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Synthesis and determination of biological activities of new series of azetidinones

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ABSTRACT

A series of aryl hydrazones cyclization with chloroacetyl chloride, dioxin at temperature of 5°c affords newer azetidinones, namely1-anilino 4,4 diphenyl azetidone ***(AZ01),*** *1-anilino 4-benzoyl 4-phenyl azetidone, 2-one* ***(AZ02),*** *aniline,4-(p-dimethyl amino phenyl azetidine-2 one* ***(AZ03),*** *4-((P-dimethyl amino phenyl)1-phenyl-azetidine -2-one)* ***(AZ04).****These compounds have been evaluated for their antimicrobial activity using ciprofloxacin as a reference compound.*

Keywords- Aryl hydrazones, chloroacetyl chloride, dioxin, antimicrobial activity.

INTRODUCTION

Number of β-lactam antibiotics i.e. pencillins and cephalosporins are the most important naturally occurring azetidinones. It is thought that the high reactivity of ß –lactam is essential for antibiotic activity of these compounds. Literature survey reveals that various azetidinones have attracted considerable attention as they are also endowed with wide range of pharmaceutical activities [1]. In view of this and in continuation of our interest in the chemistry of newer azitidinones, the present study has been aimed to synthesize newer azitidinones and to evaluate their antimicrobial properties.

The starting materials aryl hydrazones (1- 1V) required for preparation of target compounds. They are benzo phenyl hydrazone- (**1),** benzil phenyl hydrazone-(**11),** (1-Anilino-4(P-diethyl amino benzaldehyde phenyl hydra zone – (111**),** Benzyldine aniline-(**1V). 1-IV** reaction with chloroacetyl chloride and dioxan underwent cyclization and afforded novel azetidinones (AZ01, AZ02, AZ03, AZ04).

MATERIALS AND METHODS

Experimental section

All the melting points reported were taken in open capillaries on a Cintex melting point apparatus. IR spectra were recorded in KBr on FT-IR spectrophotometer.

Preparation of starting materials [2]

Benzophenone phenyl hydrazone

A mixture of equimolar concentration of benzophenone and phenyl hydrazone (0.1ml) was heated for 30min and poured the reaction mixture into cold water then precipitate of benzophenone phenyl hydra zone was obtained

Benzil phenyl hydrazone

Mixed 4.2 gm of Benzil and 4 ml of aniline in a small evaporating dish and heated on a boiling water bath for 20min. The mixture stirred frequently with glass rod. Globules of water appeared on surface of the oil. The basin was kept in cooled water and stirred, oil crystallized rapidly. Crystals transferred to a 50ml conical flask and recrystalized from methylated spirit.

1-anilino-4(P-dimethyl amino benzaldehyde)phenyl hydrazone)

Dissolved 25 gm of colorless p-dimethyl amino benzaldehyde phenyl hydrazone hydrochloride in 250ml of water. Added 45gm of crystalline sodium acetate to cold solution and shaken. Added 0.5gm of activated carbon. Shaken filtered and transferred into dark bottle.

P-(dimethyl amino benaldehyde) phenyl hydrazone

Mixed 7.2gm of paradimethyl amino benzaldehyde and 4.65 gm of aniline in a round bottom flask and condensed for 2 hours.

Synthesis of newer azitidinones (AZ01, AZ02, AZ03, AZ04) [3]

