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Synthesis and characterization of 3-chloro-4-(substituted phenyl)-N-(4- nitro benzamido)-2-azetidinone derivatives and its antimicrobial application

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***Abstract*—**2-azetidinones are well-known and important nitrogen containing 4-membered heterocyclic compounds.Classical and efficient methods have been worked out for their synthesis.This research paper focus on efficient and operationally simple microwave method for the synthesis of a new series of 3-chloro-4-(substituted phenyl)-N-(4- nitro benzamido)-2-azetidinone. It involve the treatment of 4-nitro benzohydrazide with various substituted aryl aldehydes in DMSO under microwave irradiation for definite time to obtained Schiff base which is followed by cyclisation reaction with chloroacetyl chloride and triethyl amine in DMF under microwave irradiation for specific time to obtained 2-azetidinone. Constitution of synthesised compounds have been confirmed on the basis of elemental analysis, IR, ^{1}H NMR, Mass spectral studies.

Keywords*-*2-azetidinones,Schiff base,microwave method

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I. INTRODUCTION

Over the last 20 years there has been rapid progress in synthetic organic chemistry associated with the invention for new modified organic compound derivatives with useful properties.These compounds are mainly used in the pharmaceutical industry[1].The four-membered cyclic amides commonly known as 2-azetidinones or β-lactam occupy a eminent place in organic and medicinal chemistry since the structure of penicillin showed the presence of β-lactam ring in it and various potent activities of penicillin are due to the presence of β-lactam ring. The investigations in organic chemistry were focused on development of new innovative synthetic methodologies in construction of four-membered ring whereas the researches in medicinal chemistry focused on broadening the spectrum of antibacterial activity. The studies led to development of several novel methodologies for construction of the β-lactam ring and discovery of several β-lactam antibiotics such as, carbapenams ,cephalosporins ,monobactams ,trinems, etc[2,3]. It possess pharmacological activities such as anti-viral[4], antihyperlipidemic[5],human leukocyte elastase[6], antidepressant[7],antiparkinsonian[8],antitumor[9],tubercular[10],enzyme inhibitory[11[and antithrombotic[12].

Microwave-assisted organic synthesis is known by the special accelerations produced in many reactions .Greater yields, mild reaction conditions and shorter reaction times can be used and many processes can be improved. Even some reactions that do not take place by conventional heating can also be performed using microwaves[13]. Microwave assisted organic synthesis have great demand in pharmaceutical industry[14].
Because of biological importance of 2-azetidinone derivatives, I am reporting here a microwave method for synthesis of the series of 3-chloro-4-(substituted phenyl)-N-(4- nitro benzamido)-2-azetidinone.

II. EXPERIMENTAL DETAILS

The melting points were recorded using open capillaries. The carbon and hydrogen elemental analysis were carried out on Carlo-Erba-1106 analyser. Nitrogen estimation was carried out on Colman-N-analyser-29.The IR spectra were confirmed by a PERKIN ELMER spectrophotometer in the frequency range 4000-400 cm^{-1}in Nujol mull and as KBr pellets.^{1}HNMR 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-20E800 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 3-chloro-4-(substituted phenyl)-N-(4- nitro benzamido)-2-azetidinone have been prepared by already known methods.

Details of typical preparation are as follows:

Preparation of 4-nitro benzohydrazide

In the typical preparation of 4-nitro benzohydrazide involves, the hydrazinolysis reaction of 4-nitro ethyl benzoate with 99% hydrzine hydrate in ethanol, reaction take place at room temperature without microwave heating during dropwise addition of hydrazine hydrate to obtained yellow coloured product of 4-nitro benzohydrazide which is kept overnight for evaporation of excess amount of solvent and followed by washing and recrystallization with methanol.

