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SYNTHESIS OF SOME NEW NOVEL THIAZOLIDINONE FROM CHALCONE AND THEIR ANTI-MICROBIAL ACTIVITY

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ABSTRACT:

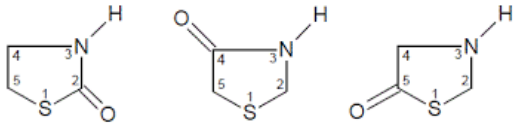
A new series of thiazolidinone derivatives (6a-c) were synthesized by the reaction of Schiff base(4a-c) with mercaptoacetic acid respectively. The chemical structure of the synthesized compounds were confirmed organic qualitative analysis and then anti-microbial activity was carried out. The different synthesis thiazolidinone derivatives from Benzyloxy benzaldehyde showed good anti bacterial activity against both gram positive and gram negative such as Staphylococcus auresus, S.typhi, Erwinia, X.Oxalopodi and Eischerchia coli. In this when compare to compound I, Compound II showed more inhibition. The average area of inhibition in millimeter (mm) was calculated and compared with that of the standard chloramphenicol.

Key words: - Chalcone, Schiff base, Mercaptoacetic acid, Thaizolidinone.

INTRODUCTION:

Thiazolidinone derivatives are five membered heterocyclic ring contain one sulphur, one nitrogen and three carbon. Thiazolidinone Derivatives of thiazolidine with a carbonyl group at the Second, Fourth, Fifth position.Many thiazolidinone and isoxazoline derivatives demonstrated a wide spectrum of biological activities [1-4]. These activities are including anti-bacterial, anti-fungi, anti-convalsant and anti-inflammatory.

The 4-thiazolidinone class represents an important analogue to thiazolidine heterocyclic compounds [5]. Derivatives of 4-thiazolidinone were synthesized by various methods. However, a conventional method for such synthesis was frequently used. It is involve the cyclo-condensation reaction one-pot method was convenient for synthesis of 4-thiazolidinone. This method includes the reaction of enaminones with ethyl-2-bromopropionate [7].



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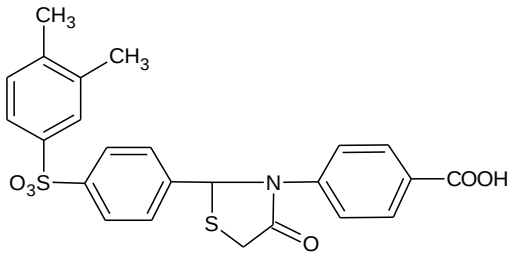
A common synthetic path for construction of iminothiazolidinones is the cyclization of thiourea or thiosemicarbazide derivatives with halo-esters or thioglycolic acids in presence of inorganic base in polar solvents. The cyclization reaction was carried out by conventional [8-14] or microwave irradiation techniques [15-18]. The classical method for synthesis isoxazoline derivatives involves a base catalyzed condensation of chalcone with hydroxylamine hydrochloride between Schiff-bases and mercaptoacetic acid [6] then in ethanol [19]. As a part of our interests towards developing novel heterocyclic compounds may be have useful biological activity, we plan to synthesis some new 4-thiazolidinones and isoxazolines have

significant structures derived from different thiosemicarbazides.

PHARMACOLOGICAL ACTIVITY

Marceli Nencki discovered 2- Thioxo-4-thiazolidinone; for the first time. In reference to its synthesis from ammonia rhodanide (in modern chemistry ammonium thiocyanate) and chloroacetic acid in water. Thiazolidinone Derivatives are an important class of heterocyclic compound known for their potential pharmaceutical applications. [19]

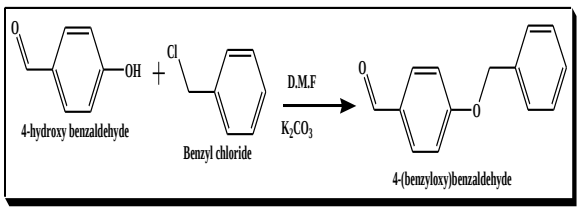
Recently, these framework containing compounds were effective against anti-microbial, antischistosomal activity, antifungal, anti-inflammatory, antimalarial, herbicidal, antiviral, antidiabetic and antioxidant activities. Thiazole derivatives are heterocyclic compound containing nitrogen and sulphur atom in their structure and are proved to be clinically useful agents against different kind of disease. [20]



MATERIALS AND METHODS:

Synthesis of Benzyloxy Benzaldehyde

General procedure for the preparation of Benzyloxy Benzaldehyde: Take 250ml round bottom flask, Take a 4- hydroxyl benzaldehyde (6.106gm, 0.005M), Dissolve this compound in Dimethyl formamide. Then add Benzyl chloride (5.72ml, 0.005M), Pottasium Carbonate (20.7gm). Refluxed the above given mixture heating is over pour the mixture in ice cold water, filter and dry the product. [21]

