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Studies of antimicrobial activity of some new-3-chloro-4-phenyl azetidine-2-ones

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Abstract
In this paper studies the Various 4-benzylideneazanyl-N or N,N-disubstituted benzene sulfonamides (3a-j) have been prepared by condensation of 4-amino-N- or N,N-disubstuted benzene sulfonamide (2) with benzaldehydes. These on cyclocondensation reaction of (3a-j) with chloroacetylchloride afforded N-(4-N or N,Ndisubstituted amino sulfonyl phenyl)-3-chloro-4-phenyl azetidine-2-ones (4a-j). Biological screening of the prepared compounds have been carried out on some strains of bacteria.

Keywords: N,N-disubstituted benzene sulfonamides, cyclocondensation, azetidine.

Introduction
Azetidine and their derivatives have been established as medicinal chemicals [1, 2]. Azetidine 2-ones also have great importance because of the use of β-lactam derivatives as an antibacterial agents [3]. More particularly and recently these types of compounds have been found in the treatment of tuberculosis and other chemotherapeutic disease [4]. The area in which these type of compound containing $–SO_2NH$-group has not received attention in spite of well defined drug activity of Sulfonamide drug. Merging of both azetidine (i.e. as anti T.B.) and sulfonamide (i.e. as antibacterial) moieties may enhance the drug activity of the compound up to some extent. Hence it was thought in term to study new sulfonamides and their azitidine derivative. The produced work is scanned in the Scheme-1.

Biological screening
Antimicrobial activities- Antimicrobial activities of all the compounds were studied against Grampositive bacteria (Bacillus subtilis and Staphylococcus aureus) and Gram-negative bacteria (Escherichia coli, Salmonella typhi, Klebsiella promioe) at a concentration of 50 µg/ml. by Agar cup plate method methanol system was used as control in this method. Under similar conditions control experiment was carried out by using sulfonamide as a standard for comparison. The area of inhibition of zone measured in cm. compounds 4e, 4h and 4j were found more active against the above microbes. Other compound found to be less or moderate active then sulfonamide (Table 2). Further work in connection with this study against human pathology is under progress.

Experimental
Melting point were determined in open capillary tubes and are uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400 D spectrophotometer and 'H NMR spectra in $CDCI_3$, on Hitachi R-1500, 60 MHz Spectrometer using TMS as an internal standard. The required 4-acetamidobenzenesulphonylchloride prepared by method. All chemicals used were of laboratory grade.

Preparation of 4-acetamido-N- or N,N-disubstituted benzene sulfonamide (1)
General procedure-Primary or secondary amine (0.05 mole) was dissolved in a mixture of 40 ml anhydrous acetone and 1 ml of dry pyridine in 250 ml flask and 11.67 gms (0.05 mole) of pure 4-acetamidobenzenesulfonylchloride (ASC) was

Table 1: Analytical and spectral data of compound (4a-j)

Compd.	Molecular Formula	Yield (%)	M.P.	Analysis % Found (Calcd.)				PMR
				%C	%H	%N	%S	
4a	$C_{17}H_{17}CIN_2O_3S$	52	142	56.02 (56.4)	4.50 (4.67)	7.48 (7.67)	8.65 (8.79)	2.39 (6H,S, 2CH), 2.5 (1H,d,C_4-H), 7.5-8.0 (9H, m, aromatic proton)
4b	$C_{19}H_{21}CIN_2O_3S$	48	123	58.06 (58.16)	5.23 (5.35)	7.02 (7.14)	8.02 (8.16)	1.2-1.5 (6H,t,2CH,). 2.6 (1H,D,C_4-H), 3.0 (1H, d. C_3-H), 3.4-3.6 (4H, q. $2CH_2$), 6.9-7.5 (9H, m,aromatic protons)
4c	$C_{27}H_{21}CIN_2O_3S$	50	138	63.60 (63.65)	4.06 (4.12)	5.35 (5.50)	6.15 (6.28)	2.3 (1H,d.C_4-H), 3.4 (1H,d, C_3-H), 6.8.-7.9 (19H, m, aromatic proton)
4d	$C_{21}H_{16}CIN_2O_3S$	38	120	61.05 (61.16)	4.04 (4.12)	6.65 (6.79)	7.65 (7.76)	2.1(1H,d, C_4- H), 3.2 (1H,d, C_3-H), 7.5-8.0 (14H,m, aromatic proton), 11.4 (1H,S,-$NHSO_2$)
4e	$C_{21}H_{16}CI_2N_2O_3S$	54	162	56.35 (56.50)	3.42 (3.58)	6.15 (6.27)	7.04 (7.17)	2.3 (1H,d, C_4-H), 3.0 (1H,d, (13,m, aromatic proton), 11.2 (1)
4f	$C_{21}H_{15}CI_3N_2O_3S$	60	158	52.40 (52.50)	3.04 (3.12)	5.75 (5.83)	6.54 (6.66)	2.4 (1H,d, C_4-H), 3.3 (1H,d, (12,m, aromatic proton), 11.4 (1)
4g	$C_{21}H_{17}CI_3N_2O_3S$	48	145	52.30 (52.50)	2.98 (3.12)	5.72 (5.38)	6.56 (6.66)	2.1 (1H,d, C_4-H), 3.2 (1H,d, (12,m, aromatic proton), 11.2 (1)
4h	$C_{22}H_{19}CIN_2O_4S$	42	136	56.15 (56.25)	3.68 (3.79)	6.13 (6.25)	7.05 (7.14)	2.5 (1H,d, C_4-H), 3.4 (1H,d,C_3-OH), 6.8-7.2 (13,m, aromat) (1H,s-$NHSO_2$)
4i	$C_{22}H_{19}CIN_2O_3S$	54	148	59.05 (59.19)	4.12 (4.26)	6.15 (6.27)	7.01 (7.17)	2.4 (3H,s, CH_3), 2.3 (1H,d,C_4-H), 6.5-7.5 (13,m, aromatic protons, -$NHSO_2$)
4j	$C_{17}H_{17}CIN_2O_4S$	62	132	57.00 (57.14)	4.03 (4.12)	5.97 (6.06)	6.86 (6.92)	2.3 (1H,d, C_4-H), 3.6 (1H,d,C_3-OCH_2), 6.5-7.5 (13,m, aroma) (1H,s-$NHSO_2$)

