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1,5-Diarylimidazoles with strong inhibitory activity against COX-2 catalyzed PGE_2 production from LPS-induced RAW 264.7 cells

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ABSTRACT

A series of 1,5-diarylimidazoles with 4-methylsulfonylphenyl group were prepared and evaluated for the inhibitory activities against COX-2 catalyzed PGE_2 production from LPS-induced RAW 264.7 cells. Most of synthesized 1,5-diarylimidazoles exhibited strong inhibitory activities regardless of the position of the 4-methylsulfonylphenyl group. The 1,5-diarylimidazoles with a halogen atom (**3c**–**3h**, **3n**–**3p**) gave mostly excellent inhibitory activities regardless of the position and species of the halogen atom. Whereas the 1,5-diarylimidazoles with two fluorine atoms (**3k**, **3l**, **3r**, **3s**) showed rather reduced inhibitory activities.

Inflammatory process comprises of several aspects provoked by different chemicals and biologicals including proinflammatory enzymes/cytokines, small molecular chemicals such as eicosanoids and tissue degradation enzymes. Among these factors, cyclooxygenase (COX), is a key proinflammatory enzyme which catalyzes the conversion of arachidonic acid to prostaglandins (PGs). Cyclooxygenase exists in two isoforms. Cyclooxygenase-1 (COX-1) is a constitutive enzyme processing homeostasis function, while cyclooxygenase-2 (COX-2) is an inducible one and known as a major isoform found in the inflammatory lesions.[1] Therefore, COX-2 selective inhibitors are useful drugs for the treatment of acute pain and chronic inflammatory diseases with reduced side effects such as gastrotoxicity.

Extensive efforts have been reported toward the development of selective COX-2 inhibitors over the past two decades. Structural variation of the central heterocycle in the tricyclic series has been a popular area of research and diverse heterocycles have been explored.[2] From the previous SAR studies, it has been well known that the diarylheterocycle COX-2 selective inhibitors require a 4-methylsulfonylphenyl or a 4-sulfonamidophenyl group attached to an unsaturated ring system in which an additional vicinal lipophilic moiety is present to possess good activity and selectivity (Fig. 1).

Also it was well acknowledged that the nature of central scaffold is very important for the activity, therefore, the choice of the central scaffold is crucial for the activity as well as selectivity. As the central scaffold, diverse regioisomeric imidazoles such as 1,2-,[3] 1,5-[4,5,6], and 4,5-diarylimidazoles[7] have been explored, however, only 1,5-diarylimidazole made success and is pursued in further development.

As part of our research to discover novel COX-2 selective inhibitors, 1,5-diarylimidazole analogs with a 4-methylsulfonylphenyl group at 1- or 5-position were synthesized and evaluated for their inhibitory activities against COX-2 catalyzed PGE_2 production from LPS-induced RAW 264.7 cells. 5-(4-Methylsulfonylphenyl) imidazoles (**3a**–**l**) were obtained by 1,3-dipolar cycloadditions of 4-methylsulfanylbenzylidenearylamines and tosylmethyl isocyanide (TosMIC)[8–10] in the presence of K_2CO_3 as the key step followed by oxidations with oxone® as shown in Scheme 1. 4-Methylsulfanylbenzylidene arylamines (**1a**–**l**) were prepared from 4-methylsulfanylbenzaldehyde and the corresponding arylamines in good yields. 1-(4-Methylsulfonylphenyl) imidazoles were prepared following the same procedure. Reactions of *N*-(4-methylsulfanylphenyl)benzylidene amines and TosMIC followed by oxidations yielded the corresponding 1,5-diarylimidazoles **3m**–**t** (Scheme 1). The *N*-(4-methylsulfanylphenyl)benzylideneamines (**1m**–**t**) were prepared from 4-methylsulfanylaniline and the corresponding arylaldehydes in good yields. The chemical yields for each compound are summarized in Table 1.

