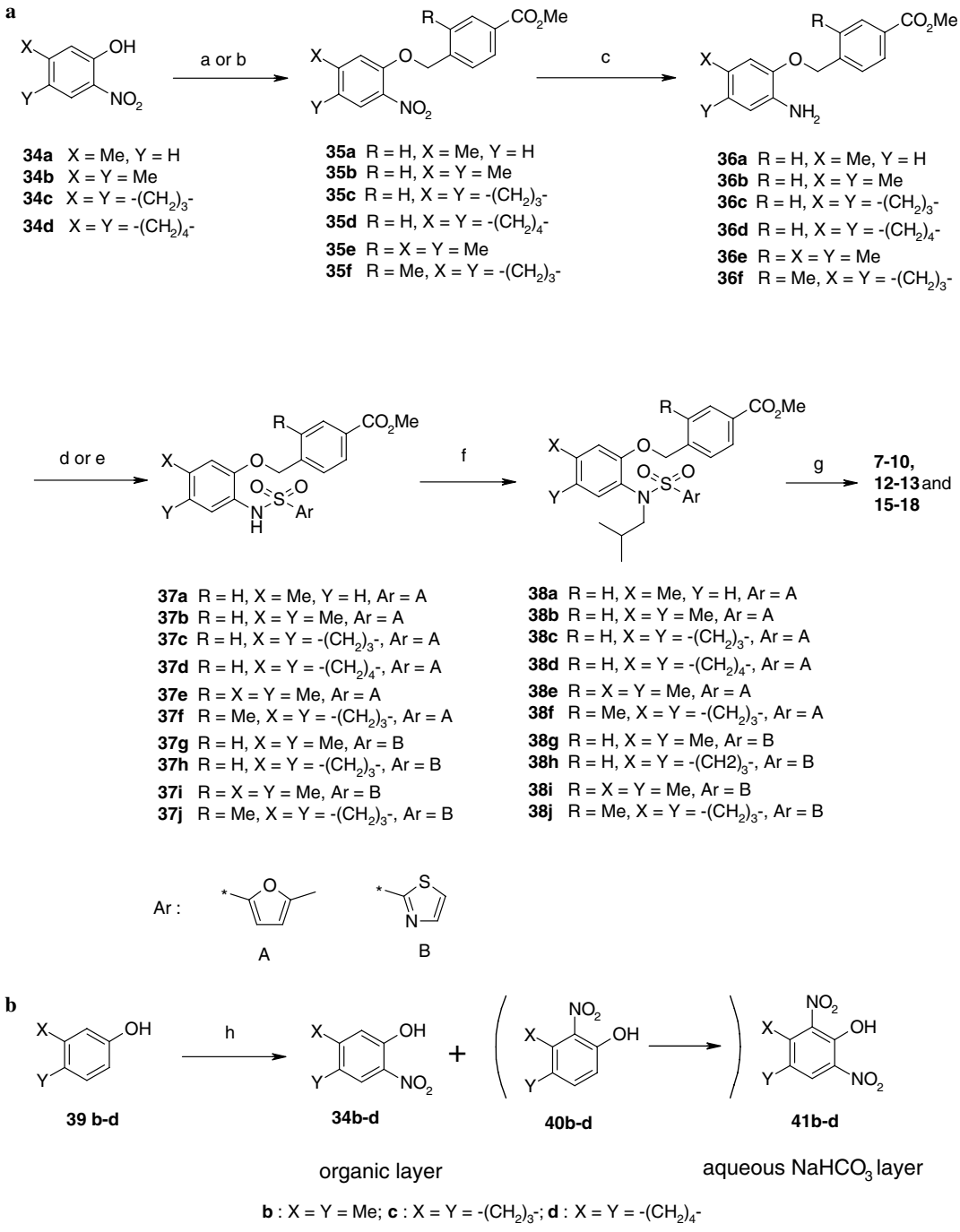
The nitrophenols **34b**–**d** were prepared as described in Scheme 3b. Nitration of phenols **39b**–**d** with 1 equiv of sodium nitrate in the presence of hydrochloric acid gave an inseparable mixture of **34b**–**d** and **40b**–**d** (1:1).[9] This synthetic problem was successfully avoided as described below. Nitration of **39b**–**d** with 2 equiv of sodium nitrate afforded a separable mixture of **34b**–**d** and **41b**–**d** (1:1) because preferential nitration of the byproducts **40b**–**d** gave dinitro compounds **41b**–**d**.

Synthesis of **11** is described in Scheme 4. O-Protection of 2-aminonaphthol **42** as TBS ether provided a TBS ether **43**. N-Sulfonylation of **43** with 5-methylfuran-2-sulfonyl chloride afforded a sulfonamide **44**, N-alkylation of which with isobutanol under Mitsunobu reaction conditions provided **45**. Deprotection of TBS ether afforded **46**. O-Alkylation of **46** with methyl 4-(bromomethyl)benzoate gave **47**, alkaline hydrolysis of which resulted in **11**.

3. Results and discussion

Further optimization of the carboxylic acid analogs was carried out because of their less potent P450 enzyme inhibition. Table 3 shows the effect of substituting the benzoic acid moiety on activity profiles. 2-Chlorobenzoic acid, 3-chlorobenzoic acid, 3-methylbenzoic acid, and 3,5-dimethylbenzoic acid analogs **3**, **4**, **5**, and **6** were tested for their receptor affinities and were found to be less potent than **1**. They were also tested for their antagonist activities. Predictably, compound **3** had nearly 15-fold less potent activity than **1**, because of the presumed masking effect of hydrophilic carboxylic acid function by the hydrophobic 2-chloro substituent, whereas 3- and/or 5-substituted benzoic acid analogs **4**–**6** without such a masking effect had equipotent antagonist activity with **1** regardless of their reduced receptor affinities.[10]

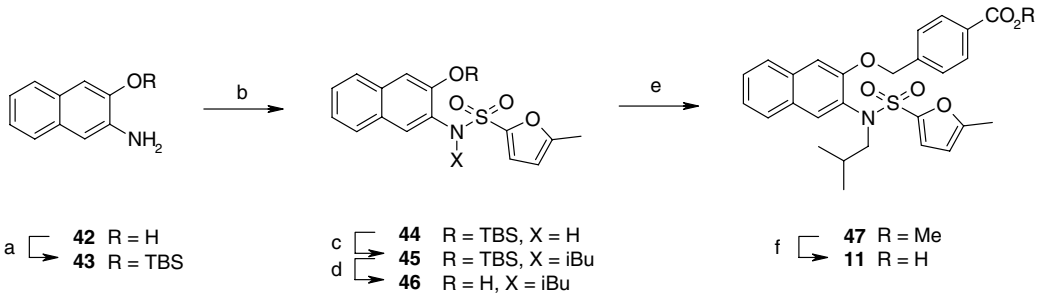
As reported in our previous paper,[6] the aminophenoxy moiety showed a tendency to prefer more hydrophobic substituents. Based on the information, 5-methyl analog **7** and 4,5-disubstituted analogs **8**–**13** were synthesized and evaluated. Table 4 shows the effect of substituting the aminophenoxy moiety on activity profiles. Replacement of the trifluoromethyl residue of **1** with a methyl residue afforded **7**, which had a 3.5-fold less potent receptor affinity and a 3-fold less potent antagonist activity. Introduction of another methyl residue into position 4 of the 2-aminophenoxy moiety of**7** produced **8**, which had a slightly more potent receptor affinity and a nearly 8-fold more potent antagonist activity. Indane analog **9** had nearly 3-fold less potent receptor affinity relative to **8**, but it had equipotent antagonist activity. Tetrahydronaphthalene analog **10** had slightly less potent activity relative to **9** with respect to both receptor affinity and antagonist activity. Naphthalene analog **11** had an increased receptor affinity relative to **10**, although it had a reduced antagonist activity. Introduction of another methyl residue into position 3 of the benzoic acid residue of **8** afforded **12**, which had a reduced receptor affinity but a similar antagonist activity. Introduction of another methyl residue into position 3 of the benzoic acid moiety of**9** produced**13**, which had a reduced receptor affinity but a nearly equipotent antagonist activity.



Scheme 3. Synthesis of **7**–**10** and **12**–**18**. Reagents: (a) methyl 4-(bromomethyl)benzoate, K_2CO_3, DMF; (b) **21c**, K_2CO_3, DMF; (c) Fe, AcOH, H_2O; (d) 5-methylfuran-2-sulfonyl chloride, pyridine, CH_2Cl_2; (e) thiazole-2-sulfonyl chloride, pyridine, CH_2Cl_2; (f) isobutyl iodide, Cs_2CO_3, DMA; (g) NaOH, MeOH, dioxane; (h) $NaNO_2$, HCl, MTBE.

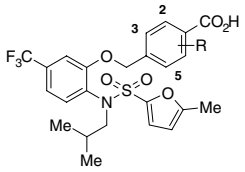
Table 5 shows the structure–activity relationships (SAR) of *N*-thiazole-2-sulfonyl analogs **14**–**18**, because *N*-thiazole-2-sulfonyl residue is one of the optimized heteroaryl sulfonyl residues as reported previously.[7] *N*-Thiazole-2-sulfonyl analogs **14**–**18** had equipotent to slightly more potent antagonist activity compared with their corresponding *N*-5-methylfuran-2-sulfonyl analogs **1**, **8**–**9**, and **12**–**13**, respectively, whereas their EP1 receptor affinities were not always consistent with the potency of their functional activities. In particular, *N*-thiazole-2-sulfonyl analogs **16**–**18** did not show increased functional activities in tandem with their increases in EP1 receptor affinities relative to their corresponding *N*-5-methylfuran-2-sulfonyl analogs **9** and **12** and **13**.

To study systemic potential of the selected compounds as EP1 receptor antagonist, they were evaluated with regard to the sulprostane-induced increase of intravesical bladder pressure in rats. Some of the analogs, **13** and **15**–**17**, which were selected on the basis of their in vitro



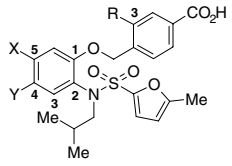
Scheme 4. Synthesis of **11**. Reagents: (a) TBSCl, imidazole, DMF; (b) 5-methylfuran-2-sulfonyl chloride, pyridine, CH_2Cl_2; (c) isobutanol, DEAD, PPh_3, THF; (d) TBAF, THF; (e) methyl 4-(bromomethyl)benzoate, K_2CO_3, DMF; (f) NaOH, MeOH, dioxane.

