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Design, synthesis, and biological evaluation of linear 1-(4-, 3- or 2-methylsulfonylphenyl)-2-phenylacetylenes: A novel class of cyclooxygenase-2 inhibitors

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Abstract—A group of regioisomeric 1-(methylsulfonylphenyl)-2-phenylacetylenes possessing a COX-2 SO_2Me pharmacophore at the *para*-, *meta*- or *ortho*-position of the C-1 phenyl ring, in conjunction with a C-2 phenyl or substituted-phenyl ring substituent (3-F, 3-OMe, 3-OH, 3-OAc, 4-Me), were designed for evaluation as selective cyclooxygenase-2 (COX-2) inhibitors. These target linear 1,2-diarylacetylenes were synthesized via a palladium-catalyzed Sonogashira cross-coupling reaction followed by oxidation of the respective 1-(methylthiophenyl)-2-phenylacetylene intermediate. In vitro COX-1/COX-2 isozyme inhibition structure–activity studies identified 1-(3-methylsulfonylphenyl)-2-(4-methylphenyl)acetylene (**12d**) as a potent COX-2 inhibitor (IC_{50} = 0.32 μM) with a high COX-2 selectivity index (SI > 320) comparable to the reference compound rofecoxib (COX-2 IC_{50} = 0.50 μM; COX-2 SI > 200). A molecular modeling study where (**12d**) was docked in the binding site of COX-2 showed that the $MeSO_2$ COX-2 pharmacophore was positioned in the vicinity of the secondary COX-2 binding site near Val^{523}. The 1-(4-methylsulfonylphenyl)-2-(3-acetoxyphenyl)acetylene (**11f**, COX-1 IC_{50} = 1.00 μM; COX-2 IC_{50} = 0.06 μM; COX-2 SI = 16.7) and 1-(3-methylsulfonylphenyl)-2-(3-acetoxyphenyl)acetylene (**12f**, COX-1 IC_{50} = 6.5 μM; COX-2 IC_{50} = 0.05 μM; COX-2 SI = 130) regioisomers exhibited comparable COX-2 inhibition, and moderately lower selective COX-2 selectivity, relative to the reference drug celecoxib (COX-1 IC_{50} = 33.1 μM; COX-2 IC_{50} = 0.07 μM; COX-2 SI = 472). The most potent anti-inflammatory agent 1-(3-methylsulfonylphenyl)-2-(4-methylphenyl)acetylene (**12d**) exhibited moderate oral anti-inflammatory activity (ED_{50} = 129 mg/kg) at 3 h postdrug administration relative to the reference drug celecoxib (ED_{50} = 10.8 mg/kg) in a carrageenan-induced rat paw edema assay. The structure–activity data acquired indicate that the acetylene moiety constitutes a suitable scaffold (template) to design novel acyclic 1,2-diarylacetylenes with selective COX-2, or dual COX-1/COX-2, inhibitory activities.

1. Introduction

The selective COX-2 inhibitors celecoxib (**1**),[1] rofecoxib (**2**),[2] valdecoxib (**3**),[3] and etoricoxib (**4**)[4,5] have been clinically validated as anti-inflammatory therapeutics for indications such as rheumatoid arthritis with less gastrointestinal and renal toxicity (see structures in Fig. 1).[6–9] Tricyclic compounds possessing 1,2-diaryl substitution on a central heterocyclic, or carbocyclic, ring system constitute a major class of selective COX-2 inhibitors. Structure–activity relationship (SAR) studies have shown that a SO_2Me or SO_2NH_2 substituent at the para-position of one of the aryl rings often provides optimum COX-2 selectivity and inhibitory potency.[10]

Despite the relatively safe pharmacological profile of selective COX-2 inhibitors, there is now increasing concern regarding their use in patients at risk for an adverse cardiovascular event such as myocardial infarction. For example, the clinical use of rofecoxib and valdecoxib were recently terminated due to adverse cardiovascular side effects associated with their use.[11] The adverse cardiovascular effects of rofecoxib and valdecoxib appear to be due to their high COX-2 selectivity. Hence, there is a need for the design of COX inhibitors based on new structural templates. Recently, we reported several investigations describing the design, synthesis, and anti-inflammatory properties for several classes of novel acyclic olefins.[12–17] The lead compound (**5**) in this group of compounds exhibited excellent in vitro inhibitory potency against COX-2 (IC_{50} = 0.014 μM) with no

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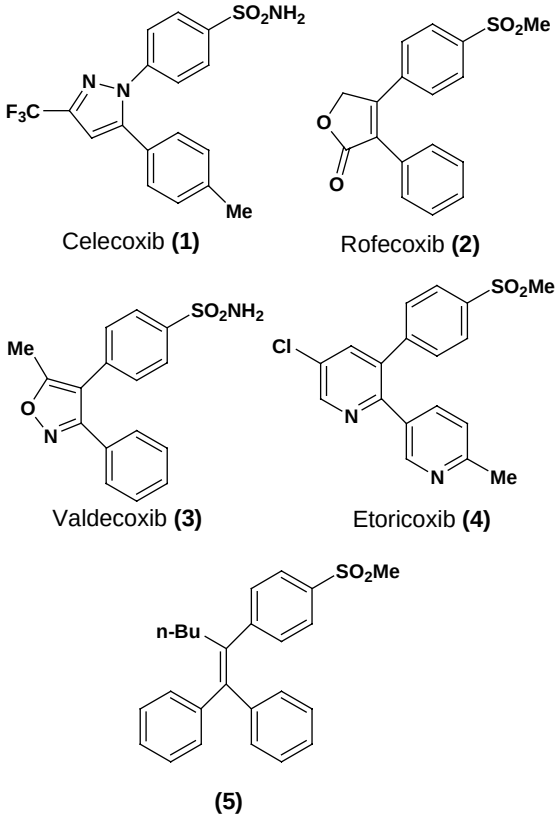
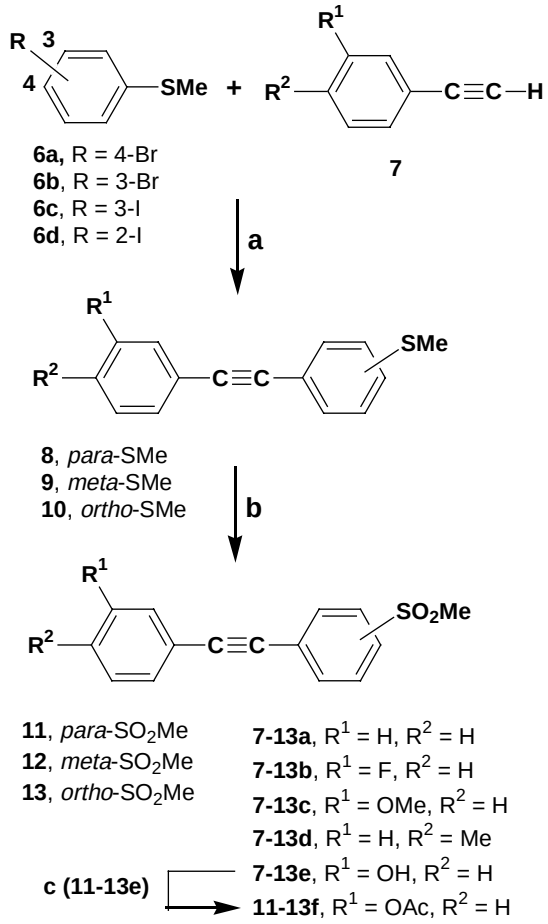


Figure 1. Some representative selective cyclooxygenase-2 (COX-2) inhibitors.

inhibition of COX-1 (IC_{50} > 100 μM). Many compounds within this group showed impressive activity in an in vivo model of inflammation. It was therefore of interest, as part of our ongoing program to design selective COX-2 inhibitors and acquire structure–activity correlations, to determine whether replacement of the double bond in this class of acyclic olefinic compounds by a linear acetylene would retain COX-2 selectivity and in vivo anti-inflammatory activity. Accordingly, we now describe the design, synthesis, in vitro COX-1 and COX-2 inhibitory activities, and in vivo anti-inflammatory activity for this class of 1-(4-,3- or 2-methylsulfonylphenyl)-2-phenylacetylene regioisomers (**11**–**13**).

