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ARTICLE

Novel arylpyridine-based 1,3,4-oxadiazoles: Synthesis, antibacterial, and anti-inflammatory evaluation

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In view of developing novel bioactive compounds, a series of 2-(5-[2-methyl-6-arylpyridin-3-yl]-1,3,4-oxadiazol-2-ylthio)-1-arylethanones **(6a–n)** were designed and synthesized in good yield. Novel compounds were evaluated for their antibacterial and anti-inflammatory activities. All synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus*, *Bascillus subtilis*, *Eschericia coli*, and *Pseudomonas aeruginosa* strains. Compounds **6a**, **6b**, **6c**, **6h**, and **6i** displayed the highest antibacterial activity with minimal inhibitory concentration (MIC) values ranging from 6.25–12.5 μg/mL in comparison with the standard Ciprofloxacin. The results of anti-inflammatory activity of carrageenan-induced footpad edema assay indicated that tested compounds exhibited remarkable anti-inflammatory activity with percentage of inhibition of 63.9–70.1% (potency 96.8–106.20% of indomethacin activity) after 3 hr. Particularly, **6c–e** and **6j–l** were found to be excellent inhibitors of inflammation, with potential higher than that of the standard, Indomethacin.

KEYWORDS

bioorganic chemistry, medicinal chemistry, organic chemistry

1 | INTRODUCTION

Antimicrobial agents have gained a lot of importance because of life-threatening infectious diseases like diphtheria, typhoid, tuberculosis, cholera, HIV, plague[1] etc caused by microbes increased to an alarming level around the world. This is mainly due to rapid development of multidrug-resistant microbial pathogens. Hence, minimizing multidrug-resistant pathogens may be an important approach to the primary prevention or treatment of these diseases. These clinical limitations such as drug resistance, toxicity, and side effects had attracted a great deal of research interest in therapeutic antimicrobial-based drug formulations.

Inflammation is a normal reaction to injury or infection. Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most frequently used medications for the treatment of pain and inflammation caused by chronic illnesses, including diabetes, cardiovascular disease, arthritis, psoriasis, infection, and cancer[2] through interacting and inhibiting the enzymatic activity.[3,4] For long-term use, NSAIDs are frequently associated with serious side effects like upper gastrointestinal (GI) irritation, bleeding, dyspepsia, ulceration, and in some cases death.[5] These side effects are due to non-selective inhibition of COXs, thereby design and development of NSAIDs with enhanced safety profile is still a necessity and challenge for the pharmaceutical industry.

In this context, considerable interest has been focused on 1,3,4-oxadiazole derivatives that has occupied a unique place in the field of medicinal chemistry. They are well known as antifungal,[6] anticancer,[7] fungicidal,[8] antidepressant,[9] hypoglycemic,[10] and anti-HIV[11] agents. Additionally, 1,3,4-oxadiazoles are very good bioisosteres of esters and amides, which help substantially to enhance the pharmacological activity by participating in hydrogen bonding interactions with the receptors. Hence, they have motivated countless researchers to study their synthesis and

pharmacological properties. Moreover, the presence of toxophoric –N=C–O– linkage in the oxadiazole core contributes to significant pharmacokinetic property like lipophilicity, which in turn increases the ability of drug to reach the target by transmembrane diffusion.[12] Besides, the literature survey reveals that the presence of alkyl or acyl, carboxamide linkage on the oxadiazole core plays an important role in biological activity by increasing the ability of penetration into the active site.[13]

On the other hand, different substituted pyridines are well documented in the literature as they have been associated with an extensive range of pharmaceutical and pesticide activities including anticancer, anti-inflammatory, analgesic,[14] antimicrobial,[15] anticonvulsant,[16] anti-TB, antidepressant,[17] phosphodiestrase-3 inhibitor,[18] HIV inhibition,[19] antihypertensive agents,[20] selective inhibitors of hepatitis C virus (HCV)[21], and insecticidal activities.[22] Additionally, Numerous studies pointed out the antimicrobial and anti-inflammatory properties of 1,3,4-oxadiazole and pyridine derivatives as promising antimicrobial and anti-inflammatory agents (Figure 1).[23–28] Additionally, there are reports that incorporation of chlorine/bromine atoms into a molecule provides compounds that exhibit superior anti-inflammatory and antimicrobial activities.[29–32] Heterocyclic compounds with a chloro-substituted/bromo-substituted phenyl ring are reported as potent analgesic used in inflammatory pain, for example, SC-558,[33] zomepirac[34] and DuP-697.[35] Furthermore, antimicrobial and anti-inflammatory activities of 1,3,4-oxadiazoles clubbed with chloro-substituted/bromo-substituted arylpyridine moieties are not even reported in the literature. In the light of above findings, we considered it of interest to synthesize a new class of heterocyclic molecules in which all of these 1,3,4-oxadiazole, pyridine, and *S*-alkyl linker moieties are present and tried to develop potential bioactive molecules. Herein, a variety of arylpyridine derivatives bearing 1,3,4-oxadiazoles, containing a diverse set of aromatic substitutions through *S*-alkyl linkage, were designed and synthesized by placing the aryl pyridine moiety at the fifth position and *S*-alkyl at the second position of the 1,3,4-oxadiazole ring and screening the results of antibacterial and anti-inflammatory activities.

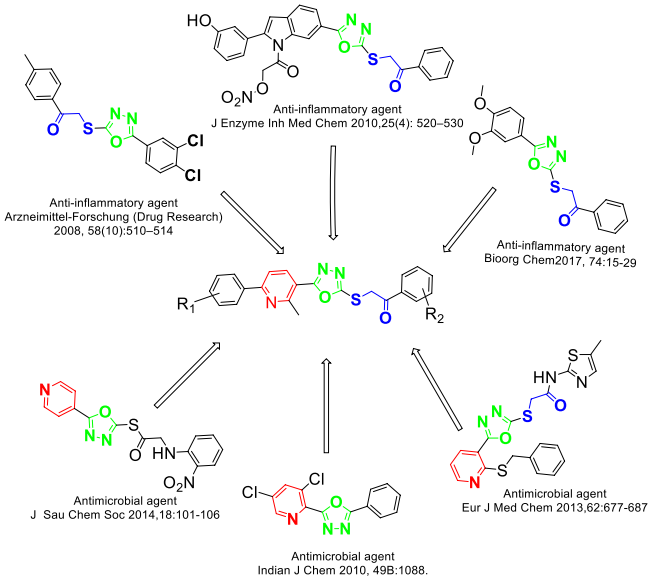
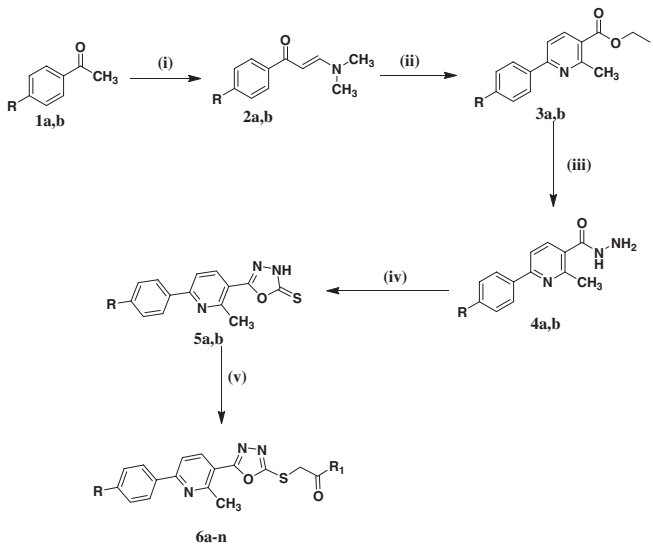


FIGURE 1 Literature reports for active 1,3,4-oxadiazole, pyridine and *S*-alkyl linker-based anti-inflammatory and antimicrobial derivatives and strategy employed for designing arylpyridine-based 1,3,4-oxadiazoles

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

In the present work, the desired arylpyridine-based 1,3,4-oxodiazoles were geared up by the series of steps and are depicted in Scheme 1. The enaminones **2a–b** were obtained by refluxing the 4-chloroacetophenone **1a** and 4-bromoacetophenone **1b** with dimethyl formamide dimethyl acetal. In a one-pot, three-component heterocylocondensation process of **2a–b**, diketoester and ammonium acetate in glacial acetic acid media furnished corresponding ethyl (6-aryl-2-methylpyridine)-3-carboxylates **3a–b**. The intermediates, **3a–b,** were then subjected to hydrazinolysis by hydrated hydrazine into corresponding arylpyridine carbohydrazides **4a–b**. 5-Arylpyridine-1,3,4-oxadiazol-2-thiones **5a–b** were synthesized by intramolecular cyclization of different arylpyridine carbohydrazides **4a–b** with carbon disulfide in the presence of sodium hydroxide in absolute ethanol, as a solvent, and finally, the preparation of target compounds was achieved via the nucleophilic substitution reaction of 5-arylpyridine-1,3,4-oxadiazol-2-thiones **5a–b** with substituted phenacyl bromides/chlorides in acetone and triethylamine. The structures of 2-(5-[2-methyl-



SCHEME 1 Outline for the synthesis. *Reagents and conditions*: (i) DMF–DMA, 90°C, 5–6 hr. (ii) ethyl acetoacetate, NH_4OAc, AcOH, reflux, 3 hr. (iii) N_2H_4, reflux, 5–6 hr. (iv) CS_2, NaOH, EtOH, reflux 4 hr. (v) Phenacyl bromide/chloride, Et_3N, acetone, reflux, 5 hr

6-arylpyridin-3-yl]-1,3,4-oxadiazol-2-ylthio)-1-arylethanones **(6a–n)** (Table 1) were ascertained by their spectral and analytical data.

