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Synthesis and biological evaluation of methanesulfonamide analogues of rofecoxib: Replacement of methanesulfonyl by methanesulfonamido decreases cyclooxygenase-2 selectivity

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Abstract—A new group of 3-(4-substituted-phenyl)-4-(4-methylsulfonamidophenyl)-2(5*H*)furanones in which the methylsulfonyl ($MeSO_2$) COX-2 pharmacophore present in rofecoxib was replaced by a methanesulfonamido ($MeSO_2NH$) moiety, and where the substituent at the *para*-position of the C-3 phenyl ring was simultaneously varied (H, F, Cl, Br, Me, OMe), were evaluated to determine the combined effects of steric and electronic substituent properties upon COX-1 and COX-2 inhibitory potency and COX isozyme selectivity. Structure–activity relationship (SAR) studies showed that compounds having a neutral (H), or electronegative halogen (F, Cl, Br), substituent at the *para*-position of the C-3 phenyl ring inhibited both COX-1 and COX-2 with COX-2 selectivity indexes in the 3.1–39.4 range. In contrast, compounds having an electron-donating Me or OMe substituent were selective inhibitors of COX-2 (COX-1 $IC_{50} > 100$ μM). These SAR data indicate the 3-aryl-4-(4-methylsulfonamidophenyl)-2(5*H*)furanone scaffold provides a suitable template to design COX inhibitors with variable COX-2 selectivity indexes.

1. Introduction

Identification of the selective cyclooxygenase-2 (COX-2) inhibitory prototype 'sulide' compound NS-398 (**1**), and the 'coxib' compound DuP 697 (**2**), served as the rationale for the original concept that a drug having a greater selectivity for the proinflammatory inducible COX-2 isozyme, relative to the cytoprotective constitutive COX-1 isozyme, would reduce the incidence of gastrointestinal bleeding and renal toxicity (see structures in Fig. 1). Subsequent drug discovery programs led to the clinical development of the selective COX-2 inhibitors nimesulide (**3**), celecoxib (**4**), and rofecoxib (**5**).[1] Later it became evident that rofecoxib may alter the balance in the cyclooxygenase pathway resulting in a decrease in the level of the vasodilatory and anti-aggregatory prostacyclin (PGI_2), in conjunction with a simultaneous increase in the level of the prothrombotic thromboxane A_2 (TxA_2), that culminated in increased incidences of an adverse cardiovascular thrombotic event.[2] The adverse cardiovascular effects of rofecoxib associated with its use, that led to its withdrawal from the market, appear to be due to its high COX-2 selectivity.[3] A thorough in vitro assessment of COX-2 selectivity, at drug concentrations that mimic

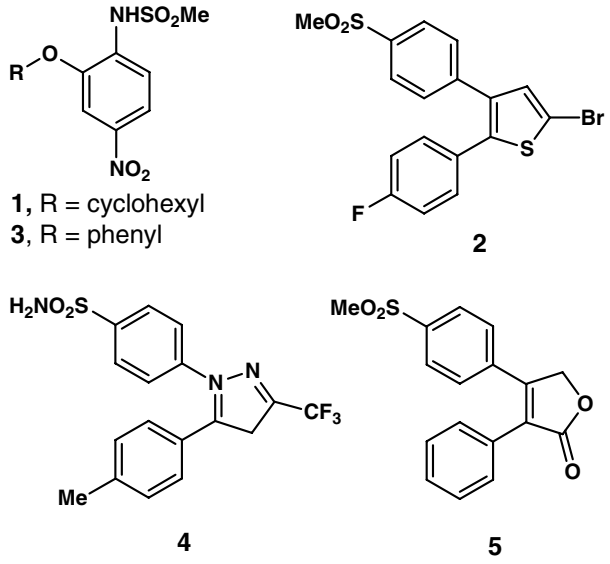

Figure 1. Structures of the selective cyclooxygenase-2 inhibitors NS-398 (**1**), DuP 697 (**2**), nimesulide (**3**), celecoxib (**4**), and rofecoxib (**5**).

