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Microwave –Assisted Efficient Synthesis of Thiazoles Containing Piperidone- 4-One Moiety as Probes for Antimicrobial Activities

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ABSTRACT

Microwave assisted organic reaction enhancements (MORE) is a simple, clean, fast, efficient, economic and environment friendly method for the synthesis of 4- piperidones. The aim of this article is to synthesize characterize and evaluate the antimicrobial activity of certain novel thiazole compounds. The synthesized compounds were characterized by elemental analysis and IR, NMR and mass spectral data. All compounds were found to exhibit a fair degree of antimicrobial activity.

Keywords: Piperidine -4-one, thioesemicarbazone, various substituted phenacyl –bromides.

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INTRODUCTION

Thiazole is a heterocyclic organic compound that has a five-member ring molecular structure (C_3H_3NS) containing three carbon atoms, one sulphur atom, and one nitrogen atom.Thiazole exhibit broad spectrum of chemotherapeutic properties such as antibacterial, antifungal and antitubercular, anti – HIV, anticonvulsant, anticancer, anti-inflammatory and analgesic.[1-7]

In the recent years, microwave assisted organic reactions have emerged as a new tool in organic synthesis. Important advantages of this technique include highly accelerated rate of the reaction, reduction in reaction time with an improvement in the yield and quality of product. Moreover the technique is considered as an important approach towards 'Green Chemistry' because of its eco-friendly nature[8-10]. Conventional methods of organic synthesis usually need longer heating time, elaborate and tedious apparatus set-up, which result in higher cost of the process and the excessive use of solvents/ reagents leads to environmental pollution.

Piperidones are active-biological compounds which possess analgesic, anti-inflammatory, anticancer and antimicrobial activities [11-14]. The heterocyclic compounds carrying piperidine skeleton are attractive targets inorganic synthesis owing to their stereo chemical and pharmacological activities. The reports indicate that the antimicrobial activities of piperidones were found to be significant in compounds possessing aromatic substituent's at 2 and 6 positions[15-17]. Due to versatile biological activities and pharmaceutical applications of 2,6-diarylpiperidin-4-ones is an important task by introducing convenience and efficient reagents.

MATERIAL AND METHODS:

The commercially available AR and LR grade chemicals were used without further purification. Chemical reagents and solvents were purchased from Sigma Aldrich. Melting points were determined in an open glass capillaries on Gallen camp apparatus and corrected. The percentage composition of the elements (CHNC) for the compounds were determined using an elemental analyzer CHNS model fission EA 1108. The infrared spectra were recorded as potassium bromide disc using a Perkin-elemer spectrophotometer GX. The ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded using JEOL JNM-ECP 400 spectrometer in DMSO-d_6 as the solvent using TMS as an internal standard, and chemical shifts are expressed as ppm. Mass spectra were recorded on micro-mass Q-TQF, and shimadzu LCMS 2010A mass spectrometer and the reactions were followed by TLC (silica gel, aluminum sheets 60 F_{235}, Merck).

Experimental Procedure:

Synthesis of 3-methyl- 2,6 –diphenylpiperidin – 4-ones

Dry ammonium acetate (0.02 mole) was dissolved in 10 ml. Ethanol and the solution were mixed with 4-substituted benzaldehyde (0.1 mole), benzaldehyde (0.1 mole) and ethyl methyl ketone (0.05 mole) was added and the reaction- mixture was placed in a conical flask, covered with a glass funnel. A petridish containing few ice pieces was kept on the funnel to prevent excess evaporation of the solvent. The reaction- mixture was irradiated with microwaves at different microwave intensities for different duration by following the pulse heating approach (irradiation in 30 s increments). A beaker containing water was also kept in the oven to serve as a 'heat sink'. To monitor the progress of the reaction, a TLC was run after every one minute of microwave irradiation using benzene ethyl acetate (7:3) solvent system.The product was recrystallized from ethanol.

Synthesis of 3-methyl-2,6-diphenyl thiosemicarbazone

To the mixture 0f 3-alkyl-2,6 –diphenyl-piperidin-4-ones (0.01 mole) in 10ml ethanol, few drops of conc. HCl were added. Thereafter thiosemicarbazide (previously dissolved in 20 ml ethanol) solution (0.01 mole) was added drop wise with stirring. The reaction – mixture was irradiated with microwaves for 5 minutes. A beaker containing water was also kept in the oven to serve as a ' heat sink'. To monitor the progress of the reaction, a TLC was run to confirm the completion of the reaction. After completion of the reaction, the solid product was filtered off and recrystallized from ethanol.

