

MICROWAVE ASSISTED SYNTHESIS VIA CHALCONES, CHARACTERIZATION AND ANTHELMINTIC SCREENING OF PYRIMIDINE DERIVATIVES

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ABSTRACT

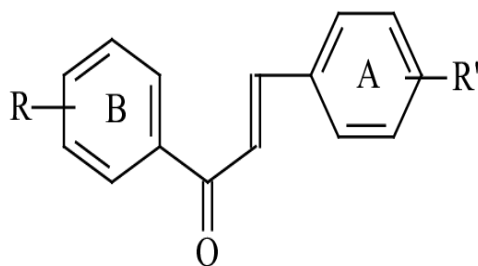
Chalcones possess a broad spectrum of biological activities including antioxidative, antibacterial, antihelmintic, amoebicidal, antiulcer, antiviral, insecticidal, antiprotozoal, anticancer, cytotoxic and immunosuppressive. Changes in their structure have offered a high degree of diversity that has proven useful for the development of new medicinal agents having improved potency and lesser toxicity and good pharmacological actions. In the present study, we focused on the environment-friendly processes used for the preparation of pyrimidine derivatives with pharmacological properties. In this regard, microwave heating is used as the alternative energy sources to synthesize a series of pyrimidine derivatives by the condensation of chalcones with urea under basic conditions. Chalcones were synthesized by Claisen

-Schmidt condensation of acetophenone with various substituted benzaldehyde in the presence of ethanolic potassium hydroxide solution. The synthesized pyrimidine derivatives were characterized by IR, ¹H NMR, Mass Spectra and CHN analyses confirmed the structure of the prepared compounds. The newly synthesized pyrimidine derivatives were screened for their antimicrobial & anthelmintic activity.

KEYWORDS: Pyrimidine, Chalcone, Anthelmintic activity.

INTRODUCTION

Chalcones are α , β -unsaturated ketones consisting of two aromatic rings such as ring A and B. Both rings are interconnected by a highly electrophilic three carbon α , β -unsaturated carbonyl system that assumes linear or planar structure.



They possess conjugated double bonds and a completely delocalized π -electron system on both benzene rings. Chemically, chalcone is 1, 3-diphenyl- 2-propene-1-one. These are coloured compounds due to presence of the chromophore, ketoethylenic group ($-\text{CO}-\text{CH}=\text{CH}-$) in their structure. Chalcones are synthesized by claisen- schmidt condensation of ketone with different aromatic aldehydes by strong bases (NaOH/KOH) or acid catalyzed followed by dehydration process. The presence of reactive α , β -unsaturated keto group in chalcones is found to be responsible for producing their biological activity. Chalcone derivatives are considered as key starting materials for the syntheses of different classes of heterocyclic compounds such as pyrazolines, oxazoles, isoxazoles, thiophenes and pyrimidines, etc. Among the heterocyclic compounds, Pyrimidine derivatives are valuable heteroaromatic compounds because of their wide spectrum of pharmacological applications such as antimalarial, anthelmintic, anticancer, antimicrobial, anti-convulsion and anti-inflammatory activities.

