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# Synthesis of 1-Acetyl-5-Substitutedaryl-3-[5'-(5''-Methoxy-3'-Indomethyl)-2'-Amino-1', 3', 4'-Thiadiazol-2'-N-Yl]-2-Pyrazoline Derivatives as Potent Anti-Inflammatory Agent

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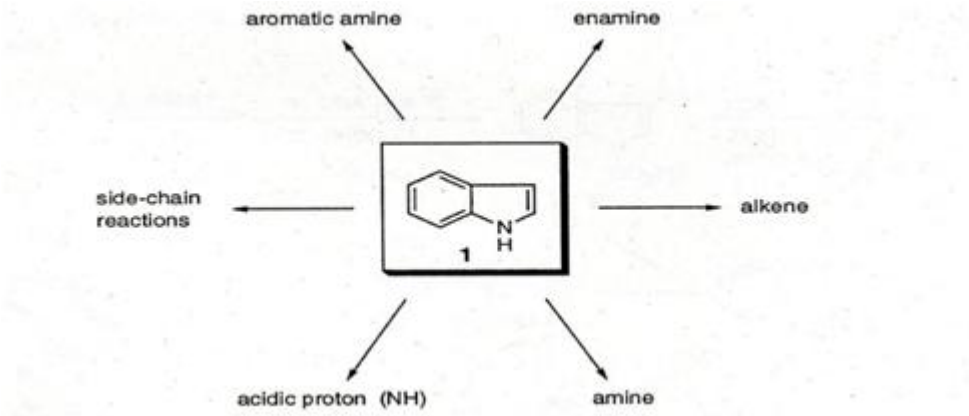
**Abstract:** ***When 5-(5'-methoxy-3'-indomethyl)--1', 3', 4'-thiadiazol-2'-amino substituted chalcones (5a-5e) undergo cyclisation in presence of 99% hydrazine hydrate and few drops of glacial acetic acid and refluxed for 12 hours, a novel series of 1-acetyl-5-substitutedaryl-3-[5'-(5''-methoxy-3'-indomethyl)-2'-amino-1', 3', 4'-thiadiazol-2'-N-yl]-2-pyrazoline can be synthesised. These compounds were characterised by IR, NMR spectroscopy and screened for their promising anti-inflammatory activity.***

**Keywords:** Thiadiazol, Indole, Chalcones, Pyrazoline, anti anti-inflammatory activity

## 1. Introduction

Hetereocyclic compounds are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics etc. A practical method for the synthesis of such compounds in of great interest in synthetic organic chemistry (1). Nitrogen containing heterocyclic compounds play an important role in medicinal chemistry and also contribute to the society by helping in different processes.

