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Synthesis and cyclooxygenase inhibitory activities of linear 1-(methanesulfonylphenyl or benzenesulfonamido)-2-(pyridyl)acetylene regioisomers

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Abstract—A group of 1-(aminosulfonylphenyl and methylsulfonylphenyl)-2-(pyridyl)acetylene regioisomers were designed such that a COX-2 SO_2NH_2 pharmacophore was located at the *para*-position of the phenyl ring, or a SO_2Me pharmacophore was placed at the *ortho*-, *meta*- or *para*-position of the phenyl ring, on an acetylene template (scaffold). The point of attachment of the pyridyl ring to the acetylene linker was simultaneously varied (2-pyridyl, 3-pyridyl, 4-pyridyl, 3-methyl-2-pyridyl) to determine the combined effects of positional, steric, and electronic substituent properties upon COX-1 and COX-2 inhibitory potency and COX isozyme selectivity. These target linear 1-(phenyl)-2-(pyridyl)acetylenes were synthesized via a palladium-catalyzed Sonogashira cross-coupling reaction. Structure–activity relationship (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_2NH_2 or SO_2Me pharmacophore on the phenyl ring, and the point of attachment of the pyridyl ring to the acetylene linker, were either individual, or collective, determinants of COX-2 inhibitory potency and selectivity. A number of compounds discovered in this study, particularly 1-(4-aminosulfonylphenyl)-2-(3-methyl-2-pyridyl)acetylene (**22**), 1-(3-methanesulfonylphenyl)-2-(2-pyridyl)acetylene (**27**), 1-(3-methanesulfonylphenyl)-2-(4-pyridyl)acetylene (**29**), 1-(4-methanesulfonylphenyl)-2-(2-pyridyl)acetylene (**30**), and 1-(4-methanesulfonylphenyl)-2-(3-pyridyl)acetylene (**31**), exhibit potent (IC_{50} = 0.04–0.33 μM range) and selective (SI = 18 to >312 range) COX-2 inhibitory activities, that compare favorably with the reference drug celecoxib (COX-2 IC_{50} = 0.07 μM; COX-2 SI = 473). The sulfonamide (**22**), and methylsulfonyl (**27** and **31**), compounds exhibited anti-inflammatory activities (ID_{50} = 59.9–76.6 mg/kg range) that were intermediate in potency between the reference drugs aspirin (ID_{50} = 128.7 mg/kg) and celecoxib (ID_{50} = 10.8 mg/kg).

1. Introduction

Cyclooxygenase (COX) inhibitors such as celecoxib (**1**)[1] and etoricoxib (**2**),[2,3] that selectively inhibit the inducible COX-2 isozyme, are effective anti-inflammatory drugs for indications such as rheumatoid arthritis with less gastrointestinal and renal toxicity (see structures in Fig. 1). Structure–activity relationship (SAR) studies showed that tricyclic compounds having 1,2-diaryl substitution on a central heterocyclic ring system represented a major class of selective COX-2 inhibitors, and that a SO_2Me or SO_2NH_2 COX-2 substituent (pharmacophore) at the *para*-position of one of the aryl rings frequently conferred optimal COX-2 selectivity and potency.[4]

Studies in our drug design program indicated that acyclic triaryl olefins (**3**) and 1,2-diaryl (*E*)-olefins (**4**), lacking a traditional central heterocyclic ring template, are potent selective COX-2 inhibitors with clinically relevant anti-inflammatory and analgesic activities.[5–7] In earlier investigations, we also described substituted-1,2-diphenylacetylene regioisomers (**5**) that are effective COX-1/2 inhibitors that exhibit in vivo anti-inflammatory activities.[8,9] It was therefore of interest to extend these latter studies to include compounds having regioisomeric 2-, 3-, and 4-pyridyl substituents. Accordingly, we now describe the design, synthesis, and in vitro COX-1 and COX-2 inhibitory and anti-inflammatory activities for a class of regioisomeric 1-(phenyl)-2-(pyridyl)acetylenes possessing a SO_2Me or SO_2NH_2 COX-2

Keywords: Linear acetylenes; $MeSO_2$ and H_2NSO_2 COX-2 pharmacophores; Sonogashira cross-coupling reaction; Cyclooxygenase-1 and -2 inhibitors; Anti-inflammatory activity.
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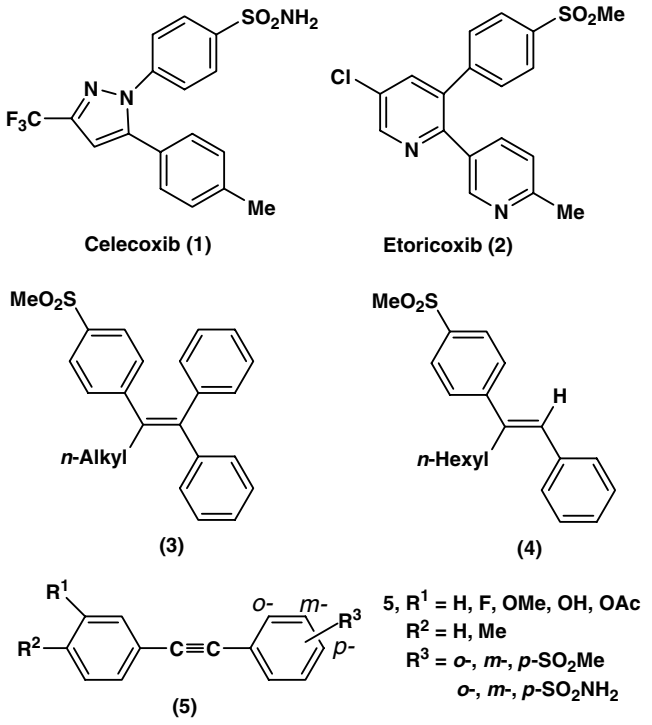
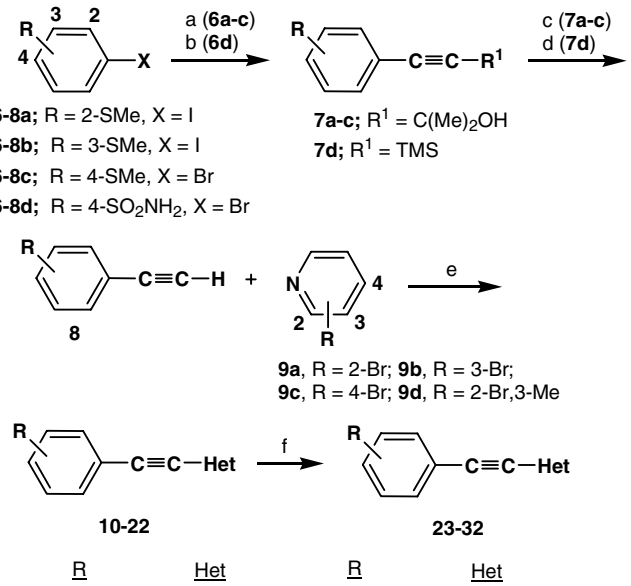


Figure 1. Some representative selective cyclooxygenase-2 (COX-2) inhibitors.

pharmacophore at the *para*-, *meta*- or *ortho*-position of the phenyl ring.

