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ANTIMICROBIAL POTENTIAL OF NOVEL SCHIFF BASE DERIVATIVES OF 2,4-THIAZOLIDINEDIONES

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Keywords:

2, 4-thiazolidinedione, Pharmacophore, Antimicrobial activity, Spectral analysis

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ABSTRACT

2, 4-thiazolidinedione is a synthetically versatile substrate, where it can be used for the synthesis of large variety of heterocyclic compounds. 2,4-Thiazolidinedione moiety can be considered as an important pharmacophore in the field of medicinal chemistry which can be used for conjugating it with other bio-active molecules such as antimicrobial, antibacterial, antifungal, antidiabetic and antioxidant activity. The aim of present work is to evaluate the antimicrobial activity of novel Schiff base derivatives of 2,4thiazolidinedione. The various derivatives of 2,4 thiazolidinedione were prepared by treating 2,4-thiazolidinedione with various amines in the presence of glacial acetic acid and formaldehyde to yield Schiff's bases and the structure of synthesized compounds were confirmed by chromatographic and spectral analysis. In the screening evaluation methods of activities of 2, 4-thiazolidinedione derivatives were tested by agar well method against gram -positive and gram-negative bacteria. Clarithromycin was employed as standard drug and zone of inhibition was calculated. The order of activity of compounds against *Staphylococcus aures, Eschericha coli* when compared with standard drug i.e. Clarithromycin is: - Comp ISS-7>Comp ISS-8>Comp ISS-9.

Introduction:

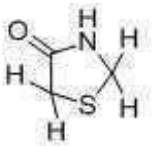
In late 1990's ,the medication class of thiazolidinediones also known as glitazones was launched as a supporting therapy for type 2 diabetes mellitus and related disease. Thiazolidinediones are pentacyclic compounds containing sulfur that are largely found throughout nature in different forms. Thiazolidinediones as well as their derivatives have drawn kind attention due to their wide clinical and biological use. Researchers are focusing on this moiety because of its involvement in the control of several physiological activities. The heterocyclic moieties that have Nitrogen and Sulfur groups attached to them are considered in broad-ranging pharmacological activities. This has made interest among researchers who have synthesized various varieties of the derivatives of thiazolidinediones and put them for screening of many biological activities. Thiazolidinedione compounds show various properties like antimicrobial, antiviral, antimycobacterium, anti-malarial, anticancer, anticonvulsant, anti-inflammatory, anti-HIV (human immunodeficiency virus), antioxidant, and antitubercular etc.

Antimicrobial agents are those chemical compounds which either kill or retard the growth of microorganisms at lower concentrations. Antimicrobial agents can be grouped into different classes on the basis of their functions or according to the microorganisms they primarily act against. In their classification on the basis of functions, agents which kill microbes are called microbicidal and those which merely inhibit their growth are called biostatic. According to another classification, those which act against bacteria are called antibiotics and those act against fungi are called antifungals. Due to emerging infectious diseases and increasing number of multi-drug resistant microbial pathogens, the treatment of infectious diseases still remains a challenging problem which demands the formation of new class of antimicrobial agents (Pfeltz and Wilkinson, 2004). The number of antimicrobial drugs available in the market is vast, but there is a need to discover novel antimicrobial agents with better pharmacodynamic and pharmacokinetic properties with lesser or no side effects. Thiazolidinedione is a potent antimicrobial agent. Looking at the pharmacological potential of 2, 4thiazolidinedione, we thought it worthwhile to synthesize some Schiff bases of 2,4 thiazolidinedione derived conjugates and finally to study their bio-activity.

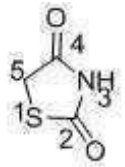
Chemistry:

Chemistry of 2, 4-Thiazolidinediones:- Thiazolidine-2, 4-diones are derivatives of Thiazolidine with a carbonyl group in the 2nd and 4th positions. Substituent in the 3rd and 5th positions may be varied, but the greatest difference in the structure and properties is exerted by the group attached to the carbon atom in the 2nd position. These groups includes alkyl or aryl (thiazolidinones), sulphur (2-thioxo-1, 3- thiazolidine-4one: rhodanine), although compounds in which alkyl or aryl groups replace the hydrogen atoms. Variations in the substituent attached to the nitrogen atom and the methylene carbon atom are also possible. 2, 4-thiazolidinedione is frequently called as

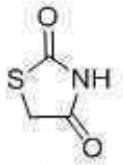
"Senfolessigsaure" in the early German literature.



