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Synthesis and Antiinflammatory Activity of 1,5-Diarylimidazoles

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A number of 1,5-diarylimidazoles has been synthesized and evaluated for their inhibitory activities of COX-2 catalyzed PGE_2 production. 1,5-Diarylimidazoles were obtained from imimes and *p*-toluenesulfonylmethyl cyanide (TosMIC). Imines were prepared from commercially available amines and aldehydes. Among the compounds tested, 1-(2,4-difluorophenyl)-5-(4-methylsulfonylphenyl)imidazole (**2r**) showed strong inhibitory activity, however, most diarylimidazoles exhibited little to low inhibitory activities against COX-2 catalyzed PGE_2 production.

Key words: 1,5-Diarylimidazoles, COX-2, Prostaglandin production inhibition, Antiinflammatory activity

INTRODUCTION

Chronic inflammation diseases such as rheumatoid arthritis are problematic therapeutic areas to overcome because their long-term therapeutic periods limit the use of therapeutic agents with side effects. Inflammatory process comprises of several aspects provoked by different chemicals/biologicals including proinflammatory enzymes/cytokines, small molecular chemicals such as eicosanoids and tissue degradation enzymes. Among these factors, cyclooxygenase (COX) catalyses the conversion of arachidonic acid to prostaglandins (PGs), a key proinflammatory eicosanoid. COX 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. Also it has been reported that COX-2 produces large quantities of PGs, deeply involved in many pathological conditions, especially inflammation-related diseases (Needleman *et al.*, 1997).

Much efforts have been reported toward the development of selective COX-2 inhibitors over the past two decades. Structural variation of the central ring in the tricyclic series has been a popular area of research and diverse heterocycles have been explored (Black, 2004). Six COX-2 selective inhibitors such as celecoxib, rofecoxib, valdecoxib, etoricoxib, parecoxib sodium and lumiracoxib have been launched in the market though rofecoxib was dropped from market recently due to its side effect (Fig. 1).

As part of our research to discover novel COX-2 selective inhibitors for the treatment of chronic inflammation diseases, 1,5-diarylimidazole analogs (Fig. 1) have been synthesized and evaluated for their inhibitory activities against COX-2 catalyzed PGE_2 production from LPS-induced RAW 264.7 cells.

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MATERIALS AND METHODS

Methanol was freshly distilled from sodium. All aldehydes and amines were purchased from Aldrich. *p*-Toluenesulfonylmethyl cyanide (TosMIC) was purchased from Lancaster. Anhydrous potassium carbonate was purchased from Yakuri Pure Chemicals. All reagents were used without further purification. All reactions were monitored by TLC on Silica gel 60 F_{254} plate (Merck). Flash column chromatography was performed on Silica gel 60 (230-400 mesh, Merck). ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) were recorded with Varian Gemini 2000 Spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard and the chemical shifts are reported as ä ppm units downfield relative to TMS. Peak splitting patterns are abbreviated as m (multiplet), s (singlet), bs (broad singlet), d (doublet), bd (broad doublet), t (triplet) and dd (doublet of doublets). The melting points were measured on