Keywords: Cyclooxygenase inhibition; Rofecoxib analogues; Methanesulfonamido pharmacophore.
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steady-state plasma levels produced at the therapeutic dose, for a group of selective COX-2 inhibitors and traditional non-steroidal anti-inflammatory drugs (NSAIDs) has been reported. In this study, rofecoxib was placed within a group of compounds having a >50-fold COX-2 selectivity relative to celecoxib and nimesulide which were placed within a group of compounds having a 5- to 50-fold COX-2 selectivity.[4]

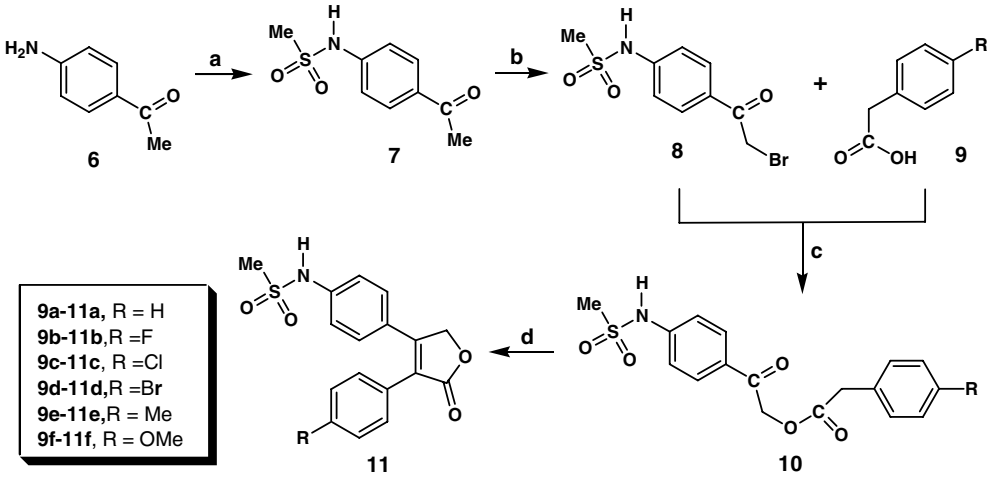
The celecoxib SO_2NH_2 and rofecoxib SO_2Me pharmacophores are believed to induce COX-2 selectivity by insertion into a secondary (2°) pocket that is present in COX-2 but absent in COX-1. The oxygen and/or nitrogen atom in these pharmacophores undergo H-bonding to arginine (Arg513) or the backbone amide NH of phenylalanine (Phe518). Replacement of histidine (His513) in COX-1 by arginine (Arg513) in COX-2 has been reported to play a key role in the hydrogen-bond network of the cyclooxygenase active site. Histidine (His90), glutamine (Gln192), and tyrosine (Tyr355) control access of ligands into the 2° COX-2 pocket.[5] The interaction of arginine (Arg513) with the bound ligand has been reported to be a requirement for the time-dependent inhibition of COX-2.[6] It was therefore of interest to exploit the presence of the arginine (Arg513) residue in the 2°-pocket of COX-2 by replacing the rofecoxib SO_2Me pharmacophore by the nimesulide $MeSO_2NH$ pharmacophore as a method to reduce the COX-2 selectivity of rofecoxib that may reduce adverse cardiovascular effects. As part of our ongoing program to acquire structure-function relationship data for COX-2 inhibitors, we now describe a group of rofecoxib analogues possessing a methylsulfonamido substituent at the *para*-position of the C-4 phenyl ring in conjunction with a variety of substituents (H, F, Cl, Br, Me, OMe) at the *para*-position of the C-3 phenyl ring (**11a–f**).

