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DESIGN, SYNTHESIS AND PHARMACOLOGICAL SCREENING OF 2-(2-(BENZO [D] OXAZOL-2-YL) PHENYLAMINO)-N-(SUBSTITUTED PHENYL) ACETAMIDES AS ANTI-INFLAMMATORY AND ANALGESIC AGENTS

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ABSTRACT

The endeavor of this study was to design, synthesize and investigate the *in vivo* anti-inflammatory and analgesic activity of some novel 2-(2-(benzo[d]oxazol-2-yl) phenylamino)-N-(substituted phenyl) acetamide (2A-2F) derivatives. 2-(2-aminophenyl) benzoxazole (D1) was synthesized by the condensation of anthranilic acid with starting material 2-aminophenol in the existence of poly phosphoric acid. A separate route was followed to obtain substituted chloroacetanilides (A1-A6) by the reaction of substituted anilines with chloroacetyl chloride. Finally title compounds were obtained by fusion of 2-(2-aminophenyl) benzoxazole (D1) and substituted chloroacetanilides (A1-A6). The newly synthesized compounds were characterized by IR, NMR and Mass spectral data. The title compounds were evaluated for *in vivo* anti-inflammatory and analgesic activities by carrageenan induced paw edema and acetic acid induced writhing method respectively. A few of the synthesized compounds manifest promising activity when compared to standard drug diclofenac sodium.

Keywords: 2-(2-aminophenyl) benzoxazole, Heterocyclic, Acetanilides, Anti-inflammatory, Analgesic

1. INTRODUCTION

Benz fused azoles are an important class of molecules and are a common heterocyclic scaffold in biologically active and medicinally significant compounds [1]. Benzoxazoles are found in a variety of natural products and are important targets in drug discovery. During recent years there have been some interesting developments in the pharmacology of benzoxazole derivatives [2].

The substituted benzoxazoles have been shown to exhibit antitumor [3], antioxidant, antihelmintic [4], cyclooxygenase inhibitory [5], antifungal [6], antitubercular [7], $5HT_3$ receptor antagonists [8], anti-inflammatory, analgesic & cyclin dependent kinase inhibitory [9], 5-lipoxygenase inhibitory [10], melatonin receptor agonist [11], anticancer [12], antibacterial [13] and anti-HIV-1 [14] activities.

Since benzoxazole derivatives are the isosters of naturally occurring nucleotides, they easily interact with the biopolymers of the living system. As a consequence of this feature, benzoxazole derivatives which have multiple biological activities have been known for a long time.

2-substituted benzoxazole were prominently studied trusting this position is decisive for the biological activity and for the same reason 2-(2-aminophenyl) benzoxazole was selected as a target compound in this research.

There are two general methods for synthesizing 2-substituted benzoxazoles. One is the coupling of 2-amino phenols with carboxylic acid derivatives, which is either catalyzed by strong acids [15] or requires microwave conditions [16]. The other is the oxidative cyclization of Phenolic Schiff bases derived from the condensation of 2-aminophenols and aldehydes. In the latter reactions, various oxidants such as $BaMnO_4$ [17], NiO_2 [18] and Pb-$(OAc)_4$ [19] have been used. However, all of these oxidants are required in stoichiometric or excess amounts relative to their respective substrates. Therefore, a more effective process is needed.

Herein we report a simple method for synthesis of benzoxazole derivatives from reaction of 2-aminophenol with anthranilic acid and their subsequent condensation with substituted acetanilides for the development of novel analgesic and anti-inflammatory agents.

2. MATERIAL AND METHODS

All melting points were determined in open capillaries and are uncorrected. The progress of the reaction and the purity of compounds were checked by TLC on percolated silica gel plates using n-Hexane, ethyl acetate, chloroform & benzene in different ratio as mobile phase. Detection of compounds was made by treatment with iodine vapours. IR spectra of compounds were recorded on FTIR 4100 type A spectrophotometer and HNMR spectra (DMSO) on Bruker FTAC spectrometer with TMS as internal standard.