2. Chemistry

A variety of synthetic approaches have been used successfully for the synthesis of 1,2-diaryl acetylene derivatives.[8–12] The synthetic strategy used in this study to prepare the target 1-(methanesulfonylphenyl or benzenesulfonamido)-2-(pyridyl)acetylenes **20–32** is illustrated in Scheme 1. 1-Ethynyl-4-methylthiobenzene (**8c**) was synthesized according to our previously reported procedure.[13] A similar procedure was used for the synthesis of 1-ethynyl-2-methylthiobenzene (**8a**)[14] and 1-ethynyl-3-methylthiobenzene (**8b**)[15] regioisomers starting from 2-iodothioanisole (**6a**) and 3-iodothioanisole (**6b**), respectively. A modified procedure[16] was used for the synthesis of 4-ethynylbenzenesulfonamide (**8d**). Thus, Sonogashira coupling of 4-bromobenzenesulfonamide (**6d**) with ethynyltrimethylsilane in the presence of Et_3N, cuprous iodide (CuI) and dichlorobis(triphenylphosphine)palladium(0) ($[PdCl_2(PPh_3)_2]$) catalyst afforded the protected 4-trimethylsilylethynylbenzenesulfonamide (**7d**). Subsequent removal of the trimethylsilyl group using tetra-*n*-butylammonium fluoride (TBAF) furnished 4-ethynylbenzenesulfonamide (**8d**) in 45% yield. A second Sonogashira cross-coupling reaction of the ethynylmethylthiobenzenes (**8a–c**) with a variety of bromopyridines (**9a–d**) was carried out under an argon atmosphere in Et_3N or Et_3N/THF using $[PdCl_2(PPh_3)_2]$/CuI as catalyst to yield the respective 1-(methylthiophenyl)-2-(pyridyl)acetylene (**10–19**) in 62–100% yield. Similar Sonogashira cross-coupling of 4-ethynylbenzenesulfonamide (**8d**) with a bromopyridine (**9a**, **9c** or **9d**) afforded the respective 1-(4-aminosulfonylphenyl)-2-(pyridyl)acetylene (**20–22**) in slightly lower yield (**20**, 83%; **21**, 44%; **22**, 86%). Subsequent oxidation of the 1-(2-, 3- or 4-methylthiophenyl)-2-(pyridyl)acetylenes (**10–19**) using Oxone® (potassium peroxymonosulfate) in 1,4-dioxane[13] afforded the target 1-(methanesulfonylphenyl)-2-(pyridyl)acetylenes (**23–32**) in 21–100% yield.



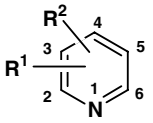
	R	Het		R	Het
10	2-SMe	2-pyridyl	**23**	2-SO_2Me	2-pyridyl
11	2-SMe	3-pyridyl	**24**	2-SO_2Me	3-pyridyl
12	2-SMe	4-pyridyl	**25**	2-SO_2Me	4-pyridyl
13	2-SMe	3-methyl-2-pyridyl	**26**	2-SO_2Me	3-methyl-2-pyridyl
14	3-SMe	2-pyridyl	**27**	3-SO_2Me	2-pyridyl
15	3-SMe	3-pyridyl	**28**	3-SO_2Me	3-pyridyl
16	3-SMe	4-pyridyl	**29**	3-SO_2Me	4-pyridyl
17	4-SMe	2-pyridyl	**30**	4-SO_2Me	2-pyridyl
18	4-SMe	3-pyridyl	**31**	4-SO_2Me	3-pyridyl
19	4-SMe	3-methyl-2-pyridyl	**32**	4-SO_2Me	3-methyl-2-pyridyl
20	4-SO_2NH_2	2-pyridyl			
21	4-SO_2NH_2	4-pyridyl			
22	4-SO_2NH_2	3-methyl-2-pyridyl			

Scheme 1. Reagents and conditions: (a) Et_3N, 2-methyl-3-butyn-2-ol, $Pd(PPh_3)_2Cl_2$, CuI, 70–75 °C, 5 h (**6a–c**); (b) Et_3N, ethynyltrimethylsilane, $Pd(PPh_3)_2Cl_2$, CuI, 90 °C, overnight (**6d**); (c) benzene, NaH, 105–110 °C, 1 h (**7a–c**); (d) THF, TBAF, 25 °C, 1 h (**7d**); (e) Et_3N or Et_3N/THF, $Pd(PPh_3)_2Cl_2$, CuI, 90 °C, 3–5 h; (f) 1,4-dioxane, aqueous Oxone®, 25 °C, 4–5 h.

3. Results and discussion

A group of 1-(aminosulfonylphenyl and methylsulfonylphenyl)-2-(pyridyl)acetylene regioisomers were designed such that a COX-2 SO_2NH_2 pharmacophore was located at the *para*-position of the phenyl ring (**20–22**), or a SO_2Me pharmacophore was placed at the *ortho*-, *meta*- or *para*-position of the phenyl ring (**23–32**), on a

Table 1. Theoretical atomic charges at each position of the pyridine ring in pyridine, 2-, 3-, and 4-ethynylpyridine, and 2-ethynyl-3-methylpyridine, and their relative charge profiles



R^1	R^2	Pyridine ring atomic charges[a]						Ring atom charge sequence
		N-1	C-2	C-3	C-4	C-5	C-6	
H	H	−0.080	−0.061	−0.152	−0.065	−0.152	−0.061	C-3 and C-5 > C-4 > C-2 and C-6
2-C≡CH	H	−0.059	0.093	−0.136	−0.066	−0.150	−0.061	C-5 > C-3 > C-4 > C-6 > C-2
3-C≡CH	H	−0.078	−0.047	0.010	−0.054	−0.150	−0.060	C-5 > C-6 > C-4 > C-2 > C-3
4-C≡CH	H	−0.078	−0.061	−0.139	0.093	−0.139	−0.061	C-3 and C-5 > C-2 and C-6 > C-4
2-C≡CH	2-Me	−0.056	0.090	−0.099	−0.075	−0.144	−0.069	C-5 > C-3 > C-4 > C-6 > C-2

[a] Charges due to open valences for each atom were calculated using the Alchemy 32 (Version 2.0, Tripos Inc., St. Louis, MO) program. The initial atomic charges calculated by the program using the Gasteiger–Marsili method were recalculated using the PM3 geometry optimization module of the Alchemy 32 computational program.

