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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ANALYSIS OF VARIOUS SUBSTITUTED 2-(3-(5-BROMOTHIOPHEN-2-YL)-1-(4-FLUOROPHENYL)-1*H*-PYRAZOL-4-YL)-3-CHLORO-4*H*-CHROMEN-4-ONE

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ABSTRACT
A easy going and skilled method has been developed for the synthesis of chlorochromones from chalcones by oxidative cyclization. The procedure is simple workup; High yield and mild reaction condition is the main feature of this method. Newly synthesized chlorochromones has been screened for their antimicrobial activity against Gram +ve and Gram –ve microorganisms.

Keywords: *chlorochromones, chalcones, antimicrobial, Gram +ve and Gram –ve microorganisms.*

INTRODUCTION
Halogenated chromones with a variety of substituents at second position are reported to have coronary antisarcom-180[1], spasmolytic and broncho-dilatory[2] properties. The 3-chlorochromones are related with antifungal and antibacterial activities. Bronchodilatory and Coronary spasmolytic activities are useful in the treatment of asthma[3-5]. The synthesis of 3-substituted chromones are important natural products like isoflavones due to this appears worthy of study and in medicines such as antiosteoporosis drug ipriflavone[6]. The different methods for the synthesis of 3-halochromones were reported by various coworkers. From enaminoketone with halogen containing reagents 3-halochromones are synthesized by Gammill[7]. The 3-Chlorochromones shows various activities like antiviral, antifungal, antibacterial and antioxidant activities[8]. Compounds of chlorochromones moieties are versatile molecules with a reactive carbonyl group having huge significance due to their biological activities[9].

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

GENERAL PROCEDURE
General Procedure for the synthesis of (*E*) 6-bromo-2-(3-(5-bromothiophen-2-yl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)-3-chloro-4H-chromen-4-one(2g): 0.25 gm, 0.0007 mmole of chalcone (1g) was dissolved in 20 ml of DMSO. Catalytic amount of cuprous chloride ($CuCl_2$) was slowly added in to the reaction mixture. The reaction mixture was heated for 4 hr at 120^{o}C in an oil bath. After the completion of reaction, (monitored by TLC) reaction mass was left overnight. Cold water about 20 ml was gradually added to the flask, solid product was obtained and this product was filtered, washed with water followed by dil. HCl for numerous times. This was again washed with water, dried out under vacuum and recrystallized in ethanol to afford **2g**. The compounds 2(a-g) were prepared by following above general procedure. Physical data of all synthesized compounds **2(a-g)** is recorded in **Table 1**. Confirmed synthesized compounds structures by 1HNMR, Mass and IR spectra.

IR (2g) (cm^{-1}):971(C-Cl), 1077(Ar-Br), 1599(C=C), 1605 (C=N), 1679(C=O).

^{1}H NMR (2g) (DMSO-d_6)δ ppm: 6.7126(s, 1H, Ar-H), 6.8199-6.8441(d, 1H, Ar-H, *J*=9.68 Hz), 6.9245-6.9869(m, 1H, Ar-H), 7.0061-7.1231(m, 2H, Ar-H), 7.2864-7.3968(m, 2H, Ar-H), 7.5439-7.6125(m, 1H, Ar-H), 7.8145-7.8654(m, 1H, Ar-H), 8.1984(s, 1H, pyrazole-H).

ES-MS (2g) (m/z):579(M+1), 581(M+3).

IR (2c) (cm^{-1}):962(C-Cl), 1081(Ar-Br), 1562(C=C), 1595 (C=N), 1668(C=O).

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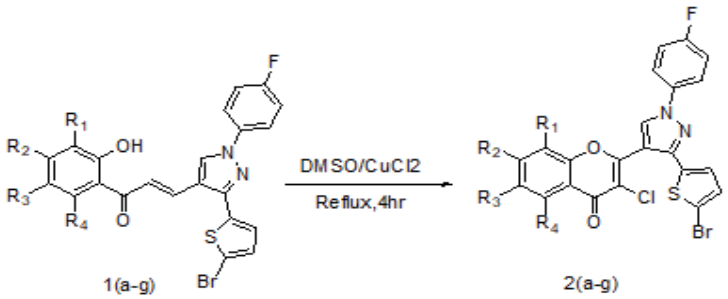
^{1}H NMR (2c) (DMSO-d_6)δ ppm: 6.5974(s, 1H, Ar-H), 6.9354-6.9564(d, 1H, Ar-H, *J*=8.4 Hz), 7.0248-7.0523(d, 1H, Ar-H, *J*=11 Hz), 7.2631-7.5864(m, 2H, Ar-H), 7.6341-7.7453(m, 2H, Ar-H), 7.7787-7.8210(m, 1H, Ar-H), 7.8564-7.9134(m,1H, Ar-H), 8.3653(s, 1H, pyrazole-H).

ES-MS (2c) (m/z):536(M+1), 538(M+3), 540(M+5).



Scheme-1: Synthesis of various (*E*) 2-(3-(5-bromothiophen-2-yl)-1-(4-fluorophenyl)-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. (^{o}C)	Yield (%)
2a	**H**	**H**	**H**	132-134	75
2b	**H**	**H**	**CH_3**	122-124	77
2c	**H**	**H**	**Cl**	144-146	68
2d	**Cl**	**H**	**Cl**	186-188	72
2e	**H**	**H**	**F**	212-214	68
2f	**H**	**CH_3**	**Cl**	168-170	75
2g	**H**	**H**	**Br**	196-198	81

RESULT AND DISCUSSION

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

Antimicrobial activity: Compounds **2(a-g)** were analyzed for their in vitro antimicrobial activity against *Escherichia coli (ATCC 25922)*, *Staphylococcus aureus (ATCC 25923)*, *Pseudomonas aeruginosa (ATCC 27853)* by paper disc diffusion method and reference standard drug is Gentamycin. Antifungal activity was analyzed against *Candida sp.* using Nystatin as standard drug. At 100 µg/ml concentration, all the tests were evaluated. Muller Hinton agar was the culture media. The region of inhibition was measured in mm after 24 hr of incubation at 37^{o}C. Microbial data for compounds 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	2a	No Zone	No Zone	No Zone	No Zone
2	2b	No Zone	No Zone	No Zone	No Zone
3	2c	No Zone	No Zone	No Zone	No Zone
4	2d	No Zone	No Zone	No Zone	No Zone
5	2e	No Zone	No Zone	No Zone	No Zone
6	2f	No Zone	No Zone	No Zone	No Zone
7	2g	No Zone	No Zone	No Zone	No Zone
8	Gentamycin	28 mm	23 mm	32 mm	--
9	Nystatin	--	--	--	23 mm

CONCLUSION

All the derivatives of chlorochromones were synthesized to good yields. The newly synthesized derivatives of chlorochromones were screened against Candida sp. and Gram positive as well as Gram negative bacterial strains. The synthesized compounds do not show any activity as compared to standard drug. The obtained data during this work shows a good concurrence between the computed and experimental spectral data.

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