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Synthesis of 2,3-diaryl-1,3-thiazolidine-4-one derivatives as selective cyclooxygenase (COX-2) inhibitors

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Abstract—A group of 2,3-diaryl-1,3-thiazolidine-4-ones, possessing a methylsulfonyl pharmacophore, were synthesized and their biological activities were evaluated for cyclooxygenase-2 (COX-2) inhibitory activity.

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of inflammation and pain is often accompanied by adverse gastrointestinal and renal side effects. Their anti-inflammatory activity results from inhibition of cyclooxygenases (COXs), which catalyzes the bioconversion of arachidonic acid to prostaglandins. However, inhibition of COXs may lead to undesirable side effects. Nowadays, it is well established that there are at least two COX isozymes, COX-1 and COX-2.[1] The constitutive COX-1 isozyme is produced in a variety of tissues and appears to be important to the maintenance of physiological functions such as gastroprotection and vascular homeostasis.[2] Alternatively, the COX-2 isozyme is induced by mitogenic and proinflammatory stimuli linking its involvement to inflammatory processes.[3] Thus, selective inhibition of COX-2 over COX-1 is useful for the treatment of inflammation and inflammation-associated disorders with reduced gastrointestinal toxicities when compared with NSAIDs. In addition to role of COX-2 in rheumatoid arthritis and osteoarthritis, it is also implicated in colon cancer and angiogenesis.[4,5] 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.[6] Diarylheterocycles, and other central ring pharmacophore templates, have been extensively studied as selective COX-2 inhibitors. All these tricyclic molecules possess 1,2 diaryl substitution on a central hetero- or carbocyclic ring system (see structures **1**–**5** in Chart 1).[7–12] Recently, we reported 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.[13,14] For example, the acyclic (*E*) 1,3-diphenylprop-2-en-1-ones possessing a 4-methylsulfonyl or 4-azido COX-2 pharmacophore group at the C-1 phenyl ring (see structure **6**) exhibited high selective COX-2 inhibition. As part of our ongoing program to design new types of tricyclic selective COX-2 inhibitors, we now report the design, synthesis, cyclooxygenase inhibitory, and some molecular modeling studies of a group of 2,3-diaryl-1,3-thiazolidine-4-ones possessing a COX-2 SO_2Me pharmacophore at the *para*-position of C-2 phenyl ring in conjunction with a substituent (H, F, Me, and OMe) at the *para*-position of the N-3 phenyl ring.

The target 2,3-diaryl-1,3-thiazolidine-4-one derivatives were synthesized via the route outlined in Scheme 1. Accordingly, an appropriate aromatic amine (**1**) was treated with 4-methylthiobenzaldehyde (**2**) and thioglycolic acid (**3**) in dry toluene under reflux to give 2-(4-methylthiophenyl)-3-(4-substitutedphenyl)-1,3-thiazolidine-4-one (**4**, 20–45%) (4, 20–45%)[18]. Oxidation of **4** using 30%

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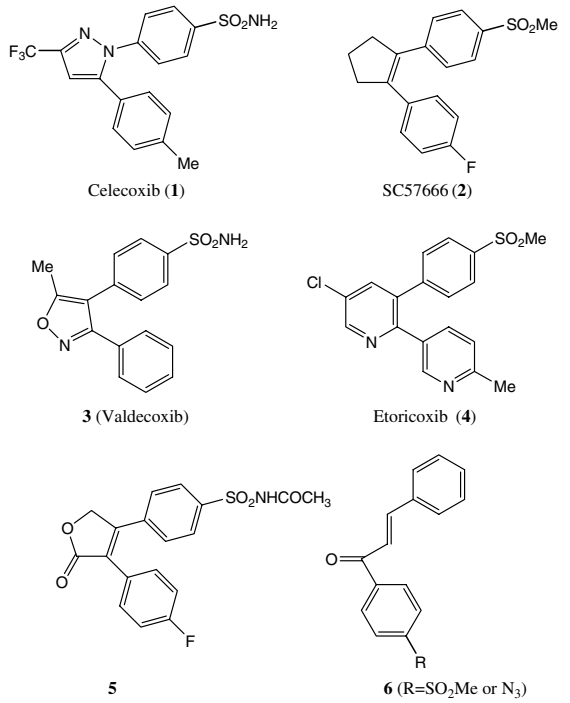
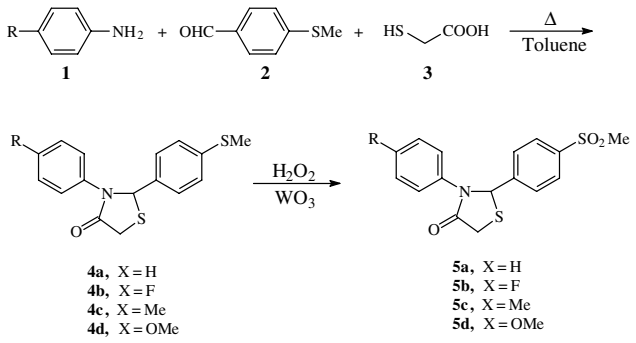


