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Synthesis, characterization and pharmacological studies of novel bis 1,3,4-oxadiazole and 1, 2,4-triazole derivatives

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ABSTRACT

*A series of 2, 2'-(5-nitrobenzene-1, 3-diyl) bis (5-alkyl-1, 3, 4-oxadiazole) (**2a-e**) 5,5'-(5-nitrobenzene-1,3-diyl)bis(1,3,4-oxadiazole-2-thiol) (**3**) and 5,5'-(5-nitrobenzene-1,3-diyl)bis(4-amino-4H-1,2,4-triazole-3-thiol(**5**) were obtained via reaction of 5-nitro iso-phthalic dihydrazide (**1**). All these newly synthesized compounds were characterized by IR, NMR and Mass, spectral studies. Newly synthesized compound displayed potent antibacterial and antinociceptive activity.*

Keywords: antibacterial activity, antinociceptive activity, Anti-inflammatory activity, alkyl bis1, 3,4-oxadiazole,bis1,2,4-triazole.

INTRODUCTION

Synthesis of novel heterocycles is an important task for heterocyclic chemists, from various points of view for the development of compounds of pharmacological and industrial importance. Oxadiazole and triazloes continue to attract great interest due to their wide spectrum of biological activity [**1**]. A generalized and efficient method for the synthesis of 1,3,4-oxadiazoles have been reported by [**2**]. Alkyl 1,3,4-oxadiazoles was synthesized by cyclization of aryl hydrazide with aromatic or aliphatic acids in the presence of phosphorus oxychloride. And 5,5'-(5-nitrobenzene-1,3-diyl)bis(1,3,4-oxadiazole-2-thiol),5,5'-(5-nitrobenzene-1,3-diyl)bis(4-amino-4*H*-1,2,4-triazole-3-thiol) was prepared in good yield, using multi-step reaction by adopting reported method [**3**] with suitable modifications. Nitrogen, oxygen, sulphur containing heterocycles like 1,3, 4-oxadiazoles and 1,2,4-triazoles are a class of heterocycles they are of

significant interest in medicine and pesticide chemistry in a number of biological targets including anti-inflammatory agents [**4-5**] antibacterial [**6-8**], tuberculostatic [**9**], anti-convulsant [**10-11**] and antimicrobial activity [**12-13**]. 1, 2, 3-oxadiazoles can also be used as HIV integrase inhibitors [**14**] or as prostaglandin receptor antagonists [**15**]. 1,3,4-oxadiazole and 1,2,4-triazole derivatives can be readily produced using dihydrazide as starting materials [**16**] showing significant antimicrobial [**17-18**] and antinociceptive activity [**19**]. Recently, our research group reported that the studies on synthesis and pharmacological activities of 3,6-disubstituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles and their dihydro analogues. And heterocyclic system containing bridgehead nitrogen atom: Synthesis and pharmacological contained activities of some substituted 1,2,4-triazolo[3,4-b]-1,3,4-oxadiazoles [**20-21**] The rapid growth in the literature dealing with the synthesis and biological activities, promoted us to report the synthesis, antibacterial and antinociceptive activities of novel of the 2,2'-(5-nitrobenzene-1,3-diyl)bis(5-alkyl-1,3,4-oxadiazole), 5,5'-(5-nitrobenzene-1,3-diyl)bis(4-amino-4*H*-1,2,4-triazole-3-thiol) and 5, 5'-(5-nitrobenzene-1,3-diyl)bis(1,3,4-oxadiazole-2-thiol) derivatives, with excellent yield, as depicted in the **scheme 1**.

