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Research Article

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF PYRIMIDINES FROM CHALCONES

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ABSTRACT

One of the most important classes of organic compounds present in nature or synthesized in the laboratory is heterocyclic systems. In the treatment of commonly occurring diseases and biological activities these compounds possess an array. Literature survey revealed that Chalcones and Pyrimidines possess a broad spectrum of biological activities like anti-inflamm atory, anti-malarial, antimicrobial, anti-depressant, anti-histamine, anti-tubercular and anti-cancer. This research is an endeavor in this direction of synthesis and characterization of such compounds based on Elemental analysis, IR, ^{1}H NMR and Mass spectroscopy. The pharmacological and anti-bacterial screening of synthesized compounds has also been included. To access many heterocyclic systems containing Nitrogen and Oxygen, chalcones afford a facile route. Hence an attempt is made to synthesize chalcones by the Claisen – Schmidt condensation from 4-Imidazolyl acetophenone with two substituted aromatic aldehydes. After purification and characterization by physical and spectral methods, the resulting chalcones have been converted successfully into Pyrimidines by treatment with Guanidine hydrochloride. Based on the reported literatureby physical and spectral methods the resultant compounds were identified also screened for antibacterial activity.

INTRODUCTION

Among pharmaceutically significant natural products and synthetic compounds the remarkable ability of heterocyclic nuclei serves both as reactive pharmacophores and biometrics. Chalcones 1, 3-diphenylpropenones, constitute one of the major classes of flavonoids with widespread distribution in fruits,vegetables, tea and soy. Prehistoric therapeutic applications of chalcones can be associated with the thousand-year old use of plants and herbs for the treatment of different medical disorders. Contemporary studies report a generous variation of significant pharmacological activities of chalcones including anti-inflammatory, anti-cancer effects, cytotoxic anti-proliferative, anti-oxidant, and anti-microbial activities[1-3]. The effect of chalcone analogues as cell cycle blockers, anti-inflammatory, anti-mitotic, anti-infective, anti-malarial, insecticidal, anti-viral, anti-fungaland cardiovascular agents. In the biosynthesis of flavones and flavanones, chalcones are important precursors and are usually synthesized from acetophenones and benzaldehydes, using base in a polar solventvia the Claisen-Schmidt condensation. Inorganic synthetic chemistry have widely popularized in "Pyrimidine" and their derivatives[4-6]. Pyrimidine does not exist in nature but in the form of its different derivatives, it is found as a part of more complex system and is widely distributed. Pyrimidine derivatives are of interest because of their pharmacological properties [7-9]. These properties include antifungal, antiprotozoal, antihypertensive, anticancer, antiviral, antihistaminic, anti-inflammatory, antibacterial and central nervous activities. In drug discoverysynthesis of new chemical entities is major bottleneck. To synthesize and antibacterial activity studies of chalcones and pyrimidines derivatives the attempt was done.

Chemistry

The melting points were recorded in melting point apparatus and were uncorrected. IR spectra were recorded using Perkin Elmer FT-IR (89258) spectrophotometer. A ^{1}HNMR spectrum was recorded using DMSO on BrukerAvance (400 MHz) and their chemical shifts are recorded in δ (parts per million) units with respect to tetramethylsilane (TMS) as internal standard. All the reagents andsolvents used were of analytical grade.

MATERIALS AND METHODS

Present research is divided into four parts:

Step I **:** Synthesis of chalcones.
Step II **:** Synthesis of Pyrimidines

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Step III **:** Characterization of derivatives
Step IV **:** Biological Evaluation

Step I: Synthesis of Chalcones

Synthesis of Chalcone -1 (Claisen- Schmidt condensation)

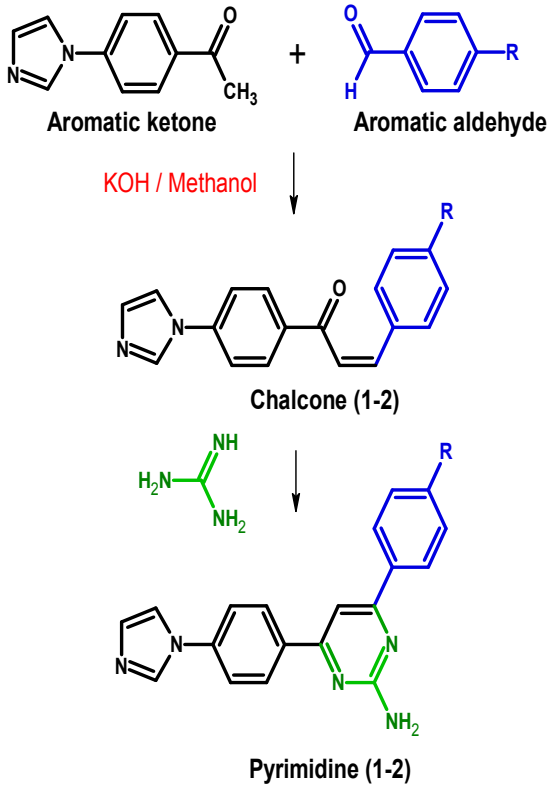
Equimolar quantities (0.003mol) of 4-imidazolyl acetophenone and 4-hydroxy benzaldehyde were mixed and dissolved in minimum amount of alcohol. To this, aqueous potassium hydroxide solution (5-10ml) was added slowly and mixed occasionally for 24 hours, at room temperature. Completion of the reaction was identified by TLC using silica gel-G. After completion of the reaction, the mixture was poured onto crushed ice, acidified if necessary with dilute hydrochloric acid, and the solid that separated was isolated by filtration, dried and recrystalised from hot ethanol [10].