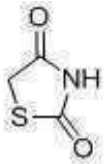
Thiazolidinedione



Thiazolidine-2,4-dione



2-Thioxo-1,3-Thiozolidine-4-one



4-thioxo-1,3-thiazolidine-2-one

Materials and methods:

MATERIALS

All the chemicals used were procured from CDH, Acros and Himedia. Melting point (m.p.) was recorded on Veego melting point apparatus and is uncorrected. All reaction were monitored by thin layer chromatography (TLC) using silica gel G (Rankem) and activated at 110 ◦ C for 30 min. The plates were developed by exposing to iodine vapors'. All reagent and solvents were purified and dried by standard techniques. Anhydrous magnesium sulphate was used as drying agent.

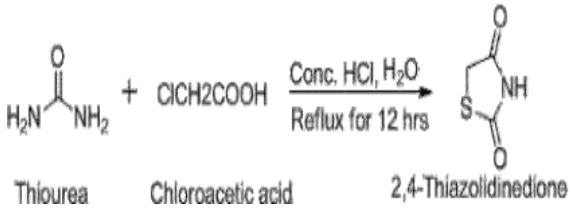
3.1 Thin Layer Chromatography

In order to ascertain the purity and homogeneity of the synthesized compounds, thin layer chromatography was carried out. The solvent system used for compounds were Chloroform: Ethanol (9:1) for the ISS-7 to ISS-9 series compounds; Silica gel-G was used as an adsorbent. The spots were located using either by the iodine vapors or under the UV lamp. Rf values were calculated for each compound by the formula-

R_f = Distance travelled by the compound / Distance travelled by the solvent front

PROPOSED SCHEME OF SYNTHESIS: -

STEP 1 :- Synthesis of 2,4-Thiazolidinedione



Thiourea Chloroacetic acid 2,4-Thiazolidinedione

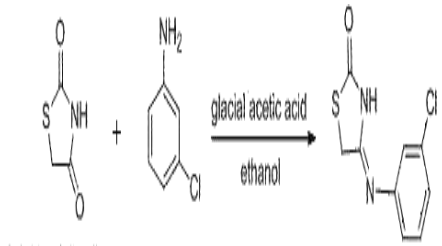
PROCEDURE:- In a 250ml three-necked flask, a solution containing 56.4g (0.6M) of chloroacetic acid in 60ml of water and 45.6g (0.6M) of thiourea was dissolved in 60ml of water. The mixture was stirred for 15 minutes till occurrence of white precipitates. To the contents of flask was now added slowly 60ml of conc. hydrochloric acid from dropping funnel to dissolve the precipitates, after which the reaction mixture was stirred and refluxed for 10-12hrs at 100-110˚C, on cooling the contents of flask were solidified to a mass of clusters of white needles. The product was filtered and washed with water to remove traces of hydrochloric acid and dried. It was recrystallised from ethanol, yield 80%, m.p. (123-125˚C).

TLC: chloroform: methanol (9:1)

R_f: 0.62

STEP 2 :- Synthesis of Schiff base derivatives of 2, 4-thiazolidinedione :

A. Synthesis of (Z)-4-(3-chlorophenylimino) thiazolidin-2-one (ISS-7)



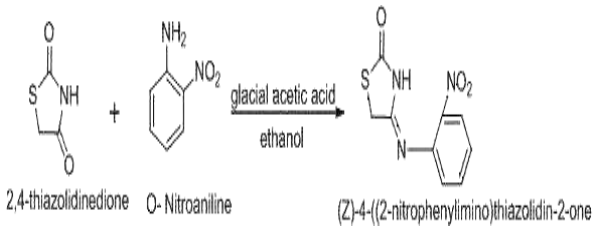
2,4-thiazolidinedione m-Chloroaniline (Z)-4-((3-chlorophenylimino)thiazolidine-2-one

PROCEDURE: - 0.01 mole of 2,4-thiazolidinedione was dissolved in minimum amount of ethanol (5ml). To this, was added 0.01 mole of m-chloroaniline, in hot ethanol (4ml). Catalytic amount of glacial acetic acid was added to the above mixture and the contents were refluxed on water bath for several times with monitoring TLC. The resulted solution was allowed to stand overnight and the precipitated solid was filtered, washed, dried and recrystallised from alcohol to yield the Schiff bases.

