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SYNTHESIS, CHARACTERIZATION AND ANALGESIC ACTIVITY OF THIAZOLIDINONE DERIVATIVES

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ABSTRACT

Substituted Thiazolidine-4-ones have received considerable attention during last one decade as they are endowed with variety of biological activities and have wide range of therapeutic properties. A series of novel thiazolidin-4-ones have been synthesized by the reaction of Ethyl benzoate with hydrazine hydrate to form Benzohydrazone (1) which reacts with substituted aromatic aldehydes in the presence of acetic acid & ethanol to produce corresponding Schiff bases.The compounds were further treated with thioglycolic acid and dry benzene results in the formation of title compounds(ks4a-ks4f).The synthesized compounds were characterized by spectral studies like IR,H^1NMR and MASS spectroscopy. Analgesic activity of the synthesized compounds showed good results at the concentration of 30mg/kg by using standard diclofenac sodium in which ks4d shown potent activity in both Acetic acid induced writhing method and Eddy's hot plate method. The results showed that incorporation of appropriately substituted aromatic aldehydes at 2nd position of Thiazolidinone nucleus can afford good analgesic activity.

Key Words: Thiazolidinone, Analgesic activity, Diclofenac sodium.

INTRODUCTION

Heterocyclic Compounds

Heterocyclic compounds are cyclic compounds in which one or more of the atoms of the ring are heteroatoms. A heteroatom is an atom other than carbon. The name comes from the Greek word heteros, which means "different". A variety of atoms, such as N, O, S, Se, P, Si, B, and As, can be incorporated in to ring structures. By far the most numerous and most important heterocyclic systems are those of five and six members.

Heterocyclic make up an exceedingly important class compounds- more than half of all known organic compounds are heterocyclic. Almost all the compounds we know as drugs, vitamins, and many other natural products are heterocyclic. (Vigorita MG *et al*., 1979).

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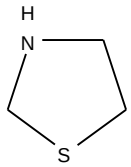
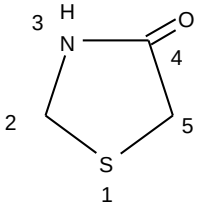
Thiazolidinones-Structure

Thiazolidinones are derivatives of thiazolidine with a carbonyl group at the 4-position .



Thiazolidine

1

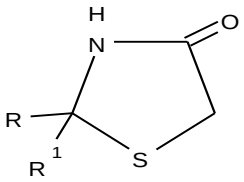


Thiazolidinone

2

Substituents in the 2-, 3-, and 5-positions may be varied, but the greatest difference in structure and properties is exerted by the group attached to the carbon atom in the 2-position (R and R' in 2 or X in3).

Variations in the substituents attached to the nitrogen atom and the methylene carbon atom are possible for the structures represented by 2 and 3.



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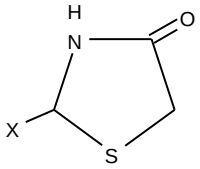


3

Heterocyclic compounds containing the thiazolidinone ring have reported to demonstrate a wide range of pharmacological activities which include antimicrobial, antifungal activity, antitubercular, antitumor, antidiabetic activity ,antiinflammatory, anticonvulsant and have been reported as novel inhibitors of the bacterial enzyme Mur B which is a precursor acting during the biosynthesis of peptidoglycan (Andres CJ & Bronson JJ *et al*., 2000) etc.

The discipline of organic and medicinal chemistry is devoted to the design, synthesis and production of molecules having value as human therapeutic agents. The combinatorial chemistry has provided access to chemical libraries based on privileged structures, with heterocyclic structures receiving special attention as they belong to a class of compounds with proven utility in medicinal chemistry (Horton DA *et al*., 2003).

There are numerous biologically active molecules with five membered rings, containing two hetero atoms. Thiazolidines an important scaffold known to be associated with several biological activities.Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five membered ring.

