

## **Design, Synthesis and Pharmacological evaluation of 2,5 di phenyl 1,3,4-oxadiazole derivatives as selective COX-2 inhibitors**

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### **Abstract**

A novel series of substituted-2,5-diphenyl-1,3,4-oxadiazole derivatives (3a-i) have been synthesized with the aim to get better anti-inflammatory and selective cox -2 inhibitor activity. Compound (2a-i) was reacted with several aryl acid hydrazides in phosphorousoxychloride to obtain the title compounds. Structures of the synthesized compounds were supported by means of IR, <sup>1</sup>H NMR and mass spectroscopy. All synthesized derivatives were determined by the carrageenan induced rat paw oedema model for Anti-inflammatory activity. The entire compound gives good response for anti-inflammatory activity for this activity indomethacine was used as standard drug and compared to new synthesized drugs. Some New Synthesized drugs have to shown better activities for anti-inflammatory. Title compounds were evaluated for their anti-inflammatory and selective cox-2 activities. These compounds also exhibited significant anti-inflammatory activity, which is comparable to that of celecoxib in the carrageenan-induced rat paw edema method. The selected compounds were evaluated for their preliminary in vitro cyclooxygenase inhibitory activity against COX-2 and COX-1 enzymes. The compounds tested showed selective inhibitory activity toward COX-2(72-5%) over COX-1 (3.5%)., amongst them compounds 3c and 3i showed appreciable COX-2 selective inhibitory activity.

**Key words:** 1,3,4-oxadiazoles ,NSAIDs, cyclooxygenase-2 inhibitors, anti-inflammatory, rat paw edema assay

### **1. Introduction**

Non-steroidal anti-inflammatory drugs (NSAIDs) still remain among the most extensively used drugs world wide and have been used in the treatment of inflammatory conditions like rheumatoid arthritis, osteoarthritis, orthopedic injuries, post operative pain, etc.<sup>1,2</sup>. However, the use of conventional NSAIDs have been restricted due to their adverse effect especially gastrointestinal toxicity and renal insufficiency<sup>3,4</sup>. A major discovery in the search of novel anti-inflammatory agents without deleterious side effects exhibited by the conventional NSAIDs came from the identification of two different isoforms of the cyclooxygenase (COX) enzyme known as COX-1 and COX-2. The common mechanism of NSAIDs involves the nonselective inhibition of cyclooxygenase thereby preventing the biosynthesis of prostaglandins (PG) which is the important lipid mediators of inflammation as well as numerous homeostatic physiological functions. COX-1 is a constitutive isoform that is involved in normal cellular functions whereas COX-2 is an inducible isoform that is expressed only after inflammatory stimulus<sup>5,6</sup>. Researchers have recently focused on selective COX-2 inhibitors which are believed to reduce inflammation without influencing normal physiologic functions of COX-1. However, recent studies has shown that COX-2 inhibitors are associated with increased thromboembolic phenomena in specific patient population such as cardiovascular disease patients challenging the benefits of selective COX-2 inhibitor. moreover, there is currently no clear evidence that COX-2 represents an independent risk of cardiovascular diseases and therefore ,clinical rationale for

