RESEARCH PAPER

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Antibacterial Screening of N-arylamino-3-chloro-4-(4'-Dimethyl Amino) Phenyl-Azetidin-2-Ones

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A number of new N-arylamino-3-chloro-4-(4'-dimethylamino) phenyl-azetidin-2-ones have been synthesised and their structures have been established on the basis of consistent elemental, IR, spectral data. Antibacterial activity has been performed using agar diffusion technique involving paper disc method against *E. coli* (445). *Pseudomonas diminuta* (MTCC 1609) and *Bacillus subtilis* (MTCC 441). All the synthesised azetidine-2-one have shown significant antibacterial activity. It has been observed that N-(4'-nitro) phenylamino-3-chloro-4-(4'-dimethylamino) phenyl azetidin-2-one is found to be more potent against *E. coli.* Molecular refractive index (M_R) correlates linearly to the drug activity with correlation coefficient of 0.99.

AZETIDINES and their derivative have been extensively explored for their applications in the field of medicine[1,2]. Likewise, azetidin-2-ones are of great importance because of the use of β-lactum derivative as antibacterial agents[3]. Recent years have witnessed a great upsurge in the treatment of tuberculosis[4]. Keeping this generalization in view, we report herein a new method of synthesis and antimicrobial activity of N-arylamino-3-chloro-4-(4'-dimethylamino) phenyl-azetidin-2-ones.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were scanned in KBr on Shimadzu 460 IR spectrophotometer. All the chemicals used were of AR grade. N-arylamino-3-chloro-4-(4' - dimethylamino) phenyl azetidin-2-ones were synthesised and characterized in the following manner.

1-Arylhydrazono-1-(4"-dimethylamino) phenylmethanes [B] (0.02 M) obtained by condensation of corresponding hydrazines [A] with p-dimethyl-amino benzaldehyde was added to a constant stirred solution of 1,4-dioxan (40 ml), triethylamine (0.02 mol) and chloroacetyl chloride (0.02 mol). The reaction mixture was mechanically stirred at 50°. The reaction vessel was kept at room temperature for 30 min and then refluxed for 8 h. On colling the precipitate so obtained was filtered off, thoroughly washed with water and dried. The product was recrystallised from dimethylformamide (DMF) as white crystals. Yield 65%.

Anal of Ia: IR bands (in cm^{-1}) at 3400 (-NH), 3070 (=C-H), 2860 (-CH) 1660 (C=C), 1740 (C=O, characteristic of 4 membered carbonyl), 1600, 1500, 860, 740 (aryl).

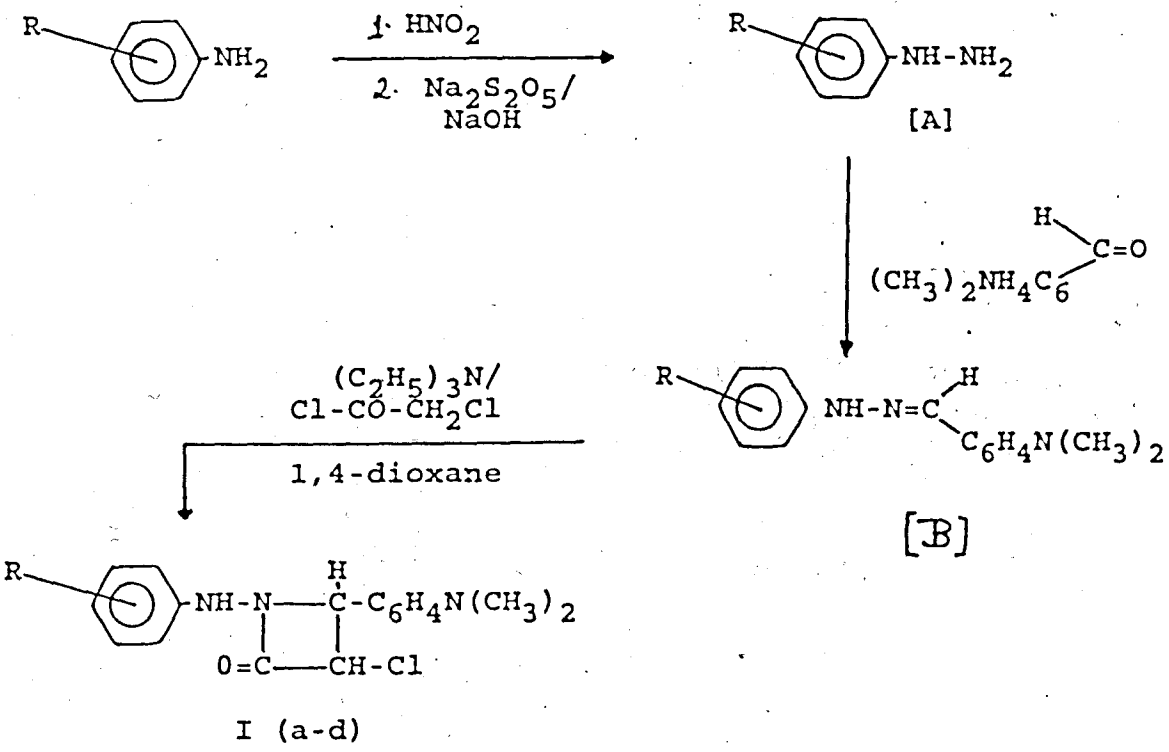
^{1}NMR (CDCL + DMSO-d_6) ppm: 1.4 (s, 3H, CH_3), 2.4 (H, CHC_6H_5),
3.2-3.4 (d, 1H, CHC_6H_5), 7.5-7.65 (m, Ar-H), 10.2 (H,NH, C_6H_5).

