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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF 2-AZETIDINONE DERIVATIVES VIA THIADIAZOLE INTERMEDIATE

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ABSTRACT

Thiadiozoles and Azetidinones are important heterocyclic molecules employed in field of research and development of newer therapeutic agents. The work focused to the antimicrobial action of azetidiones moiety (β-lactum), due to its greater resistance to enzymatic cleavage by lactomases. Various Azetidinone derivatives were synthesized via thiadiazole intermediate and screened for antimicrobial activity by agar well diffusion method using gram positive (*Bacillus subtilis*) and gram negative (*Escherichia coli*) organisms at 400µg/well and 200µg/well. The compound TDPCB (Thiadiazole-para-chloro-benzaldehyde-substituted azetidinone derivative) was found to have significant antimicrobial property.

Key words: Azetidinone, Thiadiazole, substituted aldehydes, antibacterial.

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INTRODUCTION

The development of newer and more effective antimicrobial agent made a tremendous change in the field of drug research. Newer molecules are synthesized by the combination of different heterocyclic compounds which help the clinician to develop a broad spectrum antimicrobial agent with fewer side effects. Thiadiozoles and azetidinones (Fig-1) are important heterocyclic molecules employed in field of research and development of newer therapeutic agents. Present study is focused to the antimicrobial action of azetidinones moiety (β-lactum), due to its greater resistance to enzymatic cleavage by lactamases. Thus in cooperation of these two moieties in single heterocyclic system imparts a wide variety of therapeutic benefits. The present study highlights the synthesis of Azetidinone derivatives via thiadiazole moiety to produce a significant antimicrobial agent (1-3).

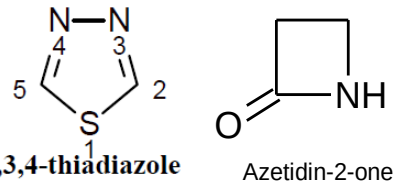


Figure-1 1, 3, 4-thiadiazole and Azetidin-2-one

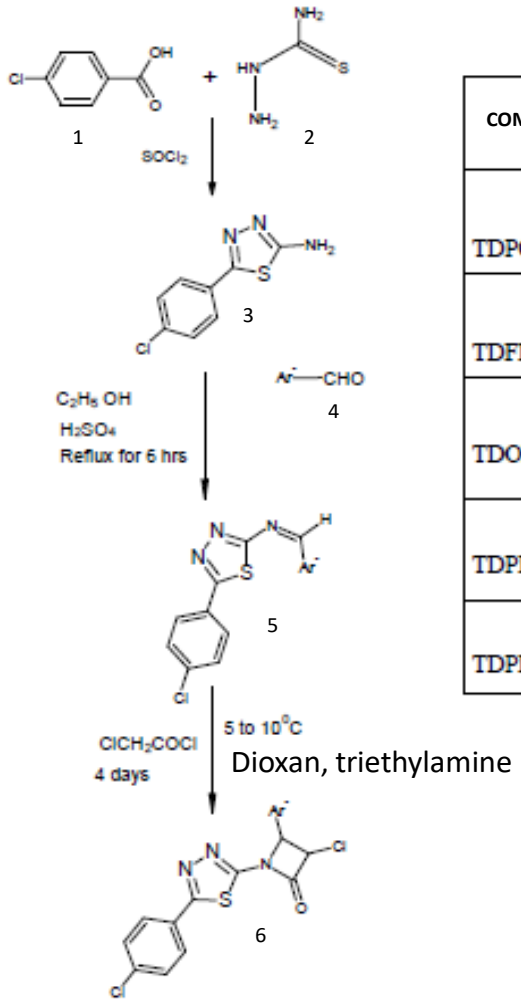
General procedure for the synthesis of 2-Azetidinone derivatives via thiadiazole (Fig-2)

Step 1-A mixture of acid (10millimole), thio semicarbazide (13 millimole) and thionyl chloride (13 millimole) were warmed at 60^0C for 1 hour.

There after the temperature was raised to 95^0C and stirred for another 2 hours. The contents were poured into a crushed ice . The pH was adjusted to 9-10 with 10 M Sodium hydroxide solution and the resulting solid was recrystallized from DMF.

Step 2-Thiadiazole (0.1 millimole) and aldehydes (0.1millimole) were dissolved in 50ml ethanol. Concentrated sulphuric acid(0.1 millimole) was added to this mixture and refluxed for 6 hours and kept for a day. The crystals of thiadiazole Schiff's base formed in the reaction mixture was filtered, dried and recrystalized using hot ethanol (95%).

Step 3-Chloroacetyl chloride was added drop wise to thiadizole Schiff's base (0.01 M) and triethyl amine(0.02M) dioxan was added to the above temperature for 3 days. The contents were filtered, recrystallized using hot ethanol (95%).



