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SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL SERIES OF BENZOXAZOLE DERIVATIVES AS NEW ANTI-INFLAMMATORY AGENTS

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ABSTRACT

Various approaches to the synthesis of novel benzoxazole derivatives are described. The products, which included 1-(2-((dialkylamino) -methyl) benzoxazole-5-carbonyl) piperazine-3,6-dionesVII) and (2-(2-((dialkylamino) methyl) benzoxazole-5-carbonyl)-2,3-dihydrophthalazine-1,4-diones IX) were screened for anti-inflammatory activity on the carrageenan-induced rat paw edema test. Some of the compounds possessed activity superior to that of diclofenac sodium

KEY WORDS

Benzoxazole derivatives, IR, NMR, Mass Spectrum, Anti-Inflammatory activity

1. INTRODUCTION:

Five- membered aromatic heterocyclic rings containing a C=N bond, such as benzoxazole, is an important structural unit in natural products, and in synthetic pharmaceutical and agrochemical compounds [1,2]. These compounds received a considerable amount of attention for their biological and therapeutic activities [3]. Inflammation evidence of many diseases is major concern for physicians throughout the word. The single most important event in this process is accumulation of large number of phagocytic cells of the site of the inflammation. Tissue injury caused by introduction of a foreign antigen, trauma, or local exposure to certain chemicals triggers complex processes of inflammation. This may consist of a fluid stasis as well as the accumulation of several cellular and no cellular elements of the immune response [4]. In most of these cases, it has been proved that the 5-substituted benzoxazole [5], substituted sulfonyl derivatives [6] and carbohydrazides [7], have promising anti-inflammatory activity. Also, benzoxazole at its 5th position [8], is more prone for its lipophilic action and therefore we go the substitution at 5th position of benzoxazole. Hence, it was planned to synthesize the 1-(2-((dialkylamino)-methyl) benzoxazole-5-carbonyl) piperazine-3,6-dionesVII) and (2-(2-((dialkylamino) methyl) benzoxazole-5-carbonyl)-2,3-dihydrophthalazine-1,4-diones IX) to get good anti-inflammatory activity.

EXPERIMENTAL

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

SYNTHESIS OF 4-CARBOMETHOXY-2-NITROPHENOL (II)

To a solution of aluminum nitrate (40grms) in acetic acid- acetic anhydride (1:1) mixture (160ml), was added an appropriate phenol (I, 40grms) in small portions, while cooling and shaking occasionally. The reaction mixture was left at room temperature for 1.5 hours while shaking the contents intermittently to complete the nitration. The resulting brown solution was diluted

to complete the nitration. The resulting brown solution was diluted with ice-cold water and acidified with concentrated Nitric acid to get a bulky, yellow precipitate. It was filtered washed with small quantity of methanol and purified by recrystallization from alcohol to get a yellow crystalline solid (44g, 85%), m.p 73^{O}C [9]

SYNTHESIS OF 4-CARBOMETHOXY-2-AMINOPHENOL (III)

4-carbomethoxy-2-nitrophenol (II, 10 grams) was dissolved in boiling alcohol (50%, 100ml) and sodium dithionite was added to this boiling alcohol solution until it becomes almost colourless. Then the alcohol was reduced to one-third of its volume by distillation and the residual liquid was triturated with crushed ice. The resulting colourless, shiny product was filtered, washed with cold water and dried in the air. Its purification was affected by recrystallization from benzene to get colourless, shiny scales (5.1 g; 60%) m.p 143^{O}C [10].

SYNTHESIS OF METHYL 2-(CHLOROMETHYL) BENZOXAZOLE-5-CARBOXYLATE (IV)

4-Carbomethoxy-2-aminophenol (III, 0.01 mol) was refluxed with chloro acetic acid in excess for 2 hours. The reaction mixture was cooled and poured into crushed ice with stirring. The obtained product was purified by recrystallization from methanol [11]

SYNTHESIS OF 2-(CHLOROMETHYL) BENZOXAZOLE-5-CARBOHYDRAZIDE (V)

A mixture of methyl 2-(chloromethyl) benzoxazole-5-carboxylate (V, 0.01mol) and hydrazine hydrate (99%) (0.01mol) were taken in 50ml of alcohol, heated under reflux on a water bath for 5hrs. The alcohol was reduced to half of its volume and cooled. The product separated was filtered and washed with small portions of cold alcohol first and then with cold water repeatedly and dried. The product was purified by recrystallization from suitable solvents. The compounds were characterized by spectral data.

