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Synthesis and Anti-Inflammatory Activity of a Novel Series of new BenzoxazoleDerivatives

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ABSTRACT

In the present investigation we have synthesized a series of new 2-arylidene-N-(benzoxazole-2-yl) hydrazine carboxamide and 2-arylidene-N-(5-chloro benzoxazole-2-yl) hydrazine carboxamide derivatives (VIIIa-VIIIf& VIIIA-VIIIE). The newly synthesized derivatives were characterized by using the data of IR, 'H NMR and Mass Spectral analysis. Thus synthesized and characterized targeted compounds were further screened for their anti-inflammatory activity by using Carrageenan - induced paw edema rat model. Among all the newly synthesized derivatives, Compounds VIIIa-c and Compounds VIIIA-C were reduced the inflammation very significantly , thus these compounds showed promising anti-inflammatory activity and compounds VIIId-VIIIf& VIIID-VIIIF showed moderate anti-inflammatory activity.

Keywords: benzoxazoles, IR,' HNMR, Mass Spectroscopy and anti-inflammatory activity

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INTRODUCTION

Non–steroidal anti-inflammatory drugs are among the most widely used of all therapeutic agents. They are commonly prescribed for 'rheumatic' muscle skeletal complaints and are often taken without prescription for minor aches and pains. There are now more than 50 different NSAIDs on the market and none of these is ideal in controlling or modifying the signs and symptoms of inflammation. Virtually all currently available NSAIDs can have significant unwanted effects, especially in elders[1]. Therefore, discovery of new safer NSAIDs represent challenging goal in the research area. In our ongoing medicinal chemistry research work, the substituted benzoxazoles have attracted much attention due to their prominent utilization as anti-inflammatory[2], anti viral[3], anti fungal[4], anti-bacterial[5], anti cancer[6], anti- tubercular[7], anticonvulsant[8] and hypoglycemic activity[15] probably resulting from its planar and compact structure. Studies showed that these benzoxazole moieties exerted there*in vivo* activity by inhibiting the synthesis of prostaglandin E_2[9] In the present study we have synthesized a series of novel derivatives with a view to screen the products for anti-inflammatory effect by carrageenan induced rat paw edema method. All the synthesized compounds were purified and the reactions were monitored by TLC. The chemical structures of the synthesized compounds (Table 1) were confirmed by IR, IH NMR and mass spectral analysis.

MATERIALS AND METHOD

Melting points of all synthesized compounds were determined by open capillary tubes and are uncorrected. The IR spectra (KBr pellets) were recorded on Spectrum BX series model spectrometer for Compounds VIIId and VIIID. ^{i}H NMR spectra were recorded for compound VIIId and VIIID on AV 300 MHz NMR Spectrometer, using TMS as internal standard. The mass spectra were recorded on -LCQ ion Mass spectrometer. The purity of the compounds were checked by Thin Layer Chromatography (TLC) on Merck Silica gel 60 F254 pre coated sheet using Chloroform and Ethyl acetate in 1:1 v/v.

Synthesis Of 4-Chloro -2-Nitrophenol (II)

To a solution of aluminium nitrate (40 g) in acetic acid : acetic -anhydride (1 : 1, v/v) mixture (160 ml) 40 g of 4-chloro phenol was added in small portions, while cooling and shaking occasionally. The reaction mixture was left at room temperature for 1.5 h while shaking the contents intermittently to complete the nitration. The resulting brown solution was diluted with ice cold water (500 ml) and acidified with conc. HNO3 (40 ml) to get a bulky yellow precipitate of 4-chloro-2-nitro phenol and recrystallized from methanol.

Synthesis Of 4-Chloro-2-Aminophenol(III)

4-Chloro-2-nitro phenol(40 g) was dissolved in boiling ethanol (400 ml) and sodium dithionite was added to this boiling alcohol solution until it becomes almost colourless. Then the solvent was reduced to one third of its volume by distillation and the residual liquid was triturated with ice cold water. The resulting colourless shiny product was filtered, washed with cold water and dried. It is recrystallized from alcohol

Synthesis Of 2-Aminobenzoxazole / 5-Chloro 2-Amino Benzoxazole(V)

To a solution of 2-amino phenol(III/IV) (0.1mol) in toluene was added a solution of Cyanogen bromide (0.02mol) in toluene with continuous stirring at room temperature and the stirring was continued for 3hr. The completion of the reaction was monitored by TLC. The solid separated was filtered and washed with carbon tetrachloride (CCl4) and air dried to give a purple colored solid , and recrystallized from ethylacetate.

