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Research Article

Synthesis, characterization and Evaluation for Antidepressant activities of some Novel 4-Thiazolidinone Derivatives

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Abstract: 4-thiazolidinone and their derivatives were possessed a wide range of pharmacological activities such as antiinflamatory , analgesic, anticonvulsant, antimicrobial (antibacterial and antifungal), local and spinal anaesthetics, CNS stimulants, hypnotics, anti HIV, hypoglycemic, anticancer, FSH receptor agonist and CFTR inhibitor etc. The objective of the present work is to synthesize N-[2-(4-substituted phenyl)-4-oxo-1, 3-thiazoldine-3-yl]-2-(naphthalene-2-yloxy) acetamide and evaluate for antidepressant activities by forced swim and tail suspension test. Three compounds were synthesized and they were characterized by FT-IR, ^{1}H-NMR and Mass Spectral studies. The determination of melting point, solubility studies were carried out. Imipramine was used as the standard drug. Two of the synthesized compounds V1 and V3 were found to be significant in Forced Swim Test, while only compound V1 was found to be significant in Tail suspension test when compared with the standard drug Imipramine.
Keywords: Thiazolidinone, Antidepressant, Forced Swim Test, Tail Suspension Test.

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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 [4]. 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.[1-2]

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

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 antidepressant activities. 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 synthesized compounds were done by TLC method. TLC plates are pre-coated silicagel (HF254-200 mesh) aluminum 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 (V1-V3).

Animals

Male mice weighing about 25-35 g were used for the study of anti-depressant activity.

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.

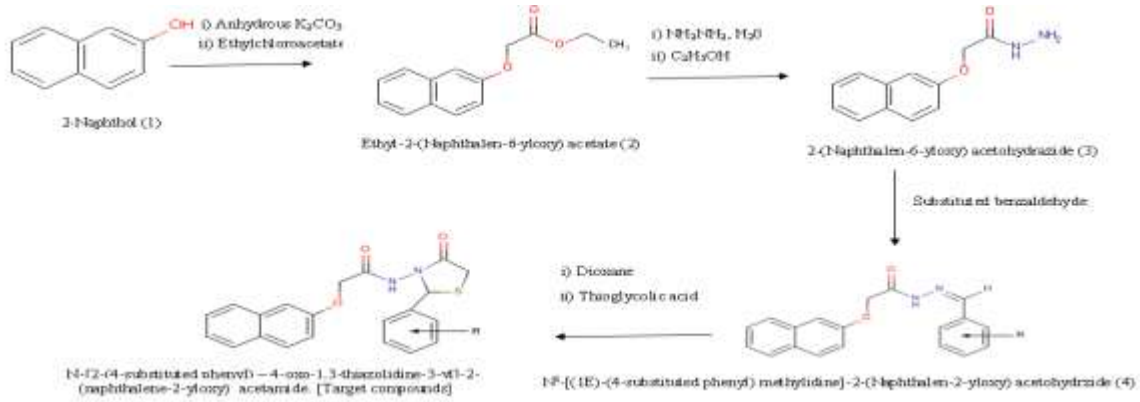

Fig- Scheme of Synthesis

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.

Screening methodology for Anti depression activity

The antidepressant activity of the test drug was evaluated using the following experimental models Forced Swim Test (FST) and Tail Suspension Test (TST) in mice.

Forced Swim Test (FST) in mice[5-7]

Antidepressant activity was evaluated by using Porsoltrd Forced Swing test in mice. This works on the basic principle of antidepressant effect statistically decrease in immobility andbehavioral despair in rodents. The Apparatus consist of a water tub of 60 cm (inner diameter) and 35 cm (height) was used. It was filled with water (27-29 °C) up to a height of 15 cm. For the evaluation of drugs, we used Porsolt's Forced Swim Test (Porsolt et al., 1977). It was a 2 day procedure. On day 1, each animal was dropped in water and was forced to swim for 6 min. It was then wiped dry and returned to home cage. On day 2, mice were treated with drugs as mention in respective groups and control receive only vehicle. After a gap of 1 hour they were subjected to the swim test. In accordance with Porsolt et al, mice were kept in water for 6 min. The duration of immobility was recorded during the last 4 minutes of the observation period because each animal showed vigorous movement during initial 2 min period. The duration of the mouse was considered immobile when it floated motionlessly or made only those moments necessary to keep its head above the water surface. The water was changed after each test. The test was conducted in a dim lighted room and each mouse was used only once in the test.

Tail Suspension Test

In Tail Suspension test used is described by Steru, *et. al*. and works on the principle of Antidepressant effect significant decrease in escape oriented movement immobility (hanging) in rodents. The animals were hung by the tail on a plastic string 50 cm above the surface with the help of an adhesive tape, placed approximately 1 cm from the tip of the tail. Each animal under test was both acoustically and visually isolated from other animals during the test. The duration of immobility was observed for a period of 8 minutes. The duration of immobility was recorded during the last 6 minutes of the observation period. Mice were considered to be immobile only when they hung passively and were completely motionless. The test was

conducted in a dim lighted room and each mouse was used only once in the test.

Study protocol

On the day of the experiment, the animals were divided randomly into five groups of six animals each.