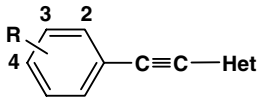
linear acetylene template (scaffold). In addition, the point of attachment of the pyridyl ring to the acetylene linker was simultaneously varied (2-pyridyl, 3-pyridyl, 4-pyridyl, 3-methyl-2-pyridyl) to determine the combined effects of positional, steric, and electronic substituent properties upon COX-1 and COX-2 inhibitory potency and COX isozyme selectivity. A comparison of the calculated pyridine ring atomic charges for the model compounds 2-, 3-, and 4-ethynylpyridine indicates the relative ring atom charge profile in order of decreasing negative charge is different for the 2-ethynylpyridine (C-5 > C-3 > C-4 > C-6 > C-2), 3-ethynylpyridine (C-5 > C-6 > C-4 > C-2 > C-3), and 4-ethynylpyridine (C-3 and C-5 > C-2 and C-6 > C-4) regioisomers (see data in Table 1). These differences are attributed to the fact that the electronic (inductive and resonance) effects of the pyridyl nitrogen atom, and the position of the ethynyl (acetylene) substituent, are determinants of the atomic charge at each position of the pyridyl ring in these three regioisomers. It is also plausible that the pyridyl nitrogen free electron-pair of the 2-, 3-, and 4-ethynylpyridine regioisomers, that could act as a hydrogen bond acceptor, would bind to a different amino acid residue(s) in the COX-1 or COX-2 isozyme binding site. Structure–activity relationship (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_2NH_2 or SO_2Me pharmacophore on the phenyl ring, and the point of attachment of the pyridyl ring to the acetylene linker, were either individual, or collective, determinants of COX-2 inhibitory potency and selectivity (see Table 2).

A comparison of the SAR data for the 1-(4-aminosulfonylphenyl)-2-(pyridyl)acetylenes (**20**–**22**) showed that the 2-pyridyl regioisomer (**20**) was a more potent and selective COX-2 inhibitor than the 4-pyridyl regioisomer (**21**), and that incorporation of a C-3 Me substituent on the 2-pyridyl ring (**22**) further enhanced COX-2 potency (COX-2 IC_{50} = 0.07 μM) that was equiactive to the reference drug celecoxib. Within the subgroups of compounds having an *o*-SO_2Me (**23**–**26**), or *m*-SO_2Me (**27**–**29**) COX-2 pharmacophore, the 2-pyridyl and 4-pyridyl regioisomers exhibited similar COX-1 and COX-2 inhibitory potencies relative to the less active 3-pyridyl regioisomer. It is notable that *m*-SO_2Me compound (**29**), which did not inhibit COX-1 (IC_{50} > 100 μM), is a more selective COX-2 inhibitor [COX-2 selectivity index (SI) > 312] than the corresponding *o*-SO_2Me regioisomer (**25**) that also inhibited COX-1 (IC_{50} = 0.26 μM; COX-2 SI = 2.4). In contrast, in the *p*-SO_2Me subgroup of compounds (**30**–**32**), the 3-pyridyl regioisomer (**31**) was a more potent inhibitor of both COX-1 (IC_{50} = 3.2 μM) and COX-2 (IC_{50} = 0.04 μM; COX-2 SI = 78) than the 2-pyridyl regioisomer (**30**, COX-1 IC_{50} = 31.7 μM, COX-2 IC_{50} = 0.33; COX-2 SI = 96.1). Insertion of a C-3 Me substituent provided the 3-methyl-2-pyridyl compound (**32**) that, unlike the 2-pyridyl compound (**30**), did not inhibit COX-1 or COX-2 (IC_{50}'s >100 μM).

The bioisosteric relationship between the *p*-SO_2NH_2 and *p*-SO_2Me COX-2 pharmacophores can be highly variable depending on which pyridyl substituent is present. In this regard, the 2-pyridyl compounds **20** (*p*-SO_2NH_2) and **30** (*p*-SO_2Me) have qualitatively similar COX-1 and COX-2 inhibitory and COX-2 SI properties, whereas the 3-methyl-2-pyridyl compound **22** (*p*-SO_2NH_2) is a potent (IC_{50} = 0.07 μM) and moderately selective COX-2 inhibitor (SI = 18.6) relative to the inactive compound **32** (*p*-SO_2Me).

The following SARs were identified when the point of attachment of the pyridyl ring to the acetylene linker was held constant and the position (*ortho*-, *meta*- *or para*-) of the SO_2Me substituent on the phenyl ring was varied. In the subgroup of compounds (**23**, **27**, and **30**) having a 2-pyridyl moiety, all compounds exhibited similar COX-2 inhibitory activity (IC_{50} = 0.20–0.33 μM range) irrespective of the position of the SO_2Me substituent to the phenyl ring. However, compounds having a *m*-SO_2Me (**27**), or *p*-SO_2Me (**30**), substituent were less potent inhibitors of COX-1 (IC_{50} = 31.6–36.7 μM range) such that their COX-2 SI's were much larger (158 and 96, respectively). A sim-

Table 2. In vitro COX-1 and COX-2 inhibition data for 1-(benzenesulfonamido)-2-(pyridyl)acetylenes (**20**–**22**) and 1-(methanesulfonylphenyl)-2-(pyridyl)acetylenes (**23**–**32**) and in vivo anti-inflammatory activities (**22**, **27**, and **31**)



20-32

Compound	R	Het	IC_{50}[a] (μM)		COX-2 SI[b]	AI activity[c] ID_{50} (mg/kg)
			COX-1	COX-2		
20	4-SO_2NH_2	2-Pyridyl	9.3	0.30	31.0	—
21	4-SO_2NH_2	4-Pyridyl	3.9	26.8	0.15	—
22	4-SO_2NH_2	3-Me–2-pyridyl	1.3	0.07	18.6	76.6
23	2-SO_2CH_3	2-Pyridyl	0.28	0.21	1.3	—
24	2-SO_2CH_3	3-Pyridyl	31.6	31.6	1	—
25	2-SO_2CH_3	4-Pyridyl	0.26	0.11	2.4	—
26	2-SO_2CH_3	3-Me–2-pyridyl	2.0	0.42	4.8	—
27	3-SO_2CH_3	2-Pyridyl	31.6	0.20	158	76.4
28	3-SO_2CH_3	3-Pyridyl	>100	31.6	>3.1	—
29	3-SO_2CH_3	4Pyridyl	>100	0.32	>312	—
30	4-SO_2CH_3	2-Pyridyl	31.7	0.33	96.1	—
31	4-SO_2CH_3	3-Pyridyl	3.2	0.04	78	59.9
32	4-SO_2CH_3	3-Me–2-pyridyl	>100	>100	—	—
Aspirin	—	—	0.35	2.4	0.15	128.7
Celecoxib	—	—	33.1	0.07	473	10.8
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 carrageenan-induced rat paw edema assay. The results are expressed as the ID_{50} value (mg/kg) at 3 h after oral administration of the test compound.

ilar comparison for the group of compounds having a 3-pyridyl moiety showed that compound **31** having a *p*-SO_2Me substituent exhibited potent (IC_{50} = 0.04 μM) and selective (SI = 78) COX-2 inhibitory activity relative to the *o*-SO_2Me (**24**) and *m*-SO_2Me (**28**) regioisomers that were either very weak or inactive inhibitors of both COX-1 and COX-2. The position of the SO_2Me moiety was a determinant of COX-2 selectivity for compounds having a 4-pyridyl moiety since the *o*-SO_2Me compound (**25**) was a potent inhibitor of both COX-1 and COX-2, whereas the *m*-SO_2Me compound (**29**) was a potent (IC_{50} = 0.32 μM) and selective (SI > 312) inhibitor of the COX-2 isozyme.