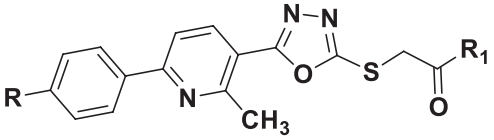
The formation of intermediates **5a–b** from corresponding carbohydrazides was confirmed by the presence of characteristic stretching vibrations for NH, C=N, and C=S groups in FT-IR. When compound **4b** was converted to the corresponding oxadiazole thione **5b**, the absorption bands due to amide carbonyl and NH/NH_2 groups disappeared, instead new absorption bands for NH, C=N, and C=S groups were observed at 3,062, 1,581, 1,332 cm^{-1}, respectively. In the ^1H NMR spectrum of compound **5b**, the presence of the pyridine ring was affirmed by two doublets at 8.03 ppm (J = 8.4 Hz) for C_4–H and 8.22 ppm (J = 8.4 Hz) for C_5-H and a sharp singlet at 2.80 ppm attributable for the methyl group on the pyridine unit. The signals resonating at 7.71 and 8.11 ppm as two doublets due to four protons supported the presence of aryl nucleus in the molecule. Furthermore, the ^{13}C NMR spectrum of **5b** confirmed the formation of the 1,3,4-oxodiazole ring by displaying signals at 177.1 and 159.4 ppm due to C-2 and C-5 carbon atoms of the 1,3,4-oxadiazole ring. The structure of new intermediate **5b** was further confirmed by its mass spectrum that displayed (M + 1), (M + 2) ion peaks at *m/z* 347.25, 349.10, respectively, which is in agreement with its molecular formula.

The formation of new arylpyridine-based 1,3,4-oxodiazole derivatives **(6a–n)** was confirmed by their spectral analysis (Supporting Information). In general, in the FT-IR spectra **(6a–n),** the bands corresponding to NH and C=S of the 1,3,4-oxadiazole-2-thione ring disappeared. Also, new characteristic peaks corresponding to C=O and C–S stretching vibrations were appeared, indicating the *S*-alkylation. Additionally, in the ^1H NMR spectra the presence of a new signal between 5.03–5.20 ppm for the S–CH_2 group clearly demonstrated the *S*-alkylation. Similarly, in the ^{13}C NMR spectra of **(6a–n)**, the signal corresponding to C=S of intermediates **5a–b** was found to be missing, instead the presence of a new signal corresponding to C=O is evidenced the formation of *S*-alkylated analogs. In particular, for the prototype **6l**, its ^1H NMR showed additional doublets at 7.80 and 7.95 ppm with coupling constants 8.4 and 2 Hz corresponding to C_3–H and C_6–H of the 2,4-dichlorophenyl ring, respectively. A doublet of doublet in the region 7.63–7.65 ppm integrating for one proton with coupling constants 8.4 and 2 Hz corresponding to C_5–H of the 2,4-dichlorophenyl ring clearly confirmed the *S*-alkylated derivative. In addition to this, the spectrum showed a singlet at 5.03 ppm integrating two protons of the S–CH_2 group, which provides the additional support for the S-substitution. The signal at 2.87 ppm attributed to the –CH_3 group attached to the pyridine moiety. Similarly, pyridine-C_4–H and C_5–H appeared as doublets at 8.05 and 8.31 ppm with a coupling constant of 8 Hz and doublet of doublets in the region at 7.72–7.74 and 8.13–8.15 ppm were attributed to the four protons of the 4-bromophenyl moiety, which further confirmed the structure. Its ^{13}C NMR further confirmed the *S*-alkylated product. The spectrum of **6l** displayed a highly deshielded signal at 193.4 ppm due to the presence of carbonyl carbon, which was absent in previous 1,3,4-oxadiazole-2-thiones. Moreover, a signal corresponding to C=S carbon of intermediate **5b** was found to be missing and it showed additional signal at 42.2 ppm corresponding to the S–CH_2 carbon, which clearly indicates the formation of target **6l**. The shifting of stretching vibration to a lower region (C–S) 1,191 cm^{-1} from (C=S) 1,332 cm^{-1} and the absence of vibration at 3,062 cm^{-1} corresponding to the NH; while a new vibration at 1,681 cm^{-1} corresponding to C=O in its IR spectrum provide additional support for the formation of target **6l** from 1,3,4-oxadiazole-2-thione derivative **5b**. The mass spectrum provided support to the structure of the compound **6l** as it displayed (M − 1), [(M − 1) + 2], and [(M − 1) + 4] ion peaks at *m/z* 532.80, 534.10, 536.80, respectively, which is in agreement with its molecular formula $C_{22}H_{14}N_3BrCl_2O_2S$, evidencing the formation of compound.

2.2 | In vitro antibacterial activity

Antibacterial potency of newly synthesized compounds was checked by performing their in vitro antibacterial activity using agar disc-diffusion method against *Eschericia coli* and *Pseudomonas aeruginosa* representative of Gram-positive and *Staphylococcus aureus*, *Bascillus subtilis* representative of Gram-negative bacterial strains. Ciprofloxacin was used as the positive control. The results of the preliminary antimicrobial activity of compounds **6a–n** are reported in Table 2. The results revealed that they showed varying degrees of inhibition against the tested microorganisms. In general, compounds **6b**, **6c**, **6h**, **6i**, and **6n** displayed the best antibacterial activity with zone of inhibition ranging between 13.6 and 16.5 mm toward Gram-positive bacteria *B. subtilis* and were considered the most sensitive among the tested microorganisms, while the other compounds were weakly active or completely inactive with the inhibition zone ≤12.5 mm. In contrast, none of the tested compounds displayed an observable inhibitory effect against *S. aureus* organism. Compounds **6h** and **6i** produced good inhibiting potency toward Gram-negative *E. coli* with the inhibition zone >13 mm, while the compound **6g** was moderately active with the inhibition zone 11.5 mm. Furthermore, compounds **6a**, **6b**, **6i**, and **6n** produced marked activity against Gram-negative *P. aeruginosa* with the inhibition zone ranging value between 12.5–14.5 mm, compared with other compounds of the series. The compounds **6d**, **6e**, **6f**, **6j**, **6k**, **6l**, and **6m** were found to be active against all bacterial strains but results were not appreciable. Based on the preliminary screening, the most active compounds were further examined for their in vitro minimal inhibitory concentration (MIC) against the same organisms using the microdilution

TABLE 1 Physical data of the newly synthesized 2-(5-(2-methyl-6-arylpyridin-3-yl)-1,3,4-oxadiazol-2-ylthio)-1-arylethanones (6**a**–**n**) via Scheme 1



6a-n

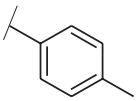
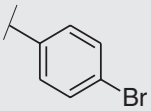
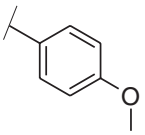
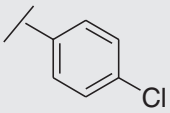
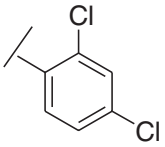
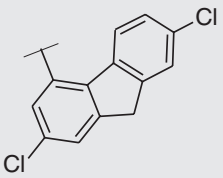
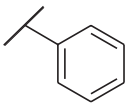
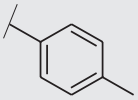
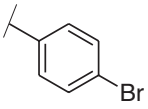
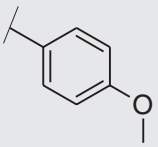
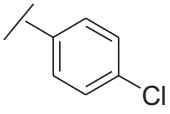
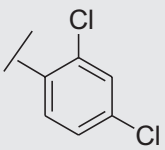
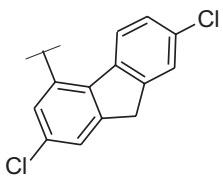
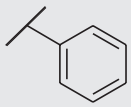
Compound	R	R_1	Mol. formula	Mol. weight	Yield (%)	Melting point (°C)
6a	Cl		$C_{23}H_{18}N_3ClO_2S$	435.08	90	180–181
6b	Cl		$C_{22}H_{15}N_3BrO_2S$	498.98	91	212–213
6c	Cl		$C_{23}H_{18}N_3ClO_3S$	451.08	98	198–199
6d	Cl		$C_{22}H_{15}N_3Cl_2O_2S$	455.03	85	209–210
6e	Cl		$C_{22}H_{14}N_3Cl_3O_2S$	488.99	73	139–140
6f	Cl		$C_{29}H_{18}N_3Cl_3O_2S$	577.02	79	147–149
6g	Cl		$C_{22}H_{16}N_3ClO_2S$	421.07	97	151–152
6h	Br		$C_{23}H_{18}N_3BrO_2S$	479.03	94	183–184
6i	Br		$C_{22}H_{15}N_3Br_2O_2S$	545.25	95	213–214
6j	Br		$C_{23}H_{18}N_3BrO_3S$	495.03	94	199–200
6k	Br		$C_{22}H_{15}N_3BrClO_2S$	498.98	98	217–218
6l	Br		$C_{22}H_{14}N_3BrCl_2O_2S$	532.94	83	144–146

