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Design, synthesis and biological evaluation of benzoxazole derivatives as new anti-inflammatory agents

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ABSTRACT

New series of N-(5-(5-(Alkylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)benzamide derivatives(VI) were synthesized by the reaction of N-(5-(5-mercapto-1,3,4-oxadiazol-2-yl)benzooxazol-2-yl) benzamides with appropriate alkyl halides. The chemical structures of the synthesized compounds were confirmed by means of IR, [1]HNMR, Mass spectral analysis. Further, the synthesized compounds (VIa-VIl) were screened for anti-inflammatory activity by using Carrageenan-induced paw edema rat model. The results showed that, compounds VId, VIe, VIf and VIh were significantly ($p<0.0001$) reduced the inflammation there by showed a promising anti-inflammatory activity; where as the compound VIb, VIg and VIi moderately reduced the inflammation. The compounds VIa, VIc, VIj, VIk and VIl showed very poor anti-inflammatory activity towards Carrageenan-induced paw edema rat.

Keywords: Benzoxazole derivatives, IR, [1]H NMR and Mass spectroscopy, N-(5-(5-(Alkylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)benzamide and anti inflammatory activity.

INTRODUCTION

Recent observations suggest that substituted benzoxazoles and related heterocycles, possess potential activity with lower toxicities in the chemotherapeutic approach in man[1,2] .Careful literature survey revealed that targets containing benzoxazole moiety, either isolated from plants or accessed by total synthesis, have remarkable biological activities.[3] For example, antihelmintic activities[4], antiviral[5], herbicidal[6], antiallergic[7], antihistaminic[8], antiparasitics[9], and antimicrobial[10]. Antiinflammatory activity of benzoxazole derivatives were also reported in the literature. The title compounds were synthesized by treating the methyl-2-aminobenzoxazole-5-carboxylate with substituted benzoyl chloride the resultant compound been subjected to a reaction with carbon-di-sulphide in alcoholic potassium hydroxide and followed by treatment with various alkyl halides to get a new series of N-(5-(5-(Alkylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)benzamide derivatives (VIa-VIl). Shown in figure1.

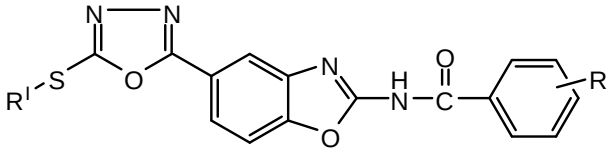


Figure:1

MATERIALS AND METHODS

All melting points were taken in open capillaries on a veego VMP-1 apparatus and are uncorrected IR spectra were recorded as KBr pellets on a Perkin-Elmer FT IR 240-c spectrometer. The ^{1}H NMR spectra were recorded on Varian-Gemini 200 MHz spectrometer in DMSO-d_6 using TMS as an internal standard and mass spectras were recorded on Schimadzu QP 5050A spectrometer. The targeted compounds were synthesized as shown in Scheme-1.

General procedure for synthesis of methyl-2-aminobenzoxazole-5-carboxylate (I)
1.3 mol of 4-carbomethoxy-2-aminophenol was dissolved in 1lit. methyl alcohol and cooled the solution to 5^OC by adding chopped ice. A cold suspension of 1.5 mol of cyanogenbromide in 1lit of water was added over a period of 5min with rapid stirring. Continued the stirring for 0.75h at room temperature, 1.3 mol of solid sodium bicarbonate in small portions over a period of 1.5 h was added to bring the p^H 6.5 -7.0. Stirring was continued for another 1h. The solid was separated by filtration, washed with cold water and on recrystallization from ethyl alcohol has resulted white solid, yield 70% m.p 238^OC.

General procedure for synthesis of methyl 2-(4-arylamido)benzoxazole-5-carboxylate (III)
To a solution of Methyl- 2-aminobenzoxazole-5-carboxylate (I) in DMF (0.15 M) NaH (2 equiv) was added slowly and the mixture was stirred vigorously for 5 min at room temperature. To the resulting solution, substituted benzoyl chloride (1.3 equiv) in 2 mL of DMF was added, and the mixture was stirred for 5 h at room temperature. The reaction mixture was quenched by addition of water and diluted with ethyl acetate. The organic layer was washed with water two times and dried over MgSO4. After filtration and concentration, the crude product was purified by column chromatography (hexane:ethyl acetate) to afford the desired amide in 60-70% yield.