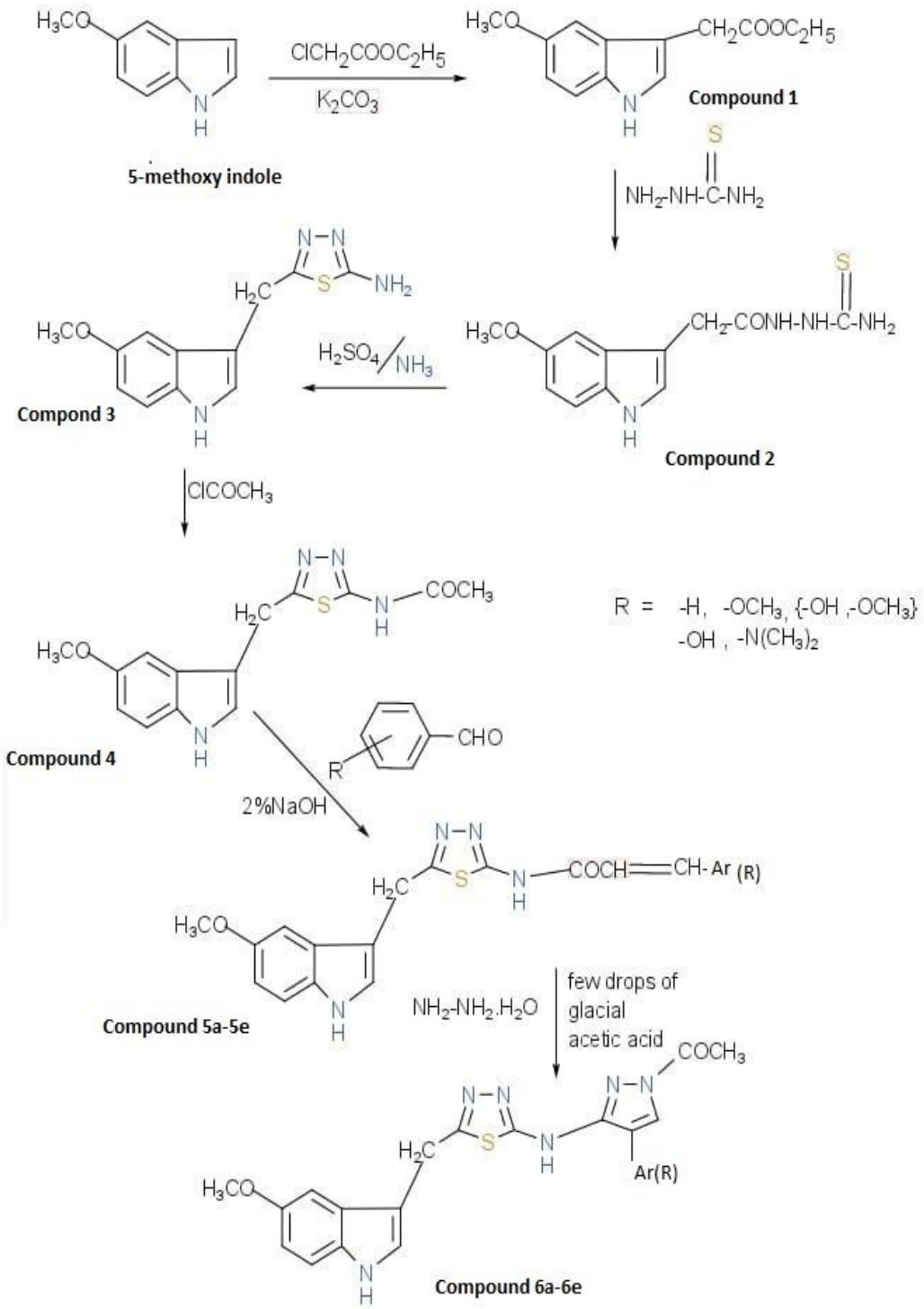
Indoles are one of the most important nitrogen containing heterocyclic compounds. The Indole nucleus is important moiety found in a large number of natural or synthetic alkaloids (2, 3). One of the naturally occurring indoles.




Indole has also known as benzypyrrole, is an aromatic organic compound composed of benzyl and a pyrrole ring. The aromatic properties of indole originate from the mobilization of its 10 π electrons throughout the indole structure. In this context, a large number of indole moieties have been investigated in the development of new efficient bioactive molecules with diverse pharmacological properties, such as antimicrobial, antiviral, anticancer, anti-inflammatory, inhibitors, and antioxidant [4-26]. Generally, indoles substituted at 2nd or 3rd position [27-29], are known to exhibit certain bioactivity.


Furthermore, various derivatives of1, 3, 4-oxadiazole [31-32], 1, 3, 4-thiadiazoles [33-34] and pyrazolines [35-36]

of different heterocyclic nuclei, are well known to exhibit potent anti-inflammatory activity. These findings prompted us to synthesise a new series of 1-acetyl-5-substituted aryl-3-[5'-(3''-indolylmethyl-5''-methoxy)-2'-amino-1', 3', 4'-thiadiazol-2'-N-yl]-2-pyrazolines. By incorporation 1, 3, 4-thiadiazolyl and pyrazolinyl moieties at 3-position of indole nucleus with a hope to develop anti-inflammatory agent with lesser side effects. The structure of all newly synthesised compounds were characterised by elemental analysis and spectral studies.




**Scheme of Work**

**Experimental Section**

**Materials:-**Solvents are carried of S. D fine chem. and E. Merck grade, were purified and dried by conventional method [31]. All other chemicals of S. D. Fine Chem and E. Merck grade have checked for their purity before use.

The homogeneity and purity of the compounds were checked over thin layer chromatography coated with silica Gel – G (thickness 0.5 mm) developing solvent acetone

/DMF (3: 1) non saturated chamber at room temp (20± $1^0$c).

The melting points of the synthesized compounds were determined by capillary method and were uncorrected. The IR spectra (in KBr) were recorded on JASCO FTIR spectrophotometer.1NMR spectra (DMSO/$CDCl_3$) were taken on VRO – 300 MHZ spectrophotometer and chemical shift expressed as ppm and TMS was used as internal standard. ε-bromoalkoxy phthalimideshave been prepared by reported methods [32].