Synthesis of (Z) -2-((3-methyl-2,6-diphenyl piperidin -4-yliene) hydrazono) -4- phenyl-2,3-dihydrothiazole

The intermediate treated with various substituted phenacyl bromide in absolute ethanol, the reaction mixture was subjected to microwave irradiation under microwave at 350W for 5 minutes. The reaction was monitored by TLC, after the completion of 12 reactions, the reaction mixture was cooled to room temperature and poured on crushed ice with constant stirring. The solid obtained was filtered and wash with water, filtered and dried, recrystallized from absolute ethanol.

RESULTS AND DISCUSSION**:**

A new microwave procedure for the rapid and efficient synthesis of thiosemicarbazide, 4-piperidones and various substituted phenacyl bromide as being developed. The microwave heating effectively reduces the reaction time from 12-16 hrs to a few minutes (10-15 minutes) by using microwave irradiation for heating, all the compounds were prepared in yields that were appreciably more than the conventional methods. The quality of the products formed was found

to be showing a less number of impurities on TLC. We are hereby reporting a simple method for synthesizing a thiazole derivative, using a microwave condition, which does not need any catalyst. The work-up procedure is simple and convenient. The structure of the compounds was established on the basis of its elemental analysis and spectral data. We have concluded that the synthesized moieties are equally potent anti-microbial and anti- fungal activities.

Hence the application of microwave technique for the synthesis of the novel compounds with an objective to reduce reaction time and increase yield was explored. The authenticity of the product was confirmed by physical, chemical and spectral analysis.

Scheme:

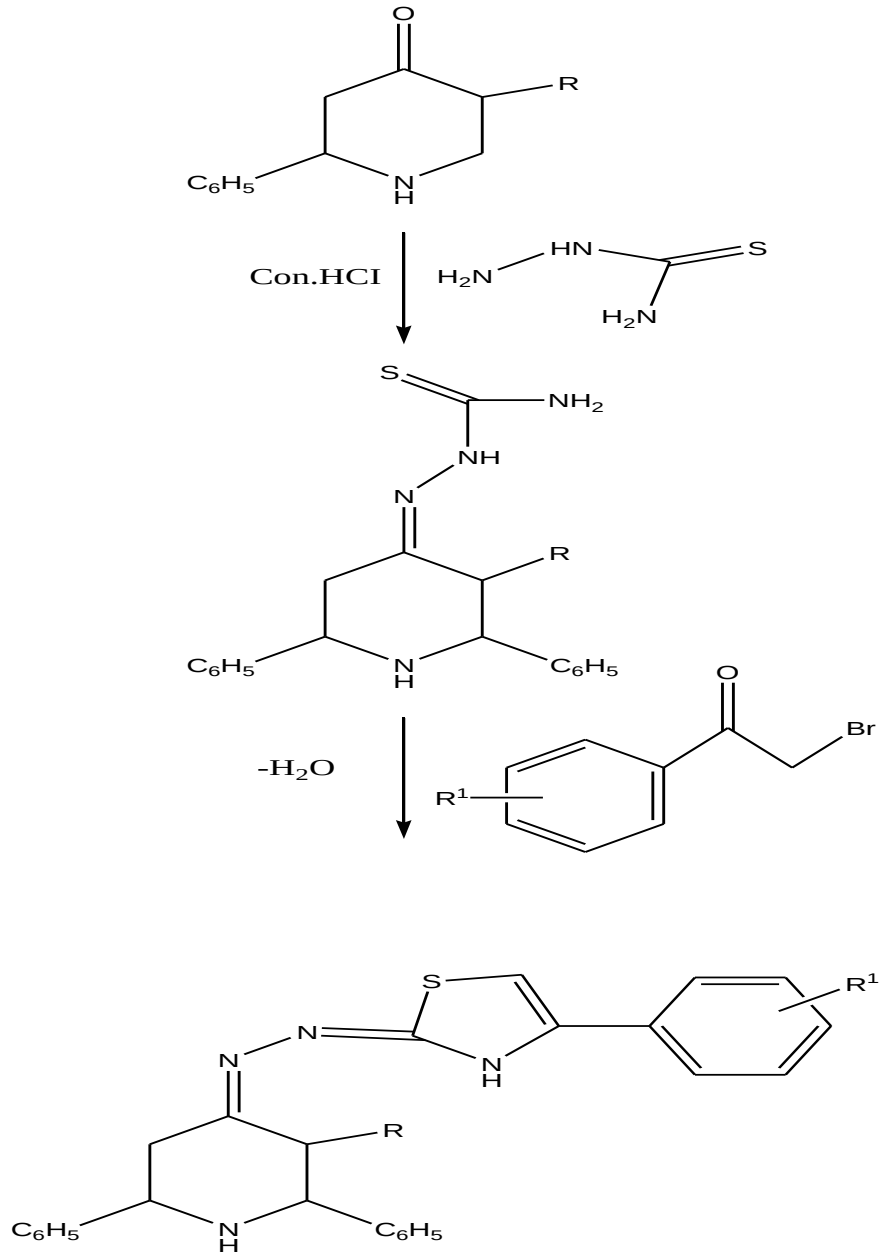


Table 1

S.No.	R1	R2	Melting point	Yield	Molecular Formula	Molecular Weight	Mass
1	CH_3	4-NO_2	150^0	79%	$C_{27}H_{25}N_5O_2S$	483.59	485
2	CH_3	H	162^0	84%	$C_{27}H_{26}N_4S$	438.59	440
3	CH_3	4-CN	170^0	82%	$C_{28}H_{25}N_5S$	463.60	465
4	CH_3	-OCH_3	124^0	78%	$C_{28}H_{28}N_4OS$	468.61	469
5	$(CH_3)_2$	4-NO_2	140^0	86%	$C_{28}H_{27}N_5O_2S$	497.61	499
6	$(CH_3)_2$	H	158^0	84%	$C_{28}H_{26}N_4S$	452.61	454
7	$(CH_3)_2$	4-CN	136^0	72%	$C_{29}H_{27}N_5S$	477.62	479
8	$(CH_3)_2$	-OCH_3	119^0	78%	$C_{29}H_{30}N_4OS$	482.64	484

Antimicrobial Activity:

The compounds were screened for their antibacterial activity against four strains of bacteria staphylococcus aureus, bacillus substilis, Escherichia coli and Candida albicans and Aspergillus Niger uses the paper disc technique. The zone of the inhibition against all the microorganisms was measured in millimeter the antifungal activity studies were carried out against Candida albicans, Aspergillus niger, Aspergillus niger fumigates, Rhizopus sps, Pencillium sps, Mucor sps. The results are present in Table 1 and 2.

Table 2 Antibacterial Activity

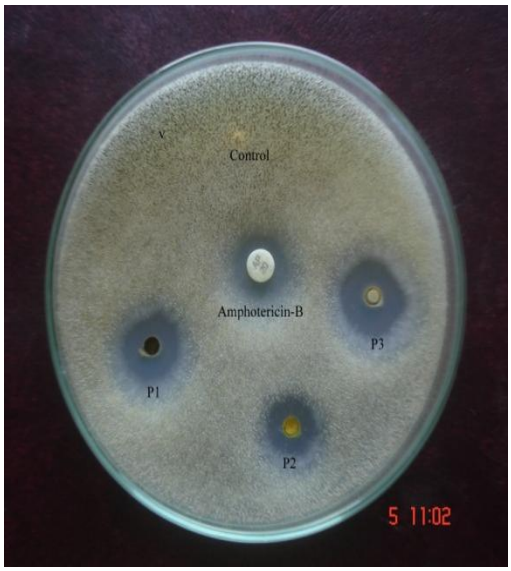
S.No	Microorganisms	Control (Solvent)	P1	P2	P3	Ciprofloxacin
1.	*Escherichia coli*	-	12	-	-	7 mm
2.	*Staphylococcus aureus*	-	14	12	10	10 mm
3.	*Klebsiella pneumoniae*	-	-	6	9	7 mm
4.	*Streptococcus faecalis*	-	9	8	14	11mm
5.	*Proteus vulgaris*	-	9	10	13	9mm
6.	*Bacillus sps*	-	11	15	11	10mm

Table-3 Antifungal Activity

S.No	Microorganisms	Control (solvent)	P1	P2	P3	Amphotericin-B
1.	*Aspergillus niger*	10mm	11mm	15mm	15mm	8 mm
2.	*Trichophyton rubrum*	10mm	8mm	14mm	14mm	15 mm
3.	*Rhizopus sps*	11mm	10mm	13mm	13mm	15mm
4.	*Candida albicans*	7mm	9mm	11mm	11mm	8mm
5.	*Mucor Sps*	13mm	12mm	15mm	15mm	10mm
6.	*Aspergillus fumigatus*	10mm	10mm	13mm	13mm	9mm

Most of the synthesized compounds exhibited mild to moderate antimicrobial activity against the tested microorganisms. The interesting results we observed that both electrons donating as well as electron withdrawing groups was found to increase the anti-microbial properties, whereas Unsubstituted derivatives exhibited a lesser degree of activity.