COMPOUND	Ar
TDPCB	
TDFMB	
TDOHB	
TDPHB	
TDPMB	

***(1) Thionly chloride, (2) Thio semicarbazide, (3) Thiodiazole intemediate,(4) Substituted aldehyde,(5) Substituted Schiff's base, (6) Product**

Figure-2 Scheme for the synthesis of 2-Azetidinone derivatives via thiadiazole.

Derivatives named TDPCB, TDFMB, TDOHB, TDPHB, TDPMB were prepared through above procedures with reasonable good yields. The structures of the derivatives TDPCB, TDPHB, TDPMB were confirmed by IR spectral studies.

Antimicrobial Screening (Agar well diffusion method) (4, 5)

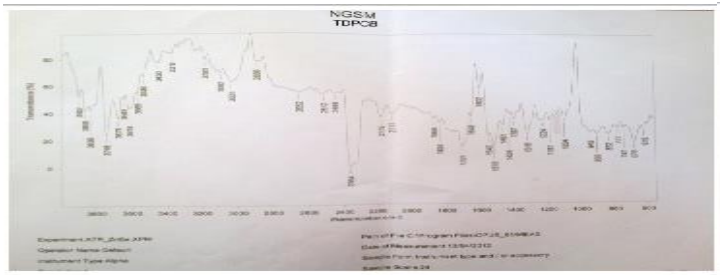
The organisms (*Bacillus subtilis, Escherichia coli*) was inoculated in Mueller Hinton agar plates and dried at room temperature. Synthesized derivatives and standard were introduced into the wells punched in the agar medium and incubated for 18-24hrs. Observations were made from zone of inhibition obtained.

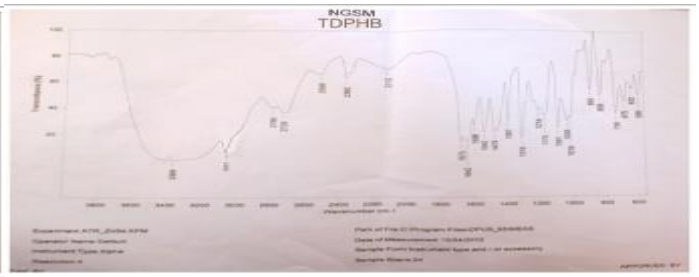
RESULT AND DISCUSSION

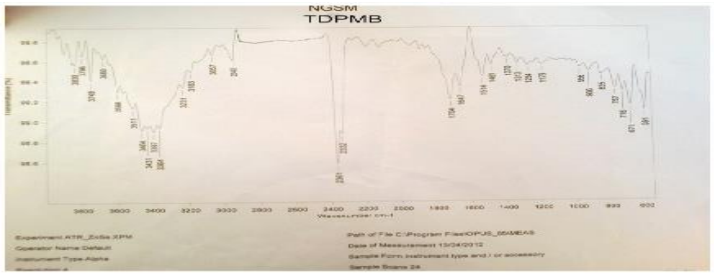
The compounds synthesized are in solid stage. The characteristics of the derivatives obtained are shown the table-1. The suggested functional groups of the derivatives were confirmed by IR spectral studies (6). The results were shown in the figure-3.

Table-1 characteristics of the derivatives synthesized

Compound code	Ar	Molecular weight	Molecular formulae	%yield	Melting point(°C)	Colour
TDPCB		438.71	$C_{18}H_{10}Cl_3N_3O_2S$	74	202	Yellow
TDFMB		418.29	$C_{19}H_{13}Cl_2N_3O_2S$	72	214	Pale yellow
TDOHB		420.26	$C_{18}H_{11}Cl_2N_3O_3S$	69	217	Light pink
TDPHB		420.26	$C_{18}H_{11}Cl_2N_3O_3S$	71	213	Puff colour
TDPMB		434.29	$C_{19}H_{13}Cl_2N_3O_3S$	73	212	Light yellow







VIBRATIONS	TDPCB (cm^{-1})	TDPHB (cm^{-1})	TDPMB (cm^{-1})
C-S stretching	2364	2362	2361
C-Cl Stretching	1094	1091	1254
C-N stretching	1316	1314	1313
C=O stretching	1701	1675	1704
Oh stretching	-	3368	-

Figure-3 IR spectral data of synthesized compounds

Antimicrobial screening

Antimicrobial screening was done by Agar well diffusion method and the results are given in table-2 and figure-4.