A number of compounds described in this study including 1-(4-aminosulfonylphenyl)-2-(3-methyl-2-pyridyl)acetylene (**22**), 1-(3-methanesulfonylphenyl)-2-(2-pyridyl)acetylene (**27**), 1-(3-methanesulfonylphenyl)-2-(4-pyridyl)acetylene (**29**), 1-(4-methanesulfonylphenyl)-2-(2-pyridyl)acetylene (**30**), and 1-(4-methanesulfonylphenyl)-2-(3-pyridyl)acetylene (**31**) exhibit potent (IC_{50} = 0.04 to 0.33 μM range) and selective (SI = 18 to >312 range) COX-2 inhibitory activities. This group of compounds, which possess SO_2NH_2 and/or SO_2Me COX-2 pharmacophores at all three isomeric positions on the phenyl ring in conjunction with a 2-pyridyl, 3-pyridyl, 4-pyridyl or 3-methyl-2-pyridyl ring attached to the acetylene linker, illustrates the value of using regioisomeric pyridine moieties as potential bioisosteres for a phenyl ring bearing aryl substituents that are traditionally used in drug design studies.

The in vivo anti-inflammatory activities of three of the more potent and selective COX-2 inhibitors (**22**, **27**, and **31**), based on in vitro enzyme inhibition data, were determined (Table 2). In a carrageenan-induced rat paw edema assay model, 1-(4-aminosulfonylphenyl)-2-(3-methyl-2-pyridyl)acetylene (**22**, ID_{50} = 76.6 mg/kg), 1-(3-methanesulfonylphenyl)-2-(2-pyridyl)acetylene (**27**, ID_{50} = 76.4 mg/kg), and 1-(4-methanesulfonylphenyl)-2-(3-pyridyl)acetylene (**31**, ID_{50} = 59.9 mg/kg) were more potent than the reference drug aspirin (ID_{50} = 128.7 mg/kg) but less potent than the selective COX-2 inhibitor celecoxib (ID_{50} = 10.8 mg/kg).

4. Conclusions

The structure–activity relationships acquired indicate that (i) a linear acetylene spacer between *vicinal* phenyl and pyridyl rings is a suitable template for the design of new acyclic COX inhibitors, (ii) the position of the COX-2 SO_2NH_2 or SO_2Me pharmacophore on the phenyl ring, and the point of attachment of the pyridyl ring to the acetylene linker, were either individual, or collective, determinants of COX-2 inhibitory potency and selectivity, (iii) regioisomeric pyridine moieties that have different ring atomic charges can be used as potential bioisosteres for a phenyl ring bearing aryl substituents that are traditionally used in drug design studies, and (iv) compounds such as 1-(3-methanesulfonylphenyl)-2-(4-pyridyl)acetylene (**29**) that exhibits similar COX-2 selectivity (SI > 312), or 1-(4-methanesulfonylphenyl)-

2-(3-pyridyl)acetylene (**31**) that exhibits similar COX-2 inhibitory potency (IC_{50} = 0.04 μM), relative to the reference drug celecoxib (COX-2 IC_{50} = 0.07 μM; COX-2 SI = 473) are readily accessible via the drug design strategy described herein.

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 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. 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). 2-Iodothioanisole (**6a**)[17] and 3-iodothioanisole (**6b**)[15] were synthesized in 91% and 76% yields, respectively, starting from 2-(methylthio)aniline and 3-(methylthio)aniline using the procedure of Ullmann.[18] 4-Bromobenzenesulfonamide (**6c**) was prepared according to a previously reported procedure.[9] All other reagents, purchased from the Aldrich Chemical Company (Milwaukee, WI), were used without further purification. The in vivo anti-inflammatory assay was carried out using a protocol approved by the Health Sciences Animal Welfare Committee at the University of Alberta.

6. General procedure for the synthesis of 2-methyl-4-(2-, 3- or 4-methylthiophenyl)but-3-yn-2-ols (7a–c)

$PdCl_2(PPh_3)_2$ (29 mg, 0.039 mmol) and CuI (8 mg, 0.042 mmol) were added to a stirred solution of a bromo- or iodothioanisole (**6a**, **6b** or **6c**, 10 mmol) and 2-methyl-3-butyn-2-ol (1.03 mL, 10.61 mmol) in Et_3N (20 mL) under an argon atmosphere at 25 °C, and the reaction was allowed to proceed at 70–75 °C for 5 h. The reaction mixture was allowed to cool to 25 °C, filtered, and excess Et_3N was removed from the filtrate in vacuo. The dark brown residue obtained was purified by silica gel column chromatography using hexanes/EtOAc (3:1, v/v) as eluent to afford the respective product **7a**, **7b** or **7c**. Spectroscopic data for **7a**–**c** are listed below.

6.1. 2-Methyl-4-(2-methylthiophenyl)but-3-yn-2-ol (7a)

Yield, 77%; reddish oil; IR (film): 3402 (OH), 2225 (C≡C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.66 (s, 6H, C*Me*$_2$), 2.13 (br s, 1H, O*H*), 2.49 (s, 3H, S*Me*), 7.07 (ddd, *J* = 7.6, 7.6, 0.9 Hz, 1H, 2- methylthiophenyl H-5), 7.13 (d, *J* = 7.6 Hz, 1H, 2-methylthiophenyl H-3), 7.29 (ddd, *J* = 7.6, 7.6, 0.9 Hz, 1H, 2-methylthiophenyl H-4), 7.37 (d, *J* = 7.6 Hz, 1H, 2-methylthiophenyl H-6).

6.2. 2-Methyl-4-(3-methylthiophenyl)but-3-yn-2-ol (7b)

Yield, 100%; reddish oil; IR (film): 3362 (OH), 2234 (C≡C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 6H, C*Me*$_2$), 2.25 (br s, 1H, O*H*), 2.48 (s, 3H, S*Me*), 7.15–7.30 (m, 4H, 3-methylthiophenyl hydrogens).

6.3. 2-Methyl-4-(4-methylthiophenyl)but-3-yn-2-ol (7c)

Yield, 79%; pale yellow solid; mp 71–73 °C (lit.[13] 70–72 °C); IR (film): 3456 (OH), 2234 (C≡C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 6H, C*Me*$_2$), 2.03 (br s, 1H, O*H*), 2.48 (s, 3H, S*Me*), 7.16 (d, *J* = 8.5 Hz, 2H, 4-methylthiophenyl H-3, H-5), 7.33 (d, *J* = 8.5 Hz, 2H, 4-methylthiophenyl H-2, H-6).

