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Synthesis, Analysis And Antibacterial Evaluation Of Thiazole Derivatives

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ABSTRACT :

Thiazoles are found in a variety of specialized products, often fused with benzene derivatives, the so-called benzothiazoles .In this study, set of thiazole derivative has been synthesized, designed and evaluated as potent antibacterial inhibitors. The synthesized compounds where characterized by using TLC, melting point and IR spectroscopy and shows satisfactory results . Among the synthesized compounds many where evaluated for their antimicrobial activity against gram positive bacteria Staphylococcus aureus and Gram negative bacteria Escherichia coli by cylinder plate method.The anisaldehyde derivative(compound 3b)showing slightly more antibacterial acivity than chloro derivative(compound 3a)

Key words: Thiazole,Antibacterial

INTRODUCTION :

Heterocyclic compounds are cyclic compounds in which one or more of the atoms of the ring are heteroatom. Heterocyclic make up an exceedingly important class compounds and more than half of all known organic compounds are heterocyclic. Almost all the compounds we know are drugs , mostly vitamins, carbohydrates and many other natural products are heterocyclics[1].

Heterocyclic intermediates are being used in the synthesis as protecting group which can be readily generated and readily removed. Heterocyclic forms the site of reaction in man enzymes and coenzymes.[2]

Thiazole, or 1,3-thiazole, is a heterocyclic compound that contains both sulfur and nitrogen; the term 'thiazole' also refers to a large family of derivatives. Thiazole itself is a pale yellow liquid with a pyridine-like odor and the molecular formula C_3H_3NS. The thiazole ring is notable as a component of the vitamin thiamine (B1).[3]

Thiazoles are found in a variety of specialized products, often fused with benzene derivatives, the so-called benzothiazoles. In addition to vitamin B1, the thiazole ring is found in epothilone. Other important thiazole dervatives are benzothiazoles, for example, the firefly chemical luciferin. Whereas thiazoles are well represented in biomolecules, oxazoles are not.[3]

Commercial significant thiazoles include mainly dyes and fungicides. Thifluzamide, Tricyclazole, and Thiabendazole are marketed for control of various agricultural pests. Another widely used thiazole derivative is the non-steroidal anti-inflammatory drug Meloxicam. The following anthroquinone dyes contain benzothiazole subunits: Algol Yellow 8, Algol Yellow G, IndanthrenRubine B, Indanthren Blue and Indanthren Blue. These thiazole dye are used for dying cotton.[4]

Various laboratory methods for the organic synthesis of thiazoles are The Hantzsch thiazole synthesis, Robinson-Gabriel synthesis, Cook-Heilbron synthesis, Herz reaction etc.

The Worldwide use of antimicrobial compounds to treat infection leads to the evolution of microbes resistant to these compounds. Antimicrobial resistance is a natural biological phenomenon of response of microbes to the selective pressure of an antimicrobial drug.[5] The Discovery of antimicrobial agents by Paul Ehrlich was one of the most remarkable discoveries that changed the face of medical practice. However, the increased global flow of antimicrobials brought with it the threat of antimicrobial resistance. As antimicrobials are frequently misused and overused in many developing countries, thus resistance to antimicrobials has led to an increase in morbidity, mortality and cost of health care.

Materials and methods

All the synthetic work was done by providing available laboratory grade reagents analytical grade solvents.TLC were performed to monitor the reactions and to determine the purity of the products. Further the compounds were purified by recrystallization using suitable solvents. The melting

points of the synthesized compounds were determined in open capillaries using Rolex VMP-1Apparatus expressed in ℃ and are uncorrected.The IR spectra of compounds were recorded on Shimadzu FT-IR-8400S spectrometer using KBr Pellet technique and are expressed in cm

SYNTHESIS:

1) Synthesis of Intermediate –I:

The first product was synthesized by cyclocondensation of 1 mole (7.61g) of thiourea with 1 mole (12.74mL) of ethyl acetoacetate in the presence of 1 millimole (1.77g) N-bromosuccimide using 1 millimole (1.815g) benzoyl peroxide as a catalyst in a round bottomed flask. The mixture was refluxed on a water bath at 80℃ for 5 hours. The flask was cooled and the crude product was filtered and washed with distilled water. Recrystallization was done using ethanol.

