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Design, synthesis, and biological evaluation of *N*-acetyl-2-(or 3-)carboxymethylbenzenesulfonamides as cyclooxygenase isozyme inhibitors

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Abstract—A group of *N*-acetyl-2-(or 3-)carboxymethylbenzenesulfonamides, possessing either a F or a substituted-phenyl ring substituent (4-F, 2,4-F_2, 4-SO_2Me, 4-$OCHMe_2$) attached to its C-4 or C-6 position, was prepared using a palladium-catalyzed Suzuki cross-coupling reaction for evaluation as selective cyclooxygenase-2 (COX-2) inhibitors. Although *N*-acetyl-3-carboxymethyl-6-fluorobenzenesulfonamide [**14**, COX-1 IC_{50} = 2.26 μM; COX-2 IC_{50} = 0.012 μM; COX-2 selectivity index (SI) = 188] and *N*-acetyl-3-carboxymethyl-6-(4-isopropoxyphenyl)benzenesulfonamide (**20c**, COX-1 IC_{50} >100 μM; COX-2 IC_{50} = 0.15 μM; COX-2 SI >667) exhibited potent in vitro COX-2 inhibitory activity and high COX-2 selectivity, both compounds were inactive anti-inflammatory agents in a carrageenan-induced rat paw edema assay. In contrast, the less potent and less selective COX-2 inhibitors *N*-acetyl-2-carboxymethyl-4-fluorobenzenesulfonamide (**12**, COX-1 IC_{50} = 4.25 μM; COX-2 IC_{50} = 0.978 μM; COX-2 SI = 4.3), *N*-acetyl-2-carboxymethyl-4-(2,4-difluorophenyl)benzenesulfonamide (**17c**, COX-1 IC_{50} = 1.02 μM; COX-2 IC_{50} = 1.00 μM; COX-2 SI = 1.02), and *N*-acetyl-3-carboxymethyl-6-(4-methanesulfonylphenyl)benzenesulfonamide (**20e**, COX-1 IC_{50} = 0.109 μM; COX-2 IC_{50} = 1.14 μM; COX-2 SI = 0.095) exhibited moderate anti-inflammatory activity where a 75 mg/kg oral dose reduced inflammation 26%, 14%, and 20%, respectively, at 3 h postdrug administration relative to the reference drug aspirin where a 50 mg/kg oral dose reduced inflammation by 25% at 3 h postdrug administration.

1. Introduction

Prostaglandins arise from the biotransformation of arachidonic acid by the action of two separate isoforms of the enzyme cyclooxygenase (COX-1 and COX-2).[1] Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin (**1**) exert their anti-inflammatory and analgesic effects via the inhibition of prostaglandin synthesis.[2] Aspirin is the only nonsteroidal anti-inflammatory drug that covalently modifies cyclooxygenases. This unique property of aspirin is derived from its ability to acetylate the Ser^{530} hydroxyl group in the primary COX binding site of COX-1 and COX-2. In this regard, aspirin is a 10- to 100-fold more potent inhibitor of COX-1 relative to COX-2.[3] Some of aspirin's beneficial therapeutic effects arise from acetylation of COX-2, whereas its antithrombotic and ulcerogenic effects result from acetylation of COX-1. Selective cyclooxygenase-2 (COX-2) inhibitors currently provide effective treatment of inflammatory disease states such as rheumatoid arthritis and osteoarthritis circumventing the ulcerogenic effect associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin that inhibit both COX-1 and COX-2.[4] However, a precautionary concern regarding the use of COX-2 inhibitors in patients at risk for an adverse cardiovascular event such as myocardial infarction has been raised and this may be due to a thromboxane A_2/prostacyclin (TxA_2/PGI_2) imbalance created by selective COX-2 inhibitors.[5] Accordingly, the ability of aspirin to inhibit blood platelet aggregation is now viewed as a clinically useful prophylactic action that can reduce the incidence of thrombus formation in individuals with cardiovascular disease. These observations were exploited in the design of the aspirin analog *o*-(acetoxyphenyl)hept-2-ynyl sulfide (APHS, **2**), that is, a selective COX-2 inhibitor.[6] In an earlier study, we reported a novel class of isomeric acetoxy analogs of rofecoxib (**3**), which are potent and

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selective COX-2 inhibitors that, like aspirin, have the potential to acetylate the COX-2 isozyme.[7]

It was therefore of interest to investigate the *N*-acetylsulfonamido ($SO_2NHCOMe$) moiety as an pharmacophore that is capable of acetylating the Ser^{530} hydroxyl moiety in the primary binding site of COX-2.[8] In this regard, incorporation of a *para* *N*-acetylsulfonamido substituent on the C-3 phenyl ring of the rofecoxib regioisomer (**4**) provided a highly potent and selective COX-2 inhibitor that has the potential to acetylate the COX-2 isozyme.[9] In a recent study, we showed that the $SO_2NHCOMe$ pharmacophore present in *N*-acetyl-2-carboxybenzenesulfonamides (**5**) is a suitable bioisostere for the acetoxy (OCOMe) group in aspirin.[10] As part of our ongoing program to design selective COX-2 inhibitors, it was of interest to acquire structure–activity relationships for structurally related homologs and regioisomers of *N*-acetyl-2-carboxybenzenesulfonamides. We now describe the synthesis and biological evaluation of a novel group of *N*-acetyl-2-(or 3-)carboxymethylbenzenesulfonamides possessing halogeno (F, Br), or a phenyl ring having a variety of *para* (H, F, *i*-PrO, SO_2Me) and *ortho* (H, F), substituents in which the interspatial distance between the COOH and COMe moieties is expected to be larger than that for the previously investigated[10] *N*-acetyl-2-carboxybenzenesulfonamide homologs (**5**) (benzoic acid vs phenylacetic acid). Alteration of this interspatial distance can be used to position the *N*-acetylsulfonamido acetylating moiety closer or further from the Ser^{530} hydroxyl group that it, like aspirin, is designed to acetylate (Fig. 1).

