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Design, synthesis, and biological evaluation of 1,3-diarylprop-2-en-1-ones: A novel class of cyclooxygenase-2 inhibitors

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Abstract—A group of regioisomeric (*E*)-1,3-diarylprop-2-en-1-one derivatives possessing a COX-2 SO_2Me pharmacophore at the *para* position of the C-1 or C-3 phenyl ring, in conjunction with a C-3 or C-1 phenyl (4-H) or substituted-phenyl ring (4-F, 4-OMe, and 4-Me), were designed for evaluation as selective cyclooxygenase-2 (COX-2) inhibitors. These target (*E*)-1,3-diarylprop-2-en-1-ones were synthesized via a Claisen–Schmidt condensation reaction. In vitro COX-1/COX-2 isozyme inhibition structure–activity studies identified (*E*)-1-(4-methanesulfonylphenyl)-3-(4-methylphenyl)prop-2-en-1-one (**9f**) as a potent COX-2 inhibitor (IC_{50} = 0.3 μM) with a high COX-2 selectivity index (SI = 106) comparable to that of the reference drug rofecoxib (COX-2 IC_{50} = 0.5 μM; COX-2 SI > 200). A molecular modeling study where **9f** was docked in the binding site of COX-2 showed that the *para*-SO_2Me substituent on the C-1 phenyl ring is oriented in the vicinity of the secondary COX-2 binding site near Val523. The structure–activity data acquired indicate that the propenone moiety constitutes a suitable scaffold to design novel acyclic 1,3-diarylprop-2-en-1-ones with selective COX-2 inhibitory activity.

1. Introduction

Selective cyclooxygenase-2 (COX-2) inhibitors frequently belong to a class of diarylheterocycles that possess vicinal diaryl moieties attached to a central heterocyclic ring scaffold in conjunction with a COX-2 pharmacophore such as a *para*-SO_2NH_2, or a *para*-SO_2Me, substituent on one of the phenyl rings.[1] Compounds possessing an acyclic *trans*-stilbenoid system have also been identified that exhibit COX inhibitory activity. Thus, resveratrol (**1**) is a naturally occurring *trans*-olefin that displays COX-1 selectivity (see structures **1**–**6** in Fig. 1).[2] In contrast, compounds possessing a *trans*-stilbene template such as the 4-methoxystilbene analogs (**2**) inhibit COX-2 mediated production of prostaglandins (PGE_2).[3] In recent studies, we showed that the acyclic triaryl olefin (**3**),[4] the 1,1,2-triaryl (*Z*)-olefin (**4**),[5] the 1,2-diaryl (*E*)-olefin (**5**),[6] and the 1,3-diphenylprop-2-yn-1-one (**6**)[7] exhibit not only potent, but also highly selective, COX-2 inhibitory activity. As part of our ongoing program to design new types of acyclic selective COX-2 inhibitors, we now report the synthesis, some structure–activity relationships, and a molecular modeling study for a group of 1,3-diarylprop-2-en-1-one regioisomers possessing a COX-2 SO_2Me pharmacophore at the *para*-position of one phenyl ring in conjunction with a substituent (H, Me, F, and OMe) at the *para*-position of the other phenyl ring.

2. Chemistry

The two sets of 1,3-diarylprop-2-en-1-one regioisomers in which the 4-methanesulfonylphenyl substituent is attached to C-3 (**9a**–**d**), or to C-1 (**9e**–**h**), were synthesized in 80–90% yield using a one-pot Claisen–Schmidt sodium hydroxide catalyzed condensation[8] of an acetophenone (**7a**–**e**) with a benzaldehyde (**8a**–**e**) using the procedure illustrated in Scheme 1. ^1H NMR spectrometry indicated that the methylsulfonyl-chalcone products (**9a**–**h**) exist as the (*E*)-stereoisomers ($J_{CH=CH}$ = 16.3–16.5 Hz range). 4-(Methanesulfonyl)acetophenone (**7e**)

