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# Discovery of new chemical leads for selective EP1 receptor antagonists

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**Abstract**—A series of 4-({2-[alkyl(phenylsulfonyl)amino]phenoxy}methyl)benzoic acids were identified as functional $PGE_2$ antagonists with selectivity for the EP1 receptor subtype starting from a chemical lead **1**, which was found while screening our in-house compound library. Discovery of the optimized analogs **21**–**23** is presented here and structure–activity relationships (SAR) are also discussed.


## 1. Introduction

Prostanoid receptors are known to be members of the G-protein coupled receptor superfamily. Recently, eight prostanoid receptors (EP1, EP2, EP3, EP4, IP, TP, DP, and FP) have been cloned and characterized.[1] The characterization of these receptors at the molecular level has resulted in renewed interest in this field,[2] but selective agonists and antagonists of human prostanoid receptors are only available in some limited field.[3–6] As a result, the correlation of specific receptors with various pathologies is currently being established by using potent but poorly selective ligands.

Recent studies have suggested that the EP1 subtype receptor mediates the induction of pain, pyrexia, allodynia[7] and diuresis.[8] Based on this information, compounds that are selective antagonists of this receptor are predicted to be useful as analgesics, antipyretics, and agents to treat hyperalgesia and pollakisuria.

A few antagonists, such as ZD-4953, ZD-6416, and ZD-6804, entered clinical development for indications related to hyperalgesia, but their development was suspended for unknown reasons.[9]

Our search for a subtype-selective EP1 receptor antagonist started with screening our in-house compound library. 4-(2-Arylsulfonylaminobenzoyl)amino benzoic acids **2**–**4** were the new chemical leads derived from the initial chemical lead **1**, which was identified by screening. Here we report on the discovery process (Fig. 1) for a new class of 4-({2-[alkyl(phenylsulfo-

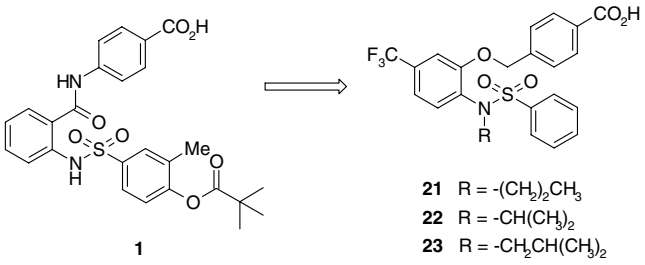


**Figure 1.** Discovery of new selective EP1 receptor antagonists **21**–**23**.

*Keywords*: Prostaglandin; EP1 receptor; Antagonist; Sulfonamide.
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nyl)amino]phenoxy}methyl)benzoic acids **21**–**23** which are potent subtype-selective EP1 receptor antagonists.

## 2. Chemistry

The test compounds listed in Tables 1–5, were synthesized as outlined in Schemes 1–5. Synthesis of **2**–**5** is described in Scheme 1. N-Sulfonylation of the aniline **26** with benzenesulfonyl chloride afforded the sulfonamide **29a**. N-Sulfonylation of the aniline **27** with benzenesulfonyl chloride and 4-chlorobensenesulfonyl chloride gave sulfonamides **29b** and **29c**, respectively. Then alkaline hydrolysis of **29a**–**c** led to benzoic acids **30a**–**c**, respectively. N-Sulfonylation of **28** with benzenesulfonyl chloride gave the sulfonamide **29d**, reduction of which afforded the aniline **30d**. Amidation of **30a**–**c** with methyl 4-aminobenzoate provided amides **31a**–**c**, alkaline hydrolysis of which resulted in the production of **2**–**4**, respectively. N-Acylation of **30d** with methyl 4-(chlorocarbonyl)benzoate gave the amide **31d**, alkaline hydrolysis of which resulted in **5**.

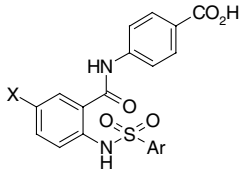
Synthesis of **6**–**9** is outlined in Scheme 2a. Wittig reaction of aldehyde **32** and a phosphonium salt **34** afforded the olefin **35** as a mixture of *E*- and *Z*-isomers. Reduction of the nitro residue of **35**, followed by separation using silica gel column chromatography, produced *Z*-isomer **36*Z*** and *E*-isomer **36*E***. N-Sulfonylation of **36*Z*** and **36*E*** with 4-chlorobenzenesulfonyl chloride, followed by alkaline hydrolysis resulted in **7** and **8**, respectively. Catalytic hydrogenation of the olefin of **8** gave the phenyl propanoic acid analog **6**. C-Acylation of an anion prepared from the phosphonium salt **34** in the presence of tertiary butoxide with an acid chloride **33** afforded betaine **37**, heating of which provided the propiolic acid derivative **38**.[10] Reduction of the nitro residue of **38** led to the aniline **39**, N-sulfonylation of which with 4-chlorobenzenesulfonyl chloride afforded the sulfonamide **41**. Alkaline hydrolysis of **41** resulted in the production of **9**.

Compound **10** was prepared as described in Scheme 2b. Sodium borohydride reduction of **32** afforded an alcohol **42**, methanesulfonylation of which provided **43**. O-Alkylation of methyl 4-hydroxybenzoate with the methanesulfonate **43** gave **44**, reduction of which led to the aniline **45**. N-Sulfonylation of **45** with 4-chlorobenzenesulfonyl chloride, followed by alkaline, hydrolysis resulted in the production of **10**.

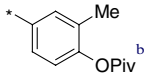
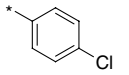
Synthesis of **11**–**12** and **15**–**25** is described in Scheme 3. Compounds **11**–**12** and **15**–**19** were prepared as outlined in Scheme 3a. O-Alkylation of nitrophenols **47a**–**f**[11] with methyl 4-(bromomethyl)benzoate in the presence of potassium carbonate provided benzyl phenyl ethers **48a**–**f**, reduction of which gave anilines **49a**–**f**, respectively. N-Sulfonylation of **49a**–**f** with benzenesulfonyl chloride, followed by alkaline hydrolysis, resulted in the production of **12** and **15**–**19**, respectively. N-Sulfonylation of **49a** with 4-chlorobenzenesulfonyl chloride led to the sulfonamide **51a**, after which alkaline hydrolysis produced **11**.

Synthesis of **20**–**25** is described in Scheme 3b. N-Alkylation of **51e** with appropriate alkyl iodides gave *N*-alkylated sulfonamides **52g**–**l**, alkaline hydrolysis of which resulted in the production of **20**–**25**, respectively.

**Table 1.** Binding affinities of chemical leads **1**–**4** for subtype receptors

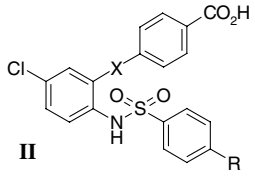



**I**

| Compound | X | Ar | Binding $K_i$ (μM) | | | |
|---|---|---|---|---|---|---|
| | | | mEPl[a] | mEP2[a] | mEP3[a] | mEP4[a] |
| **1** | H |  | 0.18 | >10 | >10 | >10 |
| **2** | H |  | 0.96 | >10 | >10 | >10 |
| **3** | Cl |  | 0.36 | >10 | >10 | >10 |
| **4** | Cl |  | 0.40 | 1.6 | >10 | >10 |

[a] mEPl-4, mouse EP1-4.
[b] Piv, pivaloyl.

**Table 2.** Effect of transformation of the carboxyamide moiety on $K_i$ values for subtype receptors and EP1 receptor antagonist activity

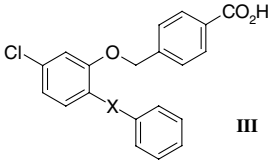


**II**

| Compound | X | R | Binding $K_i$ (μM) | | | | $IC_{50}$[a] (μM) |
|---|---|---|---|---|---|---|---|
| | | | mEPl | mEP2 | mEP3 | mEP4 | mEPl |
| **5** | –NHCO– | H | 3.6 | >10 | >10 | >10 | NT[b] |
| **6** | $-(CH_2)_2-$ | Cl | 0.33 | 1.4 | 0.57 | >10 | NT[b] |
| **7** | –CH=CH– (*Z*) | Cl | 1.2 | 0.80 | 1.2 | >10 | NT[b] |
| **8** | –CH=CH– (*E*) | Cl | 0.34 | >10 | >10 | >10 | NT[b] |
| **9** | –≡– | Cl | 0.16 | 0.047 | >10 | >10 | NT[b] |
| **10** | $-CH_2O-$ | Cl | 1.8 | 3.5 | >10 | >10 | NT[b] |
| **11** | $-OCH_2-$ | Cl | 0.076 | 0.94 | >10 | >10 | >10 |
| **12** | $-OCH_2-$ | H | 0.047 | >10 | >10 | >10 | >10 |

[a] $IC_{50}$, mEPl receptor antagonist activity.
[b] NT, not tested.

**Table 3.** Effect of transformation of the sulfonamide moiety on $K_i$ values for subtype receptors and EP1 receptor antagonist activity

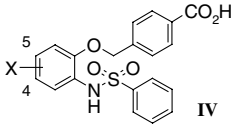


**III**

| Compound | X | Binding $K_i$ (μM) | | | | $IC_{50}$[a] (μM) |
|---|---|---|---|---|---|---|
| | | mEPl | mEP2 | mEP3 | mEP4 | mEPl |
| **12** | $-NHSO_2-$ | 0.047 | >10 | >10 | >10 | >10 |
| **13** | $-SO_2NH-$ | 0.69 | 2.9 | >10 | >10 | >10 |
| **14** | $-CH_2O-$ | 0.28 | 1.2 | >10 | >10 | NT[b] |

[a] $IC_{50}$, mEP1 receptor antagonist activity.
[b] NT, not tested.

**Table 4.** Effect of the substitution of the aminophenolxy moiety on $K_i$ values for subtype receptors and EP1 receptor antagonist activity



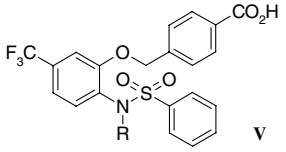
**IV**

| Compound | X | Binding $K_i$ (μM) | | | | $IC_{50}$[a] (M) |
|---|---|---|---|---|---|---|
| | | mEPl | mEP2 | mEP3 | mEP4 | mEPl |
| **12** | 5-C1 | 0.047 | >10 | >10 | >10 | >10 |
| **15** | 5-F | 0.24 | >10 | >10 | >10 | NT[b] |
| **16** | $5-CH_3$ | 0.049 | >10 | >10 | >10 | NT[b] |
| **17** | $5-OCH_3$ | 0.14 | >10 | >10 | >10 | >10 |
| **18** | $5-CF_3$ | 0.025 | >10 | >10 | >10 | >10 |
| **19** | $4-CH_3$ | 0.073 | >10 | >10 | >10 | NT[b] |

[a] $IC_{50}$, mEPl receptor antagonist activity.
[b] NT, not tested.

Compound **13** was synthesized as shown in Scheme 4. N-Sulfonylation of aniline with a sulfonyl chloride **53** afforded the sulfonamide **54**. Replacement of the fluoro residue of **54** with an alkoxide prepared from the alcohol **55** in the presence of tertiary butoxide led to the aldehyde **56**, after which oxidation produced **13**.

