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Bioorganic & Medicinal Chemistry 14 (2006) 7044–7050
Bioorganic & Medicinal Chemistry

Synthesis and biological evaluation of 1,3-diphenylprop-2-en-1-ones possessing a methanesulfonamido or an azido pharmacophore as cyclooxygenase-1/-2 inhibitors

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Received 19 April 2006; revised 7 June 2006; accepted 8 June 2006
Available online 22 June 2006

Abstract—A group of (*E*)-1,3-diphenylprop-2-en-1-one derivatives (chalcones) possessing a $MeSO_2NH$, or N_3, COX-2 pharmacophore at the *para*-position of the C-1 phenyl ring were synthesized using a facile stereoselective Claisen–Schmidt condensation reaction. In vitro COX-1/COX-2 structure–activity relationships were determined by varying the substituents on the C-3 phenyl ring (4-H, 4-Me, 4-F, and 4-OMe). Among the 1,3-diphenylprop-2-en-1-ones possessing a C-1 *para*-$MeSO_2NH$ COX-2 pharmacophore, (*E*)-1-(4-methanesulfonamidophenyl)-3-(4-methylphenyl)prop-2-en-1-one (**7b**) was identified as a selective COX-2 inhibitor (COX-2 IC_{50} = 1.0 μM; selectivity index >100) that was less potent than the reference drug rofecoxib (COX-2 IC_{50} = 0.50 μM; SI > 200). The corresponding 1,3-diphenylprop-2-en-1-one analogue possessing a C-1 *para*-N_3 COX-2 pharmacophore, (*E*)-1-(4-azidophenyl)-3-(4-methylphenyl)prop-2-en-1-one (**7f**), exhibited potent and selective COX-2 inhibition (COX-1 IC_{50} = 22.2 μM; COX-2 IC_{50} = 0.3 μM; SI = 60). A molecular modeling study where **7b** and **7f** were docked in the binding site of COX-2 showed that the *p*-$MeSO_2NH$ and N_3 substituents on the C-1 phenyl ring are oriented in the vicinity of the COX-2 secondary pocket (His90, Arg513, Phe518, and Val523). The structure–activity data acquired indicate that the propenone moiety constitutes a suitable scaffold to design new acyclic 1,3-diphenylprop-2-en-1-ones with selective COX-1 or COX-2 inhibitory activity.

1. Introduction

The clinical use of traditional nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and indomethacin for the treatment of inflammation and pain is often accompanied by adverse gastrointestinal effects. Their anti-inflammatory activity is due to inhibition of cyclooxygenases (COXs), which catalyze the bioconversion of arachidonic acid to inflammatory prostaglandins (PGs).[1,2] PGs that are produced via the inducible COX-2 isozyme are responsible for inflammation, pain, and fever, whereas the constitutively expressed COX-1 isozyme produces PGs that exhibit beneficial cytoprotective properties.[3] The initial euphoria surrounding the launch of selective cyclooxygenase-2 (COX-2) inhibitors that exhibited reduced gastrointestinal toxicity in the late 1990s[4,5] proved to be short lived. The recent withdrawal of diarylheterocyclic selective COX-2 inhibitors such as rofecoxib and valdecoxib due to their adverse cardiovascular side effects[6,7] clearly delineates the need to explore and evaluate new structural ring templates (scaffolds) possessing COX inhibitory activity.

Recently, we reported several investigations describing the design, synthesis, and anti-inflammatory properties for a novel class of compounds possessing an acyclic triaryl/diaryl olefin structural template.[8–11] For example, the acyclic 1-alkyl-1,2-diaryl (*E*)-olefin (see structure **1** in Fig. 1)[11] possessing a *trans*-stilbenoid structure with a 4-methylsulfonylphenyl COX-2 pharmacophore at the C-1 position exhibited selective cyclooxygenase-2 (COX-2) inhibition, whereas the triphenyl acyclic olefin (**2**) possessing either a methanesulfonamido ($MeSO_2NH$) or a linear azido (N_3) pharmacophore at

Keywords: Cyclooxygenase inhibition; Propenone moiety; Azido pharmacophore.
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doi:10.1016/j.bmc.2006.06.022