2.1. Reaction Scheme

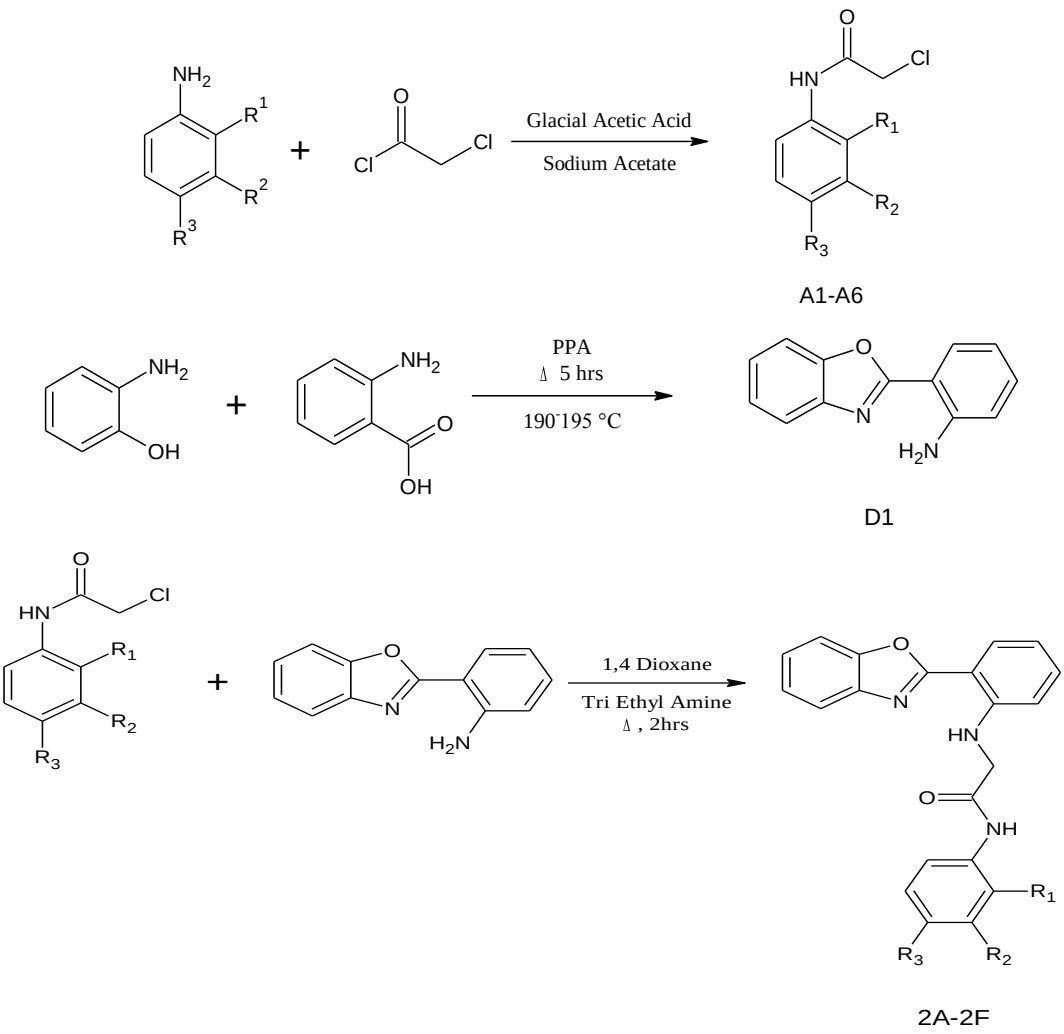

Table 1: Substitution of compounds

Compound code	R_1	R_2	R_3	Derivative's name
2A	H	H	Br	2-(2-(benzo[d]oxazol-2-yl)phenylamino)-N-(4-bromophenyl) acetamide
2B	H	H	Cl	2-(2-(benzo[d]oxazol-2-yl)phenylamino)-N-(4-chlorophenyl) acetamide
2C	Cl	H	Cl	2-(2-(benzo[d]oxazol-2-yl)phenylamino)-N-(2,4-dichloro phenyl) acetamide
2D	H	Cl	H	2-(2-(benzo[d]oxazol-2-yl)phenylamino)-N-(3-chlorophenyl) acetamide
2E	H	NO_2	H	2-(2-(benzo[d]oxazol-2-yl)phenylamino)-N-(3-nitrophenyl) acetamide
2F	H	H	H	2-(2-(benzo[d]oxazol-2-yl)phenylamino)-N-phenylacetamide

2.2. Synthesis of substituted chloroacetanilides (A1-A6)

Substituted aniline (0.1mole) was dissolved in 50ml of glacial acetic acid containing 50ml of saturated solution of sodium acetate. In case the substance did not dissolve completely, the mixture was warmed. The solution was cooled in ice bath with stirring. To this stirred solution, about 1 ml of 2-chloroacetyl chloride was added drop wise so that the vigorous reaction could not take place. After half an hour, the white product formed was separated by filtration through whatman filter paper. The solid precipitate was washed with distilled water, dried and recrystallized from aqueous alcohol [20].

2.3. Synthesis of 2-(2-aminophenyl) benzoxazole (D1)

Equimolar quantities (0.1 mole) of 2-aminophenol and anthranilic acid were refluxed in poly phosphoric acid at 190°-195°C for 4 hrs. The completion of reaction was checked by thin layer chromatography (TLC) using benzene: chloroform

(2:3) solvent system as mobile phase and iodine vapour as developing agent. The reaction mixture was poured into crushed ice, with vigorous stirring. Filtered, washed with cold water, dried and recrystalized from ethanol [21].

2.4. Synthesis of 2-(2-(benzo[d]oxazol-2-yl)phenyl-amino)-N-(substituted phenyl)acetamides (2A-2F)