MATERIALS AND METHODS

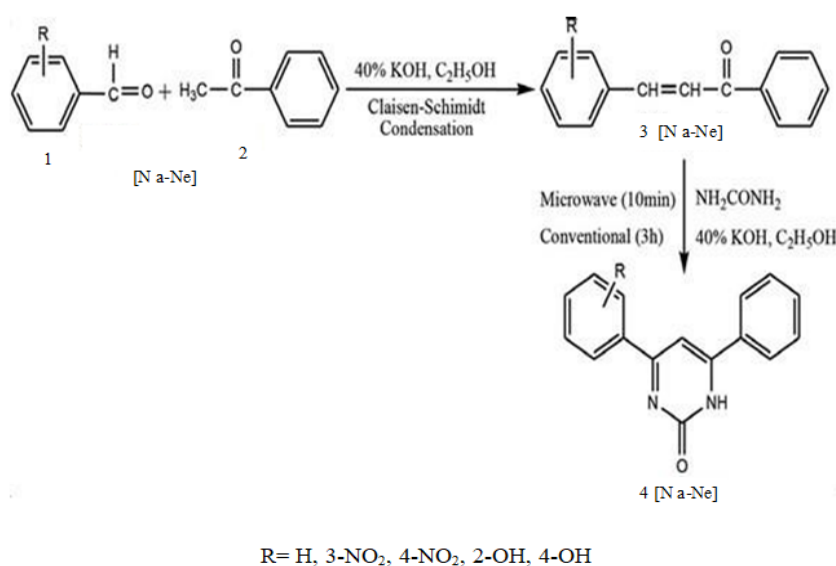
All chemicals were of synthetic grade (S. D. Fine. Chem. Ltd. Mumbai, India). Both conventional and microwave synthesis was carried out to compare reaction time and yield of product. The microwave irradiated synthesis was performed in scientific microwave oven, Catalyst System (operating between 140-700 W). All the reactions were carried out at power level-2, which corresponds to 210 W. The synthesized products were recrystallized from ethanol as a solvent. Melting points were determined in open capillary tubes, expressed in $^{\circ}\text{C}$ and are uncorrected. The time required for completion of the reaction and the purity of the compounds were checked by ascending TLC using pre-coated Silica gel-G plates and spots were observed by exposure to iodine vapours or by UV light at 254 and 366 nm. The compounds were characterized by using IR, ^1H NMR, Mass spectral and Elemental analysis. The IR spectra of the compounds were recorded on Shimadzu IR Affinity FT-IR using KBr discs and the values are expressed in cm^{-1} . The ^1H NMR spectra were recorded on a Bruker AC 400 MHz spectrometer using TMS as the internal standard in $\text{DMSO}-d_6$. The

multiplicities of the signals are denoted with the symbols s, d, t and m for singlet, doublet, triplet and multiplet, respectively. The LCMS spectra were recorded on Waters Micromass Q-Tof Micro (70 eV), a hybrid quadrupole time of flight mass spectrometer. Elemental analyses of the newly synthesized compounds were carried out on Carlo Erba 1108 analyzer.

Experimental

Synthesis of pyrimidine derivatives

1. Synthesis of chalcones (3N a-e)



Substituted benzaldehydes (1N a-e) (0.01mol) and acetophenone (2) (0.01 mol, 1.2 g) were mixed and dissolved in ethanol (10 ml). To this, 40% aqueous solution of potassium hydroxide (10 ml) was added slowly with constant stirring. The reaction mixture was stirred continuously for 3 h at room temperature. The completion of reaction was confirmed by monitoring TLC using silica gel-G. After completion of the reaction, the reaction mixture was kept in refrigerator overnight. The product was filtered and washed with cold water till the washings were neutral to litmus, if necessary acidified with dilute HCl. The product was dried and recrystallized from rectified spirit to get pale yellow colored solid chalcones (3N a-e).

2. Syntheses of 4-(substituted-phenyl)-6-phenyl- pyrimidin-2(1H)-one (4Na-e) Conventional Synthesis

A mixture of chalcone (3Na-e) (0.01 mol), urea (0.01 mol, 0.6 g) were dissolved in ethanol (10 mL, 95%). To this, 40% aqueous potassium hydroxide solution (10 ml) was added slowly

with constant stirring. The reaction mixture was allowed to reflux on water bath for 4 h. In between TLC was monitored to check the completion of reaction. After completion of reaction, the reaction mixture was cooled to room temperature and then poured into ice cold water and neutralized by adding dilute HCl. The precipitate (4Na-e) obtained was filtered, washed with water and dried. The product was recrystallized from rectified spirit. Conventional synthesis (yield 58- 65%). All the synthesized compounds were soluble in methanol, ethanol, and dimethyl sulphoxide and insoluble in nonpolar solvents. The structures of prepared pyrimidine derivatives have been elucidated by spectroscopic data and elemental analysis.

Microwave synthesis

A mixture of chalcone (3Na-e) (0.01 mol), urea (0.01 mol, 0.6 g) was dissolved in ethanol (10 ml, 95%). To this, 40% aqueous potassium hydroxide solution (10 ml) was added slowly with constant stirring. The reaction mixture was placed in microwave and irradiated at power level-2 (210 W) for 7-10 min. In between, TLC was monitored to check the completion of reaction condition-. After completion of reaction, the reaction mixture was cooled to room temperature and then poured into ice cold water and neutralized by adding dilute HCl. The precipitate obtained was filtered, washed with water and dried. The product (4Na-e) was recrystallized from rectified spirit.

Table 1: Elemental analysis of titled compound (4Na-e).

