Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry
Bioorganic & Medicinal Chemistry 13 (2005) 2459–2468

Design, synthesis, and biological evaluation of *N*-acetyl-2-carboxybenzenesulfonamides: a novel class of cyclooxygenase-2 (COX-2) inhibitors

Qiao-Hong Chen, P. N. Praveen Rao and Edward E. Knaus*

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada T6G 2N8

Received 14 December 2004; revised 21 January 2005; accepted 21 January 2005

Abstract—*N*-Acetyl-2-carboxybenzenesulfonamide (**11**), and a group of analogues possessing an appropriately substituted-phenyl substituent (4-F, 2,4-F_2, 4-SO_2Me, 4-$OCHMe_2$) attached to its C-4, or C-5 position, were synthesized for evaluation as selective cyclooxygenase-2 (COX-2) inhibitors. In vitro COX-1/COX-2 inhibition studies showed that **11** is a more potent inhibitor (COX-1 IC_{50} = 0.06 μM; COX-2 IC_{50} = 0.25 μM) than aspirin (COX-1 IC_{50} = 0.35 μM; COX-2 IC_{50} = 2.4 μM), and like aspirin [COX-2 selectivity index (S.I.) = 0.14], **11** is a nonselective COX-2 inhibitor (COX-2 S.I. = 0.23). Regioisomers having a 2,4-difluorophenyl substituent attached to the C-4 (COX-2 IC_{50} = 0.087 μM; COX-2 S.I. >1149), or C-5 (COX-2 IC_{50} = 0.77 μM, SI > 130), position of **11** exhibited the most potent and selective COX-2 inhibitory activity relative to the reference drug celecoxib (COX-1 IC_{50} = 33.1 μM; COX-2 IC_{50} = 0.07 μM; COX-2 S.I. = 472). *N*-Acetyl-2-carboxybenzenesulfonamide (**11**, ED_{50} = 49 mg/kg), and its C-4 2,4-difluorophenyl derivative (ED_{50} = 91 mg/kg), exhibited superior antiinflammatory activity (oral dosing) in a carrageenan-induced rat paw edema assay compared to aspirin (ED_{50} = 129 mg/kg). These latter compounds exhibited comparable analgesic activity to the reference drug diflunisal, and superior analgesic activity compared to aspirin, in a 4% NaCl-induced abdominal constriction assay. A molecular modeling (docking) study indicated that the $SO_2NHCOCH_3$ substituent present in *N*-acetyl-2-carboxy-4-(2,4-fluorophenyl)benzenesulfonamide, like the acetoxy substituent in aspirin, is suitably positioned to acetylate the Ser^{530} hydroxyl group in the COX-2 primary binding site. The results of this study indicate that the $SO_2NHCOCH_3$ pharmacophore present in *N*-acetyl-2-carboxybenzenesulfonamides is a suitable bioisostere for the acetoxy (OCOMe) group in aspirin.

1. Introduction

The complex biological actions exhibited by the simple salicylate class of compounds have attracted on-going attention for more than 100 years. In this context, the moderately active antiinflammatory and nonnarcotic analgesic agent acetylsalicylic acid (aspirin, **1**) continues to be a frequent first choice drug in the treatment of some arthritic disorders (see structure in Fig. 1). However, these beneficial actions of aspirin may also be accompanied by adverse effects that include tinnitus, hypersensitization, and contraindicated gastrointestinal irritation, bleeding and/or ulceration.[1] The ability of aspirin to inhibit blood platelet aggregation is now viewed as a clinically useful prophylactic action that

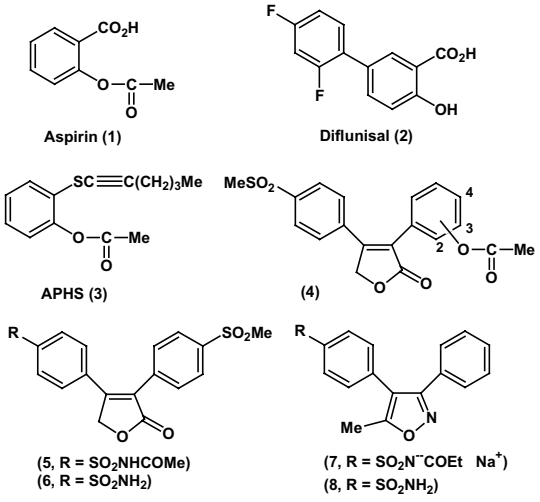


Figure 1. Some representative cyclooxygenase (COX) inhibitors.

Keywords: *N*-Acetyl-2-carboxybenzenesulfonamides; Cyclooxygenase-1 and -2 inhibition; Antiinflammatory and analgesic activities.
* Corresponding author. Tel.: +1 780 492 5993; fax: +1 780 492 1217; e-mail: eknaus@pharmacy.ualberta.ca

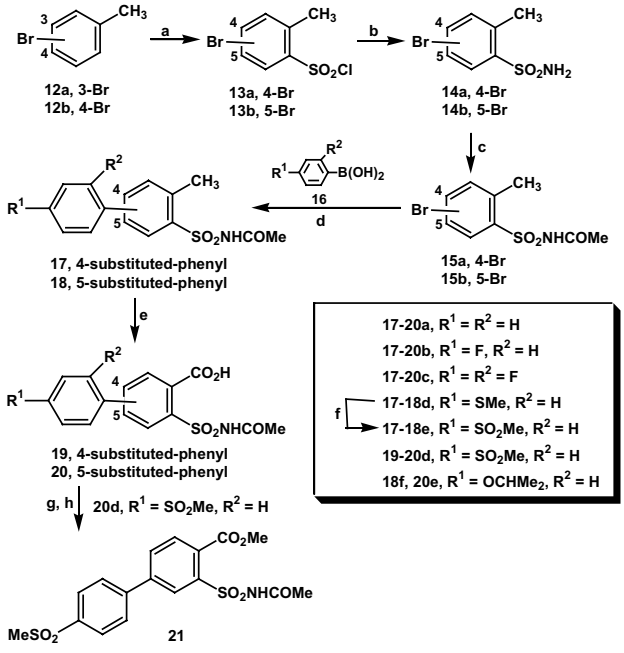
0968-0896/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2005.01.039

can reduce the incidence of thrombus formation in individuals with cardiovascular disease. The search for a clinical replacement for aspirin resulted in the development of the nonacetylating salicyclic acid derivative diflunisal (**2**) that is a more potent antiinflammatory and analgesic agent with a longer duration of action that is less ulcerogenic than aspirin.[2] The subsequent discovery[3,4] that there are two cyclooxygenase isozymes COX-1 and COX-2 provided the basis for the drug design concept that selective COX-2 inhibitors such as celecoxib[5] elicit effective antiinflammatory activity devoid of the ulcerogenic effect associated with the use of nonsteroidal antiinflammatory drugs (NSAIDs) such as aspirin that inhibit both COX-1 and COX-2. Aspirin is a unique nonselective COX inhibitor due to 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.[6] Acetylation of the weakly nucleophilic OH of Ser^{530} by aspirin is thought to result from initial binding of its COOH to the Arg^{120} residue near the mouth of the COX binding site, which positions the *ortho*-acetoxy moiety in close proximity to the Ser^{530} OH, which it acetylates. 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. These observations were exploited in the design of the aspirin analogue *o*-(acetoxyphenyl)hept-2-ynyl sulfide (APHS, **3**) that is a selective COX-2 inhibitor.[7] In an earlier study, we reported a novel class of isomeric acetoxy analogues of rofecoxib (**4**), which are potent and selective COX-2 inhibitors that, like aspirin, have the potential to acetylate the COX-2 isozyme.[8]

