Synthesis and Anti-inflammatory Activity of Some Novel 2,4-Diaryl-3,5-bis(arylimino)-1,2,4-thiadiazolidine Derivatives

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Received 1 July 2008; Accepted 21 August 2008

Abstract: A series of some novel 2,4-diaryl-3,5-bis(arylimino)-1,2,4-thiadiazolidine derivatives were synthesized and evaluated for anti-inflammatory activity. In the SAR study, the phenyl ring on 3 and 4 position of 1,2,4-thiadiazolidine ring substituted with chloro, nitro and methoxy groups showed better activity. The title compounds were synthesized from two steps; the first step involved the synthesis of diaryl substituted thioureas then, it was cyclised to give the 1,2,4-thiadiazole system in the presence of oxidizing agent (hydrogen peroxide and concentrated hydrochloric acid) in the second step. The purity of the synthesized compounds were judged by their C, H and N analysis and the structure was analyzed on the basis of IR, H$^{1}$NMR, C$^{13}$NMR and Mass spectral data. The anti-inflammatory activity of new compounds was determined by λ-Carrageenan induced mice paw edema method using diclofenac sodium as a standard. Among the compounds tested four compounds, B2 (2,4-diphenyl-3,5-bis(3-nitrophenylimino)-1,2,4-thiadiazolidine), B4 (2,4-diphenyl-3,5-bis(3-chlorophenylimino)-1,2,4-thiadiazolidine), B6 (2,4-diphenyl-3,5-bis(4-methoxyphenylimino)-1,2,4-thiadiazolidine) and B7 (2,4-diphenyl-3,5-bis(2-methoxyphenylimino)-1,2,4-thiadiazolidine) were the most active compounds in these series.

Keywords: 1,2,4-Thiadiazolidine, Carrageenan, Diclofenac sodium, Thioureas, Hydrogenperoxide

Introduction

The 1,2,4-thiadiazoles exhibit broad spectrum of biological activities, possibly due to the presence of toxophoric N-C-S moiety. 1,2,4-Thiadiazoles are an important class of heterocycles,
which have been the subject of great interest because of their biological activities. 1,2,4-thiadiazoles are highly potent inhibitors of human immunodeficiency virus type 1 (HIV-1) replication, alzheimer’s disease, cardio protective actions (delay in ischaemia-induced Na⁺ overload) and antibiotic activity, antihelicobacter pylori activity and various CNS activities.

The traditional NSAIDs (Non-steroidal anti-inflammatory drugs) in current use non-selectively inhibit COX-1 and COX-2. In fact, most of them show greater selectivity for COX-1 than COX-2. Consequently long term therapy with nonselective NSAIDs may cause gastrointestinal complications ranging from stomach irritation to life-threatening GI ulceration and bleeding. Therefore, selective COX-2 inhibitors with better safety profile have been marketed as a new generation of NSAIDs. But careful prospective examination of coxibs has revealed unexpected cardiovascular adverse effects. Thus there remains a compelling need for effective NSAIDs with an improved safety profile.

One of the most interesting reactions in organic chemistry is the oxidation of thioureas. Depending on the substitution pattern of the thiourea, the oxidizing agent, the polarity of the medium variety of products are formed.

In the present study, 2,4-diaryl-3,5-bis(arylimino)-1,2,4-thiadiazolidines synthesized from two steps; the first step involved the synthesis of N,N’-diaryl thioureas which is prepared by heating a mixture of primary aromatic amine and carbon disulphide in absolute ethanol and in the second step N,N’-diarylthioureas were cyclised to give the 2,4-diaryl-3,5-bis (arylimino)-1,2,4-thiadiazolidine system in the presence of oxidizing agent (hydrogen peroxide and concentrated hydrochloric acid). The titled compounds were evaluated for anti-inflammatory property by 𝜆-Carrageenan-induced mice paw edema method.