Compound Code	Molecular formula	Elemental Analysis (%)							
		Calculated				Found			
		C	H	N	O	C	H	N	O
4Na	C ₁₆ H ₁₂ N ₂ O	77.40	4.87	11.28	6.44	77.33	4.85	11.23	6.43
4Nb	C ₁₆ H ₁₁ N ₃ O ₃	65.53	3.78	14.33	16.37	65.20	3.69	14.36	16.39
4Nc	C ₁₆ H ₁₁ N ₃ O ₃	65.53	3.78	14.33	16.37	65.80	3.79	14.30	16.38
4Nd	C ₁₆ H ₁₂ N ₂ O ₂	72.72	4.58	10.60	12.11	72.18	4.71	10.63	12.09
4Ne	C ₁₆ H ₁₂ N ₂ O ₂	72.72	4.58	10.60	12.11	72.90	4.54	10.58	12.10

Table 2: Physical Characterization Data and Comparison between Conventional and Microwave Assisted Synthesis of Pyrimidine Derivatives (4Na-e).

Comp. Code	Structure (R)	Rf Value	M.P. (°C)	Conventional Method			Microwave Assisted Method			
				Time (h)	Energy (Temp. °C)	Yield (%)	Time (min.)	Energy (Power. Watt)	Yield (%)	Atom Economy
4Na	H	0.64	88-91	3	98-100	60.65	7	210	78.48	65.52 %
4Nb	3-NO ₂	0.66	201-204	4	98-100	60.85	9	210	82.73	71.47%

4Nc	4-NO ₂	0.68	176-179	4	98-100	62.85	8	210	82.33	69.35%
4Nd	2-OH	0.56	197-200	4	98-100	65.31	10	210	86.82	73.83%
4Ne	4-OH	0.50	185-190	3	98-100	62.56	9	210	81.66	68.28%

The synthesized compounds were analyzed by their physical and chromatographic parameters. Further analysis by IR, NMR, and Mass spectroscopy was carried out to interpret the structure of the above synthesized compounds. The mobile phase selected for TLC study was n-hexane: ethyl acetate (70:30). The spectra of chalcones show usually a peak, near 1638-1670 cm^{-1} , characteristic of α,β unsaturated carbonyl group. The α -H and β -H of chalcones resonate at δ 6.7-7.4 and δ 7.3-7.7 as two doublets ($J=17$ H) in the ^1H NMR spectra. The IR spectrum of pyrimidine derivatives (4Na-e) showed absorption at δ max 2961-2991 cm^{-1} (Ar-C-H), 1601 and 1610, 3316 cm^{-1} (pyrimidine-NH Str.), 3293-3302 cm^{-1} (Ar-OH) respectively. In the ^1H NMR spectrum, the proton of the -CH and -NH of pyrimidine nucleus resonated as a sharp singlet at δ 3.61 and 8.24 respectively. The aromatic protons were seen as a multiple at δ 6.74-8.02. The mass spectra of the pyrimidine derivatives exhibited molecular ion peak corresponding to their molecular formula. Compound 4ya and 4yb showed molecular ion peak at m/z 250 and 295 respectively. All the synthesized compounds showed significant anthelmintic activity. Among the tested compounds, 4Ne showed potential anthelmintic activity 27 ± 0.66 and 35 ± 0.76 min for paralysis and death respectively as compared to the standard drug.

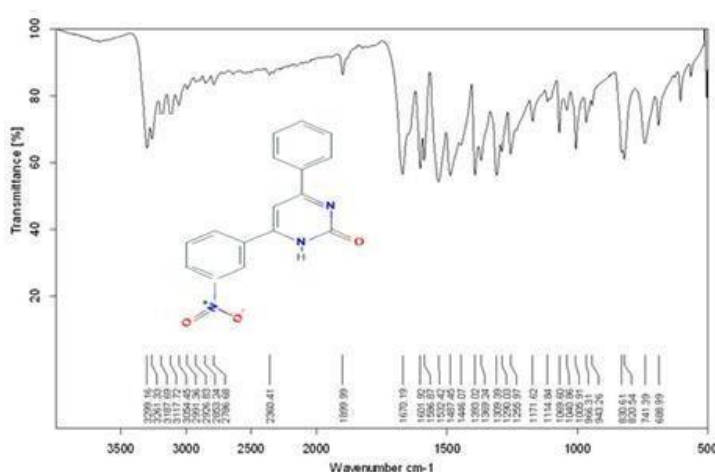


Figure No. 1: I.R Spectra of 4-(3-nitro-phenyl)-6-phenyl-pyrimidin-2(1H)-one (4Nb).

