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Synthesis and Estimation of Novel Heterocyclic Compounds with its Biological Properties

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Abstract: *Chalcones were synthesized by the condensation product of DHA in combination with aromatic aldehydes in presence of strong base. It was found that the synthesized chalcones were having prominent role in modern coordination chemistry. The chalcone synthesized by base catalyzed condensation of 3-acetyl-6-methyl-2H-pyran-2,4-(3H) dione (DHA) with different aromatic aldehyde. These chalcones were used for synthesis of derivatives i.e. flavones. The synthesized compounds were characterized by IR, ^{1}HNMR and mass spectral analysis. The derivatives were further used for the estimation of its biological properties. It was found that the derivative possesses efficient antimicrobial properties. From the study it was found that the synthesized compounds are efficient for further research work.*

Keywords: Chalcone, Flavone, IR, HNMR, Mass Spectroscopy, Biological Properties

I. INTRODUCTION

Chalcones are the special ligand molecules that used for the synthesis of complexes with desired properties. The complexes are having variations in physical, chemical and biological properties. The existence of the α, β-unsaturated ketonemoiety in chalconesis a common part found in a large number of biological active compounds[1],Therefore, chalcone derivatives from nature or synthetic origin exhibit diverse pharmacological activities, such as antimicrobial[2], antitumor[3], anticancer[4], radical scavenger[5]and inhibitor of topoisomerase[6]

Flavones are important naturally occurring organic compounds possessing a wide range of biological activities used in the treatment of various diseases [7]. Different methods are used for the synthesis of flavones, includes Allan-Robinson synthesis, synthesis from chalcones and via intramolecular witting reaction [8]. The most common method used involves Baker- Venkatramn arrangement. In this method 2- hydroxyacetophenone are converted to benzoyl ester, which in presence of base (pyridine/KOH) form 1,3 diketones. The diketones are further cyclized under strong acidic condition to afford the flavones [9]. In recent development of such dehydrative cyclization it includes the use of Amberlyst15, CoIII(sulpr)OH, FeCl3, Br2/CHCl3, EtOH/HCl, clay, NaOAc/AcOH and H2SO4 under microwave irradiation [10].Prenylatedflavanone is a unique class of naturally occurring flavonoids characterized by the presence of a Prenylated side chain in the flavonoid skeleton. It was reported that one phenolic group and certain degree of lipophilicity are required for the activity of the flavonoids Substitution of the flavonoid ring system with prenyl groups would increase their lipophilicity and consequently enhance their interaction with cellular membranes [11]. 4′ ,5,7-Trihydroxy-3′ - prenylflavanone has been isolated for the first time in 1989 from the chloroform extract of the stem bark of Erythrinaeriotriocha. The chemical and pharmaceutical industries are always under the pressure to find out environmental friendly organic reaction methodologies. Microwave irradiation is used for a variety of organic reactions due to their use in a rapid and cleaner synthesis of organic compounds [12].

Flavones are a class of flavonoid based on the backbone of2-phenyl chromene-4-one,(2-phenyl-1-benzopyrane-4-one).They are polyphenolic compound which constitute one of the most numerous and ubiquitous group of plant metabolites, flavonoids are generally present as glycosylated conjugates in fruit, vegetables and other plant products consumed in a normal diet[13].

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The immediate family members of flavonoids include flavones, flavanones, flavanols, anthocynidins & catechins. Luteolin is a flavonoids more specifically, it is thought to play an important role in the human body as an antioxidant, a free radical scavenger, an agent in the prevention of inflammation, a promoter of carbohydrate metabolism, and an immune system modulator. These characteristics of lutelin are also believed to play an important part in the prevention of cancer multiple research eexperiments describe luteolin as a biochemical agent that can dramatically reduce inflammation and the symptoms of septic shock[14].Luteolin is most often found in leaves, but it is also seen in rinds, barks, clover, blossom& ragweed pollen. It has also been isolated from salvia tomentosa. Dietary sources include celery, green pepper, perilla and camomile tea. Flavonoids have the same basic skeleton and the key feature which distinguishes one structural type from the other is the oxidation level of the various carbon in the heterocyclic ring, chromanones & flavones are integral part of human diet & have been reported to exhibit a wide range of biological effects. They also demonstrate, antibacterial,abortionist, cytotoxic, antimicrobial, antimalarial & antihypertensive activities [15].

