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DESIGN, SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF NEW SUBSTITUTED THIAZOLIDIN-4-ONE DERIVATIVES

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Abstract:

4-thiazolidinones are among the most extensively investigated class of organic compounds. Thiazolidin-4-one has been considered as magic moiety, which is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities.They are widely used as anti-inflammatory, anticonvulsant, analgesic, antimicrobial,anti-HIV,CNS depressant, carcinostatic, antihypertensive and cytotoxic. In view of the wide spectrum activities of condensed 4-thiazolidinones, it was thought worthwhile to undertake the synthesis of heterocyclic systems in which 4-thiazolidinone nucleus is linked to another biologically active moiety.Semicarbazide/Thiosemicarbazide was reacted with benzoyl chloride to obtain N-hydrazinocarbonyl benzene-1-carboxamide/N-hydrazinocarbothioylbenzene-1 carboxamide respectively.These were then condensed with various aldehydes to yield the intermediate Schiff bases. Thiazolidin-4-ones were prepared by the reaction of Schiff bases with mercaptoacetic acid in dry benzene by refluxing for 16-18 hours.

The purity of the compounds synthesized was established by TLC.The synthesized derivatives were characterized by FT-IR,[1]HNMR and Mass spectral analysis. All the derivatives synthesized were screened for their anti-bacterial and antifungal activities using cup-plate method against Bacillus subtilis, Salmonella typhi, Escherichia coli, Staphylococcus aureus, Aspergillus niger and Candida albicans at 100µg/ml using ciprofloxacin and clotrimazole as reference standard drugs respectively.The compounds belonging to series (3A1-3A6) have shown promising antibacterial and antifungal activity and those belonging to series (3B1-3B6) were moderate compared to standard.

The antimicrobial activity data reveals that, the compounds bearing the phenyl carbonyl urea in their structure, were found to be more potent than the phenyl carbonyl thiourea containing derivatives, indicating the influence of oxygen in enhancing the antimicrobial potency.

Keywords: *Schiffbases,Thiazolidin-4-one,Antimicrobial.*

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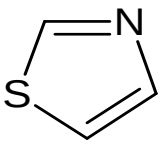
INTRODUCTION:

The history of 4- thiazolidinone can be traced back to the early work on thiazoles**. (1)**

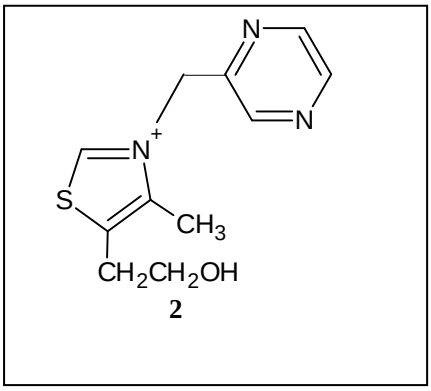


1

Compound containing a simple thiazole nucleuses were first reported by Hantzch[1] in a series of paper beginning from 1887. After this pioneering work, knowledge of the thiazole system developed shortly. Many thiazole derivatives were found to have biological and commercial interest. Green[2] in 1888 described a yellow primuline base and dihydro-thio-*p*-toludine. These were obtained by fusion of *p*-toludine with sulfur. These compounds were recognized as benzothiazole derivatives. Subsequently many related compound were prepared.

In 1935, Williams et al [3]demonstrated the existence of a simple thiazole moiety in the structure of Vitamin B1 **(2).**It was combined with 4-thiazolidinone with a view to increase the antibacterial activity [4].

The historical importance of thiazole derivatives was further emphasized during the period 1941-45, when work on the structure of penicillins (**3**) showed the thazolidine ring in it. The occurrence of thiazole derivative in nature was reported in 1952 when actithiazic acid **(4),** an antibiotic was found to be a 4-thiazolidinone derivative[5,6].



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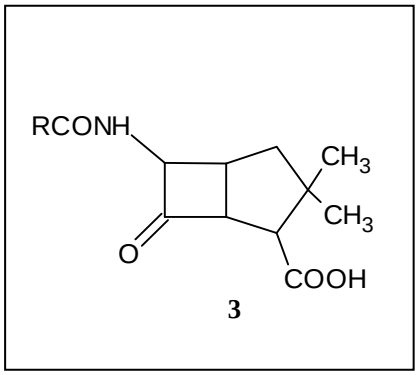

