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Synthesis and *in vivo* Anti-inflammatory and Analgesic activities of Oxadiazoles clubbed with Benzothiazole nucleus

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ABSTRACT
The aim of the present work is to synthesize and evaluate the anti-inflammatory and analgesic activity of 2-(5-substituted-1,3,4-oxadiazole-2-yl)-1,3-benzathiazole derivatives. In the present investigation, a series of 2-(5-substituted-1,3,4-oxadiazole-2-yl)-1,3-benzathiazole derivatives (**3a$_1$-3a$_9$**) were synthesized by condensing benzothiazolyl carboxyhydrazide and appropriate aryl acids in the presence of phosphorous oxychloride. Structures of synthesized compounds were established on the basis of IR, ^{1}H NMR, and Mass spectroscopy. All the synthesized compounds were screened for their in-vivo anti-inflammatory and analgesic activities at the dose of 50 mg/kg and 10 mg/kg po. The biological result shows that some compounds were good in their anti-inflammatory and analgesic actions.

Key Words: 1,3,4-oxadiazole derivatives, synthesis, aryl acids, anti-inflammatory activity, analgesic activity, spectroscopy.

INTRODUCTION

Benzothiazole is a heterocyclic compound, weak base, having varied biological activities. It is of great scientific interest due to its potential pharmacological and pharmaceutical applications. Benzothiazole and oxadiazole derivatives have been widely researched in bioorganic and medicinal chemistry with applications in drug discovery. Both the nucleuses are well acknowledged to possess a wide range of pharmaceutical, agrochemical, and biological applications. Substituted-oxadiazoles show wide variety of biological activities; anti-inflammatory (Ali *et al.*, 2014) and (Husain and Ajmal, 2009) analgesic (Ali *et al.*, 2010) and (Badiadka *et al.*, 2005) antibacterial (Shridhar *et al.*, Desai *et al.*, 2014, Sahin *et al.*, 2002) antifungal (Oliveira *et al.*, 2013) and anticancer activities (Abu-Zaied *et al.*, 2012 and Valente *et al.*, 2014). Benzothiazole derivatives have also reported to show anti-inflammatory (Abbas *et al.*, 2013 and Patil *et al.*, 2015) analgesic (Sharma *et al.*, 2013 and Sharma *et al.*, 2013a) antifungal (Liu *et al.*, 2013) anticancer (Gurdal *et al.*, 2015) and antimicrobial (Sigmundova *et al.*, 2007 and. Singh *et al.*, 2013) activities. Non-steroidal anti-inflammatory drugs NSAIDs configuration a class of therapeutic agents that are most generally used because of their anti-inflammatory, analgesic and anti-microbial effects.

In view of these observations, it was considered worthwhile to prepare hybrid derivatives of benzothiazole with oxadiazole with an aim to get potential anti-inflammatory and analgesic compounds.

MATERIALS AND METHODS

Experimental

^{1}H NMR (DMSO/$CDCl_3$) was taken on Varian E-360 MHz (Perkin-Elmer, USA) or and Brucker spectrometer DPX-300MHz (Bruker, Germany). Mass Spectra was taken on LCMS Shimadzu Spectrophotometer. From open capillary tubes the melting point was determined and all are uncorrected. All the compounds have presented satisfactory chemical analysis. All solvents were distilled previous to use.

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General Method for the synthesis of Ethyl-2-benzothiazole carboxylate (I)