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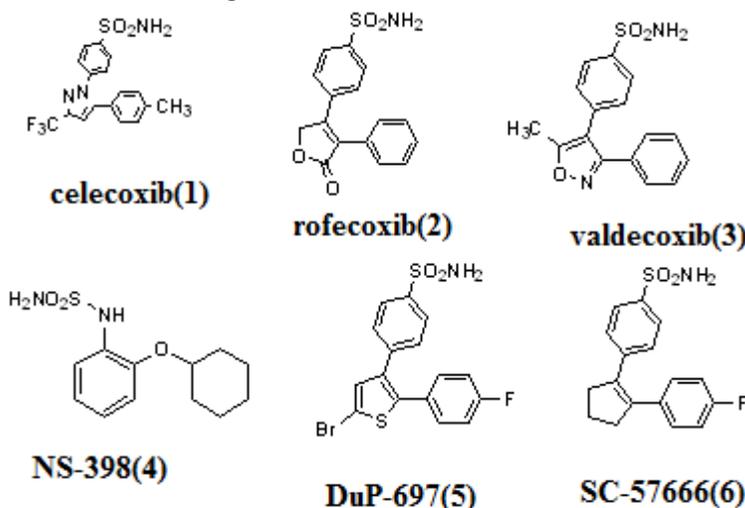
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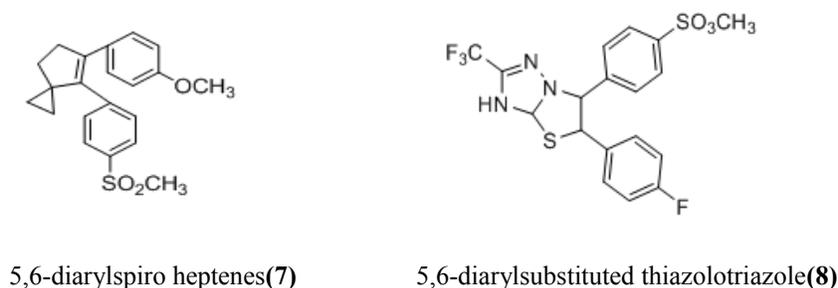
developing compounds with selective COX-2 inhibition still remains to be established. In addition to this role of COX-2 inhibitors in clinical uses are also on addition and appreciable interest and should be continued for further more extensive investigation because recently it has also documented in cancer chemotherapy and neurological diseases such as Alzheimer's and Parkinson disease .

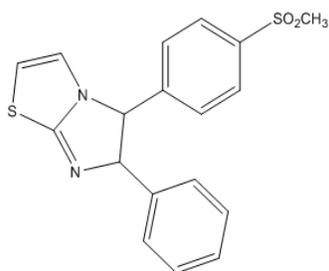
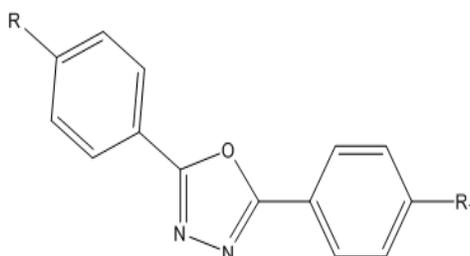
The marketed coxibs are characterized by a 1,2-diarylheterocycle. Generally, the heterocycle is a five-membered ring such as thiophene (DuP- 697),<sup>14</sup> furanone (rofecoxib),<sup>15</sup> pyrazole (celecoxib),<sup>16</sup> oxazole (JTE-522),<sup>17</sup> isoxazole (valdecoxib, parecoxib),<sup>18,19</sup> thiazole,<sup>20</sup> imidazole,<sup>21,22</sup> pyrrole,<sup>23</sup> or oxazolone.<sup>24</sup> Some coxibs such as etoricoxib<sup>25</sup> have a six-membered ring as central heterocycle (pyranone, pyridine and pyridazinone).<sup>26,27</sup> Recently, rofecoxib was voluntarily withdrawn from the market because of an increased risk of cardiovascular adverse events with a probability linked to the dose and the duration of treatment.<sup>28,29</sup> For targeting COX-2 isoform, it is therefore interesting to design new molecule scaffolds different from 1,2-diaryl heterocyclic type derivatives such as rofecoxib. During recent past several attempts have been made to develop safer COX-2 selective inhibitors containing fused heterocyclic ring system in place of a regular central single heterocycle. Now several different classes of COX-2 inhibitors have been reported, like 5,6-diarylspiro heptenes<sup>30</sup> (7) and 5,6-diarylsubstituted thiazolotriazole derivatives (8).<sup>31</sup> Recently, a novel series of 5,6-diarylimidazo[2,1-b]thiazole derivatives (9) have been reported as potent, orally active, selective COX-2 inhibitors<sup>32</sup> indicating the increasing scope of alteration in the central ring that may lead to development of newer, safer, selective COX-2 inhibitors (see Fig. 2). A common structural backbone of most COX-2 selective inhibitors consists of two aryl groups linked to adjacent atoms of a central ring which can be homocyclic or heterocyclic, one of the aryl groups is substituted in the para position with either an aminosulfonyl (SO<sub>2</sub>NH<sub>2</sub>) or a methyl sulfonyl (SO<sub>2</sub>CH<sub>3</sub>) group. There are also examples of potent COX-2 inhibitors that possess cycloalkyl, alkoxy or phenoxy moieties in the non-sulfonyl containing 'aryl' region<sup>33-34</sup> Some of the commonly found central rings within this class of molecules are thiophene, pyrazole, furanone, isoxazole, and cyclopentene as shown in Figure 1.