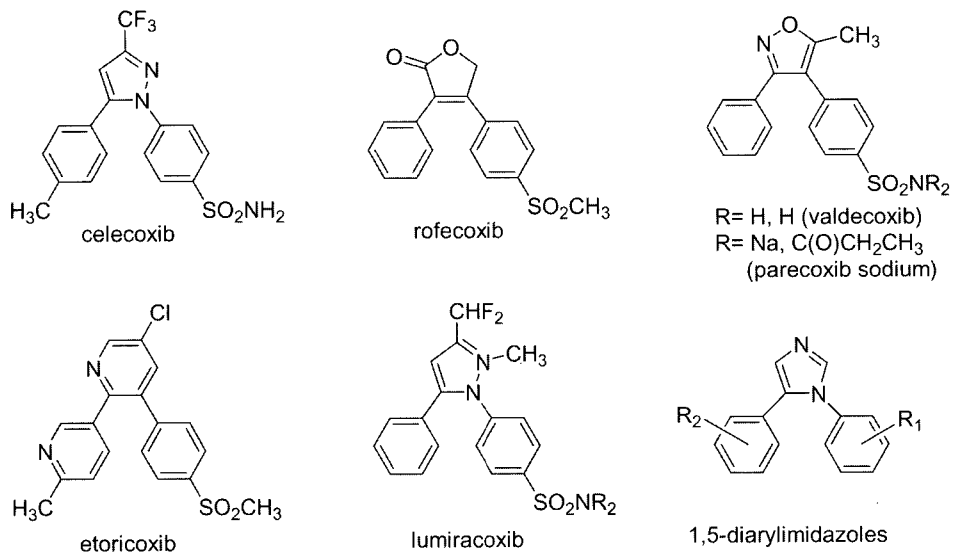


Fig. 1. Chemical structures of celecoxib, rofecoxib, valdecoxib, etoricoxib, parecoxib, lumiracoxib, and 1,5-diarylimidazoles

Fisher-Johns melting point apparatus and were uncorrected.

General procedure for imine formation

To an amine (dissolving in ethanol 95% if amine is solid,) was added aldehyde (dissolving in ethanol 95% if aldehyde is solid,) with vigorous stirring at room temperature, the product was appeared as precipitate, it was purified by ethanol 95%.

N-Phenylbenzylideneamine (1a)

The product was obtained in 90% yield as a colorless solid; m.p. 51°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.47 (s, 1H, CH-imine), 7.91 (m, 2H, Ar-H), 7.5-7.2 (m, 8H, Ar-H).

N-Phenyl-4-methylbenzylideneamine (1b)

The product was obtained in 90% yield as a yellowish solid; m.p. 65-66°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.42 (s, 1H, CH-imine), 7.8 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.43-7.18 (m, 7H, Ar-H), 2.42 (s, 3H, CH_3).

N-Phenyl-4-methoxybenzylideneamine (1c)

The product was obtained in 94% yield as a yellowish solid; m.p. 60-61°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.39 (s, 1H, CH-imine), 7.85 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.38 (m, 2H, Ar-H), 7.21 (m, 3H, Ar-H), 6.99 (d, *J*= 8.8 Hz, 2H, Ar-H).

N-Phenyl-4-chlorobenzylideneamine (1d)

The product was obtained in 91% yield as a white solid; m.p. 59°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.43 (s, 1H, CH-imine), 7.85 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.47-7.37 (m, 4H, Ar-H), 7.28-7.22 (m, 1H, Ar-H), 7.21 (d, *J* = 8.6 Hz, 2H, Ar-H).

N-(4-Tolyl)-4-methylbenzylideneamine (1e)

The product was obtained in 75% yield as a white solid; m.p. 90~91°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.42 (s, 1H, CH-imine), 7.78 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.29-7.1 (m, 6H, Ar-H), 2.41 (s, 3H, CH_3), 2.36 (s, 3H, CH_3).

N-(4-Tolyl)-3-nitrobenzylideneamine (1f)

The product was obtained in 79% yield as a white solid; m.p. 94-95°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.73 (s, 1H, Ar-H), 8.56 (s, 1H, CH-imine), 8.29 (m, *J* = 2.4, 7.6, 8.2 Hz, 2H, Ar-H), 7.65 (t, *J* = 7.6, 8.2 Hz, 1H, Ar-H), 7.21 (m, 4H, Ar-H), 2.39 (s, 3H, CH_3).

N-(4-Fluorophenyl)-4-methylbenzylideneamine (1g)

The product was obtained in 76% yield as a yellowish solid; m.p. 65°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.4 (s, 1H, CH-imine), 7.78 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.3-7.02 (m, 6H, Ar-H), 2.41 (s, 3H, CH_3).

