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Synthesis and Characterization of 3-Chloro-1-(7-nitrobenzothiazole-2-yl) - 4 - substituted phenyl azetidin- 2 - one

KEYWORDS: Schiff's base, ionic Liquid, 2-azetidinone

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ABSTRACT *Novel 3-Chloro-1-(7- nitrobenzothiazole-2-yl)- 4- substituted phenyl azetidin-2-one compounds were synthesized by condensing Chloroacetyl chloride with Schiff's base using ionic Liquid. The resulting compounds were characterized by IR, 1H-NMR and Mass spectroscopy. All the compounds have been screened for their antimicrobial activities.*

Introduction
2-Azetidinones, commonly known as β-lactams, are well-known heterocyclic compounds among the organic and medicinal chemists[1-3]. The activity of the famous antibiotics such as penicillins, cephalosporins and carbapenems are attributed to the presence of 2-azetidinone ring in them. Recently, some other types of biological activity besides the antibacterial activity have been reported in compounds containing 2-azetidinone ring[4,5] . Such biological activities include antifungal, antitubercular, antitumor, cholesterol absorption inhibition and enzyme inhibition activity. The β-lactams also serve as synthons for many biologically important classes of organic compounds. In organic synthesis Schiff bases serves as an intermediate and also useful in forming azetidinones[6,7] . Schiff bases were found to posses lot of pharmacological activities such as antimicrobial, antidiabetic, antitubercular, antitumor, antiviral, antimalarial, anticonvulsant, anti-HIV . It has been reported that Schiff bases were prepared by condensing primary amine (or diamine) with aldehyde by conventional, microwave or by simple grinding in presence of catalysts such as glacial acetic acid, conc. Sulphuric acid , DMF , zinc chloride in presence of solvents such as ethanol, methanol, water or in solvent-free conditions . Ionic liquid finds a wide application as green catalyst and medium for a variety of reactions. It has been reported that usage of ionic liquid results in better yield and easy separation of product. By considering the various applications and various preparative routes of Schiff's bases, we aimed to synthesize Schiff's bases from various primary amines and aldehydes in presence of ionic liquid at room temperature by simple stirring. Subsequently, the substituted 2 -Azetidinones were prepared from Schiff's bases.

Experimental
Synthesis of 2- amino substituted benzothiazole:
0.02mole of substituted aniline and 0.02mole of KSCN was dissolved in 20ml glacial acetic acid stirred for 20 min in an ice bath. To this 0.05M bromine in glacial acetic acid was added in small quantities for about 105min with constant stirring at 0^0C. After the complete addition of bromine, the mixture was stirred for 2 hrs in cold condition. Then the reaction mixture was left overnight. To the reaction mixture 6 ml of water was added and heated in water bath at 85^0C for about 30 min and filtered in hot condition. The residue was placed in reaction vessel and to it 10 ml of glacial acetic acid was added and heated at 85^0C in water bath for about 30 min and filtered. The above water and glacial acetic acid filtrate was mixed and cooled. To that conc. ammonia was added at 0^0C till the pH becomes 6. Then the precipitate obtained was filtered and dried.

Preparation of Ionic liquid [$AMPS^-$ $N(Et_3)$]:
The [$AMPS^-$ N (Et_3)] ionic liquid was prepared by the reaction of equal amount of AMPS and triethylamine. The mixture was stirred at room temperature, resulting a viscous liquid.

I. Preparation of 3-Chloro-1-(7- nitrobenzothiazolyl)- 4-methoxy phenylazetidin-2-one (2a)
(i) Synthesis of 7-nitro-[2-(4'-methoxyphenyl)-methylene] aminobenzothiazole (Schiff bases) ,(1a):
A mixture containing 0.01 mole of 7-nitro-2-aminobenzothiazole and 0.01mole of p-Methoxy benzaldehyde and 0.05g of ionic liquid in 10ml ethanol was stirred at room temperature for 3hrs and the resultant mixture was washed with water, filtered and dried.

(ii) Formation of 3-Chloro-1-(7- nitrobenzothiazolyl)- 4-methoxy phenylazetidin-2-one from Schiff's base(2a)
To 0.005 mole of 7-nitro-[2-(4'-methoxyphenyl)-methylene] amino benzothiazole in 15 ml of ethanol and 0.005 mole of triethylamine was added drop wise at room temperature . To this, 0.005mole of chloroacetyl chloride was added in drops for 1 hr and stirred further for 4 hrs. Then the reaction mixture was poured into ice-cold water. The precipitate was filtered and dried.

