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RESEARCH ARTICLE

Study on Synthesis of Some Novel Azetidinone Derivatives

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ABSTRACT

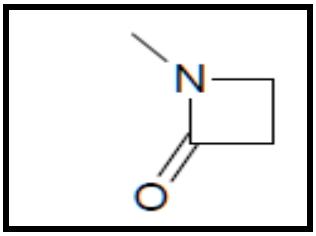
A series of five novel azetidinones were synthesized by cyclocondensation of various Schiff bases of naphthylamine with Chloroacetylchloride in the presence of triethylamine. Schiff's bases preparing from naphthylamine moiety by reacting the hydrazide of the parent compound with different aromatic or 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 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, antiinflammatory, anticonvulsant & antitubercular activities. They also function as enzyme inhibitors & are effective on the central nervous system[1-3]. These are the carbonyl derivatives of azetidines containing carbonyl group at the position-2 and 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].



Azetidinone Moiety

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

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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. Panisidine, 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 ß-lactam heterocyclic 2-azetidinones are still the most prescribed antibiotics used in medicine. A large number of 3-chloro monocyclic ß-lactam having substituents at position 4 possess powerful antimicrobial, antibacterial, sedative and 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 ß-lactam moiety, its activity is greatly influenced by different substituents. A large number of 3-chloromonocylic ß-lactam possess powerful antibacterial, antiinflammatory, antifungal, antimicrobial, analgesic, sedative, anticonvulsant antitubercular and herbicidal activities.

EXPERIMENTAL

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 spectra were recorded on Shimadzu LCMS 2010A.