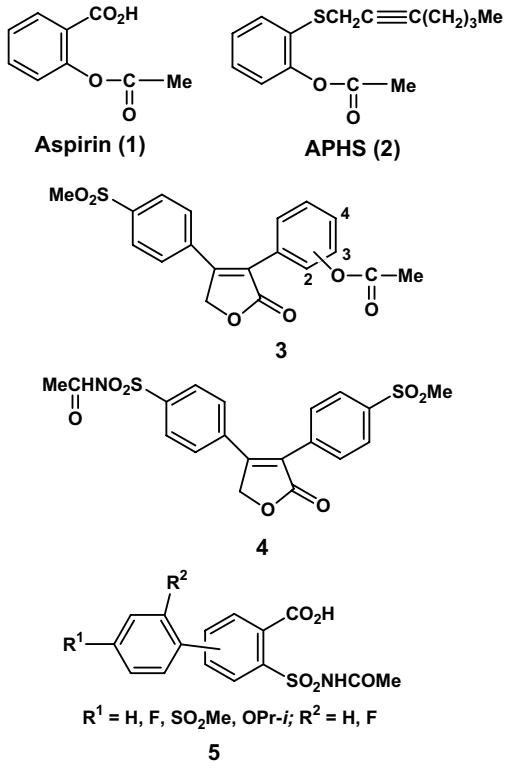
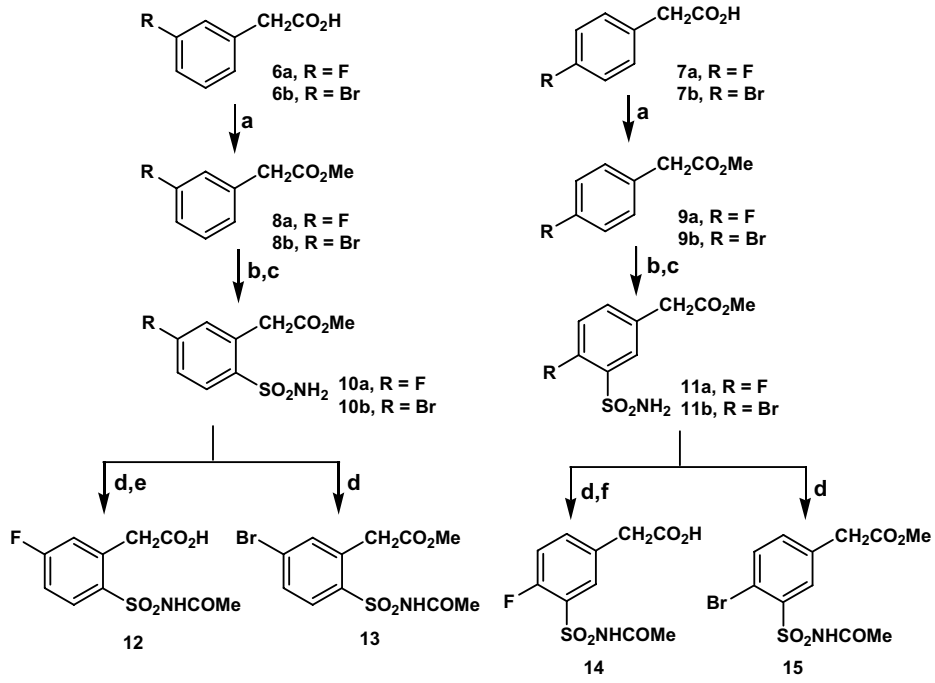


Figure 1. Some representative cyclooxygenase (COX) inhibitors.

2. Chemistry

N-Acetyl-2-(or 3-)carboxymethylbenzenesulfonamides (**12**, **14**) and *N*-acetyl-2-(or 3-)methoxycarbonylmethylbenzenesulfonamides (**13**, **15**) were synthesized using the reaction sequences illustrated in Scheme 1. Esterification of the 3-halo (**6a**,**b**), and 4-halo (**7a**,**b**), phenylacetic acids using MeOH in the presence of a catalytic amount of H_2SO_4 afforded the respective methyl 3-halophenylacetates (**8a**,**b**) and methyl 4-halophenylacetates (**9a**,**b**). Chlorosulfonation of the 3-halo compounds **8a**,**b** using chlorosulfonic acid at ice-salt bath temperature, followed by ammonolysis in THF under a stream of ammonia gas, afforded the respective 4-halo-2-methoxycarbonylmethylbenzenesulfonamide [**10a** (36%) or **10b** (64%)]. It is important to carry out this chlorosulfonation reaction at low temperature since chlorosulfonation of methyl 3-bromophenyl acetate (**8b**) at 25 °C followed by ammonolysis also produced the 2-bromo-4-methoxycarbonylmethylbenzenesulfonamide regioisomer (about 33% yield) that could not be separated from **10b** by silica gel column chromatography. In contrast, chlorosulfonation of the methyl 4-halophenylacetates (**9a**,**b**), and then ammonolysis of the intermediate sulfonyl chloride product, afforded the respective 6-halo-3-methoxycarbonylmethylbenzenesulfonamide [**11a** (14%) or **11b** (36%)]. The subsequent *N*-acetylation, and then hydrolysis of the methyl ester, of **10a** and **11a** yielded the corresponding *N*-acetyl-2-carboxymethyl-4-fluorobenzenesulfonamide (**12**, 76%) and *N*-acetyl-3-carboxymethyl-6-fluorobenzenesulfonamide (**14**, 93%). During the course of these studies, it was observed that the methyl ester moiety present in **10a** was more difficult to hydrolyze (NaOH, MeOH) than the methyl ester group present in the **11a** regioisomer (K_2CO_3, MeOH). The *N*-acetyl-4-bromo-2-methoxycarbonylmethylbenzenesulfonamide (**13**, 86%) and *N*-acetyl-6-bromo-3-methoxycarbonylmethylbenzenesulfonamide (**15**, 84%) regioisomers were similarly prepared by acetylation of the sulfonamide substituent present in **10b** and **11b**. The regiochemistry (relative position of the substituents on the phenyl ring) of compound **11b** was determined by ^1H NMR nuclear Overhauser enhancement (NOE) studies. The observation that NOE interactions occurred between CH_2 and H-2 (6.7%), and between CH_2 and H-4 (4.3%), in conjunction with the coupling constants (*J* values) and chemical shift positions (δ values) of the three phenyl hydrogens in the ^1H NMR spectrum of **11b**, indicates that the sulfonamide moiety is attached to the 1-position of the phenyl ring (see Fig. 2).

The target *N*-acetyl-2-(or 3-)carboxymethylbenzenesulfonamides (**17a–d**, **19**, **20a–e**) having a variety (R^1 = H, F, SMe, SO_2Me, $OCHMe_2$; R^2 = H, F) of substituents at the *ortho* and/or *para* position of a phenyl ring were prepared using a palladium-catalyzed Suzuki cross-coupling reaction[11,12] according to the reaction sequences shown in Schemes 2 and 3. The cross-coupling reaction between an aryl bromide (**13**, **15**) and a substituted-phenylboronic acid (**16**) in the presence of 2 M aqueous sodium carbonate in ethylene glycol dimethyl ether, using tetrakis(triphenylphosphine)palladium(0) as a catalyst, afforded the respective title compounds (**17**, **18**, **20**).



Scheme 1. Reagents and conditions: (a) MeOH, H_2SO_4, 80 °C, 3 h; (b) $ClSO_3H$, ice-salt bath, 5 h; (c) NH_3 (gas), THF, 30 min; (d) Ac_2O, pyridine, DMAP, 25 °C, overnight; (e) NaOH, MeOH, H_2O, 80 °C, 3 h; (f) K_2CO_3, MeOH, H_2O, 80 °C, 3 h.

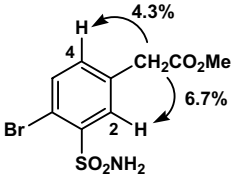
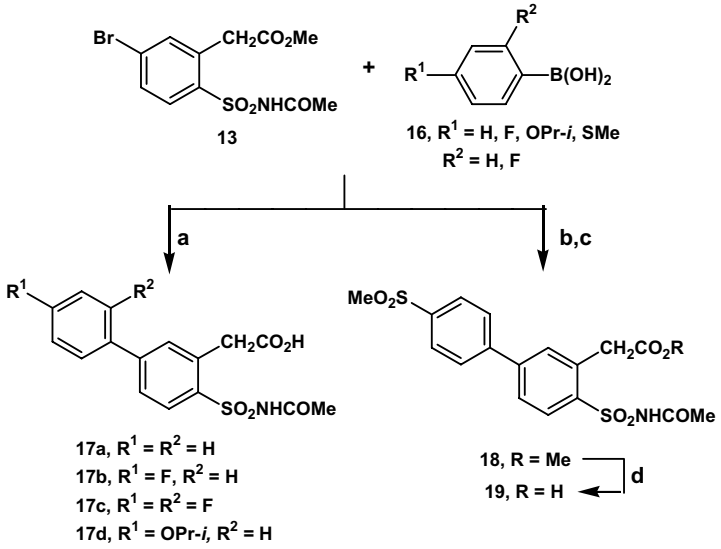
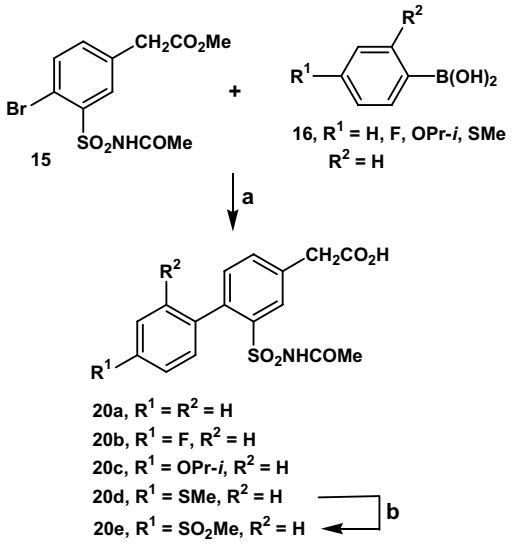


Figure 2. Some NOE studies to determine the relative substituent positions (regiochemistry) of compound **11b**.

