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Original research paper

Studies in 3,4-diaryl-1,2,5-oxadiazoles and their *N*-oxides: Search for better COX-2 inhibitors

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A series of 3,4-diaryl-1,2,5-oxadiazoles and 3,4-diaryl--1,2,5-oxadiazole *N*-oxides were prepared and evaluated for COX-2 and COX-1 binding affinity *in vitro* and for anti--inflammatory activity by the rat paw edema method. *p*--Methoxy (*p*-OMe) substituted compounds **9**, **21**, **34**, **41**, **42** showed COX-2 enzyme inhibition higher than that showed by compounds with other substituents. 3,4-Di(4--methoxyphenyl)-1,2,5-oxadiazole *N*-oxide (**42**) showed COX-2 enzyme inhibition of 54% at 22 μmol L^{-1} and COX-1 enzyme inhibition of 44% at 88 μmol L^{-1} concentrations, but showed very low *in vivo* anti-inflammatory activity. Its deoxygenated derivative (**21**) showed lower COX-2 enzyme inhibition (26% at 22 μmol L^{-1}) and higher COX-1 enzyme inhibition (53% at 88 μmol L^{-1}) but, marked *in vivo* anti-inflammatory activity (71% at 25 mg kg^{-1}) *vs.* celecoxib (48% at 12.5 mg kg^{-1}). Molecular modeling (docking) studies showed that the methoxy group is positioned in the vicinity of COX-2 secondary pocket and it also participates in hydrogen bonding interactions in the COX-2 active site. These preliminary studies suggest that *p*-methoxy (*p*-OMe) group in one of benzene rings may give potentially active leads in this series of oxadiazole/*N*-oxides.

Keywords: 1,2,5-oxadiazole, 1,2,5-oxadiazole *N*-oxide, COX-2 inhibitor

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Discovery of two cyclooxygenase (COX) isoenzymes, a constitutive COX-1, serving as homeostatic prostanoid producing agent, and COX-2, responsible for pro-inflammatory prostanoid production, led to the development of new nonsteroidal anti-inflammatory drugs (NSAIDs), selective COX-2 inhibitors, promising minimal NSAID-typical toxicity with full anti-inflammatory efficacy. COX-2 inhibitors have been successful in treating inflammatory diseases like acute pain, rheumatoid arthritis and osteoarthritis; a few of them are also being studied for treating different types of cancer and Alzheimer's disease (1). Despite a few recent cautionary reports, the coxib treatment has a high degree of benefit over risk, and strategies for using NSAIDs have been described by Antman *et al.* (2).

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A wide variety of carbocycles and heterocycles can serve as templates for COX-2 inhibitors, *i.e.*, cyclopentene [SC-57666] (3) pyrazole [celecoxib (4), SC-58125 (5)], furan [rofecoxib (6)], isoxazole [valdecoxib (7), paracoxib sodium (8)], and pyridine [etoricoxib (9)]. In an ongoing research program in this department on COX-2 inhibitors with improved biological profile, we synthesized (10) a series of 3,4-diaryl-1,2,5-oxadiazoles and 3,4-diaryl-1,2,5-oxadiazole *N*-oxides. The compounds are novel in that the vicinal diaryl heterocyclic (five membered ring) pharmacophore of the coxibs has been incorporated with the nitric oxide releasing group (1,2,5-oxadiazole *N*-oxide) into one single entity in the compounds synthesized. In this paper, we report the synthesis, preliminary biological evaluation and molecular docking studies of some of these oxadiazoles and their *N*-oxides as selective COX-2 inhibitors.

1,2,5-oxadiazole *N*-oxides (furoxans) are reported (11) to be thiol dependent NO donors, whose biological activity is produced by action on the soluble guanylate cyclase--cyclic guanosine monophosphate (sGC-cGMP) pathway. Furoxans are considered to possess favorable bioactivity since they cause a slow release of NO resulting in longer duration of action without development of tolerance. Granik and Grigor (12) proposed the mechanism for the release of NO from 1,2,5-oxadiazole *N*-oxides. It is also reported that release of NO from a nitric oxide donor drug produces beneficial effects such as reduction in blood pressure and prevention of atherosclerosis (11). NSAIDs possessing nitric oxide releasing capabilities are considered to be more promising drugs than the coxibs as these would be devoid of potential cardiovascular side effects associated with coxibs (11). Recently, a report has been published discussing the synthesis of some monosubstituted 3,4-diaryl-1,2,5-oxadiazoles (**11)** and *N*-oxides (**35**) as selective COX-2 inhibitors, expecting them to be free from adverse cardiovascular effects (13), but we claimed synthesis of these compounds much earlier (10).

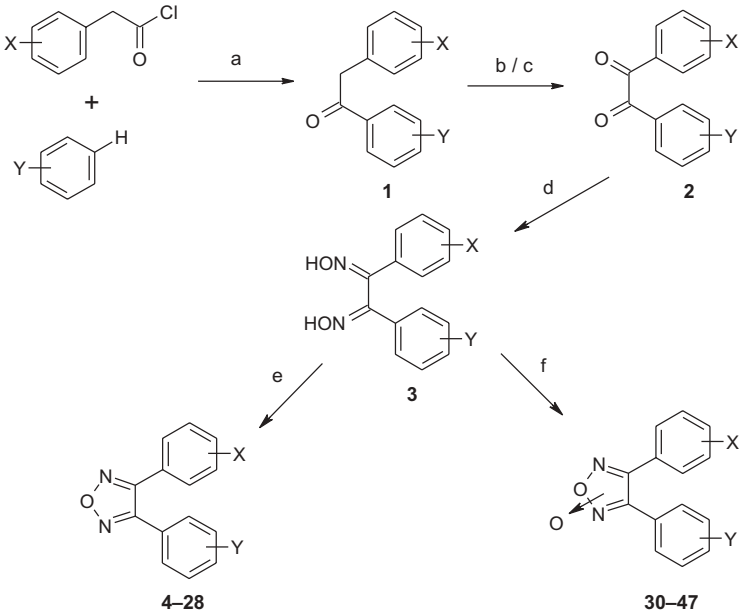
EXPERIMENTAL

The yields reported here are un-optimized. Melting points were determined using a heating block-type melting point apparatus and are uncorrected. The IR spectra were recorded using the KBr disc method on an FT-IR model 8300 (Shimadzu, Japan). The ^{1}H NMR spectra on a 300 MHz spectrometer (Brucker, USA) were recorded in $CDCl_3$ (chemical shifts in δ ppm). Assignment of exchangeable protons (NH) was confirmed by the D_2O exchange. Selenium dioxide oxidations were carried out in an R-330F microwave oven (Sharp, Carousel, Thailand). Final compounds were purified by passing through a silica gel H (100-200 mesh, s. d. fine chemicals, India) purifying column using a mixture of ethyl acetate and petroleum ether or chloroform alone as eluents.