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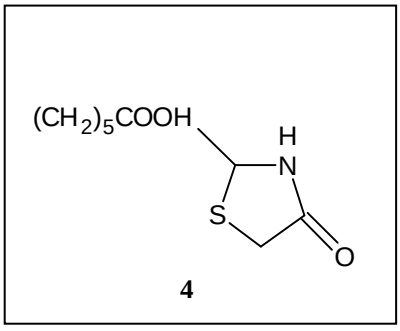

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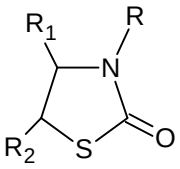
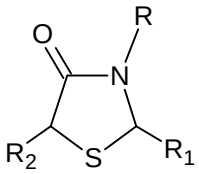
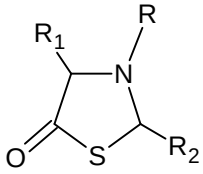
Thiazolidinones[7,8] are derivatives of thiazolidine,which belongs to an important group of heterocyclic compounds.Thiazolidinones with a carbonyl group at position 2,4 or 5 have been subject of extensive study in recent years [9-14].



2 – thiazolidinone



4 - thiazolidinone



5 - thiazolidinone

In recent years, 4-thiazolidinones and 2,4-thiazolidinediones have been among the most extensively investigated classes of organic compounds.

Thiazolidine derivatives are reported to show a variety of biological activities.

The presence of a thiazolidine ring in penicillin and related derivatives was the first recognition of its occurrence in nature[15].Thiazolidine-4-one represents a prevalent scaffold in drug discovery [16] . Thiazolidine-4-ones have many interesting activity profiles, namely COX-1inhibitors[17]' inhibitors of the bacterial enzyme MurB, which was a precursor acting during the biosynthesis of peptidoglycan[18], non-nucleoside inhibitors of HIV-RT [19] and anti-histaminic agents[20]. Thiazolidinones has been considered as magic moiety (wonder nucleus), which is a core structure in various synthetic pharmaceuticals displaying a broad spectrum biological activities [21-23].

Condensed 4-thiazolidinones have received interest and attention from a large number of organic chemists, pharmacologists and biologists world over , on account of significant threupetic and other properties associated with thiazolidinone nucleus.Applications of 4-thiazolidinones are manifold and versatile.

They are Widely Used As anticonvulsant [24], antimicrobial [25],anti-inflammatory [26], antihypertensive [27],hypnotic [28],antidiabetic [29],antifungal [30],antibacterial [31],antitumor[32],anti-HIV [33],antiviral [34],anticancer [35],cardiotonic [36]' antitubercular [37], etc.

Condensed 4-thiazolidinones have also found applications in the synthesis of cyanine and merocyanine dyes and it has been reported that the introduction of arylidene moieties at different positions of the thiazolidinone ring enhanced biological activity [38-40]. Some authors examined the ability of this ligand structure to form complexes with some radionuclides for potential use in nuclear medicine [41].

OBJECTIVES

The search for an ideal chemotherapeutic agent has began long ago. Molecular modification of a promising lead compound is still a major line of approach for the discovery of new drug.

Molecular modification involves substituting, eliminating, or adding new moieties to a parent lead compound, there by making gradual changes in the structure of the compound resulting in gradual changes in the physico-chemical properties of the parent compound and thus biological activity of the compound. It is clear from the literature review that a number of substituted thiazolidinones derivatives are known to posse's antituberculor, analgesic,anti-microbial,anti HIV,anticonvusant,antifungal activities. It has been reported that thiazolidinones also possess analgesic, anti- inflammatory and antimicrobial activities.

Thiazolidinones are of great interest due to their exceptional biological activity. The treatment of pain continues to be the subject of considerable Pharmaceutical and clinical research in recent years. A systematic investigation of this class of heterocycle revealed that thiazolidinones containing pharmacoactive agent play important role in medicinal chemistry.Chemotherapeutic analgesic and anti inflammatory drugs are prescribed simultaneously in normal practice.

By considering the above factors, in the present investigation it was planned to undertake the research work as below:

1. To synthesize some of the thiazolidin-4-one derivatives and to characterize the new compounds by analytical spectral methods viz,Infrared (IR), Mass spectra and Nuclear Magnetic Resonance (NMR).
2. To assess the acute toxicity of the derivatives synthesized following (OECD Guidelines - 420).
3. To screen few of the derivatives for their analgesic activities using Eddy's hot plate method.
4. To screen few of the derivatives for their anti-inflammatory activities using Carrageenan induced rat paw edema method.