MATERIALS AND METHODS

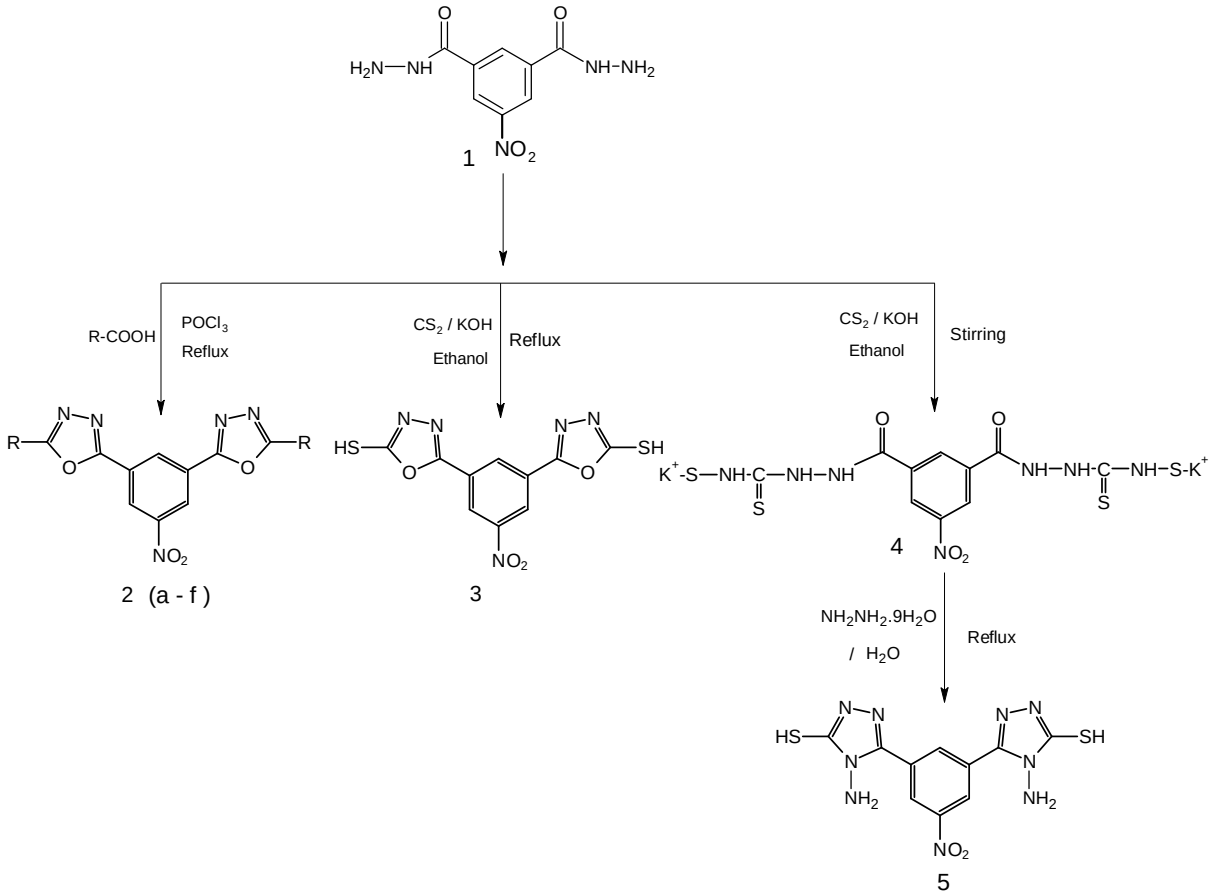
All analytical grade chemicals of were used directly. Melting points were determined in scientific melting point apparatus and uncorrected. The progress of reaction was monitored by TLC using silica gel coated plates (0.5 mm thickness, Merck) and spots visualized under UV radiation. Synthesized compounds were recrystalized using suitable solvent. Infra-Red spectra were recorded on Perkin Elmer-spectrum RX-1model spectrophotometer using KBr pellets. NMR spectra was recorded by Bruker DRX400 MHz spectrometer and acquired on a Bruker Avance-2 model spectrophotometer using $CDCl_3$/DMSO as a solvent and TMS as an internal reference.