**Experimental**

The melting points of the compounds were determined in open capillary tubes on a Thomas hoover melting point apparatus (Perfit) and are uncorrected. IR spectra were recorded in KBr pellets on JASCO FT IR-5300 infrared spectrophotometer (Japan). ¹H-NMR spectra were determined at 300.40 MHz JEOL-AL 300 (Fourier Transformer, Japan) and mercury plus Varian (400 MHz) spectrometers with tetramethyl silane as internal standard. The FT ¹³C NMR recorded in CDCl₃ at 25.2MHz. Mass spectra were recorded on JOEL SX 102/DA-6000 Mass Spectrometer (Japan). U.V/Visible spectra were taken in the region of 200-600nm, on Jasco UV-Visible spectrophotometer (Japan). The elemental analysis of the compounds was performed by Perkin Elmer model 240C analyzer (U.S.A).

**Step 1**

Synthesis of N,N’-diarylthiourea derivatives from various substituted aromatic amines (Scheme 1).

![Scheme 1.](attachment:Scheme_1.png)

- A₁ = R = H, R₂ = H, A₂ = R = m-NO₂, R₁ = m-NO₂
- A₃ = R = o-NO₂, R₁ = m-NO₂
- A₄ = R = m-Cl, R₁ = m-Cl
- A₅ = R = p-Cl, R₁ = p-Cl
- A₆ = R = p-OCH₃, R₁ = p-OCH₃
- A₇ = R = o-OCH₃, R₁ = o-OCH₃

**Scheme 1.**
In a one liter round bottomed flask provided with an efficient double surface condenser, placed 0.04 mol of substituted aniline, 15 g (40 mL, 0.66 mL) of carbon disulphide, 63.5 mL of rectified spirit and 3 g of potassium hydroxide pellets (to reduce the reaction time) then the apparatus was kept in the fume cupboard. The reaction mixture was refluxed in an electric mantle for six hours. When the reaction was completed, arranged the condenser downward distillation and the excess of carbon disulphide and alcohol were removed. The residue in the flask was shaken with excess of dilute hydrochloric acid (1:10) to remove any excess aniline was present and filtered at the pump. Then, washed with water and dried. The crude product was recrystallised by dissolving it under reflux in boiling rectified spirit and added hot water until the solution just became cloudy and cooled. The pure diarylthioureas were separated as colorless needle.

Thioureas (A1-A8) were confirmed by IR, due to the presence of peaks at 3279-3271(NH), 3031-3033(Ar=CH), 1533-1534(N-C=S), 1494-1450(C-N), 1226-1222(C=S), 1070, 680,645(Ar-H bending vibrations).

Step 2
Synthesis of 2,4-diaryl-3,5-bis (arylimino)-1,2,4-thiadiazolidine derivatives N,N'-diarylthiourea derivatives (Scheme 2)

\[ \text{C}_2\text{H}_5\text{OH} \quad \begin{array}{c} \text{H}_2\text{O}_2 \\ \text{HCl} \end{array} \]

\[ \begin{array}{c} \text{R} \\ \text{R}_1 \\ \text{R}_2 \\ \text{R}_3 \\ \text{R}_4 \\ \text{R}_5 \\ \text{R}_6 \\ \text{R}_7 \end{array} \]

B₁ = R₁H, R₂H, R₃H, R₄H, B₂ = R₁m-NO₂, R₂m-NO₂, R₃m-NO₂, R₄m-NO₂
B₃ = R₁p-NO₂, R₂p-NO₂, R₃p-NO₂, R₄p-NO₂
B₄ = R₁m-Cl, R₂m-Cl, R₃m-Cl, R₄m-Cl
B₅ = R₁p-Cl, R₂p-Cl, R₃p-Cl, B₆ = R₁p-OCH₃, R₂p-OCH₃, R₃p-OCH₃, R₄p-OCH₃
B₇ = R₁o-OCH₃, R₂o-OCH₃, R₃o-OCH₃, R₄o-OCH₃