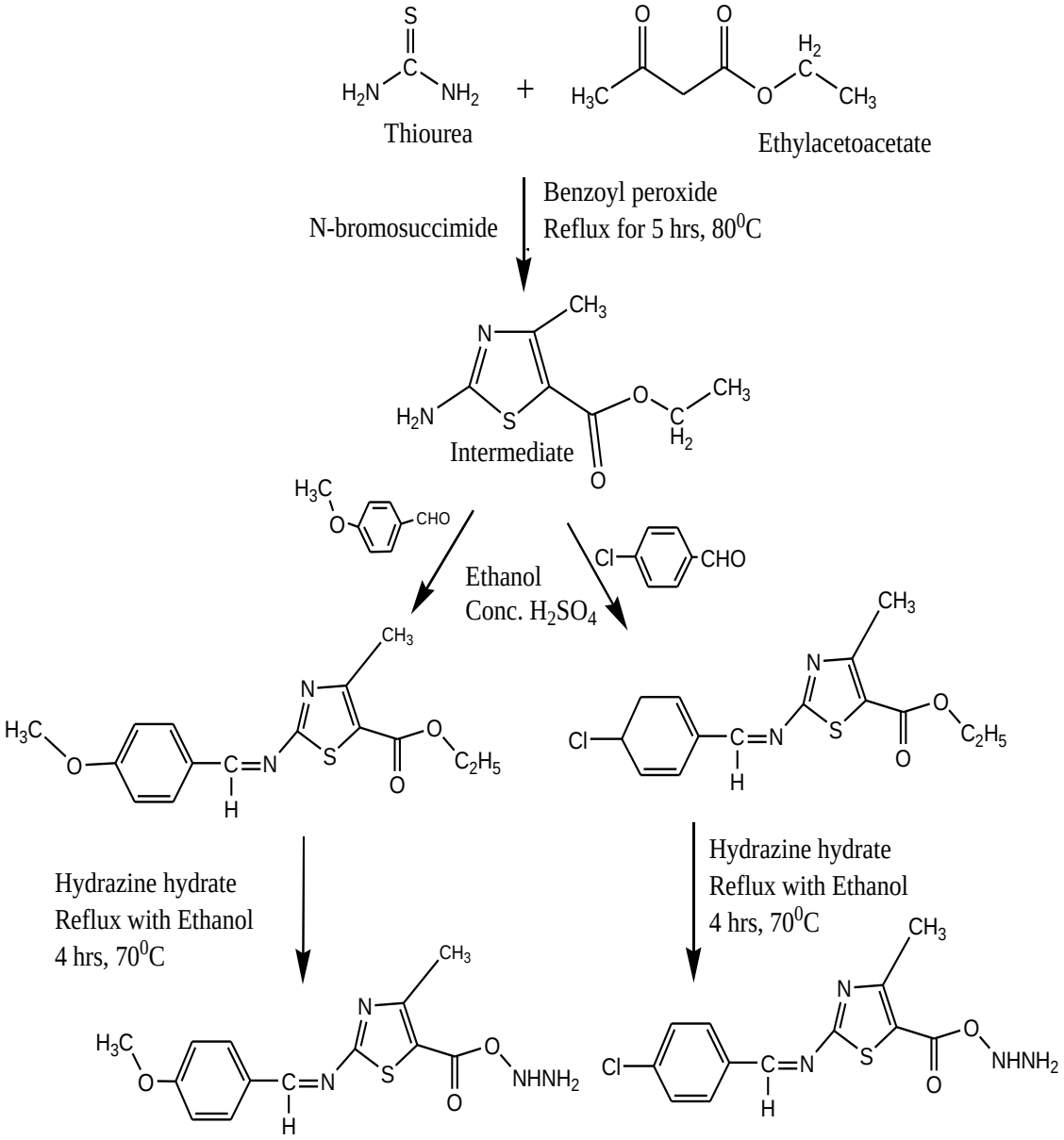
2) Synthesis of different substituted aryl aldehydes:

The intermediate compound was divided equally into two beakers and both were treated with different substituted aryl aldehydes ; I mole (7g) of p-chlorobenzaldehyde was added to one beaker and I mole (12ml) of anisaldehyde was added to the other, in the presence of ethanol and concentrated sulphuric acid to yield derivatives of ethyl-4-methyl-2-(aryl derivatives of methyleneamino) thiazole-5- carboxylate, 2a-b.

3)Synthesis of hydrazine hydrate derivatives of substituted aryl aldehydes:

To each of the above obtained products was added an equimolar amount hydrazine hydrate. The mixture was then refluxed for 10 minutes. Alcohol was then added to the mixture till both the layers were miscible and the mixture was further refluxed for 4 hours. The excess of alcohol and hydrazine hydrate were distilled out and the solid obtained was recrystallized to obtain the final products, 4-methyl-5-hydrazine hydrate-2-(aryl aldehyde derivatives of methyleneamino) thiazole-5-carboxylate , 3a-b

SCHEME:



EVALUATION OF INVITRO ANTI MICROBIAL ACTIVITY

The microbiological screening is based upon a comparison of the inhibition of by growth of bacteria by measured concentrations of the compound to be examined with that of activity produced by known concentration of a standard drug. Various methods with their own advantages and limitations have been used from time to time to evaluate the anti-microbial activity of the drugs. The anti-microbial activity can be evaluated by the following techniques:

1. Agar streak dilution method.
2. Serial dilution method.
3. Agar diffusion method.

a. Cup plate method.

b. Cylinder method.

c. Paper disc method.

4. Turbidimetric method.

In the present study, the cylinder plate or cup plate method was used to evaluate the in vitro anti-microbial activity of the synthesized compounds.

Cylinder-Plate or Cup Plate Method:

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

Standard drug selection:

Chloramphenicol is used as standard drug, chemically it is 2,2-dichloro-N-[1'3-dihydroxy-1-(4-nitrophenyl)propan-2-yl]acetamide. It is a bacteriostatic antimicrobial.

1. It is used as a prototype of drug
2. It is a broad spectrum antibiotic

Mechanism: Chloramphenicol is a bacteriostatic drug that stops bacterial growth by inhibiting protein synthesis. Chloramphenicol prevents protein chain elongation by inhibiting the peptidyl transferase activity of the bacterial ribosome. It specifically binds to A2451 and A2452 residues in the 23S rRNA of the 50S ribosomal subunit, preventing peptide bond formation.[23] While chloramphenicol and the macrolide class of antibiotics both interact with ribosomes, chloramphenicol is not a macrolide. It directly interferes with substrate binding, whereas macrolides sterically block the progression of the growing peptide.

Requirements:

- Standardized culture of test organism
- Gram positive bacteria – Staphylococcus aureus (NCIM 2079)
- Gram negative bacteria – Escherichia coli (NCIM 2065)
- Nutrient agar
- Petri dishes
- Sterile pipettes
- Test compounds
- Standard drug: Chloramphenicol
- Solvent (control): DMSO

Procedure

1. Sterile nutrient agar plates were prepared, by pouring the sterile agar into the Petri-dishes in aseptic conditions.
2. 0.1 ml of each standardized test organism culture was spread onto agar plates.
3. Cavity was done by using a sterile borer of diameter 6mm.
4. 100µg/well of the test compounds as well as the standard drug solutions and DMSO solvents were placed in the cavity separately.
5. Then the plates were maintained at +4 ℃ for 1hour to allow the diffusion of solution into the medium.
6. All the bacterial plates were incubated at 37℃ for 24hours.
7. After the Incubation period,the zone of inhibition was measured in mm.