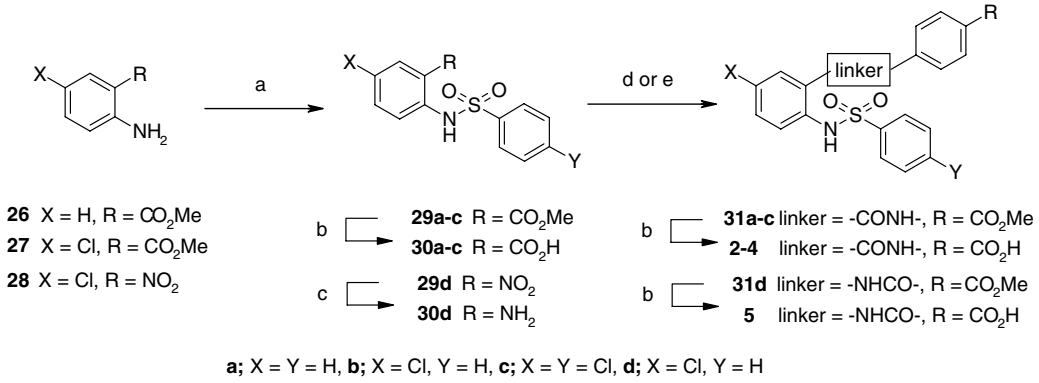
**Table 5.** Effect of N-alkylation on $K_i$ values for subtype receptors and EP1 receptor antagonist activity



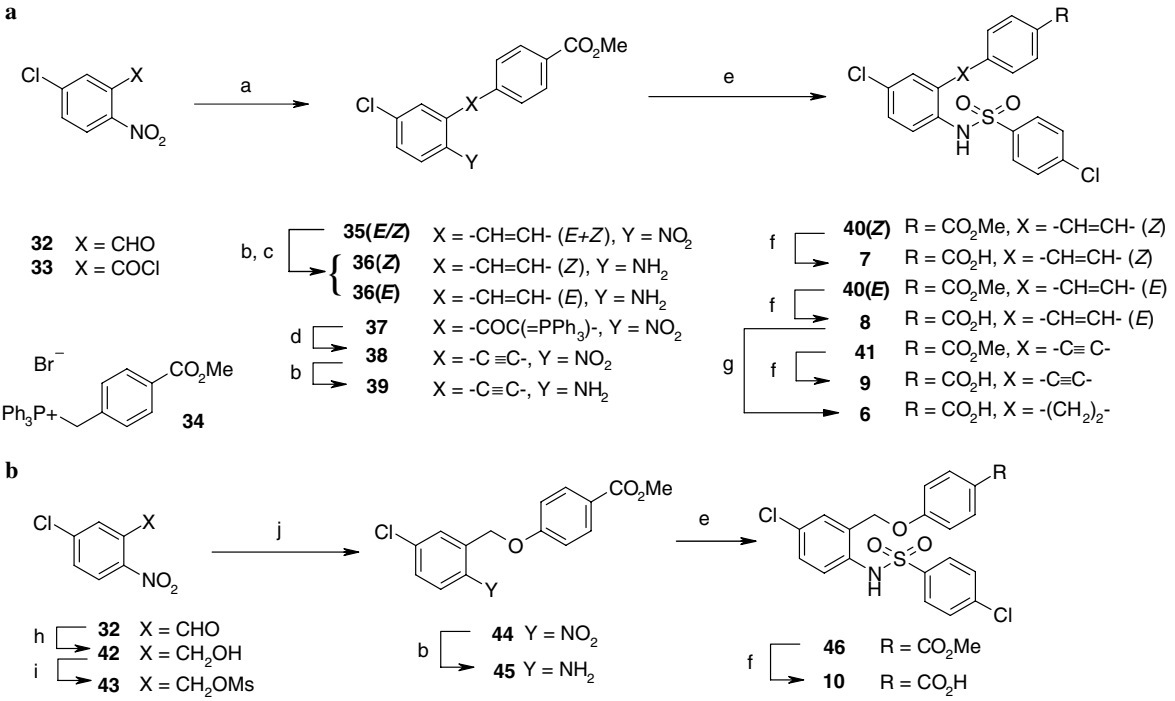
**V**

| Compound | R | Binding $K_i$ (μM) | | | | $IC_{50}$[a] (μM) |
|---|---|---|---|---|---|---|
| | | mEPl | mEP2 | mEP3 | mEP4 | mEPl |
| **18** | –H | 0.025 | >10 | >10 | >10 | >10 |
| **20** | $-CH_2CH_3$ | 0.0029 | >10 | >10 | >10 | 0.68 |
| **21** | $-(CH_2)_2CH_3$ | 0.00080 | >10 | 0.72 | >10 | 0.30 |
| **22** | $-CH(CH_3)_2$ | 0.0016 | >10 | >10 | >10 | 0.38 |
| **23** | $-CH_2CH(CH_3)_2$ | 0.00050 | >10 | 0.41 | >10 | 0.13 |
| **24** | $-CH_2C(CH_3)_3$ | 0.026 | >10 | 0.87 | 4.1 | NT[b] |
| **25** | $-CH_2$-$^c$Pentyl | 0.0066 | 6.2 | 0.46 | >10 | 1.1 |

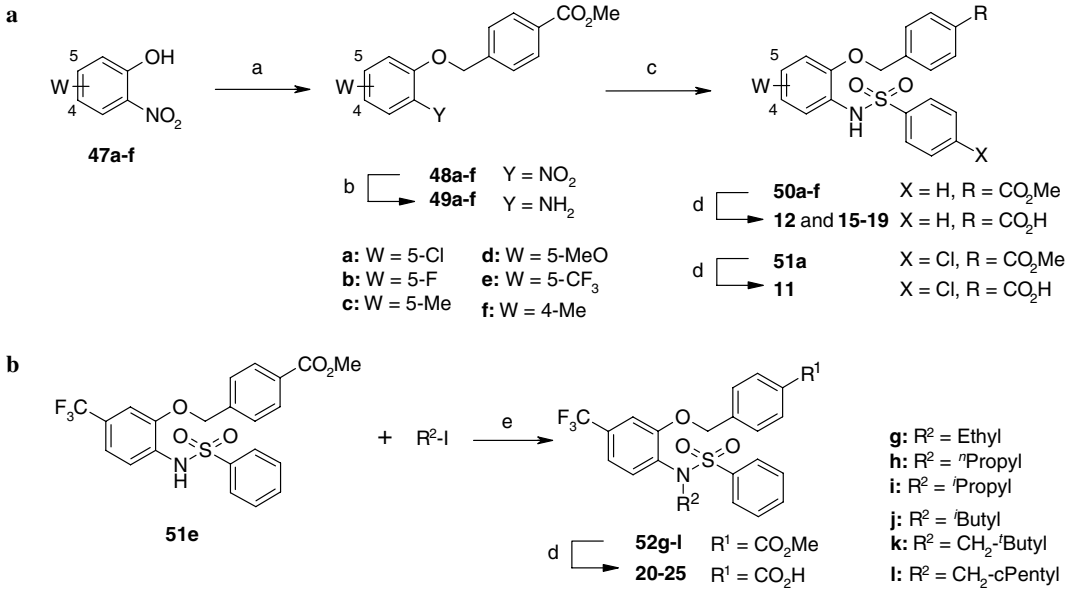
[a] $IC_{50}$, mEPl receptor antagonist activity.
[b] NT, not tested.



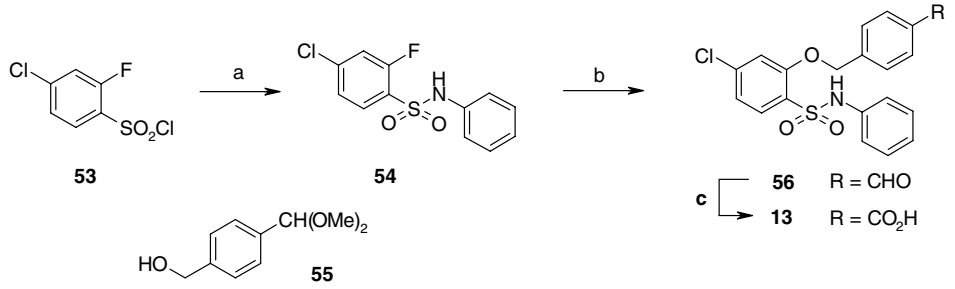

**Scheme 1.** Synthesis of **2**–**5**. Reagents: (a) $ArSO_2Cl$, pyridine, $CH_2Cl_2$; (b) NaOH, MeOH; (c) Fe, AcOH; (d) methyl 4-aminobenzoate, EDC, THF for **31a**–**c**; (e) methyl 4-(chlorocarbonyl)benzoate, pyridine, $CH_2Cl_2$ for **31d**.



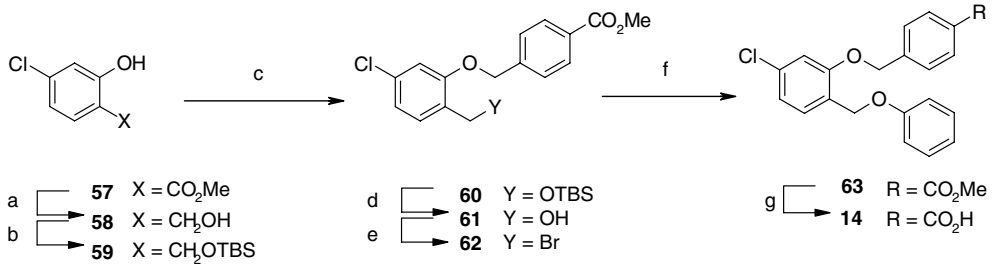

**Scheme 2.** Synthesis of **6**–**10**. Reagents: (a) **34**, $^t$BuOK, THF; (b) Fe, HCl, THF, $H_2O$; (c) separation; (d) *o*-dichlorobenzene, heat; (e) 4-Cl-$PhSO_2Cl$, pyridine, $CH_2Cl_2$; (f) NaOH, MeOH; (g) $H_2$, $PtO_2$, THF; (h) $NaBH_4$, EtOH; (i) MsCl, $Et_3N$, $CH_2Cl_2$; (j) methyl 4-hydroxybenzoate, $K_2CO_3$, acetone.




**Scheme 3.** Synthesis of **11**–**12** and **15**–**25**. Reagents: (a) methyl 4-(bromomethyl)benzoate, $K_2CO_3$, DMF; (b) Fe, AcOH; (c) $ArSO_2Cl$, pyridine, $CH_2Cl_2$; (d) NaOH, MeOH; (e) $K_2CO_3$, DMF.




**Scheme 4.** Synthesis of **13**. Reagents: (a) aniline, pyridine, $CH_2Cl_2$; (b) **55**, $^tBuOK$, DMA and then HCl; (c) $NaClO_2$, isobutene, $NaH_2PO_4$, $CH_3CN$, $H_2O$.




**Scheme 5.** Synthesis of **14**. Reagents: (a) LAH; (b) TBSCl, $Et_3N$, DMAP, THF; (c) methyl 4-(bromomethyl)benzoate, $K_2CO_3$, acetone; (d) TBAF, THF; (e) $CBr_4$, $PPh_3$, $CH_2Cl_2$; (f) PhOH, $K_2CO_3$, acetone; (g) NaOH, MeOH.

Synthesis of **14** is outlined in Scheme 5. Lithium aluminum hydride reduction of the ester **57** provided the alcohol **58**, which was protected as a TBS ether **59**. O-Alkylation of **59** with methyl 4-(bromomethyl)benzoate afforded the ether **60**, which was deprotected with TBAF to give the alcohol **61**. Bromination of **61** with carbon tetrachloride and triphenylphosphine led to the bromide **62**. O-Alkyaltion of phenol with **62** provided **63**, after which alkaline hydrolysis resulted in the production of **14**.

## 3. Results and discussion

The compounds listed in Tables 1–5 were biologically evaluated for their inhibition of the specific binding of a radiolabeled ligand [$^3$H]$PGE_2$ to membrane fractions prepared from cells stably expressing each mouse prostanoid receptor.[12] The EP1 antagonist activity of these compounds was determined by a $Ca^{2+}$ assay using the mouse EP1 receptor (mEP1) expressed in mouse CHO cells in the presence of 0.1% of bovine serum albumin (BSA).

During the course of screening our in-house compound library, compound **1** was found to show subtype-selective EP1 receptor affinity (Table 1). Removal of the metabolically unstable *para*-ester moiety and the *meta*-methyl residue of **1** afforded **2**, which showed 5.0-fold less potent EP1 receptor affinity. Introduction of a 4-chloro residue into the anthranilic acid moiety of **2** afforded **3**, which had 2.7-fold more potent receptor affinity.

Replacement of the phenylsulfonyl moiety of **3** with a 4-chlorophenylsulfonyl moiety provided **4**, which retained its EP1 receptor affinity and showed more potent EP2 receptor affinity. Further optimization was initiated with the chemical modification of **3** and **4**. Optimization of the carboxyamide moiety of the chemical leads was carried out as shown in Table 2. Transformation of the carboxyamide moiety of **3** into an aminocarbonyl moiety gave **5**, which showed 10-fold less potent EP1 receptor affinity. Replacement of the carboxyamide moiety of **4** with an ethylene moiety produced **6**, which retained EP1 receptor affinity and showed increased affinity for the EP3 receptor. Replacement of the carboxyamide moiety of **4** with a *cis*-double bond and *trans*-double bond led to **7** and **8**, respectively. The *trans*-isomer **8**, which is relatively close to the carboxyamide structure, showed more potent EP1 receptor affinity than the *cis*-isomer **7** and compound **8** retained potent EP1 receptor affinity. Replacement of the carboxyamide moiety of **4** with a triple bond led to **9**, which had 2.5-fold more potent EP1 receptor affinity and showed a marked increase of EP3 receptor affinity. Replacement of the carboxyamide moiety of **4** with methyleneoxy and oxymethylene moieties provided **10** and **11**, respectively, with 4.5-fold less potent and 5.3-fold more potent EP1 receptor affinity, respectively. Removal of the chloro residue from the more potent ether analog **11** gave **12**, which had 1.6-fold more potent EP1 receptor affinity. Compounds **11** and **12** did not exhibit antagonist activity at 10 μM, although both showed higher EP1 receptor affinity than the other compounds listed in Tables 1 and 2. Overall, phenylsulfonylamino analogs **3** and **12** tended to show better subtype selectivity than the corresponding 4-chlorophenylsulfonyl analogs **4** and **11**, respectively.