2. Chemistry

The target 1-(methylsulfonylphenyl)-2-phenylacetylenes (**11a**–**f**, **12a**–**f**, and **13a**–**f**) having a variety (R^1 = H, F, OMe, OH, OAc; R^2 = H, Me) of substituents at the *meta*- and/or *para*-position of the C-2 phenyl ring were prepared using a palladium-catalyzed Sonogashira cross-coupling reaction[18] as a key reaction step according to the reaction sequence shown in Scheme 1. The cross-coupling reaction between a bromo- or iodothioanisole (**6**) and a substituted-phenylacetylene (**7**) under an argon atmosphere in triethylamine, using dichlorobis(triphenylphosphine)palladium(0)/cuprous iodide as catalysts, afforded the respective 1-(methylthiophenyl)-2-phenylacetylenes (**8**–**10**). The high reactivity of the 3-iodo (**6c**) and 2-iodothioanisole (**6d**) in the Sonogashira



Scheme 1. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, reflux or 50 °C, overnight; (b) Oxone®, THF, MeOH, H_2O, 25 °C, overnight; (c) CH_3COCl, Et_3N, THF, 25 °C, 2 h.

cross-coupling reaction provides an effective method for the preparation of a wide variety of functionally substituted 1-(methylthiophenyl)-2-phenylacetylenes in excellent yield. This is particularly relevant in the case of 1-(2-methylthiophenyl)-2-phenylacetylenes (**10**) which generally cannot be synthesized using the less reactive 2-bromothioanisole. Subsequent oxidation of the methylthio intermediates (**8–10**) using Oxone® (potassium peroxymonosulfate) furnished the target 1-(methylsulfonylphenyl)-2-phenylacetylenes (**11a**–**e**, **12a**–**e**, and **13a**–**e**). During the course of these studies, it was observed that the *ortho*-methylthio moiety present in **10a**–**e** was more difficult to oxidize (5 equiv. Oxone®, overnight) than the *para*- or *meta*-methylthio group present in the **8a**–**e** and **9a**–**e** regioisomers (2 equiv. Oxone[reg], 2 h). Thus, it was necessary to increase the amount of Oxone® (5 equiv.) and prolong the reaction time (overnight) in order to completely oxidize the *ortho*-methylthio compounds (**10a**–**e**) to the desired *ortho*-methylsulfonyl target products (**13a**–**e**) since oxidation of the *ortho*-methylthio compounds (**10a**–**e**) using 2 equiv of Oxone®s for 2 h yielded the methylsulfoxide product rather than the desired methylsulfones. Acetylation of the 1-(methylsulfonylphenyl)-2-(3-hydroxyphenyl)acetylenes (**11e**, **12e**, and **13e**) using acetyl chloride in the presence of Et_3N yielded the corresponding

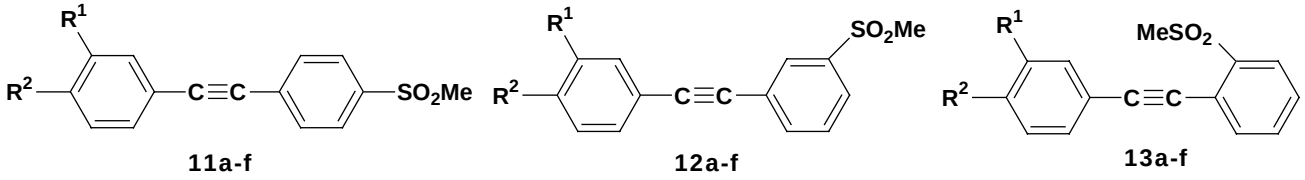
1-(methylsulfonylphenyl)-2-(3-acetoxyphenyl)acetylene regioisomers (**11f**, **12f**, and **13f**).

3. Results and discussion

A group of 1-(methylsulfonylphenyl)-2-phenylacetylene regioisomers (**11**–**13**) were designed such that the COX-2 SO_2Me pharmacophore was located at the *para*-, *meta*- or *ortho*-position of the C-1 phenyl ring on a linear acetylene template (scaffold). In addition, the substituent on the C-2 phenyl ring was simultaneously varied (H, 3-F, 3-OMe, 3-OH, 3-OAc, and 4-Me) to determine the combined effects of positional, steric, and electronic substituent properties upon COX-1 and COX-2 inhibitory potency and COX isozyme selectivity. SAR data (IC_{50} values) acquired by determination of the in vitro ability of the title compounds to inhibit the COX-1 and COX-2 isozymes showed that the position of the COX-2 SO_2Me pharmacophore on the C-1 phenyl ring and the nature of the C-2 phenyl substituent were either individual, or collective, determinants of COX-2 inhibitory potency and selectivity (see Table 1).

A comparison of the SAR data for the 1-(4-, 3-, and 2-methylsulfonylphenyl)-2-phenylacetylene regioisomers (**11a**–**13a**) showed that the COX isozyme selectivity shifts as one moves from the 4-$MeSO_2$ (**11a**, selective COX-2 inhibitor) → 3-$MeSO_2$ (**12a**, mixed COX-1/COX-2 inhibitor) → 2-$MeSO_2$ (**13a**, selective COX-1 inhibitor). A similar isozyme selectivity profile was observed for the C-2 3-fluorophenyl regioisomers (**11b**–**13b**) as the position of the $MeSO_2$ pharmacophore on the C-1 phenyl ring is transposed from 4-$MeSO_2$ (**11b**, selective COX-2 inhibitor) → 3-$MeSO_2$ (**12b**, selective COX-2 inhibitor) → 2-$MeSO_2$ (**13b**, non-selective COX-1/COX-2 inhibitor). In contrast, the relative activity/selectivity profile for the C-2 3-methoxyphenyl regioisomers (**11c**–**13c**) did not give rise to COX-1 inhibitory activity as one moved the $MeSO_2$ substituent on the C-1 phenyl ring [4-$MeSO_2$ (**11c**, inactive COX-1/COX-2 inhibitor) → 3-$MeSO_2$ (**12c**, selective COX-2 inhibitor) → 2-$MeSO_2$ **13c**, selective COX-2 inhibitor]. The effect of a C-2 4-methylphenyl substituent in regioisomers **11d**–**13d** as a function of the $MeSO_2$ substituent position on the C-1 phenyl ring was highly variable [4-$MeSO_2$ (**11d**, equipotent inhibitor of COX-1 and COX-2) → 3-$MeSO_2$ (**12d**, selective COX-2 inhibitor) → 2-$MeSO_2$ (**13d**), significantly more potent and selective inhibitor of COX-1]. Although regioisomers **11e**–**13e** having a C-2 3-hydroxyphenyl substituent and **11f**–**13f** having a C-2 3-acetoxyphenyl substituent inhibited both COX-1 and COX-2, all compounds were more potent and selective inhibitors of the COX-2 isozyme irrespective of the position of the $MeSO_2$ substituent on the C-1 phenyl ring.

