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Original article

Design, synthesis and biological evaluation of new (*E*)- and (*Z*)-1,2,3-triaryl-2-propen-1-ones as selective COX-2 inhibitors

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ABSTRACT

A group of (*E*)-and (*Z*)-1,2,3-triaryl-2-propen-1-one derivatives possessing a methylsulfonyl COX-2 pharmacophore at the *para* position of the C-1 phenyl ring were synthesized and evaluated as selective COX-2 inhibitors. In vitro COX-1/COX-2 structure–activity relationships were determined by varying the substituents on the C-3 propenone moiety. Among the 1,2,3-triaryl-2-propen-1-ones, (*Z*)-1-(4-(methylsulfonyl)phenyl)-2,3-diphenylprop-2-en-1-one (**3b**) showed the most potency and selectivity on COX-2 inhibition (COX-2 $IC_{50} = 0.07$ μM; selectivity index = 201). The *Z*-propenones were also found to be more potent and selective than their *E*-isomers for COX-2 inhibitory activity. The structure–activity data acquired indicate that the geometry of propenone and also the type of substituents on the C-3 propenone are important for COX-2 inhibitory activity.

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used therapeutics. Through their anti-inflammatory, anti-pyretic and analgesic activities, they represent a choice of treatment in various inflammatory diseases such as arthritis, rheumatisms as well as to relieve the pains of everyday life [1]. Despite the wide use of NSAIDs over the last century, their mechanism of action was not fully understood until 1971 when Vane identified their molecular target, the COX enzyme [2]. In the early 1990s, a second isoform (COX-2) was discovered, distinct from the first one, then renamed COX-1 [3]. COX-1 is expressed constitutively in many tissues and PGs produced by COX-1 mediate the "housekeeping" functions such as cytoprotection of gastric mucosa, regulation of renal blood flow and platelet aggregation. In contrast, COX-2 is not detected in most normal tissues, but its expression is rapidly induced by stimuli such as proinflammatory cytokines, lipopolysaccharides, mitogenes and oncogenes, growth factors, hormones and disorders of water-electrolyte hemostasis, resulting in increased synthesis of PGs in inflamed and neoplastic tissues. Thus the inducible isozyme has been implicated in pathological processes such as inflammation and various cancer types [4,5]. Because of their non-specific inhibition of both COX isoforms, classical NSAIDs reduce the production of proinflammatory PGs at sites of injury (via COX-2 inhibition) but also the formation of physiological PGs in the stomach and the kidney (via COX-1 inhibition). These observations provided a rationale for the development of COX-2 selective inhibitors that should retain the potent anti-inflammatory and analgesic effects of classical NSAIDs with less GI adverse effects [6]. In addition to role of COX-2 in rheumatoid arthritis and osteoarthritis, it is also implicated in colon cancer and angiogenesis [7,8]. Recent studies have shown that the progression of Alzheimer's disease is reduced among some users of NSAIDs. Chronic treatment with selective COX-2 inhibitors may therefore slow the progress of Alzheimer's disease without causing gastrointestinal damage [9]. Selective 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 [10]. Celecoxib (**1**) and rofecoxib (**2**) are two typical selective COX-2 inhibitors in this class (COXIBs). However, the recent market withdrawal of some COXIBs such as rofecoxib due to its adverse cardiovascular side effects [11] clearly delineates the need to explore and evaluate alternative templates with COX-2 inhibitory activity. For this reason, several compounds possessing acyclic central systems have also been designed and identified that exhibit COX-2 inhibitory activity [12–16]. In this regard, compounds having an acyclic triaryl olefinic structure (see structure **3** in Fig. 1) showed high potency and selectivity on COX-2 inhibition. Recently, we also reported

Abbreviations: COX, Cyclooxygenase; NSAIDs, Nonsteroidal anti-inflammatory drugs.