N-(4-Fluorophenyl)-3-nitrobenzylideneamine (1h)

The product was obtained in 86% yield as a yellow solid; m.p. 85~86°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.74 (s, 1H, Ar-H), 8.54 (s, 1H, CH-imine), 8.32 (m, 1H, Ar-H), 8.24 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.67 (t, *J* = 7.8, 8 Hz, 1H, Ar-H), 7.26 (m, 2H, Ar-H), 7.11 (m, 2H, Ar-H).

N-(4-Fluorophenyl)-4-chlorobenzylideneamine (1i)

The product was obtained in 50% yield as a yellow solid; m.p. 56°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.4 (s, 1H, CH-imine), 7.83 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.45 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.24-7.03 (m, 4H, Ar-H).

N-(2,4-Difluorophenyl)-4-methylbenzylideneamine (1j)

The product was obtained in 59% yield as a white solid;

m.p. 63~64°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.47 (s, 1H, CH-imine), 7.8 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.27 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.12 (m, 1H, Ar-H), 6.89 (m, 2H, Ar-H).

***N*-(4-Fluorophenyl)-4-benzyloxybenzylideneamine (1k)**
The product was obtained in 69% yield as a white solid; m.p. 135°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.36 (s, 1H, CH-imine), 7.83 (d, *J* = 9 Hz, 2H, Ar-H), 7.42-7.33 (m, 5H, Ar-H), 7.2-7.01 (m, 6H, Ar-H), 5.13 (s, 2H, CH_2).

***N*-(4-Fluorophenyl)-2-hydroxy-benzylideneamine (1l)**
The product was obtained in 92% as an orange solid; m.p. 80~81°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 13.08 (s, 1H, OH), 8.59 (s, 1H, CH-imine), 7.38 (m, 2H, Ar-H), 7.26 (m, 2H, Ar-H), 7.15-6.91 (m, 4H, Ar-H).

***N*-(4-Fluorophenyl)-4-fluorobenzylideneamine (1m)**
The product was obtained in 61% as a colorless solid; m.p. 62~63°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.4 (s, 1H, CH-imine), 7.89 (m, 2H, Ar-H), 7.22-7.03 (m, 6H, Ar-H).

***N*-(4-Fluorophenyl)-4-bromobenzylideneamine (1n)**
The product was obtained in 87% as a yellowish solid; m.p. 62°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.39 (s, 1H, CH-imine), 7.76 (m, 2H, Ar-H0, 7.61 (m, 2H, Ar-H), 7.24-7.03 (m, 4H, Ar-H).

***N*-(4-Fluorophenyl)-3,4-dichlorobenzylideneamine (1o)**
The product was obtained in 70% as a yellowish solid; m.p. 68~69°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.37 (s, 1H, CH-imine), 8.01 (d, *J* = 2 Hz, 1H, Ar-H), 7.7 (dd, *J* = 2, 8.2 Hz, 1H, Ar-H), 7.54 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.24-7.04 (m, 4H, Ar-H).

***N*-(2,4-Difluorophenyl)-3,4-dichlorobenzylideneamine (1p)**
The product was obtained in 43% as a yellow solid; m.p. 50~51°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.46 (s, 1H, CH-imine), 8.03 (d, *J* = 1.8 Hz, 1H, Ar-H), 7.73 (dd, *J* = 1.8, 8.2 Hz, 1H, Ar-H), 7.55 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.16 (m, 1H, Ar-H), 6.98-6.87 (m, 2H, Ar-H).

***N*-(2,4-Difluorophenyl)-4-methylthiobenzylideneamine (1q)**
The product was obtained in 89% as a yellowish solid; m.p. 83°C, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.45 (s, 1H, CH-imine), 7.81 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.3 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.13 (m, 1H, Ar-H), 6.95-6.84 (m, 2H, Ar-H), 2.53 (s, 3H, CH_3).