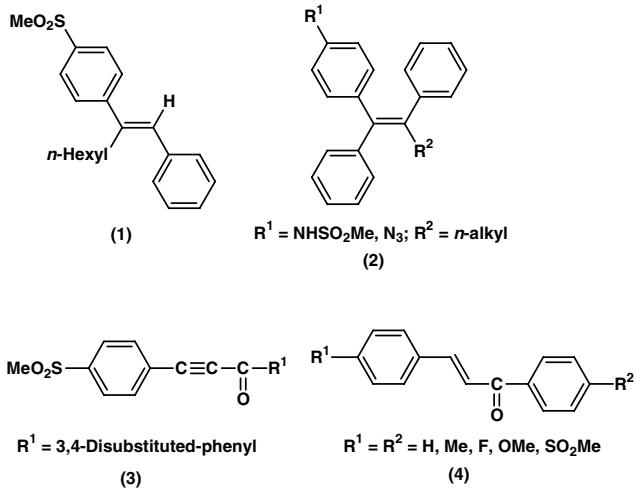


Figure 1. Some representative examples of novel acyclic structural templates (scaffolds) that exhibit cyclooxygenase-1/2 inhibition.

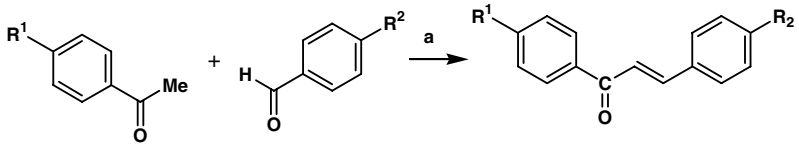
the *para*-position of one of the phenyl rings showed selective COX-2 inhibition with good in vivo anti-inflammatory activities.[9] In addition, 1,3-diphenylprop-2-yn-1-ones (**3**) possessing a central propynone moiety display potent COX inhibition.[12] It was also reported that 1,3-diphenylprop-2-en-1-one regioisomers (**4**) possessing a SO_2Me COX-2 pharmacophore at the *para*-position of one of the phenyl rings constitute a suitable template to design a new class of COX inhibitors.[13] Some structurally related chalcones to treat inflammation have been described.[14,15] Accordingly, we now describe the synthesis and biological evaluation of a group of acyclic 1,3-diphenylprop-2-en-1-ones (**7a**–**h**) possessing either a C-1 *para*-methanesulfonamido ($MeSO_2NH$), or a linear azido (N_3), COX-2 pharmacophore in conjunction with various substituents (H, Me, F, and OMe) at the *para*-position of the C-3 phenyl ring.

2. Chemistry

A one-step Claisen–Schmidt condensation was used to prepare the target 1,3-diphenylprop-2-en-1-ones in which a methanesulfonamido, or an azido, substituent was attached to the C-1 phenyl ring (**7a**–**h**).[13] The sodium hydroxide catalyzed condensation of an acetophenone (**5a**–**b**) with a *para*-substituted-benzaldehyde (**6a**–**d**) afforded the 1,3-diphenylprop-2-en-1-ones (**7a**–**h**) in moderate to high yield (45–80%) as illustrated in Scheme 1. The acetophenone precursor **5a** was prepared by treating 4-aminoacetophenone with methanesulfonyl chloride according to a previously reported procedure.[16] Diazotization of 4-aminoacetophenone with sodium nitrite, followed by reaction of the diazonium salt with sodium azide according to a previously reported method,[17] afforded the *para*-azido substituted acetophenone (**5b**). ^1H NMR spectrometry indicated that the chalcone products **7a**–**h** exist as the (*E*)-stereoisomers ($J_{CH=CH}$ = 15.4–15.6 Hz range).

3. Results and discussion

A group of 1,3-diphenylprop-2-en-1-ones (**7a**–**h**), possessing either a *para*-methanesulfonamido ($MeSO_2NH$), or an azido (N_3), substituent on the C-1 phenyl ring, were synthesized. In this study, the substituents on the C-3 phenyl ring were simultaneously varied (H, Me, F, and OMe) to determine the combined effects of steric and electronic substituent properties upon COX-1 and COX-2 inhibitory potency and 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 COX inhibition was sensitive to the nature of both the C-1 and C-3 phenyl substituents. Our recent studies for a class of acyclic triphenyl olefins have shown that potent and selective COX-2 inhibition can be obtained by replacing the traditional *p*-SO_2Me COX-2 pharmacophore with a *p*-$MeSO_2NH$ bioisostere.[9] Accordingly, among the subgroup of 1,3-diphenylprop-2-en-1-enes **7a**–**d** possessing a C-1 *p*-$MeSO_2NH$ COX-2 pharmacophore, compound **7a** possessing an unsubstituted C-3 phenyl ring exhibited equipotent and nonselective inhibition of the COX isozymes (COX-2 IC_{50} = 3.0 μM; COX-1 IC_{50} = 3.2 μM) as shown in Table 1. However, the introduction of a C-3 *p*-Me substituent gave compound **7b** that exhibited good COX-2 inhibitory potency (COX-2 IC_{50} = 1.0 μM; COX-1 IC_{50} > 100 μM) and selectivity (COX-2