Equimolar quantities (0.1mole) of compound 2-(2-aminophenyl) benzoxazole (D1) and substituted chloroacetanilide (A_1-A_6) were mixed in 25 ml of 1, 4-dioxane. To this 0.001 ml of triethylamine (TEA) was added and the reaction mixture was refluxed for 2 hours. The completion of reaction was checked by TLC using ethyl acetate: n-hexane (1:3) solvent system in iodine vapour. It was then cooled and poured into crushed ice. The solid product thus obtained was filtered, washed with 1% potassium bicarbonate followed by distilled water, dried & recrystallized with ethanol [20].

2.5. Biological Activity

The synthesized derivatives were evaluated for anti-inflammatory activity using Carrageenan induced hind paw oedema and analgesic activity was determined by acetic acid induced writhing method in mice.

2.5.1. Determination of Acute Toxicity

The acute toxicity of synthesized derivatives was determined by using male wistar strain rats (200-250gm) and albino mice (25-30 g) maintained under standard experimental conditions and divided into three groups of six animals each.
The animals were fasted overnight prior to the experiment and acute oral toxicity (as per OECD guideline no.423) was determined.

Animals were administered with different doses (50 mg/kg, 100 mg /kg and 250 mg/kg, 500 mg/kg and 1000mg/kg) of test compounds and observed individually & critically for a period of 14 days at every pre-determined fragment of time. During this period the mortality and/or the moribund status of the animal were noted.

2.5.2. Anti-inflammatory Study

Male wistar rats, weighing about 200-250 gm were used for the study. All animals were kept and maintained under laboratory conditions of temperature (22±2°C) & humidity (45±5°C) as per CPCSEA guidelines. Animals were allowed free access to standard pellet diet and water *ad libitum*. The study was approved by Institutional Animal Ethical Committee of Teerthanker Mahaveer College of Pharmacy, Moradabad, India.

The anti-inflammatory evaluations were performed using carrageenan induced hind paw oedema in male wistar rats. The animals were divided into eight groups as per the description below and were fasted for a period of 24 h prior to the study.