As illustrated in Table 3, the effect on $K_i$ value of transformation of the phenylsulfonylamino moiety of **12** was investigated. The corresponding phenylaminosulfonyl analog **13** demonstrated a 15-fold decrease of receptor affinity. Replacement of the sulfonylamino moiety of **12** with an oxymethyl moiety led to **14**, with 6.0-fold less potent EP1 receptor affinity and increased affinity for the EP2 receptor. As a result, the phenylsulfonylamino moiety was confirmed to be an optimum structure.

As shown in Table 4, the effect on $K_i$ values of substituting the aminophenoxy moiety of **12** was investigated. The 5-methyl analog **16** and the 5-trifluoromethyl analog **18** respectively retained or had slightly more potent receptor affinity than **12**, while the 5-fluoro analog **15**, 5-methoxy analog **17**, and 4-methyl analog **19** all showed a decrease of receptor affinity. Among the compounds tested, the 5-trifluoromethyl analog **18** showed the most potent EP1 receptor affinity.

The effect of N-alkylation of **18** on receptor affinity and EP1 receptor antagonist activity was investigated as shown in Table 5. N-Ethylation of **18** afforded **20**, which had 8.6-fold more potent EP1 receptor affinity. In addition, **20** exhibited EP1 receptor antagonist activity ($IC_{50}$ = 0.68 μM), while **18** did not show antagonist activity at 10 μM. Replacement of the *N*-ethyl moiety of **20** with an *N*-*n*-propyl moiety gave **21**, with a significant increase of both EP1 receptor affinity and antagonist activity. The corresponding *N*-isopropyl analog **22** was slightly less potent in terms of both receptor affinity and antagonist activity. Replacement of the *N*-ethyl moiety of **20** with *N*-isobutyl moiety afforded **23**, which showed 5.8-fold more potent EP1 receptor affinity and 5.2-fold more potent antagonist activity. Replacement of the *N*-ethyl moiety of **20** with an *N*-neopentyl moiety led to **24**, which had reduced EP1 receptor affinity, and showed weak affinity for the EP3 and EP4 receptors.

*N*-Cyclopentylmethyl analog **25** exhibited 2.3-fold less potent receptor affinity and 1.6-fold less potent antagonist activity. Among the compounds tested, the *N*-isobutyl analog **23** showed the most potent EP1 receptor affinity and antagonist activity.

In summary, a series of 4-({2-[alkyl(phenylsulfonyl)amino]phenoxy}methyl)benzoic acids **21**–**23** were identified as new chemical leads for selective mEP1 receptor antagonists after optimization starting from the newly found chemical leads **3**–**4** (Table 1) that were derived from the initial chemical lead **1**. During this process, the oxymethyl moiety and *N*-alkylsulfonamide moiety were found to be essential for both enhanced mEP1 receptor affinity and receptor antagonist activity. Further optimization will be reported in due course.

## 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. 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 were 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), diethylether ($Et_2O$), 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. General procedure for the preparation of methyl 2-[(phenylsulfonyl)amino]benzoate analogs (29a–c)

**4.2.1. Methyl 2-[(phenylsulfonyl)amino]benzoate (29a).** To a stirred solution of methyl 2-aminobenzoate **26** (1.51 g, 10 mmol) and pyridine (2.4 mL, 30 mmol) in $CH_2Cl_2$ (10 ml) was added a solution of benzenesulfonyl chloride (2.3 g, 13 mmol) in $CH_2Cl_2$ (5 ml) at room temperature under argon atmosphere. The reaction mixture was stirred for 3 h, the reaction mixture was quenched with water and 1 M HCl, and extracted with $CH_2Cl_2$, dried over $MgSO_4$. The organic layer was concentrated in vacuo. The resulting residue was recrystallized from EtOAc and hexane to yield **29a** (2.5 g, 86%). TLC $R_f = 0.40$ (EtOAc/hexane, 1:2); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 10.65 (br s, 1H), 7.91 (dd, $J = 7.8$, 1.8 Hz, 1H), 7.88–7.83 (m, 2H), 7.70 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.560–7.40 (m, 4H), 7.04 (dt, $J = 8.4$, 1.8 Hz, 1H), 3.87 (s, 3H).

According to the same procedure as described above, **29b–c** were prepared from the aniline **27**.

**4.2.2. Methyl 5-chloro-2-[(phenylsulfonyl)amino]benzoate (29b).** Yield 94%; TLC $R_f = 0.30$ (EtOAc/hexane, 1:4); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 10.51 (s, 1H), 7.90–7.78 (m, 3H), 7.68 (d, $J = 9.0$ Hz, 1H), 7.60–7.37 (m, 4H), 3.88 (s, 3H).

**4.2.3. Methyl 5-chloro-2-{[(4-chlorophenyl)sulfonyl]-amino}benzoate (29c).** Yield 88%; TLC $R_f = 0.41$ (EtOAc/hexane, 1:4); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 10.53 (s, 1H), 7.90 (d, $J = 2.5$ Hz, 1H), 7.76 (d, $J = 8.5$ Hz, 2H), 7.49–7.37 (m, 3H), 3.89 (s, 3H).

### 4.3. General procedure for the preparation of 2-[(phenylsulfonyl)amino]benzoic acids (30a–c)

**4.3.1. 2-[(Phenylsulfonyl)amino]benzoic acid (30a).** To a stirred solution of **29a** (2 g, 6.87 mmol) in MeOH (20 ml)—DME (10 ml)—THF (5 ml) was added 2 M NaOH (13.8 ml, 27.6 mmol) at 50 °C. The reaction mixture was stirred for 5 h, cooled to room temperature and acidified with 2 M HCl. The resulting precipitates were collected by filtration and dried in vacuo at 70 °C for overnight to yield **30a** (1.9 g, 95%). TLC $R_f = 0.20$ (MeOH/$CHCl_3$, 1:3); $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 13.83 (br s, 1H), 11.11 (br s, 1H), 7.87 (d, $J = 7.2$ Hz, 1H), 7.82–7.74 (m, 2H), 7.63–7.44 (m, 5H), 7.10–7.03 (m, 1H).

According to the same procedure as described above, **30b–c** were prepared from the corresponding esters **29b–c**, respectively.

**4.3.2. 5-Chloro-2-[(phenylsulfonyl)amino]benzoic acid (30b).** Yield 100%; $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 10.31 (s, 1H), 7.99 (d, $J = 2.5$ Hz, 1H), 7.87 (m, 2H), 7.70 (d, $J = 9.0$ Hz, 1H), 7.63–7.42 (m, 4H).

**4.3.3. 5-Chloro-2-{[(4-chlorophenyl)sulfonyl]amino}-benzoic acid (30c).** Yield 98%; TLC $R_f = 0.24$ (MeOH/$CHCl_3$, 1:4); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 11.06 (br s, 1H), 7.84–7.76 (m, 3H), 7.64–7.56 (m, 3H), 7.49 (d, $J = 8.7$ Hz, 1H).

### 4.4. *N*-(4-Chloro-2-nitrophenyl)benzenesulfonamide (29d)

The title compound **29d** was prepared from **28** in 19% yield according to the same procedure as described for the preparation of **29a** from **26**. TLC $R_f = 0.37$ (EtOAc/hexane, 1:5); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 9.85–9.65 (br s, 1H), 8.10 (d, $J = 2.0$ Hz, 1H), 7.90–7.78 (m, 3H), 7.68–7.44 (m, 4H).

### 4.5. *N*-(2-Amino-4-chlorophenyl)benzenesulfonamide (30d)

To a stirred solution of **29d** (172 mg, 0.55 mmol) in AcOH (4 ml) was added iron (325 mesh, 154 mg, 2.75 mmol) at room temperature. The reaction mixture was heated at reflux for 2 h, cooled to room temperature, and diluted with EtOAc. Insoluble substance was removed by filtration through a pad of Celite. The filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **30d** (92 mg, 59%). TLC $R_f = 0.34$ (EtOAc/hexane, 1:2); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 7.80–7.70 (m, 2H), 7.70–7.44 (m, 3H), 6.73 (d, $J = 2.0$ Hz, 1H), 6.46 (dd, $J = 8.0$, 2.0 Hz, 1H), 6.33 (d, $J = 8.0$ Hz, 1H), 6.15 (br s, 1H), 4.50–3.90 (br s, 2H).

### 4.6. General procedure for the preparation of methyl 4-({2-[(phenylsulfonyl)amino]benzoyl}amino)benzoate analogs (30a–c)

**4.6.1. Methyl 4-({2-[(phenylsulfonyl)amino]benzoyl}amino)benzoate (31a).** To a stirred suspension of **30a** (2 g, 7.21 mmol) and methyl 4-aminobenzoate (1.2 g, 7.94 mmol) in $CH_2Cl_2$ (40 ml) were added EDC·HCl (1.3 g, 7.21 mmol) and 4-DMAP (44 mg, 0.361 mmol). The reaction mixture was stirred for 4 days at room temperature, quenched with water and extracted with EtOAc. The organic layer was washed with water, then brine, dried over $MgSO_4$ and concentrated in vacuo to afford a residue, which was purified by column chromatography on silica gel to yield **31a** (722 mg, 21%). TLC $R_f = 0.47$ (EtOAc/hexane, 2:1); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 10.14 (br s, 1H), 8.05 (d, $J = 6.8$ Hz, 2H), 7.74 (m, 4H), 7.59 (d, $J = 6.8$ Hz, 2H), 7.26–7.51 (m, 5H), 7.15 (m, 1H), 3.93 (s, 3H).

According to the same procedure as described above, **31b–c** were prepared from the corresponding carboxylic acids **30b–c**, respectively.

**4.6.2. Methyl 4-({5-chloro-2-[(phenylsulfonyl)amino]benzoyl}amino)benzoate (31b).** Yield 40%; TLC $R_f = 0.29$ (EtOAc/benzene, 1:9); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 10.40 (s, 1H), 9.889 (m, 1H), 8.03 (dd, $J = 8.5$, 2.5 Hz, 2H), 7.83–7.70 (m, 4H), 7.63 (dd, $J = 8.5$, 2.5 Hz, 1H), 7.53–7.27 (m, 5H), 3.93 (s, 3H).

**4.6.3. Methyl 4-[(5-chloro-2-{[(4-chlorophenyl)sulfonyl]amino}benzoyl)amino]benzoate (31c).** Yield 48%; TLC $R_f = 0.32$ (EtOAc/hexane, 3:7); $^1$H NMR (200 MHz, $CD_3OD$) $\delta$ 8.05 (d, $J = 8.5$ Hz, 2H), 7.74–7.58 (m, 6H), 7.47 (dd, $J = 8.5$, 2.5 Hz, 1H), 7.27 (d, $J = 8.5$ Hz, 2H), 3.95 (s, 3H).

### 4.7. Methyl 4-[({5-chloro-2-[(phenylsulfonyl)amino]phenyl}amino)carbonyl]benzoate (31d)

To a stirred solution of **30d** (90 mg, 0.319 mmol) and pyridine (0.05 ml, 0.637 mmol) in $CH_2Cl_2$ (5 ml) was added methyl 4-(chlorocarbonyl)benzoate (70 mg, 0.35 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 6 h, quenched with water and extracted with EtOAc (3×). The combined organic layers were washed with water, brine, dried over $MgSO_4$ and evaporated. The resulting residue was crystallized from EtOAc and hexane to yield **31d** (112 mg, 79%). TLC $R_f = 0.55$ (EtOAc/hexane, 1:1); $^1$H NMR (200 MHz, $CDCl_3$ + DMSO-$d_6$) $\delta$ 9.41 (br s, 1H), 8.93 (br s, 1H), 8.22 (d, $J = 2.0$ Hz, 1H), 8.15 (d, $J = 9.0$ Hz, 2H), 7.98 (d, $J = 9.0$ Hz, 2H), 7.72–7.62 (m, 2H), 7.58–7.45 (m, 1H), 7.44–7.32 (m, 2H), 6.96 (dd, $J = 8.5$, 2.0 Hz, 1H), 6.82 (d, $J = 8.5$ Hz, 1H), 3.98 (s, 3H).