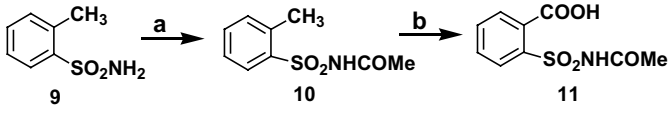
It is known that the $SO_2NHCOCH_3$ moiety is a 10^5–10^6 more reactive acetylating agent of enzyme serine hydroxyls than simple amides.[9] In a recent study, it was shown that the incorporation of a *para*-*N*-acetylsulfonamido substituent on the C-3 phenyl ring of the rofecoxib regioisomer (**5**) provided a highly potent and selective COX-2 inhibitor that has the potential to acetylate the COX-2 isozyme.[10] After acetylation of the COX-2 Ser^{530} OH by compound **5**, compound (**6**) having a free SO_2NH_2 compound would be released that could also exhibit COX-2 inhibitory activity. This rationale is based on observation that the water soluble nonnarcotic analgesic agent parecoxib sodium (**7**)[11] is a prodrug to the selective COX-2 inhibitor valdecoxib (**8**).[12] Accordingly, the $SO_2NHCOCH_3$ pharmacophore could serve the dual role of acetylation agent and prodrug. As part of our on-going research program to design selective COX-2 inhibitors, we describe herein the synthesis and biological evaluation of a novel group of *N*-acetyl-2-carboxybenzenesulfonamides possessing an appropriately substituted-phenyl substituent attached to its C-4, or C-5, position that were designed to be potential bioisosteres of aspirin.

2. Chemistry

N-Acetyl-2-carboxybenzenesulfonamide (**11**) was synthesized using a two-step reaction sequence that involved *N*-acetylation of 2-methylbenzenesulfonamide (**9**) followed by oxidation of the aryl C-2 methyl substituent using $KMnO_4$ in 0.5 N aqueous NaOH as illustrated in Scheme 1. The target *N*-acetyl-2-carboxybenzenesulfonamides (**19a–d**, **20a–e**) having a variety (R^1 = H, F, SO_2Me, $OCHMe_2$; R^2 = H, F) of substituted-phenyl substituents at the C-4 or C-5 positions were prepared using a palladium-catalyzed Suzuki cross-coupling reaction according to the reaction sequence shown in Scheme 2. Chlorosulfonation of 3-bromotoluene (**12a**), and 4-bromotoluene (**12b**), at 0 °C followed by amminolysis using aqueous ammonium hydroxide in dioxane afforded the respective sulfonamide (**14a**,**b**) in good yield. The subsequent acetylation of **14a**,**b** yielded the corresponding



Scheme 2. Reagents and conditions: (a) $ClSO_3H$, $CHCl_3$, 0 °C, 4 h; (b) 30% w/v NH_4OH, dioxane, 0 °C, 6 h; (c) Ac_2O, DMAP, pyridine, 25 °C, overnight; (d) $Pd(PPh_3)_4$, Na_2CO_3, THF, reflux, 5 h; (e) $KMnO_4$, 0.5 N NaOH, 60 °C, 4 h; (f) Oxone®, THF, MeOH, H_2O, 25 °C, 2 h; (g) MeOH, H_2SO_4, 80 °C, overnight; (h) Ac_2O, pyridine, DMAP, 25 °C, overnight.



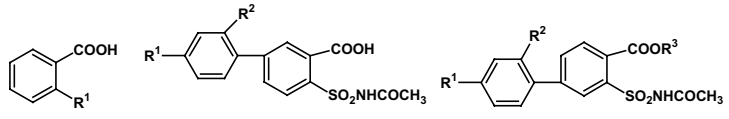
Scheme 1. Reagents and conditions: (a) Ac_2O, DMAP, pyridine, 25 °C, overnight; (b) $KMnO_4$, 0.5 N aqueous NaOH solution, 60 °C, 6 h.

N-acetyl-4-(or 5-)bromo-2-methylbenzenesulfonamide (**15a**,**b**). The Suzuki cross-coupling reaction[13,14] between an aryl bromide (**15a**,**b**) and a substituted-phenylboronic acid (**16**) in the presence of 2 M aqueous sodium carbonate in tetrahydrofuran, using tetrakis(triphenylphosphine)palladium(0) as a catalyst, afforded the respective biaryl derivative (**17**, **18**). Subsequent oxidation of the C-2 methyl aryl substituent present in **17** and **18** using $KMnO_4$ in 0.5 N aqueous NaOH at 60 °C for 6 h yielded the desired C-4 (**19**), or C-5 (**20**) substituted-phenyl derivative of *N*-acetyl-2-carboxybenzenesulfonamide. Methylation of the 2-carboxy compound **20d** followed by reacetylation furnished 2-methoxycarbonyl-5-(4-methylsulfonylphenyl)benzenesulfonamide (**21**).It was necessary to reacetylate the sulfonamide substituent since it undergoes *N*-deacetylation during the acid catalyzed esterification reaction employed to convert the C-2 carboxyl substituent to the C-2 methyl ester.

3. Results and discussion

A group of *N*-acetyl-2-carboxybenzenesulfonamides possessing an appropriately substituted-phenyl substituent attached to its C-4, or C-5, position were designed to determine (i) whether the *N*-acetylsulfonamido moiety (**11**) is a suitable bioisostere of the acetoxy substituent in aspirin (**1**), and (ii) if a substituted-phenyl moiety attached to the C-4 or C-5 position of the parent 2-carboxybenzenesulfonamido ring will provide the additional steric size required to confer COX-2 selectivity. In vitro COX-1/COX-2 inhibition studies (see data in Table 1) showed that *N*-acetyl-2-carboxybenzenesulfonamide (**11**) is a more potent inhibitor of COX-1 and COX-2 [COX-1 $IC_{50} = 0.06\ \mu M$; COX-2 $IC_{50} = 0.25\ \mu M$; COX-2 selectivity index (S.I.) = 0.23] than aspirin (COX-1 $IC_{50} = 0.35\ \mu M$; COX-2 $IC_{50} = 2.4\ \mu M$; COX-2 S.I. = 0.14). Introduction of a C-4 phenyl substituent (**19a**) increased COX-2 inhibitory potency and selectivity (COX-1 $IC_{50} = 0.33\ \mu M$; COX-2 $IC_{50} = 0.03\ \mu M$, S.I. = 10). In contrast, incorporation of a C-5 phenyl substituent (**20a**) did not appreciably change COX-1 inhibitory activity but COX-2 inhibitory activity and selectivity was decreased (COX-1 $IC_{50} = 0.03\ \mu M$; COX-2 $IC_{50} = 1.2\ \mu M$; COX-2 S.I. = 0.02). The point of attachment of a 4-fluorophenyl substituent is a determinant of selectivity since the C-4 compound (**19b**) selectively inhibits COX-1, whereas the C-5 regioisomer (**20b**) is a selective COX-2 inhibitor. Similarly, the C-4 4-methanesulfonylphenyl regioisomer (**19d**) was a selective COX-1 inhibitor, while the C-5 regioisomer (**20d**) was a selective COX-2 inhibitor. On the other hand, placement of a 2,4-difluorophenyl substituent at either the C-4 position (**19c**, COX-2 $IC_{50} = 0.087\ \mu M$; COX-2 S.I. = >1149), or C-5 position (**20c**, COX-2 $IC_{50} = 0.77\ \mu M$; COX-2 S.I. = >130) provided compounds with superior COX-2 selectivity with the C-4 difluorophenyl regioisomer (**19c**) being a ninefold more potent and selective COX-2 inhibitor than the C-5 regioisomer (**20c**). Accordingly, *N*-acetyl-2-carboxy-4-(2,4-difluorophenyl)benzenesulfonamide (**19c**) (i) is a significantly more potent and selective COX-2 inhibitor than the reference drug aspirin (COX-1 $IC_{50} > 0.35\ \mu M$; COX-2 $IC_{50} = 2.4\ \mu M$; COX-2 S.I. = 0.14), and (ii) a slightly less potent but more selective COX-2 inhibitor than celecoxib (COX-1 $IC_{50} = 33.1\ \mu M$; COX-2 $IC_{50} = 0.07\ \mu M$, S.I. = 472). Other structure–activity

