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Synthesis, Molecular Docking, Analgesic, and Anti-Inflammatory Activities of New 1,2,4-Oxadiazolo-Sulfonamides[1]

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Abstract—In the present study novel 1,2,4-oxadiazolo sulfonamides **3a–3o** are synthesized by an efficient method based on the reaction of 1,2,4-oxadiazole amines with aryl sulfonyl chlorides. Structures of the synthesized compounds are confirmed by IR, NMR and Mass spectra. Molecular interactions of the obtained compounds are studied by Discovery Studio v3.5, molecular docking with COX-2 enzyme. The compounds with high LibDock score are screened for their *in vivo* analgesic and anti inflammatory activities. The compound **3l** demonstrates the highest activity.

Keywords: 1,2,4-oxadiazole sulfonamide, molecular docking, analgesic, anti inflammatory activity

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INTRODUCTION

Various side effects such as gastrointestinal bleeding, ulceration and heart failure are associated with long term use of ibuprofen, aspirin, indomethacin, diclofenac, nimesulide, celecoxib, and other drugs. Search of potent safe anti-inflammatory drugs is one of top objectives of contemporary studies in organic synthesis. The 1,2,4-oxadiazole scaffold is a core structure found in a broad class of natural and synthetic compounds. This cycle was the basis for design of therapeutically important molecules. Several 1,2,4-oxadiazole derivatives possess anti-inflammatory activity [1].

Heterocycles containing sulfonamido moieties have attracted very close attention due to their significant biological properties and their role as pharmacophores [2–7]. Sulfonamides are well known as antibacterial [8–10], anticancer [11–13], anti-inflammatory, analgesic [14–16], antifungal [17], and antiviral [18] agents. 1,2,4-Oxadiazoles with long hydrocarbon chains at C^5 possess not only anti-inflammatory but also antitumor activities [19].

In view of the above, we have synthesized 1,2,4-oxadiazole-sulfonamide hybrids **3a–3o** in the coupling reaction of substituted 1,2,4 oxadiazole amines **1a–1d** with aryl sulfonylchlorides **2a–2d** (Scheme1). The novel 1,2,4-oxadiazolo-sulfonamides were screened for their *in vivo* analgesic and antiinflammatory activities.

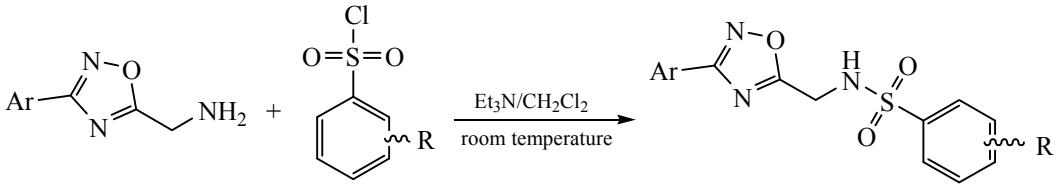
RESULTS AND DISCUSSION

In the present study, we have synthesized 1,2,4-oxadiazole sulfonamides via coupling reaction of 1,2,4-oxadiazole amines with aryl sulfonylchlorides at room temperature. Initial (3-aryl-1,2,4-oxadiazol-5-yl)-methan-amines were synthesized by alkylation of potassium phthalimide with 5-(chloromethyl)-3-aryl-1,2,4-oxa-diazoles in DMF followed by the reaction with $NH_2 \cdot NH_2 \cdot H_2O$ in ethanol. Structures of the title compounds **3a–3o** were elucidated from IR, ^1H NMR and MS data.

Molecular docking studies. All synthesized com-pounds have been docked with Structure of celecoxib bound at the COX-2 active site (PDB ID: 3LN1) for determining binding affinities and molecular interac-tions (Table 1 anf figure). The Lib dock scores of the compounds were measured. All 1,2,4-oxadiazole sulfon-amide analogues displayed better Lib dock scores than aspirin and indomethacin but lower than celecoxib.

[1] The text was submitted by the authors in English.

Scheme 1. Synthesis of 1,2,4-oxadiazolo-sulfonamides.



1a–1d **2a–2d** **3a–3o**

R = H (**2a, 3a, 3e, 3i, 3m**), 4-CH_3 (**2b, 3b, 3f, 3j, 3n**), R = 4-Cl (**2c**), 4-OCH_3 (**2d, 3d, 3h, 3l**); Ar = 4-fluoro phenyl (**1a, 3a, 3b–3d**), 4-methyl phenyl (**1b**, **3e**, **3f–3h**), R = 4-Cl (**3c, 3g, 3k, 3o**), 4-methoxy phenyl (**1c**, **3i–3l**), 2-chloro phenyl (**1d**, **3m–3o**).

