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SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL POTENTIAL OF QUINAZOLONES, Beta- LACTUM AND PRIMIDINE MOIETIES

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ABSTRACT

Since 1900, medicinal and pharmaceutical fields are taking benefits of Beta Lactam derivatives for their wide spectrum of biological activities. They are 4-membered cyclic amides though the first member was synthesized by Staudinger in 1907, the Beta lactams has got better attraction since the discovery of penicillin which contains preparation of Anthranilic acid to Iodo Anthranilic acid. The present study was aimed for the synthesis of Quinazolones, 6- Lactum and Primidine moieties and its different Schiff Bases using different aldehyde like (1) Veratraldehyde, (2) 3,4- Dicloro Benzaldehyde, (3) 3 Nitro Benzaldehyde, (4) Salisaldehyde, (5) 4-Flouro Benzaldehyde. The synthetic compounds were confirmed for their preparation using FTIR. Antimicrobial activity was also checked against *Staphylococcus Sp., Aureus, E. Coli* and *Pseudomonas*. The derivatives of Beta Lectam synthesised in the lab found significant activity against the pathogens and need further research to develop important antibiotic in future after completing advance drug testing studies.

KEYWORDS: Antimicrobial activity, Quinazolones, 6- Lactum, Primidine, Schiff Base.

INTRODUCTION

Beta Lactam derivatives are very important in medicinal and pharmaceutical fields because of their wide spectrum of biological activities. From the literature survey up to date, Synthesis and biological activity of Beta lactam derivatives have also been reported by different

authors.[1-13] The Beta lactams are 4-membered cyclic amides though the first member was synthesized by Staudinger in 1907, the Beta lactams as a class acquired importance since the discovery of penicillin which contains Beta lactam unit as an essential structural feature of its molecule, this interest continued unabated because of the therapeutic importance of Beta lactam antibiotics and recent findings of new naturally occurring Beta lactams. As a result of vigorous research, a vast literature has been accumulated over the years, and the chemistry of azetidinones continues to be blossoming field. The utility of azetidinones as synthons for various biologically active compounds, as well as their recognition as antibacterial, antifungal,[14,15] anticancer,[16] and cholesterol absorption inhibitors[17,18] has given impetus to these studies. The new synthesized novel Beta lactam derivatives were evaluated for antibacterial activity. Those compounds which showed significant antibacterial activity were selected for minimum inhibitory concentration studies.

Resistance to number of antimicrobial agents among a variety of clinically significant bacteria is becoming increasingly important. There are various problems arising with the use of antimicrobials such as local tissue irretation, interference with wound healing process, hypersensitivity reaction, system toxicity and narrow antimicrobial spectrum. So, the increasing clinical importance of drug resistant microbial pathogens has addetional urgency in microbiological and antifungal research. A wide variety of heterocyclic systems have been explored for developing pharmaceutically important molicules. Quinazolinone derivatives have been found to exhibit diverse biological activities such as antimicrobial[l1-13], antifungal[4], antibacterial[5], anti inflammatory[6], insecticidal[7], CNS depressants[8] etc. Similarly, thiazole[9-13] and thiazolidinone[14-16] derivatives have also been found to exhibit antibacterial and antifungal activity. In light of above observations it was thought worthwhile to synthesized some new substituted quinazolinone derivatives by in corporation of thiazole and thiazolidinone moieties with the hope to get better antimicrobial agents.

MATERIALS AND METHODS

Preparation of Anthranilic acid to Iodo Anthranilic acid: A solution of Anthranilic acid (25g) in water (500ml) containing KOH (15g) was added to a solution of iodine (46.5g) in water (250 ml) having KOH (24.75g). To this solution glacial acetic acid (100ml) was added and the reaction mixture immediately diluted with water (120ml). A solid separated was filtered. Washed with $NaHSO_3$ (25ml) and recrystallization product of methanol and take MP - 210˚C.