Table 1. In vitro COX-1 and COX-2 inhibition data for *N*-acetyl-2-carboxybenzenesulfonamides (**11**, **19**, **20**) and the 2-methoxycarbonyl derivative (**21**)



Compound	R^1	R^2	R^3	IC_{50} (μM)[a]		COX-2 S.I.[b]
				COX-1	COX-2	
11	$SO_2NHCOCH_3$	—	—	0.06	0.25	0.23
19a	H	H	—	0.33	0.03	10.3
19b	F	H	—	0.68	>100	<0.007
19c	F	F	—	>100	0.087	>1149
19d	SO_2CH_3	H	—	0.17	>100	<0.002
20a	H	H	H	0.03	1.2	0.02
20b	F	H	H	>100	3.8	>25
20c	F	F	H	>100	0.77	>130
20d	SO_2CH_3	H	H	2.17	0.3	7.4
20e	$(CH_3)_2CHO$	H	H	>100	>100	N/A
21	SO_2CH_3	H	CH_3	>100	>100	N/A
1 (Aspirin)	$OCOCH_3$	—	—	0.35	2.4	0.14
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}).

relationships acquired show that (i) introduction of a C-5 4-isopropoxyphenyl substituent (**20e**) abolishes both COX-1 and COX-2 inhibitory activity (IC_{50} values >100 μM), and (ii) a C-2 carboxyl substituent is essential since its elaboration (**20d**) to a C-2 methoxycarbonyl substituent (**21**) destroys both COX-1 and COX-2 inhibitory activity.

A molecular modeling experiment was carried out to determine the binding interactions of *N*-acetyl-2-carboxy-4-(2,4-difluorophenyl)benzenesulfonamide (**19c**) in the COX-2 binding site (Fig. 2). The parent aromatic ring possessing the C-2 carboxyl and *N*-acetylsulfonamido substituents was oriented such that the carboxylic acid moiety is positioned near the mouth of COX-2 binding site where it forms a salt bridge (electrostatic interaction) with the guanidino group of Arg^{120} (distance < 3 Å). The *N*-acetylsulfonamido-substituent is located in a region comprised of nonpolar amino acids such as Ala^{527}, Val^{349}, Leu^{359}, Leu^{531}, and Leu^{117}. Interestingly, the C═O of the $SO_2NHCOMe$ substituent forms a favorable hydrogen bonding interaction with the O*H* of Tyr^{355} close to the mouth of COX-2 channel (distance = 1.7 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 7.03 Å. These observations suggest that the $SO_2NHCOMe$ moiety present in **19c** is suitably orientated to potentially acetylate (covalent bond formation) Ser^{530} present in the COX-2 isozyme.

The 2,4-difluorophenyl ring present in **19c** is oriented toward the COX-2 secondary pocket in the vicinity of amino acid residues Val^{523}, Asp^{515}, Arg^{513}, Gln^{192}, Thr^{94}, and His^{90} (Fig. 2). In this context, the distance between 4-fluoro atom of the 2,4-difluorophenyl ring and the N*H*$_2$ (guanidino group) of Arg^{513} is about 5.64 Å, and it is positioned about 5.90 Å from the N*H*$_2$ of Gln^{192}. The 2-fluoro atom of the 2,4-difluoro-phenyl ring is positioned near Thr^{94}, Gly^{354}, and Tyr^{355} (distance < 5 Å) close to the entrance of the COX-2 secondary pocket.

Pharmacological studies were carried out to assess the in vivo antiinflammatory and analgesic activities of *N*-acetyl-2-carboxybenzenesulfonamide (**11**), and some of the most potent and selective COX-2 inhibitors (**19c**, **20b**, and **20c**), based on in vitro enzyme inhibition data (see data in Table 2). In the carrageenan-induced rat paw edema assay model, the parent compound **11** was the most potent antiinflammatory agent (ED_{50} = 49 mg/kg) within this group of compounds at 3 h postdrug administration (oral dose). This high in vivo antiinflammatory activity shown by **11**, relative to **19c**, **20b**, and **20c**, is attributed to the fact that **11** inhibits both COX-1 and COX-2 whereas the latter compounds inhibit only COX-2. Credence for this explanation is based on observation that the more potent and selective in vitro COX-2 inhibitor *N*-acetyl-2-carboxy-4-(2,4-difluorophenyl)benzenesulfonamide (**19c**) is a less potent antiinflammatory agent in vivo (ED_{50} = 91 mg/kg, oral dose) than **11** (ED_{50} = 49 mg/kg, oral dose). These structure–activity data indicate that the $SO_2NHCOMe$ moiety present in **11** is a suitable bioisostere, with respect to antiinflammatory activity, of the acetoxy (OCOMe)

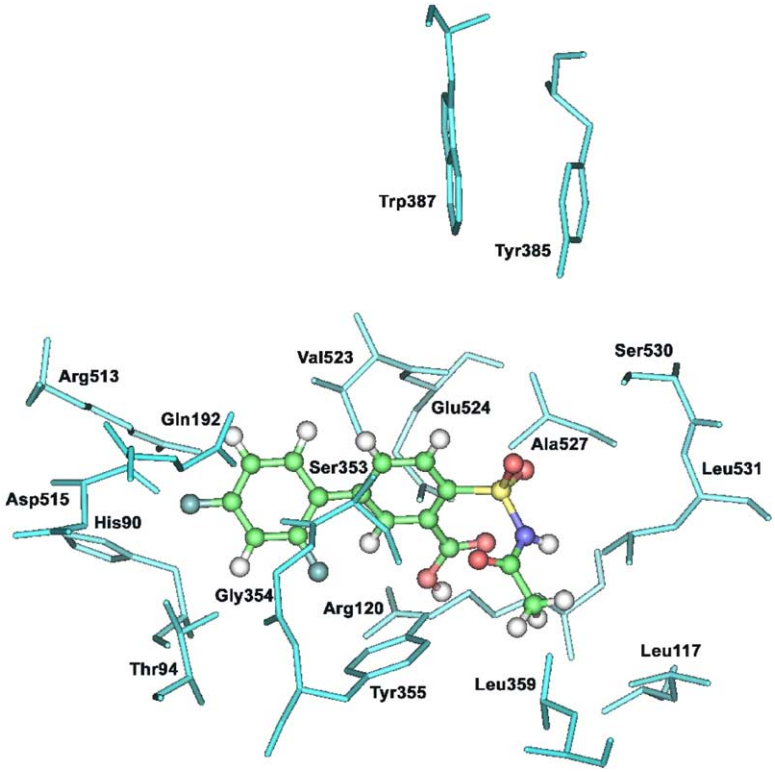
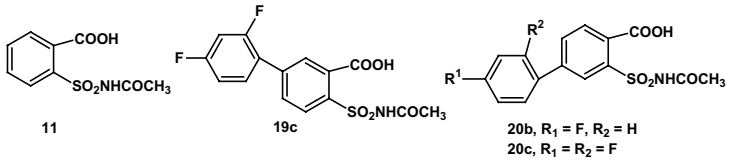


Figure 2. Docking of *N*-acetyl-2-carboxy-4-(2,4-difluorophenyl)benzenesulfonamide (**19c**) (ball-and-stick) in the active site of murine COX-2. Hydrogens atoms of the amino acid residues have been removed to improve clarity.