II. Result And Discussion

The chalcones of DHA were synthesized by claisen-schmidt condensation and characterized as good to excellent yield. The structures of all the compounds were established from IR, ^{1}HNMR and mass spectral analysis is mentioned above. The IR spectrum of chalcones gives a broad band for OH group at (3000-3125 cm^{-1}) sharp and strong bands were observed at 1700-1750 $cm^{-1}$for lactone carbonyl group. Another sharp band was observed at 1598-1650 cm^{-1}due to the presence of carbonyl group and carbon- carbon band of α, β unsaturated chalconesystem.

The structure of synthesized compounds were converted to the corresponding flavones (MBFI to MBFV) by oxidative cyclisation of chalcones. All these flavones did not gave violet colouration with ferric chloride solution and pink colouration with conc. Sulphuric acid. The IR spectra of flavones shows absences of band in the region 3000-3100 cm^{-1} (OH group).The ^{1}HNMR Spectra showed singlet at δ6.2 – 6.8 due to COCH proton and absence of singlet in the region δ15-16 due to proton of hydroxyl group. In conclusion, we have reported that the synthesized chalcones derivatives using DHA (3-acetyl-6-methyl-2H-pyran-2,4-(3H) dione possessing a good to moderate biological properties. These compounds will be having application in pharmaceutical, agriculture, medical field for drug development.

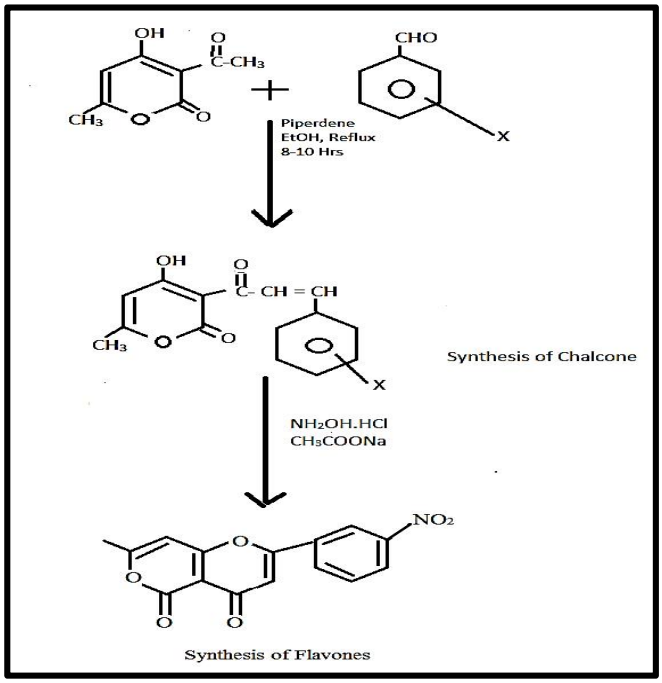

Figure 1: Schematic representation of synthesized chalcone and Isoxazoline.

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III. MATERIAL AND METHODOLOGY

Synthesis of substituted 3-Cinnamoyl-4-Hydroxy-6- Methyl-2-Pyrones (MBCI-V)

10 m mol solutions of dehydroacetic acid and the10 mmolof aromatic aldehyde were taken and in to that 8-10 drop of piperedine was added as a catalyst. The solutions was dissolved in 30 ml of ethanol solvent, the reaction mixture was then refluxed for a reaction time of 12-15 hrs. After reaction the compounds were checked by TLC. Then the mixture were filtered, dried and recrystallized with suitable solvent i.e.chloroform.[16]

The characterizations were carried out further of synthesized compounds. Melting points were determined in open capillary and are uncorrected. IR spectra were recorded on FT-IR spectrometer using potassium bromide pellet as standard, ^{1}HNMR's were determined on a New AVANCE-500 MHz spectrometer against TMS as internal standard. The mass analysis was also carried out using Shimazu Machine. Purity of compounds was checked by thin layer chromatography(TLC).