TABLE 1 (Continued)

Compound	R	R_1	Mol. formula	Mol. weight	Yield (%)	Melting point (°C)
6m	Br		$C_{29}H_{18}N_3BrCl_2O_2S$	620.35	76	168–169
6n	Br		$C_{22}H_{16}N_3BrO_2S$	465.01	96	153–154

method. Results are summarized in Table 3. It was observed that the results were in agreement with the preliminary screening results. The tested compounds displayed moderate to good inhibitory activity with the MIC values ranging from 100 to 6.25 μg/mL. Among the tested compounds, **6i** (R = Br and R_1 = 4-bromophenyl) showed highest inhibition with an MIC value of 6.25 μg/mL toward *B. subtilis* and *E. coli* strain and good activity toward *P. aeruginosa* with an MIC value of 12.5 μg/mL. Furthermore, tested **6b**, **6h** and **6i** exhibited good activity with an MIC value of 12.5 μg/mL and compound **6g** showed moderate activity toward *B. subtilis* with an MIC value of 25 μg/mL. Replacement of bromine by chlorine in **6i** led to compound **6b** (R = Cl and R_1 = 4- bromophenyl), whose activity was reduced to MIC values of 12.5 and 100 μg/mL toward *P. aeruginosa* and *E. coli*, respectively. Furthermore, among the tested compounds, **6c** (R = Cl and R_1 = 4-methoxyphenyl) exhibited highest inhibition against *B. subtilis* strain with an MIC value of 6.25 μg/mL, which displayed reduction in inhibition activity toward *P. aeruginosa* and *S. aureus* organisms with an MIC value 50 μg/mL. Compound **6h** (R = Br and R_1 = 4-methylphenyl) displayed good activity against *B. subtilis* and *E. coli* with an MIC value of 12.5 μg/mL and it showed moderate activity toward *P. aeruginosa.* Replacement of bromine in **6h** by chlorine, that is compound **6a** (R = Cl and R_1 = 4-methylphenyl) led to significant loss of activity toward *B. subtilis* and *E. coli.* However, it showed increased activity against *P. aeruginosa* with an MIC value of 12.5 μg/mL. Rest of the tested compounds exhibited weak to moderate activity against the tested organisms with MIC values ranging from 25–100 μg/mL. Thus, it was clear that the introduction of chlorine did not improve the potency. Additionally, activity results revealed that halo, methoxy, or methylphenacyl substituents in the aryl part are essential for the antibacterial activity.

TABLE 2 Antibacterial activity of synthesized compounds 6**a**–**n** using the agar cup plate method

Antibacterial activity data of the target 6a–n in terms of the zone of inhibition				
	Antibacterial activity diameter of growth inhibition zone[a]			
	Gram positive		Gram negative	
Sample	***S. aureus***	***B. subtilis***	***E. coli***	***P. aeruginosa***
Control	—	—	—	—
6a	14 ± 0	11.5 ± 0.5	8 ± 0	14.5 ± 0
6b	10.5 ± 0.5	15.5 ± 0.5	5 ± 0	13.5 ± 0.5
6c	7.5 ± 0.5	16.5 ± 0.5	8 ± 0	8.5 ± 0.5
6d	6.5 ± 0.5	12.5 ± 0.5	10 ± 0	9.5 ± 2.5
6e	11.5 ± 0.5	11.5 ± 0.5	10 ± 0	9 ± 0
6f	10.5 ± 0.5	10.5 ± 0.5	8 ± 0	8 ± 0
6g	11 ± 1	11 ± 1	11.5 ± 0.5	10.5 ± 0.5
6h	8.5 ± 0.5	15.5 ± 0.5	13 ± 0	8.5 ± 0.5
6i	9.5 ± 0.5	15.5 ± 0.5	13.5 ± 0.5	13.5 ± 0.5
6j	8.5 ± 0.5	10.5 ± 0.5	9.5 ± 0.5	10.5 ± 0.5
6k	11.5 ± 0.5	9.5 ± 0.5	6.5 ± 0.5	8.5 ± 0.5
6l	13 ± 1	10.5 ± 0.5	7 ± 1	10.5 ± 0.5
6m	11 ± 1	12 ± 0	7 ± 1	13 ± 1
6n	7 ± 1	13.5 ± 0.5	7.5 ± 0.5	12.5 ± 0.5
Ciprofloxacin	31 ± 1	17 ± 1	14.5 ± 0.5	15.5 ± 0.5

[a] Results are expressed as mean ± *SEM* (n = 5).

2.3 | In vivo anti-inflammatory activity

Based on the antibacterial potency, compounds **6c**–**6e**, **6g**, **6j**–**6l**, and **6n** were evaluated for their anti-inflammatory activity by employing the carrageenan-induced paw edema bioassay in rats and acute toxicity. We used a well-known anti-inflammatory agent, Indomethacin, as the standard.

TABLE 3 Antibacterial activity of the selected target molecules in terms of MIC

Antibacterial activity MIC in μg/mL			
Sample	***B. subtilis***	***E. coli***	***P. aeruginosa***
Control	—	—	—
6a	50	100	12.5
6b	12.5	100	12.5
6c	6.25	50	50
6g	50	25	50
6h	12.5	12.5	50
6i	12.5	6.25	6.25
6n	25	100	25
Ciprofloxacin	2	2	4

TABLE 4 Anti-inflammatory effect of the selected compounds (50 mg/kg) and indomethacin (10 mg/kg) against carrageenan-induced paw edema in rats

Sample	Anti-inflammatory activity: Change in paw volume (mL) after drug treatment (±*SEM*) (% inhibition)				Potency[a] (%)
	0 hr	1 hr	2 hr	3 hr	3 hr
Control	0.139 ± 0.0077 (0)	0.283 ± 0.0161 (0)	0.306 ± 0.0186 (0)	0.368 ± 0.0136 (0)	0
6a	ND	ND	ND	ND	ND
6b	ND	ND	ND	ND	ND
6c	0.11 ± 0.0037 (20.9)***	0.135 ± 0.0043 (52.3)***	0.11 ± 0.0026 (64.1)***	0.11 ± 0.0045 (70.1)***	106.2
6d	0.112 ± 0.0031 (19.4)***	0.135 ± 0.0043 (52.3)***	0.12 ± 0.0052 (60.8)***	0.112 ± 0.0031 (69.7)***	105.6
6e	0.107 ± 0.0033 (23.0)***	0.158 ± 0.007 (44.2)**	0.117 ± 0.0021 (61.8)***	0.112 ± 0.0017 (69.6)***	105.5
6f	ND	ND	ND	ND	ND
6g	0.117 ± 0.0021 (15.8)**	0.161 ± 0.0043 (42.4)	0.158 ± 0.0045 (48.3)*	0.130 ± 0.0021 (64.7)*	98
6h	ND	ND	ND	ND	ND
6i	ND	ND	ND	ND	ND
6j	0.112 ± 0.004 (19.4)***	0.143 ± 0.0042 (49.5)***	0.12 ± 0.0026 (60.8)***	0.115 ± 0.0022 (68.8)***	104.2
6k	0.115 ± 0.0043 (17.3)***	0.132 ± 0.0048 (53.4)***	0.13 ± 0.0068 (57.5)***	0.12 ± 0.0026 (67.4)***	102.1
6l	0.107 ± 0.0033 (23.0)***	0.13 ± 0.0026 (54.1)***	0.118 ± 0.004 (61.4)***	0.115 ± 0.0043 (68.8)***	104.2
6m	ND	ND	ND	ND	ND
6n	0.119 ± 0.007(14.3)**	0.164 ± 0.0026 (42)	0.162 ± 0.0031(47)	0.133 ± 0.0043 (63.9)*	96.8
Indomethacin	0.12 ± 0.0059 (13.7)	0.15 ± 0.0072 (47)	0.15 ± 0.0075 (51.0)	0.125 ± 0.0067 (66.0)	100

Differences between means at *$p < 0.01$; **$p < 0.005$; and ***$p < 0.0001$ were regarded significant. ND: not determined.
[a] Potency is expressed as % of edema inhibition of the tested compounds relative to % of edema inhibition of indomethacin at 3 hr.