General procedure for the Synthesis of aryl 3- nitro iso-phthalic acid dihydrazide

The Hydrazine hydrate (0.2 M) was added drop-wise to the solution of iso-phthalic ester in (0.1 M) in 30 ml of dire ethanol with vigorous stirring. The resulting mixture was refluxed for 4-6 hrs. The Excess ethanol was distilled out and the contents were cooled to a room temperature. The progress of the reaction was monitored by TLC petroleum ether, ethyl acetate (1:1) as the eluting solvent and visualized in a UV light. The yellow solid mass formed was filtered, washed thoroughly with brine solution and the resultant dried.

General procedure for the Synthesis of 2, 2'-(5-nitrobenzene-1, 3-diyl) bis (5-alkyl-1, 3, 4-oxadiazole) (2a-e)

A suspension of 5-nitrobenzene-1,3-dicarbohydrazide (1 mmol) and the appropriate long chain fatty acids (2 mmol) in $POCl_3$ (10 ml) was refluxed for 6-8 hrs. The progress of the reaction was monitored on TLC by using silica gel plates using petroleum ether and ethyl acetate (7:3) as the eluting system and visualized in UV light. The reaction mixture allowed cooled to room temperature, slowly poured over crushed ice kept overnight. The solid thus, separated out was neutralized with anhydrous sodium bicarbonate, filtered, washed with water and recrystalized using ethanol. The physical and spectral properties are given below.



Entry	*R*
a	$(CH_2)6CH_3$
b	$(CH_2)8CH_3$
c	$(CH_2)10CH_3$
d	$(CH_2)12CH_3$
e	$(CH_2)14CH_3$
f	$(CH_2)16CH_3$

General procedure for the Synthesis of Potassium dithiocabazinate (4)

Mixture of 5-nitrobenzene-1,3-dicarbohydrazide (1mmol) was added to Ethanolic KOH solution (3 mmol), with constant stirring in 10- 15 ^{0}C.To this, carbon disulfide (5 mmol) was added in small portions with constant stirring. The reaction mixture was agitated continuously for a period of 15 hrs. It was diluted with anhydrous ether. The precipitated potassium dithiocabazinate was collected by filtration. The precipitate was further washed with anhydrous ether (100 ml) and dried under vacuum. The potassium salt, thus obtained was in quantitative yield and was used in the next step without further purification.

General procedure for the Synthesis of 5,5'-(5-nitrobenzene-1,3-diyl)bis(4-amino-4H-1,2,4-triazole-3-thiol) (5)

A suspension of potassium dithiocabazinate of respective aromatic ester (2), (1 mml) in water (5 ml) and hydrazine hydrate (3 mml) was refluxed for 6-8 h with occasional shaking. The color of the reaction mixture changed to green with the evolution of H_2S gas (lead acetate paper and

odor). A homogenous reaction mixture was obtained during the reaction process. The completion of the reaction was monitored by TLC using silica gel plate's ethyl acetate and petroleum ether (1:1) as a eluting solvent and TLC visualized in UV light. The reaction mixture was cooled to room temperature and diluted with water (100 ml). On acidification with concentrated hydrochloric acid, the required triazole was precipitated out. It was filtered, washed thoroughly with cold water and recrystallized from ethanol. Physical data of these compounds summarized in **Table 1.**

RESULTS AND DISCUSSION

Spectral data of synthesized compound
2, 2'-(5-nitrobenzene-1, 3-diyl) bis (5-alkyl-1, 3, 4-oxadiazole) (2a-e)

2a IR (V max, $cm^{-1)}$ = 2849 (C-H), 1630(C=N), 1507 (NO_2), 2921(aliphatic chain), ^1H NMR ($CDCl_3$) (δ ppm) = 0.7(t, 6H, Aliphatic CH_3), 1.2-1.3(br, S, 12H, CH2) 1.36(m, 4H, CH_2) 1.45(m, 4H, CH_2)1.9 (m, 4H, CH_2) 3.0(t, 4H, CH_2) 9.0(d, 2H, Ar-H), 9.03 (t, 1H, Ar-H). MS *m/z* = 457.25 (M^+) ^{13}C NMR ($CDCl_3$) (δ ppm) = 14.6, 23.1, 26.0-32.4 (aliphatic- C) 124.0, 127.4, 130.1, 149.6, (Ar- C), 162.6 (C_5 of oxadiazole), 168.8 (C_2 of oxadiazole