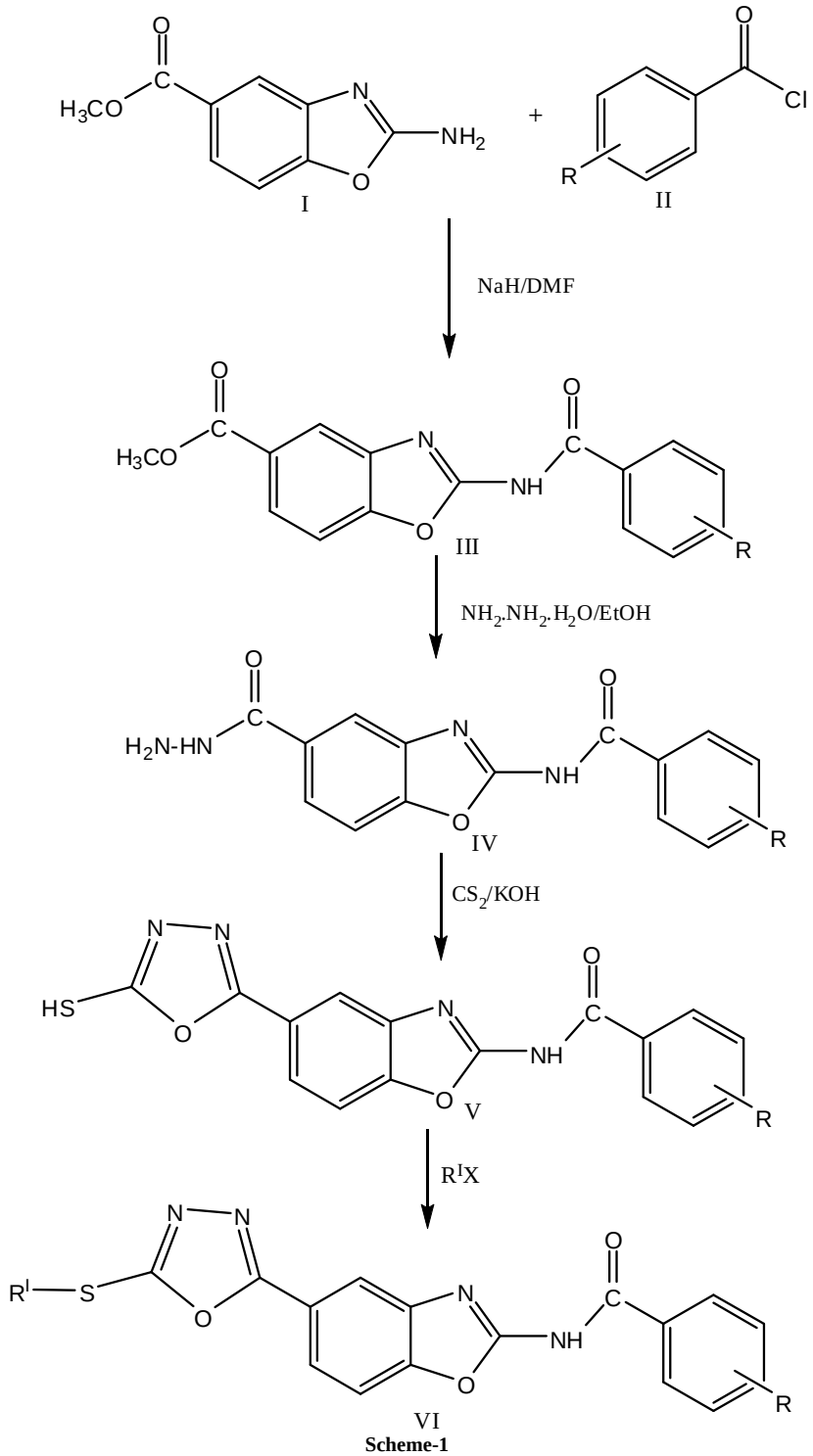
General procedure for synthesis of N-(5-(hydrazinecarbonyl)benzoxazol-2-yl)-4-substituted benzamide(IV)
A mixture of Methyl 2-(4-substituted benzamido)benzoxazole-5-carboxylate (**III** 0.01 mol) and hydrazine hydrate (0.02 mol) in ethanol (25ml) was refluxed on water bath for 6 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled; the solid that separated was filtered and recrystallized from ethanol to furnish **N-**(5-(hydrazinecarbonyl)benzoxazol-2-yl)-4-substituted benzamide (IV).

