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# Synthesis and Antiinflammatory Activity of Some New Benzoxazole Derivatives

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A series of some new 5-substituted benzoxazoles were synthesized and were characterized by elemental analysis, IR, $^1$H NMR and mass spectra. These compounds were also screened for its antiinflammatory activity.

**Key Words: Benzoxazole derivatives, Antiinflammatory activity.**

## INTRODUCTION

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 other than cellular elements of the immune response[1-6].

In most of these cases, it has been proved that the 5-substituted benzoxazole[7], substituted sulfonyl derivatives[8] and carbohydrazides[9] have promising antiinflammatory activity. Also, benzoxazole at its 5th position[10] is more prone for its lipophilic action and therefore, the authors are more interested for the substitution at 5th position of benzoxazole. In present investigation, a series of N′-[substituted sulfonyl]-1,3-benzoxazole-5-carbohydrazide (**VIa-h**) were synthesized using appropriate synthetic route and screened for its antiinflammatory activity.

## EXPERIMENTAL

Porous silica gel plates activated at 110 °C for 0.5 h were used for thin layer chromatography (TLC) and were developed with iodine vapours. IR spectra of compounds were recorded using KBr pellets on FTIR. $^1$H NMR

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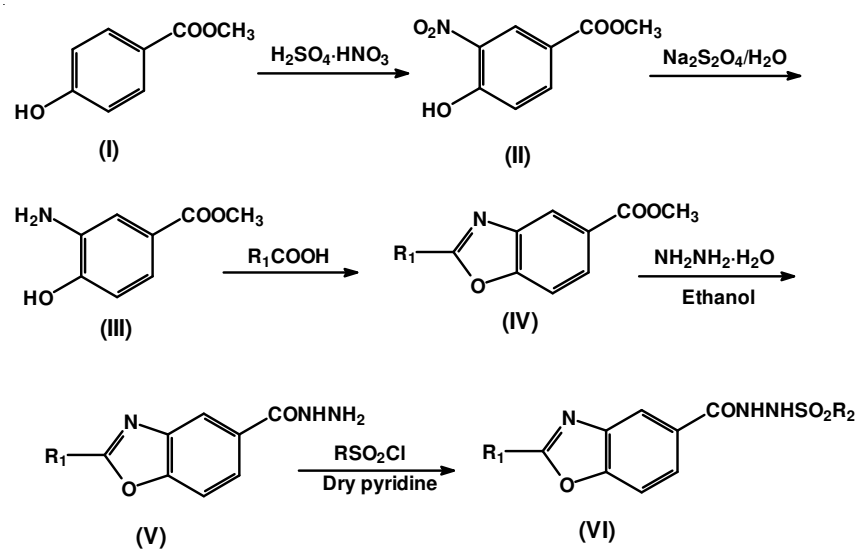
spectra (solvents) were recorded on Varian EM 390 spectra (chemicals shift in δ ppm). Mass spectra of the synthesized compounds were recorded on (FAB-MS) at National Chemical Laboratory, Pune.

All chemicals were used as purchased pure from Hi-Media, E-Merck, Collegens, *etc.* *p*-Hydroxy methyl benzoate (**I**) as starting material undergoes electrophilic substitution reaction, nitration by using concentrated nitric acid and concentrated sulphuric acid gives 4-hydroxy-3-nitro-benzoic acid methyl ester (**II**) this reaction is carried out at 0-10 ºC and recrystallized by methanol. Compound **II** undergoes reduction by using sodium dithionate as reducing agent in mixture with methanol gives good yield of 3-amino-4-hydroxybenzoic acid methyl ester (**III**). This was recrystallised by using methanol. On further reaction of compound **III** with aliphatic acid like formic and acetic acid gives corresponding compounds 2-subtituted benzoxazole-5-carboxylic acid methyl ester (**IVa-b**). Both these products were recrystallised from alcohol. Compounds (**IVa-b**) on reaction with hydrazine hydrate and mixture with ethanol gives corresponding 2-substituted benzoxazole-5-carboxylic acid hydrazides (**Va-b**) also both these products was recrystallized from alcohol. And finally compounds (**Va-b**) on further reaction with substituted sulfonyl chlorides by using pyridine as catalyst which traps HCl gas in compounds gives corresponding N`-[substituted sulfonyl]-1,3-benzoxazole-5-carbohydrazide (**VIa-h**) compounds (**Scheme-I**). Finally, these eight compounds were recrystallized by ethanol give pure compounds. The physical data of the synthesized compounds is given in Table-1.