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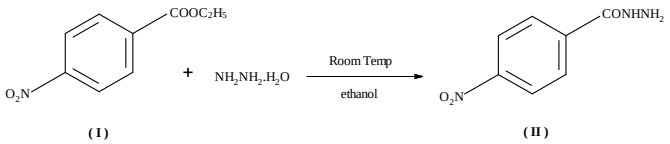
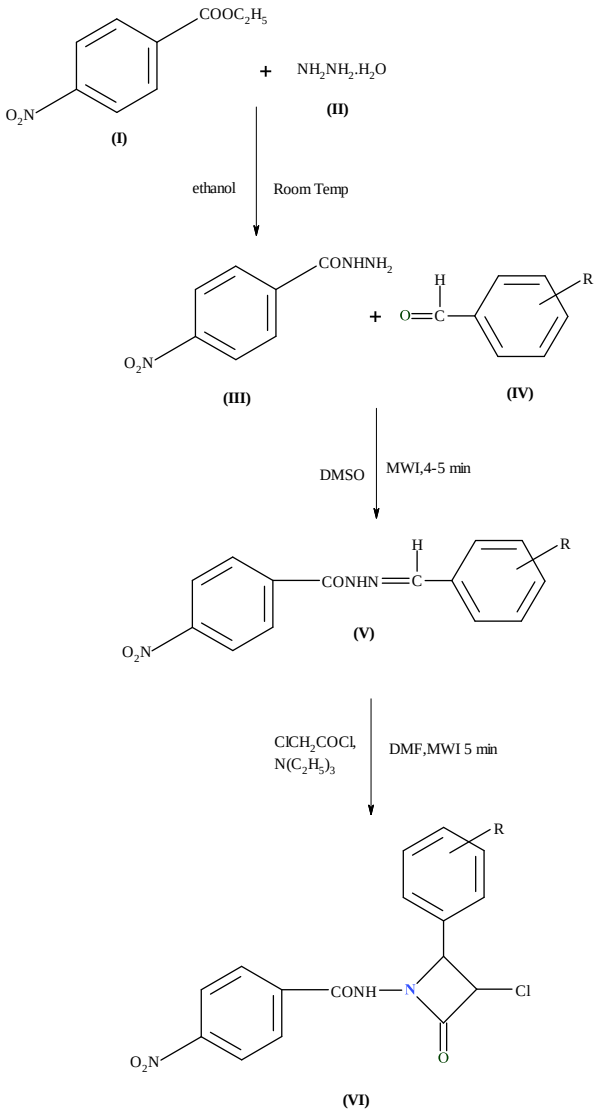


(I) (II)

Properties of compound (II)

1) The compound is yellow crystalline solid.
2) It is soluble in some solvents like DMSO, DMF, chloroform and acetone.
3) Melting point of compound is found to be 130^0C.

III. REACTION SCHEME



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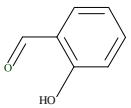
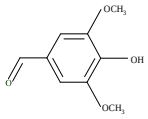
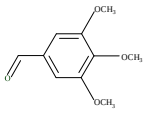
1 = 

2 = 

3 = 

IV. RESULT AND DISCUSSION

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

STEP I:

Preparation of (Schiff base)

The equimolar quantity of 4-nitro benzohydrazide(II) (0.01 mol) and various aryl aldehydes(0.01 mol),were taken in 50 ml of conical flask with 15ml of DMSO and then the reaction mixture was irradiated to microwave power for 7 mins at 300 watt(80%). The product obtained was poured over ice cold water. Separated solid t was filtered, washed with water and recrystallized from ethanol.

Step II:

Preparation of substituted-2-azetidinone

A mixture (Schiff base) (0.01 mol) and chloroacetyl chloride (0.01 mol) were taken in 50 ml of conical flask with 15ml of DMF and triethyl amine (0.01mol),then the reaction mixture was subjected to microwave irradiation for 5 min. The product obtained is cooled at room temperature and was poured over ice water. The solid separated out was filtered, washed with water and recrystallized from ethanol,

The product was found soluble in alcohol DMF, acetone, chloroform and benzene. The purity of compound was checked by TLC using solvent system petroleum ether: ethyl acetate (3:3)