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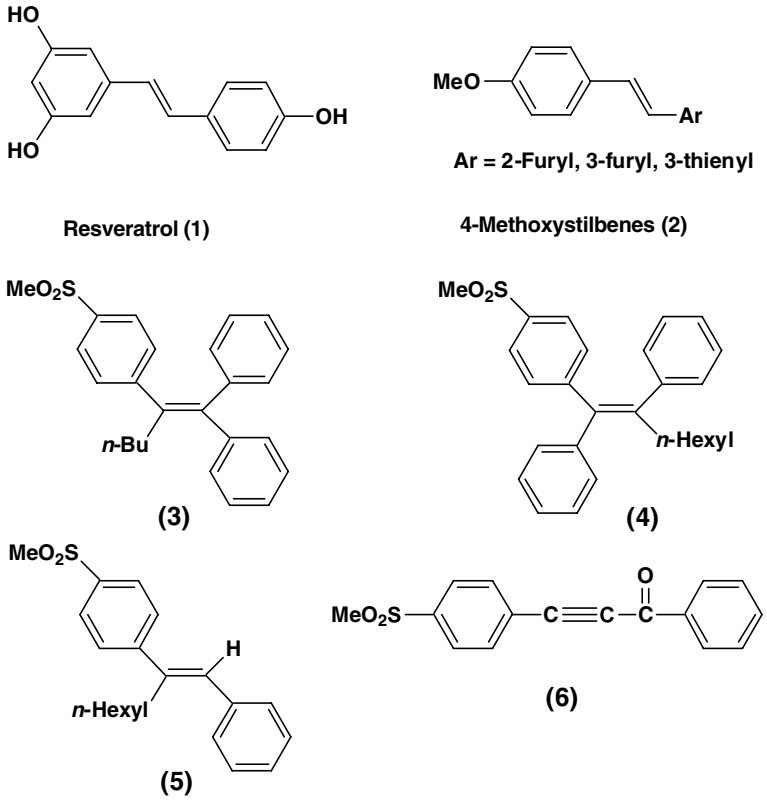
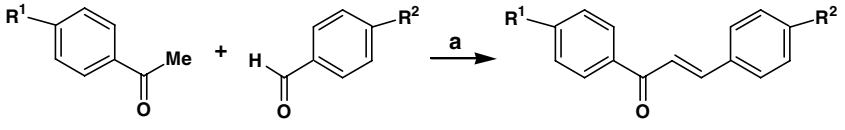


Figure 1. Some representative examples of a selective cyclooxygenase-1 (**1**) and cyclooxygenase-2 (**2**–**6**) inhibitors.



7a, R^1 = H
7b, R^1 = Me
7c, R^1 = F
7d, R^1 = OMe
7e, R^1 = SO_2Me

8a, R^2 = SO_2Me
8b, R^2 = H
8c, R^2 = Me
8d, R^2 = F
8e, R^2 = OMe

9a, R^1 = H, R^2 = SO_2Me
9b, R^1 = Me, R^2 = SO_2Me
9c, R^1 = F, R^2 = SO_2Me
9d, R^1 = OMe, R^2 = SO_2Me
9e, R^1 = SO_2Me, R^2 = H
9f, R^1 = SO_2Me, R^2 = Me
9g, R^1 = SO_2Me, R^2 = F
9h, R^1 = SO_2Me, R^2 = OMe

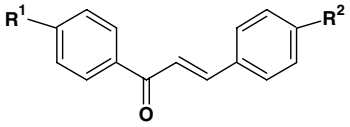
Scheme 1. Reagents and conditions: (a) NaOH, MeOH, 25 °C, 1–2 h.

was prepared according to a literature procedure by Friedel–Crafts acylation of thioanisole and then oxidation of the thiomethyl substituent to a methanesulfonyl substituent using Oxone®.[9]

