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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL HETEROCYCLIC CHALCONE DERIVATIVES

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ABSTRACT

Chalcones are an important class of natural products and are considered as the precursors of flavonoids and isoflavonoids. Some novel heterocyclic derivatives of chalcones were synthesized by condensing benzaldehyde derivatives with hydroxyl acetophenone in dilute Ethanolic sodium hydroxide solution at room temperature according to Claisen – Schmidt condensation. The structures of these compounds were characterized by TLC, infrared spectroscopy and nuclear magnetic resonance spectroscopy. The antimicrobial activity of the novel products was evaluated by disc diffusion method. The *in vitro* antibacterial and antifungal screening of the chalcone derivative revealed that C4 and C6 showed potent activity.

KEYWORDS: Chalcones, Thiazines, Oxazole, Pyrazole, Antimicrobial activity.

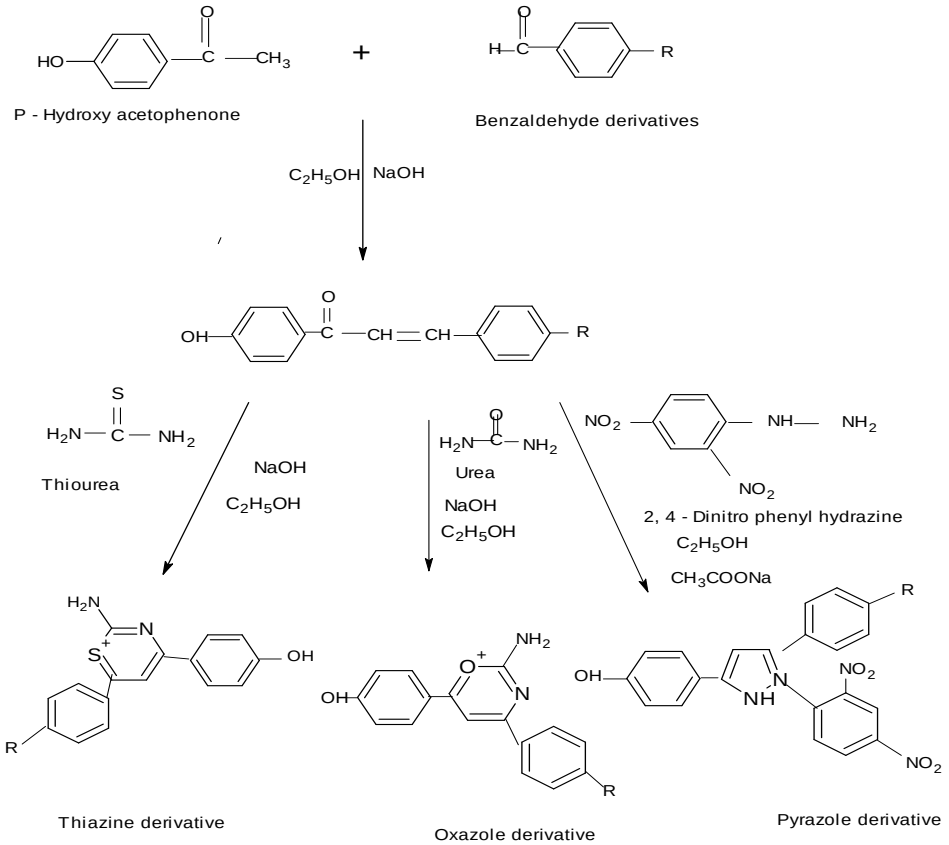
INTRODUCTION

Chalcones are aromatic ketones that form the central core for a variety of important biological compounds. The highly electrophilic three carbon α,β – unsaturated carbonyl system in chalcone has assumed importance because of their versatility in synthesis of main heterocyclics. Chalcones prepared by condensing arylketones with aromatic aldehydes in presence of suitable condensing agents. Chemically, they consist of open chain flavanoids in which the two aromatic rings are joined by a three carbon α .β unsaturated carbonyl system The presence of a reactive α, β unsaturated keto function in chalcones is found to be responsible for their antimicrobial activity.[1] Literature review reveals that chalcone derivatives exhibit diverse pharmacological activities such as anti-bacterial.[2] antiulcer.[3] antifungal.[4] antioxidant.[5] vasodilatory.[6] antimitotic.[7] antimalarial.[8] antileshmanial[9] and inhibition of chemical mediators release, inhibition of leukotriene B4.[10] inhibition of tyrosinase[11,12] and inhibition of aldose reductase[13] activities. Chalcone bears a very good synthon for the synthesis of variety of heterocyclic compounds like thaizine, oxazine, isoxazole, pyrazole, diazepine, pyridine, pyrimidine. Therefore, the synthesis of chalcones continues to attract much interest in organic chemistry. Based on the above observation, some new heterocyclic derivatives of chalcones were synthesized.