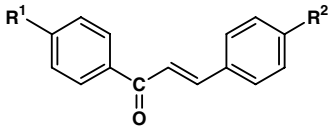
5a, $R^1 = NHSO_2Me$
5b, $R^1 = N_3$

6a. R^2 = H
6b, R^2 = Me
6c, R^2 = F
6d, R^2 = OMe

7a, $R^1 = NHSO_2Me$, R^2 = H
7b, $R^1 = NHSO_2Me$, R^2 = Me
7c, $R^1 = NHSO_2Me$, R^2 = F
7d, $R^1 = NHSO_2Me$, R^2 = OMe
7e, $R^1 = N_3$, R^2 = H
7f, $R^1 = N_3$, R^2 = Me
7g, $R^1 = N_3$, R^2 = F
7h, $R^1 = N_3$, R^2 = OMe

Scheme 1. Reagents and conditions: (a) NaOH, MeOH, 25 °C, 30 min to 2 h.

Table 1. In vitro COX-1 and COX-2 enzyme inhibition assay data for 1,3-diphenylprop-2-en-1-one derivatives **7a**–**h**



Compound	R^1	R^2	IC_{50}[a] (μM)		Selectivity index (SI)[b]
			COX-1	COX-2	
7a	$NHSO_2Me$	H	3.0	3.2	0.9
7b	$NHSO_2Me$	Me	>100	1.0	>100
7c	$NHSO_2Me$	F	3.3	>100	—
7d	$NHSO_2Me$	OMe	1.0	10.0	0.1
7e	N_3	H	>100	3.4	>29
7f	N_3	Me	22.2	0.3	60
7g	N_3	F	4.2	10.0	0.4
7h	N_3	OMe	0.4	3.6	—
Rofecoxib			>100	0.5	>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}).

SI > 100). In contrast, incorporation of a C-3 *p*-fluoro substituent (**7c**, R^2 = F) resulted in a dramatic loss in COX-2 inhibition (COX-2 IC_{50} > 100 μM) with a gain in COX-1 inhibition and potency (COX-1 IC_{50} = 3.3 μM; Table 1). This loss of COX-2 inhibitory activity for the fluoro compound **7c**, relative to the methyl analog **7b**, may be due to the electronegativity of the fluoro substituent and/or its ability to participate in a H-bonding interaction. In comparison, the presence of a C-3 *p*-MeO-phenyl substituent (**7d**, R^2 = OMe) increased COX-2 inhibition (COX-2 IC_{50} = 10 μM) although **7d** was not as potent and selective as **7b**.

It has been reported that replacement of His513 in COX-1 by Arg513 in COX-2 plays a key role in the hydrogen-bond network of the COX-2 binding site. Access of ligands to the secondary pocket of COX-2 is controlled by histidine (His90), glutamine (Gln192), and tyrosine (Tyr355), and interaction of Arg513 with the bound drug is a requirement for time-dependent inhibition of COX-2.[18] Recently we exploited, for the first time, the amino acid Arg513 to design selective COX-2 inhibitors having a dipolar azide (N_3) pharmacophore that can undergo an electrostatic (ion–ion) interaction with Arg513 in the COX-2 secondary pocket.[9,19,20] Accordingly, the subgroup of 1,3-diphenylprop-2-en-1-ones possessing a C-1 *p*-azido COX-2 pharmacophore (**7e** and **7f**) exhibited good COX-2 inhibitory potency and selectivity as shown in Table 1. For example, the chalcone derivative **7e** (R^2 = H) exhibited moderate COX-2 inhibition (COX-2 IC_{50} = 3.4 μM) with no inhibition of COX-1 at 100 μM (COX-2 SI > 29). However, **7e** was a less potent inhibitor of the COX-2 isozyme compared to the reference drug rofecoxib (COX-2 IC_{50} = 0.50 μM). Introduction of a C-3 *p*-methyl substituent provided potent COX-2 inhibition since compound **7f** (R^2 = Me) was a 1.6-fold more potent inhibitor of the COX-2 isozyme (COX-2 IC_{50} = 0.30 μM) than the reference drug rofecoxib (COX-2 IC_{50} = 0.50 μM). However, **7f** showed COX-1 inhibition (COX-1 IC_{50} = 22.2 μM; COX-2 SI = 60) and was not as selective as rofecoxib (COX-1 IC_{50} > 100 μM; COX-2 SI > 200). Although **7g** (R^2 = F) exhibited both COX-1 and COX-2 isozyme inhibition, it was a 2.5-fold more potent inhibitor of COX-1. Incorporation of a C-3 *p*-OMe substituent resulted in a dramatic increase in COX-1 inhibition with compound **7h** (R^2 = OMe) exhibiting potent and selective inhibition of the COX-1 isozyme (COX-1 IC_{50} = 0.40 μM; COX-2 IC_{50} = 30.6 μM).