General procedure for 1,5-diarylimidazoles:
To the solution of imine (2 mmol) in dried methanol (10 ml) was added anhydrous potassium carbonate (0.83 g, 6 mmol) and 0.39 g (2 mmol) of *p*-toluenesulfonylmethyl isocyanide (TosMIC). The reaction mixture was reflux overnight. After cooling, the solvent was distilled off under reduced pressure, and the residue was extracted with ether. After washing the ether layer with brine, the ether extract was dried over magnesium sulfate. The solvent was distilled off under reduced pressure and the residue was purified by silica gel column chromatography with chloroform:methanol (20:1) as eluent.

1,5-Diphenylimidazole (2a)
The product was obtained in 20% yield as a white solid; m.p. 124~125°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.71 (s, 1H, H_2-imidazole), 7.41-7.12 (m, 10H, Ar-H), 7.24 (s, 1H, H_4-imidazole); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 137.6, 130.8, 130.1, 129.6, 129.1, 128.8, 128.5, 128.4, 128.1, 126.3, 126.2.

1-Phenyl-5-(4-tolyl)imidazole (2b)
The product was obtained in 11% yield as a white solid; m.p. 82-83°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.69 (s, 1H, H_2-imidazole), 7.41-7.16 (m, 7H, Ar-H), 7.04 (s, 1H, H_4-imidazole), 7.05-6.99 (m, 2H, Ar-H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 136.8, 136.2, 134.8, 132.6, 128.8, 128.6, 128.0, 127.5, 125.9, 125.0, 122.3, 20.5.

1-Phenyl-5-(4-methoxyphenyl)imidazole (2c)
The product was obtained in 35% yield as a white solid; m.p. 154~155°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.54 (s, 1H, H_2-imidazole), 7.5 (m, 5H, Ar-H), 7.2 (s, 1H, H_4-imidazole), 7.04 (d, J = 8 Hz, 2H, Ar-H), 6.85 (d, J = 8 Hz, 2H, Ar-H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 160.0, 137.8, 136.1, 129.7, 129.5, 129.4, 127.6, 125.9, 125.4, 125.2, 113.8, 54.7.

1-Phenyl-5-(4-chlorophenyl)imidazole (2d)
The product was obtained in 30% yield as a white solid; m.p. 148~149°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.7 (s, 1H, H_2-imidazole), 7.41 (m, 2H, Ar-H), 7.25-7.18 (m, 7H, Ar-H), 7.04 (s, 1H, H_4-imidazole); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 138.6, 135.8, 131.7, 129.0, 128.6, 128.5, 128.1, 127.7, 127.3, 125.0, 113.9.

1,5-Di(4-tolyl)imidazole (2e)
The product was obtained in 15% yield as a white solid; m.p. 149~150°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.66 (s, 1H, H_2-imidazole), 7.21-7.09 (m, 8H, Ar-H), 7.04 (s, 1H, H_4-imidazole), 2.38 (s, 3H, CH_3), 2.31 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 50 MHz) ä 137.4, 136.7, 134.3, 133.7, 132.2, 129.4, 129.2, 128.5, 127.4, 126.0, 124.8, 20.5, 20.4.

1-(4-Tolyl)-5-(3-nitrophenyl)imidazole (2f)
The product was obtained in 29% as a yellow solid; m.p. 128~129°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.07 (m, 1H, Ar-

H), 8.01 (s, 1H, Ar-H), 7.73 (s, 1H, H_2-imidazole), 7.44-7.06 (m, 7H, Ar-H), 7.1 (s, 1H, H_4-imidazole), 2,41 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 148.8, 139.6, 134.1, 131.8, 131.0, 130.7, 130.6, 130.0, 128.7, 126.1, 123.0, 122.6, 122.2, 21.6.

1-(4-Fluorophenyl)-5-(4-tolyl)imidazole (2g)
The product was obtained in 20% yield as a yellowish solid; m.p. 121~122°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.68 (s, 1H, H_2-imidazole), 7.21-6.98 (m, 8H, Ar-H), 7.04 (s, 1H, H_4-imidazole), 2.32 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 159.8, 144.3, 138.3, 133.4, 129.9, 128.8, 128.1, 128.0, 126.8, 117.3, 116.9, 21.8.