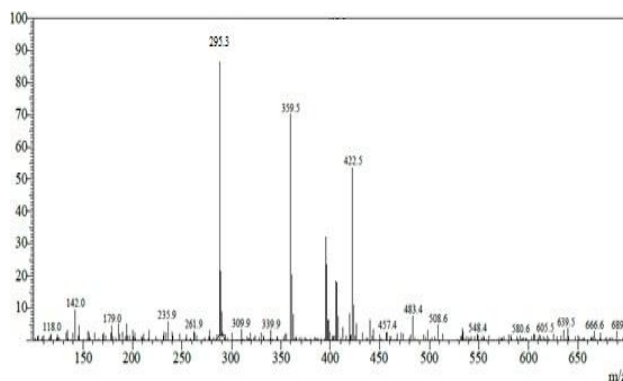


Figure No. 2: Mass Spectra of (4Nb).

Biological evaluation

Antibacterial and Antifungal evaluation

Material and Methods

Test samples

Pyrimidine Derivatives synthesized by conventional method are used for screening purpose. The test samples were dissolved in dimethylsulphoxide (DMSO) and the corresponding concentrations were expressed in terms of μg of compound per ml of solvent ($\mu\text{g}/\text{ml}$).

Test organisms

Clinically isolated four bacterial strains namely *Staphylococcus aureus*, *Bacillus subtilis*, *E. coli*, *Pseudomonas aeruginosa* and three different fungal strains namely, *Aspergillus niger*, and *Candida albicans* were collected from Department of Microbiology, M. R. Medical College, Gulbarga, India. The bacterial strains were grown in Mac Conkey agar plates at 37 °C and maintained on nutrient agar slants, while fungi were grown at 30 °C and maintained in Saboraud glucose agar slants.

Screening for antimicrobial activity

The test was performed by disc diffusion assay as per NCCLS, 1993. The nutrient agar plates containing an inoculum size of 10^6 cfu / ml for bacteria and 2×10^5 spores for fungi on Saboraud glucose agar plates were used. Previously prepared compound impregnated disc (6mm in diameter) at the concentrations of 200 $\mu\text{g}/\text{ml}$ for bacterial and 200 $\mu\text{g}/\text{ml}$ for fungal strains were placed aseptically on sensitivity plates with appropriate controls Ciprofloxacin (200 $\mu\text{g}/\text{ml}$) and Griseofulvin (200 $\mu\text{g}/\text{ml}$) were used as standard antibacterial and antifungal antibiotics respectively. Plates were incubated at 37 °C for 24 hours for bacteria and 30 °C for 72 hours for fungal inoculums. Sensitivity was recorded by measuring the clean zone of growth inhibition on agar surface around the disc.

Determination of Minimum Inhibitory Concentration(MIC) by broth dilution method

MIC was determined by broth dilution method for each of the test organism. To 0.5 ml of varying concentrations of the compounds (0-200 µg/ml for bacterial strains and 0-200 µg/ml for fungal strains), 2ml of nutrient broth was added and then a loopful of test organism was introduced into the tubes. The procedures were repeated on the test organisms using standard antibiotics Ciprofloxacin and Griseofulvin. A tube containing nutrient broth only seeded with the test organisms served as control. Tubes containing bacterial cultures were then incubated at 37 °C for 24 hours for bacteria and 30 °C for 72 hours for fungal spores. After incubation the tubes were examined for microbial growth by observing the turbidity through spectroscopic method.

Table No. 3: Antibacterial activity of synthesized compounds.