Table 3. Effect of the substitution of the benzoic acid moiety



Compound	R	Binding K_i (μM)				IC_{50} (μM)
		mEPl	mEP2	mEP3	mEP4	mEPl
3	2-Cl	0.0026	>10	0.057	>10	0.29
4	3-Cl	0.0035	2.6	0.062	>10	0.014
5	3-Me	0.0036	4.2	0.19	>10	0.015
6	3,5-DiMe	0.0072	5.8	0.18	>10	0.045

Table 4. Effect of substitution of the benzoic acid and aminophenoxy moieties



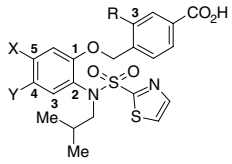
Compound	X	Y	R	Binding K_i (μM)				IC_{50} (μM)
				mEPl	mEP2	mEP3	mEP4	mEPl
7	Me	H	H	0.00070	>10	1.2	>10	0.058
8	Me	Me	H	0.00032	>10	0.34	>10	0.0072
9	–$(CH_2)_3$–		H	0.0011	3.6	0.32	>10	0.0074
10	–$(CH_2)_4$–		H	0.0017	2.0	1.9	>10	0.015
11	–(CH=CH)$_2$–		H	0.00071	2.6	0.70	>10	0.032
12	Me	Me	Me	0.0042	>10	>10	>10	0.0078
13	–$(CH_2)_3$–		Me	0.0051	3.3	0.34	>10	0.0041

EP1 receptor affinity, were evaluated for their in vivo potency after intraduodenal (id) administration as described in Table 6. These four analogs were found to be effective in an animal model after id administration (1 mg/kg). Their potency was equipotent or slightly more potent relative to **2**.

Table 7 describes the binding affinities of **13** and **15**–**17** for the other prostanoid receptors, hTP, hDP, mFP, and hIP. These analogs were also evaluated for their ability to antagonize the hEP1 receptor. As expected, all the compounds were proved to have potent hEP1 receptor antagonist activity, whereas **13** and **16**–**17** had weak affinity for the mFP receptor and **15** did not show any affinity at a concentration of 10 μM. As a result, all the selected analogs were found to be highly selective EP1 receptor antagonist.

As shown in Table 8, **13** and **15**–**17** were tested for their inhibition of cytochrome P450 isozymes.[11] Compound **13** produced 24% and 13% inhibition against 2C9 and 3A4, respectively, whereas **15** produced stronger inhibition (44%) against 2C9 and weaker inhibition (18%) against 2C19. Compound **17** exhibited weak inhibitory

Table 5. Activity profiles of *N*-thiazole-2-sulfonyl analogs



Compound	X	Y	R	Binding *N* (μM)				IC_{50} (μM)
				mEPl	mEP2	mEP3	mEP4	mEPl
14[7]	CF_3	H	H	0.00058	>10	0.73	>10	0.035
15	Me	Me	H	0.0013	>10	0.81	>10	0.0035
16	–$(CH_2)_3$–		H	0.00063	>10	0.72	>10	0.0040
17	Me	Me	Me	0.00039	5.6	0.56	>10	0.0043
18	–$(CH_2)_3$–		Me	0.00014	>10	2.6	6.6	0.0056

Table 6. In vivo efficacy of **13** and **15–17** with respect to the sulprostone-induced increase of intravesical bladder pressure in rats

Compound	In vivo EP1 function 1 mg/kg id (% inh)
1	37 ± 5
2	74 ± 13
13	77 ± 10
15	68 ± 7
16	82 ± 7
17	76 ± 9

Table 7. Receptor affinities of **13** and **15–17** for hTP, hDP, mFP, and hIP, and antagonist activities for the hEPl receptor

Compound	Binding K_i (μM)				IC_{50} (μM)
	hTP	hDP	mFP	hIP	hEPl
13	>10	>10	0.59	>10	0.0050
15	>10	>10	>10	>10	0.011
16	>10	>10	2.6	>10	0.0094
17	>10	>10	2.0	>10	0.0070

Table 8. Inhibitory activities of **13** and **15–17** against cytochrome P450 isozymes

Compound	P450 % inhibition (μM)				
	1A2	2C9	2C19	2D6	3A4
13	0.80	24	−0.40	−17.3	13
15	13	44	18	−2.3	3.1
16	8.9	47	14	−0.9	3.5
17	8.7	13	4.5	−4.8	9.7

activity (13%) against 2C9. Benzoic acid analogs **15** and **16** had significantly stronger inhibitory activity than **1**, and 3-methylbenzoic analogs **13** and **17** had equipotent to slightly less potent inhibitory activity against 2C9 relative to **15** and **16**. Analogs **13** and **15–17** had significantly weaker inhibitory activity against 2C9 and 2C19 relative to **2**. These analogs seem to be particularly promising as drug candidates because of their reduced inhibitory activity against 3A4, given that the 3A4 isozyme is known to metabolize many drugs.[12] On the basis of the data provided above, the potential risk of harmful drug interactions and/or risk of tolerance developing for **13** and **15–17** could be significantly less than that for **2**.

In conclusion, we have discovered EP1 receptor-selective antagonists **13** and **15–17**, which are promising clinical candidates, starting with a molecular design based on the structural hybridization of **1** and **2**, which show moderate in vivo activity with no P450 inhibition and an increased in vivo activity with strong P450 inhibition, respectively. The 4,5-dimethylbenzene moiety of **8**, **12**, **15**, and **17**, and the indane moiety of **9**, **13**, **16**, and **18** were newly identified as surrogates for a trifluoromethylbenzene moiety of **1** and **2**. As illustrated by **13** and **17**, 3-methylbenzoic acid analogs were found to have slightly reduced P450 inhibitory activity with preserved antagonist activity.

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), methyl *tert*-butyl ether (MTBE), dimethylsulfoxide (DMSO), ethyl acetate (EtOAc), dimethylformamide

(DMF), dichloromethane (CH_2Cl_2), diisopropylethylamine ($^iPr_2NEt$), chloroform ($CHCl_3$), methanol (MeOH), acetic acid (AcOH), hydrochloric acid (HCl), triethylamine (TEA), *tert*-butyl dimethylsilyl chloride (TBSCl), and tetrabutylammonium fluoride (TBAF).

4.2. Methyl 2-chloro-4-methylbenzoate (20a)

To a stirred suspension of **19a** (2.5 g, 17.5 mmol) and pyridine (2 mL) in CH_2Cl_2 (10 mL) was added triflic anhydride (3.5 mL, 21 mmol) at 0 °C under argon atmosphere. After being stirred for 4 h at room temperature, the reaction mixture was quenched with 1 N HCl and extracted with CH_2Cl_2. The organic layers were washed with aqueous $NaHCO_3$, water, and brine, dried over $MgSO_4$, and evaporated to afford a light yellow oil. To the stirred solution of the resultant and Et_3N (5.6 mL) in DMSO (53 mL) and MeOH (26 mL) were added $Pd(OAc)_2$ (121 mg, 0.54 mmol) and dppf (222 mg, 0.54 mmol) under carbon monoxide atmosphere. After being stirred for 2 h at 70 °C, the reaction mixture was quenched with water and extracted with EtOAc. The extract 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 **20a** (2.1 g, 62%). TLC $R_f = 0.59$ (EtOAc/hexane, 1:2); MS (APCI, Pos.) *m/e* 185 $(M+H)^+$.

4.3. Methyl 3-chloro-4-methylbenzoate (20b)

Compound **20b** was prepared from **19b** according to the same procedure as described for the preparation of **20a** from **19a**. Yield 88%; TLC $R_f = 0.64$ (EtOAc/hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.82 (d, $J = 7.5$ Hz, 1H), 7.30 (d, $J = 7.5$ Hz, 1H), 3.91 (s, 3H), 2.43 (s, 3H).

4.4. Methyl 4-(bromomethyl)-2-chlorobenzoate (21a)

To a stirred solution of **20a** (1 g, 5.4 mmol) in CCl_4 (10 mL) were added *N*-bromosuccinimide (1.06 g, 6.0 mmol) and benzoyl peroxide (13 mg, 0.054 mmol) under argon atmosphere. After being stirred for 5 h at reflux temperature, the resulting precipitates were removed by filtration and the filtrate was concentrated in vacuo to yield **21a** (1.86 g, 100%). TLC $R_f = 0.36$ (EtOAc/hexane, 1:5); ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, $J = 7.8$ Hz, 1H), 7.49 (s, 1H), 7.32 (d, $J = 7.8$ Hz, 1H), 4.43 (s, 2H), 3.93 (s, 3H).

4.5. Methyl 4-(bromomethyl)-3-chlorobenzoate (21b)

Compound **21b** was prepared from **20b** according to the same procedure as described for the preparation of **21a** from **20a**. Yield 100%; TLC $R_f = 0.56$ (EtOAc/hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.91 (d, $J = 8.1$ Hz, 1H), 7.52 (d, $J = 8.1$ Hz, 1H), 4.60 (s, 2H), 3.93 (s, 3H).

4.6. (4-Bromo-2-methylphenyl)methanol (23)

To a stirred suspension of $LiAlH_4$ (1.94 g, 51.2 mmol) in THF (50 mL) was added **22** (10 g, 46.5 mmol) under argon atmosphere. After being stirred for 10 min at room temperature, the reaction mixture was quenched with MeOH and aqueous Na_2SO_4. The resulting precipitates were removed by filtration 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 **23** (4.4 g, 47%). TLC $R_f = 0.41$ (EtOAc/hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.18 (m, 3H), 4.65 (s, 2H), 2.32 (s, 3H).

4.7. Methyl 4-(hydroxymethyl)-3-methylbenzoate (24)

Compound **24** was prepared from **23** according to the same procedure as described for the preparation of **20a** from **19a**. Yield 61%; TLC $R_f = 0.42$ (EtOAc/hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, $J = 8.1$ Hz, 1H), 7.85 (s, 1H), 7.48 (d, $J = 8.1$ Hz, 1H), 4.75 (s, 2H), 2.91 (s, 3H), 2.36 (s, 3H).

