

## SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF THIAZOLIDINONES

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### ABSTRACT

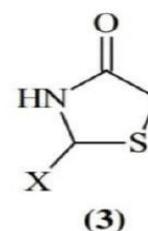
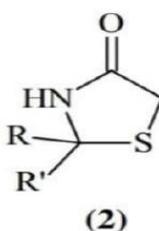
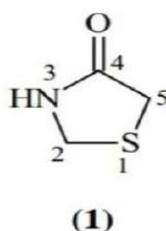
Thiazolidinones, five membered heterocyclic ring and a saturated form of thiazole with carbonyl group on fourth carbon has been considered a magic moiety (wonder nucleus) which possess almost broad spectrum of biological activities such as anti-inflammatory, antitroliferative, antihistamic, anti-HIV, hypnotic, anaesthetic, anthelmintic, antifungal and antiviral agents as well as CNS stimulants, hence the researchers has synthesized these condensed heterocyclic through different complex pathways as target structures for biological studies. Thiazolidinones are the compound synthesized by following steps such as condensation followed by cyclization of shiff's, either in a step wise manner or in a one pot under different conditions. Mercatoacetic acid, thiolactic acid, chloroacetyl chloride, potassium thiocyanate, ethylchloro acetate and ammonium thiocyanate are the most common reagents used the synthesis thiazolidinones appended of different heterocyclic skeletons. Heterocyclic compounds are promissory drugs due to its reported biological activities, for this reasons, thiazolidinones and its derivatives are presented as a new alternatives not only for its inhibitory activities against the parasite but also for its high selectivity level with high therapeutic index. Thiazolidinones have been reported as a building block in organic chemistry as a scaffolds for drug discovery. Structure of synthesis compounds was confirmed by means of their IR, NMR Spectral data and elemental analysis. Investigation of antimicrobial and antifungal activities of compound was done by liquid dilution method used for the determination of minimum inhibitory concentration. Bacterial strains of *Aspergillus niger* and *Candida albicans* were use to as certain the activity used as the standard positive control for antibacterial and antifungal activity respectively.

**KEYWORDS:** antitroliferative, antihistamic, anti-HIV, hypnotic, anaesthetic.

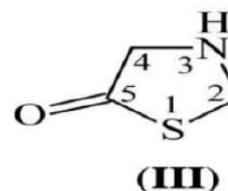
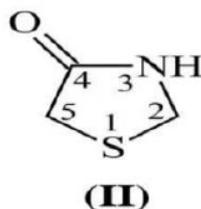
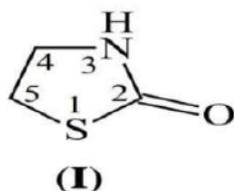
### CHAPTER 1- INTRODUCTION

Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring. A lot of research work on thiazolidinones has been done in the past. The nucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities. Numbers of methods for synthesis by using various agents are available in the references.

This array of biological response profile has attracted the attention of scientists' the world over to further investigate the potential of this organic motif. 4-Thiazolidinones are derivatives of thiazolidine with a carbonyl group at the 4-position (1). 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 in 3). Variations in the substituents attached to the nitrogen atom and the methylene carbon atom are possible for the structures represented by 2 and 3.



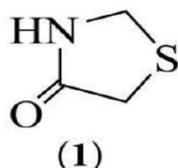
Thiazolidinones, which belong to an important group of heterocyclic compounds have been extensively explored for their application in the field of medicine. Thiazolidinones, with a carbonyl group at position 2 (I),



Antimicrobial activity is potent activity of thiazolidine-4-one. Antibacterial activity is strongly dependent on the nature of the substituent at C-2 and N-3 position. It also to possess various other activities such as anti-diarrheal, antiplatelet factor, antihistaminic, antimicrobial, antidiabetic, cyclooxygenase inhibitory, Ca Channel blocker, PAF antagonist and Follicle stimulating Hormone(FSH) receptor agonist activity and CFTR inhibitor Activity.