Thiazole is structurally related to thiophene, thiazole was first described by Hantzcs and Weber in 1887. Thiazolidine is a sulfur analogue of oxazolidine. It gives out different derivatives with all different types of biological activities**.** Thiazolidines may be synthesized by a condensation reaction between a thiol and an aldehyde or ketone. It is a reversible reaction. Therefore many thiazolidines are labile towards hydrolysis in aqueous solution. Hydrolysis of the thiazolidine generates the thiol and an aldehyde from which it was synthesized (Vigorita MG *et al*., 1979).

Therapeutic Importance

The thiazolidinone ring system represents a privileged structure in drug discovery. A large number of bioactive compounds containing this ring system are so vast that the complete range of their biological activities can be hardly classified.

MATERIAL AND METHOD

All the chemicals were purchased by S.D fine , Melting points of synthesized compounds were determined in open capillaries using Veego VMP-1 melting point apparatus and lab-India digital melting point apparatus expressed in ^{0}C and are uncorrected.The IR spectra of the compounds were recorded on FTIR spectrophotometer using KBr pellets technique and are expressed in cm^{-1}.The NMR spectra of the compounds were recorded in a VARIAN DP-200 spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded on an Electron impact Mass spectrometer at 70 eV using direct insertion probe. The molecular weight was calculated in positive mode by standard addition method.

Experimental

The title compounds were synthesised by using procedure

General Planning

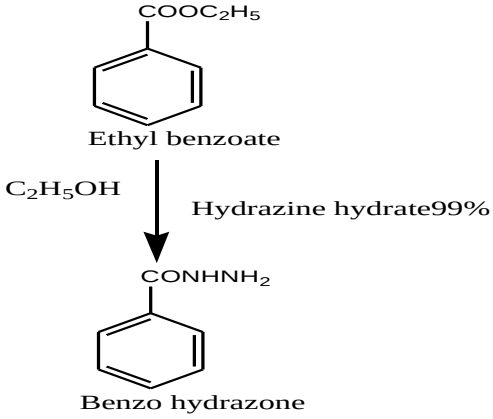
In the present work Ethyl benzoate and Hydrazine hydrate have been chosen as starting materials. The formations of the final products were monitored by TLC. The completed products show significant colour under UV light. All the compounds prepared were purified by recrystallization with suitable solvents.

General method for the Synthesis of Title Compounds

The procedure for the synthesis of compounds consists of three steps

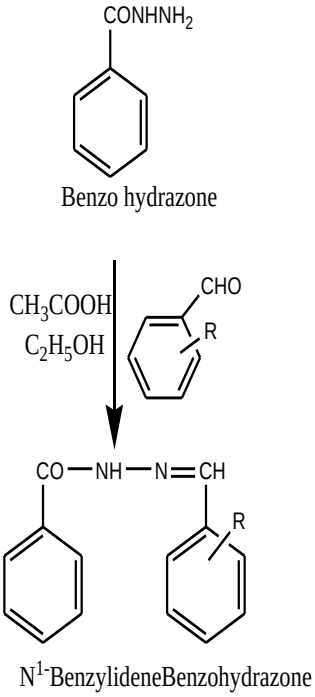
Step 1:

Take 0.01M of Ethyl benzoate and 0.02M of hydrazine hydrate in 20 ml of ethanol was refluxed for about 5hrs on a waterbath. After cooling, the resulting solid was filtered, dried and recrystallised to obtain Benzohydrazone, white solid (Nareshvarma S and Shrivastava SP *et al*., 2011).