SYNTHESIS OF 1-(2-(CHLOROMETHYL) BENZOXAZOLE-5-CARBONYL) PIPERAZINE-3,6-DIONE (VI)

A mixture of 2-(chloromethyl) benzoxazole-5-carbohydrazide (0.01mol) and succinic anhydride (0.01mol) in glacial acetic acid was refluxed for 4 hrs with stirring. The resulted mixture was poured in cold water with stirring then the separated solid was filtered, washed twice with distilled water (30mL), dried and finally purified by recrystallization from ethanol [12].

SYNTHESIS OF 1-(2-((DIALKYLAMINO)METHYL) BENZOXAZOLE-5-CARBONYL) PIPERAZINE-3,6-DIONES (VII)

To a solution of 1-(2-(chloromethyl) benzoxazole-5-carbonyl) piperazine-3,6-dione (VI, 0.01mol) in 20 ml of dry Acetone, N, N-dialkylamine (0.01mol) was added and the reaction mixture was refluxed for 5hrs on a water bath. The colorless products formed were recrystallized by suitable solvents. The compounds were characterized as the 1-(2-((dialkylamino)methyl) benzoxazole-5-carbonyl) piperazine-3,6-diones (VII) by their spectral data.

Adopting this procedure, we have synthesized five compounds and their physical data showed in Table 1.

SYNTHEIS OF 2-(2-(CHLOROMETHYL) BENZOXAZOLE-5-CARBONYL)-2,3-DIHYDROPHTHALAZINE-1,4-DIONE (VIII)

A mixture of 2-(chloromethyl) benzoxazole-5-carbohydrazide (0.01mol) and phthaleic anhydride (0.01mol) in glacial acetic acid was refluxed for 4 hrs with stirring. The resulted mixture was poured in cold water with stirring then the separated solid was filtered, washed twice with distilled water (30mL), dried and finally purified by recrystallization from ethanol.

SYNTHESIS OF 2-(2-((DIALKYLAMINO) METHYL) BENZOXAZOLE-5-CARBONYL)-2,3-DIHYDROPHTHALAZINE-1,4-DIONES(IX)

To a solution of 1-(2-(chloromethyl) benzoxazole-5-carbonyl) piperazine-3,6-dione (VI, 0.01mol) in 20 ml of dry Acetone, N, N-dialkylamine (0.01mol) was added and the reaction mixture was refluxed for 5hrs on a water bath. The colorless products formed were recrystallized by suitable solvents. The compounds were characterized as the 1-(2-((dialkylamino)methyl) benzoxazole-5-carbonyl) piperazine-3,6-diones (VII) by their spectral data.

Adopting this procedure, we have synthesized five compounds and their physical data showed in Table 2.

Spectral Data

1-(2-((dimethyl amino) methyl) benzoxazole-5-carbonyl) piperazine-3,6-dione (VIIa)

IR Spectral Data: (KBr, cm^{-1}) :3177(NH), 1688(N-C=O), 1605(C=N), 1339(C-N), 1508(Ar,C=C), 794(Ar,C-H)

^{1} H NMR spectral data: 8.8 (s, 1H, Ar-H), 8.1(d, 1H, Ar-H), 8.0 (d, 1H, Ar-H), 7.7(s, 1H, NH), 3.6 (s,2H, CH_2), 2.6(s,4H, $(CH_2)_2$, piperazine ring), 2.1(s,6H, $(CH_3)_2$).

M/z peak observed at 316 and M+1 peak was observed at 317.

1-(2-((diethylamino)methyl) benzoxazole-5-carbonyl) piperazine-3,6-dione (VIIb)

IR Spectral Data: (KBr, cm^{-1}) :3167(NH), 1668(N-C=O), 1585(C=N), 1319(C-N), 1488(Ar,C=C), 754(Ar,C-H)

^{1} H NMR spectral data: 8.9 (s, 1H,Ar-H), 8.2(d, 1H,Ar-H), 8.1(d, 1H,Ar-H), 7.9(s, 1H,NH), 3.6 (s,2H,CH_2), 2.8(s,4H,$(CH_2)_2$, piperazine ring), 2.6(s,4H, $(CH_2)_2$), 1.1(s, 6H, $(CH_3)_2$).

M/z peak observed at 344 and M+1 peak was observed at 345

1-(2-(piperidin-1-ylmethyl) benzoxazole-5-carbonyl) piperazine-3,6-dione (VIIc)

IR Spectral Data: (KBr, cm^{-1}) :3192(NH), 1699(N-C=O), 1630(C=N), 1364(C-N), 1533(Ar,C=C), 794(Ar,C-H)

^{1} H NMR spectral data: 8.6 (s, 1H,Ar-H), 7.9 (d, 1H,Ar-H), 7.8 (d, 1H,Ar-H), 7.8 (s, 1H,NH), 3.7 (s,2H,CH_2), 2.7(s,4H,$(CH_2)_2$, piperazine ring), 2.4(t,4H, $(CH_2)_2$ piperidine ring), 1.5(m, 6H, $(CH_3)_2$ piperidine ring).