***In vivo* analgesic and anti-inflammatory activities.** Analgesic activity of the newly synthesized oxadiazole fused sulfonamides **3d, 3f, 3l, 3n** were evaluated by the hot plate and tail immersion methods using male albino wistar rats Tables 2, 3). Aspirin was used as a standard. Anti-inflammatory activity of the compounds was tested by the carrageenan induced rat paw edema method using indomethacin as a standard (Tables 4, 5). All target compounds were tested at the doses of 20 and 40 mg/kg p.o., and demonstrated high analgesic

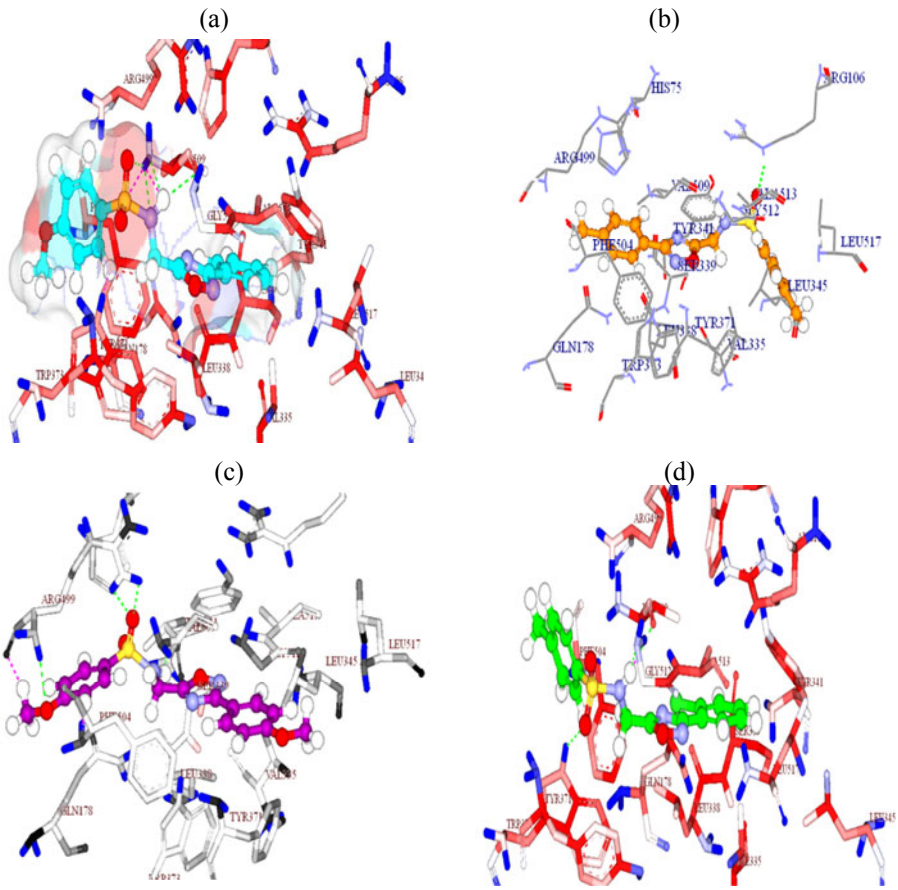
Table 1. LibDforock scores of the compounds

Compound	Libdock score	Compound	Libdock score	Compound	Libdock score
3a	101.188	**3g**	87.979	**3m**	102.781
3b	100.800	**3h**	106.181	**3n**	107.362
3c	100.297	**3i**	96.712	**3o**	98.904
3d	104.068	**3j**	107.095	Celecoxib	145.691
3e	81.071	**3k**	104.448	Aspirin	71.885
3f	108.545	**3l**	110.482	Indomehacin	103.714

Table 2. Analgesic activity as tested by the hot plate method

Compound	Time, min						
	dose	0	30	60	90	120	180
Control	1% CMC[a]	5.50±0.22	6.00±0.26	6.16±0.17	6.66±0.21	6.50±0.22	6.33±0.21
Standard	10	6.67±0.21[b]	10.00±0.81[c]	13.50±1.69[c]	23.17±2.32[d]	15.83±1.74[c]	13.33±1.68[c]
3d	20	5.50±0.32	5.80±0.29[b]	6.70±0.57	8.70±0.30[b]	6.00±0.31	5.80±0.46
	40	5.50±0.34	5.80±0.32	7.03±0.36[b]	11.80±0.88	7.90±0.42[b]	6.20±0.22
3f	20	5.60±0.25	6.30±0.35[b]	7.50±0.04[b]	9.50±0.32[b]	6.90±0.36	6.00±0.35
	40	5.60±0.47	6.98±0.34[b]	8.07±0.39[b]	13.7±0.60[b]	8.50± .47[b]	7.20±0.37
3l	20	5.70±0.26	6.60±0.41[b]	8.10±0.36[c]	10.00±0.25[c]	7.00±0.45	6.30±0.58
	40	5.70±0.35	7.22±0.49[b]	8.34±0.28[c]	14.30±0.28[c]	9.30±0.58[b]	7.60±0.74
3n	20	5.60±0.22	6.00±0.28[b]	7.00±0.45[b]	9.00±0.33[b]	6.40±0.38	5.90±0.49
	40	5.60±0.41	6.79±0.30[b]	7.98±0.32[b]	12.90±0.49[b]	8.00±0.79[b]	6.50±0.69

[a] (CMC) Carboxy methyl cellulose, values are expressed as mean ± SEM, (n = 6) and analyzed by ANOVA using Graph pad prism 7.
[b] $p < 0.05$; [c] $p < 0.01$; [d] $p < 0.001$.



