



SYNTHESIS AND ANTIBACTERIAL STUDIES ON SOME NOVEL DERIVATIVES OF AZETIDIN-2-ONES

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Abstract

Isoniazid condensed with different derivatives of acetophenone to form hydrazones, using Vilsmeier-Haack reagent to form free aldehyde. The free aldehyde reacts with different free amide (R-NH₂) group to form imines(C=N) which on react with Chloro acetyl chloride and Triethylamine to gives Azetid-2-one derivatives. The structures of the newly synthesized compounds have been established on the basis of their spectral data and elemental analysis. Selected compound were evaluated for antibacterial activity.

Key words: Azetid-2-one, Vilsmeier-Haack Reagent, Imines.

Introduction

Azetidin-2-one is carbonyl derivatives of azetidines containing carbonyl group at the position-2. These are also known as azetid-2-ones or commonly known as β -lactams, are well-known heterocyclic compounds among the organic and medicinal chemists. The β -lactam Heterocycles are still the most prescribed antibiotics used in medicine. They are considered as an important contribution of science to humanity. The most widely used antibiotics such as the penicillins, cephalosporins, carumonam, ztreonam, thienamycine and the nocardicins all contain β -lactam rings. The long-term use of β -lactam antibiotics exerts selective pressure on bacteria and permits the proliferation of resistant organisms. A comparative study of current antibiotics with those from previous decades shows an alarming increase in bacterial resistance to β -lactam antibiotics. The development of several synthetic and semi-synthetic β -lactam antibiotics by the pharmaceutical industry was due to the growing resistance of bacteria towards the β -lactam antibiotics and the need for medicines with a more specific antibacterial activity.

An interesting group of β -lactams are the monocyclic β -lactams, which are molecules that do not contain another ring fused to the β -lactam. Recently, some other types of biological activity besides the antibacterial activity have been reported in compounds containing azetidines-2-one ring. A large number of 3-chloro monocyclic β -lactams possess powerful antimicrobial¹⁻⁸, antihistaminic⁹, antihelmentic¹⁰, antiamebic¹¹, antiparasitic¹², antiprotozoal¹³, anticancer¹⁴, anti-tubercular¹⁵⁻¹⁸, anti-inflammatory^{19,20}, CNS, anti-HIV²¹, anti-diabetic²², anti-convulsant^{23,24} and analgesic activities.

Materials and Methods

Melting points were determined in open capillaries and are uncorrected. Purity of the all newly synthesized compounds was routinely checked by TLC using plates coated with silica gel-G. UV spectra were recorded on ELICO SL 169 spectrophotometer. IR spectra were recorded using SHIMADZU IR spectrophotometer. NMR spectra were recorded using BRUKER 300MHZ NMR spectrophotometer.

Experimental Procedure

Preparation of N-(1-(4-substituted phenyl ethylidene) Isonicotinic acid hydrazide

An equal molar (0.036 mol) solution of isonicotinic acid hydrazide and substituted acetophenone in ethanol were taken in a round bottom flask.²⁵ Add