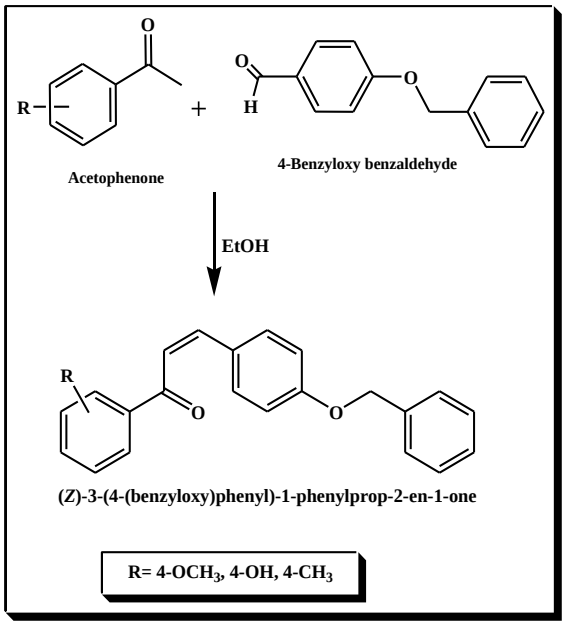


Reaction Scheme no. 1d

Synthesis of Chalcone:

General procedure for the preparation of various substituted chalcone (2a-c):

In a 250ml capacity beaker, take benzyloxy benzaldehyde (9.9830gm, 0.05M) (1a), 4-methyl acetophenone (6ml, 0.05M) (1b), 4-methoxy acetophenone (1c), 4-hydroxy acetophenone (1d) are treated in presence of 40 ml Ethanol. Dissolve the compound then add the prepared NaOH solution (3.6gm, 0.09M).Stirred well the above given mixture for 1-2 hours. After the complete stirring of reaction, mixture was filter and dried: recrystallise by ethanol. [22]



Reaction Scheme no.2: Synthesis of Chalcone

Synthesis of Schiff base:

General procedure for the preparation of Schiff base: Take 250ml round bottom flask, take prepared substituted Chalcone (2a-c), Dissolve in Ethanol then add p-amino benzoic

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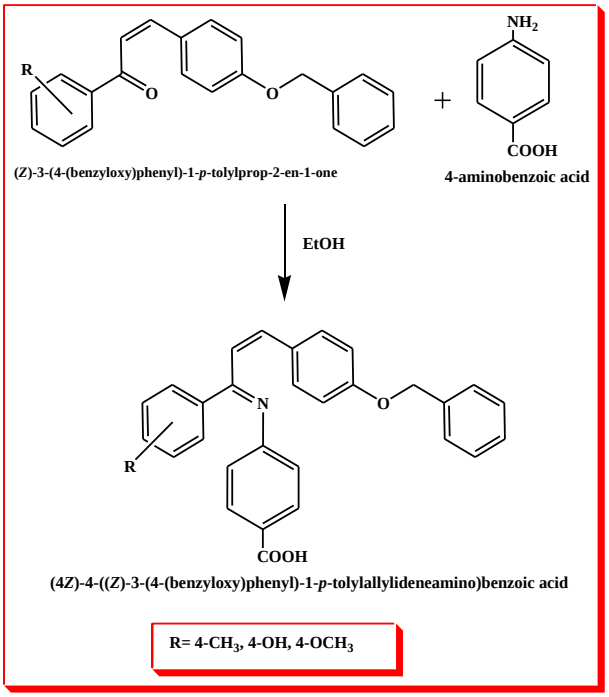
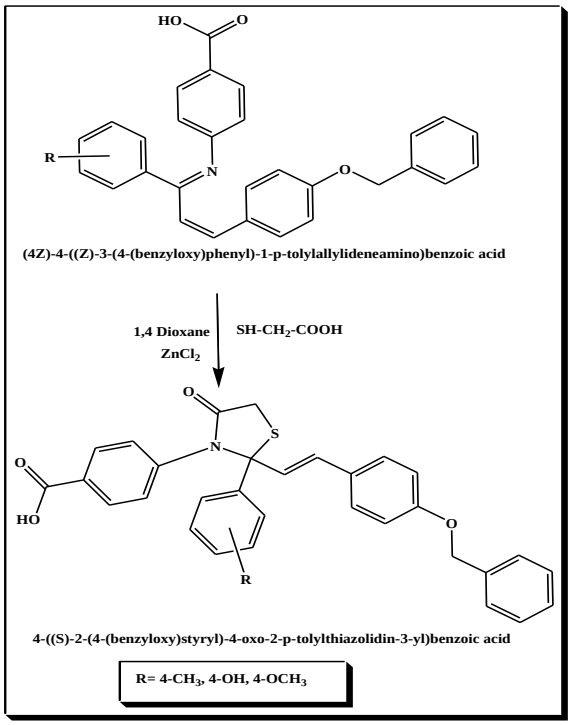
acid (5gm,0.036M) and Acetic acid. Refluxed the above given mixture for 4-5 hours heating. After the complete heating is over pour the mixture in ice cold water, Filter and dry the product. [23-24]



