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# Synthesis and antimicrobial screening of some novel chromones and chlorochromones incorporated with 2-bromothiophene.

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**ABSTRACT**

*The title compounds Chromones **4(a-h)** and Chorochromones **5(a-h)** have been synthesized from chemical transformation of Chalcones by using DMSO/$I_2$ & DMSO/$CuCl_2$ respectively. The structures of all newly synthesized compounds have been confirmed by IR, $^1$H NMR and Mass spectral data. The synthesized compounds have been screened for their antimicrobial activity. Some of the compounds show moderate antimicrobial activity as compared to the reference drugs Ciprofloxacin and Fluconazole.*

**Keywords**: Chalcones**,** chromones, chlorochromones, antimicrobial activity

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## INTRODUCTION

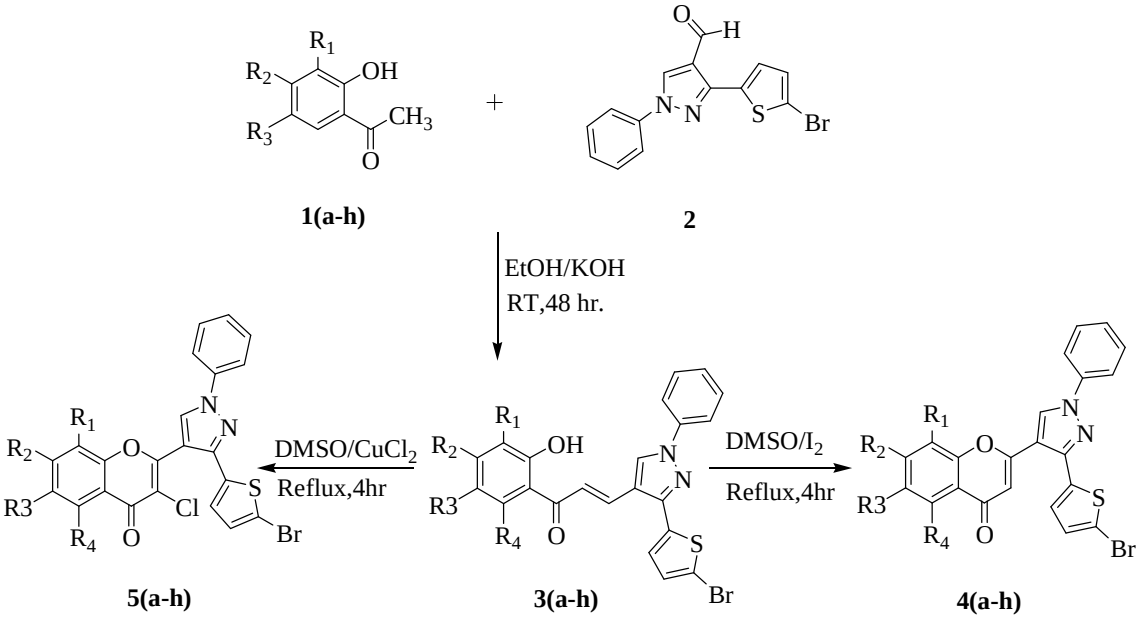
Heterocyclic compounds are widely distributed in natural products and comprise a huge number of biologically active compounds. Amongst the various heterocyclic systems, chromones are the most widely investigated. Chromones [1] have been the subject of the considerable chemical interest in the past decades. Chromones constitute one of the major classes of naturally occurring compounds and interest in their chemistry continues unabated because of their usefulness as biologically active agents [2] as well as pharmacological active agents [3]. Some of the biological activities attributed to chromone derivatives include cytotoxic (anticancer) [4-6], neuroprotective [7], HIV-inhibitory [8], antimicrobial [9-10], antifungal [11] and antioxidant activity [12]. Due to their abundance in plants and their low mammalian toxicity, chromone derivatives are present in large amounts in the diet of humans [13]. Flavonoids [14] are the chromones that are also most abundantly distributed in nature. Peucenin [15], Eugenitol [16] and Isoeugenitol [17] are some commonly occurring chromones. The chromones are also well known for their antioxidant [18], biocidal [19], wound healing [20], anti-inflammatory [21], antiulcer [22], and immune stimulatory [23] activities. Recently, some chromones are also reported as anti-HIV agents [24].

Some of the chromones, especially those having heterocyclic substituents at C-2 and C-3 positions have good pharmacological activities *viz*. coronary spasmolytic and bronchodilatory activities useful in the treatment of asthma [25-30]. The synthesis of 3-substituted chromones appears worthy of study because they are important natural products like isoflavones and in medicines such as ipriflavone, an antiosteoporosis drug [31].

