Biological Evaluation of Some Newly Synthesized Thiazolidinone Derivatives for their Analgesic Activity

Pravesh Gangwar*, Pankaj Sharma, Birendra Shrivastava, Jaya Sharma, Shikha Sharma
Department of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India.
*E-mail: pravesh.gangwar_pharma@yahoo.com

Abstract
Two new thiazolidinone derivatives were prepared by brominating 1-acetylnaphthalene in chloroform followed by condensation with substituted benzaldehyde thiosemicarbazones using ethanol to get 4-naphthalen-1-yl-2-{2-[(substituted phenyl)methylidene]hydrazino}-1,3-thiazoles. These diazole derivatives were then cyclized to title compounds by reacting with thiomalic acid in dioxane using ZnCl₂. All the synthesized compounds were characterized on the basis of their IR, melting point. The analgesic activity of thiazolidinones was performed on normal rats by acid induced writhing method.

Key words: Thiazolidinones, Analgesic activity.

Introduction
Heterocyclic chemistry is the chemistry which deals with the compound having heteroatom such as oxygen, nitrogen and sulphur also attached to carbon atom[1]. Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulfur an nitrogen in a five member ring.[2] Thiazolidinone derivatives are known to possess several promising pharmacological actions such as antimicrobial[3-5], antidiabetic[6-8] anticonvulsant[9-10], anti-cancer[11-12] activities, anti-inflammatory[13-15], analgesic[16-17]. Therefore, the investigation of chemistry and biology of these compounds continue to appeal the synthetic and medicinal organic researches.

Chemistry
According to the reaction scheme1 two new Thiazolidinone compounds have synthesized and characterized. 1-actynaphthalene on brominating with chloroform gives 1-bromoactynaphthalene which was reacted with substituted benzaldehyde thiosemicarbazone in ethanol as a solvent give 4-naphthalen-1-yl-2-{2-[(substituted phenyl)methylidene]hydrazino}-1,3-thiazole(TA₁-TA₂).This compound on addition reaction with thioglycolic acid in presence of zinc chloride as a catalyst and dioxane as a solvent gives the final compounds(TB₁-TB₂). All the synthesized compounds were purified by recrystallization. Melting points were determined in open capillaries and all uncorrected. IR spectra (KBr pellet technique) were recorded using a Shimazdu spectrophotometer.

Experimental
Chemistry All the synthesized compounds were purified by recrystallization. Melting points were determined in open capillaries and all uncorrected. IR spectra (KBr pellet technique) were recorded using a Shimadzu spectrophotometer.

Synthesis of 1-bromoacetyl naphthalene:
1-Acetylnaphthalene (0.02 moles) was taken in 20 mL of chloroform in a 250 mL conical flask. A solution of bromine (0.04 moles) in chloroform was prepared. The bromine solution was added to flask containing 1-acetylnaphthalene solution, dropwise with stirring. The chloroform mixture was distilled on a water bath. The solid obtained was washed with petroleum ether and then recrystallized from benzene yielding 1-bromoacetyl naphthalene.
All the synthesized compounds were purified by recrystallization. Melting points were determined in open capillaries and all uncorrected. IR spectra (KBr pellet technique) were recorded using a Shimazdu spectrophotometer.

**Scheme 1:**

**Synthesis of 1-bromoacetyl naphthalene:**
1-Acetylnaphthalene (0.02 moles) was taken in 20 mL of chloroform in a 250 mL conical flask. A solution of bromine (0.04 moles) in chloroform was prepared. The bromine solution was added to flask containing 1-acetylnaphthalene solution, dropwise with stirring. The chloroform mixture was distilled on a water bath. The solid obtained was washed with petroleum ether and then recrystallized from benzene yielding 1-bromoacetyl naphthalene.
4-(naphthalen-1-yl)-2-[(2E)-2-(4-nitrobenzylidene)hydrazinyl]-1,3-thiazole (TA1) M.P.: 224-225; % Yield: 81; IR (KBr) cm⁻¹: 1602 (C=C- str), 696 (CH₂-S- str), 1341 (CN str), 1590 (C=N- str), 1566 (NH str), 840 (1,4-Disubstitution) (para), 1512 (NO₂ str). 4-(naphthalen-1-yl)-2-[(2E)-2-(2-nitrobenzylidene)hydrazinyl]-1,3-thiazole (TA2) M.P.: 215-216; % Yield: 81; IR (KBr) cm⁻¹: 1614 (C=C- str), 696 (CH₂-S- str), 1338 (CN str), 1590 (C=N- str), 1554 (NH str), 738 (1,4-Disubstitution) (ortho), 1518 (NO₂ str).

General method for synthesis of 4-Thiazolidinone
A mixture of respective thiazole derivative (0.01 mole) and thiomalic acid (0.015 mole) in 25 mL of dioxane was taken in a 100 mL round bottom flask. To this solution 25 mg of ZnCl₂ was added and the reaction mixture was refluxed for 6-10 h. The mixture was then poured on crushed ice and solid so obtained was filtered, washed with water, dried and recrystallized from dioxane.

3-[[4-(naphthalen-1-yl)-1,3-thiazol-2-yl]amino]-2-(2-nitrophenyl)-1,3-thiazolidin-4-one (TB1) M.P.: 233-234; % Yield: 81; IR (KBr) cm⁻¹: 1498 (C=C- str), 696 (CH₂-S- str), 1338 (CN str), 1350 (CN str), 1590 (C=N- str), 1566 (NH str), 738 (1,4-Disubstitution) (ortho), 1518 (NO₂ str). 3-[[4-(naphthalen-1-yl)-1,3-thiazol-2-yl]amino]-2-(4-nitrophenyl)-1,3-thiazolidin-4-one (TB2) M.P.: 219-220; % Yield: 81; IR (KBr) cm⁻¹: 1608 (C=C- str), 690 (CH₂-S- str), 1284 (CN str), 1320 (CN str), 1560 (NH str), 1590 (C=N- str), 843 (1,4-Disubstitution) (para), 1476 (NO₂ str).

Pharmacology
Two new compounds of thiozolidinone derivatives have been synthesized following scheme 1. The analgesic activity of the synthesized compounds were examined. Both the compounds (TB₁ - TB₂) showed good analgesic activity by acid induced writhing method.

Results and Discussion
Analgesic Activity:
The study was aimed at evaluating the analgesic effect of compounds on rats. Male Wister albino mice (n = 3) of either sex selected by random sampling technique (25-30 g) were used for the study. The standard drug Diclofenac sodium at a dose level of 25 mg/kg served as standard drug for comparison were administered. The test compounds at 200 mg/kg (suspended in 1% CMC) were administered orally by intragastric tube 30 min prior to intraperitoneal administration of the writhing agent (0.6 % v/v aqueous acetic acid–1ml/100g). The analgesic screening is based upon a comparison of the activity produced by compound to be examined with that of activity produced by known concentration of a standard drug.

Pharmacological Study
Analgesic Activity: The analgesic activity of new synthesized compound (TB₁ - TB₂) revealed that both of the compound exhibited significant analgesic activity as compared to standard drug diclofenac sodium.

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Analgesic activity</th>
<th>Mean Writhings</th>
<th>% Protection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>39.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>7.5</td>
<td>81.01</td>
<td></td>
</tr>
<tr>
<td>TB₁</td>
<td>22.80</td>
<td>42.27</td>
<td></td>
</tr>
<tr>
<td>TB₂</td>
<td>23.71</td>
<td>39.97</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion
From the above result it has been concluded that thiazolidinones derivatives (TB₁ - TB₂) may be used as lead compounds for analgesic activity and may further be evaluated for toxicological profile.
References