Hydrogen bond interactions of selected compounds [(a) **3d**, (b) **3f**, (c) **3l**, and (d) **3n**] with the structure of celecoxib bound at the COX-2 active site (PDB ID: 3LN1). H-bonds are presented as green-dotted lines and blue or grey letters indicate the amino acids involved in the bonding.

and anti-inflammatory activity at the higher dose (Table 4). Various potencies of the compounds suggested their structure dependent activity. The compound **3l** exhibited the highest analgesic and anti- inflammatory activity. Compound **3f** demonstrated the lowest activity.

EXPERIMENTAL

All materials and solvents were industrially available and used as purchased. Melting points were recorded on a Polmon instrument, India (model MP96). IR spectra (KBr discs) were recorded on a Perkin-Elmer 337 Spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker 400 MHz spectrometer in $CDCl_3$ using TMS as an internal standard. Mass spectra were measured on an Agilent 6310 ion trap mass spectrometer, USA. All synthesized compounds were purified by recrystallization or column chromatography on silica gel (60–120 mesh, Spectrochem, Mumbai, India).

Synthesis of *N*-{[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]methyl}benzenesulfonamide (3a). To a mixture of (3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)methylamine 1a (0.3g, 1.55 mmol) with DCM (20 mL) was added TEA (0.5 mL). The mixture was stirred for 15 min. Benzene sulfonylchloride 2a (0.41g, 2.32 mmol) was added and stirring continued at room temperature for 2 h. Upon completion of the process, according to TLC, the reaction mixture was quenched with 30 mL of H_2O, extracted by DCM (2×30 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by column chromatography using petether : ethylacetate (6 : 4) as an eluent to accumulate the pure compound as white solid. Off white solid, yield 81%, mp 213–215°C. IR spectrum, ν, cm^{-1}: 1225 (C–N), 1584 (C=N), 3262 (NH). ^{1}H NMR spectrum, δ, ppm: 4.54 d (5-CH_2), 5.38 t (NH), 7.12–7.16 m ($H^{3'}$, $H^{5'}$), 7.42–7.52 m ($H^{2'}$, $H^{6'}$), 7.86–7.94 m ($H^{2''}$ to $H^{6''}$). ^{13}C NMR spectrum, δ, ppm: 38.8 (5-CH_2), 127.2 ($C^{3'}$, $C^{5'}$), 127.2 ($C^{1'}$), 129.5 ($C^{2'}$, $C^{6'}$), 129.6 ($C^{3''}$, $C^{5''}$), 129.7 ($C^{2'}$, $C^{6'}$), 136.1 ($C^{4''}$), 141.8

Table 3. Analgesic activity as tested by the tail immersion method

Compound	Time, min						
	dose	0	30	60	90	120	180
Control	1% CMC[a]	4.00±0.26	4.17±0.31	4.00±0.37	4.00±0.37	3.67±0.33	4.33±0.33
Standard	10	4.50±0.22	6.17±0.48[b]	9.17±1.14[c]	11.33±0.21[c]	7.83±0.79[b]	6.67±0.21
3d	20	4.00±0.52	4.50±0.72[b]	5.00±0.65[b]	6.00±0.65[b]	4.50±0.26[b]	4.00±0.25
	40	4.17±0.65	5.00±0.68	6.83±0.24[b]	7.00±0.24[b]	5.00±0.59[b]	4.50±0.38
3f	20	4.17±0.53	5.00±0.53[b]	5.50±0.65[b]	6.33±0.62[b]	5.33±0.81[b]	4.50±0.47
	40	4.33±0.23	5.33±0.48	7.17±0.91[b]	7.50±1.05[b]	5.83±0.28[b]	5.00±0.56
3l	20	4.17±0.31	5.33±0.41[b]	5.67±0.28[b]	6.50±1.08[b]	5.50±0.44[b]	4.50±0.62
	40	4.50±0.22	5.67±0.48[b]	7.33±0.55[b]	8.00±1.13[b]	6.00±0.73[b]	5.17±0.30
3n	20	4.00±0.42	4.95±0.62[b]	5.33±0.58[b]	6.17±0.86[b]	5.00±0.36[b]	4.33±0.61
	40	4.33±0.42	5.17±0.58	7.00±0.64[b]	7.33±0.94[b]	5.33±0.29[b]	5.00±0.37

[a] (CMC) Carboxy methyl cellulose, values are expressed as mean ± SEM, (n = 6) and analyzed by ANOVA using Graph pad prism 7. [b] $p < 0.05$; [c] $p < 0.01$.