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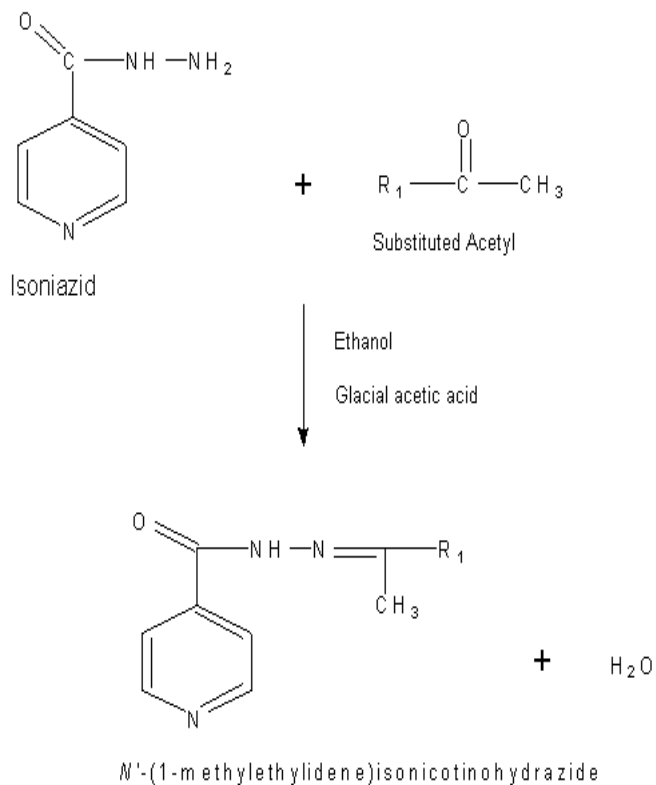
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2 drops of glacial acetic acid and refluxed for 4 hours. The solid separated on cooling filtered and washed with cold ethanol. Finally solids recrystallized from chloroform.

Preparation of 1 - isonicotinoyl- 3 - (4 - substituted phenyl) 1H-pyrazole-4- carbaldehyde

The N-(1-(4-substituted phenyl) ethylidene) isonicotinic acid hydrazide (0.009mole) was added to a vilsmeier Haack reagent³⁰ (20 ml) { prepared by drop wise addition of 1.2 ml phosphorous oxychloride to ice cooled dimethyl formamide (10 ml)} was added portion wise and the reaction mixture was heated to 60°C for about 4 hr and poured into crushed ice. The mixture was then neutralized with sodium hydrogen carbonate, heated to 50-60°C, cooled and acidified to pH-6 with 10 M HCl. ²⁶⁻²⁹ The solid thus separated was filtered and recrystallized from chloroform.

Scheme-I Step-1



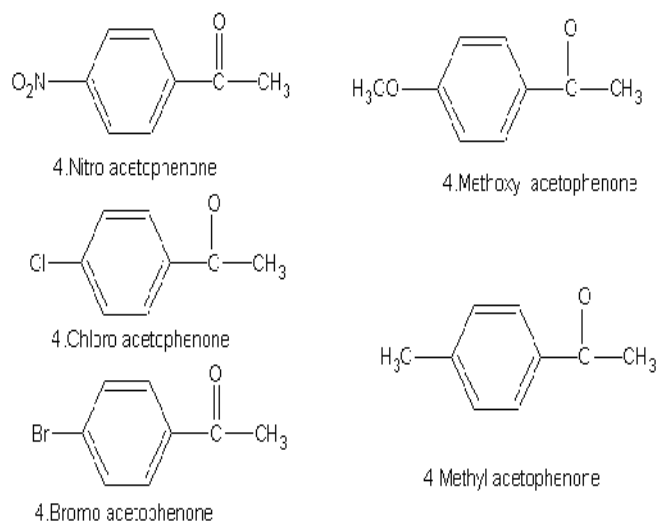
Preparation of N'-((1-isonicotinoyl-3-(4-substituted phenyl) 1H-pyrazol-4-Yl) methylene) Free Amines

An equal molar (0.007mole) solution of free amines and 1-isonicotinoyl-3-(4-methylphenyl) 1h-pyrazole-4-carbaldehyde in ethanol were taken in a round bottom flask. Add 2 drops of glacial acetic acid and refluxed for 4 hours. The solid separated on cooling filtered and washed with cold ethanol.³⁰ Finally solids recrystallized from chloroform.

