AMERICAN JOURNAL OF PHARMTECH RESEARCH

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Synthesis and Antimicrobial Evaluation of some 2-Azetidinone derivatives

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ABSTRACT

A new series of azetidinone derivatives have been synthesized due to the growing resistance of bacteria towards the â-lactam antibiotics. In our present study Oxadiazole is synthesized from semicarbazide is on condensation with substituted aldehyde to form Schiff base. The schiff bases are cyclized with chloroacetylchloride in triethylamine to yield the corresponding 2-azetidinones. Structures of synthesized compounds are confirmed by physical & spectral analysis. The compounds have screened for antimicrobial activity.

Keywords: 2- Azetidinone, Schiff base, chloroacetylchloride, triethylamine, antimicrobial activity.

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Received 14 October 2016, Accepted 15 November 2016

Please cite this article as: Sarathlal PS *et al.*, Synthesis and Antimicrobial Evaluation of some 2-Azetidinone derivatives. American Journal of PharmTech Research 2016.

INTRODUCTION

The development of newer and more effective antimicrobial agent made a tremendous change in field of drug treatment and discovery. Understanding the chemistry of the older antimicrobial agent helps clinician to develop a new antimicrobial spectrum with less side effect. Newer antibiotics are developed by small changes on the functional groups and / or side chain leading to dramatic differences in their antimicrobial spectrum[1].

Azetidinone (*β*-lactum) chemistry is of great important because of use of *β*- lactum derivatives as antibacterial agents. Since the discovery (in 1945) that the structure of penicillin contains a *β* lactum functions, a vast amount of effort has been devoted to producing other *β*-lactum antibiotics with a wider spectrum of activity and a greater resistance to enzymatic cleavage by *β*-lactomases[2].

General procedure for synthesis of 2-azetidinone derivatives

Step 1

16.41g Sodium acetate and 11.16g Semicarbazide Hydrochloride (0.01M) was stirred in 20ml of distilled water in a iodine flask .In another beaker, 14.92g aldehyde (0.1M) was mixed with ethanol. This ethanolic aldehyde solution was added slowly to the solution of semicarbazide hydrochloride. The precipitate obtained was separated by filtration, dried and recrystalised from 95% hot ethanol.

Step 2

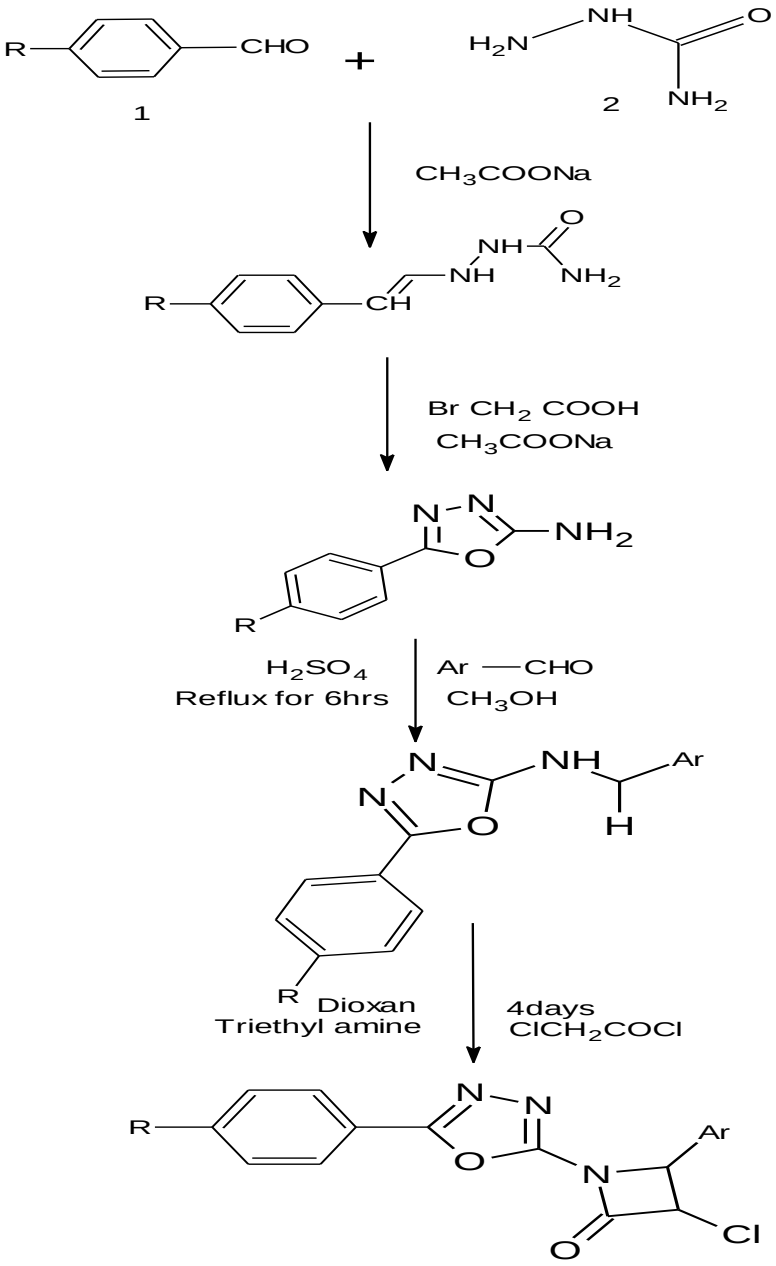
16.406g Sodium acetate (0.02M) and 20.6g Semicarbazone (0.1M) was mixed with 400ml Glacial acetic acid with continuous stirring. Bromine (Bromine: Glacial acetic acid,7:50) was added to this solution and stirred for an hour then poured on crushed ice. The resulting solid was separated, dried and recrystallised from hot ethanol.

