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Design and synthesis of 1,3-diarylurea derivatives as selective cyclooxygenase (COX-2) inhibitors

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Abstract—A group of 1,3-diarylurea derivatives, possessing a methylsulfonyl pharmacophore at the *para*-position of the N-1 phenyl ring, in conjunction with a N-3 substituted-phenyl ring (4-F, 4-Cl, 4-Me, 4-OMe), were designed and synthesized for evaluation as selective cyclooxygenase-2 (COX-2) inhibitors. In vitro COX-1/COX-2 isozyme inhibition structure–activity studies identified 1-(4-methylsulfonylphenyl)-3-(4-methoxyphenyl) urea (**4e**) as a potent COX-2 inhibitor (IC_{50} = 0.11 μM) with a high COX-2 selectivity index (SI = 203.6) comparable to the reference drug celecoxib (COX-2 IC_{50} = 0.06 μM; COX-2 SI = 405). The structure–activity data acquired indicate that the urea moiety constitutes a suitable scaffold to design new acyclic 1,3-diarylurea derivatives with selective COX-2 inhibitory activity.

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin exhibit their anti-inflammatory effects by inhibiting cyclooxygenase (COX) which catalyzes the bioconversion of arachidonic acid to prostaglandins. However, inhibition of COXs may lead to undesirable side effects such as gastric ulceration, bleeding, and renal function suppression. Nowadays, it is well established that there are at least two COX isozymes, COX-1 and COX-2.[1,2] The isozyme COX-1 is constitutive and responsible for the physiological production of prostaglandins, while the COX-2 isozyme is inducible and responsible for the elevated production of prostaglandins during inflammation.[3,4] 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.[5,6] 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.[7] 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).[8–14] The recent withdrawal of some diarylheterocyclic selective COX-2 inhibitors such as rofecoxib and valdecoxib due to their adverse cardiovascular side effects[15,16] 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 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, 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 selective COX-2 inhibitors, we now report the synthesis, some structure–activity relationships, and a molecular modeling study for a group of 1,3-diarylurea derivatives possessing a COX-2 SO_2Me pharmacophore at the *para*-position of phenyl ring in

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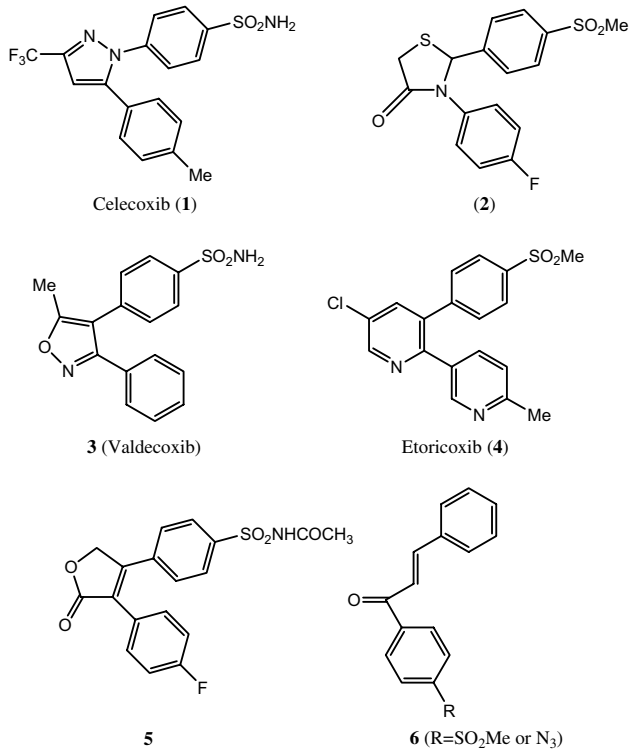


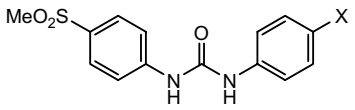
Chart 1. Representative examples of selective COX-2 inhibitors.

conjunction with various substituents (H, F, Cl, Me, and OMe) at the *para*-position of the N-3 phenyl ring.