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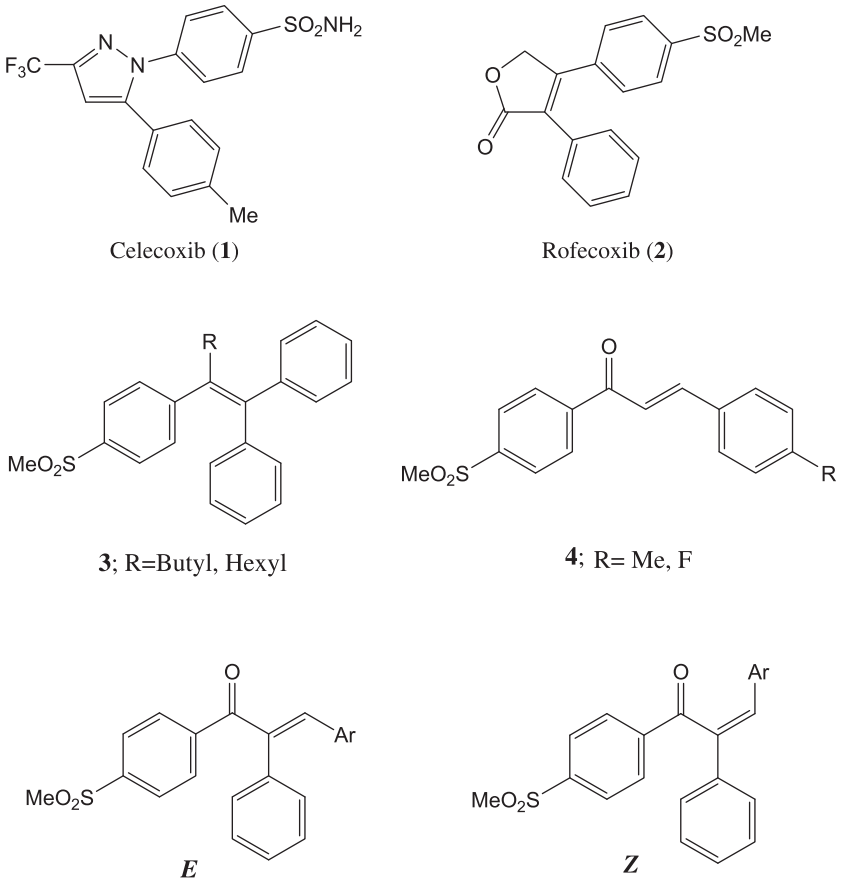
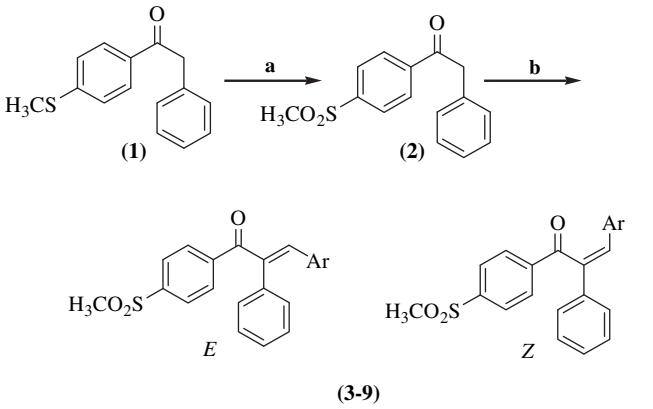


Fig. 1. Some representative examples of COXIBs (celecoxib and rofecoxib), Triarylolefines (**3**) and 1,3-diarylprop-2-en-1-ones (**4**) lead compounds and our designed scaffolds.

several investigations describing the design, synthesis, and COX inhibitory activities of a novel class of compounds possessing an acyclic 1,3-diarylprop-2-en-1-one structural template [17,18]. For example, [(*E*)-1-(4-methylsulfonylphenyl)-3-(4-methylpheny) prop-2-en-1-one] (see structure **4** in Fig. 1) identified as potent and selective COX-2 inhibitor compared with reference drug celecoxib. Accordingly, we now describe the synthesis and biological evaluation of a group of acyclic (*E*) and (*Z*)-1,2,3-triaryl-2-propen-1-ones possessing a methylsulfonyl COX-2 pharmacophore at the *para* position of the C-1 phenyl ring in conjunction with various aryl substituents at C-3 propenone moiety. In these designed compounds we utilized prop-2-en-1-one scaffold instead of olefin moiety in 1,1,2-triaryl olefins. The choice of acyclic analogues, which can exist as *E*- and *Z*-isomers, appeared particularly fruitful for an investigation of geometrical effect of this series of compounds on COX-2 inhibitory potency and selectivity.

2. Chemistry

The target *E*- and *Z*-1,2,3-triarylprop-2-en-1-ones were synthesized via Aldol condensation between 1-(4-(methylsulfonyl) phenyl)-acetophenone and appropriate benzaldehyde as outlined in Scheme 1. During Aldol condensation the products were obtained in moderate to good yield (37–60%) as a mixture of *E*- and *Z*-isomers. The *E*/*Z* ratio depends on the type of substituent at C-3 prop-2-en-1-one moiety. The crude products were crystallized in methanol if possible, mainly to give the *E*-isomers. Crystals were filtered and filtrates were purified by plate chromatography to give the *Z* isomers [19]. Geometrical assignments of 1,2,3-triarylprop-2-en-1-one isomers were carried out essentially on the basis of their IR and UV data according to literature [20]. It is quite well established that there is steric inhibition of the enone resonance in *Z*-triarylprop-2-en-1-ones which results in the appearance of their carbonyl absorption bands at relatively higher wavenumbers than those in the *E*-isomers. For this reason, the *E*-isomers have higher λ_{max} than the *Z* isomers as well. The carbonyl absorption band positions (ν) and the λ_{max} of the triarylprop-2-en-1-one isomers are