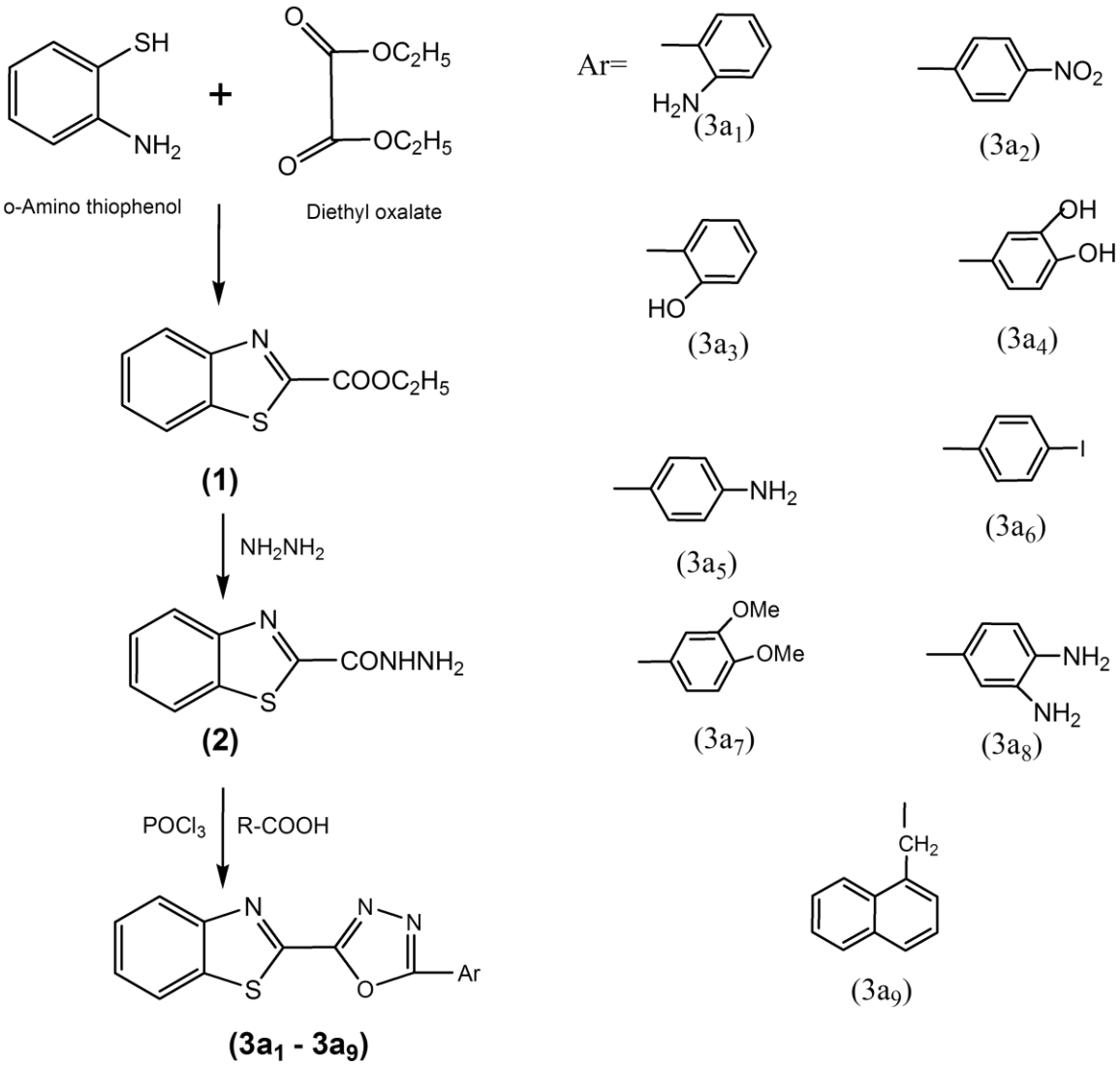
A mixture of o-aminothiophenol (0.1 mol) and diethyl oxalate (0.2 mol) upon heating on reflux for 5 hours, during experiment the temperature was decreased from 146 to 92°C. After cooling, the mixture was added into a solution of 50 ml of conc. HCl, 150 ml of water and 70 ml of ethanol with stirring, the oil dissolved and a solid formed. The mixture was cooled; the product was filtered and washed with aq. ethanol then dried and finally recrystallized from pet ether.

General Method for the synthesis of 1, 3-benzothiazole-2-carboxyhydrazide (II)

In a dry 100 ml round bottomed flask (RBF) the ethyl-2-benzothiazole carboxylate **(I)** (0.01 mole) was dissolved in ethanol (60ml). The hydrazine hydrate (0.02 mole) (99%) was added drop by drop with constant stirring and the contents were refluxed for 8 hrs, cooled at room temperature. The solid separated was filtered and washed with water and dried, and finally recrystallized from ethanol.

General Method for the synthesis of 2-(5-substituted-1,3,4-oxadiazole-2-yl)-1,3-benzothiazole (3a$_1$-a$_9$)

A mixture of 1,3-benzothiazole-2-carboxyhydrazide (II) (0.01 mol), suitable aromatic acid (0.02 mol) and phosphoryl chloride (10 ml) was refluxed on steam bath for 5-6 hours. After standing at room temperature it was added into the crushed ice with continuous stirring. The solid crystals obtained, were filtered, washed with water and recrystallized from ethanol to obtain final compound (3a$_1$-3a$_9$). The physicochemical parameters of these compounds are presented in **table 1** and synthesis pathway of resulted compounds is given in **Scheme 1.**



Scheme 1: Synthesis pathway of all resultant compounds (3a1-3a9).

