**International Research Journal of Pharmaceutical and Applied Sciences (IRJPAS)**
Available online at **www.irjpas.com**
Int. Res J Pharm. App Sci., 2013; 3(5):88-93

**Research Article**

# SYNTHESIS, CHARACTERIZATION AND EVALUATION FOR ANTI-ARTHRITIC ACTIVITY OF SOME NOVEL 4-THIAZOLIDINONE DERIVATIVES

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**Abstract** The objective of the present work is to synthesis of N-[2-(4-substituted phenyl)-4-oxo-1,3-thiazoldine-3-yl]-2-(naphthalene-2-yloxy) acetamide and evaluate for anti-arthritic activity. Based on this a new series of compounds have been planned to synthesize by reacting β-napthol, ethyl chloroacetate, hydrazinemonohydrate, ethyl alcohol and various aromatic aldehydes. The anti-arthritic activity was evaluated using *In-vitro* Bovine serum Albumin denaturation method and *In-Vivo* Formaldehyde induced arthritis in rats. In result it was found that tested drugs inhibited Protein denaturation *in-vitro* which are comparable with standard diclofenec . In Formaldehyde induced arthritis , tested compounds decreased the paw volume and improved haematological parameters. This result suggest the synthesized compounds posses good anti-arthritic activity.
Key**words:** 4-Thiazolidinone Derivatives, Bovine serum Albumin denaturation, Formaldehyde induced arthritis in rats.

## INTRODUCTION

4-thiazolidinones are derivatives of thiazolidine with a carbonyl group at the 4 position. Several methods for syntheses are available. The synthesis of 2-imino-4-thiazolidinones-4-C has been reported by using thiourea and sodium salt of labeled monochloroacetic acid.[1] Another method of synthesis of 4-thiazolidinones is by use of thiocyanate, alkyl isothiocyanate with hydrazide/acetamide followed by the treatment with ethyl bromoacetate and sodium acetate.[2]

The literature survey revealed that 4-thiazolidinone and their derivatives were possessed a wide range of pharmacological activities such as anti-inflammatory , analgesic, anticonvulsant, antimicrobial (antibacterial and antifungal), local and spinal anesthetics, CNS stimulants, hypnotics, anti HIV, hypoglycemic, anticancer, FSH receptor agonist and CFTR inhibitor, anxiolytic and anti-depressant activity etc. [3-6]

The objective of the present work is to synthesis of N-[2-(4-substituted phenyl)-4-oxo-1,3-thiazoldine-3-yl]-2-(naphthalene-2-yloxy) acetamide and anti-arthritic activity. Based on this a new series of compounds have been planned to synthesize by reacting β-napthol, ethyl chloroacetate, hydrazinemonohydrate, ethyl alcohol and various aromatic aldehydes.

## MATERIALS AND METHODS

The all chemicals used for the synthesis were of laboratory grade and analytical grade. The melting points of newly synthesized thiazolidinone compounds were determined by open capillary method. The IR spectra of synthesized compounds were recorded by ABB Bomen FT-IR spectrometer MB 104 IR spectra recorder with KBr pellets. The $H^1$-NMR spectra of synthesized compounds were recorded by BRUKER NMR spectrometer in DMSO. The Mass spectra of synthesized compounds were recorded by JEOL GCmate. The purification of newly synthesiszed compounds were done by TLC method. TLC plates are pre-coated silicagel (HF254-200 mesh) aluminium plate using ethyl acetate and n-hexane as an solvent system and spots were visualized under U.V chamber. The IR, $H^1$-NMR and Mass spectra were assigned to elucidate the structure of synthesized compounds (U1-U3).

### Animals

Wister rats of either sex weighing about 150-200 g

### Steps involved in the Synthesis of Compounds

**Step 1: Preparation of ethyl-2-naphthalene-6-yloxy acetate**

2-napthol (1.44 gm, 10 mmol), anhydrous potassium carbonate (1gm) and ethylchloroactate (1.67gm, 10mmol) in 50ml of anhydrous acetone were refluxed on oil bath for 6 hours. The reaction mixure was filtered and the excess solvent was removed by distillation under pressure.