Preparation of 2-(4-methylbenzamido)-5-iodobenzoic acid: A mixture of 5-iodoanthranilic acid[4] (2.63 g, 0.01mol) and p-tolylchloride (1.54 g, 0.01mol) in dry pyridine (15ml) was heated under reflux for 24h. The reaction mixture was cooled and treated with icy hydrochloric acid. The separated solid was filtered, washed with water, dried and crystallized from ethanol.[6]

Preparation of 6-iodo-2-ptolyl-4H-benzo [1,3]oxazin-4-one: A mixture of compound 2-(4-methylbenzamido)-5-iodobenzoic acid (0.01mol) and acetic anhydride (15ml) was heated under reflux for 2h. The reaction mixture was concentrated, cooled and crystallized from ethanol.[7]

3-amino-2-(4-tolyl)-quinazolin-4(3H)-one: Fusion of a mixture of compound 6-iodo-2- p-tolyl-4H-benzo [1, 3] oxazin-4-one (2.63 g, 0.01mol) and neat hydrazine hydrate 95% (0.03mol) for 30 min gave compound (6). The reaction mixture was washed with water, cooled. The separated solid was crystallized from ethanol.[8]

Preparation of Different Schiff Bases: A mixture of compound 6-iodo-2-ptolyl-4H-benzo [1,3]oxazin-4-one (0.01 mole) and veratraldehyde (0.01 mole) dissolve in ethanol and Reflux 4 hrs. Reaction take a room temperature and pore the cold water and wash the product sodium by sulphate to remove unreacted aldehyde.[9]

Preparation of different Schiff base by using different aldehyde

(1) Veratraldehyde

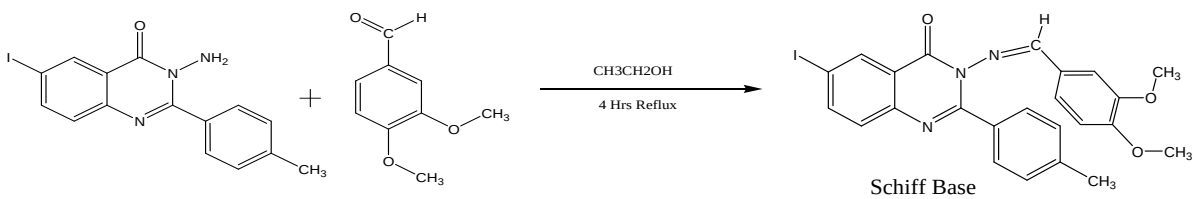
(2) 3,4-Dicloro Benzaldehyde

(3) 3 Nitro Benzaldehyde

(4) Salisaldehyde

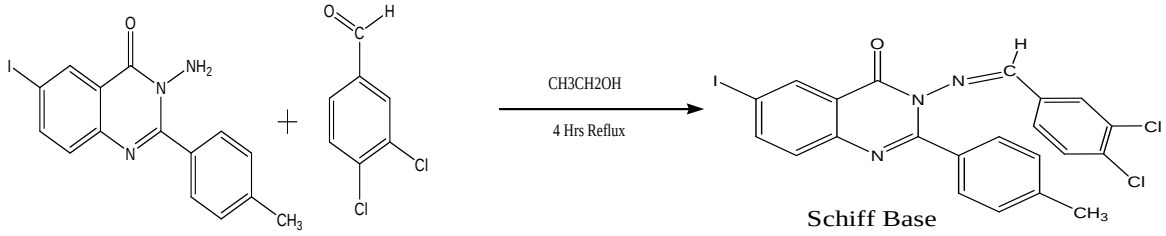
(5) 4-Flouro Benzaldehyde

Scheme of Step-4(a).