Interestingly, the ester hydrolysis of the C-2 methoxycarbonylmethyl compounds is more difficult relative to those compounds having a C-3 methoxycarbonylmethyl moiety. In order to prepare the corresponding phenylacetic acid compounds **17a–d**, it is necessary to change the solvent from DME to MeOH–H_2O (1:1, v/v) to perform the ester hydrolysis reaction after completion of the cross-coupling reaction. In contrast, the desired phenylacetic acid compounds (**20a–d**) can be obtained via the conversion of the C-3 methoxycarbonylmethyl substituent to a C-3 carboxymethyl group during the one-pot cross-coupling reaction. To circumvent cyclization[13] of *ortho*-methoxycarbonylmethylbenzenesulfonamide compound under acidic oxidation reaction conditions, the methylsulfonyl compound **18** was synthesized via a two-step process involving a palladium-



Scheme 2. Reagents and conditions: (a) $Pd(PPh_3)_4$, Na_2CO_3, DME, reflux overnight, and then MeOH, H_2O, reflux 1.5 h; (b) $Pd(PPh_3)_4$, Na_2CO_3, DME, reflux 5 h; (c) Oxone®, MeOH, THF, H_2O, 25 °C, 1.5 h; (d) K_2CO_3, MeOH, H_2O, 25 °C, 1.5 h.



Scheme 3. Reagents and conditions: (a) $Pd(PPh_3)_4$, Na_2CO_3, DME, reflux overnight; (b) Oxone®, MeOH, H_2O, 25 °C, 1.5 h.

catalyzed Suzuki cross-coupling reaction followed by oxidation of the thiomethyl to a methylsulfonyl substituent in situ. Subsequent ester hydrolysis of the methylsulfonyl compound **18** in the presence of K_2CO_3 furnished the target methylsulfonyl compound **19**. Oxidation of **20d** using aqueous Oxone solution provided the corresponding methylsulfonyl compound **20e.**

3. Results and discussion

In our recent study,[10] a group of *N*-acetyl-2-carboxybenzenesulfonamides (**5**) possessing an appropriately substituted-phenyl substituent attached to its C-4 or C-5 position, was designed for evaluation as selective cyclooxygenase-2 (COX-2) inhibitors. In vitro COX-1 and COX-2 isozyme inhibition structure–activity studies identified *N*-acetyl-2-carboxy-4-(2,4-difluorophenyl)-benzenesulfonamide as a highly potent (COX-2 IC_{50} = 0.087 μM), and a highly selective (COX-2 SI >1149), COX-2 inhibitor that showed superior anti-inflammatory activity (ED_{50} = 91 mg/kg) relative to aspirin (ED_{50} = 129 mg/kg). This initial study has now been extended to include the design of *N*-acetyl-2-(or 3-)carboxymethylbenzenesulfonamide homologs, possessing either a F, or an appropriately substituted-phenyl substituent (4-F, 2,4-F_2, 4-SO_2Me, 4-$OCHMe_2$), attached to the C-4 or C-6 position of the parent benzenesulfonamide ring system.

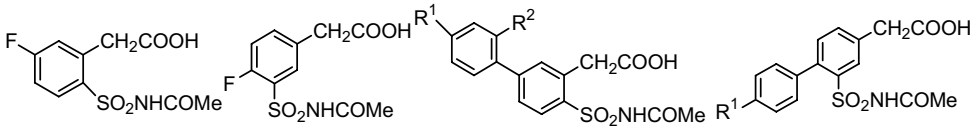
In vitro enzyme inhibition studies for the *N*-acetyl-2-carboxymethylbenzenesulfonamide subgroups (**12**, **17**, **19**) showed a wide range of COX-2 inhibitory activities (IC_{50} values in the 0.83 to >100 μM range) with low-to-moderate COX-2 selectivity indices (see data in Table 1). In this subgroup, a C-4 *p*-fluorophenyl substituent (**17b**) abolished COX-2 inhibitory activity, but COX-1 inhibitory activity was maintained (COX-1 IC_{50} = 2.2 μM, see data in Table 1). In contrast, introduction of a C-4 *p*-methanesulfonylphenyl substituent (**19**) abolished COX-1 inhibitory activity but exhibited low COX-2 inhibition (COX-1 IC_{50} >100 μM; COX-2 IC_{50} = 31.5 μM). The subgroup of *N*-acetyl-3-carboxymethylbenzenesulfonamides (**14**, **20**) showed good to excellent COX-2 inhibitory activity (IC_{50} values in the 0.012–1.76 μM range) with *N*-acetyl-3-carboxymethyl-6-(4-isopropoxyphenyl)benzenesulfonamide (**20c**), showing the best combination of COX-2 inhibitory potency and selectivity (COX-2 IC_{50} = 0.15 μM; SI >667) as shown in Table 1. In addition, the *N*-acetyl-3-carboxymethyl-6-fluorobenzenesulfonamide (**14**) is a more potent but less selective COX-2 inhibitor (COX-1 IC_{50} = 2.26 μM; COX-2 IC_{50} = 0.012 μM; COX-2 SI = 188) relative to the reference drugs rofecoxib (COX-2 IC_{50} = 0.50 μM; SI >200) and celecoxib (COX-2 IC_{50} = 0.07 μM; SI = 472). Compounds having a C-6 phenyl substituent (**20a**, COX-1 IC_{50} = 0.92 μM; COX-2 IC_{50} = 1.76 μM) or a C-6 *p*-methanesulfonylphenyl substituent (**20e**, COX-1 IC_{50} = 0.109 μM; COX-2 IC_{50} = 1.14 μM) exhibit similar COX-1 and COX-2 inhibition profiles to aspirin (COX-1 IC_{50} = 0.35 μM; COX-2 IC_{50} = 2.4 μM). In contrast, incorporation of a C-6 *p*-fluorophenyl substituent (**20b**) did not appreciably change COX-2 inhibitory activity but COX-1 inhibitory activity was abolished (COX-1 IC_{50} >100 μM; COX-2 IC_{50} = 1.52 μM).

A molecular modeling experiment was carried out to determine the binding interactions of *N*-acetyl-3-carboxymethyl-6-(4-isopropoxyphenyl)benzenesulfonamide (**20c**) in the COX-2 binding site (Fig. 3). The parent aromatic ring possessing the carboxyl and *N*-acetyl- sulfonamido substituents is surrounded by nonpolar amino acids such as Leu^{352}, Phe^{518}, Val^{523}, and Ala^{527}. The *N*-acetylsulfonamido-substituent is positioned at the top of the COX-2 binding site in a region comprised of the amino acids Tyr^{385}, Tyr^{348}, and Ser^{530}. One of the oxygen atoms of the SO_2 ($SO_2NHCOMe$) participates in a favorable hydrogen bonding interaction with the O*H* of Ser^{530} (distance = 1.83 Å). The distance between the *O*H of Ser^{530}, which is the acetylation site for aspirin, and *C*=O of the $SO_2NHCOMe$ moiety is about 4.61 Å. These observations suggest that the $SO_2NHCOMe$ moiety present in **20c** is suitably orientated to potentially acetylate (covalent bond formation) Ser^{530} present in the COX-2 isozyme.