METHODOLOGY:

The importance of thiazolidin-4-one moiety has been discussed in the previous chapter. Among the many methods available for the synthesis of thiazolidinone derivatives , in the present chapter a convenient and versatile methodology

has been adopted for the synthesis of thiazolidin-4-one derivatives.In the present case semicarbazide/Thiosemicarbazide was reacted with benzoyl chloride to obtain N-hydrazinocarbonylbenzene-1-carboxamide/*N*-hydrazinocarbothioylbenzene-1 carboxamide respectively.These were then condensed with various aldehydes to yield the intermediate Schiff bases. Thiazolidin-4-ones were prepared by the reaction of Schiff bases with mercaptoacetic acid in dry benzene by refluxing for 16-18.hrs.

All the reactions were carried out under prescribed laboratory conditions and we are monitored by TLC technique using Precoated TLC plates .The products were purified by recrystallization. Melting points were determined by capillary method and were uncorrected.

^{1}HNMR spectra of the final compounds were recorded on Bruker Avance II 300 NMR spectrometer (300 MHZ). All spectra were obtained in a mixture of DMSO. Furtherevidence about the structure was obtained by recording the mass spectrum of few typical compounds, along with their IR spectra and ^{1}HNMR.

Material and Methods

a) The entire chemicals used were procured from Qualingens, Himedia and Loba- chemicals. Purity of starting materials used for reaction was confirmed by checking their melting point or boiling point and by thin layer chromatography.

b) Melting points were determined in open capillary tube using precision melting point apparatus and uncorrected.

c) The FT-IR a spectra of the synthesized compounds has been obtained from **NGSM Institute of Medical Sciences Deralakatte, Mangalore.** The IR spectra were carried out by SHIMADZU PERKIN EKMER 8201 PC IR SPECTROMETER using a thin film on potassium bromide pellets.

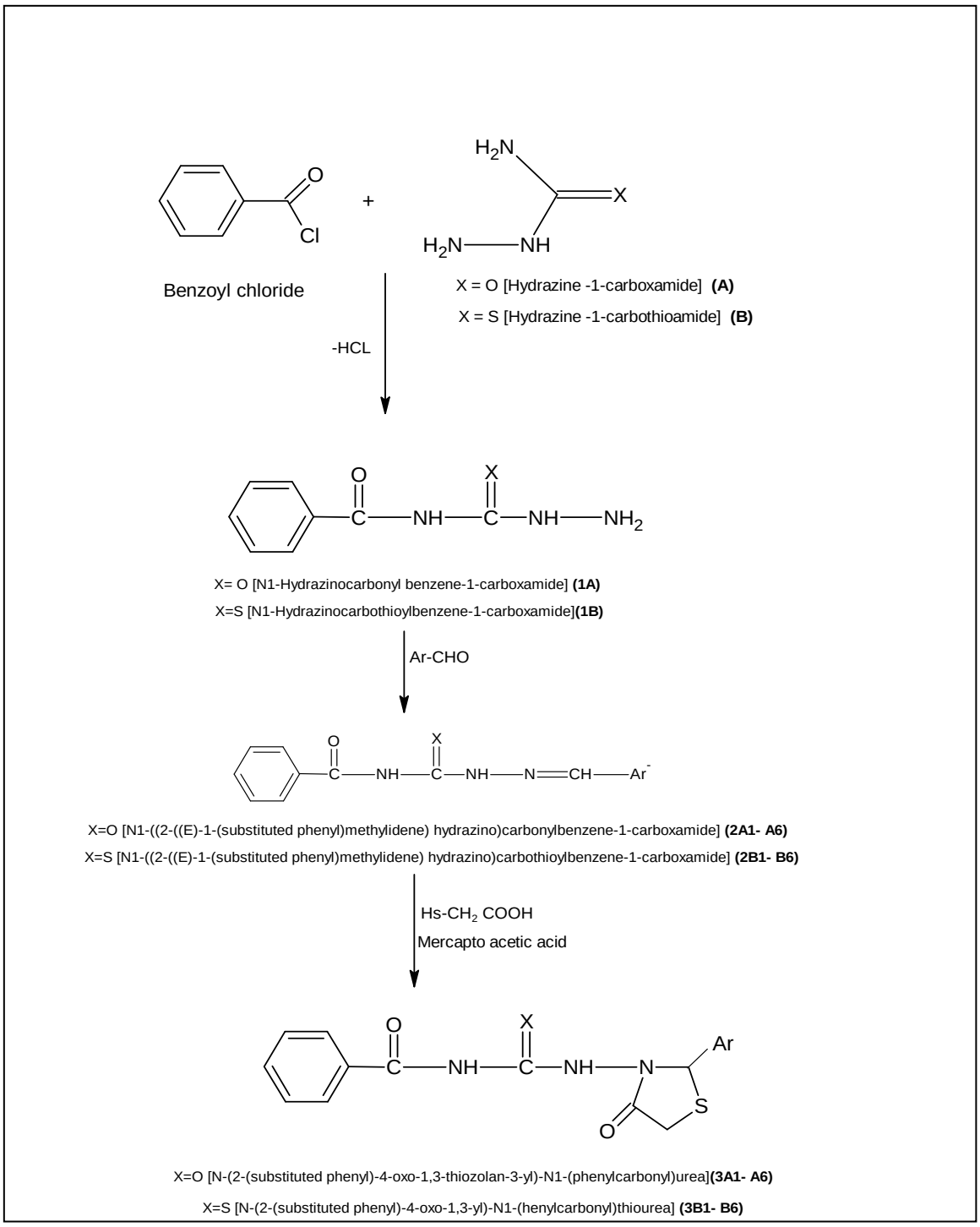
d) The ^{1}HNMR spectra of the selected compounds has been obtained from **Indian Institute of Chemical Technology Hyderabad.**The PMR spectra were recorded on **BRUKER AVANCE II 300 NMR SPECTROMETER** in a mixture of DMSO**.** Chemical shift values are reported as values in ppm relative to TMS (d=0) as internal standard.