Reaction Scheme no.3: Synthesis of Schiff base

Synthesis of Thiazolidinone:

General Procedure for the preparation of Thiazolidinone: In a 250ml capacity Round bottom flask, Take Schiff base (4gm, 0.009M) (4a-c) Add 1,4-Dioxane dissolve the compound to the clear solution. Then add the Thioglycollic acid (1ml, 0.009M) and Anhydrous ZnCl2. refluxed the above given mixture directly heating for 8 hours. After the complete heating is over pour the mixture in saturated sodium bicarbonate solution and ice cold water, filter and dry the product. [25]



Reaction Scheme no. 4: Synthesis of Thiazolidinone

RESULT AND DISCUSSION:

The Synthesis of the novel derivatives of **thiazolidinone (6a-c)** is describe in reaction Schemes. The newly Synthesized compounds have been confirmed on the basis of organic qualitative analysis such as preliminary test, Melting point, Element detection functional group. All compounds purified by solvent recrystalization. A.R. grade chemical is use for Synthesis of various substituted Thiazolidinone.

BIOLOGICAL AND MEDICAL SIGNIFICANCE OF THIAZOLIDINONE

Although they have been known from long ago to be biologically active, their varied biological features are still of great scientific interest. Given below is a brief account of various alterations conducted oxazole ring and their associated biological activities.

Anti-Microbial Activity

Thiazolidinone derivatives by a convenient one-pot synthesis of enaminones with ethyl-2-bromopropionate. The antimicrobial activities of these compounds were screened *in vitro* against

Gram-positive bacteria, Gram-negative bacteria and fungi. Thiazolidinone derivatives showed potent antimicrobial activity. Antibacterial activity was assessed by the disc diffusion or cup plate method against *E. Erveneia, X. Oxalopodis*, *S. aureus, S.typhimurium,* and *E. coli.* Strains were inoculated in BHI medium and chloramphenicol was used as standard drug. These bacteria were inoculated in Sabouraud Dextrose broth medium. Nystatin was used as standard drug. The *in vitro* study results demonstrate that the compound was found to be most active. [26]Antimicrobial of following synthesized compounds is shown in fig (1). [26]

Anti-Oxidant Property/Activity

Among many methods employed for evaluating antioxidant activity of synthesized compounds as well as phytoconstituents, reducing power capacity and nitric oxide radical scavenging activity model will be used as they are simple, cheap and can be carried out under normal laboratory conditions.

The following in-vitro models were used to evaluate antioxidant activity. [27]

1. Reducing power model.
2. Nitric oxide radical scavenging model.

Reducing power: The reducing power of test samples was determined according to the method of **Oyaizu (Oyaizu, 1986).**This method is based on the principle of increase in the absorbance of the reaction mixture. Increase in absorbance indicates increase in the antioxidant activity. In this method antioxidant compound gives a colored complex with potassium ferricyanide, trichloroacetic acid and ferric chloride, which is measured at 700 nm. Increase in absorbance of the reaction mixture indicates the reducing power of the samples.

Preparation of Reagents:

1. **Phosphate buffer pH 6.6:** 2.72 gm of potassium di-hydrogen orthophosphate was dissolved in 100 ml of distilled water. The pH of this solution was adjusted to 6.6 by using 0.2 N NaOH solution.
2. **Potassium ferricyanide 1% w/v solution:** Prepared by dissolving 1 gm in 100 ml of distilled water.
3. **Trichloroacetic acid 10% w/v:** Prepared by dissolving 10 gm in 100 ml distilled water.
4. **Ferric chloride solution 0.1% w/v:** Prepared by dissolving 0.1 gm in 100 ml distilled water.
5. **Test solutions:** 50 mg of test compound was dissolved in 50 ml of suitable solvent. 1,2,3,4 and 5 ml of the test solution was pipetted out into 10 ml volumetric flasks and further diluted up to 10 ml with distilled water. This gave final concentration as 2.5, 5, 7.5,10 and 12.5 pg/ml respectively.
6. **Blank solution:** Phosphate buffer solution.
7. **Concentration of test solutions:** The concentration of test solutions is adjusted in such a way that the required concentrations were obtained in final solution.