## 2. Experimental Method

**A. Synthesis of 5-methoxy-3-indole ethyl acetate (1):** Ethyl chloro acetate (0.1 mole) and anhydrous $_{K2CO3}$ (5.0 gm) were added to the solutionof 5-methoxy indole (0.1 mole) in $CH_3OH$ (60 ml). Thereaction mixture was refluxedfor 10 hours, ccooled and excess of solvent was removed. The solid thus obtainedwas filtered and washed with water and recrystallised from ethanol to get product.

**Yield:** 70 %, **M. P.**$48^0$ C, **Colour**: Colourless solid shining crystals

**Molecular Formula**: $C_{13}H_{15}O_3N$, **Molecular weight** = 233

**Elemental analysis (Calculated %**) C = 66.90 (66.95), H = 6.38 (6.43), N = 5.93 (6.0)

**IR (KBr) (in $Cm^{-1}$)** 3145 (N-H str), 3005 (C-H str, Ar-H), 2925 (C-H aliphatic), 1735 (C=O str), 1580 (C=C of aromatic ring).

**$^1$H-NMR ($CDCl_3$) (δ-ppm):** 7.65-7.40 (m, 5H, Ar-H), 8.20 (s, 1H, NH of indole, exchangeable with $D_2O$), 6.80 (s, 2H, CH2 attached to indole nucleus), 4.20 (q, 2H, J= 7Hz,-$COOCH_2$-$CH_3$), 1.40 (s, 3H, J= 7Hz,-$COOCH_2$-$CH_3$), 3.85 (s, 3H, Ar-$OCH_3$).

**B. Synthesis of 1-(5'-methoxy-3'-acetylindolyl)-thiosemicarbazide (2):** A mixture of Compound (1) [0.075 mole] and thiosemicarbazide (0.075 mole) in $CH_3OH$ (60 ml) was refluxed for 10 hours on steam bath. After removing the excess solvent under reduced pressure, gives solid compound on coolingin ice bath, which was filtered, dried and washed with water. The product was recrystallised from ethanol and water.

**Yield:** 65%, **M. P**.$230^0$ C, **Colour**: Colourless needle like crystals

**Molecular Formula:** $C_{12}H_{14}N_4O_2S$, **Molecular weight** =378

**Elemental analysis (Calculated %)** C = 51.70 (51.79), H = 5.0 (5.03), N = 20.10 (20.14)

**IR (KBr) (in $Cm^{-1}$)** 3160 (NH str), 3025 (C-H str, Ar-H), 2920 (C-H aliphatic) 1695 (C=O str), 1600 (C=c of aromatic ring), 1180 (C=S).

**$^1$H-NMR ($CDCl_3$) (δ-ppm):** 7.60-7.40 (m, 5H, Ar-H), 8.30 (s, 1H, NHof indole, exchangeable with $D_2O$), 6.85 (s, 2H, $CH_2$ attached to indole nucleus), 7.95 (m, 4H, $NHNHCSNH_2$, exchangeable with $D_2O$), 3.47 (s, 3H, Ar-$OCH_3$)

**C. Synthesis of 3-[4-(1H-4-methyl benzimidazol-2-yl)-2-hydroxy phenyl]-2-phenyl-1, 3-thiazolidin-4-one (Compound 3):** A mixture of compound (2) and mercapto acetic acid in equimolar ratio in equivalent amount in 200ml DMF with a pinch of anhydrous $ZnCl_2$ was refluxed for 12-14 hours on steam bath. . After concentration and on cooling, a solid compound was obtained, which was filtered, dried and washed with water. The product was recrystallised from methanol.

**Yield:** 45%, **M. P.**$102^0$ C, **Colour:** Colourless crystals

**Molecular Formula:** $C_{23}H_{19}N_3O_2S$, **Molecular weight** = 401

**Elemental analysis (Calculated %)** C = 68.75 (68.82), H = 4.67 (4.73), N = 10.40 (10.47)

**IR (KBr) (in $Cm^{-1}$)** 3380 (NH str), 3020 (C-H str, Ar-H), 1730 (C=O str), 1596 (C=N, str), 767 (C-S-C, str).

**$^1$H-NMR ($CDCl_3$) (δ-ppm):** 10.53 (s, 1H, NH), 7.98-6.34 (m, 11H, Ar-H), 4.2 (s, 2H, $CH_2$), 2.4 (3H, s, $CH_3$), 5.7 (1H, s, OH).