Synthetic pathway is presented in Schemes 1 and 2, and physicochemical and spectral data for the synthesized compounds are given in Tables I and II.

The starting compounds, 1,2-diaryl-1,2-ethanediones (**2**) (benzils), were prepared by two routes. The first route involved benzoin condensation followed by oxidation (14, 15) while the second involved Friedel-Crafts acylation followed by selenium dioxide oxidation (16).

Syntheses of 1,2-diaryl-1,2-ethanedione dioximes (**3**). *General procedure*. – A mixture of 1,2-diaryl-1,2-ethanediones (**2**) (benzils) (10 mmol), hydroxylamine hydrochloride (60

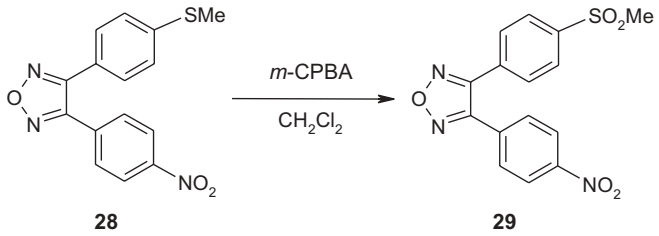


X = H, 2-Cl, 4-Cl, 4-F, 4-Me, 4-OMe, NO_2

Y = H, 4-Cl, 4-Br, 4-F, 4-Me, 4-OMe, 4-Sme, 4-SO_2Me, 3,4-di-OMe

Reagents and conditions: a – $AlCl_3$, CH_2Cl_2, 0–60 °C, 3–4 h; b – SeO_2, Ac_2O, reflux, 1–8 h; c – SeO_2, DMSO, microwave irradiation, 30–90 s; d – $NH_2OH \times HCl$, C_6H_5N, reflux, 7–8 h; e – $(-CH_2CO)_2O$, 180–5 °C, 10 min; f – aq. NaOCl (20%), 5–20 °C, 14–16 h

Scheme 1



Scheme 2

mmol) and pyridine (10 mL) was refluxed on an oil bath for 7 h. The reaction mixture was poured onto crushed ice containing concentrated hydrochloric acid (10 mL). The precipitate obtained was filtered, washed with cold water and dried. The crude materials were used as such for the next step without further purification.

*Table I. Characterization data of 3,4-diaryl-1,2,5-oxadiazoles (**4**–**29**)*

Compd. No.	X	Y	M.p. (°C)	Yield (%)	Molecular formula (M_r) and mass (*m*/*z*)	Elemental analysis, found/calcd. (%)			IR (ν, cm^{-1})	^1H NMR (δ, ppm)
						C	H	N		
4	H	H	93–96[a]	49	$C_{14}H_{10}N_2O$ (222.25) 223 (M+H)	–	–	–	1577 (C=N-O), 1442 (N-O)	7.56–7.37 (m, 10H, ArH)
5	H	4′-Cl	83–84	21	$C_{14}H_9ClN_2O$ (256.69) 256 (M^+)	65.38 65.51	3.74 3.53	10.67 10.91	1597 (C=N-O), 1447 (N-O)	7.62–7.35 (m, 9H, ArH)
6	H	4′-Br	111–113	28	$C_{14}H_9BrN_2O$ (301.14) 302 (M+H)	56.12 55.84	2.79 3.01	9.48 9.30	1596 (C=N-O), 1446 (N-O)	7.59–7.39 (m, 9H, ArH)
7	H	4′-F	85–87	33	$C_{14}H_9FN_2O$ (240.24) 240 (M^+)	69.88 70.00	3.53 3.78	11.87 11.66	1605 (C=N-O), 1454 (N-O)	7.56–7.40 (m, 7H, ArH), 7.15–7.09 (m, 2H, 3′,5′-ArH)
8	H	4′-Me	57–59	30	$C_{15}H_{12}N_2O$ (236.28) 236 (M^+)	75.96 76.25	4.87 5.12	11.59 11.86	1605 (C=N-O), 1450 (N-O)	7.54–7.20 (m, 9H, ArH), 2.40 (s, 3H, $ArCH_3$)
9	H	4′-OMe	67–69	36	$C_{15}H_{12}N_2O_2$ (252.28) 252 (M^+)	71.77 71.42	4.64 4.79	10.97 11.10	1613 (C=N-O), 1456 (N-O), 1250 (Ar-O-Me, asym), 1025 (Ar-O-Me, sym)	7.55–7.37 (m, 7H, ArH), 6.91–6.88 (m, 2H, 3′,5′-ArH), 3.82 (s, 3H, $ArOCH_3$)
10	H	4′-SMe	83–84	27	$C_{15}H_{12}N_2OS$ (268.34) 269 (M+H)	67.47 67.14	4.35 4.51	10.62 10.44	1602 (C=N-O), 1435 (N-O)	7.54–7.40 (m, 7H, ArH), 7.26–7.23 (m, 2H, 3′,5′-ArH), 2.50 (s, 3H, $ArSCH_3$)
11	H	4′-SO_2Me	142–143[b]	47	$C_{15}H_{12}N_2O_3S$ (300.34)	60.26 59.99	4.32 4.03	9.16 9.33	1600 (C=N-O), 1448 (N-O), 1308 (SO_2 asym), 1149 (SO_2 sym)	8.03–8.00 (m, 2H, 3′,5′-ArH), 7.78–7.75 (m, 2H, 2′,6′ArH), 7.57–7.44 (m, 5H, ArH), 3.11 (s, 3H, $ArSO_2CH_3$)