### 4.8. General procedure for the preparation of 4-({2-[(phenylsulfonyl)amino]benzoyl}amino)benzoic acids (2–5)

**4.8.1. 4-({2-[(Phenylsulfonyl)amino]benzoyl}amino)benzoic acid (2).** To a stirred solution of **31a** (715 mg, 1.74 mmol) in EtOH (8 ml) was added 5 M NaOH (1.1 ml) at room temperature. The reaction mixture was stirred for 3.5 days, acidified with 2 M HCl (3.0 ml) and extracted with EtOAc. The organic layer was washed with water, then brine, dried over $MgSO_4$ and concentrated in vacuo to yield **2** (677 mg, 98%). TLC $R_f = 0.50$ (MeOH/$CHCl_3$/AcOH, 10:100:1); $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 12.76 (br s, 1H), 10.57 (s, 1H), 10.49 (s, 1H), 7.95 (d, $J = 8.8$ Hz, 2H), 7.77 (m, 5H), 7.62–7.28 (m, 5H), 7.24 (m, 1H); IR (KBr) 3390, 2989, 1686, 1595, 1532, 1501, 1331, 1288, 1253, 1175, 1092 cm$^{-1}$; MS (APCI, Neg.) *m/e* 395 $(M-H)^-$.

According to the same procedure as described above, **3–5** were prepared from the corresponding esters **31b–d**, respectively.

**4.8.2. 4-({2-[(5-Chlorophenylsulfonyl)amino]benzoyl}amino)benzoic acid (3).** Yield 69%; TLC $R_f = 0.32$ (MeOH/$CHCl_3$, 3:17); $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 12.74 (br s, 1H), 10.61 (s, 1H), 10.40 (s, 1H), 7.95 (2H, d, $J = 8.6$ Hz, 2H), 7.85–7.71 (m, 5H), 7.64–7.35 (m, 5H); IR (KBr) 3323, 3153, 1689, 1595, 1533, 1480, 1421, 1386, 1323, 1290, 1253, 1167 cm$^{-1}$; MS (APCI, Neg.) *m/e* 429 $(M-H)^-$.

**4.8.3. 4-[(5-Chloro-2-{[(4-chlorophenyl)sulfonyl]amino}benzoyl)amino]benzoic acid (4).** Yield 100%; TLC $R_f = 0.27$ (MeOH/$CHCl_3$, 3:17); $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 12.70 (br s, 1H), 10.59 (s, 1H), 10.30 (s, 1H), 7.83–7.65 (m, 5H), 7.62–7.47 (m, 3H), 734 (d, $J = 9.0$ Hz, 2H); IR (KBr) 3332, 3150, 1689, 1595, 1532, 1478, 1421, 1387, 1325, 1285, 1254, 1166 cm$^{-1}$; MS (APCI, Neg.) *m/e* 463 $(M-H)^-$.

**4.8.4. 4-[({5-Chloro-2-[(phenylsulfonyl)amino]phenyl}amino)carbonyl]benzoic acid (5).** Yield 100%; TLC $R_f = 0.36$ (EtOAc/hexane/AcOH, 8:10:1); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 13.00 (br s, 1H), 9.80 (br s, 1H), 9.65 (s, 1H), 8.09 (d, $J = 8.5$ Hz, 2H), 7.87 (d, $J = 8.5$ Hz, 2H), 7.81 (d, $J = 2.5$, 1H9), 7.65–7.50 (m, 3H), 7.40 (t, $J = 7.5$ Hz, 2H), 7.22 (dd, $J = 8.5$, 5.2 Hz, 1H), 7.14 (d, $J = 8.5$ Hz, 1H).IR (KBr) 3321, 1693, 1657, 1590, 1524, 1491, 1425, 1330, 1924, 1163, 1097 cm$^{-1}$; MS (FAB, Pos.) 431 $(M+H)^+$.

### 4.9. Methyl 4-[(*E*/*Z*)-2-(5-chloro-2-nitrophenyl)vinyl]-benzoate (35*E*) and (35*Z*)

To a stirred suspension of [4-(methoxycarbonyl)benzyl](trimethyl)phosphonium bromide **34** (4.83 g, 10 mmol) in THF (20 ml) and MeOH (0.2 ml) was added potassium *tert*-butoxide (1.12 g, 10 mmol) at room temperature under argon atmosphere. After 1.5 h, 5-chloro-2-nitrobenzaldehyde **33** (742 mg, 4.00 mmol) was added to the reaction mixture and stirring was continued for additional 30 min at room temperature. The reaction mixture was quenched with 1 M HCl and extracted with EtOAc (2×). 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 a mixture of **35*E*** and **35*Z*** (680 mg, 56%). TLC $R_f = 0.44$ (EtOAc/hexane, 1:4); MS (EI, Pos.) *m/e* 317 $(M^+)$.

### 4.10. Methyl 4-[(*E*)-2-(2-amino-5-chlorophenyl)vinyl]benzoate (36*E*) and methyl 4-[(*Z*)-2-(2-amino-5-chloro-phenyl)vinyl]benzoate (36*Z*)

To a stirred solution of a mixture of **35*E*** and **35*Z*** (525 mg, 1.62 mmol) in THF (4 ml) and water (1.5 ml) were added 2 M HCl (0.4 ml) and iron (325 mesh, 884 mg, 15.8 mmol) at room temperature under argon. After 4 days, the reaction mixture was diluted with EtOAc. Insoluble substance was removed by filtration. The filtrate was washed with $NaHCO_3$aq, brine, dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **36*E*** (116 mg, 25%) and **36*Z*** (321 mg, 69%). **36*E***: TLC $R_f = 0.37$ (EtOAc/benzene, 1:19); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.03 (d, $J = 8.5$ Hz, 2H), 7.55 (d, $J = 8.5$ Hz, 2H), 7.39

(d, $J$ = 2.5 Hz, 1H), 7.18 (d, $J$ = 16.0 Hz, 1H), 7.07 (dd, $J$ = 8.5, 2.5 Hz, 1H), 7.01 (d, $J$ = 16.0 Hz, 1H), 6.56 (d, $J$ = 8.5 Hz, 1H), 3.93 (s, 3H), 3.83 (br s, 2H); **36*Z***: TLC $R_f$ = 0.41 (EtOAc/benzene, 5:95); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.88 (d, $J$ = 8.5 Hz, 2H), 7.27 (d, $J$ = 8.5 Hz, 2H), 7.05 (dd, $J$ = 8.5, 2.0 Hz, 1H), 7.00 (d, $J$ = 2.0 Hz, 1H), 6.71 (d, $J$ = 12.0 Hz, 1H), 6.62 (d, $J$ = 8.5 Hz, 1H), 6.54 (d, $J$ = 12.0 Hz, 1H), 3.88 (s, 3H), 3.71 (br s, 2H).

### 4.11. Methyl 4-[(*Z*)-2-(5-chloro-2-{[(4-chlorophenyl)sulfonyl]amino}phenyl)vinyl]benzoate (40*Z*)

The title compound **40*Z*** was prepared from **36*Z*** in 95% yield according to the same procedure as described for the preparation of **29a** from **26** using 4-chlorobenzenesulfonyl chloride instead of benzenesulfonyl chloride. TLC $R_f$ = 0.23 (EtOAc/benzene, 1:24); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.82 (d, $J$ = 8.0 Hz, 2H), 7.57 (d, $J$ = 9.0 Hz, 2H), 7.46 (d, $J$ = 9.0 Hz, 1H), 7.33 (d, $J$ = 9.0 Hz, 2H), 7.24 (dd, $J$ = 9.0, 2.0 Hz, 1H), 7.06 (d, $J$ = 2.0 Hz, 1H), 6.99 (d, $J$ = 8.0 Hz, 2H), 6.72 (d, $J$ = 12.0 Hz, 1H), 6.48 (s, 1H), 6.20 (d, $J$ = 12.0 Hz, 1H), 3.90 (s, 3H).

### 4.12. 4-[(*Z*)-2-(5-Chloro-2-{[(4-chlorophenyl)sulfonyl]amino}phenyl)vinyl]benzoic acid (7)

The title compound **7** was prepared from **40*Z*** in 46% yield according to the same procedure as described for the preparation of **2** from **31a**. TLC $R_f$ = 0.46 (MeOH/$CHCl_3$, 3:17); $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 10.05 (br s, 1H), 7.79–7.67 (m, 4H), 7.55 (d, $J$ = 8.5 Hz, 2H), 7.30 (dd, $J$ = 8.5, 2.5 Hz, 1H), 7.15 (d, $J$ = 8.5 Hz, 1H), 7.00 (d, $J$ = 8.0 Hz, 2H), 6.91 (d, $J$ = 2.5 Hz, 1H), 6.64 (m, 2H); IR (KBr) 3336, 3096, 1692, 1608, 14808, 1412, 1323, 1293, 1167 cm$^{-1}$; MS (APCI, Neg.) *m/e* 446 $(M-H)^-$.

### 4.13. Methyl 4-[(*E*)-2-(5-chloro-2-{[(4-chlorophenyl)sulfonyl]amino}phenyl)vinyl]benzoate (40*E*)

The title compound **40*E*** was prepared from **36*E*** in 98% yield according to the same procedure as described for the preparation of **29a** from **26** using 4-chlorobenzenesulfonyl chloride instead of benzenesulfonyl chloride. TLC $R_f$ = 0.15 (EtOAc/benzene, 1:24); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.02 (d, $J$ = 8.5 Hz, 2H), 7.63 (d, $J$ = 8.5 Hz, 2H), 7.51 (s, 1H), 7.41–7.30 (m, 4H), 7.26–7.22 (m, 2H), 6.91 (d, $J$ = 16.0 Hz, 1H), 6.81 (d, $J$ = 16.0 Hz, 1H), 6.63 (s, 1H), 3.95 (s, 3H).

### 4.14. 4-[(*E*)-2-(5-Chloro-2-{[(4-chlorophenyl)sulfonyl]amino}phenyl)vinyl]benzoic acid (8)

The title compound **8** was prepared from **40*E*** in 92% yield according to the same procedure as described for the preparation of **2** from **31a**. TLC $R_f$ = 0.46 (MeOH/$CHCl_3$, 3:17); $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 10.11 (br s, 1H), 7.96 (d, $J$ = 8.0 Hz, 2H), 7.80 (d, $J$ = 2.5 Hz, 1H), 7.59 (d, $J$ = 9.0 Hz, 2H), 7.52–7.41 (m, 4H), 7.36 (dd, $J$ = 8.5, 2.5 Hz, 1H), 7.20 (d, $J$ = 8.5 Hz, 1H), 7.15 (d, $J$ = 16.0 Hz, 1H), 7.08 (d, $J$ = 16.0 Hz, 1H); IR (KBr) 3220, 1688, 1606, 1478, 1425, 1330, 1293, 1092 cm$^{-1}$; MS (APCI, Neg.) *m/e* 446 $(M-H)^-$.

### 4.15. 4-[2-(5-Chloro-2-{[(4-chlorophenyl)sulfonyl]amino}-phenyl)ethyl]benzoic acid (6)

A suspension of **8** (54 mg, 0.12 mmol) and platinum dioxide (3 mg, 0.013 mmol) in THF (4 ml) was stirred vigorously at room temperature under hydrogen atmosphere. After 2 h, the catalyst was removed by filtration through a pad of Celite. The filtrate was concentrated in vacuo. The resulting residue was washed with a mixture of $CH_2Cl_2$ and hexane to yield **6** (46 mg, 85%). TLC $R_f$ = 0.42 (MeOH/$CHCl_3$, 3:17); $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 12.75 (br s, 1H), 9.88 (s, 1H), 7.84 (d, $J$ = 8.5 Hz, 2H), 7.72–7.57 (m, 4H), 7.32 (d, $J$ = 2.5 Hz, 1H), 7.23 (d, $J$ = 8.5 Hz, 2H), 7.18 (d, $J$ = 8.5 Hz, 2H), 6.88 (d, $J$ = 9.0 Hz, 1H). IR (KBr) 3285, 29676, 2667, 2538, 1684, 1611, 1484, 1398, 1337, 1288, 1169, 1095 cm$^{-1}$; MS (APCI, Neg) *m/e* 448 $(M-H)^-$.