2. Chemistry

The target 3,4-diaryl-2(5*H*)furanones (**11a–f**) were synthesized using the sequence of reactions illustrated in Scheme 1. Accordingly, reaction of 4-aminoacetophenone (**6**) with methanesulfonyl chloride in the presence of triethylamine with dichloromethane as solvent afforded 4-(methylsulfonamido)acetophenone (**7**, 70%). Bromination of **7** using bromine in chloroform in the presence of a catalytic quantity of $AlCl_3$ furnished the bromoacetyl derivative (**8**, 81%). Condensation of **8** with a 4-substituted-phenylacetic acid (**9a–f**) in the presence of triethylamine with acetonitrile as solvent yielded the respective phenacyl phenylacetate product (**10a–f**, 78–84%). Cyclization of the esters (**10a–f**) using NaH in DMSO gave the respective 4-(4-methylsulfonamidophenyl)-3-(4-substituted-phenyl)-2(5*H*)furanone product (**11a–f**, 31–42%).

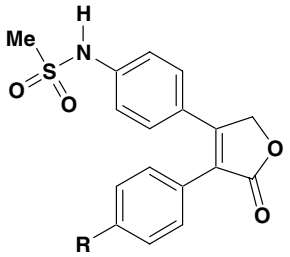
3. Results and discussion

A group of rofecoxib analogues (**11a–f**) in which the methylsulfonyl ($MeSO_2$) COX-2 pharmacophore was replaced by a methanesulfonamido ($MeSO_2NH$) moiety, and where the substituent at the *para*-position of the C-3 phenyl ring was simultaneously varied (H, F, Cl, Br, Me, OMe), were evaluated to determine the combined effects of steric and electronic substituent properties upon COX-1 and COX-2 inhibitory potency and COX isozyme selectivity. SAR studies (IC_{50} values) to determine the in vitro ability of the title compounds to inhibit the COX-1 and COX-2 isozymes showed that replacement of $MeSO_2$ (rofecoxib) by $MeSO_2NH$ (**11a**) reduced COX-2 potency and selectivity (see data in Table 1). Compounds **11a–d** having a neutral (H), or electronegative (F, Cl, Br), R-substituent at the *para*-position of the C-3 phenyl ring inhibited both COX-1 (IC_{50} values in the 10.0–35.5 μM range) and COX-2 (IC_{50} values in the 0.8–3.2 μM range) with COX-2 selectivity indexes in the 3.1–39.4 range. In contrast, compounds having an electron-donating R = Me (**11e**), or R = OMe (**11f**), substituent were selective inhibitors of COX-2 (COX-1 IC_{50} values >100 μM). Although the chloro (**11c**, R = Cl), and methyl (**11e**, R = Me), compounds were equipotent inhibitors of COX-2, the methyl



Scheme 1. Reagents and conditions: (a) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0 → 25 °C, 3 h; (b) Br_2, $CHCl_3$, 0 °C, 30 min; (c) NEt_3, MeCN, 25 °C, 30 min; and (d) NaH, DMSO, 25 °C, 4 h.

Table 1. In vitro COX-1 and COX-2 enzyme inhibition data for 3,4-diaryl-2(5*H*)furanones **11a–f**



Compound	R	IC_{50}[a] (μM)		Selectivity index (SI)[b]
		COX-1	COX-2	
11a	H	31.6	1.7	18.5
11b	F	10.0	3.2	3.1
11c	Cl	31.5	0.8	39.4
11d	Br	35.5	3.2	11.1
11e	Me	>100	0.9	>111
11f	OMe	>100	31.5	>31
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}).

compound **11e** was a selective inhibitor of COX-2 with a selectivity index >111. Accordingly, **11e** is a selective inhibitor like rofecoxib, whereas **11c** differs from rofecoxib since it inhibits both of the COX isozymes.