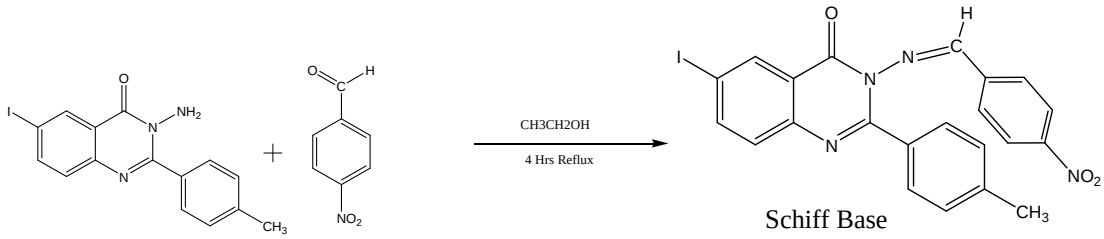


Schiff Base

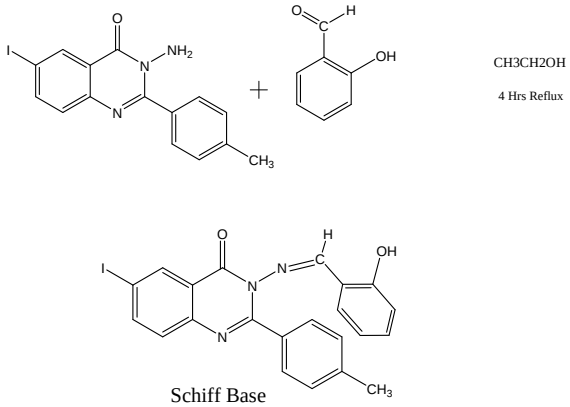
Scheme of Step-4(b)



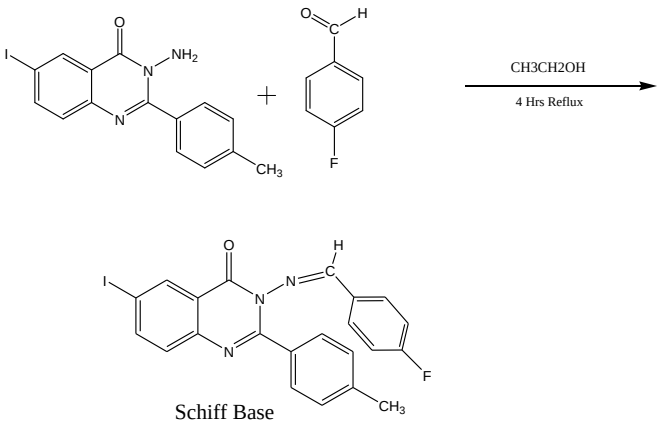
Scheme of Step-4(c)



Scheme of Step-4(d)

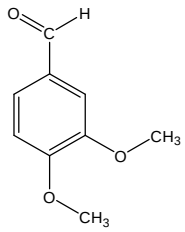
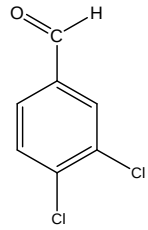
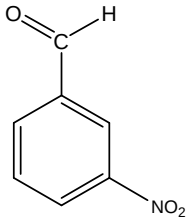
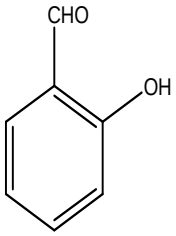
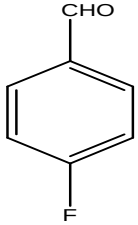


Scheme of Step-4(e)