Table 1. In vitro COX-1 and COX-2 inhibition data for 1-(methylsulfonylphenyl)-2-phenylacetylenes (**11a**–**f**, **12a**–**f**, and **13a**–**f**)



Compounds	R^1	R^2	IC_{50} (μM)[a]		COX-2 S.I.[b]
			COX-1	COX-2	
11a	H	H	⩾100	0.89	⩾113
11b	F	H	⩾100	6.0	⩾16
11c	OMe	H	⩾100	⩾100	N/A
11d	H	Me	0.32	0.32	1.0
11e	OH	H	11.3	0.21	54
11f	OAc	H	1.0	0.06	17
12a	H	H	1.0	3.2	0.32
12b	F	H	>100	1.9	>54
12c	OMe	H	>100	3.4	>30
12d	H	Me	>100	0.32	>320
12e	OH	H	0.82	0.32	2.6
12f	OAc	H	6.5	0.05	130
13a	H	H	31.6	>100	<0.31
13b	F	H	1.7	0.32	5.3
13c	OMe	H	>100	4.8	>21
13d	H	Me	0.10	31.6	0.003
13e	OH	H	31.6	3.5	8.9
13f	OAc	H	1.0	0.14	7.0
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}).

The effect of a 3-substituent on the C-2 phenyl ring, with respect to COX-2 selectivity, varied according to the position of the $MeSO_2$ substituent on the C-1 phenyl ring where the relative COX-2 selectivity indexes (SI) for the 4-$MeSO_2$-phenyl compounds (**11**) were H > OH > OAc > F >> OMe (inactive), for the 3-$MeSO_2$-phenyl compounds (**12**) were OAc > F > OMe > OH > H, and for the 2-$MeSO_2$-phenyl compounds (**13**) were OMe >OH ⩾ OAc ⩾ F >> H. These latter SAR data indicate that the $MeSO_2$ COX-2 pharmacophore on the C-1 phenyl ring, and the 3-subsitutent on the C-2 phenyl ring, are cooperative determinants of selective COX-2 inhibition.

A number of compounds such as 1-(4-methylsulfonylphenyl)-2-phenylacetylene (**11a**, IC_{50} = 0.89 μM; SI > 113) and 1-(3-methylsulfonylphenyl)-2-(4-methylphenyl)acetylene (**12d**, IC_{50} = 0.32 μM; SI > 320) were potent and selective COX-2 inhibitors relative to the reference compound rofecoxib (IC_{50} = 0.50 μM; SI > 200). In comparison, the 1-(4-methylsulfonylphenyl)-2-(3-acetoxyphenyl)acetylene (**11f**, COX-1 IC_{50} = 1.00 μM; COX-2 IC_{50} = 0.06 μM; COX-2 SI = 16.7), and 1-(3-methylsulfonylphenyl)-2-(3-acetoxyphenyl)acetylene (**12f**, COX-1 IC_{50} = 6.5 μM; COX-2 IC_{50} = 0.05 μM; COX-2 SI = 130) regioisomers, having a C-2 3-acetoxyphenyl substituent, exhibited equipotent 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) as showed in Table 1.

A molecular modeling experiment was carried out to determine the binding interactions of 1-(3-methylsulfonylphenyl)-2-(4-methylphenyl)acetylene (**12d**) in the COX-2 binding site (Fig. 2). Analysis of the most stable enzyme–ligand conformation shows that the 3-$MeSO_2$-phenyl moiety is oriented in the vicinity of COX-2 secondary pocket where it is surrounded by the amino acids Leu^{352}, Ser^{353}, Ala^{516}, Phe^{518}, Val^{523}, and His^{90}. One of the SO_2Me oxygen-atoms undergoes a weak hydrogen bonding interaction with the N*H* of Phe^{518} (distance = 3.66 Å). The SO_2*Me* methyl group is suitably positioned to undergo a van der Waal's interaction with the methyl side chain of Ala^{516} (distance = 4.00 Å). The linear acetylene scaffold, that is surrounded by Gly^{526}, Ala^{527}, and Val^{349}, serves to orient the *p*-tolyl ring in a region comprising of Tyr^{348}, Ser^{530}, and Leu^{531}. The interspatial distance between the center of the *p*-tolyl ring and the *O*H of Ser^{530} is about 4.76 Å. The CH_3 substituent of the 4-Me-C_6H_4-moiety is oriented in a small lipophilic region where it can undergo van der Waal's interactions with the side chains of amino acid residues such as Leu^{534}, Val^{344}, and Ile^{345} (distance <5 Å).

Pharmacological studies were carried out to access the in vivo anti-inflammatory and analgesic activities of 1-(3-methylsulfonylphenyl)-2-(4-methylphenyl)acetylene (**12d**), and two of the most potent COX-2 inhibitors (**11f** and **12f**), based on in vitro enzyme inhibition data (see data in Table 2). In the carrageenan-induced rat paw edema assay, compound **12d** was the most potent anti-inflammatory agent (ED_{50} = 129.3 mg/kg) within this group of compounds at 3 h postdrug administration (oral dose) relative to the reference drug celecoxib (ED_{50} = 10.8 mg/kg). One plausible explanation for the observation that the 2-(3-acetoxyphenyl)-compound

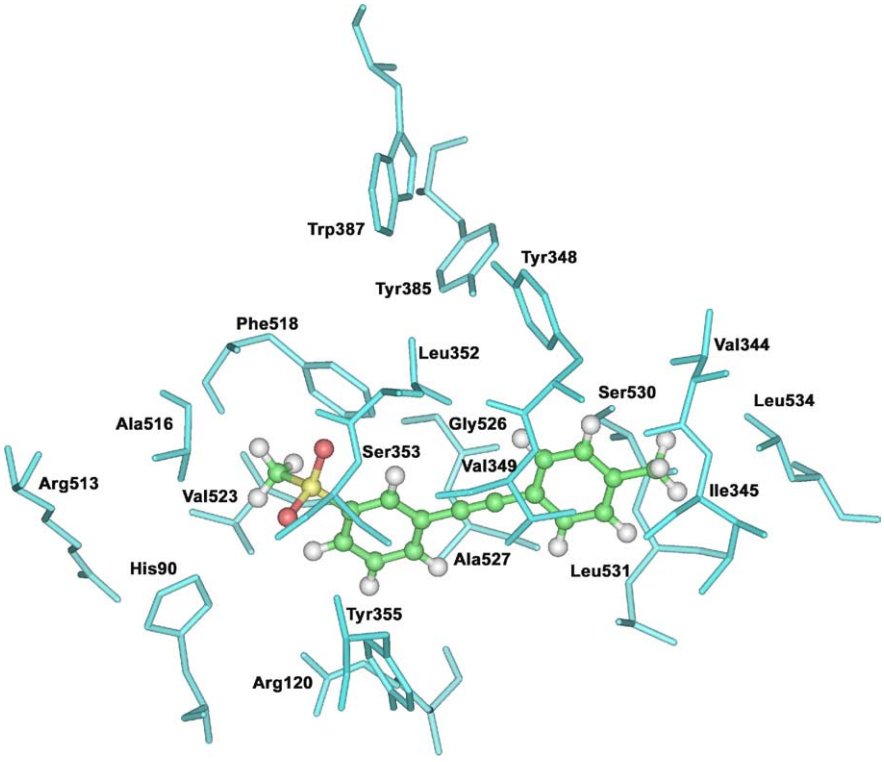
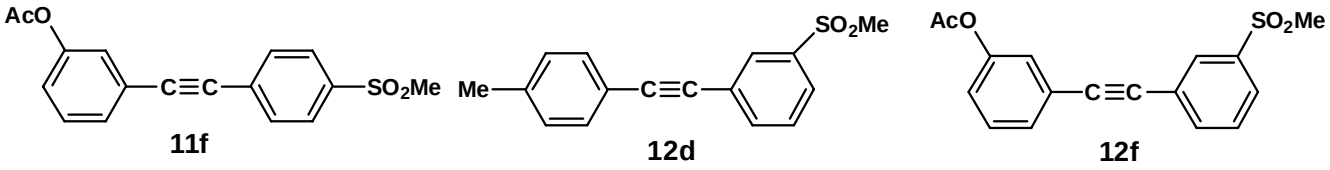


Figure 2. 1-(3-Methylsulfonylphenyl)-2-(4-methylphenyl)acetylene (**12 d**) (ball and stick) docked in the active site of murine COX-2. Hydrogen atoms of the amino acid residues have been removed to improve clarity.