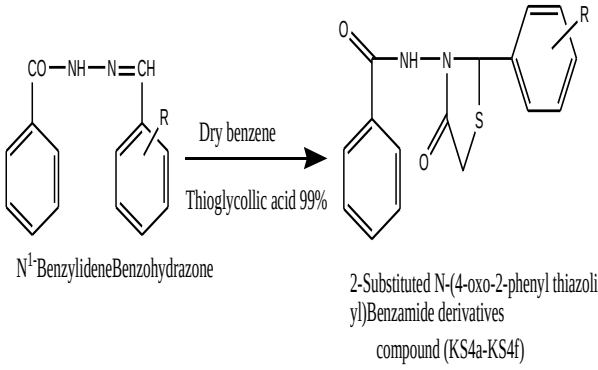
Step 2:

A mixture of the above obtained compound (0.01M), Substituted Aromatic aldehyde (0.01M), anhydrous sodium acetate (0.02M) and glacial CH_3COOH (20ml),were taken in a RBF kept under stirring and reflux for 5hrs.The reaction mixture was cooled and poured into crushed ice with vigorous stirring. The precipitated solid obtained was filtered off and recrystallized from ethanol (P.Sudhir kumar *et al*., 2010).



Step 3:

A mixture of different substituted Schiff bases (0.001M)in dry benzene(25ml) was added to Thioglycolic acid(0.01M).The reaction mixture was refluxed for 6hrs.A solid ppt was obtained after cooling . (P.Sudhir kumar et al.,2010).



Acute Toxicity Results

Acute toxicity study carried out by the method described by up/down method. Swiss albino mice were divided into 6 groups each contains 10 animals. Drugs were administered by oral route in different concentrations i.e. 25, 50, 100, 250, 500, 1000 and 2000 mg/kg body weight. After action all the animals were monitored for abnormalities up to 2 hrs and the mortality was observed after 24hr period. The LD50 values calculated by median lethal dose calculations. From this study it was found that, the LD50 values of drugs in the range not more than 100 mg/ kg body weight.

ANALGESIC ACTIVITY

Acetic acid induced writhing model

1. From the results the synthesized derivatives screened at 30 mg/kg body weight. KS4a has shown 66.51% of percentage inhibition which is more potent whencompared to control and less potent than standard (76.42%) due to unsubstituted aldehyde.
2. The result of KS4b revealed that 69.10% of percentage inhibition which is less potent activity to that of standard Diclofenac and more potent than KS4a.This is due to the presence of electron withdrawing group (chlorine) at *para* position.
3. KS4c has given 63.85% percentage inhibition which is less potent than standard and KS4b. This is due to the fact that electrion releasing group like hydroxy always posses less potent activity.
4. The KS4d has shown percentage inhibition of 72.88% which is more potent than all other derivatives but less potent than standard Diclofenac.The KS4d is highly potent which is comparable with standard diclofenac.
5. The compound KS4e shown percentage inhibition of 64.61% which is more potent than KS4c and less potent than other derivatives and standard. This may be due to the presence of *p*- methoxy and *m*-hydroxy groups.
6. The percentage inhibition of KS4f has shown 61.56% which is less potent than all other derivatives and standard. This may be due to the presence of bulky substitution of 2 methoxy groups to the aldehyde
7. KS4d shown good activity when compared to all other derivatives and less potent than standard.

All derivatives which are screen by Acetic acid induced model where also screen for their Analgesic activity using Eddy's hot plate method at different time intervals (30, 60, and 90 min).The results at various reaction time of all the derivatives are noted As the reaction time increases the time taken for the Jumping also increases.

1. Among all the Substituted Thiazolidinone derivatives KS4d and KS4e have shown more potent activity when compared to control and almost equipotent to that of standard. This may be due to the presence of nitro group of KS4d at *ortho* position and *para* and *meta* substitution of methoxy group and hydroxyl group of KS4e might be favoured this activity.
2. All the derivatives have shown good activity.Among all, KS4a have shown less activity than all other derivatives.

Statistical Analysis

Analgesic activity of synthesized derivatives was measured in Acetic acid induced writhing Pain in Mice. Data are expressed as the Mean±SEM (n=6) of Number of abdominal writhing(s). $^{***}p<0.0001$, based on one-way analysis of variance (ANOVA) followed by the Dunnett's test.