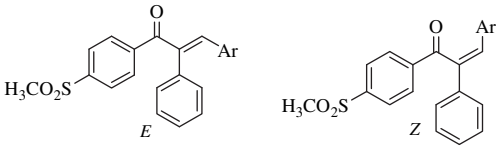
Scheme 1. Reagents and conditions: (a) Oxone, THF/H_2O, 25 °C (b) ArCHO, dry benzene, AcOH, piperidine, reflux, 16–26 h.

shown in Table 1. The starting material 1-(4-(methylthio)phenyl)-2-phenylethanone **1** was prepared by reaction of phenylacetylchloride and thioanisole in prescence of $AlCl_3$ according to a previously reported procedure [21]. Oxidation of **1** using oxone in hydromethanol afforded (1-(4-(methylsulfonyl)phenyl)-acetophenone **2** [22].

3. Results and discussion

A group of *E*- and *Z*-1,2,3-triarylprop-2-en-1-ones (3–9), possessing a methylsulfonyl COX-2 pharmacophore at the *para* position of the C-1 phenyl ring were synthesized and evaluated as selective COX-2 inhibitors. In vitro COX-1/COX-2 structure–activity relationships were determined by varying the substituents on the C-3 propenone moiety. As shown in Table 1, among the 1,2,3-triaryl-2-propen-1-ones, (*Z*)-1-(4-(methylsulfonyl)phenyl)-2,3-diphenylprop-2-en-1-one (**3b**) showed the most potency and selectivity on COX-2 inhibition (COX-2 IC_{50} = 0.07 μM; selectivity index = 201). The *Z*-propenones were also found to be more potent and selective than the *E*-isomers for COX-2 inhibitory activity. Our results showed that the size and nature of substituent at the *para* position of the C-3 phenyl ring can affect the COX-2 inhibitory potency and selectivity. Accordingly, among the 1,2,3-triaryl-2-propen-1-one derivatives (**3**–**7**), compounds **3a**, **3b** and **4a**, **4b** possessing an unsubstituted or small substituent phenyl ring attached to C-3 of the propenone moiety exhibited higher COX-2 inhibitory potency and selectivity. However, the introduction of a methyl or methoxy substituent gave compounds **5a**, **5b** or **6a**, **6b** that exhibited low COX-2 inhibitory potency. In contrast, incorporation of a C-3 *p*-hydroxy phenyl substituent (**7**) resulted a single *E* isomer with high COX-2 inhibitory potency and selectivity (COX-2 IC_{50} = 0.08 μM; selectivity index = 184.9). The increase of COX-2 inhibitory activity for the *p*-fluoro (**4**) or *p*-hydroxy (**7**) compounds, relative to the methyl (**5**) and methoxy analogs (**6**), may be due to the ability of the fluoro or hydroxyl substituent to participate in a H-bonding interaction. In comparison, the presence of a heterocyclic ring on the C-3 propenone (**8a**, **8b**, **9**) showed moderate to good COX-2 inhibitory activity although it was not possible to isolate the *E*- and *Z*-isomers of **9** and therefore the mixture was evaluated. These results indicated that the geometry of propenone and type of substituent at the C-3 of the propenone moiety are important for COX-2 inhibition.

Table 1
In vitro COX-1 and COX-2 enzyme inhibition assay data for (*E*)- and (*Z*)-1,2,3-triaryl-2-propen-1-ones **3**–**9**.



Compound	Ar	Geometry	IC_{50} (μM)[a]		Selectivity index (SI)[b]
			COX-1	COX-2	
3a	Phenyl	*E*	13.27	0.11	120.6
3b	Phenyl	*Z*	14.27	0.07	201
4a	4-F-phenyl	*E*	12.59	0.19	66.2
4b	4-F-phenyl	*Z*	30.94	0.16	193.4
5a	4-Methylphenyl	*E*	10.37	0.28	37.0
5b	4-Methylphenyl	*Z*	12.21	0.21	58.1
6a	4-Methoxyphenyl	*E*	10.68	0.22	48.5
6b	4-Methoxyphenyl	*Z*	18.38	0.21	87.5
7	4-Hydroxyphenyl	*E*	14.42	0.08	184.9
8a	2-Thienyl	*E*	13.12	0.13	100.1
8b	2-Thienyl	*Z*	ND[c]	ND[c]	ND[c]
9	4-Pyridyl	*E* & *Z*	12.37	0.07	171.8
Celecoxib			24.3	0.06	405

[a] Values are means of two determinations acquired using an ovine COX-1/COX-2 assay kit 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] Not determined.