3. Results and discussion

A group of (*E*)-1,3-diarylprop-2-en-1-ones having a $MeSO_2$ group at the *para*-position of the C-3 phenyl ring containing a variety of substituents (H, Me, F, and OMe) at the *para*-position of the C-1 phenyl ring (**9a**–**d**), and the corresponding regioisomers (**9e**–**h**), were synthesized to investigate the effect of these substituents on COX-2 selectivity and potency. SAR data (IC_{50} μM 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 and the nature of the *para*-substituents on the C-1 or C-3 phenyl ring were either individual, or collective, determinants of COX-2 inhibitory potency and selectivity. In vitro COX-1/COX-2 inhibition studies showed that compounds having a $MeSO_2$ group at the *para*-position of the C-1 phenyl ring (**9e**–**h**) were more selective COX-2 inhibitors compared to their corresponding regioisomers (**9a**–**d**). These results also showed that incorporation of a methyl (Me) substituent at the *para*-position of the C-1 or C-3 phenyl ring

Table 1. In vitro COX-1 and COX-2 enzyme inhibition data for compounds **9a**–**h**



Compound	R^1	R^2	IC_{50} (μM)[a]		COX-2 SI[b]
			COX-1	COX-2	
9a	H	SO_2Me	1.1	0.8	1.4
9b	Me	SO_2Me	1.0	0.3	3.3
9c	F	SO_2Me	4.2	10.0	0.4
9d	OMe	SO_2Me	3.2	4.9	0.6
9e	SO_2Me	H	21.5	1.0	21.5
9f	SO_2Me	Me	32.0	0.3	106
9g	SO_2Me	F	31.6	0.6	52
9h	SO_2Me	OMe	3.3	3.2	1.0
Rofecoxib			>100	0.5	>200

[a] Values are mean values of two determinations acquired using an ovine COX-1/COX-2 assay kit, where 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}).

provided the equipotent regioisomers **9b** and **f** that were more potent COX-2 inhibitors (COX-2 IC_{50} = 0.3 μM) than the reference drug rofecoxib (IC_{50} = 0.5 μM; see data in Table 1). Moreover, these compounds showed moderate (**9b**, SI = 3.3) to good (**9f**, SI = 106) COX-2 selectivity. In contrast, an introduction of a methoxy (MeO) group at the *para*-position of C-1 phenyl (**9d**) and C-3 phenyl (**9h**) resulted in an approximately equipotent inhibition of both COX-1 (**9d**, IC_{50} = 3.2 μM; **9h**, IC_{50} = 3.3 μM) and COX-2 (**9d**, IC_{50} = 4.9 μM; **9h**, IC_{50} = 3.2 μM). On the other hand, compound **9g** possessing a *para*-fluoro (F) substituent on the C-3 phenyl ring showed high COX-2 inhibitory activity (IC_{50} = 0.6 μM) with a respectable COX-2 selectivity index of 52. In contrast, the C-1 4-fluorophenyl regioisomers **9c** was a more potent and selective COX-1 inhibitor. Although the two regioisomers having an unsubstituted C-1 phenyl (**9a**), or C-3 phenyl (**9e**), ring were approximately equipotent inhibitors of COX-2, the (*E*)-1-(4-methanesulfonylphenyl)-3-phenylprop-2-en-1-one regioisomer (**9e**) was a more selective COX-2 inhibitor (SI = 21.5). The structure–activity data acquired suggest that (*E*)-1-(4-methanesulfonylphenyl)-3-(4-methylphenyl)prop-2-en-1-one (**9f**), which showed the optimal combination of COX-2 inhibitory potency and selectivity, should inhibit the synthesis of inflammatory prostaglandins via the cyclooxygenase pathway at sites of induced inflammation and be devoid of ulcerogenicity due to its reduced level of COX-1 inhibition.