A molecular modeling (docking) study showed that the selective COX-2 inhibitor 3-(4-methylphenyl)-4-(4-methylsulfonamidophenyl)-2(5*H*)furanone (**11e**) binds in the center of the primary binding site of the COX-2 isozyme such that the $NHSO_2Me$ COX-2 pharmacophore inserts into the COX-2 secondary pocket (Val523, Arg513, Phe518, and His90) as illustrated in Figure 2. One of the O-atoms of the $NHSO_2Me$ moiety is positioned about 5.16 Å from the N*H*$_2$ (guanidine group) of Arg513. A hydrogen-bonding interaction was observed between the other O-atom of the $NHSO_2Me$ group and the N*H* of His90 (distance ≈ 3.17 Å). In addition, the backbone C=O of Leu352 is located about 3.72 Å from the N*H* of the $NHSO_2Me$ group. The terminal Me of $NHSO_2Me$ is oriented toward Ala516 and Gly519 within the COX-2 2°-pocket (distance < 5 Å). The C-3 4-methylphenyl moiety is oriented in a hydrophobic region at the apex of the COX-2 channel where it is in close contact with Leu352, Trp387, Leu384, Gly526, and Tyr385 (distance < 5 Å). The ring O-atom of the central furanone ring is about 4.32 Å removed from the O*H* of Tyr355 at the mouth of the COX-2 channel, and the distance between the N*H*$_2$ of Arg120 and the O-atom of the central furanone ring is about 6.31 Å. Interestingly, the furanone C=O forms a hydrogen bond with the O*H* of Ser530 (distance = 3.53 Å). These observations, together with the in vitro COX-2 inhibitor data, provide a rational explanation for the high COX-2 selectivity and potency exhibited by 3-(4-methylphenyl)-4-(4-methylsulfonamidophenyl)-2(5*H*)furanone (**11e**).

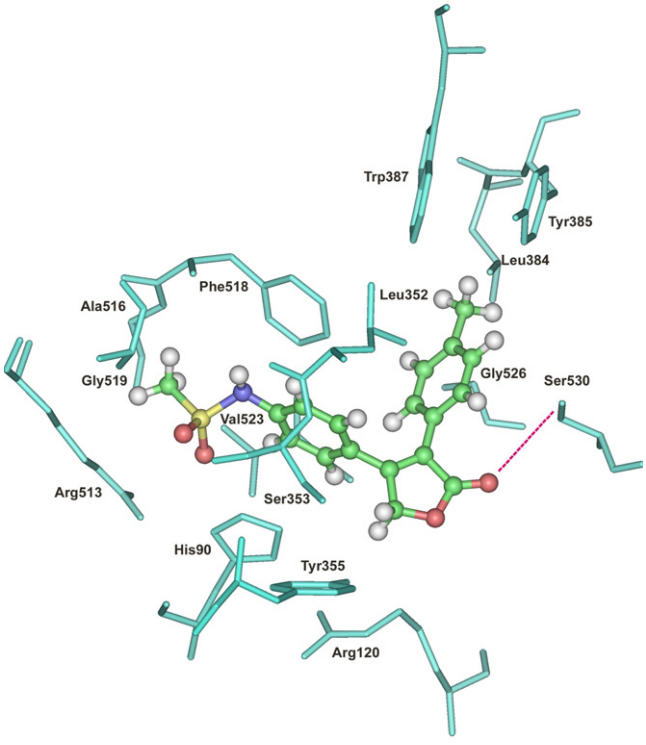


Figure 2. 3-(4-Methylphenyl)-4-(4-methylsulfonamidophenyl)-2(5*H*)uranone (**11e**) (ball and stick) docked in the binding site of murine COX-2. Hydrogen atoms of the amino acid residues have been removed to improve clarity.

4. Conclusions

A group of 3-(4-substituted-phenyl)-4-(4-methylsulfonamidophenyl)-2(5*H*)furanones were synthesized to determine their ability to inhibit the COX-1 and

COX-2 isozymes. In vitro enzyme inhibition structure–activity studies indicated that (i) replacement of the $MeSO_2$ pharmacophore in rofecoxib by a $MeSO_2NH$ bioisostere provides a suitable scaffold (template) to modulate the COX-2 selectivity index that is dependent upon the specific substituent present at the *para*-position of the C-3 phenyl ring, and (ii) compounds having a neutral (H), or electronegative halogen (F, Cl, Br), substituent at the *para*-position of the C-3 phenyl ring inhibited both COX-1 and COX-2. In contrast, compounds having an electron-donating Me or MeO substituent at the same position were selective inhibitors of COX-2.