3.1 General method for the synthesis of Flavones

A solution of substituted 2-hydroxy chalcone was dissolved in DMSO (Dimethyl sulfoxide) ,a catalytic amount of iodine was added and the reaction mixture was refluxed for 2 to hrs till the starting material had completely undergone conversion .Reaction was monitored by TLC, the reaction mixture was cooled at room temperature and sodium thiosulphate solution (10%) was added to decompose excess of iodine. The solid so obtained was filtered and dried. The dry solid on crystallization from alcohol afforded flavone. The M.P. & Yield are listed in table. The structures of flavones were confirmed by spectral analysis (IR, ^{1}HNMR & mass).

3.2 Characteristic Test

The compound does not give violet coloration with FeCl3 solution & Wilson test was negative.

Synthesis of Flavones

A solution of 1-(4-hydroxy-6-methyl-2-oxa-2H-pyran-3-yl)-3-(2-fluorophenyl)-2-propenone (0.001mol) and a crystal of iodine was added to it .The reaction mixture was refluxed for 1-2 hrs, the completion of reaction was checked by TLC. After completion of the reaction, the mixture was cooled at room temperature and diluted with water; the excess of iodine was decomposed with saturated sodium thiosulphate solution. The solid thus obtained was filtered & washed with cold water & recrystallized from ethanol to get product name

Similarly other compounds of the series were also synthesized by same procedure. The physical data of synthesized compounds are listed in table no. 1 and 2.

Spectroscopic data of synthesized Flavone derivatives (MBFI-MBFV)

MBFI: 7-methyl-2-(3-nitrophenyl) pyrano [4,3-b] pyran-4,5-dione

IR (KBr, cm-1); 1650 (C=O), 1722(C=O Lactone), 2990 (C-H str. Of –CH3)

^{1}HNMR (CDCl3, δ/ ppm): 2.2 (3H, s, CH3), 6.5 (1H, s, COCH), 6.0 (1H, s, pyran ring), 6.8 to 8.4 (4H, m, Ar-H)

Mass (m/z): (M+1) 300.

MBFII: 7-methyl-2-(3,4,5-trimethoxyphenyl) pyrano [4,3-b] pyran-4,5-dione

IR (KBr, cm-1); 1648 (C=O), 1716 (C=O Lactone), 2950 (C-H str. Of –CH3)

^{1}HNMR (CDCl3, δ/ ppm): 2.0 (3H, s, CH3), 3.8-4.2 (9H, s, 3XOCH$_3$), 6.2 (1H, s, COCN) 6.0 1H, s, pyran ring), 6.4 to 8.4 (2H, m, Ar-H)

Mass (m/z): (M+1) 345.

MBFIII: 7-methyl-2-(3-methoxyphenyl) pyrano [4,3-b] pyran-4,5-dione

IR (KBr, cm-1); 1658 (C=O), 1720 (C=O Lactone), 2978 (C-H str. Of –CH3)

^{1}HNMR (CDCl3, δ/ ppm): 2.3 (3H, s, CH3), 3.9 (3H, s, OCH3), 6.8 (1H, s, COCH), 5.9 (1H, s, pyran ring), 6.8 to 8.2 (4H, m, Ar-H)

Mass (m/z): (M+1) 283.

