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Synthesis and Antimicrobial Studies of Azetidinone Derivatives from Naphthylamine Moiety

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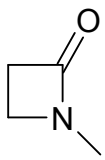
Abstract: A series of five novel azetidinones SAz1 -5 were synthesized by cyclocondensation of various Schiff bases of naphthylamine with chloroacetylchloride in the presence of triethylamine. Schiff's bases preparing from naphthylamine moiety by reacting the hydrazide of the parent compound with different aromatic or heterocyclic aldehydes under acidic conditions in ethanol and cyclocondensation of Schiff's bases with chloracetyl chloride in the presence of triethylamine and dioxane resulted in the formation of corresponding azetidinone derivatives. The newly synthesized compounds were characterized by IR, and mass spectra. The synthesized compounds were evaluated for antibacterial and antifungal activities by Agar diffusion method. All the compounds SAz1 -5 at a concentration of 1000,500,250,125 and 62.5µg/ml and compounds were screened for their antibacterial activity against *Staphylococcus aureus, Bacillus subtilis* (Gram positive bacteria) *Escherichia coli, Pseudomonas aeruginosa* (Gram-negative bacteria) by disk diffusion method. Compounds showed good anti-bacterial activity against *Staphylococcus aureus* and *Bacillus subtilis*. Compounds SAz1 -5 exhibited good antifungal activity against *Candida albicans* fungus.
Keywords: Azetidinones, naphthylamine, anti-bacterial, anti-fungal.

INTRODUCTION:

Azetidinones which are part of antibiotics structure are known to exhibit interesting biological activities. A large number of 3-chloro monocyclic ß-lactam possesses powerful antibacterial, antimicrobial, anti-inflammatory, anticonvulsant & antitubercular activities. They also function as enzyme inhibitors & are effective on the central nervous system. [1-3]



Azetidinone Moiety

They are the carbonyl derivatives of azetidines containing carbonyl group at the position-2. These are also known as 2-azetidinones or more commonly ß-lactam. Azetidinones or ß-lactam chemistry is of great importance because of the use of ß-lactam derivatives as antibacterial agents.[4, 5]

Cycloaddition of monochloroacetylchloride with imines (Schiff base) result in formation of 2-azetidinone (ß -lactam). The reaction involves direct acylation of imine with monochloroacetylchloride. The reaction is carried out with base as triethylamine gives β-lactams.[5] Although variety of drugs have been developed for treating bacterial and fungal diseases, the basic difficulty experienced with these infections are the rapid development of drug résistance to the infectious strains. Review of literature reveals that 2-

azetidinones are reported to possess significant antitubercular, antibacterial & antifungal activities. P-anisidine, which is aniline derivative have been found to be biologically interesting compound for many years. Since 2- azetidinones of p-anisidine are not available, these derivatives can be done and resulting analogues are tested for their antimicrobial activity. The β-lactam heterocyclic 2-azetidinones are still the most prescribed antibiotics used in medicine. A large number of 3-chloro monocyclic β-lactam having substituents at position land 4 possess powerful antimicrobial antibacterial, sedative, anticonvulsant activity. They also function as central nervous system. In recent past these derivative are also found to be moderately active against several types of cancer and HIV.

Large number of 2-azetidinones containing β-lactam moiety, its activity is greatly influenced by different substituents. A large number of 3-chloromonocylic β-lactam possess powerful antibacterial, anti-inflammatory, antifungal, antimicrobial, analgesic, sedative, anticonvulsant antitubercular and herbicidal activities.

EXPERIMENTAL:[6-11]

In the present study, some azetidinone derivatives have been synthesized and screened for their biological activities. The progress of reaction was monitored by thin layer chromatography using plate coated silica gel G of 0.25 mm thickness. Eluents used were methanol: glacial acetic acid: water (4:1:5) as a solvent system and ethanolic sulphuric acid 0.1 M solution was used as spraying agent. Spot were visualized through iodine chamber. Solubility of newly synthesized azetidinone derivatives was determined in various organic solvents at 27± 2 ^{0}C. Melting points was recorded in open glass capillary tubes and are uncorrected. Solvents were purified and dried by standard procedure before use. The IR spectra were recorded on KBr on FTIR Shimadzu perkin-Elmer infrared spectrophotometer. Mass spectras were recorded on Shimadzu LCMS 2010A.