3 g of A1 –A9 was dissolved in 25 mL of methanol. 2 mL of conc. hydrochloric acid and excess of hydrogen peroxide solution (about 30 mL 6%, volumes) were added in to the above mixture. The reaction mixture was cooled intermittently, as during the addition of hydrogen peroxide solution as the temperature was tend to rise. The light yellow sticky mass obtained was removed by filtration and the resulting filtrate was basified with ammonia solution. The precipitate obtained (B1-B7) was filtered, washed with cold water and dried. Physical constant of the compounds are given in the Table1.
### Table 1. Physical data of 2,3,4,5-tetra aryl substituted 1,2,4-thiadiazolidines.

| S.No | Comp. | R1  | R2  | R3  | R4  | % Yield | M.P, °C | Mol. Formula | Mol. Wt | Rf\(^a\) | Rm\(^b\) |
|------|-------|-----|-----|-----|-----|---------|---------|--------------|---------|---------|---------|
| 1    | D1    | H   | H   | H   | H   | 75.5    | 152     | C\(_{26}\)H\(_{20}\)N\(_4\)S | 420.5288 | 0.728   | -0.4276 |
| 2    | D2    | 3-NO\(_2\) | 3-NO\(_2\) | 3-NO\(_2\) | 3-NO\(_2\) | 82.0 | 103 | C\(_{26}\)H\(_{18}\)N\(_4\)O\(_5\)S | 600.51904 | 0.864   | -0.8029 |
| 3    | D3    | 2-NO\(_2\) | 2-NO\(_2\) | 2-NO\(_2\) | 2-NO\(_2\) | 80.0 | 68 | C\(_{26}\)H\(_{16}\)N\(_4\)O\(_5\)S | 600.51904 | 0.782   | -0.5650 |
| 4    | D4    | 3-Cl  | 3-Cl  | 3-Cl  | 3-Cl  | 70.5 | 110 | C\(_{26}\)H\(_{16}\)Cl\(_4\)N\(_2\)OS | 558.30904 | 0.850   | -0.7535 |
| 5    | D5    | 4-Cl  | 4-Cl  | 4-Cl  | 4-Cl  | 72.0 | 144 | C\(_{26}\)H\(_{16}\)Cl\(_4\)N\(_2\)OS | 558.30904 | 0.874   | -0.8411 |
| 6    | D6    | 4-OCH\(_3\) | 4-OCH\(_3\) | 4-OCH\(_3\) | 4-OCH\(_3\) | 69.0 | 210 | C\(_{30}\)H\(_{28}\)N\(_4\)O\(_5\)S | 540.63272 | 0.892   | -0.9169 |
| 7    | D7    | 2-OCH\(_3\) | 2-OCH\(_3\) | 2-OCH\(_3\) | 2-OCH\(_3\) | 65.0 | 196 | C\(_{30}\)H\(_{28}\)N\(_4\)O\(_5\)S | 540.63272 | 0.861   | -0.7919 |

\(^a\) The solvent system used for TLC was chloroform:methanol (8:2) for all the compounds \(^b\) Rm = log \([(1/Rf)-1]\)
Compound B1
UV (λmax) nm in ethanol: 246, (IR) υmax (KBr cm⁻¹): 3096-3005 (Ar=CH), 2362 (C-N), 1594 (C=N), 1526, 1438 (aromatic skeleton), 1253 (C-S), 1110 (N-C-N), 802, 734 (Ar-H bending vibration), 669 (N-S-C), 1H-NMR (δ-ppm): 6.9-7.4 (m, 3H, meta, para hydrogens of aryl Ar), 8.127-8.229 (m, 2H’s ortho to imino nitrogen on adjacent carbon of Ar)