Further, incorporation of $–NO_2$, -CN group in the phenyl ring, increased lipophilicity as well as a remarkably increased the antibacterial and antifungal activity. Basically the introduction of thiazole moiety in the piperdone ring has increased the antifungal activity.



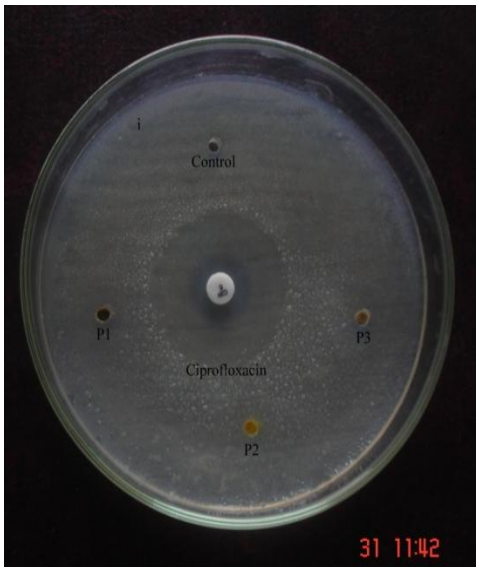
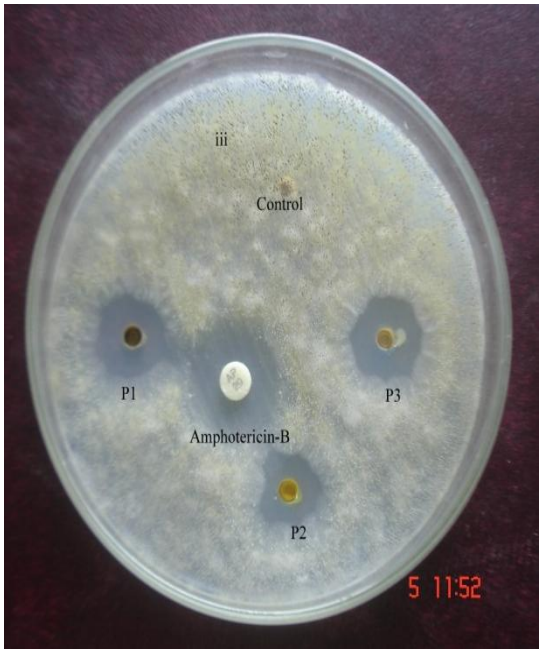


Figure 1& 2: Antibacterial Activity



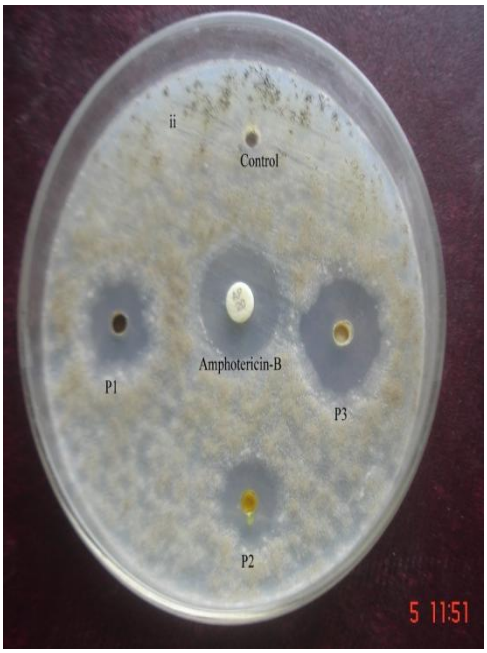


Figure 3& 4Antifungal Activity

CONCLUSION:

The main aim of the present study is to synthesize and investigate the antimicrobial activity of new heterocyclic derivatives containing piperidone-4-onemoieties, with the hope of discovering new structures serving as potential broad spectrumanti-microbial agents.

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