The results are summarized in Table 4, as for activity, the tested compounds possess significant inhibition of inflammation that is, paw edema, when compared to the normal control group at a dose level of 50 mg/kg. The treatment with doses of 50 mg/kg of **6c** having the 4-chlorophenyl moiety attached to the pyridine ring and the 4-methoxyphenyl ring attached to the other extreme end of the 1,3,4-oxadiazole ring resulted a most active compound by exhibiting significant inhibition of paw-edema 70.1%, when compared to the normal control group and was more effective than the standard-treated group 66% at a test dose of 10 mg/kg, their potency being nearly equal to 106.2% that of Indomethacin. Furthermore, replacing the 4-chlorophenyl group with 4-bromophenyl in **6c** led to compound **6j** displaying a significant activity. It must be noted that its inhibiting potency was decreased to 68.8%, indicating that the 4-bromophenyl substituent was less efficient when compared to the 4-chlorophenyl group. Acute treatment with the compound **6d** having the 4-chlorophenyl substituent on both extreme ends emerged as a good anti-inflammatory agent by exhibiting the percentage inhibition value of 69.7%, this effect was significant ($p < 0.001$) when compared to the standard-treated group. Meanwhile, replacing the 4-chlorophenyl substituent in the pyridine ring of **6d** with the 4-bromophenyl substituent resulted in compound **6k**, which emerged as a potent compound with a percentage inhibition of 67.4% notably, which promoted a decrease in the inhibition of inflammation with their potency being nearly equal to 102.1% that of Indomethacin. However, when compared to **6d**, the activity was slightly less, which clearly indicates the efficacy of the 4-chloro substituent on the anti-inflammatory activity. Furthermore, introduction of one more chloro substituent in **6d** and **6k** decreased their activity from 69.7 to 68.8%, i.e., compounds **6e** and **6l** displayed good anti-inflammatory activity, but lower than that of the starting compounds **6d** and **6k**. Additionally, among the tested compounds, animals treated with compounds **6g** and **6n** with an unsubstituted phenyl ring exhibited the lowest anti-inflammatory activity.

When we correlate the structures of tested compounds and their activity, it is clear that anti-inflammatory activity is sensitive to structural changes that is, the chlorophenyl substituent on pyridine and electron donating p-methoxyphenacyl spacer on other end of the oxadiazole moiety imparted superior activity than the other phenacyl spacer derivatives. Furthermore, derivatives with the chlorophenyl substituent on the pyridine ring considerably enhanced the anti-inflammatory activity when compared to the oxadiazoles with bromophenyl on the pyridine ring. While the addition of the dichlorophenacyl spacer decreased the anti-inflammatory activity compared to the monochlorophenacyl derivatives. Meanwhile, the unsubstituted phenacyl moiety did not affect the reduction in the edema thickness.

The acute toxicity study demonstrated that none of the screened compounds induce any appreciable behavioral change at the administered doses during the observation period.

3 | CONCLUSIONS

In conclusion, a series of 2-(5-[2-methyl-6-arylpyridin-3-yl]-1,-3,4-oxadiazol-2-ylthio)-1-arylethanones **(6a–n)** were prepared in good yield and their anti-inflammatory and antimicrobial activity were investigated. Evaluation of anti-inflammatory

activity revealed that most of the synthesized compounds showed a significant decrease in inflammation induced by carrageenan in rat's paws. Compound **6c** induced amazing anti-inflammatory activity by exhibiting the highest percentage of inhibition of 70.1% (with potency 106.2% to that of indomethacin), whereas the reference drug Indomethacin displayed percentage of inhibition of 66%. Furthermore, compounds **6d**, **6e**, **6k,** and **6l** exhibited significant anti-inflammatory activity compared to the standard drug. Moreover, the activity results demonstrated that halogen atoms particularly chlorophenyl on the pyridine ring and the methoxyphenacyl spacer have made good contribution to potency. In addition to this, the in vitro antimicrobial profile evidenced that among the series, compounds **6c** and **6i** emerged as more potent antibacterial agents. Furthermore, compounds **6a**, **6b,** and **6h** displayed good antibacterial activity compared with the standard. The investigation confirmed that the design is successful in generating members of the antibacterial and anti-inflammatory agent family.

4 | EXPERIMENTAL

All the chemicals and reagents were purchased from Merck, S.D. Fine, and Sigma-Aldrich Company and used as received. The purity of compounds was checked by thin layer chromatography (TLC) analyses performed on silica gel-G-coated aluminum plates (Merck) and spots were visualized by UV light. Melting points were determined in open glass capillaries and are uncorrected. FT (ATR)-IR absorption spectra were acquired on apparatus Thermo Nicolet, Avatar 370 in the 4,000–400 cm^{-1} range. The ^{1}H and ^{13}C NMR spectra were recorded for d_6-DMSO solution on Bruker Avance III, 400 and 100 MHz, respectively, with TMS as the internal standard. Elemental analysis (C, H, and N) of compounds was carried out using CHNS Elementar Vario EL III. The mass spectra were recorded using a Water, synapt G2 high detection mass spectrometer and are uncorrected.

4.1 | Synthesis of ethyl 2-methyl-6-arylnicotinate (3a–b)

A mixture of enaminones **2a**–**b** (2 mmol), ethylacetoacetate (2.2 mmol), and ammonium acetate (40 mmol) was refluxed for 5 hr. in glacial acetic acid media. The progress of reaction was monitored via TLC till single spot. After cooling, poured into ice-cold water, residue formed was collected by filtration and washed with petroleum ether and dried. The residue was purified by recrystallization in ethanol to afford compound **3a–b** as brown solids.

4.2 | Ethyl 6-(4-chlorophenyl)-2-methylpyridine-3-carboxylate (3a)

Brown solid. Yield: 98%, mp. 42–43°C. FT IR (ATR, cm^{-1}): 1,723 (C=O), 1,641 (C=N), 1,579 (C=C), and 823 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.34 (t, 3H, J = 7.4 Hz, $–CH_3$), 2.77 (s, 3H, $–CH_3$), 4.29–4.34 (q, 2H, J = 7.2 Hz, $–CH_2$), 7.53–7.55 (dd, 2H, ^{1}J = 8.8 Hz, ^{2}J = 2 Hz, C_3 and C_5–H of 4-ClC_6H_4), 7.95 (d, 1H, J = 8.4 Hz, C_4–H of pyridine), 8.04–8.06 (dd, 2H, ^{1}J = 8.8 Hz, ^{2}J = 2 Hz, C_2 and C_6–H of 4-ClC_6H_4), and 8.24 (d, 1H, J = 8.4 Hz, C_4–H of pyridine); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 165.7, 158.6, 156.4, 139.2, 136.5, 135.7, 129.5, 128.1, 123.6, 117.4, 60.8, 24.6, and 14.1; MS: calculated for $C_{15}H_{14}NClO_2$ is 275.07; found: (M +) 275.75, (M + 2) 277.75 *m/z*; Anal. Calc. for $C_{15}H_{14}NClO_2$: C, 65.34; H, 5.12; and N, 5.08%. Found: C, 65.49; H, 5.56; and N, 5.06%.

4.3 | Ethyl 6-(4-bromophenyl)-2-methylpyridine-3-carboxylate (3b)

Brown solid. Yield: 98%, mp. 49–51°C. FT IR (ATR, cm^{-1}): 1,724 (C=O), 1,641 (C=N), 1,581(C=C), and 775 (C–Br); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.34 (t, 3H, J = 7.4 Hz, $–CH_3$), 2.78 (s, 3H, $–CH_3$), 4.30–4.35 (q, 2H, J = 7.2 Hz, $–CH_2$), 7.70–7.72 (dd, 2H, ^{1}J = 8.8 Hz, ^{2}J = 2 Hz, C_3 and C_5–H of 4-BrC_6H_4), 7.95 (d, 1H, J = 8.4 Hz, C_4–H of pyridine), 8.08–8.10 (dd, 2H, ^{1}J = 8.8 Hz, ^{2}J = 2 Hz, C_2 and C_6–H of 4-BrC_6H_4), and 8.25 (d, 1H, J = 8.4 Hz, C_5–H of pyridine); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 165.8, 158.6, 156.4, 139.4, 136.5, 131.7, 128.9, 123.9, 123.6, 117.4, 60.9 ($–CH_2$), 24.6 ($–CH_3$), and 14 ($–CH_3$); MS: calculated for $C_{15}H_{14}NBrO_2$ is 319.02; found: (M+) 319.20, (M + 2) 321.20 *m/z*; Anal. Calc. for $C_{15}H_{14}NBrO_2$: C, 56.27; H, 4.41; and N, 4.37%. Found: C, 56.49; H, 4.56; and N, 4.20%.

4.4 | Synthesis of 2-methyl-6-arylnicotinohydrazide 4a–b

A mixture of hydrazine hydrate (99%, 6 mL) and ethyl 2-methyl-6-arylnicotinate **3a**–**b** (6 mmol) was heated under reflux condition for 6 hr and allowed to cool to room temperature. The resultant solid was filtered and washed with water and dried, and recrystallized from dioxane.