## MATERIALS AND METHODS

All the chemicals required for the synthesis of the compounds were obtained from Sigma Aldrich and SDFine chemicals. Melting points were recorded in open capillaries and are uncorrected. $^1$H NMR spectra were recorded on Varian 400 MHz and Varian Mercury YH 300 MHz spectrophotometers in $CDCl_3$, DMSO-$d_6$ and TMS as an internal standard. The infra-red spectra were recorded as potassium bromide disk using Schimadzu-FT-IR Spectrophotometer. Mass spectra were recorded on Micromass mass spectrophotometer. The purity of the synthesized compounds was checked by TLC silica gel coated plates obtained from Merck as stationary phase and solvent mixture of ethyl acetate/hexane (20:80) as mobile phase.

**General procedure for the synthesis of 2-(3-(5-bromothiophen-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)-6-chloro-4*H*-chromen-4-one (4c)**: (0.25 gm, 0.0005mmole) of chalcone **3c** was dissolved in 15 mL of DMSO. To this reaction mixture catalytic amount of iodine ($I_2$) was added. The reaction mixture was heated in an oil bath for 4 hr at 120$^o$C. After completion of reaction (monitored by TLC), reaction mass was left overnight. 10 mL cold water was slowly added to the flask and the separated product was filtered, washed with water followed by dil. sodium thiosulphate solution for several times. It was again washed with water, dried under vacuum and crystallized from ethanol to yield **4c.** The compounds **4(a-h)** were prepared by following the general procedure. Physical data are recorded in **Table I**. Their structures have been confirmed by IR, $^1$H NMR and Mass spectra.**IR (4c)** (cm$^{-1}$):715(C-Cl), 1076(Ar-Br), 1257(C-O), 1529(C=N), 1560(Ar-C=C), 1602(C=C), 1652(C=O); **$^1$H NMR (4c)** ($CDCl_3$)δ ppm: 6.626(s, 1H, Chromone-H), 7.077-7.084(d, 1H, Ar-H, *J* =2.8 Hz),7.165-7.172(d, 1H, Ar-H, *J* =2.9 Hz),7.401-7.422(d, 2H, Ar-H, *J*=8.5 Hz), 7.512-7.531(t, 2H, Ar-H, *J* =7.6 Hz),7.625-7.646(d, 1H, Ar-H, *J* =8.1 Hz), 7.764-7.784(d, 2H, Ar-H, *J*=7.7 Hz), 8.196(s, 1H, Ar-H), 8.380(s, 1H, Pyrazole-H); **ES-MS (4c)** (m/z):483(M+1), 485(M+3), 487(M+5).




**Scheme 1**

**Table I: Physical data of compounds (4a-h) & (5a-h)**

| Comp. | $R_1$ | $R_2$ | $R_3$ | M.P. (°C) | Yield (%) |
|---|---|---|---|---|---|
| **4a** | **H** | **H** | **H** | 265-267 | 86 |
| **4b** | **H** | **H** | **$CH_3$** | 248-250 | 87 |
| **4c** | **H** | **H** | **Cl** | 240-242 | 52 |
| **4d** | **Cl** | **H** | **Cl** | 290-292 | 81 |
| **4e** | **H** | **H** | **F** | 280-282 | 91 |
| **4f** | **H** | **$CH_3$** | **Cl** | 250-252 | 84 |
| **4g** | **H** | **H** | **Br** | 270-272 | 84 |
| **4h** | **$CH_3$** | **H** | **$CH_3$** | 285-287 | 64 |

| | | | | | |
|---|---|---|---|---|---|
| **5a** | **H** | **H** | **H** | 110-112 | 47 |
| **5b** | **H** | **H** | **$CH_3$** | 180-182 | 76 |
| **5c** | **H** | **H** | **Cl** | 190-192 | 80 |
| **5d** | **Cl** | **H** | **Cl** | 130-132 | 72 |
| **5e** | **H** | **H** | **F** | 320-322 | 40 |
| **5f** | **H** | **$CH_3$** | **Cl** | 125-127 | 76 |
| **5g** | **H** | **H** | **Br** | 205-207 | 66 |
| **5h** | **$CH_3$** | **H** | **$CH_3$** | 170-172 | 74 |