The target 1,3-diarylurea derivatives were synthesized via the route outlined in Scheme 1. Accordingly, 4-methylthioaniline (**1**) was treated with an appropriate phenylisocyanate (**2**) in dry THF under reflux to give 1-(4-methylthiophenyl)-3-(4-substituted-phenyl) urea (**3**, 42–60%).[19] Oxidation of **3** using oxone in THF/H_2O afforded the 1-(4-methylsulfonylphenyl)-3-(4-substituted-phenyl) urea (**4**, 53–90%).[17,22]

A group of 1,3-diarylurea derivatives possessing a methylsulfonyl pharmacophore at the *para*-position of the N-1 phenyl ring having a variety of substituents (H, F, Cl, Me, OMe) at the *para*-position of the N-3 phenyl ring (**4a**–**e**) 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 nature of the *para*-substituents on the N-3 phenyl ring was determinant of COX-2 inhibitory potency and selectivity. The ability of the 1,3-diarylurea derivatives **4a**–**e** to inhibit the COX-1 and COX-2 isozymes was determined using chemiluminescent enzyme assays according to our previously reported method[14] (see enzyme inhibition data in Table 1). In vitro COX-1/COX-2 inhibition studies showed that all compounds **4a**–**e** were selective inhibitors of the COX-2 isozyme with IC_{50} values in the highly potent 0.11–0.33 μM range, and COX-2 selectivity indexes (SI) in the >54 to >203 range. According to these results, 1-(4-methylsulfonylpheny)-3-(4-methoxyphenyl) urea **4e** was the most potent (IC_{50} = 0.11 μM), and selective (SI > 203), COX-2 inhibitor among the synthesized compounds. The structure–activity relationship study of these compounds indicated that the order of COX-2 selectivity was OMe > F > Cl > H > Me. These results showed that the presence of a hydrogen acceptor group such as methoxy or fluorine substituent at the *para*-position of the N-3 phenyl ring may improve selectivity and potency for COX-2 inhibition. These data suggest that the com-

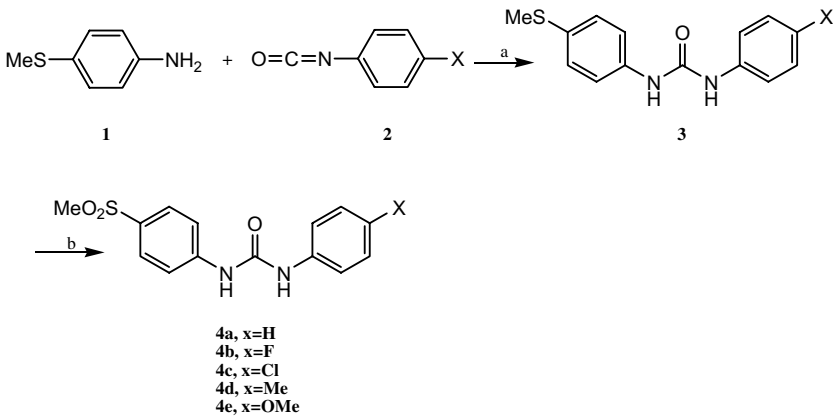
Table 1. In vitro COX-1 and COX-2 enzyme inhibition data



Compound	R	IC_{50}[a] (μM)		COX-2 SI[b]
		COX-1	COX-2	
4a	H	9.2	0.17	54.1
4b	F	21.8	0.13	167.7
4c	Cl	21.5	0.27	79.6
4d	Me	12.5	0.33	37.9
4e	OMe	22.4	0.11	203.6
Celecoxib		24.3	0.06	405

[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}).



Scheme 1. Reagents and conditions: (a) dry THF, reflux, 3 h; (b) Oxone®, THF/H_2O, 12 h.