Synthesis of Phenyl Benzoxazole-2-Yl / Phenyl 5-Chloro Benzoxazole-2-Yl Carbamate (VI)

To a solution of phenyl chloroformate (0.1mol) in chloroform (40 ml) was added 2-amino-benzoxazole(V) (0.1 mol) and triethylamine (0.1mol) drop-wise and stirred at room temperature for 6hr.The reaction mixture was then concentrated and after cooling 40-50ml of petroleum ether was added to give a precipitate, which was filtered and washed with large quantity of water and the separated solid was air dried. Recrystallized from absolute alcohol to give pale pink color needle- like crystals.

Synthesis of N-(Benzoxazole-2-Yl) / N-(5-Chloro Benzoxazole-2-Yl)Hydrazine Carboxamide(VII)

The compound above (VI)(0.1 mol) in absolute ethanol (20ml), hydrazine hydrate (99%,0.2mol) was added, followed by a catalytic amount of glacial acetic acid (3drops). Then the mixture was refluxed for 3 hrs. Excess solvent was removed by distillation and poured on to crushed ice to give a white color solid recrystallized from ethanol.

microwave synthesis of 2-arylidene-n-(5-chloro benzoxazole / benzoxazole -2-yl) hydrazine carboxamide(VIII)

The compound above(VII) (0.01 mole) and appropriate aromatic aldehydes (0.015 mole) were taken in a conical flask and were dissolved in 10ml of absolute alcohol. The conical flask was subjected to microwave irradiation for 5 min in microwave oven. The reaction mixture was cooled and triturated with crushed ice ; the separated solid was purified by recrystallization.

Adopting this procedure totally we have synthesized twelve benzoxazole derivatives. The yields, melting points and physical data of newly synthesized compounds were summarized in

Table 1-Physical data of 2-arylidene-N-(5-chloro benzoxazole / benzoxazole -2-yl) hydrazine carboxamide (VIII)

S.no	Compound	R	R'	Molecular Formula	M.Wt	Melting Point(^{0}C)	%Yield
1	VIII a	H	Thiophenyl	C13H10N402S	286	193-195	90
2	VIII b	H	Salicyl	C15H12N403	296	200-203	88
3	VIII c	H	Furfuryl	C13H10N403	270	185-188	85
4	VIII d	H	Phenyl	C15H12N402	280	190-192	85
5	VIII e	H	Anisyl	C16H14N403	310	191-193	92
6	VIII f	H	Cinnamyl	C17H14N402	306	202-205	84
7	VIII A	Cl	Thiophenyl	C13H9N402SCl	319	203-206	91
8	VIIIB	Cl	Salicyl	C15H11N403Cl	329	210-212	86
9	VIIIC	Cl	Furfuryl	C13H9N403Cl	303	200-202	84
10	VIIID	Cl	Phenyl	C15H11N402Cl	313	205-207	82
11	VIIIE	Cl	Anisyl	C16H13N403Cl	343	212-215	88
12	VIIIF	Cl	Cinnamyl	C17H13N402Cl	339	208-210	86