M/z peak observed at 356 and M+1 peak was observed at 357

1-(2-(piperazin-1-ylmethyl) benzoxazole-5-carbonyl) piperazine-3,6-dione (VIId)

IR Spectral Data: (KBr, cm^{-1}) :3192(NH), 1699(N-C=O), 1620(C=N), 1354(C-N), 1533(Ar,C=C), 791(Ar,C-H)

^{1} H NMR spectral data: 8.8 (s, 1H,Ar-H), 8.1 (d, 1H,Ar-H), 8.0 (d, 1H,Ar-H), 7.9 (s, 1H,NH), 3.5 (s,2H,CH_2), 2.7(t,4H,$(CH_2)_2$, piperazine ring), 2.4(t,4H, $(CH_2)_2$ piperidine ring), 2.1(s, 1H, NH, piperidinyl ring).

M/z peak observed at 357 and M+1 peak was observed at 358.

1-(2-(morpholinomethyl) benzoxazole-5-carbonyl) piperazine-3,6-dione (VIIe)

IR Spectral Data: (KBr, cm^{-1}) : 3194(NH), 1697(N-C=O), 1622(C=N), 1352(C-N), 1535(Ar,C=C), 789(Ar,C-H)

^{1} H NMR spectral data: 8.7 (s, 1H,Ar-H), 8.2 (d, 1H,Ar-H), 8.0 (d, 1H,Ar-H), 7.9 (s, 1H,NH), 3.7 (t, 4H, $(CH_3)_2$ morpholinyl ring), 3.6 (s,2H,CH_2), 2.6(t,4H,$(CH_2)_2$, piperazine ring), 2.5(t,4H, $(CH_2)_2$ morpholinyl).

M/z peak observed at 358 and M+1 peak was observed at 359.

2-(2-((dimethylamino) methyl) benzoxazole-5-carbonyl)-2,3-dihydrophthalazine-1,4-dione (IXa)

IR Spectral Data: (KBr, cm^{-1}): 3199(NH), 1692(N-C=O), 1627(C=N), 1347(C-N), 1540(Ar,C=C), 784(Ar,C-H)

^{1} H NMR spectral data: 8.8 (s, 1H, Ar-H), 8.2 (d, 1H, Ar-H), 8.1 (d, 1H, Ar-H), 8.0 (s, 1H, NH), 7.8(m, 4H, Ar-H), 3.6(s,2H, CH_2), 2.1(s,6H, $(CH_3)_2$,).

M/z peak observed at 364 and M+1 peak was observed at 365

2-(2-((diethylamino)methyl) benzoxazole-5-carbonyl)-2,3-dihydrophthalazine-1,4-dione(IXb)

IR Spectral Data: (KBr, cm^{-1}) :3183(NH), 1682(N-C=O), 1611(C=N), 1333(C-N), 1514(Ar,C=C), 788(Ar,C-H)

^{1} H NMR spectral data: 8.8 (s, 1H,Ar-H), 8.2 (d, 1H,Ar-H), 8.1 (d, 1H,Ar-H), 8.0 (s, 1H,NH), 7.8(m, 4H,Ar-H), 3.6(s,2H,CH_2), 2.9(m,4H,$(CH_2)_2$), 1.1 (t, 6H, $(CH_3)_2$).

M/z peak observed at 392 and M+1 peak was observed at 393

2-(2-(piperidin-1-ylmethyl) benzoxazole-5-carbonyl)-2,3-dihydrophthalazine-1,4-dione (IXc)

IR Spectral Data: (KBr, cm^{-1}) :3184(NH), 1681(N-C=O), 1612(C=N), 1332(C-N), 1515(Ar,C=C), 787(Ar,C-H)

^{1} H NMR spectral data: 8.8 (s, 1H,Ar-H), 8.2 (d, 1H,Ar-H), 8.1 (d, 1H,Ar-H), 8.0 (s, 1H,NH), 7.8(m, 4H,Ar-H), 3.6(s,2H,CH_2), 2.5(t,4H,$(CH_2)_2$), 1.5 (m, 6H, $(CH_2)_3$).