**Step 2: Preparation of 2-(naphthalene-6-yloxy) acetohydrazide**

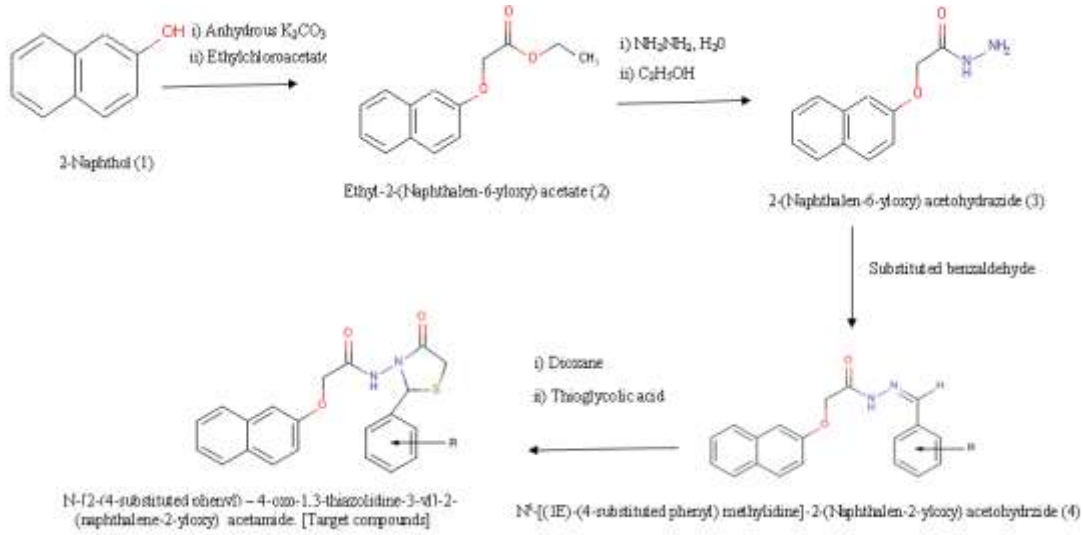
The residue and 1gm hydrazine monohydrate (20 mmol) were dissolved in 50 ml of absolute ethanol and refluxed on a steam bath for 1 hour. The solute must was filtered and dried and recrystalized from ethanol.

**Step 3: Preparation of substituted benzaldehyde derivatives**

0.01mol of substituted banzaldehyde and 0.01mol of substance and 2-3 drops of glacial acetic acid and 20ml of ethanol were taken in round bottom flask and reflux for 6 hours on water bath. After cooling add ice cold water to the mixture to give solid white mass. Filtered and dried. Recrystalized from chloroform-methanol mixture.

**Step 4: General method of synthesis of thiazolidinone derivatives**

A mixture of Schiff base (0.001mmol) and Thioglycolic acid (0.001mol) dissolved in 1,4-dioxane (20ml), anhydrous zinc chloride (0.5mg) was added and refluxed for 8 hours. The reaction was then cooled to 30°C and the result solid was washed with sodium bicarbonate solution. The compound recrystalized from absolute ethanol.




**Pharmacological Evaluation**

**Acute Oral Toxicity Study**

In the present study acute oral toxicity of the synthesized compounds were performed by acute toxic class method 423 Guideline. In this method the toxicity of synthesized compounds were tested using a step wise procedure, each step using three mice of single sex (female). The mice were fasted prior to dosing (food but water should be with held) for three to four hours. Following the period of fasting the animal should be weighted and synthesized compounds were administered initially at a dose of 2000mg/kg b.w. and 1% CMC (p. o.) and were observed for 14 days for acute toxicity.

***In-Vitro* Anti-arthritic Activity using Bovine serum albumin denaturation method [6]**

**Preparation of reagents**

i. **5% Bovine serum albumin (BSA):** Dissolved 5 g of BSA in 100 ml of water.

ii. **Phosphate buffer saline pH 6.3:** Dissolved 8 g of sodium chloride (NaCl), 0.2 g of potassium chloride (KCl), 1.44 g of disodium hydrogen phosphate (Na2HPO4), 0.24 g of potassium dihydrogen phosphate (KH2PO4) in 800 ml distilled water. The pH was adjusted to 6.3 using 1N HCl and make up the volume to 1000 ml with distilled water.