Table 2. In vivo anti-inflammatory and analgesic activities for 1-(methylsulfonylphenyl)-2-phenylacetylenes (**11f**, **12d**, and **12f**)



Compounds	Anti-inflammatory activity[a]		Analgesic activity[b]	
	% inhibition at 3 h (75 mg/kg po dose)	ED_{50} (mg/kg)	% inhibition at 30 min	% inhibition at 60 min
11f	Inactive	—	—	—
12d	38.9 ± 3.5	129.3	43.7 ± 19.8	65.8 ± 7.1
12f	28.5 ± 5.0	—	—	—
Celecoxib	79.9 ± 1.9[c]	10.8	69.3 ± 12.1[c]	79.5 ± 2.0[c]

[a] Inhibitory activity in a carrageenan-induced rat paw edema assay. The results are expressed as the means ± SEM ($n = 4$) following a 75 mg/kg oral dose of the test compound.

[b] Inhibitory activity in the rat 4% NaCl-induced abdominal constriction assay. The results are expressed as the means ± SEM ($n = 4$) following a 75 mg/kg oral dose of the test compound.

[c] 50 mg/kg oral dose.

(**11f**) is an effective in vitro inhibitor of both COX-1 and COX-2, but that it is an inactive anti-inflammatory agent at a 75 mg/kg oral dose, is that **11f** undergoes in vivo O-deacetylation to an inactive phenolic metabolite. On the other hand, the corresponding regioisomer **12f** showed modest anti-inflammatory activity where a 28% inhibition of inflammation was observed following a 75 mg/kg oral dose. In a rat model 4% NaCl-induced abdominal constriction assay, a 75 mg/kg po dose of 1-(3-methylsulfonylphenyl)-2-(4-methylphenyl)acetylene (**12d**) exhibited good analgesic activity where writhing was reduced by 43 and 66% at 30 and 60 min postdrug administration relative to the reference drug celecoxib (69 and 79% inhibition at 30 and 60 min postdrug administration for a 50 mg/kg oral dose).

4. Conclusions

A new class of linear 1,2-diarylacetylenes was designed for evaluation as COX-2 inhibitors. In vitro enzyme inhibition structure–activity studies indicated that (i) the acetylene moiety present in the 1-(methylsulfonylphenyl)-2-phenylacetylene structure is a suitable scaffold (template) to design COX-2 inhibitors, (ii) SAR data for the 1-(4-, 3- and 2-methylsulfonylphenyl)-2-phenylacetylene regioisomers (**11a**–**13a**) showed that the COX isozyme selectivity shifts as one moves from the 4-$MeSO_2$ (selective COX-2 inhibitor) → 3-$MeSO_2$ (mixed COX-1/COX-2 inhibitor) → 2-$MeSO_2$ (selective COX-1 inhibitor), and (iii) 1-(3-methylsulfonylphenyl)-2-(4-methylphenyl)acetylene (**12d**) was a selective in vitro COX-2 inhibitor (COX-2 $IC_{50} = 0.32$ μM; SI > 320) that exhibited moderate in vivo anti-inflammatory ($ED_{50} = 129.3$ mg/kg po) and analgesic (60% inhibition at 60 min postdrug administration for a 75 mg/kg oral dose) activities.

5. Experimental section

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 DMSO-d_6 with TMS as the internal standard, where J (coupling constant) values are estimated in hertz (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 (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). 3-Iodothioanisole (**6c**) was synthesized in 54% yield starting from 3-(methylthio)aniline using the procedure of Ullmann.[19] 2-Iodothioanisole (**6d**) was prepared in 63% yield via a two-step halogen exchange reaction [(i) t-BuLi, -78 °C; (ii) I_2] employing 2-bromothioanisole.[20] All other reagents, purchased from the Aldrich Chemical Company (Milwaukee, WI), were used without further purification. Male Sprague–Dawley rats, used in the anti-inflammatory and 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.

6. General procedure for the synthesis of 1-(4-, 3-, and 2-methylthiophenyl)-2-phenylacetylenes (8–10)

Cuprous iodide (35 mg, 0.18 mmol) was added to a solution of dichloro-bis(triphenylphosphine)palladium (63 mg, 0.09 mmol), a bromothioanisole **6a** or **6b** (609 mg, 3 mmol) or an iodothioanisole **6c** or **6d** (750 mg, 3 mmol), and an acetylene **7a**–**e** (4.5 mmol) in Et_3N (8 mL). The reaction was allowed to proceed overnight with stirring at 90 °C (for bromothioanisole **6a** and **6b**) or 50 °C (for iodothioanisole **6c** and **6d**) under an argon atmosphere, cooled to 25 °C, and then Et_3N was removed under reduced pressure. The residue obtained was purified by silica gel column chromatography using hexane/dichloromethane as the eluent to furnish the respective title compound (**8**, **9**, or **10**). Some physi-

cal and spectroscopic data for **8a**–**e**, **9a**–**e**, and **10a**–**e** are listed below.

6.1. 1-(4-Methylthiophenyl)-2-phenylacetylene (8a)

The product was obtained as yellow crystals using a Sonogashira coupling reaction of **7a** with 4-bromothioanisole in 47% yield; mp 86–87 °C (Lit.[21] 83–84 °C); IR (film): 2218 (C≡C), 1593, 1492 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.49 (s, 3H, SCH_3), 7.21 (d, J = 8.2 Hz, 2H, 4-methylthiophenyl H-3, H-5), 7.36–7.41 (m, 3H, phenyl H-3, H-4, H-5), 7.45 (d, J = 8.2 Hz, 2H, 4-methylthiophenyl H-2, H-6), 7.52 (m, 2H, phenyl H-2, H-6).

6.2. 1-(4-Methylthiophenyl)-2-(3-fluorophenyl)acetylene (8b)

The product was obtained as a yellow solid using a Sonogashira coupling reaction of **7b** with 4-bromothioanisole in 55% yield; mp 66–68 °C; IR (film): 2200 (C≡C), 1575, 1502 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60 (s, 3H, SCH_3), 7.09–7.55 (m, 8H, 4-methylthiophenyl and 3-fluorophenyl hydrogens). Anal. calcd for $C_{15}H_{11}FS$: C, 74.35; H, 4.58. Found: C, 74.03; H, 4.72.

6.3. 1-(4-Methylthiophenyl)-2-(3-methoxyphenyl)acetylene (8c)

The product was obtained as a yellow oil by a Sonogashira coupling reaction of **7c** with 4-bromothioanisole in 54% yield; IR (film): 2206 (C≡C), 1595, 1499 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51 (s, 3H, SCH_3), 3.83 (s, 3H, OCH_3), 6.90 (dd, J = 8.2, 2.7 Hz, 1H, 3-methoxyphenyl H-4), 7.12 (br s, 1H, 3-methoxyphenyl H-2), 7.13 (br d, J = 8.2 Hz, 1H, 3-methoxyphenyl H-6), 7.21 (d, J = 8.2 Hz, 2H, 4-methylthiophenyl H-3, H-5), 7.26 (t, J = 8.2 Hz, 1H, 3-methoxyphenyl H-5), 7.45 (d, J = 8.2 Hz, 2H, 4-methylthiophenyl H-2, H-6).