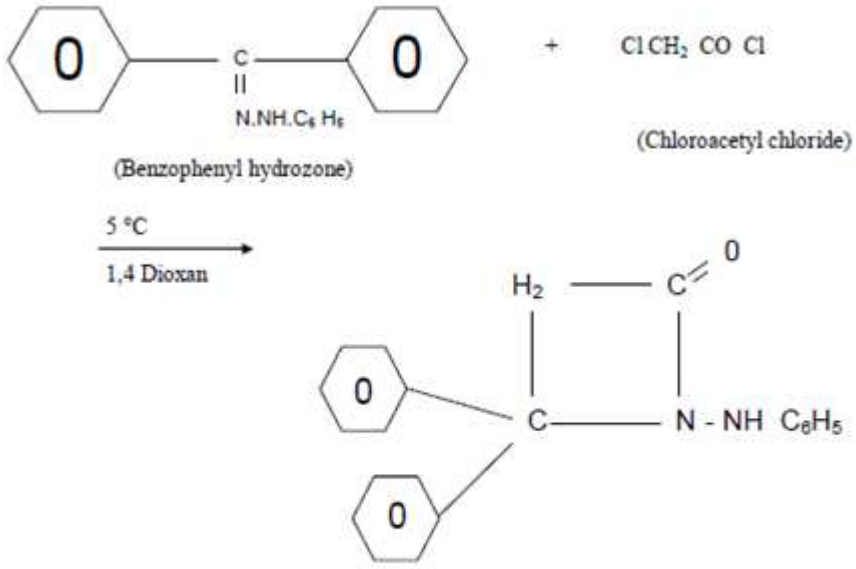
The starting compound benzophenone phenyl hydrazone, benzyl phenyl hydrazone, 1-anilino 4-(p-dimethyl amino benzaldehyde) phenyl hydrazone, P-dimethyl amino benzaldehyde) phenyl hydrazone were dissolved separately in 35ml of dioxan and chloroacetyl chloride, kept in separate ice bath. After 20min mixed both the solutions which afforded newer azitidinones. The percentage yield, melting point and thin layer chromatography were carried out and tabulated.

Table -1 Physical characteristics of newer azitidinones

S.No	Code	Chemical name	% of yield	Melting point	Rf value	Description
1	AZ01	1-anilino-4,4 diphenyl azetidine -2-one	75%	120ºc	0.75	Light brownish amorphous compound
2	AZ02	1-anilino-4(p-dimethyl amino phenyl –azetidine-2-one	83%	96ºc	0.65	Yellowish amorphous compound
3	AZ03	1-anilino-4(p dimetyl amino phenyl –azetidine -2-one	65%	100ºc	0.92	Light red amorphous compound
4	AZ04	4(p-dimetyl amino phenyl-azetidine -2-one	62%	65ºc	0.80	Brick red crystalline compound

Mobile phase for TLC: - Ethyl acetate: Benzene (1:10) Detector for TLC: - Iodine chamber

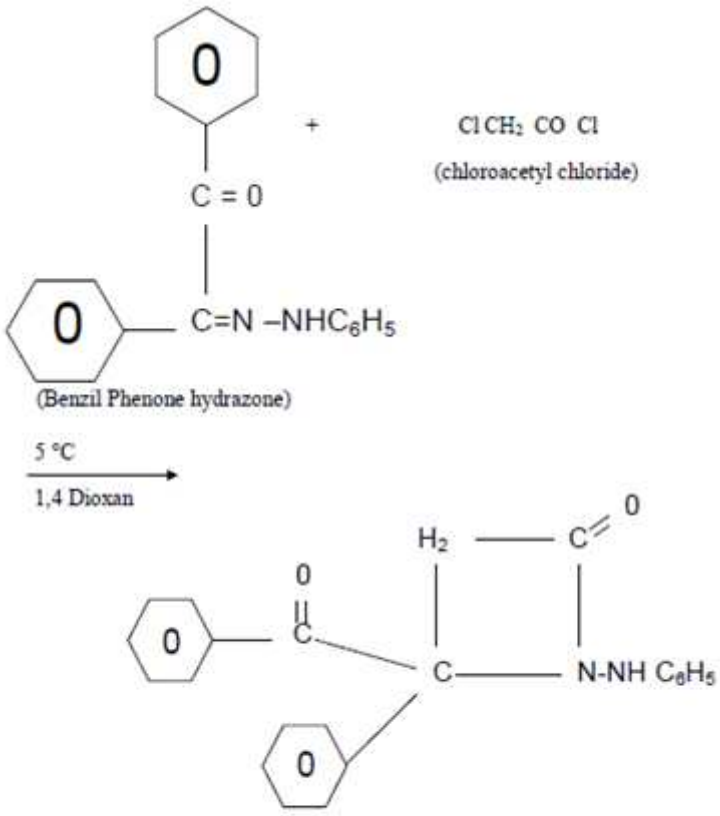
The scheme for the synthesized compounds AZO1, AZ02, AZ03, and AZ04 are given below.