Group I: Control (1% Tween 80; 10ml/kg, p.o)

Group II: Test1 (V1; 100mg/kg in 1% Tween 80)

Group III: Test2 (V2; 100mg/kg in 1% Tween 80)

Group IV: Test3 (V3; 100mg/kg in 2% Tween 80)

Group V: Standard (Imipramine; 10mg/kg, p.o. in 1% Tween 80)

Behavioural evaluation was carried out 60 minutes post drug/vehicle administration.

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.

RESULTS AND DISCUSSIONS

Characterization of the synthesized Compounds

Compound V1: 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}): 1624.11cm^{-1}(Ar-C=C),3177.12cm^{-1}(aliph-N-H),1026.57cm^{-1}(N-N), 747.42cm^{-1}(C-S),3610.57cm^{-1}(O-H-phe),1689.24cm^{-1}(C=O),1269.54cm^{-1}(C-N),1728.62cm^{-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 V2: 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: 172^0C , R_f value0.46, Freely soluble in DMF, DMSO, Yield: 65.2%, IR (KBr) ν (cm^{-1}): 1611.20cm^{-1} (Ar-C=C) ,3186.99cm^{-1} (Aliph-N-H), 1086.99cm^{-1}(N-N) ,695.56cm^{-1} (C-S) ,1668.87cm^{-1}(C=O), 1267.68cm^{-1} (C-N) ,750.35cm^{-1} (Ar-C-Cl) ,1716.32cm^{-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 V3: 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.

Antidepressant Activity

Table-1:

Effect of drugs on duration of immobility in Forced Swim Test (FST)

Group	Drug Treatment	Duration of Immobility (sec.) Mean ± SEM
I	Control (1% Tween 80)	153.5±3.55
II	Test1 (V1; 100mg/kg in 1% Tween 80)	88.83±5.24***
III	Test2 (V2; 100mg/kg in 1% Tween 80)	146.0±3.99^{ns}
IV	Test3 (V3; 100mg/kg in 1% Tween 80)	121.8±3.00**
V	Standard (Imipramine; 10mg/kg, p.o in2% Tween 80)	74.67±3.82***

Values are in Mean ± S.E.M (n=6); ns -Non Significant, *p<0.05, **p<0.01, ***p<0.001 when compared with Control using One way ANOVA followed by Dunnett" s multiple "t" test

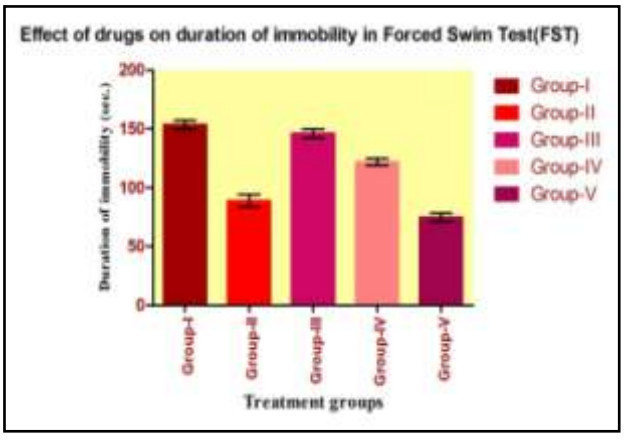

Fig. 1: Effect on duration of immobility in Forced Swim Test (FST)

Table 2: Effect on duration of immobility in Tail Suspension Test (TST)

1.

Group	Drug Treatment	Duration of Immobility (sec.) Mean ± SEM
I	Control (1% Tween 80; 10ml/kg, p.o)	170.0±2.80
II	Test1 (V1; 100mg/kg in 1% Tween 80, p.o.)	101.0±6.69***
III	Test2 (V2; 100mg/kg in 1% Tween 80, p.o.)	158.8±4.11^{ns}
IV	Test3 (V3; 100mg/kg in 1% Tween 80, p.o.)	150.0±5.62*
V	Standard (Imipramine; 10mg/kg, p.o in 1% Tween 80)	72.33±2.69***

Values are in Mean ± S.E.M (n=6); ns -Non Significant, *p<0.05, **p<0.01, ***p<0.001 when compared with Control using One way ANOVA followed by Dunnett‟ s multiple “t” test

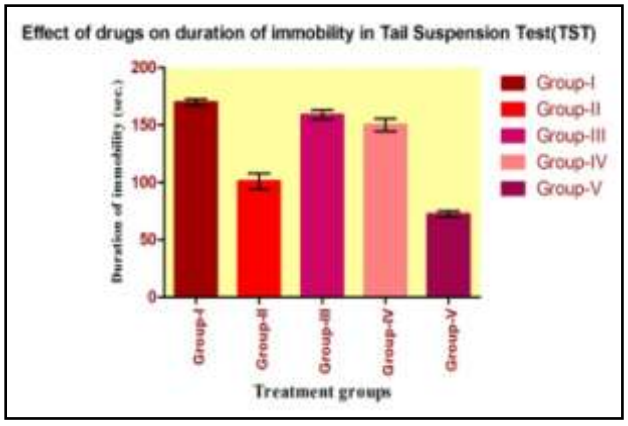

Fig. 2: Effect on duration of immobility in Tail Suspension Test (TST)

CONCLUSION

Two of the synthesized compounds V1 and V3 were found to be significant in Forced Swim Test, while only compound V1 was found to be significant in Tail suspension test when compared with the standard drug Imipramine. Finally, it can be concluded that, 4-thiazolidone derivatives produces anti-depressant like activity.

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