SYNTHESIS AND CHARACTERIZATION OF NEW 2-AZETIDINONE DERIVATIVES AS ANTIMICROBIAL AGENTS

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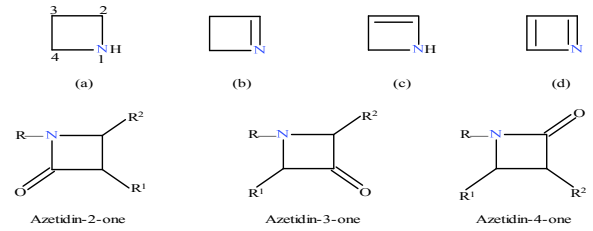
ABSTRACT

The 2-azetidinone is an important biological scaffold. A series of 3-chloro-4-(substituted phenyl)- N-(4-methoxy benzamido)-2-azetidinone were synthesized from 4-methoxy benzohydrazide which on reaction with different aromatic aldehydes in DMSO and subjected to microwave irridation to give the Schiff bases. These Schiff bases formed undergoes cyclisation when treated with chloroacetyl chloride and base triethyl amine in DMF in microwave oven for specific time period to give the titled azetidinone derivatives. Constitution of synthesised compounds have been delineated on the basis of elemental analysis, IR, 1H NMR, Mass spectral studies.

Key Words: 2-Azetidinones, schiff bases, chloroacetyl chloride

I. INTRODUCTION

2-Azetidinones are also known as β-lactams which are derivatives of 1. Azetidine 2. Azetine 3. 2 Azetine and 4. Azete derived from nitrogen derivatives of cyclobutane, cyclobutene and cyclobutadiene[1]. 2-azetidinones have become popular because it is integral part of famous antibiotics such as penicillins and cephalosporins.



Since the advent of penicillin, the β-lactam antibiotics have been the subject of much discussion and investigation, within both the scientific and public sectors. The primary biological targets of the β-lactam antibacterial drugs are the penicillin binding proteins, a group of transpeptidases anchored within the bacterial cellular membrane, which mediate the final step of cell wall biosynthesis. The chemistry of β-lactams has taken an important place in organic chemistry since the discovery of penicillin by Sir Alexander Fleming in 1928 and shortly thereafter cephalosporin which were both used as successful antibiotics. Even now the research in this area is stimulated because of development of bacterial resistance to widely used antibiotics of this type. There is a need for functionalized β-lactams or for new active principles in β-lactam series[2].

Bringing about slight modifications in the parent compound often serves to enrich the activity of the compound and also in most cases eliminates adverse effects or toxicity associated with the parent drug[3]. 2-azetidinone exhibit interesting biological activities such as carbonic anhydrase inhibitors[4], sedatives[5], antimicrobial[6], thrombin inhibitors[7], analgesic[8], chymase inhibitory activity[9] and antitubercular[10]. Cycloaddition of monochloroacetyl chloride with imines (Schiff base) result in formation of 2-azetidinone (β-lactam). The reaction involves direct acylation of imine with monochloroacetylchloride. The reaction is carried out with base as triethylamine gives β-lactam[11].

Microwave chemistry is becoming increasingly popular both in industry and in academia. Microwave assisted organic synthesis has brought great revolution in organic synthesis. Small molecules can be built in a fraction of the time required by classical

thermal methods. As a result, this technique has rapidly gained acceptance as a valuable tool for accelerating drug discovery and development processes[12].

In view of the utility of series of 3-chloro-4-(substituted phenyl)- N-(4-methoxy benzamido)-2-azetidinone and as a part of wider programme, here a microwave method for synthesis of 3-chloro-4-(substituted phenyl)- N-(4-methoxy benzamido)-2-azetidinone has been reported.