Table I. Continued

Compd. No.	X	Y	M.p. (°C)	Yield (%)	Molecular formula (M_r) and mass (m/z)	Elemental analysis, found/calcd. (%)			IR (ν, cm^{-1})	^1H NMR (δ, ppm)
						C	H	N		
12	2-Cl	H	59–60	26	$C_{14}H_9ClN_2O$ (256.69)	65.06 65.51	4.87 4.53	10.74 10.94	1600 (C=N-O), 1434 (N-O)	7.51–7.31 (m, 9H, ArH)
13	2-Cl	4′-Me	117–118	38	$C_{15}H_{11}ClN_2O$ (270.72)	66.90 66.55	3.79 4.10	10.55 10.35	1613 (C=N-O), 1435 (N-O)	7.51–7.39 (m, 4H, ArH), 7.37–7.34 (m, 2H, 2′,6′-ArH), 7.16–7.13 (m, 2H, 3′,5′-ArH), 2.35 (s, 3H, $ArCH_3$)
14	2-Cl	4′-OMe	107–108	39	$C_{15}H_{11}ClN_2O_2$ (286.72) 287 (M^+)	62.48 62.84	3.50 3.87	9.99 9.77	1611 (C=N-O), 1437 (N-O), 1253 (Ar-O-Me, asym), 1029 (Ar-O-Me, sym)	7.53–7.39 (m, 6H, ArH), 6.88–6.83 (m, 2H, 3′,5′-ArH), 3.80 (s, 3H, $ArOCH_3$)
15	2-Cl	3′,4′-di-OMe	77–79	60	$C_{16}H_{13}ClN_2O_3$ (316.75) 316 (M^+)	60.48 60.67	3.86 4.14	9.12 8.84	1605 (C=N-O), 1440 (N-O), 1256 (Ar-O-Me, asym), 1019 (Ar-O-Me, sym)	7.52–7.43 (m, 4H, ArH), 7.08–7.087 (dd, 1H, 2′-ArH), 7.02–6.98 (dd, 1H, 6′-ArH), 6.81–6.78 (dd, 1H, 3′-ArH), 3.87 (s, 3H, $ArOCH_3$), 3.71 (s, 3H, $ArOCH_3$)
16	4-Cl	4′-F	101–103	27	$C_{14}H_8FClN_2O$ (274.68)	60.82 61.22	3.22 2.94	10.38 10.20	1601 (C=N-O), 1447 (N-O)	7.54–7.48 (m, 2H, 2′,6′-ArH), 7.46–7.41 (m, 4H, ArH), 7.19–7.11 (m, 2H, 3′,5′-ArH)
17	4-Cl	4′-Me	137–139	19	$C_{15}H_{11}ClN_2O$ (270.72)	66.91 66.55	4.26 4.10	10.53 10.35	1602 (C=N-O), 1445 (N-O)	7.50–7.41 (m, 4H, ArH), 7.37–7.34 (m, 2H, 2′,6′-ArH), 7.16–7.13 (m, 2H, 3′,5′-ArH), 2.46 (s, 3H, $ArCH_3$)
18	4-Cl	4′-OMe	98–100	26	$C_{15}H_{11}ClN_2O_2$ (286.72)	62.57 62.84	4.28 3.87	9.95 9.77	1614 (C=N-O), 1451 (N-O), 1253 (Ar-O-Me, asym), 1027 (Ar-O-Me, sym)	7.51–7.40 (m, 6H, ArH), 6.98–6.93 (m, 2H, 3′,5′-ArH), 3.86 (s, 3H, $ArOCH_3$)

Table I. Continued

Compd. No.	X	Y	M.p. (°C)	Yield (%)	Molecular formula (M_r) and mass (m/z)	Elemental analysis, found/calcd. (%)			IR (ν, cm^{-1})	^1H NMR (δ, ppm)
						C	H	N		
19	4-F	4′-SO_2Me	155–157	32	$C_{15}H_{11}FN_2O_3S$ (318.33)	56.33 56.60	3.86 3.48	8.56 8.80	1606 (C=N-O), 1310 (SO_2 asym), 1151 (SO_2 sym)	8.05–8.02 (m, 2H, 3′,5′-ArH), 7.77–7.74 (m, 2H, 2′,6′ArH), 7.53–7.49 (m, 2H, 2,6-ArH), 7.20–7.14 (m, 2H, 3,5-ArH), 3.12 (s, 3H, $ArSO_2CH_3$)
20	4-Me	4′-SO_2Me	141–142	43	$C_{16}H_{14}N_2O_3S$ (314.37)	61.48 61.13	4.24 4.49	9.02 8.91	1610 (C=N-O), 1451 (N-O), 1307 (SO_2 asym),1150 (SO_2 sym)	8.03–8.00 (m, 2H, 3′,5′-ArH), 7.78–7.75 (m, 2H, 2′,6′-ArH), 7.39–7.35 (m, 2H, 2,6-ArH), 7.28–7.25 (m, 2H, 3,5-ArH), 3.10 (s, 3H, $ArSO_2CH_3$), 2.43 (s, 3H, $ArCH_3$)
21	4-OMe	4′-OMe	123–125	26	$C_{16}H_{14}N_2O_3$ (282.30) 283 (M+H)	67.83 68.08	4.66 5.00	10.16 9.92	1612 (C=N-O), 1444 (N-O), 1257 (Ar-O-Me, asym), 1026 (Ar-O-Me, sym)	7.53–7.45 (m, 4H, ArH), 6.97–6.92 (m, 4H, 3,3′,5,5′-ArH), 3.86 (s, 6H, $ArOCH_3$)
22	4-NO_2	H	139–142	22	$C_{14}H_9N_3O_3$ (267.25) 267 (M^+)	63.24 62.92	3.02 3.39	15.58 15.72	1602 (C=N–O), 1515 (NO_2, asym), 1448 (N–O), 1350 (NO_2, sym)	8.31–8.28 (m, 2H, 3,5-ArH), 7.78–7.74 (m, 2H, 2,6-ArH), 7.58–7.45 (m, 5H, ArH)
23	4-NO_2	4′-Cl	168–170	53	$C_{14}H_8ClN_3O_3$ (301.69)	55.52 55.74	2.98 2.67	13.77 13.93	1601 (C=N–O), 1515 (NO_2, asym), 1448 (N–O) and 1350 (NO_2, sym)	8.34–8.31 (m, 2H, 3,5-ArH), 7.77–7.73 (m, 2H, 2,6-ArH), 7.50–7.43 (m, 4H, ArH)
24	4-NO_2	4′-Br	185–186	30	$C_{14}H_8BrN_3O_3$ (346.14)	48.16 48.58	2.66 2.33	12.38 12.14	1600 (C=N–O), 1517 (NO_2, asym), 1442 (N–O) and 1346 cm^{-1} (NO_2, sym)	8.34–8.30 (m, 2H, 3,5-ArH), 7.77–7.72 (m, 2H, 2,6-ArH), 7.65–7.60 (m, 2H, 2′,6′- ArH), 7.40–7.36 (m, 2H, 3′,5′-ArH)

