SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITIES OF 2-AZETIDINONE DERIVATIVES

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Abstract:

β-lactam antibiotics are among the most important and widely used antimicrobials and are comprised of a large family of compounds, obtained by chemical modifications of the common scaffolds. A series of N-substituted phenyl –(3',4'-methylenedioxyphenyl)-3 chloro-2-azetidinones was synthesized and antimicrobial properties of the title compounds were investigated and many of them have potent antibacterial activity.

Keywords: Azetidinone derivatives, antibiotics, antibacterial activity,

Introduction:

The discovery of antimicrobials like penicillin paved the way for better health for millions around the world. Azetidinone are more commonly known as β lactams which has ring system having internal amide linkage[1]. When a carbon, β to the carbonyl group is attached to the nitrogen in order to form the cyclic amide, it is referred to as beta lactam. Ring system has been known since 1907 but the investigation of its Chemistry only followed the discovery of powerful activity of penicillin and clinically more useful cephalosporin. The basic skeleton commonly encountered in β-lactam antibiotics are the penam and cepham and high reactivity of β-lactam ring system is essential for the antibiotic activity of those compounds[2]. β lactam drugs are most widely prescribed antibiotics used in medicine. 2-azetidinone derivatives possess wide therapeutic activity such as antimicrobial[3], antitubercular[4], anticonvulsant [5], antidepressant [6], herbicidal [7], antifungal[8], anti-inflammatory[9]and cholesterol absorption inhibitors[10].

Experimental:

General Procedure:

The chemicals used were of A.R grade for synthesis and purity of synthesized compounds were checked by TLC.IR spectrum of synthesized compounds was recorded on FT-IR spectrophotometer, Schimadzu Make -8101, Japan and Ultraviolet spectrum was recorded on UV-VIS spectrophotometer, Schimadzu Make -2401 PC at department of pharmaceutical Sciences, Nagpur University, Nagpur. PMR spectrum was recorded on AMX -400 MHZ High Resolution multinuclear FT-NMR spectrometer at regional Sophisticated Instrument Facility Center, department of Chemistry, Indian Institute of Science Bangalore.

Synthesis Procedure:

A mixture of 3,4- methylenedioxyphenylidine-4'chloro aniline (0.01M) and chloroacetyl chloride (0.01M) was dissolved in 20 ml benzene in presence of 2 ml of triethylamine. The mixture was refluxed for 8 hrs. It was then cooled; sticky mass was obtained. The solvent was evaporated on hot water bath. The product was triturated with petroleum ether and crystallized from 40% ethanol to yield N-4'-chloro phenyl –4-(3',4'-methylenedioxyphenyl)-3 chloro-2-azetidinones (Figure 1).

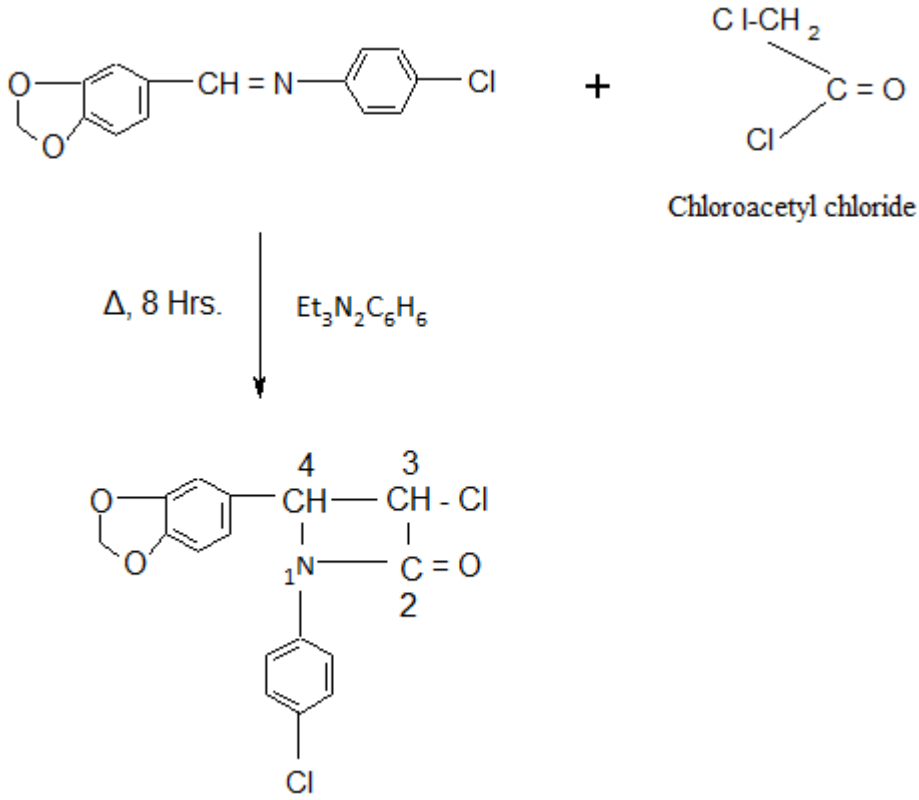


Figure 1. Scheme of reactions used in the synthesis

Antimicrobial activities:

The synthesised compounds were tested against the pathogenic bacteria using minimum inhibitory concentration (MIC) were determined using broth macro-broth dilution method. The organisms used for this method were *Staphylococcus aureus*, *Bacillus megatherium*, *Bacillus subtilis*, *Pemphigus vulgaris*, *Escherichia coli* and *Pseudomonas aeruginosa*. Two fold serial dilutions of Chloramphenicol (range 400 µg/ml to 12.5 µg/ml) and test compound (N-4'-chloro phenyl –4-(3',4'-methylenedioxyphenyl)-3 chloro-2-azetidinones) (range 500 µg/ml to 31.25 µg/ml) were prepared in Luria Broth (LB). The cultures were activated in LB for overnight (OD 0.5 at 600 nm). The activated cultures were harvested and washed with sterile saline. 200 the test compounds and Chloramphenicol was used as standard drug. The antimicrobial activity was determined as the zone of inhibition for various compounds against different test compounds recorded.

Results

Properties of Compound:

1. It is greenish colored crystalline solid compound. M.P 148^0 C
2. From analytical data, molecular formula was found to be $C_{16}H_{11}O_3NCl_2$. The molecular weight was found to be 336
3. UV-VIS spectrum was recorded in methanol solvent[11-13]. λ_{max} values are 351nm and 210 nm corresponding to n to π* and π to π* transition in azetidinones.

Table 1: Characterization of IR Data:

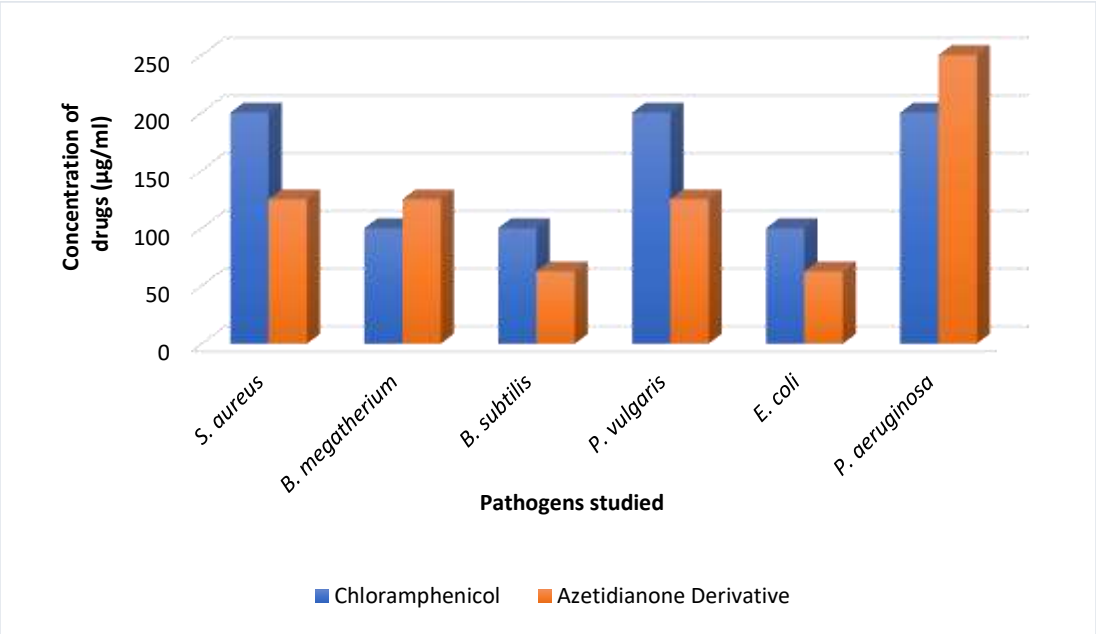
Literature value (cm^{-1})	Absorption Observed (cm^{-1})	Assignment
3300-3200	3288	-OH stretching Enol form
2790-2770 (m)	2780	-O-CH2-O stretching
1710-1630	1708	C=O stretching azetidinone
1585-1570	1550	C-H stretching
1520-1480	1510	C=C stretching
1220-1020	1172	C-N stretching
1125-1090	1074	C-H def
1070-1000	1036	C-O streching
835-810	814	C-H opp def
800-650 (s)	740	C-Cl streching

Table 2: Characterization of NMR Data:

The chemical shifts can be corelated as follows:

Peak observed in (delta)	Multiplicity	Inference
5.90	S	$-CH_2$, 2H
6.12	Dd	1H,-CH (HA)
6.30	Dd	1H, -CH (HB)
7.0-8.5	M	7H, Ar-H
9.9	S	-OH, 1H, enol

Antimicrobial activity:



Conclusion:

In this study new 2-azetidionone derivatives have been designed and synthesized and structures of all new compounds were proved using spectral methods. The compounds were evaluated for their antimicrobial activity. Some compounds show potent microbial activity compared with standard drug used.

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