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Invitro Anti-Inflammatory Activity Of Synthesized Thiazolidinone Derivatives

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ABSTRACT :

Substituted Thiazolidinones have a variety of biological activities and have wide range of therapeutic properties. A series of novel thiazolidinones have been synthesized by the reaction of ethyl benzoate with hydrazine hydrate to form benzohydrazone which reacts with substituted aromatic aldehydes in the presence of acetic acid &ethanol to produce corresponding Schiff bases. These compounds were further treated with thioglycolic acid and dry benzene results in the formation of title compounds(ks4a-ks4f).The synthesized compounds were characterised by spectral studies like IR, H^1NMR & Mass spectroscopy. Invitro Anti-inflammatory activity of the synthesized compounds showed good results at the concentration of 50 and

100µg/ml by using standard Diclofenac sodium by HRBC membrane stabilisation method. The compounds show the good anti inflammatory activity but less than that of standard diclofenac sodium.

KEYWORDS: Thiazolidinones, Schiff bases, HRBC method, Anti-inflammatory.

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. 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.

Thiazolidinones -Structure

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

Fig:1 Title molecule -Thiazolidinone

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).

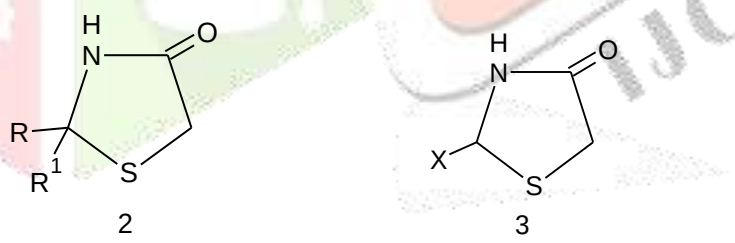


Fig:2 Substituted Thiazolidinones.

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. 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. 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.

Materials and methods:

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 ºC 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 CDCl3 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. 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.

RESULTS AND DISCUSSION:

Results of Anti Inflammatory Activity by HRBC Method for the Synthesized Compounds in µg/ml. The % Stabilisation of compounds by using HRBC method

Compound code	Conc.µg/ml	Absorbance(nm)	%Stabilization
control	-	0.805	99%
Standard	50	0.224	72.2%
	100	0.354	56.1%
KS4a	50	0.512	36.4%
	100	0.372	53.8%
KS4b	50	0.492	38.9%
	100	0.362	55.1%
KS4c	50	0.572	29%
	100	0.394	51.1%
KS4d	50	0.598	25.8%
	100	0.432	46.4%
KS4e	50	0.664	18%
	100	0.442	45.1%

KS4f	50	0.416	48.4%
	100	0.376	53.3%

Fig:3 Tabular representation of %stabilisation of compounds by using HRBC Method.

EXPERIMENTAL SECTION:

Scheme The schematic representation of the procedure is as follows

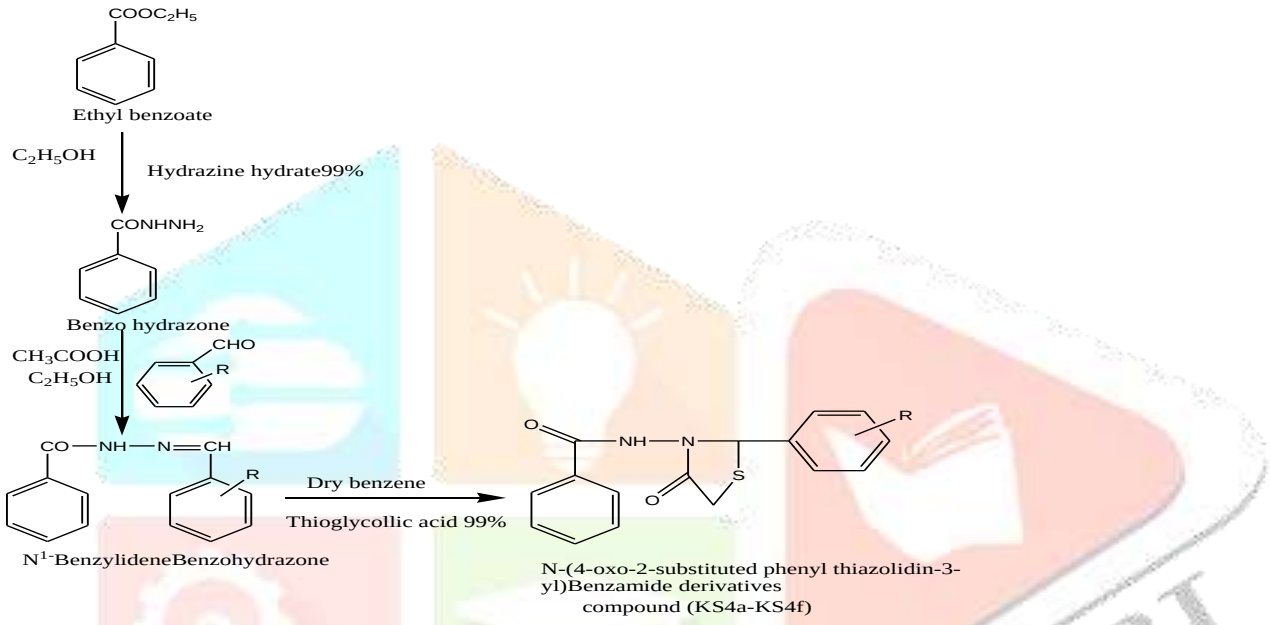


Fig:4 Schematic representation of Stepwise synthesis of Title compounds.

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:Synthesis of Benzohydrazone

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 Seelam and S. P. Shrivastava et al.,2011).

Step 2:Preparation of N^1-Benzylidene Benzohydrazone

A mixture of the above obtained compound (0.01M),Substituted Aromatic aldehyde (0.01M),anhydrous sodium acetate(0.02M) and glacial CH 3 COOH(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:Preparation of N-(4-oxo-2-substituted phenyl thiazolidin-3-yl)Benzamide derivatives

A mixture of different substituted Schiff bases (0.001M)in dry benzene(25ml) wasadded 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).

IR spectroscopy

Infra red spectrum (IR spectrum) gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption bands which provides information about the functional

groups present in an organic compound. Each functional group in the compound absorbs infra red radiations at definite frequencies and produce characteristic absorption bands. These absorption bands help to identify the characteristic functional groups in the compound (Sharma YR, 2009).

IR Characterization:

Compound(ks4a)C=C stretching in aromatic ring 1843, C-H stretch in Aromatic ring 3020,C=O stretch 1647.21,1635.64,C-S stretch 750.31, C-N stretch 1446.61, -NH stretch 3466.08 Base peak 208 , M + 1 peak 224.

Compound(ks4b) C=C stretching in aromatic ring 1780.30,C-H stretch in Aromatic ring 3194,C=O stretch 1714.72, C-S stretch 952, C-N stretch 1446, -NH stretch 3323.35

Compound(ks4c) C=C stretching in aromatic ring 1683.86,C=O stretch 1743.65,C-S stretch 952.84,C-N stretch 1436.97,-NH stretch 3394.72,-OH stretch 3454.51,C-H stretch 3204 Molecular ion peak-314,Base peak-240

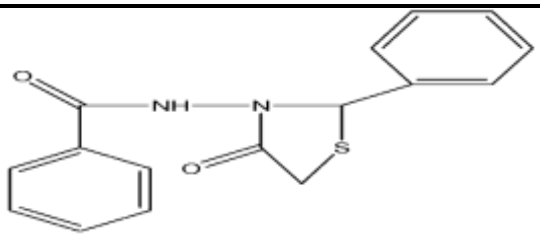
Compound(ks4d) C=C stretching in aromatic ring 1869.02,C=O stretch 1730.15,C-S stretch 667.37, C-N stretch 1423.47,-NH stretch 3419.79,NO_2 in aromatic ring 1550.77, C-H stretch 3185, Molecular ion peak-344,Base peak-210.

Compound(ks4e) C=C stretching in aromatic ring 1651.07,C=O stretch 1724, C-S stretch 752,C-N stretch 1456.2 -NH stretch 3250,OH stretch in aromatic ring 2550, -OCH3 in aromatic ring 2834, C-H stretch 3192

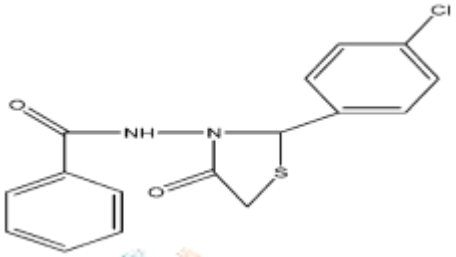
Compound(ks4f) C=C stretch in aromatic ring 1755,1864**,**C=O stretch 1743**,**C-S stretch 745**,**C-N stretch 1423**,-**NH stretch 3274**,-**OCH 3 group 2820,2834**,**C-H stretch 3188.