**Method**

1. Test solution (0.5ml) consist of 0.45ml of Bovine serum albumin (5%W/V aqueous solution) and 0.05ml of test solution of various concentrations.
2. Test control solution (0.5ml) consist of 0.45ml of bovine serum albumin (5%W/V aqueous solution) and 0 .05ml of distilled water.
3. Product control (0.5ml) consists of 0.45ml of distilled water and 0.05 ml of test solution.
4. Standard solution (0.5ml) consists of 0.45ml of Bovine serum albumin (5%w/v aqueous solution) and 0.05ml of Diclofenac sodium of various concentrations.

Various concentrations (100, 250, 500 µg/ml) of test dugs and standard drug diclofenac sodium ( 100, 250, 500 µg/ml) were taken respectively. All the above solutions were adjusted to pH 6.3 using 1N HCl. The samples were incubated at 37°c for 20 minutes and the temperature was increased to keep the samples at 57°c for 3 minutes. After cooling, add 2.5 ml of phosphate buffer to the above solutions. The absorbance was measured using UV-Visible spectrophotometer at 416nm. The control represents 100% protein denaturation. The results were compared with Diclofenac sodium. All determinations were done in triplicate. The percentage inhibition of protein denaturation can be calculated as-

***Percentage Inhibition = 100 – [{(optical density of test solution – optical Density of product control)/optical density of test control} × 100]***

***In-vivo* Formaldehyde induced arthritis in rats [7-8]**

**Experimental Design:**

(Animals: Rats (Either Sex), weight (150-200g), Total Groups=6, (n=6, No. of animals in each group)

Group I Normal (Vehicle, 10 ml/kg ,1% Tween 80, p.o)

Group II Control (Vehicle, 10 ml/kg, 1% Tween 80 , p.o)+ Formaldehyde

Group III Test Drug- U1 (100 mg/kg , p.o) )+ Formaldehyde

Group IV Test Drug –U2 (100mg/kg , p.o) + Formaldehyde
Group V Test Drug –U3 (100mg/kg , p.o) + Formaldehyde
Group VI Standard (Ibuprofen, 50 mg/kg p.o) + Formaldehyde

**Experimental procedure:**
Wister albino rats of either sex, (150-200 g) were divided in six groups of 6 animals each. The Group I which serves as Normal and Group II serves as control receives vehicle orally and treated with Formaldehyde 0.1 ml (2% V/V) into the hind paw, while other groups III, IV, V receives Test Drug U1, U2 and U3 at 100 mg/kg, and group VI received Ibuprofen, standard drug .The animals were treated with drugs by oral route and subsequently after one hour of treatment intoxicated with 0.1 ml of Formaldehyde (2% v/v). Daily the paw volume was measured for the next 10 days with Plethysmometer.

**Estimation of Hematological parameters**
The Test drugs (U1, U2 and U3) on hematological parametersin Formaldehye induced arthritis model were carried out. The estimation of hematological parameters was carried out. Blood of approximately 1 ml was collected on $11^{th}$ day from each group of the animal by retro-orbital puncture in to the EDTA coated tubes of accurately 1ml and shakes the tubes immediately, to mix up with the EDTA. Then the blood containing tubes are subjected to hemocytometer for the determination of White Blood Cells (W.B.C), Red Blood Cells (R.B.C), Hemoglobin (Hb) Platelets

**Statistical Analysis**
The data were expressed as mean ± standard error mean (SEM). The data were analyzed by using Graph pad software version5 by one way analysis of variance (ANOVA). The test was followed by Dennett's't'-test, p values less than 0.05 were considered as significance.