Compound B2
(IR) υmax (KBr cm⁻¹): 3095-3007 (Ar=CH), 2360 (C-N), 1593 (C=N), 1525, 1437 (aromatic skeleton), 1354 (C-NO₂), 1251 (C-S), 1112 (N-C-N), 802, 734 (Ar-H bending vibration), 669 (N-S-C), 1H-NMR (δ-ppm): 8.29 (m, 2H meta, para to NO₂ of Ar), 9.68 (m, 2H’s ortho NO₂ of Ar)

Compound B3
UV (λmax) nm in ethanol: 268.1. (IR) υmax (KBr cm⁻¹): 3094-3007 (Ar=CH), 2359 (C-N), 1592 (C=N), 1522, 1438 (aromatic skeleton), 1358 (C-NO₂), 1252 (C-S), 1083 (N-C-N), 805, 733 (Ar-H bending vibration), 669 (N-S-C), 1H-NMR (δ-ppm): 7.33 (m, H’s meta, para to NO₂ of Ar long range coupling), 9.34 (m, H’s ortho to nitro group on the phenyl ring attached to thiadiazolidine ring)

Compound B4
UV (λmax) nm in ethanol: 252. (IR) υmax (KBr cm⁻¹): 3064 (Ar=CH), 2360 (C-N), 1514, 1473 (aromatic skeleton), 1244 (C-S), 1074 (N-C-N), 781 (C-Cl), 852 (Ar-H bending vibration) 664 (N-S-C), 1H-NMR (δ-ppm): 7.46-7.50 (m, hydrogens ortho to phenyl ring), 8.60-7.72 (m, 2H ortho to imino nitrogen on adjacent carbon of Ar, long range coupling)

Compound B5
UV (λmax) nm in ethanol: 269. (IR) υmax (KBr cm⁻¹): 3062 (Ar=CH), 2359 (C-N), 1623 (C=N), 1513, 1472 (aromatic skeleton), 1246 (C-S), 1074 (N-C-N), 779 (C-Cl), 851 (Ar-H bending vibration) 665 (N-S-C), 1H-NMR (δ-ppm): 7.46-7.50 (m, 2H, hydrogens ortho to phenyl ring), 8.60-7.72 (m, 2H ortho to imino nitrogen on adjacent carbon of Ar)

Compound B6
UV (λmax) nm in ethanol: 368.5. (IR) υmax (KBr cm⁻¹): 3059 (Ar=CH), 2948 (CH₃), 2357 (C-N), 1621 (C=N), 1514, 1471 (aromatic skeleton), 1269 (C-O), 1245 (C-S), 1071 (N-C-N), 782, 850 (Ar-H bending vibration) 663 (N-S-C), 1H-NMR (δ-ppm): 1.81 (s, 3H of O-CH₃) 7.71 (dd, 2H, ortho to imino nitrogen on adjacent carbon of Ar) 8.86 (dd, 2H, ortho to O-CH₃ of Ar)

Compound B7
UV (λmax) nm in ethanol: 369. (IR) υmax (KBr cm⁻¹): 369, 3060 (Ar=CH), 2948 (CH₃), 2349 (C-N), 1621 (C=N), 1513, 1472 (aromatic skeleton), 1271 (C-O), 1244 (C-S), 1072 (N-C-N), 780, 853 (Ar-H bending vibration) 664 (N-S-C), 1H-NMR (δ-ppm): 1.76 (s, 3H of O-CH₃) 7.12 (m, H’s ortho, meta to imino nitrogen of Ar) 8.94 (m, H’s ortho, meta to -OCH₃ of phenyl ring)

13C–NMR spectrum
The 13C–NMR spectrum of 5-imino-N, 4-diphenyl-1,2,4-thiadiazolidine-3-amine exhibited (B1) the two thiadiazole ring carbons at positions 3 and 5 absorb at δ 186.4 and 173.1, respectively. The four signals at δ 128.1, 128.7, 130.2 and 132.7 are assigned to the phenyl ring carbons.
Mass spectrum