Table I. Continued

Compd. No.	X	Y	M.p. (°C)	Yield (%)	Molecular formula (M_r) and mass (m/z)	Elemental analysis, found/calcd. (%)			IR (ν, cm^{-1})	^1H NMR (δ, ppm)
						C	H	N		
25	4-NO_2	4′-F	137–138	46	$C_{14}H_8FN_3O_3$ (285.24)	58.55 58.95	2.59 2.83	14.59 14.73	1608 (C=N–O), 1519 (NO_2, asym), 1448 (N–O) and 1350 (NO_2, sym)	8.33–8.30 (m, 2H, 3,5-ArH), 7.76–7.73 (m, 2H, 2,6-ArH), 7.53–7.49 (m, 2H, 2′,6′-ArH), 7.21–7.15 (m, 2H, 3′,5′-ArH)
26	4-NO_2	4′-Me	113–114	39	$C_{15}H_{11}N_3O_3$ (281.27)	64.46 64.05	3.66 3.94	15.19 14.94	1602 (C=N–O), 1517 (NO_2, asym), 1448 (N–O) and 1346 cm^{-1} (NO_2, sym)	8.32–8.27 (m, 2H, 3,5-ArH), 7.78–7.74 (m, 2H, 2,6-ArH), 7.39–7.37 (m, 4H, ArH), 2.43 (s, 3H, $ArCH_3$)
27	4-NO_2	4′-OMe	125–126	32	$C_{15}H_{11}N_3O_4$ (297.27)	60.95 60.61	3.51 3.73	13.98 14.14	1610 (C=N–O), 1519 (NO_2, asym), 1436 (N–O), 1350 (NO_2, sym), 1249 (Ar–O) and 1024 cm^{-1} (O–Me)	8.31–8.28 (m, 2H, 3,5-ArH), 7.78–7.75 (m, 2H, 2,6-ArH), 7.45–7.41 (m, 2H, 2′,6′-ArH), 6.99–6.95 (m, 2H, 3′,5′-ArH), 3.87 (s, 3H, $ArOCH_3$)
28	4-NO_2	4′-SMe	135–136	34	$C_{15}H_{11}N_3O_3S$ (313.34)	57.12 57.50	3.85 3.54	13.28 13.41	1598 (C=N–O), 1519 (NO_2, asym), 1438 (N–O), 1350 cm^{-1} (NO_2, sym)	8.33–8.29 (m, 2H, 3,5-ArH), 7.79–7.74 (m, 2H, 2,6-ArH), 7.43–7.39 (m, 2H, 2′,6′-ArH), 7.31–7.27 (m, 2H, 3′,5′-ArH), 2.53 (s, 3H, $ArSCH_3$)
29	4-NO_2	4′-SO_2Me	172–173	59	$C_{15}H_{11}N_3O_5S$ (345.34)	51.83 52.17	3.52 3.21	12.34 12.17	1531 (NO_2 asym), 1353 (NO_2 sym), 1302 (SO_2 asym), 1149 cm^{-1} (SO_2 sym)	8.36–8.33 (m, 2H, 3,5-ArH), 8.09–8.06 (m, 2H, 3′,5′-ArH), 7.77–7.73 (m, 4H, ArH), 3.13 (s, 3H, $ArSO_2CH_3$)

[a] Lit. m.p. 94 °C (22), 67–70 °C (13).
[b] Lit. m.p. 135–137 °C (13).

Table II. Characterization data of 3,4-diaryl-1,2,5-oxadiazole N*-oxides (**30–47**)*

Compd. No.	X	Y	M.p. (°C)	Yield (%)	Molecular formula (M_r) and mass (*m*/z)	Elemental analysis, found/calcd. (%)			IR (ν, cm^{-1})	^1H NMR (δ, ppm)
						C	H	N		
30	H	H	114–117[a]	65	$C_{14}H_{10}N_2O_2$ (238.25)	–	–	–	1592 (C=N^+-O^-), 1419 (=N^+(O^-)-O)	7.55–7.35 (m, 10H, ArH)
31	H	4′-Cl	104–105	33	$C_{14}H_9ClN_2O_2$ (272.69)	61.35 61.66	3.59 3.33	10.54 10.27	1591 (C=N^+-O^-), 1434 (=N^+(O^-)-O)	7.56–7.39 (m, 9H, ArH)
32	H	4′-F	113–115	30	$C_{14}H_9FN_2O_2$ (256.24) 256 (M^+)	65.47 65.62	3.79 3.54	11.12 10.93	1588 (C=N^+-O^-), 1429 (=N^+(O^-)-O)	7.56–7.40 (m, 7H, ArH), 7.17–7.08 (m, 2H, 3′,5′-ArH)
33	H	4′-Me	104–106	53	$C_{15}H_{12}N_2O_2$ (252.28) 252 (M^+)	71.09 71.42	4.48 4.79	11.35 11.10	1600 (C=N^+-O^-), 1429 (=N^+(O^-)-O)	7.54–7.38 (m, 7H, ArH), 7.25–7.18 (m, 2H, 3′,5′-ArH), 2.42 and 2.40 (s, 3H, $ArCH_3$)
34	H	4′-OMe	103–105	49	$C_{15}H_{12}N_2O_3$ (268.27)	67.42 67.16	4.82 4.51	10.57 10.44	1591 (C=N^+-O^-), 1425 (=N^+(O^-)-O), 1252(Ar-O-Me, asym), 1026 (Ar-O-Me, sym)	7.54–7.40 (m, 7H, ArH), 6.94–6.89 (m, 2H, 3′,5′-ArH), 3.84 and 3.83 (s, 3H, $ArOCH_3$)
35	H	4′-SO_2Me	125–127[b]	35	$C_{15}H_{12}N_2O_4$ (316.34) 316 (M^+)	57.33 56.95	3.67 3.82	8.67 8.86	1594 (C=N^+-O^-), 1448 (=N^+(O^-)-O), 1307 (SO_2 asym), 1150 cm^{-1} (SO_2 sym)	8.03–8.00 (m, 2H, 3′,5′-ArH), 7.79–7.74 (m, 2H, 2′,6′-ArH), 7.58–7.44 (m, 5H, ArH), 3.11 and 3.09 (s, 3H, $ArSO_2CH_3$)
36	2-Cl	4′–Me	139–140	66	$C_{15}H_{11}ClN_2O_2$ (286.72)	62.66 62.84	3.47 3.87	9.52 9.77	1592 (C=N^+-O^-), 1423 (=N^+(O^-)-O)	7.56–7.11 (m, 8H, ArH), 2.36 and 2.34 (s, 3H, $ArCH_3$)
37	2-Cl	4′-OMe	114–117	53	$C_{15}H_{11}ClN_2O_3$ (302.72)	59.91 59.52	3.82 3.66	9.07 9.25	1590 (C=N^+-O^-), 1426 (=N^+(O^-)-O), 1253 (Ar-O-Me, asym), 1029 (Ar-O-Me, sym)	7.57–7.37 (m, 6H, ArH), 6.88–6.84 (m, 2H, 3′,5′-ArH), 3.81 and 3.80 (s, 3H, $ArOCH_3$)