The chemistry of heterocycles lies at the heart of drug discovery<sup>1</sup>. 4-Thiazolidinone is one of the most intensively investigated classes of five member heterocycles<sup>2,3</sup>. 4-Thiazolidinones are the heterocyclic compounds having nitrogen and sulfur atoms and are known for a long time for their wide range of interesting biological activities namely anticonvulsant activity, anti-inflammatory activity, anti-tubercular activity, anthelmintic activity, antiviral activity, antifungal activity, antibacterial activity, anticancer activity and anti-HIV activity<sup>4-12</sup> etc. There are many protocols for the synthesis of 4-thiazolidinone. Present work deals with the synthesis of thiazolidinone derivatives and their characterization by spectral analysis (IR, <sup>1</sup>H NMR).

Thiazolidinones are classified as doubly unsaturated heterocyclic compounds contain one nitrogen, one sulphur and three carbon atoms including a carbonyl group.



There are many protocols for the synthesis of 4-thiazolidinones. 4-thiazolidinones can be synthesized either by cyclisation of acyclic compounds or by simple condensation of thioglycolic acid with Schiff's bases. The reaction undergoes by the attack of mercaptoacetic acid upon the C=N group, with the -S-CH<sub>2</sub>-COOH adding to the carbon atom followed by the capture of a proton by nitrogen and subsequent cyclisation. The nucleophilic attack of mercaptoacetic acid anion on carbon of azomethine, which has got positive character, is evidenced. Simultaneous removal of water as it forms

4 (II) or 5 (III), have been subjects of extensive study in the recent past. Numerous reports have appeared in the literature, which highlight their chemistry and use.

in reaction helps in condensation and determination of the reaction time.

4-thiazolidinones may be considered as phosphate bioesters and therefore inhibit the bacterial enzyme MurB which is involved in the biosynthesis of peptidoglycan layer of the cell wall. In addition, some thiazolidinones were recently reported as novel Inhibitor of mycobacterial rhamnose synthetic enzyme, this rhamnose is found in human, has been shown to be essential for mycobacterial cell wall synthesis.

4-Thiazolidinone ring also occurs in nature; thus actithiazic acid [(-) 2-(5-carboxypentyl) thiazolidine-4-one] isolated from *Streptomyces* strains exhibits highly specific in vitro activity against *Mycobacterium tuberculosis*.

### 1.1 Biological importance of Thiazolidinones

The development in the field of bio-inorganic chemistry has increased the interest in Thiazolidinones complexes, since it has been recognized that many of these complexes may serve as models for biologically important species. Thus, we report them in the following.

#### 1.1.1 Anticonvulsant Activity

Most of the compound were found to exhibit protection against pentylenetetrazole – induced seizures, and the degree of protection ranged upto 80%. However, no definite structure activity relationship could be observed regarding the anticonvulsant activity possessed by thiazolidinones.

#### 1.1.2 Hypnotic Activity

Several 2-(arylimino)-3-(2-pyrimidyl)-4-thiazolidinones and 2-(arylimino)-3-(3-(N-morpholino)-propyl)-4-thiazolidinones were evaluated for their ability to potentiate pentobarbital-induced hypnosis in mice at a dose of 100 mg/kg. All thiazolidinones were found to potentiate pentobarbital sleeping time.

#### 1.1.3 Respiratory Activity

A number of 4-thiazolidinones were investigated for their inhibitory effects on the oxidation of the substrates of the tricarboxylic acid cycle and  $\beta$ -hydroxy-butyrate by rat brain homogenate.

#### 1.1.4 Antiinflammatory, Antiproteolytic, and Antihemolytic Properties

Newbould studied the antiinflammatory activity of 2-[(butoxycarbonyl)methylene]-4-thiazolidinone. The compound was found to be devoid of activity against most models of acute inflammation. However, it partially inhibited carrageenin-induced edema in the rat and prevented completely the development of secondary lesions in the rats injected with adjuvant in the footpad.

#### 1.1.5 Antitubercular Activity

Litvinchuk reported antitubercular activity with low toxicity associated with a few derivatives of 2-imino-4-thiazolidinones. Repeated therapeutic doses were found to possess antituberculous activity comparable to streptomycin or pthivazid. A few derivatives were found to inhibit the growth of human tubercle bacilli, H37Rv strain, in a concentration of 12.5 µg/mL.

