Synthesis Characterization and Biological Activity of Some Novel Schiff Base Azitidinones

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ABSTRACT

Azitidinone derivatives are found to exhibit various pharmacological activities.on the basis of literature study the main objective of the present work was to synthesise new potent bioactive azitidinone derivatives.I have prepared 6 noval novel schiff base azitidinones. The newly synthesised compounds were analysed IR,NMR,Mass spectral analysis.the entire series of compounds were evaluated for their biological activitiesA total 6 synthesized Azetidinone Derivative compounds were evaluated for anti-bacterial activity bycup plate method at concentrationsof 100,200, and 300µg/ml.Standard was used as Streptomycin,Control was used DMSO.among 6 out of 3are showed the good biological activity.

Keywords: Azitidinone, Schiff base, ß-lactam, Denaturation

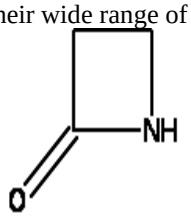
Introduction

Azetidinones

Azetidinone is a four member heterocyclic compound having one nitrogen and one oxygen atom. It is also called as *monocyclic ß-lactam*. Present in antibiotics like penicillin, cephalosporins, carbapenams and monobactums(1).

ß-lactam – An overview

Azetidinone commonly known as ß-lactam, are well known heterocyclic compound among the organic and medicinal chemists. The ß-lactams also serve as synthons for many biologically important class of organic compound(2).The 2-carbonyl derivative of azetidine (fourmember heterocyclic ring with nitrogen as the heteroatom) is designated as 2-azetidinone or, more commonly, ß-lactam.. Azetidines are considered significant owing to their wide range of biological applications.



Schiff bases are the products of condensation of arylamines and carbonyl compounds(3). They are quite stable and versatile intermediates for preparation of a number of important medicinal compounds. Applying principle of condensation on Schiff bases along with chloroacetyl chloride and triethylamine in the presence of 1, 4-dioxan, azetidines are produced(4). Azetidines are widely used in the areas of fine chemicals and medical Submission. Cycloaddition of monochloro acetyl chloride with imine (schiff base) result in formation of azetidinone(ß-lactam). The reaction involves direct acylation of imine with mono chloroacetylchloride(5). The reaction is carried out with base as triethylamine gives -lactams.

Materials and methods

Synthesis of Azetidinone and their derivatives

The Azetidinonederivatives are prepared by Ethyl Nicotinate, Hydrazine Hydrate, 50% Ethanol, Ethyl acetate, Ethanol, Substituted Benzaldehydes, Glacial acetic acid, 1,4- Dioxane, Triethyl amine, chloro acetic acid, crushed ice. And the Procedure involves 3 Steps

Step: 1 Synthesis of Compound: Nicotino Hydrazide

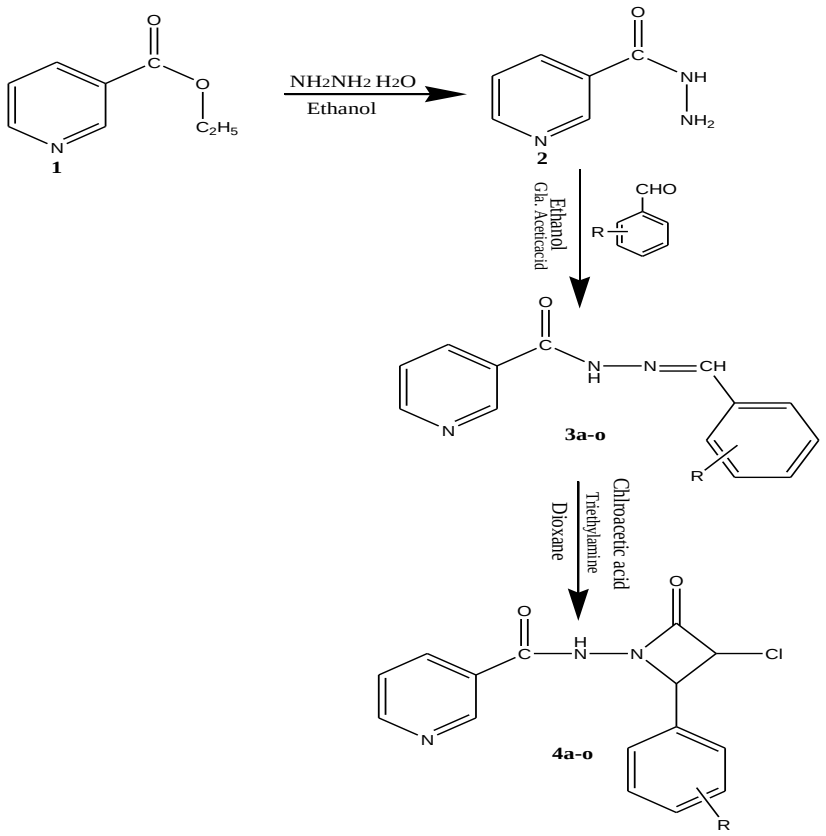
A mixture of 0.1 M (15.1gm) of ethyl nicotinate (compound 1) and 0.2 M(10gm) of hydrazine hydrate with 50% ethanol taken in round bottomed flask and then refluxed for 16 hours. Then the reaction mixture concentrated to half volume and poured it into the crushed ice(6).

