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Microwave assisted synthesis and antimicrobial activity of 3-chloro-4-methyl-1-(substituted phenyl)-4-(10H-phenothiazin-8-yl) azetidin-2-one

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Abstract : A new synthesis of 3-chloro-4-methyl-1-(substituted phenyl)-4-(10h-phenothiazin-8-yl) azetidin-2-one **(III a-h)** were synthesized by reacting different phenothiazine Schiffs bases **(IIa-h)** with 2-Chloroacetylchloride under microwave irradiation. The newly synthesized compounds were characterized by IR, 1H NMR, mass spectroscopy, elemental analysis and tested for their antibacterial and antifungal activity. Some compounds showed promising activities.
Key word : Synthesis, 2-Azetidinone; Phenothiazine; Chalcones; Antimicrobial activity.

Introduction

Azetidinones are very important class of compounds possessing wide range of biological activities such as anti-inflammatory [1], antifungal [2], antibacterial [3], antihyperlipidemic [4], antitubercular [5], anticancer [6], antihyperglycemic [7], anticonvulsant [8], CNS activity [9], tryptase inhibitory [10], human leukocyte elastase inhibitory [11], vasopressin v1a antagonist [12], and antitumor [13], enzyme inhibitors [14], cytotoxic [15], cholesterol absorption inhibitors [16] and elastase inhibitors [17].

A literature survey reveals that compounds containing phenothiazine skeleton possessing wide spectrum diverse biological activities such as anti-inflammatory [18], antimalarial [19], antipsychotropic [20], antimicrobial [21-24], antitubercular [25] and antitumor [26] properties.

Microwave heating is becoming a widely accepted tool for synthetic chemists. It is possible to improve product yields and enhance the rate of reactions as well as being a safe and convenient method for heating reaction mixtures to elevated temperatures [27-29].

These examples prompted to synthesize microwave irradiated synthesis of some new phenothiazine 2-azetidinone derivatives and evaluate for its antimicrobial activities.

Materials and Methods

All chemicals were purchased from Aldrich and Merck chemicals, Mumbai (India), and were used without further purification. Melting points were determined in open capillaries using a Toshniwal melting point apparatus and are uncorrected.

Formation of product was routinely checked by TLC. A Perkin - Elmer FT-IR spectrometer (vmax in cm-1) was used to record IR Spectra; and for NMR spectra a Brucker 300MHz instrument was used. ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as internal standard (chemical shifts in δ, ppm), Mass spectra were

obtained on LCQ davantage Therma Finiger spectrometer and Carlo Erba 1108 analyzer was used for elemental analysis.

General procedure for IIIa-h

3-chloro-4-methyl-4-(10H-phenothiazin-8-yl)-1-phenyl azetidin-2-one (IIIa)

A mixture of (Z)-N-(1-(10H-phenothiazin-8-yl) ethylidene) (10mmol) **(IIa),** Chloroacetyl Chloride (10mmol) and Triethyl amine (10mmol) were taken in 100 ml erylemer flask and the reaction was irradiated under microwave at 300W for 5 minutes. The product obtained was purified by using ethanol as solvent. IR (KBr) cm-1: 3039 (Ar-H), 2932 (C-H), 1728 (C=O), 1598(C=C), 1380 (C-N); 1H NMR (CDCl3): δ 8.09 - 6.35 (m, 13H, Ar-*H*), 1.96 (d, 1H, Cl-C*H*=CH), 1.61 (m, 1H, Cl-CH=C*H*), 1.09 (d,3H, C*H*$_3$CH); Mass (m/z) : 392. Anal.cald. for $C_{22}H_{17}N_2OSCl$: C, 67.25; H, 4.36; N, 7.13. Found: C, 67.40; H, 4.58; N, 7.18%.

Similarly, III**b-h** were synthesized by using different schiffs bases IIb-h.