**Figure 1: Selective cox-2 inhibitors**



**Figure 2: Recently reported selective cox-2 inhibitors.**



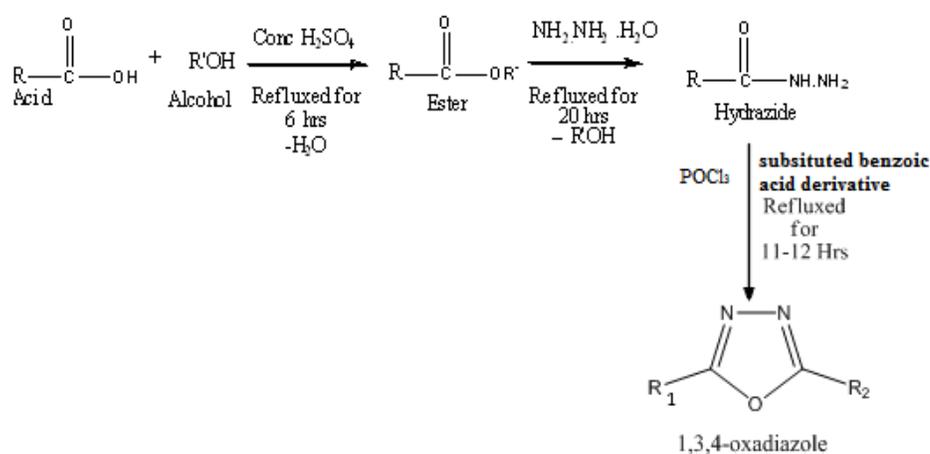
5,6-diarylimidazo[2,1-b]thiazole (**9**)2,5-diphenyl-1,3,4-oxadiazole (**3a-j**)

## 2. Experimental

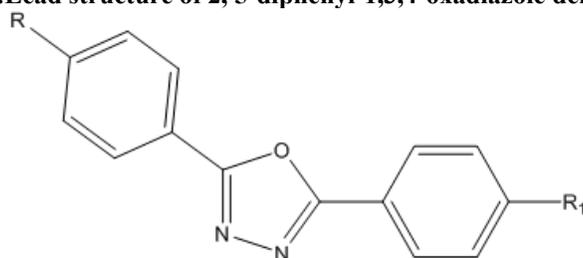
Melting points were determined with a Reichert–Jung hot-stage microscope and are uncorrected. Infrared spectra were recorded on a Nicolet Magna 550-FT spectrometer.  $^1\text{H}$  NMR (400 MHz) spectra were measured on a Varian Unity plus 400 spectrometer in  $\text{CDCl}_3$  or  $\text{DMSO-d}_6$  with TMS as the internal standard, where  $J$  (coupling constant) values are estimated in Hertz. Spin multiples are given as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and br (broad). Mass spectra were obtained with a Finnigan Mat TSQ-70 spectrometer. Elemental microanalyses were carried out with a Perkin-Elmer 240-C apparatus and were within  $\pm 0.4\%$  of the theoretical values for C, H, and N. All solvents and reagents were purchased from the Fluka, Aldrich or Merck Chemical Company. Albino rats, used in the anti-inflammatory screens, and experiments were carried out using protocols approved by the Ethics Committee of Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research, Balawala, Dehradun, India.