The binding interactions of the most potent and selective COX-2 inhibitor compounds (**7b** and **7f**) within the COX-2 binding site were investigated. The most stable enzyme–ligand complex of the potent and selective COX-2 inhibitor compound **7b** [(*E*)-1-(4-methanesulfonamidophenyl)-3-(4-methylphenyl)prop-2-en-1-one] possessing a C-1 *p*-$MeSO_2NH$ COX-2 pharmacophore within the COX-2 binding site (Fig. 2) shows that the *p*-$MeSO_2NH$-phenyl moiety is oriented toward the COX-2 secondary pocket (Val523, Phe518, Ile517, Arg513, Thr94, and His90). The methyl group of the $MeSO_2NH$ moiety is involved in a hydrophobic binding interaction with Phe518, Ile517, and Ala516 (distance <5 Å), whereas one of the *O*-atoms of the $MeSO_2$ moiety is about 4.66 Å away from N*H*$_2$ of Arg513. The distance between the *N*H of $MeSO_2NH$ and N*H*$_2$ of Arg513 is about 5.72 Å. In addition, a hydrogen bonding interaction is observed between the N*H* of $MeSO_2NH$ and N^{δ} of His90 at the entrance to the COX-2 secondary pocket (distance ≈ 2.70 Å). The C=*O* of the central α,β-unsaturated-carbonyl moiety is oriented toward the entrance to the COX-2 binding site (Tyr355 and Arg120). The distance between the C=*O* and the O*H* of Tyr355 is about 5.12 Å, whereas the distance between the C=*O* and N*H*$_2$ of Arg120 is about 6.15 Å. The *trans* C=C olefinic bond, which is surrounded by Val349, Leu352, and Ala527, positions the C-3 4-tolyl substituent toward the apex of the COX-2 binding site (Phe205, Thr206, Tyr348, Phe381, Tyr385, and Ser530). The C-3 *p*-methyl substituent is within van der Waal's contact range of Thr206, Tyr348, and Tyr385 (distance <5 Å). The distance between the centre of the C-3 phenyl ring and the *O*H of Ser530 is about 4.60 Å. A similar investigation of the selective COX-2 inhibitor compound **7f** [(*E*)-1-(4-azidophenyl)-3-(4-methylphenyl)prop-2-en-1-one] docked in the COX-2 active site (Fig. 3) shows that it binds in the primary binding site such that the *para*-azido substituent on the C-1 phenyl ring is oriented in the vicinity of the secondary pocket present in COX-2 (Val523, Phe518, Ile517, Ala516, Arg513, Ser353, Thr94, and His90). The linear dipolar azido substituent, as proposed, is involved in an ion–ion (electrostatic) interaction with Arg513. The distance between the terminal *N*-atom of the azido substituent and the N*H*$_2$ of Arg513 is about 5.71 Å, whereas the distance between the N^2-atom of the azido substituent and the N*H* of His90 is about 4.18 Å. Interestingly, the C=*O* of the central α,β-unsaturated-carbonyl moiety is oriented toward the entrance of the COX-2 binding site (Tyr355 and Arg120) similar to that observed for the methanesulfonamido derivative (**7b**). The C=*O* par-