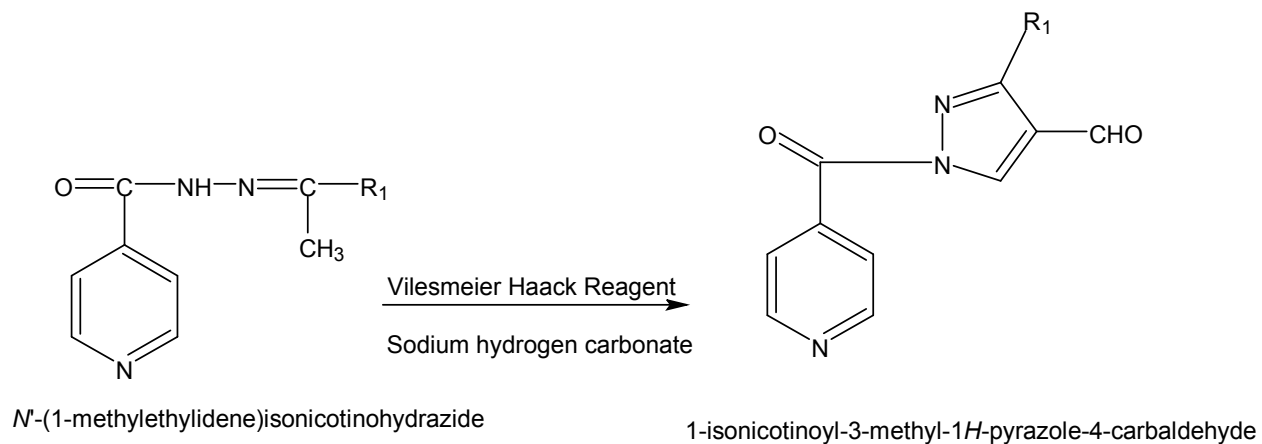
Preparation of different azetidin-2-one derivatives

All freeamines Compounds (0.01mol) was dissolved in N,N-dimethyl formamide (40ml) and triethylamine (2.80ml,0.02ml) was add to it. Chloroacetylchloride (1.60ml, 0.02mol) was added drop wise over a period of 15min.The reaction mixture was refluxed for 8 hours .The reaction mixture was concentrated, cooled and poured into crushed ice.³¹⁻³² The solid was obtained, washed with water and recrystallized with chloroform.