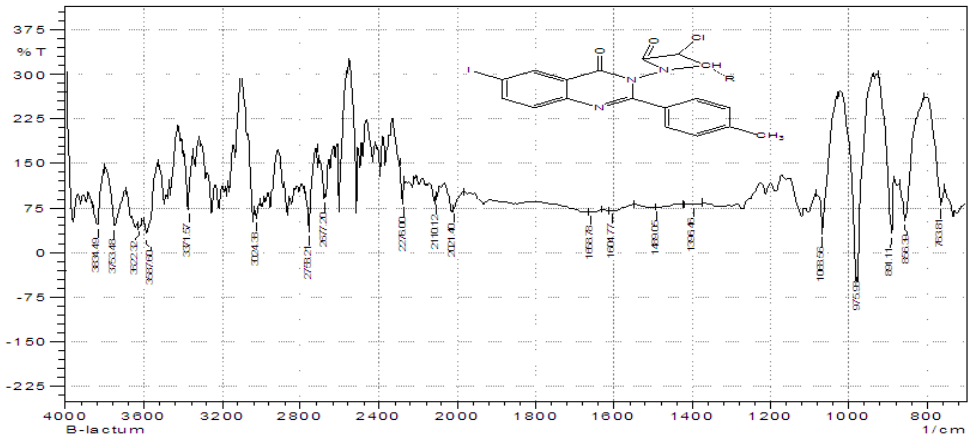


Preparation of Different types of β-Lactums

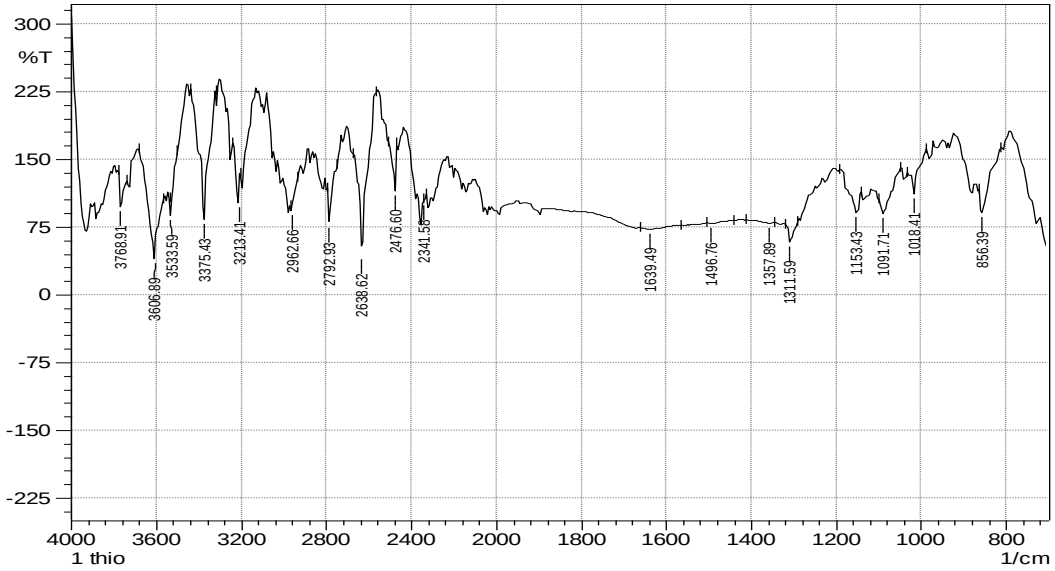
Triethylamine (0.01 mol) in 1,4-dioxane, chloroacetyl chloride (0.01 mol) Was added drop wise to a solution of the compound 3-a (0.005) and at room temperature. The reaction mixture was stirred for 30 min. The mixture was then refluxed for 3h on a water bath. The solid obtained after removal of 1,4-dioxane was re-crystallized from ethanol and take a Mp.

Compound	R	Molecular Formula	Mol. Wt	Mp (^{0}C)	%Yield
4-a		C26H20O2N3Cl1I1	595	242	78%
4-b		C24H14O2N3Cl3I	603	225	69%
4-c		C28H17N5O5I	585	234	70%
4-d		C27H19N4O4I	578	220	68%
4-e		C27H18N4O3IF	598	239	72%

Characterization of sample 4-a in FTIR



Characterization of sample 4-b in FTIR



β-Lactum Sample FTIR (Cm^{-1})

3024 (Ar-C-H str.),

2855 (C-H str.),

1600-1700 (C=O str. B-Lactum),

1489 (C-N),

2276 (N-N str.),

Preparation of indol-3-carboxaldehyde to 1-schiff base: 0.03 mole of indol-3-carboxaldehyde will be dissolved in methanol (20 ml) & add 0.03 mole benzocaine portion wise to if in RBF shake well & then add few drops of glacial acetic acid to clean the suspension then reflux this mixture for 1 hrs at this point color will be change (pale yellow)

keep result mixture at room temperature cold it. Pour this reaction mixture in ice-cold water with staring solid product can be separated out. Re crystallizing ethanol and take M.p. ^{0}C.

Preparation of Schiff base to its hydrazide: 0.01 mole of compound (1a-h) and dissolved in ethanol and add 0.5-1ml of glacial acetic acid reaction mixture shake well and add after shaking 0.015 mole of hydrazine hydrate in RBF and after adding reaction mixture was reflux 3 hrs. After heating reaction monitoring of TLC in every 1 hrs reaction will be complete product will be poor in a ice-cold water and add dilute HCl of some amount so solid product can be formed. Separate product filtrate and recrystallization of ethanol and take M.p. ^{0}C.

Preparation of second schiff base using different types of aldehyde: A mixture of compound 2a-h (0.01mol) and Veratraldehyde (0.01mole) will be dissolved in a ethanol shake well and adding few drop of glacial acetic acid in RBF was heated under reflux for 3-4h. The reaction mixture was concentrated, cooled and poor ice-cold water and wash sodium by sulfate solution solid product will be formed filter it and wash cold water and crystallized from ethanol and take M.P.