5. Experimental

Melting points were determined using a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded as films with NaCl plates on a Nicolet 550 Series II Magna FT-IR spectrometer. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AM-300 spectrometer in which coupling constants (J) were estimated in Hz. Elemental analyses, performed for C, H, and N (Microanalytical Laboratory, Department of Chemistry, University of Alberta), were within ±0.4% of theoretical values. Silica-gel column chromatography was performed using Merck silica gel 60 ASTM (70-230 mesh). All reagents were purchased from Aldrich Chemical Company (Milwaukee, WI), which were used without further purification.

5.1. 4-(Methylsulfonamido)acetophenone (7)

Methanesulfonyl chloride (1.8 mL, 24 mmol) was added dropwise with vigorous stirring to a solution of 4-aminoacetophenone (**6**, 2.72 g, 20.0 mmol) and triethylamine (4.2 mL, 30 mmol) in CH_2Cl_2 (150 mL) at 0 °C, the cooling bath was removed, and the reaction was allowed to proceed for 3 h at 25 °C. Water (150 mL) was added, the organic layer was separated and washed with an aqueous $NaHCO_3$ solution, and the organic fraction was dried (Na_2SO_4). Removal of the solvent in vacuo gave a residue that was recrystallized from petroleum ether–ethyl ether to afford **7** (3.0 g, 70%) as white crystals; mp 150–152 °C (lit.[7], mp 156.5–158.5 °C); IR (film): 3285 (NH), 1680 (C=O), 1335, 1150 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.60 (s, 3H, CH_3CO), 3.11 (s, 3H, SO_2CH_3), 6.75 (s, 1H, N*H*), 7.26 (d, J = 8.4 Hz, 2H, phenyl H-3, H-5), 7.98 (d, J = 8.4 Hz, 2H, phenyl H-2, H-6).

5.2. 4-Methylsulfamidophenacyl bromide (8)

A catalytic amount of $AlCl_3$ (10 mg), and then a solution of bromine (0.5 mL, 12.5 mmol) in $CHCl_3$ (5 mL), was added to a solution of **7** (3.0 g, 14.1 mmol) in $CHCl_3$ (100 mL) at 0 °C with vigorous stirring. The reaction was allowed to proceed for 30 min with stirring prior to addition of water (100 mL). The aqueous and organic layers were separated, the aqueous fraction was extracted with $CHCl_3$ (2 × 30 mL), the two organic fractions were combined, and dried (Na_2SO_4). Removal of the solvent in vacuo gave a residue that was recrystallized from EtOAc–hexane (1:2, v/v) to furnish **8** (3.2 g, 81%) as white crystals; mp 189–191 °C (lit.[7] mp 190–191); IR (film): 3380 (NH), 1705 (C=O), 1370, 1150 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.24 (s, 3H, SO_2CH_3), 4.44 (s, 2H, CH_2Br), 6.61 (s, 1H, N*H*), 7.51 (d, J = 8.2 Hz, 2H, phenyl H-3, H-5), 8.12 (d, J = 8.2 Hz, 2H, phenyl H-2, H-6).

5.3. 4-Methylsulfonamidophenacyl phenylacetate (10a): General procedure

4-Methylsulfamidophenacyl bromide **8** (582 mg, 2.0 mmol) was added to a solution of phenylacetic acid **9a** (272 mg, 2.0 mmol) in acetonitrile (10 mL) containing triethylamine (0.6 mL, 4.4 mmol) at 25 °C with stirring. The reaction was allowed to proceed for 1 h at 25 °C with stirring, the solvent was removed in vacuo, and water (40 mL) was added to the residue. Extraction with CH_2Cl_2 (3 × 50 mL). washing the combined organic extracts with dilute hydrochloric acid, drying the organic fractions (Na_2SO_4), and removal of the solvent in vacuo gave a residue that was recrystallized from petroleum ether–ethyl ether to afford **10a** (560 mg, 81%) as white needles; mp 118–119 °C; IR (film): 3200 (NH), 1730, 1695 (C=O), 1375, 1150 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.10 (s, 3H, SO_2CH_3), 3.83 (s, 2H, $OCOCH_2$), 5.32 (s, 2H, OCH_2CO), 7.0 (s, 1H, N*H*), 7.26 (d, J = 8.5 Hz, 2H, 4-methylsulfonamidophenyl H-3, H-5), 7.23–7.36 (m, 5H, phenyl), 7.88 (d, J = 8.5 Hz, 2H, 4-methylsulfonamidophenyl H-2, H-6).

