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Der Pharma Chemica, 2010, 2(4): 219-223
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X

Synthesis and antimicrobial activities of 2-azetidinone and its derivatives

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ABSTRACT

In present research work , 2-aminobenzothiazole is condensed with different aromatic aldehydes in ethanol to yield corresponding Schiff bases. The Schiff bases were cyclised with chloroacetyl choride in triethyl amine to yield the corresponding 2-Azetidinones. The structures of synthesized compounds were confirmed by elemental and spectral analysis such as IR, NMR, Mass, GC-MS. The compounds were evaluated for their antimicrobial properties against micro-organisms such as S. aureus , B. substilis., B megatherium, E. coli, S. typhie, P.aeruginosa.

Key words: 2 -Aminobenzothiazole, 2-azetidinone, schiff bases, antimicrobial activity.

INTRODUCTION

Azetidinone is commonly known as β-lactum. Monocyclic β -lactum are an important class of heterocyclic compounds because of their use in the synthesis of biologically active classical or non- classical β -lactum antibiotics.[1-3] A large number of 3- chloro monocyclic β -lactum possesses powerful antibacterial, antimicrobial, anti-inflammatory, anticonvulscent and antitubercular activities. They are also function as enzyme inhibitors and are effective on the central nervous system[4-5]. Azetidinones[6-9] have played an important role in the medicinal chemistry. Azetidinone or β -lactum chemistry is of great importance because of the use of β -lactum derivative as antibacterial agent.[10-11]We have previously reported antibacterial activity of 1,4 diaryl-2-Azetidinone[12]against Gram -ve bacteria and fungi has been observed.

Previous studies on 1,4 diaryl-azetidinone[13]demonstrated the possibility of using the system for designing cytotonic compounds by employing a variety of aromatic and heterocyclic ring system in position 1 and 4.

Recently anticancer activity of mono and bicyclic β -lactum system[14-16]are discovered the penicillin and cephalosporin antibiotics posses cis- β -lactum units where as thienamycins and trinems have trans- β -lactum moieties. The effective synthesis of desirable goal based on the discovery of penicillin and cephalosporin.[17]

Some β -lactum derivatives have also been recognized as Inhibitors of human leukocytes elastase[18]and against with new biological activities.

Cycloaddition of mono chloroacetyl chloride with Schiff base result in formation of 2-Azetidinone (β - Lactum). The reaction involves direct acylation of imines with mono chloroacetyl chloride. The reaction carried out with base triethylamine gives β –lactum.
Although variety of drugs have been developed for treating bacterial and fungal disease, the basic difficulty experienced with these infections are the rapid development of drug resistance to the infectious strains.

A rapid, convenient microwave assisted and conventional synthesis of novel azetidinones derivatives were studied by Jignesh P. et.al.[19] The Vilsmeier reagent is useful and versatile reagent for the synthesis of azetidinones was studied by Jarrahpour A. et.al.[20] Parmar S.J.et.al. were synthesized and evaluated some novel optically active 3-chloro 1-4(-(4-[(5)-(4 -chlorophenyl) (phenyl)methyl]-1-piperaziyl}acetyl)] -4-aryl -azetidinones derivatives.[21] The synthesis of azetidinones substituted 1,3,4-thiazdiazole- 2-yl derivatives were studied by Vabarmathy J. et.al.[22]

The synthesis of some 2- azetidnones derivatives of 2-methyl benzimidazole by conventional and microwave assisted and evaluation of their antimicrobial efficiency were studied by Sonwane S K. et.al.[23], Shanmugapandiyan P. et.al.[24] can synthesized and studied biological activity of 2 - (thiazolidin-4-one)phenyl] -1H-phenylbenzimidazoles.

Toraskar M. et.al[25] were studied the azetidinones as bioactive moiety. The synthesis, characterization and biological evaluation of some azetidinones derivatives with naphthalene moiety were studied by Mishra S. K. et.al.[26] The synthesis and characterizations of certain novel azetidinones derivatives studied Sahoo U. et.al[27-28].

Review of literature reveals that, 2- Azetidinone are reported to posses significant antitubercular, antibacterial, antifungal activities. 2-aminobenzothiazole have been found to be biologically interesting compounds for many years. Since 2- azetidinones derivatives of 2 -aminobenzothiazole using various aldehydes were not synthesized yet. Hence, it was thought of interest to synthesized and study of biological activities of 2-azetidinones and its derivatives.

MATERIALS AND METHODS

Melting point were determined in an open capillary tube using Precision Digital Melting Point Apparatus- Model MP-D and are uncorrected. The IR spectra were recorded on a Perkin Elmer IR Spectrometer using KBr disc of the sample. The NMR spectra were recorded as 400MHz FT-NMR Spectrometer in DMSO using TMS as an internal standard. Chemical shift is given in δ ppm.

Synthesis of Schiff Bases:

A mixture of 2-Amino benzothiazole (0.01M) and various aldehydes (0.01M) was dissolved in 20-25 ml absolute ethanol and 2,3 drop of concentrated sulphuric acid (H_2SO_4) were added. The mixture was refluxed for 4-5 hours. It was then cooled, dilute with ice cold water and resulting solid was crystallized from ethanol to yield Schiff bases.