Table II. Continued

Compd. No.	X	Y	M.p. (°C)	Yield (%)	Molecular formula (M_r) and mass (m/z)	Elemental analysis, found/calcd. (%)			IR (ν, cm^{-1})	^1H NMR (δ, ppm)
						C	H	N		
38	2-Cl	3′,4′-di-OMe	110–111	35	$C_{16}H_{13}ClN_2O4$ (332.75)	57.51 57.76	3.62 3.94	8.28 8.40	1601 (C=N^+-O^-), 1438 (=N^+(O^-)-O), 1264 (Ar-O-Me, asym), 1025 (Ar-O-Me, sym)	7.59–7.42 (m, 4H, ArH), 7.17–7.14 (m, 1H, 2′-ArH), 7.07–7.04 (m, 1H, 6′-ArH), 6.84–6.78 (m, 1H, 3′-ArH), 3.87, 3.72 and 3.63 (s, 6H, $ArOCH_3$)
39	4-Cl	4′-F	113–115	52	$C_{14}H_8ClFN_2O_2$ (290.68) 290 (M^+)	57.41 57.85	3.02 2.77	9.82 9.64	1605 (C=N^+-O^-), 1440 (=N^+(O^-)-O)	7.54–7.41 (m, 6H, ArH), 7.19–7.13 (m, 2H, 3′,5′-ArH)
40	4-Cl	4′-Me	121–123	37	$C_{15}H_{11}ClN_2O_2$ (286.72) 286 (M^+)	62.56 62.84	3.59 3.87	9.59 9.77	1589 (C=N^+-O^-), 1436 (=N^+(O^-)-O)	7.50–7.37 (m, 6H, ArH), 7.27–7.24 (m, 2H, 3′,5′-ArH), 2.42 and 2.40 (s, 3H, $ArCH_3$)
41	4-Cl	4′-OMe	142–144	53	$C_{15}H_{11}ClN_2O_3$ (302.72)	59.88 59.52	3.87 3.66	9.42 9.25	1591 (C=N^+-O^-), 1450 (=N^+(O^-)-O), 1254 (Ar-O-Me, asym), 1025 (Ar-O-Me, sym)	7.51–7.40 (m, 6H, ArH), 6.97–6.94 (m, 2H, 3′,5′-ArH), 3.86 and 3.85 (s, 3H, $ArOCH_3$)
42	4-OMe	4′-OMe	110–114	56	$C_{16}H_{14}N_2O_4$ (298.30) 299 (M+H)	64.66 64.42	4.99 4.73	9.17 9.39	1600 (C=N^+-O^-), 1443 (=N^+(O^-)-O)1261 (Ar-O-Me, asym), 1022 (Ar-O-Me, sym)	7.50–7.43 (m, 4H, ArH), 6.97–6.92 (m, 4H, 3′,5′-ArH), 3.85 and 3.84 (s, 6H, $ArOCH_3$)
43	4-NO_2	4′-Cl	156–158	78	$C_{14}H_8ClN_3O_4$ (317.69)	52.59 52.93	2.72 2.54	13.42 13.23	1591 (C=N^+–O^-), 1516 (NO_2, asym), 1440 (=N^+(O^-)–O), 1350 (NO_2, sym)	8.35–8.30 (m, 2H, 3,5-ArH), 7.77–7.71 (m, 2H, 2,6-ArH), 7.50–7.42 (m, 4H, ArH)

Table II. Continued

Compd. No.	X	Y	M.p. (°C)	Yield (%)	Molecular formula (M_r) and mass (m/z)	Elemental analysis, found/calcd. (%)			IR (ν, cm^{-1})	^1H NMR (δ, ppm)
						C	H	N		
44	4-NO_2	4′-Br	170–172	30	$C_{14}H_8BrN_3O_4$ (362.14)	46.22 46.43	2.49 2.23	11.45 11.60	1585 (C=N^+–O^-), 1521 (NO_2, asym), 1444 (=N^+(O^-)–O), 1350 cm^{-1} (NO_2, sym)	8.34–8.29 (m, 2H, 3,5-ArH), 7.77–7.71 (m, 2H, 2,6-ArH), 7.65–7.60 (m, 2H, 2′,6′-ArH), 7.40–7.35 (m, 2H, 3′,5′-ArH)
45	4-NO_2	4′-F	127–128	26	$C_{14}H_8FN_3O_4$ (301.24)	55.66 55.82	2.42 2.68	14.22 13.95	1589 (C=N^+–O^-), 1519 (NO_2, asym), 1440 (=N^+(O^-)–O), 1350 cm^{-1} (NO_2, sym)	8.34–8.29 (m, 2H, 3,5-ArH), 7.77–7.72 (m, 2H, 2,6-ArH), 7.53–7.48 (m, 2H, 2′,6′-ArH), 7.21–7.13 (m, 2H, 3′,5′-ArH)
46	4-NO_2	4′-Me	146–148	80	$C_{15}H_{11}N_3O_4$ (297.27)	60.27 60.61	3.97 3.73	14.29 14.14	1586 (C=N^+–O^-), 1540 (NO_2, asym), 1439 (=N^+(O^-)–O), 1350 (NO_2, sym)	8.31–8.26 (m, 2H, 3,5-ArH), 7.78–7.72 (m, 2H, 2,6-ArH), 7.39–7.35 (m, 4H, ArH), 2.44 and 2.42 (s, 3H, $ArCH_3$)
47	4-NO_2	4′-SO_2Me	156–158	46	$C_{15}H_{11}N_3O_6S$ (361.34)	49.69 49.84	2.78 3.06	11.49 11.62	1600 (C=N^+–O^-), 1523 (NO_2, asym), 1444 (=N^+(O^-)–O), 1350 (NO_2, sym), 1311 (SO_2, asym), 1153 cm^{-1} (SO_2, sym)	8.37–8.31 (m, 2H, 3,5-ArH), 8.10–8.04 (m, 2H, 3′,5′-ArH), 7.76–7.71 (m, 4H, ArH), 3.13 and 3.11 (s, 3H, $ArSO_2CH_3$)

[a] Lit. m.p 118 °C (22), Lit. 104–105 °C (13).
[b] Lit. m.p. 121–123 °C (13).