The compounds that were synthesised are represented below:

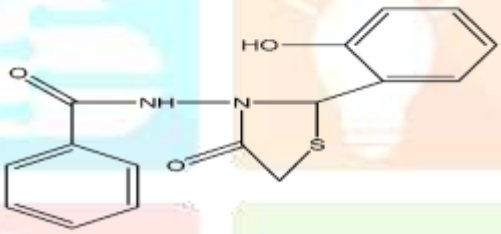
1. Compound code : KS4a **IUPAC name**: N-(4-oxo-2-Phenyl thiazolidin-3-yl)Benzamide



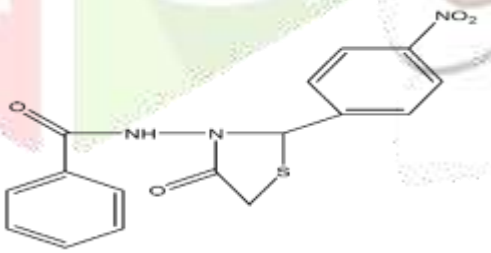
2. Compound code : KS4b **IUPAC name**: N-(2-(4-chloroPhenyl)-4-oxothiazolidin-3-yl)Benzamide



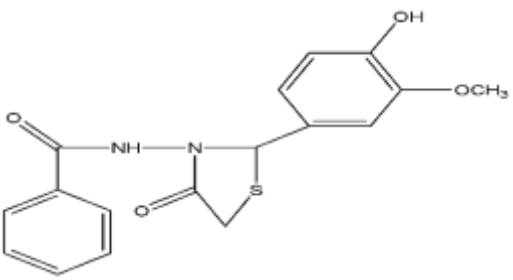
3. Compound code : KS4c **IUPAC name**:N-(2-(2-hydroxyPhenyl)4-oxo thiazolidin-3-yl)Benzamide



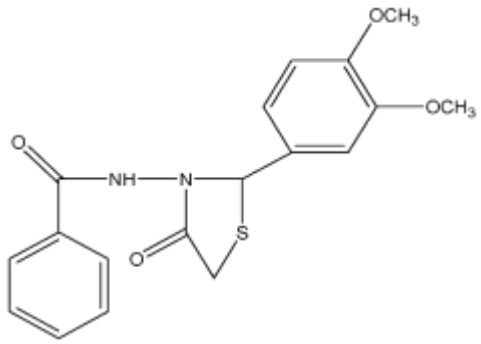
4. Compound code : KS4d **IUPAC name**: N-(2-(4-nitroPhenyl)-4-oxothiazolidin-3-yl)Benzamide.



5. Compound code: KS4e **IUPAC name**: N-(2-(4-hydroxy-3-methoxy phenyl)-4-oxo thiazolidin-3-yl)Benzamide



6. Compound code : KS4f **IUPAC name**: N-(2-(3,4-dimethoxyphenyl)-4-oxothiazolidin-3-yl)Benzamide.



Invitro Anti-inflammatory Activity

Antiinflammatory activity of the compounds were evaluated by HRBC Membrane Stabilization Method.

HRBC Membrane Stabilization Method

The human red blood cell membrane stabilization method (HRBC) has been used as a method to study the invitro anti-inflammatory activity. Blood was collected from healthy human volunteer who was not taken any NSAIDS for 2 weeks prior to the experiment. The collected blood was mixed with equal volume of sterilized Alsever solution (2% dextrose,0.8% sodium citrate, 0.05% citric acid and 0.42% NaCl in water) and centrifuged at 3,000 rpm. The packed cells were washed with isosaline (0.85%, pH 7.2) and a 10% (v/v) suspension was made with isosaline[8].Various concentrations of compounds were prepared (50 and 100 µg/ml) using distilled water and to each concentration 1 ml of phosphate buffer (0.15M, pH 7.4), 2 ml of hypo saline (0.36%)and 0.5 ml of HRBC suspension were added. It is incubated at 36^0c for 30 min and centrifuged at 3,000rpm for 20 min. The haemoglobin content in the supernatant solution was estimated spectro photometrically at 560 nm. Diclofenac sodium (50 & 100 µg/ml) was used as a reference standard and a control (distilled water) was prepared omitting the compounds. The percentage hemolysis was calculated by assuming the hemolysis produced in presence of distilled water of as 100%. The percentage of HRBC membrane stabilization or hemolysis was calculated using the formula[6,7].