General procedure for synthesis of N-(5-(5-mercapto-1, 3, 4-oxadiazol-2-yl) benzoxazol-2-yl) benzamides (V)
Each of the Methyl 2-(4-substituted benzamido)benzoxazole-5-carboxylate(IV) was been subjected to a reaction with carbon-di-sulphide in alcoholic potassium hydroxide by heating under reflux for 5hrs , the resulted solid was acidified with 10% hydrochloric acid to get a colourless product. It was purified by alcohol and characterized as N-(5-(5-mercapto-1,3,4-oxadiazol-2-yl)benzooxazol-2-yl) benzamide (V) based on its analytical and spectral data.

General procedure for synthesis of N-(5-(5-(alkylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)benzamides(VI)
Each of the N-(5-(5-mercapto-1,3,4-oxadiazol-2-yl)benzooxazol-2-yl) benzamide (0.01m, V) was treated with 0.01mol of methyl iodide, ethylbromide, n-propyl iodide and n-butylbromide. This reaction mixture was stirred in alcoholic potassium hydroxide (5%) for 5hrs. The product obtained on workout, in each case was purified by recrystallization from suitable solvent(s) and characterized as respective N-(5-(5-(Alkylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)benzamides (VI), by its satisfactory physical given in table1.

Anti inflammatory activity
Carrageenan-induced rat paw edema method[11] was employed for evaluating the anti inflammatory activity of the synthesized compounds (VIa-Vll).

Wister Albino rats of either sex weighing approx 200-350 gm, were housed in clean polypropylene cages and kept under room temperature (25 ± 2^OC), and relative humidity 40-50% in a 12 h light-dark cycle. Food was withdrawn 12 h before and during experimental hours. In this study, the animals were divided into groups as shown in the Table-2. Acute inflammation was produced by sub plantar injection of 0.1ml of 1% suspension of Carrageenan with 2% gum acacia in normal saline, in the right hind paw of the rats. After oral administration of the test compounds, the paw volume was measured Plethysmometrically at 1, 2, 3, and 4 h intervals. Diclofenac sodium 10mg/ml of 2% gum acacia in normal saline was used as standard drug.



Scheme-1

RESULTS AND DISCUSSION

The targeted compounds were synthesized according to the Scheme-1. The required starting material, methyl- 2-aminobenzoxazole-5-carboxylate in DMF, NaH was added slowly and the mixture was stirred vigorously for 5 min at room temperature. To the resulting solution, substituted benzoyl chloride in DMF was added, was prepared in

good yield (85%). A mixture of methyl 2-(4-substituted benzamido)benzoxazole-5-carboxylate and hydrazine hydrate in ethanol was refluxed. Each of the Methyl 2-(4-substituted benzamido)benzoxazole-5-carboxylate has been subjected to a reaction with carbon-di-sulphide in alcoholic potassium hydroxide by heating under reflux, the resulted solid was acidified with 10% hydrochloric acid to get a colourless product. Each of the N-(5-(5-mercapto-1,3,4-oxadiazol-2-yl)benzooxazol-2-yl) benzamide (0.01m, V) was treated with 0.01mol of methyl iodide, ethylbromide, n-propyl iodide and n-butylbromide. This reaction mixture was stirred in alcoholic potassium hydroxide (5%). The yields, melting points and physical data of newly synthesized compounds are summarized in Table-1. The formations of N-(5-(5-(Alkylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)benzamides were confirmed by means of IR, ^{1}HNMR, Mass spectral analysis. The investigation of anti inflammatory activity revealed that the tested compounds VId, VIe, VIf and VIh were significantly ($p<0.0001$) reduced the inflammation there by showed a promising anti-inflammatory activity; where as the compound VIb, VIg and VIi moderately reduced the inflammation. The compounds VIa, VIc, VIj, VIk and VIl showed very poor anti-inflammatory activity towards Carrageenan – induced paw edema rat model when compared to the standard drug Diclofenac Sodium (10mg/ml).