**D. Synthesis of 2-acetylamino-5-(5'-methoxy-3'-indolylmethyl)-1, 3, 4-Thiadiazole (Compound 4):** A solution of acetyl chloride (0.02 mole) in dry chloroform (20 ml) was added drop wise at 0-$5^0$C to the vigorously stirred solution of 2-amino-5-(5'-methoxy-3'-indolylmethyl)-1, 3, 4-thidiazole (compound 3) (0.02mole) in dry chloroform (50 ml). The reaction mixture further stirred with the help of magnetic stirrer for about 2 hours at room temperature and then refluxed for 6 hours on water bath. The excess of solvent was distilled off, cooled and poured into crushed ice. The resulting mixture was filtered to afford solid product. which was filtered, dried and washed with petroleum ether. The product is recrystallized from ethyl alcohol-water.

**Yield:** 80%, M. P.$260^0$ C, **Colour:** White crystals

**Molecular Formula**: $C_{14}H_{14}N_4O_2S$, **Molecular weight** = 302

**Elemental analysis (Calculated %)** C = 55.35 (55.58), H = 4.41 (4.55), N = 18.49 (18.59)

**IR (KBr) (in $Cm^{-1}$)** 3150 (NH str), 3010 (C-H str, Ar-H), 2930 (C-H aliphatic),, 1705 (C=O str), 1540 (C=C of aromatic ring), 735 (C-S-C, str), 1047 (N-N), 1590 (C=N).

**$^1$H-NMR ($CDCl_3$) (δ-ppm):** 7.55-7.35 (m, 5H, Ar-H), 8.15 (s, 1H, NH of indole, exchangeable with $D_2O$), 6.80 (s, 2H, $CH_2$ attached to indole nucleus), 8.45 9s, 2H, NHCO exchangeable with $D_2O$),, 2.45 (3H, s, $COCH_3$), 2.55 (s, 3H, $OCH_3$).

**E. Synthesis of 5-(5'-methoxy-3'-indolylmethyl)-1, 3, 4-thiadiazolyl-2-amino (p-dimethylaminophenyl) chalcone (Compound (5d):** To a solution of compound 4 (0.01 mole) in $CH_3OH$ (50 ml), p-dimethylaminobenzaldehyde (0.01 mole) was added in presence of 2% NaOH solution. The reaction mixture was heated under reflux for 12 hours. The excess of solvent distilled off, and contents were cooled. The resulting product was filtered and wased with cold water and recrystallised with ethanol-water.

**Yield:** 60%, M. P.228$^0$ C, **Colour:** White crystals

**Molecular Formula**: $C_{23}H_{23}N_5O_2S$, **Molecular weight** =433

**Elemental analysis (Calculated %)** C = 63.68 (63.74), H = 5.26 (5.31), N = 16.10 (16.16)

**IR (KBr) (in Cm$^{-1}$)** 3160 (NH str), 3050 (C-H str, Ar-H), 2920 (C-H aliphatic),, 1700 (C=O str), 1530 (C=C of aromatic ring), 1600 (C=N), 1062 (N-N) 1140 (C-S-C, str).

**$^1$H-NMR ($CDCl_3$) (δ-ppm):** 7.70-7.20 (m, 9H, Ar-H), 8.18 (s, 1H, NH of indole, exchangeable with $D_2O$), 6.90 (s, 2H, $CH_2$ attached to indole nucleus), 8.50 (s, 2H, NHCO exchangeable with $D_2O$), 6.40 (d, 1H, COCH=), 9.15 (d, 1H, =CH-Ar), 2.15 (s, 6H, N $(CH_3)_2$).