II .Preparation of 3-Chloro-1-(7- nitrobenzothiazolyl)- 4-methylphenylazetidin-2-one (2b)
(i) Synthesis of 7-nitro-[2-(4'-methylphenyl)-methylene] aminobenzothiazole (Schiff bases) ,(1b):
A mixture containing 0.01 mole of 7-nitro-2-aminobenzothiazole and 0.01mole of p-Methyl benzaldehyde and 0.05g of ionic liquid in 10ml ethanol was stirred at room temperature for 3hrs and the resultant mixture was washed with water, filtered and dried.

(ii) Formation of 3-Chloro-1-(7- nitrobenzothiazolyl)- 4-methyl phenylazetidin-2-one from Schiff's base(2b)
To 0.005 mole of 7-nitro-[2-(4'-methylyphenyl)-methylene] amino benzothiazole in 15 ml of ethanol and 0.005 mole of triethylamine was added drop wise at room temperature . To this, 0.005mole of chloroacetyl chloride was added in drops for 1 hr and stirred further for 4 hrs. Then the reaction mixture was poured into ice-cold water. The precipitate thus formed was filtered and dried.

III .Preparation of 3-Chloro-1-(7- nitrobenzothiazolyl)- 4-p-hydroxy phenylazetidin-2-one (2c)
(i) Synthesis of 7-nitro-[2-(4'-hydroxy phenyl)-methylene] aminobenzothiazole (Schiff bases) ,(1c):
A mixture containing 0.01 mole of 7-nitro-2-aminobenzothiazole and 0.01mole of p-hydroxy benzaldehyde and 0.05g of ionic liquid in 10ml ethanol was stirred at room temperature for 3hrs and the resultant mixture was washed with water, filtered and dried.

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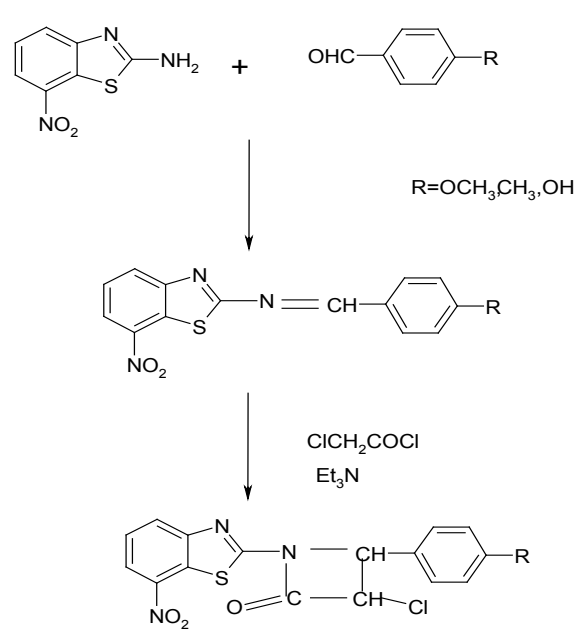
(ii) Formation of 3-Chloro-1-(7- nitrobenzothiazolyl)- 4-hydroxy phenylazetidin-2-one from Schiff's base(2c)
To 0.005 mole of 7-nitro-[2-(4'-hydroxyphenyl)-methylene] amino benzothiazole in 15 ml of ethanol and 0.005 mole of triethylamine was added drop wise at room temperature . To this , 0.005mole of chloroacetyl chloride was added in drops for 1 hr and stirred further for 4 hrs. Then the reaction mixture was poured into ice-cold water. The precipitate thus formed was filtered and dried.

Antimicrobial studies:
Test-microorganisms
Gram negative Klebsiella pneumoniae and Pseudomonas aeruginosa, Gram positive Bacillus subtilis and Staphylococcus aureus and Candida albicans were used for in vitro antimicrobial activity. These selected pathogenic strains were obtained from clinical microbiological laboratory (R&D Centre, Jayagen Biologics, Chennai).

In vitro antimicrobial activity
The antimicrobial activity was determined by agar well diffusion (Perez et al., 1990). About 25 mL of molten Mueller Hinton Agar was poured into a sterile Petri plate (Himedia, Mumbai, India). The plates were allowed to solidify, after which 18 h grown (OD adjusted 0.6)100 µl of above said pathogenic cultures were transferred onto plate and made culture lawn by using sterile L-rod spreader. After five min setting of the bacteria, there were five wells made in the plates using the sterile cork-borer (5 mm). The test samples were dissolved in 10% Dimethyl sulfoxide (DMSO) at various concentrations (i.e. 25, 50, 100 and 200 µg/mL). The wells were loaded with various concentrations of test samples and Streptomycin (30 µg/mL) added well served as control. The plates were incubated at 37°C in a 40 W florescent light source (~ 400 nm) for 24 h. The antimicrobial activity was determined by measuring the diameter of the zone of inhibition around the well using antibiotic zone scale (Himedia, Mumbai, India).