**RESULT AND DISCUSSION**
**Characterization of the synthesized Compounds**
**Compound U1:** N-[2-(4-hydroxyphenyl]-4-oxo-1,3-thiazolidin-3-yl-2-(naphthalene-2-yloxylacetamide, Molecular formula: $C_{21}H_{18}N_2O_4S$, Melting point: $180^0$ C, $R_f$ value: 0.55 (Ethyl acetate: n- hexane: 2:3); Freely soluble in DMF, DMSO, Yield: 62%, IR (KBr) ν ($cm^{-1}$): 1624.11$cm^{-1}$(Ar-C=C),3177.12$cm^{-1}$(aliph-N-H),1026.57$cm^{-1}$(N-N), 747.42$cm^{-1}$(C-S),3610.57$cm^{-1}$(O-H-phe),1689.24$cm^{-1}$(C=O),1269.54$cm^{-1}$(C-N),1728.62$cm^{-1}$(C=O-thiazolidine); $^1$H-NMR δ (ppm): 8.0(1H,-NH-),6.8-7.9(11H,Ar-H),5.92(1H,-N-CH-S-),5.21(1H,Ar-OH),5.0(2H,-O-$CH_2$-CO-), 3.8(2H,-S-$CH_2$); Mass (m/e value): 394.5(30%) ($M^+$).

**Compound U2:** N-[2(4-chlorophenyl-4-oxo-1,3-thiazolidin-3-yl]-2-(naphthalene-2-yloxy)acetamide; Molecular formula: $C_{21}H_{17}ClN_2O_3S$; Melting point: $172^0$C , $R_f$ value0.46, Freely soluble in DMF, DMSO, Yield: 65.2%, IR (KBr) ν ($cm^{-1}$): 1611.20$cm^{-1}$ (Ar-C=C) ,3186.99$cm^{-1}$ ( Aliph-N-H), 1086.99$cm^{-1}$(N-N) ,695.56$cm^{-1}$ (C-S) ,1668.87$cm^{-1}$(C=O), 1267.68$cm^{-1}$ (C-N) ,750.35$cm^{-1}$ (Ar-C-Cl) ,1716.32$cm^{-1}$ (C=O- thiazolidine); $^1$H-NMR δ (ppm): 8.3 (1H,-NH-) ,6.8-7.9 (11H,Ar-H) ,5.80 (1H,-N-CH-S-) ,5.0 (2H,-O-$CH_2$-CO-), 3.3(2H,-S-$CH_2$); Mass (m/e value): 412.9 (24%)($M^+$).

**Compound U3:** N-[2-(4-fluorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-2-(naphthalene) acetamide., Molecular formula: $C_{21}H_{17}FN_2O_3S$, Melting point: $175^0$ C, $R_f$ value: 0.48 (Ethyl acetate: n- hexane: 2:3); Freely soluble in DMF, DMSO, Yield: 55.7%, IR (KBr) ν ($cm^{-1}$): 1609.09cm-1(Ar-C=C), 3194.42cm-1(Aliph-N-H), 1026.76cm-1(N-N), 1256.34cm-1(C-N),705.10cm-1(C-S),1662.09cm-1(C=O),1000.62cm-1(Ar-C-F),1721.94cm-1(C=O-thiazolidine); $^1$H-NMR δ (ppm): 8.20(1H,-NH-),6.8-7.9(11H,Ar-H),6.0(1H,-N-CH-S-),4.90(2H,-O-$CH_2$-CO-),3.5(2H,-S-$CH_2$-); Mass (m/e value): 396.5(13%)($M^+$).

**Acute oral toxicity studies**
No sign of toxicity observed at 2000 mg/kg b.w. in the experimental animals, the $LD_{50}$ value of the title compounds (V1-V3) expected to exceed 2000 mg/kg b. w. and represented as class 5 (2000 mg/kg < $LD_{50}$ < 2500 mg/kg). Thus, 100 mg/k.g. b.w. was considered as the dose for the further studies.

**Results of Anti-arthritic Activity**
The *In-vitro* anti-arthritic results are using Bovine serum albumin denaturation method is given in Table-1 and plotted in Fig-1. The *In-vivo* anti-arthritic activity using formaldehyde induced paw edema, the results are given in Table-2 and plotted in Fig-2. The influence of drugs in hematological parameters in Formaldehyde induced arthritis are given in Table-3.