Chart 1. Representative examples of selective COX-2 inhibitors.

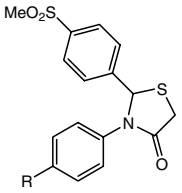


Scheme 1. Reagents and conditions: (a) Toluene, reflux, 48 h; (b) H_2O_2 30%, WO_3, 25 °C, 12 h.

H_2O_2 in hydromethanol in the presence of a trace amount of WO_3 afforded the 2-(4-methylsulfonylphenyl)-3-(4-substitutedphenyl)-1,3-thiazolidine-4-one (**5**, 60–80%).[15,19]

It is well established for the diarylheterocyclic class of COX-2 inhibitors, that a *para*-methylsulfone substituent on one of the phenyl rings is a requirement for good COX-2 potency and selectivity. Accordingly, a group of 2,3-diaryl-1,3-thiazolidine-4-one analogues having different substituents at *para*-position of the N-3 phenyl ring (**5a**–**d**) were prepared to investigate the effect of different substituents on COX-2 selectivity and potency. The ability of the 1,3-thiazolidine-4-ones **5a**–**d** to inhibit the COX-1 and COX-2 isozymes was determined using chemiluminescent enzyme assays (see enzyme inhibition data in Table 1). In vitro COX-1/COX-2 inhibition studies showed that all compounds **5a**–**d** were selective inhibitors of the COX-2 isozyme with IC_{50} values in the highly potent 0.12–0.20 μM range, and COX-2 selectivity indexes (SI) in the >359 to >833 range. In addition, compounds **5b** and **5d** did not inhibit COX-1 at a concentration of 100 μM (IC_{50} values > 100 μM). However, compounds **5a** and **5c** showed less selectivity for COX-2 isozyme compared with compounds **5a** and **5c**. According to these results, 3-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)-1,3-thiazolidine-4-one **5b** was the most potent (IC_{50} = 0.12 μM), and selective (SI > 833), COX-2 inhibitor among the synthesized compounds. It was also more selective COX-2 inhibitor than the parent reference compound celecoxib (SI > 403). These data suggest that the compound **5b** should inhibit the synthesis of inflammatory prostaglandins via the cyclooxygenase pathway at sites of inflammation and be devoid of ulcerogenicity due to the absence of COX-1 inhibition.

Table 1. In vitro COX-1 and COX-2 enzyme inhibition data



Compound	R	IC_{50}[a] (μM)		COX-2 SI[b]
		COX-1	COX-2	
5a	H	96.1	0.20	480.5
5b	F	>100	0.12	>833
5c	Me	53.9	0.15	359.3
5d	OMe	>100	0.16	>625
Celecoxib		24.3	0.06	> 403

[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}).

The orientation of the highly potent and selective COX-2 inhibitor, 3-(4-fluorophenyl)-2-(4-methylsulfonylphenyl)-1,3-thiazolidine-4-one **5b** in the COX-2 active site,

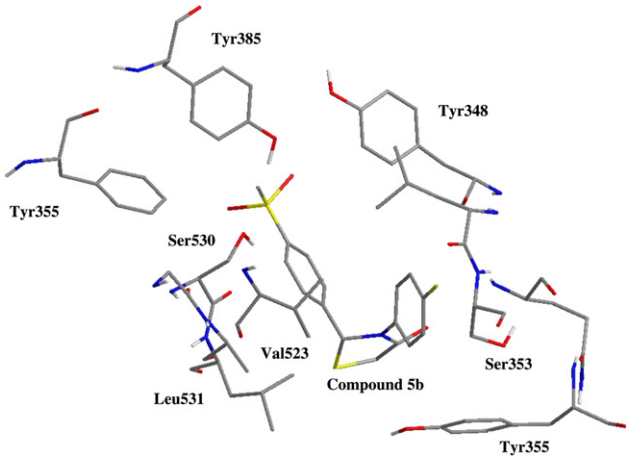


Figure 1. Compound **5b** 3-(4-fluorophenyl)-(2-(4-methylthiophenyl)-1,3-thiazolidine-4-one docked in the active site of murine COX-2 isozyme.