Group 1: Control
Group 2; Standard reference
Group 3-8: Test

Group 1 was treated as control and received 1% CMC in normal saline orally; Group 2 received diclofenac sodium (50mg/kg/ml) suspended in 1% carboxymethyl cellulose (orally) and Group 3-8 were treated with 100 mg/kg of synthesized derivatives suspended in carboxymethyl cellulose. Edema was induced by injecting 0.1 ml of a 1% solution of carragenan in saline into the subplantar region of the right hind paw of the rats. The vehicle, synthesized derivatives and the standard drugs were administered 60 min before carragenan injection. The volumes of oedema were measured at 1, 2, 3 & 4^{th} hr time duration using a plethysmometer to calculate the percentage of paw edema inhibition.

The percent inhibition was calculated using the relation, % inhibition = 1-(Vt /Vc)×100, where, vt and vc are the mean relative changes in the volume of paw edema in the test and control, respectively.

2.5.3. Analgesic Activity

The analgesic activity was determined by acetic acid induced writhing method-using wistar albino mice (n = 6) of either sex selected by random sampling technique (25-30 g). Diclofenac sodium at a dose level of 25 mg/kg served as standard drug for comparison. The negative control received solvent only (1% CMC). The test compounds at 100 mg/kg (suspended in 1% CMC) were administered orally 30 min prior to intraperitoneal administration of the writhing agent (0.6 % v/v aqueous acetic acid–1ml/100g). The writhing produced in the animal was observed for 20 minutes and the percentage protection was calculated by following formula for analgesic activity.

$$\% \text{ Protection} = 1-(Vt/Vc)\times 100$$

Where, Vt and Vc are the mean writhings in the test and control, respectively.

2.5.4. Statistical Analysis

The results were presented as mean ± SEM of six observations. One way analysis of variance (ANOVA) followed by Dunnett's *t*-test for multiple comparisons were used for statistical evaluation. p value ($p < 0.05$) was considered as significant.

3. RESULTS AND DISCUSSION

Substituted chloroacetanilides (A_1-A_6) were prepared by suitably substituted aromatic amine and chloroacetyl chloride in glacial acetic acid, as catalyst. 2-(2-aminophenyl) benzoxazole (D1) was synthesized according to illustrated procedure [22] and was used as preparatory material**.** It was reacted with substituted α-chloro acetanilides (A_1-A_6) in the existence of dioxane and Tri ethyl amine (TEA) as catalyst to attain the title compounds *i.e.* 2-(2-(benzo [d] oxazol-2-yl)

phenylamino)-n-(substituted phenyl) acetamides (2A-2F). All the synthesized compounds were obtained in adequate yield. The structures of the synthesized compounds were assigned on the bases of their spectral data and elemental analysis.

2-(2-aminophenyl) benzoxazole (D1):

Compound D1 was found as Reddish brown solid. Yield = 69%, mp 115-120°C. IR (KBr, cm^{-1}) υ; 1420 (Ar.C=C Str.); 3060(Ar.C-H Str.); 753 (Ar.C-H bend $_{out\ plane}$); 1152 (Ar.C-H bend $_{in\ plane}$); 1302 (Ar. C-N Str.); 1589 (Ar. C=N Str.); 1753 (Ar. C-O Str.); 3374 (Ali. 1° N-H Str.). ^{1}H NMR (400.13 MHz, DMSO) δ; 7.2057- 7.7392 (5H, m, Ar.H), 6.5177, 6.6812, 6.7392 (3H, s, Ar.H), 4.4257- 4.4976 (2H, d, Ali NH_2). Anal. for $C_{13}H_{10}N_2O$, Calcd (%) C C, 74.27; H, 4.79; N, 13.33; O, 7.61%, Found C, 74.25; H, 4.77; N, 13.31; O, 7.59%.