Pharmacology

The animals used in the examination were sheltered in congruence of the Vivek College of Technical education Unit, which follows the guidelines and regulation set by the committee for the control and administration of experiments on animals (CPCSEA), Ministry of social justice and empowerment, Government of India. The studies were attempted with previous approval from the Institutional Animal Ethics committee (IAEC) and ultimate care was taken to establish that the animals were handling in the most kind and satisfactory manner. Wistar rats and albino mice of either sex (Vivek College of Technical education, India), weighing 150-200 gm and 20-25 gm, respectively, were used. Pregnant females were eliminated.

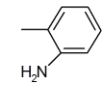
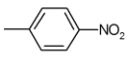
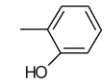
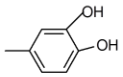
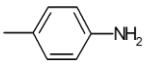
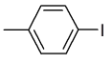
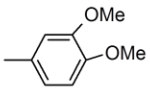
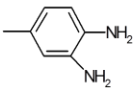
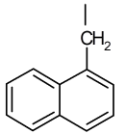
Anti-inflammatory Activity

Anti-inflammatory activity was carried on the Wistar rats (Winter *et al.*, 1968). The animals were divided into 6 groups each having six animals. Albino rats of either sex weighing 150-200 gm were selected. They were maintained on standard pellet diet and free access to water. The normal control, Diclofenac and test compounds were administered to the rats 30 minutes before the injection of 0.1ml of 1% carrageenan suspension in normal saline. Carrageenan suspension was injected into the sub-planar region of the left hind paw, and the right hind paw served as reference. Immediately thereafter the oedema volume of the injected paws was measured plethysmographically. Anti-inflammatory activity was carried out by (Roy *et al.*, 1980) mercury displacement method.

Analgesic Activity

The compounds that display good anti-inflammatory active (>50%) were protected for analgesic activity. Analgesic activity was carried out by Eddy's hot plate mathod (Kulkarni, 1999). Six groups of albino mice of either sex each comprising of four animals, weighing between 20-25 gms were deprived of food and water for 18hrs prior to the experiment. The animal with a basal reaction time of less than 8 seconds were considered for the study. The hot plate was stabilized at 55±1°C, the animals are placed on the hot plate and the time until either licking or jumping response with the animals is

Table 1: Characterization of the synthesized compounds.

Compound number	R	M.p. (°C)	Yield (%)	Mol Formula/ Mol. Mass	Spectral Data		
					IR (KBr) (v, cm-1)	^{1}H NMR (CDCl$_3$, DMSO, δ, ppm)	Mass Spectra (m/z)
3a1		160-162	69	$C_{15}H_{10}N_4OS$ (294)	3055 (C-H) 3310 (N-H)	6.12-7.23 (m, 8H, Ar-H) 3.93 (s, 2H, -NH$_2$)	294 (M+)
3a2		240-242	65	$C_{15}H_8N_4O_3S$ (324)	3025 (C-H) 1315 (-NO$_2$)	6.23-8.11 (m, 8H, Ar-H)	nr
3a3		242-244	63	$C_{15}H_9N_3O_2S$ (295)	3010 (C-H) 3100 (-OH)	6.12-7.81 (m, 8H, Ar-H), 9.27 (s, 1H, -OH)	295 (M+)
3a4		170-174	74	$C_{15}H_9N_3O_3S$ (311)	3020 (C-H) 3210 (-OH)	6.93-7.46 (m, 7H, Ar-H), 9.28 (s, 2H, -OH)	nr
3a5		210-212	71	$C_{15}H_{10}N_4OS$ (294)	3055 (C-H) 3410 (-NH$_2$)	6.31-7.58 (m, Ar-8H, Ar-H) 3.94 (s, 1H, -NH$_2$)	294 (M+)
3a6		180-182	70	$C_{15}H_8IN_3OS$ (405)	3045 (C-H) 1325 (-I)	6.11-7.64 (m, Ar-8H ,Ar-H)	nr
3a7		178-180	67	$C_{17}H_{13}N_3O_3S$ (339)	3110 (C-H) 2850 (C-H, ali)	6.24-7.35 (m, 7H, Ar-H), 1.28-2.0835 (m, 6H, -CH$_3$)	nr
3a8		100-104	72	$C_{15}H_{11}N_5OS$ (309)	3130 (C-H) 3490 (-NH$_2$)	6.81-7.94 (m, 7H, Ar-H), 3.84-4.26 (m, 4H, -NH$_2$)	309 (M+)
3a9		106-110	51	$C_{20}H_{13}N_3OS$ (343)	3052 (C-H) 2872 (C-H, ali)	6.13-7.78 (m, 11H, Ar-H), 1.84 (s, 2H, -CH$_2$)	nr

S - singlet, d - doublet, t - triplet, q - quarter, m - multiplet, nr - not recorded

recorded by a stopwatch, the time taken as the end point. The reaction time was recorded at prefixed time interval *i.e.*, 0, 20, 40, 60, 80, 100 and 120 minutes following oral or subcutaneous administration of the standard or the test compound.