The mass spectrum exhibits a molecular ion at m/z 420 which is consistent with the molecular weight of B1 molecular formula \([\text{C}_{26}\text{H}_{20}\text{N}_{4}\text{S}]^{+}\) (MW 420.5288) and base peak due to cleavage of \([\text{C}_{12}\text{H}_{10}\text{N}_{2}\text{S}]^{+}\) at m/z = 226 and two intense peaks at m/z 194 due to desulfuration from base peak with relative intensity of 9% and a peak at m/z 167 with relative intensity of 11% due to cleavage of HCN from \([\text{C}_{12}\text{H}_{10}\text{N}_{2}]^{+}\).

Compounds B2 and B3 exhibit a molecular ion at m/z 604 molecular formula \([\text{C}_{30}\text{H}_{16}\text{N}_{8}\text{O}_{8}\text{S}]^{+}\) (MW 604) and base peak due to cleavage of \([\text{C}_{13}\text{H}_{9}\text{N}_{6}\text{O}_{4}\text{S}]^{+}\) at m/z = 317 and two intense peaks at m/z 287 due to desulfuration from base peak with relative intensity of 12% and a peak at m/z 227 due to liberation of 2NO with relative intensity of 17%. Followed by peak at m/z = 171 due to cleavage of 2CO then the liberation of HCN to at m/z = 144.

Compounds B4 and B5 exhibit a molecular ion at m/z 558, molecular formula \([\text{C}_{26}\text{H}_{16}\text{Cl}_{14}\text{N}_{4}\text{S}]^{+}\) (MW 558.30) and base peak due to cleavage of \([\text{C}_{13}\text{H}_{8}\text{Cl}_{2}\text{N}_{2}\text{S}]^{+}\) at m/z = 265 and two intense peaks at m/z 195 due to desulfuration from base peak with relative intensity of 13% and a peak at m/z 125 due to liberation of -2Cl with relative intensity of 16% and the cleavage of HCN from the above leads to peak at 98.

Furthermore, the presence of a chlorine atom in a molecule can be characterized by the presence of a P+2 peaks, which is due to a fragment containing natural abundance of isotopic 37.5Cl atom. The intensity of the P+2 peaks appeared as 1/3 less intense than of the molecular ion for the existence of one chlorine atom in the molecule.

Compounds B6 and B7 exhibit a molecular ion at m/z 541 which is consistent with the molecular weight of D6 and D7 molecular formula \([\text{C}_{30}\text{H}_{28}\text{N}_{4}\text{O}_{4}\text{S}]^{+}\) (MW 541) and base peak due to cleavage of \([\text{C}_{15}\text{H}_{15}\text{N}_{2}\text{O}_{2}\text{S}]^{+}\) at m/z = 225 due to desulfuration from base peak at m/z 287 and two intense peaks at m/z 255 due to desulfuration from base peak at m/z 225 due to liberation of 2CH with relative intensity of 21%. Followed by peak at m/z = 171 due to cleavage of 2CO then the liberation of HCN to at m/z = 144.

Biological investigation

Experimental protocols and procedures used in this study were approved by the Animal Ethics Committee of the Allahabad Agricultural Institute-Deemed University, Allahabad.

Animals

Wister rats of both sexes weighing 250–300 g were used. The animals were kept and maintained under laboratory conditions of temperature, humidity, and light; and were allowed free access to food (standard pellet diet) and water ad libitum. The animals were divided into – synthesized 1,2,4-thiadiazolidine, reference drug treated ‘test’, and distilled water-treated ‘control’ groups of six animals per group.