**Scheme-I**

TABLE-1
PHYSICAL DATA OF SYNTHESIZED COMPOUNDS
N′-[SUBSTITUTED SULFONYL]-1,3-BENZOXAZOLE-5-CARBOHYDRAZIDE (**VIa-h**)

| Compd. | $R_1$ | $R_2$ | m.f. | m.p. (ºC) uncorrected | Yield (%) | $R_f$ |
|---|---|---|---|---|---|---|
| **VIa** | H | 4-Methyl phenyl | $C_{15}H_{13}N_3O_4S$ | 72-74 | 38 | 0.63 |
| **VIb** | $CH_3$ | 4-Methyl phenyl | $C_{16}H_{15}N_3O_4S$ | 78-80 | 57 | 0.60 |
| **VIc** | H | 4-Acetamido phenyl | $C_{16}H_{14}N_4O_5S$ | 92-94 | 72 | 0.57 |
| **VId** | $CH_3$ | 4-Acetamido phenyl | $C_{17}H_{16}N_4O_5S$ | 88-90 | 40 | 0.54 |
| **VIe** | H | 4-Chloro phenyl | $C_{14}H_{10}N_3O_4SCl$ | 110-112 | 75 | 0.53 |
| **VIf** | $CH_3$ | 4-Chloro phenyl | $C_{15}H_{12}N_3O_4SCl$ | 102-104 | 72 | 0.64 |
| **VIg** | H | Benzene | $C_{14}H_{11}N_3O_4S$ | 69-70 | 30 | 0.62 |
| **VIh** | $CH_3$ | Benzene | $C_{15}H_{13}N_3O_4S$ | 66-68 | 40 | 0.72 |

## Spectral data

**Compound VIa:** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3390 (-NH- *str.*), 3085 (Ar-H *str.*), 1730 (-CO- *str.*), 1625 (C-N *str.*), 1315 and 1398 (-S-O *str.*), 1165 (ether group in ring), 835 (C=C bending). $^1H$ NMR ($CDCl_3$) δ: 7.34-7.95 (m, 8H), 8.0 (s, 2H), 2.35 (d, 3H). FAB-MS: (m/z, 100 %): 331 ($M^+$). Elemental analysis for $C_{15}H_{13}N_3O_4S$: Calculated (%): C: 52.9, H: 4.04, N: 13.08, Found (%): C: 52.5, H: 4.04, N: 13.12.

**Compound VIb:** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3319 (-NH- *str.*), 3010 (Ar-H *str.*), 2230 (C-C *str.*) 1730 (-CO- *str.*), 1625 (C=N *str.*), 1315 (-S-O *str.*), $^1H$ NMR ($CDCl_3$) δ: 7.34-7.95 (m, 7H), 8.0 (s, 2H), 2.35 (d, 6H). FAB-MS: (m/z, 100 %): 345 [$M^+$], Elemental analysis for $C_{16}H_{15}N_3O_4S$: Calculated (%): C: 55.6, H: 4.34, N: 12.07, Found (%): C: 55.5, H: 4.38, N: 12.10.

**Compound VIc:** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3327 (-NH- *str.*), 3010 (Ar-H *str.*), 1730 (-CO- *str.*), 1352 (-SO *str.*), 1116 and 1172 $cm^{-1}$ (CONH *str.*), $^1H$ NMR ($CDCl_3$) δ: 7.44-7.95 (m, 8H), 8.0 (s, 3H), 2.02 (d, 3H). FAB-MS: (m/z, 100 %): 374 ([$M^+$], (100 %) Elemental analysis for $C_{16}H_{14}N_4O_5S$: Calculated (%): C: 53.63, H: 3.91, N: 15.64, Found (%): C: 53.65, H: 3.87, N: 15.76.

**Compound VId:** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3324 (-NH- *str.*), 1322 (-S-O *str.*), 1730 (-CO- *str.*), 1629 (C=N *str.*), 3110 (Ar-H *str.*), 3180 (CONH *str.*). $^1H$ NMR ($CDCl_3$) δ: 7.44-7.95 (m, 7H), 8.0 (s, 3H), 2.02 and 2.35 (d, 6H). FAB-MS: (m/z, 100 %): 388 [$M^+$], Elemental analysis for $C_{17}H_{16}N_4O_5S$: Calculated (%): C: 52.57, H: 4.12, N: 14.43, Found (%): C: 52.560, H: 4.16, N: 14.47.

**Compound VIe:** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3216 (-NH- *str.*), 3090 (Ar-H *str.*), 1339 (-S-O *str.*), 772 (C-Cl *str.*), $^1H$ NMR ($CDCl_3$) δ: 7.44-7.95 (m, Ar-H, 8H), 8.0 (s, 2H). FAB-MS: (m/z, 100 %): 351.50 [$M^+$], Elemental analysis for $C_{14}H_{10}ClN_3O_4S$: Calculated (%): C: 45.94, H: 2.94, N: 12.37, Found (%): C: 45.97, H: 2.98, N: 12.40.