Table 2: Antimicrobial activity of compound (4a-j)

Inhibitions zone of compound	Gram +ve		Gram –ve		Escherichia coli
	Bacillus subtillis	Staphlococcus aureus	Klebsiella Promioe	Salmonella typhi	
4a	++	+	++	+	++
4b	+	++	+++	++	+++
4c	+++	+++	+++	+++	+++
4d	+++	+++	++	+++	++
4e	+++	++	+++	++	++
4f	++	+	+++	++	+
4g	+	+++	+	+	+++
4h	+++	+++	+++	++	+++
4i	++	+	+++	++	+
4j	++	+++	++	+	+++
sulfonamid	+++	+	+++	++	+++
+++ highly active	++ moderately active				+ less active

slowly added into it. Sodium bicarbonate was added as an acid acceptor. The reaction mixture is set aside overnight and almost pure 4-acetamido-N-or N,N-disubstituted benzene sulfonamide is filtered off and washed with cold water and air dried. It was then recrystallised form methylated spirit to give white product (1) in 60-75% yields.

Preparation of 4-amino-N- or N,N-disubstituted benzene sulfonamide (2)

General procedure- 4-acetamido-N- or N,N disubstituted benzene sulfonamide was hydrolyzed by refluxing with 75 ml of ethanol containing 15 ml conc. HCl for 4-5 hrs. It was then poured into ice cold water and finally just alkaline with liq. ammonia. The resultant product 4-amino-N-or N,N-disubstituted benzene sulfonamide is filtered off and washed with water and air dried. It was then recrystallized from ethanol to give white product (2a-j) in 55-60% yield.