Table 4. Anti-inflammatory activity as tested by the carrageenan induced rat paw edema method

Group	Treatment	Dose, mg/kg	Mean paw edema volume ± SEM, mL			
			1 h	3 h	5 h	7 h
I	Control	1% CMC[a]	0.45±0.024	0.65±0.029	0.68±0.027	0.59±0.029
II	Standard	10	0.26±0.032[c]	0.19±0.031[d]	0.32±0.038[d]	0.36±0.03[d]
III	**3d**	20	0.41±0.014[b]	0.39±0.034[c]	0.45±0.028[b]	0.50±0.018[b]
IV		40	0.36±0.024[b]	0.33 ±0.049[b]	0.44±0.069[b]	0.48±0.038[b]
V	**3f**	20	0.38±0.011[b]	0.35±0.026[c]	0.43±0.022[c]	0.47±0.043[b]
VI		40	0.32±0.034[b]	0.30±0.074[c]	0.40±0.045[c]	0.45±0.044[b]
VII	**3l**	20	0.37 ±0.025[b]	0.34±0.029[c]	0.42±0.043[c]	0.46±0.022[b]
VIII		40	0.31±0.067[c]	0.29±0.085[c]	0.38±0.046[c]	0.43±0.067[b]
IX	**3n**	20	0.40±0.092[b]	0.37±0.037[c]	0.44±0.054[b]	0.49±0.017[b]
X		40	0.34±0.075[b]	0.32±0.091[b]	0.41±0.660[b]	0.47±0.039[b]

[a] (CMC) Carboxy methyl cellulose, values are expressed as mean ± SEM, (n = 6) and analyzed by ANOVA using Graph pad prism 7. [b] $p < 0.05$; [c] $p < 0.01$; [d] $p < 0.001$.

($C^{1''}$), 144.0 ($C^{4'}$), 168.1 (C^{5}), 174.4 (C^{3}). DIPMS: *m/z*: 332 [M – 1].

The compounds **3b–3o** were synthesized according to the method presented above for **3a**.

***N*-{[3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl]-methyl}-4-methylbenzenesulfonamide (3b).** White solid, yield 77%, mp 221–223°C. IR spectrum, ν, cm^{-1}: 1235 (C–N), 1580 (C=N), 3246 (NH). ^{1}H NMR spectrum, δ, ppm: 2.25 s (4''-CH_3), 4.51 d (5-CH_2), 5.42 t (NH), 7.13–7.22 m ($H^{3'}$, $H^{3''}$, $H^{5'}$, $H^{5''}$), 7.71–7.73 m ($H^{2''}$, $H^{6''}$), 7.90–7.94 m ($H^{2'}$ to $H^{6'}$). ^{13}C NMR spectrum, δ, ppm: 21.5 (4''-CH_3), 38.9 (5-CH_2), 127.2 ($C^{3'}$, $C^{5'}$), 127.2 ($C^{1'}$), 129.5 ($C^{2'}$, $C^{6'}$), 129.6 ($C^{3''}$, $C^{5''}$), 129.7 ($C^{2'}$, $C^{6'}$), 136.1 ($C^{4''}$), 141.8 ($C^{1''}$), 144.0 ($C^{4'}$), 168.1 (C^{5}), 174.4 (C^{3}). DIPMS: *m/z*: 348 [M + 1].

Table 5. Inhibition of acute inflammation (carrageenan-induced paw edema)

Compound	Dose	Inhibition of acute inflammation, %			
		1 h	3 h	5 h	7 h
Control	1% CMC[a]	0	0	0	0
Standard	10	44	70.7	52.9	38.9
3d	20	8.9	40.0	33.8	15.3
	40	20.0	49.2	35.3	18.6
3f	20	15.6	46.2	36.8	20.3
	40	28.9	53.8	41.1	23.7
3l	20	17.8	47.7	38.2	22.0
	40	31.1	55.4	44.1	27.1
3n	20	11.1	43.1	35.3	16.9
	40	24.4	50.8	39.7	20.3

[a] (CMC) Carboxy methyl cellulose, values are expressed as mean ± SEM, (n = 6) and analyzed by ANOVA using Graph pad prism 7.

4-Chloro-*N*-{[3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl]methyl}benzenesulfonamide (3c). Light yellow solid, yield 79%, mp 195–196°C. IR spectrum, ν, cm^{-1}: 1225 (C–N), 1581 (C=N), 3268 (NH) ^{1}H NMR spectrum, δ, ppm: 4.56 d (5-CH_2), 5.71 t (NH), 7.13–7.18 m ($H^{3'}$, $H^{5'}$), 7.39–7.41 m ($H^{3''}$, $H^{5''}$), 7.78–7.80 m ($H^{2'}$ to $H^{6'}$), 7.89–7.92 m ($H^{2''}$, $H^{6''}$). ^{13}C NMR spectrum, δ, ppm: 38.8 (5-CH_2), 116.0 ($C^{3'}$, $C^{5'}$), 116.2 ($C^{1'}$), 128.6 ($C^{2''}$, $C^{6''}$), 129.4 ($C^{3''}$, $C^{5''}$), 129.6 ($C^{2'}$, $C^{6'}$), 137.8 ($C^{4''}$), 139.7 ($C^{1''}$), 165.9 ($C^{4'}$), 167.4 (C^5), 174.6 (C^3). DIPMS: *m/z*: 368 [*M* + 1].