**Tale-1: Result of *In-vitro* anti-arthritic activity of drugs in BSA denaturation method**

| Drug | Conc. (µg/ml) | % inhibition |
|---|---|---|
| Test Control | - | - |
| Product Control | - | - |
| Test Drug (U1) | 100 | 23.4±2.4 |
| | 250 | 34.5±3.2 |
| | 500 | 43.5±2.2 |
| Test Drug (U2) | 100 | 17.6±1.4 |
| | 250 | 28.5±1.5 |
| | 500 | 38.3±2.3 |
| Test Drug (U3) | 100 | 43.6±3.1 |
| | 250 | 56.7±4.2 |
| | 500 | 66.8±3.2 |
| Diclofenac | 100 | 56.3±1.5 |
| | 250 | 72.4±2.5 |
| | 500 | 87.7±2.3 |

**Values are in Mean ± SD, n=3.**

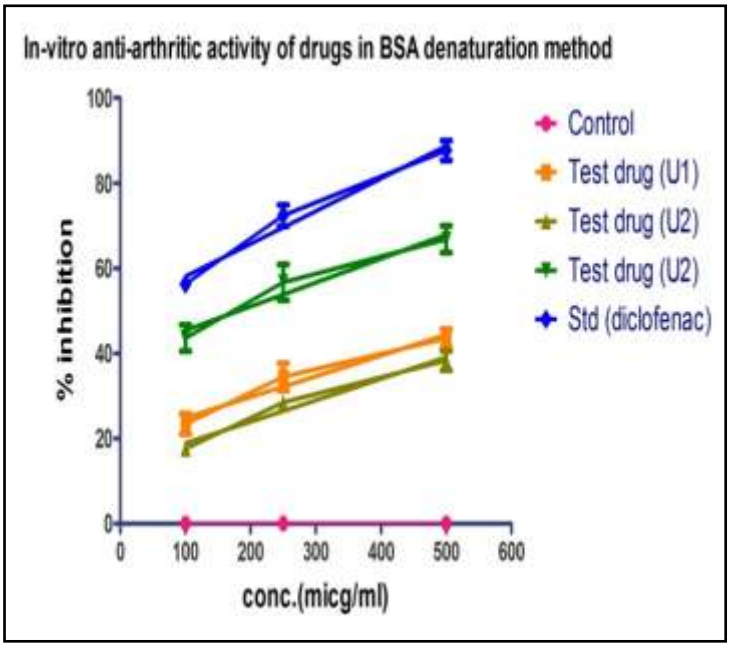



**Fig1: Result of *In-vitro* anti-arthritic activity of drugs in BSA denaturation method**

**Table-2: Result of Anti-arthritic activity of Test Compounds on Formaldehyde-induced arthritis in rats**

| Group No. | Treatment | Paw Volume in different time interval in ml (Mean ± SEM) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **0 day** | **1 day** | **2 day** | **3 day** | **4 day** | **5 day** | **6 day** | **7 day** | **8 day** | **9 day** | **10 day** |
| I | Normal (1% Tween 80) | 0.82 ± 0.02 | 0.83± 0.01 | 0.82± 0.01 | 0.82± 0.01 | 0.82± 0.01 | 0.82± 0.01 | 0.82± 0.01 | 0.82± 0.01 | 0.82± 0.01 | 0.82± 0.01 | 0.82± 0.01 |
| II | Control ( 1% Tween 80) | 0.83 ± 0.01$^{ns}$ | 1.73± 0.02$^{a}$ | 1.73± 0.02$^{a}$ | 1.72± 0.01$^{a}$ | 1.70± 0.02$^{a}$ | 1.67± 0.02$^{a}$ | 1.66± 0.02$^{a}$ | 1.58± 0.01$^{a}$ | 1.43± 0.02$^{a}$ | 1.39± 0.02$^{a}$ | 1.18± 0.02$^{a}$ |
| III | Test Drug U1 (100 mg/kg p.o) | 0.82 ± 0.12$^{ns}$ | 1.71± 0.02$^{ns}$ | 1.68± 0.02$^{ns}$ | 1.66± 0.02$^{ns}$ | 1.64± 0.02$^{ns}$ | 1.53± 0.02$^{ns}$ | 1.52± 0.02$^{ns}$ | 1.46± 0.02$^{ns}$ | 1.32± 0.02$^{ns}$ | 1.22± 0.01* | 1.00± 0.02$^{ns}$ |
| IV | Test Drug U2 (100 mg/kg p.o) | 0.83 ± 0.12$^{ns}$ | 1.70± 0.02$^{ns}$ | 1.68± 0.02$^{ns}$ | 1.65± 0.02$^{ns}$ | 1.57± 0.01* | 1.53± 0.02* | 1.47± 0.02* | 1.40± 0.02** | 1.27± 0.01** | 1.16± 0.01** | 0.98± 0.01* |
| V | Test Drug U3 ( 100 mg/kg p.o) | 0.82 ± 0.12$^{ns}$ | 1.72± 0.01$^{ns}$ | 1.67± 0.02$^{ns}$ | 1.63± 0.02$^{ns}$ | 1.56± 0.02* | 1.43± 0.02* | 1.30± 0.01* | 1.29± 0.02* | 1.23± 0.01* | 1.00± 0.01** | 0.91± 0.01* |
| VI | Ibuprofen, 50 mg/kg p.o) | 0.82 ± 0.02$^{ns}$ | 1.37± 0.01*** | 1.35± 0.01*** | 1.22± 0.02*** | 1.29± 0.02*** | 1.10± 0.02*** | 1.07± 0.02*** | 1.12± 0.02*** | 1.00± 0.01*** | 0.92± 0.02*** | 0.92± 0.02*** |

