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SYNTHESIS AND BIOLOGICAL EVALUATION OF THIAZOLIDINONE DERIVATIVES

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ABSTRACT

A new series of thiazolidinone derivatives were synthesized by the reaction of schiff base (2-aminopyridine and 4-dimethyl amino benzaldehyde) with mercaptoacetic acid respectively. The chemical structures of the synthesized compounds were confirmed by means of IR. The different synthesized thiazolidinone derivatives derived from benzaldehyde showed good antibacterial activity against both gram positive and gram negative such as *Staphylococcus aureus* and *Eischerchia coli*. In this when compare to compound I, compound II showed more inhibition. The average area of inhibition in millimetre (mm) was calculated and compared with that of the standards gentamycin.

KEYWORDS

Schiff Bases, Thiazolidinone, *Staphylococcus aureus and Escherichia coli*.

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INTRODUCTION

There are numerous biologically active molecules which contain various hetero atoms such as nitrogen, sulphur and oxygen, always drawn the attention of chemist over the years mainly because of their biological importance. Thiazolidine derivatives (Figure No.1) and have an atom of sulfur at position 1, an atom of nitrogen at position 3 and a carbonyl group at position 2, 4, or 5. However, its derivatives

belong to the most frequently studied moieties and its presence in penicillin was the first recognition of its occurrence in nature[1,2]. Similarly 1, 3-thiazolidin-4-ones are heterocyclic nucleus that have an atom of sulfur and nitrogen at position 1 and 3, respectively and a carbonyl group at position 4have been subjected to extensive study in the recent years. The 4- thiazolidinone is very versatile and has featured in a number of clinically used drugs. They have found uses as anti-tubercular, anti-microbial, anti-inflammatory and as anti-viral agents, especially as anti-HIV agents. It has been extensively reported that presence of arylazo, sulfamoylphenylazo or phenylhydrazono[3,4] moieties at different positions of the thiazolidone ring enhanced anti-microbial activity and its antibacterial activity may be due to its inhibitory activity of enzyme Mur B which is precursor acting during the biosynthesis of peptidoglycan. The thiazolidinones ring has been incorporated into a broad range of known biologically active compounds, either as a substitutuent group or as a replacement of another ring inspired researchers to synthesize several compounds containing this moiety. Thiazolidinones with C-2 and N-3 substituted positions possess diverse degrees of inhibition against bacteria and fungi. The dramatically rising prevalence of multi-drug resistant microbial infections in the past few decades has become a serious health problem. Approximately all the positions of 4-thiazolidinone have been explored to improve the antibacterial and antifungal activity. The SAR studies of thiazolidinone derivatives showed that they are more effective on gram-negative bacteria as compared to gram-positive bacteria. The search for new antimicrobial agents will consequently remain as an important and challenging task for medicinal chemists.

Thiazolidinone derivatives (Figure No.2) were reported to possess antibacterial, antifungal, antitumor antituberculor activity, anti-HIV, analgesic, anti inflammatory[5], and ulcerogenic activity. Pyridine derivatives were reported to possess antimicrobial[6] activities. Therefore it was envisaged that compounds containing both the chemical moieties would result in compounds of interesting biological activities. In this present study 2-aminopyridines were treated with 4-dimethyl amino benzaldehyde to produce Schiff base. The Schiff bases were subjected to addition reaction with thioglycollic acid in the presence of 1, 4 dioxane,anhydrous zinc chloride to produce 4-thiazolidinone derivative respectively[7]. The chemical structures of the synthesized compounds were confirmed by means of IR, 1H-NMR. The synthesized compounds were screened for antibacterial activity against gram positive and gram negative bacteria[8].