***N*-{[3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl]-methyl}-4-methoxybenzenesulfonamide (3d).** Light orange solid, yield 83%, mp 232–233°C. IR spectrum, ν, cm^{-1}: 1222 (C–N), 1577 (C=N), 3273 (NH). ^{1}H NMR spectrum, δ, ppm: 3.71 s (4''-OCH_3), 4.50 d (J = 5.2 Hz, 5-CH_2), 5.41 t (NH), 6.86 d.d (J = 2.4 Hz, J = 2 Hz, $H^{3''}$, $H^{5''}$), 7.13 d.d (J = 8.8 Hz, J = 8.8 Hz, $H^{3'}$, $H^{5'}$), 7.76 d.d (J = 2 Hz, J = 2.4 Hz, $H^{2''}$, $H^{6''}$), 7.91 d.d (J = 5.2 Hz, J = 5.2 Hz, $H^{2'}$, $H^{6'}$). ^{13}C NMR spectrum ($CDCl_3$, 100.6 MHz), δ, ppm: 38.9 (5-CH_2), 55.3 (4''-OCH_3), 114.3 ($C^{3'}$, $C^{5'}$), 115.9 ($C^{1'}$), 116.1 ($C^{2'}$, $C^{6'}$), 122.3 ($C^{3''}$, $C^{5''}$), 129.5 ($C^{2'}$, $C^{6'}$), 129.7 ($C^{4''}$), 130.5 ($C^{1''}$), 131.1 ($C^{4'}$), 165.9 (C^5), 174.8 (C^3). DIPMS: *m/z*: 364 [*M* + 1].

***N*-{(3-*p*-Tolyl-1,2,4-oxadiazol-5-yl]methyl}-benzenesulfonamide (3e).** White solid, yield 82%, mp 179–181°C. IR spectrum, ν, cm^{-1}: 1224 (C–N), 1573 (C=N), 3249 (NH). ^{1}H NMR spectrum, δ, ppm: 2.41 s (4'-CH_3), 4.53 d (J = 5.6 Hz, 5-CH_2), 5.36 t (NH), 7.25–7.27 m ($H^{3'}$, $H^{5'}$), 7.44–7.47 m ($H^{3''}$, $H^{4''}$, $H^{5''}$), 7.79–7.81 m ($H^{2''}$, $H^{6''}$), 7.85–7.88 m ($H^{2'}$, $H^{6'}$). ^{13}C NMR spectrum, δ, ppm: 24.9 (4'-CH_3), 38.9 (5-CH_2), 115.9 ($C^{2'}$, $C^{6'}$), 116.1 ($C^{1'}$), 122.3 ($C^{3''}$, $C^{5''}$), 127.1 ($C^{3'}$, $C^{5'}$), 129.1 ($C^{2''}$, $C^{6''}$), 129.6 ($C^{4''}$), 133.0 ($C^{4'}$), 139.2 ($C^{1''}$), 167.4 (C^5), 174.8 (C^3). DIPMS: *m/z*: 330 [*M* + 1].

4-Methyl-*N*-[(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)-methyl]benzenesulfonamide (3f). Off white solid, yield 78%, mp 209–210°C. IR spectrum, ν, cm^{-1}: 1239 (C–N), 1572 (C=N), 3240 (NH). ^{1}H NMR spectrum, δ, ppm: 2.24 s (4'-CH_3), 2.41 s (4''-CH_3), 4.50 d (J = 4.4 Hz, 5-CH_2), 5.48 t (NH), 7.19 d.d ($H^{3'}$, $H^{5'}$), 7.25 d.d ($H^{3''}$, $H^{5''}$), 7.71 d.d ($H^{2''}$, $H^{6''}$), 7.78 d.d ($H^{2'}$, $H^{6'}$). ^{13}C NMR spectrum, δ, ppm: 24.9 (4'-CH_3), 25.5 (4''-CH_3), 38.8 (5-CH_2), 125.3 ($C^{2'}$, $C^{6'}$), 127.2 ($C^{1'}$), 129.8 ($C^{2''}$, $C^{6''}$), 130.9 ($C^{3'}$, $C^{5'}$), 131.9 ($C^{3''}$, $C^{5''}$), 133.3 ($C^{4'}$), 136.1 ($C^{4''}$), 144.0 ($C^{1''}$), 166.9 (C^5), 174.3 (C^3). DIPMS: *m/z*: 344 [*M* + 1].