Compounds **10b–f** were prepared using a similar procedure to that described above for **10a** except that **9b–f** were used in place of **9a**. The physical and spectral data of **10b–f** are listed below.

5.4. 4-Methylsulfonamidophenacyl 4-fluorophenylacetate (10b)

Compound **10b** was obtained as white needles in 81% yield; mp 123 °C; IR (film): 3240 (NH), 1725, 1685 (C=O), 1340, 1150 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.11 (s, 3H, SO_2CH_3), 3.81 (s, 2H, $OCOCH_2$), 5.32 (s, 2H, OCH_2CO), 6.86 (s, 1H, N*H*), 7.05 (d, J_{HCCF} = 8.4 of d, J_{HCCH} = 8.4 Hz, 2H, 4-fluorophenyl H-3, H-5), 7.25 (d, J = 8.4 Hz, 2H, 4-methylsulfonamidophenyl H-3, H-5), 7.32 (d, J_{HCCF} = 8.4 Hz of d, J_{HCCH} = 5.4 Hz, 2H, 4-fluorophenyl H-2, H-6), 7.90 (d, J = 8.4 Hz, 2H, 4-methylsulfonamidophenyl H-2, H-6).

5.5. 4-Methylsulfonamidophenacyl 4-chlorophenylacetate (10c)

Compound **10c** was obtained as white needles in 79% yield; mp 158–159 °C; IR (film): 3325 (NH), 1730, 1705 (C=O), 1375, 1150 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.12 (s, 3H, SO_2CH_3), 3.80 (s, 2H, $OCOCH_2$), 5.34 (s, 2H, OCH_2CO), 6.86 (s, 1H, N*H*), 7.25 (d, J = 8.4 Hz, 2H, 4-methylsulfonamidophenyl H-3, H-5), 7.33 (d, J = 8.2 Hz, 2H, 4-chlorophenyl H-2, H-6), 7.49 (d, J = 8.2 Hz, 2H, 4-chlorophenyl H-3, H-5), 7.98 (d, J = 8.4 Hz, 2H, 4-methylsulfonamidophenyl H-2, H-6).

5.6. 4-Methylsulfonamidophenacyl 4-bromophenylacetate (10d)

Compound **10d** was obtained as white needles in 78% yield; mp 160–161 °C; IR (film): 3315 (NH), 1750, 1710 (C=O), 1375, 1155 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.13 (s, 3H, SO_2CH_3), 3.78 (s, 2H, $OCOCH_2$), 5.34 (s, 2H, OCH_2CO), 6.86 (s, 1H, NH), 7.23 (d, J = 8.4 Hz, 2H, 4-methylsulfonamidophenyl H-3, H-5), 7.47 (d, J = 8.3 Hz, 2H, 4-bromophenyl H-2, H-6), 7.51 (d, J = 8.3 Hz, 2H, 4-bromophenyl H-3, H-5), 7.98 (d, J = 8.4 Hz, 2H, 4-methylsulfonamidophenyl H-2, H-6).

5.7. 4-Methylsulfonamidophenacyl 4-methylphenylacetate (10e)

Compound **10e** was obtained as white needles in 82% yield; mp 158–159 °C; IR (film): 3325 (NH), 1740, 1705 (C=O), 1365, 1165 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.35 (s, 3H, CH_3), 3.10 (s, 3H, SO_2CH_3), 3.79 (s, 2H, $OCOCH_2$), 5.31 (s, 2H, OCH_2CO), 6.83 (s, 1H, NH), 7.18 (d, J = 7.8 Hz, 2H, 4-methylphenyl H-3, H-5), 7.21 (d, 2H, J = 7.8 Hz, 4-methylphenyl H-2, H-6), 7.26 (d, J = 8.4 Hz, 2H, 4-methylsulfonamidophenyl H-3, H-5), 7.89 (d, J = 8.4 Hz, 2H, 4-methylsulfonamidophenyl H-2, H-6).