TLC: Chloroform: ethanol (9:1)

Rf: 0.8

B. Synthesis of (Z)-4-((2-nitrophenylimino) Thiazolidine-2-one (ISS-8)

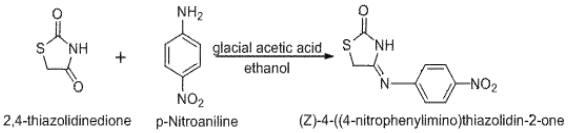


PROCEDURE: - 0.01 mole of 2, 4-thiazolidinedione was dissolved in minimum amount of ethanol (5ml). To this, was added 0.01 mole of O-Nitroaniline , in hot ethanol (4ml). Catalytic amount of glacial acetic acid was added to the above mixture and the contents were refluxed on water bath for several times with monitoring TLC. The resulted solution was allowed to stand overnight and the precipitated solid was filtered, washed, dried and recrystallised from alcohol to yield the Schiff bases.

TLC: Chloroform: ethanol (9:1)

R_f: 0.73

Synthesis of (Z)-4-(4-nitrophenylimino) thiazolidin-2-one (ISS-9)

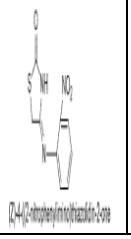
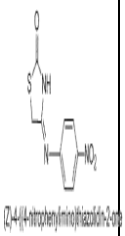


PROCEDURE: - 0.01 mole of 2, 4-thiazolidinedione was dissolved in minimum amount of ethanol (5ml). To this, was added 0.01 mole of p-Nitroaniline , in hot ethanol (4ml). Catalytic amount of glacial acetic acid was added to the above mixture and the contents were refluxed on water bath for several times with monitoring TLC. The resulted solution was allowed to stand overnight and the precipitated solid was filtered, washed, dried and recrystallised from alcohol to yield the Schiff bases.

TLC: Chloroform: ethanol (9:1) Rf: 0.79

ANALYTICAL PROFILE AND SPECTRAL REPORTS OF SYNTHESIZED COMPOUNDS :

TABLE: - Physicochemical data for compounds

	Compound ISS-7 Profile	**Compound ISS-8 Profile**	**Compound ISS-9 Profile**
Molecular formula	$C_9H_7N_2OSCl$	C9H7N3O3S	C7H7N3O3S
Molecular mass	226.68	237.24	237.02
Chemical name	(Z)-4-((3-chlorophenylimino)thiazolidin- 2-one	(Z)-4-((2-nitrophenyl imino) thiazolidin-2-one	(Z)-4-((4-nitrophenyl imino) thiazolidin-2-one
Appearance	Dark reddish brown	Yellow	Pale Yellow
%yield	67	83	77
Melting point	155-158	157-160	149-153
R_f value	0.8	0.73	0.79
			

In vitro Antimicrobial Screening :

Agar-well method

Clarithromycin is a macrolide antibiotic used to treat pharyngitis, tonsillitis, acute maxillary sinusitis, acute bacterial exacerbation of pneumonia (especially atypical pneumonia associated with Chlamydophila pneumoniae), skin infections. It was taken as standard as it is broad spectrum antibiotic active against both gram-positive *Staphylococcus aureus* and gram negative *Eschericha coli*. All of the newly synthesized compound derivatives were subjected to antimicrobial screening by the in vitro agar well method using Clarithromycin as positive controls. The Gram-positive bacteria Staphlococcus aureus was proved to be sensitive towards all the compounds, but most active was ISS-7.

Procedure:-

The biological evaluation of synthesized compound was performed using the in vitro agarwell method and MBC values were calculated . In the present study one gram-positive and one gramnegative bacterium were selected. The gram-positive strain was *Staphylococcus aureus* and gram negative was *Escherichia coli*. The selected strains were preserved by periodical subculturing on agar slant and storing them under frozen conditions ; for the study fresh 24 hours broth cultures were used.