was examined by a docking experiment (Fig. 1).[16,17] This molecular modeling shows that it binds in the primary binding site such that the C-2 *para*-SO_2Me substituent inserts into the 2° pocket present in COX-2. One of the O-atoms of *p*-SO_2Me forms a hydrogen bonding interaction with hydroxyl group (O*H*) of Tyr^{385} (distance < 2) whereas the other O-atom is close to O*H* of Ser^{530} (distance = 2.7). The C=*O* of the central thiazolidine-4-one forms hydrogen bond (distance = 4.4) with the O*H* of Ser^{353}. It was interesting to note that, the *para*-fluoro substituent of N-3 phenyl ring was forming a hydrogen bond with amide hydrogen (N*H*) of Ser^{353} (distance = 4.4). These observations together with experimental results provide a good explanation for the potent and selective inhibitory activity of **5b**.

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16. Docking studies were performed using Autodock software Version 3.0. The coordinates of the X-ray crystal structure of the selective COX-2 inhibitor SC-558 bound to the murine COX-2 enzyme was obtained from the RCSB Protein Data Bank (1c × 2) and hydrogens were added. The ligand molecules were constructed using the Builder module and were energy minimized for 1000 iterations reaching a convergence of 0.01 kcal/mol Å. The energy minimized ligands were superimposed on SC-558 in the PDB file 1c × 2 after which SC-558 was deleted. The purpose of docking is to search for favorable binding configuration between the small flexible ligands and the rigid protein. Protein residues with atoms greater than 7.5 Å from the docking box were removed for efficiency. Searching is conducted within a specified 3D docking box using annealing based on the Monte Carlo method and MMFF94 molecular mechanics force field for 8000 iterations. These docked structures were very similar to the minimized structures obtained initially. The quality of the docked structures was evaluated by measuring the intermolecular energy of the ligand-enzyme assembly.
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18. Analytical data for **4a**. Yield, 45%; white crystalline powder; mp 105–106 °C; IR (KBr): υ cm^{-1} 1680 (C=O); MS: *m/z* (%): 301 (M^+, 60), 226(55), 177(75), 134(100), 104(45), 91(30), 77(40); ^1H NMR ($CDCl_3$): δ ppm 2.48 (S, 3H, SCH_3), 3.90 (d, 1H, CH_2, J = 15.8 Hz), 4.04 (d, 1H, CH_2, J = 15.8 Hz), 6.10 (S, 1H, CH), 7.18 (d, 2H, 4-methylthio phenyl H_3 and H_5, J = 8.4 Hz), 7.19–7.23 (m, 3H, phenyl H_3—H_5), 7.25 (d, 2H, 4-methylthio phenyl H_2 and H_6, J = 8.4 Hz), 7.33 (dd, 2H, phenyl H_2 and H_6, J = 7.8 Hz); Anal. $C_{16}H_{15}NOS_2$ (C, H, and N).
Compound **4b**. Yield, 35%; white crystalline powder; mp 97 °C; IR (KBr): υ cm^{-1} 1670 (C=O); MS: *m/z* (%): 319 (M^+, 30), 243(40), 228(20), 177(45), 134(100), 94(70), 77(40); Anal. $C_{16}H_{14}FNOS_2$ (C, H, and N).
Compound **4c**. Yield, 20%; white crystalline powder; mp 101–102 °C; IR (KBr): υ cm^{-1} 1680 (C=O); MS: *m/z* (%): 315 (M^+, 60), 240(70), 178(100), 135(90), 91(90), 77(30); Anal. $C_{17}H_{17}NOS_2$ (C, H, and N).
Compound **4d**. Yield, 35%; white crystalline powder; mp 103–104 °C; IR (KBr): υ cm^{-1} 1670 (C=O); MS: *m/z* (%): 331 (M^+, 25), 257(45), 242(50), 178(45), 135(100), 77(30); Anal. $C_{17}H_{17}NOS_2$ (C, H, and N). Satisfactory analysis for C, H, N was obtained for all the compounds within ±0.4% of the theoretical values.
19. Analytical data for **5a**. Yield, 60%; white crystalline powder; mp 238–239 °C; IR (KBr): υ cm^{-1} 1670 (C=O), 1300, 1120 (SO_2); MS: *m/z* (%): 333 (M^+, 15), 259(45), 179(30), 123(70), 77(100); ^1H NMR ($CDCl_3$): δ ppm 3.23 (S, 3H, SO_2CH_3), 3.92 (d, 1H, CH_2, J = 16.5 Hz), 4.08 (d, 1H, CH_2, J = 16.5 Hz), 6.71 (S, 1H, CH), 7.25–7.50 (m, 5H, phenyl), 7.82 (d, 2H, 4-methylsulfonyl phenyl H_2 and