CompoundVIa: N-(5-(5-(methylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)benzamide
IR (KBr, cm-1): 3363(NH), 1682 (C=O), 1575 (C=N), 1565 (C=C), 1442 (C-N),1195 (C-S); ^{1}H-NMR (DMSO-d6) δ: 12.4 (s, 1H, NH), 8.1 (s, 1H, Ar-H), 8.0(d, 2H, Ar-H), 7.8(d, 1H, Ar-H), 7.7(d, 1H, Ar-H), 7.6(t, 2H, Ar-H), 7.5(t, 1H, Ar-H) 2.5(s, 3H, CH_3); MS (*m/z):* M^+: 353.0

Compound VIb:N-(5-(5-(ethylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)benzamide
IR (KBr, cm-1): 3366(NH), 1678 (C=O), 1582 (C=N), 1558 (C=C), 1450 (C-N),1187 (C-S); ^{1}H-NMR (DMSO-d6) δ: 12.1 (s, 1H, NH), 8.2 (s, 1H, Ar-H), 8.1(d, 2H, Ar-H), 7.9(d, 1H, Ar-H), 7.8(d, 1H, Ar-H), 7.7(t, 2H, Ar-H), 7.6(t, 1H, Ar-H) 3.1(s, 2H, CH_2), 1.2(s,3H, CH_3). MS (*m/z):* M^+: 367.0

Compound VIc: N-(5-(5-(propylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)benzamide
IR (KBr, cm-1): 3361(NH), 1683 (C=O), 1576 (C=N), 1564 (C=C), 1443 (C-N),1194 (C-S); ^{1}H-NMR (DMSO-d6) δ: 12.2 (s, 1H, NH), 8.1 (s, 1H, Ar-H), 8.0(d, 2H, Ar-H), 7.9(d, 1H, Ar-H), 7.8(d, 1H, Ar-H), 7.6(t, 2H, Ar-H), 7.5(t, 1H, Ar-H) 3.1(s, 4H, 2(CH_2)), 1.1(s,3H, CH_3). MS (*m/z):* M^+: 381.0

Compound VId: N-(5-(5-(butylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)benzamide
IR (KBr, cm-1): 3371(NH), 1674 (C=O), 1587 (C=N), 1554 (C=C), 1455 (C-N),1181 (C-S); ^{1}H-NMR (DMSO-d6) δ: 12.5 (s, 1H, NH), 8.3 (s, 1H, Ar-H), 8.1(d, 2H, Ar-H), 7.9(d, 1H, Ar-H), 7.8(d, 1H, Ar-H), 7.7(t, 2H, Ar-H), 7.4(t, 1H, Ar-H) 3.1(d, 2H, CH_2), 1.6(t, 2H, CH_2), 1.4(t, 2H, CH_2), 1.1(s,3H, CH_3). MS (*m/z):* M^+: 395.0

Compound VIe : 4-chloro-N-(5-(5-(methylthio) -1, 3, 4- oxadiazol -2 –yl) benzoxazol-2-yl)benzamide
IR (KBr, cm-1): 3342(NH), 1643(C=O), 1546 (C=N), 1524 (C=C), 1414 (C-N),1140 (C-S); ^{1}H-NMR (DMSO-d6) δ: 11.9(s, 1H, NH), 8.2 (s, 1H, Ar-H), 8.0(d, 2H, Ar-H), 7.9(d, 2H, Ar-H), 7.8(d, 1H, Ar-H), 7.7(d, 1H, Ar-H), 2.3(s,3H, CH_3). MS (*m/z):* M^+: 387.0

Compound VIf: 4-chloro-N-(5-(5-(ethylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)benzamide
IR (KBr, cm-1): 3386(NH), 1673(C=O), 1526 (C=N), 1514 (C=C), 1444 (C-N),1160 (C-S); ^{1}H-NMR (DMSO-d6) δ: 12.1(s, 1H, NH), 8.3 (s, 1H, Ar-H), 8.2(d, 2H, Ar-H), 8.0(d, 2H, Ar-H), 7.8(d, 1H, Ar-H), 7.6(d, 1H, Ar-H), 3.0(d,2H, CH_2), 1.2(s, 3H, CH_3). MS (*m/z):* M^+: 401.0