MATERIALS AND METHOD

Methods of Synthesis of Thiazolidine derivatives

A mixture of 2-aminopyridine (0.01mol), 4-dimethyl amino benzaldehyde [9] (0.01mol) and a drop of acetic acid was dissolved in ethanol (25ml) and heated on a steam bath for 45-60 min or on a water bath for 2-3 hrs. The reaction mixture was allowed to stand at room temperature for 24h. The product separated out was filtered, dried under vacuum and recrystallized by using warm ethanol. The Schiff bases and thiazolidine-4-one derivatives were prepared by the method of [10]. To a mixture of schiff base (0.01mol) and thioglycolic acid (0.01mol) dissolved in 1, 4 dioxane (20ml), anhydrous zinc chloride (0.004 mol) was added and refluxed for 8hours. The reaction mixture was cooled, filtered, washed with water, vacuum dried and recrystalised using absolute ethanol [11].

Anti microbial activity of thiazolidinone derivatives

The bacterial screening is based upon a comparison of the inhibition of growth of bacteria by measured concentrations of the compound to be examined with that of activity produced by known concentration of a standard drug.

List of compounds subjected for anti-bacterial Studies

- Nutrient Agar / Sabourd Dextrose Broth
- Petri dishes
- Sterile Pipettes
- Test Compounds
- Standard Drug: Gentamycin

- Solvent (control): DMSO

Cylinder-Plate or Cup Plate Method

Cup plate method is based on the diffusion of compound from a vertical cylinder or a cavity through the solidified agar layer of a petri dish or plate to an extent such that growth of the added bacteria is prevented entirely in a circular area or "zone" around the cylinder or cavity containing a solution of the compound. The compounds were tested at the concentration of 100 µg/well against one Gram-positive bacteria, three Gram-negative bacteria's.

Requirements

Standardised culture of Test organism

Gram positive - *Staphylococcus aureus*

Gram negative - *Eischerchia coli*

Inoculate a previously liquefied medium appropriate to the assay with the requisite quantity of suspension of the micro organism, add the suspension to the medium at a temperature between 40 to 50^{o}C and immediately pour the inoculated medium into petri dishes to give a depth of 3-4mm. Ensure that the layers of medium are uniform in thickness by placing the dishes or plates on a level surface.

The prepared dishes must be stored in a manner so as to ensure that no significant growth or death of the test organism occurs before the dishes are used and that the surface of the agar layer is dry at the time of use. The cavities in the agar plates are prepared be using a metal borer. The cavities formed must be uniform throughout the dish. Apply the solutions to the surface of the solid medium in sterile cavities prepared in the agar medium. The volume of solution added to each cavity must be uniform and sufficient almost to fill those holes when these are used. Leave the dishes standing for 1-4 hrs at room temperature or at 4^{o}C as appropriate as a period of pre-incubation diffusion to minimise the effects of variation in time between the applications of different solutions. Then the plates are incubated at 37±1^{o}C for 24 hrs and observed for antibacterial activity. The diameter of the zone of inhibition was measured for the plates in which the zone of inhibition was observed.

RESULTS AND DISCUSSION

The present work describes the synthesis of Schiff base and their thiazolidinone derivative along with their antibacterial activities. The reaction completion was confirmed by TLC and the synthesised compounds were purified by recrystallisation (Figure No.3). The structures of the synthesised compounds were assigned on the basis of the spectral data. The infra red, nuclear magnetic resonance spectra of these Schiff bases and thiazolidinone compound showed the expected frequencies and signals. The antimicrobial activity of the thiazolidinone derivative was screened by the cup plate method with the standard drug Gentamycin, control (solvent DMSO) and the sample. It showed that the compound had antibacterial activity towards Gram +ve and Gram – ve organisms. The standard used was Gentamycin. When compare to compound I, compound II showed more inhibition. The average area of inhibition in millimetre (mm) was calculated and compared with that of the standards as shown in the Table No.1 below:

Compound – I

(Z)-N-(4-(dimethylamino)benzylidene)pyridin-2-amine

IR (KBr) cm-1: 1663(C=N), 899(CH-Ph), 1379(N-methyl), 1589(CH3).

Compound – II

2-(4-(dimethylamino)phenyl)-3-(pyridin-2-yl)thiazolidinone

IR (KBr) cm-1:1671(C=O), 1441(CH2 Bending), 1232(C-N), 936(CH- Ph), 1362 (Nmethyl), 1441 (CH3).