4.8. Methyl 4-(bromomethyl)-3-methylbenzoate (21c)

To a stirred solution of **24** (529 mg, 2.93 mmol) in MTBE (5 mL) was added PBr_3 (0.11 mL, 1.17 mmol) at −6 °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 aqueous $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated in vacuo to yield **21c** (672 mg, 95%). TLC $R_f = 0.78$ (EtOAc/hexane, 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.84 (d, $J = 7.8$ Hz, 1H), 7.37 (d, $J = 7.8$ Hz, 1H), 4.51 (s, 2H), 3.91 (s, 3H), 2.46 (s, 3H).

4.9. General procedure for the preparation of 2-aminophenols (34b–d)

4.9.1. 6-Nitroindan-5-ol (34c). To a stirred solution of $NaNO_3$ (63.3 g, 745 mmol) in water (90 mL) was added concd HCl (90 mL) below 10 °C. To this stirred solution was added a solution of **39c** (50 g, 373 mmol) in MTBE (150 mL) below 12 °C. After being stirred for 2.5 h at room temperature, the organic layer of the reaction mixture was diluted with toluene (500 mL). The organic layer was washed with aqueous Na_2CO_3 (2× 300 mL), water, and brine, dried over $MgSO_4$, and concentrated in vacuo to yield **34c** (32 g, 48%). TLC $R_f = 0.45$ (EtOAc/hexane, 1:4); ^1H NMR (300 MHz, $CDCl_3$) δ 10.73 (s, 1H), 7.91 (s, 1H), 6.98 (s, 1H), 2.96–2.86 (m, 4H), 2.17–2.07 (m, 2H).

Compounds **34b** and **34d** were prepared from **39b** and **39d**, respectively, according to the same procedure as described for the preparation of **34c** from **39c**.

4.9.2. 4,5-Dimethyl-2-nitrophenol (34b). Yield 33%; TLC $R_f = 0.50$ (EtOAc/hexane, 1:4); ^1H NMR (300 MHz, $CDCl_3$) δ 10.47 (s, 1H), 7.83 (s, 1H), 6.92 (s, 1H), 2.30 (s, 3H), 2.24 (s, 3H).

4.9.3. 3-Nitro-5,6,7,8-tetrahydronaphthalen-2-ol (34d). Yield 23%; TLC $R_f = 0.58$ (EtOAc/hexane, 1:9); ^1H NMR (300 MHz, $CDCl_3$) δ 10.36 (s, 1H), 7.80 (s, 1H), 6.48 (s, 1H), 2.82–2.65 (m, 4H), 1.85–1.70 (m, 4H).

4.10. General procedure for the preparation of methyl 4-[(2-nitrophenoxy)methyl]benzoate analogs (35a–f)

4.10.1. Methyl 4-[(5-methyl-2-nitrophenoxy)methyl]benzoate (35a). A heterogeneous mixture of **34a** (2 g, 13.1 mmol), methyl 4-(bromomethyl)benzene (3.3 g, 14.4 mmol), and K_2CO_3 (3.6 g, 26.1 mmol) in DMF (40 mL) was stirred at 50 °C. After being stirred for 4 h, the reaction mixture was diluted with EtOAc and precipitates were removed by filtration through a pad of Celite. The filtrate was concentrated in vacuo. The resulting residue was crystallized from EtOAc and hexane to yield **35a** (3.03 g, 77%). TLC $R_f = 0.24$ (EtOAc/hexane, 1:5); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.07 (d, $J = 8.0$ Hz, 2H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.56 (d, $J = 8.0$ Hz, 2H), 6.90 (s, 1H), 6.86 (d, $J = 8.0$ Hz, 1H), 5.27 (s, 2H), 3.93 (s, 3H), 2.40 (s, 3H).

Compounds **35b–d** were prepared from **34b–d**, respectively, according to the same procedure as described for the preparation of **35a** from **34a**.

4.10.2. Methyl 4-[(4,5-dimethyl-2-nitrophenoxy)methyl]benzoate (35b). Yield 81%; TLC $R_f = 0.32$ (EtOAc/hexane, 1:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, $J = 8.4$ Hz, 2H), 7.72 (s, 1H), 7.55 (d, $J = 8.4$ Hz, 2H), 6.87 (s, 1H), 5.25 (s, 2H), 3.93 (s, 3H), 2.29 (s, 3H), 2.24 (s, 3H).

4.10.3. Methyl 4-{[(6-nitro-2,3-dihydro-1*H*-inden-5-yl)oxy]methyl}benzoate (35c). Yield 100%; TLC $R_f = 0.34$ (EtOAc/hexane, 1:4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, $J = 8.7$ Hz, 2H), 7.74 (s, 1H), 7.55 (d, $J = 8.7$ Hz, 2H), 6.95 (s, 1H), 5.25 (s, 2H), 3.92 (s, 3H), 2.98–2.87 (m, 4H), 2.13 (m, 2H).

4.10.4. Methyl 4-{[(3-nitro-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]methyl}benzoate (35d). Yield 96%; TLC $R_f = 0.46$ (EtOAc/hexane, 3:7); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, $J = 8.7$ Hz, 2H), 7.65 (s, 1H), 7.55 (d, $J = 8.7$ Hz, 2H), 6.76 (s, 1H), 5.23 (s, 2H), 3.92 (s, 3H), 2.80–2.68 (m, 4H), 1.83–1.75 (m, 4H).

Compounds **35e–f** were prepared from **34b–c**, respectively, according to the same procedure as described for the preparation of **35a** from **34a** using **21c** instead of methyl 4-(bromomethyl)benzoate.

4.10.5. Methyl 4-[(4,5-dimethyl-2-nitrophenoxy)methyl]-3-methylbenzoate (35 e). Yield 95%; TLC $R_f = 0.46$ (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, $J = 8.1$ Hz, 1H), 7.88 (s, 1H), 7.71 (s, 1H), 7.63 (d, $J = 8.1$ Hz, 1H), 6.90 (s, 1H), 5.17 (s, 2H), 3.91 (s, 3H), 2.30 (s, 3H), 2.31 (s, 3H), 2.24 (s, 3H).

4.10.6. Methyl 3-methyl-4-{[(6-nitro-2,3-dihydro-1*H*-inden-5-yl)oxy]methyl}benzoate (35f). Yield 98%; TLC $R_f = 0.38$ (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98–7.83 (m, 2H), 7.74 (s, 1H), 7.62 (d, $J = 7.7$ Hz, 1H), 6.98 (s, 1H), 5.18 (s, 2H), 3.98 (s, 3H), 3.05–2.81 (m, 4H), 2.41 (s, 3H), 2.25–2.02 (m, 2H).

4.11. General procedure for the preparation of methyl 4-[(2-aminophenoxy)methyl]benzoate analogs (36a–f)

4.11.1. Methyl 4-[(2-amino-5-methylphenoxy)methyl]benzoate (36a). To a stirred solution of **35a** (3 g, 9.97 mmol) in AcOH (20 mL) and water (2 mL) was added iron powder (2.78 g, 49.8 mmol) under argon atmosphere. After being stirred for 1 h, the reaction mixture was diluted with EtOAc and the precipitates were removed by filtration through a pad of Celite. The filtrate was washed with aqueous $NaHCO_3$ (3×), water, brine, dried over $MgSO_4$ and concentrated in vacuo to yield **36a** (2.71 g, 100%). TLC $R_f = 0.47$ (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, $J = 8.7$ Hz, 2H), 7.51 (d, $J = 8.7$ Hz, 2H), 6.70–6.60 (m, 3H), 5.13 (s, 2H), 3.93 (s, 3H), 3.71 (br s, 2H), 2.24 (s, 3H).

Compounds **36b–f** were prepared from **35b–f**, respectively, according to the same procedure as described for the preparation of **36a** from **35a**.

4.11.2. Methyl 4-[(2-amino-4,5-dimethylphenoxy)methyl]benzoate (36b). Yield 100%; TLC $R_f = 0.32$ (EtOAc/hexane, 1:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, $J = 8.4$ Hz, 2H), 7.50 (d, $J = 8.4$ Hz, 2H), 6.67 (s, 1H), 6.57 (s, 1H), 5.11 (s, 2H), 3.93 (s, 3H), 3.66 (br s, 2H), 2.14 (s, 6H).

4.11.3. Methyl 4-{[(6-amino-2,3-dihydro-1*H*-inden-5-yl)oxy]methyl}benzoate (36c). Yield 100%; TLC $R_f = 0.42$ (EtOAc/hexane, 3:7); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, $J = 8.7$ Hz, 2H), 7.53 (d, $J = 8.7$ Hz, 2H), 6.93 (s, 1H), 6.77 (s, 1H), 5.16 (s, 2H), 3.93 (s, 3H), 2.82 (t, $J = 7.5$ Hz, 4H), 2.68 (br, 2H), 2.12–1.98 (m, 2H).

4.11.4. Methyl 4-{[(3-amino-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]methyl}benzoate (36d). Yield 79%; TLC $R_f = 0.41$ (EtOAc/hexane, 3:7); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, $J = 8.7$ Hz, 2H), 7.50 (d, $J = 8.7$ Hz, 2H), 6.52 (s, 1H), 6.47 (s, 1H), 5.10 (s, 2H), 3.93 (s, 3H), 3.92–3.40 (br, 2H), 2.67–2.57 (m, 4H), 1.80–1.67 (m, 4H).

4.11.5. Methyl 4-[(2-amino-4,5-dimethylphenoxy)methyl]-3-methylbenzoate (36e). Yield 100%; TLC $R_f = 0.44$ (EtOAc/hexane, 3:7) ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.88 (d, $J = 8.1$ Hz, 1H), 7.52 (d, $J = 8.1$ Hz, 2H), 6.65 (s, 1H), 6.57 (s, 1H), 5.06 (s, 2H), 3.92 (s, 3H), 3.63 (br s, 2H), 2.41 (s, 3H), 2.16 (s, 3H), 2.14 (s, 3H).

