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SYNTHESIS, CHARACTERIZATIONS AND ANTIMICROBIAL ACTIVITY OF SOME 3-CHLOROFLAVONE DERIVATIVES

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ABSTRACT

Flavanoids are important biosynthetic precursors for the synthesis of flavones, isoflavones, flavonols, flavonone and 3-chloroflavone. The 3-chloroflavone skeleton is present in a wide range of synthetic and naturally occurring products exhibiting various interesting pharmacological activities. In the present investigation, a series of some 3-Chloro-2-(4′-dimethylamino-phenyl)-4*H*-chromen-4-ones**,(2a-j)** have been synthesized by oxidative cyclization of 1-(substituted-2-hydroxy-phenyl)-3-(4′-dimethylamino-phenyl)-prop-2-en-1-ones (2-hydroxychalcones) **(1a-j)** with $CuCl_2$ using DMSO as a solvents with good yield of 3-Chloroflavone (72%). The products were tested for purity by TLC and structures of synthesized compounds were confirmed by IR, ^{1}H NMR and Mass spectral analysis. All these synthesized compounds were evaluated for their antimicrobial activity.

Keywords: 2-hydroxychalcone, 3-Chloroflavone, Antimicrobial Activities

INTRODUCTION

Flavonoids are well known group of naturally occurring aromatic oxygen-bearing heterocyclic compounds. They have a broad distributed in higher plants kingdom and are found in many fruits, vegetables, tea and red wine. They constitute most of yellow, red and blue colour in flowers and fruits. Flavonoids are yellow color pigments. In Latin Flavus means Yellow colour. The interaction of dietary flavonoids shows great medicinal value[1-2]. The family members of flavonoids include, flavones, 3-Chloroflavones, isoflavones and flavanones. Antimicrobial activity refers to the process of killing or inhibiting the disease causing microbes. Various types of antimicrobial agents are synthesized and used against this type of microbes. Antimicrobial may be anti-bacterial, anti-fungal or antiviral[3-4]. They all have different modes of action by which they act to suppress the infection of disease[5-6]. The naturally occurring and synthesized flavonoids and are display important biological and pharmacological properties such as antioxidant[7-8], anticancer[9], anti-inflammatory[10-11], cytotoxicity[12], anti-HIV[13], antidepressant activities[14]. They may act as chemo

preventive agents against the development of cancer[15-16]. In this context it would seen advantageous if more studies were to appear on these 3-Chloroflavone derivatives synthesis and study of their biological properties[17-18].

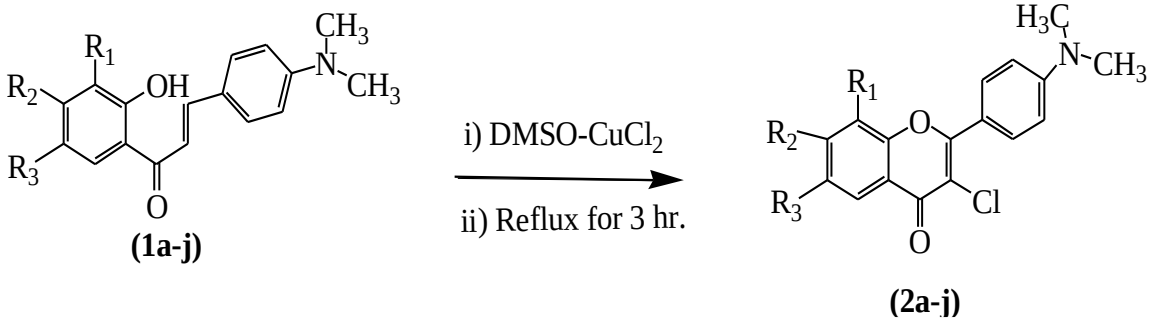
In view of these observations, in the present investigation we report here, the synthesis of number of 3-Chloro-2-(4′-dimethylamino-phenyl)-4*H*-chromen-4-ones**, (2a-j)** having chloro, bromo, iodo, hydroxy and methyl groups with an aim to find new most active antibacterial and antifungal agents. We have synthesized a series of 3-Chloroflavone derivatives. The substituted 2-hydroxychalcones reflux in DMSO/$CuCl_2$. The structures of the synthesized compounds **(2a-j)** were established on the basis of IR, ^{1}H NMR, and Mass spectral data. All the synthesized compounds were tested for their antibacterial activity against *Escherichia coli, Salmonella typhi, Staphylococcus aureus*and *Bacillus subtilis* and antifungal activity against *Aspergillus niger, Penicillium chrysogenum, Fusarium moneliforme* and *Aspergillus flavus,* using standard (Penicillin and Greseofulvin) drugs.