5.8. 4-Methylsulfonamidophenacyl 4-methoxyphenylacetate (10f)

Compound **10f** was obtained as white needles in 84% yield; mp 151–152 °C; IR (film): 3310 (NH), 1740, 1710 (C=O), 1365, 1155 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.03 (s, 3H, SO_2CH_3), 3.69 (s, 2H, $OCOCH_2$), 3.73 (s, 3H, OCH_3), 5.22 (s, 2H, OCH_2CO), 6.62 (s, 1H, NH), 6.80 (d, J = 8.4 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.16 (d, J = 8.4 Hz, 2H, 4-methylsulfonamidophenyl H-3, H-5), 7.19 (d, 2H, J = 8.4 Hz, 4-methoxyphenyl H-2, H-6), 7.89 (d, J = 8.4 Hz, 2H, 4-methylsulfonamidophenyl H-2, H-6).

5.9. 4-(4-Methylsulfonamidophenyl)-3-phenyl-2(5H)furanone (11a): General procedure

A solution of **10a** (517 mg, 1.5 mmol) in dimethylsulfoxide (5 mL) was added dropwise to a stirred suspension of sodium hydride (100 mg, 4.2 mmol) in dimethylsulfoxide (2 mL) at 25 °C. The reaction was allowed to proceed for 4 h at 25 °C prior to pouring into water (20 mL). Extraction with ethyl acetate (3 × 25 mL), washing the combined ethyl acetate extracts with water, drying the organic fraction (Na_2SO_4), and removal of the solvent in vacuo afforded a residue. Purification of this residue by silica-gel column chromatography using ethyl acetate:hexane (1:1, v/v) as eluent furnished **11a** (201 mg, 41%) as yellow needles; mp 206–207 °C; IR (film) 3255 (NH), 1735 (furanone CO), 1330, 1155 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.06 (s, 3H, SO_2CH_3), 5.36 (s, 2H, CH_2), 7.14 (d, J = 8.4 Hz, 2H, 4-methylsulfonamidophenyl H-3, H-5), 7.28–7.48 (m, 7H total, 4-methylsulfonamidophenyl H-2, H-6; phenyl hydrogens), 10.15 (s, 1H, NH). Anal. Calcd for $C_{17}H_{15}NO_4S \cdot 1/5H_2O$: C, 61.32; H, 4.66; N, 4.21. Found: C, 60.97; H, 4.52; N, 4.10.

5.10. 3-(4-Fluorophenyl)-4-(4-methylsulfonamidophenyl)-2(5H)furanone (11b)

Compound **11b** was obtained as a yellow solid in 31% yield; mp 92–93 °C; IR (film) 3330 (NH), 1730 (furanone CO), 1375, 1155 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.07 (s, 3H, SO_2CH_3), 5.35 (s, 2H, CH_2), 7.16 (d, J = 8.4 Hz, 2H, 4-methylsulfonamidophenyl H-3, H-5), 7.23–7.50 (m, 6H total, 4-fluorophenyl hydrogens, 4-methylsulfonamidophenyl H-2, H-6), 10.18 (s, 1H, NH). Anal. Calcd for $C_{17}H_{14}FNO_4S \cdot 2/3H_2O$: C, 56.82; H, 4.30; N, 3.90. Found: C, 56.85; H, 4.41; N, 3.54.

5.11. 3-(4-Chlorophenyl)-4-(4-methylsulfonamidophenyl)-2(5H)furanone (11c)

Compound **11c** was obtained as a yellow solid in 42% yield; mp 108–110 °C; IR (film) 3305 (NH), 1750 (furanone CO), 1320, 1155 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6): 3.07 (s, 3H, SO_2CH_3), 5.35 (s, 2H, CH_2), 7.16 (d, J = 8.4 Hz, 2H, 4-methylsulfonamidophenyl H-3, H-5), 7.31 (d, J = 8.4 Hz, 2H, 4-methylsulfonamidophenyl H-2, H-6), 7.36 (d, 2H, J = 7.5 Hz, 4-chlorophenyl H-3, H-5), 7.51 (d, J = 7.5 Hz, 2H, 4-chlorophenyl H-2, H-6), 10.19 (s, 1H, NH). Anal. Calcd for $C_{17}H_{14}ClNO_4S$: C, 56.12; H, 3.88; N, 3.85. Found: C, 56.40; H, 4.17; N, 3.68.