**General Procedure for the synthesis of 2-(3-(5-bromothiophen-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)-3-chloro-4*H*-chromen-4-one (5c):** (0.25 gm, 0.0007 mmole) of chalcone **3c** was dissolved in 15 mL of DMSO. To 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$^o$C. After completion of reaction (monitored by TLC), reaction mass was left overnight. 10 mL cold water was slowly 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 under vacuum and crystallized from ethanol to afford **5c**. The physical data of the compounds **5(a-h)** is recorded in **Table I**. Their structures have been confirmed by IR, $^1$H NMR and Mass spectra.**IR (5c)** (cm$^{-1}$): 717(C-Cl), 1080(Ar-Br), 1597, 1612(C=C), 1653(C=O); **$^1$H NMR (5c)** ($CDCl_3$)δ ppm: 6.955-6.964(d, 1H, Ar-H, *J*=3.6 Hz), 7.003-7.012(d, 1H, Ar-H, *J*=3.6 Hz), 7.261-7.280(d, 1H, Ar-H, *J*=7.6 Hz), 7.393-7.430(m, 1H, Ar-H),7.516-7.555(m, 1H, Ar-H), 7.638-7.644(d, 1H, Ar-H, *J*=2.4 Hz),7.660-7.667(d, 1H, Ar-H, *J*=2.8 Hz),7.778-7.795(m, 2H, Ar-H),8.266-8.272(d, 1H, Ar-H, *J*=2.4 Hz),8.591(s, 1H, Pyrazole-H); **ES-MS (5c)** (m/z): 517(M+1), 519(M+3), 521(M+5), 523(M+7).

## RESULTS AND DISCUSSION

The Chromone derivatives were synthesized successfully in moderate to good yields. The 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:** Compounds **4(a-h), 5(a-h)** were screened for their in vitro antimicrobial activity against *Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 27853), Staphylococcus aureus(ATCC 25923), Staphylococcus albus, Klebsiella pnuemoniae* using Ciprofloxacin as a reference standard drug by paper disc diffusion method. Antifungal activity was evaluated against *Candida sp.* using Fluconazole as standard drug. All the tests were evaluated at 100 µg/ml concentration. The culture media was Muller Hinton agar. The zone of inhibition was measured in mm after 24 hr of incubation at 37$^o$C. DMSO is used as control.

Microbial data for corresponding compounds is summarized in **Table II.**

**Table II: Antimicrobial Analysis Data**

| Sr. No. | Comp. No. | Inhibition Zone Diameter (mm) | | | | | |
|---|---|---|---|---|---|---|---|
| | | *Candida sp.* | *S. aureus* | *S. albus* | *Klebsiella pnuemoniae* | *E. coli* | *Pseudomonas sp.* |
| 1 | 4a | 5 | 6.4 | 7 | 10 | 6 | 5 |
| 2 | 4b | 6.4 | 6 | 9 | 12.3 | 6.4 | 4 |
| 3 | 4c | 6.4 | 6 | 4 | 11 | 6.7 | 6.5 |
| 4 | 4d | - | - | 4.2 | 9.8 | 6.9 | 5.8 |
| 5 | 4e | - | - | 5 | 9.5 | 5 | - |
| 6 | 4f | 8 | - | 4.6 | 9 | 4.9 | 5.8 |
| 7 | 4g | 3.6 | - | - | 14 | 11 | 9 |
| 8 | 4h | - | - | 4.6 | 9.7 | 6.8 | 6.8 |
| 9 | 5a | 8.7 | - | 7 | 1 | 12 | 9 |
| 10 | 5b | 7.4 | - | 11 | 6 | 13 | 12 |
| 11 | 5c | 5 | - | 15 | 9.4 | 10 | - |
| 12 | 5d | 9 | 9 | 9 | 5 | - | - |
| 13 | 5e | 10 | 8 | - | 2.5 | 7 6 | - |
| 14 | 5f | 8 | 8.6 | 10 | 3.5 | 9 | - |
| 15 | 5g | - | 8.5 | 9 | 8 | 9 | - |
| 16 | 5h | 5.6 | 8 | - | - | - | - |
| 17 | Control | 8 | 3 | 3 | 4 | 6 | 10 |
| 18 | Ciprofloxacin | --- | 20 | 22 | 22 | 21 | 23 |
| 19 | Fluconazole | 23 | --- | --- | --- | --- | --- |

## CONCLUSION

The synthesized compounds were tested against Candida sp. and Gram positive as well as Gram negative bacterial strains. Among them, the compound 4b, 4c, 4f, 4g, 5b, 5c, 5f exhibited moderate activity against all the tested bacteria. The other compounds have shown good activity compared to standard drug.

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