1-aninilino-4,4 diphenyl azetidine – 2 - one

AZO1

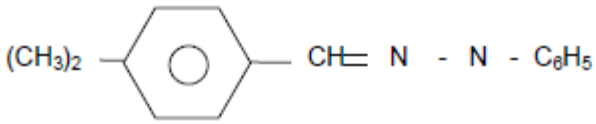
Scheme – I



1 – Anilino - 4 benzoyl - 4 Phenyl - azetidine – 2 one

AZO2

Scheme - II



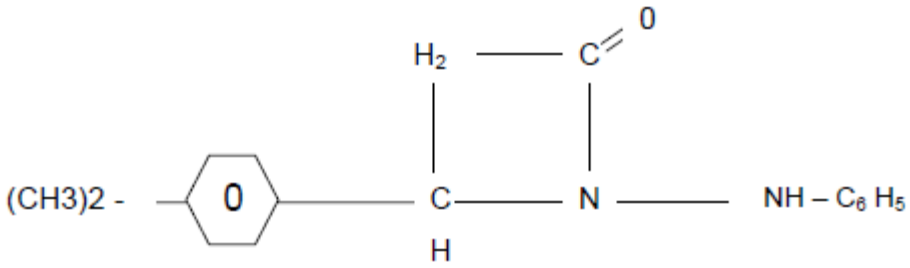
1-anilino 4(p,dimethyl amino benzaldehyde) phenyl hydra zone

+ Cl CH_2 CO Cl

(chloroacetyl chloride)

5 °C

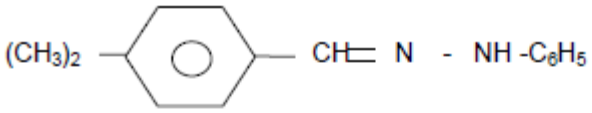
1,4 Dioxan



1- Anilino – 4 (P-Dimethyl amino phenyl – Azetidine -2- one)

AZO3

Scheme – III

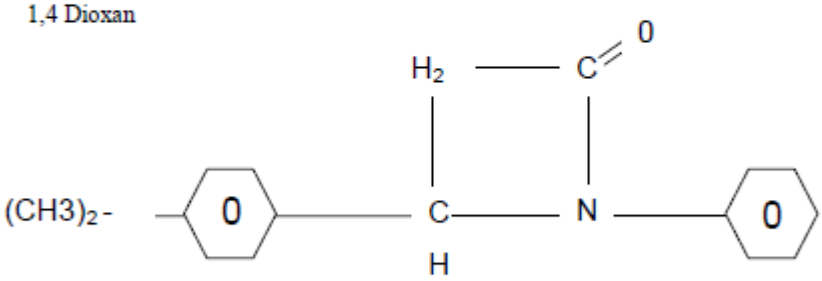


(P – Dimethyl amino phenyl) Phenyl hydrozone + Cl CH_2 CO Cl

(chloroacetyl chloride)