4.5 | 6-(4-Chlorophenyl)-2-methylpyridine-3-carbohydrazide (4a)

White solid. Yield: 97%, mp. 179–180°C. FT IR (ATR, cm^{-1}): 3,325, 3,296 (NH_2), 3,192 (NH), 1,640 (C=O), 1,585 (C=N), 1,516 (C=C), and 824 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.60 (s, 3H, $–CH_3$), 4.54 (s, 2H, $–NH_2$), 7.54 (d, 2H, J = 8.4 Hz, C_3 and C_5–H of 4-ClC_6H_4), 7.79 (d, 1H, J = 8 Hz, C_4–H of pyridine), 7.87 (d, 1H,

J = 8.4 Hz, C_5–H of pyridine) 8.05 (d, 2H, J = 8.4 Hz, C_2 and C_6–H of 4-ClC_6H_4), and 9.64 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 167.1, 155.7, 154.3, 137.3, 136.5, 135.7, 130.7, 129.2, 128.2, 117.1, and 22.9 (–CH_3); MS: calculated for $C_{13}H_{12}N_3ClO$ is 261.07; found: (M+) 261.75, (M + 2) 263.75 *m/z*; Anal. Calc. for $C_{13}H_{12}N_3ClO$: C, 59.66; H, 4.62; and N, 16.06%. Found: C, 59.49; H,4.56; and N, 16.06%.

4.6 | 6-(4-Bromoophenyl)-2-methylpyridine-3-carbohydrazide (4b)

White solid. Yield: 98%, mp. 182–183°C. FT IR (ATR, cm^{-1}): 3,326, 3,294 (NH_2), 3,195 (NH), 1,641 (C=O), 1,583 (C=N), 1,506 (C=C), and 784 (C–Br); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.60 (s, 3H, –CH_3), 4.54 (s, 2H, NH_2), 7.71 (d, 2H, J = 8.4 Hz, C_3 and C_5–H of 4-BrC_6H_4), 7.79 (d, 1H, J = 8 Hz, C_4–H of pyridine), 7.87 (d, 1H, J = 8.4 Hz, C_5–H of pyridine) 8.07 (d, 2H, J = 8.4 Hz, C_2 and C_6–H of 4-BrC_6H_4), and 9.63 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 167.0, 155.7, 154.5, 137.1, 136.5, 131.7, 129.4, 128.6, 122.9, 117.0, and 22.9 (–CH_3); MS: calculated for $C_{13}H_{12}N_3BrO$ is 305.02; found: (M + 1) 306.02, [(M + 1) + 2] 308.02 *m/z*; Anal. Calc. for $C_{13}H_{12}N_3BrO$: C, 51.00; H, 3.95; and N, 13.72%. Found: C, 50.49; H, 3.56; and N, 13.06%.

4.7 | 5-[2-methyl-6-arylpyridin-3-yl]-1,3,4-oxadiazole-2(3H)-thione 5a–b

2-methyl-6-arylnicotinohydrazide **4a**–**b** (1 mmol) was dissolved in absolute ethanol. Carbon disulfide (2 mmol) was added, followed by the addition of sodium hydroxide (2 mmol). The mixture was heated until the evolution of H_2S ceased (6–7 hr). After completion of the reaction, the mixture was cooled, diluted with water, and was neutralized by dilute hydrochloric acid. The precipitated product was filtered off, washed with cold water and dried, and recrystallized from ethanol-water.

4.8 | 5-[6-(4-Chlorophenyl)-2-methylpyridin-3-yl]-1,3,4-oxadiazole-2(3H)-thione (5a)

Off White solid. Yield: 96%, mp. 218–220°C. FT IR (ATR, cm^{-1}): 3,092 (NH), 1,585 (C=N), 1,507 (C=C), 1,336 (C=S), 1,287 (C–O–C), and 836 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.81(s, 3H, –CH_3), 7.59 (d, 2H, J = 8.4 Hz, C_3 and C_5–H of 4-ClC_6H_4), 8.03 (d, 1H, J = 8.4 Hz, C_4–H of pyridine), 8.19 (d, 2H, J = 8.8 Hz, C_2 and C_6–H of 4-ClC_6H_4), and 8.24 (d, 1H, J = 8.4 Hz, C_5–H of pyridine); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 177.6 (C=S), 159.9, 156.9,156.2, 137.6, 136.5, 135.3, 129.4, 129.1, 118.2, 116.9, and 25.4 (–CH_3); MS: calculated for $C_{14}H_{10}N_3ClOS$ is 303.02; found: (M+) 303.77, (M + 2) 305.77 *m/z*; Anal. Calc. for $C_{14}H_{10}N_3ClOS$: C, 55.35; H, 3.32; and N, 13.83%. Found: C, 55.49; H, 3.56; and N, 13.06%.

4.9 | 5-[6-(4-Bromophenyl)-2-methylpyridin-3-yl]-1,3,4-oxadiazole-2(3H)-thione (5b)

Off White solid. Yield: 98%, mp. 2,111–212°C. FT IR (ATR, cm^{-1}): 3,062 (NH), 1,581 (C=N), 1,508 (C=C), 1,332 (C=S), 1,299 (C–O–C), and 761 (C–Br); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.80 (s, 3H, –CH_3), 7.71 (d, 2H, J = 8.4 Hz, C_3 and C_5–H of 4-BrC_6H_4), 8.01(d, 1H, J = 8.4 Hz, C_4–H of pyridine), 8.11 (d, 2H, J = 8.4 Hz, C_2 and C_6–H of 4-BrC_6H_4), and 8.22 (d, 1H, J = 8.4 Hz, C_5–H of pyridine); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 177.1 (C=S), 159.4, 156.4, 155.7, 137.1, 136.3, 131.8, 128.8, 123.7, 117.6, 116.1, and 24.9 (–CH_3); MS: calculated for $C_{14}H_{10}N_3BrOS$ is 346.97; found: (M+) 347.25, (M + 2) 349.10 *m/z*; Anal. Calc. for $C_{14}H_{10}N_3BrOS$: C, 48.29; H, 2.89; and N, 12.07%. Found: C, 48.49; H, 2.56; and N, 12.06%.

4.10 | General procedure for synthesis of 2-(5-[2-methyl-6-arylpyridin-3-yl]-1,3,4-oxadiazol-2-ylthio)-1-arylethanone 6a–n

Triethylamine (1 mmol) was added as a base to a suspension of 1,3,4-oxadiazole-2-thione **5a**–**b** (1 mmol) in acetone, stirred for 15 min. Then, appropriate phenacyl bromide/chloride (1 mmol) was added and the mixture was heated under reflux for 3 hr. Completion of the reaction was monitored by TLC. After completion, the reaction mixture was poured to ice cold water, the resulting solid was collected and recrystallized from ethanol.

4.11 | 2-({5-[6-(4-Chlorophenyl)-2-methylpyridin-3-yl]-1,3,4-oxadiazol-2-yl}thio)-1-(p-tolyl)Ethan-1-one (6a)

Off White solid. Yield: 90%, mp. 180–181°C. FT IR (ATR, cm^{-1}): 1,668 (C=O), 1,583 (C=N), 1,471 (C=C), 1,176 (C–S–C), 1,091 (C–O), and 815 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.42 (s, 3H, –CH_3), 2.86 (s, 3H, –CH_3), 5.16 (s, 2H, –CH_2), 7.42 (d, 2H, J = 8 Hz, C_2 and C_6–H of 4-MeC_6H_4), 7.61 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_3 and C_5–H of 4-ClC_6H_4), 7.96 (d, 2H, J = 8 Hz, C_3 and C_5–H of 4-MeC_6H_4), 8.04 (d, 1H, J = 8.4 Hz, C_4–H of pyridine), 8.22 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_2 and C_6–H of 4-ClC_6H_4), and 8.32 (d, 1H, J = 8.4 Hz, C_5–H of pyridine); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 193.4 (C=O), 164.4, 163.2, 156.4, 155.3, 139.1, 137.8, 136.1, 134.8, 133.4, 131.6, 129.6, 129.2, 128.9, 128.4, 116.8, 42.3 (–CH_2), 25.9 (–CH_3), and 24.9 (–CH_3); MS: calculated for $C_{23}H_{18}N_3ClO_2S$ is 435.08; found: (M+) 435.55, (M + 2) 437.55 *m/z*; Anal. Calc. for $C_{23}H_{18}N_3ClO_2S$: C, 63.37; H, 4.16; and N, 9.64%. Found: C, 63.49; H, 4.56; and N, 9.06%.