2b IR (V max ,$cm^{-1)}$ = 2849 (C-H), 1630(C=N), 1507 (NO_2), 2921(aliphatic chain) ^1H NMR ($CDCl_3$) (δ ppm) = 0.7(t, 6H, Aliphatic CH_3), 1.2-1.3(br,S,16 H, CH_2) 1.36(m, 4H, CH_2) 1.45(M, 4H, CH_2)1.9 (m, 4H, CH_2) 3.0(t, 4H, CH_2) 9.0(d, 2H, Ar-H), 9.03 (t, 1H, Ar-H). MS *m/z* = 510.37 (M^-)

2c IR (V max ,$cm^{-1)}$ = 2849 (C-H), 1630(C=N), 1507 (NO_2), 2921(aliphatic chain) ^1H NMR ($CDCl_3$) (δ ppm) = 0.7(t, 6H, Aliphatic CH_3), 1.2-1.3(br,S, 32H, CH_2) 1.36(m, 4H, CH_2) 1.45(m, 4H, CH_2)1.9 (m, 4H, CH_2) 3.0(t, 4H, CH_2) 9.0(d, 2H, Ar-H), 9.03 (t, 1H, Ar-H). MS *m/z* = 568.7 (M^+)

2d IR (V max, $cm^{-1)}$ = 2849 (C-H), 1630(C=N), 1507 (NO_2), 2921(aliphatic chain) ^1H NMR ($CDCl_3$) (δ ppm) = 0.7(t, 6H, Aliphatic CH_3), 1.2-1.3(br,S, 44H, CH_2) 1.36(m, 4H, CH_2) 1.45(m, 4H, CH_2)1.9 (m, 4H, CH_2) 3.0(t, 4H, CH_2) 9.0(d, 2H, Ar-H), 9.03 (t, 1H, Ar-H). MS *m/z* = 625.51(M^+)

2e IR (V max, $cm^{-1)}$ = 2849 (C-H), 1630(C=N), 1507 (NO_2), 2921(aliphatic chain) ^1H NMR ($CDCl_3$) (δ ppm) = 0.7(t, 6H, Aliphatic CH_3), 1.2-1.3(br,S, 44H, CH_2) 1.48(m, 4H, CH_2) 1.9 (m, 4H, CH_2) 3.0(t, 4H, CH_2) 9.0(d, 2H, AR-H), 9.03 (t, 1H, Ar-H). MS *m/z* = 680.9 (M^+)

2f IR (V max, $cm^{-1)}$ = 2849 (C-H), 1630(C=N), 1507 (NO_2), 2921(aliphatic chain) ^1H NMR ($CDCl_3$) (δ ppm) = 0.7(t, 6H, Aliphatic CH_3), 1.2-1.3(br,S, 44H, CH_2) 1.36(m, 4H, CH_2) 1.45(M, 4H, CH_2)1.9 (m, 4H, CH_2) 3.0(t, 4H, CH_2) 9.0(d, 2H, AR-H), 9.03 (t, 1H, Ar-H). MS *m/z* = 737.07(M^+)

3 IR (V max, $cm^{-1)}$ = 2849 (C-H), 2852.7 cm^{-1} (SH), 1676 (C=N) ^1H NMR (DMSO – d6) (δ ppm) = 8.5 (t, 1H Ar-H), 8.7(d.2H), (δ ppm) = 13.9 (s,2H,SH) MS *m/z* = 222.0 (M^-) ^{13}C NMR (DMSO) (δ ppm) = 110.6, 114.2, 124.9,151.2 (Ar-C)160.8 (C_5 of oxadiazole), 163.1 (C_2 of oxadiazole)

4 IR (V max,$cm^{-1)}$ = 2849 (C-H), 3291 (NH stretching), 1613 (C]N stretching), 3130 (aromatic CH stretching), 2586 (SH), ^{1}H NMR (DMSO – d6) (δ ppm) = 8.5 (t, 1H Ar-H), 8.7(d.2H Ar-H), 5.5 - 5.7(4H, NH_2),13.9 (s,2H,SH) MS *m/z* = 350.0 (M^-) ^{13}C NMR (DMSO) (δ ppm) = 110.6, 114.2, 124.9,151.2 (Ar-C),160.8 (C_5 of oxadiazole), 163.1 (C_2 of oxadiazole)

Table 1. Physical parameters of newly synthesized compounds.