1. SYNTHESIS OF SCHIFF'S BASES:

Naphthylamine moiety was converted in to respective shiff's bases:

STEP- 1: PREPARATION OF NAPHTHYLAMINE MOIETY ETHYL ACETAT

A mixture of naphthylamine moiety (0.1 mole), ethylchloroacetate (0.1 mole) and anhydrous potassium carbonate (19.5 gm, 0.15 mole) in dry ethanol was refluxed on a water bath for 24 hours at 70 ^{0}C. The resultant reaction mixture was cooled and filtered. Excess of ethanol was then removed by distillation from this filtrate. This reaction mixture was poured on to the ice-cold water and stirred well. The organic layer was allowed to extract with ether and ether layer was then washed with 5% HC1 and dried over anhydrous sodium sulphate. The ether layer was evaporated on water bath. Finally the resultant liquid was collected and purified under reduced pressure to give pure naphthylamine ethylacetate.

STEP-II: PREPARATION OF NAPHTHYLAMINE ACETYL HYDRAZIDE:

A mixture of naphthylamine ethylacetate (0.05 moles), hydrazine hydrate (99%, 0.07 mole) in ethanol (100 ml) was refluxed for 6 hours. From the resultant mixture, excess of ethanol was removed by distillation. On cooling, white needle like crystals of naphthylamine acetyl hydrazide began to separate from the resultant mixture. The crystals so obtained, were recrystallized with ethanol, collected and then again recrystallized from ethanol.

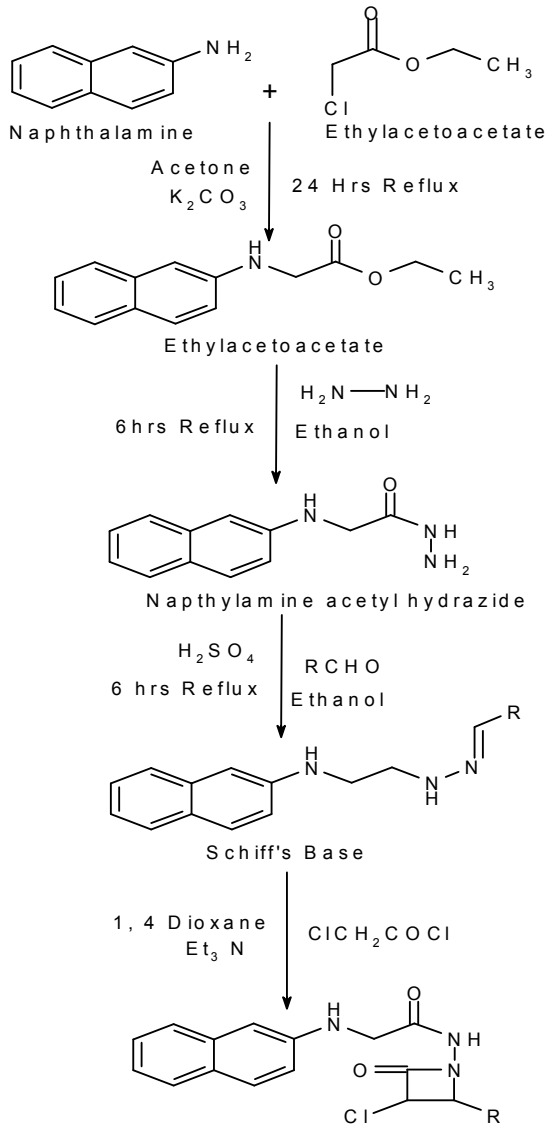
STEP-III: PREPARATION OF SCHIFF'S BASES OF A NAPHTHYLAMINE ACETYL HYDRAZIDE:

Naphthylamine acetyl hydrazide (0.01 mole) was dissolved in 10 ml of ethanol and different aromatic or heterocyclic aldehydes (0.01 mol, dissolved in minimum quantity of ethanol (10 ml)) were refluxed together by employing sulphuric acid (0.01 moles) as catalyst in a round bottom flask on water bath for 6 hours. The precipitate, so obtained, was then filtered, washed with ice-cold water and recrystalized by with ethanol.

2. SYNTHESIS OF AZETIDINONE ANALOGS:

Chloroacetylchloride was added drop wise to Schiff's base (0.01 moles) and triethylamine (0.02 ml) in dioxane (25 ml) was added to this at 5-10 ^{0}C. The reaction mixture was then stirred for 20 hours and kept at room temperature for three days. The obtained product was filtered, dried and recrystallized by using ethanol.