4.11.6. Methyl 4-{[(6-amino-2,3-dihydro-1*H*-inden-5-yl)oxy]methyl}-3-methylbenzoate (36f). Yield 96%; TLC $R_f = 0.33$ (AcOEt/toluene, 1:9); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.80 (m, 2H), 7.51 (d, $J = 8.4$ Hz, 1H), 6.75 (s, 1H), 6.66 (s, 1H), 5.06 (s, 2H), 3.91 (s, 3H), 3.48 (s, 2H), 2.14–1.94 (m, 2H), 2.88–2.71 (m, 4H), 2.40 (s, 3H).

4.12. General procedure for the preparation of methyl 4-({2-[(arylsulfonyl)amino]phenoxy}methyl)benzoate analogs (37a–j)

4.12.1. Methyl 4-[(5-methyl-2-{[(5-methyl-2-furyl)sulfonyl]amino}phenoxy)methyl]benzoate (37a). To a stirred solution of **36a** (2.08 g, 7.68 mmol) and pyridine (1.55 mL) in CH_2Cl_2 (8 mL) was added a solution of 5-methylfuran-2-sulfonyl chloride (1.66 mg, 9.22 mmol) in CH_2Cl_2 (2 mL) at room temperature under argon atmosphere. The reaction mixture was stirred for 1 h, quenched with water, and extracted with EtOAc. The organic layer was washed with water, brine, dried over $MgSO_4$, and evaporated in vacuo to yield **37a** (2.95 g, 92%). TLC $R_f = 0.38$ (EtOAc/hexane, 3:7); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, $J = 8.4$ Hz, 2H), 7.41 (d, $J = 8.1$ Hz, 1H), 7.38 (d, $J = 8.4$ Hz, 2H), 7.02 (s, 1H), 6.84 (d, $J = 3.3$ Hz, 1H), 6.75 (d, $J = 8.1$ Hz, 1H), 6.62 (s, 1H), 6.00 (d, $J = 3.3$ Hz, 1H), 5.06 (s, 2H), 3.94 (s, 3H), 2.26 (s, 3H), 2.22 (s, 3H).

Compounds **37b–f** were prepared from **36b–f**, respectively, according to the same procedure as described for the preparation of **37a** from **36a**.

4.12.2. Methyl 4-[(4,5-dimethyl-2-{[(5-methyl-2-furyl)sulfonyl]amino}phenoxy)methyl]benzoate (37b). Yield 69%; TLC $R_f = 0.50$ (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07–8.03 (m, 2H), 7.37 (d, $J = 8.7$ Hz, 2H), 7.30 (s, 1H), 6.97 (s, 1H), 6.84 (d, $J = 3.3$ Hz, 1H), 6.58 (s, 1H), 6.00 (dd, $J = 3.3$, 0.9 Hz, 1H), 5.02 (s, 2H), 3.94 (s, 3H), 2.21 (s, 3H), 2.17 (s, 3H), 2.15 (s, 3H).

4.12.3. Methyl 4-{[(6-{[(5-methyl-2-furyl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-5-yl)oxy]methyl}benzoate (37c). Yield 88%; TLC $R_f = 0.32$ (EtOAc/hexane, 3:7); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, $J = 8.4$ Hz, 2H), 7.40–7.36 (m, 3H), 7.03 (s, 1H), 6.85 (d, $J = 3.3$ Hz, 1H), 6.67 (s, 1H), 6.01 (m, 1H), 5.04 (s, 2H), 3.94 (s, 3H), 2.87–2.75 (m, 4H), 2.22 (s, 3H), 2.09–1.98 (m, 2H).

4.12.4. Methyl 4-{[(3-{[(5-methyl-2-furyl)sulfonyl]amino}-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]methyl}benzoate (37d). Yield 98%; TLC $R_f = 0.32$ (EtOAc/hexane, 3:7); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, $J = 8.7$ Hz, 2H), 7.37 (d, $J = 8.7$ Hz, 2H), 7.21 (s, 1H), 6.99 (s, 1H), 6.87 (d, $J = 3.3$ Hz, 1H), 6.48 (s, 1H), 6.00 (m, 1H), 5.02 (s, 2H), 3.94 (s, 3H), 2.71–2.58 (m, 4H), 2.22 (s, 3H), 1.80–1.67 (m, 4H).

4.12.5. Methyl 4-[(2-{[(5-methyl-2-furyl)sulfonyl]amino}-4,5-dimethylphenoxy)methyl]-3-methylbenzoate (37e). Yield 100%; TLC $R_f = 0.42$ (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.88 (d, $J = 7.8$ Hz, 1H), 7.32 (d, $J = 7.8$ Hz, 1H), 7.31 (s, 1H), 6.95 (br s, 1H), 6.85 (d, $J = 3.6$ Hz, 1H), 6.61 (s, 1H), 6.00 (m, 1H), 4.98 (s, 2H), 3.93 (s, 3H), 2.36 (s, 3H), 2.20 (s, 3H), 2.18 (s, 3H), 2.17 (s, 3H).

4.12.6. Methyl 3-methyl-4-{[(6-{[(5-methyl-2-furyl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-5-yl)oxy]methyl}benzoate (37f). Yield 64%; TLC $R_f = 0.56$ (EtOAc/toluene, 1:4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.87 (d, $J = 8.0$ Hz, 1H), 7.40 (s, 1H), 7.32 (d, $J = 8.0$ Hz, 1H), 7.02 (s, 1H), 6.86 (d, $J = 3.3$ Hz, 1H), 6.70 (s, 1H), 6.05–6.00 (m, 1H), 4.99 (s, 2H), 3.93 (s, 3H), 2.90–2.75 (m, 4H), 2.36 (s, 3H), 2.21 (s, 3H), 2.10–2.00 (m, 2H).

Compounds **37g–j** were prepared from **36b–c** and **e–f**, respectively, according to the same procedure as described for the preparation of **37a** from **36a** using thiazole-2-sulfonyl chloride instead of 5-methylfurane-2-sulfonyl chloride.

4.12.7. Methyl 4-({4,5-dimethyl-2-[(1,3-thiazol-2-ylsulfonyl)amino]phenoxy}methyl)benzoate (37g). Yield 72%; TLC $R_f = 0.58$ (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, $J = 8.4$ Hz, 2H), 7.89 (d, $J = 3.0$ Hz, 1H), 7.53 (d, $J = 3.0$ Hz, 1H), 7.40 (s, 1H), 7.32 (d, $J = 8.4$ Hz, 2H), 6.55 (s, 1H), 4.97 (s, 2H), 3.94 (s, 3H), 2.18 (s, 3H), 2.14 (s, 3H).

4.12.8. Methyl 4-[({6-[(1,3-thiazol-2-ylsulfonyl)amino]-2,3-dihydro-1*H*-inden-5-yl}oxy)methyl]benzoate (37h). Yield 66%; TLC $R_f = 0.40$ (EtOAc/hexane, 2:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06–8.01 (m, 2H), 7.90 (d, $J = 3.3$ Hz, 1H), 7.54 (d, $J = 3.3$ Hz, 1H), 7.49 (s, 1H), 7.33 (d, $J = 8.7$ Hz, 2H), 7.27 (m, 1H), 6.64 (s, 1H), 4.98 (s, 2H), 3.94 (s, 3H), 2.85 (t, $J = 7.5$ Hz, 2H), 2.79 (t, $J = 7.5$ Hz, 2H), 2.10–1.98 (m, 2H).

4.12.9. Methyl 4-({4,5-dimethyl-2-[(1,3-thiazol-2-ylsulfonyl)amino]phenoxy}methyl)-3-methylbenzoate (37i). Yield 96%; TLC $R_f = 0.30$ (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92–7.80 (m, 3H), 7.52 (d, $J = 3.3$ Hz, 1H), 7.42 (s, 1H), 7.30–7.12 (m, 2H), 6.95 (s, 1H), 4.93 (s, 2H), 3.93 (s, 3H), 2.33 (s, 3H), 2.19 (s, 3H), 2.17 (s, 3H).

4.12.10. Methyl 3-methyl-4-[({6-[(1,3-thiazol-2-ylsulfonyl)amino]-2,3-dihydro-1*H*-inden-5-yl}oxy)methyl]benzoate (37j). Yield 57%; TLC $R_f = 0.22$ (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.87 (d, $J = 3.0$ Hz, 1H), 7.86 (d, $J = 8.7$ Hz, 1H), 7.54 (d, $J = 3.0$ Hz, 1H), 7.51 (s, 1H), 7.26 (s, 1H), 7.25 (d, $J = 8.7$ Hz, 1H), 6.68 (s, 1H), 4.94 (s, 2H), 3.93 (s, 3H), 2.90–2.76 (m, 4H), 2.33 (s, 3H), 2.11–1.98 (m, 2H).

4.13. General procedure for the preparation of methyl 4-({2-[(arylsulfonyl)(isobutyl)amino]phenoxy}methyl)benzoate analogs (38a–j)

4.13.1. Methyl 4-[(2-{isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-methylphenoxy)methyl]benzoate (38a). To a stirred solution of **37a** (1 g, 2.41 mmol) in DMA (5 mL) were added Cs_2CO_3 (1.73 g, 5.30 mmol) and isobutyl iodide (0.40 mL, 3.62 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 **38a**

(1.13 g, 100%). TLC $R_f = 0.48$ (EtOAc/hexane, 3:7); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, $J = 8.4$ Hz, 2H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.16 (d, $J = 7.5$ Hz, 1H), 6.78 (m, 1H), 6.72–6.68 (m, 2H), 5.92 (m, 1H), 5.10–4.90 (m, 2H), 3.93 (s, 3H), 3.49 (d, $J = 7.2$ Hz, 2H), 2.32 (s, 3H), 2.12 (s, 3H), 1.67 (m, 1H), 0.91 (d, $J = 6.6$ Hz, 3H), 0.90 (d, $J = 6.6$ Hz, 3H).

Compounds **38b–j** were prepared from **37b–j**, respectively, according to the same procedure as described for the preparation of **38a** from **37a**.