Step: 2 Synthesis of Schiff Bases

A mixture of compound 2 (1.47 gm, 0.001 M) and substituted benzaldehydes (0.001M) Were dissolved in absolute ethanol(40 ml) by the addition of a few drops of glacial acetic acid and refluxed for 6 hrs.

Step-3

A Mixture of compounds (step-2) (0.01 mole) in dioxane (10 ml) and triethylamine (0.025 mole) was added chloro aceticacid (0.025 mole) drop wise at 5-10^{0}C(6). Then the reaction mixture was poured into crushed ice. The solid separated was dried and that is recrystallized from ethanol.The purity of the compounds were detected by Thin layer chromatography(TLC).



Physical properties of the synthesized compounds (IV B1-B6)

Comp. Code	Mol.Formula	Mol.Weight (g/mol)	M.P(^{0}C)	%Yield	R_fValue*
B1	$C_{15}H_{11}N_3O_2Cl_2$	336.1	135-137^{0}C	68.51%	0.63
B2	$C_{15}H_{11}N_3O_2ClBr$	380.5	270-272^{0}C	78.92%	0.68
B3	$C_{15}H_{11}N_4O_4Cl$	346.5	278-280^{0}C	72.41%	0.71
B4	$C_{15}H_{12}N_3O_3Cl$	317.5	192-194^{0}C	76.61%	0.72
B5	$C_{15}H_{11}N_3O_2ClF$	319.5	220-222^{0}C	71.35%	0.56
B6	$C_{17}H_{17}N_4O_2Cl$	344.5	264-266^{0}C	69.20%	0.69

Anti Micribial Evaluation

All the synthesized compounds were screened for antibacterial and antifungal activities by agar disc diffusion method with reference to standard drug Streptomycin[7,12].

zone of inhibition by cup plate method of Synthesized Azetidinone Derivatives compounds.

S.No	Comp.Code	Gram+ve			Gram-Ve		
		Bacillus Subtilis(B.S)$^{++}$			*Proteus vulgaris(P.V1)*$^{++}$		
		100µg/ml	**200µg/ml**	**300µg/ml**	**100µg/ml**	**200µg/ml**	**300µg/ml**
1	B1	-	-	-	7	11*	16**
2	B2	9	11	12	-	-	-
3	B3	7	10	15	6	9	13*
4	B4	-	-	-	-	-	-
5	B5	9	13*	16*	-	-	-
6	B6	-	-	-	4	7	10
Control	DMSO	-	-	-	-	-	-
Standard	**streptomycin**	**13**	**15**	**18**	**9**	**13**	**15**

(*)Significant Zone of inhibition;(**) Highly significant Zone of inhibition;
$^{++}$corrected Zone of inhibition:Total zone size –Bore size(8mm)

Anti-Inflammatory Activity by egg albumin denaturation method[13,14]:

A total of 6 Synthesized Azetidinone derivative Compounds were evaluated for anti-inflammatory activity by egg albumin denaturation method at concentrations 100, 200, 300,400 and 500 µg/ml. Diclofenac was used as standard. Phosphate buffer was used as control[8].The results were shown in table

Anti-inflammatory activity of synthesized Compounds(B_1-B_6)

S.NO	Comp.Code	% In 100	%In 200	%In 300	%In 400	%In 500
1	B1	31.6	43.06	51.98	63.87	71.47
2	B2	19.49	33.14	41.85	64.86	78.19
3	B3	23.12	42.07	51.65	67.73	75.99
4	B4	34.8	50.33	57.81	65.96	73.89
5	B5	25.33	41.74	54.07	61.89	76.54
6	B6	34.25	43.17	53.63	66.62	61.34
Standard	Diclofenac	42.4	55.72	65.19	73.89	87

Result & Discussion

A. Synthesis &characterization

Total six azetidinone derivatives were synthesized, those had better yield characterized. The compounds were named based on the structural nomenclature and each compound characteristics are given below;