A molecular modeling study of the most selective COX-2 inhibitor compound **9f** [(*E*)-1-(4-methanesulfonylphenyl)-3-(4-methylphenyl)prop-2-en-1-one] docked in the COX-2 active site (Fig. 2) shows that it binds in the primary binding site such that the *para*-SO_2Me substituent

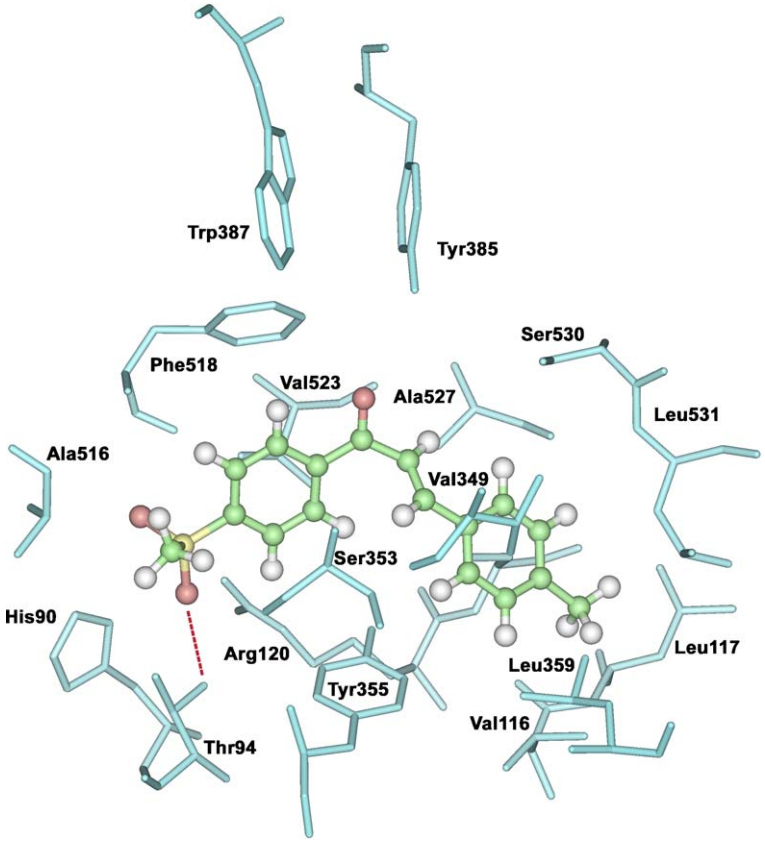


Figure 2. (*E*)-1-(4-Methanesulfonylphenyl)-3-(4-methylphenyl)prop-2-en-1-one (**9f**) (ball and stick) docked in the active site of murine COX-2. Hydrogen atoms of the amino acid residues have been removed to improve clarity.

on the C-1 phenyl ring is oriented in the vicinity of the secondary pocket present in COX-2 (Phe518, Ala516, Val523, His90, Ser353, and Thr94). One of the *O*-atoms of the SO_2Me moiety forms a *H*-bond with the O*H* of Thr94 (distance = 1.79 Å), whereas the other *O*-atom is closer to the NH_2 of Arg120 (distance = 2.42 Å). The methyl group of the SO_2Me moiety undergoes a van der Waals interaction with the side chain of Ala516 (distance = 3.79 Å). Interestingly, the C=*O* of the central α,β-unsaturated-carbonyl moiety is oriented toward the apex of the COX-2 binding site where it participates in a weak hydrogen bonding interaction with the O*H* of Tyr385 (distance = 3.78 Å). The trans stereochemistry about the C=C olefinic bond positions the C-1 4-tolyl substituent in a hydrophobic pocket comprised of Val116, Leu117, Ser121, Val349, Leu359, and Leu531 within the COX-2 active site. The methyl group of the 4-tolyl substitutent is located within van der Waals contact range of Leu117, Leu359, and Leu531 (distance < 5 Å). This computational study shows that the stereochemical disposition of substituted aryl rings about the C=C bond controls the optimal protein–ligand binding interactions in the active site of COX-2. The COX-2 isozyme has an additional secondary pocket, which is absent in the COX-1 isozyme, that is formed by a conformational change at Tyr355 due to the presence of Ile523 in COX-1 relative to Val523 having a smaller side chain in COX-2.[10] The SO_2Me pharmacophore in selective COX-2 inhibitors induces COX-2 selectivity by insertion into the secondary pocket of COX-2.[1] Accordingly, **9f** is a selective COX-2 inhibitor since the COX-1 isozyme does not have a secondary pocket into which the $MeSO_2$ pharmacophore present in **9f** can insert. These observations together with experimental results provide a good explanation for the potent and selective inhibitory activity exhibited by **9f**.