#### 1.1.6 Anthelmintic Activity

3-Methyl-5-[(4-nitrophenyl)azol] rhodanine, nitro dan, was reported as a potent anthelmintic compound which was effective when administered in feed against *Hymenolepis nana* and *Syphacia obuelata* infections in mice, *Asceridia galli* infections in chickens, and *Toxocera canis*, *Ancylostoma caninum*, and *Uncinaria stenocephala* infections in dogs, pigs, and horses. 2-Imino-3-(2-acetamidophenyl)-4-thiazolidinone derivatives have been found to be effective in vitro against horse Strongyloids at concentration of  $10^{-3}$  to  $10^{-6}$  M Hussain et al. synthesized a few azorhodanine derivatives in search of potent anthelmintics and found only 2-thiono-3-(4-chlorophenyl)-5-[[4-(4-methylpiperazino)phenyl]azo]-4-thiazolidinone possessing anthelmintic activity against *N. dubius* in mice.

#### 1.1.7 Cardiovascular Effects

Nagar et al. studied the cardiovascular effects of a series of 2-cyclopentyl(cyclohexylimino)-3-aryl-4-thiazolidinone-5-ylacetic acids on adult cats of either sex. All substituted thiazolidinones induced hypotension of varying degree. The duration of hypotensive activity observed with most of these compounds was less than 15 min.

#### 1.1.8 Antibacterial Activity

Several 2-[(dichlorophenyl)imino]-4-thiazolidinones and 2-(arylhydrazono)-4-thiazolidinones and their corresponding 5-arylidene derivatives were tested against

*Staphylococcus aureus*. The antibacterial activity of 5-arylidene derivatives of both 2-[(dichlorophenyl)imino]/2-(arylhydrazono)-4-thiazolidinones was found to be greater than that of the parent compounds. The screening data of more than 50 thiazole and thiazolidinone derivatives against some common bacteria revealed that the thiazolidinones were more active than the thiazoles. An enhancement in activity was observed with mercurated thiazolidinone derivatives as compared to nonmercurated derivatives.

#### 1.1.9 Antifungal Activity

Antifungal activity of some mercurated derivatives of 4-thiazolidinones against *Aspergillus niger*. Various 2-(4'-arylthiazolyl-2'-imino)-3-aryl-4-thiazolidinones have also been found to be sufficiently active against *Aspergillus niger* and *Alternaria tenuis*. Matolcsy have found very high antifungal activity associated with the derivatives of 2-thiono-4-thiazolidinones against

*Alternaria tenuis* and *Botrytis allii*. Several 2-(o-methylphenyl)imino]-3-aryl-4-thiazolidinones and their 5-phenylazo derivatives have been found to be very good fungicidal agents against *Helminthosporium euphorbiae*. Chaubey et al. screened various 1,1-dioxides and 5-phenylazo derivatives of 2-(arylimino)-3-aryl-4-thiazolidinones against *Aspergillus niger* and found the compounds to be fungistatic and not fungicidal.

#### 1.1.10 Antiviral Activity

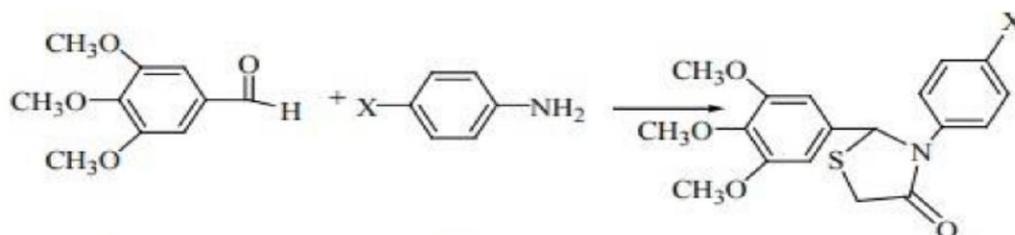
2,4-Dioxo-5-thiazolidinylacetic acid prevents in high dilution the cytopathogenic changes in cell culture of human embryonic kidneys infected with Herpes simplex virus and poliovirus type I. This compound prevented the cytopathogenic changes with these viruses if added simultaneously with virus to the cell culture medium or even if added at different time intervals after the cells have been infected. Schauer et al. investigated a number of 4-oxo-5-thiazolidinylacetic acid derivatives for their activity against Herpes simplex in order to find out a relationship between their antiviral activity.