Various other 5-(5'-methoxy-3'-indolylmethyl)-1, 3, 4-thiadiazolyl-2-amino substituted chalcone 5a, 5b, 5c and 5e were prepared with different aromatic aldehydes by the above mentioned method. Their Physical and analytical data are given in Table 1**.**

**Physical Data of Compounds 5a-5e**

| S. No. | Substituted (R) Aromatic aldehyde | Yield | Recrystallization Solvent | M. P. ($^0$C) | Molecular Formula | Found (Calculated) % | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| **5a** | H | 60 | DMF | 282 | $C_{21}H_{18}O_2N_4S$ | 64.70 (64.61) | 4.56 (4.61) | 14.62 (14.35) |
| **5b** | p-$OCH_3$ | 58 | Acetic Acid | 231 | $C_{22}H_{20}O_3N_4S$ | 62.90 (62.85) | 4.82 (4.76) | 13.38 (13.33) |
| **5c** | m-$OCH_3$, p-OH | 65 | Methanol-water | 248 | $C_{22}H_{20}O_4N_4S$ | 60.65 (60.55) | 4.67 (4.58) | 12.90 (12.84) |
| **5d** | p-N $(CH_3)_2$ | 60 | Ethanol-water | 228 | $C_{23}H_{23}O_2N_5S$ | 63.60 (63.74) | 5.25 (5.31) | 16.03 (16.16) |
| **5e** | p-OH | 48 | Acetone-pet. ether | 246 | $C_{21}H_{18}O_3N_4S$ | 61.93 (62.06) | 4.30 (4.43) | 13.65 (13.79) |

**F. Synthesis of 1-acetyl-5-(p-dimethylaminophenyl)-3-[5-(5''-methoxy-3''-indolylmethyl)-2'-amino-1', 3', 4'-thiadiazolyl-2'N-yl]-2-pyrazoline (Compound 6d):** Hydrazine hydrate 99% (0.04 mole) was added to a solution of compound 5d (0.02 mole) in ethanol (40 ml) in presence of few drops of glacial acetic acid and the reaction mixture was refluxed for 12 hours. distilled off and cooled the contents. The separated solid was filtered, washed with water and recrystallised with acetone/ pet. ether.

**Yield:** 50%, M. P.235$^0$ C, **Colour:** dull White needle crystals

**Molecular Formula**: $C_{25}H_{27}N_7O_2S$, **Molecular weight** = 489

**Elemental analysis (Calculated %)** C = 61.28 (61.34), H = 5.46 (5.52), N = 19.96 (20.0)
**IR (KBr) (in Cm$^{-1}$)** 3130 (NH str), 3040 (C-H str, Ar-H), 2922 (C-H aliphatic),, 1710 (C=O str), 1530 (C=C of aromatic ring), 1603 (C=N), 1050 (N-N) 746 (C-S-C, str).

**$^1$H-NMR ($CDCl_3$) (δ-ppm):** 7.70-7.25 (m, 9H, Ar-H), 8.20 (s, 1H, NH of indole, exchangeable with $D_2O$), 6.92 (s, 2H, $CH_2$ attached to indole nucleus), 5.70 (bs, 2H, NH, exchangeable with $D_2O$), 5.25 (d, 2H, $CH_2$ of pyrazoline ring), 6.60 (t, 1H, CH-Ar of pyrazoline ring), 2.50 (s, 3H, $COCH_3$), 2.20 (s, 6H, N $(CH_3)$ 2), 2.58 (s, 3H, $OCH_3$).
Other 1-acetyl-5-substitutedaryl-3-[5'-(5''-methoxy-3''-indolylmethyl)-2'-amino-1'3', 4'-thiazol-2'-N-yl]-2-pyrazolines 6a, 6b, 6c and 6e were synthesised by the same method as given above. Their physical and analytical data are given in Table 2.

**Physical Data of Compounds 6a-6e**

| S. No. | Substituted (R) Aromatic aldehyde | Yield | Recrystallization Solvent | M. P. ($^0$C) | Molecular Formula | Found (Calculated) % | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| **6a** | H | 45 | Acetic acid | 228 | $C_{23}H_{22}O_2N_6S$ | 61.80 (61.88) | 4.85 (4.93) | 18.75 (18.85) |
| **6b** | p-$OCH_3$ | 60 | Methanol-water | 208 | $C_{24}H_{24}O_3N_6S$ | 60.44 (60.50 | 4.90 (5.04) | 17.58 (17.64) |
| **6c** | m-$OCH_3$, p-OH | 48 | Ethanol-water | 221 | $C_{24}H_{24}O_4N_6S$ | 58.42 (58.53) | 4.80 (4.87) | 16.96 (17.07) |
| **6d** | p-N $(CH_3)_2$ | 50 | Acetone-pet. ether | 235 | $C_{25}H_{27}O_2N_7S$ | 61.25 (61.34) | 5.44 (5.32) | 19.99 (20.04) |
| **6e** | p-OH | 50 | Acetic acid | 245 | $C_{23}H_{22}O_3N_6S$ | 59.65 (59.74) | 4.70 (4.76) | 18.03 (18.18) |