Inhibition of COX-2 catalyzed PGE_2 production from LPS-induced RAW 264.7 cells by 1,5-diarylimidazoles was determined according to the published procedure.[11] RAW 264.7 cells obtained from American Type Culture Collection were cultured with DMEM

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Table 1
Yields of each compounds and % inhibitory activities of 1,5-diarylimidazoles (**3a**–**3s**) against COX-2 catalyzed PGE_2 production from LPS-induced RAW 264.7 cell

Code No.	R^1 or R^2	Yields (%)	% Inhibition (10 μM)
1a/2a/3a	4-H	94/70/95	91
1b/2b/3b	4-CH_3	90/75/90	99
1c/2c/3c	4-F	97/64/93	93
1d/2d/3d	3-F	95/85/97	86
1e/1e/3e	2-F	93/63/96	96
1f/2f/3f	4-Cl	98/85/96	100
1g/2g/3g	3-Cl	95/92/99	100
1h/2h/3h	4-Br	90/92/97	100
1i/2i/3i	4-OCH_3	93/30/95	98
1j/2j/3j	4-SO_2CH_3	89/40/80	13
1k/2k/3k	2,4-F_2	89/25/90	89
1l/2l/3l	3,4-F_2	92/90/91	55
1m/2m/3m	4-CH_3	90/73/89	90
1n/2n/3n	4-F	95/65/92	100
1o/2o/3o	4-Cl	93/75/89	100
1p/2p/3p	4-Br	92/80/92	84
1q/2q[12]**/3q**[13]	4-OCH_3	96/80/90	100
1r/2r/3r	2,4-F_2	93/86/93	90
1s/2s/3s	3,4-F_2	94/83/97	97
References	Celecoxib/NS-398		99/100

(a) All compounds were treated at 10 μM. Treatment of LPS to RAW cells increased PGE_2 production (10.0 μM) from the basal level of 0.5 μM. (b)% Inhibition = 100 × [1 − (PGE_2 of LPS with the flavones treated group- PGE_2 of the basal)/(PGE_2 of LPS treated group- PGE_2 of the basal)]. (c) Celecoxib and NS-398 were used as the reference compound. (d) All data are the arithmetic means ± S.D. (n = 3).

supplemented with 10% FBS and 1% CO_2 at 37 °C and activated with LPS. Briefly, cells were plated in 96-well plates (2×10^5 cells/well). Each 1,5-diarylimidazole and LPS (1 g/ml) were added and incubated for 24 h. Cell viability was assessed with MTT assay based on the experimental procedures described previously. PGE_2 concentration in the medium was measured using EIA kit for PGE_2 according to the manufacture's recommendation. All experiments were carried out at least twice and they gave similar results. The inhibitory activities of imidazoles on COX-2 catalyzed PGE_2 production from LPS-induced RAW 264.7 cells were estimated and the results are shown in Table 1.

As demonstrated in Table 1, most 1,5-diarylimidazole analogs exhibited strong inhibitory activities against COX-2 catalyzed PGE_2 production from LPS-induced RAW 264.7 cells regardless of the position of the 4-methylsulfonylphenyl group. Surprisingly the 1,5-diarylimidazole (**3j**) with 4-methylsulfonylphenyl group at both 1- and 5-positions totally lost its inhibitory activity. The 1,5-diarylimidazoles with a halogen atom (**3c**–**3h**, **3n**–**3p**) gave mostly excellent inhibitory activities regardless of the position and species of the halogen atom. Whereas the 1,5-diarylimidazoles with two fluorine atoms (**3k**, **3l**, **3r**, **3s**) showed rather reduced inhibitory activities. Our results are quite different from those of the previously reported results that introduction of a small substituent at the β-position of 4-methylsulfonylphenyl group showed remarkable inhibitory activities.[3,6]