## CHAPTER 2- METHODOLOGY

### 2.1. Synthesis of 4-thiazolidinones

#### 2.1.1. SYNTHESIS-

Turgut et al. prepared 4-thiazolidinones by the Katti cabodiimide (DCC) mediated one-pot three component condensation reaction of an aromatic amine, an aldehyde and mercaptoacetic acid.



### 2.1.2. CHARACTERIZATION

Characterized by means of their IR, NMR Spectra and UV-visible Spectra.

### 2.1.3. ANTIMICROBIAL EVALUTION

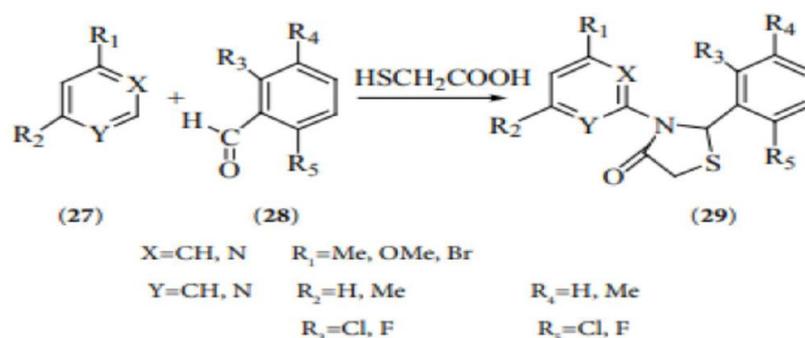
Antimicrobial Activity of the 4-thiazolidinones was studied against the nine microorganism including seven bacterial strains *B. subtilis*, *Staphylococcus aureus*, *Pseudomonas fluorescens*, *E. coli*, *Micrococcus luteus* And two fungal strains *A. niger* and *Penicillium chrysogenum*.

Reference- Ashrf Mashrai And Ayaz Mahmood Dar, Article in Medicinal Chemistry, Januar 2016.

## 2.2. Synthesis Of 2,3-diaryl-1,3-thiazolidin-4-ones

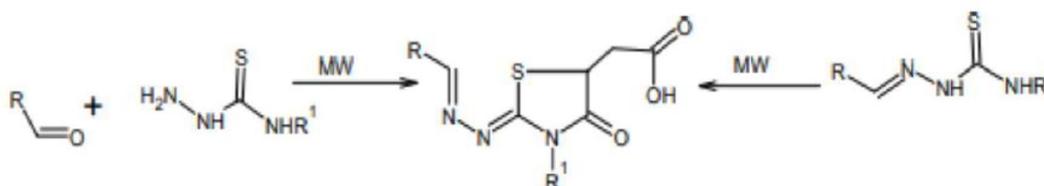
### 2.2.1. SYNTHESIS-

Monforte et al. reported the synthesis of 2,3-diaryl-1,3-thiazolidin-4-ones by reacting an aromatic aldehyde with an equimolar amount of (hetero) aromatic amine in the presence of an excess of mercaptoacetic acid. The microwave-irradiation dramatically shortened the reaction times, affording the desired products in high yields.



### 2.2.2. CHARACTERIZATION

Melting point were taken in open capillaries and are uncorrected IR,  $^1\text{H}$  NMR can recorded.



### 2.2.3. ANTIMICROBIAL EVALUTION

The antibacterial activity invitro against pathogenic bacterial strains such as *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus typhi* employing the nutrient agar disc diffusion method.

Reference- Andres, c.J.; Brinson, J.J.; D'Andrea, S.V.; Deshpande, M.S.; Falk, P.J.; Grant-Young, K.A.; Harte, W.E.; Ho, H, T.; Miscon, P.E.; Robertson, J.G.; Yaxinongsm, D.S.; Walsh, A.W. *Bioorg. Med. Chem. Lett.* 200, 10, 715.

## 2.3. Synthesis Of 2-hydrozoly-4-thiazolidinones

### 2.3.1. SYNTHESIS

Saiz C. et al. reported this reaction. An efficient tandem procedure for the synthesis of 2-hydrozoly-4-thiazolidinones under microwave conditions was reported. Different solvents and various reaction equivalents were explored until good isolated yields of thiazolidinones were obtained. 9 Microwave heating for the synthesis of thiazolidinone resulted in a significantly better yield compared to thermal conditions (75% vs 40%). Microwave irradiation also allowed for a faster

conversion. For tandem reactions, the best yields were obtained when a solvent mixture of PhMe/DMF (1:1) was used. Thiazolidinone was prepared in 68% yield using a stepwise sequence and in 82% yield under tandem conditions.