4. Conclusions

This study indicates that (i) a new class of triaryl propenones can be prepared via a simple Aldol condensation reaction, (ii) the propenone moiety is a suitable scaffold (template) to design COX-1/-2 inhibitors, (iii) in this class of compounds COX-1/-2 inhibition is sensitive to the geometry of propenone and type of substituent at the C-3 of the propenone moiety (iv) (*Z*)-1-(4-(methylsulfonyl) phenyl)-2,3-diphenylprop-2-en-1-one (**3b**) showed the most potency and selectivity on COX-2 inhibition.

5. Experimental section

5.1. Chemistry

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 1420 spectrometer. A Bruker FT-500 MHz instrument (Brucker Biosciences, USA) was used to acquire ^{1}HNMR spectra with TMS as internal standard. Chloroform-D and DMSO-D_6 were used as solvents. 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). The mass spectral measurements were performed on a 6410Agilent LC-MS triple quadrupole mass spectrometer (LC-MS) with an electrospray ionization (ESI) interface. Microanalyses, determined for C and H, were within ±0.4% of theoretical values.

5.1.1. Preparation of (**1**): 1-(4-(methylthio)phenyl)-2-phenylethanone (**1**)

2 ml (15.13 mmol) phenylacetylchloride was added to a suspension of 2.1 g (15.84 mmol) $AlCl_3$ in 25 ml dichloromethane under argon atmosphere. The temperature was kept at 0–5 °C. After 30 min, 1.5 ml (11.97 mmol) thioanisole was added drop wise to the mixture. After 2 h, the temperature was let to approach the room temperature and stirring continued overnight. Then the reaction mixture was added to crushed ice and extracted with dichloromethane. The organic phase was washed 3 times with saturated $NaHCO_3$ and dried with anhydrous Na_2SO_4 and concentrated in vacuo. The product was recrystallized in ethanol. Yield: 84%; mp: 96–97 °C [21,22].

5.1.2. Preparation of 1-(4-(methylsulfonyl)phenyl)-2-phenylethanone (**2**)

1g (4.13 mmol) of (1) was dissolved in 20 ml THF, and 6g Oxone® in THF/water was added. The solution was stirred at room temperature overnight. THF was evaporated and the residue was extracted with chloroform. The organic phase was washed 3 times with saturated $NaHCO_3$ and dried with anhydrous Na_2SO_4 and concentrated in vacuo. A white crystalline solid formed. Yield: 71%; mp: 169–170 °C [22].

5.2. Preparation of (E)- and (Z)-1,2,3-triarylprop-2-en-1-ones (**3**–**9**): General procedure

Equimolar proportions of 1-(4-(methylsulfonyl)phenyl)-2-phenylethanone and arylaldehydes were dissolved in anhydrous benzene (usually 100 ml for each 50 mmol of reactants) and refluxed in a Dean–Stark assembly in the presence of catalytic amounts of glacial AcOH and piperidine (2.8 and 1.0 ml, respectively, for each 50 mmol of the reactants) for 12–24 h. After the completion of the reaction, the mixtures were cooled and mixed with equal proportions of water. The organic layers were separated, washed twice with water, dried with anhydrous Na_2SO_4 and concentrated in vacuo. The crude products were crystallized in methanol if possible, mainly to give the *E*-isomers. Crystals were filtered and filtrates were purified by plate chromatography to give the *Z* isomers [20]. The yields of the reactions varied from 37 to 60%.

5.2.1. (E)-1-(4-(Methylsulfonyl)phenyl)-2,3-diphenylprop-2-en-1-one (**3a**)

Pale yellow powder; mp 166–167 °C; UV (λ_{max}): 314 nm; IR (KBr disk): υ(cm^{-1}) 1651 (C=O), 1315, 1150 (SO_2); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 3.13 (s, 3H, SO_2CH_3), 7.13 (d, 2H, 3-phenyl H_2 & H_6, J = 7.5 Hz), 7.24 (t, 2H, 2-phenyl H_2 & H_6, J = 7.5 Hz), 7.29–7.31 (m, 3H, 3-phenyl H_3–H_5), 7.35 (s, 1H, =CH), 7.41–7.43 (m, 3H, 2-phenyl H_3–H_5), 7.99 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, J = 8.3 Hz), 8.06 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, J = 8.3 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 43.8, 126.1, 126.6, 128.1, 128.3, 128.6, 128.9, 129.5, 131.2, 132.6, 135, 135.9, 142.1, 142.8, 144.7, 195.5; LC-MS (ESI) m/z: 385 (M + 23) (100); Anal. Calcd. for $C_{22}H_{18}O_3S$: C, 72.90; H, 5.01. Found: C, 72.72; H, 5.21.