Table 2. In vivo antiinflammatory and analgesic activities for *N*-acetyl-2-carboxybenzenesulfonamides



Compound	Antiinflammatory activity[a]		Analgesic activity[b]	
	% Inhibition (50 mg/kg)	ED_{50} (mg/kg)	% Inhibition at 30 min	% Inhibition at 60 min
11	51.1 ± 5.2	49	48.0 ± 9.7	78.0 ± 1.4
19c	41.7 ± 5.2	91	33.7 ± 10.1	60.0 ± 10.3
20b	Inactive	—	38.0 ± 19.7	53.3 ± 22.2
20c	Inactive	—	58.3 ± 11.8	33.3 ± 18.0
Diflunisal (**2**)	60.8 ± 0.9[c]	17	52.8 ± 20.7	58.3 ± 10.2
Aspirin (**1**)	25.2 ± 3.3	129	29.7 ± 10.7	46.4 ± 14.1

[a] Inhibitory activity in a carrageenan-induced rat paw edema assay. The results are expressed as mean ± SEM ($n = 4$) at 3 h following a 50 mg/kg oral dose of the test compound, or as the ED_{50} value when it was determined.

[b] Inhibitory activity in the rat 4% NaCl-induced abdominal constriction assay. The results are expressed as mean ± SEM ($n = 4$) following a 5 mg/kg oral dose of the test compound.

[c] 30 mg/kg oral dose.

substituent present in aspirin (ED_{50} = 129 mg/kg, oral dose).

In a rat model 4% NaCl-induced abdominal constriction assay, a 5 mg/kg po dose of compounds **11**, **19c**, **20b**, and **20c** exhibited good analgesic activities (33–78% inhibition range) at 30 or 60 min postdrug administration relative to the reference drugs diflunisal (52–58% inhibition) and aspirin (30–46% inhibition).

4. Conclusions

In vitro COX-1/COX-2 isozyme inhibition, and in vivo antiinflammatory and analgesic, data acquired for this novel class of *N*-acetyl-2-carboxybenzenesulfonamides showed that (i) the $SO_2NHCOCH_3$ moiety is a suitable bioisostere of the OAc substituent present in aspirin, (ii) incorporation of a 2,4-difluorophenyl substituent at the C-4 position of *N*-acetyl-2-carboxybenzenesulfonamide provided the most potent (IC_{50} = 0.087 μM) and selective (S.I. >1149) inhibition of COX-2, and that this compound could serve as a useful probe to study the function and catalytic activity of the COX-2 isozyme, and (iii) a compound, which inhibits both COX-1 and COX-2 such as *N*-acetyl-2-carboxybenzenesulfonamide exhibits superior in vivo antiinflammatory activity relative to compounds that are more potent and selective inhibitors of COX-2.

5. Experimental

Melting points were determined on a Thomas–Hoover capillary apparatus and are uncorrected. Infrared (IR) spectra were recorded on 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 Hz. Spin multiples are given as s (singlet), d (double), t (triplet), q (quartet), m (multiplet), and br (broad). 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, purchased from the Aldrich Chemical Company (Milwaukee, WI), were used without further purification. Male Sprague–Dawley rats, used in the antiinflammatory-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. *N*-Acetyl-2-methylbenzenesulfonamide (10)

Acetic anhydride (1.7 mL, 18 mmol) and 4-dimethylaminopyridine (219 mg, 1.8 mmol) were added to a solution of 2-methylbenzenesulfonamide (**9**, 1.03 g, 6 mmol) in pyridine (3 mL) and the reaction was allowed to proceed at 25 °C with stirring for 6 h. EtOAc (300 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 **10** (962 mg, 60%) as colorless needles; mp 130–132 °C; IR (film) 1704 (C=O), 1465 (Ar), 1341 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.09 (s, 3H, $NHCOCH_3$), 2.68 (s, 3H, C-2, CH_3), 7.35 (d, J = 7.7 Hz, 1H, H-3), 7.40 (t, J = 7.7 Hz, 1H, H-5), 7.55 (t, J = 7.7 Hz, 1H, H-4), 8.15 (d, J = 7.7 Hz, 1H, H-6), 8.66 (br s, 1H, *NH*).

5.2. *N*-Acetyl-2-carboxybenzenesulfonamide (11)

$KMnO_4$ (1.9 g, 12 mmol) was added to a solution of *N*-acetyl-2-methylbenzenesulfonamide (**10**, 426 mg, 2 mmol) in aqueous NaOH (24 mL of 0.5 N), and the reaction was allowed to proceed at 60 °C with stirring for 6 h prior to quenching with acetone. The insoluble material was removed by filtration, and the filtrate was

diluted with H_2O (150 mL) prior to acidification to pH 3 using 5% HCl. Extraction with CH_2Cl_2 (2 × 100 mL), washing the combined CH_2Cl_2 extracts with water (3 × 50 mL), drying the organic fraction (Na_2SO_4), and removal of the solvent in vacuo afforded **11** (306 mg, 63%) as a pale yellow solid; mp 178–180 °C; IR ($CHCl_3$) 3669–2497 (COOH), 3273 (NH), 3157 (Ar–H), 1721 (C═O), 1620, 1470 (Ar), 1380 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO): δ 1.95 (s, 3H, NHCOCH_3), 7.50 (m, 2H, H-4, H-5), 7.66 (dd, J = 7.8, 1.6 Hz, 1H, H-3), 8.10 (dd, J = 7.3, 1.2 Hz, 1H, H-6), 10.40 (br s, 1H, *NH*). Anal. Calcd for $C_9H_9O_5NS$: C, 44.44; H, 3.73; N, 5.76. Found: C, 44.37; H, 3.51; N, 5.65.

5.3. General procedure for the synthesis of 4-bromo-2-methylbenzenesulfonyl chloride (13a) and 5-bromo-2-methylbenzensulfonyl chloride (13b)

Chlorosulfonic acid (2.5 mL, 4.38 g, 37.6 mmol) was added slowly to a cold solution (0 °C) of either 3-bromotoluene (**12a**, 1.03 g, 6 mmol), or 4-bromotoluene (**12b**, 1.03 g, 6 mmol), in $CHCl_3$ (10 mL). The reaction was allowed to proceed with stirring for 4 h at 0 °C prior to pouring onto crushed ice (250 mL), and then extraction with $CHCl_3$ (3 × 150 mL). The combined $CHCl_3$ extracts were washed with water (3 × 100 mL), the organic fraction was dried (Na_2SO_4), and the solvent was removed in vacuo to yield the respective arylsulfonyl chloride product (**13a** or **13b**). Some physical and spectroscopic data for **13a**,**b** are listed below.

5.4. 4-Bromo-2-methylbenzenesulfonyl chloride (13a)

Yield, 99%; white crystals; mp 63–64 °C; IR (film) 1577, 1547, 1472 (Ar), 1375 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.77 (s, 3H, CH_3), 7.57 (d, J = 8.5 Hz, 1H, H-5), 7.60 (s, 1H, H-3), 7.93 (d, J = 8.6 Hz, 1H, H-6).