II. METHODS AND MATERIAL

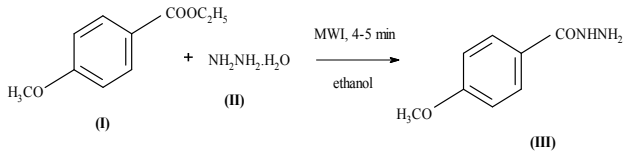
Experimental

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.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.

Details of typical preparation are as follows :-

Preparation of 4- methoxy benzohydrazide[13,14]

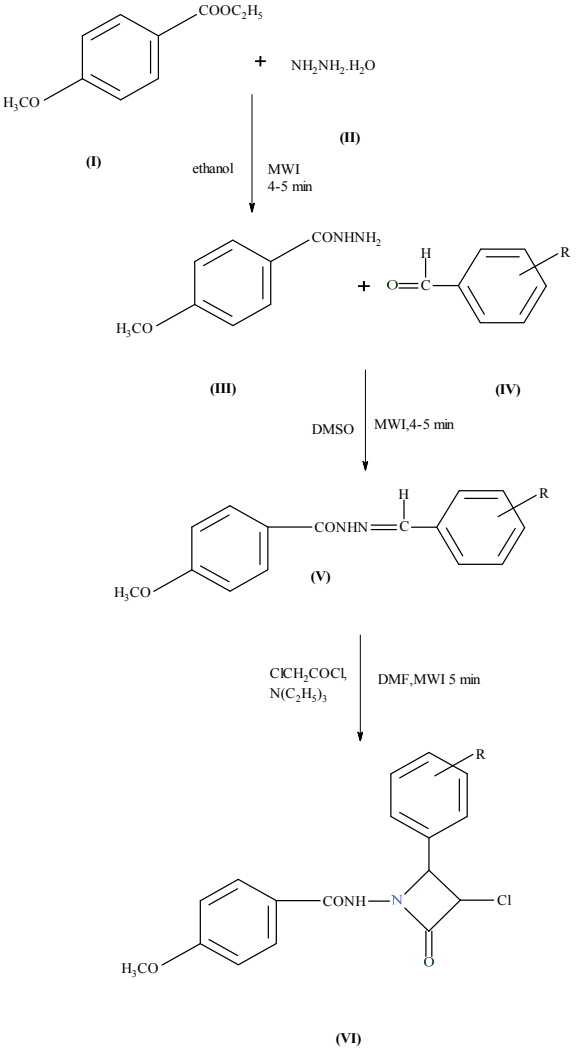
4-methoxy ethyl benzoate(I) (0.01 mol) in ethanol and hydrazine hydrate (99%) (II) (0.012 mol) were taken in 100 ml conical flask. The reaction mixture was irradiated under microwaves for 4 - 5 min at 80% power at 300 watt. Then reaction mixture was cooled and excess of ethanol was distilled off and contents were poured into ice cold water and precipitated hydrazides were filtered, dried and recrystallized from methanol.



Properties of compound (III)

1) Compound is white crystalline solid.
2) It is highly soluble in organic solvents like DMSO, DMF, chloroform and acetone.
3) Melting point of compound is found to be 190^0C.

Interaction of 4- methoxy benzohydrazide with different aryl aldehydes to obtain Schiff base and followed by cyclisation:



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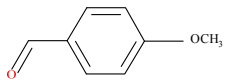
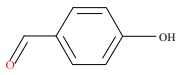
a = 

b = 

Preparation of 3-chloro-4-(4-substituted phenyl)- N-(4-methoxy benzamido)-2-azetidinone (VIa)

STEP I :Preparation of N'-(4-substituted benzylidene)-4-methoxy benzohydrazide (Schiff base) (Va)

4-methoxy benzohydrazide(III) (0.01mol) was dissolved in 5 ml DMSO. 4-subsituted benzaldehyde(IVa) (0.01mol) was added to the reaction mixture. then it is subjected to microwave irridation (70%) power for 4 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-(4-substituted phenyl)- N-(4-methoxy benzamido)-2-azetidinone(VIa)

To a stirred solution of N'-(4-substituted benzylidene)-4-methoxy benzohydrazide (Schiff base)(Va) (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 15 min and then irridated to microwave power (70%) for 2 min. Excess of solvent distilled off and the residue was poured into ice-cold water. A solid obtained was filtered and recrystallized from ethanol,

III. RESULT AND DISCUSSION

Spectral analysis of compound VIa

IR Spectrum

The IR[15-20] spectral analysis of compound **VIa** showed the presence of following absorption bands.