2-(2-(benzo[d]oxazol-2-yl)phenylamino)-N-(4-bromo phenyl) acetamide (2A):

Compound 2A was found as light brown solid. Yield = 63%, mp 150-160°C. IR (KBr, cm^{-1}) υ; 1485 (Ar.C=C Str.); 3089 (Ar.C-H Str.); 741 (Ar.C-H bend $_{out\ plane}$); 1152 (Ar.C-H bend $_{in\ plane}$); 1320 (Ar. C-N Str.); 1614 (Ar. C=N Str.); 1740 (Ar. C-O Str.); 1550 (Ali. C=O Str.); 3370 (Ar. 2° N-H Str.); 2825 (Ali.C-H Str.); 531(Ar. C-Br. Str.). ^{1}H NMR (400.13 MHz, DMSO) δ; 7.29 (s, 5H, ArH), 7.53 (d, 2H, CH), 7.41 (m, 2H, Ar-H), 6.64-6.69 (m, 2H, Ar-H), 4.13 (d, 3H CH_2NH), 8.0 (s, 1H, NH). Anal. for $C_{21}H_{16}BrN_3O$, Calcd (%) C, 59.73; H, 3.82; Br, 18.92; N, 9.95; O, 7.58%, Found C, 59.70; H, 3.79; Br, 18.89; N, 9.92; O, 7.55%

2-(2-(benzo[d]oxazol-2-yl)phenylamino)-N-(4-chloro phenyl) acetamide (2B):

Compound 2B was found as reddish brown solid. Yield = 62%, mp 135-140°C. IR (KBr, cm^{-1}) υ; 1499 (Ar. C=C Str.); 3078 (Ar. C-H Str.); 821 (Ar.C-H bend $_{out\ plane}$); 1243 (Ar.C-H bend $_{in\ plane}$); 1282 (Ar. C-N Str.); 1590 (Ar. C=N Str.); 1755 (Ar. C-O Str.); 1544 (Ali. C=O Str.); 3299 (Ar. 2° N-H Str.); 2952 (Ali.C-H Str.); 1042 (Ar. C-Cl. Str.). ^{1}H NMR (400.13 MHz, DMSO) δ; 7.26 (s, 5H, C_6H_5), 7.25 (m, 2H, p-Cl Ar-H), 6.64-6.49 (d, 2H, ArH) 4.23 (d, 3H, CH_2NH) 8.23 (s, 1H, NH). Anal. for $C_{21}H_{16}ClN_3O_2$, Calcd (%)C, 66.76; H, 4.27; Cl, 9.38; N, 11.12; O, 8.47%, Found C, 66.72; H, 4.23; Cl, 9.34; N, 11.10; O, 8.44%.

2-(2-(benzo[d]oxazol-2-yl)phenylamino)-N-(2,4-di chlorophenyl) acetamide (2C):

Compound 2C was found as reddish brown solid. Yield = 65%, mp 82-85°C. IR (KBr, cm^{-1}) υ; 1508 (Ar.C=C Str.); 3046 (Ar.C-H Str.); 753 (Ar.C-H bend $_{out\ plane}$); 1254 (Ar.C-H bend $_{in\ plane}$); 1272 (Ar. C-N Str.); 1601 (Ar. C=N Str.); 1725 (Ar. C-O Str.); 1664 (Ali. C=O Str.); 3266 (Ar. 2° N-H Str.) 2952 (Ali.C-H Str.); 1089 (Ar. C-Cl. Str.). ^{1}H NMR (400.13 MHz, DMSO) δ; 7.32-7.37 (m, 5H, C_6H_5), 6.69-6.72 (d, 2H, ArH), 7.13 (s, 1H, p-Cl), 7.26 (s, 1H, O-Cl), 4.12 (s, 3H, CH_2NH), 8.32 (s, 1H, NH). Anal. for $C_{21}H_{15}Cl_2N_3O_2$, Calcd (%)C, 61.18; H, 3.67; Cl, 17.20; N, 10.19; O, 7.76%, Found C, 61.14; H, 3.64; Cl, 17.18; N, 10.18; O, 7.75%.

