New series of 2-methyl-N-(substituted arylidene) benzoxazole-5-carbohydrazide derivatives were synthesized by the reaction of Schiff bases of 2-methyl benzoxazole-5-carbohydrazide with appropriate aromatic aldehydes. The chemical structures of the synthesized compounds were confirmed by means of IR, 1HNMR, Mass spectral analysis. Further, the synthesized compounds (VIa-VIf) were screened for anti-inflammatory activity by using Carrageenan – induced paw edema rat model. The results showed that, compound VI c was significantly (p<0.0001) reduced the inflammation there by means of IR, 1HNMR, Mass spectral analysis. Further, the synthesized compounds (VIa-VIf) were screened for anti-inflammatory activity by using methyl benzoxazole-5-carbohydrazide with appropriate aromatic aldehydes.

**Key words:** Benzoxazole derivatives, IR, 1H NMR, Mass spectroscopy 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, antimicrobial[4], antihistaminic[5], antiparasitics[6], herbicidal[7], antiviral[8], ant allergic[9] and anthelmintic activities[10], antifungal[11], Cyclooxygenase Inhibiting[12], antitumor[13], antiulcer[14], anticonvulsant[15], hypoglycemic[16], anti-inflammatory[17,18] and anti-tubercular activity[19] Anti-inflammatory activity of benzoxazole derivatives were also reported in the literature. The title compounds were synthesized by treating the 2-methyl benzoxazole-5-carbohydrazide with appropriate aromatic aldehydes to get a new series of 2-methyl-N-(substituted arylidene) benzoxazole-5-carbohydrazide (VI a-VI f).

**MATERIALS AND METHODS**
All the reagents and solvents used were of laboratory grade. The melting points of synthesized compounds were determined by open capillary method and were uncorrected. The purity and homogeneity of compounds were checked using TLC technique. IR spectra[20] of compounds were recorded using KBr pellets on Perkin Elmer 337 spectrophotometer. 1H-NMR spectra[21] were recorded on Bruker Avance-300 MHz Spectrophotometer using dimethyl sulfoxamide as solvent at Apptuit laurus, hyderabad. Mass Spectra of the synthesized compounds were recorded on Liquid Chromatography Mass Spectrometer at Apptuit laurus, hyderabad.

**SYNTHESIS AND CHARACTERIZATION OF COMPOUNDS:**

1) 4-Hydroxy-3-nitro-benzoic acid methyl ester (II)
In a 1 ltr. three necked round bottom flask equipped with reflux condenser, mechanical stirrer and thermometer, of p-hydroxy methyl benzoate (10 g, 0.74 mol) was placed. A mixture of concentrated sulphuric acid (6.2 ml) and concentrated nitric acid (6.2 ml) in a dropping funnel, cool the flask in an ice bath to 0-10°¢ and then run in the nitrating mixture in p-hydroxy methyl benzoate with stirring, while maintaining the temperature of the reaction between 5 to 15°¢; the addition continued up to 1 h. Poured the reaction mixture in to of crushed ice (70 g). Filtered off the crude m-nitro, p-hydroxy methyl benzoate at the pump and wash with cold water. Transfer the solids into 500 ml flask and stirred it with ice cold methanol in order to remove a small amount of ortho isomer and other impurities. The mixture was filtered with suction and washed with little methanol and dried in the air. Then the product was recrystallised using methanol as solvent.(22)

**Percentage Yield-** 84%. **M.P.** 65-67°, **Rf-0.76** (Ethyl acetate: methanol, 1:1).

2) 3-Amino-4-hydroxy-benzoic acid methyl ester (III)
In a 500 ml three necked flat bottom flask equipped with reflux condenser with guard tube, compound II (10 g) was dissolved in boiling alcohol (50%, 100 ml) and sodium dithionate was added to this boiling alcohol solution until it becomes almost colorless. Then the alcohol was reduced to one third of its volume by distillation and the residual liquid was triturated with ice cold water. The resulting colorless, shiny product was filtered, washed with cold water, dried and recrystalise using methanol as solvent.(23) **Percentage Yield-** 70%, **M.P.** 110-112°, **Rf-0.67** (Saturated methanol),