**Compound VIf:** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3204 (-NH- *str.*), 3180 (CONH *str.*), 3097 (Ar-H *str.*), 1730 (-CO- *str.*), 1354 and 1329 (-S-O *str.*), 767 (C-Cl *str.*), $^1H$ NMR ($CDCl_3$) δ: 7.44-7.95 (m, 7H), 8.0 (s, 2H), 2.35 (d, 3H) FAB-MS: (m/z, 100 %): 317.50 [$M^+$], Elemental analysis for $C_{15}H_{12}ClN_3O_4S$: Calculated (%): C: 47.81, H: 3.73, N: 11.81, Found (%): C: 47.78, H: 3.75, N: 11.84.

**Compound VIg:** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3350 (-NH- *str.*), 3174 (CONH *str.*), 3097 (Ar-H *str.*), 1730 1 (-CO- *str.*), 1329 (-S-O *str.*), 674 (C-C bending) $^1H$ NMR ($CDCl_3$) δ: 7.03-7.95 (m, Ar-H, 9H), 8.0 (s, 2H). FAB-MS: (m/z, 100 %): 317 [$M^+$], Elemental analysis for $C_{14}H_{11}N_3O_4S$: Calculated (%): C: 51.31, H: 3.28, N: 13.81, Found (%): C: 51.33, H: 3.32, N: 13.85.

**Compound VIh:** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3204 (-NH- *str.*), 3085 (Ar-H *str.*), 2990 (C-C *str.*), 1346 (-S-O *str.*), 1730 (-CO- *str.*), 1625 (C=N *str.*), $^1H$ NMR ($CDCl_3$) δ: 7.03-7.95 (m, 8H), 8.0 (s, 2H), 2.35 (d, 3H). FAB-MS: (m/z, 100 %): 331 [$M^+$], Elemental analysis for $C_{15}H_{13}N_3O_4S$: Calculated (%): C: 53.31, H: 3.75, N: 13.12, Found (%): C: 53.34, H: 3.77, N: 13.16.

## Pharmacological screening

$LD_{50}$ of test compounds was performed at National Toxicological Center, Pune and determined on mice as per the OECD Guidelines[11] 423. As per studies 2000 mg/kg dose was considered as $LD_{50}$. 1/10th of the $LD_{50}$ was considered as an effective dose *i.e.* 200 mg/kg.

TABLE-2
ANTIINFLAMMATORY ACTIVITY DATA OF THE SYNTHESIZED COMPOUNDS (**IVa-h**)

| Group | Test material (dose) | Mean increase in paw volume and % inhibition | | |
|---|---|---|---|---|
| | | 1 h | 2 h | 3 h |
| 1 | Control | 1.29 ± 0.152 | 1.73 ± 0.200 | 1.90 ± 0.116 |
| 2 | **VIa** 200 mg/kg | 1.06 ± 0.116 (17.82%) | 1.38 ± 0.019 (20.23%) | 1.66 ± 0.168 (18.63%) |
| 3 | **VIb** 200 mg/kg | 1.13 ± 0.212 (12.40%) | 1.38 ± 0.200 (20.23%) | 1.51 ± 0.292 (20.52%) |
| 4 | **VIc** 200 mg/kg | 1.19 ± 0.364 (7.75%) | 1.24 ± 0.167 (14.45%) | 1.50 ± 0.342 (21.05%) |
| 5 | **VId** 200 mg/kg | 1.22 ± 0.0740 (5.42%) | 1.58 ± 0.081 (12.45%) | 1.68 ± 0.223 (11.57%) |
| 6 | **VIe** 200 mg/kg | 1.28 ± 0.98 (0.77%) | 1.48 ± 0.305 (14.45%) | 1.50 ± 0.340 (21.05%) |
| 7 | **VIf** 200 mg/kg | 1.09 ± 0.0659 (15.50%) | 1.35 ± 0.100 (21.96%) | 1.22 ± 0.189 (30.78%) |
| 8 | **VIg** 200 mg/kg | 1.47 ± 0.285 (21.63%) | 0.57 ± 0.158 (26.35%) | 1.07 ± 0.328 (40.05%) |
| 9 | **VIh** 200 mg/kg | 1.10 ± 0.0815 (14.72%) | 1.22 ± 0.169 (35.78%) | 1.00 ± 0.145 (42.19%) |
| 10 | Standard Ibuprofen 50 mg/kg) | 0.95 ± 0.158 (26.35%) | 1.09 ± 0.178 (36.99%) | 1.03 ± 0.163 (45.78%) |

**Antiinflammatory activity:** The antiinflammatory activities of these compounds were done by using carrageenan induced rat paw edema method[12]. Antiinflammatory activity data are summarized in Table-2.

## RESULTS AND DISCUSSION

5-Substituted benzoxazole has proved to be a promising moiety for antiinflammatory activity. The test compounds (**VIa-h**) showed significant antiinflammatory activity compared with the standard drug ibuprofen. Among these compounds **VId** and **VIe** possesses good and compound **VIb**, **VIc** and **VIf** possess moderate antiinflammatory activity. All the significant compounds also possess antiinflammatory activity with reduced toxicity.

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