e) The Mass spectrum of the selected synthesized compounds has been performed in **Indian Institute of Chemical Technology Hyderabad.** The FAB mass spectra were recorded on **JEOL SX-102/DA-6000 Mass Spectrometer** using Argon/Xenon (6Kv, 10Ma) as the FAB gas.

f) Purity of compounds was checked on "Silica Gel G" coated on laboratory micro slides prepared by dipping method or precoated plates, eluent was the mixture of different polar and non-polar solvents in varying proportions and detection was done either by observing in UV (ultra-violet) light or exposure to iodine vapours as required. The absence of TLC spots for starting materials and appearance of new TLC spot at different R_f value ensured the completion of reaction.

EXPERIMENTAL:

SCHEME



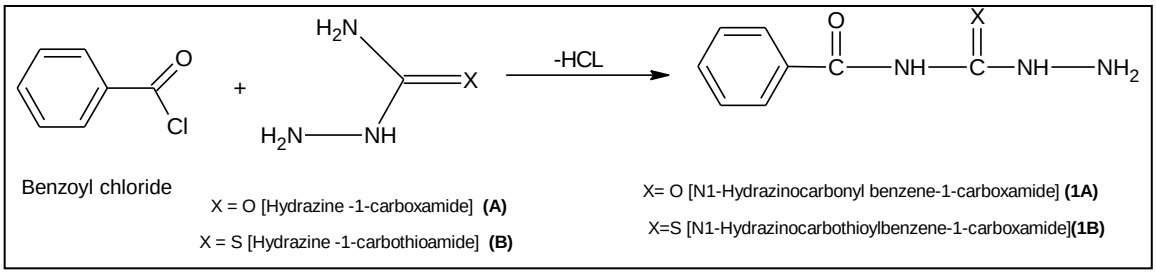
X = 0	X = S	Ar
3A1	3B1	-H
3A2	3B2	4-NO_2
3A3	3B3	4-OCH_3
3A4	3B4	4-F
3A5	3B5	4-Cl
3A6	3B6	4-Br

SYNTHETIC STUDIES:

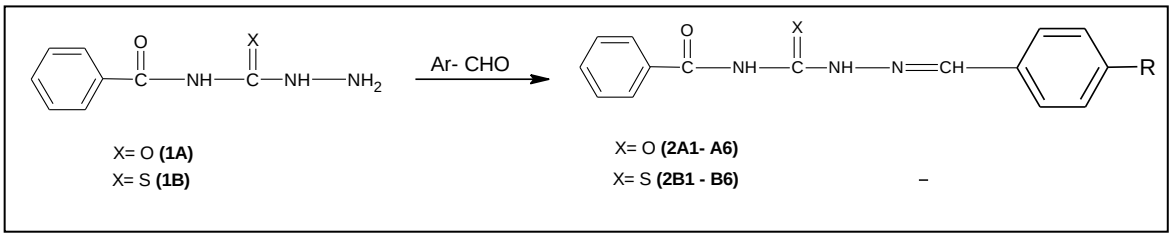
In the present dissertation by the condensation of semicarbazide or thiosemicarbazide with benzoyl chloride, substituted thiazolidine-4-ones derivatives synthesized. The synthesis consists of three steps, which are as follows:

Preperation of *N*-hydrazinocarbonylbenzene-1-carboxamide/N–hydrazinocarbothioyl benzene-1-carboxamide (1A and 1B):

The mixture of Semicarbazide (0.1 mol) and Thiosemicarbazide (0.1mol) in benzoyl chloride (0.1 mol) in 75 ml of dry alcohol was refluxed for 3-4 hours. The excess of alcohol was removed by distillation and the contents of the flask were poured onto crushed ice.The product seperated was filtered,washed with water dried overnight and recrystallized from aqous ethanol. The purity of all the compounds was established by single spot on TLC plate using silica gel G. Solvent system used: Acetone:Benzene (1:1).



Preperation of N^1-((2-((*E*)-1-(Substituted Phenyl)methylidene)hydrazino) carbonyl benzene-1-carboxamide (2A1-2A6) / N^1-((2-((*E*)-1-(SubstitutedPhenyl) methylidene) hydrazino)carbothioyl benzene-1-carboxamide (2B1-2B6):



To a mixture of N-hydrazinocarbonylbenzene-1-carboxamide/-hydrazino carbothioylbenzene-1-carboxamide (0.1mol) and aromatic aldehyde (0.1 mol) in dry ethanol (25 ml), 2-3 drops of Conc H_2SO_4 was added and was refluxed for 3-4 hours. The contents are poured onto crushed.

The solid**,** N^1-((2-((*E*)-1-**(**Substituted Phenyl) methylidene) hydrazino) carbonylbenzene-1-carboxamide/N^1-((2-((*E*)-1-(Substituted Phenyl) methylidene) hydrazino) carbothioylbenzene-1-carboxamide formed was filtered, dried and recrystallized from ethanol to obtain the compound in pure form. The purity of all the compounds was established by single spot on TLC plate using silica gel G. Solvent system used: Acetone:Benzene (1:1).

Preparation of *N*-(2-(substituted phenyl)-4-oxo-1,3-thiazolan-3-yl)-N^1- (phenylcarbonyl) urea (3A1-3A6)/*N*-(2-(substitutedphenyl)-4-oxo-1,3-thiazolan-3-yl)-N^1-(phenylcarbonyl) thiourea (3B1-3B6):

To a mixture Schiff bases (0.1mol)**(2A1-2A6&2B1-2B6)** obtained as above mercapto acetic acid (0.1) in dry benzene(75ml) was added slowly to the above flask Dean stark apparatus was set to remove the water continuously which was formed during the course of reaction,then the reaction mixture was refluxed for 15-16 hrs and the excess of benzene was distilled off to get solid thiazolidin-4-ones derivatives.The solid product was filtered, dried and recrystallised from absolute alcohol. The purity of all the compounds was established by single spot on TLC plate using silica gel G.

Solvent system used: Acetone: Benzene (1:1).

BIOLOGICAL ACTIVITY:

Antimicrobial activity[42,43]:

In general, any compound or drug inhibits the growth or causes the death of microorganisms, known as antimicrobial agents. Any drug which inhibits the growth of bacteria or fungi, it is said to possess bacteriostatic and fungi static activity respectively. If it kills the bacteria or fungi, it said to possess bactericidal and fungicidal activity.

In- vitro tests are used as screening procedure for new antimicrobial agents and for testing the

susceptibility of individual isolates from infections, to determine which of the available drugs might be useful therapeutically. Sensitivity testing is done to determine the range of microorganisms that are susceptible to the compound under specified conditions. It can be done by disk diffusion method and **Cup-plate** method .These method are suitable for the organisms that grow well overnight such as most of the common aerobes and facultative anaerobes and rapidly growing fungi. Several forms of disk diffusion methods have been advocated.

Biological evaluation involves testing of microbial susceptibility to chemotherapeutic agents. Determination of antimicrobial effectiveness against pathogens is essential for therapy. Testing can show the efficiency of antimicrobial against a pathogen and give an estimate of proper therapeutic dose. The idea of the effectiveness of a chemotherapeutic agent against a specific pathogen can be obtained from the minimum inhibitory concentration (MIC).

The MIC is the lowest concentration of the drug that can prevent the growth of the pathogen.

The important factors to be controlled in the testing of the antimicrobial activity are as follows,

1. Type of test organism.
2. Temperature and time of incubation.
3. Composition and pH of culture.
4. Inoculums concentration.