6.4. 1-(4-Methylthiophenyl)-2-(4-methylphenyl)acetylene (8d)

The product was obtained as a pale yellow solid employing the Sonogashira coupling reaction of **7d** with 4-bromothioanisole in 26% yield; mp 100–101 °C; IR (film): 2220 (C≡C), 1609, 1519 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (s, 3H, Ar-CH_3), 2.50 (s, 3H, SCH_3), 7.16 (d, J = 7.6 Hz, 2H, 4-methylphenyl H-3, H-5), 7.20 (d, J = 8.2 Hz, 2H, 4-methylthiophenyl H-3, H-5), 7.42 (d, J = 7.6 Hz, 2H, 4-methylphenyl H-2, H-6), 7.43 (d, J = 8.2 Hz, 2H, 4-methylthiophenyl H-2, H-6). Anal. calcd for $C_{16}H_{14}S$: C, 80.63; H, 5.92. Found: C, 80.57; H, 5.87.

6.5. 1-(4-Methylthiophenyl)-2-(3-hydroxyphenyl)acetylene (8e)

The product was obtained as a yellow foam using the Sonogashira coupling reaction of **7e** with 4-bromothioanisole in 42% yield; mp 90–92 °C; IR (film): 3421 (OH), 2209 (C≡C), 1603, 1437 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51 (s, 3H, SCH_3), 4.83 (br s, 1H, OH, exchanges with D_2O), 6.83 (dd, J = 7.9, 2.4 Hz, 1H, 3-hydroxyphenyl H-4), 6.99 (t, J = 2.4 Hz, 1H, 3-hydroxyphenyl H-2), 7.11 (d, J = 7.6 Hz, 1H, 3-hydroxyphenyl H-6), 7.20–7.26 (m, 3 H, 4-methylthiophenyl H-3, H-5, 3-hydroxyphenyl H-5), 7.44 (d, J = 8.2 Hz, 2H, 4-methylthiophenyl H-2, H-6). Anal. calcd for $C_{15}H_{12}OS$: C, 74.97; H, 5.03. Found: C, 74.63; H, 5.03.

6.6. 1-(3-Methylthiophenyl)-2-phenylacetylene (9a)

The product was obtained as a pale yellow liquid by the Sonogashira coupling reaction of **7a** with 3-bromothioanisole in 65% yield; IR (film): 2220 (C≡C), 1602, 1581, 1499 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H, SCH_3), 7.21–7.56 (m, 9H, 3-methylthiophenyl and phenyl hydrogens). Anal. calcd for $C_{15}H_{12}S$: C, 80.31; H, 5.39. Found: C, 80.39; H, 5.38.

6.7. 1-(3-Methylthiophenyl)-2-(3-fluorophenyl)acetylene (9b)

The product was obtained as a pale yellow oil using the Sonogashira coupling reaction of **7b** with 3-iodothioanisole in 84% yield; IR (film): 2209 (C≡C), 1612, 1584, 1483 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H, SCH_3), 7.02–7.41 (m, 8H, 3-methylthiophenyl and 3-fluorophenyl hydrogens). Anal. calcd for $C_{15}H_{11}FS$: C, 74.35; H, 4.58. Found: C, 74.16; H, 4.40.

6.8. 1-(3-Methylthiophenyl)-2-(3-methoxyphenyl)acetylene (9c)

The product was obtained as a pale yellow solid by the Sonogashira coupling reaction of **7c** with 3-bromothioanisole in 47% yield; IR (film): 2213 (C≡C), 1595, 1567, 1492 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51 (s, 3H, SCH_3), 3.82 (s, 3H, OCH_3), 6.89–7.41 (m, 8H, 3-methylthiophenyl and 3-methoxyphenyl hydrogens).

6.9. 1-(3-Methylthiophenyl)-2-(4-methylphenyl)acetylene (9d)

The product was obtained as a pale yellow oil using the Sonogashira coupling reaction of **7d** with 3-bromothioanisole in 48% yield, or by the Sonogashira coupling reaction of **7d** with 3-iodothioanisole in 85% yield; IR (film): 2227 (C≡C), 1588, 1567, 1506 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (s, 3H, Ar-CH_3), 2.51 (s, 3H, SCH_3), 7.15–7.45 (m, 8H, 3-methylthiophenyl and 4-methylphenyl hydrogens). Anal. calcd for $C_{16}H_{14}S$: C, 80.63; H, 5.92. Found: C, 81.02; H, 6.27.

6.10. 1-(3-Methylthiophenyl)-2-(3-hydroxyphenyl)acetylene (9e)

The product was obtained as a yellow oil employing the Sonogashira coupling reaction of **7e** with 3-iodothioanisole in 90% yield; IR (film): 3377 (OH), 2215 (C≡C), 1592, 1502 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51 (s, 3H, SCH_3), 5.16 (br s, 1H, OH, exchanges with D_2O), 6.84 (dd, J = 7.9, 2.5 Hz, 1H, 3-hydroxyphenyl H-4), 7.01 (s, 1H, 3-hydroxyphenyl H-2), 7.12 (d, J = 7.6 Hz, 1H, 3-hydroxyphenyl H-6), 7.20–7.31 (m,

4H, 3-methylthiophenyl H-4, H-5, H-6, 3-hydroxyphenyl H-5), 7.40 (s, 1H, 3-methylthiophenyl H-2). Anal. calcd for $C_{15}H_{12}OS$: C, 74.97; H, 5.03. Found: C, 74.67; H, 4.93.

6.11. 1-(2-Methylthiophenyl)-2-phenylacetylene (10a)

The product was obtained as a yellow liquid either by the Sonogashira coupling reaction of **7a** with 2-bromothioanisole in 25% yield, or by the Sonogashira coupling reaction of **7a** with 2-iodothioanisole in 89% yield; IR (film): 2206 (C≡C), 1602, 1499 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.53 (s, 3H, SCH_3), 7.10–7.63 (m, 9H, 2-methylthiophenyl and phenyl hydrogens).

6.12. 1-(2-Methylthiophenyl)-2-(3-fluorophenyl)acetylene (10b)

The product was obtained as a yellow oil using the Sonogashira coupling reaction of **7b** with 2-iodothioanisole in 86% yield; IR (film): 2200 (C≡C), 1621, 1584, 1492 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.53 (s, 3H, SCH_3), 7.02–7.50 (m, 8H, 2-methylthiophenyl and 3-fluorophenyl hydrogens). Anal. calcd for $C_{15}H_{11}FS$: C, 74.35; H, 4.58. Found: C, 74.58; H, 4.61.

6.13. 1-(2-Methylthiophenyl)-2-(3-methoxyphenyl)acetylene (10c)

The product was obtained as a yellow oil from the Sonogashira coupling reaction of **7c** with 2-iodothioanisole in 70% yield; IR (film): 2200 (C≡C), 1603, 1575, 1492 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H, SCH_3), 3.84 (s, 3H, OCH_3), 6.89–7.51 (m, 8H, 2-methylthiophenyl and 3-methoxyphenyl hydrogens).

6.14. 1-(2-Methylthiophenyl)-2-(4-methylphenyl)acetylene (10d)

The product was obtained as a pale yellow oil using the Sonogashira coupling reaction of **7d** with 2-iodothioanisole in 72% yield; IR (film): 2209 (C≡C), 1593, 1520, 1465 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (s, 3H, Ar-CH_3), 2.52 (s, 3H, SCH_3), 7.12 (dt, J = 7.6, 1.2 Hz, 1H, 2-methylthiophenyl H-4), 7.18 (d, J = 8.2 Hz, 1H, 2-methylthiophenyl H-6), 7.17 (d, J = 8.2 Hz, 2H, 4-methylphenyl H-3, H-5), 7.30 (dt, J = 7.6, 1.5 Hz, 1H, 2-methylthiophenyl H-5), 7.48 (d, J = 7.9 Hz, 3H, 2-methylthiophenyl H-3, 4-methylphenyl H-2, H-6). Anal. calcd for $C_{16}H_{14}S \cdot 1/8H_2O$: C, 79.87; H, 5.97. Found: C, 79.79; H, 6.01.