Using different types of aldehyde and formed different types of Schiff base

(1) Veratraldehyde(3a)

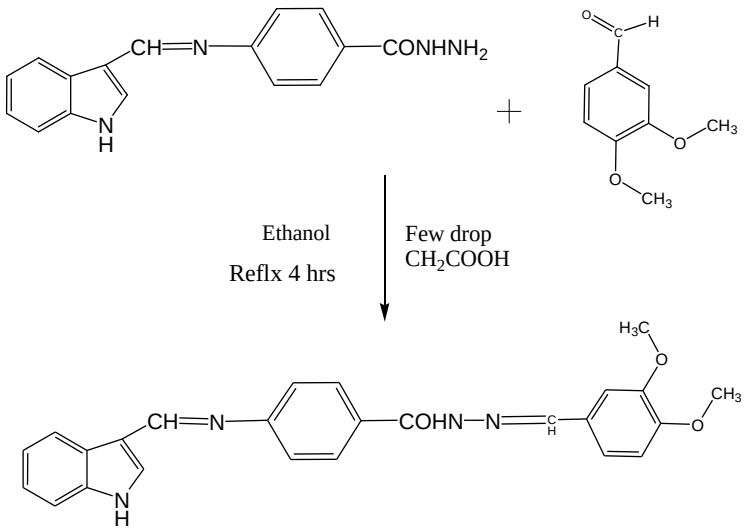
(2) 3,4-dicloro Benzaldehyde(3b)

(3) 3-nitro Benzaldehyde(3c)

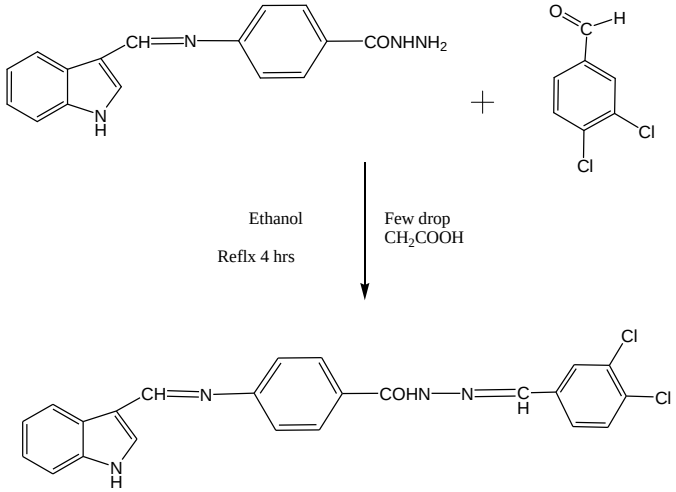
(4) Salisaldehyde(3d)

(5) 4-fluoro Benzaldehyde(3e)

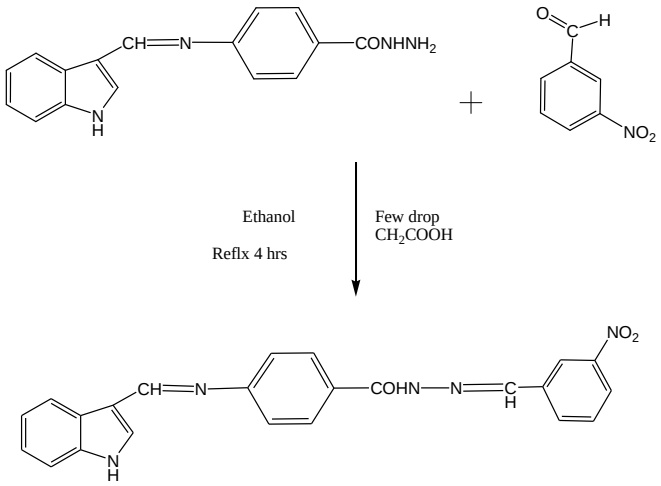
Scheme of Step-3(a)