4.12 | 1-(4-Bromophenyl)-2-({5-[6-(4-chlorophenyl)-2-methylpyridin-3-yl]-1,3,4-oxadiazol-2-yl} thio)Ethan-1-one (6b)

Off White solid. Yield: 91%, mp. 212–213°C. FT IR (ATR, cm^{-1}): 1,660 (C=O), 1,581(C=N), 1,485 (C=C), 1,176 (C–S–C), 1,091 (C–O), 830 (C–Cl) ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.86 (s, 3H, –CH_3), 5.12 (s, 2H, –CH_2), 7.62 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_3 and C_5–H of 4-ClC_6H_4), 7.78 (d, 2H, J = 8 Hz, C_3 and C_5–H of 4-BrC_6H_4), 7.98 (d, 2H, J = 8 Hz, C_2 and C_6–H of 4-BrC_6H_4), 8.06 (d, 1H, J = 8.4 Hz, C_4–H of pyridine), 8.22 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_2 and C_6–H of 4-ClC_6H_4), and 8.34 (d, 1H, J = 8.4 Hz, C_5–H of pyridine); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 193.7 (C=O), 165.4, 163.7, 156.4, 155.7, 137.2, 136.7, 135.1, 133.5, 132.0, 131.7, 130.3, 128.7, 128.5, 124.0, 116.8, 42.3 (–CH_2), and 24.9 (–CH_3); MS: calculated for $C_{22}H_{15}N_3BrO_2S$ is 498.98; found: (M+) 499.55, (M + 2) 500.55, and (M + 4) 502.55 *m/z*; Anal. Calc. for $C_{22}H_{15}N_3BrO_2S$: C, 52.76; H, 3.02; and N, 8.39%. Found: C, 53.49; H, 3.06; and N, 8.26%.

4.13 | 2-({5-[6-(4-Chlorophenyl)-2-methylpyridin-3-yl]-1,3,4-oxadiazol-2-yl}thio)-1-(4-methoxy phenyl)Ethan-1-one (6c)

Off White solid. Yield: 98%, mp. 198–199°C. FT IR (ATR, cm^{-1}): 1,667 (C=O), 1,583 (C=N), 1,493 (C=C), 1,176 (C–S–C), 1,091 (C–O), and 836 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.87 (s, 3H, –CH_3), 3.79 (s, 3H, –OCH_3), 5.14 (s, 2H, –CH_2), 7.05 (d, 2H, J = 8 Hz, C_3 and C_5–H of 4-$OMeC_6H_4$), 7.62 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_3 and C_5–H of 4-ClC_6H_4), 7.98 (d, 2H, J = 8 Hz, C_3 and C_5–H of 4-$OMeC_6H_4$), 8.06 (d, 1H, J = 8.4 Hz, C_4–H of pyridine), 8.21 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_2 and C_6–H of 4-ClC_6H_4), and 8.30 (d, 1H, J = 8.4 Hz, C_5–H of pyridine); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 194.4 (C=O), 163.4, 162.2, 160.4, 156.4, 152.3, 136.8, 136.1, 134.2, 131.6, 131.1, 128.8, 128.6, 128.4, 116.6, 114.1, 55.5(–OCH_3), 42.5 (–CH_2), and 25.9 (–CH_3); MS: calculated for $C_{23}H_{18}N_3ClO_3S$ is 451.08; found: (M+) 451.93, (M + 2) 453.07 *m/z*; Anal. Calc. for $C_{23}H_{18}N_3ClO_3S$: C, 61.13; H, 4.01; and N, 9.30%. Found: C, 61.49; H, 3.56; and N, 9.06%.

4.14 | 1-(4-Chlorophenyl)-2-({5-[6-(4-chlorophenyl)-2-methylpyridin-3-yl]-1,3,4-oxadiazol-2-yl} thio)Ethan-1-one (6d)

Off White solid. Yield: 85%, mp. 209–210°C. FT IR (ATR, cm^{-1}): 1,666 (C=O), 1,585 (C=N), 1,483 (C=C), 1,176 (C–S–C), 1,089 (C–O), and 821 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.87 (s, 3H, –CH_3), 5.06 (s, 2H, –CH_2), 7.52 (d, 2H, J = 8 Hz, C_3 and C_5–H of 4-ClC_6H_4), 7.73 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_3 and C_5–H of 4-ClC_6H_4), 7.84 (d, 2H, J = 8 Hz, C_3 and C_5–H of 4-ClC_6H_4), 8.06 (d, 1H, J = 8.4 Hz, C_4–H of pyridine), 8.12 (dd, 2H, ^1J = 6.8 Hz, $2J$ = 2 Hz, C_2 and C_6–H of 4-ClC_6H_4), and 8.22 (d, 1H, J = 8.4 Hz, C_5–H of pyridine); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 193.7 (C=O), 164.6, 163.2, 156.7, 155.6, 137.8, 136.4, 135.7, 134.8, 133.4, 131.6, 130.2, 129, 128.9, 128.4, 116.8, 42.2 (–CH_2), and 24.9 (–CH_3); MS: calculated for $C_{22}H_{15}N_3Cl_2O_2S$ is 455.03; found: (M + 1) 455.97, (M + 2) 457.96, and (M + 4) 459.96 *m/z*; Anal. Calc. for $C_{22}H_{15}N_3Cl_2O_2S$: C, 57.90; H, 3.31; and N, 9.21%. Found: C, 56.98; H, 3.56; and N, 9.16%.

4.15 | 2-({5-[6-(4-Chlorophenyl)-2-methylpyridin-3-yl]-1,3,4-oxadiazol-2-yl}thio)-1-(2,4-dichloro phenyl)Ethan-1-one (6e)

Brown solid. Yield: 73%, mp. FT IR (ATR, cm^{-1}): 139–140°C. 1,683 (C=O), 1,581 (C=N), 1,477 (C=C), 1,191 (C–S–C), 1,095 (C–O), and 833 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.87 (s, 3H, –CH_3), 5.03 (s, 2H, –CH_2), 7.60 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_3 and C_5–H of 4-ClC_6H_4), 7.65 (dd, 1H, ^1J = 8.8 Hz, ^2J = 2.4 Hz, C_5–H of 2,4-$Cl_2C_6H_3$), 7.80 (d, 1H, J = 2 Hz, C_3–H of 2,4-$Cl_2C_6H_3$), 7.95 (d, 1H, J = 8.4 Hz, C_6–H of 2,4-$Cl_2C_6H_3$), 8.05 (d, 1H, J = 8.4 Hz, C_4–H of pyridine), 8.22 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_2 and C_6–H of 4-ClC_6H_4), and 8.31 (d, 1H, J = 8.4 Hz, C_5–H of pyridine); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 193.4 (C=O), 164.2, 163.1, 156.5, 155.7, 137.5, 137.1, 136.1, 134.8, 134.7, 131.8, 131.5,130.3, 128.9, 128.6, 127.6, 117.7, 116.9, 42.2 (–CH_2), 24.9 (–CH_3); MS: calculated for $C_{22}H_{14}N_3Cl_3O_2S$ is 488.99; found: (M+) 489.30, (M + 2) 491.35, and (M + 4) 492.80 *m/z*; Anal. Calc. for $C_{22}H_{14}N_3Cl_3O_2S$: C, 53.84; H, 2.88; and N, 8.56%. Found: C, 53.49; H, 2.86; and N, 8.46%.

4.16 | 2-({5-[6-(4-Chlorophenyl)-2-methylpyridin-3-yl]-1,3,4-oxadiazol-2-yl}thio)-1-(1,7-dichloro-9H-fluoren-2-yl))Ethan-1-one (6f)

Brown solid. Yield: 79.2%, mp. FT IR (ATR, cm^{-1}): 147–149°C. 1,668 (C=O), 1,583 (C=N), 1,482 (C=C), 1,176 (C–S–C), 1,092 (C–O), and 836 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.86 (s, 3H, –CH_3), 3.96 (s, 2H, C_9–H of 2,7-dichloro-9*H*-fluorene), 5.16 (s, 2H, –CH_2), 7.40–7.43 (m, 2H, C6 and C8-H of 2,7-dichloro-9*H*-fluorene), 7.61 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_3 and C_5–H of 4-ClC_6H_4), 7.71–7.75 (m, 2H, C_3, C_5–H of 2,7-dichloro-9*H*-fluorene), 8.04 (d, 1H, J = 8.4 Hz, C_4–H of pyridine), 8.22 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_2 and C_6–H of 4-ClC_6H_4), and 8.32 (d, 1H, J = 8.4 Hz, C_5–H of pyridine); ^{13}C NM R (100 MHz, DMSO-d_6, δ, ppm): 193.6 (C=O), 165.6, 165.2, 156.5, 155.7, 143.6, 143.1, 143, 139.8, 137.5, 134.7, 134.5, 133.1, 132.9, 130.6, 128.9,128.7, 128.6,

128.3, 127.8, 126.5, 116.9, 42.3 (–CH_2), 36.7, 24.9 (–CH_3); MS: calculated for $C_{29}H_{18}N_3Cl_3O_2S$ is 577.02; found: (M + 1) 578.09, (M + 2) 579.02, (M + 4) 581.02, and (M + 6) 583.03 *m/z*; Anal. Calc. for $C_{29}H_{18}N_3Cl_3O_2S$: C, 60.17; H, 3.13; and N, 7.26%. Found: C, 60.19; H, 3.10; and N, 7.16%.