Step II : Synthesis of Pyrimidines

Synthesis of pyrimidine from chalcone

Chalcone -1 (0.001 mol) was condensed with guanidine hydrochloride (0.001 mol) in the presence of potassium hydroxide (0.002 mol) in absolute ethanol (5 ml) at reflux temperature for 6 hours. The solvent was evaporated and crushed ice was added to the residue to obtain a bright yellow solid separated out. This solid was filtered under vacuum, dried and recrystalized from hot ethanolic solution to give pure pale yellow solid [11].

Scheme

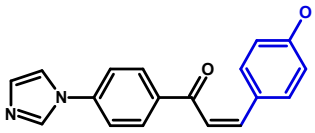
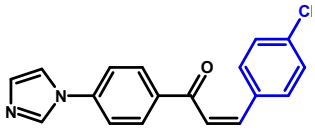
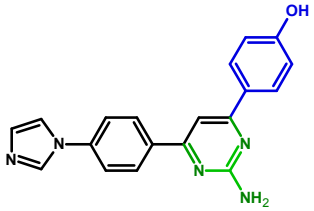
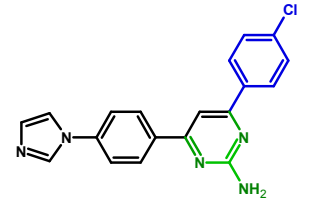


Scheme shows the detailed Structures of Chalcones and Pyrimidines

Step III: Characterization of derivatives

Spectral data

Table 1 shows the spectral data of the given compounds

COMPOUND	SPECTRA
 CHALCONE 1	**EIMS (m/z %):** 289(M^+, 100) **^{1}H NMR (DMSO):** δ 7.93 (s, 1H), 7.85 (d, 1H), 7.82 (d, 1H), 7.1-7.9 (d, Ar-8H), 6.8-6.9 (d, β-1H), 6.63(d, α-1H) **IR (KBr, cm^{-1}):** 2853.49 (Al C-H), 1645.79 (Al C=C), 1056.91 (Al C-C), 1752.89 (C=O), 3132 (O-H), 1371.79 (C-O), 1675.04 (C=N), 1189.82 (C-N), 1291.28 (Ar C=C), 1056.91 (Ar C-C), 2626.34 (Ar C-H).
 CHALCONE 2	**EIMS (m/z %):** 309(M^+, 100) **^{1}H NMR (DMSO):** δ 7.92-7.97 (d, Ar- 4H), 7.86 (s, 1H), 7.7 (d, 1H), 7.6 (d, 1H), 7.50-7.51 (d, β-1H), 7.4-7.5 (d, Ar-4H), 5.22-5.25 (d, α-1H) **IR (KBr, cm^{-1}):** 2853.77 (Al C-H), 1655.54 (Al C=O), 1605.01 (C=N), 1188.65 (C-N), 2615.91 (Ar C-H), 768.68 (C-Cl).
 PYRIMIDINE 1	**EIMS (m/z %):** 330(M^+, 100) **^{1}H NMR (DMSO):** δ 8.0-8.4 (d, Ar 4H), 7.87 (s, 1H), 7.87 (d, Ar-2H), 7.81 (d, 1H), 7.6 (d, Ar-2H), 6.86 (d,1H), 6.61 (s, Ar-1H) **IR (KBr, cm^{-1}):** 3118.68 (Ar C-H), 1606.34 (Ar C=C), 1667.27 (Ar C=N), 3315.71 (O-H), 1169.60 (C=O).
 PYRIMIDINE 2	**EIMS (m/z %):** 348(M^+, 100) **^{1}H NMR (DMSO):** δ 8.40-8.41(d, Ar-2H), 8.38(s, 1H), 8.30-8.28 (d, Ar-2H), 7.88-7.83 (d, Ar-4H), 7.26-7.59 (d, 1H), 7.16 (s, Ar-1H), 6.82 (d, 1H) **IR (KBr, cm^{-1}):** 3109.84 (Ar C-H), 1612.84 (Ar C=C), 1679.69 (C=N), 731.29 (C-Cl).