M/z peak observed at 404and M+1 peak was observed at 405

2-(2-(piperazin-1-ylmethyl) benzoxazole-5-carbonyl)-2,3-dihydrophthalazine-1,4-dione (IXd)

IR Spectral Data: (KBr, cm^{-1}) :3186(NH), 1679(N-C=O), 1614(C=N), 1330(C-N), 1517(Ar,C=C), 785(Ar,C-H)

^{1} H NMR spectral data: 8.8 (s, 1H,Ar-H), 8.2 (d, 1H,Ar-H), 8.1 (d, 1H,Ar-H), 8.0 (s, 1H,NH), 7.8(m, 4H,Ar-H), 3.6(s,2H,CH_2), 2.7(t,4H,$(CH_2)_2$ piperazinyl), 2.4 (t, 4H, $(CH_2)_2$ piperazinyl), 2.0(s,1H, NH piperazinyl).

M/z peak observed at 405 and M+1 peak was observed at 406

2-(2-(morpholinomethyl) benzoxazole-5-carbonyl)-2,3-dihydrophthalazine-1,4-dione(IXe)

IR Spectral Data: (KBr, cm^{-1}) :3188(NH), 1677(N-C=O), 1616(C=N), 1328(C-N), 1519(Ar,C=C), 783(Ar,C-H)

^{1} H NMR spectral data: 8.8 (s, 1H,Ar-H), 8.2 (d, 1H,Ar-H), 8.1 (d, 1H,Ar-H), 8.0 (s, 1H,NH), 7.8(m, 4H,Ar-H), 3.7 (t, 4H, $(CH_2)_2$ morpholinyl), 3.5(s,2H,CH_2), 2.5(t,4H,$(CH_2)_2$ morpholinyl).

Mass spectrum: M/z peak observed at 406 and M+1 peak was observed at 407.

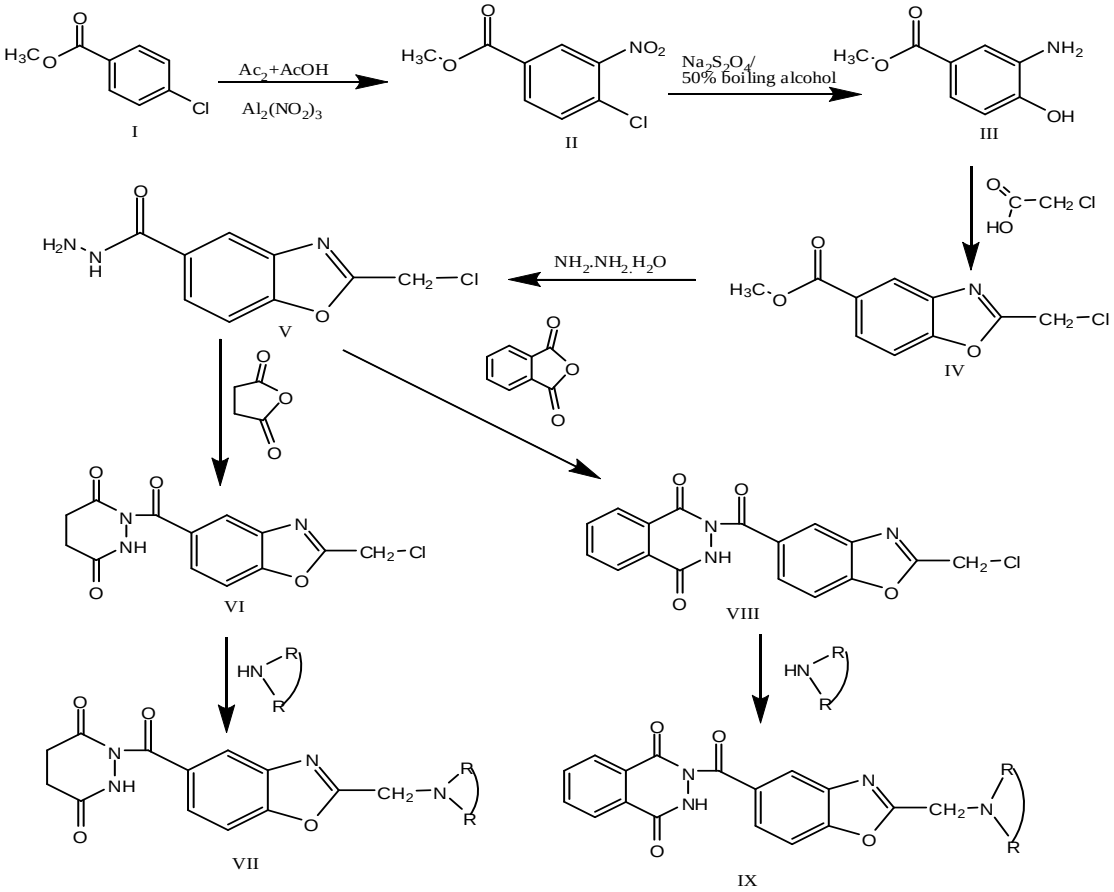
ANTI INFLAMMATORY ACTIVITY [13]:

Carrageenan - induced rat paw edema method (Winter et al) was employed for evaluating the anti-inflammatory activity of the synthesized compounds 1-(2-((dialkylamino) -methyl) benzoxazole-5-carbonyl) piperazine-3, 6-diones (VII) and 2- (2-((dialkylamino) methyl) benzoxazole-5-carbonyl)-2, 3-dihydrophthalazine-1, 4-diones (IX). Wister Albino rats

of either sex weighing approx. 200- 350 gm, were housed in clean polypropylene cages and kept under room temperature (25±2^{O}C), 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. 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.