### 4.16. Methyl 4-[2-(5-chloro-2-nitrophenyl)-2-oxo-1-(triphenylphosphoranylidene)ethyl]benzoate (37)

To a stirred suspension of [4-(methoxycarbonyl)benzyl]-(triphenyl)phosphonium bromide (1.17 g, 2.38 mmol) in THF (8 ml) was added potassium $^t$butoxide (246 mg, 2.19 mmol) at 0 °C under argon atmosphere. After 30 min, a solution of 5-chloro-2-nitrobenzoyl chloride **33** (218 mg, 0.992 mmol) in THF (4 ml)was added dropwise. The reaction mixture was allowed to warm up to room temperature and stirred for additional 3 h. The reaction mixture was diluted with $CHCl_3$, washed with $NH_4Cl$aq, water, brine and dried over $MgSO_4$. The organic layer was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **37** (619 mg, 100%). TLC $R_f$ = 0.26 (MeOH/$CHCl_3$, 1:100); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.80–7.40 (m, 18H), 7.07 (m, 2H), 6.93 (dd, $J$ = 8.0 Hz, 2H), 3.80 (s, 3H); IR (neat) 3065, 1715, 1521, 1436, 1348, 1275, 1103 cm$^{-1}$; MS (APCI, Pos.) *m/e* 594 $(M+H)^+$.

### 4.17. Methyl 4-[(5-chloro-2-nitrophenyl)ethynyl]benzoate (38)

A solution of **37** (513 mg, 0.865 mmol) was heated at 180 °C with stirring. After 9 h, the reaction mixture was concentrated in vacuo and the resulting residue was purified by column chromatography on silica gel to yield **38** (189 mg, 69%). TLC $R_f$ = 0.40 (EtOAc/hexane, 1:7); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.09 (d, $J$ = 8.8 Hz, 1H), 7.72 (d, $J$ = 2.4 Hz, 1H), 7.66 (d, $J$ = 8.6 Hz, 2H), 7.46 (dd, $J$ = 8.8, 2.4 Hz, 1H), 3.94 (s, 3H); IR (KBr) 3424, 2225, 1713, 1606, 1516, 1346, 1278, 1108 cm$^{-1}$; MS (FAB, Pos.) *m/e* 316 $(M+H)^+$.

### 4.18. Methyl 4-[(2-amino-5-chloro-phenyl)ethynyl]benzoate (39)

The title compound **39** was prepared from **38** in 88% yield according to the same procedure as described for

the preparation of **36*Z*** and **36*E*** from the mixture of **35*E*** and **35*Z***. TLC $R_f = 0.22$ (EtOAc/hexane, 1:5); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.03 (d, $J = 8.8$ Hz, 2H), 7.57 (d, $J = 8.8$ Hz, 2H), 7.34 (d, $J = 2.6$ Hz, 1H), 7.11 (dd, $J = 8.8$, 2.6 Hz, 1H), 6.66 (d, $J = 8.8$ Hz, 1H), 4.29 (br s, 2H), 23.93 (s, 3H); IR (KBr) 3481, 3382, 2203, 1713, 1620, 1604, 1488, 1438, 1279, 1252, 1150, 1111 cm$^{-1}$; MS (APCI, Neg.) *m/e* 284 $(M-H)^-$.

### 4.19. Methyl 4-[(5-chloro-2-{[(4-chlorophenyl)sulfonyl]-amino}phenyl)ethynyl]benzoate (41)

The title compound **41** was prepared from **39** in 94% yield according to the same procedure as described for the preparation of **29a** from **26** using 4-chlorobenzenesulfonyl chloride instead of benzenesulfonyl chloride. TLC $R_f = 0.50$ (EtOAc/hexane, 1:3); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.07 (d, $J = 8.4$ Hz, 2H), 7.67 (d, $J = 8.6$ Hz, 2H), 7.58 (d, $J = 8.8$ Hz, 1H), 7.49 (d, $J = 8.4$ Hz, 2H), 7.39 (d, $J = 2.4$ Hz, 1H), 7.34 (d, $J = 8.6$ Hz, 2H), 7.32 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.07 (br s, 1H), 3.96 (s, 3H).; MS (APCI, Pos.) *m/e* 460 $(M+H)^+$.

### 4.20. 4-[(5-Chloro-2-{[(4-chlorophenyl)sulfonyl]amino}-phenyl)ethynyl]benzoic acid (9)

The title compound **9** was prepared from **41** in 94% yield according to the same procedure as described for the preparation of **2** from **31a**. TLC $R_f = 0.43$ (MeOH/$CHCl_3$/AcOH, 5:100:1); $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 13.16 (br s, 1H), 10.32 (br s, 1H), 8.00 (d, $J = 8.4$ Hz, 2H), 7.65 (d, $J = 8.6$ Hz, 2H), 7.59 (d, $J = 2.6$ Hz, 1H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.50 (dd, $J = 8.5$ Hz, 2.6 Hz, 1H), 7.43 (d, $J = 8.6$ Hz, 2H), 7.35 (d, $J = 8.5$ Hz, 1H); IR (KBr) 3455, 3270, 2845, 2545, 1688, 1608, 1481, 1425, 1392, 1347, 1314, 1285, 1172, 1093 cm$^{-1}$; MS (EI, Pos.) *m/e* 445 ($M^+$), 382, 368, 356, 270.

### 4.21. (5-Chloro-2-nitrophenyl)methanol (42)

To a stirred solution of methyl 5-chloro-2-nitrobenzaldehyde **32** (800 mg, 4.31 mmol) in EtOH (20 ml) was added $NaBH_4$ (170 mg, 4.49 mmol) at 0 °C. After 30 min, the reaction mixture was quenched with 1 M HCl and extracted with EtOAc. The organic layer was washed with $NaHCO_3$aq, brine, dried over $MgSO_4$ and concentrated in vacuo to yield **42** (792 mg, 97%). TLC $R_f = 0.47$ (EtOAc/hexane, 1:2); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.09 (d, $J = 8.6$ Hz, 1H), 7.82 (d, $J = 2.4$ Hz, 1H), 7.34 (dd, $J = 8.6$, 2.4 Hz, 1H), 5.08–4.98 (br s, 2H), 2.50–2.34 (br s, 1H).

### 4.22. 5-Chloro-2-nitrobenzyl methanesulfonate (43)

To a stirred solution of **42** (400 mg, 2.13 mmol) in $CH_2Cl_2$ (6 ml) were added $Et_3N$ (0.6 ml, 4.30 mmol) and methanesulfonyl chloride (0.25 ml, 3.2 mmol) at −10 °C under argon atmosphere. After 15 min, the reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with 2 M HCl, brine, dried over $MgSO_4$ and evaporated. The resulting residue was concentrated in vacuo to yield **43** (600 mg). TLC $R_f = 0.36$ (EtOAc/hexane, 1:2); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.17 (d, $J = 8.6$ Hz, 1H), 7.76 (d, $J = 2.4$ Hz, 1H), 7.53 (dd, $J = 8.6$, 2.4 Hz, 1H), 5.66 (s, 2H), 3.16 (s, 3H).

### 4.23. Methyl 4-[(5-chloro-2-nitrobenzyl)oxy]benzoate (44)

To a stirred solution of **43** (600 mg) in acetone (20 ml) were added methyl 4-hydroxybenzoate (425 mg, 2.79 mmol) and $K_2CO_3$ (900 mg, 6.51 mmol). After being stirred for 22 h at room temperature under argon atmosphere, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **44** (464 mg, 67% in 2 steps). TLC $R_f = 0.26$ (EtOAc/hexane, 1:2); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.18 (d, $J = 8.8$ Hz, 1H), 8.04 (d, $J = 9.2$ Hz, 2H), 7.91 (d, $J = 2.2$ Hz, 1H), 7.48 (dd, $J = 8.8$, 2.2 Hz, 1H), 7.05 (d, $J = 9.2$ Hz, 1H), 5.53 (s, 2H), 3.90 (s, 3H).

### 4.24. Methyl 4-[(2-amino-5-chlorobenzyl)oxy]benzoate (45)

The title compound **45** was prepared from **44** according to the same procedure as described for the preparation of **36*E*** and **36*Z*** from the mixture of **35*E*** and **35*Z***. TLC $R_f = 0.23$ (EtOAc/hexane 1:2); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.01 (d, $J = 8.8$ Hz, 2H), 7.19 (d, $J = 2.4$ Hz, 1H), 7.13 (dd, $J = 8.4$, 2.4 Hz, 1H), 7.00 (d, $J = 8.8$ Hz, 2H), 6.67 (d, $J = 8.4$ Hz, 2H), 5.02 (s, 2H), 3.89 (s, 3H).

### 4.25. Methyl 4-[(5-chloro-2-{[(4-chlorophenyl)sulfonyl]amino}benzyl)oxy]benzoate (46)

The title compound **46** was prepared from **45** in 47% yield according to the same procedure as described for the preparation of **29a** from **26** using 4-chlorobenzenesulfonyl chloride instead of benzenesulfonyl chloride. TLC $R_f = 0.45$ (EtOAc/benzene, 1:9); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.01 (d, $J = 8.8$ Hz, 1H), 7.62 (d, $J = 8.8$ Hz, 2H), 7.40 (d, $J = 8.8$ Hz, 2H), 7.32–7.26 (m, 3H), 7.11 (br s, 1H), 6.90 (d, $J = 8.8$ Hz, 2H), 4.80 (s, 2H), 3.90 (s, 3H).

### 4.26. 4-[(5-Chloro-2-{[(4-chlorophenyl)sulfonyl]amino}benzyl)oxy]benzoic acid (10)

The title compound **10** was prepared from **46** in 67% yield according to the same procedure as described for the preparation of **2** from **31a**. TLC $R_f = 0.51$ (EtOAc); $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 10.05 (br s, 1H), 7.90 (d, $J = 8.7$ Hz, 2H), 7.69 (d, $J = 9.0$ Hz, 2H), 7.61 (d, $J = 9.0$ Hz, 2H), 7.49 (d, $J = 2.4$ Hz, 1H), 7.36 (dd, $J = 8.5$, 2.4 Hz, 1H), 7.01 (d, $J = 8.5$ Hz, 1H), 6.92 (d, $J = 8.7$ Hz, 2H), 5.02 (s, 2H); IR (KBr) 3500, 3215, 1679, 1607, 1431, 1330, 1295, 1247, 1173, 1155, 1092, 1042, 1015 cm$^{-1}$; MS (APCI, Neg.) *m/e* 450 $(M-H)^-$.

### 4.27. General procedure for the preparation of methyl 4-(2-nitrophenoxy)methylbenzoate analogs (48a–f)

**4.27.1. Methyl 4-[(5-chloro-2-nitrophenoxy)methyl]benzoate (48a).** To a stirred suspension of 5-chloro-2-nitrophenol **47a** (4.0 g, 23.1 mmol) and $K_2CO_3$ (3.83 g, 27.7 mmol) in DMF (40 ml) was added methyl 4-(bromomethyl)benzoate (5.83 g, 25.4 mmol) under argon atmosphere. The resulting mixture was stirred for 1 h at 50 °C, then quenched by the addition of 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 yielded **48a** (7.11 g, 99%). TLC $R_f = 0.49$ (EtOAc/hexane, 1:10); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.10 (d, $J = 8.6$ Hz, 2H), 7.87 (d, $J = 8.2$ Hz, 1H), 7.54 (d, $J = 8.6$ Hz, 2H), 7.12–7.02 (m, 2H), 5.28 (s, 2H), 3.93 (s, 3H).

According to the same procedure as described above, **48b–f** were prepared from **47b–f**, respectively.

**4.27.2. Methyl 4-[(5-fluoro-2-nitrophenoxy)methyl]benzoate (48b).** Yield 93%; TLC $R_f = 0.26$ (EtOAc/hexane, 1:5); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.09 (d, $J = 8.4$ Hz, 2H), 8.05 (dd, $J = 9.0$, 6.0 Hz, 1H), 7.55 (d, $J = 8.4$ Hz, 2H), 6.81 (dd, $J = 9.6$, 2.1 Hz, 1H), 6.76 (ddd, $J = 9.0$, 7.2, 2.1 Hz, 1H), 5.28 (s, 2), 3.93 (s, 3H).