The carboxylate moiety present in the parent aromatic ring, is positioned close to Tyr^{355} and Arg^{120} near the mouth of the COX-2 binding site (hydrogen bonding and electrostatic interactions). This orientation properly orients the *N*-acetylsulfonamide substituent closer to Ser^{530}, the acetylation site for aspirin. In this regard, the O*H* of the carboxylate is located about 1.99 Å from the NH_2 (guanidine moiety) of Arg^{120}, whereas the distance between the C=*O* of the COOH and the O*H* of Tyr^{355} is about 4.07 Å.

Interestingly, the 4-isopropoxyphenyl ring is oriented in a lipophilic pocket comprised of Leu^{384}, Trp^{387}, Leu^{507}, Met^{522}, Leu^{525}, and Gly^{526} at the upper apex of the

Table 1. In vitro COX-1/COX-2 enzyme inhibition assay data for **12, 14, 17a–d, 19**, and **20a–c,e**, in vivo anti-inflammatory assay data for **12**, **14**, **17c**, **20a**, **20c**, and **20e** and analgesic activity assay data for **17c** and **20e**



12 **14** **17a-d, 19** **20a-c, e**

Compds	R^1	R^2	IC_{50} (μM)[a]		COX-2 SI[b]	AI activity[c] % inhibition (75 mg/kg)	Analgesic activity[d]	
			COX-1	COX-2			% Inhibition (30 min)	% Inhibition (60 min)
12	—	—	4.25	0.978	4.3	26.3 ± 18.5[e]	—	—
14	—	—	2.26	0.012	188	Inactive	—	—
17a	H	H	2.83	0.83	3.4	—	—	—
17b	F	H	2.20	>100	<0.02	—	—	—
17c	F	F	1.02	1.00	1.02	14.3 ± 1.9	69.8 ± 6.8	68.7 ± 8.3
17d	$OCH(CH_3)_2$	H	3.74	3.16	1.18	—	—	—
19	SO_2CH_3	H	>100	31.5	>3.17	—	—	—
20a	H	—	0.92	1.76	0.52	Inactive	—	—
20b	F	—	>100	1.52	>65.8	—	—	—
20c	$OCH(CH_3)_2$	—	>100	0.15	>667	Inactive	—	—
20e	SO_2CH_3	—	0.109	1.14	0.095	20.0 ± 3.0[e]	73.77 ± 11.4	68.22 ± 7.6
1 (Aspirin)	—	—	0.35	2.4	0.14	25.2 ± 3.3[f]	56.52 ± 9.8[f]	64.30 ± 13.7[f]
Celecoxib			33.1	0.07	472	—	—	—
Rofecoxib			>100	0.50	>200	—	—	—

[a] Values are means of two determinations acquired using an ovine COX-1/COX-2 assay kit (Catalog No. 560101, Cayman Chemicals Inc., Ann Arbor, MI, USA) and the deviation from the mean is <10% of the mean value.
[b] In vitro COX-2 selectivity index (COX-1 IC_{50}/COX-2 IC_{50}).
[c] Inhibitory activity in a carrageen-induced rat paw edema assay. The results are expressed as mean ± SEM ($n = 4$) at 3 h following a 75 mg/kg oral dose of the test compound.
[d] Inhibitory activity in the rat 4% NaCl-induced abdominal constriction assay. The results are expressed as mean ± SEM ($n = 6$) following a 75 mg/kg oral dose of the test compound.
[e] $n = 3$ animals.
[f] 50 mg/kg oral dose.

COX-2 binding site. This small lipophilic region has been exploited in the design of selective COX-2 inhibitors.[14] Accordingly, the *p*-$OCH(CH_3)_2$ substituent may undergo van der Waal's interactions with side chains of amino acid residues such as Leu^{384}, Leu^{525}, and Met^{522} (distance <5 Å).

In vivo pharmacological evaluation of a small group of compounds was carried out to assess their potential anti-inflammatory and analgesic activities. Initial compound selection for in vivo screening was based on in vitro COX-1/COX-2 enzyme inhibition data. Qualitative structure–activity relationship data, acquired using the anti-inflammatory rat paw edema assay, showed that some of the *N*-acetyl-2-(or 3-)carboxymethylbenzenesulfonamides exhibited moderate anti-inflammatory activity while others were inactive (inactive to 26% inhibition range for a 75 mg/kg oral dose) (Table 1). *N*-Acetyl-2-carboxymethyl-4-fluorobenzenesulfonamide (**12**) and *N*-acetyl-3-carboxymethyl-6-(4-methanesulfonylphenyl)-benzenesulfonamide (**20e**) were the most potent anti-inflammatory agents within this group of compounds, producing a 26% and 20% reduction in inflammation at 3 h postdrug administration (75 mg/kg oral dose), respectively, relative to the reference drug aspirin where a 50 mg/kg oral dose reduced inflammation by 25% at 3 h postdrug administration. In contrast, *N*-acetyl-3-carboxymethyl-6-fluorobenzenesulfonamide (**14**) and *N*-acetyl-3-carboxymethyl-6-(4-isopropoxyphenyl)benzenesulfonamide (**20c**), which exhibited high in vitro COX-2 potency and selectivity, were inactive anti-inflammatory agents (see data in Table 1). Further pharmacological studies using systemic routes of administration may help to explain these observed differences between in vitro COX-2 inhibition and in vivo anti-inflammatory activity.

In a rat model, 4% NaCl-induced abdominal constriction assay, a 75 mg/kg po dose of compounds **17c** and **20e** exhibited good analgesic activities (68–74% inhibition range) at 30 or 60 min postdrug administration relative to the reference drug aspirin (57% and 64% inhibition) at 30 and 60 min postdrug administration for a 50 mg/kg oral dose (see data in Table 1).

4. Conclusions

A new class of *N*-acetyl-2-(or 3-)carboxymethylbenzenesulfonamides were designed to develop further structure–activity relationship data. In vitro enzyme inhibition studies showed that COX-2 inhibitory potency and selectivity was dependent upon the point of attachment of the $SO_2NHCOCH_3$ moiety. In this regard, the *N*-acetyl-3-carboxymethylbenzenesulfonamides **14** and **20c** are selective COX-2 inhibitors, while

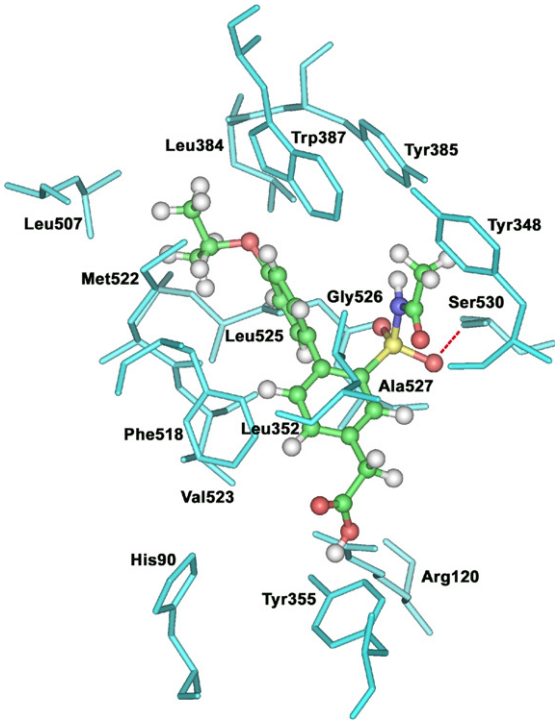


Figure 3. Docking of *N*-acetyl-3-carboxymethyl-6-(4-isopropoxyphenyl)benzenesulfonamide (**20c**) (ball and stick) in the active site of murine COX-2. Hydrogen atoms of the amino acid residues have been removed to improve clarity.