RESULTS AND DISCUSSION :

Structure, Molecular formula and IUPAC Name of Synthesized Compounds.Table-I

S.NO	SYNTHESIZED COMPOUND	MOLECULAR FORMULA	IUPAC NAME

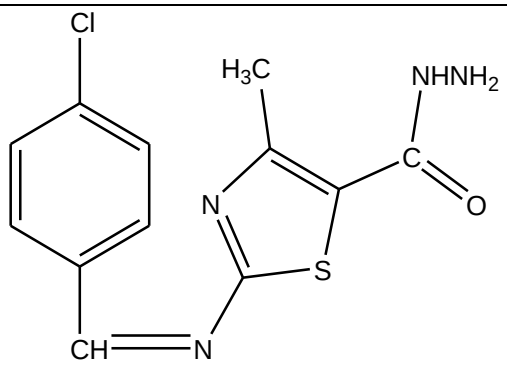
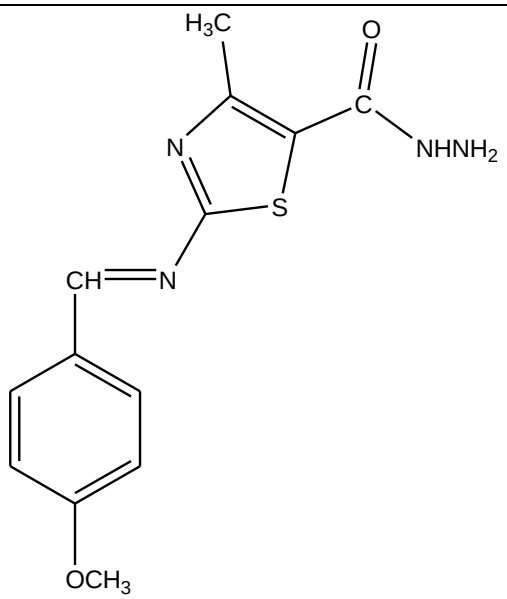
1		C12H11ClN4OS	2-(4'-chloro benzylidene amino)-4methyl thiazole-5-carbohydrazide
2		C13H14N4O2S	-(4'-methoxybenzylidene amino)-methyl thiazole-5-carbohyrazide

Table-II

R_fValue = Distance travelled by the solute

Distance travelled by the solvent front

Mobile phase = Chloroform : Benzene

(3 : 2)

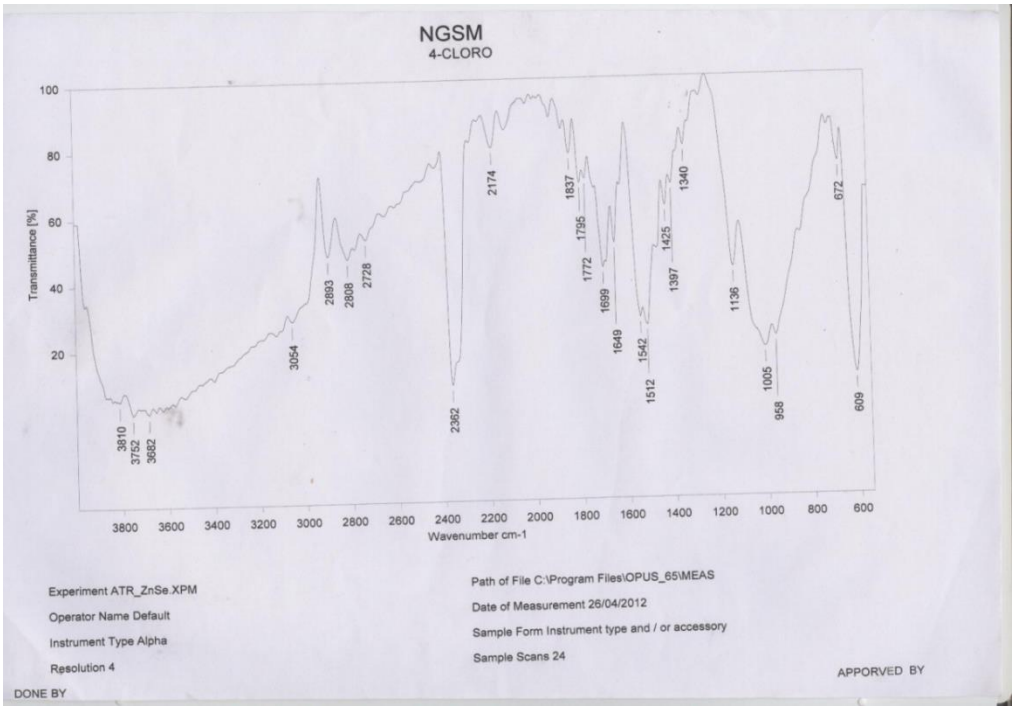
S.No	Compound	**Molecular Weight**	Percentage Yield	RfValue	Melting Point (℃)
1	3a	294.03	45.32	0.75	250-252 (uncorrected)
2	3b	290.34	50.25	0.84	165-167 (uncorrected)