**4.27.3. Methyl 4-[(5-methyl-2-nitrophenoxy)methyl]benzoate (48c).** Yield 77%; TLC $R_f = 0.24$ (EtOAc/hexane, 1:5); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 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).

**4.27.4. Methyl 4-[(5-methoxy-2-nitrophenoxy)methyl]benzoate (48d).** Yield 97%; TLC $R_f = 0.45$ (EtOAc/hexane, 1:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.10–8.00 (m, 3H), 7.56 (d, $J = 8.1$ Hz, 2H), 6.60–6.50 (m, 2H), 5.26 (s, 2H), 3.92 (s, 3H), 3.85 (s, 3H).

**4.27.5. Methyl 4-{[2-nitro-5-(trifluoromethyl)phenoxy]methyl}benzoate (48e).** Yield 89%; TLC $R_f = 0.38$ (EtOAc/hexane, 1:5); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.10 (d, $J = 8.4$ Hz, 2H), 7.95 (d, $J = 8.7$ Hz, 1H), 7.54 (d, $J = 8.4$ Hz, 2H), 7.40–7.25 (m, 2H), 5.33 (s, 2H), 3.94 (s, 3H).

**4.27.6. Methyl 4-[(4-methyl-2-nitrophenoxy)methyl]benzoate (48f).** Yield 77%; TLC $R_f = 0.24$ (EtOAc/hexane, 1:5); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.06 (d, $J = 8.5$ Hz, 2H), 7.69 (d, $J = 1.5$ Hz, 1H), 7.54 (d, $J = 8.5$ Hz, 2H), 7.30 (dd, $J = 8.5$, 1.5 Hz, 1H), 7.98 (d, $J = 8.5$ Hz, 1H), 5.26 (s, 2H), 3.92 (s, 3H), 2.35 (s, 3H).

### 4.28. General procedure for the preparation of methyl 4-(2-aminophenoxy)methylbenzoate analogs (49a–f)

**4.28.1. Methyl 4-[(2-amino-5-chlorophenoxy)methyl]benzoate (49a).** To a stirred solution of **48a** (7.1 g, 23 mmol) in AcOH (70 ml) and water (4.7 ml) was added iron (325 mesh, 6.41 g, 115 mmol) under argon atmosphere. The reaction mixture was stirred for 3 h at 50 °C, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo, diluted with $NaHCO_3$aq and extracted with EtOAc. The organic layer was washed with water, brine and dried over $MgSO_4$ and concentrated in vacuo to yield **49a** (6.45 g, 100%). TLC $R_f = 0.27$ (EtOAc/benzene, 1:19); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.07 (d, $J = 8.0$ Hz, 2H), 7.49 (d, $J = 8.0$ Hz, 2H), 6.84–6.75 (m, 2H), 6.65 (d, $J = 9.0$ Hz, 1H), 5.12 (s, 2H), 3.93 (s, 3H), 3.83 (br s, 2H).

According to the same procedure as described above, **49b–f** were prepared from **48b–f**, respectively.

**4.28.2. Methyl 4-[(2-amino-5-fluorophenoxy)methyl]benzoate (49b).** Yield 28%; TLC $R_f = 0.65$ (EtOAc/hexane, 1:1); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.07 (d, $J = 8.5$ Hz, 2H), 7.50 (d, $J = 8.5$ Hz, 2H), 6.72–6.46 (m, 3H), 5.12 (s, 2H), 3.93 (s, 3H); MS (APCI, Pos.) *m/e* 276 $(M+H)^+$.

**4.28.3. Methyl 4-[(2-amino-5-methylphenoxy)methyl]benzoate (49c).** Yield 100%; TLC $R_f = 0.47$ (EtOAc/hexane, 1:2); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.06 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.5$ Hz, 2H), 6.65 (s, 3H), 5.13 (s, 2H), 3.93 (s, 3H), 3.75 (br s, 2H), 2.24 (s, 3H).

**4.28.4. Methyl 4-[(2-amino-5-methoxyphenoxy)methyl]benzoate (49d).** Yield 100%; TLC $R_f = 0.39$ (EtOAc/hexane, 1:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.05 (d, $J = 8.7$ Hz, 2H), 7.50 (d, $J = 8.7$ Hz, 2H), 6.69 (d, $J = 8.7$ Hz, 1H), 6.47 (d, $J = 2.7$ Hz, 1H), 3.79 (dd, $J = 8.7$, 2.7 Hz, 1H), 3.93 (s, 3H), 3.72 (s. 3H), 1.19 (s, 2H).

**4.28.5. Methyl 4-{[2-amino-5-(trifluoromethyl)phenolxy]methyl}benzoate (49e).** Yield 85%; TLC $R_f = 0.50$ (EtOAc/hexane, 1:5); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 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).

**4.28.6. Methyl 4-[(2-amino-4-methylphenoxy)methyl]benzoate (49f).** Yield 100%; TLC $R_f = 0.52$ (EtOAc/hexane, 1:2); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.05 (d, $J = 8.0$ Hz, 2H), 7.50 (d, $J = 8.0$ Hz, 2H), 6.70 (d, $J = 8.0$ Hz, 1H), 6.59 (d, $J = 1.5$ Hz, 1H), 6.49 (dd, $J = 8.0$, 1.5 Hz, 1H), 5.11 (s, 2H), 5.00–3.50 (br s, 2H), 3.92 (s, 3H), 2.22 (s, 3H).

### 4.29. General procedure for methyl 4-({2-[(phenylsulfonyl)amino]phenoxy}methyl)benzoate analogs (50a–f)

According to the same procedure as described for the preparation of **29a–c** from the corresponding anilines, **50a–f** were prepared from the corresponding anilines **49a–f**, respectively.

**4.29.1. Methyl 4-({5-chloro-2-[(phenylsulfonyl)amino]phenoxy}methyl)benzoate (50a).** Yield 85%; TLC $R_f = 0.31$ (EtOH/benzene, 1:19); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.03 (d, $J = 8.5$ Hz, 2H), 7.70 (m, 2H), 7.56–6.50 (m, 2H), 7.40 (m, 2H), 7.16 (d, $J = 8.5$ Hz, 2H),

6.95 (dd, $J$ = 8.5, 2.0 Hz, 1H), 6.86 (s, 1H), 6.73 (d, $J$ = 2.0 Hz, 1H), 4.88 (s, 2H), 3.95 (s, 3H).

**4.29.2. Methyl 4-({5-fluoro-2-[(phenylsulfonyl)amino]phenoxy}methyl)benzoate (50b).** Yield 88%; TLC $R_f$ = 0.59 (EtOAc/hexane, 2:3); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.03 (d, $J$ = 8.5 Hz, 2H), 7.70–7.50 (m, 4H), 7.45–7.32 (m, 2H), 7.11 (d, $J$ = 8.0 Hz, 2H), 6.73 (br s, 1H), 6.75–6.63 (m, 1H), 6.45 (dd, $J$ = 10.0, 2.5 Hz, 1H), 4.82 (s, 2H), 3.95 (s, 3H).

**4.29.3. Methyl 4-({5-methyl-2-[(phenylsulfonyl)amino]phenoxy}methyl)benzoate (50c).** Yield 87%; TLC $R_f$ = 0.43 (EtOAc/hexane, 1:2); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.01 (d, $J$ = 8.0 Hz, 2H), 7.74–7.64 (m, 2H), 7.60–7.45 (m, 2H), 7.44–7.32 (m, 2H), 7.14 (d, $J$ = 8.0 Hz, 2H), 6.81 (br s, 1H), 6.85–6.73 (m 1H), 6.53 (s, 1H), 4.84 (s, 2H), 3.95 (s, 3H), 2.25 (s, 3H).

**4.29.4. Methyl 4-({5-methoxy-2-[(phenylsulfonyl)amino]phenoxy}methyl)benzoate (50d).** Yield 88%; TLC $R_f$ = 0.25 (EtOAc/hexane, 1:2); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.99 (d, $J$ = 8.5 Hz, 2H), 7.66–7.45 (m, 4H), 7.35 (d, $J$ = 8.0 Hz, 2H), 7.08 (d, $J$ = 8.0 Hz, 2H), 6.61 (s, 1H), 6.50 (dd, $J$ = 9.0, 2.0 Hz, 1H), 6.26 (d, $J$ = 2.5 Hz, 1H), 4.76 (s, 2H), 3.95 (s, 3H), 3.74 (s, 3H).

**4.29.5. Methyl 4-{[2-[(phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (50e).** Yield 86%; TLC $R_f$ = 0.76 (acetone/benzene, 1:9); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 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).

**4.29.6. Methyl 4-({4-methyl-2-[(phenylsulfonyl)amino]phenoxy}methyl)benzoate (50f).** Yield 88%; TLC $R_f$ = 0.43 (EtOAc/hexane, 1:2); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.00 (d, $J$ = 8.5 Hz, 2H), 7.75–7.65 (m, 2H), 7.60–7.40 (m, 1H), 7.46–7.30 (m, 3H), 7.14 (d, $J$ = 8.5 Hz, 2H), 6.90 (br s, 1H), 6.81 (dd, $J$ = 8.5, 2.0 Hz, 1H), 6.58 (d, $J$ = 8.5 Hz, 1H), 4.85 (s, 2H), 3.94 (s, 3H), 2.28 (s, 3H).

### 4.30. Methyl 4-[(5-chloro-2-{[(4-chlorophenyl)sulfonyl]amino}phenoxy)methyl]benzoate (51a)

The title compound **51a** was prepared from **49a** in 98% yield according to the same procedure as described for the preparation of **29a** from **26** using 4-chlorobenzenesulfonyl chloride instead of benzenesulfonyl chloride. TLC $R_f$ = 0.30 (EtOAc/benzene, 1:24); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.06 (d, $J$ = 8.5 Hz, 2H), 7.59 (d, $J$ = 8.5 Hz, 2H), 7.53 (d, $J$ = 9.0 Hz, 1H), 7.34 (d, $J$ = 8.5 Hz, 2H), 7.18 (d, $J$ = 8.5 Hz, 2H), 6.96 (dd, $J$ = 9.0, 2.0 Hz, 1H), 6.82 (br s, 1H), 6.76 (d, $J$ = 2.0 Hz, 1H), 4.89 (s, 2H), 3.96 (s, 3H).

### 4.31. General procedure for methyl 4-{[2-[alkyl(phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}-benzoate analogs (52g–l)

**4.31.1. Methyl 4-{[2-[ethyl(phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (52g).** To a stirred solution of **51e** (250 mg, 0.54 mmol) in DMF (3 ml) were added $K_2CO_3$ (89 mg, 0.64 mmol) and ethyl iodide (0.51 ml, 0.64 mmol). The reaction mixture was stirred overnight at room temperature, then 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 **52g** (280 mg, 100%). TLC $R_f$ = 0.64 (EtOAc/benzene, 1:9); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.00 (d, $J$ = 8.4 Hz, 2H), 7.70–7.60 (m, 2H), 7.50–7.10 (m, 8H), 4.89 (s, 2H), 3.95 (s, 3H), 3.67 (q, $J$ = 7.2 Hz, 2H), 1.09 (t, $J$ = 7.2 Hz, 3H); MS (APCI, Pos) $m/e$ 494 $(M+H)^+$.

According to the same procedure as described above, **52h–l** were prepared from **51e**.

**4.31.2. Methyl 4-{[2-[(phenylsulfonyl)(propyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (52h).** Yield 100%; TLC $R_f$ = 0.73 (EtOAc/hexane, 1:9); $^1$H NMR (200 MHz, CDCl3) $\delta$ 8.01 (d, $J$ = 8.4 Hz, 2H), 7.70–7.60 (m, 2H), 7.50–7.10 (m, 8H), 4.87 (s, 2H), 3.95 (s, 3H), 3.58 (t, $J$ = 7.6 Hz, 2H), 1.60–1.40 (m, 2H), 0.8 (t, $J$ = 7.6 Hz, 3H); MS (APCI, Pos.) $m/e$ 508 $(M+H)^+$.

**4.31.3. Methyl {[2-[isopropyl(phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (52i).** Yield 75%; TLC $R_f$ = 0.58 (EtOAc/hexane, 1:2); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.07 (d, $J$ = 8.2 Hz, 2H), 7.79 (m 2H), 7.56–7.32 (m, 5H), 7.23 (m, 3H), 5.09 (s, 2H), 4.37 (sept, $J$ = 6.6 Hz, 1H), 3.94 (s, 3H), 1.05 (d, $J$ = 6.6 Hz, 6H).