the corresponding regioisomers *N*-acetyl-2-carboxymethylbenzenesulfonamides **12** and **17d**, like aspirin, are nonselective COX-2 inhibitors. *N*-Acetyl-3-carboxymethyl-6-(4-isopropoxyphenyl)benzenesulfonamide (**20c**) exhibited optimal COX-2 inhibitory potency (IC_{50} = 0.15) and selectivity (COX-2 SI >667). In vivo anti-inflammatory studies showed that replacement of the carboxyl substituent in **5** by a homologous acetic acid substituent that provided *N*-acetyl-2-(or 3-)carboxymethylbenzenesulfonamides resulted in a significant reduction of in vivo anti-inflammatory activity.

5. Experimental

Melting points were determined on a Thomas–Hoover capillary apparatus and are uncorrected. Infrared (IR) spectra were recorded as films on NaCl plates using a Nicolet 550 Series II Magna FT-IR spectrometer. ^{1}H NMR spectra were measured on a Bruker AM-300 spectrometer in $CDCl_3$ or $CDCl_3$ + DMSO-d_6 with TMS as the internal standard, where *J* (coupling constant) values are estimated in Hertz. Spin multiples are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). The NOE studies were performed under steady-state conditions using the Bruker NOE DIFF.AU software program (signal:noise ratio of 136 for a single pulse). Microanalyses were performed for C, H, N (MicroAnalytical Service Laboratory, Department of Chemistry, University of Alberta) and were within ±0.4% of theoretical values. Silica gel column chromatography was performed using Merck silica gel 60 ASTM (70–230 mesh). All reagents were purchased from the Aldrich Chemical Company (Milwaukee, WI) and used without further purification. Male Sprague–Dawley rats, used in the anti-inflammatory-analgesic screens, were purchased from Animal Health Services at the University of Alberta, and experiments were carried out using protocols approved by the Animal Welfare Committee, University of Alberta.

5.1. General procedure for the synthesis of methyl 3-(or 4)-halophenylacetates (8a,b and 9a,b)

Concentrated H_2SO_4 (5 mL) was added dropwise at ice-bath temperature to a stirred solution of **6a**, **6b**, **7a**, or **7b** (1.0 g) in methanol (50 mL). The reaction mixture was refluxed for 3 h, cooled to 25 °C, and EtOAc (350 mL) was added. This solution was washed with water (3 × 60 mL), the organic fraction was dried (Na_2SO_4), and the solvent was removed in vacuo to afford the respective title compound (**8a**,**b**, **9a**, or **9b**) for which some physical and spectral data are listed below.

5.1.1. Methyl 3-fluorophenylacetate (8a). Yield, 95%; colorless liquid; IR (film): 1727 (C=O), 1622, 1592, 1480 (Ar) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.63 (s, 2H, CH_2COO), 3.71 (s, 3H, OCH_3), 6.94–7.04 (m, 3H, H-2, H-4, H-6), 7.27–7.34 (m, 1H, H-5).

5.1.2. Methyl 3-bromophenylacetate (8b). Yield, 89%; pale yellow liquid; IR (film): 1746 (C=O), 1597, 1498 (Ar) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.60 (s, 2H, CH_2COO), 3.71 (s, 3H, OCH_3), 7.17–7.45 (m, 4H, phenyl hydrogens).

5.1.3. Methyl 4-fluorophenylacetate (9a). Yield, 100%; colorless liquid; IR (film): 1735 (C=O), 1600, 1570 (Ar) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 2H, CH_2COO), 3.70 (s, 3H, OCH_3), 7.02 (t, *J* = 8.5 Hz, 2H, H-3, H-5), 7.26 (dd, *J* = 8.5, 5.5 Hz, 2H, H-2, H-6).

5.1.4. Methyl 4-bromophenylacetate (9b). Yield, 96%; colorless liquid; IR (film): 1750 (C=O), 1600, 1547, 1465 (Ar) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.59 (s, 2H, CH_2COO), 3.70 (s, 3H, OCH_3), 7.16 (d, *J* = 8.2 Hz, 2H, H-2, H-6), 7.46 (d, *J* = 8.2 Hz, 2H, H-3, H-5).

5.2. General procedure for the synthesis of 4-fluoro (or 4-bromo)-2-methoxycarbonylmethylbenzenesulfonamide (10a,b) and 6-fluoro (or 6-bromo)-3-methoxycarbonylmethylbenzenesulfonamide (11a,b)

Chlorosulfonic acid (10 mL) was added slowly at ice-salt bath temperature to a flask containing a 3-halo (**8a**,**b**) or 4-halo (**9a**,**b**) methyl phenylacetate (1.0 g). The reaction was allowed to proceed with stirring for 5 h at the same low temperature prior to pouring onto crushed ice (300 mL), and then extracted with CH_2Cl_2 (3 × 150 mL). The combined CH_2Cl_2 extracts were washed with water (3 × 100 mL), and the organic fraction was dried (Na_2SO_4). Removal of the solvent in vacuo gave the respective arylsulfonyl chloride intermediate, which was dissolved in THF (50 mL). This solution was stirred under a stream of gaseous ammonia

for 30 min at 25 °C, the insoluble material was removed by filtration, and the solvent was removed from the filtrate in vacuo to yield the respective sulfonamide (**10a**,**b**, **11a**, or **11b**). Some physical and spectral data for the title compounds are listed below.

5.2.1. 4-Fluoro-2-methoxycarbonylmethylbenzenesulfonamide (10a). Yield, 64%; pale yellow solid; mp 108–110 °C; IR (film): 3670 (NH_2), 1727 (C=O), 1607, 1585, 1457 (Ar), 1352 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.68 (s, 3H, OCH_3), 4.11 (s, 2H, CH_2COO), 6.05 (br s, 2H, NH_2), 6.99 (dd, J = 9.16, 2.4 Hz, 1H, H-3), 7.06 (dt, J = 8.5, 2.4 Hz, 1H, H-5), 8.03 (dd, J = 8.5, 5.5 Hz, 1H, H-6). Anal. Calcd for $C_9H_{10}FNO_4S$: C, 43.72; H, 4.08; N, 5.67. Found: C, 43.72; H, 4.10; N, 5.51.

5.2.2. 4-Bromo-2-methoxycarbonylmethylbenzenesulfonamide (10b). Yield, 36%; white solid; mp 126–128 °C; IR (film): 3407 (NH_2), 1727 (C=O), 1592, 1555, 1457 (Ar), 1352 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.76 (s, 3H, OCH_3), 4.18 (s, 2H, CH_2COO), 5.44 (br s, 2H, NH_2), 7.50 (d, J = 1.8 Hz, 1H, H-3), 7.61 (dd, J = 8.2, 1.8 Hz, 1H, H-5), 7.95 (d, J = 8.2 Hz, 1H, H-6). Anal. Calcd for $C_9H_{10}BrNO_4S$: C, 35.08; H, 3.27; N, 4.55. Found: C, 35.44; H, 2.99; N, 4.34.

