Pergamon

Bioorganic & Medicinal Chemistry 9 (2001) 1977–1984

BIOORGANIC & MEDICINAL CHEMISTRY

Structure–Activity Relationship of Cinnamic Acylsulfonamide Analogues on the Human EP_3 Prostanoid Receptor

Hélène Juteau, Yves Gareau,* Marc Labelle, Claudio F. Sturino, Nicole Sawyer, Nathalie Tremblay, Sonia Lamontagne, Marie-Claude Carrière, Danielle Denis and Kathleen M. Metters

Merck Frosst Canada & Co., PO Box 1005, Pointe-Claire-Dorval, Québec, Canada H9R 4P8

Received 5 February 2001; accepted 28 February 2001

Abstract—Potent and selective antagonists of the human EP_3 receptor have been identified. The structure–activity relationship of the chemical series was conducted and we found several analogues displaying sub-nanomolar K_i values at the EP_3 receptor and micromolar activities at the EP_1, EP_2 and EP_4 receptors. The effect of added human serum albumin (HSA) on the binding affinity at the EP_3 receptor was also investigated.

Introduction

In response to various extracellular stimuli, prostaglandins are rapidly generated through the consecutive action of the cyclo-oxygenases and distinct synthases on membrane arachidonic acid and exert their action in close proximity to the site of their synthesis. The eight known human prostanoid receptors have been cloned and their sequences determined.[1] PGE_2 will bind preferentially to the EP_1, EP_2, EP_3 and EP_4 receptors, PGD_2 to the DP receptor, $PGF_{2\alpha}$ to the FP receptor, PGI_2 to the IP receptor and TXA_2 to the TP receptor.[2,3] The pharmacological action of the prostanoids at their respective receptors results ultimately in a variety of biological responses in different tissues. PGE_2 binding to the EP_3 receptor has been found to play a key role in the regulation of ion transport, smooth muscle contraction of the GI tract, acid secretion, uterine contraction during fertilization and implantation, fever generation and PGE_2-mediated hyperalgesia. The EP_3 receptor has been detected in many organs such as the kidney, the gastrointestinal tract, the uterus and the brain.[4] So far, studies for understanding the roles of EP_3 have been conducted mainly with PGE_2 and other prostanoid-like compounds.[5] However, these compounds behave as agonists and cross react with other prostanoid receptors. The lack of selective and specific EP_3 antagonists has become a crucial issue for the characterization of the EP_3 receptor pharmacology.

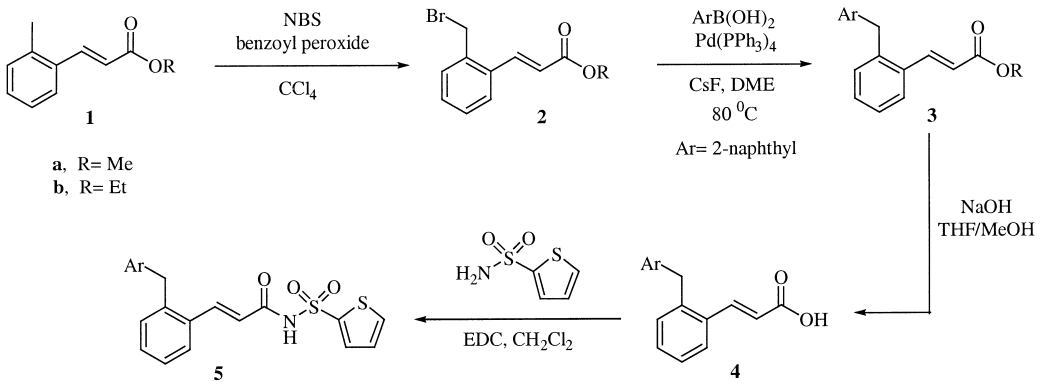
Results and Discussion

Recently, we have reported a new class of EP_3 antagonist based on the arylmethyl cinnamic acid skeleton **4**.[6] This series was found to be active at the EP_3 receptor with K_i values between 20 and 100 nM for the most potent analogues.[7] The three step synthesis of this class of compounds is illustrated in Scheme 1. A Suzuki coupling reaction was first performed between the benzyl bromide **2** and an aryl boronic acid. Hydrolysis under basic conditions gave the desired arylmethyl cinnamic acid **4** with a K_i of 20 nM on the EP_3 receptor when Ar = 2-naphthyl. In an effort to improve the potency in this series, an extensive SAR study was carried out focusing on four different positions. These positions are the top and bottom ring, the methylene linker and the carboxylic acid moiety, the latter being the first position investigated.

The acidic character of the molecule is essential for activity. Neutral compounds were found to be inactive on EP_3. We thus focused our effort on identifying acid surrogates with improved binding affinity. Tetrazole is probably the most widely used replacement for carboxylic acid. The tetrazole analogue of **4** (Ar = 2-naphthyl) was

*Corresponding author. Tel.: +1-514-428-3001; fax: +514-428-4900; e-mail: yves_gareau@merck.com

0968-0896/01/$ - see front matter
PII: S0968-0896(01)00110-9



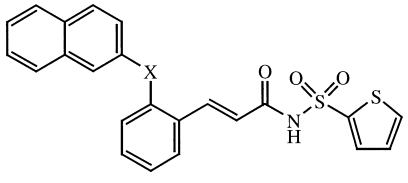
Scheme 1.

prepared from the nitrile and was found to be 10-fold less active with a K_i of 190 nM on EP_3. This series was no longer pursued.

Among various changes looked at, we found that incorporation of 2-thiophenesulfonamide to form an acylsulfonamide such as **5** would greatly improve the potency of compound **4**. The adduct **5** was 1.1 nM on the EP_3 receptor and very selective over the other EP receptors (Table 1). The high shift in the presence of HSA was the major drawback of this compound. The K_i value at the EP_3 receptor in the presence of 0.05% human serum albumin (HSA) was 263 nM (>200-fold shift). We decided at this time to carry out further SAR studies with the 2-thiophene acyl sulfonamide and to re-investigate the issue of protein shift later on. Acylsulfonamide **5** was easily prepared from carboxylic acid **4** and 2-thiophenesulfonamide in the presence of a coupling reagent (EDC) according to Scheme 1.