4.17 | 2-({5-[6-(4-Chlorophenyl)-2-methylpyridin-3-yl]-1,3,4-oxadiazol-2-yl}thio)-1-phenylethan-1-one (6g)

Brown solid. Yield: 97%, mp. 151–152°C. FT IR (ATR, cm^{-1}): 1,670 (C=O), 1,583 (C=N), 1,452 (C=C), 1,180 (C–S–C), 1,000 (C–O), and 819 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.85 (s, 3H, –CH_3), 5.06 (s, 2H, –CH_2), 7.61 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_3 and C_5–H of 4-ClC_6H_4), 7.71–7.75 (m, 3H, C_3, C_4 and C_5–H of C_6H_5), 8.04 (d, 1H, J = 8.4 Hz, C_4–H of pyridine), 8.21 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_2 and C_6–H of 4-ClC_6H_4), 8.13–8.15 (m, 2H, C_2 and C_6–H of C_6H_5), and 8.32 (d, 1H, J = 8.4 Hz, C_5–H of pyridine); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 194.1 (C=O), 164.5, 163.3, 156.2, 155.3, 137.8,136.6, 135.5, 134.8, 131.6, 128.9, 128.8, 128.6, 128.2, 127.9, 116.8, 42.3 (–CH_2), 24.9 (–CH_3); MS: calculated for $C_{22}H_{16}N_3ClO_2S$ is 421.07; found: (M+) 421.9, (M + 2) 423.9 *m/z*; Anal. Calc. for $C_{22}H_{16}N_3ClO_2S$: C, 62.63; H, 3.82; and N, 9.96%. Found: C, 62.49; H, 3.65; and N, 9.76%.

4.18 | 2-({5-[6-(4-Bromophenyl)-2-methylpyridin-3-yl]-1,3,4-oxadiazol-2-yl}thio)-1-(p-tolyl)Ethan-1-one (6h)

Cream solid. Yield: 94%, mp. 183–184°C. FT IR (ATR, cm^{-1}): 1,664 (C=O), 1,583 (C=N), 1,481 (C=C), 1,176 (C–S–C), 1,091 (C–O), and 715 (C–Br); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.42 (s, 3H, –CH_3), 2.87 (s, 3H, –CH_3), 5.05 (s, 2H, –CH_2), 7.42 (d, 2H, J = 8 Hz, C_2 and C_6–H of 4-MeC_6H_4), 7.74 (dd, 2H, ^1J = 6.8 Hz, ^2J = 1.6 Hz, C_3 and C_5–H of 4-BrC_6H_4), 7.96 (d, 2H, J = 8 Hz, C_3 and C_5–H of 4-MeC_6H_4), 8.06 (d, 1H, J = 8 Hz, C_4–H of pyridine), 8.13 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_2 and C_6–H of 4-BrC_6H_4), and 8.32 (d, 1H, J = 8 Hz, C_5–H of pyridine); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 193.4 (C=O), 165.8, 165.4, 156.7, 155.8, 139.1,137.5, 134.7, 133.4, 131.8, 129.6, 129.2, 128.9, 123.6, 116.9, 42.2 (–CH_2), 25.9 (–CH_3), and 24.9 (–CH_3); MS: calculated for $C_{23}H_{18}N_3BrO_2S$ is 479.03; found: (M + 1) 480.38, (M + 2) 481.38 *m/z*; Anal. Calc. for $C_{23}H_{18}N_3BrO_2S$: C, 57.51; H, 3.78; and N, 8.75%. Found: C, 57.49; H, 3.86; and N, 8.76%.

4.19 | 1-(4-Bromophenyl)-2-({5-[6-(4-bromophenyl)-2-methylpyridin-3-yl]-1,3,4-oxadiazol-2-yl} thio)Ethan-1-one (6i)

Off white solid. Yield: 95%, mp. 213–214°C. FT IR (ATR, cm^{-1}): 1,666 (C=O), 1,587 (C=N), 1,483 (C=C), 1,180 (C–S–C), 1,071 (C–O), and 698 (C–Br); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.86 (s, 3H, –CH_3), 5.13 (s, 2H, –CH_2), 7.74 (dd, 2H, ^1J = 6.8 Hz, ^2J = 1.6 Hz, C_3 and C_5–H of 4-BrC_6H_4), 7.78 (d, 2H, J = 8 Hz, C_3 and C_5–H of 4-BrC_6H_4), 7.98 (d, 2H, J = 8 Hz, C_2 and C_6–H of 4-BrC_6H_4) 8.03 (d, 1H, J = 8 Hz, C_4–H of pyridine), 8.16 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_2 and C_6–H of 4-BrC_6H_4), and 8.32 (d, 1H, J = 8 Hz, C_5–H of pyridine); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 193.3 (C=O), 165.8, 165.5, 156.8, 155.5, 137.5, 134.7, 132.0, 131.8,130.3, 128.9, 124, 123.6, 116.9, 42.3 (–CH_2), 24.9 (–CH_3); MS: calculated for $C_{22}H_{15}N_3Br_2O_2S$ is 545.25; found: (M + 1) 546.35, (M + 2) 547.35, and (M + 4) 549.35 *m/z*; Anal. Calc. for $C_{22}H_{15}N_3Br_2O_2S$: C, 48.46; H, 2.77; and N, 7.71%. Found: C, 48.49; H, 2.86; and N, 7.66%.

4.20 | 2-({5-[6-(4-Bromophenyl)-2-methylpyridin-3-yl]-1,3,4-oxadiazol-2-yl}thio)-1-(4-methoxy phenyl)Ethan-1-one (6j)

Off white solid. Yield: 94%, mp. 199–200°C. FT IR (ATR, cm^{-1}): 1,668 (C=O), 1,583 (C=N), 1,471 (C=C), 1,176 (C–S–C), 1,091 (C–O), and 712 (C–Br); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.88 (s, 3H, –CH_3), 3.79 (s, 3H, –OCH_3), 5.13 (s, 2H, –CH_2), 7.05 (d, 2H, J = 8 Hz, C_3 and C_5–H of 4-$OMeC_6H_4$), 7.74 (dd, 2H, ^1J = 6.8 Hz, ^2J = 1.6 Hz, C_3 and C_5–H of 4-BrC_6H_4), 7.98 (d, 2H, J = 8 Hz, C_3 and C_5–H of 4-$OMeC_6H_4$), 8.05 (d, 1H, J = 8 Hz, C_4–H of pyridine), 8.15 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_2 and C_6–H of 4-BrC_6H_4), and 8.31 (d, 1H, J = 8 Hz, C_5–H of pyridine); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 193.4 (C=O), 165.8, 165.4, 160.4, 156.7, 155.8, 137.5, 134.7, 131.8, 131.1, 128.9, 128.7, 123.6, 116.9, 114, 55.5 (–OCH_3), 42.2 (–CH_2), and 24.9 (–CH_3); MS: calculated for $C_{23}H_{18}N_3BrO_3S$ is 495.03; found: (M + 1) 496.35, (M + 2) 497.35 *m/z*; Anal. Calc. for $C_{23}H_{18}N_3BrO_3S$: C, 55.65; H, 3.66; and N, 8.47%. Found: C, 55.49; H, 3.76; and N, 8.46%.

4.21 | 2-({5-[6-(4-Chlorophenyl)-2-methylpyridin-3-yl]-1,3,4-oxadiazol-2-yl}thio)-1-(4-chlorophenyl)Ethan-1-one (6k)

Off white solid. Yield: 98%, mp. 217–218°C. FT IR (ATR, cm^{-1}): 1,666 (C=O), 1,585 (C=N), 1,483 (C=C), 1,176 (C–S–C), and 1,089 (C–O), 712 (C–Br); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.83 (s, 3H, –CH_3), 5.16 (s, 2H, –CH_2), 7.52 (d, 2H, J = 8 Hz, C_3 and C_5–H of 4-ClC_6H_4), 7.75 (dd, 2H, ^1J = 6.8 Hz, ^2J = 1.6 Hz, C_3 and C_5–H of 4-BrC_6H_4), 7.84 (d, 2H, J = 8 Hz, C_3 and C_5–H of 4-ClC_6H_4), 8.07 (d, 1H, J = 8 Hz, C_4–H of pyridine), 8.14 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_2 and C_6–H of 4-BrC_6H_4), and 8.32 (d, 1H, J = 8 Hz, C_5–H of pyridine); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 193.4 (C=O), 165.9, 165.5, 156.6, 155.4, 137.5, 134.6, 135.7, 133.5, 131.5, 130.2,

129, 128.7, 123.6, 116.9, 42.2 (–CH_2), 25.2 (–CH_3); MS: calculated for $C_{22}H_{15}N_3BrClO_2S$ is 498.98; found: (M + 1) 499.95, (M + 2) 500.95, and (M + 4) 502.95 *m/z*; Anal. Calc. for $C_{22}H_{15}N_3BrClO_2S$: C, 52.76; H, 3.02; and N, 8.39%. Found: C, 52.74; H, 3.01; and N, 8.36%.