2-(2-(benzo[d]oxazol-2-yl)phenylamino)-N-(3-chloro phenyl) acetamide (2D):

Compound 2D was found as reddish brown solid. Yield = 64%, mp 80-85°C. IR (KBr, cm^{-1}) υ; 1507 (Ar.C=C Str.); 3045 (Ar C-H Str.); 753 (Ar.C-H bend $_{out\ plane}$); 1230 (Ar.C-H bend $_{in\ plane}$); 1299 (Ar. C-N Str.); 1582 (Ar. C=N Str.); 1702 (Ar. C-O Str.); 1633 (Ali. C=O Str.); 3350 (Ar. 2° N-H Str.) 2870 (Ali.C-H Str.); 1096 (Ar. C-Cl. Str.). ^{1}H NMR (400.13 MHz, DMSO) δ; 8.1104, 7.6054, 7.3046, 6.7778, 6.5540 (5H, s, Ar.H); 7.0475-7.0854 (2H, d, Ar.H); 4.0089-4.2089 (2H, d, Ar.NH); 7.4556-7.2431(6H, m, Ar.H). Anal. for $C_{21}H_{16}ClN_3O_2$, Calcd (%)C, 66.76; H, 4.27; Cl, 9.38; N, 11.12; O, 8.47%, Found C, 66.73; H, 4.25; Cl, 9.35; N, 11.11; O, 8.44%.

2-(2-(benzo[d]oxazol-2-yl)phenylamino)-N-(3-nitro-phenyl) acetamide (2E):

Compound 2E was found as reddish brown solid. Yield = 63%, mp 150-155°C. IR (KBr, cm^{-1}) υ; 1507 (Ar.C=C Str.); 3045 (Ar C-H Str.); 753 (Ar.C-H bend $_{out\ plane}$); 1230 (Ar.C-H bend $_{in\ plane}$); 1299 (Ar. C-N Str.); 1582 (Ar. C=N Str.); 1702 (Ar. C-O Str.); 1633 (Ali. C=O Str.); 3350 (Ar. 2° N-H Str.) 2870 (Ali.C-H Str.); 1096 (Ar. C-Cl. Str.). ^{1}H NMR (400.13 MHz, DMSO) δ; 8.6692, 7.227, 6.6586, 6.5272 (4H, s, Ar.H); 7.824-7.2272 (8H, m, Ar.H); 4.9089-4.9557 (2H, d, Ar.NH). Anal. for $C_{21}H_{16}ClN_3O_2$, Calcd (%)C, 64.94; H, 4.15; N, 14.43; O, 16.48%, Found C, 64.92; H, 4.14; N, 14.40; O, 16.46%.

2-(2-(benzo[d]oxazol-2-yl)phenylamino)-N-phenyl acetamide (2F):

Compound 2F was found as reddish brown solid. Yield = 65%, mp 146-150°C. IR (KBr, cm^{-1}) υ; 1520 (Ar.C=C Str.); 3051 (Ar. C-H Str.); 805 (Ar.C-H bend $_{out\ plane}$); 1176 (Ar.C-H bend $_{in\ plane}$); 1297 (Ar.C-N Str.); 1593, 1606 (Ar.C=N Str.); 1737 (Ar.C-O Str.); 1770 (Ali.C=O Str.); 3360 (Ar.2° N-H Str.); 2886 (Ali.C-H Str.). ^{1}H NMR (400.13 MHz, DMSO) δ; 7.21-7.64 (9H, ArH), 6.64-6.69 (d, 2H, Ar NH), 4.29-4.32 (d, 3H, CH_2NH). Anal. for $C_{21}H_{16}ClN_3O_2$, Calcd (%) C, 73.45; H, 4.99; N, 12.24; O, 9.32%, Found C, 73.42; H, 4.97; N, 12.23; O, 9.30%.