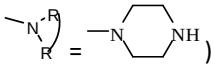
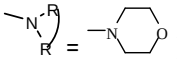
RESULTS AND DISCUSSION:

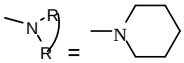
The target compounds were synthesized according to the **Scheme-1**. The required starting material, Methyl-3-amino-4-hydroxybenzoate **(III)** was prepared in good yield (85%) according to reported procedure. The resultant compound was treated with chloroacetic acid to get the precursor methyl 2-(chloromethyl) benzoxazole-5-carboxylate (V) which was treated with hydrazine hydrate(99%) followed by treatment with succinic anhydride and pthalic anhydride, finally the resultant intermediates refluxed with various secondary amines to get the targeted compounds i.e 1-(2 ((dialkylamino)- methyl)benzoxazole-5-carbonyl) piperazine- 3, 6-diones (VIIa-e) and 2-(2-((dialkylamino) methyl) benzoxazole-5-carbonyl)- 2, 3-dihydrophthalazine-1, 4-diones (IXa-e) respectively. All the targeted compounds was characterized by their spectral data and physical data showed in table 1 and 2.

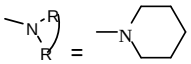
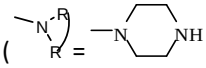


Scheme-1

All the synthesized compounds were screened for Anti-inflammatory activity by carageenan induced rat paw edema method. All the compounds 1-(2-((dialkylamino) -methyl) benzoxazole-5-carbonyl) piperazine-3,6-diones(VIIa-e) showed (Table 3a and 3b) moderate to good anti-inflammatory activity in the range of 66.03 to 80.50 percentage inhibition of Carrageenan induced rat paw edema. Comparatively more activity with 80.50

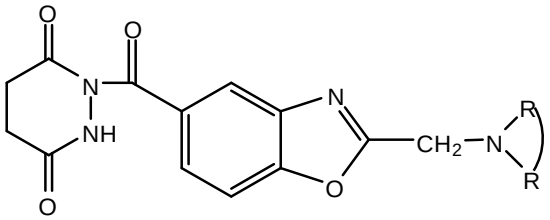
percentage of inhibition was observed for compound VIId () at 4th hour among all the test compounds of this series. compounds VIIa ( = -$N(CH_3)_2$) and VIIe () with percentage inhibition of 78.93 and 78.61 respectively were in next line.

Compound VIIb ( =-$N(CH_2CH_3)_2$) and compound VIIc ()showed good percentage of inhibition with 66.03 and 67.29 respectively when comparing with the standard Diclofenac sodium with percentage of inhibition of 74.52.

All the compounds 2-(2-((dialkylamino) methyl) benzoxazole-5-carbonyl)-2,3-dihydrophthalazine-1,4-diones (IXa-e) showed (Table 4a and 4b) mild to good anti-inflammatory activity in the range of 36.19 to 75.23 percentage inhibition of Carrageenan induced rat paw edema. Comparatively more activity with 75.23 percentage of inhibition was observed for compound IXc () at 4th hour among all the test compounds of this series. compounds IXe ( = ) and IXd () with percentage inhibition of 70.15 and 67.61 respectively were in next line.

Compound IXb ( =-$N(CH_2CH_3)_2$) showed good percentage of inhibition with 64.76 and compound IXa ( = -$N(CH_3)_2$) showed very poor percentage of inhibition with 36.19 when comparing with the standard Diclofenac sodium with percentage of inhibition of 74.52.

