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SYNTHESIS AND BIOLOGICAL EVALUATION OF CERTAIN NEW 3-CHLORO-4-(3-BROMO PHENYL)- N-(4-METHOXY BENZAMIDO)-2-AZETIDINONE DERIVATIVES

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ABSTRACT

The chemistry of heterocyclic compounds is a field of organic and pharmaceutical chemistry which is being continuously explored for the synthesis and biological evaluation of new chemical entities in search of better lead molecules. This paper deals with a novel, convenient microwave synthesis for preparation of 3-chloro-4-(3-bromo phenyl)- N-(4-methoxy benzamido)-2-azetidinone by the interaction of 4-methoxy benzohydrazide with 3-bromobenzaldehyde and followed by cyclization to obtain titled 2-azetidinone. Constitution of synthesised compounds have been delineated on the basis of elemental analysis, IR, ¹H NMR, Mass spectral studies.

Keywords: 2-azetidinone, microwave synthesis, cyclisation, elemental analysis

I. INTRODUCTION

2-azetidinone commonly known as β -lactams, are well-known heterocyclic compounds among the organic and medicinal chemists mainly because of their antimicrobial and diverse pharmacological activities. The β -lactam antibiotics are still the most prescribed antibiotics used in medicine. They are considered as an important contribution of science to humanity^{1,2}. The most widely used antibiotics such as the Penicillins, Cephalosporins, Carumonam, Aztreonam, Thienamycine and the Nocardicins contain β -lactam (azetidin-2-one) rings³. The long-term use of β -lactam antibiotics exert selective pressure on bacteria and permit the proliferation of resistant organisms⁴. A comparative study of current antibiotics with those from previous decades shows an alarming increase in bacterial resistance to β -lactam antibiotics^{5,6}. The development of several synthetic and semi-synthetic β -lactam antibiotics by the pharmaceutical industry was due to the growing resistance of bacteria towards the β -lactam antibiotics and the need for medicines with a more specific antibacterial activity⁷. A large number of antibiotics contain amide linkage. Several derivatives of amides were prepared and found to possess antimicrobial activities. Literature survey reveals that various drugs e.g. penicillin⁸ (antibacterial), pyrazinamide⁹ (antitubercular), indinavir¹⁰, ritonavir¹¹. (Protease inhibitors as anti-AIDS) etc contain their particular activities due to the amide linkage present in their structure. 2-Azetidinones are the monocyclic β -lactams, are well-known heterocyclic compounds among the organic and medicinal chemists^{12,13}. In recent years, renewed interest has been focused on the synthesis and modification of β -lactam ring to obtain compounds with diverse pharmacological activities like antitubercular¹⁴, anticonvulsant¹⁵, antibacterial¹⁶, sedative¹⁷, anticancer¹⁸, antiparkinsonian¹⁹, antidiabetic²⁰, anti-inflammatory²¹, cholesterol absorption inhibitors²², anti-HIV²³. It also possesses enzyme inhibitor²⁴, hypoglycemic²⁵ and human leukocytase elastase inhibitor activity²⁶.

II. RESULT AND DISCUSSION

Experimental

- The melting points of all synthesized compounds were recorded using open capillaries and are uncorrected.
- The carbon and hydrogen analysis were carried out on Carlo-Erba-1106 analyser. Nitrogen estimation was carried out on Colman-N-analyser-29.
- The IR spectra were recorded on a PERKIN ELMER spectrophotometer in the frequency range 4000-400 cm⁻¹ in Nujol mull and as KBr pellets.

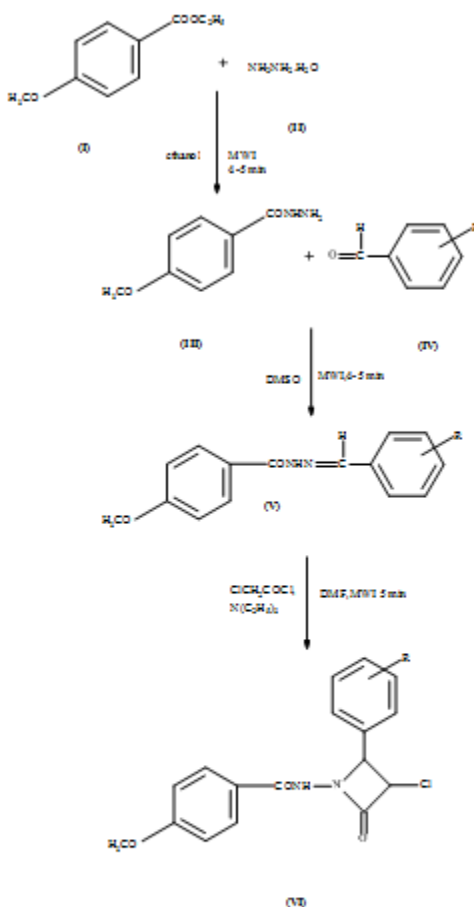
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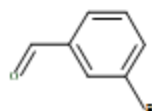
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- ^1H NMR spectra were recorded on BRUKER AVANCE II 400 spectrometer with TMS as internal standard using DMSO as solvents.
- All the compounds are synthesised in domestic microwave oven Godrej SLGX-20E 800 Watt.
- Chemicals used were of AR grade. Purity of the compounds were checked on pre coated silica-G plates by TLC