**2.1 General procedure:** In present described experimental conditions the heterocyclization reaction reached completion with a relative simple operation giving high yield (65-95%) at shorter time (1.5-3.0 h) compared to the other reported cyclization methods for 1,3,4-oxadiazole ring. In this method 20gm (0.145 moles) of substituted benzoic acid, 65 ml of absolute ethanol and 2.85 ml of conc.  $\text{H}_2\text{SO}_4$  refluxed for 6 hours., excess alcohol was distilled off on water bath and allowed to cool. The residue was poured into crushed ice and the oily layer that deposited was extracted with diethyl ether. Then washed with the strong solution of sodium hydrogen carbonated. Filtered and collected the pure liquid mass of ester(1a-1i).Synthesized ester (0.0527moles) and 2.63 ml (0.05257 moles) of hydrazide hydrate was placed in a 250 ml round bottom flask (RBF), containing the sufficient amount of  $\text{C}_2\text{H}_5\text{OH}$ . Mixture was refluxed for 20 hours.. After completion of reaction, excess amount of alcohol was distilled off on water bath and solution was poured crushed ice. The obtained white crystals of hydrazide was collected, dried and recrystallised from ethyl alcohol. Substituted Hydrazide 1.36 gm (0.01 moles) and  $\text{POCl}_3$  (5 ml ), 1.37 gm (0.01 moles)of 4-amino benzoic acid was placed in a 100 ml round bottom flask (RBF) and refluxed for 11-13 hours. The reaction was monitored by TLC, using chloroform: methanol (10:90) as a solvent system and the spot was observed in iodine vapours. After completion, the reaction mixture was poured into the beaker containing the crushed ice. A Clear solution was obtained. The solution was made alkaline by sodium carbonate solution (5%) until no further evolution of  $\text{CO}_2$  occurs and a resulting solid was filtered, dried and recrystallized from a mix of ethanol and DMF .

**Scheme 1 (a) Conc. H<sub>2</sub>SO<sub>4</sub>, Ethanol, Reflux 4hr; (b) Hydrazine Hydrate, Ethanol, Reflux 20 hr; (c) Substituted benzoic acid ), Phosphorous Oxychloride, Reflux 2-3 hr.( hetero-cyclization reaction)**



**Table 1 :Lead structure of 2, 5-diphenyl-1,3,4-oxadiazole derivatives:**



S. No	R	R1
3a	H	H
3b	H	SO <sub>2</sub> NH <sub>2</sub>
3c	CH <sub>3</sub>	SO <sub>2</sub> NH <sub>2</sub>
3d	SO <sub>2</sub> CH <sub>3</sub>	H
3e	SO <sub>2</sub> CH <sub>3</sub>	CH <sub>3</sub>
3f	C <sub>2</sub> H <sub>5</sub>	SO <sub>2</sub> NH <sub>2</sub>
3g	C <sub>2</sub> H <sub>5</sub>	SO <sub>2</sub> CH <sub>3</sub>
3h	OCH <sub>3</sub>	SO <sub>2</sub> CH <sub>3</sub>
3i	OCH <sub>3</sub>	SO <sub>2</sub> NH <sub>2</sub>

**2.2. 2,5-diphenyl-1,3,4-oxadiazole (3a) :** Yield, 35%; mp 238 °C (methanol); IR (KBr): 2938(C-H),1731(C=O),1674(C=N) cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ : 7.36( m,2H,H-9,15 phenyl),7.53( m,4H,H-8,10,,14,16 phenyl),8.07(m,4H,H-7,11,13,17); MS m/z (%) 222[M+1} Anal. calcd for C<sub>14</sub>H<sub>10</sub>N<sub>2</sub>O: C, 75.66; H, 4.54; N, 12.60; O, 7.20. Found: C, 75.01; H, 5.01; N, 12.45; O, 8.01.

**2.3 4-(5-phenyl-1,3,4-oxadiazol-2-yl)benzenesulfonamide (3b) :** Yield, 65%; mp 330°C (methanol); IR (KBr): 2960(C-H),1741(C=O),1648(C=N) cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ : 2.05 (s,2H,H-18,19),7.36 ( m,1H,H-15 phenyl),7.53( m,2H,H-14,16

phenyl), 7.81 (m, 2H, H-8, 10 phenyl), 8.07 (m, 4H, H-7, 11, 13, 17); MS m/z (%) 301.01 [M+1] Anal. calcd for C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>S: C, 55.80; H, 3.68; N, 13.95; O, 15.93; S, 10.64. Found: C, 56.01; H, 3.89; N, 14.03