MATERIALS AND METHODS

All the reagents and solvents used were of analytical grade and were used as supplied unless otherwise stated. Progress of the reactions was monitored using TLC, performed on aluminium plates precoated with silica gel-G, using chloroform: methanol (92:8) as the solvent systems and the spots were visualized by exposure to iodine vapors.The melting points were recorded in open sulphuric acid or oil bath using thermometer and were uncorrected. IR spectra were recorded using Perkin-Elmer FTIR-RX1 spectrophotometer. A 1HNMR spectrum was recorded using CDCl3 on Bruker Avance (400 MHz) and their chemical shifts are recorded in δ (parts per million) units with respect to tetramethyl silane (TMS) as internal standard.

Scheme I
Synthesis of Chalcone Derivative



General procedure for the synthesis of differently substituted chalcone derivative (C1-C6).

STEP I
Synthesis of chalcone

Benzaldehyde derivative (0.01 mol) and acetophenone (0.01 mol) were dissolved in ethanol (25ml). Sodium hydroxide solution, 10 % (25 ml) was added slowly and the mixture stirred for 4 hrs then it was poured into 400 ml of water with constant stirring for 1hr and left overnight in refrigerator. The precipitate obtained was filtered, washed and recrystallized using ethanol.

STEP II
Preparation of Thiazine/Oxazine derivatives

A mixture of chalcone (0.02 mol), thiourea/urea (0.02 mol) were dissolved in Ethanolic sodium hydroxide solution (10 ml) and stirred for 3 hours, then it was poured into 400 ml of cold water with continuous strirring for 1 hour then left overnight. The precipitate formed was filtered, washed and recrystallized using ethanol.

Preparation of Pyrazole derivatives

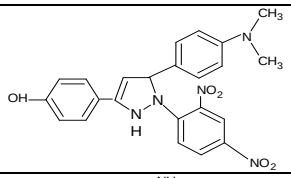
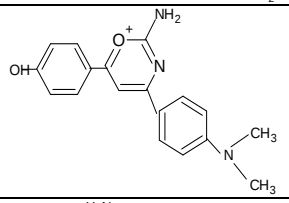
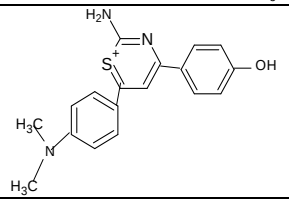
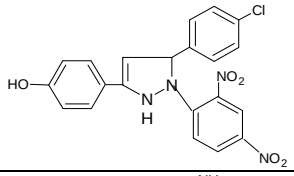
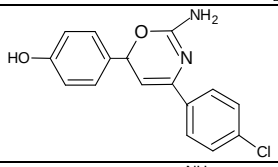
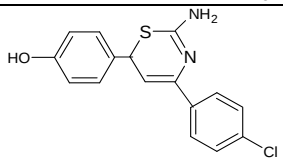
A mixture of Chalcone, I & II (0.02 mol), 2,4dinitro phenyl hydrazine (0.02) and sodium acetate in ethanol (25 ml) was refluxed for 6 hours. The mixture was concentrated by distilling out the solvent under reduces pressure and poured into ice water. The precipitate obtained was filtered, washed and recrystallized using ethanol. The completion of the reaction was monitored by TLC

RESULT AND DISCUSSION

Different Types of Aldehydes
Table-1.

S. NO.	Compounds	R	R1	R2	R3	R4	R5
1	P–Dimethylaminobenzaldehyde	H	H	H	H	N-$(CH_3)_2$	H
2	P–4 Chlorobenzaldehyde	H	H	H	H	Cl	H

General Properties of Synthesized Compounds
Table-2.