4-Chloro-*N*-[(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)-methyl]benzenesulfonamide (3g). Light yellow solid, yield 79%, mp 193–195°C. IR spectrum, ν, cm^{-1}: 1217 (C–N), 1571 (C=N), 3261 (NH). ^{1}H NMR spectrum, δ, ppm: 2.41 s (4'-CH_3), 4.55 d (J = 4.4 Hz, 5-CH_2), 5.51 t (NH), 7.28–7.31 m ($H^{3'}$, $H^{5'}$), 7.39–7.41 m ($H^{3''}$, $H^{5''}$), 7.77–7.80 m ($H^{2''}$, $H^{6''}$, $H^{2'}$, $H^{6'}$). ^{13}C NMR spectrum, δ, ppm: 24.8 (4'-CH_3) 38.8 (5-CH_2), 125.1 ($C^{2'}$, $C^{6'}$), 127.6 ($C^{1'}$), 129.5 ($C^{2''}$, $C^{6''}$), 131.9 ($C^{3'}$, $C^{5'}$), 132.9 ($C^{3''}$, $C^{5''}$), 134.3 ($C^{4'}$), 137.1 ($C^{4''}$), 144.2 ($C^{1''}$), 166.7 (C^5), 174.1 (C^3). DIPMS: *m/z*: 364 [*M* + 1], 366 (M+H+2).

4-Methoxy-*N*-[(3-*p*-tolyl-1,2,4-oxadiazol-5-yl)-methyl]-benzenesulfonamide (3h). Light orange solid, yield 75%, mp 222–223°C. IR spectrum, ν, cm^{-1}: 1225 (C–N), 1576 (C=N), 3237 (NH). ^1H NMR spectrum, δ, ppm: 2.41 s (4'-CH_3), 3.68 s (4"-OCH_3), 4.50 d (J = 5.2 Hz, 5-CH_2), 5.49 t (NH), 6.84 d.d (J = 2.4 Hz, J = 2 Hz, $H^{3"}$, $H^{5"}$), 7.25 d.d (J = 8.8 Hz, J = 8.8 Hz, $H^{3'}$, $H^{5'}$), 7.76–7.81 m ($H^{2"}$, $H^{6"}$, $H^{2'}$, $H^{6'}$). ^{13}C NMR spectrum, δ, ppm: 21.5 (4'-CH_3), 38.9 (5-CH_2), 55.6 (4"-OCH_3), 114.3 ($C^{3"}$, $C^{5"}$), 123.2 ($C^{1'}$), 127.4 ($C^{2'}$, $C^{6'}$), 129.5 ($C^{2"}$, $C^{6"}$), 130.5 ($C^{3'}$, $C^{5'}$), 131.1 ($C^{4'}$), 141.8 ($C^{1"}$), 163.2 (C^5), 168.2 ($C^{4'}$), 174.5 (C^3). DIPMS: *m/z*: 360 [M + 1].

***N*-{[3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl]-methyl}benzenesulfonamide (3i).** Off white solid, yield 81%, mp 198–199°C. IR spectrum, ν, cm^{-1}: 1255 (C–N), 1597 (C=N), 3253 (NH). ^1H NMR spectrum, δ, ppm: 3.86 s (4'-OCH_3), 4.52 d (J = 5.6 Hz, 5-CH_2), 5.68 t (NH), 6.94–6.96 m ($H^{3'}$, $H^{5'}$), 7.42–7.49 m ($H^{3"}$, $H^{4"}$, $H^{5"}$), 7.84–7.88 m ($H^{2"}$, $H^{6"}$, $H^{2'}$, $H^{6'}$). ^{13}C NMR spectrum, δ, ppm: 38.9 (5-CH_2), 58.9 (4'-OCH_3), 115.9 ($C^{2'}$, $C^{6'}$), 116.1 ($C^{1'}$), 122.3 ($C^{3"}$, $C^{5"}$), 127.1 ($C^{3'}$, $C^{5'}$), 129.1($C^{2"}$, $C^{6"}$), 129.6 ($C^{4"}$), 133.0 ($C^{4'}$), 139.2 ($C^{1"}$), 167.4 (C^5), 174.8 (C^3). DIPMS: *m/z*: 346 [M + 1].

***N*-{[3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl]-methyl}-4-methylbenzene sulfonamide (3j).** White solid, yield 78%, mp 213–215°C. IR spectrum, ν, cm^{-1}: 1254 (C–N), 1574 (C=N), 3249 (NH). ^1H NMR spectrum, δ, ppm: 2.25 s (4"-CH_3), 3.86 s (4'-OCH_3), 4.50 d (J = 4.4 Hz, 5-CH_2), 5.46 t (NH), 6.95 d.d (J = 2 Hz, J = 2.4 Hz, $H^{3'}$, $H^{5'}$), 7.25 d.d (J = 8 Hz, J = 8 Hz, $H^{3"}$, $H^{5"}$), 7.71 d.d (J = 8.4 Hz, J = 8.4 Hz, $H^{2"}$, $H^{6"}$), 7.78 d.d (J = 2 Hz, J = 2 Hz, $H^{2'}$, $H^{6'}$). ^{13}C NMR spectrum, δ, ppm: 24.9 (4"-CH_3), 38.8 (5-CH_2), 55.4 (4'-OCH_3), 114.2 ($C^{3'}$, $C^{5'}$), 118.4 ($C^{1'}$), 127.1 ($C^{2'}$, $C^{6'}$), 129.0 ($C^{2"}$, $C^{6"}$), 129.1 ($C^{3"}$, $C^{5"}$), 133.0 ($C^{4"}$), 139.2 ($C^{1"}$), 162.1 ($C^{4'}$), 167.9 (C^5), 174.3 (C^3). DIPMS: *m/z*: 360 [M + 1].