4.13.2. Methyl 4-[(2-{isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-4,5-dimethylphenoxy)methyl]benzoate (38b). Yield 98%; TLC $R_f = 0.39$ (EtOAc/hexane, 1:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, $J = 8.1$ Hz, 2H), 7.37 (d, $J = 8.1$ Hz, 2H), 7.04 (s, 1H), 6.70 (d, $J = 3.3$ Hz, 1H), 6.68 (s, 1H), 5.92 (m, 1H), 4.98 (br s, 2H), 3.93 (s, 3H), 3.48 (d, $J = 6.6$ Hz, 2H), 2.21 (s, 3H), 2.18 (s, 3H), 2.11 (s, 3H), 1.67 (m, 1H), 0.92 (d, $J = 6.6$ Hz, 6H).

4.13.3. Methyl 4-{[(6-{isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-5-yl)oxy]methyl}benzoate (38c). Yield 100%; TLC $R_f = 0.44$ (EtOAc/hexane, 3:7); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, $J = 8.4$ Hz, 2H), 7.38 (d, $J = 8.4$ Hz, 2H), 7.12 (s, 1H), 6.76 (s, 1H), 6.71 (d, $J = 3.3$ Hz, 1H), 5.93 (m, 1H), 5.15–4.80 (m, 2H), 3.93 (s, 3H), 3.60–3.40 (m, 2H), 2.85 (t, $J = 7.2$ Hz, 4H), 2.18 (s, 3H), 2.15–2.00 (m, 2H), 1.67 (m, 1H), 1.00–0.82 (br s, 6H).

4.13.4. Methyl 4-{[(3-{isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]methyl}benzoate (38d). Yield 100%; TLC $R_f = 0.44$ (EtOAc/hexane, 3:7); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, $J = 8.4$ Hz, 2H), 7.37 (d, $J = 8.4$ Hz, 2H), 6.96 (s, 1H), 6.71 (d, $J = 3.3$ Hz, 1H), 6.56 (s, 1H), 5.92 (m, 1H), 5.05–4.87 (m, 2H), 3.93 (s, 3H), 3.47 (d, J = 7.5 Hz, 2H), 2.74–2.60 (m, 4H), 2.11 (s, 3H), 1.82–1.60 (m, 5H), 0.91 (d, $J = 6.3$ Hz, 6H).

4.13.5. Methyl 4-[(2-{isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-4,5-dimethylphenoxy)methyl]-3-methylbenzoate (38e). Yield 95%; TLC $R_f = 0.54$ (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89–7.85 (m, 2H), 7.38 (d, $J = 8.1$ Hz, 1H), 7.04 (s, 1H), 6.73–6.69 (m, 2H), 5.93 (d, $J = 3.3$, 0.9 Hz, 1H), 4.91 (br, 2H), 3.92 (s, 3H), 3.48 (d, $J = 6.6$ Hz, 2H), 2.35 (s, 3H), 2.23 (s, 3H), 2.18 (s, 3H), 2.09 (s, 3H), 1.67 (sept, $J = 6.6$ Hz, 1H), 0.90 (d, $J = 6.6$ Hz, 6H).

4.13.6. Methyl 4-{[(6-{isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-5-yl)oxy]methyl}-3-methylbenzoate (38f). Yield 86%; TLC $R_f = 0.48$ (EtOAc/hexane, 3:7); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90–7.80 (m, 2H), 7.40 (d, $J = 8.7$ Hz, 1H), 7.12 (s, 1H), 6.78 (s, 1H), 6.71 (d, $J = 3.3$ Hz, 1H), 5.95–5.90 (m, 1H), 5.00–4.80 (m, 2H), 3.92 (s, 3H), 3.49 (br, 2H), 2.87 (t, $J = 7.5$ Hz, 4H), 2.34 (s, 3H), 2.15–2.00 (m, 5H), 1.80–1.60 (m, 1H), 0.90 (br s, 6H).

4.13.7. Methyl 4-({2-[isobutyl(1,3-thiazol-2-ylsulfonyl)amino]-4,5-dimethylphenoxy}methyl)-3-methylbenzoate (38g). Yield 84%; TLC $R_f = 0.70$ (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, $J = 8.7$ Hz, 2H), 7.67 (d, $J = 3.0$ Hz, 1H), 7.32 (d, $J = 3.0$ Hz, 1H), 7.27 (d, $J = 8.7$ Hz, 2H), 7.07 (s, 1H), 6.65 (s, 1H), 5.00–4.65 (m, 2H), 3.94 (s, 3H), 3.80–3.68 (m, 2H), 2.21 (s, 3H), 2.17 (s, 3H), 1.70 (sept, $J = 6.9$ Hz, 1H), 1.10–0.86 (m, 6H).

4.13.8. Methyl 4-[({6-[isobutyl(1,3-thiazol-2-ylsulfonyl)amino]-2,3-dihydro-1*H*-inden-5-yl}oxy)methyl]benzoate (38h). Yield 73%; TLC $R_f = 0.75$ (EtOAc/toluene, 1:4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, $J = 8.4$ Hz, 2H), 7.68 (d, $J = 3.0$ Hz, 1H), 7.33 (d, $J = 3.0$ Hz, 1H), 7.29 (d, $J = 8.4$ Hz, 2H), 7.15 (s, 1H), 6.74 (s, 1H), 5.00–4.90 (m, 1H), 4.80–4.70 (m, 1H), 3.94 (s, 3H), 3.80–3.63 (m, 1H), 3.63–3.50 (m, 1H), 2.85 (t, $J = 7.2$ Hz, 4H), 2.20–2.00 (m, 2H), 1.80–1.60 (m, 1H), 1.05–0.85 (m, 6H).

4.13.9. Methyl 4-({2-[isobutyl(1,3-thiazol-2-ylsulfonyl)amino]-4,5-dimethylphenoxy}methyl)-3-methylbenzoate (38i). Yield 66%; TLC $R_f = 0.25$ (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90–7.82 (m, 2H), 7.67 (d, $J = 3.0$ Hz, 1H), 7.32 (d, $J = 3.0$ Hz, 1H), 7.26–7.20 (m, 1H), 7.06 (s, 1H), 6.68 (s, 1H), 4.95–4.65 (m, 2H), 3.93 (s, 3H), 3.75–3.45 (m, 2H), 2.32 (s, 3H), 2.23 (s, 3H), 2.18 (s, 3H), 1.78–1.62 (m, 1H), 1.05–0.82 (m, 6H).

4.13.10. Methyl 4-[({6-[isobutyl(1,3-thiazol-2-ylsulfonyl)amino]-2,3-dihydro-1*H*-inden-5-yl}oxy)methyl]-3-methylbenzoate (38j). Yield 93%; TLC $R_f = 0.43$ (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, $J = 7.8$ Hz, 1H), 7.85 (s, 1H), 7.68 (d, $J = 3.0$ Hz, 1H), 7.33 (d, $J = 3.0$ Hz, 1H), 7.25 (d, $J = 7.8$ Hz, 1H), 7.15 (s, 1H), 6.76 (s, 1H), 4.97–4.60 (m, 2H), 3.93 (s, 3H), 3.80–3.44 (m, 2H), 2.94–2.77 (m, 4H), 2.31 (2, 3H), 2.16–2.00 (m, 2H), 1.81–1.64 (m, 1H), 1.08 –0.78 (m, 6H).

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

A heterogeneous mixture of **21a** (464 mg, 1.32 mmol), **25** (226 mg, 0.60 mmol), and K_2CO_3 249 mg (1.8 mmol) in acetone 2.4 mL was stirred under argon atmosphere. After being stirred for 7 h at 50 °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 **26a** (227 mg, 68%). TLC $R_f = 0.38$ (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.88 (d, $J = 6.9$ Hz, 1H), 7.41 (d, $J = 6.9$ Hz, 1H), 7.39 (d, $J = 6.9$ Hz, 1H), 7.26 (dd, $J = 6.9$, 1.5 Hz, 1H), 7.18 (d, $J = 1.5$ Hz, 1H), 6.73 (d, $J = 3.3$ Hz, 1H), 6.00–6.85 (m, 1H), 5.01 (s, 2H), 3.93 (s, 3H), 3.49 (d, $J = 7.2$ Hz, 2H), 2.39 (s, 3H), 2.13 (d, $J = 0.6$ Hz,

3H), 1.70–1.55 (m, 1H), 0.88 (d, $J = 6.6$ Hz, 6H); MS (MALDI, Pos.) *m/e* 582 $(M+Na)^+$.

4.15. Methyl 3-chloro-4-{[2-{isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoate (26b)

Compound **26b** was prepared from **21b** and **25** according to the same procedure as described for the preparation of **26a** from **21a** and **25**. Yield 81%; TLC $R_f = 0.50$ (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.98 (d, $J = 8.4$ Hz, 1H), 7.58 (d, $J = 8.4$ Hz, 1H), 7.43 (d, $J = 8.1$ Hz, 1H), 7.33–7.25 (m, 1H), 7.19 (s, 1H), 6.77 (d, $J = 3.3$ Hz, 1H), 5.99 (d, $J = 3.3$ Hz, 1H), 5.20–5.07 (m, 2H), 3.95 (s, 3H), 3.52 (d, $J = 7.5$ Hz, 2H), 2.17 (s, 3H), 1.72–1.60 (m, 1H), 0.90 (d, $J = 6.6$ Hz, 6H).

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

Compound **26c** was prepared from **21c** and **25** according to the same procedure as described for the preparation of **26a** from **21a** and **25**. Yield 61%; TLC $R_f = 0.38$ (EtOAc/hexane, 1:3).

4.17. 3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-naphthylamine (43)

To a stirred solution of **42** (635 mg, 3.99 mmol) and imidazole (310 mg, 4.55 mmol) in DMF (88 mL) was added TBSCl (686 mg, 4.55 mmol) under argon atmosphere. After being stirred overnight at room temperature, 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 **43** (950 mg, 87%). TLC $R_f = 0.76$ (EtOAc/hexane, 1:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (t, $J = 8.1$ Hz, 2H), 7.29–7.15 (m, 2H), 7.08 (s, 1H), 7.03 (s, 1H), 1.06 (s, 9H), 0.32 (s, 6H).

4.18. *N*-(3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-naphthyl)-5-methylfuran-2-sulfonamide (44)

Compound **44** was prepared from **43** according to the same procedure as described for the preparation of **38a** from **37a**. Yield 86%; TLC $R_f = 0.60$ (EtOAc/hexane, 1:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.76–7.67 (m, 1H), 7.40–7.30 (m, 3H), 7.10 (s, 1H), 7.01 (d, $J = 3.6$ Hz, 1H), 6.00–5.96 (m, 1H), 2.25 (s, 3H), 1.08 (s, 9H), 0.31 (s, 6H).