5.2.2. (Z)-1-(4-(Methylsulfonyl)phenyl)-2,3-diphenylprop-2-en-1-one (**3b**)

White powder; mp 122–124 °C; UV (λ_{max}): 283 nm; IR (KBr disk): υ(cm^{-1}) 1661 (C=O), 1310, 1145 (SO_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.05 (s, 3H, SO_2CH_3), 7.23–7.25 (m, 3H, 3-phenyl H_3–H_5), 7.28–7.30 (m, 3H, 3-phenyl H_2 & H_6 & =CH), 7.38–7.43 (m, 3H, 2-phenyl H_3–H_5), 7.49 (d, 2H, 2-phenyl H_2 & H_6, J = 7.1 Hz), 7.96 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, J = 8.3 Hz), 8.16–8.18 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, J = 8.3 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 43.6, 126.0, 126.5, 128.0, 128.2, 128.5, 128.8, 129.5, 131.1, 132.4, 134.8, 135.7, 140.9, 142.7, 144.6, 197.5; LC-MS (ESI) m/z: 385 (M + 23) (100); Anal. Calcd. for $C_{22}H_{18}O_3S$: C, 72.90; H, 5.01. Found: C, 72.76; H, 5.30.

5.2.3. (E)-3-(4-Fluorophenyl)-1-(4-(methylsulfonyl)phenyl)-2-phenylprop-2-en-1-one (**4a**)

White powder; mp 171–173 °C; UV (λ_{max}): 315 nm; IR (KBr disk): υ(cm^{-1}) 1653 (C=O), 1310, 1160 (SO_2); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 3.13 (s, 3H, SO_2CH_3), 6.92 (t, 2H, 4-fluorophenyl H_3 & H_5, J = 8.6 Hz), 7.12(dd, 2H, 4-fluorophenyl H_2 & H_6, J_{HH} = 8.7 Hz, J_{HF} = 5.5 Hz), 7.27–7.29 (m, 2H, phenyl H_2 & H_6), 7.32 (s, 1H, =CH), 7.41–7.44 (m, 3H, phenyl H_3–H_5), 7.97 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, J = 8.2 Hz), 8.05 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, J = 8.2 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 43.9, 115.7, 126.5, 127.8, 128.6, 129.2, 129.9, 130.8, 131.4, 132.6, 135.9, 141.2, 142.9, 144.9, 162.1, 195.8; LC-MS(ESI) m/z: 403 (M + 23) (100); Anal. Calcd. for $C_{22}H_{17}O_3SF$: C, 69.46; H, 4.50. Found: C, 69.77; H, 4.30.

5.2.4. (Z)-3-(4-Fluorophenyl)-1-(4-(methylsulfonyl)phenyl)-2-phenylprop-2-en-1-one (**4b**)

Yellow oil liquid; UV (λ_{max}): 281 nm; IR ($CHCl_3$): υ(cm^{-1}) 1676 (C=O), 1325, 1160 (SO_2); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 3.07 (s, 3H, SO_2CH_3), 6.94(t, 2H, 4-fluorophenyl H_3 & H_5, J = 8.6 Hz), 7.26–7.30 (m, 3H, 4-fluorophenyl H_2 & H_6 & =CH), 7.38–7.43 (m, 3H, phenyl H_3–H_5), 7.45–7.47 (m, 2H, phenyl H_2 & H_6), 7.98 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, J = 8.5 Hz), 8.16 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, J = 8.5 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 43.9, 115.1, 126.2, 127.5, 128.3, 128.8, 129.9, 130.6, 131.3, 132.6, 135.7, 140.9, 141.7, 144.8, 160.9, 197.5; LC-MS(ESI) m/z: 403 (M + 23) (100); Anal. Calcd. for $C_{22}H_{17}O_3SF$: C, 69.46; H, 4.50. Found: C, 69.71; H, 4.68.

5.2.5. (E)-1-(4-(Methylsulfonyl)phenyl)-2-phenyl-3-p-tolylprop-2-en-1-one (**5a**)

White powder; mp 168–170 °C; UV (λ_{max}): 324 nm; IR (KBr disk): υ(cm^{-1}) 1642 (C=O), 1300, 1150 (SO_2); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 2.34 (s, 3H, CH_3), 3.13 (s, 3H, SO_2CH_3), 7.01 (d, 2H, 4-methylphenyl H_3 & H_5, J = 8.2 Hz), 7.05(d, 2H, 4-methylphenyl H_2 & H_6, J = 8.2 Hz), 7.29 (m, 2H, phenyl H_2 & H_6), 7.34 (s, 1H, =CH), 7.42–7.44 (m, 3H, phenyl H_3–H_5), 7.97 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, J = 8.4 Hz), 8.06 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, J = 8.4 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 23.9, 44.0, 126.3, 126.6, 127.9, 128.5, 128.9, 129.3, 130.9, 131.9, 132.5, 135.7, 137.5, 140.8, 142.9, 144.5, 194.9; LC-MS(ESI) m/z: 377 (M + 1), 399 (M + 23); Anal. Calcd. for $C_{23}H_{20}O_3S$: C, 73.38; H, 5.35. Found: C, 73.67; H, 5.08.