Table 1: PHYSICAL DATA OF COMPOUNDS 1-(2-((DIALKYLAMINO) -METHYL) BENZOXAZOLE-5-CARBONYL) PIPERAZINE-3,6-DIONES (VII)



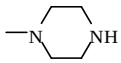
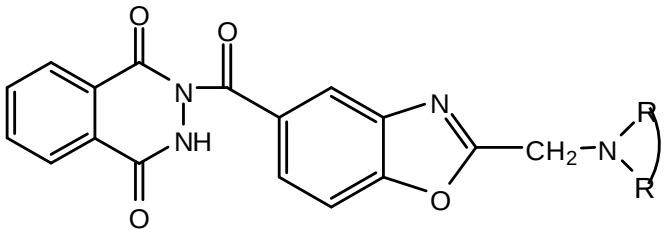
S.N	Compound		Chemical Formula M	Melting (^{0}C)	Point	Yield (%)
1	VIIa	-$N(CH_3)_2$	$C_{15}H_{16}N_4O_4$	198		69
2	VIIb	-$N(CH_2CH_3)_2$	$C_{17}H_{20}N_4O_4$	172		65
3	VIIc		$C_{18}H_{20}N_4O_4$	264		66
4	VIId		$C_{17}H_{19}N_5O_4$	228		68
5	VIIe		$C_{17}H_{18}N_4O_5$	245		60

Table 2: PHYSICAL DATA OF COMPOUNDS 2-(2-((DIALKYLAMINO) METHYL) BENZOXAZOLE-5-CARBONYL)-2,3-DIHYDROPHTHALAZINE-1,4-DIONES (IXa-e)



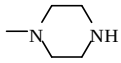
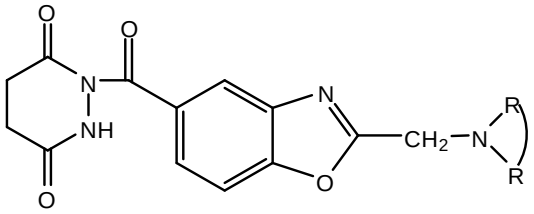
S. N	Compound		Chemical Formula M	Melting Point (^{0}C)	Yield (%)
1	IXa	-N(CH_3)$_2$	$C_{19}H_{16}N_4O_4$	224	65
2	IXb	-N(CH_2CH_3)$_2$	$C_{21}H_{20}N_4O_4$	272	67
3	IXc		$C_{22}H_{20}N_4O_4$	252	65
4	IXd		$C_{21}H_{19}N_5O_4$	219	68
5	IXe		$C_{21}H_{18}N_4O_5$	276	69

Table 3a: Showing the Mean ± SD of the paw volume of the Compounds in Scheme – 1 (1-(2-((dialkylamino) -methyl) benzoxazole-5-carbonyl) piperazine-3,6-dionesVII) (Comp VIIa –VIIe) by Carrageenan induced rat paw oedema method. (n = 6)



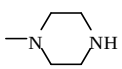
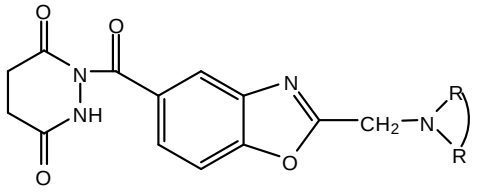
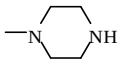
Time		1.0hr	2.0hr	3.0hr	4.0hr
Carraggenan	--	2.74 ± 0.242	2.87±0.254	3.12±0.289	3.15±0.291
Diclofenac sodium	--	2.56±0.310	1.84±0.350***	1.06±0.375***	0.81±0.356***
VIIa	-N(CH_3)$_2$	2.61±0.364	2.06±0.314*	1.54±0.348***	0.67±0.314***
VIIb	-N(CH_2CH_3)$_2$	2.68±0.358	2.26±0.391*	1.94±0.319***	1.08±0.389***
VIIc		2.66±0.394	2.04±0.351**	1.56±0.385***	1.04±0.315***
VIId		1.14±0.298***	1.2±0.321***	0.85±0.351***	0.62±0.384***
VIIe		2.66±0.393	2.54±0.393	2.16±0.284***	1.54±0.291***

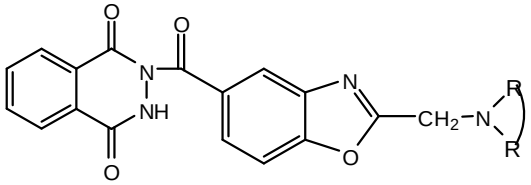
Table 3b: Percentage inhibition of paw volume of the Compounds in Scheme – 1 (1-(2-((dialkylamino) -methyl) benzoxazole-5-carbonyl) piperazine-3,6-diones VII) (Comp VIIa –VIIe) by Carrageenan induced rat paw oedema method. (n = 6).