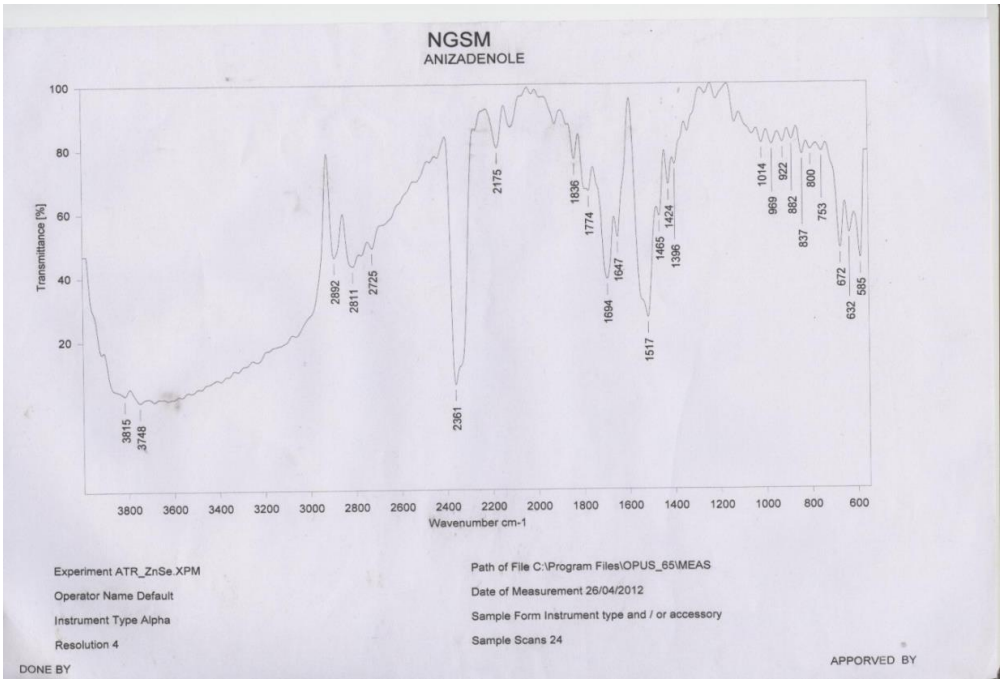
SPECTRAL STUDIES

The Infrared spectral values of the synthesized compounds are shown in the table below:

S.NO	COMPOUND	INFRARED SPECTRA	
		Position of bad in cm^{-1}	Type of vibration
1	3a	1699	C=O stretching(aryl alkyl ketones)