4.19. *N*-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-naphthyl)-*N*-isobutyl-5-methylfuran-2-sulfonamide (45)

To a stirred solution of 44 (344 mg, 0.82 mmol), isobutanol (0.23 mL, 2.5 mmol), and PPh_3 (648 mg, 2.5 mmol) in THF (1 mL) was added 40% solution of DEAD in toluene (1.12 mL, 2.5 mmol) at room temperature under argon atmosphere. After being stirred overnight, the reaction mixture was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **45** (390 mg, 100%). TLC $R_f = 0.68$ (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.62 (m, 2H), 7.51 (s, 1H), 7.46–7.39 (m, 1H), 7.36–7.28 (m, 1H), 7.21 (s 1H), 6.78(d, $J = 3.3$ Hz, 1H), 6.11–6.07 (m, 1H), 3.65–3.43 (m, 2H), 2.40 (s, 3H), 1.74–1.66 (m, 1H), 1.07 (s, 9H), 0.94–0.80 (m, 6H), 0.35 (s, 6H).

4.20. *N*-(3-Hydroxy-2-naphthyl)-*N*-isobutyl-5-methylfuran-2-sulfonamide (46)

To a stirred solution of **45** (382 mg 0.81 mmol) in THF (2 mL) was added 1 M solution of TBAF in THF (0.97 mL, 0.97 mmol). After being stirred for 1 h at room temperature, 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 **46** (211 mg, 73%). TLC $R_f = 0.43$ (EtOAc/toluene, 1:9); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, $J = 8.1$ Hz, 1H), 7.56 (d, $J = 8.1$ Hz, 1H), 7.48–7.40 (m, 1H), 7.41 (s, 1H), 7.34–7.27 (m, 1H), 7.17 (s, 1H), 6.78 (d, $J = 3.3$ Hz, 1H), 6.50 (s, 1H), 6.13–6.09 (m, 1H), 3.96–3.18 (m, 2H), 2.41 (s, 3H), 1.74–1.60 (m, 1H), 1.13–0.77 (m, 6H).

4.21. Methyl 4-{[(3-{isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-2-naphthyl)oxy]methyl}benzoate (47)

Compound **47** was prepared from **46** according to the same procedure as described for the preparation of **35a** from **34a**. Yield 88%; TLC $R_f = 0.35$ (EtOAc/toluene, 1:9); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, $J = 8.7$ Hz, 2H), 7.79 (s, 1H), 7.77 (d, $J = 7.8$ Hz, 1H), 7.69 (d, $J = 7.8$ Hz, 1H), 7.51–7.34 (m, 2H), 7.51–7.34 (m, 2H), 7.17 (s, 1H), 6.69 (d, $J = 3.3$ Hz, 1H), 5.97–5.92 (m, 1H), 5.29–4.95 (m, 2H), 3.94 (s, 3H), 3.75–3.46 (m, 2H), 2.14 (s, 3H), 1.79–1.64 (m, 1H), 1.02–0.82 (m, 6H).

4.22. General procedure for the preparation of 4-({2-[(arylsulfonyl)(isobutyl)amino]phenoxy}methyl)benzoic acids (3–5, 7–13, and 15–18)

4.22.1. 2-Chloro-4-{[2-{isobutyl[(5-methyl-2- furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (3). To a stirred solution of **26a** (225 mg, 0.40 mmol) in MeOH (2 mL) and dioxane (2 mL) was added 1 N NaOH (1.2 mL, 1.2 mmol) at room temperature. After being stirred for 1.5 h, the reaction mixture was quenched with 1 N HCl and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated in vacuo to yield **3** (188 mg, 86%). TLC $R_f = 0.33$ (MeOH/$CHCl_3$, 1:7); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, $J = 7.8$ Hz, 1H), 7.49 (s, 1H), 7.45–7.34 (m, 2H), 7.32–7.22 (m, 1H), 7.16 (s, 1H), 6.80–6.00 (m, 2H), 5.06 (br s, 2H), 3.49 (d, $J = 7.2$ Hz, 2H), 2.19 (s, 3H), 1.72–1.57 (m, 1H), 0.90 (d, $J = 6.6$ Hz, 6H); IR (KBr) 3428, 2964, 1704, 1609, 1508, 1429, 1332, 1256, 1211, 1173, 1134, 1084,

1049 cm^{-1}; MS (FAB, Pos.) *m/e* 546 $(M+H)^+$; HRMS (Pos.) calcd for $C_{24}H_{24}ClF_3NO_6S$: 546.0965; found: 546.0927.

Compounds **4**–**5**, **7**–**13**, and **15**–**18** were prepared from **26b**–**c**, **38a**–**d**, **47**, and **38e**–**j**, respectively, according to the same procedure as described for the preparation of **3** from **26a**.

4.22.2. 3-Chloro-4-{[2-{isobutyl[(5-methyl-2- furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (4). Yield 87%; TLC R_f = 0.28 ($MeOH/CHCl_3$, 1:9); ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J = 1.5 Hz, 1H), 8.05 (dd, J = 8.1, 1.5 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.32–7.15 (m, 2H), 6.78 (d, J = 3.3 Hz, 1H), 6.00 (d, J = 3.3 Hz, 1H), 5.23–5.09 (m, 2H), 3.52 (d, J = 7.5 Hz, 2H), 2.19 (s, 3H), 1.63–1.59 (m, 1H), 0.90 (d, J = 6.9 Hz, 6H); IR (KBr) 2963, 1692, 1510, 1430, 1334, 1132, 1043 cm^{-1}; MS (FAB, Pos.) *m/e* 546 $(M+H)^+$; Anal. Calcd for $C_{24}H_{23}ClF_3NO_6S$: C, 52.80; H, 4.25; N, 2.57; S, 5.87. Found: C, 53.08; H, 4.26; N, 2.42; S, 5.84.

4.22.3. 4-{[2-{Isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy]methyl}-3-methylbenzoic acid (5). Yield 61%; TLC R_f = 0.40 ($MeOH/CHCl_3$, 1:10); ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.20 (s, 1H), 6.76 (d, J = 3.6 Hz, 1H), 5.99 (dd, J = 3.6, 1.2 Hz, 1H), 5.05 (s, 2H), 3.50 (d, J = 7.5 Hz, 2H), 2.41 (s, 3H), 2.15 (s, 3H), 1.64 (m, 1H), 0.88 (d, J = 6.6 Hz, 6H); IR (KBr) 2964, 1685, 1509, 1429, 1334, 1217, 1164, 1133, 1046 cm^{-1}; MS (APCI, Neg.) *m/e* 524 $(M-H)^-$; Anal. Calcd for $C_{25}H_{26}F_3NO_6S$: C, 57.14; H, 4.99; N, 2.67; S, 6.10. Found: C, 57.30; H, 5.05; N, 2.62; S, 6.25.

4.22.4. 4-[(2-{Isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-methylphenoxy)methyl]benzoic acid (7). Yield 67%; TLC R_f = 0.56 ($MeOH/CHCl_3$, 1:9); ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.1 Hz, 1H), 6.79 (m, 1H), 6.75–6.69 (m, 2H), 5.94 (m, 1H), 5.20–4.85 (m, 2H), 3.51 (d, J = 7.2 Hz, 2H), 2.33 (s, 3H), 2.14 (s, 3H), 1.67 (m, 1H), 0.91 (d, J = 6.6 Hz, 6H); IR (KBr) 3434, 2962, 2924, 2870, 1687, 1608, 1506, 1420, 1359, 1314, 1287, 1180, 1129, 1072, 1044, 1019 cm^{-1}; MS (APCI, Neg.) *m/e* 524 $(M-H)^-$; Anal. Calcd for $C_{24}H_{27}NO_6S$: C, 63.00; H, 5.95; N, 3.06; S, 7.01. Found: C, 62.69; H, 5.97; N, 3.19; S, 6.96.

4.22.5. 4-[(2-{Isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-4,5- dimethylphenoxy)methyl]benzoic acid (8). Yield 77%; TLC R_f = 0.38 ($MeOH/CHCl_3$, 1:109); ^1H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H), 7.04 (s, 1H), 6.72 (d, J = 3.3 Hz, 1H), 6.69 (s, 1H), 5.95–5.92 (m, 1H), 5.01 (br s, 2H), 3.50 (br d, J = 6.9 Hz, 2H), 2.22 (s, 3H), 2.18 (s, 3H), 2.13 (s, 3H), 1.78–1.60 (m, 1H), 0.92 (br d, J = 6.3 Hz, 6H); IR (KBr) 3434, 2962, 2924, 2870, 1687, 1608, 1506, 1420, 1359, 1314, 1287, 1180, 1129, 1072, 1044, 1019 cm^{-1}; MS (APCI, Neg.) *m/e* 524 $(M-H)^-$; Anal. Calcd for $C_{25}H_{29}NO_6S$: C, 63.68; H, 6.20; N, 2.97; S, 6.80. Found: C, 63.80; H, 6.25; N, 3.05; S 6.98.

4.22.6. 4-{[(6-{Isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-5-yl)oxy]methyl}benzoic acid (9). Yield 72%; TLC R_f = 0.45 ($MeOH/CHCl_3$, 1:9); ^1H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 7.12 (s, 1H), 6.77 (s, 1H), 6.73 (d, J = 3.3 Hz, 1H), 5.94 (m, 1H), 5.15–4.85 (br, 2H), 3.60–3.40 (br, 2H), 2.86 (t, J = 7.2 Hz, 4H), 2.14 (s, 3H), 2.13–2.00 (m, 2H), 1.68 (m, 1H), 1.02–0.82 (br, 6H); IR (KBr) 3417, 2959, 1689, 1614, 1496, 1414, 1356, 1282, 1218, 1178, 1135, 1056, 1021 cm^{-1}; MS (APCI, Neg.) *m/e* 482 $(M-H)^-$; Anal. Calcd for $C_{26}H_{29}NO_6S$: C, 64.58; H, 6.04; N, 2.90; S, 6.63. Found: C, 64.61; H, 6.13; N, 2.98; S 6.70.