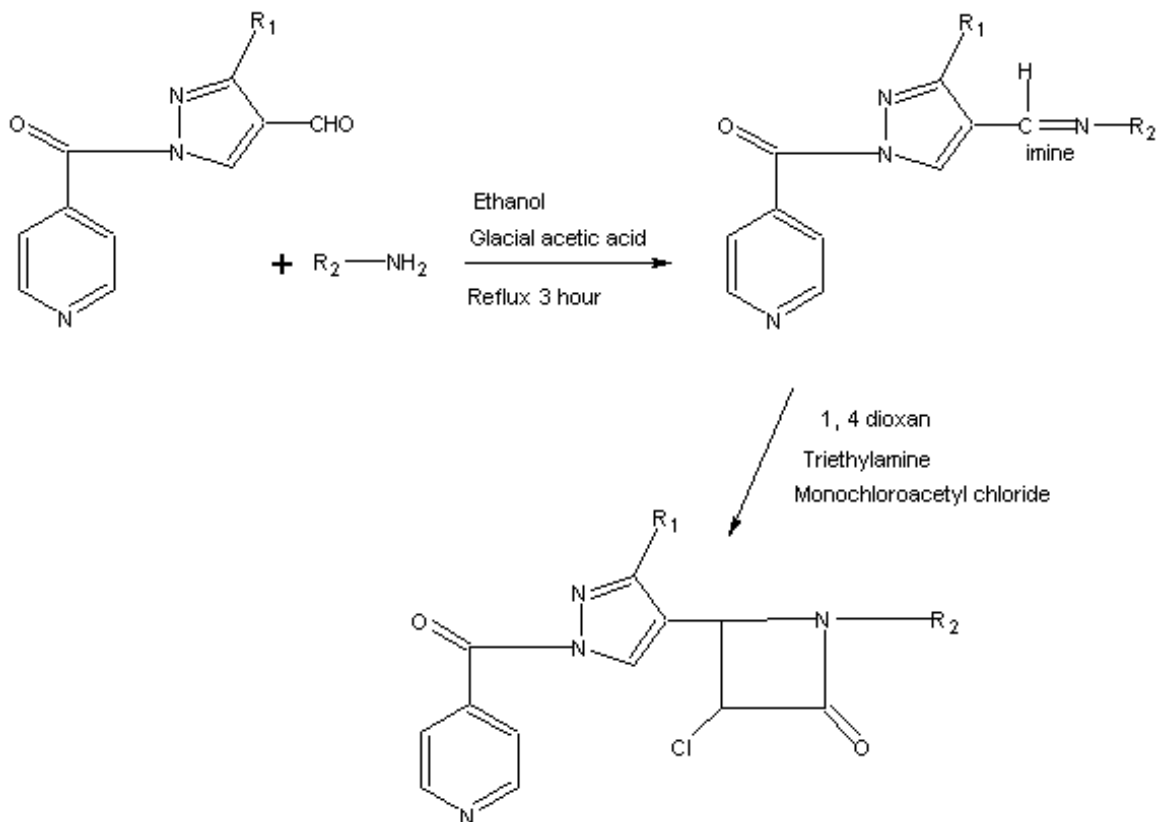
R₁

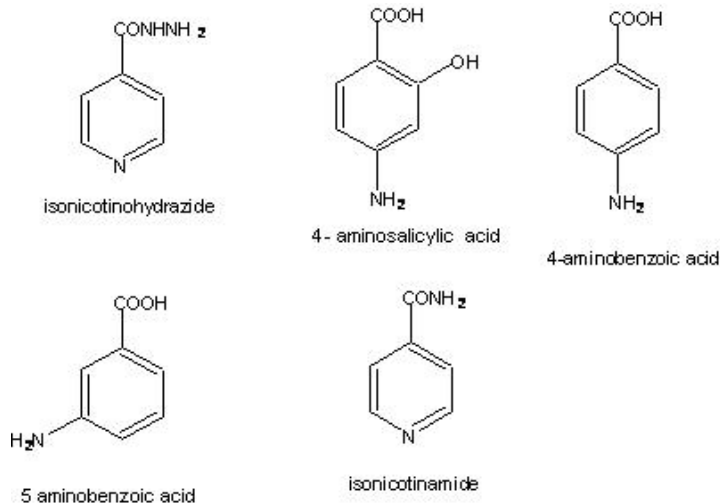


Step 2



Scheme II



R₂

Spectral Studies of Prototype Compounds

Structures of Azetidin-2-ones synthesized were established on the basis of IR, NMR, Mass spectral data.

3-Chloro-1-isonicotinohydrazide-4-(1-isonicotinyl-3-ethylphenyl-1H-pyrazol-4-yl) azetidin-2-One (Am)

IR - NH_{str} (3350.1), Methyl C-H_{str} (2937.4), C-H_{str} Aromatic (3000-3300), C=O_{str} (1720), C=N_{str} (1590) N=O_{str} (1527.5), C=C_{str} in pyridine moiety (1610), C=C_{str} in aromatic ring (1450), C-N_{str} (1280), C-O_{str} (1101.3), C-N_{str} for Ar NO₂ (856.3), Out of plane bend C-H_{str} (750.3).

¹HNMR - 7.416 – 7.440 (4H of Benzene ring), 4.816 (1H of Azetidinone), 3.30 (1H of CH-Cl Azetidinone), 2.441 (3H of Methyl).

¹³CNMR – 166.96 (C=O of Azetidinone), 139.12 (C of benzene), 49.64 (CH of Azetidinone).

3-Chloro-1-isonicotinyl-4-(1-isonicotinyl-3-methylphenyl-1H-pyrazol-4-yl) azetidin-2-One (Br)

IR - 3031.89-3448.49 (Ar C-H stretching and N-H stretching), 1660.60 (C=O stretching), 1290.29 (C=C stretching in aromatic), 869.84 (C-H stretching), 58.90 (C-Cl stretching).