### 2.3.2. CHARACTERIZATION-

The structure of this newly synthesized compound are confirmed by IR,  $^1\text{H}$  NMR, mass spectra and C, H, N elemental analysis.

### 2.3.3. ANTIMICROBIAL EVALUTION

The antimicrobial activity of this compound against *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus mutans*, *Pseudomonas aeruginosa* and *Escherichia coli*. The Turbidometric method and Agar diffusion method are used to know the antifungal and antibacterial activity.

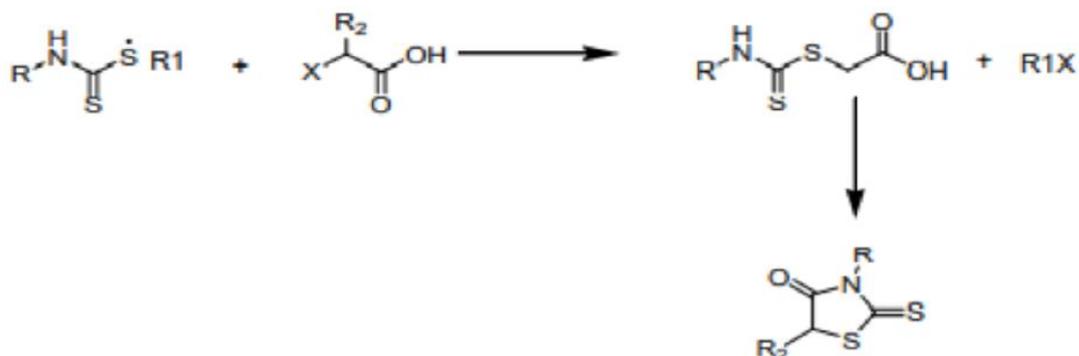
Reference- subhas S. karki and Mitul Prajapati, *International Journal Of Pharma Sciences And Reserch (IJPSR)*

## 2.4. Synthesis of substituted 2-thiono-4-thiazolidinones

### 2.4.1. SYNTHESIS

The dithiocarbamates formed by the reaction of primary

amine with carbon disulfide in the presence of base react with haloalkanoic acid in the presence of NaHCO<sub>3</sub> to give substituted 2-thiono-4-thiazolidinones as presented in the scheme. (Cunico W. et al., 2007).



### 2.4.2. CHARACTERIZATION

Characterized by IR, NMR and Mass Spectroscopy studies.

### 2.4.3. ANTIMICROBIAL EVALUTION

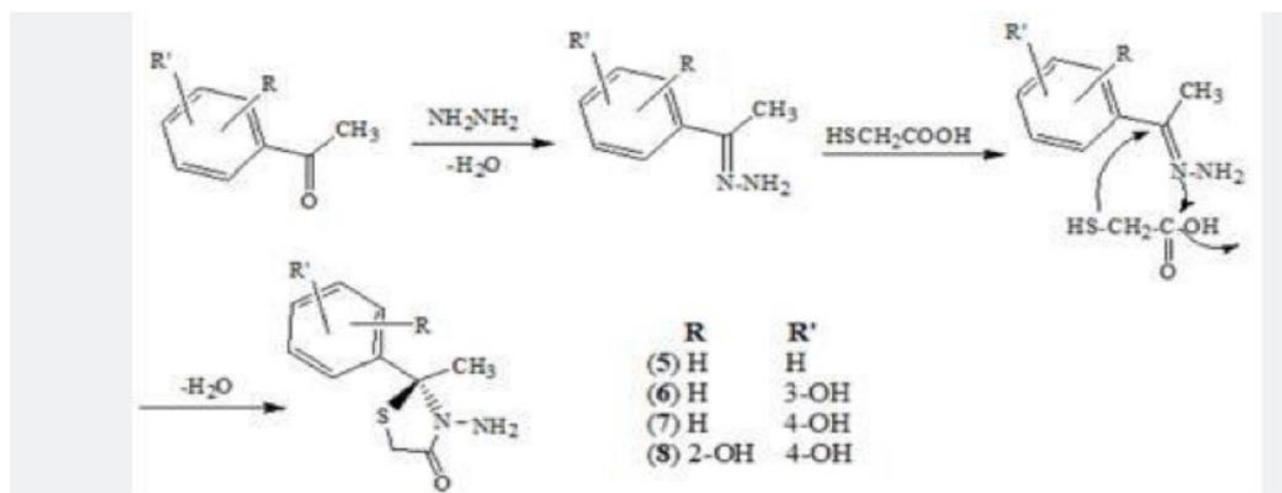
The antibacterial activity was studied with *Bacillus pumilus*, *Escherichia coli*. Antifungal Strains including *Aspergillus niger* And *Penicillium chrysogenum*.