The second position we looked at for the SAR was the methylene linker. Replacement by heteroatoms such as oxygen and sulfur did not improve the binding affinity. The oxygen linker **6a** was surprisingly less potent on EP_3 with a K_i of 153 nM when compared to the sulfur **6b** ($K_i = 6.7$ nM) or the methylene tether **5**. This loss of potency may be attributed to the difference in conformation between the oxygen and the methylene linker (the conjugation of the oxygen lone pair with the aromatic rings slow down the rotation around this bond). Among the analogues that we prepared, the sulfone **6d** turned out to be the least shifted (20-fold) but the potency on EP_3 was not improved. We could have used the sulfone linker to investigate the top aromatic ring but decided, for practical reasons, to continue SAR with the methylene moiety. Next, the naphthyl group was replaced by a phenyl and the substitution of the ring was looked at. We first noticed that polarity played an important role in this region of the molecule. Strong electron-withdrawing groups such as sulfoxide **7b** and sulfone **7c** at the 4-position were not tolerated at all, which resulted in dramatic losses of potency with activities of 3.7 and 1.3 μM, respectively. On the other hand, lipophilic groups such as chlorine and thioether were better tolerated. The K_i values of these analogues ranged from 1.9 to 6.3 nM and they were also quite selective over the other EP receptors (**7a**, **8a**, **8b**, and **8c**). The 3,4-dichlorophenyl **8c** gave the best substitution on the

Table 1. Binding affinity of cinnamic analogues bearing various tether

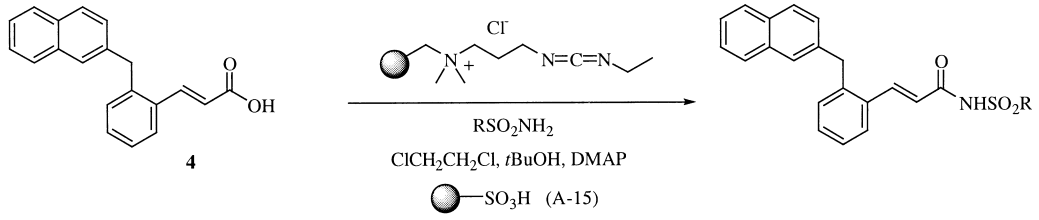


		K_i (nM)[a]				
Compound	X	EP_1	EP_2	EP_3	EP_3 (+0.05% HSA)	EP_4
5	CH_2	>5000	>5000	1.1	263	1236
6a	O	>5000	2000	153	1500	1300
6b	S	>5000	3333	6.7	356	1300
6c	SO	>5000	>5000	17	200	>5000
6d	SO_2	>5000	>5000	2.1	41	1567
6e	OCH_2	>5000	>5000	9.9	1794	1380

[a] K_i determinations are averages based on at least two experiments.

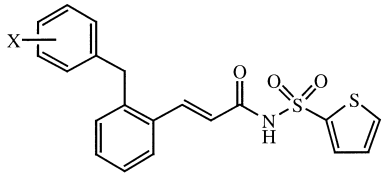
ring with a K_i of 1.9 nM but was highly shifted in the presence of HSA to 1.7 μM (1000-fold shift).

We then directed our efforts to find a thiophene replacement. This was accomplished with a solid supported reagent to simplify the work up procedure and speed up the process. The carboxylic acid **4** was coupled to various aryl and alkyl sulfonamides using a polymer-supported coupling reagent (EDC, Scheme 2).[8] Typically, the reaction was performed using an excess of the coupling reagent and DMAP (the latter being used due to the low reactivity of the sulfonamide nucleophile). To avoid any unreacted sulfonamide contamination at the end of the reaction, we used 0.8 equivalents of sulfonamide (with 1 equivalent of the carboxylic acid). The excess of carboxylic acid remains bound to the resin and does not diminish product purity. Amberlyst-15 was also used at the end of the reaction as a proton source to protonate the acylsulfonamide and to remove the DMAP from the solution. The work up of this reaction involved a simple filtration to remove the resin bound reagent and the DMAP. Overall, 62 compounds were prepared with this procedure with high yields and purities. We were able to find a thiophene replacement that showed superior activity and better behavior in the presence of HSA. The 5-bromo-2-methoxybenzene sulfonamide **9** was the best analogue in terms of potency with a K_i of 0.3 nM on EP_3. It was shifted only 14-fold in the presence of HSA (Table 2). This part of the molecule was kept constant and a new SAR was initiated on the naphthyl and phenyl group. The *para* position to the methylene group on the aromatic ring of the cinnamoyl moiety was investigated next. Substituting with heteroatoms such as fluorine, chlorine or methoxy (**10a**, **10b**, **10c**) resulted in no gain of potency. Although the fluoro analogue showed a smaller shift in the presence of HSA, the selectivity against EP_4 ($K_i = 715$ nM) was reduced. Also, increasing the size of the group from hydrogen, chlorine, methoxy to allyl **10d** yielded less potent antagonists on EP_3. We decided to carry on the SAR on the naphthyl group with the chlorine substituent since this analogue **10b** was more selective over the other EP receptors. Quinoline analogues such as **11c** were looked at but were rapidly abandoned due to the lack of improvement on the binding affinity. We then looked at substituted naphthyl derivatives; two representatives (**11a** and **11b**) are shown in Table 3. Substitution on the naphthyl moiety with fluorine or chlorine resulted in very potent compounds on the EP_3 receptor and highly selective over the PGE receptors with only 10-fold shift in the presence of HSA. The synthesis of these compounds is outlined in Scheme 3.[9] First, the zinc derivative of 3-(2-bromomethyl-5-chlorophenyl)-acrylic acid ethyl ester was prepared from the corresponding halide. The zinc intermediate **12** was then coupled to the corresponding substituted naphthyl



Scheme 2.

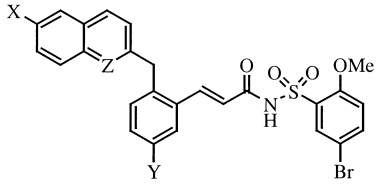
Table 2. Binding affinity of substituted phenyl analogues



Compound	X	K_i (nM)[a]				
		EP_1	EP_2	EP_3	EP_3 (+0.05% HSA)	EP_4
7a	4-SME	> 5000	> 5000	5.1	1045	> 5000
7b	4-SOMe	> 5000	> 5000	3750	ND[b]	> 5000
7c	4-SO_2Me	> 5000	> 5000	1300	ND[b]	> 5000
8a	4-Cl	> 5000	> 5000	6.3	1890	4750
8b	2,4-Cl	> 5000	> 5000	2.5	579	3700
8c	3,4-Cl	> 5000	> 5000	1.9	1690	2522
8d	3,5-Cl	> 5000	> 5000	26	3856	3700

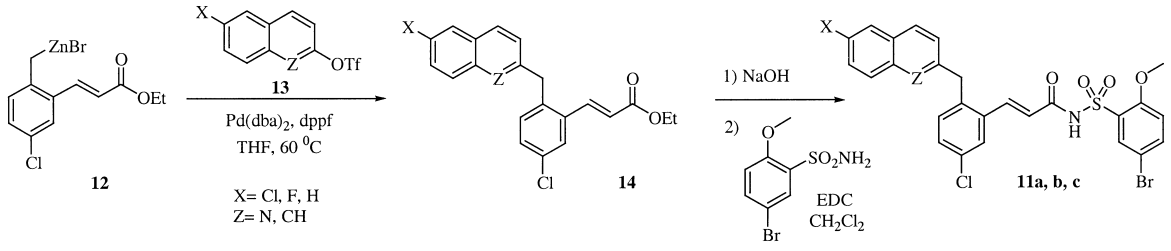
[a]K_i determinations are averages based on at least two experiments.
[b]Not determined.