S. No.	Cpd. Code	Chemical structure	Molecular formula	Molecular Weight (g)	Yield (%)	Melting point	Rf value
1	C1		$C_{23}H_{20}N_5O_5$	446	90 %	98°C	0.83
2	C2		$C_{18}H_{23}N_3O_2$	297	83%	103°C	0.78
3	C3		$C_{18}H_{23}N_3O_1S_1$	329	89%	110°C	0.88
4	C4		$C_{21}H_{14}N_4Cl_1O_5$	437.5	90%	99°C	0.89
5	C5		$C_{16}H_{16}N_2Cl_1O_2$	303.5	87%	105°C	0.96
6	C6		$C_{16}H_{16}N_2Cl_1O_1S_1$	319.5	85%	112°C	: 0.81

Spectral Data of Synthesized Compounds
Table-3.

Compound code	IR (KBr) ν cm-1	1H NMR (d6-DMSO) δ ppm
C1	1294(C-N,str),1608.1(NH),1525(Ar-=C), 1519(Ar-NO_2)	13.6(NH),7.48(d-Ar-H),7.33(t,Ar-H),5.09(s,CH)
C2	1612.4(1° NH_2),1246(C-N,str),1475(Ar-C=C), 1394 (Ar-C-O)	2.4(s,$N(CH_3)_2$),7.30(t,Ar-H), 4.4(s,CH), 2.0(s,NH_2)
C3	1615.3(1°NH_2),2368(C-S-C),1487(Ar-C=C), 3239(Ar-OH)	2.47(s,$N(CH_3)_2$),7.1-7.8(m,Ar-H), 5.71(s,CH),1353(NH)
C4	1099(C-N,str),1448(Ar-C=C),1519(Ar-NO_2), 3350(Ar-CH)	5.0(s,Ar-OH), 13.53(NH), 6.78(s,CH), 7.34(d,Ar-H)
C5	680(C-Cl str),1599(C=C str),3073(Ar-C-H str), 1611.7(NH_2)	6.14(s,CH),5.2(s,Ar-OH),3.5(s,1H),6.8-7.9(m,Ar-H)
C6	2370(C-S-C), 1655(C=C), 1624(C=N), 1610(NH_2)	2.1(s, NH_2),3.5(s,1H),6.8-7.9(m,Ar-H) 4.7(s,CH)

In Vitro Antimicrobial Screening

The antimicrobial activity of all the synthesized compounds (C1-C6) were examined against different Gram-positive (Bacillus subtilis and Staphylococcus aureus) and Gram-negative.

(Escherichia coli and Salmonella typhii) and fugal strains Aspergillus niger and Candida albicans organisms by measuring zone of inhibition. The antimicrobial activity was performed by Disc diffusion method at the concentration level of 200µg/ml. Amoxycillin and ketoconazole as standard drug at a concentration of 200µg/ml. Nutrient agar was used as culture media for antibacterial activity and Sabouraud dextrose agar was used as culture media for antifungal activity and DMSO as control. The results of the antimicrobial activity are shown in Table 4.

Zone of inhibition (mm) data of synthesized compounds

Table-4.

Compound	Zone of Inhibition (mm)					
	Gram Positive		Gram Negative		Antifungal activity	
	B.Subtilis	S.aureus	E.Coli	S.typi	C.Albicans	A.niger
C1	10	12	11	9	13	14
C2	12	13	12	11	15	12
C3	11	14	15	12	13	13
C4	13	15	13	10	15	16
C5	15	11	12	15	14	11
C6	20	19	18	15	17	20
Amoxycillin	26	18	27	30	-	-
Ketocanazole	-	-	-	-	27	24

CONCLUSION

In the present work chalcones were used to prepare various heterocyclic compounds by cyclization with urea/thiourea/2,4-dinitrophenylhydrazine in presence of ethanolic sodium hydroxide/ sodium acetate gives good yields. A facile method under mild conditions has been developed for the synthesis of the title compounds. All the compounds synthesized were characterized by physically (Rf values, melting point, molecular weight, molecular formula) and the compounds were characterized by spectral data (IR, 1H-NMR,). The compounds C6 and C4 have significant antibacterial and antifungal activities .The Activity data obtained in this study can certainly useful to go for further research for drug designing and also for heterocyclic moieties.

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