5.12. 3-(4-Bromophenyl)-4-(4-methylsulfonamidophenyl)-2(5H)furanone (11d)

Compound **11d** was obtained as a yellow solid in 36% yield; mp 115–116 °C; IR (film) 3300 (NH), 1745 (furanone CO), 1315, 1150 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6): 3.08 (s, 3H, SO_2CH_3), 5.35 (s, 2H, CH_2), 7.17 (d, J = 8.4 Hz, 2H, 4-methylsulfonamidophenyl H-3, H-5), 7.31 (d, J = 8.4 Hz, 2H, 4-methylsulfonamidophenyl H-2, H-6), 7.35 (d, 2H, J = 7.5 Hz, 4-bromophenyl H-2, H-6), 7.62 (d, J = 7.5 Hz, 2H, bromophenyl H-3, H-5), 10.19 (s, 1H, NH). Anal. Calcd for $C_{17}H_{14}BrNO_4S \cdot 1/2\ H_2O$: C, 48.93; H, 3.52; N, 3.36. Found: C, 48.55; H, 3.14; N, 3.11.

5.13. 3-(4-Methylphenyl)-4-(4-methylsulfonamidophenyl)-2(5H)furanone (11e)

Compound **11e** was obtained as yellow needles in 42% yield; mp 199–200 °C; IR (film) 3250 (NH), 1740 (furanone CO), 1340, 1150 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6): 2.34 (s, 3H, CH_3), 3.06 (s, 3H, SO_2CH_3), 5.33 (s, 2H, CH_2), 7.13–7.16 (m, 4H, 4-methylsulfonamidophenyl H-3, H-5; 4-methylphenyl H-3, H-5), 7.22 (d, J = 8.8 Hz, 2H, 4-methylphenyl H-2, H-6), 7.35 (d, J = 8.4 Hz, 2H, 4-methylsulfonamidophenyl H-2, H-6), 10.1 (s, 1H, NH). Anal. Calcd for $C_{18}H_{17}NO_4S \cdot 1/2\ H_2O$: C, 61.35; H, 5.10; N, 3.97. Found: C, 61.25; H, 4.74; N, 3.75.

5.14. 3-(4-Methoxyphenyl)-4-(4-methylsulfonamidophenyl)-2(5H)furanone (11f)

Compound **11f** was obtained as a yellow solid in 39% yield; mp 123–124 °C; IR (film) 3250 (NH), 1750 (furanone CO), 1335, 1150 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.06 (s, 3H, SO_2CH_3), 3.78 (s, 3H, OCH_3), 5.31 (s, 2H, CH_2), 7.01 (d, $J = 8.7$ Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.15 (d, $J = 8.4$ Hz, 2H, 4-methylsulfonamidophenyl H-3, H-5), 7.31 (d, $J = 8.4$ Hz, 2H, 4-methylsulfonamidophenyl H-2, H-6), 7.37 (d, 2H, $J = 8.7$ Hz, 4-methoxy phenyl H-2, H-6), 10.14 (s, 1H, NH). Anal. Calcd for $C_{18}H_{17}NO_5S$: C, 60.15; H, 4.77; N, 3.90. Found: C, 60.51; H, 4.46; N, 3.98.

6. Molecular modeling (docking) study

The docking experiment was performed using Insight II software Version 2000.1 (Accelrys Inc.) running on a Silicon Graphics Octane 2 R1400A workstation according to a previously reported method.[8]

7. 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 immunoassay (EIA) kit (catalog number 560101, Cayman Chemical, Ann Arbor, MI, USA) according to our previously reported method.[9]

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