5.5. 5-Bromo-2-methylbenzenesulfonyl chloride (13b)

Yield, 78%; colorless liquid; IR (neat) 3091 (Ar–H), 1374 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.73 (s, 3H, CH_3), 7.31 (d, J = 8.2 Hz, 1H, H-3), 7.72 (dd, J = 8.2, 1.8 Hz, 1H, H-4), 8.19 (d, J = 1.8 Hz, 1H, H-6).

5.6. General procedure for the synthesis of 4-bromo-2-methylbenzenesulfonamide (14a) and 5-bromo-2-methylbenzenesulfonamide (14b)

An aqueous solution of NH_4OH (30 mL of 30% w/v) was added to a cold (0 °C) solution of the arylsulfonyl chloride (**13a** or **13b**, 0.59 g, 2.2 mmol) in dioxane (15 mL) with vigorous stirring, and the reaction was allowed to proceed for 6 h at 0 °C with continued stirring. The insoluble material was removed by filtration, washed with water (3 × 10 mL), and recrystallized from hexanes–acetone to yield the respective product (**14a** or **14b**).

5.7. 5-Bromo-2-methylbenzenesulfonamide (14a)

Yield, 78%; white needles; mp 176–177 °C; IR (film) 3362, 3242 (NH_2), 1592, 1547 (Ar), 1315 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.67 (s, 3H, CH_3), 4.81 (br s, 2H, NH_2), 7.47 (d, J = 8.2 Hz, 1H, H-5), 7.51 (s, 1H, H-3), 7.88 (d, J = 8.2 Hz, 1H, H-6).

5.8. 5-Bromo-2-methylbenzenesulfonamide (14b)

Yield, 80%; white needles; mp 164–165 °C (lit.[15] 164–165 °C); IR (film) 3397, 3281 (NH_2), 1291 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.63 (s, 3H, CH_3), 4.79 (br s, 2H, NH_2), 7.21 (d, J = 8.0 Hz, 1H, H-3), 7.58 (dd, J = 8.0, 2.1 Hz, 1H, H-4), 8.15 (d, J = 2.1 Hz, 1H, H-6).

Compounds **15a**,**b**, for which the physical and spectroscopic data are listed below, were prepared using an acetylation procedure similar to that described previously for the synthesis of compound **10**.

5.9. *N*-Acetyl-4-bromo-2-methylbenzenesulfonamide (15a)

Yield, 80%; pale yellow crystals; mp 150–152 °C; IR (film) 1704 (C═O), 1597, 1547, 1440 (Ar), 1349 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.09 (s, 3H, NHCOCH_3), 2.65 (s, 3H, C-2 CH_3), 7.52 (s, 1H, H-3), 7.54 (d, J = 8.5 Hz, 1H, H-5), 8.00 (d, J = 8.5 Hz, 1H, H-6), 8.36 (br s, 1H, *NH*). Anal. Calcd for $C_9H_{10}BrNO_3S$: C, 37.00; H, 3.45; N, 4.79. Found: C, 37.28; H, 3.34; N, 4.62.

5.10. *N*-Acetyl-5-bromo-2-methylbenzenesulfonamide (15b)

Yield, 82%; pale yellow crystals; mp 179–180 °C; IR (film) 1668 (C═O), 1473 (Ar), 1333 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.12 (s, 3H, NHCOCH_3), 2.62 (s, 3H, C-2, CH_3), 7.22 (d, J = 8.3 Hz, 1H, H-3), 7.65 (dd, J = 8.3, 2.1 Hz, 1H, H-4), 8.26 (d, J = 2.1 Hz, 1H, H-6), 8.60 (br s, 1H, N*H*). Anal. Calcd for $C_9H_{10}BrNO_3S$: C, 37.00; H, 3.45; N, 4.79. Found: C, 37.13; H, 3.34; N, 4.68.

5.11. General procedure for the synthesis of *N*-Acetyl-2-methyl-4-(substituted-phenyl)benzenesulfonamides (17a–d) and *N*-acetyl-2-methyl-5-(substituted-phenyl)benzenesulfonamides (18a–d,f)

The aryl bromide (**15a** or **15b**, 0.58 g, 2.0 mmol) and the appropriately substituted-phenylboronic acid (**16**, 3.0 mmol) were dissolved in THF (30 mL), and then aqueous Na_2CO_3 (3.0 mL of 2 M) followed by tetrakis(triphenylphosphine)palladium (70 mg, 0.06 mmol) were added. The reaction was allowed to proceed at reflux for 3–5 h, cooled to 25 °C, water was added (150 mL), the mixture was acidified to pH 3 using 5% w/v HCl, and the mixture was extracted with EtOAc (3 × 100 mL). The combined EtOAc extracts were washed with water (3 × 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 (100:3, v/v) as eluant furnished the respective title compound (**17a–d**, **18a–d**,**f**).

5.12. *N*-Acetyl-2-methyl-4-phenylbenzenesulfonamide (17a)

Yield, 90%; white needles; mp 168–169 °C; IR ($CHCl_3$) 3393 (NH), 3155 (Ar–H), 1722 (C=O), 1603, 1474 (Ar), 1380, 1350 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.13 (s, 3H, NHCOCH_3), 2.74 (s, 3H, C-2, CH_3), 7.40–8.27 (m, 8H, Ar–H), 8.62 (br s, 1H, *NH*). Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.23; N, 4.84. Found: C, 62.20; H, 5.19; N, 4.69.

5.13. *N*-Acetyl-2-methyl-5-phenylbenzenesulfonamide (18a)

Yield, 53.5%; pale yellow crystals; mp 183–185 °C; IR (film) 1682 (C=O), 1480, 1435 (Ar), 1310 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.12 (s, 3H, NHCOCH_3), 2.71 (s, 3H, C-2, CH_3), 7.37–7.51 (m, 4H, H-3, phenyl H-3, H-4, H-5), 7.62 (dd, J = 8.4, 1.2 Hz, 2H, phenyl H-2, H-6), 7.76 (dd, J = 8.0, 1.8 Hz, 1H, H-4), 8.33 (br s, 1H, *NH*), 8.37 (d, J = 1.8 Hz, 1H, H-6). Anal. Calcd for $C_{15}H_{15}NO_3S{\cdot}1/4H_2O$: C, 61.31; H, 5.31; N, 4.77. Found: C, 61.34; H, 5.31; N, 4.73.

5.14. *N*-Acetyl-4-(4-fluorophenyl)-2-methylbenzenesulfonamide (17b)

Yield, 87%; pale yellow crystals; mp 175–176 °C; IR ($CHCl_3$) 3382 (NH), 3019 (Ar–H), 1723 (C=O), 1602, 1474 (Ar), 1387 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.12 (s, 3H, NHCOCH_3), 2.73 (s, 3H, C-2, CH_3), 7.18 (t, J = 8.5 Hz, 2H, fluorophenyl H-3, H-5), 7.50 (br s, 1H, H-3), 7.58 (m, 3H, H-5, fluorophenyl H-2, H-6), 8.21 (d, J = 8.4 Hz, 1H, H-6), 8.57 (br s, 1H, *NH*). Anal. Calcd for $C_{15}H_{14}FNO_3S$: C, 58.62; H, 4.59; N, 4.56. Found: C, 58.60; H, 4.34; N, 4.37.

5.15. *N*-Acetyl-5-(4-fluorophenyl)-2-methylbenzenesulfonamide (18b)

Yield, 75%; pale yellow solid; mp 120–122 °C; IR ($CHCl_3$) 3388 (NH), 3130 (Ar–H), 1723 (C=O), 1620, 1461 (Ar), 1380 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.10 (s, 3H, NHCOCH_3), 2.70 (s, 3H, C-2, CH_3), 7.16 (t, J = 8.4 Hz, 2H, fluorophenyl H-3, H-5), 7.41 (d, J = 8.0 Hz, 1H, H-3), 7.57 (dd, J = 8.4, 5.2 Hz, 2H, fluorophenyl H-2, H-6), 7.70 (dd, J = 8.0, 1.8 Hz, 1H, H-4), 8.33 (d, J = 2.1 Hz, 1H, H-6), 8.34 (br s, 1H, *NH*). Anal. Calcd for $C_{15}H_{14}FNO_3S$: C, 58.62; H, 4.59; N, 4.56. Found: C, 58.78; H, 4.48; N, 4.43.