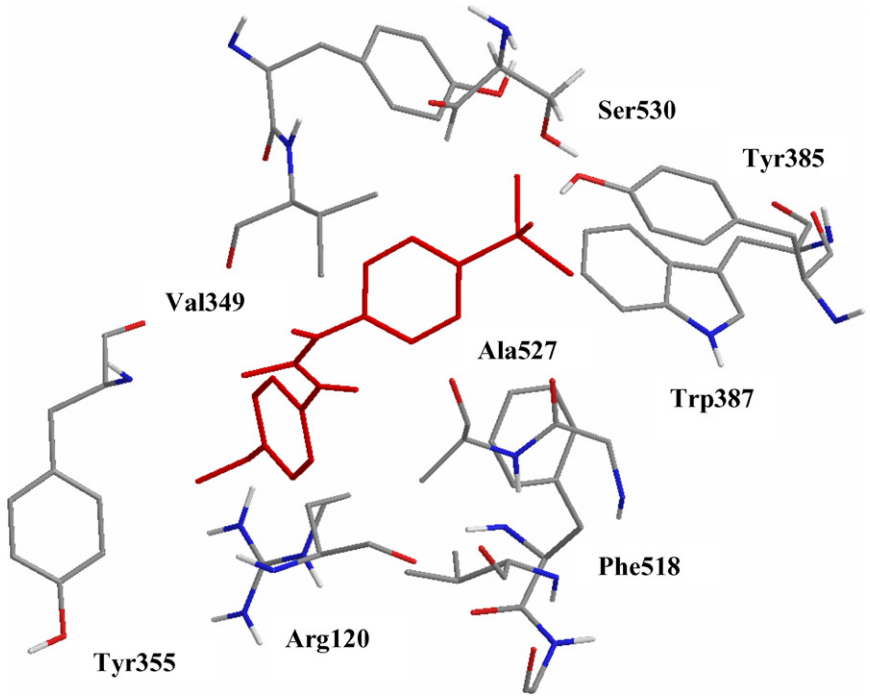


Figure 1. Compound **4e** 1-(4-methylsulfonylpheny)-3-(4-methoxyphenyl) urea docked in the active site of murine COX-2 isozyme.

pound **4e** 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.

The orientation of the most potent and selective COX-2 inhibitor, 1-(4-methylsulfonylpheny)-3-(4-methoxyphenyl) urea **4e**, in the COX-2 active site was examined by a docking experiment (Fig. 1).[20,21] This molecular modeling shows that it binds in the primary binding site such that the N-1 *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 Ser^{530} (distance = 2.6) whereas the other *O*-atom is close to O*H* of Tyr^{385} (distance = 2.8). The C=*O* of the central urea moiety forms hydrogen bond (distance = 3.8) with the N*H* of Tyr^{355}. The N_1H can form hydrogen bond (distance = 3.4) with C=*O* of Val^{349} while the N_3H is almost close to C=*O* group of Ala^{527} (distance < 6). These observations together with experimental results provide a good explanation for the potent and selective inhibitory activity of **4e**.