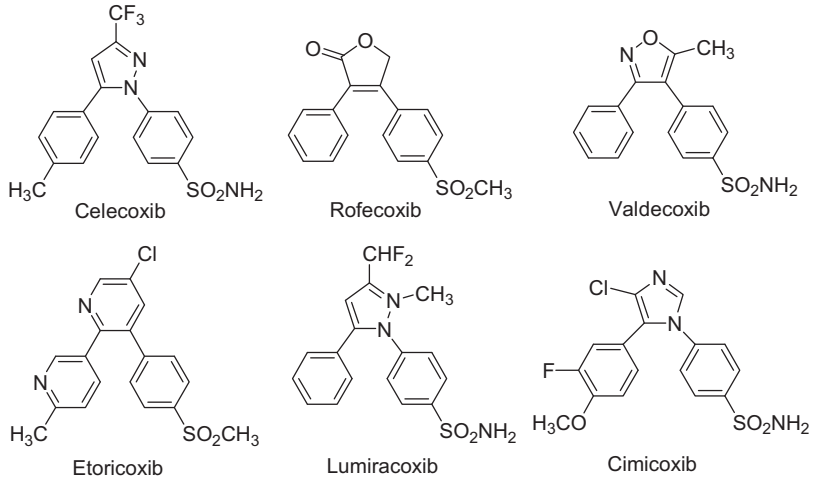
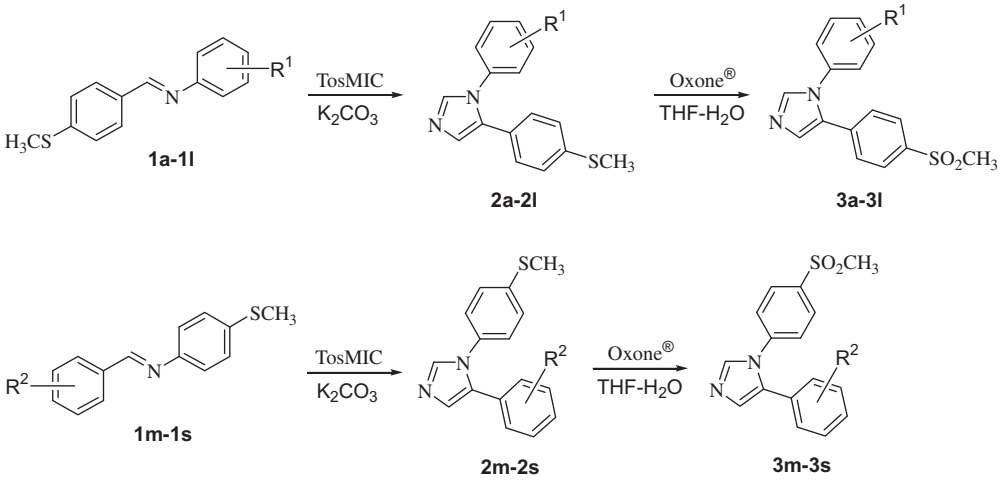


Figure 1. Structures of COX-2 inhibitors in the market.



Scheme 1. Synthesis of 1,5-diarylimiazoles with a 4-methylsulfonyphenyl group.

In conclusion, introduction of a halogen atom and a 4-methylsulfony group to any aryl groups of the 1,5-diarylimidazole improved bioactivity. Further COX-2 and COX-1 inhibitory activity tests of the synthesized 1,5-diarylimidazoles are under investigation to determine the COX-2 versus COX-1 selectivity.

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12. *Reaction conditions for 1-(4-methylthiophenyl)-5-(4-methoxyphenyl)imidazole* (**2q**): To the solution of an imine (2 mmol) in anhydrous MeOH (10 mL) was added anhydrous K_2CO_3 (0.83 g, 6 mmol) and 0.39 g (2 mmol) of *p*-toluenesulfonylmethylisocyanide (TosMIC).The reaction mixture was refluxed for overnight. After cooling, the solvent was distilled off under reduced pressure, and the residue was extracted with ether.
After washing with brine, the ethereal extract was dried over $MgSO_4$. The solvent was distilled off under reduced pressure. Purification of the residue by silica gel column chromatography with $CHCl_3$/MeOH (20:1) yielded product in 80% yield as a white solid. mp 150–151 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70 (s, 1H, H_2-imidazole), 7.27–7.20 (m, 2H, Ar-H), 7.12–7.03 (m, 4H, Ar-H), 7.11 (s, 1H, H_4-imidazole), 6.84–6.77 (m, 2H, Ar-H), 3.78 (s, 3H, OCH_3), 2.49 (s, 3H, SCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.0, 140.0, 138.7, 136.1, 134.1, 130.3, 127.9, 127.5, 126.6, 122.1, 114.7, 55.9, 16.1; *m*/*z* 297 (M^+, 74), 296 (100), 282 (45), 281 (80), 269 (49), 258 (61), 254 (57).
13. *Reaction conditions for 1-(4-methylsulfonylphenyl)-5-(4-methoxyphenyl)imidazole* (**3q**): To the solution of the methylthioimidazole (**2q**, 1 mmol) in THF (10 mL) at −10 °C, Oxone® (1.6 g, 2.6 mmol) in H_2O (14 mL) was added dropwise. The resulting mixture was stirred at 23 °C for 24 h. The reaction mixture was quenched with ice, extracted with CH_2Cl_2, washed with brine and dried over $MgSO_4$. After filtration, the filtrate was evaporated under reduced pressure. The residue was recrystallized in ethyl acetate to give the title product in 90% yield as white solid. mp 186–187 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.77 (s, 1H, H_2-imidazole), 7.36 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.22 (s, 1H, H_4-imidazole), 7.04 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.83 (d, *J* = 8.4 Hz, 2H, Ar-H), 3.80 (s, 3H, OCH_3), 3.08 (s, 3H, SO_2CH_3); *m*/*z* 328 (M^+, 34), 296 (100), 283 (56), 240 (43).