Sl. No	Compound code (200 µg/ml)	<i>S. aureus</i> (mm)	<i>B. subtilis</i> (mm)	<i>E. coli</i> (mm)	<i>P. aeruginosa</i> (mm)
1	4Na	15.85 ± 0.10	13.29 ± 0.34	13.38 ± 0.01	12.19 ± 0.88
2	4Nb	14.68 ± 0.34	13.90 ± 0.25	14.57 ± 0.48	13.02 ± 0.00
3	4Nc	13.42 ± 0.20	13.44 ± 0.08	14.80 ± 0.01	13.65 ± 0.00
4	4Nd	12.33 ± 0.65	12.00 ± 0.00	12.21 ± 0.30	14.66 ± 0.10
5	4Ne	13.00 ± 0.23	14.72 ± 0.55	13.38 ± 0.07	15.33 ± 0.07
6	3Na	11.30 ± 0.23	11.21 ± 0.66	10.44 ± 0.40	12.12 ± 0.22
7	Ciprofloxacin	16.90 ± 0.10	14.95 ± 0.14	15.00 ± 0.09	17.00 ± 0.11

All values are expressed as mean ± S.E.M. of three replications

Table No. 4: Antifungal activity of synthesized compounds.

Sl. No.	Compound code (200 µg/ml)	<i>A. niger</i> (mm)	<i>C. albicans</i> (mm)
1	4Na	12.21 ± 0.34	12.39 ± 0.00
2	4Nb	11.06 ± 0.07	09.88 ± 0.23
3	4Nc	14.18 ± 0.88	10.18 ± 0.78
4	4Nd	12.08 ± 0.59	10.00 ± 0.43
5	4Ne	15.43 ± 0.88	13.88 ± 0.88
6	3Na	10.23 ± 0.08	10.38 ± 0.02
7	Griseofulvin	16.50 ± 0.99	14.00 ± 0.14

All values are expressed as mean ± S.E.M. of three replications

Table No. 5: MIC of synthesized compounds for bacterial strains.

Sl. No.	Compound code (200 µg/ml)	<i>Staphylococcus aureus</i>	<i>Bacillus subtilis</i>	<i>E. coli</i>	<i>Pseudomonas aeruginosa</i>
1	4Na	20	30	100	20
2	4Nb	80	50	-	60
3	4Nc	30	40	60	30
4	4Nd	60	80	80	50

5	4Ne	40	30	10	40
6	3Na	40	40	30	-
7	Ciprofloxacin	10	-	20	20

Table No. 6: MIC of Synthesized compounds for fungal strains.

Sl. No.	Compound code (200 µg/ml)	<i>A. niger</i>	<i>C. albicans</i>
1	4Na	50	40
2	4Nb	60	90
3	4Nc	10	40
4	4Nd	60	80
5	4Ne	30	60
6	3Na	60	20
7	Griseofulvin	10	20

From the data of the Table No 5 and Table No 6 of antibacterial and antifungal activity it is clearly concluded that the synthesized compounds are significant and moderate antibacterial and antifungal agents. The substituted Pyrimidine moieties are already known for different biological activities. Here we have synthesized some Pyrimidine analogues combining with different substituted aromatic system with view to get a good antibacterial and antifungal agents with less toxic and side effects. As per the results of screening it is clearly indicated that the compounds 4Na, 4Nb, 4Nc, 4Nd and 4Ne have shown significant antibacterial and compounds 4Na, 4Nb, 4Nc, 4Nd and 4Ne has shown significant antifungal activity with the standard drugs. This is because of the presence of different groups like – NO₂, -OH at the 4th positions of phenyl nucleus which is attached to Pyrimidine molecule. From the above results one can establish that the synthesized substituted Pyrimidine molecule can be rich source for the exploitation. Therefore in search of new generation of the active compounds, it may be worthwhile to explore the possibility in this area by introducing different functional groups or by cyclization as substitutions. Which may results into better pharmacological agents? The objective of the present work is to synthesize some Pyrimidine derivatives and to study their antibacterial, antifungal activity, and antimicrobial activity thus an attempt has been made in this direction. As expected Pyrimidine derivatives exhibited significant and moderately antibacterial, antifungal activity and antimicrobial activity when compared with standard drugs respectively. Therefore further a detailed study of toxicity is necessary. There is no such a thing as completely safe drug. Drugs are powerful tools, which alter physiological processes for the better or for the worse. A society that wishes to benefit from them will not achieve all the benefits open to it, if it ignores the fact and seeks for impossible standards of harmlessness. Further the detailed structural activity relationship studies are required along

with the molecular manipulation i.e. molecular modeling may give better drugs. Molecules prepared for the biological testing do not always turn out as potential new drugs, but may be intended to serve as models for evaluation of hypothesis.