6.15. 1-(2-Methylthiophenyl)-2-(3-hydroxyphenyl)acetylene (10e)

The product was obtained as a pale yellow oil using the Sonogashira coupling reaction of **7e** with 2-iodothioanisole in 92% yield; IR (film): 3375 (OH), 2200 (C≡C), 1658, 1575, 1437 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H, SCH_3), 6.82–7.49 (m, 8H, 2-methylthiophenyl and 3-hydroxyphenyl hydrogens). Anal. calcd for $C_{15}H_{12}OS$: C, 74.97; H, 5.03. Found: C, 74.64; H, 4.76.

6.16. General procedure for the synthesis of 1-(4-methylsulfonylphenyl)-2-phenylacetylenes (11a–e) and 1-(3-methylsulfonylphenyl)-2-phenylacetylenes (12a–e)

An aqueous solution of Oxone® (1.28 g, 2 mmol, 9 mL) was added to a stirred solution of a 1-(4-, or 3-methylthiophenyl)-2-phenylacetylene compound (**8** or **9**, 1 mmol) in methanol (15 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 (200 mL), extraction with EtOAc (3 × 80 mL), drying the combined EtOAc extracts (Na_2SO_4), and removal of the solvent in vacuo afforded the crude product. Purification of the product by recrystallization from hexanes/acetone, or silica gel column chromatography using hexanes/acetone (3:1) as eluent, gave the respective title compound (**11a**–**e** and **12a**–**e**) in 80–95% yield. The physical and spectral data for **11a**–**e** and **12a**–**e** are summarized below.

6.17. 1-(4-Methylsulfonylphenyl)-2-phenylacetylene (11a)

Yield, 83%; pale yellow crystals; mp 158–160 °C; IR (film): 2227 (C≡C), 1650, 1561, 1451 (Ar), 1320 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.08 (s, 3H, SO_2 CH_3), 7.29–7.41 (m, 3H, phenyl H-3, H-4, H-5), 7.53–7.59 (m, 2H, phenyl H-2, H-6), 7.71 (d, J = 8.5 Hz, 2H, 4-methylsulfonylphenyl H-2, H-6), 7.93 (d, J = 8.5 Hz, 2H, 4-methylsulfonylphenyl H-3, H-5).

6.18. 1-(4-Methylsulfonylphenyl)-2-(3-fluorophenyl)acetylene (11b)

Yield, 82%; pale yellow solid; mp 130–132 °C; IR (film): 2296 (C≡C), 1609, 1588, 1499 (Ar), 1320 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.08 (s, 3H, SO_2 CH_3), 7.07–7.14 (m, 1H, 3-fluorophenyl H-4), 7.24 (dd, J = 8.0, 1.8 Hz, 1H, 3-fluorophenyl H-2), 7.33–7.40 (m, 2H, 3-fluorophenyl H-5, H-6), 7.71 (d, J = 8.2 Hz, 2H, 4-methylsulfonylphenyl H-2, H-6), 7.94 (d, J = 8.2 Hz, 2H, 4-methylsulfonylphenyl H-3, H-5). Anal. calcd for $C_{15}H_{11}FO_2S$: C, 65.69; H, 4.02. Found: C, 65.39; H, 4.14.

6.19. 1-(4-Methylsulfonylphenyl)-2-(3-methoxyphenyl)acetylene (11c)

Yield, 82%; pale yellow needle; mp 137–139 °C; IR (film): 2207 (C≡C), 1570, 1487 (Ar), 1315 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.08 (s, 3H, SO_2 CH_3), 3.84 (s, 3H, OCH_3), 6.96 (dd, J = 8.0, 2.1 Hz, 1H, 3-methoxyphenyl H-4), 7.09 (d, J = 2.1 Hz, 1H, 3-methoxyphenyl H-2), 7.16 (d, J = 8.0 Hz, 1H, 3-methoxyphenyl H-6), 7.30 (t, J = 8.0 Hz, 1H, 3-methoxyphenyl H-5), 7.71 (d, J = 8.2 Hz, 2H, 4-methylsulfonylphenyl H-2, H-6), 7.93 (d, J = 8.2 Hz, 2H, 4-methylsulfonylphenyl H-3, H-5). Anal. calcd for $C_{16}H_{14}O_3S$: C, 67.11; H, 4.93. Found: C, 66.97; H, 4.80.

6.20. 1-(4-Methylsulfonylphenyl)-2-(4-methylphenyl)acetylene (11d)

Yield, 90%; pale yellow needles, mp 193–194 °C; IR (film): 2234 (C≡C), 1567, 1513 (Ar), 1313 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (s, 3H, Ar-CH_3), 3.08 (s, 3H,

SO_2 CH_3), 7.20 (d, J = 7.6 Hz, 2H, 4-methylphenyl H-3, H-5), 7.46 (d, J = 7.6 Hz, 2H, 4-methylphenyl H-2, H-6), 7.70 (d, J = 8.5 Hz, 2H, 4-methylsulfonylphenyl H-2, H-6), 7.92 (d, J = 8.5 Hz, 2H, 4-methylsulfonylphenyl H-3, H-5). Anal. calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22. Found: C, 70.72; H, 5.20.

6.21. 1-(4-Methylsulfonylphenyl)-2-(3-hydroxyphenyl)acetylene (11e)

Yield, 90%; pale brown crystals; mp 196–198 °C; IR (film): 3429 (OH), 2131 (C≡C), 1595, 1567, 1451 (Ar), 1306 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO) δ 3.06 (s, 3H, SO_2CH_3), 6.87 (dd, J = 8.2, 1.2 Hz, 1H, 3-hydroxyphenyl H-4), 7.02–7.05 (m, 2H, 3-hydroxyphenyl H-2, H-6), 7.19 (t, J = 7.9 Hz, 1H, 3-hydroxyphenyl H-5), 7.67 (d, J = 8.2 Hz, 2H, 4-methylsulfonylphenyl H-2, H-6), 7.90 (d, J = 8.2 Hz, 2H, 4-methylsulfonylphenyl H-3, H-5), 8.40 (br s, 1H, OH, exchanges with D_2O). Anal. calcd for $C_{15}H_{12}O_3S$: C, 66.16; H, 4.44. Found: C, 65.79; H, 4.60.

6.22. 1-(4-Methylsulfonylphenyl)-2-(3-acetoxyphenyl)acetylene (11f)

Acetyl chloride (0.1 mL, 1.5 mmol) and Et_3N (0.1 mL, 0.75 mmol) were added to a solution of 1-(4-methylsulfonylphenyl)-2-(3-hydroxyphenyl)acetylene (**11e**, 204 mg, 0.75 mmol) in THF (6 mL), and the reaction was allowed to proceed at 25 °C with stirring for 2 h. Then EtOAc (200 mL) was added and this solution was washed with H_2O (2 × 60 mL). The organic fraction was dried ($NaSO_4$), and the solvent was removed in vacuo to afford **11f** (190 mg, 80% yield) as pale yellow crystals; mp 122–123 °C; IR (film): 2220 (C≡C), 1767 (C=O), 1602, 1574, 1478 (Ar), 1300 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3H, COCH_3), 3.08 (s, 3H, SO_2 CH_3), 7.11–7.15 (m, 1H, 3-acetoxyphenyl H-4), 7.29 (br s, 1H, 3-acetoxyphenyl H-2), 7.31–7.44 (m, 2H, 3-acetoxyphenyl H-5, H-6), 7.70 (d, J = 8.5 Hz, 2H, 4-methylsulfonylphenyl H-2, H-6), 7.90 (d, J = 8.5 Hz, 2H, 4-methylsulfonylphenyl H-3, H-5). Anal. calcd for $C_{17}H_{14}O_4S$: C, 64.95; H, 4.49. Found: C, 64.61; H, 4.67.