MATERIAL AND METHOD

All the solvents and reagents were obtained from commercial sources and were used without further purification. The melting points were determined by Open Capillary method and are uncorrected. The mass spectra were obtained with a Shimadzu GC-MS spectrophotometer. The IR spectra in KBr were recorded on Shimadzu Spectrophotometer and ^{1}HNMR spectra were recorded in DMSO on Avance 300 MHz Spectrometer using TMS as internal standard. The chemical shift values are expressed in part per million (ppm) downfield from the internal standard and signals are quoted as, s (singlet), d (doublet), t (triplet) and m (multiplet). TLC was used to monitor the progress of all reactions and to check the purity of compounds by using ethyl acetate and petroleum ether as an eluent in the ratio of (3:7 v/v). All the compounds were tested for their antibacterial and antifungal activities by agar diffusion method.

General procedure for Synthesis of 3, 6-dichloro-2-(4'-dimethylamino-phenyl)-7-methyl-*4H*-chromen-4-one (3-Chloroflavone)

A mixture of 1-(5-chloro-2-hydroxy-4-methyl-phenyl)-3-(4'-dimethylamino-phenyl)-prop-2-en-1-one (**1i**) (0.315 gm, 0.001 mol) was dissolved in dimethyl sulfoxide (DMSO). To this reaction mixture, excess of $CuCl_2$ (about 2gm) was added: contents were heated under mild reflux condition for 3 hours. The completion of reaction was checked by TLC, and the reaction mixture was left over night, the 100 ml of cold water was slowly added to the flask and the separated product was filtered and washed with cold water followed by diluted HCl several time, again it was washed with cold water. The solid products precipitated out was filtered, washed several time with cold water, dried and recrystllised by using ethanol to afford 3, 6-dichloro-2-(4'-dimethylamino-phenyl)-7-methyl-4*H*-chromen-4-one(**2i)**



(1a-j) **(2a-j)**

Table-1: Physical data of synthesized 3-Chloroflavone derivatives (2a-j)

Sr. No.	Entry	R_1	R_2	R_3	Molecular formula	Yield in (%)	Melting point ^{0}C
1	**2a**	I	H	I	$C_{17}H_{12}O_2I_2NCl$	71	120
2	**2b**	I	H	CH_3	$C_{18}H_{15}O_2INCl$	74	140
3	**2c**	Cl	H	Cl	$C_{17}H_{12}O_2Cl_3N$	68	235
4	**2d**	I	H	Cl	$C_{17}H_{12}O_2ICl_2N$	70	110
5	**2e**	Br	H	CH_3	$C_{18}H_{15}O_2BrNCl$	68	201
6	**2f**	Br	H	Cl	$C_{17}H_{12}O_2BrCl_2N$	70	130
7	**2g**	Br	H	Br	$C_{17}H_{12}O_2Br_2NCl$	66	245
8	**2h**	I	H	Br	$C_{17}H_{12}O_2BrINCl$	68	198
9	**2i**	H	CH_3	Cl	$C_{18}H_{15}O_2Cl_2N$	70	230
10	**2j**	H	H	Br	$C_{17}H_{12}O_2BrNCl$	72	151