Reaction Scheme:

Where R is



- **STEP I : Preparation of N'-(3-bromo benzylidene)-4-methoxy benzohydrazide (Schiff base) (V)**

4-methoxy benzohydrazide(III) (0.01mol) was dissolved in 10 ml DMSO. 3-bromo benzaldehyde(IV) (0.01mol) was added to the reaction mixture, then it was subjected to microwave irradiation (80%) power for 4.5 min, cooled to

room temperature and then poured into crushed ice. The solid obtained was filtered, washed with water and recrystallized with ethanol.

• **STEP II :**

Preparation of 3-chloro-4-(3-bromo phenyl)- N-(4-methoxy benzamido)-2-azetidinone (VI)

To a stirred solution of N'-(3-bromo benzylidene)-4-methoxy benzohydrazide (Schiff base)(V) (0.01mol), in DMF (15ml), triethylamine (0.01mol) and chloroacetylchloride (0.01mol) were added drop wise with constant stirring at room temperature. The reaction mixture was kept for 10 min and then irradiated to microwave power (80%) for 3.5 min. Excess of solvent distilled off and the residue was poured into ice-cold water. A solid obtained was filtered and recrystallized from ethanol, m.p.90⁰ C having molecular formula C₁₇H₁₄O₃N₂ClBr . The product was found soluble in DMF, acetone, chloroform. The purity of compound was checked by TLC using solvent system chloroform:benzene:ethyl acetate (4:4:2)and its R_f value was 0.82.

Spectral analysis of compound

IR Spectrum

The IR spectral analysis of compound VI showed the presence of following absorption bands.

Table 1. IR Spectrum

Absorption observed (cm ⁻¹)	Assignment	Absorption expected (cm ⁻¹)
3066	Ar-H stretching	3100 – 3000
1477,1509	C=C stretching	1600 – 1450
3531	N-H stretching	3500 – 3100
726	C-Cl stretching	730 – 550
1679	C=O stretching of β-lactam	1760 – 1730
1344	C-N stretching	1350 – 1280
1026,1254	C-O-C stretching	symm 1040, asymm ~ = 1250
681	C-Br stretching	690 – 550

¹H-NMR Spectrum

The ¹H-NMR spectral analysis of compound VI showed the presence of following peaks. The chemical shift can be correlated as below:

Table 2. ¹H-NMR Spectrum

Signal	Signal Position (δppm)	Relative No. of H-atoms	Multiplicity	Assignment of Signal
1	7.0 – 8.4	8H	Multiplet	Ar-H
2	11.8	1H	Singlet	CO-NH
3	1.4	1H	Doublet	CH
4	3.8	3H	Singlet	OCH ₃
5	4.5	1H	Doublet	CH-Cl

Mass Spectrum

The mass spectral analysis of compound **VI** showed the presence of following molecular ion peaks.

Table 3. Mass Spectrum

Ion	M/Z
M ⁺	408
M+1	409
[M-Br] ⁺	329

Antimicrobial activity

Various methods have been proposed and adopted for the measurement of antimicrobial activity¹⁹. In present antimicrobial study the newly synthesised compound was screened for their antimicrobial study using “Kirby-Bauer Disc Diffusion Method” (by Well method).

Table 4. Antimicrobial activity

Compound	Antibacterial				Antifungal	
	<i>E. coli</i>	<i>S. aureus</i>	<i>B. subtilis</i>	<i>S. typhi</i>	<i>A. niger</i>	<i>T. viride</i>
VI	16	R	12.5	18	R	23
Streptomycin	22	24	16.5	16	18	16
Penicillin	R	26	18	20	19	18
Griseofulvin	15	18	20	18	16	19

III. CONCLUSION

The objective of the present work was to synthesize, purify, characterize and evaluate the antimicrobial activity of novel derivatives. The yields of different synthesized compounds were found to be in the range of 60-80% and the characterization was done by melting point. Characteristic IR bands show several functional vibrational modes which confirm the completion of reaction. The test compound showed good, moderate and poor biological activity.

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