1-(4-Fluorophenyl)-5-(3-nitrophenyl)imidazole (2h)
The product was obtained in 25% yield as a yellow solid; m.p. 171~173°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 8.1 (m, 1H, Ar-H), 8.02 (s, 1H, Ar-H), 7.73 (s, 1H, H_2-imidazole), 7.43 (m, 3H, Ar-H), 7.19 (m, 3H, Ar-H), 7.18 (s, 1H, H_4-imidazole); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 165.4, 148.9, 140.6, 134.1, 131.5, 130.8, 130.2, 128.3, 128.1, 123.1, 122.9, 117.8, 117.3.

1-(4-Fluorophenyl)-5-(4-chlorophenyl)imidazole (2i)
The product was obtained in 40% yield as a yellowish solid; m.p. 118~120°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.87 (s, 1H, H_2-imidazole), 7.29-7.03 (m, 8H, Ar-H), 7.16 (s, 1H, H_4-imidazole); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 165.3, 160.3, 134.6, 132.3, 130.0, 129.5, 128.5, 128.2, 128.0, 117.5, 117.1.

1-(2,4-difluorophenyl)-5-(4-tolyl)imidazole (2j)
The product was obtained in 30% yield as a yellow solid; m.p. 132~133°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.76 (s, 1H, H_2-imidazole), 7.29-6.9 (m, 7H, Ar-H), 7.03 (s, 1H, H_4-imidazole), 2.32 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 164.9, 160.3, 155.0, 138.6, 130.3, 130.1, 130.0, 128.3, 126.4, 121.4, 113.0, 112.5, 106.1, 21.8.

1-(4-Fluorophenyl)-5-(4-benzyloxyphenyl)imidazole (2k)
The product was obtained in 15% yield as a white solid; m.p. 144~145°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.64 (s, 1H, H_2-imidazole), 7.38 (m, 5H, Ar-H), 7.18-7.07 (m, 6H, Ar-H), 7.03 (s, 1H, H_4-imidazole), 6.87 (m, 2H, Ar-H), 5.03 (s, 2H, CH_2); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 159.8, 159.0, 139.1, 137.3, 133.4, 130.7, 130.2, 129.3, 128.8, 128.2, 128.0, 122.5, 117.3, 116.9, 115.5, 70.6.

1-(4-Fluorophenyl)-5-(2-hydroxyphenyl)imidazole (2l)
The product was obtained in 22% yield as a yellowish solid; m.p. 178~179°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.74 (s, 1H, H_2-imidazole), 7.22-6.77 (m, 8H, Ar-H), 7.03 (s, 1H, H_4-imidazole); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 165.1, 160.1, 155.6, 133.2, 132.0, 131.1, 129.4, 127.3, 127.2, 120.5, 117.2, 117.0, 116.7, 116.2, 115.2.

1,5-Di(4-fluorophenyl)imidazole (2m)
The product was obtained in 20% yield as a white solid; m.p. 139~140°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.66 (s, 1H, H_2-imidazole), 7.23-6.92 (m, 8H, Ar-H), 7.06 (s, 1H, H_4-imidazole); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 165.3, 160.3, 139.5, 133.0, 130.6, 129.4, 128.1, 128.0, 125.9, 117.2, 116.3.

1-(4-Fluorophenyl)-5-(4-bromophenyl)-1*H*-imidazole (2n)
The product was obtained in 62% as a white solid; m.p. 117~118°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.67 (s, 1H, H_2-imidazole), 7.4 (m, 2H, Ar-H), 7.18-7.06 (m, 4H, Ar-H), 7.01-6.97 (m, 2H, Ar-H), 6.96 (s, 1H, H_4-imidazole); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 165.1, 160.1, 139.7, 132.9, 132.5, 132.5, 129.6, 128.6, 127.8, 122.3, 116.9.