5.2.6. (Z)-1-(4-(Methylsulfonyl)phenyl)-2-phenyl-3-p-tolylprop-2-en-1-one (**5b**)

Yellow powder; mp 116.5–118 °C; UV (λ_{max}): 288 nm; IR (KBr disk): υ(cm^{-1}) 1664 (C=O), 1315, 1145 (SO_2); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 2.30 (s, 3H, CH_3), 3.06 (s, 3H, SO_2CH_3), 7.04 (d, 2H, 4-methylphenyl H_3 & H_5, J = 8.0 Hz), 7.18 (d, 2H, 4-methylphenyl H_2 & H_6, J = 8.0 Hz), 7.37 (s, 1H, =CH), 7.37–7.42 (m, 3H, phenyl H_3–H_5), 7.46–7.48 (m, 2H, phenyl H_2 & H_6), 7.96 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, J = 8.5 Hz), 8.17 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, J = 8.5 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 22.9, 44.1, 126.1, 126.5, 127.7, 128.3, 128.8, 129.2, 130.6, 131.5, 132.5, 135.5, 137.1, 139.7, 142.8, 144.4, 196.7; LC-MS(ESI) m/z: 377 (M + 1), 399 (M + 23); Anal. Calcd. for $C_{23}H_{20}O_3S$: C, 73.38; H, 5.35. Found: C, 73.57; H, 5.16.

5.2.7. (E)-3-(4-Methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-2-phenylprop-2-en-1-one (**6a**)

Pale yellow powder; mp 200–202 °C; UV (λ_{max}): 344 nm; IR (KBr disk): υ(cm^{-1}) 1652 (C=O), 1295, 1155 (SO_2); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 3.13 (s, 3H, SO_2CH_3), 3.81 (s, 3H, OCH_3), 6.75 (d, 2H, 4-methoxyphenyl H_3 & H_5, J = 8.9 Hz), 7.06 (d, 2H, 4-methoxyphenyl H_2 & H_6, J = 8.9 Hz), 7.29–7.31 (m,2H, phenyl H_2 & H_6), 7.34 (s, 1H, =CH), 7.42–7.45 (m, 3H, phenyl H_3-H_5), 7.94 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, J = 8.3 Hz), 8.05 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, J = 8.3 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 44.2, 55.6, 114.5, 126.5, 127.4, 127.8, 128.2, 128.6, 129.0, 130.9, 131.6, 135.8, 140.8, 142.7, 144.4, 159.7, 196.9; LC-MS(ESI) m/z: 393 (M + 1), 415 (M + 23); Anal. Calcd. for $C_{23}H_{20}O_4S$: C, 70.39; H, 5.14. Found: C, 70.67; H, 5.36.

5.2.8. (Z)-3-(4-Methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-2-phenylprop-2-en-1-one (**6b**)

Yellow powder; mp 136–137 °C; UV (λ_{max}): 299 nm; IR (KBr disk): υ(cm^{-1}) 1666 (C=O), 1315, 1150 (SO_2); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 3.06 (s, 3H, SO_2CH_3), 3.78 (s, 3H, OCH_3), 6.76 (d, 2H, 4-methoxyphenyl H_3 & H_5, J = 8.8 Hz), 7.23 (d, 2H, 4-methoxyphenyl H_2 & H_6, J = 8.8 Hz), 7.28 (s, 1H, =CH), 7.35 (m,1H, phenyl H_4), 7.38–7.41 (m, 2H, phenyl H_3 & H_5), 7.42–7.46 (m, 2H, phenyl H_2 & H_6), 7.97 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, J = 8.5 Hz), 8.18 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, J = 8.5 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 44.3, 55.5, 114.3, 126.2, 127.1, 127.6, 128.0, 128.4,

128.8, 130.6, 131.3, 135.7, 138.9, 142.6, 144.3, 159.6, 195.8; LC-MS (ESI) *m/z*: 393 (M + 1), 415 (M + 23); Anal. Calcd. for $C_{23}H_{20}O_4S$: C, 70.39; H, 5.14. Found: C, 70.64; H, 4.95.