4.22 | 2-({5-[6-(4-Bromophenyl)-2-methylpyridin-3-yl]-1,3,4-oxadiazol-2-yl}thio)-1-(2,4-dichloro phenyl)Ethan-1-one (6l)

Brown solid. Yield: 83%, mp. 144–146°C. FT IR (ATR, cm^{-1}): 1,681 (C=O), 1,581 (C=N), 1,475 (C=C), 1,191 (C–S–C), 1,064 (C–O), and 763 (C–Br); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.87 (s, 3H, –CH_3), 5.03 (s, 2H, –CH_2), 7.63 (dd, 1H, ^1J = 8.4 Hz, ^2J = 2 Hz, C_5–H of 2,4-$Cl_2C_6H_3$), 7.74 (dd, 2H, ^1J = 6.8 Hz, ^2J = 1.6 Hz, C_3 and C_5–H of 4-BrC_6H_4), 7.80 (d, 1H, J = 2 Hz, C_3–H of 2,4-$Cl_2C_6H_3$), 7.95 (d, 1H, J = 8.4 Hz, C_6–H of 2,4-$Cl_2C_6H_3$), 8.05 (d, 1H, J = 8 Hz, C_4–H of pyridine), 8.15 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_2 and C_6–H of 4-BrC_6H_4), and 8.31 (d, 1H, J = 8 Hz, C_5–H of pyridine); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 193.4 (C=O), 165.8, 165.4, 156.7, 155.8, 137.5, 137.2, 134.7, 131.8, 131.5, 130.3, 128.9, 127.6, 125.1, 123.6, 117.7, 116.9, 42.2 (–CH_2), 24.9 (–CH_3); MS: calculated for $C_{22}H_{14}N_3BrCl_2O_2S$ is 532.94; found: (M+) 490.35, (M + 2) 491.35, and (M + 4) 493.35 *m/z*; Anal. Calc. for $C_{22}H_{14}N_3BrCl_2O_2S$: C, 49.37; H, 2.64; and N, 7.85%. Found: C, 49.49; H, 2.86; and N, 7.46%.

4.23 | 2-({5-[6-(4-Bromophenyl)-2-methylpyridin-3-yl]-1,3,4-oxadiazol-2-yl}thio)-1-(1,7-dichloro-9H-fluoren-2-yl))Ethan-1-one (6m)

Pale yellow solid. Yield: 76%, mp. 168–169°C. FT IR (ATR, cm^{-1}): 1,668 (C=O), 1,583 (C=N), 1,477 (C=C), 1,180 (C–S–C), 1,098 (C–O), and 736 (C–Br); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.84 (s, 3H, –CH_3), 3.96 (s, 2H, C_9–H of 2,7-dichloro-9*H*-fluorene), 5.12 (s, 2H, –CH_2), 7.40–7.43 (m, 2H, C6 and C8–H of 2,7-dichloro-9*H*-fluorene), 7.70–7.75 (m, 4H, C_3, C_5–H of 4-BrC_6H_4 and 2,7-dichloro-9*H*-fluorene), 8.06 (d, 1H, J = 8 Hz, C_4–H of pyridine), 8.16 (dd, 2H, ^1J = 6.8 Hz, ^2J = 2 Hz, C_2 and C_6–H of 4-BrC_6H_4), and 8.32 (d, 1H, J = 8 Hz, C_5–H of pyridine); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 193.6 (C=O), 165.6, 165.2, 156.5, 155.7, 143.6, 143.1, 143, 139.8, 137.5, 134.7, 133.1, 132.9, 131.8, 130.6, 128.9, 128.7, 128.3, 127.8, 126.5, 123.6, 116.9, 42.2 (–CH_2), 36.7, 24.9 (–CH_3); MS: calculated for $C_{29}H_{18}N_3BrCl_2O_2S$ is 620.35; found: (M+) 620.96, (M + 2) 622.90, (M + 4) 624.90, and (M + 6) 626.96 *m/z*; Anal. Calc. for $C_{29}H_{18}N_3BrCl_2O_2S$: C, 55.88; H, 2.91; and N, 6.74%. Found: C, 55.79; H, 2.86; and N, 6.76%.

4.24 | 2-({5-[6-(4-Bromophenyl)-2-methylpyridin-3-yl]-1,3,4-oxadiazol-2-yl}thio)-1-phenylethan-1-one (6n)

Brown solid. Yield: 96%, mp. 153–154°C. FT IR (ATR, cm^{-1}): 1,681 (C=O), 1,581 (C=N), 1,475 (C=C), 1,176 (C–S–C), 1,064 (C–O), and 719 (C–Br); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.85 (s, 3H, –CH_3), 5.20 (s, 2H, –CH_2), 7.59–7.63 (m, 2H, C_3 and C_5–H of C_6H_5), 7.71–7.75 (m, 3H, J = 8 Hz, C_3 and C_5–H of 4-BrC_6H_4 and C_4–H of C_6H_5), 8.04 (d, 1H, J = 8 Hz, C_4–H of pyridine), 8.07–8.15 (m, 4H, C_2, C_6–H of 4-BrC_6H_4 and C_6H_5), and8.32 (d, 1H, J = 8 Hz, C_5–H of pyridine); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 193.4 (C=O), 165.8, 165.4, 156.7, 155.8, 137.5, 135.6, 134.7, 131.8, 130.1, 128.9, 128.7, 128.5, 123.6, 116.9, 42.2 (–CH_2), 24.9 (–CH_3); MS: calculated for $C_{22}H_{16}N_3BrO_2S$ is 465.01; found: (M+) 465.55, (M + 2) 467.50 *m/z*; Anal. Calc. for $C_{22}H_{16}N_3BrO_2S$: C, 56.66; H, 3.46; and N, 9.01%. Found: C, 56.49; H, 3.48; and N, 9.02%.

4.25 | In vitro antimicrobial activity assay

The newly synthesized compounds were screened for their antibacterial activity against four bacterial strains namely *P. aeruginosa*, *E. coli* representative of Gram Positive and *B. subtilis*, *S. aureus* representative of Gram Negative bacterial strains. Ciprofloxacin was used as positive control. The primary screening was carried out using the Agar cup plate method.[36]

The sterilized nutrient agar medium was distributed 100 mL each in two 250 mL conical flasks and allowed to cool to room temperature. To these media, 18–24 hr grown bacterial subcultures were added and shaken thoroughly to ensure uniform distribution of organisms throughout the medium. Then, this agar medium was distributed in equal portions, in sterilized petri dishes, ensuring that each petri dish contains about 45–50 mL of the medium. The medium was then allowed for solidification. Then, cups were made with the help of a sterile cork borer (6 mm diameter) punching into the set of agar media. The solutions of required concentrations (100 μg/mL) of test compounds were prepared by dissolving the compounds in DMSO filled into the cups with 1 mL of respective solution. Then, the petri dishes were kept for incubation in an inverted position for 24–48 hr at 37°C in an incubator. When growth inhibition zones were developed surrounding each cup, their diameter in mm was measured and compared with that of the standard drug. The MIC for the potent compounds **6a**, **6b**, **6c**, **6g**, **6h**, **6i**, and **6n** against the same microorganisms used in the primary screening was used according to the reported Broth dilution method.[37]

4.26 | In vivo anti-inflammatory assay

The rats were divided into ten groups of six animals each. Group I (negative control) received 1 mL of normal saline,

Group II (Standard) received 10 mg/kg p.o. indomethacin, and Group III-IX received synthetic compounds 50 mg/kg. After 1 hr, the rats were challenged with subcutaneous injection of 0.1 mL of 1% w/v solution of carrageenan (Sigma chemical co, St. Louis MO, USA) into the plantar side of the left hind paw. The paw was marked in the cup of the apparatus with water. The digital plethysmograph apparatus was used for the measurement of rat paw volume. The paw volume was measured every hour for 3 hr after injection of carrageenan to each group to determine the change in the paw edema thickness. The difference between the initial and subsequent reading gave the actual edema volume.

4.27 | Animals

Animal Wistar rats of either sex and of approximately the same age, weighing about 125–150 g, were used for the study and were housed in polypropylene cages and fed with standard pellet diet and water ad libitum. The animals were under alternate cycle of 12 hr of darkness and light each. Before each test, the animals were fasted for at least 12 hr.

4.28 | Acute toxicity study

Acute toxicity study[38] on Wister albino rats was carried out using the standard method at an oral dose of 100–1,000 mg/kg body weight as per OECD 425 guidelines. The control group receives 1% tween 80 suspension. All the animals were observed continuously for 8 hr for any signs of acute toxicity such as tremors, ataxia, and convulsions. Animals were kept under fasting conditions prior to dosing.

4.29 | Statistical analysis

Statistics were performed with one-way analysis of variance ANOVA and expressed as Mean ± *SEM* followed by Dunnett's test. The differences between mean at $*p < 0.01$, $**p < 0.005$, and $***$ $p < 0.0001$ were considered to be significant.

Anti-inflammatory activity was calculated as percentage of inhibition in the edema thickness induced by carrageenan was obtained from the following relation.

$$\%\text{inhibition} = (V_c - V_t)/V_c \times 100,$$

where V_c and V_t are volumes of paw edema in control and drug treated groups, respectively.

4.30 | Ethics

The experimental protocols according to the CPCSEA guidelines and IAEC clearance were taken prior to the commencement of the study. The animal treatment protocol was approved by Reg. No. SCSCP/IEEC/09/2016-17.

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CONFLICTS OF INTEREST

The authors declare no potential conflict of interests.

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