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Synthesis of Some Novel Chlorochromones Containing Pyrazole Moiety

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ABSTRACT

A mild and proficient method has been developed for the synthesis of chlorochromones from oxidative cyclization of chalcones. High yield, simple workup procedure and mild reaction condition are main feature of this method. All synthesized chlorochromones has been evaluated for their antimicrobial activity against Gram +ve and Gram –ve microorganisms.

Kewords: Chalcones, Chlorochromones, Antimicrobial, Gram +Ve And Gram –Ve Microorganisms.

I. INTRODUCTION

Heterocyclic compounds are widely distributed in natural products and comprise a huge number of biologically active compounds. Halogenated chromones with a variety of substituents at second position are reported to have coronary spasmolytic, broncho-dilatory and antisarcom-180 properties. The 3-chlorochromones are related with antibacterial and antifungal activities[1-3]. Chalcones are starting materials for the synthesis of chlorochromones. Chalcones and their analogues having an-unsaturated carbonyl system are very adaptable β, α substrates for the evaluation of a variety of organic reactions.[4] The chalcones were initiate to have good antibacterial, analgesic and anti-inflammatory activities.[5] The chalcones, intermediates for the synthesis of a variety of heterocyclic compounds, are well-known for their antiinfective, particularly antibacterial and antifungal activities, since a long time [6].

The diverse methods for the synthesis of 3-halochromones were reported by different coworkers. Gammill[7] synthesized 3-halochromone from enaminoketone with halogen containing reagents. The 3-Chlorochromones are allied with antifungal, antibacterial, antiviral and antioxidant activities [8]. Compounds containing chlorochromone moiety are synthetically versatile molecules with a reactive carbonyl group having large significance for their biological activities[9-10]

II. MATERIALS AND METHODS

All the chemicals necessary for the synthesis of the compounds were obtained from Sigma Aldrich and SD Fine chemicals. Melting points were recorded in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on Bruker Avance II 400 MHz NMR Spectrophotometer in DMSO-d_6 and TMS as an internal standard. Using FT-IR Spectrophotometer Model RZX (Perkin Elmer) the infra-red spectra were recorded as potassium bromide disk. Mass spectra were recorded on Macromass mass spectrophotometer (Waters) by electro-spray method (ES). Using TLC silica gel coated plates obtained from Merck as stationary phase and solvent mixture of ethyl acetate/hexane (20:80) as mobile phase, purity of the synthesized compounds was checked.

III. GENERAL PROCEDURE

General Procedure for the synthesis of (*E*)6-bromo-2-(3-(3-bromothiophen-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)-3-chloro-4*H*-chromen-4-one (2g): (0.25 gm, 0.0007 mmole) of chalcone as starting material was dissolved in 15 ml of DMSO. In this reaction mixture catalytic amount of cuprous chloride ($CuCl_2$) was added. The reaction mixture was heated in an oil bath for 4 hr

at 120°C. After completion of reaction (monitored by TLC) reaction mass was left overnight. 10 ml cold water was gradually added to the flask and the separated product was filtered, washed with water followed by dil. HCl for several times. It was again washed with water, dried out under vacuum and crystallized from ethanol to afford 2g. The physical data of the compounds 2(a-g) is recorded in Table 1.Their structures have been confirmed by ^{1}HNMR, Mass and IR spectra.

IR (2g) (cm^{-1}):960(C-Cl), 1076(Ar-Br), 1562(C=C), 1595 (C=N), 1649(C=O).

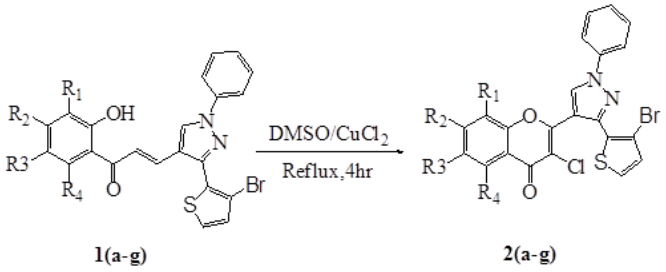
^{1}H NMR (2g) (DMSO-d_6)δ ppm: 6.5266(s, 1H, Ar-H), 7.0051-7.0274(d, 1H, Ar-H, *J*=8.92 Hz), 7.1473-7.1606(d, 1H, Ar-H, *J*=5.32 Hz), 7.4278-7.4648(dd, 1H, Ar-H, *J*=7.36 & 7.44Hz), 7.5332-7.6022(m, 2H, Ar-H), 7.7881-7.8145(dd, 1H, Ar-H, *J*=5.32 & 6.84Hz), 7.8521-7.9210 (m,1H, Ar-H), 7.9584-8.0046(dd, 2H, Ar-H, *J*=10.76 & 7.72Hz), 8.1861-8.1922(d,1H, Ar-H, *J*=2.44 Hz), 8.2097(s, 1H, pyrazole-H).