Compound VIg:4-chloro-N-(5-(5-(propylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)benzamide
IR (KBr, cm-1): 3376(NH), 1662(C=O), 1514 (C=N), 1501 (C=C), 1430 (C-N),1145 (C-S); ^{1}H-NMR (DMSO-d6) δ: 12.4(s, 1H, NH), 8.2 (s, 1H, Ar-H), 8.1(d, 2H, Ar-H), 8.0(d, 2H, Ar-H), 7.9(d, 1H, Ar-H), 7.8(d, 1H, Ar-H), 3.1(d,2H, CH_2), 1.4(t, 2H, CH_2), 1.0 (s,3H, CH_3). MS (*m/z):* M^+: 415.0

Compound VIh: 4-chloro-N-(5-(5-(butylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)-benzamide
IR (KBr, cm-1): 3364(NH), 1649(C=O), 1524 (C=N), 1501 (C=C), 1413 (C-N),1135 (C-S); ^{1}H-NMR (DMSO-d6) δ: 12.0(s, 1H, NH), 8.3 (s, 1H, Ar-H), 8.1(d, 2H, Ar-H), 7.9(d, 2H, Ar-H), 7.8(d, 1H, Ar-H), 7.7(d, 1H, Ar-H), 3.1(d,2H, CH_2), 1.6(t, 2H, CH_2),1.4(t, 2H, CH_2), 1.0 (s,3H, CH_3). MS (*m/z):* M^+: 430.0

Compound VIi : N-(5-(5-(methylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)-4-nitrobenzamide
IR (KBr, cm-1): 3333(NH), 1659(C=O), 1525 (C=N), 1511 (C=C), 1423 (C-N),1145 (C-S); ^{1}H-NMR (DMSO-d6) δ: 12.3(s, 1H, NH), 8.5 (d, 2H, Ar-H), 8.2(d, 2H, Ar-H), 8.1(s, 1H, Ar-H), 8.0(d, 1H, Ar-H), 7.9(d, 1H, Ar-H), 2.8 (s,3H, CH_3). MS (*m/z):* M^+: 398.0

Compound VIj :N-(5-(5-(ethylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)-4-nitrobenzamide
IR (KBr, cm-1): 3334(NH), 1661(C=O), 1528 (C=N), 1515 (C=C), 1428 (C-N),1151 (C-S); ^{1}H-NMR (DMSO-d6) δ: 12.2(s, 1H, NH), 8.4 (d, 2H, Ar-H), 8.3(d, 2H, Ar-H), 8.0(s, 1H, Ar-H), 7.9(d, 1H, Ar-H), 7.8(d, 1H, Ar-H), 2.9(d,2H, CH_2),1.7 (s,3H, CH_3). MS (*m/z):* M^+: 412.0

CompoundVIk:4-nitro-N-(5-(5-(propylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)benzamide
IR (KBr, cm-1): 3344(NH), 1671(C=O), 1538 (C=N), 1515 (C=C), 1438 (C-N),1161 (C-S); ^{1}H-NMR (DMSO-d6) δ: 12.1(s, 1H, NH), 8.4 (d, 2H, Ar-H), 8.3(d, 2H, Ar-H), 7.9(s, 1H, Ar-H), 7.8(d, 1H, Ar-H), 7.7(d, 1H, Ar-H), 2.7(d,2H, CH_2),1.4(d,2H, CH_2),1.1 (s,3H, CH_3). MS (*m/z):* M^+: 426.0

Compound VIl: N-(5-(5-(butylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)-4-nitrobenzamide
IR (KBr, cm-1): 3343(NH), 1673(C=O), 1541 (C=N), 1519 (C=C), 1443 (C-N),1167 (C-S); ^{1}H-NMR (DMSO-d6) δ: 12.4(s, 1H, NH), 8.5 (d, 2H, Ar-H), 8.4(d, 2H, Ar-H), 8.0(s, 1H, Ar-H), 7.9(d, 1H, Ar-H), 7.8(d, 1H, Ar-H), 2.9(d,2H, CH_2),1.7(d,2H, CH_2),1.5(d,2H, CH_2),1.0 (s,3H, CH_3). MS (*m/z):* M^+: 440.0