Synthesis of Substituted 2-Azetidinones :

A mixture of Schiff bases and choroacetyl chloride was dissolved in 20 ml of Dioxane in presence of 2 ml of triethyl amine. The mixture was refluxed for 14-15 hours. It was then cooled sticky mass was obtained, when the solvent was evaporated on hot water bath. The product was triturated with petroleum ether and crystallized from ethanol to yield substituted Azetidinones.

Table -1

Compound	Aldehyde
II a	2- Nitro bezaldehyde
IIIa	p- methoxy bezaldehyde
IVa	Furfuraldehyde
Va	3,4 -methylenedioxy bezaldehyde
VIa	3- Nitro bezaldehyde

Spectral analysis:

Compound Ia: IR(υ in cm^{-1}) : 3019 (Ar-H), 1613(CH=N Stretching), 1588(=CH-H Stretching), 1530(C=C Stretching), 1216(C-N Stretching), 2912(C-H Stretching). NMR (δ in ppm): 8.84 (s, CH=N, 1H), 2.03(s, N-$(CH_3)_2$, 6H), 6.5-8 (m, Ar-H, 8H).

Compound Ib: IR(υ in cm^{-1}): 2958 (C-H), 1528 (C=C), 1216 (C-N), 1061(C-H), 1638(C=O), 775(C-Cl), 1036(C-O). NMR (δ in ppm) : 6.5-8(m, Ar-H, 8H), 6.12 (dd, CH H_A 1H), 6.30 (dd, CH H_B 1H), 2.03(s, N-$(CH_3)_2$, 6 H).

Table-2: Physical parameters of synthesized Schiff bases

Comp.	Mol. wt.	Melting point	% yield	Colour	Molecular formula
Ia	281.38	180^0	77%	Yellow	$C_{16}H_{15}N_3S$
IIa	283.309	162^0	70%	Yellowish green	$C_{14}H_9N_3SO_2$
IIIa	268.338	186^0	65%	Grey	$C_{15}H_{12}N_2SO$
IVa	228.273	185^0	65%	Pale yellow	$C_{12}H_7N_2SO$
Va	282.321	188^0	67%	Greenish yellow	$C_{15}H_{10}NSO_2$
VIa	283.309	162^0	70%	Yellowish green	$C_{14}H_9N_3SO_2$

Table-3: Physical parameters of synthesized 2-Azetidinone derivatives

Comp.	Mol. wt.	Melting point	% yield	Colour	Molecular formula
Ib	357.863	135^0	80%	Brown	$C_{18}H_{16}N_3SOCl$
IIb	366.786	165^0	80%	Reddish brown	$C_{16}H_{10}N_3SO_3Cl$
IIIb	344.82	175^0	70%	Greenish yellow	$C_{17}H_{13}N_2SO_2Cl$
IVb	380.733	145^0	85%	Voilet	$C_{13}H_9N_2SO_2Cl$
Vb	358.803	195^0	70%	Orange	$C_{17}H_{12}N_2SO_3Cl$
VIb	360.786	165	70%	Reddish	$C_{16}H_{10}N_3SO_3Cl$

Antimicrobial screening:

The synthesized compounds were subjected to antimicrobial screening by broth dilution method. Minimum inhibitory concentration (MIC) value of synthesized compounds against various organism are tabulated in Table -4 and 5.

For conveniences, titled compound were graded a highly active with MIC > 3 to 12.5 µg /ml, moderately active with MIC value 25-50 µg/ml, poorly active with MIC value 100-200 µg /ml. The majority of the compound show moderate activity with MIC value is an range of > 12.5 to 200 µg/ml for both +ve and -ve bacteria.

Table-4

Compounds(µg/ml)	*S.aures*	*B.substalis*	*B.megatherium*	*E.coli*	*S.typhi*	*P.aeruginosa*
Ia	50	100	100	50	100	50
IIa	25	25	25	25	25	50
IIIa	50	50	50	50	50	50
IVa	25	50	50	25	25	50
Va	100	100	200	200	100	50
VIa	25	25	50	50	50	50
Chloromphenicol	50	50	50	50	50	50

Table-5

Compound(µg/ml)	*S.aures*	*B.substalis*	*B.megatherium*	*E.coli*	*S.typhi*	*P.aeruginosa*
Ib	50	25	50	25	50	50
IIb	100	50	200	100	200	200
IIIb	12.5	25	50	50	25	25
IVb	50	50	100	50	100	50
Vb	25	25	25	25	25	25
VIb	100	50	200	50	100	50
Chloromphenicol	50	50	50	50	50	50

RESULT AND DISCUSSION

All synthesized compounds were first purified by successive recrystalisation using appropriate solvent. The synthesized compounds were subjected to spectral analysis to confirm the structures. All the analytical details show satisfactory results. The IR peak at 1638 cm^{-1}, (C=O), 775 cm^{-1}(C-Cl),1216 cm^{-1},(C-N) and for 1HNMR spectra the peaks at 1.4 ppm and 2.12-2.18 ppm for C-CH-Cl, N-CH-Cl groups have confirmed the formation of 2 -Azetidinones.

Since our such title compounds are known to posses antimicrobial activity. The compounds were screened for their antimicrobial activity by broth dilution method. Three gram positive bacteria such as *S.aures B. substilis , B. megatherium* and three gram negative bacteria such as *E. coli , S.typhi , P. aeruginos.* are tested for activities . All compounds shown moderate activities.

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