ES-MS (2g) (m/z):561(M+1), 563(M+2), 565(M+3), 567(M+5).

IR (2c) (cm^{-1}):958(C-Cl), 1079(Ar-Br), 1558(C=C), 1598 (C=N), 1652(C=O).

^{1}H NMR (2c) (DMSO-d_6)δ ppm: 6.6725(s, 1H, Ar-H), 7.0231-7.0325(d, 1H, Ar-H, *J*=3.76 Hz), 7.2451-7.2899(d, 1H, Ar-H, *J*=17.92 Hz), 7.4485-7.4688(dd, 1H, Ar-H, *J*=7.86 & 7.97Hz), 7.6231-7.6564(m, 2H, Ar-H), 7.7968-7.8234(dd, 1H, Ar-H, *J*=7.32 & 8.84Hz), 7.8651-7.9482(m,1H, Ar-H), 7.9651-8.0023(dd, 2H, Ar-H, *J*=9.75 & 7.84Hz), 8.2131-8.2436(d,1H, Ar-H, *J*=12.2 Hz), 8.2713(s, 1H, pyrazole-H).

ES-MS (2c) (m/z):517(M+1), 519(M+2), 521(M+3), 523(M+5).



Scheme 1. Synthesis of various (E) 6-bromo-2-(3-(3-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-3-chloro-4H-chromen-4-one

Table 1. Physical data of compounds 2(a-g)

Comp.	R_1	R_2	R_3	M.P. (°C)	Yield (%)
2a	H	H	H	158-160	71
2b	H	H	CH_3	192-194	69
2c	H	H	Cl	176-178	73
2d	Cl	H	Cl	210-212	79
2e	H	H	F	208-210	69
2f	H	CH_3	Cl	164-166	78
2g	H	H	Br	188-190	82

IV. RESULT AND DISCUSSION

The chlorochromones derivatives were synthesized successfully in reasonable to good yields. All newly synthesized compounds were identified on the basis of melting point range, IR, ^{1}H NMR, Mass spectral analysis. All the newly synthesized derivatives were screened for antimicrobial activity using disc diffusion method.

Antimicrobial activity: Compounds1 and 2(a-g) were screened for their in vitro antimicrobial activity against Staphylococcus aureus (ATCC 25923), Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 27853) by paper disc diffusion method using Gentamycin as a reference standard drug. Antifungal activity was screened against Candida sp. using Nystatin as standard drug. At 100 µg/ml concentration all the tests were evaluated. The culture media was Muller Hinton agar. The region of inhibition was measured in mm after 24 hr of incubation at 37°C.Microbial data for copounds 1 & 2(a-g)are summarized below in Table 2.

Table 2. Antimicrobial Analysis Data

Sr. No.	Comp.No.	Escherichia coli (ATCC 25922)	Pseudomonas aeruginosa (ATCC 27853)	Staphylococcus aureus (ATCC 25923)	Candida sp.
1	2	No Zone	No Zone	No Zone	No Zone
2	2a	No Zone	No Zone	No Zone	No Zone
3	2b	No Zone	No Zone	No Zone	No Zone
4	2c	No Zone	No Zone	No Zone	No Zone
5	2d	No Zone	No Zone	No Zone	No Zone
6	2e	No Zone	No Zone	No Zone	No Zone
7	2f	No Zone	No Zone	No Zone	No Zone
8	2g	No Zone	No Zone	No Zone	No Zone
9	Gentamycin	28 mm	23 mm	32 mm	--
10	Nystatin	--	--	--	23 mm

V. CONCLUSION

The newly synthesized compounds were screened against Candida sp. and Gram positive as well as Gram negative bacterial strains. The synthesized compounds do not shown any activity compared to standard drug. The data obtained during the present work shows a good agreement between the experimental and computed spectral data.

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