EVALUATION OF ANTIBACTERIAL ACTIVITY:

Antibacterial activity is determined based on the *in vitro* activity in pure cultures. *In vitro* susceptibility test are done by the cup-plate method. The antibacterial activity of thiazolidinone derivatives was evaluated by cup-plate method against the strains of common pathogens,gram-negative organisms ***Escherichia coli, Salmonella typhi*** Gram-positive organisms ***Staphylococcus aureus, Bacillus subtilis.*** Ciprofloxacin were used as standard drug at the concentration of **100 µg/ml.**

The microorganisms used in the present screening were procured from the Department of Microbiology, Gulbarga University, Gulbarga.

Test organisms (bacteria):

Staphylococcus aureus (Gram-positive bacteria)
Bacillus subtilis (Gram-positive bacteria)
Escherichia coli (Gram-negative bacteria)
Salmonella typhi (Gram-negative bacteria)

All the synthesized compounds were screened for antibacterial activity against the above-mentioned strains by cup-plate method.

The following materials ware used for the testing:

1. Nutrient agar
2. Sterilized petridishes, pipettes and beakers
3. Sterilized 6 mm cork borer
4. 18-24 hr. old growth culture in nutrient broth.
5. Sterilized test tubes containing solution of test compounds in desired concentration

Preparation of Nutrient Agar medium:

Nutrient agar media (40g), bacteriological peptone (1g), beef extract (5g) and sodium chloride (5g) were dissolved in distilled water (1000 ml). The pH of the solution was adjusted to 7 to 7.4 by using sodium hydroxide solution (40%, approximately 0.25 ml for 100 ml of nutrient broth) and then sterilized for 30 min. at 15 lbs pressure in an autoclave.

Preparation of sub culture:

One day prior to test the microorganisms were inoculated into the sterilized nutrient broth and incubated at 37^0C for 24 hr. On the day of testing, the organisms ware subcultured into sterile nutrient broth. After incubating for 3 hr, the growth thus obtained was used as inoculums for the test.

Sterilization of media and glasswares:

The media used in the present study, nutrient agar and nutrient broth were sterilized in a conical flask of suitable capacity by autoclaving the same at 15 lbs pressure for 20 min. The cork borer, petridishes, test tubes and pipettes, were sterilized by employing hot air oven at 160^0C for 1 hr.

Preparation of solution of test compound:

The test compound (5 mg each) was dissolved in freshly distilled DMF (5 ml) in serially labeled sterile test tubes, thus giving a final concentration of 100 µgm/0.1 ml

Preparation of solution of standard compound:

The standard compound Ciprofloxacin (5 mg each) was dissolved in freshly distilled DMF (5 ml) in serially labeled sterile test tubes, thus giving a final concentration of 100 µgm/0.1 ml

Method of testing

The method depends on the diffusion of an antibiotic from a cavity through the solidified agar layer in a petridish to an extent such that growth of the added microorganisms is prevented entirely in a circular area or zone around the cavity containing a solution of test compound. About 15-20 ml of molten nutrient agar was poured into each of the sterile petridishes. The cups were made by scooping out nutrient agar with a sterile cork borer. The agar plates so prepared were divided into different set and each set of the plates were inoculated with the suspension of particular organism by spread plate technique.

The cups of inoculated plates were then filled

with 0.1 ml of the test solution; the plates were then incubated at 37^0C for 24 hours. The zone of inhibition(diameter in mm) developed, if any, was then measured for the particular compound with each organism. The solvent DMF was used as negative –control to know the activity of the solvent. The results of antibacterial testing are summarized in the following table no.5

Antifungal activity:
The antifungal activity of Thiazolidinones, derivatives were carried out by cup & plate method, in comparison with that of standard antifungal drugs, clotrimazole. The fungi culture used were ***Candida albicans*** and ***Aspergillus niger.***

MATERIAL AND METHODS:

Cup -plate diffusion method: Antifungal activity of the test compounds was assessed against the above strains of fungi by cup plate diffusion method. The following materials were used:

1. Sabourauds agar
2. Sterilized Petri-dishes and pipettes of 0.1 ml and 0.2 ml
3. Cultures grown in Sabourauds broth
4. Sterilized test tubes for preparation of solution of the test compounds in desired concentration.

Preparation of media:
Sabourauds agar:
Bacteriological peptone (1 g) and glucose (4 g) were dissolved in distilled water (100 ml) and filtered. Agar powder (2 g) was added and sterilized for 30 min. at 15lbs pressure.