6.4. General procedure for the synthesis of 1-ethynyl-2-, 3- or 4-methylthiobenzenes (8a–c)

Sodium hydride (24 mg, 1 mmol) was added to a solution of 2-methyl-4-(2-, 3- or 4-methylthiophenyl)but-3-yn-2-ol (**7a**, **7b** or **7c**, 7.28 mmol) in benzene (6 mL), and the reaction mixture was heated at 105–110 °C for 1 h. Removal of the solvent in vacuo gave a dark brown oil which was purified by silica gel column chromatography using hexanes/EtOAc (3:1, v/v) as eluent to afford the respective product **8a**, **8b** or **8c**. Some physical and spectroscopic data for **8a**–**c** are listed below.

6.5. 1-Ethynyl-2-methylthiobenzene (8a)

Yield, 95%; pale yellow oil; IR (film): 2099 (C≡C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 3H, S*Me*), 3.49 (s, 1H, C≡C*H*), 7.10 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H, 2-methylthiophenyl H-5), 7.18 (d, *J* = 7.9 Hz, 1H, 2-methylthiophenyl H-3), 7.33 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1H, 2-methylthiophenyl H-4), 7.47 (dd, *J* = 7.6, 1.2 Hz, 1H, 2-methylthiophenyl H-6).

6.6. 1-Ethynyl-3-methylthiobenzene (8b)

Yield, 79%; pale yellow oil; IR (film): 2106 (C≡C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H, S*Me*), 3.09 (s, 1H, C≡C*H*), 7.20–7.33 (m, 3H, 3-methylthiophenyl H-4, H-5, H-6), 7.37 (s, 1H, 3-methylthiophenyl H-2).

6.7. 1-Ethynyl-4-methylthiobenzene (8c)

Yield, 91%; yellow brown oil; IR (film): 2105 (C≡C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H, S*Me*), 3.08 (s, 1H, C≡C*H*), 7.18 (d, *J* = 8.5 Hz, 2H, 4-methylthiophenyl H-3, H-5), 7.41 (d, *J* = 8.5 Hz, 2H, 4-methylthiophenyl H-2, H-6).

6.8. 4-Ethynylbenzenesulfonamide (8d)

$PdCl_2(PPh_3)_2$ (351 mg, 0.5 mmol) and CuI (191 mg, 1 mmol) were added to a solution of 4-bromobenzenesulfonamide (**6d**, 3.50 g, 14.83 mmol) and (trimethylsilyl)acetylene (2.47 mL, 17.8 mmol) in Et_3N (62 mL) under an argon atmosphere with stirring at 25 °C, and the reaction was allowed to proceed at 90 °C overnight. The reaction mixture was cooled to 25 °C, filtered, and the excess Et_3N was removed from the filtrate in vacuo

to furnish 4-trimethylsilylethynylbenzenesulfonamide (**7d**) as a dark brown solid that was dissolved in THF (125 mL). A solution of TBAF (1 M in THF, 12 mL) was added and this mixture was stirred at 25 °C for 1 h. Removal of the solvent in vacuo gave a residue that was purified by silica gel column chromatography using hexanes/acetone (2:1, v/v) as eluent to afford 4-ethynylbenzenesulfonamide (**8d**). Yield, 45%; pale brown solid; mp 177–179 °C; IR (film): 3355, 3261 (NH_2), 2065 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$+ DMSO-d_6) δ 3.11 (s, 1H, C≡C*H*), 6.65 (br s, 2H, SO_2NH_2), 7.21 (d, J = 8.2 Hz, 2H, benzenesulfonamido H-3, H-5), 7.52 (d, J = 8.2 Hz, 2H, benzenesulfonamido H-2, H-6).

6.9. General procedure for the synthesis of 1-(methylthiophenyl)-2-(pyridyl)acetylenes (10–19) and 1-(benzenesulfonamido)-2-(pyridyl)acetylenes (20–22)

CuI (24 mg, 0.12 mmol) was added with stirring to a solution containing $PdCl_2(PPh_3)_2$ (42 mg, 0.06 mmol), a bromopyridine **9a**, **9b**, **9c** or **9d** (2 mmol), and either an ethynylmethylthiobenzene **8a**, **8b** or **8c**, or 4-ethynylbenzenesulfonamide **8d** (3 mmol), in Et_3N (5 mL) under an argon atmosphere. In the case of **8d**, dry THF (5 mL) was also added along with Et_3N. The reaction mixture was heated at 90 °C for 3–5 h, cooled to 25 °C, and filtered to remove the inorganic salts. The solvent from the filtrate was removed in vacuo, and the residue obtained was purified by silica gel column chromatography using either hexanes/EtOAc (1:1, v/v) as eluent to furnish the respective product **10**–**19**, or hexanes/acetone (1:1, v/v) as eluent to furnish the respective product **20**–**22**. Some physical and spectroscopic data for **10**–**22** are listed below.

6.10. 1-(2-Methylthiophenyl)-2-(2-pyridyl)acetylene (10)

The product was obtained as a reddish oil using the Sonogashira coupling reaction of **8a** with 2-bromopyridine (**9a**) in 100% yield; IR (film): 2213 (C≡C), 1588, 1561, 1471 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.53 (s, 3H, S*Me*), 7.11 (dd, J = 7.6, 7.6 Hz, 1H, phenyl H-5), 7.18 (d, J = 7.6 Hz, 1H, phenyl H-3), 7.26 (dd, J = 8.5, 4.8 Hz, 1H, pyridyl H-5), 7.36 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H, phenyl H-4), 7.54–7.62 (m, 2H, phenyl H-6, pyridyl H-3), 7.72 (ddd, J = 8.5, 8.5, 1.8 Hz, 1H, pyridyl H-4), 8.63 (br d, J = 4.8 Hz, 1H, pyridyl H-6).

6.11. 1-(2-Methylthiophenyl)-2-(3-pyridyl)acetylene (11)

The product was obtained as a reddish oil using the Sonogashira coupling reaction of **8a** with 3-bromopyridine (**9b**) in 94% yield; IR (film): 2233 (C≡C), 1560, 1479 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.53 (s, 3H, S*Me*), 7.14 (dd, J = 7.6, 7.6 Hz, 1H, phenyl H-5), 7.18 (d, J = 7.6 Hz, 1H, phenyl H-3), 7.28–7.40 (m, 2H, pyridyl H-5, phenyl H-4), 7.50 (d, J = 7.6 Hz, 1H, phenyl H-6), 7.90 (d, J = 8.5 Hz, 1H, pyridyl H-4), 8.5–9.1 (br resonance, 2H total, pyridyl H-2, H-6).