¹HNMR - 7.41 – 7.57 (4H of Benzene ring), 4.818 (1H of Azetidinone), 3.308 (1H of CH-Cl Azetidinone), 2.438 (3H of Methyl).

¹³CNMR - 169.81, (C=O of Azetidinone), 137.28 (C of benzene), 49.64 (CH of Azetidinone).

3-Chloro-1-benzoic acid-4-(1-isonicotinyl-3-methylphenyl-1H-pyrazol-4-yl) azetidin-2-One (Al)

IR - 2864.09-3016.46 (Ar C-H stretching and N-H stretching), 1666.38 (C=O stretching), 1334.65 (C=C stretching in aromatic), 844.76 (C-H stretching), 675.04 (C-Cl stretching).

¹HNMR - 7.318 – 7.426 (4H of Benzene ring), 4.43 (1H of Azetidinone), 3.308 (1H of CH-Cl Azetidinone), 2.437 (3H of Methyl).

¹³CNMR - 170.70 (C=O of Azetidinone), 139.11 (C of benzene), 49.64 (CH of Azetidinone).

3-Chloro-4-[1-isonicotinoyl-3-(4-chlorophenyl)-1H-pyrazol-4-yl]-1-isonicotinamido-azetidin-2-one (a-Azt)

IR - 'H' bonded, coupled, Ar C-H_{str}, Lactum C-H and N-H_{str} (2400-3400), C=O_{str} (1710), C=N_{str} (1494) N=O_{str} (1535), C=C_{str} in pyridine moiety (1590), C=C_{str} in aromatic ring (1400) C-N_{str} (1249), C-O_{str} (1101), C-N_{str} for Ar NO₂ (846), C-Cl (866), Out of plane bend C-H_{str} (750). ¹HNMR 2.5 (-CH-CH- LACTUM), 3.4 (-NH), 4.6 (-CH Cl), 7.7 (Ar. benzene proton), 8.7 (Pyridine proton), 10.2 (Tautomeric enolic OH).

3-Chloro-4-[1-isonicotinoyl-3-(4-chlorophenyl)-1H-pyrazol-4-yl]-1-(2-hydroxy benzoic acid) azetidin-2-one (b-Azt)

IR - 'H' bonded, coupled, Ar C-H_{str}, Lactum C-H and N-H_{str} (2400-3400), C=O_{str} (1740), C=N_{str} (1477), C=C_{str} in pyridine moiety (1570), C=C_{str} in aromatic ring (1398), C-N_{str} (1290), C-O_{str} (1090), C-Cl (850), Out of plane bend C-H_{str} (759).

¹HNMR 2.4 (-CH-CH- Lactum), 3.4 (-NH), 4.7 (-CH Cl), 7.8(Ar.benzene proton), 8.7(Pyridine proton), 10.2 (Tautomeric enolic OH).

3-Chloro-4-[1-isonicotinoyl-3-(4-chlorophenyl)-1H-pyrazol-4-yl]-1-benzoic acid) azetid-2-one (c-Azt)

IR - 'H' bonded, coupled, ArC-H_{str}, Lactum C-H and N-H_{str} (2400-3400), C=O_{str}(1700), C=N_{str}(1494) N=O_{str} (1535), C=C_{str} in pyridine moiety(1624), C=C_{str} in aromatic ring(1570)C-N_{str}(1319), C-O_{str}(1014), C-Br (1249), C-Cl(866), Out of plane bend C-H_{str}(759).

¹HNMR 2.5 (-CH-CH- Lactum), 3.4 (-NH), 4.7 (-CH Cl), 7.7(Ar.benzene proton), 8.8(Pyridine proton). **EI -MS:** 283(M⁺).