**Biological activity**

**Anti-inflammatory activity**

Anti-inflammatory activity (34) of all newly synthesized derivatives was determined by the carrageenan-induced rat paw oedema model. Albino rats (80-140 g) were divided into 3 groups as control, test and standard (six animals per group). Overnight fasted animals were used and during that period only tap water was given. Generally, Phenylbutazone was used as standard drug. Both test and standard drugs were suspended in 1% carboxymethyl cellulose (CMC) and administered orally through gastric gavage needle. One percent of CMC was administered in control group. After 1 h of administrating the compound, we induced the carrageenan (1%) by the sub planner surface of the right hind paws of animals. The initial paw volume and also the paw volume after 3 and 6 h of administrating carrageenan were measured. Percent paw oedema inhibition was calculated according to the formula given below-

% anti-inflammatory activity = $(1\text{-}V_t/V_c) \times 100$

Where $V_t$ and $V_c$ are volume of oedema in drug treated and control group respectively.

## 3. Result and Discussion

SAR study of indole nucleus has revealed that substitution at 3-position of indole nucleus markedly enchanced the anti-inflammatory activity. Furthermore, indole was substituted with thiadiazolyl moieties at its 3-position. These compounds further converted into different substituted chalcones and finally cyclised into their corresponding pyrazolines. It was noticed that the chalcones showed mild to moderate anti-inflammatory activity. The inflammation inhibiting property increased on cyclisation of chalcones 5a-5e into their corresponding pyrazolines6a-6e. Moreover, It has been observed that when compound 6c were substituted at 5-position of pyrazoline ring with phenyl group having methoxy group at meta position and hydroxyl group at para position, they showed maximum percentage inhibition of rat's paw oedema (47.6%). On the other hand compound 6 b substituted at 5-position of pyrazoline ring with phenyl ring having methoxy group at para position, has shown substantive anti-inflammatory activity (40.4%).

Hence, it may be concluded that the substitution in chalcones (5a-5e) and pyrazolines (6a-6e) with phenyl group at meta position and hydroxyl group at para position show maximum anti-inflammatory activity, while the substitution in chalcones and pyrazolines with phenyl group possess minimum anti-inflammatory activity.

All newly synthesised compounds (5a-5e and 6a-6e) were screened for their anti –inflammatory activity at a dose at 50 mg/kg p. o. . The results of study are showmn in table 3. Most of these congeners showed potent anti-inflammatory activity ranging from 24.3% to 49% and were found statistically significant. All these compounds were compared with standard drug (Phenylbutazone), which provided with 45.6% inhibition of oedema at the identical dose. Compound 6c exhibited most potent anti-inflammatory activity (47.6%) and exhibited higher inflammation inhibiting property in comparison to phenylbutazone at 50 mg/kg p. o., by considering their potentiality, compound 6c and standard drug were further tested for their anti-inflammatory activity at three grades doses i.e.25, 50, 100 mg/kg p. o. and results are given in table 3.

**Anti-inflammatory study:**

**Anti-inflammatory activities of compounds (5a-5e) and (6a-6e)**

| Compounds | Dose mg/kg | Inhibition of paw oedema after 3 h (%) 1 | Inhibition of paw oedema after 6 h (%) 2 |
|---|---|---|---|
| **12** | 50 | 3.28 ± 0.28 | 25.4 |
| **5b** | 50 | 2.48 ± 0.23 | 36.5 |
| **5c** | 50 | 3.46 ± 0.22 | 40.8 |
| **5d** | 50 | 1.62 ± 0.27 | 28.6 |
| **5e** | 50 | 1.10±0.20 | 33.5 |
| **6a** | 50 | 3.45 ± 0.28 | 28.8 |
| **6b** | 50 | 2.49 ± 0.23 | 40.8 |
| **6c** | 50 | 3.86 ± 0.22 | 28.5<br>47.8<br>67.0 |
| **6d** | 50 | 1.45 ± 0.27 | 31 |
| **6e** | 50 | 1.63 ± 0.20 | 37.3 |
| **Phenylbutazone** | | | 26.7<br>46.8<br>66.2 |

1: Dose for 1-7: 50 mg/Kg b. wt; 2: Dose for phenylbutazone 50 mg/Kg b. wt; mean ± SEM; n+6

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