Each bacterial pure culture was transferred into 100mL of Sabouraud's dextrose broth. The inoculated broths were incubated at 37° Celsius for 24hours. Muller Hinton agar media was prepared by suspending 19g of media in 500mL . They were boiled to dissolve completely. It was then sterilized by autoclaving at 15lbs. pressure (121° Celsius for 15mins). The prepared Muller Hinton agar medium was transferred into sterile petri plates.

Standardized bacterial inoculums were spreaded on medium using sterile cotton swab. 5 wells were made by means of a cork borer and the underside of the plates being marked to permit subsequent identification of the cups. The synthesized test compound derivatives (ISS-7 to ISS-9) and standard Clarithromycin were dissolved in DMSO to obtain a concentration of 200 µg/mL gives 1000 µg/mL). Cylindrical plugs were removed from agar plate using a streile cork borer and all the cups were filled by sample solution using a pipette. Plates inoculated with tested bacteria were incubated at 37° Celsius. Results were taken after 24hours of incubation and were recorded as average diameter of the inhibition zone in mm.

TABLE Zone of Inhibition of some Schiff bases of 2,4 thiazolidinedione.

For antibacterial activity on a) ***Staphlococcus aureus*** **and b)** ***Eschericha coli*** **:-**

Compound 250µg/ml	***Staphlococcus aureus*** **(zone of inhibition in mm)**	***Eschericha coli*** **inhibition in mm)**
. Control	0	0
Standard	20	17
ISS-7	15	13
ISS-8	7	6
ISS-9	16	5

Figure: Anti-bacterial activity of some novel Schiff bases of 2,4, thiazolidinedione

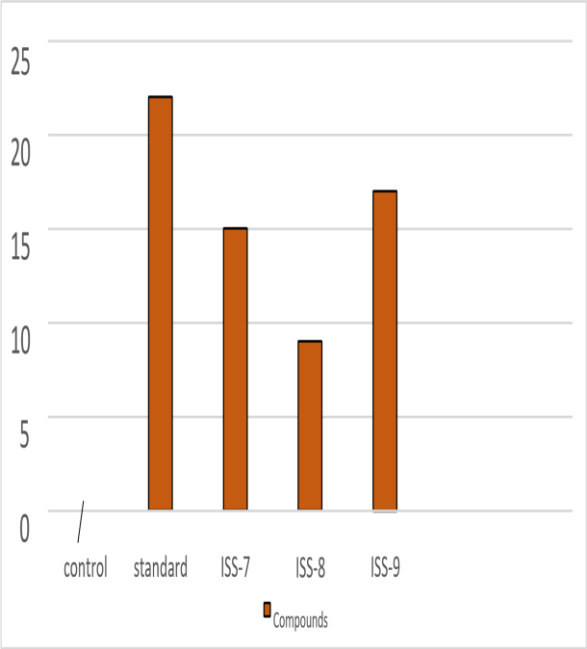


Figure: Graphical presentation of antibacterial activity of some novel Schiff bases of 2,4 thiazolidinedione (ISS-7 to ISS-9) against *Staphlococcus aureus*

Compounds were also active against the gram-negative bacteria *Eschericha coli*. Compound ISS-7 showed a maximum activity.

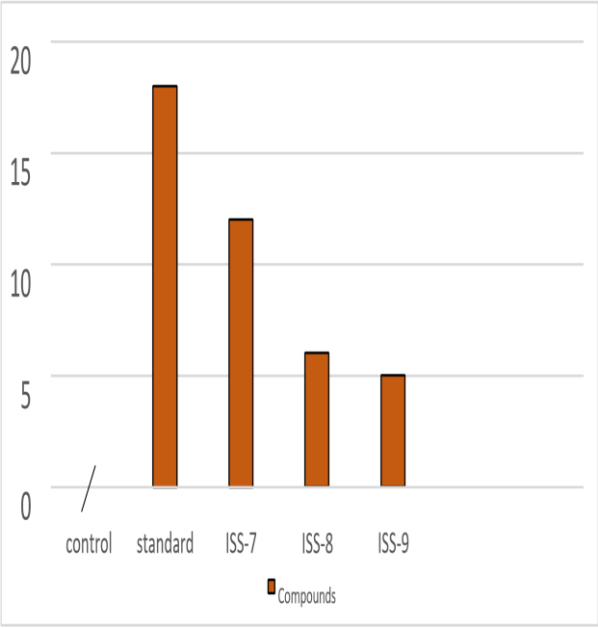


Figure: Graphical presentation of antibacterial activity of some novel Schiff bases of 2,4 thiazolidinedione(ISS-7 to ISS-9) against *Eschericha coli*