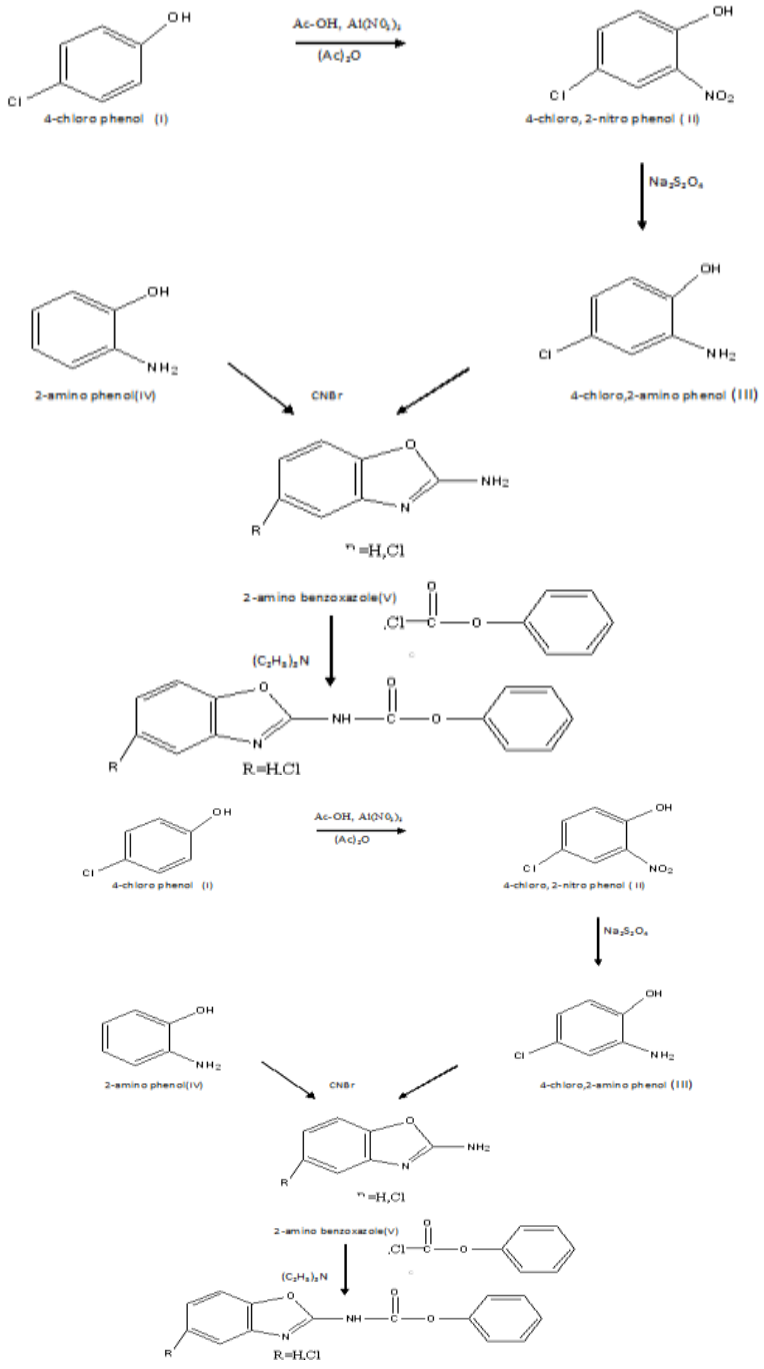
Anti inflammatory activity

Carrageenan - induced rat paw edema method[10] was employed for evaluating the anti inflammatory activity of the synthesized compounds**.** Wister Albino rats of either sex weighing approx 200- 300 gm, were housed in clean polypropylene cages and kept under room temperature (25±2°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 as shown in the **Table-2.** Acute inflammation was produced by sub plantar injection of 0.1ml of 1% suspension of Carrageenan 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. Indomethacin 5mg/kg in normal saline was used as standard drug.

Table 2: Anti inflammatory activity of 2-arylidene-N-(5-chloro benzoxazole / benzoxazole -2-yl) hydrazine carboxamide (VIII)

Compound	1hr	%inhibition	2hr	%inhibition	3hr	%inhibition	4hr	%inhibition
VIIIa	0.55	35.29	0.53	45.91	0.51	60.7	0.46	74.4
VIIIb	0.65	23.5	0.61	37.7	0.56	56.9	0.48	73.3
VIIIc	0.70	17.6	0.66	32.6	0.55	57.6	0.53	70.5
VIIId	0.73	14.1	0.68	30.6	0.63	51.5	0.55	69.4
VIIIe	0.75	11.7	0.70	28.5	0.63	51.5	0.55	69.4

VIIIf	0.71	16.4	0.68	30.6	0.65	50	0.56	68.8
VIIIA	0.53	37.6	0.51	47.9	0.48	63.07	0.45	75
VIIIB	0.61	28.2	0.58	40.8	0.50	61.5	0.43	76.1
VIIIC	0.68	20	0.63	35.7	0.53	59.2	0.46	74.4
VIIID	0.68	20	0.65	33.6	0.56	56.9	0.48	73.3
VIIIE	0.68	20	0.63	35.7	0.58	55.3	0.51	71.6
VIIIF	0.73	14.1	0.71	27.5	0.61	53.07	0.53	70.5
Indomethacin	0.63	25.8	0.53	45.9	0.48	63.07	0.43	76.1
Control	0.85	-	0.98	-	1.3	-	1.8	-



Scheme

N-(Benzoxazole-2-Yl) / N-(5-Chloro Benzoxazole-2-Yl)Hydrazine Carboxamide(VII)

The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands (cm^{-1}) at: 3752 (NH2), 3650(NH),3323 (C-H), 1620 (C=O).PMR spectrum (DMSO-d_6) of the compound has been found to exhibit proton signals (δ ppm) at: 6.9-7.1(d, 2H,Ar-H), 6.9-7.1(d,2H,Ar-H), 4.1 (d, 2H ,NH_2), 7.4 (s, 1H, NH),8.1(t,1H,NH).Mass spectrum of compound (VII) recorded its molecular ion peak at m/z 192.2(calculated value is 192).