Table 1. Results showing Analgesic Activity of novel thiazolidinone

S.No.	Compound Group	Dosage	Number of abdominal Writhing (Mean±SEM)	Percentage inhibition (%)
1	Control	-	71.06± 1.032	0
2	Standard (Diclofenac)	35 mg/kg	16.66±0.557***	76.42
3	KS4a	30 mg/kg	23.66±1.115***	66.51
4	KS4b	30 mg/kg	21.83±1.046***	69.10
5	KS4c	30 mg/kg	25.66±0.666***	63.85
6	KS4d	30 mg/kg	19.16±0.703***	72.88
7	KS4e	30 mg/kg	25.00±1.341***	64.61
8	KS4f	30 mg/kg	27.16±0.792***	61.56

Figure 1. Therapeutic importance of thiazolidinone moiety

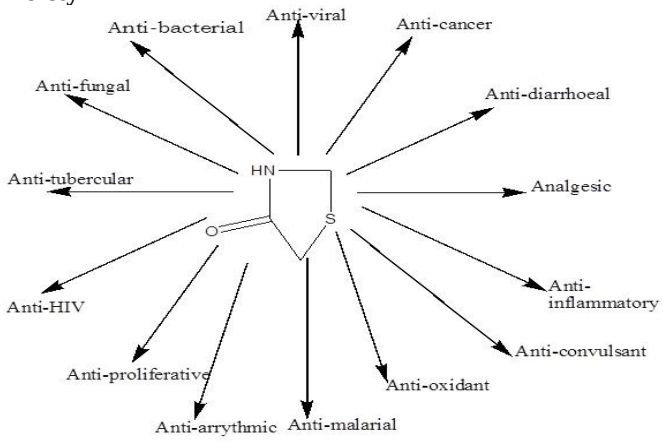
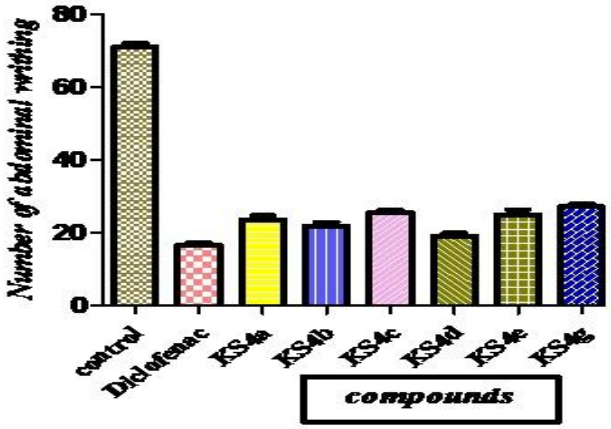


Figure 2. Bar diagram showing Analgesic activity using Acetic acid induced writhing Pain in Mice



RESULT AND DISCUSSION

The wide literature survey kept in view for the present research work and it has been carried out to synthesize the substituted Thiazolidinone derivatives and their evaluation for the in-vitro Analgesic activities respectively."Some Substituted Thiazolidinone derivatives" were synthesized by three step facile procedure. Six derivatives were synthesized, characterized and evaluated for analgesic, activity. In this activity two models were screened in both models against control, Diclofenac Sodium used as standard drug. The purity of the title compounds was checked by recrystallisation. Structural characterization was performed by IR, ^{1}H NMR, Mass and elemental analytical data.

CONCLUSION

All the title compounds (KS4a to KS4f) were synthesized and characterized by analytical data and screened for their analgesic activity. Among all the derivatives the compound KS4d was found to be more potent against control in Acetic acid induced writhing model and all the derivatives were less potent than the standard. The compounds KS4d and KS4e have shown more potent analgesic activity when compared to control using Eddy's hot plate method. If the research is continued by varying pharmacophore groups at thiazolidinone might give more potent activity than existing one. Further this research need to be carried out to know the relationship between structure and their activities.

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