4. Conclusions

A new class of linear (*E*)-1,3-diarylprop-2-ene-1-ones, that are readily accessible via a simple one-step Claisen–Schmidt reaction, was designed for evaluation as COX-2 inhibitors. In vitro enzyme inhibition structure–activity studies indicated that: (i) the propenone moiety present in a 1,3-diarylprop-2-en-1-one structure is a suitable scaffold (template) to design COX-2 inhibitors and (ii) (*E*)-1-(4-methanesulfonylphenyl)-3-(4-methylphenyl)prop-2-en-1-one (**9f**) is not only a potent, but also a selective, COX-2 inhibitor.

5. Experimental section

All chemicals and solvents used in this study were purchased from Merck AG and Aldrich Chemical. Melting points were determined with a Thomas–Hoover capillary apparatus. Infrared spectra were acquired using a Perkin Elmer Model 550 SE spectrometer. A Bruker AM-300 NMR spectrometer was used to acquire ^{1}H NMR spectra with TMS as internal standard. Coupling constant (*J*) values are estimated in hertz (Hz) and spin multiples are given as s (singlet), d (double), t (triplet), q (quartet), m (multiplet), and br (broad). Low-resolution mass spectra were acquired with an MAT CH5/DF (Finnigan) mass spectrometer that was coupled online to a Data General DS 50 data system. Electron-impact ionization was performed at an ionizing energy of 70 eV with a source temperature of 250 °C. Elemental microanalyses, determined for C and H, were within ±0.4% of theoretical values.

6. General procedure for the synthesis of (*E*)-1,3-diarylprop-2-en-1-ones (9a–h)

A 4-substituted acetophenone (one of **7a**–**e**, 1 mmol) and a 4-substituted benzaldehyde (one of **8a**–**e**, 1 mmol) were dissolved in a minimum volume of methanol (3–5 mL), a single NaOH pellet (about 100 mg) was then added to this solution, and the reaction mixture was stirred at 25 °C. In most cases, an off-white to pale yellow solid was formed within a few minutes but the reaction was allowed to proceed for 2 h. The solid product **9** was collected on a filter, washed with cold methanol, and the product was recrystallized from EtOAc/hexane (3:7, v/v).

6.1. (*E*)-3-(4-Methanesulfonylphenyl)-1-phenylprop-2-en-1-one (9a)

Yield, 81%; white crystals; mp 110–111 °C; IR (KBr disk): 1680 (C=O), 1630, 1580, 1460 (Ar), 1300, 1150 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.10 (s, 3H, SO_2CH_3), 7.28–7.40 (m, 3H, phenyl H_3, H_4, H_5), 7.51–7.59 (m, 2H, phenyl H_2, H_6), 7.68 (d, *J* = 16.5 Hz, 1H, COC*H*=CH), 7.77 (d, *J* = 16.5 Hz, 1H, COCH=C*H*), 7.96 (d, *J* = 8.7 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 8.05 (d, *J* = 8.7 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5); MS: *m*/*z* (%) 286.1 (M^+, 20), 207.2 (40), 182 (25), 105 (100), 77 (75). Anal. Calcd for $C_{16}H_{14}O_3S$: C, 67.11; H, 4.93. Found: C, 66.80; H, 5.11.