Statistical analysis

The animal experimental data were indicated as mean±SEM. Statistical characteristic between the treatments and the standard were approved by one-way ANOVA pursue by Dunnett's multiple comparison test.

RESULTS AND DISCUSSION

The synthetic compounds (**3a$_1$ - 3a$_9$**) were designed for the benzothiazole analogues and has been accomplished starting from the Ethyl-2-benzothiazole carboxylate (I) which was dissolve in ethanol, hydrazine hydrate was added drop by drop with constant stirring and the contents were refluxed for 8 hrs, cooled at room temperature. The solid of 1,3-benzothiazole-2-carboxyhydrazide (II) was separated. To it suitable aromatic acid and phosphoryl chloride (10 ml) was added and refluxed on steam bath for 5-6 hours. After standing at room temperature it was added into the crushed ice with continuous stirring. The solid crystals obtained, were filtered, washed with water and recrystallized from ethanol to obtain final compounds (**3a$_1$-3a$_9$**).

All final compounds were pure and well balanced. The structure elucidation was proved by IR, NMR and Mass spectroscopy. IR spectral peaks of the final compounds were accepted from 3375-3200 cm^{-1} for N-H stretching, 3000-3200 cm^{-1} for NH$_2$, 3075-2850 cm^{-1} for C-H aliphatic and aromatic, 3200-3325 cm^{-1} for -OH and 1300-1400 cm^{-1} for NO$_2$, respectively **(table 1).** In ^{1}HNMR spectra typical proton signals for C-H aliphatic and aromatic were found near 2.36-3.68, 8.06-6.30 δ ppm. Mass spectra chanced correct molecular ion peaks.

Compounds (3a$_1$-3a$_9$) were assessing for their in *vivo* anti-inflammatory activity by the carrageen an induced rat paw edema method. The compounds were assessing at an oral dose 200 mg/kg and differentiate with the standard drug Diclofenac Sodium. All the compounds showed good anti-inflammatory activities were tested for analgesic activity. All compounds were assessing at 10 mg/kg dose as a standard drug Pentazocin. Examination of the results showed that the compound having 1, 3-benzothiazole-2-carboxyhydrazide substitution at the 5th position of oxadiazole ring display outstanding analgesic activity **(table 2)**.

Table 2: Data showing anti-inflammatory activity of benzothiazole derivatives (3a1-a9) in (Carrageenan induced acute rat paw oedema model).

Gp.	Treatment	Dose mg/kg	Paw oedema volume							
			After 1st hour		After 2nd hour		After 3rd hour		After 4th hour	
			Mean/±SEM	% ROV	Mean/±SEM	% ROV	Mean/±SEM	% ROV	Mean/±SEM	% ROV
1	Control	1.5 ml	0.70±0.025	-	0.76±0.006	-	0.61±0.026	-	0.84±0.015	-
2	Standard	50	0.25±0.018	64.28	0.20±0.009	73.60	0.15±0.009	74.09	0.15±0.014	82.14
3	3a1	200	0.25±0.023	64.28	0.21±0.009	72.36	0.15±0.010	75.40	0.20±0.010	76.19
4	3a2	200	0.30±0.014	57.14	0.25±0.015	67.10	0.17±0.009	71.31	0.15±0.010	81.91
5	3a3	200	0.31±0.012	55.71	0.29±0.012	61.84	0.23±0.009	62.29	0.25±0.023	69.28
6	3a4	200	0.30±0.020	56.00	0.25±0.023	66.05	0.20±0.012	67.20	0.16±0.014	80.23
7	3a5	200	0.33±0.009	52.42	0.28±0.018	62.76	0.22±0.009	63.11	0.17±0.014	79.16
8	3a6	200	0.30±0.023	56.00	0.25±0.022	66.05	0.20±0.007	67.20	0.16±0.007	80.23
9	3a7	200	0.31±0.016	55.71	0.28±0.011	62.72	0.21±0.009	66.22	0.23±0.009	70.50
10	3a8	200	0.30±0.020	57.14	0.25±0.018	67.10	0.16±0.020	73.32	0.15±0.009	81.54
11	3a9	200	0.32±0.018	51.12	0.28±0.023	61.70	0.23±0.009	66.80	0.18±0.014	79.08

Animals: Albino rat, Route: P.O, Dose: 20, 25 mg/kg for anti-inflammatory activity. Mean ± SEM, n = 4

Table 3: Data showing analgesic activity of benzothiazole derivatives (3a1-3a9).