5.16. *N*-Acetyl-4-(2,4-difluorophenyl)-2-methylbenzenesulfonamide (17c)

Yield, 86%; pale gray crystals; mp 146–147 °C; IR ($CHCl_3$) 3382 (NH), 3153 (Ar–H), 1716 (C=O), 1622 (Ar), 1387 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.13 (s, 3H, NHCOCH_3), 2.73 (s, 3H, C-2, CH_3), 6.95 (m, 2H, difluorophenyl H-3, H-5), 7.38–7.53 (m, 2H, H-3, H-5), 8.20 (d, J = 8.2 Hz, 1H, H-6), 8.52 (br s, 1H, *NH*). Anal. Calcd for $C_{15}H_{13}F_2NO_3S$: C, 55.38; H, 4.03; N, 4.31. Found: C, 55.41; H, 3.96; N, 4.23.

5.17. *N*-Acetyl-5-(2,4-difluorophenyl)-2-methylbenzenesulfonamide (18c)

Yield, 69%; pale yellow needles; mp 162–164 °C; IR ($CHCl_3$) 3385 (NH), 3010 (Ar–H), 1720 (C=O), 1600, 1490 (Ar), 1380 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.12 (s, 3H, NHCOCH_3), 2.71 (s, 3H, C-2, CH_3), 6.95 (m, 2H, difluorophenyl H-3, H-5), 7.42 (d, J = 8.2 Hz, 1H, H-3), 7.45 (m, 1H, difluorophenyl H-6), 7.70 (br d, J = 8.2 Hz, 1H, H-4), 8.28 (br s, 1H, H-6), 8.53 (br s, 1H, *NH*). Anal. Calcd for $C_{15}H_{13}F_2NO_3S$: C, 55.38; H, 4.03; N, 4.31. Found: C, 55.45; H, 3.82; N, 4.21.

5.18. *N*-Acetyl-2-methyl-4-(4-methylthiophenyl)benzenesulfonamide (17d)

Yield, 90%; white crystals; mp 162–163 °C; IR (film) 1697 (C=O), 1600, 1442 (Ar), 1300 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.12 (s, 3H, NHCOCH_3), 2.54 (s, 3H, SCH_3), 2.73 (s, 3H, C-2, CH_3), 7.34 (d, J = 8.4 Hz, 2H, methylthiophenyl H-3, H-5), 7.52–7.58 (m, 4H, H-3, H-5, methylthiophenyl H-2, H-6), 8.19 (d, J = 8.6 Hz, 1H, H-6), 8.46 (br s, 1H, *NH*). Anal. Calcd for $C_{16}H_{17}NO_3S_2$: C, 57.29; H, 5.11; N, 4.18. Found: C, 57.42; H, 5.08; N, 3.98.

5.19. *N*-Acetyl-2-methyl-5-(4-methylthiophenyl)benzenesulfonamide (18d)

Yield, 89%; pale yellow solid; mp 173–175 °C; IR (film) 1696 (C=O), 1602, 1481 (Ar), 1347 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.10 (s, 3H, NHCOCH_3), 2.53 (s, 3H, SCH_3), 2.69 (s, 3H, C-2, CH_3), 7.33 (d, J = 8.2 Hz, 2H, methylthiophenyl H-3, H-5), 7.40 (d, J = 8.2 Hz, 1H, H-3), 7.54 (d, J = 8.5 Hz, 2H, methylthiophenyl H-2, H-6), 7.73 (dd, J = 8.2, 1.8 Hz, 1H, H-4), 8.35 (d, J = 1.8 Hz, 1H, H-6), 8.58 (br s, 1H, *NH*). Anal. Calcd for $C_{16}H_{17}NO_3S_2$: C, 57.29; H, 5.11; N, 4.18. Found: C, 57.34; H, 4.93; N, 4.01.

5.20. *N*-Acetyl-5-(4-isopropoxyphenyl)-2-methylbenzenesulfonamide (18f)

Yield, 82%; white needles; mp 150–151 °C; IR ($CHCl_3$) 3388 (NH), 3031, 3024 (Ar–H), 1726 (C=O), 1602, 1485 (Ar), 1205 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.38 [d, J = 6.1 Hz, 6H, OCH(CH_3)$_2$], 2.10 (s, 3H, NHCOCH_3), 2.69 (s, 3 H, C-2, CH_3), 4.61 [m, 1H, OCH(CH$_3$)$_2$], 6.98 (d, J = 8.7 Hz, 2H, isopropoxyphenyl H-3, H-5), 7.37 (d, J = 8.0 Hz, 1H, H-3), 7.53 (d, J = 8.7 Hz, 2H, isopropoxyphenyl H-2, H-6), 7.71 (dd, J = 8.2, 1.8 Hz, 1H, H-4), 8.32 (d, J = 1.8 Hz, 1H, H-6), 8.62 (br s, 1H, *NH*). Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.34; H, 6.10; N, 3.94.

5.21. General procedure for the synthesis of *N*-acetyl-4-(4-methanesulfonylphenyl)-2-methylbenzenesulfonamide (17e) and *N*-acetyl-5-(4-methanesulfonylphenyl)-2-methylbenzenesulfonamide (18e)

An aqueous solution of Oxone® (1.9 g, 3.03 mmol, 15 mL) was added to a stirred solution of the methylthiophenyl

compound (**17d** or **18d**, 574 mg, 1.71 mmol) in methanol (6 mL) and THF (15 mL), and the reaction was allowed to proceed with stirring at 25 °C for 1.5 h. Addition of H_2O (100 mL), extraction with CH_2Cl_2 (3×80 mL), drying the combined CH_2Cl_2 extracts (Na_2SO_4), and removal of the solvent in vacuo afforded the crude product. The ^1H NMR of this product showed that the *N*-acetyl group has undergone partial hydrolysis. To circumvent this, the title compounds were isolated following acetylation of the crude product employing the same acetylation procedure described previously for the synthesis of compound **10**. The physical and spectral data for **17**–**18e** are summarized below.

5.22. *N*-Acetyl-4-(4-methanesulfonylphenyl)-2-methylbenzenesulfonamide (17e)

Yield, 89%; pale orange crystals; mp 206–208 °C; IR ($CHCl_3$) 1716 (C=O), 1595, 1441 (Ar), 1313 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO): δ 1.84 (s, 3H, NHCOCH_3), 2.56 (s, 3H, C-2, CH_3), 2.94 (s, 3H, SO_2CH_3), 7.35 (s, 1H, H-3), 7.39 (d, J = 8.2 Hz, 1H, H-5), 7.62 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.85 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.04 (d, J = 8.2 Hz, 1H, H-6), 11.7 (br s, 1H, *NH*). Anal. Calcd for $C_{16}H_{17}NO_5S_2$: C, 52.30; H, 4.66; N, 3.81. Found: C, 52.38; H, 4.38; N, 3.71.