Table 3. Binding affinity of substituted phenyl analogues



Compound	Z	X	Y	K_i (nM)[a]				
				EP_1	EP_2	EP_3	EP_3 (+0.05% HSA)	EP_4
9	CH	H	H	> 5000	> 5000	0.3	4.2	916
10a	CH	H	F	> 5000	> 5000	0.3	1.2	715
10b	CH	H	Cl	> 5000	> 5000	0.8	9.2	> 5000
10c	CH	H	OMe	> 5000	> 5000	1.5	28.1	2050
10d	CH	H	Allyl	> 5000	> 5000	48	400	4600
11a	CH	F	Cl	> 5000	> 5000	0.5	4.7	5350
11b	CH	I	Cl	> 5000	> 5000	0.6	4.1	> 5000
11c	N	H	Cl	> 5000	> 5000	1.5	22.1	1557

[a] K_i determinations are averages based on at least two experiments.



Scheme 3.

triflate **13** with $Pd(dba)_2$ and dppf to yield the desired adduct **14**. Basic hydrolysis of the ester followed by the sulfonamide coupling afforded compounds **11a** and **11b**.

Conclusion

We have described the SAR studies in the arylmethyl cinnamic acylsulfonamide series that allowed identification of compounds with nanomolar potency on the human EP_3 receptor and high selectivity over the other EP receptors.[10] One of them, compound **11b**, was 0.6 nM at the EP_3 receptor and 4.1 nM in the presence of HSA (7-fold shift). This compound was also highly selective over the other EP receptors. Pharmacological studies of this compound will be disclosed elsewhere.

Experimental

Biological assays

See ref 2 for stable expression of prostanoid receptors in the human embryonic kidney (HEK) 293 (EBNA) cell line and also for prostanoid receptor binding assays.

Chemistry

General procedure for the preparation of cinnamate ester. Methyl-3-(2-methylphenyl)-2-propenoate (1a). To a solution of 2-methylcinnamic acid (100.0 g, 617 mmol) in 1.2 L of DMF was added DBU (112.6 g, 740 mmol). After 15 min, methyl iodide (131.3 g, 925 mmol) was added dropwise and the mixture was stirred overnight. The solution was then diluted in ether and washed with HCl (10%), water and brine. The solvent was removed to give 106.8 g (98%) of the title compound **1a**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, $J = 15.1$ Hz, 1H), 7.52 (d, $J = 8.0$ Hz, 1H), 7.22 (m, 3H), 6.35 (d, $J = 15.1$ Hz, 1H), 3.80 (s, 3H), 2.41 (s, 3H). The ethyl ester **1b** was prepared in a different fashion. To 2-methyl benzaldehyde (5.0 g, 41.6 mmol) and triethyl phosphonoacetate (9.9 mL, 50.0 mmol) in 150 mL of toluene at 0 °C, was added sodium hydride (2.52 g, 63.0 mmol, 60% w/w in oil) portionwise. After 2 h of stirring, the mixture was quenched with an ammonium acetate solution (25%) and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$ and the solvent removed to give 7.1 g (90%) of the desired ethyl cinnamate. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, $J = 15.1$ Hz, 1H), 7.52 (d, $J = 8.0$ Hz, 1H), 7.20 (m, 3H), 6.35 (d,

$J = 15.1$ Hz, 1H), 4.23 (q, $J = 7.3$ Hz, 2H), 2.39 (s, 3H), 1.33 (t, $J = 7.3$ Hz, 3H).

General procedure for the preparation of benzylic bromide. 3-(2-bromomethyl-phenyl)-acrylic acid methyl ester (2a). To **1a** (18.5 g, 105 mmol) and NBS (19.6 g, 110.3 mmol) in refluxing CCl_4 was added benzoyl peroxide (1.27 g, 5.24 mmol). The solution was stirred 12 h under reflux then cooled to rt and filtered. The solvent was removed and the crude oil purified by silica gel chromatography using 5% ethyl acetate in hexane to yield 14.2 g (53%) of the title compound **2a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, $J = 15.2$ Hz, 1H), 7.57 (m, 1H), 7.30 (m, 3H), 6.45 (d, $J = 15.2$ Hz, 1H), 4.60 (s, 2H), 3.85 (s, 3H).

General procedure for the Suzuki coupling reaction. 3-(2-naphthalen-2-ylmethyl-phenyl)-acrylic acid methyl ester (3a). A mixture of benzyl bromide **2a** (0.50 g, 1.86 mmol), 2-naphthylboronic acid (0.63 g, 3.71 mmol), CsF (1.13 g, 7.43 mmol) and $(Ph_3P)_4Pd$ (0.11 g, 0.09 mmol) in 10 mL of DME was heated to reflux for 10 h. The mixture was cooled to rt, quenched with an ammonium acetate solution (25%) and extracted with ethyl acetate. The organic phases were combined, dried and the solvent removed. Purification by silica gel chromatography using 10% ethyl acetate in hexane afforded 0.35 g (63%) of the title compound **3a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, $J = 15.4$ Hz, 1H), 7.75 (m, 3H), 7.60 (d, $J = 7.0$ Hz, 1H), 7.52 (s, 1H), 7.41 (m, 2H), 7.25 (m, 4H), 6.32 (d, $J = 15.5$ Hz, 1H), 4.25 (s, 2H), 3.75 (s, 3H).