**2.4 4-(5-p-tolyl-1,3,4-oxadiazol-2-yl)benzenesulfonamide (3c):** Yield, 56%; mp 358°C (methanol); IR (KBr): 2955(C-H), 1735(C=O), 1660(C=N) cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ : 2.03 (s, 2H, H-18, 19), 2.35 (s, 3H, H-20, 21, 22), 7.36 (m, 1H, H-15 phenyl), 7.53 (m, 2H, H-14, 16 phenyl), 7.81 (m, 2H, H-8, 10 phenyl), 8.07 (m, 4H, H-7, 11, 13, 17); MS m/z (%) 315.07 [M+1] Anal. calcd for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>S: C, 57.13; H, 4.16; N, 13.33; O, 15.22; S, 10.1, 15.93; S, 10.64: found C, 58.12; H, 5.12; N, 13.21

**2.5 2-(4-(methylsulfonyl)phenyl)-5-phenyl-1,3,4-oxadiazole(3d):** Yield, 56%; mp 358°C (methanol); IR (KBr): 2955(C-H), 1735(C=O), 1660(C=N) cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ : 3.34 (s, 2H, H-18, 19, 20), 7.46 (m, 1H, H-15 phenyl), 7.58 (m, 2H, H-14, 16 phenyl), 7.98 (m, 2H, H-8, 10 phenyl), 8.12 (m, 4H, H-7, 11, 13, 17); MS m/z (%) 300.06 [M+1] Anal. calcd for C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>S: C, 59.99; H, 4.03; N, 9.33; O, 15.98; S, 10.68: found C, 60.12; H, 4.02; N, 9.32; O, 16.03; S, 10.21

**2.6 2-(4-(methylsulfonyl)phenyl)-5-p-tolyl-1,3,4-oxadiazole(3e):** Yield, 63%; mp 358°C (methanol); IR (KBr): 2934(C-H), 1767(C=O), 1678(C=N) cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ : 2.35 (s, 3H, H-18, 19, 20), 3.34 (s, 3H, H-20, 21, 22), 7.26 (m, 2H, H-14, 15 phenyl), 7.88 (m, 4H, H-8, 10, 13, 17 phenyl), 8.12 (m, 2H, H-7, 11, 13, 17); MS m/z (%) 314.21 [M+1] Anal. calcd for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>S: C, 61.13; H, 4.49; N, 8.91; O, 15.27; S, 10.20: found C, 61.13; H, 4.49; N, 8.91; O, 15.27; S, 10.20

**2.7 4-(5-(4-ethylphenyl)-1,3,4-oxadiazol-2-yl)benzenesulfonamide (3f):** Yield, 63%; mp 358°C (methanol); IR (KBr): 2944(C-H), 1757(C=O), 1679(C=N) cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ : 1.56 (m, 3H, H-21-23), 2.35 (s, 2H, H-18, 19), 3.34 (s, 3H, H-20, 21, 22), 7.26 (m, 2H, H-14, 15 phenyl), 7.88 (m, 4H, H-8, 10, 13, 17 phenyl), 8.12 (m, 2H, H-7, 11, 13, 17); MS m/z (%) 329.08 [M+1] Anal. calcd for C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>S: C, 58.34; H, 4.59; N, 12.76; O, 14.57; S, 9.74: found C, 57.94; H, 5.09; N, 12.32; O, 13.21; S, 8.91

**2.8 2-(4-ethylphenyl)-5-(4-(methylsulfonyl)phenyl)-1,3,4-oxadiazole (3g):** Yield, 59%; mp 378°C (methanol); IR (KBr): 2945(C-H), 1710(C=O), 1649(C=N) cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ : 1.24 (s, 3H, -CH<sub>3</sub>), 2.47 (m, 2H, -CH<sub>2</sub>), 2.89 (m, 3H, -SO<sub>2</sub>NH<sub>2</sub>), 3.56 (m, 3H, H-23-25), 3.89 (m, 3H, H-22, 23, 24), 7.06 (m, 2H, H-14, 16), 7.83 (m, 2H, H-8, 10 phenyl), 8.08 (m, 4H, H-8, 11, 13, 17 phenyl) MS m/z (%) 328.36 [M+1] Anal. calcd for C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>S: C, 62.18; H, 4.91; N, 8.53; O, 14.62; S, 9.76 found C, 61.23; H, 5.10; N, 8.13; O, 13.48; S, 10.21