2-Arylidene-N-(5-Chloro Benzoxazole / Benzoxazole -2-Yl) Hydrazine Carboxamide (VIIId)

The IR Spectrum (KBr) of the compound exhibited characteristic absorption bands (cm^{-1}) at: 3650(NH),3323 (C-H), 1620 (C=O), 1676 (C=N).PMR spectrum (DMSO-d_6) of the compound has been found to exhibit proton signals (δ ppm) at: 6.6 (S, 5H, Ar-H), 7.5 (s, 1H ,Ar-NH), 6.0(s,1H,=CH),7-7.1(d,2H,Ar-H), 7-7.1(d,2H,Ar-H), 8.1(S,1H,NH).Mass spectrum of compound (VIII d) recorded its molecular ion peak at m/z 280.1(calculated value is 280).

RESULTS AND DISCUSSION

The preliminary studies on anti-inflammatory activity of the new2-arylidene-N-(5-chloro benzoxazole/benzoxazole-2-yl)hydrazine carboxamide(VIII) have generated some interesting data.

Anti-inflammatory activity

All the synthesized new benzoxazole derivatives were evaluated for their anti-inflammatory activity by using the standard indomethacin for the period of four hours with one hour interval.

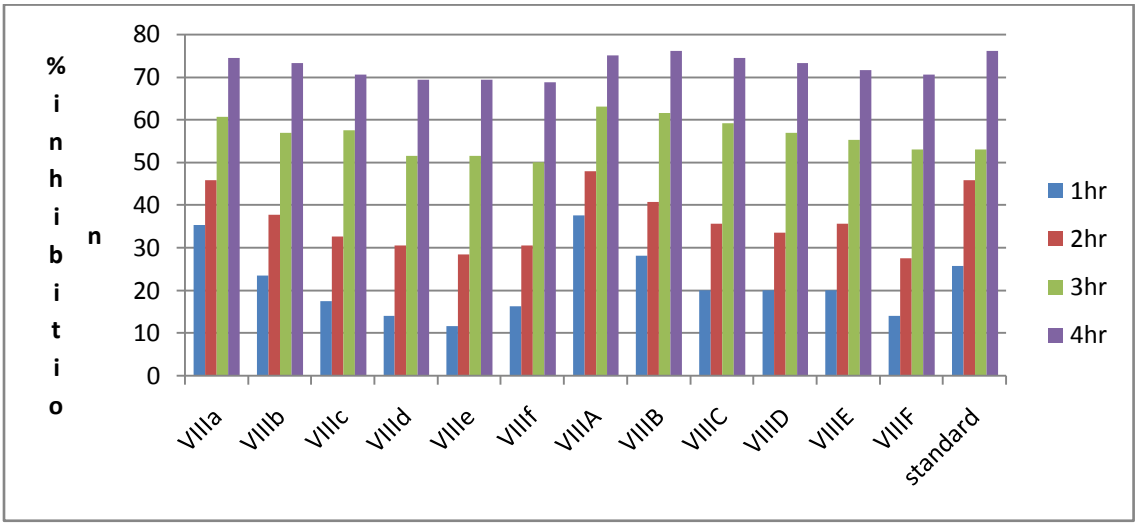


Figure1: Graph showing Antiinflammatory activity of 2-arylidene-N-(5-chloro benzoxazole / benzoxazole -2-yl) hydrazine carboxamide (VIII)

The investigation of anti-inflammatory activity revealed that the tested compounds VIII a & VIIIA(R'=thiophenyl), VIIIb & VIIIB (R'=salicyl) and VIIIc & VIIIC (R'=furfuryl) significantly reduced the inflammation, there by showed a promising anti-inflammatory activity, whereas the compound VIIId& VIIID (R'=phenyl), VIIIe&VIIIE (R'=anisyl) and VIIIf& VIIIF (R'=cinnamyl) moderately reduced the inflammation towards carrageenan induced paw edema rat model, when compared to the standard drug indomethacin.

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 benzoxazolemoiety which is comparable with standard drug. It has been observed that the increased anti-inflammatory activity is attributed to the presence of pharmacologically active groups like semicarbazide side chain. Chloro derivatives of benzoxazoles were more potent than derivatives without chloro group.

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