Reference- Amit Gupta, Rajendra Singh, Pankaj k. Sonar, *Biochemistry Research International* Volume 2016, Article.

## 2.5. Synthesis of 3-amino-2-methyl-2-phenyl thiazolidine-4-one

### 2.5.1. SYNTHESIS

Acetophenone and its derivatives (1 mmol), hydrazine hydrate (1 mmol), mercaptoacetic acid (3.0 mmol) and few drops of conc. HCl were reflux in ethanol for 5 h. The progress and completion of the reaction was monitored by TLC. After completion of reaction, the excess solvent was reduced to three fourths of the original volume under reduced pressure. The reaction mixture was then taken in ether, washed with water and dried over anhydrous sodium sulfate. Evaporation of solvents and crystallization from methanol afforded the corresponding thiazolidinone.



: Proposed mechanism of formation 3-amino-2-methyl-2-phenyl thiazolidin-4-one derivatives [5-8].

### 2.5.2. CHARACTERIZATION

Characterized by Melting Point, IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, electronic data, FT-IR, LS spectral analysis.

### 2.5.3. ANTIMICROBIAL EVALUTION

The synthesized Compound were screened for their in vitro antibacterial activity against *Staphylococcus*

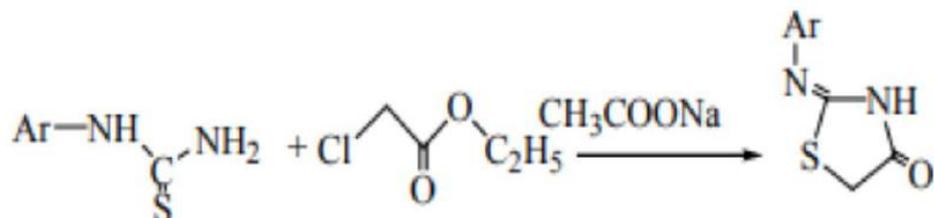
*aureus*, *Salmonella typhi*. And antifungal activity Against the *Aspergillus niger* and *Candida albicans*. Antimicrobial activity performed by cup-plate method.

Reference- Shafia Mir, Masrat Jan, Praveen Kumar And Ayaz Mahmood Dar, *Research Article* Volume 8 Issue October 2018.

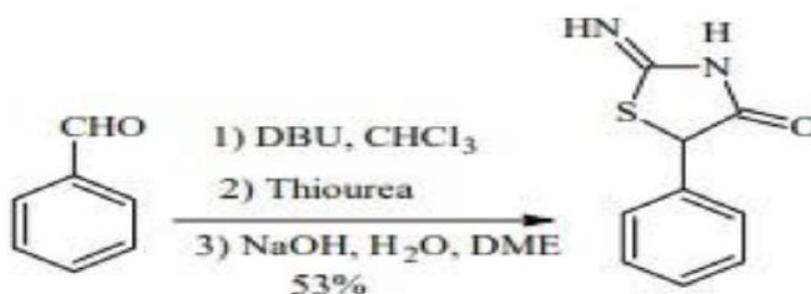
## 2.6. Synthesis of Thiazolidinones derivatives by using Thiourea

### 2.6.1. SYNTHESIS

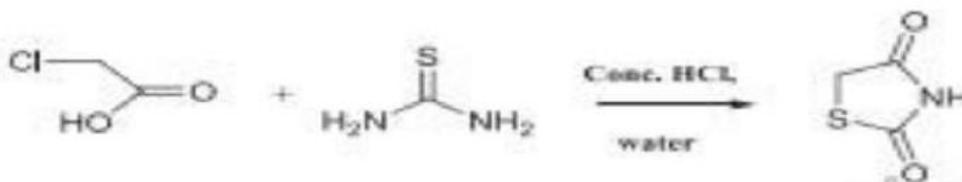
1) Shiradkar reported that various aryl-thioureas on treatment with ethyl chloroacetate and fused sodium acetate in a ethanol gave 2-arylimino-4-thiazolidinones.