Table- 2 Zone of inhibition in bacterial strains

Compound code	Escherichia coli			Bacillus subtilis		
	200µg/well	400µg/well	Standard (50µg/well)	200µg/well	400µg/well	Standard (50µg/well)
TDPCB	14	19	29	13	19	27
TDFMB	11	14	26	12	18	26
TD0HB	13	16	25	14	18	25
TDPHB	15	18	28	13	16	27
TDPMB	13	16	27	14	19	29

Note: Solvent: DMSO, (Diameter of zone of inhibition: 17mm & above: Sensitive, 13-16mm: Moderately sensitive, <12mm: resistant)

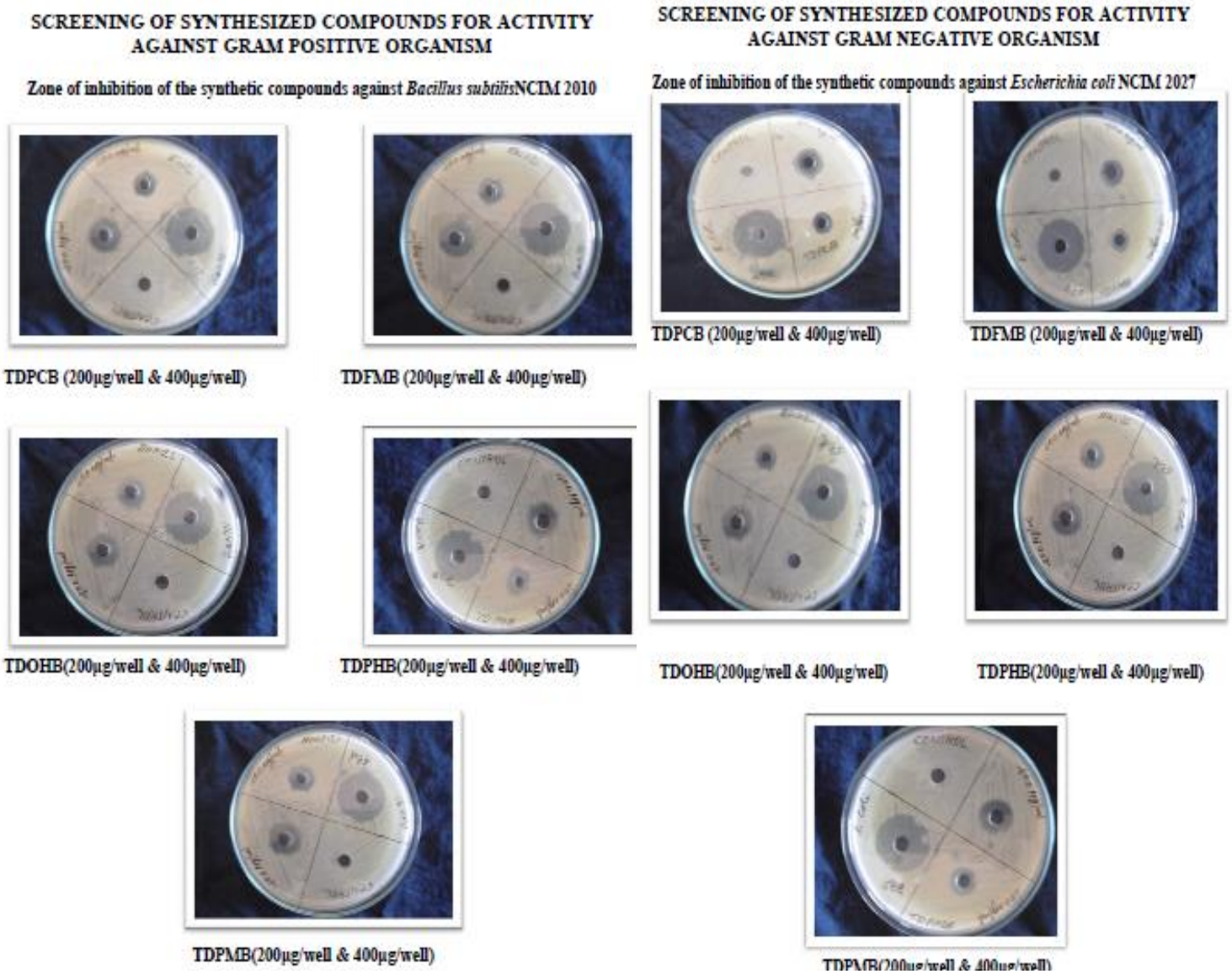


Figure-4 Antibacterial screening of synthesized compounds in bacterial strains

Compound TDPCB was found to be sensitive in both strains of bacteria. And others are moderately sensitive.

CONCLUSION

The work highlights about the synthesis of 2-Azetidinone derivatives via thiadiazole. All the synthesized derivatives were screened for gram positive (*Bacillus subtilis*) and gram negative (*Escherichia coli*) organisms at 400µg/well and 200µg/well. The compound TDPCB (Thiadiazole Para chloro benzaldehyde substituted azetidinone derivative) was found to have significant antimicrobial property.

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