6.12. 1-(2-Methylthiophenyl)-2-(4-pyridyl)acetylene (12)

The product was obtained as a reddish oil using the Sonogashira coupling reaction of **8a** with 4-bromopyridine (**9c**) in 85% yield; IR (film): 2220 (C≡C), 1593, 1542 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.53 (s, 3H, S*Me*), 7.14 (dd, J = 7.6, 7.6 Hz, 1H, phenyl H-5), 7.20 (d, J = 7.6 Hz, 1H, phenyl H-3), 7.36 (dd, J = 7.6, 7.6 Hz, 1H, phenyl H-4), 7.48 (d, J = 5.5 Hz, 2H, pyridyl H-3, H-5), 7.52 (d, J = 7.6 Hz, 1H, phenyl H-6), 8.60 (d, J = 5.5 Hz, 2H, pyridyl H-2, H-6).

6.13. 1-(2-Methylthiophenyl)-2-(3-methyl-2-pyridyl)acetylene (13)

The product was obtained as a reddish oil using the Sonogashira coupling reaction of **8a** with 2-bromo-3-methylpyridine (**9d**) in 79% yield; IR (film): 2220 (C≡C), 1589, 1562, 1471, 1441 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O) δ 2.53 (s, 3H, S*Me*), 2.60 (s, 3H, pyridyl C-3 *Me*), 7.12–7.28 (m, 3H, phenyl H-3 and H-5, pyridyl H-5), 7.36 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H, phenyl H-4), 7.52–7.65 (m, 2H, phenyl H-6, pyridyl H-4), 8.48 (d, J = 4.0 Hz, 2H, pyridyl H-6).

6.14. 1-(3-Methylthiophenyl)-2-(2-pyridyl)acetylene (14)

The product was obtained as a reddish oil using the Sonogashira coupling reaction of **8b** with 2-bromopyridine (**9a**) in 81% yield; IR (film): 2234 (C≡C), 1586, 1560, 1539 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51 (s, 3H, S*Me*), 7.22-7.33 (m, 3H, phenyl H-4, H-5, H-6), 7.34–7.70 (m, 3H, phenyl H-2, pyridyl H-3, H-5), 7.78 (br resonance, 1H, pyridyl H-4), 8.66 (br resonance, 1H, pyridyl H-6).

6.15. 1-(3-Methylthiophenyl)-2-(3-pyridyl)acetylene (15)

The product was obtained as a reddish oil using the Sonogashira coupling reaction of **8b** with 3-bromopyridine (**9b**) in 62% yield; IR (film): 2234 (C≡C), 1586, 1559, 1479 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H, S*Me*), 7.20–7.36 (m, 4H, phenyl H-4, H-5, H-6, pyridyl H-5), 7.41 (s, 1H, phenyl H-2), 7.96 (d, J = 7.5 Hz, 1H, pyridyl H-4), 8.5–9.0 (br resonance, 2H total, pyridyl H-2, H-6).

6.16. 1-(3-Methylthiophenyl)-2-(4-pyridyl)acetylene (16)

The product was obtained as a reddish oil using the Sonogashira coupling reaction of **8b** with 4-bromopyridine (**9c**) in 71% yield; IR (film): 2234 (C≡C), 1593, 1559 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H, S*Me*), 7.20–7.36 (m, 3H, phenyl H-4, H-5, H-6), 7.42 (s, 1H, phenyl H-2), 7.50–7.63 (m, 2H, pyridyl H-3, H-5), 8.50–9.50 (br resonance, 2H total, pyridyl H-2, H-6).

6.17. 1-(4-Methylthiophenyl)-2-(2-pyridyl)acetylene (17)

The product was obtained as a reddish oil using the Sonogashira coupling reaction of **8c** with 2-bromopyridine (**9a**) in 100% yield; IR (film): 2213 (C≡C), 1578, 1560, 1487 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.50 (s, 3H, S*Me*), 7.22 (d, J = 8.5 Hz, 2H, H-3, H-5), 7.28 (dd, J = 8.5, 4.8 Hz, 1H, pyridyl H-5), 7.51 (d, J = 8.5 Hz, 2H, phenyl H-2, H-6), 7.56 (d, J = 8.5 Hz,

1H, pyridyl H-3), 7.75 (ddd, J = 8.5, 8.5, 1.8 Hz, 1H, pyridyl H-4), 8.64 (d, J = 4.8 Hz, 1H, pyridyl H-6).

6.18. 1-(4-Methylthiophenyl)-2-(3-pyridyl)acetylene (18)

The product was obtained as a reddish solid using the Sonogashira coupling reaction of **8c** with 3-bromopyridine (**9b**) in 100% yield; mp 73–75 °C; IR (film): 2227 (C≡C), 1577, 1558, 1494 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51 (s, 3H, S*Me*), 7.20 (d, J = 8.5 Hz, 2H, phenyl H-3, H-5), 7.32 (dd, J = 8.5, 4.8 Hz, 1H, pyridyl H-5), 7.50 (d, J = 8.5 Hz, 2H, phenyl H-2, H-6), 7.82 (d, J = 8.5 Hz, 1H, pyridyl H-4), 8.54 (d, J = 4.8 Hz, 1H, pyridyl H-6), 8.76 (s, 1H, pyridyl H-2).

6.19. 1-(4-Methylthiophenyl)-2-(3-methyl-2-pyridyl)acetylene (19)

The product was obtained as reddish crystals using the Sonogashira coupling reaction of **8c** with 2-bromo-3-methylpyridine (**9d**) in 91% yield; mp 55–57 °C; IR (film): 2220 (C≡C), 1581, 1563, 1491 (Ar) cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O) δ 2.51 (s, 3H, S*Me*), 2.52 (s, 3H, pyridyl C-3 *Me*), 7.16 (dd, J = 8.5, 4.8 Hz, 1H, pyridyl H-5), 7.25 (d, J = 8.5 Hz, 2H, phenyl H-3, H-5), 7.52 (d, J = 8.5 Hz, 2H, phenyl H-2, H-6), 7.58 (d, J = 8.5 Hz, 1H, pyridyl H-4), 8.46 (d, J = 4.8 Hz, 1H, pyridyl H-6).

6.20. 1-(4-Aminosulfonylphenyl)-2-(2-pyridyl)acetylene (20)

The product was obtained as pale yellow solid using the Sonogashira coupling reaction of **8d** with 2-bromopyridine (**9a**) in 83% yield; mp 163–165 °C; IR (film): 3316, 3259 (NH_2), 2223 (C≡C), 1568, 1450 (Ar), 1333 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 7.25–7.50 (m, 2H, SO_2NH_2 that exchanges with D_2O), 7.32 (dd, J = 8.5, 4.8 Hz, 1H, pyridyl H-5), 7.52 (d, J = 8.5 Hz, 1H, pyridyl H-3), 7.66 (d, J = 8.5 Hz, 2H, phenyl H-2, H-6), 7.74 (dd, J = 8.5, 8.5 Hz, 1H, pyridyl H-4), 7.84 (d, J = 8.5 Hz, 2H, phenyl H-3, H-5), 8.56 (d, J = 4.8 Hz, 1H, pyridyl H-6). Anal. Calcd for $C_{13}H_{10}N_2O_2S{\cdot}1/4H_2O$: C, 59.42; H, 4.00; N, 10.66. Found: C, 59.76; H, 3.98; N, 10.27.