*5.2.9. (E)-3-(4-Hydroxyphenyl)-1-(4-(methylsulfonyl)phenyl)-2-phenylprop-2-en-1-one (**7**)*

Pale yellow powder; mp 181–183 °C; UV (λ_{max}): 342 nm; IR (KBr disk): υ(cm^{-1}) 3600–3200 (OH), 1620 (C=O), 1305, 1150 (SO_2); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 3.14 (s, 1H, SO_2CH_3), 5.34 (s, 1H, OH), 6.68 (d, 2H, 4-hydroxyphenyl H_3 & H_5, J = 8.7 Hz), 7.01 (d, 2H, 4-hydroxyphenyl H_2 & H_6, J = 8.7 Hz), 7.29–7.31 (m, 2H, phenyl H_2 & H_6), 7.33 (s, 1H, =CH), 7.41–7.45 (m, 3H, phenyl H_3–H_5), 7.94 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, J = 8.4 Hz), 8.05 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, J = 8.4 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 44.1, 116.1, 126.4, 127.7, 127.9, 128.1, 128.8, 129.1, 131.1, 132.4, 135.9, 140.7, 142.9, 144.6, 158.4, 196.1; LC-MS *m/z*:379 (M + 1), 401 (M + 23); Anal. Calcd. for $C_{23}H_{20}O_4S$: C, 70.39; H, 5.14. Found: C, 70.71; H, 5.43.

*5.2.10. (E)-1-(4-(Methylsulfonyl)phenyl)-2-phenyl-3-(thiophen-2-yl)prop-2-en-1-one (**8a**)*

Cream powder; mp 195.5–197 °C; UV (λ_{max}): 345 nm; IR (KBr disk): υ(cm^{-1}) 1644 (C=O), 1310, 1145 (SO_2); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 3.15 (s, 3H, -SO_2CH_3), 7.01 (dd, 1H, thiophene H_4, J = 5.1 Hz), 7.18 (d, 1H, thiophene H_5, J = 3.48 Hz), 7.35–7.38 (m, 3H, thiophene H_3 & phenyl H_2 & H_6), 7.53–7.55 (m, 3H, phenyl H_3–H_5), 7.64 (s, 1H, =CH), 7.94 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, J = 8.4 Hz), 8.08 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, J = 8.4 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 44.2, 126.4, 127.2, 127.9, 128.2, 128.6, 128.9, 130.6, 130.9, 131.9, 132.4, 137.4, 141.5, 142.8, 144.6, 196.5; LC-MS(ESI) *m/z*: 369 (M + 1), 391 (M + 23); Anal. Calcd. for $C_{20}H_{16}O_3S_2$: C, 65.19; H, 4.38. Found: C, 65.38; H, 4.53.

*5.2.11. (Z)-1-(4-(Methylsulfonyl)phenyl)-2-phenyl-3-(thiophen-2-yl)prop-2-en-1-one (**8b**)*

Yellow powder; mp 144 °C; UV (λ_{max}): 312 nm; IR (KBr disk): υ (cm^{-1}) 1662 (C=O), 1310, 1150 (SO_2); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 3.08 (s, 3H, SO_2CH_3), 6.96 (dd, 1H, thiophene H_4, J = 5.0 Hz), 7.10 (d, 1H, thiophene H_5, J = 3.45 Hz), 7.24 (d, 1H, thiophene H_3, J = 5.0 Hz), 7.36–7.39 (m, 1H, phenyl H_4), 7.40–7.42 (m, 3H, phenyl H_3 & H_5 & =CH), 7.42–7.46 (m, 2H, phenyl H_2 & H_6), 8.01 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, J = 8.5 Hz), 8.23 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, J = 8.5 Hz); ^{13}CNMR ($CDCl_3$, 100 MHz): δ 44.3, 126.2, 127.0, 127.6, 128.0, 128.4, 128.7, 130.2, 130.6, 131.0, 132.2, 137.2, 141.2, 142.6, 144.3, 197.6; LC-MS(ESI) *m/z*: 369 (M + 1), 391 (M + 23); Anal. Calcd. for $C_{20}H_{16}O_3S_2$: C, 65.19; H, 4.38. Found: C, 64.88; H, 4.60.

*5.2.12. (E & Z)-1-(4-(Methylsulfonyl)phenyl)-2-phenyl-3-(pyridin-4-yl)prop-2-en-1-one (**9**)*

Two isomers (*E*/*Z* ratio: 3:1) were obtained. cream powder; mp 58–60 °C; UV (λ_{max}): 284 nm; IR (KBr disk): υ(cm^{-1}) 1658 (C=O), 1300, 1150 (SO_2); ^{1}HNMR ($CDCl_3$, 500 MHz): δ 3.07 (s, 3H, SO_2CH_3), 3.12 (s, 3H, SO_2CH_3), 6.98 (d, 2H, phenyl H_2 & H_6, J = 5.6 Hz), 7.17 (d, 2H, phenyl H_2 & H_6, J = 5.6 Hz), 7.19 (s, 1H, =CH), 7.21 (s, 1H, =CH), 7.27–7.49 (m, 10H, phenyl H_3–H_5, pyridine H_3 & H_5), 8.00 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, J = 8.3 Hz), 8.02 (d, 2H, 4-methylsulfonylphenyl H_2 & H_6, J = 8.3 Hz), 8.05 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, J = 8.3 Hz), 8.15 (d, 2H, 4-methylsulfonylphenyl H_3 & H_5, J = 8.3 Hz), 8.50 (d, 4H, pyridine H_2 & H_6, J = 3.9 Hz); LC-MS *m/z*: 364 (M + 1) (100).