Procedure: The standard drug and test compounds were dissolved in dimethyl formamide (DMF) so as to get different concentrations (25 pg/ml, 50 pg/ml, 75 pg/ml, 100 pg/ml, 125 pg/ml). This was mixed with 2.5 ml of (pH 6.6) 0.2 mol phosphate buffer and 2.5 ml of 1 % potassium ferricyanide [K_3Fe (CN)r,]. The mixture was incubated at 50 °C for 20 minutes. 2.5 ml of 10 % trichloroacetic acid was added to the mixture, which was then centrifuged for 10 minutes at 1000 rpm. 2.5 ml upper layer of solution was mixed with 2.5 ml of distilled water and 0.5 ml of 0.1 % ferric chloride. The absorbance was measured at 700 nm. The absorbance of the blank was also measured in similar manner. The results (table-no 6a) were compared with ascorbic acid, which was used as a reference standard antioxidant. The percentage increase in absorbance was calculated by using the formula given below.

Antioxidant activity of some representative compounds are given in Table **1**

$$\% \text{ increase in absorbance} = \frac{\text{Test O.D.-Control O.D.}}{\text{Control O.D.}} \times 100$$

Anti-Bacterial Activity

The novel synthesized heterocyclic compounds such as were screened for their *in vitro* antimicrobial activity using agar cup plate method against two gram positive bacterial strains, *S. aureus* and three gram negative strains, *E. coli* and *E. ervinia* ,*S.typhi,* Chloramphenicol were used as standard drugs for bacteria. The details of the relevant procedures and the results of the biological screening are discussed in this part of the thesis. [28]

General Procedure

Determination of Zone of Inhibition by Agar Cup plate method:

Test solutions were prepared with known weight of compound in dimethyl sulphoxide (DMSO) and diluted suitably to give the resultant concentration of 125, 250, 500 and 1000µg/mL.*In vitro* antibacterial activity was determined by using Nutrient broth Agar.

Twenty-four hours old culture of selected bacterial strain was mixed with physiological saline and the turbidity was corrected by adding sterile physiological saline and sub cultured on Sabouraud Dextrose and suspended in sterile distilled water to an absorbance of 0.6 at 450 nm. Petri plates were prepared by pouring 10 ml of Mueller Hinton Agar for bacteria containing microbial culture was allowed to solidify. The Bore method were then applied and the plates were incubated at 37 ˚C for 24h (bacteria) and the inhibition zone was measured as diameter in four directions and expressed as mean. The results were compared using Chloramphenicol as a standard antibacterial agent. The results of antibacterial activity (i.e. Zone of inhibition in mm) of some of the synthesized compounds s are given in the Table **2.**

CONCLUSION:

In conclusion, a rapid, high yield, simple, practical, economic, readily available system, and convenient procedure for the synthesis of substituted Thiazolidinone, (6a-c). The chemistry of Thiazolidinone with N, S, O bond considered to be the key factor played the major role. Living organism finds difficulty in construction of N, S, O bonds and so the natural abundance of compounds having such bonds is less. Therefore synthesis of novel Thiazolidinone derivatives(6a-c) and investigation of their chemical have gained more importance for medical purposes. The new substituted Thiazolidinone described in this project work are very stable compounds, and show antibacterial and antioxidant a property which may render them especially useful substances in drug research.

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Table no.1: Antioxidant activity of some synthesized compounds

Sr. No.	Compound Code	Absorbance					% increase in absorbance				
		20 µg/ml	40 µg/ml	60 µg/ml	80 µg/ml	100 µg/ml	20 µg/ml	40 µg/ml	60 µg/ml	80 µg/ml	100 µg/ml
1	Control	0.200					—				
2	Standard (Ascorbic acid)	0.254	0.265	0.262	0.282	0.288	54	65	62	82	88
3	4a	0.208	0.229	0239	0.252	0.265	08	29	39	52	65
4	4b	0.224	0.236	0.242	0.276	0.288	24	36	42	76	88
5	4c	0.224	0.246	0.256	0.273	0.289	24	46	56	73	89
7	5a	0.230	0.244	0.262	0.279	0.294	30	44	62	79	94
8	6b	0.203	0.212	0.214	0.229	0.237	03	12	14	29	37
9	6c	0.232	0.255	0.263	0.276	0.281	32	55	63	76	81

Table 2: Anti-Bacterial activity of some synthesized compounds

Sr. No.	Name of Compound	Concentrations (µg/ml)	Zone of inhibition in mm			
			Antibacterial activity			
			S. areus	*E. coli*	*S.Typhi*	*E. Erveneia*
1.	Chloramphenicol	1000	30	20	20	16
		500	27	18	20	17
		250	21	17	16	16
		125	17	17	15	15
2.	4-(2-(4-(benzyloxy)styryl)-2-(4-methoxyphenyl)-4-oxothiazolidine-3-yl)benzoic acid) (6b)	1000	18	13	17	17
		500	15	13	12	15
		250	09	10	15	17
		125	10	11	13	12

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Fig.(1) Anti-Microbial Activity of following synthesized componds