6.23. 1-(3-Methylsulfonylphenyl)-2-phenylacetylene (12a)

Yield, 89%; pale yellow solid; mp 100–102 °C; IR (film): 2227 (C≡C), 1603, 1492 (Ar), 1327 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.09 (s, 3H, SO_2CH_3), 7.34–7.41 (m, 3H, phenyl H-3, H-4, H-5), 7.52–7.60 (m, 3H, phenyl H-2, H-6, 3-methylsulfonylphenyl H-5), 7.79 (d, J = 7.6 Hz, 1H, 3-methylsulfonylphenyl H-6), 7.90 (br d, J = 7.9 Hz, 1H, 3-methylsulfonylphenyl H-4), 8.12 (t, J = 1.2 Hz, 1H, 3-methylsulfonylphenyl H-2). Anal. calcd for $C_{15}H_{12}O_2S$: C, 70.29; H, 4.72. Found: C, 70.50; H, 4.97.

6.24. 1-(3-Methylsulfonylphenyl)-2-(3-fluorophenyl)acetylene (12b)

Yield, 95%; pale brown oil; IR (film): 2218 (C≡C), 1603, 1584, 1483 (Ar), 1318 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.09 (s, 3H, SO_2CH_3), 7.06–7.13 (m, 1H, 3-fluorophenyl H-4), 7.25 (d, J = 8.5 Hz, 1H, 3-fluorophenyl H-2), 7.31–7.39 (m, 2H, 3-fluorophenyl H-5, H-6), 7.59 (t, J = 7.9 Hz, 1H, 3-methylsulfonylphenyl H-5), 7.79 (d, J = 7.9 Hz, 1H, 3-methylsulfonylphenyl H-6), 7.92 (d, J = 7.9 Hz, 1H, 3-methylsulfonylphenyl H-4), 8.12 (s, 1H, 3-methylsulfonylphenyl H-2). Anal. calcd for $C_{15}H_{11}FO_2S$: C, 65.68; H, 4.04. Found: C, 65.48; H, 4.02.

6.25. 1-(3-Methylsulfonylphenyl)-2-(3-methoxyphenyl)acetylene (12c)

Yield, 80%; yellow oil; IR (film): 2227 (C≡C), 1609, 1574, 1492 (Ar), 1320 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.08 (s, 3H, SO_2CH_3), 3.84 (s, 3H, OCH_3), 6.94 (dd, J = 8.0, 2.7 Hz, 1H, 3-methoxyphenyl H-4), 7.07 (br s, 1H, 3-methoxyphenyl H-2), 7.14 (dt, J = 7.6, 1.2 Hz, 1H, 3-methoxyphenyl H-6), 7.29 (t, J = 7.6 Hz, 1H, 3-methoxyphenyl H-5), 7.57 (t, J = 7.9 Hz, 1H, 3-methylsulfonylphenyl H-5), 7.79 (dt, J = 7.9, 1.2 Hz, 1H, 3-methylsulfonylphenyl H-6), 7.90 (dt, J = 7.9, 1.2 Hz, 1H, 3-methylsulfonylphenyl H-4), 8.11 (t, J = 1.2 Hz, 1H, 3-methylsulfonylphenyl H-2). Anal. calcd for $C_{16}H_{14}O_3S1/8H_2O$: C, 66.59; H, 4.98. Found: C, 66.46; H, 4.84.

6.26. 1-(3-Methylsulfonylphenyl)-2-(4-methylphenyl)acetylene (12d)

Yield, 88%; pale solid; mp 94–96 °C; IR (film): 2234 (C≡C), 1602, 1526 (Ar), 1313 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.39 (s, 3H, Ar-CH_3), 3.09 (s, 3H, SO_2CH_3), 7.20 (d, J = 7.9 Hz, 2H, 4-methylphenyl H-3, H-5), 7.45 (d, J = 7.9 Hz, 2H, 4-methylphenyl H-2, H-6), 7.56 (t, J = 7.6 Hz, 1H, 3-methylsulfonylphenyl H-5), 7.78 (d, J = 7.6 Hz, 1H, 3-methylsulfonylphenyl H-6), 7.89 (d, J = 7.6 Hz, 1H, 3-methylsulfonylphenyl H-4), 8.10 (s, 1H, 3-methylsulfonylphenyl H-2). Anal. calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22. Found: C, 70.75; H, 5.14.

6.27. 1-(3-Methylsulfonylphenyl)-2-(3-hydroxyphenyl)acetylene (12e)

Yield, 90%; white crystals; mp 99–100 °C; IR (film): 3422 (OH), 2220 (C≡C), 1581, 1492 (Ar), 1306 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.09 (s, 3H, SO_2CH_3), 5.02 (br s, 1H, OH, exchanges with D_2O), 6.88 (dd, J = 7.9, 2.4 Hz, 1H, 3-hydroxyphenyl H-4), 7.02 (br s, 1H, 3-hydroxyphenyl H-2), 7.13 (d, J = 7.9 Hz, 1H, 3-hydroxyphenyl H-6), 7.25 (t, J = 7.9 Hz, 1H, 3-hydroxyphenyl H-5), 7.57 (t, J = 7.9 Hz, 1H, 3-methylsulfonylphenyl H-5), 7.78 (d, J = 7.9 Hz, 1H, 3-methylsulfonylphenyl H-6), 7.90 (d, J = 7.9 Hz, 1H, 3-methylsulfonylphenyl H-4), 8.11 (br s, 1H, 3-methylsulfonylphenyl H-2). Anal. calcd for $C_{15}H_{12}O_3S$: C, 66.16; H, 4.44. Found: C, 65.83; H, 4.13.

6.28. 1-(3-Methylsulfonylphenyl)-2-(3-acetoxyphenyl)acetylene (12f)

Acetyl chloride (0.1 mL, 1.5 mmol) and Et_3N (0.1 mL, 0.75 mmol) were added to a solution of 1-(3-methylsulfonylphenyl)-2-(3-hydroxyphenyl)acetylene (**12e**,

185 mg, 0.68 mmol) in THF (6 mL), and the reaction was allowed to proceed at 25 °C with stirring for 2 h. EtOAc (200 mL) was added and this solution was washed with H_2O (2 × 60 mL). The organic fraction was dried ($NaSO_4$), and the solvent was removed in vacuo to afford **12f** (190 mg, 89%) as a white solid; mp 78–79 °C; IR (film): 2218 (C≡C), 1768 (C=O), 1658, 1566 (Ar), 1318 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3H, CO CH_3), 3.09 (s, 3H, SO_2CH_3), 7.11–7.14 (m, 1H, 3-acetoxyphenyl H-4), 7.29 (br s, 1H, 3-acetoxyphenyl H-2), 7.36-7.43 (m, 2H, 3-acetoxyphenyl H-5, H-6), 7.58 (t, J = 7.9 Hz, 1H, 3-methylsulfonylphenyl H-5), 7.78 (d, J = 7.9 Hz, 1H, 3-methylsulfonylphenyl H-6), 7.91 (d, J = 7.9 Hz, 1H, 3-methylsulfonylphenyl H-4), 8.10 (br s, 1H, 3-methylsulfonylphenyl H-2). Anal. calcd for $C_{17}H_{14}O_4S$: C, 64.95; H, 4.49. Found: C, 64.66; H, 4.35.