5.3. In vitro cyclooxygenase (COX) inhibition assays

The assay was performed using an enzyme chemiluminescent kit (Cayman chemical, MI, USA) according to our previously reported method [23]. The Cayman chemical chemiluminescent COX (ovine) inhibitor screening assay utilizes the heme-catalyzed hydroperoxidase activity of ovine cyclooxygenases to generate luminescence in the presence of a cyclic naphthalene hydrazide and the substrate arachidonic acid. Arachidonate-induced luminescence was shown to be an index of real-time catalytic activity and demonstrated the turnover inactivation of the enzyme. Inhibition of COX activity, measured by luminescence, by a variety of selective and nonselective inhibitors showed potencies similar to those observed with other in vitro and whole cell methods.

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References

[1] S. Fiorucci, R. Meli, M. Bucci, G. Cirino, Biochem. Pharmacol. 62 (2001) 1433–1438.
[2] J.R. Vane, Nature 231 (1971) 232–237 239.
[3] J.Y. Fu, J.L. Masferrer, K. Seibert, A. Raz, P. Needleman, J. Biol. Chem. 265 (1990) 16736–16737.
[4] C.S. Williams, R.N. DuBois, Am. J. Physiol. 270 (1996) 393–400.
[5] P.C. Konturek, J. Kania, G. Burnat, E.G. Hahn, S.J. Konturek, J. Physiol. Pharmacol. 56 (2005) 57–73.
[6] M.M. Goldenberg, Clin. Ther. 21 (1999) 1497–1513.
[7] T. Kawamori, C.V. Rao, K. Seibert, B.S. Reddy, Cancer Res. 58 (1998) 409.
[8] M. Katori, M. Majima, Inflamm. Res. 295 (2000) 802–809.
[9] J.R. Vane, R.M. Botting, Inflamm. Res. 47 (1998) S78–S87.
[10] J.J. Talley, Prog. Med. Chem. 36 (1999) 201–234.
[11] J.M. Dogné, C.T. Supuran, D. Pratico, J. Med. Chem. 48 (2005) 2251–2257.
[12] M.J. Uddin, P.N. Praveen Rao, E.E. Knaus, Bioorg. Med. Chem. Lett. 14 (2004) 1953–1956.
[13] M.J. Uddin, P.N. Praveen Rao, E.E. Knaus, R. McDonald, J. Med. Chem. 47 (2004) 6108–6111.
[14] M.J. Uddin, P.N. Praveen Rao, M.A. Rahim, R. McDonald, E.E. Knaus, Bioorg. Med. Chem. Lett. 14 (2004) 4911–4914.
[15] P.N. Praveen Rao, Q.H. Chen, E.E. Knaus, Bioorg. Med. Chem. Lett. 15 (2005) 4842–4845.
[16] A. Zarghi, S. Kakhgi, A. Hadipoor, B. Daraee, O.G. Dadrass, M. Hedayati, Bioorg. Med. Chem. Lett. 18 (2008) 1336–1339.
[17] A. Zarghi, S. Arfaee, P.N. Praveen Rao, E.E. Knaus, Bioorg. Med. Chem. 14 (2006) 2600–2605.
[18] A. Zarghi, T. Zebardast, F. Hakimion, F.H. Shirazi, P.N. Praveen Rao, E.E. Knaus, Bioorg. Med. Chem. 14 (2006) 7044–7050.
[19] S. Mittal, S. Durani, R.S. Kapil, J. Med. Chem. 28 (1985) 492–497.
[20] P.J. Duke, D.W. Boykin, J. Org. Chem. 37 (1972) 1436–1439.
[21] M. Therien, J.Y. Gauthier, Y. Leblanc, S. Leger, H. Perrier, P. Prasit, Z. Wang, Synthesis 12 (2001) 1778–1779.
[22] S.K. Singh, V. Saibaba, V. Ravikumar, C.S. Rao, V. Akhila, Y.K. Rao, Bioorg. Med. Chem. 12 (2004) 1881–1893.
[23] A. Zarghi, L. Najafnia, B. Daraee, O.G. Dadrass, M. Hedayati, Bioorg. Med. Chem. Lett. 17 (2007) 5634–5637.