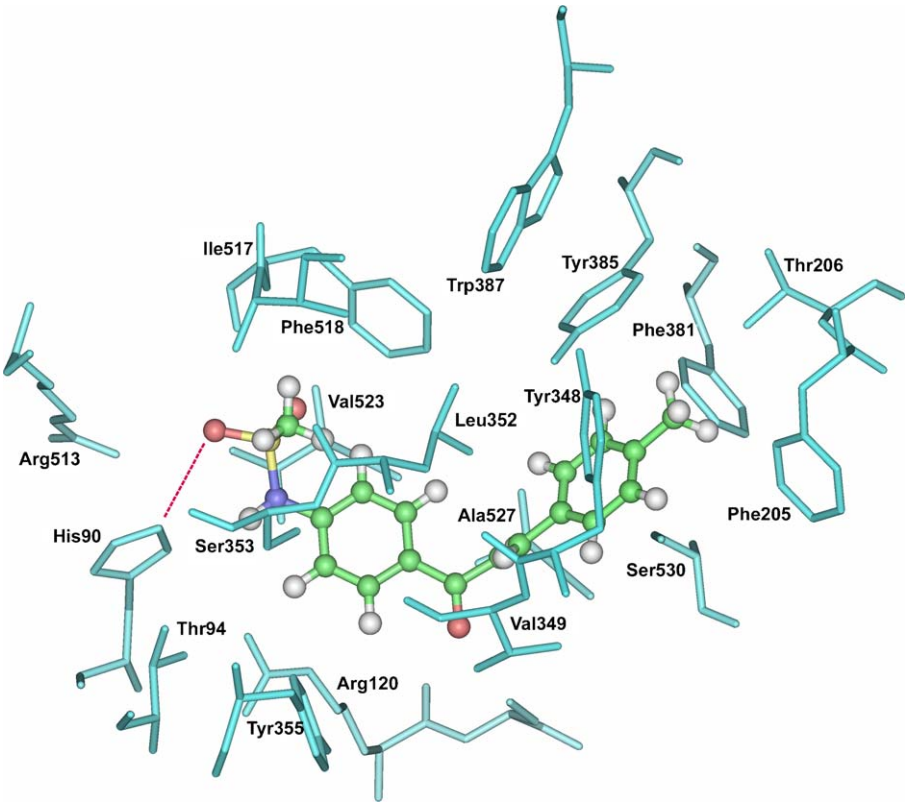


Figure 2. Docking (*E*)-1-(4-methanesulfonamidophenyl)-3-(4-methylphenyl)prop-2-en-1-one (**7b**) (ball and stick) in the active site of murine COX-2. Hydrogen atoms of the amino acid residues have been removed to improve clarity.