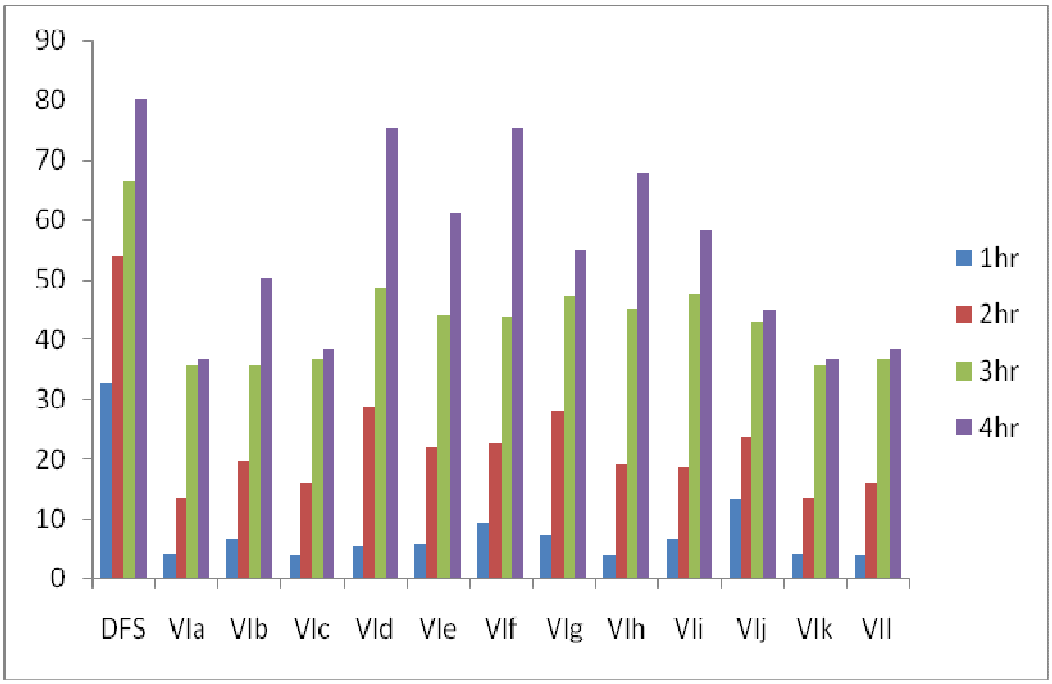
Table1: Physical data of N-(5-(5-(Alkylthio)-1,3,4-oxadiazol-2-yl)benzoxazol-2-yl)benzamides (VI).

SNo	Compound	R	R^I	Chemical formula	Melting Point (^{O}C)	Yield (%)	Elemenyal analysis (C; N; H; O,S,Cl)
1	VIa	H	methyl	$C_{17}H_{12}N_4O_3S$	183	74	56.76,14.38,2.91,12.90,8.19,-
2	VIb	H	ethyl	$C_{18}H_{14}N_4O_3S$	171	81	58.90,14.29,2.84,12.94,7.97,-
3	VIc	H	n-propyl	$C_{19}H_{16}N_4O_3S$	201	64	58.17,13.29,3.41,11.84,7.78,-
4	VId	H	n-butyl	$C_{20}H_{18}N_4O_3S$	196	80	59.95.13.90,3.91,11.34,7.62,-
5	VIe	Cl	methyl	$C_{17}H_{11}ClN_4O_3S$	184	71	51.01,1.27,13.85,11.10,7.75,8.10-
6	VIf	Cl	ethyl	$C_{18}H_{13}ClN_4O_3S$	172	63	52.38,12.29,2.49,10.94,7.01,7.91
7	VIg	Cl	n-propyl	$C_{19}H_{15}ClN_4O_3S$	195	64	54.30,12.20,2.90,10.94,6.64,7.66
8	VIh	Cl	n-butyl	$C_{20}H_{17}ClN_4O_3S$	207	72	55.54,12.80,3.56,10.46,6.64,7.02
9	VIi	NO_2	methyl	$C_{17}H_{11}N_5O_5S$	205	71	50.07,16.19,1.92,19.01,7.14,-
10	VIj	NO_2	ethyl	$C_{18}H_{13}N_5O_5S$	195	65	51.10,16.05,2.46,18.75,6.37,-
11	VIk	NO_2	n-propyl	$C_{19}H_{15}N_5O_5S$	197	55	52.10,15.60,3.01,17.91,6.84,-
12	VIl	NO_2	n-butyl	$C_{20}H_{17}N_5O_5S$	189	71	53.83,14.26,2.91,17.31,6.34,-