2) One pot three component synthesis containing aldehyde, thiourea and chloroform to give 2-amino-4-thiazolidinone derivatives was also reported. Various imino 8 thiazolidinones were developed by using different reagents with different reaction conditions. (Jieping Z. et al., 2004).



3) Synthesis of thiazolidine-2,4-dione using thiourea as the starting material.



### 2.6.2. CHARACTERIZATION-

Compound have established on the basis of their elemental analysis And Spectral Data.

### 2.6.3. ANTIMICROBIAL EVALUTION

The compound Screened as Antituberculosis activity and Antiviral activity. Also they show the Antimicrobial activity of both Antifungal and Antibacterial activity.

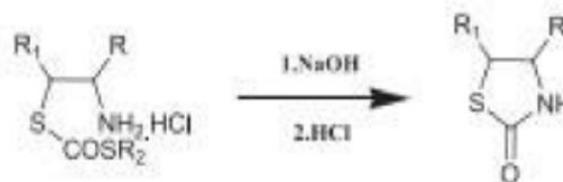
Reference- Sonam Nirwan and Rita Kakkar, Article in Journal of Heterocyclic Chemistry, March 2019.

## 2.7. Synthesis of 2-Thiazolidinones

### 2.7.1. SYNTHESIS

The treatment of 2-aminoethyl benzyl dithiocarbamate hydrochloride with 1 N NaOH solution, followed by neutralization with HCl, resulted in the formation of 2-thiazolidinones. In an effort to study the biological significance of the not much explored 2-thiazolidinone moiety, a group of researchers synthesized C-3 substituted 2-thiazolidinones. They used a fragment-based drug design approach to arrive at these scaffolds

and then synthesized them using multiple steps, as shown in Figure. In continuation of their efforts, the group also synthesized some sulfonamide substituted 2-thiazolidinone derivatives using similar steps.



### 2.7.2. CHARACTERIZATION-

Characterized by <sup>1</sup>H NMR, IR Spectra, FT-IR, LCMS, HPLC analysis, UV absorption. They also show a Column chromatography.

### 2.7.3. ANTIMICROBIAL EVALUTION-

They have antibacterial activity against *S. aureus* And *P.aeruginosa*.

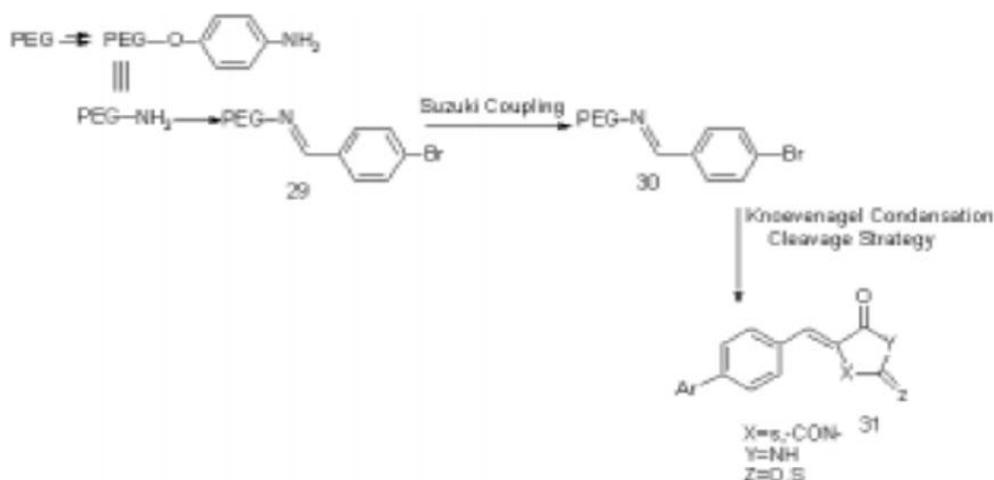
Reference-Journal of Pharmaceutical and Biomedical

Sciences by Murugesan Sugumaran et al. /JPBMS, 2012, 16(13).