Time		1.0hr	2.0hr	3.0hr	4.0hr
Carraggenan	--	NA	NA	NA	NA
Diclofenac sodium	--	2.91	35.88***	64.90***	74.52***
VIIa	$-N(CH_3)_2$	6.56	28.22*	49.00***	78.93***
VIIb	$-N(CH_2CH_3)_2$	4.74	21.25*	35.76***	66.03***
VIIc		2.18	28.91**	48.34***	67.29***
VIId		58.39***	59.18***	72.76***	80.50***
VIIe		2.18	28.22	55.62***	78.61***

*** = p<0.001; ** = p<0.01; * = p<0.05

Table 4a: Showing the Mean ± SD of the paw volume of the Compounds in Scheme – 1 (2-(2-((dialkylamino) methyl) benzoxazole-5-carbonyl)-2,3-dihydrophthalazine-1,4-diones IX) (Comp Ixa –IXe) by Carrageenan induced rat paw oedema method. (n=6)



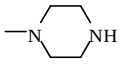
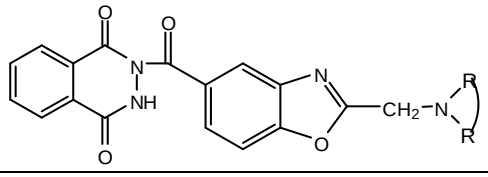
Time		1.0hr	2.0hr	3.0hr	4.0hr
Carraggenan	--	2.74 ± 0.242	2.87±0.254	3.12±0.289	3.15±0.291
Diclofenac sodium	--	2.56±0.310	1.84±0.350***	1.06±0.375***	0.81±0.356***
IXa	$-N(CH_3)_2$	2.38±0.325	2.04±0.383**	2.02±0.371***	2.01±0.309***
IXb	$-N(CH_2CH_3)_2$	2.34±0.325	2.12±0.378*	1.84±0.345***	1.11±0.325***
IXc		2.49±0.361	2.22±0.301**	1.76±0.281***	0.78±0.254***
IXd		2.59±0.299	2.05±0.322***	1.61±0.291***	0.78±0.385***
IXe		2.58±0.351	2.24±0.301*	1.75±0.299***	1.22±0.351***

Table 4b: Percentage inhibition of paw volume of the Compounds in Scheme – 1 (2-(2-((dialkylamino) methyl) benzoxazole-5-carbonyl)-2,3-dihydrophthalazine-1,4-diones IX) (Comp IXa –IXe) by Carrageenan induced rat paw oedema method. (n = 6)



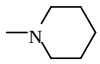
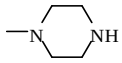
Time		1.0hr	2.0hr	3.0hr	4.0hr
Carraggenan	--	NA	NA	NA	NA
Diclofenacsodium	--	2.91	35.88***	64.90***	74.52***
IXa	$-N(CH_3)_2$	13.13	28.91**	35.25***	36.19***
IXb	$-N(CH_2CH_3)_2$	14.59	26.13*	41.02***	64.76***
IXc		9.12	22.64**	43.58***	75.23***
IXd		3.64	19.16*	45.19***	67.61***
IXe		7.66	19.51	57.05***	70.15***

Figure 1: Graphical representation of percentage inhibition of paw volume of ((1-(2-((dialkylamino)-methyl) benzoxazole-5-carbonyl) piperazine-3,6-dionesVIIa-e) compounds by carrageenan induced rat paw edema method.

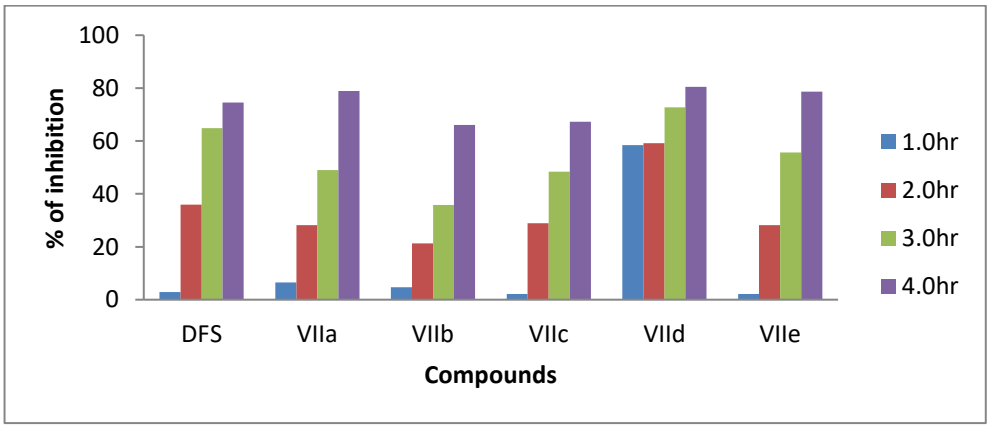
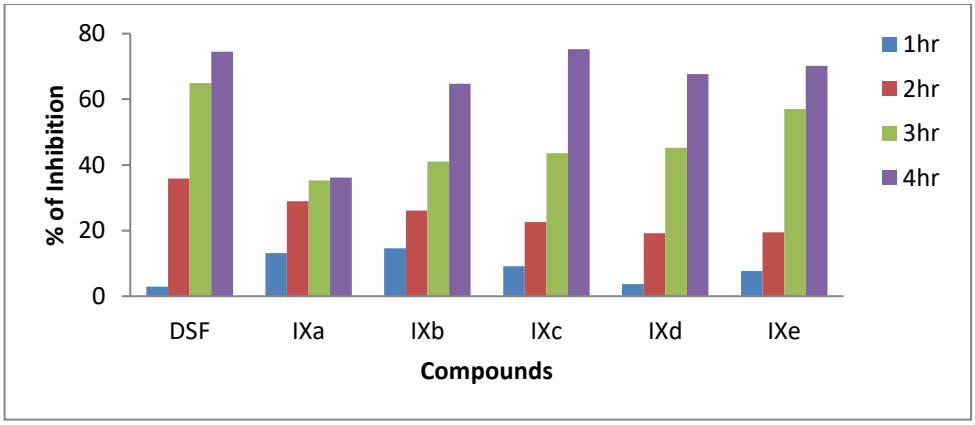