4.22.7. 4-{[(3-{Isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5,6,7,8-tetrahydronaphthalen-2-yl)oxy]methyl}benzoic acid (10). Yield 78%; TLC R_f = 0.45 ($MeOH/CHCl_3$, 1:9); ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H), 6.95 (s, 1H), 6.73 (d, J = 3.3 Hz, 1H), 6.57 (s, 1H), 5.93 (m, 1H), 5.15–4.82 (br, 2H), 3.48 (d, J = 7.2 Hz, 2H), 2.77–2.60 (m, 4H), 2.13 (s, 3H), 1.82–1.60 (m, 5H), 0.92 (d, J = 6.6 Hz, 6H); IR (KBr) 2926, 1685, 1613, 1508, 1420, 1350, 1313, 1287, 1259, 1219, 1189, 1179, 1135, 1067, 1018 cm^{-1}; MS (FAB, Pos.) *m/e* 498 $(M+H)^+$; HRMS (Pos.) calcd for $C_{27}H_{32}NO_6S$: 498.1950; found: 498.1955.

4.22.8. 4-{[(3-{Isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-2-naphthyl)oxy]methyl}benzoic acid (11). Yield 78%; TLC R_f = 0.33 ($MeOH/CHCl_3$, 1:9); ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 8.4 Hz, 2H), 7.82–7.75 (m, 3H), 7.53 (d, J = 8.4 Hz, 2H), 7.51–7.35 (m, 3H), 6.71 (d, J = 3.3 Hz, 1H), 6.05 (m, 1H), 5.42–4.95 (br, 2H), 3.62 (d, J = 7.5 Hz, 1H), 2.13 (s, 3H), 1.79–1.61 (m, 2H), 0.94 (d, J = 6.3 Hz, 6H); IR (KBr) 2961, 1697, 1505, 1474, 1362, 1257, 1181, 1136, 1060, 1020 cm^{-1}; MS (APCI, Neg.) *m/e* 492 $(M-H)^-$; Anal. Calcd for $C_{27}H_{27}NO_6S$: C, 65.70; H, 5.51; N, 2.84; S, 6.50. Found: C, 65.78; H, 5.47; N, 2.92; S, 6.60.

4.22.9. 4-[(2-{Isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-4,5-dimethylphenoxy)methyl]-3-methylbenzoic acid (12). Yield 85%; TLC R_f = 0.35 ($MeOH/CHCl_3$, 1:19); ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 7.8 Hz, 1H), 7.93 (s, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.04 (s, 1H), 6.74–6.70 (m, 2H), 5.94 (dd, J = 3.3, 0.9 Hz, 1H), 4.94 (br, 2H), 3.48 (d, J = 6.6 Hz, 2H), 2.37 (s, 3H), 2.24 (s, 3H), 2.19 (s, 3H), 2.11 (s, 3H), 1.68 (sept, J = 6.6 Hz, 1H), 0.91 (d, J = 6.6 Hz, 6H); IR (KBr) 3442, 2961, 1687, 1612, 1578, 1514, 1347, 1271, 1185, 1136, 1063 cm^{-1}; MS (APCI, Neg.) *m/e* 484 $(M-H)^-$; Anal. Calcd for $C_{26}H_{31}NO_6S$: C, 64.31; H, 6.43; N, 2.88; S, 6.60. Found: C, 64.42; H, 6.54; N, 2.98; S 6.72.

4.22.10. 4-{[(6-{Isobuty[(5-methyl-2-furyl)sulfonyl]amino}-2,3-dihydro-1*H*-inden-5-yl)oxy]methyl}-3-methylbenzoic acid (13). Yield 83%; TLC R_f = 0.53 (MeOH/

$CHCl_3$, 1:9); ^1H NMR (300 MHz, DMSO-d_6) δ 12.88 (s, 1H), 7.80–7.72 (m, 2H), 7.36 (d, J = 8.1 Hz, 1H), 7.08 (s, 1H), 6.98 (s, 1H), 6.83 (d, J = 3.3 Hz, 1H), 6.16 (d, J = 3.3 Hz, 1H), 5.06 (br, 1H), 4.92 (br, 1H), 3.37 (d, J = 6.6 Hz, 2H), 2.90–2.76 (m, 4H), 2.32 (s, 3H), 2.09 (s, 3H), 2.08–1.98 (m, 2H), 1.52 (sept, J = 6.6 Hz, 1H), 0.94–0.78 (br, 6H); IR (KBr) 3313, 2957, 2871, 1720, 1612, 1495, 1449, 1420, 1216, 1174, 1131, 1055 cm^{-1}; MS (FAB, Pos.) *m/e* 489 $(M+H)^+$; Anal. Calcd for $C_{27}H_{31}NO_6S$: C, 65.17; H, 6.28; N, 2.81; S, 6.44. Found: C, 65.31; H, 6.24; N, 2.79; S 6.72.

4.22.11. 4-({2-[Isobutyl(1,3-thiazol-2-ylsulfonyl)amino]-4,5- dimethylphenoxy}methyl)-3-methylbenzoic acid (15). Yield 73%; TLC R_f = 0.56 (MeOH/$CHCl_3$, 1:9); ^1H NMR (300 MHz, DMSO-d_6) δ 7.97 (dd, J = 3.0, 0.3 Hz, 1H), 7.94 (d, J = 7.8 Hz, 2H), 7.85 (dd, J = 3.0, 0.3 Hz, 1H), 7.34 (d, J = 7.8 Hz, 2H), 6.94 (s, 1H), 6.92 (s, 1H), 5.02 (br s, 1H), 4.81 (br s, 1H), 3.46 (br s, 2H), 2.20 (s, 3H), 2.12 (s, 3H), 1.65–1.45 (m, 1H), 0.85 (br d, J = 6.6 Hz, 6H); IR (KBr) 2959, 2640, 1717, 1613, 1508, 1456, 1420, 1361, 1313, 1264, 1179, 1147, 1116, 1054, 1007 cm^{-1}; MS (APCI, Neg.) *m/e* 473 $(M-H)^-$; Anal. Calcd for $C_{23}H_{26}N_2O_5S_2$: C, 58.21; H, 5.52; N, 5.90; S, 13.51. Found: C, 58.25; H, 5.53; N, 5.99; S 13.45.

4.22.12. 4-[({6-[Isobutyl(1,3-thiazol-2-ylsulfonyl)amino]-2,3- dihydro-1*H*-inden-5-yl}oxy)methyl]benzoic acid (16). Yield 94%; TLC R_f = 0.35 (MeOH/$CHCl_3$, 1:10); ^1H NMR (300 MHz, DMSO-d_6) δ 8.10 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 3.0 Hz, 1H), 7.38–7.31 (m, 3H), 7.15 (s, 1H), 6.75 (s, 1H), 5.05–4.90 (m, 1H), 4.85–4.70 (m, 1H), 3.80–3.65 (m, 1H), 3.65–3.50 (m, 1H), 2.86 (t, J = 7.8 Hz, 4H), 2.15–2.00 (m, 2H), 1.82–1.65 (m, 1H), 1.05–0.85 (m, 6H); IR (KBr) 2960, 1717, 1615, 1581, 1492, 1419, 1360, 1313, 1261, 1174, 1147, 1101, 1077, 1045 cm^{-1}; MS (APCI, Neg.) *m/e* 485 $(M-H)^-$; Anal. Calcd for $C_{24}H_{26}N_2O_5S_2$: C, 59.24; H, 5.39; N, 5.76; S, 13.18. Found: C, 59.38; H, 5.23; N, 5.83; S 13.28.

4.22.13. 4-({2-[Isobutyl(1,3-thiazol-2-ylsulfonyl)amino]-4,5-dimethylphenoxy}methyl)-3-methylbenzoic acid (17). Yield 82%; TLC R_f = 0.27 (MeOH/$CHCl_3$, 1:9); ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, J = 7.8 Hz, 1H), 7.93 (s, 1H), 7.70 (d, J = 3.0 Hz, 1H), 7.35 (d, J = 3.0 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.06 (s, 1H), 6.69 (s, 1H), 4.97–4.67 (m, 2H), 3.75–3.47 (m, 2H), 2.34 (s, 3H), 2.23 (s, 3H), 2.18 (s, 3H), 1.71 (m, 1H), 1.05–0.83 (m, 6H); IR (KBr) 2966, 1712, 1510, 1362, 1295, 1179, 1149, 1056 cm^{-1}; MS (APCI, Neg.) *m/e* 487 $(M-H)^-$; Anal. Calcd for $C_{24}H_{28}N_2O_5S_2$: C, 59.00; H, 5.78; N, 5.73; S, 13.12. Found: C, 59.11; H, 5.80; N, 5.88; S 13.34.

4.22.14. 4-[({6-[Isobutyl(1,3-thiazol-2-ylsulfonyl)amino]-2,3- dihydro-1*H*-inden-5-yl}oxy)methyl]-3-methylbenzoic acid (18). Yield 80%; TLC R_f = 0.41 (MeOH/$CHCl_3$,1:9); ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 8.4 Hz, 1H), 7.92 (s, 1H), 7.71 (d, J = 3.0 Hz, 1H), 7.35 (d, J = 3.0 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.15 (s, 1H), 6.77 (s, 1H), 5.02–4.64 (m, 2H), 3.81–3.43 (m, 2H), 2.95–2.76 (m, 4H), 2.34 (s, 3H), 2.17–2.01 (m, 2H), 1.82–1.64 (m, 1H), 1.08–0.83 (m, 6H); IR (KBr) 3426, 2958, 1712, 1692, 1613, 1492, 1419, 1361, 1275, 1210, 1175, 1146, 1101, 1053 cm^{-1}; MS (APCI, Neg.) *m/e* 499 $(M-H)^-$; Anal. Calcd for $C_{25}H_{28}N_2O_5S_2$: C, 59.98; H, 5.64; N, 5.60; S, 12.81. Found: C, 60.07; H, 5.68; N, 5.71; S 12.84.