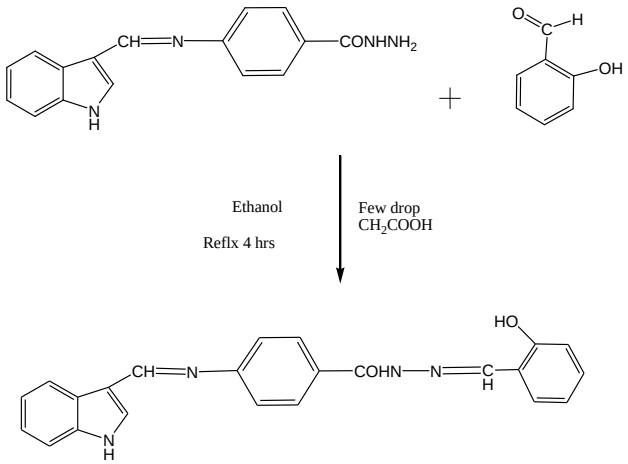
Scheme of Step-3(b)



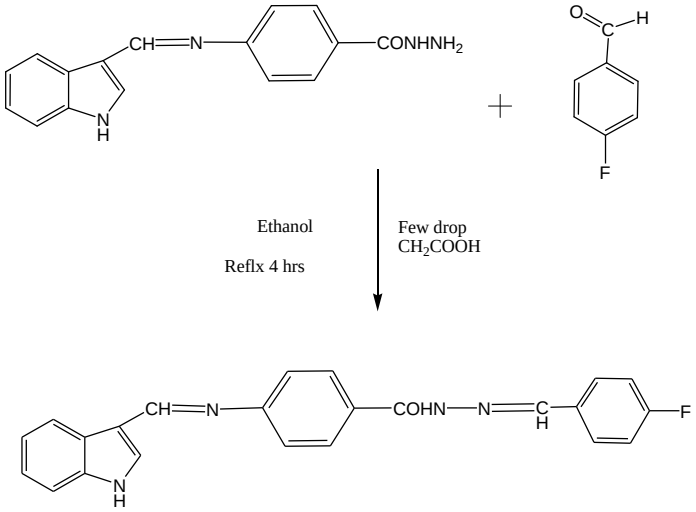
Scheme of Step-3(c)



Scheme of Step-3(d)

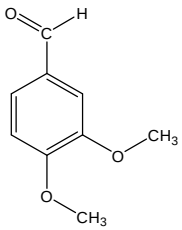
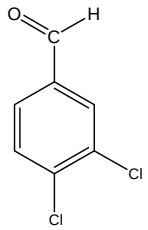
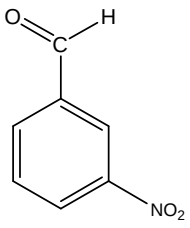


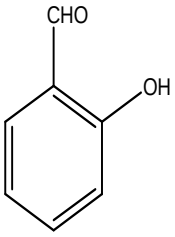
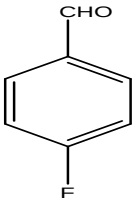
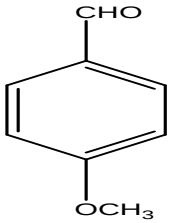
Scheme of Step-3(e)



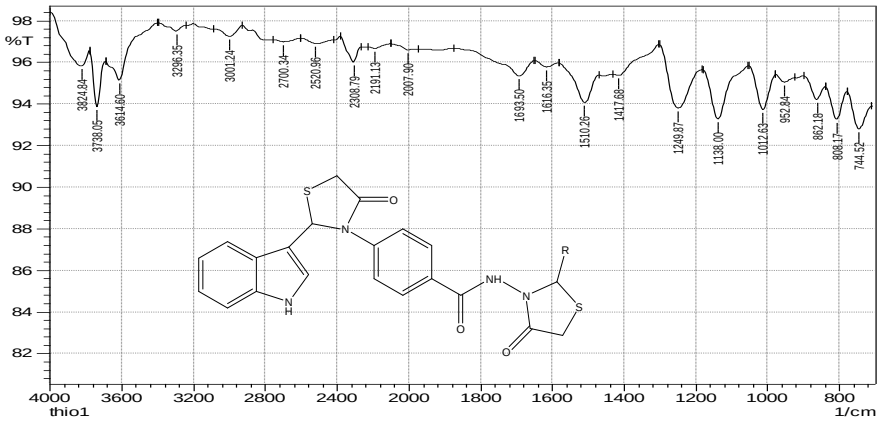
Preparation of different types of 4-Thiazolidinone

A mixture of Schiff Base (0.01 Mole) and Thioglycolic acid (0.02 Mole) are dissolve in 1,4-Dioxane in RBF and reflux 18 hrs(100-110˚C). After the reaction are complete pore the product cold $NaHCO_3$ saturated solution so remove un-reacted Thioglycolic acid and wash it with cold water filtrate it and re crystallization and take Mp.