## 2.8. Synthesis Via Suzuki Coupling Reaction and Knoevenagel Condensation

### 2.8.1. SYNTHESIS

An efficient method for the soluble polymer-supported synthesis of 5-arylidene thiazolidinones and



### 2.8.2. CHARACTERIZATION

Characterized melting point, TLC, IR, NMR.

### 2.8.3. ANTIMICROBIAL EVALUTION

They are tested in vitro for their antimycobacterial activity, Antimicrobial activity, Cytotoxicity. Antibacterial strains such as E. coli.

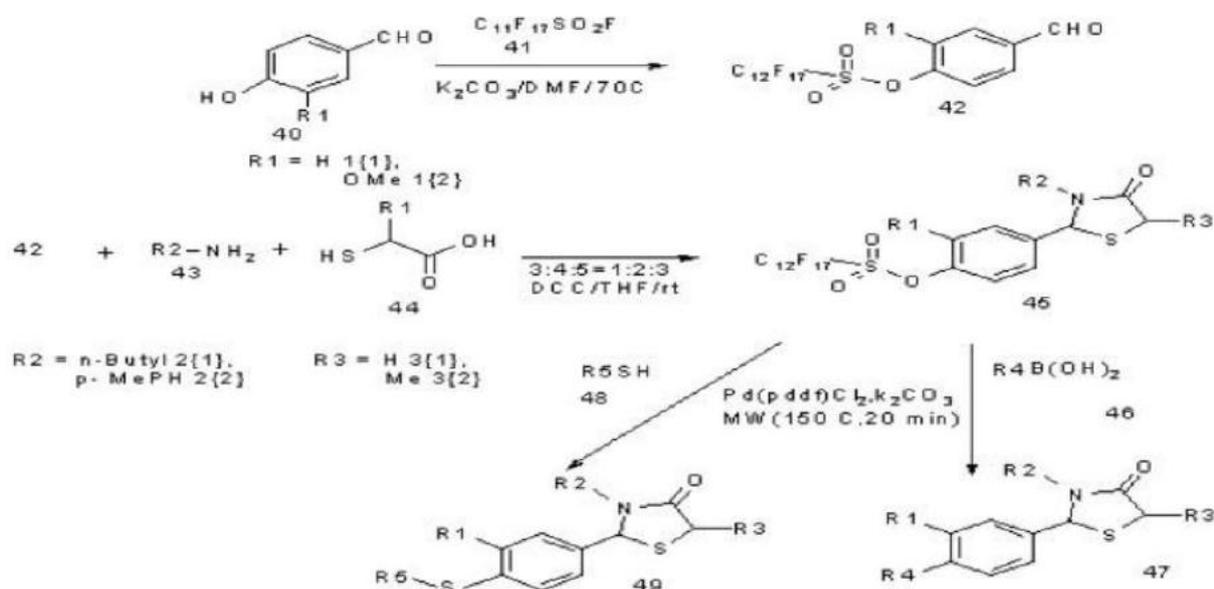
Reference- Dr. R. P. Gore / Journal of Pharmacy Research 2014.

pyrimidinones using aniline as a traceless linker was described. Aldehyde substrates were attached to the polyethylene glycol (PEG) bound aniline via an imine linkage, and after the subsequent PEG-promoted Suzuki coupling reaction for the diversification, Knoevenagel condensation was readily employed as the cleavage strategy. Zhang Liu et al, 2008.

## 2.9. Synthesis from Fluoroussulfonate 42

### 2.9.1. SYNTHESIS

Synthesis of 2-aryl-substituted 4-thiazolidinone and 4-thiazinanone libraries as drug candidates. Fluoroussulfonate tag 42 was introduced and performed 41 functions during the syntheses: as a phase tag for the purification of intermediates 45, and as an activated leaving group for cross-coupling reactions to form the final products of the library Bin Yan et al 2008.





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