Preparation of sub cultures:
One day prior to the test, inoculation of the microorganism **(Candida Albicans & Aspergillus Niger)** was made in sabourauds broth and incubated at 37^0C for 18 hr.

Sterilization of media and glasswares:
The media used in the present study was sterilized in conical flask of suitable capacity by autoclaving at 15 lbs pressure for about 20 min. The cork borer, petridishes, test tubes and pipettes were sterilized in hot air oven at 160^0C for one hour.

Preparation of solution:

1. Clotrimazole: 5 mg of the clotimazole was dissolved in 5 ml, of DMF (dimethylformamide) to get a concentration of 1000 µg/1 ml.
2. Compounds: 5 mg of each test compounds was dissolved in 5 ml of DMF in Serially and suitably labeled in sterile test tubes thus giving a final concentration of 1000 µg/1 ml.

Method of testing: Cup-plate method: This method depends on the diffusion of an antifungal agent from a cavity through the solidified agar layer in a petridish to an extent such that growth of the added microorganism is prevented in a circular area or zone around the cavity containing a solution of antifungal agent.
A previously liquefied medium was inoculated appropriate to the assay with the requisite of the suspension of the microorganisms between 40-500C and inoculated medium was poured into petridishes to give a depth of 3 to 4 mm. Ensured that the layer of medium were uniform in thickness by placing the dishes on a leveled surface. With the help of a cork borer, scooped out the set agar from each petridish. Using sterile pipettes, the standard and the sample solution (0.1 ml) of known concentrations ware fed into the bored cups. The dishes ware left standing for 1 to 4 hrs at room temperature as a period of pre-incubation diffusion. These were then incubated for 48 hr. at 37^0C. The zone of inhibition developed, if any was then accurately measured in mm growth of the added micro-organism is prevented in circular area or zone around the cavity containing a solution of antifungal agent.

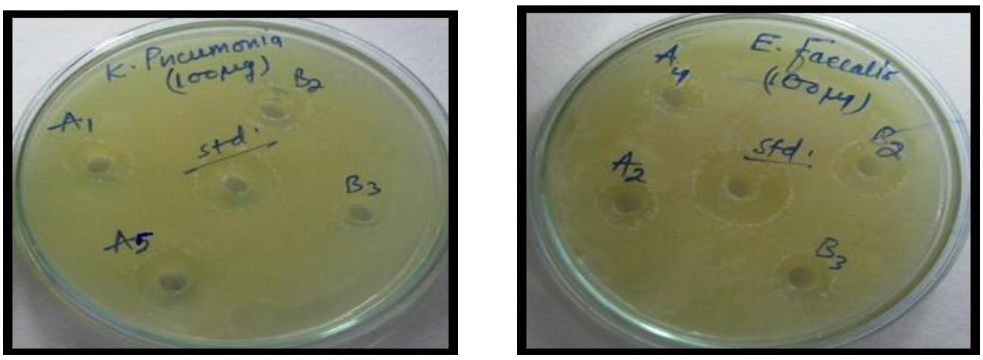


Fig. 1: Antibacterial activity

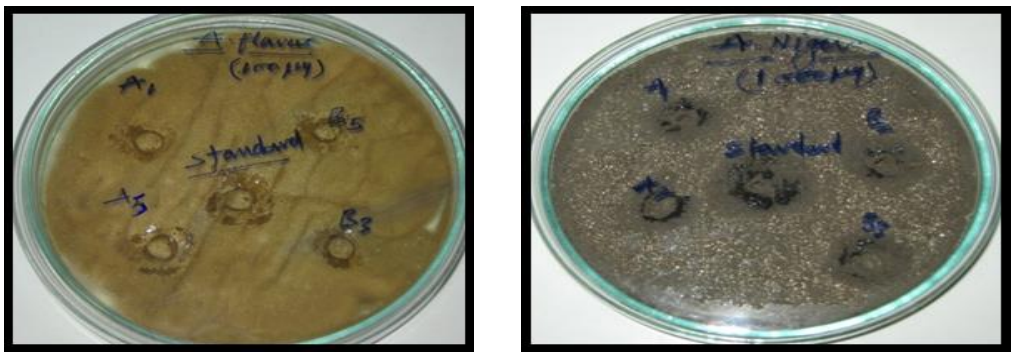


Fig. 2: Antifungal activity

Note: -denotes no activity and, 12-19 mm moderate activity, 20-25 mm good activity.