Compound	R	m.p (^oC)	recrystallizing solvent	Yield (%)	Molecular formula /Molecular wt
2a	$(CH_2)_6CH_3$	58-59	Ethanol /H_20	63	$C_{24}H_{33}N_5O_4$/455.54
2b	$(CH_2)_8CH_3$	64-65	Ethanol /H_20	67	$C_{29}H_{45}N_5O_4$/511.65
2c	$(CH_2)_{10}CH_3$	66-67	Ethanol /H_20	65	$C_{32}H_{49}N_5O_4$/567.76
2d	$(CH_2)_{12}CH_3$	72-74	Ethanol /H_20	60	$C_{36}H_{57}N_5O_4$/623.86
2e	$(CH_2)_{14}CH_3$	76-78	Ethanol /H_20	57	$C_{40}H_{65}N_5O_4$/679.97
2f	$(CH_2)_{16}CH_3$	82-84	Ethanol /H_20	64	$C_{44}H_{73}N_5O_4$/736.08
3	-	242-243	DMF/ H_20	84	$C_{10}H_5N_5OS_2$/323.307
5	-	263-264	DMF/ H_20	63	$C_{10}H_9N_9O_2S_2$/351.36

Pharmacological activity

In vitro antibacterial screening

All the newly synthesized compounds were evaluated for their antimicrobial properties MIC's were recorded as the minimum concentration of compound, which inhibits the growth of tested microorganisms. Antibacterial activities were determined by the well-diffusion method [**22**]. Compounds exhibited moderate to better activity against all bacteria viz., *Pseudomonas aeruginosa* (ATCC-20852), *Klebsiella pneumoniae* (ATCC-618), *Staphylococcus aureus* (ATCC 29737), *Salmonella typhi* (ATCC-19430), *Salmonella paratyphi* (ATCC-9150) and *Escherchia coli* (ATCC-25922). The results revealed that 100 µg of compound in 100 µL of 10% DMF with distilled water v/v was found to be the minimum inhibition concentration at which they showed inhibition of bacteria under study. Compounds 2a–f showed comparatively good activity against all the strains, which is attributed to the presence of groups having inductively electron withdrawing but mesomerically electron donating substituents on phenyl group. It has been observed that compound **3** and **5** having 5, 5'-(5-nitrobenzene-1,3-diyl)bis(1,3,4-oxadiazole-2-thiol) and 5,5'-(5-nitrobenzene-1,3-diyl)bis(4-amino-4*H*-1,2,4-triazole-3-thiol) moiety has have higher antibacterial activity against all the strains, containing parallel polar groups SH and NH_2 [**23**]. In case of compound 3 and 5 has shown very good activity against all the test organisms with NO2 substituent while same substituent in alkyl 1,3,4- oxadiazole system has moderate activity (compound 2a-f). The results are summarized in Table2 and Table 3.

Table 2. Clinical strains Minimal inhibitory concentrations (MIC) of anti bacterial activity

Clinical strains Minimal inhibitory concentrations(MIC)				
Compounds	*Staphylococcus aureus*	*Klebsiella pneumoniae*	*Pseudomonas aureginosa*	*Escherchia coli*
3	**8.5**	**9.0**	**10.00**	**12.00**
5	**7.0**	**9.5**	**8.0**	**9.5**
Ciproflaxin	**5.5**	**6.0**	**5.5**	**5.8**

Table 3 In vitro antibacterial activity of newly synthesized compounds against Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, Salmonella typhi, Salmonella paratyphi and Escherchia coli