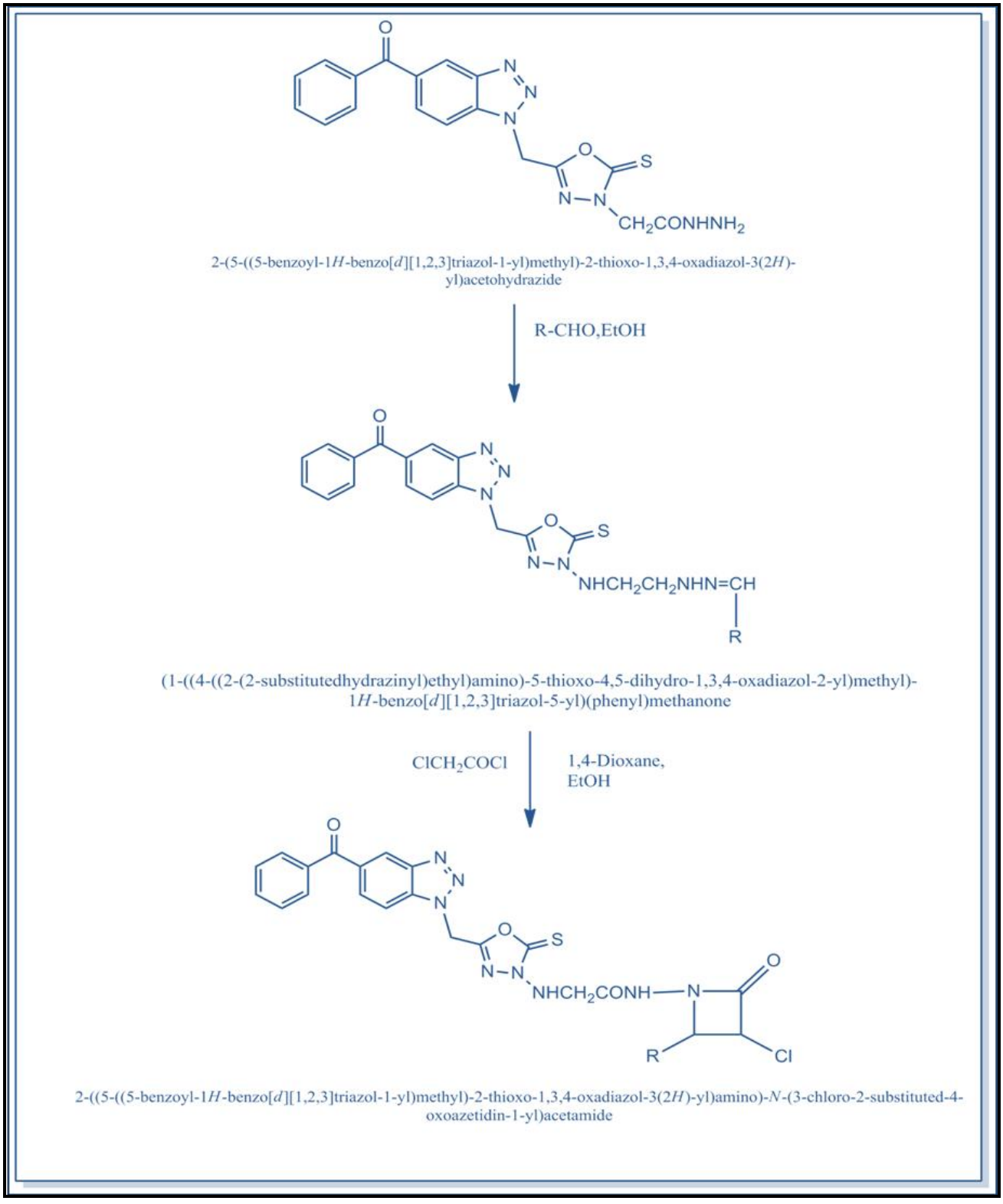
Synthesis of Azetidinone Analogs

Chloroacetylchloride was added drop wise to Schiff's base (0.02 moles) and triethylamine (0.04 ml) in dioxane (25 ml) was added to this at 5-10 ^{0}C. The reaction mixture was then stirred for 21 hours and kept at room temperature for three days. The obtained product was filtered, dried and recrystallized by using ethanol.

Table 1: Physical data of Azetidinone derivatives

Sr.No	Compounds	Physical State	Rf Values	M.P. (^{0}C)	% Yield
1.	Phenyl	Yellow Crystal	0.53	270-200^{0}C	75
2.	4-bromophenyl	Orange Crystal	0.66	230-215^{0}C	63
3.	4-methoxyphenyl	Yellow Crystal	0.60	259-263^{0}C	80

Reaction Scheme



Where R: Phenyl,4-bromophenyl,4-methoxyphenyl

RESULTS AND DISCUSSION

2-(5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetohydrazide

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).

(1-((4-((2-(2-substitutedhydrazinyl)ethyl)amino)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)-1H-benzo[d][1,2,3]triazol-5-yl)(phenyl)methanone

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 (CN stretching), 896.5, 750.5 and 677.8(C=C bending), 679.8 (C-Cl stretching).

2-((5-((5-benzoyl-1H-benzo[d][1,2,3]triazol-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)amino)-N-(3-chloro-2-substituted-4-oxoazetidin-1-yl)acetamide

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(CN stretching), 894.5, 750.5 and 677.8 (C=C bending), 677.8 (C-Cl stretching).

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.

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.

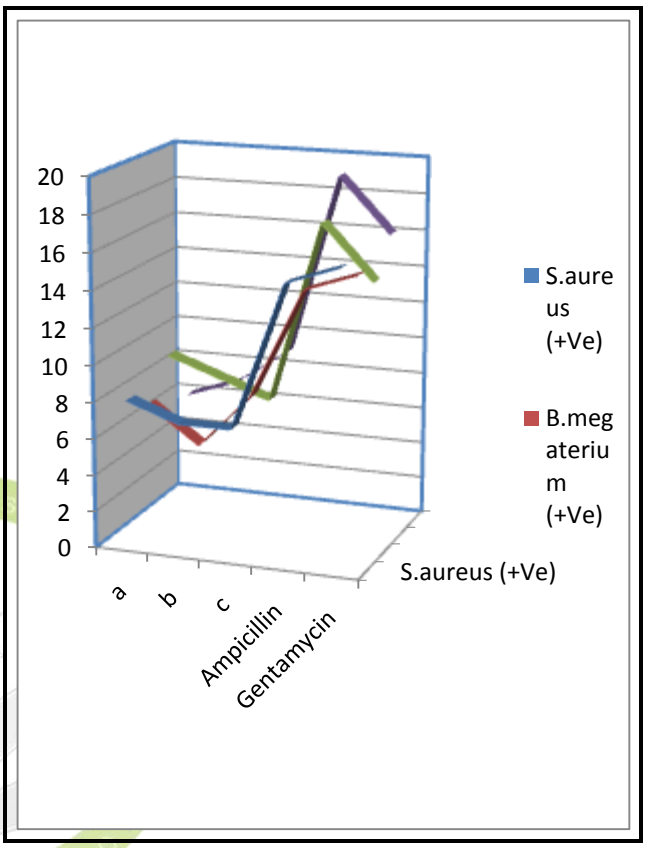


Figure 1: The bacterial screening indicated that among the compound no. C moderately activities against all tested bacterial strain

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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Table 2: Data of antimicrobial activity of Azetidinone derivatives

Samples	***S.aureus (+Ve)***	***B.megaterium (+Ve)***	***E.coli (-Ve)***	***P.vulgaris (-Ve)***
a	8	7	9	6
b	7	5	8	7
c	7	8	7	9
Ampicillin	**15**	**14**	**17**	**19**
Gentamycin	**16**	**15**	**14**	**16**

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