5 °C

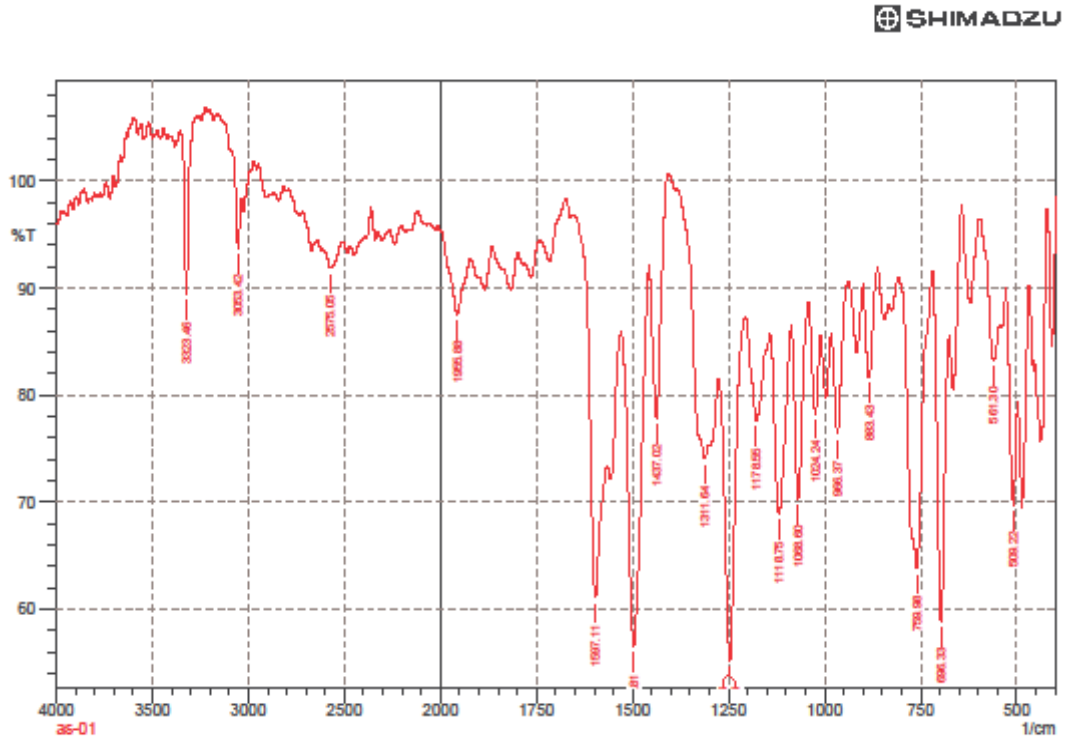
1,4 Dioxan



4((P- Dimethyl amino phenyl)1-phenyl – Azetidine- 2-one)

AZO4

Scheme-IV



	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	509.22	69.737	13.623	528.51	497.65	3.415	1.161
2	561.3	83.25	6.851	596.02	542.02	2.801	0.686
3	696.33	58.87	29.414	719.47	677.04	5.606	3.356
4	759.98	63.8	27.581	808.2	719.47	9.503	6.018
5	883.43	81.628	9.409	900.79	862.21	2.446	0.886
6	966.37	76.372	11.127	983.73	937.44	3.617	1.065
7	1024.24	78.288	8.677	1041.6	1010.73	2.572	0.728
8	1068.6	70.321	17.111	1087.89	1041.6	4.542	1.883
9	1118.75	68.885	17.144	1141.9	1087.89	6.175	2.661
10	1178.55	77.6	9.057	1205.55	1141.9	5.465	1.464
11	1247.99	55.171	28.602	1274.99	1207.48	9.675	4.7
12	1247.99	55.171	28.675	1276.92	1205.55	9.99	4.716
13	1311.64	74.059	1.484	1323.21	1301.99	2.666	0.086
14	1437.02	77.865	17.939	1458.23	1408.08	2.765	1.959
15	1496.81	56.471	32.36	1529.6	1458.23	10.181	6.608
16	1597.11	61.043	20.633	1653.05	1566.25	8.876	2.419
17	1955.88	87.545	6.359	2013.75	1921.16	3.481	1.109
18	2575.05	91.865	1.725	2600.13	2509.47	2.917	0.396
19	3053.42	93.736	6.154	3086.21	3036.06	0.401	0.524
20	3323.46	89.379	15.81	3354.32	3271.38	-0.223	1.661

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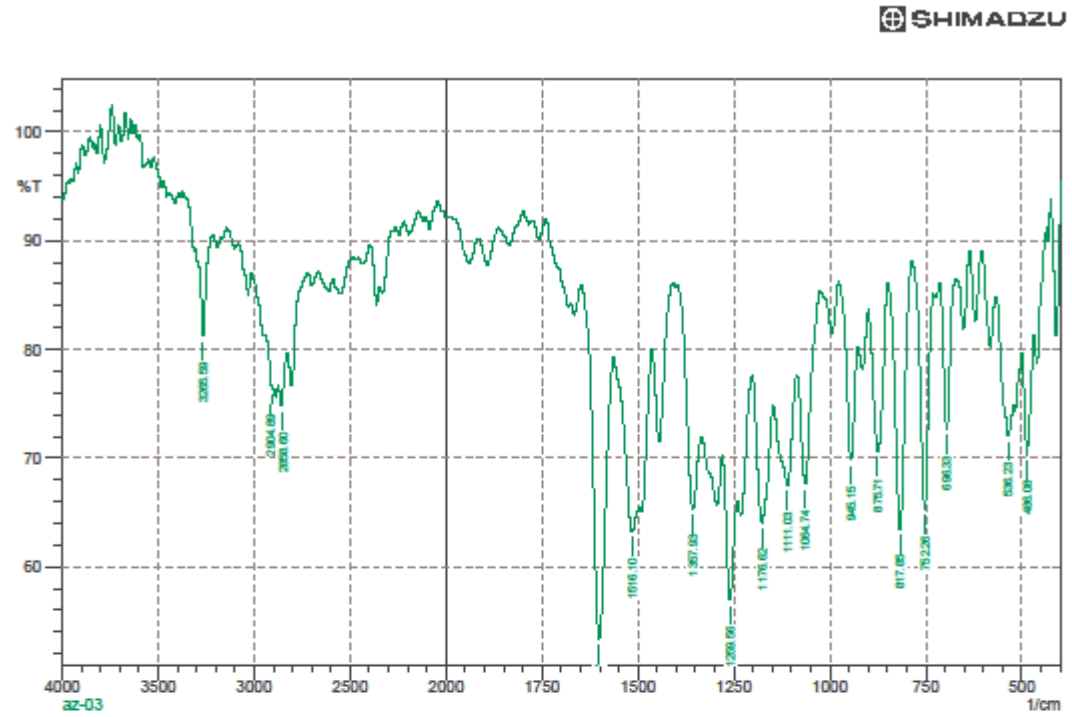