Absorption observed (cm^{-1})	Assignment	Absorption expected (cm^{-1})
3017	Ar-H stretching	3100 – 3000
1463,1511	C=C stretching	1600 – 1450
3429	N-H stretching	3500 – 3100
710	C-Cl stretching	730 – 550
1720	C=O stretching of β-lactam	1760 – 1730
1310	C-N stretching	1350 – 1280
1033,1257	C-O-C stretching	symm 1040, asymm ≈ 1250

1H-NMR Spectrum

The 1H-NMR[15-21] spectral analysis of compound **VIa** showed the presence of following peaks. The chemical shift can be correlated as below:

Signal	Signal Position (δppm)	Relative No. of H-atoms	Multiplicity	Assignment of Signal
1	6.9 – 8.4	8H	Multiplet	Ar-H
2	11.6	1H	Singlet	CO-NH
3	2.5	1H	Doublet	CH
4	3.8	6H	Singlet	OCH_3

Mass Spectrum

The mass[17,20,22] spectral analysis of compound **VIa** showed the presence of following molecular ion peaks.

Ion	M/Z
M^+	360
M-1	359
$[M-C_6H_4OCH_3]^+$	252

Spectral analysis of compound VIb

IR Spectrum

The IR[15-20] spectral analysis of compound **VIb** showed the presence of following absorption bands.

Absorption observed (cm^{-1})	Assignment	Absorption expected (cm^{-1})
3037	Ar-H stretching	3100 – 3000
1462,1508	C=C stretching	1600 – 1450
3211	N-H stretching	3500 – 3100
701	C-Cl stretching	730 – 550
1772	C=O stretching of β-lactam	1760 – 1730

1315	C-N stretching	1350 – 1280
1033,1225	C-O-C stretching	symm 1040, asymm ≤ 1250
3079	Ar-OH stretching	3400 – 3200

1H-NMR Spectrum

The 1H-NMR[15-21] spectral analysis of compound **VIb** showed the presence of following peaks. The chemical shift can be correlated as below:

Signal	**Signal Position (δppm)**	**Relative No. of H-atoms**	**Multiplicity**	**Assignment of Signal**
1	6.8 – 8.3	8H	Multiplet	Ar-H
2	11.5	1H	Singlet	CO-NH
3	2.5	1H	Doublet	CH
4	3.8	3H	Singlet	OCH_3
5	9.7	1H	Singlet	Ar-OH

Mass Spectrum

The mass[17,20,22] spectral analysis of compound **VIb** showed the presence of following molecular ion peaks.

Ion	**M/Z**
M^+	346
$[M\text{-}OCH_3]^+$	315
$[M\text{-}OCH_3,C_6H_4OH]^+$	222

The compounds synthesised were screened for their microbial activity against comman pathogens like *Escherichia coli, Salmonella typhi, Bacillus subtilis and Staphylococcus aureus* and for antifungal activity against *Aspergillus niger and Trichoderma viride* and they were screened for their antimicrobial study using "Kirby-Bauer Disc Diffusion Method" (by Well method).