Spectral analysis of compound 1

IR Spectrum

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

Absorption observed (cm^{-1})	**Assignment**	**Absorption expected (cm^{-1})**
3050	Ar-H stretching	3100 – 3000
1467,1488,1525	C=C stretching	1600 – 1450
3421	N-H stretching	3500 – 3100
1332	Ar-NO_2 stretching	1355 – 1315
2855	Aliphatic C-H stretching	2960 – 2850
711	C-Cl stretching	730 – 550
1655	C=O stretching of β-lactam	1760 – 1730

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[1]HNMR Spectrum

The 1HNMR[15-21] spectral analysis of compound 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 – 8.6	7H	Multiplet	Ar-H
2	4.1	1H	Doublet	CH-Cl
3	12.37	1H	Singlet	CO-NH
4	4.1	1H	Singlet	Ar-OH

MASS Spectrum

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

Ion	M/Z
M^+	361
$[M\text{-}OH]^+$	344
$[M\text{-}OH,Cl]^+$	309

Spectral analysis of compound II

IR Spectrum

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

Absorption observed (cm^{-1})	Assignment	Absorption expected (cm^{-1})
2937	Ar-H stretching	3100 – 3000
1423,1463,1516	C=C stretching	1600 – 1450
3435	N-H stretching	3500 – 3100
1329	Ar-NO_2 stretching	1355 – 1315
2851	Aliphatic C-H stretching	2960 – 2850
712	C-Cl stretching	730 – 550
1649	C=O stretching of β-lactam	1760 – 1730
1329	C-N stretching	1350 – 1280
1062,1248	C-O-C stretching	symm 1040, asymm ~= 1250

[1]HNMR Spectrum

The [1]HNMR[15-21] spectral analysis of compound 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 – 8.8	4H	Multiplet	Ar-H
2	4.6	1H	Doublet	CH-Cl
3	11.9	1H	Singlet	CO-NH
4	3.8	6H	Singlet	OCH_3

MASS Spectrum

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

Ion	M/Z
M^+	421
$[M\text{-}NO_2]^+$	375
$[M\text{-}NO_2,OH,$ β lactam ring$]^+$	255

Spectral analysis of compound III

IR Spectrum

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

Absorption observed (cm^{-1})	Assignment	Absorption expected (cm^{-1})
3002	Ar-H stretching	3100 – 3000
1417, 1463 & 1524	C=C stretching	1600 – 1450
3195	N-H stretching	3500 – 3100
1330	Ar-NO_2 stretching	1355 – 1315
2942	Aliphatic C-H stretching	2960 – 2850
712	C-Cl stretching	730 – 550
1651	C=O stretching of β-lactam	1760 – 1730
1296	C-N stretching	1350 – 1280
1064, 1235	C-O-C stretching	symm 1040, asymm ~= 1250

[1]HNMR Spectrum

The [1]HNMR[15-21] spectral analysis of compound 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 – 8.4	6H	Multiplet	Ar-H
2	3.8	1H	Doublet	CH-Cl
3	12.0	1H	Singlet	CO-NH
4	3.3	9H	Singlet	OCH_3

MASS Spectrum

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

Ion	M/Z
M^+	435
$[M\text{-}NO_2]^+$	389
$[M\text{-}NO_2,OCH_3]^+$	358

The compounds synthesised were screened and studied for their microbial activity against common pathogens like *Escherichia coli, Salmonella typhi, Bacillus subtilis and Staphylococcus aureus* and for antifungal activity against *Aspergillus niger and Trichoderma viride*

Table - Antimicrobial activity test of 3-chloro-4-(substituted phenyl)-N-(4- nitro benzamido)-2-azetidinone (I-III).

Compound	Antibacterial				Antifungal	
	E.coli	***S. aureus***	***B. subtilis***	***S.typhi***	***A.niger***	***T. viride***
1	22	18	19	16	--	16
2	18	24	18	20	19	17
3	20	22	20	18	23	18

V. CONCLUSION

All the compounds synthesized by effective microwave method and screened for various antimicrobial activity..Some compounds shows more potent activity as compared to standard drugs.

Acknowledgement

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