3-Chloro-4-[1-isonicotinoyl-3-(4-nitrophenyl)-1H-pyrazol-4-yl]-1-(2-hydroxy benzoic acid) azetid-2-one (Bm)

IR - 'H' bonded, coupled, Ar C-H_{str} and N-H_{str} (3000-3400), Methyl C-H_{str} (2933.5), C=O_{str} (1690), C=N_{str} (1580) C=C_{str} in pyridine moiety(1560.3), C=C_{str} in aromatic ring(1411) C-N_{str}(1284), C-O_{str}(1101), C-Cl_{str} (993), Out of plane bend C-H_{str}(752).

¹HNMR 2.6 (-CH-CH- Lactum), 3(-CHCl), 3.75 (COOH), 4.7 (Ar.OH) 8.4 and 8.6 (Ar. benzene proton), 7.9 (Pyridine proton).

3-Chloro-4-[1-isonicotinoyl-3-(4-bromophenyl)-1H-pyrazol-4-yl]-1-isonicotinamido-azetid-2-one (Ap)

IR - 'H' bonded, coupled, Ar C-H_{str} and N-H_{str} (3000-3400), Methyl C-H_{str} (2933.5), C=O_{str} (1690), C=N_{str} (1580) C=C_{str} in pyridine moiety(1560.3), C=C_{str} in aromatic ring(1411) C-N_{str}(1284), C-O_{str}(1101), C-Cl_{str} (993), Out of plane bend C-H_{str}(752).

¹HNMR 2.3 (-CH-CH-Lactum), 3.4 (-CH Cl), 4 (COOH), 4.9 (Ar.OH), 5.9 (Pyrazole CH) 8.3(Ar.benzene proton), 8.9 (Pyridine proton).

3-Chloro-4-[1-isonicotinoyl-3-(4-bromophenyl)-1H-pyrazol-4-yl]-1-(2-hydroxy benzoic acid) azetid-2-one (Bp)

IR - 'H' bonded, coupled, Ar C-H_{str} and N-H_{str} (3000-3400), Methyl C-H_{str} (2935.5), C=O_{str}(1745), C=N_{str} (1519) C=C_{str} in pyridine moiety(1590), C=C_{str} in aromatic ring(1420) C-N_{str} (1280), C-O_{str}(1105), C-Br_{str} (1220), Out of plane bend C-H_{str} (752).

¹HNMR 2.5 (-CH-CH- Lactum), 3.6(-CH-Cl), 11(COOH),

7.3 (Pyrazole CH) 9(Ar. benzene proton), 9.5 (Pyridine proton).

3-Chloro-4-[1-isonicotinoyl-3-(4-bromophenyl)-1H-pyrazol-4-yl]-1-benzoic acid) azetid-2-one (Cp)

IR - 'H' bonded, coupled, Ar C-H_{str} and N-H_{str} (3000-3400), C=O_{str}(1745), C=N_{str}(1510) C=C_{str} in pyridine moiety(1678), C=C_{str} in aromatic ring(1350), C-N_{str} (1299), C-Br_{str} C-O_{str}(1105), Out of plane bend C-H_{str}(750).

¹HNMR 2.4 (-CH-CH-Lactum), 3.3(-CH Cl), 11 (COOH), 8.9(Ar. benzene proton), 9.4(Pyridine proton). **EI -MS:** 299(M⁺).

Antibacterial Screening

Mueller-Hinton agar plates were prepared aseptically to get a thickness of 5- 6 mm. The plates were allowed to solidify and inverted to prevent the concentrate falling on the agar surface. The plates were dried at 37° C before inoculation. The organisms are inoculated in the plates prepared earlier, by dipping a sterile swab in the previously standardized inoculum, removing the excess of inoculum by pressing and rotating the swab firmly against the sides of the culture tube, above the level of the liquid and finally streaking the swab all over the surface of the medium three times, rotating the plates through an angle of 60° C after each application. Finally press the swab round the edge of the agar surface. Leave it to dry at room temperature with the lid closed. The sterile disc containing test drugs, standard and blank were placed on the previously inoculated surface of the Mueller – Hinton agar plate and were kept in the refrigerator for one hour to facilitate uniform diffusion of the drug. Plates were prepared in triplicate and it was then incubated for 18 – 24 hours. Observations were made for zone of inhibition around the drugs and compared with that of standard. All the compounds synthesized were tested for antibacterial activity against 1 gram - positive and gram -negative bacteria. The antibacterial data are shown in Table 01.