**2.9 2-(4-methoxyphenyl)-5-(4-(methylsulfonyl)phenyl)-1,3,4-oxadiazole (3h):** Yield, 49%; mp 308°C (methanol); IR (KBr): 2946(C-H), 1776(C=O), 1643(C=N) cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ : 3.24 (s, 3H, H-23-25), 3.84 (s, 3H, H-22, 23, 24), 7.06 (m, 2H, H-14, 16), 7.83 (m, 2H, H-8, 10 phenyl), 8.08 (m, 4H, H-8, 11, 13, 17 phenyl) MS m/z (%) 330.36 [M+1] Anal. calcd for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>S: C, 58.17; H, 4.27; N, 8.48; O, 19.37; S, 9.71: found C, 58.07; H, 4.76; N, 8.72; O, 20.12; S, 9.42

**2.10 4-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)benzenesulfonamide (3i):** Yield, 52%; mp 382°C (methanol); IR (KBr): 2953 (C-H), 1754 (C=O), 1664 (C=N) cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>) δ : 2.04 (s, 2H, H-23-25), 3.84 (s, 3H, H-22, 23, 24), 7.06 (m, 2H, H-14, 16), 7.83 (m, 2H, H-8, 10 phenyl), 8.08 (m, 4H, H-8, 11, 13, 17 phenyl) MS m/z (%) 331.06 [M+1] Anal. calcd for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O<sub>4</sub>S: C, 54.37; H, 3.95; N, 12.68; O, 19.31; S, 9.68: found C, 53.12; H, 3.01; N, 11.54; O, 19.31; S, 10.54

### 3. Biological evaluation

#### 3.1 *In vivo* anti-inflammatory activity.

The preliminary *in vivo* anti-inflammatory activity was evaluated using carrageenan-induced rat paw edema assay model of inflammation by adopting the method of Winter et al. [36] for the selected compounds listed in Table 2. Male albino rats (170–220 g) were fasted with free access to water at least 12 h prior to experiments and divided randomly into nine groups of six each. Control group received 1 mL of vehicle (0.5% methyl cellulose and 0.025% Tween 20), standard group received 10 mg/kg of celecoxib, and test groups received 10 mg/kg of synthesized compounds. The rats were dosed orally, 1 h later, a subplantar injection of 0.05 mL of 1% solution of carrageenan in 0.9% sterile solution was administered to the left hind foot pad of each animal. The paw edema volume was measured with a digital plethysmometer (Ugo-Basile, Italy) at 0, 2, 4 h after carrageenan injection. Paw edema volume was compared with vehicle control group and percent reduction was calculated as 1 - (edema volume in the drug treated group / edema volume in the control group) × 100

### 3.2 *In vitro* cyclooxygenase inhibition studies.

The selected compounds listed in Table 3 were tested for their ability to inhibit *in vitro* COX-1 and COX-2 using a colorimetric COX (ovine) inhibitor screening kit (Catalog No. 760 111, Cayman Chemicals Inc., Ann Arbor, MI, USA) using the previously established method.<sup>37</sup>

**Table2: % inhibition of different compounds**

S. No	compound	No. of animals used.	Average Body Weight (gms)	Dose (mg/kg)	Mean Paw Swelling±S.D	Inhibition %
1.	Control	5	264	50	0.286±0.052	-----
2.	Ibuprofen	5	230	50	0.064±0.017	77.63%
3.	Compound 3a	5	200	50	0.088±0.027	69.23%
4.	Compound3b	5	268	50	0.096±0.017	66.43%
5.	Compound 3c	5	224	50	0.076±0.036	73.42%
6.	Compound 3d	5	212	50	0.104±0.033	63.64%
7.	Compound 3e	5	270	50	0.100±0.024	65%
8.	Compound3f	5	220	50	0.084±0.026	70.63%
9.	Compound3g	5	256	50	0.089±0.015	69.23%
10.	Compound3h	5	245	50	0.102±0.033	60.1%
11.	Compound3i	5	237	50	0.057±0.016	78.4%