Treatment	No. of mice	Avg. wt. (g)	Average Dose (mg)	Basal reaction time (sec.) after						
				0 min	20 min	40 min	60 min	80 min	100 min	120 min
Control (gum acacia)	4	22	-	3.9±0.367	4.12±0.473	4.12±0.553	4.22±0.503	4.27±0.324	3.88±0.372	5.20±0.647
Standard(Pentazocin (10 mg/kg)	4	23.6	0.236	6.53±0.889	12.87±1.332	12.91±1.320	13.87±0.279	13.65±0.851	11.83±1.042	12.33±0.918
Compound(3a1)	4	24.33	2.433	3.36±0.521	4.2±0.351	10.16±1.837	9.53±1.080	12.273±1.093	11.326±1.374	11.18±1.955
Compound(3a2)	4	22.33	2.233	3.433±0.212	13.373±0.521	13.073±1.219	11.866±1.611	14.493±0.320	13.24±1.111	10.39±0.610
Compound(3a3)	4	25	2.5	4.093±0.239	4.26±0.130	12.976±0.645	12.243±0.850	11.136±1.145	10.116±1.520	9.146±0.938
Compound(3a4)	4	26	2.6	4.116±0.748	12.47±1.600	11.903±1.498	13.23±0.202	12.446±1.176	10.986±0.516	11.663±0.757
Compound(3a5)	4	20.66	2.066	5.156±0.299	7.106±0.431	12.203±0.866	14.55±0.284	12.991±0.938	14.793±0.130	13.2±1.138
Compound(3a6)	4	23.33	2.333	3.836±0.202	6.066±0.368	7.31±0.719	10.59±0.628	12.76±0.774	14.04±0.450	13.42±0.912
Compound(3a7)	4	24.33	2.433	4.977±0.540	5.497±0.417	10.990±1.075	13.063±0.897	13.607±0.881	13.693±0.826	12.093±1.143
Compound(3a8)	4	24.33	2.433	3.36±0.521	4.2±0.351	10.16±1.837	9.53±1.080	12.273±1.093	11.326±1.374	11.18±1.955
Compound(3a9)	4	26	2.6	4.116±0.748	12.47±1.600	11.903±1.498	13.23±0.202	12.446±1.176	10.986±0.516	11.663±0.757

Dose: 20, 25 mg/kg for analgesic activity. Mean ± SEM, n = 4

Biological Studies

From the literature survey it reveals that novel benzothiazole have been reported for number of pharmacological activities and some molecules have shown significant activities and some compounds shows moderate and good activities. Here we have synthesized some novel benzothiazole analogues and screened them for their anti-inflammatory and analgesic activities. All compounds at dose of 200 mg/ kg exhibited significant anti-inflammatory activity in acute inflammatory models in rats. Results are tabulated in **table 3**. Compounds $3a_1$, $3a_2$, $3a_3$, $3a_4$, $3a_5$, $3a_6$, $3a_7$, $3a_8$, and $3a_9$ exhibited maximum inhibition with 76.19%, 81.91%, 69.28%, 80.23%, 79.16%, 80.23%, 70.50%, 81.54% and 79.08%, respectively, whereas standard Diclofenac Sodium showed reduction in oedema volume by 82.14% in carrageenan induced rat hind paw oedema model. The synthesized compounds have shown a significant Analgesic activity. Results are tabulated in **table 3**. The compounds $3a_5$ and $3a_7$ have shown potent Analgesic activity. The compounds $3a_3$, $3a_4$, $3a_9$ showed a moderate analgesic activity. The other compound $3a_1$ and $3a_2$ and $3a_6$ also showed a significant analgesic activity till 120 minutes.

CONCLUSION

From the above result it has been concluded that a series of nine compounds were prepared by reacting substituted Ethyl-2-benzothiazole carboxylate and 3-benzothiazole-2-carboxyhydrazide to form 2-(5-substituted-1,3,4-oxadiazole-2-yl)-1,3-benzothiazole derivatives. Adopting easy and useful method and characterized by TLC, M.P and spectral analysis. Synthesized compounds were screened for their *in vivo* anti-inflammatory and Analgesic activities. Compounds $3a_2$, $3a_4$, $3a_6$, $3a_8$, showed potent anti-inflammatory activity and the compounds $3a_5$, $3a_7$ has shown potent Analgesic activity.

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