In the IR spectra of 2-(2-aminophenyl) benzoxazole (D1), occurrence of absorption band at 1302 cm^{-1} and at 3374 cm^{-1} strappingly recommended the existence of C-N and NH group respectively in the molecule, while the bands at 1420-1589cm^{-1} recommended the company of C=C and C=N ring stretching respectively. Other significant peaks were observed at 1753 cm^{-1} for C-O and 3060 cm^{-1} for C-H stretching bands.

Table2: Anti-inflammatory activity of benzoxazole derivatives

S.No.	Group	Change in paw volume (ml) Mean±SEM				% Inhibition			
		1 hr	2 hr	3 hr	4 hr	1 hr	2 hr	3 hr	4 hr
1	Control	0.73±0.017	0.96±0.014	1.82±0.037	1.91±0.015	---	----	----	---
2	Diclofenac sodium	0.17±0.022	0.26±0.009	0.50±0.040	0.39±0.014	76.71[a]	72.92[a]	72.53[a]	79.58[a]
3	2A	0.54±0.020	0.81±0.017	1.02±0.063	1.19±0.033	26.02[a]	15.63[b]	43.96[a]	37.69[a]
4	2B	0.47±0.012	0.79±0.015	1.17±0.058	1.20±0.061	35.62[a]	17.71[a]	35.71[a]	37.17[a]
5	2C	0.45±0.018	0.79±0.029	0.86±0.044	1.38±0.023	38.36[a]	17.71[a]	52.75[a]	27.75[a]
6	2D	0.55±0.021	0.83±0.010	0.87±0.058	1.35±0.046	24.66[a]	13.54[b]	52.19[a]	29.32[a]
7	2E	0.55±0.009	0.68±0.020	0.89±0.023	1.43±0.061	24.66[a]	29.17[a]	51.09[a]	25.13[a]
8	2F	0.56±0.006	0.60±0.021	1.02±0.037	1.28±0.032	23.29[a]	37.50[a]	43.96[a]	32.98[a]

[a]shows significant difference at P < 0.001 in comparison with control group
[b]shows significant difference at P < 0.01 in comparison with control group

Table 3: Analgesic activity of benzoxazole derivatives

S. No.	Group	Mean writhing±SEM	% Protection
1	Control	37.77±0.49	-------
2	Diclofenac Sodium	7.400±0.57	80.41[b]
3	2A	9.88±0.50	73.84[b]
4	2B	14.57±0.85	61.42[b]
5	2C	18.33±0.75	51.47[b]
6	2D	23.30±0.65	38.31[b]
7	2E	14.98±0.69	60.34[b]
8	2F	26.22±1.56	30.58[b]

[b]shows significant difference at P < 0.01 in comparison with control group

The emergence of absorption band in the IR spectrum of the compound 2A for 2° N-H and C-Br were observed at 3370 cm^{-1} and 531 cm^{-1} respectively. The appearance of absorption band in IR spectrum of compound 2A appears for (C=O) and (C=N) at 1550 cm^{-1} & 1614 cm^{-1} respectively. Spectra of all the other compounds were found to be in full consignment with the assigned structure.

All the synthesized derivatives were evaluated for their anti-inflammatory potential. The derivatives exhibited moderate to good anti-inflammatory activity having higher percentage inhibition by compound 2C during third hour and the least percentage inhibition of edema by 2D during second hour (table 2).

The highest analgesic activity was exhibited by compound 2A while least activity was demonstrated by compound 2F (table 3). All other compounds displayed moderate to good analgesic activity against acetic acid induced writhing.

4. CONCLUSION

The benzoxazole moiety independently has been reported to possess potent varied pharmacological activities. In the present work authors have provided a convenient synthetic method for the synthesis of newer benzoxazole compounds by utilizing various substituted anilines imparting condensation of these with 2-(2-aminophenyl) benzoxazole.

The results of anti-inflammatory and analgesics screening were encouraging. Further investigations with appropriate structural modifications of title compounds may result in therapeutically useful outcomes for future researchers.