% inhibition of Hemolysis= 100× (OD1- OD2)/ OD1

Where OD1 and OD2 are absorbance of control, Diclofenac sodium or test compounds respectively.

The percentage of membrane stability was calculated as follows:

$$\text{Percentage stabilization} = 100 - \left(\frac{\text{OD of test solution} - \text{OD of product control}}{\text{OD of test solution}}\right) \times 100$$

Graphical Representation:

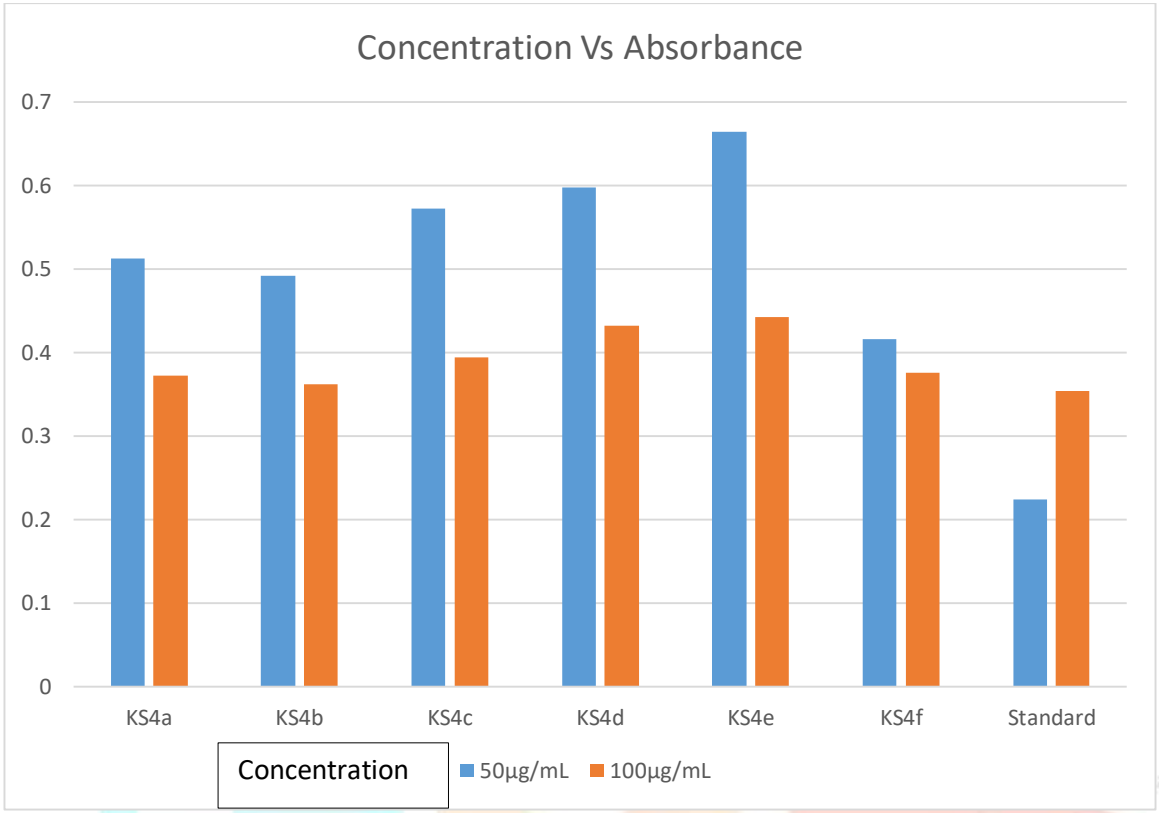


Fig-5:Graphical representation of Invitro Anti-inflammatory activity of Thiazolidinone derivatives by HRBC Membrane Stabilisation Method using Standard - Diclofenac sodium.

Conclusion: The invitro anti inflammatory potential of the all synthesized compounds were evaluated by method namely Human Red Blood Cell Membrane Stabilisation(HRBC Membrane stabilisation method) using Diclofenac sodium as a internal standard.From the results the derivative KS4f which possess Meta and Para methoxy substitution showed significant anti inflammatory activity (%Stabilisation values 48.4% and 53.3% respectively) and all derivatives are less potent than the standard diclofenac sodium.

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