Results and Discussion

All the newly synthesized compounds were synthesized with good yields (65-72%). All the synthesized compounds exhibited antibacterial. All the analytical details (Table 02) show satisfactory results. After analyzing the results, the following conclusions were

made, All the compounds showed considerable antibacterial activity against Gram-positive and Gram-negative organisms.

The micro organism *Staphylococcus aureus* was found to be sensitive to **AM** and **CP** and moderate sensitive to **BP** at 500 µg/disc concentration. The micro organism *Bacillus subtilis* was found to be sensitive to **A-AZT** at 500µg/disc concentration. The micro-organism *Pseudomonas aeruginosa* was found to be sensitive to **A-AZT** and **C-AZT** and resistant to **CM** and **AP** at 500 µg/disc concentration. The micro organism *Escherichia coli* were found to be sensitive to **A-AZT** and **C-AZT** at 500 µg/disc concentration. The micro organism *Klebisella aeruginosa* was found sensitive **A-AZT** and **C-AZT** at 500 µg/disc concentration.

Antipseudomonal Activity

Compounds A-AZT and C-AZT showed significant

activity against *Pseudomonas aeruginosa* and clinically isolated culture of *Pseudomonas* species at 500, 250 µg/disc concentration by Agar diffusion method.

In case of NCIM culture (non pathogenic) the activity was significantly greater than the clinical isolated culture (due to resistance commonly seen in clinical pathogenic culture. The activity of A-AZT against the NCM culture at 250µg/disc strength was greater than that of C-AZT at 250 µg/disc strength which was greater than the reference standard cefotaxime at 10 µg/disc strength. Similarly result was observed against the clinical culture also.

This observation clearly shows that the Azetidin-2-ones (especially NO₂ and Br substituted) may be used as important lead molecule in synthesizing potent Antibacterial agents having *Pseudomonas* coverage. The anti pseudomonal data are shown in Table 03.

Table 01: Quantitative Screening of Compounds for Antibacterial Activity

S.No	Compound Code	Diameter of zone of inhibition in mm 500µg/disc)			
		Gram-positive organisms		Gram-negative organisms	
		<i>S.aureus</i>	<i>B.subtilis</i>	<i>E. coli</i>	<i>K.aeruginosa</i>
1	AM	23 mm	-	-	-
2	BM	-	10 mm	-	-
3	CM	-	-	-	-
4	AL	-	-	-	-
5	CL	-	-	-	-
6	AP	-	-	-	-
7	BP	16 mm	-	-	-
8	CP	18 mm	-	-	-
9	AR	-	-	-	-
10	DR	-	-	-	-
11	A-AZT	-	20 mm	20 mm	21 mm
12	B-AZT	-	-	-	-
13	C-AZT	-	-	24 mm	24 mm
14	Water : Ethanol (80:20) Blanks	-	-	-	-
15	Std (10 µg/disc)	24 mm (Amoxycillin)	28 mm (Amoxycillin)	18 mm (Amoxycillin)	23 mm (Amoxycillin)

All the compounds were prepared at 500 µg/disc concentration.

(-) indicates no zone of inhibition.