**4.31.4. Methyl {[2-[isobutyl(phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (52j).** Yield 100%; TLC $R_f$ = 0.70 (EtOAc/benzene, 1:9); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 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 $(M+H)^+$.

**4.31.5. Methyl {[2-[neopentyl (phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (52k).** Yield 39%; TLC $R_f$ = 0.64 (EtOAc/hexane, 3:7); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.04 (d, $J$ = 8.4 Hz, 2H), 7.60–7.40 (m, 4H), 7.30–7.20 (m, 5H), 7.07 (d, $J$ = 1.6 Hz, 1H), 4.98 (d, $J$ = 12.2 Hz, 1H), 4.67 (d, $J$ = 12.2 Hz, 1H), 3.95 (s, 3H), 3.57 (d, $J$ = 14.4 Hz, 1H), 3.48 (d, $J$ = 14.4 Hz, 1H), 0.85 (s, 9H); MS (APCI, Pos.) $m/e$ 536 $(M+H)^+$.

**4.31.6. Methyl {[2-[(cyclopentylmethyl)(phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoate (52l).** Yield 100%; TLC $R_f$ = 0.51 (EtOAc/hexane, 1:3); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.01 (d, $J$ = 8.4 Hz, 2H), 7.63–7.58 (m, 2H), 7.48–7.25 (m, 5H), 7.17 (d, $J$ = 8.4 Hz, 2H), 7.09 (d, $J$ = 1.4 Hz, 1H), 4.83 (br s, 2H), 3.95 (s, 3H), 3.50–3.40 (m, 2H), 1.92–1.09 (m, 9H); MS (APCI, Pos.) $m/e$ 548 $(M+H)^+$.

### 4.32. Synthesis of 11–12 and 15–25

Compounds **11**–**12** and **15**–**25** were prepared by the usual alkaline hydrolysis of their corresponding esters.

**4.32.1. 4-[(5-Chloro-2-{[(4-chlorophenyl)sulfonyl]amino}phenoxy)methyl]benzoic acid (11).** Yield 97%; TLC $R_f = 0.43$ (MeOH/$CHCl_3$, 3:17); $^1H$ NMR (200 MHz, DMSO-$d_6$) $\delta$ 9.89 (br s, 1H), 7.93 (d, $J = 8.0$ Hz, 2H), 7.60 (d, $J = 8.5$Hz, 2H), 7.42 (d, $J = 8.5$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.06 (d, $J = 2.0$ Hz, 1H), 7.01 (dd, $J = 8.0$, 2.0 Hz, 1H), 4.98 (s, 2H); IR (KBr) 3331, 2877, 1689, 1595, 1498, 1424, 1395, 1353, 1252, 1172, 1123, 1095 $cm^{-1}$; MS (APCI, Neg.) *m/e* 450 $(M-H)^-$.

**4.32.2. 4-({5-Chloro-2-[(phenylsulfonyl)amino]phenolxy}methyl)benzoic acid (12).** Yield 89%; TLC $R_f = 0.39$ (MeOH/$CHCl_3$, 1:4); $^1H$ NMR (200 MHz, DMSO-$d_6$) $\delta$ 12.98 (s, 1H), 9.78 (s, 1H), 7.92 (d, $J = 8.0$ Hz, 2H), 7.65 (d, $J = 8.5$ Hz, 2H), 7.55 (t, $J = 8.5$ Hz, 1H), 7.41 (t, $J = 8.5$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 2H), 7.28 (d, $J = 8.5$ Hz, 1H), 7.04 (d, $J = 2.0$ Hz, 1H), 6.98 (dd, $J = 8.5$, 2.0 Hz, 1H), 4.98 (s, 2H); IR (KBr) 3260, 2996, 2887, 1687, 1598, 1426, 1339, 1290, 1265, 1168 $cm^{-1}$; MS (APCI, Neg.) *m/e* 416 $(M-H)^-$.

**4.32.3. 4-({5-Fluoro-2-[(phenylsulfonyl)amino]phenolxy}methyl)benzoic acid (15).** Yield 85%; TLC $R_f = 0.42$ (EtOAc/hexane/AcOH, 6:13:1); $^1H$ NMR (200 MHz, DMSO-$d_6$) $\delta$ 12.95 (br s, 1H), 9.65 (br s, 1H), 7.91 (d, $J = 8.5$ Hz, 2H), 7.60 (d, $J = 7.0$ Hz, 2H), 7.52 (t, $J = 7.0$ Hz, 1H), 7.39 (d, $J = 7.5$ Hz, 2H), 7.35 (d, $J = 7.5$ Hz, 2H), 7.26 (dd, $J = 7.0$, 6.5 Hz, 1H), 6.84 (dd, $J = 11.0$, 2.5 Hz, 1H), 6.75 (dt, $J = 8.5$, 2.5 Hz, 1H), 4.90 (s, 2H); IR (KBr) 3267, 1686, 1616, 1459, 1449, 1398, 1336, 1284, 1163, 1093, 1041, 1019 $cm^{-1}$; MS (FAB, Pos.) *m/e* 402 $(M+H)^+$.

**4.32.4. 4-({5-Methyl-2-[(phenylsulfonyl)amino]phenolxy}methyl)benzoic acid (16).** Yield 86%; TLC $R_f = 0.43$ (EtOAc/hexane/AcOH, 7:12:1); $^1H$ NMR (200 MHz, DMSO-$d_6$) $\delta$ 7.91 (d, $J = 8.5$ Hz, 2H), 7.62 (d, $J = 7.0$ Hz, 2H), 7.57–7.45 (m, 1H), 7.44–7.30 (m, 4H), 7.14 (d, $J = 8.0$ Hz, 1H), 6.75 (s, 2H), 6.71 (d, $J = 8.0$ Hz, 1H), 4.89 (s, 2H), 2.21 (s, 3H); IR (KBr) 3266, 2867, 1685, 1614, 1579, 1510, 1449, 1415, 1337, 1286, 1160, 1122, 1093, 1048, 1020 $cm^{-1}$; MS (FAB, Pos.) *m/e* 398 $(M+H)^+$.

**4.32.5. 4-({5-Methoxy-2-[(phenylsulfonyl)amino]phenolxy}methyl)benzoic acid (17).** Yield 89%; TLC $R_f = 0.40$ (MeOH/$CHCl_3$, 1:4); $^1H$ NMR (200 MHz, DMSO-$d_6$) $\delta$ 7.90 (d, $J = 8.5$ Hz, 2H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.51 (t, $J = 8.0$ Hz, 1H), 7.44–7.28 (m, 4H), 7.15 (d, $J = 8.5$ Hz, 1H), 6.54–6.47 (m, 2H), 4.86 (s, 2H), 3.69 (s, 3H); IR (KBr) 3293, 3006, 1686, 1614, 1510, 1450, 1398, 1337, 1200, 1166 $cm^{-1}$; MS (APCI, Neg.) *m/e* 412 $(M-H)^-$.

**4.32.6. 4-{[2-[(Phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (18).** Yield 99%; TLC $R_f = 0.52$ (MeOH/$CHCl_3$/AcOH, 5:100:1); $^1H$ NMR (200 MHz, DMSO-$d_6$) $\delta$ 12.95 (s, 1H), 10.10 (br s, 1H), 7.93 (d, $J = 8.0$ Hz, 2H), 7.75 (m, 2H), 7.59 (m, 1H), 7.53–7.40 (m, 5H), 7.27 (m, 2H), 5.14 (s, 2H); IR (KBr) 3379, 3297, 3072, 2671, 1694, 1415, 1522, 1443, 1353, 1334, 1286, 1169, 1123, 1090, 1011 $cm^{-1}$; MS (FAB, Pos.) *m/e* 452 $(M+H)^+$.

**4.32.7. 4-({4-Methyl-2-[(phenylsulfonyl)amino]phenolxy}methyl)benzoic acid (19).** Yield 82%; TLC $R_f = 0.43$ (EtOAc/hexane/AcOH, 7:12:1); $^1H$ NMR (200 MHz, DMSO-$d_6$) $\delta$ 7.89 (d, $J = 8.0$ Hz, 2H), 7.66 (d, $J = 7.0$ Hz, 2H), 7.60–7.48 (m, 1H), 7.41 (d, $J = 8.0$ Hz, 2H), 7.35 (d, $J = 8.0$ Hz, 2H), 7.11 (d, $J = 2.0$ Hz, 1H), 6.90 (dd, $J = 8.0$, 2.0 Hz, 1H), 6.76 (d, $J = 8.0$ Hz, 1H), 4.88 (s, 2H), 2.19 (s, 3H); IR (KBr) 3289, 2919, 1687, 1615, 1579, 1511, 1458, 1424, 1390, 1335, 1295, 1222, 1175, 1127, 1092, 1035, 1018 $cm^{-1}$; MS (FAB, Pos.) *m/e* 398 $(M+H)^+$.

**4.32.8. 4-{[2-[Ethyl(phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (20).** Yield 76%; TLC $R_f = 0.43$ (MeOH/$CHCl_3$, 1:9); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 8.09 (d, $J = 7.4$ Hz, 2H), 7.70–7.60 (m, 2H), 7.50–7.20 (m, 7H), 7.15 (d, $J = 1.6$ Hz, 1H), 4.94 (s, 2H), 3.69 (q, $J = 7.4$ Hz, 2H), 1.11 (t, $J = 7.4$ Hz, 3H); IR (KBr) 2981, 2360, 1694, 1614, 1510, 1429, 1332, 1219, 1172, 1127, 1087, 1019 $cm^{-1}$; MS (FAB, Pos.) *m/e* 480 $(M+H)^+$.

**4.32.9. {[2-[(Phenylsulfonyl)(propyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (21).** Yield 70%; TLC $R_f = 0.50$ (MeOH/$CHCl_3$, 1:9); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 8.09 (d, $J = 8.2$ Hz, 2H), 7.70–7.60 (m, 2H), 7.50–7.20 (m, 7H), 7.14 (s, 1H), 4.92 (s, 2H), 3.59 (t, $J = 7.4$ Hz, 2H), 1.60–1.40 (m, 2H), 0.88 (t, $J = 7.4$ Hz, 3H); IR (KBr) 2970, 1694, 1614, 150,1428, 1332, 1171, 1127, 1087, 1018 $cm^{-1}$; MS (FAB, Pos.) *m/e* 494 $(M+H)^+$.

**4.32.10. {[2-[Isopropyl(phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (22).** Yield 78%; TC $R_f = 0.44$ (MeOH/$CHCl_3$/AcOH, 5:100:1); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 8.15 (d, $J = 8.6$ Hz, 2H), 7.81 (m, 2H), 7.52 (m, 3H), 7.38 (m, 2H), 7.24 (m 3H), 5.13 (s, 2H), 4.4 0 (sept, $J = 6.8$ Hz, 1H9, 1.06 (d, $J = 6.8$ Hz, 6H); IR (KBr) 3423, 2982, 1698, 1426, 1332, 1294, 1218, 1172, 1127, 1088, 1034 $cm^{-1}$, MS (FAB, Pos.) *m/e* 494 $(M+H)^+$, 353.

**4.32.11. {[2-[Isobutyl(phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (23).** Yield 80%; TLC $R_f = 0.53$ (MeOH/$CHCl_3$, 1:9); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 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, $J = 6.6$ Hz, 6H); IR (KBr) 2963, 1694, 1510, 1448, 1427, 1331, 1289, 1257, 1213, 1169, 1127, 1086, 1019 $cm^{-1}$; MS (FAB, Pos.) *m/e* 508 $(M+H)^+$.

**4.32.12. {[2-[Neopentyl (phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (24).** Yield 80%; TLC $R_f = 0.50$ (MeOH/$CHCl_3$, 1:9); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 8.12 (d, $J = 8.0$ Hz, 2H), 7.60–7.40 (m, 4H), 7.40–7.20 (m, 5H), 7.09 (d, $J = 1.8$ Hz, 1H), 5.02 (d, $J = 12.4$ Hz, 1H), 4.72 (d, $J = 12.4$ Hz, 1H), 3.53 8s, 2H), 0.86 (s, 9H); IR (KBr) 2961, 1694, 1614, 1581, 1510, 1478, 1448, 1427, 1329, 1279, 1234, 1201, 1168, 1129, 100, 1019 $cm^{-1}$; MS (EI, Pos.) *m/e* 521 $(M^+)$.