Table: Antimicrobial activity test of 3-chloro-4-(substituted phenyl)- N-(4-methoxy benzamido)-2-azetidinone

Compound	**Antibacterial**				**Antifungal**	
	E.coli	***S. aureus***	***B. subtilis***	***S.typhi***	***A.niger***	***T. viride***
VIa	16.2	22	16	--	16	16
VIb	18	16	22	18	22	26
Streptomycin	22	24	16.5	16	18	16
Penicillin	R	26	18	20	19	18
Griseofulvin	15	18	20	18	16	19

(Diameter of inhibition zone in mm)

IV. CONCLUSION

The compounds synthesised were screened for their antimicrobial activity (Table 6.5). Compounds (VIa), (VIb) were found to be moderately sensitive against the organisms *E.coli* and *B.subtilis* where as compounds (VIa) and (VIb) were found to be highly sensitive against the organism *S.aureus*. Compounds (VIb) was found to be moderately sensitive against the organism *S.typhi.* (VIb) was found to be highly sensitive against the organism *T.viride*

V. ACKNOWLEDGEMENT

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VI. REFERENCES

[1] A. R. Guru Prasad, K. R. Raju1, B. S. Kumar and L. R. K. R. Ravindranath, *Journal of Clinical and Analytical Medicine*,(2014).

[2] S. D. Sharma and S. Bandari, *Indian Journal of Heterocyclic Chemistry*,**11,**221-224(2002).

[3] K. Basavaraj and K. Asifiqbal, *UJPB.*, **02 (01)**, 43-50(2014).

[4] K.V. A. Kumar and B. Gopalakrishna, *RRJPPS.*, **3(1)**, (2014).

[5] D. Kumar and A. Kumar, *Journal of Chemistry*,**2014**, 8(2014).

[6] M. I. Konaklieva**,** *Antibiotics, 3***,** 128-142(2014).

[7] N. A. A. Elkanzi**,** *World Journal of Organic Chemistry*, **1(2)**, 24-51(2013).

[8] S. R. Desai, U. V. Laddi, R. S. Bennur and S. C. Bennur, *Indian Journal of Pharmaceutical Sciences,* (2011).

[9] P. D. Mehta and A. K. Pathak, *Int.J. PharmTech Res.,* **4(2),**(2012).

[10] R. Basawaraj, L. Amith, T. VijayKumar, M. Havangirao and C.H. Upendra, *Int.J. ChemTech Res.*, **2(3)**, (2010).

[11] K. M. Pandya and P. S. Desai, *IJPSR.,* **2(4),** (2013).

[12] S. Ravichandran and E. Karthikeyan**,** *Int.J. ChemTech Res.*, **3(1)**(2011).

[13] A. Saha, R.Kumar, R. Kumar and C. Devkumar, *Indian J. Chem.,***49(B),**526-531(2010).

[14] A. Thirugnanasambanthan, S. Venkatraman and M. S. Palaniappan, *J. Chem. Pharm. Res*., **4(2),**1217-1221(2012).

[15] R. M.Silverstein, G. C. Bassler and T. C. Morrill, "Spectroscopic Identification of Organic Compounds", 5th Ed., John Wiley and Sons, INC, New York, (1991).

[16] Margareta Avram and G. H. Mateeseu, "Infrared Spectrpscopy Application in Organic Chemistry", John Wiley and Sons, INC, New York,(1970).

[17] D. H. Williams and I. Fleming, "Spectroscopic Methods in Organic Chemistry", 4th Ed. Tata McGrawHill Publication, New Delhi, (1988).

[18] N. B. Colthup, L. H. Daly and S. E. Wibereley, "Introduction to Infrared and Raman Spectroscopy", Academic Press, New York,(1964).

[19] J. R. Dyer, "Application of Absorption Spectroscopy of Organic Compounds", 8th Ed., Prentice Hall (1991).

[20] Donald L. Pavia, Gary M. Lampman, George S. Kriz and James R. Vyvyan, "Spectroscopy", Cengage Learning,New Delhi.

[21] R. M. Silverstein, G. C. Bassler and T. C. Morrill, "Spectroscopic Identification of Organic Compounds", 4th Ed., John Wiley and Sons, INC, New York, (1981).