	Zone of inhibition (mm)					
Compounds (10µg/ 10 µL)	*Staphylococcus aureus*	*Klebsiella pneumoniae*	*Pseudomonas aureginosa*	*Salmonella typhi*	*Salmonella paratyphi*	*Escherchia coli*
2a	**16**	**14**	**14**	**11**	**15**	**14**
2b	**15**	**11**	**14**	**19**	**17**	**16**
2c	**13**	**09**	**20**	**17**	**14**	**14**
2d	**15**	**15**	**19**	**20**	**17**	**17**
2e	**17**	**16**	**17**	**19**	**14**	**16**
2f	**18**	**17**	**16**	**16**	**16**	**14**
3	**33**	**29**	**26**	**22**	**23**	**26**
5	**35**	**27**	**29**	**24**	**25**	**31**
Ciproflaxin	**44**	**35**	**36**	**34**	**35**	**37**

Antinociceptive activity

Antinociceptive activity of the newly synthesized compounds was carried out using adult Swiss albino mice (6 animals per group) by abdominal constriction method [**24**]. Mice of either sex were housed individually in polypropylene cages with paddy husk as bedding. Animals were maintained at a temperature of 25-27°C and relative humidity of 30-70%. Mice were procured from Virus Diagnostic Laboratory, Shimoga. Five groups of six mice each (25-30 g) was selected and 0.6% acetic acid (dose 10 ml/kg) was injected intraperitoneally. The number of writhes was counted for 20 min after 5 min of injection of acetic acid to each mouse. This reading was taken as control. Next day, the same groups of mice were used for evaluating antinociceptive activity. Each group administered orally with the suspension of test compounds (100 mg/kg body weight) in gum tragacanth (1% w/v) with 1 h early injection of acetic acid. After 5 min, the mice were observed for the number of writhes for the duration of 20 min.

The mean value for each group was calculated and compared with the control. Acetyl salicylic acid was used as a standard for the comparison of antinociceptive activity**.** Percent protection was calculated using the formula $(1-V_c/V_t) \times 100$, where: V_t = Mean number of writhing in test animals, V_c = Mean number of writhing in control. Results expressed the mean ± S.E.M. of 6 animals per group. The data was statistically analyzed by turkey's *t*-test for significance level of $^*P < 0.05$, $^{**} P < 0.01$ as compared to control group. The number of writhing observed during a 20 min period in control group was 71.33 ± 1.91. Compound **3** (18.67 ± 0.71) and Compound **5** (22.17 ± 0.98) showed significant antinociceptive activity than the Compounds belonging to group 2 derivatives. Whereas, Compound **3** showed activity comparable to the standard drug acetyl salicylic acid (14.5 ± 1.26).We also observed that animals treated with Compound **3** and Compound **5** showed delayed onset of writhing (after 35-52 min) when compared to the control (1 min). However, with the animals treated with the Compounds belonging to group 2 in which onset of writhes was observed within 5 min. The results of antinociceptive activity are depicted in Table 4**.**

Table 4. Antinociceptive activity of newly synthesized compounds by abdominal writhing

Compounds	Concentration	No. of writhes	Incubation time
Control(Gum tragacanth	1% w/v	71.33±1.91	1 min
Acetyl salicylic acid	100mg/kg	14.5±1.26 **	69 min
2a	100mg/kg	31.83±1.45**	2 min
2b	100mg/kg	53.33±1.28**	2 min
2c	100mg/kg	49.83±0.79**	3 min
2d	100mg/kg	47.17±0.6**	5 min
2e	100mg/kg	56.33±1.31**	1 min
2f	100mg/kg	53.33±1.05**	1 min
3	100mg/kg	18.67±0.71**	52 min
5	100mg/kg	22.17±0.98**	35 min

Values are the mean ±S.E.M. of six mice. Symbols represent statistical significance.
**P < 0.05, ** P < 0.01 as compared to control group*