Results and discussion
The schematic representations of Azetidin-2-ones are shown below:

compound	R (aldehyde)
1a,2a 1b,2b 1c,2c	p –methoxy benzaldhyde p-methyl benzaldehyde p-hydroxy benzaldehyde



The synthesized compounds were characterized by IR, NMR and Mass spectroscopy.

I. 3-Chloro-1-(7- nitrobenzothiazolyl)- 4- methoxy phenylazetidin-2-one
The 3-Chloro-1-(7- nitrobenzothiazolyl)- 4- methoxy phenylazetidin-2-one was prepared by condensation of 7-nitro-[2-(4'-methoxyphenyl)-methylene] amino benzothiazole with chloroacetyl chloride .The spectral characterizations are as follows:

IR spectral values (cm^{-1}) :C-N(1030);C-NO_2(1523); C-S(610); Ar C-H(3065);C=O(1628);C-Cl(739);N-CH (970);OCH_3(1258)

^{1}H-NMR spectral values (δ): 3.59 for (S ,3H,-OCH_3) ;4.33 for (S ,1H, CH –Cl); 7.6-7.9(m , 7H ,Ar CH); 8.59 (S, 1H, N=CH-Ar).

Mass (m/z) : 389,358,354,343,282,207,182(100 %), 155,109, 100 and 92 .

II. 3-Chloro-1-(7- nitrobenzothiazolyl) - 4- methyl phenylazetidin-2-one
The 3-Chloro-1-(7- nitrobenzothiazolyl)- 4 - methyl phenylazetidin-2-one was prepared by condensation of 7-nitro-[2-(4'-methylphenyl)-methylene] amino benzothiazole with chloroacetyl chloride .The spectral characterizations are as follows:

IR spectral values (cm^{-1}) : C-N(1030);C-NO_2(1532); C-S(610); Ar C-H(3065);C=O(1682);C-Cl(739);N-CH (970);CH_3(2910)

^{1}H-NMR spectral values(δ):2.48 (3H,-CH_3); 4.33 for (S,1H, CH –Cl); 7.6-7.9(m , 7H ,Ar CH); 8.59 (S,1H, N=CH-Ar).

Mass (m/z) : 373,358,338, ,282, 247, 191, 182(100%) ,145 and 100 .

III. 3-Chloro-1-(7- nitrobenzothiazolyl)- 4- hydroxy phenylazetidin-2-one
The 3-Chloro-1-(7- nitrobenzothiazolyl)- 4- hydroxy phenylazetidin-2-one was prepared by condensation of 7-nitro-[2-(4'-hydroxy phenyl)-methylene] amino benzothiazole with chloroacetyl chloride .The spectral characterizations are as follows:

IR spectral values (cm^{-1}) : Phenolic OH(3380); C-Cl(737) ;C-S(1178,678); C=O(1626); C-NO_2(1527); Ar C-H(3010)

^{1}H-NMR spectral values(δ): 4.3 for (S,1H, CH –Cl); 7.4-7.9(m , 7H ,Ar CH); 8.8 (S, 1H, N=CH-Ar); 11.0((S, 1H,Ar-OH).

Mass (m/z) : 375,358,340,323,282 , 236, 182(100%) , 141 and 100 .

Organism Name	Antimicrobial activity of given sample zone of inhibition (mm)											
	35 BAC (µg/mL)				46 BAC (µg/mL)				47 BAC (µg/mL)			
	25	50	100	200	25	50	100	200	25	50	100	200
Bacillus subtilis	0	0	9	14	12	15	17	19	11	14	16	17
Staphylococcus aureus	9	10	12	14	8	9	11	13	9	11	13	14
Pseudomonas aeruginosa	7	9	9	11	0	7	8	10	6	6	7	9
Klebsiella pneumoniae	0	0	6	7	0	0	6	6	6	7	8	10
Candida albicans	0	7	9	11	0	8	10	12	0	7	7	9

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Antimicrobial studies:
The antimicrobial activity profile of test samples is given in Table 1. The given samples were capable to kill all the tested pathogens ranging from 6 mm to 19 mm of zone of inhibition .Among the bacterial pathogens the test materials active against Gram positive bacteria than Gram negative. Among all the three compounds Hydroxy substituted Azetidin-2-one are more active against both bacteria and fungi.

Table1. Antimicrobial activity of Azetidin-2-ones: (Methoxy(35) , Methyl(46), Hydroxy (47)

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