General procedure for ester hydrolysis. 3-(2-naphthalen-2-ylmethyl-phenyl)-acrylic acid (4). Hydrolysis of the previous ester **3a** (0.33 g, 1.10 mmol) was performed in THF/MeOH (6:3 mL) with a 2 N sodium hydroxyde solution (1.1 mL, 2.20 mmol). After 4 h, the solution was diluted with ethyl acetate and quenched with HCl (10%). The organic phase was dried over Na_2SO_4 and the solvent removed. Purification was done by a trituration with hexane to yield 0.21 g (66%) of the title compound **4**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, $J = 15.1$ Hz, 1H), 7.73 (m, 3H), 7.62 (d, $J = 7.5$ Hz, 1H), 7.52 (s, 1H), 7.40–7.21 (m, 6H), 6.32 (d, $J = 15.1$ Hz, 1H), 4.29 (s, 2H); elemental analysis calcd for $C_{20}H_{16}O_2.1/4H_2O$: C, 82.16; H, 5.63; found: C, 81.70; H, 5.66.

General procedure for the acylsulfonamide preparation. Thiophene-2-sulfonic acid [3-(2-naphthalen-2-ylmethyl-phenyl)-acryloyl]-amide (5). To the acid **4** (100 mg; 0.35 mmol), 2-thiophenesulfonamide (60 mg; 0.37 mmol) and DMAP (86 mg; 0.70 mmol) in 2 mL of CH_2Cl_2, was added EDCI (134 mg; 0.70 mmol). The mixture was stirred overnight. The solution was then diluted with ethyl acetate, quenched with HCl (10%) and washed with brine. The organic phase was dried over Na_2SO_4 and the solvent removed. Purification by silica gel chromatography using 5% methanol in dichloromethane afforded 87 mg (57%) of the title compound **5**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, $J = 15.2$ Hz, 1H), 7.84 (m, 1H), 7.81–7.15 (m, 12H), 7.02 (m, 1H), 6.31 (d, $J = 15.2$ Hz, 1H), 4.24 (s, 2H); elemental analysis calcd for the sodium salt $C_{24}H_{18}NNaO_3S_2.H_2O$: C, 60.87; H, 4.22; N, 2.96; S, 13.54; found: C, 60.36; H, 4.25; N, 3.29; S, 12.53.

Thiophene-2-sulfonic acid {3-[2-(naphthalen-2-yloxy)-phenyl]-acryloyl}-amide (6a). A mixture of 2-naphthol (3.50 g, 24.2 mmol), 2-fluorobenzaldehyde (3.05 g, 24.2 mmol) and potassium carbonate (3.71 g, 26.6 mmol) in 30 mL of dimethylacetamide was stirred under reflux for 2 h.[11] After cooling down to rt, the mixture was diluted with ethyl acetate and washed with water and brine. The organic phase was dried over $MgSO_4$ and evaporated to dryness. Purification on silica gel using 10% ethyl acetate in hexane afforded 3.42 g (57%) of 2-(naphthalen-2-yloxy)-benzaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.05 (m, 1H), 7.92 (m, 2H), 7.75 (d, $J = 7.1$ Hz, 1H), 7.52 (m, 3H), 7.35 (s, 1H), 7.31 (m, 1H), 7.25 (m, 1H), 6.95 (d, $J = 7.1$ Hz, 1H). Olefination to the α,β-unsaturated ester using triethylphosphonoacetate followed by hydrolysis and coupling with 2-thiophenesulfonamide as previously described for compound **5** afforded the title compound **6a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (m, 2H), 7.92 (m, 2H), 7.74 (m, 2H), 7.55–7.40 (m, 3H), 7.37 (m, 1H), 7.29 (dd, $J = 8.8$ and 2.0 Hz, 1H), 7.24 (m, 1H), 7.15 (dd, $J = 4.5$ and 4.0 Hz, 1H), 6.97 (d, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 16.0$ Hz, 1H); HR-MS calcd for the sodium salt $C_{23}H_{16}NNaO_4S_2 + H^+$: 458.0497; found: 458.0497.

Thiophene-2-sulfonic acid {3-[2-(naphthalen-2-sulfanyl)-phenyl]-acryloyl}-amide (6b). A mixture of 2-naphthalenethiol (5.33 g, 33.0 mmol), 2-fluorobenzaldehyde (3.71 g, 30.0 mmol) and potassium carbonate (4.62 g, 33.0 mmol) in 28 mL of isopropanol was stirred overnight under reflux.[12] After cooling down to rt, the mixture was diluted with ethyl acetate and washed with water and brine. The organic phase was dried over $MgSO_4$ and evaporated to dryness. Purification on silica gel using 10% ethyl acetate in hexane afforded 7.82 g (99%) of 2-(naphthalen-2-ylsulfanyl)-benzaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.05 (s, 1H), 7.85 (m, 4H), 7.52 (m, 2H), 7.45 (m, 1H), 7.35 (m, 2H), 7.11 (d, $J = 7.1$ Hz, 1H). Olefination to the α,β-unsaturated ester using triethylphosphonoacetate afforded 3-[2-(naphthalen-2-ylsulfanyl)-phenyl]-acrylic acid ethyl ester. Hydrolysis followed by coupling with 2-thiophenesulfonamide afforded the title compound **6b**. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.31 (d, $J = 15.5$ Hz, 1H), 7.82 (m, 7H), 7.47 (m, 2H), 7.41 (m, 3H), 7.33 (m, 1H), 7.12 (m, 1H), 6.66 (d, $J = 15.5$ Hz, 1H); HR-MS calcd for the sodium salt $C_{23}H_{16}NO_3S_3Na + H^+$: 474.0268; found: 474.0270.

Thiophene-2-sulfonic acid {3-[2-(naphthalene-2-sulfinyl)-phenyl]-acryloyl}-amide (6c). To a solution of 3-[2-(naphthalen-2-ylsulfanyl)-phenyl]-acrylic acid ethyl ester (2.98 g, 9.05 mmol) in 45 mL of CH_2Cl_2 at 0 °C was added m-CPBA (1.72 g, 9.91 mmol). After 1 h, the reaction was quenched with a sodium thiosulfate solution and extracted with ethyl acetate. The organic phase was washed with water, brine and dried over $MgSO_4$. After evaporation to dryness and purification on silica gel using 30% ethyl acetate in hexane, 2.35 g (74%) of 3-[2-(naphthalene-2-sulfinyl)-phenyl]-acrylic acid ethyl

ester was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.25 (d, J = 15.5 Hz, 1H), 8.12 (d, J = 7.9 Hz, 1H), 7.85 (m, 1H), 7.81 (m, 2H), 7.55 (m, 4H), 7.45 (m, 2H), 6.33 (d, J = 15.3 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). Hydrolysis followed by coupling with 2-thiophenesulfonamide afforded the title compound **6c**. ^{1}H NMR (400 MHz, CD_3OD-d_4) δ 8.17 (s, 1H), 8.12 (d, J = 7.3 Hz, 1H), 7.99 (d, J = 15.4 Hz, 1H), 7.85–7.72 (m, 4H), 7.67 (d, J = 7.9 Hz, 1H), 7.55 (m, 2H), 7.45 (m, 3H), 7.22 (dd, J = 8.7 and 1.8 Hz, 1H), 7.12 (m, 1H), 6.19 (d, J = 15.4 Hz, 1H); elemental analysis calcd for the sodium salt $C_{23}H_{16}NNaO_4S_3.1/2H_2O$: C, 55.36; H, 3.40; N, 2.81; S, 19.27; found: C, 55.00; H, 3.62; N, 2.81; S, 18.18.