4-Chloro-*N*-{[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]methyl}benzenesulfonamide (3k). Off white solid, yield 83%, mp 182–184°C. IR spectrum, ν, cm^{-1}: 1258 (C–N), 1575 (C=N), 3289 (NH). ^1H NMR spectrum, δ, ppm: 3.86 s (4'-OCH_3), 4.53 d (J = 4.4 Hz, 5-CH_2), 5.75 t (NH), 6.95–6.97 m ($H^{3'}$, $H^{5'}$), 7.38–7.41 m ($H^{3"}$, $H^{5"}$), 7.78–7.84 m ($H^{2"}$, $H^{6"}$, $H^{2'}$, $H^{6'}$). ^{13}C NMR spectrum, δ, ppm: 38.8 (5-CH_2), 54.8 (4'-OCH_3) 125.1 ($C^{2'}$, $C^{6'}$), 127.6 ($C^{1'}$), 129.5 ($C^{2"}$, $C^{6"}$), 131.9 ($C^{3'}$, $C^{5'}$), 132.9 ($C^{3"}$, $C^{5"}$), 134.3 ($C^{4'}$), 137.1 ($C^{4"}$), 144.2 ($C^{1"}$), 166.7 (C^5), 174.1 (C^3). DIPMS: *m/z*: 380 [M + 1].

4-Methoxy-*N*-{[(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]methyl}benzenesulfonamide (3l). Off white solid, yield 75%, mp 225–226°C. IR spectrum, ν, cm^{-1}: 1259 (C–N), 1573 (C=N), 3251 (NH). ^1H NMR spectrum, δ, ppm: 3.69 s (4'-OCH_3), 3.87 s (4"-OCH_3), 4.49 d (J = 5.2 Hz, 5-CH_2), 5.48 t (NH), 6.84 d.d (J = 2.4 Hz, J = 2 Hz, $H^{3'}$, $H^{5'}$), 7.25 d.d (J = 8.8 Hz, J = 8.8 Hz, $H^{3"}$, $H^{5"}$), 7.76 d.d (J = 2.4 Hz, J = 2 Hz, $H^{2"}$, $H^{6"}$) 7.92 d.d (J = 8.8 Hz, J = 8.8 Hz, $H^{2'}$, $H^{6'}$). ^{13}C NMR spectrum, δ, ppm: 38.9 (5-CH_2), 55.5 (4'-OCH_3), 55.6 (4"-OCH_3), 114.2 ($C^{3'}$, $C^{5'}$), 114.3 ($C^{3"}$, $C^{5"}$), 118.4 ($C^{1'}$), 129.4 ($C^{2'}$, $C^{6'}$), 130.5 ($C^{2"}$, $C^{6"}$), 131.1 ($C^{1"}$), 162.1 ($C^{4'}$), 163.1 (C^5), 167.8 ($C^{4"}$), 174.4 (C^3). DIPMS: *m/z*: 376 [M + 1].

***N*-{[3-(2-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-methyl}benzenesulfonamide (3m).** Light yellow solid, yield 80%, mp 173–175°C. IR spectrum, ν, cm^{-1}: 1247 (C–N), 1570 (C=N), 3254 (NH). ^1H NMR spectrum, δ, ppm: 4.58 d (5-CH_2), 5.61 t (NH), 7.11–7.15 m ($H^{3'}$, $H^{5'}$), 7.32–7.48 m ($H^{2'}$, $H^{6'}$), 7.82–7.92 m ($H^{2"}$ to $H^{6"}$). ^{13}C NMR spectrum, δ, ppm: 38.8 (5-CH_2), 127.2 ($C^{5'}$), 127.2 ($C^{3'}$), 129.5 ($C^{3"}$, $C^{5"}$), 129.6 ($C^{4'}$), 129.7 ($C^{2"}$, $C^{6"}$), 130.1 ($C^{4'}$), 136.1 ($C^{2'}$), 141.8 ($C^{1'}$), 144.0 ($C^{1"}$), 168.1 (C^5), 174.4 (C^3). DIPMS: *m/z*: 350 [M + 1].

***N*-{[3-(2-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-methyl}-4-methylbenzenesulfonamide (3n).** Off white solid, yield 72%, mp 184–185°C. IR spectrum, ν, cm^{-1}: 1332 (C–N), 1592 (C=N), 3293 (NH). ^1H NMR spectrum, δ, ppm: 2.31 s (4"-CH_3), 4.56 d (5-CH_2), 5.51 t (NH), 7.22–7.24 m ($H^{3"}$, $H^{5"}$), 7.34–7.38 m ($H^{4'}$), 7.41–7.46 m ($H^{5'}$), 7.51 d.d (J = 1.2 Hz, J = 1.2 Hz, $H^{2'}$), 7.71–7.74 m ($H^{6'}$, $H^{2"}$, $H^{6"}$). ^{13}C NMR spectrum, δ, ppm: 21.5 (4"-CH_3), 38.9 (5-CH_2), 127.2 ($C^{3'}$, $C^{5'}$), 127.2 ($C^{1'}$), 129.5 ($C^{2'}$, $C^{6'}$), 129.6 ($C^{3"}$, $C^{5"}$), 129.7 ($C^{2'}$, $C^{6'}$), 136.1 ($C^{4"}$), 141.8 ($C^{1"}$), 144.0 ($C^{4'}$), 168.1 (C^5), 174.4 (C^3). DIPMS: *m/z*: 364 [M + 1].