Syntheses of 3,4-diaryl-1,2,5-oxadiazoles (**4**–**28**). *General procedure*. – A mixture of 1,2-diaryl-1,2-ethanedione dioximes (**3**) (4 mmol) and succinic anhydride (20 mmol) was heated at 180–185 °C for 10 min in an oil-bath. The molten product was cooled, suspended in water and a sufficient quantity of sodium bicarbonate was added to neutralize the acid. The resulting mixture was extracted with successive quantities of chloroform (3 × 25 mL). The combined organic extract was washed with water (3 × 50 mL), dried and the solvent was recovered. The product obtained was crystallized from methanol to yield the title compounds.

Preparation of 3-(4-methylsulfonylphenyl)-4-(4-nitrophenyl)-1,2,5-oxadiazole (**29**). – To a cooled solution of **28** (0.2 g, 0.64 mmol) in CH_2Cl_2 (20 mL), *m*-chloroperbenzoic acid (*m*-CPBA) (1.0 g, 58 mmol, 55–75%) was added under stirring. Stirring was continued at room temperature overnight. The reaction mixture was cooled to 0 °C and filtered at the pump to remove benzoic acid. Aqueous sodium metabisulphite (20 mL, 10%, *m*/*V*) was added to the filtrate and stirred for 15 min. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extract was washed with aqueous sodium bicarbonate solution (5%, 2 × 10 mL) followed by water (3 × 5 mL). The CH_2Cl_2 layer was dried over anhydrous sodium sulphate and recovered. The resulting solid was crystallized from benzene to yield the title compound.

Syntheses of 3,4-diaryl-1,2,5-oxadiazole N-*oxides* (**30**–**47**). *General procedure*. – 1,2-Diaryl-1,2-ethanedione dioxime (**3**) (0.5 g) was dissolved in methanol (10 mL). A freshly prepared sodium hypochlorite solution (10 mL, 20%) was added dropwise to the above solution at a temperature below 10 °C under stirring over a period of 30 min keeping the temperature below 10 °C. After complete addition, the reaction mixture was further stirred for 1 h at a temperature below 10 °C and refrigerated overnight. The reaction mixture was poured onto crushed ice and the solid obtained was filtered and dried. Crystallization from methanol afforded the title compounds.

In vitro *COX inhibition assay*

The final compounds were evaluated for their ability to inhibit ovine COX-1 and COX-2 enzymes [percent inhibition at a fixed molar concentration (μmol L^{-1})] (17). Inhibition of the enzymes was determined with the colorimetric COX (ovine) inhibitor screening assay kit (Cayman Chemicals, USA) using ELISA reader following the procedure described in the catalog. The experiments were performed in duplicates.

In vivo *carrageenian induced rat paw edema assay*

Anti-inflammatory activity was determined by the carrageenian-induced rat paw edema method described by Winter *et al*. (18). Male Sprague-Dawley rats weighing 150 to 200 g (6–8 weeks old) were used in groups of six animals per group for the experiments. The animals were housed in a room with temperature of 22 ± 2 °C under a 12 h light/dark cycle. They were allowed free access to food and water *ad libitum*. The protocol for the animal experiments performed was approved by the IAEC (Institute Animal Ethics Committee) registered under CPCSEA (Committee for the purpose of Control and Supervision of Experiments on Animals) Govt. of India. Compounds were administered orally as suspension in 1% carboxymethyl cellulose (CMC). Paw edema was induced by

intradermal injection of 50 μL of 1% λ-carrageenian (Sigma, USA) into the subplantar region of the right hind paw, after one hour of compound administration. The paw volume was measured immediately after injection and after 3 hours using a plethysmometer (UGO-Basile, Italy). The control group received only the vehicle. Increase in paw volume was compared with that in the control group and percent inhibition was calculated taking the values in the control group as 0% inhibition.

Molecular modeling (docking studies)

All the molecular modeling studies reported herein were performed on a Silicon Graphics Fuel Workstation running on the IRIX 6.5 operating system using SYBYL 6.9 molecular modeling software from Tripos, Inc., USA (19) and GLIDE from Schrödinger Inc., USA (20). All compounds used for docking were built from the fragments in the SYBYL database. Each structure was fully geometry optimized using the standard Tripos force field (21) with a distance-dependent dielectric function until a root mean square deviation (rms) of 4.186 J $Å^{-1}$ was achieved. Conformational search was carried out using MULTISEARCH option in SYBYL 6.9. The lowest energy conformer thus obtained was further minimized using the Tripos force field and was subsequently used in docking. The COX-2 receptor structure (pdb code: 6COX) obtained from the Protein Data Bank (USA) was refined to remove water molecules, adjust bond orders and formal charges prior to docking. Docking was performed using GLIDE software according to their previously reported protocol (20).

RESULTS AND DISCUSSION

Chemistry

The general method employed for the preparation of 3,4-diaryl-1,2,5-oxadiazoles (**4**–**28**) and 3,4-diaryl-1,2,5-oxadiazole *N*-oxides (**30**–**47**) and important intermediates **1**–**3** is illustrated in Scheme 1. Acid chlorides of phenylacetic acid and substituted phenylacetic acids were obtained by refluxing the acid with thionyl chloride or phosphorous trichloride. Excess of thionyl chloride or phosphorous trichloride was removed under vacuum and the resulting acid chlorides were used as such in Friedel-Crafts acylation reaction with benzene and monosubstituted benzenes to yield 1,2-diaryl-1-ethanones (**1**) (16). IR spectra of these ethanones showed the presence of characteristic carbonyl stretching peaks at 1690–1665 cm^{-1}. Their ^1H NMR spectra showed characteristic signals for -CH_2- at about δ 4.37 ppm.