All values are expressed as mean ± SEM, n= 6, One way Analysis of Variance (ANOVA) followed by multiple comparison Dunnett's test. The minimum value of $p<0.05$ was considered as significant. $^{a}p<0.001$ as compared to normal group; ns-non significant, *$p<0.05$, **$p<0.01$, ***$P<0.001$ as compared with control group.

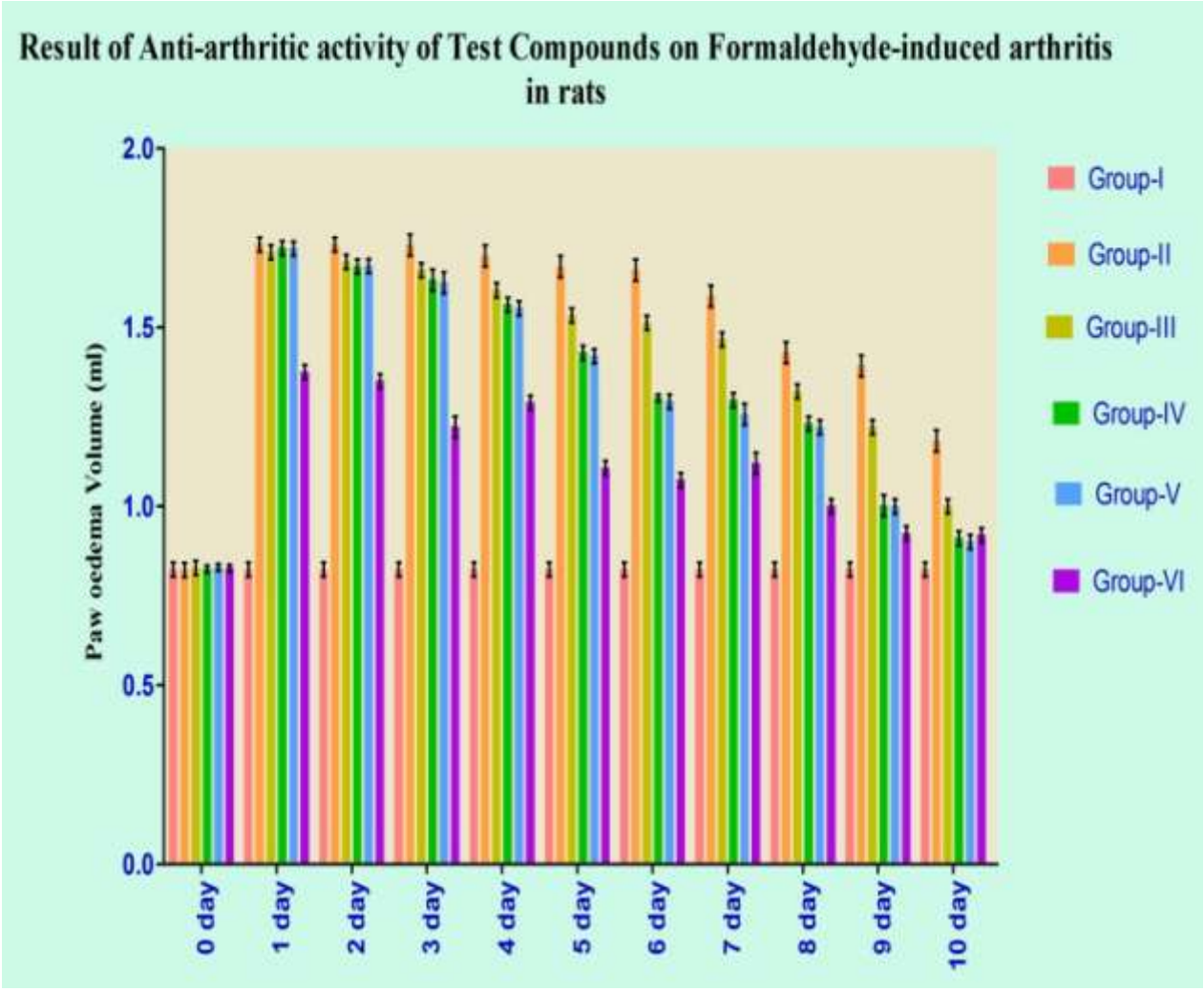



**Fig-2: Result of Anti-arthritic activity of Test Compounds on Formaldehyde-induced arthritis in rats**

**Table-3: Effect of Test Compounds on haematological parameters in Formaldehyde-induced arthritis in rats**

| Group No. | Treatment | Blood Parameter | | | |
|---|---|---|---|---|---|
| | | Hg (g %) | Total RBC Millions/mm$^3$ | Total WBC/ mm$^3$ | Platelets Lacks/ mm$^3$ |
| I | Normal (1% Tween 80) | 15.4± 0.71 | 5.2±0.32 | 8124±21.08 | 2.8±0.05 |
| II | Control+ Formaldehyde ( 1% Tween 80) | 8.5± 1.2$^{a\,**}$ | 4.1±0.30$^{a*}$ | 12980±24.13$^{a\,***}$ | 1.5±0.09$^{a\,***}$ |
| III | Test Drug U1 (100 mg/kg p.o) | 11.3±1.50$^{ns}$ | 4.4±0.32$^{ns}$ | 10740±24.45$^{ns}$ | 2.5±0.02** |
| IV | Test Drug U2 (100 mg/kg p.o) | 11.72±2.10$^{ns}$ | 4.6±0.37* | 11970±34.93$^{ns}$ | 2.3±0.04** |
| V | Test Drug U3 ( 100 mg/kg p.o) | 13.45±2.16** | 4.9±0.39$^{**}$ | 8901±50.24** | 2.3±0.02** |
| VI | Ibuprofen, 50 mg/kg p.o) | 10.8± 1.22$^{ns}$ | 4.5±0.24$^{ns}$ | 10404±34.80* | 2.1±0.05* |

All values are expressed as mean ± SEM, n= 6, One way Analysis of Variance (ANOVA) followed by multiple comparison Dunnett's test. The minimum value of $p<0.05$ was considered as significant. [a] as compared to normal group; ns-non significant, *$p<0.05$, **$p<0.01$, ***$P<0.001$ as compared with control group.

Denaturation of protein is an important of the main cause of rheumatoid arthritis is well documented. [9-11] Production of auto-antigen in certain arthritis may be due to denaturation of protein. The inhibition of denaturation of protein may one of possible target for arthritis treatment. Our present study suggests that the synthesiszed compounds inhibited protein denaturation, and can be used as anti-arthritc drug.

Moreover, formaldehyde induced inflammatory arthritis is also well documented. In our study it was found that the synthesized compounds was able to significantly reduce joint swelling in formaldehyde induced inflammatory arthritis in rats. Which suggest the activity through inhibition of prostaginin and other inflammatory mediators.[12-13]

## CONCLUSION

Finally, it can concluded that of N-[2-(4-substituted phenyl)-4-oxo-1,3-thiazoldine-3-yl]-2-(naphthalene-2-yloxy) acetamide derivatives posses good anti-arthritic activity both in-vitro and in-vivo models and suggest probable use of these derivatives as drugs.

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