The above results established the fact that benzoxazole derivatives could be a rich source of potential entities in search of new generation of biologically active compounds and be worthwhile to explore the possibility in this area by fusing differently substituted moieties which may result in better pharmacological activities.

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6. REFERENCES

1. Lokwani P, Nagori BP, Batra N, Goyal A, Gupta S, Singh N. *J. Chem. Pharm. Res.*, 2011; **3(3):**302-311.

2. Laliteshwar PS, Chawla V, Chawla P, Saraf SK. *Der Pharma Chemica*, 2010; **2(4):**206-212.
3. Tang JJX, Dou W, Zhang H, Liu W, Wang C, Zheng J. *Journal of Inorganic Biochemistry,* 2010; **104:**583-591.
4. Satyendra RV, Vishnumurthy KA, Vagdevi HM , Rajesh KP, Manjunatha H, Shruthi A. *European Journal of Medicinal Chemistry*, 2011; **46:**3078-3084.
5. Paramashivappa R, Kumar PP, Rao PVS, Rao AS. *Bioorganic & Medicinal Chemistry Letters*, 2003; **13:**657-660.
6. Ramalingan C, Balasubramanian S, Kabilan S, Vasudevan M. *European Journal of Medicinal Chemistry*, 2004; **39:**527-533.
7. Klimesova V, Koc J, Waisser K, Kaustova J, Mollmann U. *European Journal of Medicinal Chemistry*, 2009; **44:**2286-2293.
8. Yang Z , Fairfax DJ, Maeng JH, Masih L, Usyatinsky A, Hassler C et al., *Bioorganic & Medicinal Chemistry Letters*, 2010; **20:**6538-6541.
9. Sham M, Singh SN, Kumar A, Lozach O, Meijer L. *Bioorganic & Medicinal Chemistry Letters*, 2006; **14:**3758-3765.
10. Song H, Oh SR, Lee HK, Han G, Kim JH, Chang HW, Doh KE. *Bioorganic & Medicinal Chemistry,* 2010; **18:**7580-7585.
11. Sun LQ, Chen J, Bruce M, Deskus JA, Epperson JR, Johnson KTG et al., *Bioorganic & Medicinal Chemistry Letters*, 2004; **14:**3799-3802.
12. Kamal A , Reddy KS, Naseer M, Khan A , Rajesh VC, Shetti C, Ramaiah MJ et al., *Bioorganic & Medicinal Chemistry,* 2010; **18:**4747-4761.
13. Ertan T, Yildiz I , Gulbas BT, Bolelli K, Arpaci OT, Ozkan S, Kaynak F, Yalcin I, Aki E. *European Journal of Medicinal Chemistry,* 2009; **44:**501-510.
14. Rida SM, Ashour FA, Soad AM, Hawash E, Mona M, Semary E et al., *European Journal of Medicinal Chemistry*, 2005; **40:**949-959.
15. Terashima M, Ishii M, Kanaoka Y. *Synthesis,* 1982; 484.
16. (a) Bourgrin K, Loupy A, Soufiaoui M. *Tetrahedron,* 1998; **54:**8055. (b) Pottorf RS, Chadha NK, Katkevics M, Ozola V, Suna E, Ghane H et al., *Tetrahedron Lett.*, 2003; **44:**175-178.
17. Srivastava RG, Venkataramani PS. *Synth. Commun.*, 1988; **18:**1537.
18. Nakagawa K, Onoue H, Sugita. *J. Chem. Pharm. Bull.*, 1964; **12:**1135.
19. Stephens FF, Bower JD. *J. Chem. Soc.*, 1949; 2971.
20. Pattan SR, Babu SNN, Angadi JS, *Indian drugs*, 2002; **39(10):**515-518.
21. Chhonker YS, Veenu B, Hasim SR, Kaushik N, Kumar D, Kumar P. *E-journal of chemistry*, 2009; **6(S1):**S342-S346.
22. Saravanan G, Alagarsamy V, Pavitra TGV. *Inter. J. Pharm. Biosciences,* 2010; **1(3):**1-8.