Data analysis

Experimental data obtained from ‘test’ rats treated synthesized compounds (td) (B1-B7), diclofenac sodium alone, as well as those obtained from sodium carboxy methyl cellulose-treated ‘control’ mice and rats, were pooled and expressed as means (±S.E.M.). The differences standard drug treated - or synthesized compounds - treated ‘test’ rats means, and sodium carboxy methyl cellulose(NaCMC) treated ‘control’ rats means, Statistical comparisons were performed using Students ‘t’ test, to assess the level of significance of the differences between the ‘test’ and ‘control’ group data means. Values of \(P\leq0.05\) were taken to imply statistical significance.
**Method**

The rats used were divided into three broad (A, B and C) experimental groups of eight rats per group. Group A rats were used as control and each animal in this group (A) received sodium carboxy methyl cellulose (sodium CMC) (0.1% 3 mL / kg i.p.) only. Group B ‘test’ rats received the above mentioned synthesized compounds (100 mg/kg i.p.). Group C ‘test’ rats received diclofenac sodium (DIC, 100 mg/kg i.p.). The rat hind paw oedema was used as a model of acute inflammation. Acute inflammation of the hind paw was induced in each of the rat by injecting carrageenan (0.1 mL (3%)/kg) into the sub plantar surface of the right hind paw. Pedal inflammation (oedema) was always evident within 5–8 min following fresh carrageenan (0.1 mL (3%) / kg) injection. Linear diameter of the injected paw was measured (with a screw gauze) for 3 h at 30 min intervals after the administration of the phlogistic agent. Increases in the linear diameter of the right hind paws were taken as indicators of paw oedema. Oedema was assessed in terms of the difference in the ‘zero time’ (C0) linear diameter of the injected right hind paw, and its linear diameter at ‘time t’ [(Ct)—that is, 30, 60, 90, 120, 150 and 180 min] following fresh carrageenan administration.

The increases in the right hind paw diameters induced by injections of fresh carrageenan were compared with those of the contra-lateral, non-injected left hind paw diameters. Synthesized compounds (100 mg/kg i.p.) were separately administered to each of the rats in the ‘test’ Group B, 30 min before inducing inflammation with the injection of fresh carrageenan. Rats in the reference, comparative ‘test’ Group received diclofenac (DIC, 100 mg/kg i.p.); while rats in the ‘control’ Group A received sodium carboxy methylcellulose (NaCMC) (3 mL (0.1%)/kg i.p.) only. Percentage inflammation (oedema) was calculated from the formula: \( \frac{C_0}{C_t} \times 100 \); while percentage inhibition of the oedema was calculated from the formula: \( \frac{C_0-C_t}{C_0} \times 100 \) [where \( C_0 \) is the average inflammation (hind paw oedema) of the ‘control’ Group A rats at a given time; and \( C_t \) is the average inflammation of the (Group B) Compounds (td) B1-B9 or (Group C) diclofenac-treated rats at the same time]. At the doses tested 30 and 100 /kg all the compounds possessed activity at 100 mg. (Table 2)

**Results and Discussion**

The titled compounds were synthesized from two steps, the first step involved was the synthesis of diaryl substituted thioureas and in the second step diaryl substituted thioureas cyclised to give the 1,2,4-thiadiazole system in the presence of oxidizing agent (hydrogen peroxide and concentrated hydrochloric acid). Diaryl thioureas were confirmed by IR, due to the presence of stretching vibration at 1529-1511 (N-C=S). 1,2,4-thiadiazolidines, \(^1\)H NMR showed the peaks for Ar-NH, aryl protons and for proton on imino nitrogen, \(^13\)C–NMR spectrum, shown signal for the two carbons of the thiadiazole ring and the mass spectrum exhibited major fragmentation pathways involving the cleavage of weaker C-S and C-N bond.