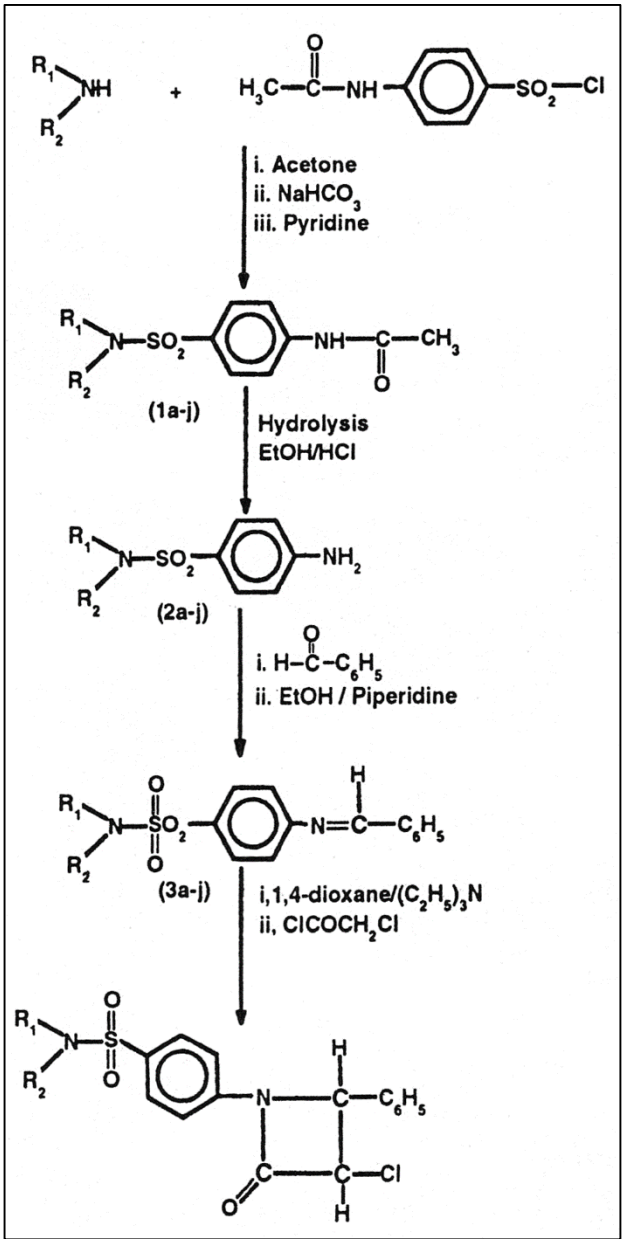

Fig 1: Scheme

Where,

	R_1	R_2		R_1	R_2
(a)	CH_3	CH_3	(f)	H	2,5-Cl-C_6H_3
(b)	$C2H_5$	$C2H_5$	(g)	H	2,4-Cl- C_6H_3
(c)	C_6H_5	C_6H_5	(h)	H	P-OH- C_6H_3
(d)	H	C_6H_5	(i)	H	P-CH_3-C_6H_3
(e)	H	P-Cl- C_5H_4	(j)	H	O-OCH_3-C_6H_3

Preparation of 4-benzylideneazanyl-N or N,N disubstituted benzene sulfonamide (3a-j)

General procedure- A mixture of equimolecular amount (0.01 mole) of 4-amino-N- or N,N-disubstituted benzene sulfonamide and one of benzaldehyde in ethanol (40 ml) and piperidine (0.3 ml) was refluxed for 3 hrs. on a water-bath. The reaction mixture was concentrated, cooled and it was poured into water and the solid obtained was filtered and recrystallised from ethanol to give yellowish white product 4-benzylideneazanyl-N or N,N-disubsituted benzene sulfonamide (3a-j) was obtained into 40-50% yield.

Preparation of N-(4-N or N,N-disubsituted amino sulfonyl phenyl)-3-chloro-4-phenyl azetidine-2-ones (4a-j)

General procedure- A mixture of 4-benzylideneazanyl-N or N,N-disubstituted benzene sulfonamide (3a-j). (0.002 mole) and triethylamine (0.004 mole) was dissolved in 1,4-dioxane (50 ml). To this well stirred cooled solution chloroacetylchloride (0.004 mole) was added drop wise during 20 minute. The reaction mixture was then stirred for further 3 hrs, and left at room temperature for 48 hours. The resultant mixture was concentrated, cooled, then poured into cold water and dried. The product thus obtained was purified by column chromatography over silica gel using 30% ethylacetate: benzene as eluent. Recrystallization from ether/n-hexane gave white powdered N-(4-N or N,N-disubstituted amino sulfonyl phenyl)-3-chloro-4-phenyl azetidine-2-ones. (4a-j) were obtained in 38.62% yield. All the compounds were characterized by analytical and spectral data (Table 1) of the compound is assigned as in Scheme 1.

Results and discussion

4-acetamido-N- or N,N-dis.ubstituted benzene sulfonamide (1) were prepared by the condensation of primary or secondary amine with 4-acetamidobenzenesulfonylchloride (ASC) in dry acetone in the presence of pyridine as a catalyst and sodium bicarbonate as an acid acceptor'. The resulted 4-acetamido-N or N,N-disubstituted benzene sulfonamide was hydrolyzed by reported method' and afforded 4-amino-N- or N,N-disubstituted benzene sulfonamide (2) 4-benzylidene azanyl-N or N,N-disubstituted benzene sulfonamide (3a-j) were obtained by the condensation of 4-amino-N- or N,N-disubstituted benzene sulfonamide (2) with benzaldehydes in ethanol in presence of piperidine as a catalyst. Other compounds of the type (3a-j) were obtained in same manner and IR data (bands at 1645 cm' assignable to γC=N) cyclocondensation of (3a-j) with chloroacetylchloride was carried out by method reported [6, 7, 8] and afforded (4a-j) and their structures were established on the basis of elemental analysis (Table 1). The product were characterized as substituted 2-azetidinones which showed bands at 1750-1740 cm^{-1} (C=0) in the IR spectra. The C,H,N analysis of all the compounds of each series are presented in Tables. The values are consistent with their predicted structure (Scheme -1). The FT-IR spectra (not shown here, and also comprises the important band)

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