3) 2-methyl benzoxazole-5-carboxylic acid methyl ester (IV)
Compound III (0.01mol) was heated with acetic acid (0.1mol) in excess under reflux for 2h. The reaction mixture was cooled and poured in crushed ice (100 gm) with stirring. The product thus separated was filtered under suction and washed with cold water. The products were recrystallised by using methanol as a solvent. **Percentage Yield-** 60%, **M.P.** 70-72°C, **Rf-0.7** (Saturated methanol),

4) 2-methyl benzoxazole-5-carboxylic acid hydrazide (V)
A mixture of an appropriate 2-substituted benzoxazole-5-carboxylic acid methyl ester IV (0.001 mol) in alcohol (25 ml) and hydrazine hydrate (99%, 0.015 mol) was heated under reflux on water bath for 4 hours. The alcohol was reduced to half of its volume and cooled. The product separated was filtered and washed with small portions of cold alcohol and then with cold alcohol...
5) Synthesis of 2-methyl-N-(substituted arylidene) benzoxazole-5-carbohydrazide(VI):
The 2-methyl benzoxazol-5-carboxylic acid hydrazides (V, 0.01mol) and appropriate aromatic aldehydes (0.015mol) in alcohol (20ml) with 2 to 3 drops of acetic acid, heated under reflux on a water bath for one hour. The solvent was removed to possible extent by distillation under reduced pressure. The product thus obtained was filtered, washed with water dried and purified by recrystallization from suitable solvent to produce the compounds GH1-GH8. The physical data of these benzoxazole derivatives were given in table 1.

### RESULTS AND DISCUSSION

Table 1: Physical data of 2-methyl-N-[substituted arylidene]-1,3-benzoxazole-5-carbohydrazide (VI a-VI f)

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Compound</th>
<th>Ar</th>
<th>Mol. Formula</th>
<th>Melting point (°C)</th>
<th>(%) Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>VI a</td>
<td>4-Hydroxy phenyl</td>
<td>C₈H₈N₂O₂</td>
<td>230</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>VI b</td>
<td>4-Dimethyl amino phenyl</td>
<td>C₈H₁₀N₂O₂</td>
<td>205</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>VI c</td>
<td>4-Methoxy phenyl</td>
<td>C₈H₁₀N₂O</td>
<td>220</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>VI d</td>
<td>4-Chlorophenyl</td>
<td>C₈H₈N₂ClO</td>
<td>224</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>VI e</td>
<td>4-Flourophenyl</td>
<td>C₈H₈N₂F₂</td>
<td>213</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>VI f</td>
<td>2-Nitrophenyl</td>
<td>C₈H₈N₂O₂</td>
<td>242</td>
<td>81</td>
</tr>
</tbody>
</table>

**Scheme of Synthesis:**

![Scheme of Synthesis](image)
RESULTS AND DISCUSSION

The target compounds were synthesized according to the Scheme-1. In the current research work, the title compounds N'[substituted sulfonyl]-1,3-benzoxazole-5-carboxyhydrazide, were synthesized by electrophilic aromatic substitution on p-hydroxy methyl benzoate (I) with concentrated nitric acid and concentrated sulfuric acid under reflux condition. Compound (II) on reduction with sodium dithionate with alcohol gives 3-amino-4-hydroxy benzoic acid methyl ester (III). Reaction of compound (III) with two appropriate aliphatic acids (formic acid and acetic acid) produced corresponding 2-substituted benzoxazole-5-carboxylic acid methyl esters. The reaction of compounds (IV) with hydrazine hydrate in ethanol on refluxing yielded the corresponding 2-substituted benzoxazole-5-carboxylic acid hydrazides. On further reaction of compounds (V) with the different aromatic aldehydes derivatives afforded the corresponding six 2-methyl-N-[substituted aryldiene]-1,3-benzoxazole-5-carboxyhydrazide. The identification and characterization of the synthesized compounds were carried out by melting point, Thin Layer Chromatography, FT-IR, NMR and Mass data to ascertain that all synthesized compounds were of different chemical nature than the respective parent compound.

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

CONCLUSION

Benzoxazole derivatives showed promising anti inflammatory activity. Compound Vle (methoxy phenyl) is found to be the most potent compound with an inhibition of paw volume of 73.70 percent after one hour of administration. The yields, melting points and physical data of newly synthesized compounds are summarized in Table-1.

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