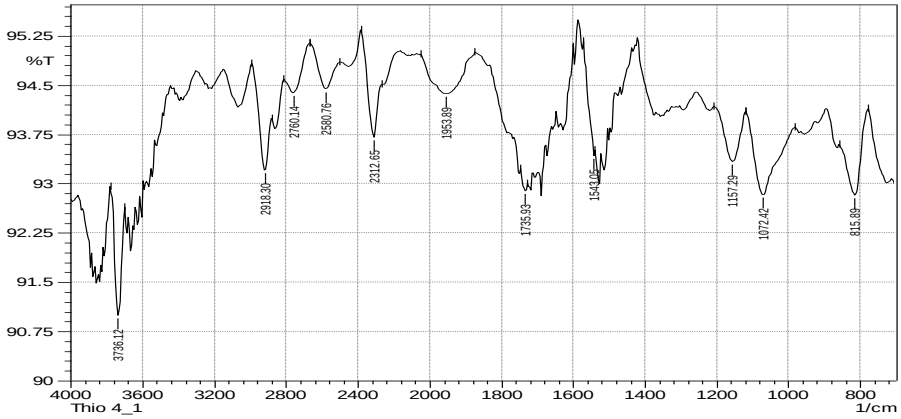
Compound	R	Mol. Formula	Mol. Wt	Mp (^{0}C)	%Yield
3a-h		C29H24O5N4S2	575	185-187	69%
3b-h		C28H16N4O3S2Cl2	583	182	72%
3c-h		C28H17N5O5S2	567	173-175	65%

3d-h		C27H19N4O4S2	534	208-210	59%
3e-h		C27H18N4O3S2F	538	137-140	63%
3e-h		C28H21N4O4S2	546	156-157	65%