METHODS

General Method for Antibacterial Screening: The method employed for antibacterial activity was the agar diffusion technique[5] involving paper disc method. Bacterial cultures used for the study were *E.coli* (445), *Pseudomonas diminuta* (MTCC 1609) and *Bacillus substilis* (MTCC 441).

*For correspondence

An overview of their synthetic pathway is depicted in Scheme-I



R =

-H, $-NO_2$, -Cl, $-CH_3$,

SCHEME 1

Antibacterial Screening

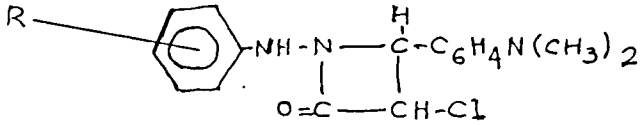
All the bacterial strains were maintained on nutrient agar slants[6]. Culture was inoculated in peptone water and incubated overnight. All the synthesised compounds were screened for antibacterial activity at 0.25 - 1.00 m/M100 ml. all the screening results were evaluated in terms of the zone of inhibition in cm. The percent inhibition has been calculated using the formula; % inhibition = ($\propto$-β) / $\propto$ x 100, where $\propto$ and β stands for inhibition zone of control drug (Sulphamethoxole has been used as the control drug) and inhibition zone of azetidin-2-one derivatives, respectively.

RESULTS AND DISCUSSION

A systematic perusal of data presented in Table-1 reveals that maximum inhibition is found against *E.coli* and in the series N-(4'-nitro) phenylamino-3-chloro-4-(4'-dimethylamino) phenyl azetidin-2-one is found to be a more potent antibacterial agent.

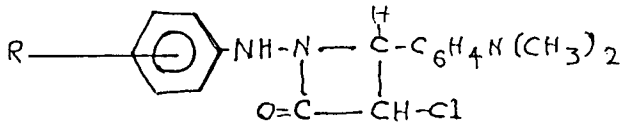
To study quantitative structure activity relationships (QSAR) molecular refractive index (M_R) has been calculated by the method of Dreishach[7] and reported in Table 2. A parasol of data reveals that M_R is correlated linearly to the drug activity [A][8] for activity against E.coli, the equation is [A] = 0.45 + 0.92 x $^{M}{}_{R}$ with correlation of cofficient of 0.992.

Table 1 : Antibacterial activity of N-arylamino-3-chloro-4-(4' dimethylamine) phenyl azetidin-2-ones



Compound		LD_{50} mg/Kg	Organism	control drug ∝cm	Azetidin -2-one cm^{β}	% inhibition ∝-β/∝ x 100
Ia		18.10	*P. dimunita*	2.2	2.3	-04.54
	-H		*B. subtilis*	2.8	2.5	+10.71
			E.coli	2.4	2.8	-16.66
Ib			*P. dimunita*	2.2	2.9	-31.81
	$-NO_2$	20.14				
			B. subtilis	2.8	2.9	-03.57
			E.coli	2.4	3.3	-37.50
Ic			P. dimunita	2.2	2.7	-22.72
	-Cl	14.14	*B.subtilis*	2.8	2.2	-21.42
			E.coli	2.4	3.5	-45.83
Id			*P. dimunita*	2.2	3.3	-50.00
	$-CH_3$	25.18				
			B. substilis	2.8	2.9	-03.57
			E.coli	2.4	2.5	-04.16

Table 2 : Characteristic data of N-arylamino-3-chloro-4-(4' dimethylamine) phenyl azetidin-2-ones



Compd	R	M_R	M.P °C	Yield %	C Calc % (found %)	H	N
Ia	H	39.100	244	62	64.86 (64.32)	5.40 (4.94)	13.35 (13.00)
Ib	$-NO_2$	45.309	249	67	56.58 (55.64)	4.71 (4.70)	15.53 (15.43)
IC	- Cl	43.976	248	60	56.04 (55.67)	4.67 (4.70)	15.38 (15.38)
Id	$- CH_3$	43.727	246	56	65.5 (65.45)	6.06 (6.00)	12.74 (12.72)

Procedure For The Determination of LD_{50}

Before screening for above activities, substituted azetidin-2-one comounds were subjected to acute toxicity studies to find out LD_{50}. During which, 10 rats were considered in each group and were observed for 72 h. According to the toxicity studies, the LD_{50} value and the magnitude of toxicity are inversely related to each other i.e. the smaller the LD_{50} value, the more toxic the chemical. All the synthesised compound did not show any toxicity upto a dose of 8.1 mg / kg in rats. LD_{50} for each synthesised compound is depicted in the table 1.

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