Table No.1: Anti-bacterial activity of synthesized thiazolidinone derivatives

S.No	Microorganism used	Concentration in µg	Zone of inhibition in mm	
			Compounds	
			Compound -I	Compound - II
1	**Gram +Positive organisms** *Staphylococcus aureus*	250	07.0	08.1
		125	04.2	06.4
2	**Gram –Negative organisms** *Eischerchia coli*	250	06.1	08.3
		125	05.0	07.3
3	**Gentamycin**	---	19.8	19.3

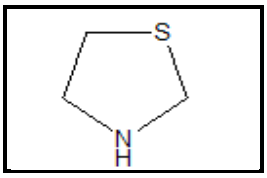

Figure No.1: Structure of Thiazolidine

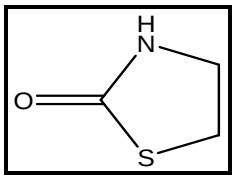

Figure No.2: Structure of Thiazolidinone

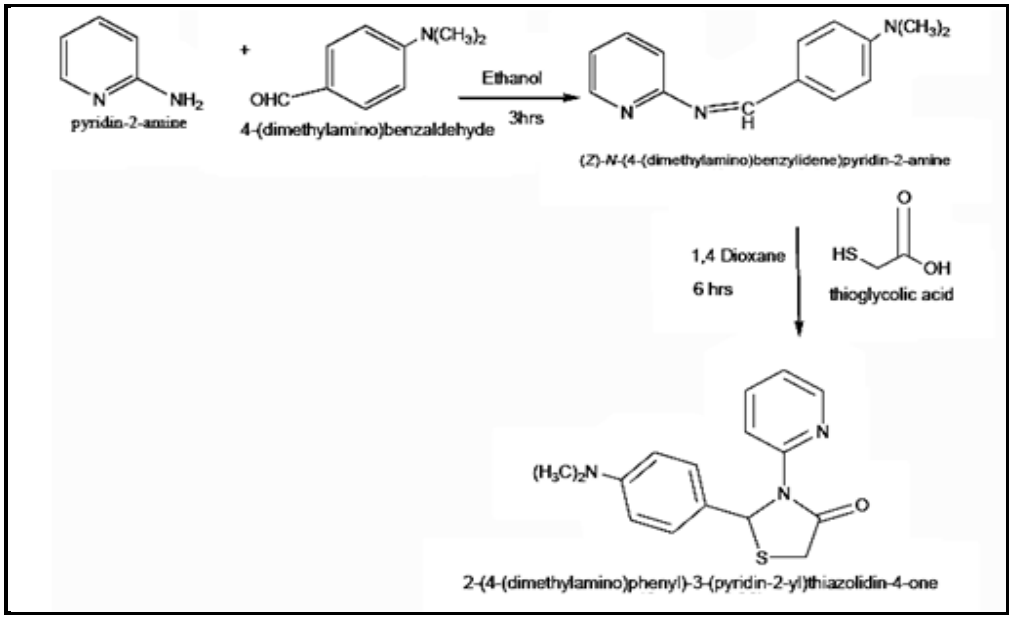

Figure No.3: General schematic synthesis of thiazolidinone derivatives

CONCLUSION

The potency of thiazolidinone nucleus is cleared from the clinically used drugs. Though the antibacterial are the major area of clinical use, other potential targets are still to be explored. Most of the positions were explored to improve the antibacterial profile of thiazolidinone. However, few derivatives with C-2 and N-3 substituted positions and the presences of electron-withdrawing substitution on aromatic ring on C-2 position of thiazolidinone presenting varied degrees of inhibition against Gram-positive and Gram-negative bacteria showing inhibition as good as to the standard drugs used. The activity of the compounds depends upon the nature and position of the substituents at the aryl moiety attached with thiazolidinone ring. Hence further investigation in this direction may yield fruitful results.

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