Figure 1: Graphical representation of percentage inhibition of paw volume of (((2-(2-((dialkylamino) methyl) benzoxazole-5-carbonyl)-2,3-dihydrophthalazine-1,4-diones IXa-e) compounds by carrageenan induced rat paw edema method



v). Agar disc diffusion assay method:

Antifungal activity of culture crude extracts of two cyanobacterial species were determined by using the agar disc diffusion assay by using Sabouraud Dextrose Agar (SDA) method [31]. The 20 ml of sterilized Sabouraud Dextrose Agar medium (Hi Media- Mumbai, India) was poured into petri plates, allowed to cool and solidify. 100 µl 5-day glucose peptone broth culture of fungal suspension was poured in each plate and inoculated with L-shaped spreader. Sterile filter paper disc (6mm) impregnated with 50 µl of crude extract were placed on the surface of the agar containing media, similarly disc (6mm) impregnated with 50 µl of respective organic solvent (Acetone, Methanol and Petroleum ether) were placed on the surface of the agar containing media were used as negative control and Nystatin 50 µg/disc was used as standard control. The plates were incubated for 48-72 hrs. at 28^0 C. At the end of incubation period the zone of inhibition was recorded in millimeters (mm) by using Hi Antibiotic Zones Scale-C™ Hi Media (Mumbai, India). Antifungal activity was evaluated by measuring the zone of inhibitions against the tested microorganisms and their mean and standard errors was calculated.

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. McKee, M. L.; Kerwin, S. M. Bioorg. Med. Chem. 2008, 16, 1775.
2. Mortimer, C. G.; Wells, G.; Crochard, J. P.; Stone, E. L.; Bradshaw, T. D.; Stevens, M. F. G.; Westwell, A. D. J. Med. Chem. 2006, 49, 179.
3. Grobler, J. A.; Dornadula, G.; Rice, M. R.; Simcoe, A. L.; Hazuda, D. J.; Miller, M. D. J. Biol. Chem. 2007, 282, 8005.
4. Mohammed Rageeb Mohammed Usman, Rana Sohil D ,Md. Abullais Md. Usman ,Shaikh Tanver Y ,Sayad Imran wahab, IOSR Journal of Pharmacy Vol. 2, Issue 3, May-June, 2012, pp.374-379.
5. Mohd A, S. Kumar, Indian Drugs, 42(2), 2005, 73-77.
6. krapcho John, United States Patent, 4156079, 1979
7. Y. Sato, M. Yamada, and K. Kobayashi, Chem. Pharm. Bull, 46(3), 1998, 445-451.
8. M. Peter, and Pojer, Aust. J. Chem., 32, 1979, 201-4.
9. Rajmohan k and N.V. Subba Rao, *Indian J. Chem.,***11** (1973) 1076.
10. Finhorn A and B.Ptyl, *Ann. Chem.,* **311** (1900) 46.
11. Reena M, kiran G, Rajyalakshmi G , Venkateshwa Rao J , Sarangapani M, Acta Pharmaceutica Sinica 2010, 45 (6): 730-734.
12. Ahlam Marouf Al-Azzawi and Ahmed Saadi Hassan, IJRPC 2014, 4(4), 755-762.
13. C.A. Winter, E.A. Risely and E.V. Nuss, *Pro. Soc. Exp. Biol. & Med.,* **111,** 544 (1962).

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