Table1. Physical data of compounds IIIa-h

Comp. no	R1	R2	R3	M.F.	% Yield	M.P
III a	H	H	H	$C_{22}H_{17}N_2OSCl$	78	111-113
III b	NO_2	H	H	$C_{22}H_{16}N_3O_3SCl$	65	121-124
III c	H	NO_2	H	$C_{22}H_{16}N_3O_3SCl$	68	114-117
III d	H	H	NO_2	$C_{22}H_{16}N_3O_3SCl$	73	138-140
III e	OCH_3	H	H	$C_{23}H_{19}N_2O_2SCl$	66	143-145
III f	H	OCH_3	H	$C_{23}H_{19}N_2O_2SCl$	71	162-165
III h	H	H	OCH_3	$C_{23}H_{19}N_2O_2SCl$	70	139-141

Antimicrobial activity

The synthesized compounds were evaluated for antimicrobial activity by using Cup Plate method. The *Escherichia coli, Bacillus subtillis* were used as Bacterial strain and *Aspergillus niger* (recultered), *Candida albicans* as fungal strain. The 100 µg solution in DMSO were prepared and used for analysis. The zone of inhibition (in mm) was measured after two days at 37^0C. Ampicillin and Fluconazole were used as internal standards. The data of antimicrobial studies are recorded in Table 2.

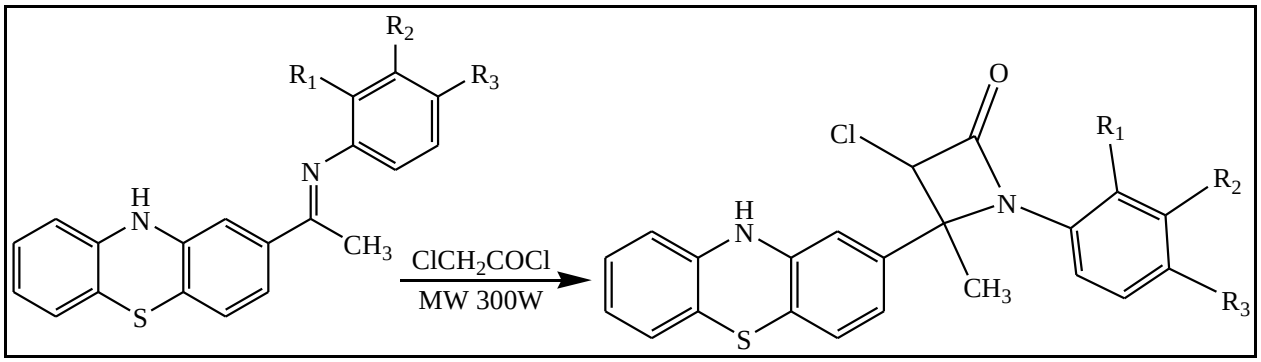
Table2. Antimicrobial activity of the compounds IIIa-h

Compounds	Bacillus subtillis	Escherichia coli	Candida albicans	Aspergillus niger
IIIa	17	15	19	16
IIIb	23	24	16	15
IIIc	27	26	20	19
IIId	26	29	18	17
IIIe	19	21	16	14
IIIf	24	25	26	26
IIIg	23	26	23	22
Ampicillin	35	34	-	-
Fluconazole	-	-	31	32

(Zone of inhibition in mm)

Results and Discussion:

Azetidin-2-one derivatives (III a-h**)** were synthesized at 300W microwave irradiation by treating various Schiff's bases (II a-h) with Chloroacetyl chloride. Formations of Azetidin-2-one derivatives were confirmed on the basis of elemental and spectral analysis. Compounds III **a** showed strong IR absorption bands at 1728 cm^{-1} (C=O) due to cyclic ketone stretching. ^{1}H NMR spectrum of compound **IIIa** showed multiplets at 8.09-6.35 due to aromatic protons, two doublets at 1.96 and 1.09 due to azetidin-2-one ring and methyl protons respectively, one multiplets at 1.61 due to ring proton. The physical data of compounds IIIa–h are recorded in Table 1. All synthesized Azetidin-2-one derivatives were screened for antimicrobial activity and compound IIIb- IIIh showed moderate to good activity.



Scheme1

Conclusions:

A simple, efficient, and convenient method was developed for the synthesis of Azetidin-2-one derivatives.

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