Anthelmintic activity

Helminthiasis is a macro parasitic disease found in humans due to parasitic worms such as Nematodes or Cestodes which are present in skin, liver, brain, lungs, lymph, eye, muscles etc. of the body. The marketed anthelmintic drugs are used to expel such parasitic worms from the body by either stunning or killing them without causing any significant damage to the host cell. Pyrimidine derived drugs such as pyrantel and morantel are commonly used as anthelmintic agents which has broad spectrum activity. Indian adult earthworms were selected to study the antihelmintic activity. The earth- worms were collected from the water logged areas of soils in Kalaburagi, Karnataka, India. Earth- worms were washed with normal saline to remove all the fecal matter and waste surrounding their body. The earth worms (*Pheritima posthuma*) 5-8 cm in length and 0.2-0.3 cm width weighing 0.8-3.04 g were used for experimental protocols. As the earthworms are resembled anatomically and physiologically with the intestinal roundworm parasites of human beings, hence they were selected to study the anthelmintic activity.

Table No. 7: Anthelmintic activity of titled compounds.

Sl. No.	Compounds	Dose	Paralysis time (Minute)	Death time (Minute)
			Mean±S.E.M	Mean±S.E.M
1	4Na	100mg/mL	20±0.5	32±0.41
2	4Nb	100mg/mL	25±0.529	32±0.36
3	4Nc	100mg/mL	30± 0.763	35±0.61
4	4Nd	100mg/mL	27±0.76	32±0.8
5	4Ne	100mg/mL	27±0.66	35±0.76
6	3Na	100mg/mL	20±1.2	22±0.78
7	Control (Normal saline)	-----	-----	-----
8	Albendazole	100mg/mL	20±1.1	21±2.1

Procedure

Gum acacia solution (1%) was prepared by using normal saline. Test solutions (100mg/ml) were prepared by using Gum acacia solution. Samples were taken in petriplates and adult healthy earth worms (n=6) were introduced into petriplates. Observations were made for the time taken to paralyze and time taken for death of the earthworms. Paralysis was said to

occur when the worms do not revive even in normal saline. Death was concluded when worms lost their motility followed by fading away of the body color and the values are summarized in Table 7 and in figure 3.

Effect of Pyrimidine Derivatives on *Pheritima Posthuma* (Earth Worms)

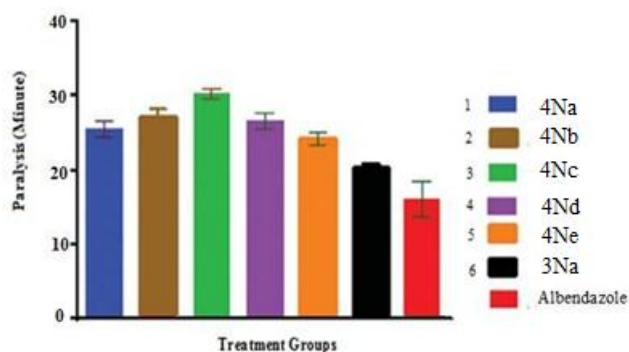


Figure No. 3: Anthelmintic activity (Paralysis time) of titled compounds.

RESULTS AND DISCUSSION

The chalcones were prepared by the Claisen Schmidt condensation of acetophenone with various substituted benzaldehyde (1Na-1Ne) in the presence of ethanolic potassium hydroxide solution. Both conventional as well as microwave assisted methods followed to prepare a series of pyrimidine derivatives via chalcones by the treatment of chalcones with urea in basic media. The prepared compounds along with their reaction time period and percentage yields were given in Table 2. It was found that the microwave assisted method is energetically favorable which requires less time with enhanced reaction rates and provides better yields (78-85%) with pure product as compared to the standard marketed miraculous drug.

CONCLUSION

In an attempt to develop new class of anthelmintic agents, a series of pyrimidine derivatives were efficiently synthesized with good yield and purity in less reaction time by microwave irradiated method as compared to conventional heating technique. Microwave irradiated synthesis is an invaluable technology which made the chemical reaction simple, rapid and eco-friendly to get the cleaner products. By the help of microwave synthesis, the yield of product was increased from 60 upto 86 % as compared to conventional synthesis which signifies the utility of green chemistry approach. Some of the synthesized compounds showed significant anthelmintic activity. Compound 4ye with electron withdrawing groups was found

to be highly potent among the series. Thus, the quest to explore many more modifications on chalcone and pyrimidine moiety needs to be continued.

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