6.21. 1-(4-Aminosulfonylphenyl)-2-(4-pyridyl)acetylene (21)

The product was obtained as pale yellow solid using the Sonogashira coupling reaction of **8d** with 4-bromopyridine (**9c**) in 44%; mp 230–232 °C; IR (film): 3349, 3261 (NH_2), 2220 (C≡C), 1568, 1450 (Ar), 1340 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 7.32–7.62 (m, 4H, pyridyl H-3, H-5; SO_2NH_2 that exchanges with D_2O), 7.7 (d, J = 8.5 Hz, 2H, phenyl H-2, H-6), 7.88 (d, J = 8.5 Hz, 2H, phenyl H-3, H-5), 8.5–9.5 (br resonance, 2H total, pyridyl H-2, H-6). Anal. Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90; N, 10.85. Found: C, 60.37; H, 4.05; N, 10.42.

6.22. 1-(4-Aminosulfonylphenyl)-2-(3-methyl-2-pyridyl)acetylene (22)

The product was obtained as pale yellow solid using the Sonogashira coupling reaction of **8d** with 2-bromo-3-methylpyridine (**9d**) in 86% yield; mp 175–177 °C; IR (film): 3328, 3254 (NH_2), 2222 (C≡C), 1568, 1450 (Ar), 1340 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 2.47 (s, 3H, pyridyl C-3 *Me*), 7.02 (br s, 2H, SO_2NH_2 that exchanges with D_2O), 7.24 (dd, J = 8.5, 4.8 Hz, 1H, pyridyl H-5), 7.58 (d, J = 8.5 Hz, 1H, pyridyl H-4), 7.64 (d, J = 8.5 Hz, 2H, phenyl H-2, H-6), 7.86 (d, J = 8.5 Hz, 2H, phenyl H-3, H-5), 8.5 (br resonance, 1H, pyridyl H-6). Anal. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.34; H, 4.47; N, 10.00.

6.23. General procedure for the synthesis of 1-(methanesulfonylphenyl)-2-(pyridyl)acetylenes (23–32)

An aqueous solution of Oxone® (50% w/v, 3 mmol) was added dropwise to a stirred solution of a 1-(methylthiophenyl)-2-(pyridyl)acetylene **10**–**19** (1 mmol) in 1,4-dioxane (10 mL) at 0 °C, and the reaction was allowed to proceed with stirring at 25 °C for 4–5 h. The reaction mixture was diluted with water (15 mL), extracted with EtOAc (3 × 25 mL), the organic phase was washed successively with water and brine, and dried ($MgSO_4$). After filtration, the solvent from the organic fraction was removed in vacuo to give a crude product which was purified by silica gel column chromatography using hexanes/EtOAc as eluent to afford the respective product **23**–**32**. The spectral and microanalytical data for compounds **23**–**32** are listed below.

6.24. 1-(2-Methanesulfonylphenyl)-2-(2-pyridyl)acetylene (23)

Yield, 66%; pale yellow solid; mp 155–157 °C; IR (film): 2224 (C≡C), 1582, 1475 (Ar), 1313 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.35 (s, 3H, SO_2Me), 7.35 (dd, J = 8.5, 4.8 Hz, 1H, pyridyl H-5), 7.53–7.72 (m, 3H, phenyl H-4, H-5, pyridyl H-3), 7.76 (dd, J = 8.5, 1.8 Hz, 1H, phenyl H-6), 7.80 (ddd, J = 8.5, 8.5, 1.2 Hz, 1H, pyridyl H-4), 8.15 (d, J = 8.5 Hz, 1H, phenyl H-3), 8.65 (d, J = 4.8 Hz, 1H, pyridyl H-6). Anal. Calcd for $C_{14}H_{11}NO_2S{\cdot}1/4H_2O$: C, 64.23; H, 4.39; N, 5.35. Found: C, 64.54; H, 4.49; N, 5.27.

6.25. 1-(2-Methanesulfonylphenyl)-2-(3-pyridyl)acetylene (24)

Yield, 59%; red syrup; IR (film): 2222 (C≡C), 1561, 1482 (Ar), 1310 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.30 (s, 3H, SO_2Me), 7.39 (dd, J = 8.5, 4.8 Hz, 1H, pyridyl H-5), 7.57 (dd, J = 8.5, 8.5 Hz, 1H, phenyl H-5), 7.68 (ddd, J = 8.5, 8.5, 1.8 Hz, 1H, phenyl H-4), 7.78 (d, J = 8.5 Hz, 1H, phenyl H-6), 7.96 (d, J = 8.5 Hz, 1H, pyridyl H-4), 8.16 (d, J = 8.5 Hz, 1H, phenyl H-3), 8.63 (d, J = 4.8 Hz, 1H, pyridyl H-6), 8.82 (s, 1H, pyridyl H-2). Anal. Calcd for $C_{14}H_{11}NO_2S{\cdot}1/5H_2O$: C, 64.45; H, 4.37; N, 5.37. Found: C, 64.64; H, 4.73; N, 5.02.

6.26. 1-(2-Methanesulfonylphenyl)-2-(4-pyridyl)acetylene (25)

Yield, 32%; pale yellow solid; mp 165–167 °C; IR (film): 2225 (C≡C), 1597, 1477, 1465 (Ar), 1310 (SO_2) cm^{-1};

^{1}H NMR ($CDCl_3$) δ 3.28 (s, 3H, SO_2Me), 7.50 (d, J = 4.8 Hz, 2H, pyridyl H-3, H-5), 7.55–7.72 (m, 2H, phenyl H-4, H-5), 7.80 (d, J = 8.5 Hz, 1H, phenyl H-6), 8.16 (d, J = 8.5 Hz, 1H, phenyl H-3), 8.67 (d, J = 4.8 Hz, 2H, pyridyl H-2, H-6). Anal. Calcd for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44. Found: C, 64.92; H, 4.63; N, 5.41.

6.27. 1-(2-Methanesulfonylphenyl)-2-(3-methyl-2-pyridyl)acetylene (26)

Yield, 38%; pale yellow solid; mp 92–94 °C; IR (film): 2219 (C≡C), 1582, 1472 (Ar), 1310 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.59 (s, 3H, pyridyl C-3 *Me*), 3.34 (s, 3H, SO_2Me), 7.23 (dd, J = 8.5, 4.8 Hz, 1H, pyridyl H-5), 7.50–7.70 (m, 3H, phenyl H-4, H-5; pyridyl H-4), 7.85 (d, J = 8.5 Hz, 1H, phenyl H-6), 8.13 (d, J = 8.5 Hz, 1H, phenyl H-3), 8.47 (d, J = 4.6 Hz, 1H, pyridyl H-6). Anal. Calcd for $C_{15}H_{13}NO_2S{\cdot}1/3H_2O$: C, 64.96; H, 4.93; N, 5.05. Found: C, 64.75; H, 4.89; N, 4.97.