1-(4-Fluorophenyl)-5-(3,4-dichlorophenyl)imidazole (2o)
The product was obtained in 30% yield as a white solid; m.p. 141~142°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.68 (s, 1H, H_2-imidazole), 7.34-7.28 (m, 3H, Ar-H), 7.2-7.1 (m, 3H, Ar-H), 7.09 (s, 1H, H_4-imidazole), 6.87 (q, 1H, Ar-H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 165.2, 160.2, 140.0, 133.2, 132.7, 132.2, 131.3, 131.0, 130.2, 129.7, 128.0, 127.5, 117.5.

1-(2,4-Difluorophenyl)-5-(3.4-dichlorophenyl)imidazole (2p)
The product was obtained in 28% yield as a white solid; m.p. 142~143°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.65 (s, 1H, H_2-imidazole), 7.28 (m, 4H, Ar-H), 7.03 (s, 1H, H_4-imidazole), 6.94 (m, 2H, Ar-H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 165.6, 160.6, 159.8, 154.7, 140.2, 133.2, 131.9, 131, 129.8, 129.6, 126.9, 120.9, 113.0, 106.3, 105.8.

1-(2,4-Difluorophenyl)-5-(4-methylthiophenyl)imidazole (2q)
The product was obtained in 25% yield as a white solid; m.p. 140~141°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.62 (s, 1H, H_2-imidazole), 7.21-6.91 (m, 7H, Ar-H), 7.06 (s, 1H, H_4-imidazole), 2.46 (s, 3H, SCH_3); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 139.9, 139.2, 130.3, 130.1, 128.8, 128.6, 126.8, 115.2, 113.1, 112.6, 106.7, 106.2, 105.7, 15.9.

1-(2,4-Difluorophenyl)-5-(4-methylsulfonylphenyl) imidazole (2r)
The solution of **2p** (0.3 g, 1 mmol) in THF (10 mL) was cooled to -10°C and oxone (1.6 g, 2.6 mmol) in H_2O (14 mL) was added dropwise to the solution of **2p**. The resulting mixture was stirred at 23° for 24 h, combined with ice and CH_2Cl_2 and washed with brine, dried over $MgSO_4$, concentrated and evaporated under reduced pressure. The residue was recrystallized in $CH_3CO_2C_2H_5$

Table I. Inhibition of COX-2 catalyzed PGE_2 production from LPS-induced RAW 264.7 cells by 1,5-diarylimidazoles

Compound	Inhibition %
2a	inactive
2b	29
2c	76
2d	inactive
2e	56
2f	inactive
2g	31
2h	inactive
2i	25
2j	49
2k	inactive
2l	inactive
2m	inactive
2n	30
2o	inactive
2p	inactive
2q	61
2r	89
celecoxib	99

a All compounds were treated at 10 μM. Treatment of LPS to RAW cells increased PGE_2 production (10.0 nM) from the basal level of 0.5 nM.

b % inhibition = 100 × (PGE_2 of the treated group – PGE_2 of the basal)/ (PGE_2 of LPS treated group – PGE_2 of the basal).

to gave a title product as a white solid in 90%; m.p. 180~181°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.87 (d, J = 8.2 Hz, 2H, Ar-H), 7.72 (s, 1H, H_2-imidazole), 7.44 (s, 1H, H_4-imidazole), 7.34 (d, J = 8.2 Hz, 2H, Ar-H), 7.29 (m, 1H, Ar-H), 7.06-6.96 (m, 2H, Ar-H), 3.07 (s, 3H, CH_3); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 166.0, 160.9, 160.0, 155.0, 141.1, 140.1, 135.2, 130.8, 130.0, 128.4, 113.0, 106.9, 106.0, 45.0.

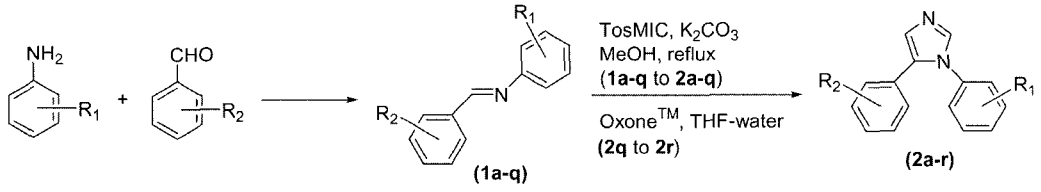
Biological evaluation

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 (Chi, 2001). RAW 264.7 cells obtained from American Type Culture Collection were cultured with DMEM 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 imidazole 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 I.