Thiophene-2-sulfonic acid {3-[2-(naphthalene-2-sulfonyl)-phenyl]-acryloyl}-amide (6d). To a solution of 3-[2-(naphthalen-2-ylsulfanyl)-phenyl]-acrylic acid ethyl ester (1.02 g, 3.05 mmol) in 15 mL of CH_2Cl_2 at 0 °C was added m-CPBA (1.58 g, 9.15 mmol). The solution was stirred 1 h. Work-up and purification were done as previously described for compound **6c** to give 853 mg (76%) of 3-[2-(naphthalene-2-sulfonyl)-phenyl]-acrylic acid ethyl ester. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.52 (d, J = 15.4 Hz, 1H), 8.35 (m, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.85 (m, 2H), 7.70 (d, J = 7.9 Hz, 1H), 7.55 (m, 5H), 6.05 (d, J = 15.3 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). Hydrolysis followed by coupling with 2-thiophenesulfonamide gave the desired compound **6d**. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.71 (d, J = 15.6 Hz, 1H), 8.66 (s, 1H), 8.32 (m, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.91 (m, 5H), 7.60 (m, 5H), 7.15 (t, J = 4.5 Hz, 1H), 6.32 (d, J = 15.6 Hz, 1H); elemental analysis calcd for the sodium salt $C_{23}H_{16}NNaO_5S_3.3/2H_2O$: C, 51.87; H, 3.57; N, 2.63; S, 18.05; found: C, 51.70; H, 3.33; N, 2.75; S, 17.70.

Thiophene-2-sulfonic acid {3-[2-(naphthalen-2-yloxymethyl)-phenyl]-acryloyl}-amide (6e). A solution of 2-naphthol (147 mg, 1.00 mmol), benzyl bromide **1b** (250 mg, 0.90 mmol) and cesium carbonate (394 mg, 1.20 mmol) in 5 mL of DMF was heated at 40 °C overnight. After cooling to rt and diluted with ethyl acetate, the organic phase was washed with water, brine and dried over $MgSO_4$. After evaporation, the product was purified over silica gel using 10% ethyl acetate in hexane to yield 245 mg (85%) of 3-[2-(naphthalen-2-yloxymethyl)-phenyl]-acrylic acid ethyl ester. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 15.2 Hz, 1H), 7.82 (m, 3H), 7.65 (m, 1H), 7.55 (m, 1H), 7.41–7.30 (m, 4H), 7.23–7.11 (m, 2H), 6.41 (d, J = 15.5 Hz, 1H), 5.30 (s, 2H), 4.25 (q, J = 7.3 Hz, 2H), 1.35 (t, J = 7.3 Hz, 3H). Hydrolysis followed by coupling with 2-thiophenesulfonamide afforded the desired compound **6e**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 15.6 Hz, 1H), 7.83 (s, 1H), 7.71 (m, 3H), 7.53 (m, 3H), 7.41 (m, 4H), 7.15 (m, 2H), 7.02 (brs, 1H), 6.39 (d, J = 15.4 Hz, 1H), 5.22 (s, 2H); elemental analysis calcd for the sodium salt $C_{24}H_{28}NNaO_4S_2.3/2H_2O$: C, 57.82; H, 4.21; N, 2.81; found: C, 58.31; H, 3.96; N, 2.91.

Thiophene-2-sulfonic acid {3-[2-(4-methylsulfanylbenzyl)-phenyl]-acryloyl}-amide (7a). The compound was prepared according to Scheme 1. The Suzuki coupling reaction with (4-methylthio)phenylboronic acid afforded 3-[2-(4-methylsulfanyl-benzyl)-phenyl]-acrylic acid ethyl ester in 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 15.3 Hz, 1H), 7.63 (d, J = 7.4 Hz, 1H), 7.25 (m, 2H), 7.15 (d, J = 7.1 Hz, 3H), 7.05 (d, J = 7.7 Hz, 2H), 6.31 (d, J = 15.4 Hz, 1H), 4.22 (q, J = 7.3 Hz, 2H), 4.06 (s, 2H), 2.43 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H). Hydrolysis followed by coupling with 2-thiophenesulfonamide afforded the title compound **7a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 15.3 Hz, 1H), 7.89 (s, 1H), 7.61 (s, 1H), 7.49 (m, 1H), 7.32–6.91 (m, 8H), 6.33 (d, J = 15.3 Hz, 1H), 4.01 (s, 2H), 2.40 (s, 3H); elemental analysis calcd for the sodium salt $C_{21}H_{18}NNaO_3S_3 \cdot 1/2H_2O$: C, 54.77; H, 4.13; N, 3.04; S, 20.88; found: C, 54.55; H, 4.01; N, 3.06; S, 20.58.

Thiophene-2-sulfonic acid {3-[2-(4-methylsulfinylbenzyl)-phenyl]-acryloyl}-amide (7b). To a solution of 3-[2-(4-methylsulfanyl-benzyl)-phenyl]-acrylic acid ethyl ester (384 mg, 1.23 mmol) in 6 mL of CH_2Cl_2 at 0 °C was added m-CPBA (233 mg, 1.35 mmol) and the mixture was stirred overnight. The solution was then diluted with ethyl acetate, washed with a sodium thiosulfate solution, water and brine. The organic phase was dried over $MgSO_4$ and evaporated to dryness. After purification on silica gel using 100% ethyl acetate, 340 mg (88%) of 3-[2-(4-methanesulfinyl-benzyl)-phenyl]-acrylic acid ethyl ester was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 15.6 Hz, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.55 (d, J = 7.5 Hz, 2H), 7.31 (m, 4H), 7.15 (d, J = 7.2 Hz, 1H), 6.32 (d, J = 15.3 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 4.23 (s, 2H), 2.70 (s, 3H), 1.33 (t, J = 7.4 Hz, 3H). Hydrolysis followed by coupling with 2-thiophenesulfonamide afforded the title compound **7b**. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.05 (d, J = 15.3 Hz, 1H), 7.95 (d, J = 4.5 Hz, 1H), 7.86 (d, J = 4.3 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 7.9 Hz, 2H), 7.42 (d, J = 6.6 Hz, 1H), 7.33 (m, 4H), 7.22 (m, 1H), 6.61 (d, J = 15.5 Hz, 1H), 4.31 (s, 2H), 2.60 (s, 3H); HR-MS calcd for the sodium salt $C_{21}H_{18}NO_4S_3Na + H^+$: 468.0374; found: 468.0373.