1,2-Diaryl-1,2-ethanediones **2** (benzils) were synthesized by selenium dioxide (SeO_2) oxidation of **1** using AcOH/Ac_2O as solvents at refluxing temperatures up to 8 h. The reaction was completed under these conditions except for nitro substituted derivatives of **1**. Therefore, a new method was developed (16) for the oxidation of 1,2-diaryl-1-ethanones **1**, which proved to be faster and more efficient. In this method, the reaction was carried out in DMSO in a microwave oven for 30 s to afford the desired diones **2** in almost pure form. ^1H NMR spectra of these diones **2** showed the absence of characteristic signals for -CH_2- at δ 4.37 ppm. Some of benzils **2** were prepared by benzoin/cross ben-

zoin condensation followed by oxidation, as per the reported procedures (14, 15). 1,2-Diphenyl-1,2-ethanedione (benzil), 1,2-di(4-methoxyphenyl)-1,2-ethanedione (anisil), 1-(2-chlorophenyl)-2-(4-methoxyphenyl)-1,2-ethanedione and 1-(2-chlorophenyl)-2-(3,4-dimethoxyphenyl)-1,2-ethanedione were prepared by this method (14, 15).

Benzils **2** were oximated into the corresponding 1,2-diaryl-1,2-ethanedione dioximes **3** using the hydroxylamine hydrochloride/pyridine system at refluxing temperatures. Most of the dioximes were isolated as solid compounds. Their TLC showed two spots and IR spectra indicated the absence of keto stretching bands. Since there is a possibility of formation of *syn* and *anti* products, no efforts were made to isolate these geometric isomers and the dioximes **3** were used as such for the next step.

Cyclization of **3** to 3,4-diaryl-1,2,5-oxadiazoles was attempted using different acidic/basic dehydrating agents but could only be effected by heating with succinic anhydride at 180–185 °C. Oxidation of **3** was carried out with aqueous sodium hypochlorite solution (20%) to obtain 3,4-diaryl-1,2,5-oxadiazole *N*-oxides. It was observed that methylsulfanyl (–SMe) also got oxidized to methylsulfonyl ($–SO_2Me$) during sodium hypochlorite treatment of compound **47**. This was confirmed by the shift of methyl signal from δ 2.50 to δ 3.11 ppm in its ^{1}H NMR spectrum. Conversion of –SMe to $–SO_2Me$ was also performed with *m*-CPBA either at 1,2-diaryl-1-ethanone **1** or at 3,4-diaryl-1,2,5-oxadiazole stages (Scheme 2). The elemental and spectral data of the synthesized compounds are given in Tables I and II.

Biological and molecular modeling studies

All compounds described herein were evaluated *in vitro* for COX-2 binding affinity at a concentration of 22 μmol L^{-1} by the colorimetric COX (ovine) inhibitor screening assay. Selected active compounds were also evaluated for COX-1 binding affinity at a higher concentration (88 μmol L^{-1}) (Table III). Compounds that showed promising COX-2 inhibitory activity were further screened for their anti-inflammatory activity (Table IV) *in vivo* using the carrageenian induced rat paw edema method.

Amongst all the compounds, methoxy (-OMe) substituted compounds **9**, **21**, **34**, **41**, **42** showed COX-2 enzyme inhibition higher than that shown by compounds with other substituents. 3,4-Di(4-methoxyphenyl)-1,2,5-oxadiazole *N*-oxide (**42**) showed COX-2 enzyme inhibition of 54% at 22 μmol L^{-1} and COX-1 enzyme inhibition of 44% at 88 μmol L^{-1} concentration, but showed mild *in vivo* anti-inflammatory activity at a 25 mg kg^{-1} dose. However, its deoxygenated analog **21** showed lower COX-2 enzyme inhibition (26% at 22 μmol L^{-1}) and higher COX-1 enzyme inhibition (53% at 88 μmol L^{-1}), but showed stronger *in vivo* anti-inflammatory activity at a 25 mg kg^{-1} dose (71%) than standard celecoxib at 12.5 mg kg^{-1} (48%). However, at the same dose level of 12.5 mg kg^{-1}, it showed much lower activity than (21%) celecoxib. This preliminary study suggests that the methoxy (-OMe) group at 4-position of one of the phenyl rings may be a suitable pharmacophore for COX-2 enzyme binding in this series of compounds. Replacement of one of the -OMe groups of compound **21** by an electron withdrawing $-NO_2$ group resulted in a complete loss of COX-2 enzyme affinity. Compounds **11**, **19**, **20**, **29** and **47** with the well known COX-2 enzyme pharmacophore (methylsulfonyl, $-SO_2Me$) failed to show COX-2 enzyme inhibition at a 22 μmol L^{-1} concentration, but compound **11** exhibited *in vivo* anti-inflammatory activity at 25 mg kg^{-1} comparable to celecoxib at 12.5 mg kg^{-1}. Compound **21** was found to be the most active compound in the series.

Table III. In vitro *COX-2 inhibition data for 3,4-diaryl-1,2,5-oxadiazoles and 3,4-diaryl-1,2,5-oxadiazole* N*-oxides (**4**–**47**)*[a]

Compd. No.	Inhibition[b] (%)	
	COX-2 (22 μmol L^{-1})	COX-1 (88 μmol L^{-1})
4	5	–
8	8	–
9	17	–
10	5	–
14	9	–
15	5	–
18	4	–
19	4	–
21	26	53
23	4	–
25	7	–
32	3	–
34	21	55
35	11	–
37	6	–
38	4	–
41	20	53
42	54	45
45	2	–
42	54	45
Celecoxib	95	–

[a] Compounds **5**–**7**, **11**–**13**, **16**, **17**, **20**, **22**, **24**, **26**–**31**, **33**, **36**, **39**, **40**, **43**, **44**, **46** and **47** were found to be inactive at the concentration of 22 μmol L^{-1}.
– Not evaluated.
[b] Experiments were performed in duplicate.