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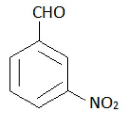
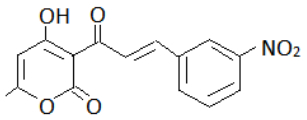
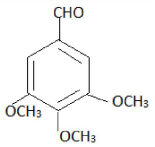
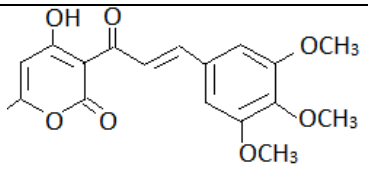
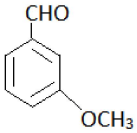
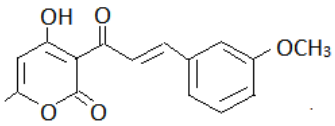
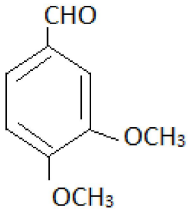
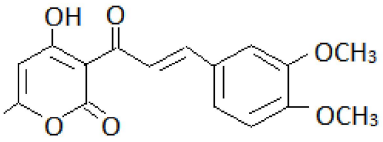
MBFIV: 7-methyl-2-(3,4-dimethoxyphenyl) pyrano [4,3-b] pyran-4,5-dione
IR (KBr, cm-1); 1651 (C=O), 1720 (C=O Lactone), 2950 (C-H str. Of –CH3)
^{1}HNMR (CDCl3, δ/ ppm): 2.1 (3H, s, CH3), 3.9-4.2 (6H, s, 2XOCH$_3$), 6.8 (1H, s, COCH), 6.0 (1H, s, pyran ring), 6.4 to 8.2 (4H, m, Ar-H)
Mass (m/z): (M+1) 315.

MBFV: 7-methyl-2-(2-florophenyl) pyrano [4,3-b] pyran-4,5-dione
IR (KBr, cm-1); 1668 (C=O), 1722 (C=O Lactone), 2990 (C-H str. Of –CH3)
^{1}HNMR (CDCl3, δ/ ppm): 2.2 (3H, s, CH3), 6.6 (1H, s, COCH), 6.0 (1H, s, pyran ring), 6.3 to 8.2 (4H, m, Ar-H)
Mass (m/z): (M+1) 273.

Biological Activity

The synthesized compounds were tested in *in vitro* for antimicrobial activity against bacterial isolates like *S. aureus*, *E. coli* and *Salmonella Typhi* and fungi species like *Fusariumoxysporum*, *Candida albicans* and *Aspergillusflavus*. The concentrations of compounds were taken as 150 µg/ml each. The antimicrobial activity was checked by agar plate diffusion method . The concentrations used for activity was confirmed after estimating the MICs of each compound. The solvent used for assay was dimethyl sulfoxide (DMSO) which further diluted with water. Nutrient agar and PDA (Potato Dextrose Agar) was used as the growth medium for the bacterial and fungal species respectively. DMSO was used as a negative control. The results were compared with standard drug penicillin for antimicrobial activity by measuring the zone of inhibition in mm using 150 µg/mL were mentioned in table no.3. Antimicrobial activity was measured as a diameter of zone of inhibition (mm) [17-18].

Table 1: Percentage yield and melting point of substituted 3-Cinnamoyl-4-Hydroxy-6- Methyl-2-Pyrones

Entry	X	Product		Yield %	Melting point °C
1		MBCI		70	190
2		MBCII		80	198
3		MBCIII		85	195
4		MBCIV		80	176

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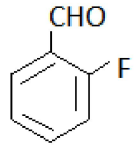
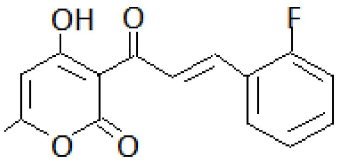
5		MBCV		84	160

Table 2: Physical data of Flavonesderivation (MBFI-MBFV)

Compounds	Molecular Formula	M. P (°C)	Yield %
MBF I	$C_{15}H_9O_6N$	210	85
MBF II	$C_{18}H_{16}O_7$	250	88
MBF III	$C_{16}H_{12}O_5$	212	65
MBF IV	$C_{17}H_{14}O_6$	205	80
MBF V	$C_{15}H_9O_4F$	260	79

Table 3: Antimicrobial activity of Flavones

Compound	Bacteria (Zone of Inhibition in mm)			Fungi (Zone of Inhibition in mm)		
	A	**B**	**C**	**D**	**E**	**F**
MBF I	14	19	**21**	13	16	14
MBF II	15	17	19	15	17	12
MBF III	18	15	18	18	15	18
MBF IV	19	18	18	12	18	17
MBF V	14	20	16	14	**20**	19
Penicillin*	11	10	12	10	12	13

standard, A-** *S. aureus* **, B-** *E. coli* **, C-** *S. Typhi* **, D-Fusariumoxysporum***, E-** *Candida albicans***, F-***Aspergillusflavus.*

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