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22. Analytical data for compound **4a**: yield, 53%; pale yellow crystalline powder; mp 184 °C; IR (KBr): υ cm^{-1} 3390 (NH), 1675 (C═O), 1300, 1150 (SO_2); ^1H NMR ($CDCl_3$): δ ppm 2.99 (S, 3H, SO_2CH_3), 6.98–7.01 (m, 3H, phenyl H_3–H_5), 7.40 (d, 2H, phenyl H_2 and H_6, J = 7.6 Hz), 7.61 (d, 2H, 4-methyl sulfonyl phenyl H_2 and H_6, J = 8.4 Hz), 7.75 (d, 2H, 4-methylsulfonyl phenyl H_3 and H_5, J = 8.4 Hz), 8.19 (S, 1H, NH), 8.64 (S, 1H, NH); Anal. $C_{14}H_{14}N_2O_3S$ (C, H, N). Compound **4b**: yield, 80%; light brown crystalline powder; mp 196–197 °C; IR (KBr): υ cm^{-1} 3380 (NH), 1670 (C═O), 1300, 1150 (SO_2); ^1H NMR ($CDCl_3$): δ ppm 3.08 (S, 3H, SO_2CH_3), 7.69 (t, 2H, 4-fluorophenyl H_3 and H_5), 7.27 (dd, 2H, 4-fluorophenyl H_2 and H_6), 7.51 (d, 2H, 4-methylsulfonyl phenyl H_2 and H_6, J = 8.5 Hz), 7.65 (d, 2H, 4-methylsulfonyl phenyl H_3 and H_5, J = 8.5 Hz), 8.19 (S, 1H, NH), 8.60 (S, 1H, NH); Anal. $C_{14}H_{13}N_2O_3FS$ (C, H, N). Compound **4c**: yield, 87%; pale yellow crystalline powder; mp 204 °C; IR (KBr): υ cm^{-1} 3350, 3280 (NH), 1670 (C═O), 1300, 1140 (SO_2); ^1H NMR ($CDCl_3$): δ ppm 3.16 (S, 3H, SO_2CH_3), 7.35 (d, 2H, 4-methylsulfonyl phenyl H_2 and H_6, J = 8.6 Hz), 7.51 (d, 2H, 4-methylsulfonyl phenyl H_3 and H_5, J = 8.6 Hz), 7.69 (d, 2H, 4-chloro phenyl H_2 and H_6, J = 8.5 Hz), 7.98 (d, 2H, 4-chlorophenyl H_3 and H_5, J = 8.5 Hz), 9.01 (S, 1H, NH), 9.26 (S, 1H, NH); Anal. $C_{14}H_{13}N_2O_3ClS$ (C, H, N). Compound **4d**: yield, 67%; pale yellow crystalline powder; mp 183 °C; IR (KBr): υ cm^{-1} 3310 (NH), 1680 (C═O), 1300, 1150 (SO_2); ^1H NMR ($CDCl_3$): δ ppm 2.15 (S, 3H, CH_3), 2.99 (S, 3H, SO_2CH_3), 6.92 (d, 2H, 4-methylphenyl H_3 and H_5, J = 8.2 Hz), 7.15 (d, 2H,4-methylphenyl H_2 and H_6, J = 8.2 Hz), 7.49 (d, 2H, 4-methylsulfonyl phenyl H_2 and H_6, J = 8.4 Hz), 7.61 (d, 2H, 4-methylsulfonyl phenyl H_3 and H_5, J = 8.4 Hz), 8.11 (S, 1H, NH), 8.62 (S, 1H, NH); Anal. $C_{15}H_{16}N_2O_3S$ (C,H, N). Compound **4e**: yield, 90%; pale yellow crystalline powder; mp 228 °C; IR (KBr): υ cm^{-1} 3310 (NH), 1670 (C═O), 1300, 1150 (SO_2); ^1H NMR ($CDCl_3$): δ ppm 3.15 (S, 3H, SO_2CH_3), 3.72 (S, 3H, OCH_3), 6.89 (d, 2H, 4-methoxyphenyl H_3 and H_5, J = 8.6 Hz), 7.37 (d, 2H, 4-methoxyphenyl H_2 and H_6, J = 8.6 Hz), 7.68 (d, 2H, 4-methylsulfonyl phenyl H_2 and H_6, J = 8.5 Hz), 7.80 (d, 2H, 4-methylsulfonyl phenyl H_3 and H_5, J = 8.5 Hz), 8.67 (S, 1H, NH), 9.15 (S, 1H, NH); Anal. $C_{15}H_{16}N_2O_4S$ (C,H, N). Satisfactory analysis for C, H, N was obtained for all the compounds within ±0.4% of the theoretical values.