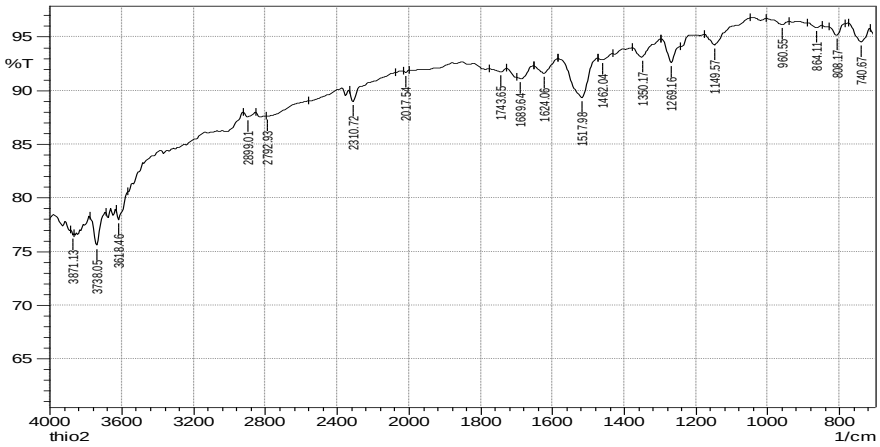
Characterization of sample 3a-h in FTIR



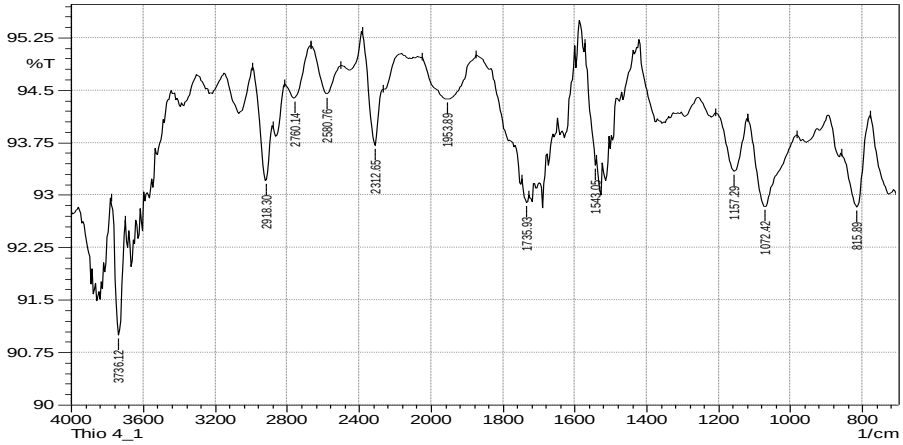
Characterization of sample 3b-h in FTIR



Characterization of sample 3c-h in FTIR



Characterization of sample 3d-h in FTIR



Thiazolidenone Sample FTIR (Cm^{-1}) :-

-: 3738-3824 (thiazolidinone ring C-S-C str.),

-: 1693 (C=O str.),

-: 1600-1510 (C=C, Ar-C-H str.),

-: 1616 (C-N),

-: 2308 (N-N str.),

Mass Spectroscopy

(1) Compound 3a-h :- 576 gm/mol

(2) Compound 3b-h :- 583 gm/mol

(3) Compound 3c-h :- 567 gm/mol

RESULTS AND DISCUSSION

Bacterial Activity of Synthesized Compound:- The antibacterial screening was performed by agar diffusion method.[19] Muller Hinton agar were used for the antibacterial screening, sterilized (autoclaved at 1210C for 30 minutes) medium (40-500C) was inoculated with the suspension of the microorganism (1 ml/ 100ml of medium) & poured into different plates (each containing 10 microlitre) with the synthesized compound dissolved in DMSO were placed on the solidified medium. The plates were pre incubated at 370C for 24 hrs.[20]

On successive synthesis the compound are dissolved in DMSO. The synthesized compounds shows different functional group are present in it. Hence the compound was screened for antibacterial activity. The result of antibacterial activity of synthesized compound are given in table 1. Zone of inhibition was measured using Himedia, Hi-antibiotic zone scale where, 1 inch is equal to 25.4 mm.

Biological activity of β-Lactums.

Solvent	Compound	Zone of inhibition		
		S. Aureus	***E. Coli***	***Pseudomonas***
DMSO	4-a	17mm	22mm	10mm
DMSO	4-b	14mm	25mm	13mm
DMSO	4-c	15mm	20mm	11mm
DMSO	4-d	13mm	19mm	12mm
DMSO	4-e	11mm	23mm	15mm

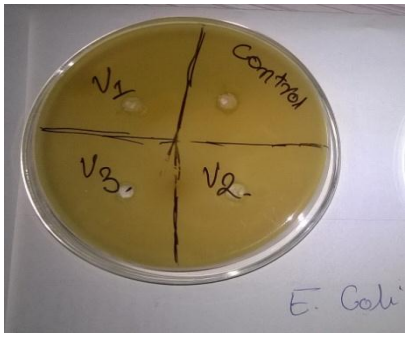
Biological activity of 4-Thiazolidinone

Solvent	Compound	Zone of inhibition		
		S. Aureus	***E. Coli***	***Pseudomonas***
DMSO	3a-h	23mm	18mm	12mm
DMSO	3b-h	22mm	16mm	20mm
DMSO	3c-h	20mm	22mm	15mm
DMSO	3d-h	21mm	19mm	17mm
DMSO	3e-h	23mm	18mm	14mm

All the synthesized final compounds were first purified by successive recrystalization using appropriate solvents. The purity of the synthesized compounds was checked by performing thin layer chromatography and determining melting points. Then the synthesized compounds were subjected to spectral analysis such as IR to confirm the structures. All the analytical details show satisfactory results. The following peaks confirmed the formation of β-LACTUMS AND 4-THIAZOLIDINONE. The peaks at 1550-1510 cm-1 1270-1200 cm-1,1580 cm-1in FTIR have shown the groups of N-H,C-O, C=C in 2-azetidinones

respectively. Since our titled compounds are known to possess antimicrobial activity, the compounds were screened for their antibacterial Activity by well diffusion method. Three bacteria such as Staphylococcus aurous, Escherichia coli and Pseudomonas aeruginosa are tested for the activities. The concentration of 2 µg/ml of our titled compounds has been used. The compounds shows the good bacterial activities.

Antimicrobial activity against *Pseudomonas Sp*.



Antimicrobial activity against *E. Coli*

Antimicrobial activity against *Staphylococcus Sp*.

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