Following compounds were synthesized using above method:

^{1}H-NMR signals of ISS-7 appeared at 4.772 (2H, s), 8.594 (1H, s, N-H), 7.210-7.665 (4H, m, aromatic proton).

Infrared spectrum of ISS-7 showed amide C=O- stretching at 1641-1618 cm^{-1}, alkane CH- stretching at 2999-2851 cm^{-1}, NH- stretching at 3344 cm^{-1}, C=N- stretching at 1664 cm^{-1}, C=C

^{1}H-NMR signals of ISS-8 appeared at 3.281 (2H, s), 8.954 (1H, s, N-H), 7.210-7.665 (4H, m, aromatic proton).

Infrared spectrum of ISS-8 showed amide C=O- stretching at 1644 cm^{-1}, alkane CH- stretching at 3062-2923 cm^{-1}, NH- stretching at 3346 cm^{-1}, C=N- stretching at 1664 cm^{-1}, C=C stretching at 1611-1493 cm^{-1}, O- disubstituted ring at 749 cm^{-1}.

Infrared spectrum of ISS-9 showed amide C=O- stretching at 1644 cm^{-1}, alkane CH- stretching at 3062-2923 cm^{-1}, NH- stretching at 3346 cm^{-1}, C=N- stretching at 1664 cm^{-1}, C=C stretching at 1611-1493 cm^{-1},NO_2- asymmetric at 1529-1493 cm^{-1}, NO_2-symmetric at 1337 cm^{-1}.

RESULT AND DISCUSSION

Thiazolidine-2, 4-diones ring being present as a pharmacophore in many natural and synthetic compounds has exhibited diversified biological and pharmacological activities such as antidiabetic, antibacterial, antimicrobial, antifungal and antioxidant activity.

2,4-thiazolidinediones is prepared from chloroacetic acid and thiourea in the presence of concentrated HCl and H_2O to give 2,4-thiazolidinedione. Then various derivatives of 2,4thiazolidinediones is prepared by treating 2,4-thiazolidinedione with various amines in the presence of glacial acetic acid, formaldehyde and DMF to yield Schiff's bases.

The formation of the compounds was determined by the TLC technique by detecting the different spots using the mixture of the solvents Chloroform: Ethanol (9:1) as the mobile phase.

Antimicrobial analysis:

In the screening evaluation methods of activities of 2, 4-thiazolidinedione derivatives were tested by agar well method against gram-positive and gram-negative bacteria. Clarithromycin was employed as standard drug and zone of inhibition was calculated.

Comp ISS-7 containing chlorine in the molecule showed the best antimicrobial activity. Thus, demonstrating the power of this atom on bacteria. when compared with that of standard drug i.e.

Clarithromycin.

Comp ISS-8 and ISS-9 having substituted nitrogen on them showed significant activity against

Staphlococcus aureus, *Eschericha coli* when compared with standard drug i.e. Clarithromycin. The order of activity of compounds is: -

Comp ISS-7>Comp ISS-8>Comp ISS-9

CONCLUSION

Schiff bases were formed by the reaction of carbonyl derived compound with the primary amine in the presence of glacial acetic acid and some alcohol group like ethanol. All the Schiff bases were prepared by conventional technique. Then, all the synthesized compounds were evaluated for various pharmacological activities. In the case of antibacterial activity compound ISS-7 was most active against *Eschericha Coli*. Compond ISS-7 showed broad spectrum activity against both the strains *Eschericha coli* and *Staphlococcus aureus* at a concentration of 200µg/mL.

It was concluded that the Schiff bases of thiazolidinediones prepared by conventional methods and also aniline derived derivatives were proved to be more potent in case of all the activities. Formation of Shiff bases can be explored to synthesize novel chemical entities with diverse biological activities.

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