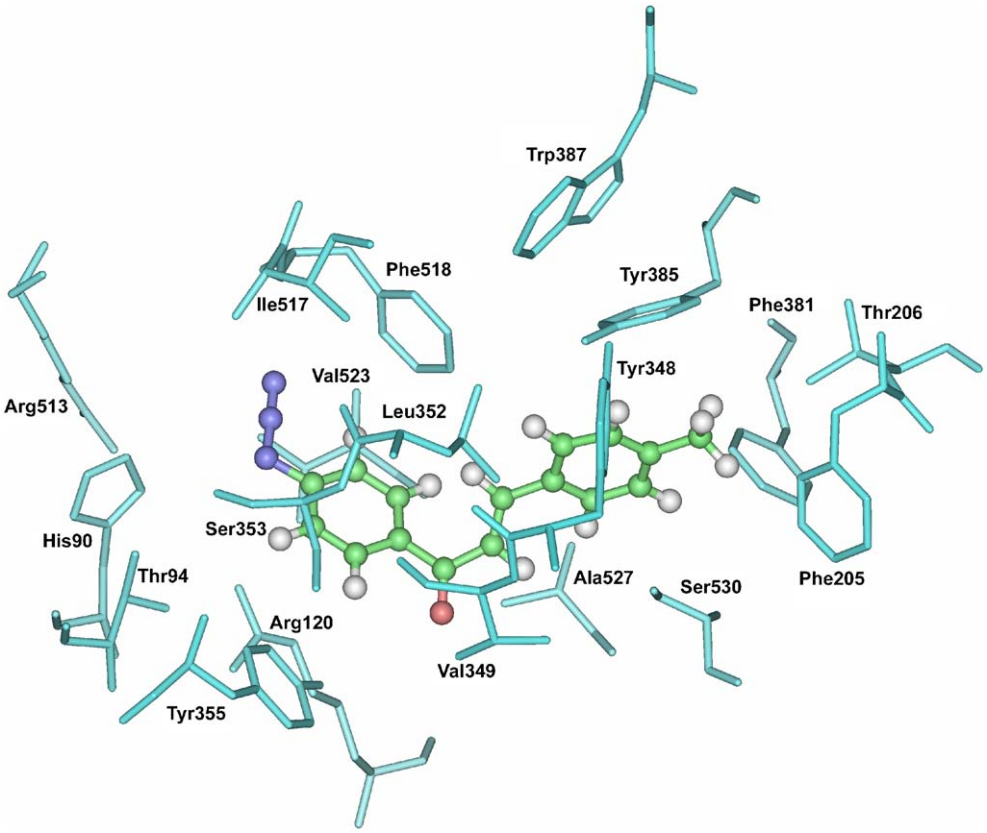


Figure 3. Docking (*E*)-1-(4-azidophenyl)-3-(4-methylphenyl)prop-2-en-1-one (**7f**) (ball and stick) in the active site of murine COX-2. Hydrogen atoms of the amino acid residues have been removed to improve clarity.

ticipates in a weak hydrogen bonding interaction with the O*H* of Tyr355 (distance ≈ 4.08 Å). The distance between the C=*O* and N*H*$_2$ of Arg120 is about 6.24 Å. The *trans* C=C olefinic bond, which is surrounded by Leu352 and Ala527, positions the C-3 4-tolyl substituent toward the apex of the COX-2 binding site (Phe205, Thr206, Tyr348, Phe381, Tyr385, and Ser530). The C-3 *p*-methyl substituent on the C-3 phenyl ring is within van der Waal's contact range of Thr206, Phe381 and Tyr385 (distance <5 Å). Accordingly, this computational study shows that the *p*-N_3 substituent present in **7f** interacts within the COX-2 secondary pocket where it acts as a suitable COX-2 pharmacophore.

4. Conclusions

This study indicates that (i) a new class of acyclic (*E*)-1,3-diphenylprop-2-en-1-ones can be prepared via a simple one-step stereoselective Claisen–Schmidt condensation, (ii) the propenone moiety is a suitable scaffold (template) to design COX-1/-2 inhibitors, (iii) in this chalcone class of compounds (**7**), the *p*-$MeSO_2NH$ and N_3 moieties proved to be suitable COX-2 pharmacophores, (iv) COX-1/-2 inhibition is sensitive to the nature of the C-3 phenyl substituents, and (v) (*E*)-1-(4-azidophenyl)-3-(4-methylphenyl)prop-2-en-1-one (**7e**) exhibited good COX-2 inhibitory potency and selectivity.

5. Experimental

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. Compounds **7e** and **7h** have been described in a previous study.[21] 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 a 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. Microanalyses, determined for C and H, were within ±0.4% of theoretical values.

6. General procedure for the synthesis of (*E*)-1,3-diphenylprop-2-en-1-ones (7a–h)

A 4-substituted-acetophenone (**5a** or **5b**, 1 mmol) and a 4-substituted-benzaldehyde (**6a**–**d**, 1 mmol) were dissolved in a minimum amount of methanol (3–5 mL). A NaOH pellet (100 mg, 2.5 mmol) was then added to this solution, and the reaction was allowed to proceed with stirring at 25 °C for a period of 30 min to 2 h prior to neutralization with 2N HCl (2–3 mL). The solid product **7** was collected on a filter, washed with cold methanol, and the product was recrystallized from ethanol. The physical and spectral data for **7a**–**h** are listed below.

6.1. (*E*)-1-(4-Methanesulfonamidophenyl)-3-phenylprop-2-en-1-one (7a)

Yield, 51%; pale yellow crystals; mp 169–170 °C; IR (KBr): 3200 (NH), 1670 (C=O), 1120, 1340 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.05 (s, 3H, SO_2CH_3), 7.25–7.36 (m, 5H, phenyl H-3, H-4, H-5 and 4-methanesulfonamidophenyl H-3, H-5), 7.45–7.60 (m, 2H, phenyl H-2, H-6), 7.71 (d, *J* = 15.6 Hz, 1H, COC*H*=CH), 7.90 (d, *J* = 15.6 Hz, 1H, COCH=C*H*), 8.14 (d, *J* = 8.0 Hz, 2H, 4-methanesulfonamidophenyl H-2, H-6), 10.36 (s, 1H, N*H*); MS: *m*/*z* (%): 301.1 (M$^+$, 20), 222.2 (20), 194.2 (25), 131 (65), 103.1 (100), 91 (40), 77.2 (65). Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.47; H, 5.25; N, 4.38.