		1600 -1500	C=O stretching in amide in presence of -NH
		2362	$-NH_2$
		800-600	C-Cl
		3054	Ar-H(-CH aromatic)
		1600-1430	C=N
		1512	C=C
2	3b	1699	C=O stretching(aryl alkyl ketones)
		1600 -1500	C=O stretching in amide in presence of -NH
		2362	$-NH_2$
		2850-2815	Methoxy($-OCH_3$),Methyl ether
		3054	Ar-H(-CH aromatic)
		1600-1430	C=N
		1512	C=C





EVALUATION OF INVITRO ANTI MICROBIAL ACTIVITY :

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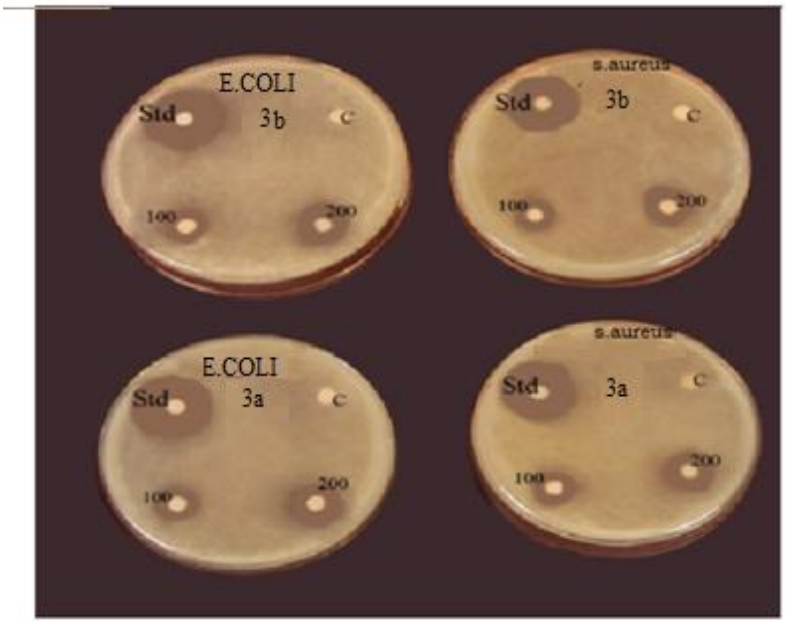
Cup Plate method is based on the diffusion of compound from a vertical cylinder or a cavity through solidified agar layer of a petri-dish plate to an extend such that growth of the added bacteria is prevented entirely in a circular area or "Zone" around the cylinder or cavity containing a solution to a compound. The compounds were tested at the concentration of 100 µg/well against three Gram Positive and three Gram negative bacteria's. Chloramphenicol is used as standard drug, is a bacteriostatic drug that stops bacterial growth by inhibiting protein synthesis.

Among the synthesized compounds selected two compounds were screened for their antibacterial activity against one gram-positive bacterium such as *Staphylococcus aureus* as well as one gram-negative bacterium such as *Escherichia coli* by cup and cylinder plate method. All the selected compounds were tested for antibacterial activity against both bacteria at the concentration 100 and 200µg/ml solutions were prepared in DMSO (solvent). Both the standard, Chloramphenicol and Solvent control were maintained for the study. The two compounds 3a and3b showed significant activity against Stapylococcus aureus and Escherichia coli at concentration about 100 and 200µg/ml.



SUMMARY AND CONCLUSION :

We synthesized some derivatives of Thiazole by using ethylacetoacetate and thiourea asstarting material. The synthesized compounds where characterized by using TLC, melting point, IR spectroscopy and shows satisfactory results.

The synthesized compounds were evaluated for their antimicrobial activity against gram positive bacteria Staphylococcus aureus and Gram negative bacteria Escherichia coli. After the incubation period,the plates were checked for Zone of inhibition.Both derivatives have antibacterial activity and showed some promising activity against gram positive bacteria and the anisaldehyde derivative(compound 3b)showing slightly more antibacterial activity than chloro derivative(3a).

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