Thiophene-2-sulfonic acid {3-[2-(4-methylsulfonylbenzyl)-phenyl]-acryloyl}-amide (7c). To a solution of 3-[2-(4-methylsulfanyl-benzyl)-phenyl]-acrylic acid ethyl ester (384 mg, 1.23 mmol) in 6 mL of CH_2Cl_2 at 0 °C was added m-CPBA (637 mg, 3.69 mmol) and the mixture was stirred 1 h. The solution was then diluted with ethyl acetate, washed with a sodium thiosulfate solution, water and brine. The organic phase was dried over $MgSO_4$ and evaporated to dryness. After purification on silica gel using 50% ethyl acetate in hexane, 390 mg (96%) of 3-[2-(4-methanesulfonyl-benzyl)-phenyl]-acrylic acid ethyl ester was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 15.4 Hz, 1H), 7.82 (d, J = 7.6 Hz, 2H), 7.60 (d, J = 7.5 Hz, 1H), 7.31 (m, 4H), 7.23 (d, J = 7.1 Hz, 1H), 6.31 (d, J = 15.6 Hz, 1H), 4.22 (q, J = 7.4 Hz, 2H), 4.22 (s, 2H), 3.05 (s, 3H), 1.33 (t, J = 7.3 Hz, 3H). Hydrolysis followed by coupling with 2-thiophenesulfonamide afforded the title compound **7c**. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.05 (m, 2H), 7.87 (d, J = 4.4 Hz, 1H), 7.82 (d, J = 7.6 Hz, 2H), 7.65 (d, J = 7.8 Hz, 1H), 7.35 (m, 5H), 7.22 (m, 1H), 6.62 (d, J = 15.3

Hz, 1H), 4.32 (s, 2H), 3.11 (s, 3H); HR-MS calcd for the sodium salt $C_{21}H_{18}NO_5S_3Na + H^+$: 484.0323; found: 484.0323.

Thiophene-2-sulfonic acid {3-[2-(4-chlorobenzyl)-phenyl]-acryloyl}-amide (8a). The compound was prepared according to Scheme 1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 15.5 Hz, 1H), 7.85 (d, J = 2.9 Hz, 1H), 7.55 (m, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.31 (m, 1H), 7.14 (m, 4H), 7.05 (m, 1H), 6.95 (d, J = 8.4 Hz, 2H), 6.34 (d, J = 15.4 Hz, 1H), 4.05 (s, 2H); HR-MS calcd for the sodium salt $C_{20}H_{16}NO_3S_2ClNa + H^+$: 440.0158; found: 440.0160.

Thiophene-2-sulfonic acid {3-[2-(2,4-dichlorobenzyl)-phenyl]-acryloyl}-amide (8b). The compound was prepared according to Scheme 1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 15.5 Hz, 1H), 7.87 (d, J = 3.8 Hz, 1H), 7.56 (d, J = 5 Hz, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.33 (s, 1H), 7.25 (m, 2H), 7.05 (m, 2H), 6.95 (d, J = 7.6 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 6.42 (d, J = 15.4 Hz, 1H), 4.11 (s, 2H); elemental analysis calcd for the sodium salt $C_{20}H_{14}Cl_2NNaO_3S_2$: C, 50.64; H, 2.97; N, 2.95; S, 13.52; found: C, 50.30; H, 3.01; N, 2.89; S, 13.75.

Thiophene-2-sulfonic acid {3-[2-(3,4-dichlorobenzyl)-phenyl]-acryloyl}-amide (8c). The compound was prepared according to Scheme 1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 15.4 Hz, 1H), 7.88 (d, J = 2.0 Hz, 1H), 7.63 (d, J = 4.9 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.32 (m, 1H), 7.24 (m, 2H), 7.07 (m, 3H), 6.85 (d, J = 8.2 Hz, 1H), 6.33 (d, J = 15.4 Hz, 1H), 4.07 (s, 2H); elemental analysis calcd for the sodium salt $C_{20}H_{14}Cl_2NNaO_3S_2.1/2H_2O$: C, 49.7; H, 3.1; N, 2.9; S, 13.27; found: C, 49.46; H, 2.9; N, 2.86; S, 13.73.

Thiophene-2-sulfonic acid {3-[2-(3,5-dichlorobenzyl)-phenyl]-acryloyl}-amide (8d). The compound was prepared according to Scheme 1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 15.4 Hz, 1H), 7.91 (d, J = 3.8 Hz, 1H), 7.72 (d, J = 3.8 Hz, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.44 (s, 1H), 7.31 (m, 2H), 7.15 (m, 3H), 6.95 (s, 2H), 6.55 (d, J = 15.4 Hz, 1H), 4.11 (s, 2H); HR-MS calcd for $C_{20}H_{15}NO_3S_2Cl_2 + H^+$: 451.9949; found: 451.9949.

5-Bromo-2-methoxy-*N*-[3-(2-naphthalen-2-ylmethyl-phenyl)-acryloyl]-benzenesulfonamide (9). Carboxylic acid **4** was coupled with 5-bromo-2-methoxybenzenesulfonamide to afford the title compound **9** in 73% yield. ^{1}H NMR (acetone-d_6-DMSO-d_6) δ 8.01 (d, J = 15.2 Hz, 1H), 7.91 (m, 5H), 7.65–7.55 (m, 2H), 7.50–7.35 (m, 4H), 7.31 (m, 1H), 7.15 (d, 1H), 6.65 (d, J = 15.2 Hz, 1H), 4.31 (s, 2H), 3.85 (s, 3H); elemental analysis calcd for the sodium salt $C_{27}H_{21}BrNNaO_4S.1/2H_2O$: C, 57.15; H, 3.88; N, 2.47; found: C, 56.88; H, 3.73; N, 2.52.