Azetidinone Derivatives

Comp. Code	Mol. Formula	Spectral data
B1	$C_{15}H_{11}N_3O_2Cl_2$	**FT-IR υmax, cm⁻1: (ATR)** 3465.65 (NH,Ar),3027.48(CH,Str),1723.00(Ar,C=Oketo), 1663.24(Ar,C=O,amide),1482.55(Ar C=C, Str), 1211.38(Ar C-N Str), 786.46(Cl).
B2	$C_{15}H_{11}N_3O_2ClBr$	**FT-IR υmax, cm⁻1: (ATR)** 3371.86(NH,Ar),3011.40(CH,Str),1701.11(Ar,C=Oketo), 1649.06(Ar,C=O,amide),1480.20(Ar C=C, Str), 1293.26 (Ar C-N Bend), 718.65(Cl Str).
B3	$C_{15}H_{11}N_4O_4Cl$	**FT-IR υmax, cm⁻1: (ATR)** 3395.04 (NH,Ar), 3021.28 (CH Str), 1715.42 (Ar,C=O keto), 1654.92 (Ar,C=O,amide), 1510.86 (Ar C=C, Str), 1348.48 (NO_2 Str) 1224.03 (Ar C-N Str), 778.85 (Cl Str), **^{1}H NMR (in DMSO-d6, δ in ppm)** ^{11}CH-Cl=3.924; ^{6}CH=3.489; ^{5}NH= 8.605; ^{4}H=9.11 **^{13}CNMR (in DMSO-d6, δ, in ppm):** ^{8}C-Cl-45.94.; ^{6}C=O(Amide)129.27; $^{10\text{-}15}$(Ar C)-149.21-146.24; ^{4}C=153.96;^{7}C=O(Keto)-162.49; ^{16}C=N=169.18; MASS M/Z – 322.25
B4	$C_{15}H_{12}N_3O_3Cl$	**FT-IR υmax, cm⁻1: (ATR)** 3432.80 (NH,Ar), 3618.37 (OH Str), 3018.13 (CH Str), 1770.57 (Ar,C=Oketo), 1645.62(Ar,C=O,amide), 1512.11 (Ar C=C, Str), 1292.99 (Ar C-N Str), 727.94 (Cl Bend). **^{1}H NMR (in DMSO-d6, δ inppm):** ^{12}CH-Cl=3.435; ^{5}NH= 8.260; ^{4}H=9.06; ^{11}OH=11.853.
B5	$C_{15}H_{11}N_3O_2ClF$	**FT-IR υmax, cm⁻1: (ATR)** 3393.62 (NH,Ar), 3003.10 (CH Str), 1757.20 (Ar,C=O keto), 1683.22 (Ar,C=O,amide), 1506.19 (Ar C=C Bend), 1300.21 (Ar C-N Str),1225.17(C-F Str) 700.04 (Cl Str).
B6	$C_{17}H_{17}N_4O_2Cl$	**FT-IR υmax, cm⁻1: (ATR)** 3436.85.62 (NH,Ar), 3019.25 (CH Str), 1775.04 (Ar,C=O keto), 1652.83 (Ar,C=O,amide), 1515.78 (Ar C=C Bend), 1289.15 (Ar C-N Str), 705.78 (Cl Str).

Anti –Bacterial activity of synthesized Azetidinone Derivatives:

A total 6 synthesized Azetidinone Derivative compounds were evaluated for anti-bacterial activity bycup plate method at concentrationsof 100,200, and 300µg/ml.Standard was used as Streptomycin,Control was used DMSO[11]. Theresults were shown The 6 synthesized derivative compounds in scheme-1,2were evaluated for anti-bacterial activity agents. In compound code B5 were shownsignificant activity against *Bacillus subtilis* at200,300µg/ml concentration, and B2,B3,were shown moderate activity. *Proteus vulgaris* and remaining compounds were shown moderate activity when compare with standard (Streptomycin). All compounds are observed dose dependent activity.

Conclusion

By using Ethyl nicotinate, Hydrazine hydrate, Dioxane, Triethyl amine, Chloro aceticacid and various aldehydes substituted azetidin-4-ones are synthesised in Scheme All the synthesised **6** derivatives of azetidin-4-ones were evaluated with physical, spectral characterization and biological evaluation such as antibacterial, antifungal and anti inflammatory activities. The 6 synthesized derivative compounds in scheme-I were evaluated for anti-bacterial activity agents. In compound code B5 were shown significant activity against *Bacillus subtilis* at 200,300µg/ml concentration, and B2,B3, were shown moderate activity. All the compounds are screened for anti- Inflammatory activity at the concentrations of 100µg/ml, 200µg/ml, 300µg/ml, 400µg/ml, and 500µg/ml. Among 6 compounds.

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