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Microwave Efficient Synthesis of 3-chloro-4-(substituted phenyl)- N-(4-methoxy benzamido)-2-azetidinone and its appilcability as a versatile drug

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Abstract— In present research paper microwave assisted greener and convenient synthesis of novel 3-chloro-4-(substituted phenyl)-N-(4-methoxy benzamido)-2-azetidinone is synthesised by cyclocondensation of Schiff bases of 4-methoxy benzohydrazide with chloroacetyl chloride in presence of triethyl amine. Schiff bases are prepared by the reaction of 4-methoxy benzohydrazide with substituted aryl aldehydes in DMSO in microwave oven for specific time period and followed by cyclocondensation of Schiff base with chloroacetyl chloride in presence of triethyl amine and DMF in microwave oven for specific time period and resulted in the formation of corresponding 2-azetidinone derivatives. Constitution of synthesised compounds have been delineated on the basis of elemental analysis, IR, ^{1}H NMR, Mass spectral studies and microbial study.

Keywords-*2-azetidinone, Schiff bases, cyclocondensation.*

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I. INTRODUCTION

The simplest β-lactam possible is 2-azetidinone in which the nitrogen atom is attached to the β-carbon relative to the carbonyl group and is a part of the several β-lactam antibiotics. The 2-azetidinone template has been widely described as a lead structure for a wide spectrum of pharmacological activities. Hence the development of new synthetic methodology incorporating the β-lactam nucleus referred as β-lactam synthon method is a vigorous research approach in the current scenario [1]. It is well established that slight alterations in the structure of certain compounds are able to bring drastic changes to yield better drug with less toxicity to the host. It is observed that chemical modification not only alters physicochemical properties but also pharmacological activities [2]. Discovery of newer and more potent analogs of molecules with already established activities form a key part of research in the pharmaceutical field. Bringing about slight modifications in the parent compound often serves to enhance 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 revolutionized 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. RESULT AND DISCUSSION

Experimental

The melting points of all syntesized 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.

The reagents used in synthesis of of 3-chloro-4-(substituted phenyl)-N-(4-methoxy benzamido)-2-azetidinone have been prepared by already known method.

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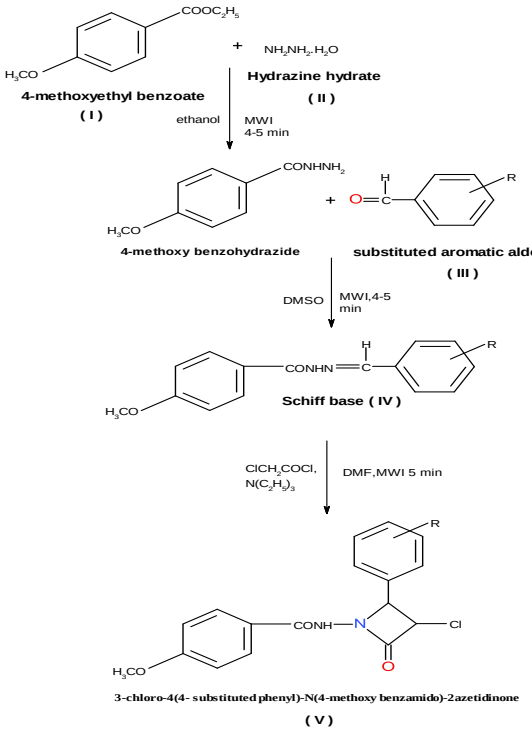

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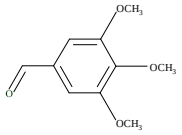

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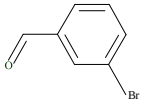

Interaction of 4- methoxy benzohydrazide with different aryl aldehydes to obtain Schiff base and followed by cyclisation:

Preparation of 3-chloro-4-(3,4,5-trimethoxy phenyl)- N-(4-methoxy benzamido)-2-azetidinone (VId)

STEP I :

Preparation of N'-(3,4,5-trimethoxy benzylidene)-4-methoxy benzohydrazide (Schiff base) (Vd)

4-methoxy benzohydrazide(III) (0.01mol) was dissolved in 10 ml DMSO. 3,4,5-trimethoxy benzaldehyde(IVd) (0.01mol) was added to the reaction mixture, then it was subjected to microwave irridation (80%) power for 2.5 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-(3,4,5-trimethoxy phenyl)- N-(4-methoxy benzamido)-2-azetidinone (VId)

To a stirred solution of N'-(3,4,5-trimethoxy benzylidene)-4-methoxy benzohydrazide (Schiff base)(Vd) (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 irridated to microwave power (80%) for 5.5 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.180^0 C having molecular formula $C_{20}H_{21}O_6N_2Cl$.

The product was found soluble in DMF, acetone, chloroform. The purity of compound was checked by TLC using solvent system chloroform:benzene:ethyl acetate (3:3:4)and its R_f value was 0.64.

Spectral analysis of compound VId

IR Spectrum

The IR [13-17] spectral analysis of compound **VId** showed the presence of following absorption bands.

Absorption observed (cm^{-1})	Assignment	Absorption expected (cm^{-1})
3050	Ar-H stretching	3100 – 3000
1463,1503	C=C stretching	1600 – 1450
3466	N-H stretching	3500 – 3100
720	C-Cl stretching	730 – 550
1641	C=O stretching of β-lactam	1760 – 1730
1332	C-N stretching	1350 – 1280
1066,1260	C-O-C stretching	symm 1040, asymm 1250

1H-NMR Spectrum

The 1H-NMR [13-17] spectral analysis of compound **VId** 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	7.0 – 8.3	6H	Multiplet	Ar-H
2	11.7	1H	Singlet	CO-NH
3	1.6	1H	Doublet	CH
4	3.8	12H	Singlet	OCH_3
5	4.6	1H	Doublet	CH-Cl

Mass Spectrum

The mass [13-17] spectral analysis of compound **VId** showed the presence of following molecular ion peaks

Ion	M/Z
M^+	420
$[M-OCH_3]^+$	389
$[M-OCH_3,C_6H_4]^+$	313

Experiment No.5:

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

STEP I :

Preparation of N'-(3-bromo benzylidene)-4-methoxy benzohydrazide (Schiff base) (Ve)

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4-methoxy benzohydrazide(III) (0.01mol) was dissolved in 10 ml DMSO. 3-bromo benzaldehyde(IVe) (0.01mol) was added to the reaction mixture, then it was subjected to microwave irridation (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 (VIe)

To a stirred solution of **N'**-(3-bromo benzylidene)-4-methoxy benzohydrazide (Schiff base)(Ve**)** (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 irridated 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.90^0 C having molecular formula $C_{17}H_{14}O_3N_2ClBr$.

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 VIe

IR Spectrum

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

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 [13-17] spectral analysis of compound **VIe** 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	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 [13-17] spectral analysis of compound **VIe** showed the presence of following molecular ion peaks.

Ion	M/Z
M^+	408
M+1	409
$[M-Br]^+$	329

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*
VId	20	--	14	16	24	R
VIe	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

(Diameter of inhibition zone in mm)

III. CONCLUSION

All the compounds prepared by microwave method are obtained with good yield and showed enhanced antimicrobial activity which cab be used as a versatile drug.

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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).

 ISSN: 2321-8169
45 – 48

[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).
[22] H. Budzikiewicz, "Strructural Elucidation of Natural Products by Mass Spectrometry" Vol.II (1964).