	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	486.08	70.314	10.059	499.58	468.72	3.816	0.905
2	536.23	72.026	6.275	565.16	520.8	5.281	0.898
3	696.33	72.67	13.571	713.69	671.25	4.013	1.293
4	752.26	65.273	20.997	785.05	731.05	5.963	2.582
5	817.85	63.492	23.556	848.71	785.05	7.338	3.512
6	875.71	70.639	14.164	900.79	848.71	5.842	2.123
7	945.15	69.806	12.625	976.01	927.79	5.281	1.435
8	1064.74	67.597	12.764	1085.96	1026.16	7.211	1.863
9	1111.03	67.458	9.028	1147.68	1085.96	9.028	1.745
10	1176.62	64.041	12.277	1201.69	1147.68	8.57	2.196
11	1259.56	56.928	11.004	1280.78	1242.2	7.858	1.424
12	1357.93	65.336	11.974	1398.44	1332.86	8.617	1.775
13	1516.1	63.217	6.313	1562.39	1496.81	10.325	0.93
14	1600.97	53.35	28.868	1647.26	1564.32	13.086	6.14
15	2858.6	74.781	2.939	2874.03	2829.67	5.084	0.34
16	2904.89	76.373	0.691	2943.47	2899.11	4.579	0.004
17	3265.59	81.232	8.593	3306.1	3217.37	5.429	1.318

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RESULTS AND DISCUSSION

The structure of AZ01, AZ02, AZ03, and AZ04 were supported by their spectral data. IR spectra in KBr showed 1597-1500cm^{-1} (β lactam) - C =O stretching, 2576cm^{-1}(saturated C-H stretching), 3323-3053 cm $^{-1}$(NH stretching), 1495-1432 cm$^{-1(}$CH deformation) 966-695 cm^{-} (aryl CH deformation).All the newly synthesized compounds gave satisfactory C, H, N analysis and spectral data

Antimicrobial activity [4]

Compounds AZ01- AZ04 were evaluated for their anti bacterial activity *in vitro* against *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus vulgaris* and *Staphylococcus aureus* using the filter paper disc method at 200µg/disc concentration. The activity was compared with known standard ciprofloxacin (100µg/disc). The results are presented in Table-2. The results indicate that all compounds were active against both the gram –negative and gram – positive bacteria .However, the degree of inhibition varied both with the test compounds as well as with bacterium. Compounds AZ01, AZ03 were most effective, while AZ02, AZ04, showed significant activity. The results also indicate that compound AZ01 showed significant activity against *Pseudomonas aeruginosa*

Table -2 Antibacterial activity of synthesized compounds AZ01-AZ04 Acknowledgements

Drug Treatment	Zone of inhibition in mm			
	Pseudomonas aeruginosa	*Escherichia coli*	*Proteus vulgaris*	*Staphylococcus aureus*
AZ01 (200 µg/disc)	18	4	3	5
AZ02 (200 µg/disc)	14	2	2	14
AZ03 (200 µg/disc)	12	5	2	6
AZ04 (200 µg/disc)	11	Nil	5	2
Standard Ciprofloxacin (100µg/disc)	16	20	20	22

Acknowledgement

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