Table 02: Physicochemical Data of Newly Synthesized Compounds

S.No	Comd. code	Mol. Formula	Mol. Wt.	M.P(°C)	% Yield	R _f Value	λ max
1	AM	C ₂₄ H ₁₆ Cl N ₇ O ₅	517.881	178	79	0.73	340
2	BM	C ₂₄ H ₁₆ Cl N ₅ O ₇	533.877	180	65	0.61	330
3	CM	C ₂₅ H ₁₆ Cl N ₅ O ₆	517.877	167	62	0.67	310
4	DM	C ₂₅ H ₁₆ Cl N ₇ O ₅	517.877	173	64	0.54	350
5	EM	C ₂₄ H ₁₅ Cl N ₆ O ₅	502.866	184	76	0.71	335
6	AL	C ₂₄ H ₁₆ Cl ₂ N ₆ O ₃	507.328	150	70	0.68	330
7	BL	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₅	523.324	160	75	0.73	345
8	CL	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₄	507.324	156	80	0.78	347
9	DL	C ₂₅ H ₁₆ Cl ₂ N ₄ O ₄	507.324	148	59	0.64	328
10	EL	C ₂₅ H ₁₅ Cl ₂ N ₅ O ₃	492.313	140	75	0.67	342
11	AP	C ₂₄ H ₁₆ BrCl N ₆ O ₃	551.779	145	72	0.61	344
12	BP	C ₂₅ H ₁₆ BrCl N ₄ O ₅	567.775	152	69	0.61	341
13	CP	C ₂₄ H ₁₆ BrCl N ₄ O ₄	551.776	190	75	0.75	329
14	DP	C ₂₅ H ₁₆ BrCl N ₄ O ₄	551.776	180	65	0.77	330
15	EP	C ₂₄ H ₁₅ BrCl N ₅ O ₃	536.765	208	66	0.67	344
16	AR	C ₂₅ H ₁₉ Cl N ₆ O ₃	486.910	195	71	0.74	329
17	BR	C ₂₆ H ₁₉ Cl N ₄ O ₅	502.906	189	60	0.52	325
18	CR	C ₂₆ H ₁₉ Cl N ₄ O ₄	486.906	158	74	0.48	335
19	DR	C ₂₆ H ₁₉ Cl N ₄ O ₄	486.906	174	79	0.67	339
20	ER	C ₂₅ H ₁₈ Cl N ₆ O ₃	471.895	197	53	0.58	328
21	A-AZT	C ₂₅ H ₁₉ Cl N ₆ O ₄	502.909	185	61	0.64	340
22	B-AZT	C ₂₆ H ₁₉ Cl N ₄ O ₆	518.905	196	78	0.51	339
23	C-AZT	C ₂₆ H ₁₉ Cl N ₄ O ₅	502.906	210	69	0.53	341
24	D-AZT	C ₂₆ H ₁₉ Cl N ₄ O ₄	486.906	198	64	0.62	341
25	E-AZT	C ₂₄ H ₁₈ Cl N ₅ O ₃	471.895	207	71	0.69	339

Table No 03: Anti-Pseudomonal Activity against *Pseudomonas aeruginosa* NCIM 5029 and Clinical Culture at 500, 250µg/disc Concentration

		Diameter of Zone of Inhibition in mm (500,250 µg/disc)			
S. No.	Compound Code	<i>Pseudomonas aeruginosa</i> NCIM 5029		Clinical culture of <i>Pseudomonas</i> species	
		500(µg/disc)	250(µg/disc)	500(µg/disc)	250(µg/disc)
1.	CM	12 mm	-	-	-
2.	AP	11 mm	-	-	-
3.	BP	9 mm	-	-	-
4.	CP	10 mm	-	-	-
5.	A-AZT	25 mm	22 mm	19 mm	16 mm
6.	C-AZT	22 mm	16 mm	17 mm	16 mm
7.	Water : Ethanol (80:20)Blanks	-	-	-	-
8.	Std (10 µg/disc)	17 mm (Cefotaxime)	15 mm (Cefotaxime)	15 mm (Cefotaxime)	15 mm (Cefotaxime)

Conclusions

In conclusion, we developed an efficient and simple method for the direct preparation of derivatives of azetidin-2-ones via the Vilsmeier-Haack reagent using the suitable catalyst in good yields and short reaction times from readily available starting materials. The

selected compounds were screened for their antibacterial activity against gram positive and gram negative organism. Compounds were found to have moderate antibacterial activity.

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