Step 3

1.406g of aldehyde and 2.04g of Oxadiazole were dissolved in 50ml ethanol. The mixture refluxed for 4 hours using concentrated sulphuric acid (0.1M) and kept for a day.

Step 4

Chloroacetyl chloride was added drop wise and 0.3ml tri-ethyl amine (0.02M) in dioxin (25ml) was added to the above at 5-10^{0}c. This mixture was stirred for 20hours and left at room temperature for 3 days. The contents were filtered, dried and recrystallised from methanol



HPOAD R= $N(CH_3)_2$: Ar = $OH(C_6H_4)CHO$

MPOAD R= $N(CH_3)_2$: Ar = $OHCH_2(C_6H_4)CHO$

CPOAD R= $N(CH_3)_2$: Ar = $Cl(C_6H_4)CHO$

Compounds named HPOAD, MPOAD, CPOAD were prepared through above procedure with reasonable good yields. The structure of the compound CPOAD were confirmed by IR spectral studies.

Antibacterial activity (Agar well diffusion method).

The test organisms *(Staphylococcus aureus, Bacillus subtilis, Escherichia coli Pseudomonas aeruginosa)* was inoculated on Mueller Hinton agar plates by means of sterile cotton swab. To the

wells 50µl of the drug solution in DMSO was added. The plates were incubated for 24 hrs at 37^0C. Antimicrobial activity was evaluated by measuring the zone of inhibition. Observations were made for zone of inhibition around the drugs and compared with that of standard.

RESULTS AND DISCUSSION

The compounds synthesized are in solid stage and suggested groups of the derivative CPOAD were confirmed by IR Spectra (presence of Absorption maxima at 3330cm^{-2} (-NH_2Stretching), 1463cm^{-2}(C=C Stretching-Aromatic), 2364cm^{-2}(C=0 Stretching), 1058cm^{-2} (C-Cl Stretching)).

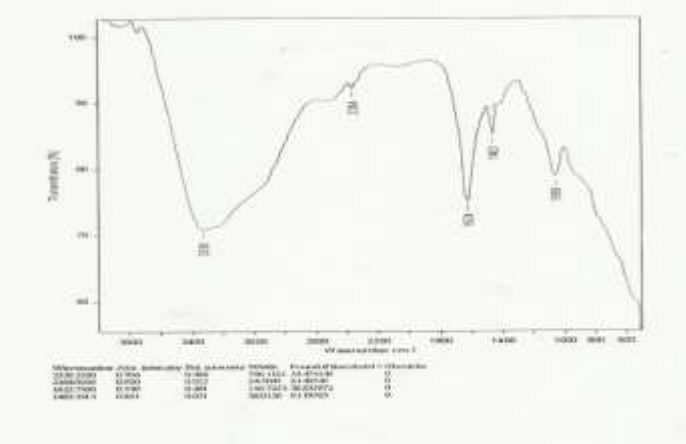


Figure 1: IR spectrum of compound CPOAD

(-) indicates no zone of inhibition, Sa: *Staphylococcus aureus*, Bs: *Bacillus subtilis*, Ec: *Escherichia coli*, Pa: *Pseudomonas aeruginosa* : (Diameter of zone of inhibition:17 mm & above: Sensitive, 13-16mm: Moderately sensitive, <12 mm: resistant).

Table: Zone of inhibition in bacterial strains

Compound code	Diameter of zone of inhibition in mm							
	Sa		Bs		Ec		Pa	
	200µg/well	400µg/well	200µg/well	400µg/well	200µg/well	400µg/well	200µg/well	400µg/well
CPOAD	13	28	13	25	17	26	13	28
MPOAD	12	24	-	24	14	24	11	24
HPOAD	11	25	14	25	11	25	11	24
Standard Ciprofloxacin (5µg/well)	31	36	30	36	36	34	34	38