6.2. (*E*)-3-(4-Methanesulfonylphenyl)-1-(4-methylpheyl)prop-2-en-1-one (9b)

Yield, 88%; white crystals; mp 174–176 °C; IR (KBr disk): 1680 (C=O), 1640, 1570, 1460 (Ar), 1300, 1150 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H, CH_3), 3.10 (s, 3H, SO_2CH_3), 7.33 (d, 2H, *J* = 7.6 Hz, 4-methylphenyl H-3, H-5), 7.60 (d, 2H, *J* = 7.6 Hz, 4-methylphenyl H-2, H-6), 7.70 (d, *J* = 16.4 Hz, 1H, COC*H*=CH), 7.78 (d, *J* = 16.4 Hz, 1H, COCH=C*H*), 8.00 (d, *J* = 8.7 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 8.10 (d, *J* = 8.7 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5); MS: *m*/*z* (%) 300.1 (M^+, 60), 285.1 (100), 272.0 (45), 220.2 (100), 178 (50), 119 (60), 91 (45). Anal. Calcd for $C_{17}H_{16}O_3S$: C, 67.98; H, 5.37. Found: C, 67.65; H, 5.05.

6.3. (*E*)-1-(4-Fluorophenyl)-3-(4-methanesulfonylphenyl)prop-2-en-1-one (9c)

Yield, 82%; white crystals; mp 152–153 °C; IR (KBr disk): 1670 (C=O), 1630, 1580, 1470 (Ar), 1300, 1150 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.10 (s, 3H, SO_2CH_3), 7.15 (d, *J* = 16.4 Hz, 1H, COC*H*=CH), 7.30 (d, *J* = 16.4 Hz, 1H, CO*C*H=C*H*), 7.70 (d, *J* = 8.8 Hz,

2H, 4-fluorophenyl H-2, H-6), 7.90 (dd, J_{HH} = 8.9 Hz, J_{HF} = 5.5 Hz, 2H, 4-fluorophenyl H-3, H-5), 8.00 (d, J = 8.6 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 8.10 (d, J = 8.6 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5); MS: *m/z* (%) 304.1 (M^+, 75), 289.1 (55), 225.0 (80), 196.1 (75), 123.0 (95), 95.1 (100), 75.1 (70). Anal. Calcd for $C_{16}H_{13}FO_3S$: C, 63.14; H, 4.31. Found: C, 63.45; H, 4.64.

6.4. (*E*)-3-(4-Methanesulfonylphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (9d)

Yield, 81%; white crystals; mp 159–160 °C; IR (KBr disk): 1680 (C=O), 1640, 1550, 1490 (Ar), 1300, 1150 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.10 (s, 3H, SO_2CH_3), δ 3.90 (s, 3H, OCH_3), 6.95 (d, J = 16.3 Hz, 1H, COC*H*=CH), 7.05 (d, J = 16.3 Hz, 1H, COCH=C*H*), 7.15 (d, J = 7.6 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.40 (d, J = 7.6 Hz, 2H, 4-methoxyphenyl H-2, H-6), 7.90 (d, J = 8.6 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 8.05 (d, J = 8.6 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5); MS: *m/z* (%) 316.2 (M^+, 80), 236.2 (45), 165.2 (40), 135.1 (100), 107.1 (40), 92.1 (55), 77.1 (85). Anal. Calcd for $C_{17}H_{16}O_4S$: C, 64.54; H, 5.10. Found: C, 64.85; H, 5.25.

6.5. (*E*)-1-(4-Methanesulfonylphenyl)-3-phenylprop-2-en-1-one (9e)

Yield, 80%; white crystals; mp 127–128 °C; IR (KBr disk): 1690 (C=O), 1630, 1580, 1470 (Ar), 1300, 1150 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.05 (s, 3H, SO_2CH_3), 7.25–7.36 (m, 3H, phenyl H-3, H-4, H-5), 7.45–7.60 (m, 2H, phenyl H-2, H-6), 7.65 (d, J = 16.5 Hz, 1H, COC*H*=CH), 7.80 (d, J = 16.5 Hz, 1H, COCH=C*H*), 7.99 (d, J = 8.6 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 8.17 (d, J = 8.6 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5); MS: *m/z* (%) 286.1 (M^+, 55), 207.2 (90), 196.2 (75), 145.1 (75), 102 (70), 91.2 (70), 76.1 (50). Anal. Calcd for $C_{16}H_{14}O_3S$: C, 67.11; H, 4.93. Found: C, 66.76; H, 5.27.