5.2.3. 6-Fluoro-3-methoxycarbonylmethylbenzenesulfonamide (11a). Yield, 14%; white solid; mp 138–140 °C; IR (film): 3415 (NH_2), 1742 (C=O), 1607, 1487 (Ar), 1345 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.59 (s, 2H, CH_2COO), 3.64 (s, 3H, OCH_3), 6.21 (br s, 2H, NH_2), 7.10 (dd, J = 9.7, 8.5 Hz, 1H, H-5), 7.38–7.43 (m, 1H, H-4), 7.74 (dd, J = 6.7, 2.1 Hz, 1H, H-2). Anal. Calcd for $C_9H_{10}FNO_4S$: C, 43.72; H, 4.08; N, 5.67. Found: C, 43.98; H, 4.42; N, 5.56.

5.2.4. 6-Bromo-3-methoxycarbonylmethylbenzenesulfonamide (11b). Yield, 36%; pale yellow oil; IR (film): 3443, 3347 (NH_2), 1739 (C=O), 1607, 1361 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 (s, 2H, CH_2COO), 3.72 (s, 3H, OCH_3), 5.22 (br s, 2H, NH_2), 7.36 (dd, J = 8.2, 2.1 Hz, 1H, H-4), 7.71 (d, J = 8.2 Hz, 1H, H-5), 8.06 (d, J = 2.1 Hz, 1H, H-2); Anal. Calcd for $C_9H_{10}BrNO_4S$: C, 35.08; H, 3.27; N, 4.55. Found: C, 35.41; H, 3.25; N, 4.38.

5.2.5. *N*-Acetyl-2-carboxymethyl-4-fluorobenzenesulfonamide (12). Acetic anhydride (0.3 mL, 3.08 mmol) and 4-dimethylaminopyridine (56 mg, 0.46 mmol) were added to a solution of 4-fluoro-2-methoxycarbonylmethylbenzenesulfonamide (**10a**, 380 mg, 1.54 mmol) in pyridine (1 mL), and the reaction was allowed to proceed overnight at 25 °C with stirring. EtOAc (200 mL) was added and this solution was washed successively with saturated aqueous NH_4Cl (2 × 50 mL) and H_2O (2 × 50 mL). The organic fraction was dried (Na_2SO_4) and the solvent was removed in vacuo to afford the intermediate *N*-acetyl-4-fluoro-2-methoxycarbonylmethylbenzenesulfonamide product, which was dissolved in MeOH (15 mL). A solution of NaOH (123 mg, 3.08 mmol) in H_2O (15 mL) was added and the reaction was allowed to proceed for 3 h at 80 °C, cooled to 25 °C, water (150 mL) was added, the mixture was acidified to pH 2–3 using 5% w/v HCl, and the mixture was extracted with EtOAc (3 × 100 mL). The combined EtOAc extracts were washed with water (2 × 50 mL), the organic fraction was dried (Na_2SO_4), and the solvent was removed in vacuo to afford **12** (320 mg, 76%) as a pale yellow solid; mp 195–197 °C; IR (film): 3670 (NH), 3600–2447 (COOH), 1720 (C=O), 1607, 1592, 1472 (Ar), 1375 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.86 (s, 3H, COCH_3), 3.96 (s, 2H, CH_2COOH), 6.96–7.02 (m, 2H, H-3, H-5), 8.08 (dd, J = 5.5, 2.7 Hz, 1H, H-6), 11.03 (br s, 1H, *NH*). Anal. Calcd for $C_{10}H_{10}FNO_5S$: C, 43.63; H, 3.66; N, 5.09. Found: C, 43.72; H, 3.49; N, 4.99.

5.2.6. *N*-Acetyl-4-bromo-2-methoxycarbonylmethylbenzenesulfonamide (13). To a solution of 4-bromo-2-methoxycarbonylmethylbenzenesulfonamide (**10b**, 919 mg, 2.98 mmol) in pyridine (3 mL) were added acetic anhydride (2.0 mL, 21 mmol) and 4-dimethylaminopyridine (109 mg, 0.89 mmol). The reaction solution was stirred overnight at 25 °C, and EtOAc (350 mL) was added. This solution was washed successively with saturated aqueous NH_4Cl (2 × 80 mL) and H_2O (2 × 80 mL). The organic fraction was dried (Na_2SO_4), and the solvent was removed in vacuo to furnish **13** (898 mg, 86%) as a pale yellow solid; mp 166–168 °C; IR (film): 3662 (NH), 1742 (C=O), 1622, 1585, 1480 (Ar), 1270 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (s, 3H, COCH_3), 3.58 (s, 3H, OCH_3), 3.98 (s, 2H, CH_2COO), 7.39 (d, J = 1.8 Hz, 1H, H-3), 7.47 (dd, J = 8.5, 1.8 Hz, 1H, H-5), 7.92 (d, J = 8.5 Hz, 1H, H-6), 11.75 (br s, 1H, *NH*). Anal. Calcd for $C_{11}H_{12}BrNO_5S$: C, 37.73; H, 3.45; N, 4.00. Found: C, 38.07; H, 3.17; N, 3.86.

5.2.7. *N*-Acetyl-3-carboxymethyl-6-fluorobenzenesulfonamide (14). Compound **14** was prepared as white crystals in 93% yield using an acetylation and hydrolysis procedure similar to that described previously for the synthesis of compound **12** where K_2CO_3 was used for base in place of NaOH during the hydrolysis; mp 180–182 °C; IR (film): 3670 (NH), 3587–2455 (COOH), 1720 (C=O), 1607, 1502 (Ar), 1375 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO) δ 1.95 (s, 3H, COCH_3), 3.56 (s, 2H, CH_2COOH), 7.07 (dd, J = 10.0, 8.5 Hz, 1H, H-5), 7.41 (ddd, J = 8.5, 4.6, 2.1 Hz, 1H, H-4), 7.86 (dd, J = 6.7, 2.1 Hz, 1H, H-2), 11.03 (br s, 1H, *NH*). Anal. Calcd for $C_{10}H_{10}FNO_5S$: C, 43.63; H, 3.66; N, 5.09. Found: C, 43.79; H, 3.50; N, 4.97.

5.2.8. *N*-Acetyl-6-bromo-3-methoxycarbonylmethylbenzenesulfonamide (15). Compound **15** was prepared as a white solid in 84% yield using an acetylation procedure similar to that described previously for the synthesis of compound **13**; mp 150–152 °C; IR (film): 3388 (NH), 1739 (C=O), 1348 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11 (s, 3H, COCH_3), 3.71 (s, 2H, CH_2COO), 3.73 (s, 3H, OCH_3), 7.44 (dd, J = 8.2, 2.1 Hz, 1H, H-4), 7.72 (d, J = 8.2 Hz, 1H, H-5), 8.20 (d, J = 2.1 Hz, 1H, H-2), 8.88 (br s, 1H, *NH*). Anal. Calcd for $C_{11}H_{12}BrNO_5S$: C, 37.73; H, 3.45; N, 4.00. Found: C, 38.00; H, 3.20; N, 3.86.