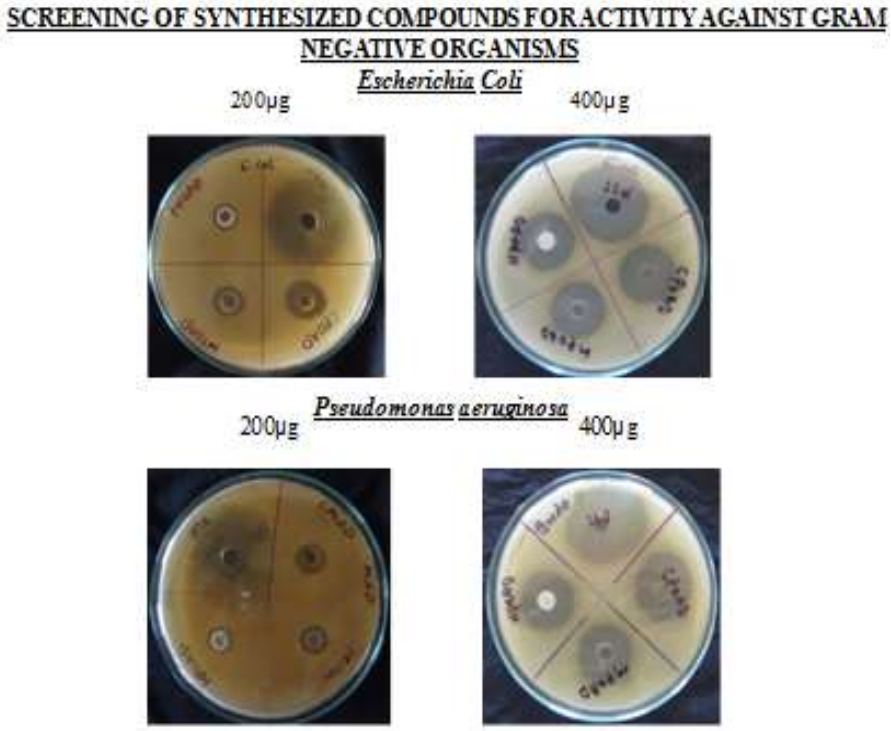


Figure 2 : zone of inhibition of gram negative bacterial strains

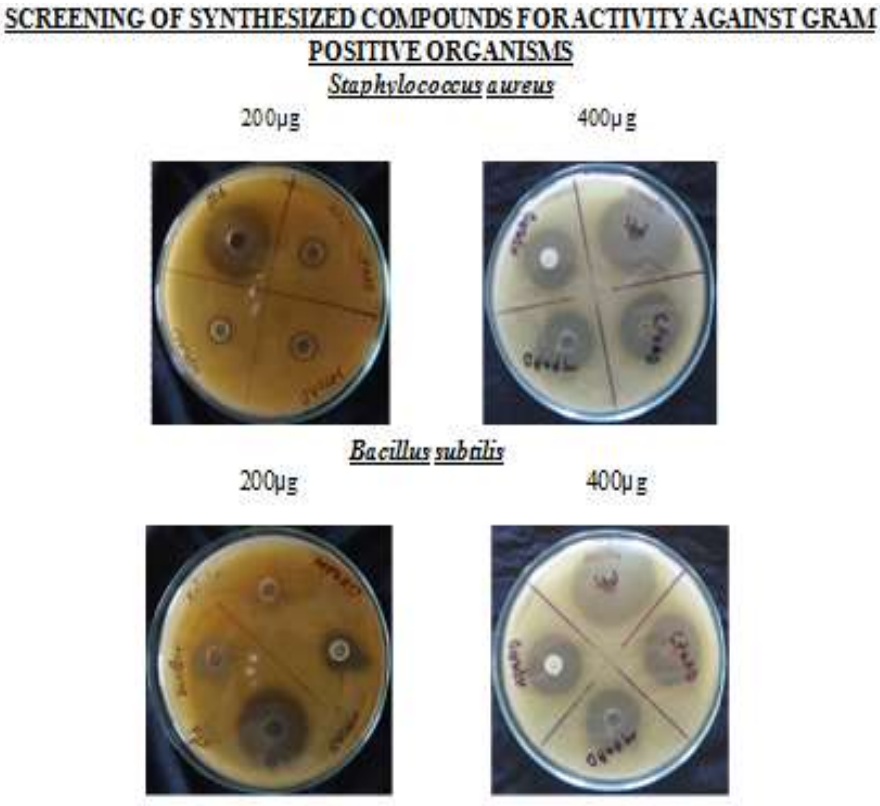


Figure 3: zone of inhibition of gram positive bacterial strains

CONCLUSION

2-Azetidinone derivatives were synthesized from aldehydes, Oxadiazole, Chloro acetyl chloride and Triethyl amine.IR spectral studies are carried out. The compound HPOAD **(**Hydroxy benzaldehyde derivative**)** was sensitive at 400µg/well & moderately sensitive 200µg/well concentration against *Bacillus subtilis.* The compound with code MPOAD (Methoxy benzaldehyde derivative**)** was found to be sensitive at 400µg/well, moderately sensitive at 200µg/well concentration against *Escherichia coli*. The compound CPOAD(Chloro aldehyde derivative**)** was sensitive at 400µg/well, moderately sensitive at 200µg/well concentration against *Pseudomonas aeruginosa.* Thus the derivatives are having good antimicrobial activities.

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