5.23. *N*-Acetyl-5-(4-methanesulfonylphenyl)-2-methylbenzenesulfonamide (18e)

Yield, 57.5%; white crystals; mp 221–222 °C; IR ($CHCl_3$) 3393 (NH), 3155 (Ar–H), 1713 (C=O), 1639, 1500 (Ar), 1380 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO): δ 1.98 (s, 3H, NHCOCH_3), 2.67 (s, 3H, C-2, CH_3), 3.05 (s, 3H, SO_2CH_3), 7.36 (d, J = 8.2 Hz, 1H, H-3), 7.67 (dd, J = 8.2, 2.2 Hz, 1H, H-4), 7.76 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.96 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.36 (d, J = 2.2 Hz, 1H, H-6), 11.7 (br s, 1H, *NH*). Anal. Calcd for $C_{16}H_{17}NO_5S_2$: C, 52.30; H, 4.66; N, 3.81. Found: C, 52.49; H, 4.74; N, 3.66.

The *N*-acetyl-2-carboxy-4-(substituted-phenyl)benzenesulfonamides (**19a**–**d**) and *N*-acetyl-2-carboxy-5-(substituted-phenyl)benzenesulfonamides (**20a**–**d**) were prepared by oxidation of the C-2 methyl substituent using $KMnO_4$ according to the procedure described previously for the preparation of compound **11**.

5.24. *N*-Acetyl-2-carboxy-4-phenylbenzenesulfonamide (19a)

Yield, 88%; white crystals; mp 195–196 °C; IR ($CHCl_3$) 3388–2475 (COOH), 1709 (C=O), 1595, 1467 (Ar), 1250 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO): δ 2.00 (s, 3H, NHCOCH_3), 7.30–7.41 (m, 3H, phenyl H-3, H-4, H-5), 7.51 (d, J = 7.5 Hz, 2H, phenyl H-2, H-6), 7.70 (dd, J = 8.4, 1.8 Hz, 1H, H-5), 7.89 (d, J = 1.8 Hz, 1H, H-3), 8.19 (d, J = 8.4 Hz, 1H, H-6), 10.45 (br s, 1H, *NH*). Anal. Calcd for $C_{15}H_{13}NO_5S$: C, 56.42; H, 4.10; N, 4.39. Found: C, 56.32; H, 3.96; N, 4.23.

5.25. *N*-Acetyl-2-carboxy-5-phenylbenzenesulfonamide (20a)

Yield, 67%; pale yellow solid; mp 274–275 °C; IR ($CHCl_3$) 3471–2513 (COOH), 1704 (C=O), 1638, 1473 (Ar), 1366 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO): δ 2.01 (s, 3H, NHCOCH_3), 7.35 (m, 3H, phenyl H-3, H-4, H-5), 7.56 (d, J = 8.0 Hz, 2H, phenyl H-2, H-6), 7.75 (dd, J = 8.2, 1.5 Hz, 1H, H-4), 7.81 (d, J = 8.2 Hz, 1H, H-3), 8.36 (d, J = 1.5 Hz, 1H, H-6), 10.30 (br s, 1H, *NH*). Anal. Calcd for $C_{15}H_{13}NO_5S$: C, 56.42; H, 4.10; N, 4.39. Found: C, 56.10; H, 4.15; N, 4.30.

5.26. *N*-Acetyl-2-carboxy-4-(4-fluorophenyl)benzenesulfonamide (19b)

Yield, 88%; white solid; mp 201–202 °C; IR ($CHCl_3$): 3409–2468 (COOH), 1709 (C=O), 1602, 1467 (Ar), 1380 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO): δ 1.92 (s, 3H, NHCOCH_3), 7.02 (t, J = 8.5 Hz, 2H, fluorophenyl H-3, H-5), 7.45 (m, 2H, fluorophenyl H-2, H-6), 7.60 (dd, J = 8.2, 1.2 Hz, 1H, H-5), 7.76 (d, J = 1.2 Hz, 1H, H-3), 8.13 (d, J = 8.2 Hz, 1H, H-6), 10.69 (br s, 1H, *NH*). Anal. Calcd for $C_{15}H_{12}FNO_5S$: C, 53.41; H, 3.59; N, 4.15. Found: C, 53.44; H, 3.51; N, 4.02.

5.27. *N*-Acetyl-2-carboxy-5-(4-fluorophenyl)benzenesulfonamide (20b)

Yield, 78%; pale yellow solid; mp 250–252 °C; IR ($CHCl_3$) 3493–2515 (COOH), 1712 (C=O), 1380 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO): δ 2.02 (s, 3H, NHCOCH_3), 7.09 (t, J = 8.5 Hz, 2H, fluorophenyl H-3, H-5), 7.56 (dd, J = 8.5, 5.2 Hz, 2H, fluorophenyl H-2, H-6), 7.74 (dd, J = 8.0, 1.8 Hz, 1H, H-4), 7.82 (d, J = 8.0 Hz, 1H, H-3), 8.35 (d, J = 1.8 Hz, 1H, H-6), 10.27 (br s, 1H, *NH*). Anal. Calcd for $C_{15}H_{12}FNO_5S$: C, 53.41; H, 3.59; N, 4.15. Found: C, 53.08; H, 3.51; N, 4.05.

5.28. *N*-Acetyl-2-carboxy-4-(2,4-difluorophenyl)benzenesulfonamide (19c)

Yield, 81%; white solid; mp 189–190 °C; IR ($CHCl_3$) 3368–2509 (COOH), 1716 (C=O), 1615, 1461 (Ar), 1380 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO): δ 1.87 (s, 3H, NHCOCH_3), 6.83 (m, 2H, difluorophenyl H-3, H-5), 7.26 (m, 1H, difluorophenyl H-6), 7.54 (br d, J = 8.2 Hz, 1H, H-5), 7.66 (br s, 1H, H-3), 8.08 (d, J = 8.2 Hz, 1H, H-6), 10.90 (br s, 1H, *NH*). Anal. Calcd for $C_{15}H_{11}F_2NO_5S$: C, 50.70; H, 3.12; N, 3.94. Found: C, 50.55; H, 2.86; N, 3.87.

5.29. *N*-Acetyl-2-carboxy-5-(2,4-difluorophenyl)benzenesulfonamide (20c)

Yield, 69%; white solid; mp 220–221 °C; IR ($CHCl_3$) 3361–2515 (COOH), 1729 (C=O), 1629, 1467 (Ar), 1380 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO): δ 2.01 (s, 3H, NHCOCH_3), 6.90 (m, 2H, difluorophenyl H-3, H-5), 7.43 (m, 1H, difluorophenyl H-6), 7.72 (br d, J = 8.0 Hz, 1H, H-4), 7.79 (d, J = 8.0 Hz, 1H, H-3), 8.28 (br s, 1H, H-6), 10.36 (br s, 1H, *NH*). Anal. Calcd

for $C_{15}H_{11}F_2NO_5S$: C, 50.70; H, 3.12; N, 3.94. Found: C, 50.66; H, 2.95; N, 3.85.

5.30. *N*-Acetyl-2-carboxy-4-(4-methanesulfonylphenyl)benzenesulfonamide (19d)

Yield, 70%; white crystals; mp 199–200 °C; IR ($CHCl_3$) 3382–2723 (COOH), 1716 (C=O), 1602, 1454 (Ar), 1306 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO): δ 1.89 (s, 3H, $NHCOCH_3$), 2.93 (s, 3H, SO_2CH_3), 7.64 (dd, J = 8.2, 1.8 Hz, 1H, H-5), 7.64 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.80 (d, J = 1.8 Hz, 1H, H-3), 7.87 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.16 (d, J = 8.2 Hz, 1H, H-6), 11.0 (br s, 1H, *NH*). Anal. Calcd for $C_{16}H_{15}NO_7S_2$: C, 48.35; H, 3.80; N, 3.52. Found: C, 48.44; H, 3.66; N, 3.42.