**Table 3: *In vitro* inhibition of purified COX-2 by 2,5-diphenyl-1,3,4-oxadiazole derivatives.**

S. No	R	R <sub>1</sub>	COX-2 inhibition (%) <sup>a</sup>	COX-1 inhibition (%) <sup>a</sup>
3a	H	H	5.24± 8.23	nt <sup>c</sup>
3b	H	SO <sub>2</sub> NH <sub>2</sub>	44.82± 3.15	nt
3c	CH <sub>3</sub>	SO <sub>2</sub> NH <sub>2</sub>	70.24±1.69	3.46 ± 8.03 (10 mM) 18.27±7.05 (100 mM)
3d	SO <sub>2</sub> CH <sub>3</sub>	H	48.61± 2.33	nt
3e	SO <sub>2</sub> CH <sub>3</sub>	CH <sub>3</sub>	27.53±2.30	nt
3f	C <sub>2</sub> H <sub>5</sub>	SO <sub>2</sub> NH <sub>2</sub>	29.74 ± 5.28	nt
3g	C <sub>2</sub> H <sub>5</sub>	SO <sub>2</sub> CH <sub>3</sub>	38.60± 2.31	nt
3h	OCH <sub>3</sub>	SO <sub>2</sub> CH <sub>3</sub>	28.19± 5.31	nt
3i	OCH <sub>3</sub>	SO <sub>2</sub> NH <sub>2</sub>	72.13± 1.31	3.45 ± 7.01 (10 mM) 17.25 ±8.02 (100 mM)
Indomethacin			91.44±0.24	71.89±6.31
Rofecoxib			66.78±2.83	13.66 ±6.66

<sup>a</sup>Data are indicated as percentage of inhibition at 10 mM\_SEM (n ¼4).

<sup>b</sup>Rofecoxib was assayed at 100 mM and 1 mM for COX-1 and COX-2, respectively.

<sup>c</sup>nt: not tested.

#### 4. Result and discussion

The compounds reported herein were tested for their ability to inhibit COX-2 and/or COX-1 using the purified colorimetric COX (ovine) method. The in vitro activity results are reported as a percentage of inhibition of the purified enzymes at 10 mM (Table 2). In this preliminary study towards new potential COX-2 selective compounds as novel drug candidates for inflammatory and related diseases, we have introduced systematic modifications to the 2,5-diphenyl-1,3,4-oxadiazole core structure. It is well established that 2,5-diphenyl-1,3,4-oxadiazole having a sulfone or sulfonamide on the 4-phenyl is a good template for selective COX-2 inhibition. Thus, taking into account this structural feature, we planned a structure–activity relationship study using the 2,5-diphenyl-1,3,4-oxadiazole core as a template. In particular, we envisaged a series of substitution on the 2 and 5 position aryl ring in order to introduce more flexibility to the template, while keeping the 1,3,4-oxadiazole which was required to maintain COX-2 selectivity. Results are shown in Table 2. In general, none of the newly synthesized derivatives proved to be endowed with the desired activity profile at COX-2, as none but two of the compounds (compound 3c and 3i) inhibited at least 50% of the COX-2 isoform during preliminary screening. Compound 3c and 3i are endowed with a p-sulfonamide on the 5-phenyl ring. We found that ethyl and methoxy substitution with phenyl ring had low COX-2 activity with respect to the sulfonamide or methylsulfonyl analogs. This preliminary results indicated that the presence of p-sulfone/sulfamoyl is important for COX-2 activity and sulfone on the 5-phenyl ring was less effective with regard to sulfamoyl at the same position which was in close agreement with literature results for related compounds [29,30]. Within the sulfonamide analogs, introduction of smaller substituents on the p-phenyl position, i.e., 3e caused a decrease in the observed COX-2 activity at 10 mM screening.

#### 5. Conclusion

The synthesis of a series of 2,5-diphenyl-1,3,4-oxadiazole derivatives substituted at R<sub>1</sub> and R<sub>2</sub> is described along with their preliminary evaluation as potential COX-2 inhibitors. Most of the compounds show no significant COX-2 inhibitory activity. Only compound 3c and 3j displayed potent and selective COX-2 inhibition. In conclusion, we feel that the preliminary in vitro activity results of this class of compounds may possess potential for design of future molecules with modifications on the aryl substituents inhibit one or more of these enzymes. Further studies are in progress.

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