SCHEME



Azetidinone Derivative

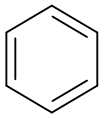
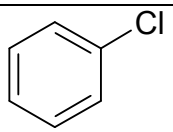
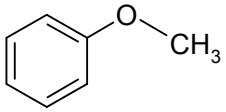
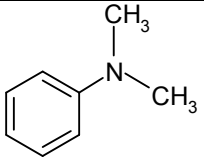
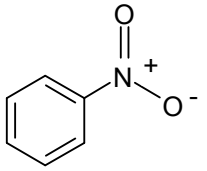
S.No.	Compounds	R
1.	SAz1	
2.	SAz2	
3.	SAz3	
4.	SAz4	
5.	SAz5	

Table 1: Physical data of Azetidinone derivatives derived from naphthalamine moiety

S.No.	Compounds	Molecular weight	Physical state	Rf values	M.P. (^{0}C)	% Yield
1	SAz1	379.50	Cream colored crystals	0.72	280-210^{0}C	65.0%
2	SAz2	414.28	Yellow orange crystals	0.54	203-205^{0}C	74.5%
3	SAz3	393.50	Brown crystals	0.62	205-207^{0}C	72.5%
4	SAz4	422.50	Reddish brown crystals	0.64	215-217^{0}C	60.5%
5	SAz5	424.50	Brown Crystals	0.69	228-230^{0}C	70.8%

RESULTS & DISCUSSION:

N^1–[3-Chloro-4phenyl-2oxo-azetidin-1-yl]-2 (-naphthylamine) acetamide (SAz1)

IR (KBr, cm^{-1}): 3228.0 (N-H stretching), 3045.0 (C-H stretching), 1749.4 (C=O stretching of azetidinone ring), 1672.2 {CO stretching of CO-NH (amidyl)}, 1420.0 (C-N stretching), 832.8 and 779.8 (C-C stretching), 689.2 (C-Cl stretching).
MS (m/z): M^+ calculated 379.50

N^1-[3-chloro-4(4-chloro-phenyl)-2-oxo-azetidin-1-yl]-2(naphthylamine)acetamide (SAz2)

IR (KBr, cm^{-1}): 3469.6 (NH stretching), 3054.0 (CH stretching), 1756.8 (C=O stretching of azetidinone ring), 1670.8 (C=O Stretching of CO-NH), 1444.4 (C-N stretching), 854.5, 689.2(C=C of aromatic ring), 689.2 (C-Cl stretching).
MS (m/z): M^+ calculated 414.28

N^1-[3-chloro-4(4-methoxyphenyl)-2-oxo-azetidin-1-yl]-2(naphthylamine) acetamide (SAz3)

IR (KBr, cm^{-1}): 3449.5 (NH stretching), 3045.0 (CH stretching); 1757.1 (C=O stretching of azetidinone ring), 1622.9 (C=O Stretching of CO-NH), 1446.7(C-N stretching), 894.5, 750.5 and 677.8 (C=C bending), 677.8 (C-Cl stretching).
MS (m/z): M^+ calculated 393.50

N^1–[3-Chloro-4-(4-dimethylaminophenyl)-1-oxo-azetidin-1-yl]-2-(naphthylamine) acetamide (SAz4)

IR (KBr, cm^{-1}): 3238.0 (N-H stretching), 3049.0 (C-H stretching), 1750.4 (C=O stretching of azetidinone ring), 1673.2 {CO stretching of CO-NH (amidyl)}, 1422.0 (C-N stretching), 834.5 and 779.8 (C-C stretching), 619.9 (C-Cl stretching).
MS (m/z): M^+ calculated 422.50

N^1–[3-Chloro-4-(4-ntrophenyl)-2-oxo-azetidin-1-yl]-2-(naphthylamine) acetamide (SAz5)

IR (KBr, cm^{-1}) 3450.5 (NH stretching), 3047.0 (CH stretching), 1754.1 (C=O stretching of azetidinone ring), 1624.9 (C=O Stretching of CO-NH), 1448.7 (C-N stretching), 896.5, 750.5 and 677.8(C=C bending), 679.8 (C-Cl stretching).
MS (m/z): M^+ calculated 424.50.

IN VITRO ANTIMICROBIAL SCREENING

The synthesized compounds were subjected to antimicrobial Screening by cup plate method for zone of inhibition. The antibacterial activity was tested against various gram positive and Gram negative bacteria and anti fungal activity against various fungal stains compared with standard drug (Ampicillin and Griseofulvin) using solvent control. The results were described in the Table: 2 & 3.

The synthesized compounds were subjected to biological evaluations. The compounds were evaluated for antibacterial and antifungal activities. The activity studies suggest that novel azetidinone derivatives compounds had showed moderate antibacterial and antifungal activity. The activity of β–lactam moiety was greatly influenced by substituents or fused rings.