4.23. 4-(Hydroxymethyl)-2,6-dimethylphenol (28)

To a stirred solution of **27** (2.25 g, 13.5 mmol) in THF (10 mL) was added CH_2N_2 in Et_2O at 0 °C until bubbling ceased. The reaction mixture was concentrated in vacuo and then diluted with THF (20 mL). To this solution was added $LiAlH_4$ (1 g, 27.1 mmol) at 0 °C under argon atmosphere. After being stirred for 1 h, the reaction mixture was diluted with Et_2O, quenched with aqueous Na_2SO_4, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was crystallized from THF and hexane to yield **28** (1.78 g, 85%). TLC R_f = 0.37 (EtOAc/hexane, 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.82 (s, 2H), 4.85 (t, J = 5.4 Hz, 1H), 4.29 (d, J = 5.4 Hz, 2H), 2.12 (s, 6H).

4.24. 4-[(Methoxymethoxy)methyl]-2,6-dimethylphenol (29)

To a stirred solution of **28** (700 mg, 4.60 mmol) and $^iPr_2NEt$ (2.4 mL, 13.8 mmol) in CH_2Cl_2 (5 mL) wad added chloromethyl methylether (0.52 mL, 6.90 mmol) under argon atmosphere. After being stirred for 3 h, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with 1 N HCl, aqueous $NaHCO_3$, water, and brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **29** (800 mg, 89%). TLC R_f = 0.41 (EtOAc/hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 6.98 (s, 2H), 4.68 (s, 2H), 4.46 (s, 2H), 3.41 (s, 3H), 2.24 (s, 6H).

4.25. Methyl 4-[(methoxymethoxy)methyl]-2,6-dimethylbenzoate (30)

Compound **30** was prepared from **29** according to the same procedure as described for the preparation of **20a** from **19a**. Yield 100%; TLC R_f = 0.49 (EtOAc/hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (s, 2H), 4.69 (s, 2H), 4.53 (s, 2H), 3.91 (s, 3H), 3.41 (s, 3H), 2.31 (s, 6H).

4.26. {4-[(Methoxymethoxy)methyl]-2,6-dimethylphenyl}methanol (31)

To a stirred solution of **30** (930 mg, 4.08 mmol) in THF (5 mL) was added $LiAlH_4$ (148 mg, 3.9 mmol) at 0 °C under argon atmosphere. After being stirred for 30 min, the reaction mixture was diluted with Et_2O, quenched with aqueous Na_2SO_4, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was crystallized from THF and hexane to yield **31** (450 mg, 53%). TLC R_f = 0.20 (EtOAc/hexane, 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (s, 2H),

4.74 (s, 2H), 4.70 (s, 2H), 4.51 (s, 2H), 3.42 (s, 3H), 2.43 (s, 6H).

4.27. *N*-Isobutyl-*N*-[2-({4-[(methoxymethoxy)methyl]-2,6-dimethylbenzyl}oxy)-4- (trifluoromethyl)phenyl]-5-methylfuran-2-sulfonamide (32)

Compound **32** was prepared from **25** and **31** according to the same procedure as described for the preparation of **45** from **44** and isobutanol. Yield 100%; TLC $R_f = 0.53$ (EtOAc/toluene, 1:5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (m, 3H), 7.07 (s, 2H), 6.67 (d, $J = 3.3$ Hz, 1H), 5.98–5.95 (m, 1H), 5.00 (s, 2H), 4.74 (s, 2H), 4.55 (s, 2H), 3.44 (s, 3H), 3.38 (d, $J = 7.5$ Hz, 2H), 2.35 (s, 6H), 2.18 (s, 3H), 0.80 (d, $J = 6.6$ Hz, 6H).

4.28. *N*-[2-{[4-(hydroxymethyl)-2,6-dimethylbenzyl]oxy}-4-(trifluoromethyl)phenyl]-*N*-isobutyl-5-methylfuran-2-sulfonamide (33)

To a stirred solution of **32** (300 mg, 0.53 mmol) in dioxane (5 mL) and water (0.5 mL) was added 4 M HCl in dioxane (0.5 mL). After being stirred for 3 h at 40 °C, the reaction mixture was quenched 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 **33** (66 mg, 24%). TLC $R_f = 0.30$ (EtOAc/hexane, 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (m, 3H), 7.08 (s, 2H), 6.68 (d, $J = 3.3$ Hz, 1H), 6.00–5.95 (m, 1H), 5.01 (s, 2H), 4.66 (s, 2H), 3.37 (d, $J = 7.5$ Hz, 2H), 2.36 (s, 6H), 2.19 (s, 3H), 1.60–1.45 (m, 1H), 0.79 (d, $J = 6.6$ Hz, 6H).

4.29. 4-({2-{Isobutyl[(5-methyl-2-furyl)sulfonyl]amino}-5-(trifluoromethyl)phenoxy}methyl)-3,5-dimethylbenzoic acid (6)

To a stirred solution of **33** (66 mg, 0.13 mmol) and Et_3N (0.11 mL, 0.75 mmol) in DMSO (1 mL) and EtOAc (2 mL) was added SO_3·Pyr (60 mg, 0.38 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 water, brine, dried over $MgSO_4$, and concentrated. To a solution of the resulting residue in ^{t}BuOH (2 mL) were added NaH_2PO_4 (15 mg, 0.13 mmol), isobutene (0.06 mL, 0.57 mL), and $NaClO_2$ (50 mg, 0.44 mmol) at room temperature. After being stirred overnight, the reaction mixture was diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was crystallized from EtOAc and hexane to yield **6** (52 mg, 77%). TLC $R_f = 0.49$ (MeOH/$CHCl_3$, 1:9); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 2H), 7.40–7.20 (m, 3H), 6.70 (d, $J = 3.3$ Hz, 1H), 6.00–5.95 (m, 1H), 5.07 (s, 2H), 3.35 (d, $J = 7.5$ Hz, 2H), 2.43 (s, 6H), 2.19 (s, 3H), 1.60–1.45 (m, 1H), 0.79 (d, $J = 6.6$ Hz, 6H); MS (APCI, Neg.) *m/e* 538 $(M-H)^-$; HRMS (Pos.) calcd for $C_{26}H_{29}F_3NO_6S$: 540.1668; found: 540.1684.

5. Biological assay method

5.1. Prostanoid mEP1–4, mDP, hTP, mFP, and hIP 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, mEP2, mEP3a, mEP4, mDP, hTP, mFP, and hIP. Membranes from CHO cells expressing prostanoid receptors were incubated with radioligands (2.5 nM [^{3}H]PGE_2 for mEP1–4; 2.5 nM [^{3}H]PGD_2 for mDP; 5.0 nM [^{3}H]-SQ29548 for hTP; 2.5 nM [^{3}H]$PGF_2\alpha$ for mFP; 5 nM [^{3}H]Iloprost for hIP) and the test compounds at various concentrations in assay buffer (10 mM KH_2PO_4–KOH buffer containing 1 mM EDTA, 10 mM $MgCl_2$, and 100 mM NaCl, pH 6.0, for mEP1–4 and mFP; 25 mM HEPES–NaOH buffer containing 1 mM EDTA, 5 mM $MgCl_2$, and 10 mM $MnCl_2$, pH 7.4, for mDP; 10 mM Tris–HCl buffer containing 100 mM NaCl, pH 7.5, for hTP; 50 mM Tris–HCl buffer containing 1 mM EDTA and 10 mM $MgCl_2$, pH 7.5, for hIP). Incubation was carried out at 25 °C for 60 min, except for mEP1 and mDP (20 min), and hTP and hIP (30 min). The incubation was terminated by filtration through mM KH_2PO_4–KOH buffer containing 0.1 mM NaCl, pH 6.0, for mEP1–4 and mFP; 10 mM Tris–HCl buffer containing 100 mM NaCl and 0.01 w/v% BSA, pH 7.4, for mDP; 10 mM Tris–HCl buffer containing 100 mM NaCl, pH 7.4, for hTP and hIP), and radioactivity on the filter was measured in 6 mL of liquid scintillation (ACSII) mixture by using a liquid scintillation counter. Nonspecific binding was achieved by adding excess amounts of unlabeled PGE_2 (for mEP1–4), unlabeled PGD_2 (for mDP), unlabeled SQ29548 (for hTP), unlabeled $PGF_2\alpha$ (for mFP) or unlabeled Iloprost (for IP) with assay buffer. The concentration of the test substance required to inhibit specific binding in the vehicle group by 50% (IC_{50} value) was estimated from the regression curve. The K_i value (M) was calculated using 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 mEP1 and hEP1 receptor antagonist activity

To confirm that the test compounds antagonize the mEP1 and hEP1 receptors and to estimate the antagonism activity for both receptors, a functional assay was performed by measuring PGE_2-stimulated changes in intracellular Ca^{2+} as an indicator of receptor function. Cells expressing mEP1 or hEP1 receptor were seeded at a density of 1×10^4 cells/well in 96-well plates and cultured for 2 days with 10% fetal bovine serum (FBS)/minimum essential Eagle's medium (alpha modification) (αMEM) in an incubator (37 °C, 5% CO_2). Cells in each well were rinsed with phosphate-buffered saline (PBS(−)), and load buffer was added. After incubation

for 1 h, the load buffer (10% FBS/αMEM containing 5 μM Fura 2/AM, 20 μM indomethacin, and 2.5 mM probenecid) was discarded. After addition of assay buffer (Hanks' balanced salt solution containing 1% (w/v) BSA, 2 μM indomethacin, 2.5 mM probenecid and 10 mM HEPES–NaOH) to each well, the cells were incubated in a dark place at room temperature for 1 h. After addition of solutions of test compound (10 μL) and PGE_2 (10 μL), which were prepared with an assay buffer, intracellular calcium concentration was measured using a fluorescence drug screening system (FDSS-4000, Hamamatsu Photonics). Two fluorescence intensities emitted at 500 nm were measured with excitation wavelengths of 340 nm and 380 nm, respectively.

Antagonist activity was defined as percentage inhibition of the increase of intracellular calcium concentration induced by PGE_2 (100 nM).

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

Female rats (Wistar) were anesthetized with 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 a pressure transducer and an 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 in micturition pressure was elicited by subcutaneous injection of diclofenac (5 mg/kg) and sulprostone (300 μg/kg). The inhibitory effect of a test compound on this increase of intravesical pressure was measured for 60 min after id administration (2 mL/kg).

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