5.3. General procedure for the synthesis of *N*-acetyl-2-carboxymethyl-4-(substituted-phenyl)benzenesulfonamides (17a–d)

N-Acetyl-4-bromo-2-methoxycarbonylmethylbenzenesulfonamide (**13**, 145 mg, 0.41 mmol) and a substituted-phenylboronic acid (**16**, 0.61 mmol) were dissolved in DME (8 mL), and then aqueous Na_2CO_3 (0.61 mL of 2 M) followed by tetrakis(triphenylphosphine)palladium (14 mg, 0.012 mmol) were added. The reaction was allowed to proceed overnight at reflux, and the solvent was removed in vacuo. MeOH (5 mL) and then water (5 mL) were added, and the reaction was continued at reflux for 1.5 h, cooled to 25 °C, water (100 mL) was added, the mixture was acidified to pH 3 using 5% w/v HCl, and the mixture was extracted with EtOAc (3×60 mL). The combined EtOAc extracts were washed with water (2×50 mL), the organic fraction was dried (Na_2SO_4), and the solvent was removed in vacuo to afford the crude product. Purification of the product by silica gel column chromatography using $CHCl_3$–MeOH (20:1, v/v) as eluant furnished the respective title compounds (**17a**–**c**, or **17d**). Some physical and spectral date for **17a**–**d** are listed below.

5.3.1. *N*-Acetyl-2-carboxymethyl-4-phenylbenzenesulfonamide (17a). Yield, 36%, white crystals; mp 194–195 °C; IR (film): 3670 (NH), 3595–2417 (COOH), 1712 (C=O), 1615, 1457 (Ar), 1247 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO) δ 1.78 (s, 3H, COCH_3), 3.94 (s, 2H, CH_2COOH), 7.16–8.00 (m, 8H, phenyl hydrogens). Anal. Calcd for $C_{16}H_{15}NO_5S$: C, 57.65; H, 4.54; N, 4.20. Found: C, 58.03; H, 4.62; N, 3.99.

5.3.2. *N*-Acetyl-2-carboxymethyl-4-(4-fluorophenyl)benzenesulfonamide (17b). Yield, 83%; pale yellow crystals; mp 202–203 °C; IR (film): 3670 (NH), 3580–2725 (COOH), 1712 (C=O), 1622, 1472 (Ar), 1247 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.79 (s, 3H, COCH_3), 3.95 (s, 2H, CH_2COOH), 6.96 (t, J = 8.6 Hz, 2H, fluorophenyl H-3, H-5), 7.33 (s, 1H, H-3), 7.40–7.50 (m, 3H, H-5, fluorophenyl H-2, H-6), 8.02 (d, J = 8.2 Hz, 1H, H-6), 11.6 (br s, 1H, *NH*). Anal. Calcd for $C_{16}H_{14}FNO_5S$: C, 54.70; H, 4.02; N, 3.99. Found: C, 55.05; H, 4.04; N, 3.69.

5.3.3. *N*-Acetyl-2-carboxymethyl-4-(2,4-difluorophenyl)-benzenesulfonamide (17c). Yield, 59%; white crystals; mp 199–200 °C; IR (film): 3670 (NH), 3587–2432 (COOH), 1720 (C=O), 1622, 1472 (Ar), 1240 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO) δ 1.70 (s, 3H, COCH_3), 3.86 (s, 2H, CH_2COOH), 6.64–6.76 (m, 2H, difluorophenyl H-3, H-5), 7.13–7.33 (m, 3H, difluorophenyl H-6, H-3, H-5), 7.92 (d, J = 8.2 Hz, 1H, H-6). Anal. Calcd for $C_{16}H_{13}F_2NO_5S$: C, 52.03; H, 3.55; N, 3.79. Found: C, 51.94; H, 3.53; N, 3.69.

5.3.4. *N*-Acetyl-2-carboxymethyl-4-(4-isopropoxyphenyl)-benzenesulfonamide (17d). Yield, 52%; white crystals; mp 193–194 °C; IR (film): 3677 (NH), 3602–2717 (COOH), 1727 (C=O), 1630, 1525, 1472 (Ar), 1240 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO) δ 1.18 [d, J = 5.6 Hz, 6H, CH(CH_3)$_2$], 1.80 (s, 3H, COCH_3), 3.95 (s, 2H, CH_2COOH), 4.43 [hept, J = 5.6 Hz, 1H, CH(CH$_3$)$_2$], 6.77 (d, J = 8.5 Hz, 2H, isopropoxyphenyl H-3, H-5), 7.34–7.41 (m, 4H, H-3, H-5, isopropoxyphenyl H-2, H-6), 8.00 (d, J = 8.2 Hz, 1H, H-6). Anal. Calcd for $C_{19}H_{21}NO_6S$: C, 58.30; H, 5.41; N, 3.58. Found: C, 58.10; H, 5.54; N, 3.32.

5.3.5. *N*-Acetyl-2-methoxycarbonylmethyl-4-(4-methanesulfonylphenyl)benzenesulfonamide (18). To a solution of the aryl bromide (**13**, 145 mg, 0.41 mmol) and 4-(methylthio)phenylboronic acid (**16**, 102 mg, 0.61 mmol) in DME (8 mL), aqueous Na_2CO_3 (0.61 mL of 2 M) followed by tetrakis(triphenylphosphine)palladium (14 mg, 0.012 mmol) were added. The reaction was allowed to proceed at reflux for 5 h, and the solvent was removed in vacuo. The residue obtained was dissolved in THF (5 mL) and MeOH (5 mL), a solution of Oxone (636 mg) in water (5 mL) was added, and the reaction was allowed to proceed at 25 °C for 1.5 h with stirring. EtOAc (100 mL) was added and this solution was washed with water (2×50 mL). The organic fraction was dried (Na_2SO_4), and the solvent was removed in vacuo. The residue obtained was purified by silica gel column chromatography using $CHCl_3$–MeOH (100:3, v/v) as eluant to afford **18** (136 mg, 77%) as white needles; mp 197–198 °C; IR (film) 1745 (C=O), 1217 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H, COCH_3), 3.12 (s, 3H, SO_2CH_3), 3.75 (s, 3H, OCH_3), 4.27 (s, 2H, CH_2COO), 7.59 (d, J = 1.5 Hz, 1H, H-3), 7.72 (dd, J = 8.6, 1.5 Hz, 1H, H-5), 7.80 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6), 8.07 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.37 (d, J = 8.6 Hz, 1H, H-6), Anal. Calcd for $C_{18}H_{19}NO_7S_2$: C, 50.81; H, 4.50; N, 3.29. Found: C, 50.88; H, 4.13; N, 3.13.

5.3.6. *N*-Acetyl-2-carboxymethyl-4-(4-methanesulfonylphenyl)benzenesulfonamide (19). An aqueous solution of K_2CO_3 (65 mg) in water (5 mL) was added to a stirred solution of *N*-acetyl-2-methoxycarbonylmethyl-4-(4-methanesulfonylphenyl)benzenesulfonamide (**18**, 100 mg, 0.23 mmol) in MeOH (5 mL). The reaction was allowed to proceed with stirring at 80 °C for 1.5 h, cooled to 25 °C, water (100 mL) was added, the mixture was acidified to pH 3 using 5% w/v HCl, and the mixture was extracted with EtOAc (3×60 mL). The combined EtOAc extracts were washed with water (2×50 mL), the organic fraction was dried (Na_2SO_4), and the solvent was removed in vacuo to give **19** (78 mg, 81%) as white crystals; mp 215–217 °C; IR (film): 3677 (NH), 3602–2440 (COOH), 1712 (C=O), 1630, 1465 (Ar), 1240 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO) δ 1.75 (s, 3H, COCH_3), 2.91 (s, 3H, SO_2CH_3), 3.96 (s, 2H, CH_2COO), 7.41 (br s, 1H, H-3), 7.45 (br d, J = 8.2 Hz, 1H, H-5), 7.61 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.81 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.06 (d, J = 8.5 Hz, 1H, H-6). Anal. Calcd for $C_{17}H_{17}NO_7S_2 \cdot 1/2H_2O$: C, 48.56; H, 4.32; N, 3.33. Found: C, 48.44; H, 4.26; N, 3.24.