6.2. (*E*)-1-(4-Methanesulfonamidophenyl)-3-(4-methylphenyl)prop-2-en-1-one (7b)

Yield, 45%; pale yellow crystals; mp 194–196 °C; IR (KBr): 3200 (NH), 1680 (C=O), 1120, 1320 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.49 (s, 3H, CH_3), 3.05 (s, 3H, SO_2CH_3), 7.27 (d, *J* = 8.1 Hz, 2H, 4-methylphenyl H-3, H-5), 7.32 (d, *J* = 8.0 Hz, 1H, 4-methanesulfonamidophenyl H-3, H-5), 7.65 (d, *J* = 8.1 Hz, 2H, 4-methylphenyl H-2, H-6), 7.70 (d, *J* = 15.6 Hz, 1H, COC*H*=CH), 7.80 (d, *J* = 15.6 Hz, 1H, COCH=C*H*), 8.10 (d, *J* = 8.0 Hz, 2H, 4-methanesulfonamidophenyl H-2, H-6), 10.05 (s, 1H, N*H*); MS: *m*/*z* (%): 315.1 (M$^+$, 40), 300 (85), 236 (100), 221.2 (35), 208.2 (75), 165.0 (50), 119.1 (55), 91 (95), 77.2 (30). Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.45; H, 5.32; N, 4.18.

6.3. (*E*)-3-(4-Fluorophenyl)-1-(4-methanesulfonamidophenyl)prop-2-en-1-one (7c)

Yield, 52%; pale yellow crystals; mp 192–195 °C; IR (KBr): 3240 (NH), 1680 (C=O), 1140, 1300 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.10 (s, 3H, SO_2CH_3), 7.28 (d, *J* = 8.1 Hz, 2H, 4-fluorophenyl H-2, H-6), 77.35 (d, *J* = 8.5 Hz, 1H, 4-methanesulfonamidophenyl H-3, H-5), 7.72 (d, *J* = 15.5 Hz, 1H, COC*H*=CH), 7.94 (dd, J_{HH} = 8.1 Hz, J_{HF} = 5.5 Hz, 2H, 4-fluorophenyl H-3, H-5), 7.88 (d, *J* = 15.5 Hz, 1H, COCH=C*H*), 8.15 (d, *J* = 8.5 Hz, 2H, 4-methanesulfonamidophenyl H-2, H-6), 10.35 (s, 1H, N*H*); MS: *m*/*z* (%): 319 (M$^+$, 15), 240.2 (20), 183 (10), 149.0 (65), 121.1 (60), 101.0 (100), 91.2 (45). Anal. Calcd for $C_{16}H_{14}FNO_3S$: C, 60.18; H, 4.42; N, 4.39. Found: C, 59.95; H, 4.65; N, 4.66.

6.4. (*E*)-1-(4-Methanesulfonamidophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (7d)

Yield, 44%; pale yellow crystals; mp 132–135 °C; IR (KBr): 3200 (NH), 1670 (C=O), 1120, 1300 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.12 (s, 3H, SO_2CH_3), 3.81 (s, 3H, OCH_3), 7.00 (d, *J* = 8.5 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.27 (d, *J* = 8.5 Hz, 2H, 4-methanesulfonamidophenyl H-3, H-5), 7.31 (d, *J* = 8.5 Hz, 2H,

4-methoxyphenyl H-2, H-6), 7.68 (d, J = 15.4 Hz, 1H, COC*H*=CH), 7.77 (d, J = 15.4 Hz, 1H, COCH=C*H*), 7.92 (d, J = 8.5 Hz, 2H, 4-methanesulfonamidophenyl H-2, H-6), 10.32 (s, 1H, N*H*); MS: *m*/*z* (%): 331.2 (M^+, 10), 213.2 (30), 198.1 (100), 119.2 (65), 106 (60), 91.2 (60), 77.2 (95). Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.61; H, 5.17; N, 4.23. Found: C, 61.35; H, 5.45; N, 4.55.