6.29. General procedure for the synthesis of 1-(2-methylsulfonylphenyl)-2-phenylacetylenes (13a–e)

An aqueous solution of Oxone® (3.07 g, 5 mmol, 9 mL) was added to a stirred solution of the 1-(2-methylthiophenyl)-2-phenylacetylene compound (**10**, 1 mmol) in methanol (15 mL) and THF (15 mL), and the reaction was allowed to proceed with stirring at 25 °C overnight. Addition of H_2O (200 mL), extraction with EtOAc (3 × 80 mL), drying the combined EtOAc extracts (Na_2SO_4), and removal of the solvent in vacuo afforded the crude product. Purification of the product by silica gel column chromatography using hexanes/acetone (3:1, v/v) as eluent gave the respective title compound (**13a–e**) in 79–86 % yield. Some of the physical and spectral data for **13a–e** are listed below.

6.30. 1-(2-Methylsulfonylphenyl)-2-phenylacetylene (13a)

Yield, 79%; pale yellow solid; mp 99–100 °C; IR (film): 2218 (C≡C), 1566, 1502 (Ar), 1309 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.33 (s, 3H, SO_2 CH_3), 7.35–7.41 (m, 3H, phenyl H-3, H-4, H-5), 7.53 (dt, J = 7.9, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-4), 7.57–7.66 (m, 3H, phenyl H-2, H-6, 2-methylsulfonylphenyl H-5), 7.74 (dd, J = 7.6, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-6), 8.15 (dd, J = 7.9, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-3). Anal. calcd for $C_{15}H_{12}O_2S$: C, 70.29; H, 4.72. Found: C, 70.09; H, 4.79.

6.31. 1-(2-Methylsulfonylphenyl)-2-(3-fluorophenyl)acetylene (13b)

Yield, 83%; pale yellow oil; IR (film): 2215 (C≡C), 1607, 1585, 1495 (Ar), 1307 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.31 (s, 3H, SO_2CH_3), 7.08–7.16 (m, 1H, 3-fluorophenyl H-4), 7.29–7.42 (m, 3H, 3-fluorophenyl H-2, H-5, H-6), 7.56 (dt, J = 7.6, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-4), 7.64 (dt, J = 7.6, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-5), 7.74 (d, J = 7.6 Hz, 1H, 2-methylsulfonylphenyl H-6), 8.16 (dd, J = 7.6, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-3). Anal. calcd for $C_{15}H_{11}FO_2S$: C, 65.68; H, 4.04. Found: C, 65.53; H, 3.84.

6.32. 1-(2-Methylsulfonylphenyl)-2-(3-methoxyphenyl)acetylene (13c)

Yield, 82%; semisolid; IR (film): 2215 (C≡C), 1607, 1570, 1487 (Ar), 1307 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.33 (s, 3H, SO_2CH_3), 3.85 (s, 3H, OCH_3), 6.96 (dd, J = 8.2, 1.8 Hz, 1H, 3-methoxyphenyl H-4), 7.14 (br s, 1H, 3-methoxyphenyl H-2), 7.21 (d, J = 7.6 Hz, 1H, 3-methoxyphenyl H-6), 7.31 (t, J = 7.6 Hz, 1H, 3-methoxyphenyl H-5), 7.53 (dt, J = 7.6, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-4), 7.63 (dt, J = 7.6, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-5), 7.74 (dd, J = 7.6, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-6), 8.13 (dd, J = 7.9, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-3). Anal. calcd for $C_{16}H_{14}O_3S$: C, 67.11; H, 4.93. Found: C, 66.96; H, 4.88.

6.33. 1-(2-Methylsulfonylphenyl)-2-(4-methylphenyl)acetylene (13d)

Yield, 83%; pale yellow solid; mp 94–95 °C; IR (film): 2222 (C≡C), 1585, 1510, 1480 (Ar), 1322 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.39 (s, 3H, Ar-CH_3), 3.32 (s, 3H, SO_2CH_3), 7.20 (d, J = 7.6 Hz, 2H, 4-methylphenyl H-3, H-5), 7.48–7.53 (m, 3H, 4-methylphenyl H-2, H-6, 2-methylsulfonylphenyl H-4), 7.61 (dt, J = 7.6, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-5), 7.72 (dd, J = 7.6, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-6), 8.14 (dd, J = 7.9, 0.9 Hz, 1H, 2-methylsulfonylphenyl H-3). Anal. calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22. Found: C, 71.03; H, 5.14.

6.34. 1-(2-Methylsulfonylphenyl)-2-(3-hydroxyphenyl)acetylene (13e)

Yield, 86%; colorless syrup; IR (film): 3407 (OH), 2215 (C≡C), 1585, 1487 (Ar), 1315 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.36 (s, 3H, SO_2CH_3), 5.56 (br s, 1H, OH, exchanges with D_2O), 6.88–6.92 (m, 1H, 3-hydroxyphenyl H-4), 7.12 (d,J = 2.4 Hz, 1H, 3-hydroxyphenyl H-2), 7.16 (dd, 1H, J = 7.6, 1.2 Hz, 3-hydroxyphenyl H-6), 7.24 (t, J = 7.6 Hz, 1H, 3-hydroxyphenyl H-5), 7.53 (dt, J = 7.6, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-4), 7.63 (dt, J = 7.6, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-5), 7.73 (dd, J = 7.6, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-6), 8.15 (dd, J = 7.9, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-3). Anal. calcd for $C_{15}H_{12}O_3S$: C, 66.16; H, 4.44. Found: C, 65.99; H, 4.33.

6.35. 1-(2-Methylsulfonylphenyl)-2-(3-acetoxyphenyl)acetylene (13f)

Acetyl chloride (0.1 mL, 1.5 mmol) and Et_3N (0.1 mL, 0.75 mmol) were added to a solution of **13e** (204 mg, 0.70 mmol) in THF (6 mL), and the reaction was allowed to proceed at 25 °C with stirring for 2 h. EtOAc (200 mL) was added and this solution was washed with H_2O (2 × 60 mL). The organic fraction was dried ($NaSO_4$), and the solvent was removed in vacuo to afford **13f** (200 mg, 85%) as a pale yellow solid; mp 129–130 °C; IR (film): 2215 (C≡C), 1757 (C=O), 1600, 1585, 1487 (Ar), 1315 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3H, $COCH_3$), 3.31 (s, 3H, SO_2CH_3), 7.13–

7.17 (m, 1H, 3-acetoxyphenyl H-4), 7.35 (t, $J = 1.8$ Hz, 1H, 3-acetoxyphenyl H-2), 7.41 (t, $J = 7.9$ Hz, 1H, 3-acetoxyphenyl H-5), 7.49 (dt, $J = 7.9$, 1.2 Hz, 1H, 3-acetoxyphenyl H-6), 7.54 (dt, $J = 7.6$, 1.5 Hz, 1H, 2-methylsulfonylphenyl H-4), 7.63 (dt, $J = 7.6$, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-5), 7.73 (dd, $J = 7.6$, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-6), 8.15 (dd, $J = 7.6$, 1.2 Hz, 1H, 2-methylsulfonylphenyl H-3). Anal. calcd for $C_{17}H_{14}O_4S$: C, 64.95; H, 4.49. Found: C, 64.62; H, 4.50.

7. 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]

8. 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 immuno assay (EIA) kit (catalog number 560101, Cayman Chemical, Ann Arbor, MI, USA) according to our previously reported method.[13]

9. Anti-inflammatory assay

Anti-inflammatory activity was performed using a method described by Winter et al.[22]

10. Analgesic assay

Analgesic activity was determined using a 4% sodium chloride-induced writhing abdominal constriction assay previously reported.[23]

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