RESULTS:

Biological activities

In view of the wide spectrum activities of the condensed 4-thiazolidinone nucleus, the synthesis of heterocyclic systems was undertaken in which 4-thiazolidinone nucleus is linked to another biologically active moiety.

The structure of the synthesized compounds were established by their IR, ^{1}HNMR and Mass spectral studies .All the synthesized compounds were evaluated for their antibacterial and antifungal activity at 100µ g/0.1ml concentration by **Cup- plate** method using ciprofloxacin and clotrimazole as standard drugs respectively.The results are summarised in **Table-1.**

Antimicrobial activity:

In the study of antibacterial and antifungal activity of the synthesized derivatives, the results showed that the compound **3A5** has shown maximum activity against all the organism followed by the compound **3A2** .The rest of the compounds belonging to **3A** series also shown good antimicrobial activity were as compounds belonging to **3B** series have shown moderate growth inhibitory activities among which **3B5** and **3B4** were found to be better compared to standard drugs.

Table-1: **Antimicrobial activity of thiazolidin-4-one derivatives**

SI.No	Compound	Conc. (µg/ml)	Diameter of zone inhibition (mm)					
			Bacillus subtilis	Salmonella typhi ATCC-29212	Escherichia coli ATCC-25923	Staphylococcus aureus ATCC -27853	Aspergillus niger	Candida albican
1	A1	100	20	22	23	22	22	20
2	A2	100	19	21	24	22	23	23
3	A3	100	22	20	23	23	21	25
4	A4	100	20	21	22	21	22	23
5	A5	100	21	23	25	22	23	26
6	A6	100	19	22	24	21	22	24
7	B1	100	16	12	17	16	15	20
8	B2	100	17	14	17	17	18	18
9	B3	100	18	15	19	16	19	21
10	B4	100	20	19	18	17	15	20
11	B5	100	18	20	21	17	19	21
12	B6	100	15	18	20	16	19	20
13	Ciprofloxacin	100	23	25	27	25	-	-
14	Clotrimazole	100	-	-	-	-	26	28
15.	Control	-	-	-	-	-	-	-

DISCUSSION

All the synthesized compounds **(3A1-3A6)** (**3B1-3B6)** have been evaluated for anti-microbial activity at 100µ g/ml concentration level which shown clear zone of inhibition. The compounds belonging to series **(3A1-3A6)** have shown promising antibacterial and antifungal activity where as the compounds belonging to series **(3B1-3B6)** were moderate when compared to that of standard antimicrobial agents. The antimicrobial activity data reveals that, the compounds bearing the phenyl carbonyl urea in their structure were found to be more potent than the phenyl carbonyl thiourea containing derivatives, indicating the influence of oxygen in enhancing the antimicrobial potency.

SUMMARY:

The object of the present work is to synthesize certain new derivatives of thiazolidine-4-one which has been considered as magic moiety and is a core structure in various synthetic pharmaceuticals displaying wide spectrum of biological activities.

The target molecules were successfully synthesized in which thiazolidin-4-one nucleus is linked to other biologically active moieties. The purity of the compounds synthesized was established by using TLC technique and the structures were established by their FT-IR, ^{1}HNMR and MASS spectrum.

All the derivatives synthesized were screened for their antibacterial and antifungal activities. Among the compounds screened for antimicrobial activities, the series of compounds which bear phenyl carbonyl urea in the structure have been found to possess potent activity; than the other series of compounds which contain phenyl carbonyl thiourea that indicates the influence of oxygen over the sulphur in enhancing the antimicrobial

potency.
All these above results only showed that the thiazolidin-4-one moiety can be rich source for further exploitation. The thiazolidin-4-one moiety needs more attention and if it is suitably exploited by molecular modification can still give better lead compounds.

CONCLUSION:

All the derivatives synthesized were screened for their antibacterial and antifungal activities. The antimicrobial activity shown by the compounds was inferior to that of standard drug, it is of significance. Even though the structural activity relationship is not emerging out, it may be predicted that the higher antimicrobial activity possessed by the compounds belonging to series **(3A1 to 3A6**) bearing phenyl carbonyl urea in their structure over the other series **(3B1 to 3B6**) which bear phenyl carbonyl thiourea (sulphur in presence of oxygen) is quite likely that the presence of oxygen (urea part) could be decesive factor in enhancing the activity.
From the above results one can establish that the synthesized substituted thiazolidinones can be rich source of exploitation.Therefore, in the search of new generation of active compounds, it may worthwhile to explore the possibility in this area by making or introducing different functional group as substitution of primary amine moieties which may result in better pharmacological agents with higher potency.

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