Anti-inflammatory activity

All the synthesized compounds were tested for their anti-inflammatory activity using carrageenan induced rat hind paw edema method of Winter et al. [**25**]. Albino rats (Wistar strain) of either sex, weighing between 150 and 200 g, were used for the experiment. Tested compounds showed weak to moderate activity ranging from 6% to 32%, while phenylbutazone, standard Showed 55% of inhibition. The animals were divided into various groups and each group consisting of six animals. One group served as control and received 0.1 ml of 1% gum acacia suspension orally. Group II served as standard and received phenylbutazone at the dose of 100 mg kg^{-1} as suspension in gum acacia orally. One hour after the administration of test compounds at the dose of 100 mg kg–1 as suspension in gum acacia, 0.1 ml of 1% carrageenan in normal saline was given subcutaneously to the sub plantar region of right hind paw. The paw volume was measured immediately (‘0’ h) and after 1–4 h, respectively, by using plethysmometer.

Table 5. Anti-inflammatory activity of compounds (2a-2f, 3,5)

Compound	change in paw value in (mL) after drug treatment (± SEM)			Anti-inflammatory activity (%inhibition)		
	1h	2h	3h	1h	2h	3h
Control	1.76± 0.07	1.92± 0.05	3.31±0.03	-	-	-
Diclofenac	1.96±0.04	2.27±0.04	2.31±0.03	27.96**	47.96**	71.30**
2a	1.76±0.04	2.32±0.06	2.16±0.06	23.87*	36.84**	60.35**
2b	1.98±0.01	2.25 ± 0.04	2.58 ± 0.04	29.11**	50.87**	71.83**
2c	1.48 ± 0.03	1.84 ± 0.03	1.43 ± 0.02	16.64^{ns}	41.35**	60.34**
2d	1.42 ± 0.03	2.00 ± 0.03	2.33 ± 0.05	20.99*	43.09**	68.62**
2e	1.34 ± 0.02	1.97 ± 0.02	2.26 ± 0.02	28.20**	48.78**	69.37**
2f	1.62 ± 0.03	2.00 ± 0.03	2.33 ± 0.05	13.54^{ns}	40.20**	60.99**
3	2.01 ± 0.02	2.32 ± 0.01	2.65 ± 0.01	30.53**	51.72**	80.07**
5	2.02 ± 0.06	2.33 ± 0.06	2.61 ± 0.06	31.38**	46.96**	72.88**

*Data analyzed by one way ANOVA followed by Dunnett’s’ test, (n = 6), *P < 0.05, **P < 0.01 significant from control; ns, not significant.*

The difference between the paw volume at 4th and 0 h measurement was calculated and taken as edema volume. Percentage inhibition in the paw edema was calculated by using the formula, percentage inhibition = 100 (1 – Vt/Vc), where Vt = mean increase in paw

Volume of test, and Vc = mean increase in paw volume of control. All newly synthesized compounds showed potent anti-inflammatory activity. Percentage inhibition shown by tested compounds is recorded in **Table 5**.

Based on findings of these preclinical results, further studies need to be carried out to investigate the other specifications, such as in vitro assays, chronic ulceroge-nicity studies, toxicological studies and mechanism by which these drugs exhibit potential analgesic, anti-inflammatory activity.

CONCLUSION

We report a convenient, economically cheaper and useful method for the synthesis of active molecules possessing anti microbial and antinociceptive property containing a series of 5,5'-(5-nitrobenzene-1,3-diyl)bis(alkyl1,3,4-oxadiazole)**,**derivatives,5,5'-(5-nitrobenzene 1,3diyl)bis (1,3,4-oxadiazole-2-thiol) and 5,5'-(5-nitrobenzene-1,3-diyl)bis(1,3,4-oxadiazole-2-thiol) most of our synthesized compounds showed potent antibacterial and antinociceptive activity. Among all the Compounds tested for antibacterial and antinociceptive activity, the Compound **3** and Compound **5** exhibited potent antinociceptive activity. The remaining test compounds showed significant activity when compared with the standard drug. Hence, it is concluded that, this class of Compounds certainly holds greater promise for discovering safer antimicrobial and antinociceptive agents.

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