RESULTS AND DISCUSSION

1,5-Diarylimidazoles can be prepared from either amines, potassium thiocyanate and hydroxy acetone (Askin *et al.*, 2000) or imines and TosMIC (Albert *et al.*, 1977; Kuwano *et al.*, 1989; John, 1998). In this study, 1,5-diarylimidazoles were synthezed in two steps from imines and TosMIC as shown in Scheme 1. Imines were prepared from amines and aldehydes following the procedure described in the reference (Stanley and Wolf, 1986). Imines and TosMIC was treated with anhydrous potassium carbonate in methanol at reflux to get the target compounds in moderate yields (10-62%). 1,5-Diarylimidazoles were purified by flash column chromatography with chloroform: methanol (20:1) as an eluent.

1,5-Diarylimidazoles which was synthesized were evaluated for their inhibitory activities against COX-2 catalyzed PGE_2 production from LPS-induced RAW 264.7 cells. For the 1,5-diarylimidazoles possessing strong COX-2 inhibitory activity, we planned to evaluate the biological activity against COX-1 enzyme inhibition to investigate the COX-



a $R_1 = R_2 = H$
b $R_1 = H$, $R_2 = 4\text{-}CH_3$
c $R_1 = H$, $R_2 = 4\text{-}OCH_3$
d $R_1 = H$, $R_2 = 4\text{-}Cl$
e $R_1 = R_2 = 4\text{-}CH_3$
f $R_1 = 4\text{-}CH_3$, $R_2 = 3\text{-}NO_2$
g $R_1 = 4\text{-}F$, $R_2 = 4\text{-}CH_3$
h $R_1 = 4\text{-}F$, $R_2 = 3\text{-}NO_2$
i $R_1 = 4\text{-}F$, $R_2 = 4\text{-}Cl$
j $R_1 = 2,4\text{-}F_2$, $R_2 = 4\text{-}CH_3$
k $R_1 = 4\text{-}F$, $R_2 = 4\text{-}OCH_2Ph$
l $R_1 = 4\text{-}F$, $R_2 = 4\text{-}OH$
m $R_1 = 4\text{-}F$, $R_2 = 4\text{-}F$
n $R_1 = 4\text{-}F$, $R_2 = 4\text{-}Br$
o $R_1 = 4\text{-}F$, $R_2 = 3,4\text{-}Cl_2$
p $R_1 = 2,4\text{-}F_2$, $R_2 = 3,4\text{-}Cl_2$
q $R_1 = 2,4\text{-}F_2$, $R_2 = 4\text{-}SCH_3$
r $R_1 = 2,4\text{-}F_2$, $R_2 = 4\text{-}SO_2CH_3$

Scheme 1. Synthesis of 1,5-diarylimidazoles

2/COX-1 selectivity. Among 1,5-diarylimidazoles tested, 1-(2,4-difluorophenyl)-5-(4-methylsulfonylphenyl)imidazole (**2r**) showed strong inhibitory activity, however, most diarylimidazoles exhibited little to low inhibitory activities against COX-2 catalyzed PGE_2 production as shown in Table I. COX-1 enzyme inhibition study for these compounds was not examined at this time. These results are similar with the biological data from other groups that the parent unsubstituted compound was completely inactive and a substantial increase in activity was seen on introduction small substituent in position 2 or 4 (Barta *et al.*, 1998; Almansa *et al.*, 2003). Our present results showed that the compound with the 4-methylsulfonyl group only exhibited strong bioactivity. Further SARs study of 1,5-diarylimidazoles containing the 4-methylsulfonyl group(s) at the aryl ring(s) is currently under investigation.

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