5.31. *N*-Acetyl-2-carboxy-5-(4-methanesulfonylphenyl)benzenesulfonamide (20d)

Yield, 81%; white solid; mp >300 °C; IR ($CHCl_3$) 3409–2468 (COOH), 1716 (C=O), 1615, 1454 (Ar), 1380 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO): δ 1.90 (s, 3H, $NHCOCH_3$), 2.95 (s, 3H, SO_2CH_3), 7.71 (m, 4H, H-3, H-4, methanesulfonylphenyl H-2, H-6), 7.89 (d, J = 8.6 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.33 (d, J = 1.0 Hz, 1H, H-6), 11.0 (br s, 1H, *NH*). Anal. Calcd for $C_{16}H_{15}NO_7S_2$: C, 48.35; H, 3.80; N, 3.52. Found: C, 48.00; H, 3.71; N, 3.42.

5.32. *N*-Acetyl-2-carboxy-5-(4-isopropoxyphenyl)benzenesulfonamide (20e)

Yield, 87%; white crystals; mp 206–208 °C; IR (film) 3430–2845 (COOH), 1735, 1727 (C=O), 1592 (Ar), 1240 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.06 [d, J = 6.1 Hz, 6H, $CH(CH_3)_2$], 1.76 (s, 3H, $NHCOCH_3$), 4.32 [m, 1H, $CH(CH_3)_2$], 6.68 (d, J = 8.7 Hz, 2H, isopropoxyphenyl H-3, H-5), 7.28 (d, J = 8.7 Hz, 2H, isopropoxyphenyl H-2, H-6), 7.48 (d, J = 8.0 Hz, 1H, H-3), 7.52 (dd, J = 8.0, 1.8 Hz, 1H, H-4), 8.09 (d, J = 1.8 Hz, 1H, H-6), 11.0 (br s, 1H, *NH*). Anal. Calcd for $C_{18}H_{19}NO_6S \cdot 1/4H_2O$: C, 56.61; H, 5.15; N, 3.67. Found: C, 56.81; H, 5.10; N, 3.64.

5.33. *N*-Acetyl-2-methoxycarbonyl-5-(4-methanesulfonylphenyl)benzenesulfonamide (21)

Concentrated H_2SO_4 (1.3 mL) was added dropwise at ice-bath temperature to a stirred solution of **20d** (100 mg, 0.25 mmol) in methanol (15 mL). The reaction mixture was refluxed for 24 h, cooled to 25 °C, and CH_2Cl_2 (100 mL) was added. This solution was washed with water (30 mL), the organic fraction was dried (Na_2SO_4), and the solvent was removed in vacuo to provide a white solid. This solid was acetylated in situ, following the procedure described previously for the synthesis of compound **10**, to afford a crude product, which was crystallized from hexanes–acetone to yield the target product **21** as pale yellow crystals (80 mg, 77%); mp 217–218 °C; IR (film): 1721 (C=O), 1597, 1448 (Ar), 1291 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO): δ 1.94 (s, 3H, $NHCOCH_3$), 2.98 (s, 3H, SO_2CH_3), 3.86 (s, 3H, OCH_3), 7.73 (d, J = 8.2 Hz, 1H, H-3), 7.78 (d, J = 8.4 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.80 (dd, J = 8.2, 1.5 Hz, 1H, H-4), 7.92 (d, J = 8.4 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.41 (d, J = 1.5 Hz, 1H, H-6), 11.40 (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, 49.55; H, 3.96; N, 3.26.

5.34. 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.[16]

5.35. In vitro cyclooxygenase inhibition assays

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 immuno assay (EIA) kit (catalog number 560101, Cayman Chemical, Ann Arbor, MI, USA) according to our previously reported method.[16]

5.36. Antiinflammatory assay

Antiinflammatory activity was performed using a method described by Winter et al.[17]

5.37. Analgesic assay

Analgesic activity was determined using a 4% sodium chloride-induced writhing (abdominal constriction assay previously reported).[18]

Acknowledgements

We are grateful to (i) the Canadian Institutes of Health Research (CIHR) (MOP-14712) for financial support of this research, (ii) the Alberta Heritage Foundation for Medical Research (AHFMR) for a postdoctoral fellowship award (to Q.H.C.), and a graduate scholarship (to P.R.), and to Rx&D-HRF/CIHR for a postdoctoral fellowship (to Q.H.C.).

References and notes

1. *The Salicylates*; Smith, M. J. H., Smith, P. K., Eds.; Wiley-Interscience: New York, 1966, and references cited therein.
2. Hannah, J.; Ruyle, W. V.; Jones, H.; Matzuk, A. R.; Kelly, K. W.; Witzel, B. E.; Holtz, W. J.; Houser, R. A.; Shen, T. Y.; Sarett, L. H. *J. Med. Chem.* **1978**, *21*, 1093.
3. Fu, J. Y.; Masferrer, J. L.; Seibert, K.; Raz, A.; Needleman, P. *J. Biol. Chem.* **1990**, *265*, 16737.
4. Xie, W.; Chipman, J.; Robertson, D. L.; Erikson, R. L.; Simmons, D. L. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 2692.
5. Goldstein, J. L.; Silverstein, F. E.; Agrawal, N. M.; Hubbard, R. C.; Kaiser, J.; Maurath, C. I.; Verburg, K. M.; Geis, G. S. *Am. J. Gastroenterol.* **2000**, *95*, 1681.
6. Meade, E. A.; Smith, W. L.; DeWitt, D. L. *J. Biol. Chem.* **1993**, *268*, 6610.

7. (a) Kalgutkar, A. S.; Crews, B. C.; Rowlinson, S. W.; Garner, C.; Seibert, K.; Marnett, L. J. *Science* **1998**, *280*, 1268; (b) Kalgutkar, A. S.; Kozak, K. R.; Crews, B. C.; Hochgesang, G. P., Jr.; Marnett, L. J. *J. Med. Chem.* **1998**, *41*, 4800; (c) Hochgesang, G. P., Jr.; Nemeth-Cawley, J. F.; Rowlinson, S. W.; Caprioli, R. M.; Marnett, L. J. *Arch. Biochem. Biophys.* **2003**, *409*, 127.
8. Rahim, M. A.; Rao, P. N. P.; Knaus, E. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2753.
9. Sykes, N. O.; Macdonald, S. J. F.; Page, M. I. *J. Med. Chem.* **2002**, *45*, 2850.
10. Zarghi, A.; Rao, P. N. P.; Knaus, E. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1957.
11. Boyer-Joubert, C.; Lorthiois, E.; Moreau, F. *Annu. Rep. Med. Chem.* **2003**, *38*, 364.
12. Talley, J. J.; Brown, D. L.; Carter, J. S.; Graneto, M. J.; Koboldt, C. M.; Masferrer, J. L.; Perkins, W. E.; Rogers, R. S.; Shaffer, A. F.; Zhang, Y. Y.; Zweifel, B. S.; Seibert, K. *J. Med. Chem.* **2000**, *43*, 775.
13. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
14. Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263.
15. Huntress, E. H.; Carten, F. H. *J. Am. Chem. Soc.* **1940**, *62*, 511.
16. Uddin, M. J.; Rao, P. N. P.; Knaus, E. E. *Bioorg. Med. Chem.* **2004**, *12*, 5929.
17. Winter, C. A.; Risley, E. A.; Nuss, G. W. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544.
18. Fukawa, K.; Kawano, O.; Hibi, M.; Misaka, N.; Ohba, S.; Hatanaka, Y. *J. Pharmacol. Methods* **1980**, *4*, 251.