5-Bromo-*N*-[3-(5-fluoro-2-naphthalen-2-ylmethyl-phenyl)-acryloyl]-2-methoxy-benzenesulfonamide (10a). The compound was prepared according to Scheme 1 using 3-(2-bromomethyl-5-fluoro-phenyl)-acrylic acid ethyl ester for the Suzuki coupling reaction and 5-bromo-2-methoxyphenylsulfonamide for the final step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (brs, 1H), 8.16 (s, 1H), 7.97 (d, J = 15.4 Hz, 1H), 7.65 (m, 4H), 7.42 (m, 3H), 7.23 (m, 3H), 7.05 (m, 1H), 6.75 (d, J = 8.6 Hz, 1H), 6.41 (d, J = 15.2 Hz, 1H), 4.17 (s, 2H), 3.70 (s, 3H); elemental analysis calcd for the sodium salt $C_{27}H_{20}BrFNNaO_4S.H_2O$: C, 54.56; H, 3.70; N, 2.36; Found C, 54.73, H, 3.61; N, 2.45.

5-bromo-*N*-[3-(5-chloro-2-naphthalen-2-ylmethyl-phenyl)-acryloyl]-2-methoxy-benzenesulfonamide (10b). The compound was prepared according to Scheme 1 using 3-(2-bromomethyl-5-chloro-phenyl)-acrylic acid ethyl ester for the Suzuki coupling reaction and 5-bromo-2-methoxyphenylsulfonamide for the final step. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 2.5 Hz, 1H), 7.91 (d, J = 15.8 Hz, 1H), 7.82 (m, 4H), 7.62 (m, 2H), 7.41 (m, 5H), 7.23 (d, J = 8.9 Hz, 1H), 6.66 (d, J = 15.7 Hz, 1H), 4.31 (s, 2H), 3.85 (s, 3H); elemental analysis calcd for the sodium salt $C_{27}H_{20}BrClNNaO_4S.H_2O$: C, 53.08; H, 3.64; N, 2.29; S, 5.25; found: C, 53.25; H, 3.89; N, 2.91; S, 4.97.

5-Bromo-2-methoxy-*N*-[3-(5-methoxy-2-naphthalen-2-yl-methyl-phenyl)-acryloyl]-benzenesulfonamide (10c). The compound was prepared according to Scheme 1 using 3-(2-bromomethyl-5-methoxy-phenyl)-acrylic acid ethyl ester for the Suzuki coupling reaction and 5-bromo-2-methoxyphenylsulfonamide for the final step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (brs, 1H), 8.15 (d, J = 2.5 Hz, 1H), 7.95 (d, J = 15.5 Hz, 1H), 7.80–7.60 (m, 3H), 7.57 (dd, J = 8.8 and 2.5 Hz, 1H), 7.37 (m, 3H), 7.20–7.10 (m, 2H), 7.02 (d, J = 2.6 Hz, 1H), 6.85 (m, 1H), 6.70 (d, J = 8.9 Hz, 1H), 6.40 (d, J = 15.5 Hz, 1H), 4.13 (s, 2H), 3.77 (s, 3H), 3.72 (s, 3H).

***N*-[3-(5-allyl-2-naphthalen-2-ylmethyl-phenyl)-acryloyl]-5-bromo-2-methoxy-benzenesulfonamide (10d).** The compound was prepared according to Scheme 1 using 3-(5-allyl-2-bromomethyl-phenyl)-acrylic acid ethyl ester for the Suzuki coupling reaction and 5-bromo-2-methoxyphenylsulfonamide for the final step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (brs, 1H), 8.20 (d, J = 2.5 Hz, 1H), 8.05 (d, J = 15.6 Hz, 1H), 7.65 (m, 4H), 7.25 (m, 7H), 6.75 (d, J = 8.9 Hz, 1H), 6.41 (d, J = 15.6 Hz, 1H), 5.92 (m, 1H), 5.10 (m, 2H), 4.22 (s, 2H), 3.75 (s, 3H), 3.35 (m, 2H); HR-MS calcd for the sodium salt $C_{30}H_{25}NO_4SBrNa_+Na^+$: 620.0483; found: 620.0481.

5-Bromo-*N*-{3-[5-chloro-2-(6-fluoro-naphthalen-2-ylmethyl)-phenyl]-acryloyl}-2-methoxybenzenesulfonamide (11a). Preparation of the zinc bromide **12**:[9] to a solution of activated zinc (389 mg, 5.95 mmol) in 3 mL of DMF was added 3-(2-bromomethyl-5-chloro-phenyl)-acrylic acid ethyl ester (1.81 g, 5.95 mmol). The reaction was heated at 100 °C for 30 min then cooled down to rt. To a solution of $Pd(dba)_2$ (137 mg, 0.24 mmol) and dppf (133 mg, 0.24 mmol) in 20 mL of THF was added trifluoromethanesulfonic acid 6-fluoro-naphthalen-2-yl ester **13**[13] (1.75 g, 5.95 mmol) followed by the solution of zinc bromide **12** previously prepared. The reaction was stirred overnight at 65 °C, diluted in ethyl acetate and quenched with HCl 10%. The organic phase was washed with brine, dried over $MgSO_4$ and evaporated to dryness. Purification by flash chromatography afforded 1.03 g (47%) of 3-[5-chloro-2-(6-fluoro-naphthalen-2-ylmethyl)-phenyl]-acrylic acid ethyl ester **14**. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.91 (d, $J=15.2$ Hz, 1H), 7.72 (s, 1H), 7.65 (d, $J=7.6$ Hz, 2H), 7.55 (s, 1H), 7.43 (s, 1H), 7.32 (d, $J=7.6$ Hz, 1H), 7.25 (m, 2H), 7.11 (d, $J=7.4$ Hz, 1H), 6.31 (d, $J=15.2$ Hz, 1H), 4.20 (q, $J=7.3$ Hz, 2H), 4.15 (s, 2H), 1.33 (t, $J=7.2$ Hz, 3H). Hydrolysis followed by coupling with 5-bromo-2-methoxyphenylsulfonamide afforded the title compound **11a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90–7.75 (m, 5H), 7.64 (m, 1H), 7.58 (d, $J=15.8$ Hz, 1H), 7.51 (s, 1H), 7.47 (m, 1H), 7.35 (m, 2H), 7.27 (d, $J=8.4$ Hz, 1H), 7.17 (d, $J=8.9$ Hz, 1H), 6.53 (d, $J=15.7$ Hz, 1H), 4.22 (s, 2H), 3.78 (s, 3H); elemental analysis calcd for the sodium salt $C_{27}H_{19}BrFClNNaO_4S.2H_2O$: C, 50.13; H, 3.58; N, 2.17; S, 4.96; found: C, 49.75; H, 3.20; N, 2.29; S, 4.62.