6.28. 1-(3-Methanesulfonylphenyl)-2-(2-pyridyl)acetylene (27)

Yield, 99%; brown solid; mp 103–105 °C; IR (film): 2231 (C≡C), 1582, 1477 (Ar), 1313 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.09 (s, 3H, SO_2Me), 7.30 (dd, J = 8.5, 4.8 Hz, 1H, pyridyl H-5), 7.58–7.67 (m, 2H, phenyl H-5, pyridyl H-3), 7.76 (ddd, J = 8.5, 8.5, 1.2 Hz, 1H, pyridyl H-4), 7.87 (d, J = 8.5 Hz, 1H, phenyl H-6), 7.94 (d, J = 8.5 Hz, 1H, phenyl H-4), 8.18 (s, 1H, phenyl H-2), 8.66 (d, J = 4.8 Hz, 1H, pyridyl H-6). Anal. Calcd for $C_{14}H_{11}NO_2S{\cdot}1/5H_2O$: C, 64.45; H, 4.37; N, 5.37. Found: C, 64.67; H, 4.38; N, 5.38.

6.29. 1-(3-Methanesulfonylphenyl)-2-(3-pyridyl)acetylene (28)

Yield, 87%; brown solid; mp 83–85 °C; IR (film): 2228 (C ≡ C), 1582, 1479, 1414 (Ar), 1310 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.10 (s, 3H, SO_2Me), 7.39 (dd, J = 8.5, 7.9 Hz, 1H, pyridyl H-5), 7.61 (dd, J = 8.5, 8.5 Hz, 1H, phenyl H-5), 7.81 (d, J = 8.5 Hz, 1H, pyridyl H-4), 7.88 (d, J = 8.5, phenyl H-6), 7.94 (d, J = 8.5 Hz, 1H, phenyl H-4), 8.14 (s, 1H, phenyl H-2), 8.60 (d, J = 4.8 Hz, 1H, pyridyl H-6), 8.78 (s, 1H, pyridyl H-2). Anal. Calcd for $C_{14}H_{11}NO_2S{\cdot}2/3H_2O$: C, 62.44; H, 4.58; N, 5.20. Found: C, 62.75; H, 4.48; N, 5.09.

6.30. 1-(3-Methanesulfonylphenyl)-2-(4-pyridyl)acetylene (29)

Yield, 21%; dark brown syrup; IR (film): 2229 (C≡C), 1597, 1478 (Ar), 1312 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.09 (s, 3H, SO_2Me), 7.42 (d, J = 5.6 Hz, 2H, pyridyl H-3, H-5), 7.61 (dd, J = 8.5, 8.5 Hz, 1H, phenyl H-5), 7.81 (d, J = 8.5 Hz, 1H, phenyl H-6), 7.95 (d, J = 8.5 Hz, 1H, phenyl H-4), 8.14 (s, 1H, phenyl H-2), 8.66 (br d, J = 5.6 Hz, 2H, pyridyl H-2, H-6). Anal. Calcd for $C_{14}H_{11}NO_2S{\cdot}1/2H_2O$: C, 63.15; H, 4.51; N, 5.26. Found: C, 63.12; H, 4.75; N, 4.91.

6.31. 1-(4-Methanesulfonylphenyl)-2-(2-pyridyl)acetylene (30)

Yield, 100%; pale green needle shaped crystals; mp 167–169 °C; IR (film): 2226 (C≡C), 1590, 1466 (Ar), 1307 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.08 (s, 3H, SO_2Me), 7.34 (dd, J = 8.5, 4.8 Hz, 1H, pyridyl H-5), 7.56 (d, J = 8.5 Hz, 1H, pyridyl H-3), 7.74 (dd, J = 8.5, 8.5 Hz, 1H, pyridyl H-4), 7.78 (d, J = 8.5 Hz, 2H, phenyl H-2, H-6), 7.95 (d, J = 8.5 Hz, 2H, phenyl H-3, H-5), 8.66 (br d, J = 4.8 Hz, 1H, pyridyl H-6). Anal. Calcd for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44. Found: C, 65.27; H, 4.68; N, 5.58.

6.32. 1-(4-Methanesulfonylphenyl)-2-(3-pyridyl)acetylene (31)

Yield, 76%; pale yellow solid; mp 142–144 °C; IR (film): 2222 (C≡C), 1582, 1475 (Ar), 1310 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.09 (s, 3H, SO_2Me), 7.38 (dd, J = 8.5, 4.8 Hz, 1H, pyridyl H-5), 7.73 (d, J = 8.5 Hz, 2H, phenyl H-2, H-6), 7.90 (dd, J = 8.5, 1.8 Hz, 1H, pyridyl H-4), 7.96 (d, J = 8.5 Hz, 2H, phenyl H-3, H-5), 8.62 (d, J = 4.8 Hz, 1H, pyridyl H-6), 8.80 (s, 1H, pyridyl H-2). Anal. Calcd for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44. Found: C, 65.43; H, 4.44; N, 5.52.

6.33. 1-(4-Methanesulfonylphenyl)-2-(3-methyl-2-pyridyl)acetylene (32)

Yield, 72%; white solid; mp 152–154 °C; IR (film): 2220 (C≡C), 1595, 1478 (Ar), 1311 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H, pyridyl C-3 *Me*), 3.08 (s, 3H, SO_2Me), 7.24 (dd, J = 8.5, 4.8 Hz, 1H, pyridyl H-5), 7.61 (d, J = 8.5 Hz, 1H, pyridyl H-4), 7.79 (d, J = 8.6 Hz, 2H, phenyl H-2, H-6), 7.95 (d, J = 8.6 Hz, 2H, phenyl H-3, H-5), 8.49 (d, J = 4.8 Hz, 1H, pyridyl H-6). $C_{15}H_{13}NO_2S{\cdot}1/4\ H_2O$: C, 65.31; H, 4.89; N, 5.08. Found: C, 65.71; H, 4.99; N, 5.21.

7. In vitro cyclooxygenase (COX) inhibition assays

The ability of the test compounds listed in Table 2 to inhibit ovine COX-1 and COX-2 (IC_{50} value, μM) was determined using an enzyme immuno assay (EIA) kit (Catalog No. 560101, Cayman Chemical, Ann Arbor, MI, USA) according to a previously reported method.[19]

8. In vivo anti-inflammatory assay

The test compounds **22**, **27**, and **31** and the reference drugs aspirin and celecoxib were evaluated using the in vivo carrageenan-induced foot paw edema model reported previously.[20]

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