5.4. General procedure for the synthesis of *N*-acetyl-3-carboxymethyl-6-(substituted-phenyl)benzenesulfonamides (20a–d)

N-Acetyl-6-bromo-3-methoxycarbonylmethylbenzenesulfonamide (**15**, 100 mg, 0.29 mmol) and a substituted-

phenylboronic acid (**16**, 0.43 mmol) were dissolved in DME (5 mL), and then aqueous Na_2CO_3 (0.42 mL of 2 M) followed by tetrakis(triphenylphosphine)palladium (10 mg, 0.0086 mmol) were added. The reaction was refluxed overnight, and the solvent was removed in vacuo. Water (80 mL) was added, the mixture was acidified to pH 3 using 5% w/v HCl, and the mixture was extracted with EtOAc (3 × 50 mL). The combined EtOAc extracts were washed with water (2 × 30 mL), the organic fraction was dried (Na_2SO_4), and the solvent was removed in vacuo to afford the crude product. Purification of the product by silica gel column chromatography using $CHCl_3$–MeOH (20:1, v/v) as eluant gave the respective title compound (**20a**–**d**). Some physical and spectral data for **20a**–**d** are listed below.

5.4.1. *N*-Acetyl-3-carboxymethyl-6-phenylbenzenesulfonamide (20a). Yield, 50%, white foam; mp 189–190 °C; IR (film): 3663 (NH), 3601–2467 (COOH), 1719 (C═O), 1623, 1478 (Ar), 1238 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO) δ 1.72 (s, 3H, CO*CH*$_3$), 3.67 (s, 2H, *CH*$_2$COOH), 7.18 (d, J = 8.0 Hz, 1H, H-5), 7.38–7.24 (m, 5H, C-6 phenyl hydrogens); 7.51 (dd, J = 8.0, 1.8 Hz, 1H, H-4), 8.11 (d, J = 1.8 Hz, 1H, H-2). Anal. Calcd for $C_{16}H_{15}NO_5S{\cdot}1/4H_2O$: C, 56.87; H, 4.62; N, 4.15. Found: C, 56.79; H, 4.52; N, 4.00.

5.4.2. *N*-Acetyl-3-carboxymethyl-6-(4-fluorophenyl)benzenesulfonamide (20b). Yield, 26%; white foam; mp 114–115 °C; IR (film): 3482 (NH), 3395–2468 (COOH), 1716 (C═O), 1635, 1461 (Ar), 1380 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO) δ 1.68 (s, 3H, CO*CH*$_3$), 3.59 (s, 2H, *CH*$_2$COOH), 6.98 (t, J = 8.6 Hz, 2H, fluorophenyl H-3, H-5), 7.08 (d, J = 8.0 Hz, 1H, H-5), 7.18 (m, 2H, fluorophenyl H-2, H-6), 7.43 (br d, J = 8.0 Hz, 1H, H-4), 8.01 (br s, 1H, H-2). Anal. Calcd for $C_{16}H_{14}FNO_5S{\cdot}1/2H_2O$: C, 53.33; H, 4.20; N, 3.89. Found: C, 53.37; H, 4.34; N, 3.63.

5.4.3. *N*-Acetyl-3-carboxymethyl-6-(4-isopropoxyphenyl)-benzenesulfonamide (20c). Yield, 54%; white powder; mp 100–102 °C; IR (film): 3388–2492 (COOH), 1716 (C═O), 1630, 1474 (Ar), 1380 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO) δ 1.39 [d, J = 5.8 Hz, 6H, CH(*CH*$_3$)$_2$], 1.80 (s, 3H, CO*CH*$_3$), 3.81 (s, 2H, *CH*$_2$COOH), 4.62 [hept, J = 5.8 Hz, 1H, *CH*(CH$_3$)$_2$], 6.97 (d, J = 8.6 Hz, 2H, isopropoxyphenyl H-3, H-5), 7.29 (d, J = 7.0 Hz, 1H, H-5), 7.32 (d, J = 8.6 Hz, 2H, isopropoxyphenyl H-2, H-6), 7.59 (br d, J = 7.0 Hz, 1H, H-4), 8.19 (br s, 1H, H-2). Anal. Calcd for $C_{19}H_{21}NO_6S{\cdot}1/4\ H_2O$: C, 57.63; H, 5.47; N, 3.54. Found: C, 57.57; H, 5.26; N, 3.29.

5.4.4. *N*-Acetyl-3-carboxymethyl-6-(4-methylthiophenyl)-benzenesulfonamide (20d). Yield, 70%; white powder; mp 172–174 °C; IR (film): 3664–2569 (COOH), 1727 (C═O), 1630, 1465 (Ar), 1375 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 (s, 3H, CO*CH*$_3$), 2.54 (s, 3H, S*CH*$_3$), 3.82 (s, 2H, *CH*$_2$COOH), 7.21–7.34 (m, 5H, H-5, methylthiophenyl H-2, H-3, H-5, H-6), 7.63 (d, J = 7.8 Hz, 1H, H-4), 8.18 (br s, 1H, H-2). Anal. Calcd for $C_{17}H_{17}NO_5S_2{\cdot}1/2H_2O$: C, 52.56; H, 4.67; N, 3.60. Found: C, 52.45; H, 4.32; N, 3.50.

5.4.5. *N*-Acetyl-3-carboxymethyl-6-(4-methanesulfonylphenyl)benzenesulfonamide (20e). An aqueous solution of Oxone (270 mg, 0.42 mmol, 5 mL) was added to a stirred solution of the methylthiophenyl compound (**20d**, 80 mg, 0.21 mmol) in methanol (5 mL), and the reaction was allowed to proceed with stirring at 25 °C for 1.5 h. Addition of H_2O (60 mL), extraction with EtOAc (3 × 50 mL), drying the combined EtOAc extracts (Na_2SO_4), and removal of the solvent in vacuo afforded **20e** (50 mg, 58%) as a pale yellow foam; mp 117–118 °C; IR (film): 3685 (NH), 3602–2492 (COOH), 1727 (C═O), 1630, 1465 (Ar), 1375 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO) δ 1.81 (s, 3H, CO*CH*$_3$), 3.10 (s, 3H, SO_2*CH*$_3$), 3.74 (s, 2H, *CH*$_2$COOH), 7.20 (d, J = 8.0 Hz, 1H, H-5), 7.55 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.59 (br d, J = 8.0 Hz, 1H, H-4), 7.95 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.19 (br s, 1H, H-2). 11.1 (br s, 1H, *NH*), Anal. Calcd for $C_{17}H_{17}NO_7S_2$: C, 49.62; H, 4.16; N, 3.40. Found: C, 49.83; H, 4.16; N, 3.31.

5.5. Molecular modeling (docking) study

Docking experiments were performed using Insight II software Version 2000.1 (Accelrys Inc.) running on a Silicon Graphics Octane 2 R14000A workstation according to a previously reported method.[15]

5.6. In vitro cyclooxygenase (COX) inhibition assay

The ability of the test compounds listed in Table 1 to inhibit ovine COX-1 and COX-2 (IC_{50} value, μM) was determined using an enzyme immunoassay (EIA) kit (catalog number 560101, Cayman Chemical, Ann Arbor, MI, USA) according to our previously reported method.[15]

5.7. Anti-inflammatory assay

Anti-inflammatory activity was performed using a method described by Winter et al.[16]

5.8. Analgesic assay

Analgesic activity was determined using a 4% sodium chloride-induced writhing (abdominal constriction) assay previously reported.[17]

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