5-Bromo-*N*-{3-[5-chloro-2-(6-chloro-naphthalen-2-ylmethyl)-phenyl]-acryloyl}-2-methoxybenzenesulfonamide (11b). The compound was prepared according to Scheme 3. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.98 (s, 1H), 7.92–7.75 (m, 5H), 7.59 (d, $J=15.1$ Hz, 1H), 7.55 (s, 1H), 7.45 (m, 2H), 7.40–7.30 (m, 2H), 7.20 (d, $J=8.0$ Hz, 1H), 6.53 (d, $J=15.1$ Hz, 1H), 4.22 (s, 2H), 3.78 (s, 3H); elemental analysis calcd for the sodium salt $C_{27}H_{19}BrCl_2NNaO_4S.2H_2O$: C, 49.01; H, 3.33; N, 2.14; found: C, 48.89, H, 3.47; N, 2.11.

5-Bromo-*N*-{3-[5-chloro-2-(6-chloroquinolin-2-ylmethyl)-phenyl]-acryloyl}-2-methoxy-benzenesulfonamide (11c). The compound was prepared according to Scheme 3. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, $J=8.9$ Hz, 1H), 8.05 (s, 1H), 7.95 (d, $J=15.4$ Hz, 1H), 7.92 (s, 1H), 7.82 (m, 2H), 7.67 (m, 1H), 7.55 (s, 1H), 7.41 (m, 3H), 7.23 (d, $J=8.8$ Hz, 1H), 6.55 (d, $J=15.3$ Hz, 1H), 4.42 (s, 2H), 3.82 (s, 3H); HR-MS calcd for the sodium salt $C_{26}H_{18}N_2O_4SCl_2BrNa + Na^+$: 648.9343; found: 648.9344.

Acknowledgements

The authors would like to thank Dr. John Colucci for proofreading this manuscript.

References and Notes

1. **EP_1**: Funk, C. D.; Furci, L.; FitzGerald, G. A.; Grygorczyk, R.; Rochette, C.; Bayne, M. A.; Abramovitz, M.; Adam, M.; Metters, K. M. *J. Biol. Chem.* **1993**, *268*, 26767. **EP_2**: Regan, J. W.; Bailey, T. J.; Pepperl, D. J.; Pierce, K. L.; Bogardus, A. M.; Donello, J. E.; Fairbairn, C. E.; Kedzie, K. M.; Woodward, D. F.; Gil, D. W. *Mol. Pharmacol.* **1994**, *46*, 213. **EP_3**: Adam, M.; Boie, Y.; Rushmore, T. H.; Muller, G.; Bastien, L.; McKee, K. T.; Metters, K. M.; Abramovitz, M. *FEBS Lett.* **1994**, *338*, 170. **EP_4**: Bastien, L.; Sawyer, N.; Grygorczyk, R.; Metters, K. M.; Adam, M. *J. Biol. Chem.* **1994**, *269*, 11873. **DP**: Boie, Y.; Sawyer, N.; Slipetz, D. M.; Metters, K. M.; Abramovitz, M. *J. Biol. Chem.* **1995**, *270*, 18910. **FP**: Abramovitz, M.; Boie, Y.; Nguyen, T.; Rushmore, T. H.; Bayne, M. A.; Metters, K. M.; Slipetz, D. M.; Grygorczyk, R. *J. Biol. Chem.* **1994**, *269*, 2632. **IP**: Boie, Y.; Rushmore, T. H.; Darmon-Goodwin, A.; Grygorczyk, R.; Slipetz, D. M.; Metters, K. M.; Abramovitz, M. *J. Biol. Chem.* **1994**, *269*, 12173. **TP**: Hirata, M.; Hayashi, Y.; Ushikubi, F.; Yokota, Y.; Kageyama, R.; Nakanishi, S.; Narumiya, S. *Nature* **1991**, *349*, 617.

2. Abramovitz, M.; Adam, A.; Boie, Y.; Godbout, C.; Lamontagne, S.; Rochette, C.; Sawyer, N.; Tremblay, N. M.; Belley, M.; Gallant, M.; Dufresne, C.; Gareau, Y.; Ruel, R.; Juteau, H.; Labelle, M.; Ouimet, N.; Metters, K. M. *Biochim. Biophys. Acta* **2000**, *1483*, 285.

3. Kiryiama, A.; Ushikubi, F.; Kobayashi, T.; Hirata, M.; Sugimoto, Y.; Narumiya, S. *Br. J. Pharmacol.* **1997**, *122*, 217.

4. Sugimoto, Y.; Narumiya, S.; Ichikawa, A. *Prog. Lipid. Res.* **2000**, *39*, 289. Narumiya, S.; Sugimoto, Y.; Ushikubi, F. *Physiol. Rev.* **1999**, *79*, 1193. Coleman, R. A.; Smith, W. L.; Narumiya, S. *Pharmacol. Rev.* **1994**, *46*, 205.

5. Shimazaki, Y.; Kameo, K.; Tanami, T.; Tanaka, H.; Ono, N.; Kiuchi, Y.; Okamoto, S.; Sato, F.; Ichikawa, A. *Bioorg. Med. Chem.* **2000**, *8*, 353.

6. Juteau, H.; Gareau, Y.; Labelle, M.; Lamontagne, S.; Tremblay, N.; Carriere, M. C.; Sawyer, N.; Denis, D.; Metters, K. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 747.

7. The subtype used for this assay was EP3-III.

8. For the methodology, see: Sturino, C. F.; Labelle, M. *Tetrahedron Lett.* **1998**, *39*, 5891.

9. Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2392. Knochel, P.; Palmer, N.; Rottlander, M. *Synlett* **1996**, 573.

10. All the compounds described in this paper behave as full antagonists.

11. Yeager, G. W.; Schissel, D. N. *Synthesis* **1995**, 28.

12. Suschitzky, H.; Bentley, R. L. *J. Chem. Soc. Perkin I* **1976**, 1725.

13. Ellingboe, J. W.; Lombardo, L. J.; Alessi, T. R.; Nguyen, T. T.; Guzzo, F.; Guinosso, C. J.; Bullington, J.; Browne, E. N. C.; Bagli, J. F.; Wrenn, J.; Steiner, K.; McCaleb, M. L. *J. Med. Chem.* **1993**, *36*, 2485. Adcock, W.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1967**, *89*, 386. Yu, K. L.; Ostrowski, J.; Chen, S.; Tramposch, K. M.; Reczek, P. R. *Bioorg. Med. Chem. Lett.* **1996**, *23*, 2865.