Step IV: Biological Evaluation

Antibacterial Activity

The antibacterial activity of all synthesized compounds was determined by disc diffusion method. All human pathogenic bacteria viz. *Escherichia coli, staphylococcus aureus* were procured from SGRRITS Dehradun. The nutrient agar medium was prepared. Preparation of nutrient broth, subculture, base layer medium and peptone water was done as per the standard procedure. The disc measuring 6.25 in diameter was punched from whatmann No.1 filter paper. Stock solution of synthesized compounds diluted in dimethylsulphoxide (1% DMSO) to give final concentration of 500µg/ml and 1000µg/ml. A reference standard for both gram positive and gram negative bacteria was made by dissolving accurately weighed quantity of ciprofloxacin (500µg/ml, 1000µg/ml) respectively in sterile distil water separately [12-14]. The incubation was carried at

33^0- 37^0C for 48 hours. All the experiment was carried out in triplicate. Simultaneously, controls were maintained by employing 0.1ml of DMSO which did not reveal any inhibition. A zone of inhibition produced by each compound was measured in and antibacterial activity (% inhibition) was calculated by using this formula. The results of antibacterial activity are shown in table 2.

$$\% \text{ inhibition} = \frac{\text{Zone of inhibition of test compound (in diameter) X100}}{\text{Zone of inhibition of standard drug (in diameter)}}$$

RESULTS AND DISCUSSION

The antibacterial activity of all synthesized compounds was determined by disc diffusion method. The results of compounds of preliminary antibacterial testing are shown in table 2.

Their comparision studies are shown in figure 1. The screening results revealed that the compounds showed significant antibacterial activity at both 500µg/ml and 1000 µg/ml concentration levels when compared with ciprofloxacin as a standard drug. It was found that compound Chalcone 1, Chalcone 2 and pyrimidine 2 showed maximum activity and pyrimidine 1 showed least activity.

Table 2 shows the physical characterization of synthesized compounds

Compound	Molecular formula	Molecular weight	% yield	Melting point
Chalcone 1	$C_{18}H_{14}N_2O_2$	290	78	187
Chalcone 2	$C_{18}H_{13}ClN_2O$	308	85	163
Pyrimidine 1	$C_{19}H_{15}N_5O$	329	83	205
Pyrimidine 2	$C_{19}H_{14}ClN_5$	342	63	218

Table 3 Results of Antibacterial activity

	Escherichia coli (Zone of inhibition in)				*Staphylococcus aureus* (Zone of inhibition i)			
Concentration (µg/ ml)	500	% Inhibition*	1000	% Inhibition*	500	% Inhibition*	1000	% Inhibition*
Chalcone 1	12	38.70	16	51.61	15	48.38	19	61.29
Chalcone 2	12	38.70	18	58.06	14	45.16	19	61.29
Pyrimidine 1	11	35.48	18	58.06	11	35.48	17	54.82
Pyrimidine 2	12	38.70	19	61.29	12	38.70	16	51.61
Ciprofloxacin	31	100	31	100	31	100	31	100

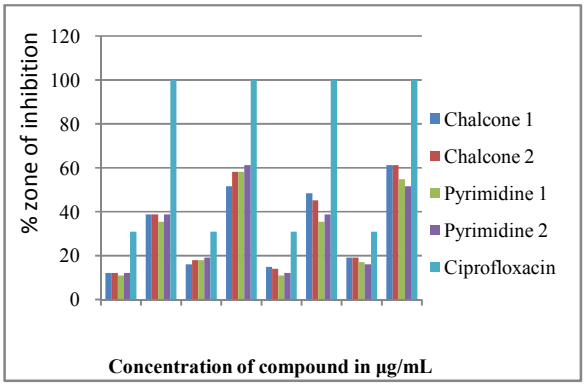


Figure 1 shows the graph of Test compounds compared with Standard drug

CONCLUSION

The main objective of research work is to synthesize a novel chalcones or pyrimidines with more efficacy towards antibacterial activity than the previously synthesized. Literature survey reveals that chalcones or pyrimidines contain electron with drawing groups have a wide variety of biological importance. From the present study by comparing all physical and spectral analysis, it can be concluded that Nitrogenous heterocyclic nucleus containing compounds (chalcones or pyrimidines) have more potent and posses significant antibacterial activity. Hence the synthesized molecules might show a broad range of pharmacological importance.

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