Table2: Anti-inflammatory activity of N-(5-(5-(Alkylthio)-1,3,4-oxadiazol-2-yl)Benzoxazol-2-yl)benzamides (VI) by carrageenan induced rat paw edema method

Time	R	R^I	1hr %red	2 hr %red	3 hr %red	4 hr %red
Carraggenan	-	-	NA	NA	NA	NA
Diclofenac sodium	-	-	32.84	54.00	66.34	80.31
VIa	H	methyl	4.01	13.58	35.57	36.50
VIb	H	ethyl	6.56	19.51	35.57	50.15
VIc	H	n-propyl	3.64	15.67	36.53	38.41
VId	H	n-butyl	5.47	28.57	48.39	75.23
VIe	Cl	methyl	5.83	21.95	43.91	61.26
VIf	Cl	ethyl	9.12	22.64	43.58	75.23
VIg	Cl	n-propyl	7.29	27.87	47.11	54.92
VIh	Cl	n-butyl	3.64	19.16	45.19	67.61
VIi	NO_2	methyl	6.56	18.46	47.43	58.09
VIj	NO_2	ethyl	13.13	23.69	42.94	44.76
VIk	NO_2	n-propyl	4.01	13.58	35.57	36.50
VIl	NO_2	n-butyl	3.64	15.67	36.53	38.41

Figure 2: Graphical representation of percentage inhibition of paw volume of N-(5-(5-(Alkylthio)-1,3,4-oxadiazol-2-yl)Benzoxazol-2-yl)Benzamides (VI) by carrageenan induced rat paw edema method



CONCLUSION

This study reports the successful synthesis of the title compounds in good yields and moderate to potent anti inflammatory activity of these derivatives containing benzoxazole moiety which is comparable with standard drug.

REFERENCES

[1] R.D. Haugwitz, R.G.Angel, G.A.Jacobs, B.V.Manner, V.L. Narayanan, L.R.Crothers and J. Szanto, *J. Med. Chem.*, **1982** (25) , 969.
[2] T. Hisano, M. Ichikawa, K. Tsumoto, M. Tasaki, *Chem. Pharm. Bull* **1982**, 30, 2996.
[3] Anita hari, Charles karan, Warren C. Rodrignes and Benjamin L. Miller, *J. Org. Chem.* **2001**, 66 , 991.
[4] B.Gopal Krishna, N. Raghunandan, J.V.Rao, S. Bari, B.Srinivas, Venkatesham and M.Sarangapani, *Indian Drugs* **2005**, 42 (6).
[5] Surendra Bahadhur and Pandey, *J. Indian Chem. Soc.*, **1981**, 58 , 883 .
[6] Peter Paul Wilhelm, Wilhelm, Sittenthales, Hans Ulrich Bernhard and Torsten Rehm, *Ger.Offen* D.E. **3**, 638685 (Cl. A. 01 N57/08), (**1980**), *Chem. Abstr.*, **1989**, 109, 110657.
[7] *Chem. Abstr.* **1992**, 117, 69856K .
[8] Yousuke Katsura, Yoshikaz Inoue, Signetaka Nishino, Masaaki Tomoi, Harunobu Itoh and Hisashi Takasugi, *Chem. Pharm. Bull.*, **1992**, 4(6) , 1424 .
[9] Qian, Xuhong, Li, Zhibin, Sorg, Gonghua, Lizhorg, *J. Chem. Res. Synop.*, **2001**, 4, 138.
[10] Sultan Nacak, Seyban Ersan, Rukiye Berkem and Tancel Ozden, *Arzneim-Forsch/ Drugs Res.*, **1997** 41, 963
[11] C.A. Winter, E.A. Risely and E.V. Nuss, *Pro. Soc. Exp. Biol. & Med.*, **1962**, 111, 544