All the synthesized compounds were energy minimized and docked in the active site of COX-2, but only a few binding interactions are discussed here. The binding interaction of 3,4-di(4-methoxyphenyl)-1,2,5-oxadiazole (**21,** 26% COX-2 inhibitory activity) was studied within the COX-2 binding site by molecular docking studies. The *para* methoxy group is oriented in the vicinity of COX-2 secondary pocket (Phe^{518}, Arg^{513}, Gln^{192}, Val^{523}, Ser^{353}) as shown in Fig. 1. The oxygen atom of the *para* substituted methoxy group to the C-3 phenyl ring is hydrogen bonded with the backbone NH of Ile^{517} (distance = 4.1 Å). The oxygen atom of the other methoxy group that is *para* substituted to C-4 phenyl ring also forms a hydrogen bond with OH of Tyr^{348} (distance = 4.9 Å). The N^2-atom of the central oxadiazole ring forms a favorable hydrogen bond with NH_2 of Arg^{120} (distance = 3.65 Å).

Table IV. In vivo *anti-inflammatory data for selected compounds*

Compd. No.	Dose (mg kg^{-1})	Paw volume (mL) (% inhibition)[a]
Control	25	0.820 ± 0.02 (0)
11	25	0.28 ± 0.06 (53)
20	25	0.57 ± 0.10 (35)
21	25	0.16 ± 0.04 (71)
41	25	0.25 ± 0.03 (31)
42	25	0.04 ± 0.01 (5)
21	12.5	0.16 ± 0.04 (21)
Celecoxib	12.5	0.39 ± 0.05 (48)

[a] Mean ± SD, $n = 6$.

Binding mode of 3,4-di(4-methoxyphenyl)-1,2,5-oxadiazole *N*-oxide (**42**, 54% COX-2 inhibitory activity) was also examined (Fig. 2). As observed in other compounds, also here the *p*-methoxy group is oriented towards the secondary pocket of the enzyme, which is similar to the orientation of $–SO_2NH_2$ in celecoxib. The central oxygen atom of the oxadiazole ring participates in hydrogen bond formation with NH_2 of Arg^{120} (distance = 2.57 Å). Oxygen atom of *N*-oxide forms a favorable hydrogen bond with NH of Leu^{531}. The methoxy group substituted on the C-3 phenyl ring forms a hydrogen bond with Tyr^{348} (distance = 4.8 Å). The methoxy group on the C-4 phenyl ring also participates in the formation of the hydrogen bond with backbone NH of Ile^{517} (distance = 3.83 Å) and NH of Gln^{192} (distance = 4.8 Å). Amongst all the compounds in the series, **42** had the lowest intermolecular energy of $–3.5 \times 10^5$ J mol^{-1}, indicating its stability in the COX-2 active site.

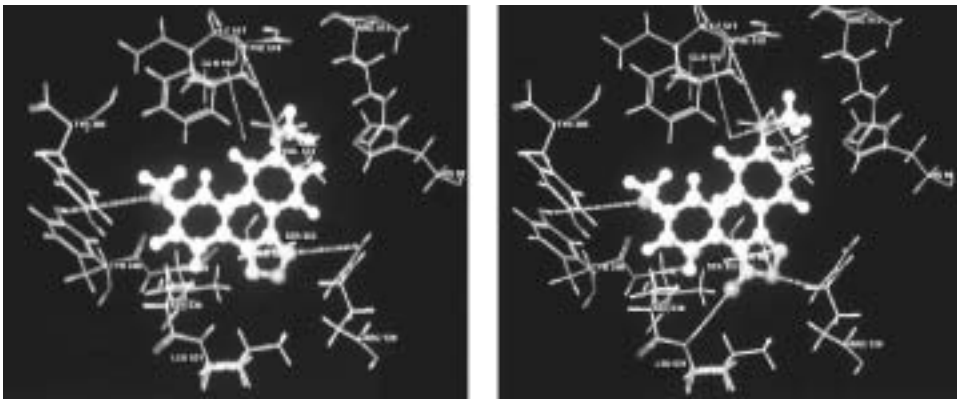


Fig. 1. Docking of compounds (ball and stick) in the active site of murine COX-2: a) 3,4-di(4-methoxyphenyl)-1,2,5-oxadiazole (**21**) and b) 3,4-di(4-methoxyphenyl)-1,2,5-oxadiazole *N*-oxide (**42**).

CONCLUSIONS

Docking studies of 3,4-diaryl-1,2,5-oxadiazoles and 3,4-diaryl-1,2,5-oxadiazole *N*-oxides indicate a favorable orientation of the methoxy group in the COX-2 active site. Lower binding energies also indicate the stability of 3,4-diaryl-1,2,5-oxadiazoles and their *N*-oxides in the active site. This supports *in vitro* and *in vivo* anti-inflammatory data. These preliminary studies suggest that the methoxy group may be acting as a pharmacophore for the COX-2 enzyme binding site in series of 1,2,5-oxadiazoles and their *N*-oxides. Further work in this direction is in progress.

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SAŽETAK

Istraživanja 3,4-diaril-1,2,5-oksadiazola i njihovih *N*-oksida: Potraga za boljim COX-2 inhibitorima

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Sintetizirana je serija 3,4-diaril-1,2,5-oksadiazola i 3,4-diaril-1,2,5-oksadiazol *N*-oksida i ocijenjena njihova sposobnost vezivanja na COX-2 i COX-1 *in vitro* i protuupalno djelovanje na edem šape štakora. Spojevi sa *p*-metoksi (*p*-OMe) supstituentom **9**, **21**, **34**, **41**, **42** bolje su inhibirali COX-2 nego ostali spojevi. 3,4-*Di*(4-metoksifenil)-1,2,5-oksadia-

zol *N*-oksid (**42**) inhibirao je COX-2 za 54% u koncentraciji od 22 μmol L^{-1}, a COX-1 za 44% u koncentraciji 88 μmol L^{-1}, ali je *in vivo* slabo djelovao protuupalno. Njegov deoksigenirani derivat **21** pokazao je slabiju inhibiciju COX-2 enzima (26% u koncentraciji 22 mmol L^{-1}) i jaču inhibiciju COX-1 (71% u koncentraciji 25 mg kg^{-1}), što je bolje od standarda celokoksiba (48% u koncentraciji 12,5 mg kg^{-1}). Molekularno je modeliranje pokazalo da je metoksi skupina smještena u blizini sekundarnog džepa na enzimu COX-2 i da utječe na vodikove veze interakcija na aktivnom mjestu COX-2. Ova preliminarna istraživanja sugeriraju da bi se u seriji oksadiazol/*N*-oksida mogao naći predvodni spoj s *p*-metoksi skupinom na benzenskom prstenu.

Ključne riječi: 1,2,5-oksadiazol, 1,2,5-oksadiazol *N*-oksid, COX-2 inhibitor

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