**4.32.13. {[2-[(Cyclopentylmethyl)(phenylsulfonyl)amino]-5-(trifluoromethyl)phenoxy]methyl}benzoic acid (25).** Yield 100%; TLC Rf = 0.40 (MeOH/$CHCl_3$/$H_2O$,

1:9:0.1); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.09 (d, $J$ = 8.2 Hz, 2H), 7.65–7.61 (m, 2H), 7.47–7.20 (m, 7H), 7.11 (d, $J$ = 1.8 Hz, 1H), 4.89 (br s, 2H), 3.59–3.51 (m, 2H), 1.93–1.10 (m, 9H), 7.11 (d, $J$ = 1.8 Hz, 1H), 4.89 (br s, 2H), 3.59–3.51 (m, 2H), 1.93–1.10 (m, 9H); IR (KBr) 2953, 2871, 1697, 1580, 1510, 1448, 1429, 1333, 1289, 1215, 1167, 1128, 1085, 1019 cm$^{-1}$; MS (APCI, Neg.) *m/e* 532 $(M-H)^-$.

### 4.33. 4-Chloro-2-fluoro-*N*-phenylbenzenesulfonamide (54)

To a stirred solution of aniline (372 mg, 4.0 mmol) in $CH_2Cl_2$ (10 ml) was added pyridine (0.40 ml, 4.0 mmol) and benzenesulfonyl chloride **53** (1.37 g, 6.0 mmol) at 0 °C under argon atmosphere. The reaction mixture was allowed to warm up to room temperature, stirred for 15 min and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **54** (964 mg, 85%); TLC $R_f$ = 0.24 (EtOAc/hexane, 1:6); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.75 (m, 1H), 7.29–7.07 (m, 7H), 6.87 (br s, 1H); MS (APCI, Neg.) *m/e* 286 $(M-H)^-$.

### 4.34. 4-Chloro-2-[(4-formylbenzyl)oxy]-*N*-phenylbenzenesulfonamide (56)

To a stirred solution of [4-(dimethoxymethyl)phenyl]methanol **55** (866 mg, 12 mmol) in DMA (3 ml) was added potassium $^t$butoxide (462 mg, 4.12 mmol) at 80 °C under argon atmosphere. After 20 min, **54** (392 mg, 1.37 mmol) was added to the reaction mixture and stirring was continued for additional 2 h at 110 °C. The reaction mixture was cooled to room temperature and quenched by the addition of water. The aqueous layer was extracted with EtOAc (2×) and the combined organic layers were washed with 2 M HCl (3×) and then brine. The organic layer was dried over $MgSO_4$ and evaporated. The resulting residue was purified by column chromatography on silica gel to yield **56** (415 mg, 76%). TLC $R_f$ = 0.24 (EtOAc/hexane, 1:6); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.06 (s, 1H), 7.98 (d, $J$ = 8.4 Hz, 2H), 7.80 (d, $J$ = 8.7 Hz, 1H), 7.71 (d, $J$ = 8.4 Hz, 2H), 7.19 (m, 2H), 7.11–6.93 (m, 5H), 6.69 (s, 1H), 5.34 (s, 2H).

### 4.35. 4-{[2-(Anilinosulfonyl)-5-chlorophenoxy]methyl}-benzoic acid (13)

To a stirred solution of **56** (413 mg, 1.03 mmol) in $CH_3CN$ (5 ml) and water (5 ml) were added 2-methyl-2-butene (0.545 ml, 5.15 mmol), $NaH_2PO_4$ (122 mg, 1.03 mmol) and $NaClO_2$ (452 mg, 4.12 mmol) at room temperature. The reaction mixture was stirred for 1.5 h under argon, diluted with water, acidified with 1 M HCl and extracted with $Et_2O$. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **13** (127 mg, 30%). TLC $R_f$ = 0.35 (MeOH/$CHCl_3$, 1:10); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.87 (d, $J$ = 8.4 Hz, 2H), 7.80 (d, $J$ = 8.7Hz, 1H), 7.52 (d, $J$ = 8.4 Hz, 2H), 7.24–7.17 (m, 3H), 7.13–7.05 (m, 3H), 6.97 (m, 1H), 5.48 (s, 2H); IR (KBr) 3215, 1707, 1587, 1499, 1479, 1408, 1386, 1320, 1239, 1156, 1136, 1064 cm$^{-1}$; MS (APCI, Neg.) *m/e* 416 $(M-H)^-$.

### 4.36. 5-Chloro-2-(hydroxymethyl)phenol (58)

To a stirred solution of methyl 4-chloro-2-hydroxybenzoate **57** (2.16 g, 11.6 mmol) in THF (20 ml) was added lithium aluminum hydride (440 mg, 11.6 mmol) at 0 °C under argon atmosphere. The reaction mixture was allowed to warm up to room temperature and stirred for additional 30 min, diluted with $Et_2O$, acidified with 2 M HCl and extracted with EtOAc. The organic layer was washed with water, brine, dried over $MgSO_4$ and concentrated in vacuo to afford **58** (1.85 g, 100%). TLC $R_f$ = 0.50 (EtOAc/hexane, 1:1); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.51 (s, 1H), 6.95 (d, $J$ = 8.2 Hz, 1H), 6.90 (d, $J$ = 2.0 Hz, 1H), 6.83 (dd, $J$ = 8.2, 2.0 Hz, 1H), 4.85 (d, $J$ = 3.0 Hz, 1H), 2.21 (br s, 1H).

### 4.37. 2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-5-chlorophenol (59)

To a stirred solution of **58** (1.85 g, 11.6 mmol) in THF (20 ml) were added $Et_3N$ (4.85 ml, 34.8 mmol), 4-DMAP (28 mg, 0.232 mmol) and TBSCl (1.92 g, 12.8 mmol) under argon atmosphere. The reaction mixture was stirred for 24 h, diluted with EtOAc. The organic layer was washed with water and then brine. The organic layer was dried over $MgSO_4$ and evaporated. The resulting residue was purified by column chromatography on silica gel to yield **59** (1.89 g, 60%); TLC $R_f$ = 0.61 (EtOAc/hexane, 1:10); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.23 (s, 1H), 6.88 (d, $J$ = 2.6 Hz, 1H), 6.85 (d, $J$ = 8.0 Hz, 1H), 6.78 (dd, $J$ = 8.0, 3.6 Hz, 1H), 4.86 (s, 2H), 0.91 (s, 9H), 0.13 (s, 6H).

### 4.38. Methyl 4-[(5-chloro-2-{[(*tert*-butyl(dimethyl)silyl)-oxy]methyl}phenoxy)methyl]benzoate (60)

To a stirred solution of **59** (1.85 g, 6.80 mmol) in acetone (20 ml) were added methyl 4-(bromomethyl)benzoate (2.03 g, 8.84 mmol) and $K_2CO_3$ (1.41 g, 10.2 mmol) under argon atmosphere. After stirred for 4 h at 50 °C, the reaction mixture was diluted with EtOAc and filtered through a pad of Celite. The filtrate was concentrated in vacuo to yield **60** (3.47 g), which was used without further purification; TLC $R_f$ = 0.32 (EtOAc/hexane, 1:20).

### 4.39. Methyl 4-{[5-chloro-2-(hydroxymethyl)phenoxy]-methyl}benzoate (61)

To a stirred solution of **60** (3.47 g, <6.80 mmol, crude) in THF (10 ml) was added 1.0 M solution of TBAF in THF (6.8 ml, 6.8 mmol). The reaction mixture was stirred for 10 min and diluted with EtOAc. The organic layer was washed with water, brine, dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was recrystallized from EtOAc and hexane to yield **61** (1.76 g, 84% in 2 steps); TLC $R_f$ = 0.58 (EtOAc/hexane, 1:1); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.99 (d, $J$ = 8.4 H, 2H), 7.59 (d, $J$ = 8.4 Hz, 2H), 7.40 (d, $J$ = 8.0 Hz, 1H), 7.09 (d, $J$ = 2.0 Hz, 1H), 7.01 (dd, $J$ = 8.0, 2.0 Hz, 1H), 5.25 (s, 2H), 5.13 (t, $J$ = 5.6 Hz, 1H), 4.55 (d, $J$ = 5.6 Hz, 1H), 3.86 (s, 3H).

### 4.40. Methyl 4-{[2-(bromomethyl)-5-chlorophenoxy]-methyl}benzoate (62)

To a stirred solution of **61** (200 mg, 0.654 mmol) in $CH_2Cl_2$ (2 ml) were added triphenylphosphine (206 mg, 0.784 mmol) and carbon tetrabromide (325 mg, 0.98 mmol) at room temperature under argon. The reaction mixture was stirred for 5 min, the reaction mixture was diluted with EtOAc. The organic layer was washed with $NaHCO_3$aq, water, brine, dried over $MgSO_4$ and concentrated in vacuo to yield **62** (759 mg, 100%), which was used without further purification. TLC $R_f = 0.71$ (EtOAc/hexane, 1:2).

### 4.41. Methyl 4-{[5-chloro-2-(phenoxymethyl)phenoxy]-methyl}benzoate (63)

To a stirred solution of **62** (759 mg, 0.654 mmol) in acetone (2 ml) were added phenol (0.057 ml, 0.654 mmol) and $K_2CO_3$ (116 mg, 0.85 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 2 days, diluted with EtOAc and filtered through a pad of Celite. The filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to yield **63** (240 mg, 96%, in 2 steps); TLC $R_f = 0.35$ (benzene/hexane, 7:3); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.04 (d, $J = 8.4$ Hz, 2H), 7.47 (d, $J = 8.4$ Hz, 2H), 7.41 (d, $J = 8.9$ Hz, 1H), 7.29 (m, 2H), 6.97 (m, 5H), 5.17 (s, 2H), 5.12 (s, 2H), 3.92 (s, 3H); IR (KBr) 1722, 1599, 1495, 1281, 1243, 1109 cm$^{-1}$.

### 4.42. 4-{[5-Chloro-2-(phenoxymethyl)phenoxy]methyl}-benzoic acid (14)

The title compound **14** was prepared from **63** in 100% yield according to the same procedure as described for the preparation of **2** from **31a**. TLC $R_f = 0.49$ (MeOH/$CHCl_3$/AcOH, 5:100:1); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.11 (d, $J = 8.2$ Hz, 2H), 7.51 (d, $J = 8.2$ Hz, 2H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.30 (m, 2H), 6.98 (m, 5H), 5.19 (s, 2H), 5.14 (s, 2H); IR (KBr) 3449, 2901, 2361, 1703, 1602, 1499, 1407, 1377, 1292 cm$^{-1}$; MS (EI, Pos.) *m/e* 368 ($M^+$), 275, 135, 107.

## 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 mouse EP1-4.

Membranes from CHO cells expressing prostanoid receptors were incubated with redioligand (2.5 nM of [$^3$H]$PGE_2$) and the 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 (20 min). Incubation was terminated by filtration through Whatman GF/B filters. The filters were then 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 amount of unlabeled $PGE_2$ with assay buffer. The concentration of the test compound required to inhibit the amount of the specific binding in the vehicle group by 50% ($IC_{50}$ value) were estimated from the regression curve. The $K_i$ value (M) was calculated according to the following equation.

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

where [L] is concentration of radiolabeled ligand; $K_d$, dissociation constant of radiolabeled ligand for the prostanoid receptors.

### 5.2. Measurement of the mEP1 receptor antagonist activity

To confirm that test compounds antagonize the mEP1 receptor and estimate potencies of antagonism for 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 $1 \times 10^4$ cells/well in 96 well plates and cultured for 2 days with 10% FBS (fetal bovine serum)/minimum essential medium Eagle alpha modification (αMEM) in the incubator (37 °C, 5% $CO_2$). The cells in each well were rinsed with phosphate buffer (PBS(minus)), 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, 2.5 mm of probenecid) was discarded. After the addition of the assay buffer (Hank's balanced salt solution (HBSS) containing 0.1% (w/v) BSA, 2 μM of indomethacin, 2.5 mm of probenecid and 10 mm of HEPES–NaOH) to each well, the cells were incubated in a dark place at room temperature for 1 h. After the addition of a test compound (10 μl) and $PGE_2$ (10 μl) which were prepared with assay buffer, intracellular calcium concentration was measured with Fluorescence drug screening system (FDSS-4000, Hamamatsu Photonics). A pair of fluorescence intensities emitted 500 nm by an excitation wavelength of each 340 and 380 nm was measured. The percent inhibition of 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 test compound (100%) to estimate the $IC_{50}$ value.

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