6.5. (*E*)-1-(4-Azidophenyl)-3-phenylprop-2-en-1-one (7e)

Yield, 72%; pale yellow crystals; mp 115–116 °C; IR (KBr): 2080 (N_3), 1670 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.13 (d, J = 8.5 Hz, 2H, 4-azidophenyl H-3, H-5), 7.42–7.44 (m, 3H, phenyl H-3, H-4, H-5), 7.52 (d, J = 15.6 Hz, 1H, COC*H*=CH), 7.64–7.66 (m, 2H, phenyl H-2, H-6), 7.82 (d, J = 15.6 Hz, 1H, COCH=C*H*), 8.05 (d, J = 8.5 Hz, 2H, 4-azidophenyl H-2, H-6); MS: *m*/*z* (%): 249.1 (M^+, 10), 222.2 (80), 194.2 (25), 120.1 (100), 103 (25), 91 (45), 77.2 (35). Anal. Calcd for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45; N, 16.86. Found: C, 72.55; H, 4.86; N, 16.95.

6.6. (*E*)-1-(4-Azidophenyl)-3-(4-methylphenyl)prop-2-en-1-one (7f)

Yield, 60%; pale yellow crystals; mp 128 °C; IR (KBr): 2080 (N_3), 1670 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.40 (s, 3H, C*H*$_3$), 7.13 (d, J = 8.5 Hz, 2H, 4-azidophenyl H-3, H-5), 7.22 (d, J = 7.9 Hz, 2H, 4-methylphenyl H-3, H-5), 7.48 (d, J = 15.6 Hz, 1H, COC*H*=CH), 7.55 (d, J = 7.9 Hz, 2H, 4-methylphenyl H-2, H-6), 7.80 (d, J = 15.6 Hz, 1H, COCH=C*H*), 8.05 (d, J = 8.5 Hz, 2H, 4-azidophenyl H-2, H-6); MS: *m*/*z* (%): 263.2 (M^+, 5), 237 (100), 221.1 (35), 145 (30), 120 (100), 91 (45). Anal. Calcd for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 73.25; H, 5.12; N, 16.10.

6.7. (*E*)-1-(4-Azidophenyl)-3-(4-fluorophenyl)prop-2-en-1-one (7g)

Yield, 70%; pale yellow crystals; mp 138–139 °C; IR (KBr): 2120 (N_3), 1670 (C=O)cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.12 (d, J = 8.4 Hz, 2H, 4-fluorophenyl H-2, H-6), 7.13 (d, J = 8.5 Hz, 2H, 4-azidophenyl H-3, H-5), 7.43 (d, J = 15.5 Hz, 1H, COC*H*=CH), 7.94 (dd, J_{HH} = 8.4 Hz, J_{HF} = 5.5 Hz, 2H, 4-fluorophenyl H-3, H-5), 7.78 (d, J = 15.5 Hz, 1H, COCH=C*H*), 8.05 (d, J = 8.5 Hz, 2H, 4-azidophenyl H-2, H-6); MS: *m*/*z* (%): 267.2 (M^+, 5), 200.9 (80), 165.9 (45), 116.9 (100), 94 (35). Anal. Calcd for $C_{15}H_{10}FN_3O$: C, 67.41; H, 3.77; N, 15.72. Found: C, 67.35; H, 3.95; N, 15.55.

6.8. (*E*)-1-(4-Azidophenyl)-3-(4-methoxyphenyl)prop-2-ene-1-one (7h)

Yield, 71%; yellow crystals; mp 121–122 °C; IR (KBr): 2100 (N_3), 1670 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.86 (s, 3H, OC*H*$_3$), 6.94 (d, J = 8.4 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.12 (d, J = 8.5 Hz, 2H, 4-azidophenyl H-3, H-5), 7.39 (d, J = 15.6 Hz, 1H, COC*H*=CH), 7.61 (d, J = 8.4 Hz, 2H, 4-methoxyphenyl H-2, H-6), 7.79 (d, J = 15.6 Hz, 1H, COCH=C*H*), 7.80 (d, J = 8.5 Hz, 2H, 4-azidophenyl H-2, H-6); MS: *m*/*z* (%): 279.1 (M^+, 10), 253.2 (100), 238.1 (40), 207 (35), 120 (100), 91.2 (50). Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05. Found: C, 68.55; H, 4.85; N, 15.26.

6.9. Molecular modeling (docking) studies

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.[22]

6.10. In vitro cyclooxygenase (COX) inhibition assays

The ability of the test compounds listed in Table 1 to inhibit ovine COX-1 and COX-2 (IC_{50} value, μM) was determined using an enzyme immuno assay (EIA) kit (catalog number 560101, Cayman Chemical, Ann Arbor, MI, USA) according to our previously reported method.[22]

Acknowledgment

We are grateful to the Canadian Institutes of Health Research (CIHR) (MOP-14712) for financial support of this research.

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