The percentage of protection against carrageenan induced inflammation shown at the end of 180 minutes by the 2,3,4,5-tetra substituted thiadiazolidine derivatives (% protection). All the compounds showed significant activity in comparison between the negative control group and the positive control group treated with diclofenac sodium.
### Table 2. Anti-inflammatory activity of 1,2,4-thiazolidine derivatives (D1-D7).

| Experimental group (N) | Dose   | 30      | 60      | 90      | 120     | 150     | 180     |
|------------------------|--------|---------|---------|---------|---------|---------|---------|
|                        |        | Time (in min) and paw diameter (in mm) |         |         |         |         |         |
| Group A (Untreated)    | 0      | 10.38±0.40 | 12.44±0.32 | 15.36±0.44 | 13.56±0.34 | 12.36±0.38 | 11.48±0.31 |
| Group B SodC MC treated | 3 mL/Kg | 10.38±0.35 (0.00%) | 12.43±0.36 (0.08%) | 15.34±0.41 (0.13%) | 13.53±0.40 (0.22%) | 13.53±0.40 (0.22%) | 12.34±0.37 (0.16%) |
| B1                     | 100 mg/Kg | 6.54±0.28** (43.93%) | 6.22±0.32** (49.95%) | 5.91±0.28** (61.47%) | 4.54±0.12*** (66.44%) | 4.12±0.24** (69.54%) | 3.71±0.39** (69.93%) |
| B2                     | 100 mg/Kg | 5.82±0.36** (27.36%) | 5.42±0.43*** (56.48%) | 4.84±0.38*** (68.45%) | 4.12±1.5** (69.54%) | 3.58±0.28** (73.54%) | 3.21±0.41** (73.98%) |
| B3                     | 100 mg/Kg | 6.41±0.31** (44.12%) | 6.12±0.40** (61.06%) | 5.81±0.35*** (62.25%) | 4.82±1.11*** (64.59%) | 4.31±1.01*** (65.12%) | 4.01±0.11*** (67.50) |
| B4                     | 100 mg/Kg | 5.12±0.31** (50.67) | 4.84±0.29** (61.06) | 4.12±1.7** (73.14) | 3.46±1.41*** (74.42) | 3.23±1.21*** (76.12) | 2.89±1.12*** (76.58) |
| B5                     | 100 mg/Kg | 6.34±0.12* (46.44%) | 6.12±0.35** (61.06%) | 5.82±0.42** (62.56%) | 4.83±0.32** (64.29) | 4.14±0.21** (68.12) | 3.89±0.29** (68.94) |
| B6                     | 100 mg/Kg | 5.41±0.44*** (47.88%) | 5.13±0.43*** (58.72%) | 4.74±0.40** (69.10) | 4.12±0.32** (71.84) | 3.81±0.35*** (73.90) | 3.22±0.12*** (73.97) |
| B7                     | 100 mg/Kg | 4.98±0.34** (52.02%) | 4.51±0.25** (63.71%) | 4.14±0.12* (73.01) | 3.56±0.43*** (73.68) | 3.32±0.28** (75.54) | 3.20±0.26** (73.97) |
| DIC                    | 100 mg/Kg | 4.22±0.31*** (69.24%) | 4.00±0.40*** (67.04%) | 3.26±0.35*** (78.13) | 2.10±0.11*** (85.25) | 0.73±0.10*** (94.28) | 0.05±0.28** (99.56) |

* P < 0.05; **P < 0.01; ***P < 0.001 vs. control. N= 6 animals each group
The compounds B2 (2,4-diphenyl-3,5-bis(3-nitrophenylimino)-1,2,4-thiadiazolidine) and B4 (2,4-diphenyl-3,5-bis(3-chlorophenylimino)-1,2,4-thiadiazolidine) which are meta substituted on the phenyl rings with the −Cl and −NO\(_2\) respectively, the compounds B6 (2,4-diphenyl-3,5-bis(4-methoxyphenylimino)-1,2,4-thiadiazolidine) which is para substituted with the −OCH\(_3\) and B7 (2,4-diphenyl-3,5-bis(2-methoxyphenylimino)-1,2,4-thiadiazolidine) which is ortho substituted with −OCH\(_3\) on the phenyl ring also showed significant increase in the anti inflammatory activity (Table 2).

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