6.6. (*E*)-1-(4-Methanesulfonylphenyl)-3-(4-methylphenyl)prop-2-en-1-one (9f)

Yield, 79%; pale yellow crystals; mp 170 °C; IR (KBr disk): 1660 (C=O), 1630, 1580, 1460 (Ar), 1300, 1150 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H, CH_3), 3.10 (s, 3H, SO_2CH_3), 7.23 (d, J = 16.4 Hz, 1H, COC*H*=CH), 7.39 (d, J = 7.6 Hz, 2H, 4-methylphenyl H-3, H-5), 7.55 (d, J = 16.4 Hz, 1H, COCH=C*H*), 7.61 (d, J = 7.6 Hz, 2H, 4-methylphenyl H-2, H-6), 8.05 (d, J = 8.7 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 8.15 (d, J = 8.7 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5); MS: *m/z* (%) 300.1 (M^+, 50), 285.2 (100), 221.2 (65), 178.2 (50), 145.1 (85), 115.1 (90), 91.2 (73), 76.1 (48). Anal. Calcd for $C_{17}H_{16}O_3S$: C, 67.98; H, 5.37. Found: C, 68.25; H, 5.60.

6.7. (*E*)-3-(4-Fluorophenyl)-1-(4-methanesulfonyl phenyl)prop-2-en-1-one (9g)

Yield, 81%; white crystals; mp 201–202 °C; IR (KBr disk): 1670 (C=O), 1650, 1580, 1470 (Ar), 1300, 1150 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.10 (s, 3H, SO_2CH_3), 7.10 (d, J = 16.4 Hz, 1H, COC*H*=CH), 7.25 (d, J = 16.4 Hz, 1H, COCH=C*H*), 7.60 (d, J = 8.8 Hz, 2H, 4-fluorophenyl H-2, H-6), 7.75 (dd, J_{HH} = 8.7 Hz, J_{HF} = 5.4 Hz, 2H, 4-fluorophenyl H-3, H-5), 8.05 (d, J = 8.6 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 8.15 (d, J = 8.6 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5); MS: *m/z* (%) 304.1 (M^+, 85), 225.1 (95), 196.2 (80), 149.1 (100), 121.1 (95), 101.1 (90), 75.1 (75). Anal. Calcd for $C_{16}H_{13}FO_3S$: C, 63.14; H, 4.31. Found: C, 63.50; H, 4.70.

6.8. (*E*)-1-(4-Methanesulfonylphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (9h)

Yield, 79%; white crystals; mp 165–166 °C; IR (KBr disk): 1670 (C=O), 1630, 1560, 1480 (Ar), 1300, 1150 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.10 (s, 3H, SO_2CH_3), 3.85 (s, 3H, OCH_3), 7.05 (d, J = 16.4 Hz, 1H, COC*H*=CH), 7.15 (d, J = 16.4 Hz, 1H, COCH=C*H*), 7.25 (d, J = 7.7 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.45 (d, J = 7.7 Hz, 2H, 4-methoxylphenyl H-2, H-6), 7.95 (d, J = 8.6 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 8.10 (d, J = 8.6 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5); MS: *m/z* (%) 316.2 (M^+, 75), 236.2 (55), 165.2 (45), 135.1 (85), 107.1 (45), 92.1 (70), 77.1 (100). Anal. Calcd for $C_{17}H_{16}O_4S$: C, 64.54; H, 5.10. Found: C, 64.80; H, 5.40.

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.[11]

8. In vitro cyclooxygenase (COX) inhibition assay

The ability of the test compounds listed **9a**–**h** in Table 1 to inhibit ovine COX-1 and COX-2 (IC_{50} value, μM) was determined using an enzyme immunoassay (EIA) kit (Catalog No. 560101, Cayman Chemical, Ann Arbor, MI, USA) according to our previously reported method.[12]

Acknowledgment

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