Table 2: Data of antimicrobial activity of azetidinone derivatives

S. No.	Compound	Diameter of zone of inhibition (mm)				
		B .subtilis	*S. aureus*	*E .coli*	*P. aerugenosa*	*C .albicans*
1	SAz 1	12	12	12	10	8
2	SAz 2	15	18	16	15	16
3	SAz 3	14	19	17	14	15
4	SAz4	14	18	15	15	12
5	SAz5	12	12	12	10	14
Ampicillin		16	20	18	15	--
Griseofulvin		--	--	--	--	16

Table 3: Data of antibacterial and antifungal activity of synthesized azetidinone derivatives

S. No.	Comp. No.	*B. subtilis*				*S. aureus*				*E. coli*				*P. aeruginosa*				*C .albicans*			
Dilution		I	II	III	IV-V	I	II	III	IV-V	I	II	III	IV-V	I	II	III	IV-V	I	II	III	IV-V
1	SAz 1	-	+	+	+	-	-	+	+	-	+	+	+	-	-	+	+	-	-	+	+
2	SAz 2	-	-	-	+	-	-	-	+	-	-	-	+	-	-	-	-	-	-	-	+
3	SAz 3	-	-	-	+	-	-	-	+	-	-	-	+	-	-	-	+	-	-	-	+
4	SAz 4	-	-	-	+	-	-	-	+	-	-	+	+	-	-	-	+	-	-	+	+
5	SAz 5	-	-	-	+	-	-	+	+	-	-	+	+	-	-	-	+	-	-	+	+
Ampicillin		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
Griseofulvin																		-	-	-	-

I-1000µg/ml, II-500µg/ml, III-250µg/ml, IV-125µg/ml, V-62.5µg/ml
(-) indicates absence of growth; (+) indicates presence of growth.

Fig I- The bacterial screening indicated that among the compound no. SAz2, SAz3 & SAz4 moderately activities against all tested bacterial strain *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa*.

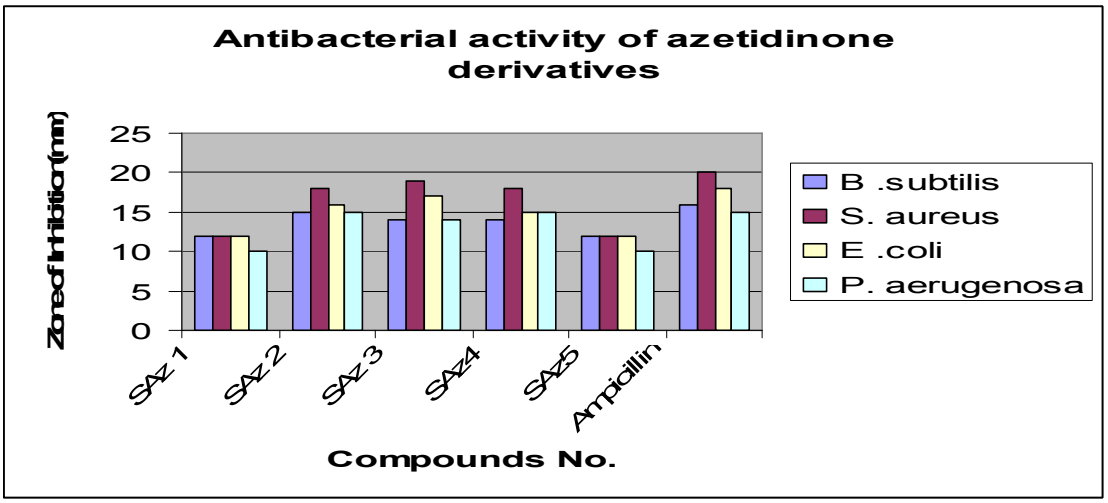
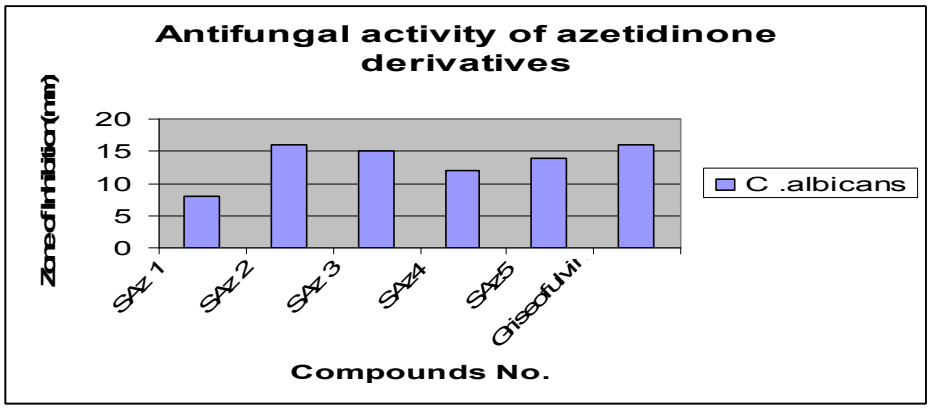


Fig. II- Antifungal screening indicated that among the compound no. SAz2, SAz3 & SAz5 reveled that the test compounds showed moderate activity against *Candida albicans*



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Based on the above observation, it may be postulated the presences of nitro and methoxy group on the azetidinone may be responsible for significant antimicrobial activity.

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