4-Chloro-*N*-{[3-(2-chlorophenyl)-1,2,4-oxadiazol-5-yl]methyl}benzenesulfonamide (3o). Off white solid, yeield 86%, mp 195–196°C. IR spectrum, ν, cm^{-1}: 1277 (C–N), 1586 (C=N), 3254 (NH). ^1H NMR spectrum, δ, ppm: 4.60 d (5-CH_2), 5.84 t (NH), 7.13–7.18 m ($H^{4'}$, $H^{5'}$), 7.39–7.41 m ($H^{3'}$, $H^{6'}$), 7.51 d.d (J = 1.2 Hz, J = 1.2 Hz, $H^{5"}$), 7.67 d.d (J = 2 Hz, J = 2 Hz, $H^{3"}$), 7.78–7.80 m ($H^{2"}$, $H^{6"}$). ^{13}C NMR spectrum, δ, ppm: 38.8 (5-CH_2), 116.0 ($C^{3'}$, $C^{5'}$), 116.2 ($C^{1'}$), 128.6 ($C^{2"}$, $C^{6"}$), 129.4 ($C^{3"}$, $C^{5"}$), 129.6 ($C^{2'}$, $C^{6'}$), 137.8 ($C^{4"}$), 139.7 ($C^{1"}$), 165.9 ($C^{4'}$), 167.4 (C^5), 174.6 (C^3). DIPMS: *m/z*: 385 [M + 1], 387 (M+H+2).

Molecular docking. Molecular docking method was used for studying the binding modes and affinities of the synthesized compounds with *Musmusculus*

COX 2 (PDB ID: 3LN1). All the ligands were targeted to celecoxib bound at the COX-2 site. The three dimensional structure of celecoxib bound at the COX-2 active site (PDB ID: 3LN1) was retrieved from the Brookhaven Protein Data Bank (PDB), USA (http://www.rcsb.org/pdb). Protein and ligand preparation wizard were used, respectively. Initially, ions, water molecules, and all the internal ligands were removed and missing atoms were inserted before minimization of the target protein. Alternative conformations (disorder) were removed. The best ligand conformation was chosen on the base of Lib Dock score and highly interacting amino acid residues. Of ten conformations generated for each compound, the compound with the highest Lib Dock score was chosen for interaction analysis of the hydrogen bonding.

***In vivo* analgesic activity.** *a. Hot plate method:* The hot-plate test was performed to measure response latencies according to the method described by Eddy and Leimbach (1953) [20]. Swiss albino male wistar rats (170–210 g body weight) were divided into groups of six animals each. Group I served as control; group II served as standard, received aspirin (10 mg/kg); Groups III and IV served as test samples, received 20 and 40 mg/kg of **3d**, **3f**, **3l**, **3n** test samples respectively. The animals were placed on the hot plate, maintained at 55±2°C. The pain threshold was considered to be reached when the animals lifted and licked their paws or attempted to jump out of the hot plate. Time needed for the rats to react in this fashion was considered as basal reaction time. A latency period of 30 s (cut-off) was defined as complete analgesia, and the measurement was terminated if it exceeded the latency period in order to avoid injury. The reaction time was reinvestigated at 30, 60, 120, and 180 min after the treatment and changes in the reaction time were noted.

b. Tail immersion method. Young Male Albino Wistar rats (170–210 g body weight) are used. The lower 5 cm portion of the tail was marked. This part of the tail was immersed in a cup of freshly filled water at 55°C. Within a few seconds the rat reacted by withdrawing the tail. After each determination the tail was dried. The reaction time was determined before and periodically after oral administration of the test substance (30, 60, 90, 120, 180 min). The cut off time of the immersion was 15 s.

***In vivo* anti-inflammatory activity by Carrageenan induced rat paw edema method.** Anti-inflammatory activity of synthesized compounds was assessed by the carrageenan-induced rat paw edema method [21]. The animals were housed under standard environmental conditions, one week before the start and also during the experiment as per the rules and regulations of the institutional ethics committee (registered no. RBVRR1328/01/2017/CPCSEA).

CONCLUSIONS

Herein, we report simple and efficient method of synthesis of fused 1,2,4-oxadiazolo-sulfonamides via the coupling reaction. Molecular docking studies indicated high binding affinity of the compounds with 3LN1. *In vivo* analgesic and anti-inflammatory tests demonstrated that 4-methoxy-*N*-{[(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]methyl}benzenesulfonamide had the highest activity. If the phenyl ring contained the electron releasing substituents, like methoxy and methyl groups, the compounds demonstrated high Lib Dock scores, as well as significant analgesic and anti inflammatory activities.

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