RESULTS AND DISCUSSION

This paper presents synthesis of halogen substituted and 3-Chloro-2-(4′-dimethylamino-phenyl)-4*H*-chromen-4-ones, (**2a-j**) were synthesized by oxidative cyclization of corresponding 2-hydroxychalcones (**1a-j**), and DMSO/$CuCl_2$. All these 3-Chloro-2-(4′-dimethylamino-phenyl)-4*H*-chromen-4-ones, compounds didn't give violet coloration with $FeCl_3$ solution and pink coloration with concentrated H_2SO_4. The structures of newly synthesized compounds have been confirmed by spectral data. IR spectrum of compounds **2i** showed a peak 717 cm^{-1} due to C_3-Cl streaching, ^{1}H NMR shows the absence of proton at **C2** (C_2-H absent) in pyrone ring which clearly indicates the formation of 3-chloro chromones[19-20]. Mass spectrum of **2i** compound showed (M+1) 347. All the newly synthesized compounds were screened for their antibacterial activity against four different selected pathogens, such as *Escherichia coli, Salmonella typhi, Staphylococcus aureus* and *Bacillus subtilis* . All the compounds of 3-Chloroflavone (**2a-j)** does not showed activity against *E. coli* the compound **2b** showed good activity against *S. typhi*, but other compounds showed moderate activity. The compounds **2a, 2f, 2g** and **2h** showed significant activity against *S. aureus.* While another compounds showed moderate activity. The compound **2b** and **2g** are most active against *B. subtilis* and another compounds moderate activity as comparison with standard drugs (Penicillin).The results revealed that most of the newly synthesized 3-Chloroflavone compounds exhibited good antifungal activity as comparison with (Greseofulvin) as standard drugs against four different pathogens such as *Aspergillus niger, Penicillium chrysogenum, Fusarium moneliforme and Aspergillus flavus*. The presence of 3-Chloroflavone moiety, the substituent's particularly bromo, chloro, iodo and methyl groups in phenyl ring may be responsible for antimicrobial activity for this class of compounds.

6, 8-dichloro-2-(4′-(dimethylamino-phenyl)-3-Chloro-4*H*-chromen-4-one (2c):- Yield 68 % Melting point 235 ^{0}C. **IR (KBr):-** 1614 cm^{-1} (C=O), 1522 cm^{-1} (C=C), 1260 cm^{-1} (C-O-C), 718 cm^{-1} (C-Cl) ^{1}**H NMR (DMSO)**:- δ 2.2-2.3 (s, 3H, CH_3), δ 3.0-3.2 (s, 6H, $(CH_3)_2$) δ 6.8-7.7 (m, 6H, Ar-H), **MS (m/z)**: (M+1) =367

6-bromo-8-methyl-2-(4′-dimethylamino-phenyl)-3-Chloro-4*H*-chromen-4-one (2e):- Yield 68 % Melting Point 201 ^{0}C, **IR (KBr):-** 1618 cm^{-1} (C=O), 1530 cm^{-1} (C=C), 1254 cm^{-1} (C-O-C), 722 cm^{-1} (C-Cl), ^{1}**H NMR (DMSO)**:- δ 2.2-2.3 (s, 3H, CH_3), δ 3.0-3.2 (s, 6H, $(CH_3)_2$) δ 6.8-7.7 (m, 6H, Ar-H), **MS (m/z)**: (M+1) =392

6-chloro-7-methyl-2-(4′-(dimethylamino-phenyl)-3-Chloro-4*H*-chromen-4-one (2i):- Yield 70 % Melting point 230 ^{0}C, **IR (KBr):-** 1612 cm^{-1} (C=O), 1527 cm^{-1} (C=C), 1257 cm^{-1} (C-O-C), 717 cm^{-1} (C-Cl), ^{1}**H NMR (DMSO)**:- δ 2.1-2.2 (s, 3H, CH_3), δ 3.0-3.3 (s, 6H, $(CH_3)_2$) δ 6.7-7.8 (m, 6H, Ar-H), **MS (m/z)**: (M+1) =347

8-bromo-2-(4′-dimethylamino-phenyl)-3-Chloro-4*H*-chromen-4-one (2j):- Yield 72 % Melting point 151 ^{0}C, **IR (KBr)**:- 1608 cm^{-1} (C=O),1525 cm^{-1} (C=C), 1560 cm^{-1} (C-O-C),721 cm^{-1} (C-Cl) ^{1}**H NMR (DMSO)**: δ 2.9-3.3 (s, 6H, $(CH_3)_2$), δ 6.7-7.9 (m, 7H, Ar-H), **MS (m/z):** (m/z):(M+1)=379

Table 2: Antimicrobial activity of synthesized 3-Chloroflavone derivatives (2a-j)