H_6, J = 8.4 Hz), 8.01 (d, 2H, 4-methylsulfonyl phenyl H_3 and H_5, J = 8.4 Hz); Anal. $C_{16}H_{15}NO_3S_2$ (C, H, and N). Compound **5b**. Yield, 65%; white crystalline powder; mp 234 °C; IR (KBr): υ cm^{-1} 1670 (C=O), 1310, 1120 (SO_2); MS: *m*/*z* (%): 351 (M^+, 5), 277(100), 197(60), 122(60), 95 (90), 77(50); ^1H NMR ($CDCl_3$): δ ppm 3.24 (S, 3H, SO_2CH_3), 3.74 (d, 1H, CH_2, J = 17.0 Hz), 4.41 (d, 1H, CH_2, J = 17.0 Hz), 6.66 (S, 1H, CH), 7.27 (t, 2H, 4-fluorophenyl H_3 and H_5, J = 8.8 Hz), 7.53 (dd, 2H, 4-fluorophenyl H_2 and H_6, J_{HH} = 8.6 Hz, J_{HF} = 4.9 Hz), 7.81 (d, 2H, 4-methylsulfonyl phenyl H_2 and H_6, J = 8.3 Hz), 7.99 (d, 2H, 4-methylsulfonyl phenyl H_3 and H_5, J = 8.3 Hz); Anal. $C_{16}H_{14}FNO_3S_2$ (C, H, and N). Compound **5c**. Yield, 75%; white crystalline powder; mp 236–237 °C; IR (KBr): υ cm^{-1} 1680 (C=O), 1300, 1110 (SO_2); MS: *m*/*z* (%): 347 (M^+, 5), 273(100), 193(60), 118(60), 91 (100), 77(50); ^1H NMR ($CDCl_3$): δ ppm 2.26 (S, 3H, CH_3), 3.23 (S, 3H, SO_2CH_3), 3.71 (d, 1H, CH_2, J = 17.0 Hz), 4.39 (d, 1H, CH_2, J = 17.0 Hz), 6.67 (S, 1H, CH), 7.21 (d, 2H, 4-methylphenyl H_3 and H_5, J = 8.4 Hz), 7.38 (d, 2H, 4-methylphenyl H_2 and H_6, J = 8.4 Hz), 7.80 (d, 2H, 4-methylsulfonyl phenyl H_2 and H_6, J = 8.3 Hz), 7.98 (d, 2H, 4-methylsulfonyl phenyl H_3 and H_5, J = 8.3 Hz); Anal. $C_{17}H_{17}NO_3S_2$ (C, H, and N).

Compound **5d**. Yield, 80%; white crystalline powder; mp 205–206.5 °C; IR (KBr): υ cm^{-1} 1670 (C=O), 1300, 1100 (SO_2); MS: *m*/*z* (%): 363 (M^+, 5), 289(100), 274(75), 195(40), 91 (90), 77(30); ^1H NMR ($CDCl_3$): δ ppm 3.23 (S, 3H, SO_2CH_3), 3.70 (d, 1H, CH_2, J = 17.2 Hz), 3.75 (S, 3H, OCH_3), 4.38 (d, 1H, CH_2, J = 17.2 Hz), 6.65 (S, 1H, CH), 6.96 (d, 2H, 4-methoxyphenyl H_3 and H_5, J = 8.9 Hz), 7.37 (d, 2H, 4-methoxyphenyl H_2 and H_6, J = 8.9 Hz), 7.81 (d, 2H, 4-methylsulfonyl phenyl H_2 and H_6, J = 8.3 Hz), 7.98 (d, 2H, 4-methylsulfonyl phenyl H_3 and H_5, J = 8.3 Hz); Anal. $C_{17}H_{17}NO_4S_2$ (C, H, and N). Satisfactory analysis for C, H, N was obtained for all the compounds within ±0.4% of the theoretical values.