		Antibacterial activity (Zone of Inhibition in mm)				**Antifungal activity (Zone of Inhibition in mm)**			
Sr. No	**Entry**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**
1	**2a**	--	--	22	12	-ve	-ve	-ve	-ve
2	**2b**	--	16	17	16	-ve	-ve	-ve	RG
3	**2c**	--	14	13	14	-ve	-ve	RG	RG
4	**2d**	--	12	18	15	-ve	-ve	-ve	-ve
5	**2e**	--	--	13	13	-ve	-ve	RG	RG
6	**2f**	--	11	22	14	-ve	-ve	-ve	RG
7	**2g**	--	12	26	16	-ve	-ve	RG	-ve
8	**2h**	--	11	21	12	-ve	-ve	-ve	RG
9	**2i**	--	13	16	--	-ve	-ve	RG	-ve
10	**2j**	--	11	17	14	-ve	-ve	-ve	-ve
+ve Control DMSO		**-ve**	**-ve**	**-ve**	**-ve**	**+ve**	**+ve**	**+ve**	**+ve**
Penicilline		**12**	**20**	**34**	**22**	**X**	**X**	**X**	**X**
-ve Control (Griseofulvin)		**X**	**X**	**X**	**X**	**-ve**	**-ve**	**-ve**	**-ve**

Zone of Inhibition in mm)

A = Escherichia coli, B = Salmonella typhi, C = Staphylococcus aureus,

D = Bacillus subtilis E = Aspergillus niger, F =penicillium chrysogenum,

G = Fusarium moneliforme, H = Aspergillus flavus

-- = No Antibacterial activity, RG = Reduced Growth (Moderate Activity)

-ve = Growth (Antifungal Activity Observed), X = Not Applicable

ANTIMICROBIAL ACTIVITY

All the newly synthesized 3-Chloro-2-(4′-dimethylamino-phenyl)-4*H*-chromen-4-ones, compounds **(2a-j)** were assessed for their antibacterial and antifungal activities against four different strains of bacteria such as *E. coli*, *S typhi*, *S. aureus* and *B. subtilis* and four fungi like *Aspergillus niger*, *Penicillium chrysogenum*, *Fusarium moneliforme and Aspergillus flavus*. The test for antibacterial activity was carried by agar cup method[21-22] (cup size 8mm) with nutrient agar as medium whereas antifungal activity was carried out by using potato-dextrose agar (PDA) medium by same agar cup plate method. All newly synthesized compounds were dissolved in DMSO and used as control concentration of each test compound was 25µg/ml. The experiments were performed in triplicate in order to minimize the errors. Zone of inhibition were recorded after incubation at 37 ^{0}C for 24 hrs, zone of inhibition produced by each compound was measured in mm. By using Standard drugs like Peniciline and Greseofulvin were used for comparison purpose. The biological data of compounds as shown in **Table.2** from the data of antimicrobial activity indicate that compounds of 3-Chloroflavone (**2a-j)** do not show activity against *E. coli.* The compound **2b** showed good activity against *S. typhi,* but other compounds showed moderate activity. The compounds **2a, 2f, 2g** and **2h** showed significant activity against *S. aureus.* While another compounds showed moderate activity. The compound **2b** and **2g** are most active against *B. subtilis* and another compounds moderate activity as comparison with standard drugs (Penicillin). The results revealed that the newly synthesized compounds exhibited moderates to good antifungal activity as comparison with (Greseofulvinas) standard drugs.

CONCLUSION

In this work, we have demonstrated the synthesis of 3-Chloro-2-(4′-dimethylamino-phenyl)-4*H*-chromen-4-ones, **(2a-j)** compounds using simple experimental procedure with high yields, relatively short reaction time, easily work up and low cost. All the synthesized compounds were screened for their antibacterial and antifungal activities. From the result of antibacterial and antifungal activities, it can be concluded that the title compounds and the ring system, presence of halogen, hydroxyl, dimethylamino groups and methyl group of 3-Chloroflavone ring are responsible for the antibacterial and antifungal effects. The obtained results in all these assays during the study will be certainly useful to go for further research for drug designing might provide interesting and additional synthesizing of new effective derivatives.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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