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# Eco-Friendly Synthesis and in vitro Antibacterial Activities of Some Novel Chalcones[1]

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**Abstract**—Chalcone derivatives have been synthesized by reaction of 1-(2,5-dimethyl-furan-3-yl)-ethanone with corresponding active aldehyde in ethanolic NaOH in microwave oven. The structure of these compounds was established by elemental analysis, IR, $^1$H NMR, $^{13}$C NMR, and EI-MS spectral analysis. The anti-bacterial activity of these compounds was first tested in vitro by the disc diffusion assay against two Gram-positive and two Gram-negative bacteria, and then the minimum inhibitory concentration (MIC) was determined with the reference of standard drug chloramphenicol. The results showed that pyrazol containing chalcone (compound **8**) inhibited both types of bacteria (Gram-positive and Gram-negative) better than chloramphenicol.

*Keywords: chalcones, anti-bacterial activity, chloramphenicol*

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## INTRODUCTION

The rapid rise in the pathogen infections such as food poisoning, rheumatic, salmonellosis, and diarrhea have become the topic of concern for many researchers. These serious health problems are caused by Staphylococcus aureus, *Staphylococcus pyogenes, Salmonella typhimurium*, and *Escherichia coli* [1]. Amoxicillin, norfloxacin, and ciprofloxacin are the principal drugs of choice in the treatment of these bacterial infections. These drugs are found to be effective against intestinal and extraintestinal wall infection, but there are various side effects such as nausea, metallic taste, dizziness, hypertension, etc. associated with these drugs. The rise in the bacterial resistance to these drugs has encouraged the continuing search for new classes of compounds with novel modes of antibacterial activity [2]. Chalcones (*trans*-1,3-diphenyl-2-propen-1-one) are carbonyl systems; they consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α,β-unsaturated system [3]. Chalcones have been reported to possess many useful properties, including anti-inflammatory, antimicrobial, antifungal, antioxidant, cytotoxic, antitumor, and anticancer activities [4–9]. Recent developments in anti-bacterial agents involve structural modification of chalcones to improve their bioavailability and study the role of various substituents on aryl or heteroaryl rings [10]. Introduction of a heterocyclic ring into chalcones dramatically increases the diversity of certain biological properties such as antibacterial, antiviral, and antiamoebic activities [11]. Various synthetic methods have been reported so far, such as refluxing in an organic solvent [12], solvent-free solid-phase reaction [13], ultrasonication [14], and microwave radiation [15]. Microwave radiation has attracted the attention of medicinal chemists due to its unique advantages. In view of these findings, herein we describe a simple and convenient method for the synthesis of chalcones under microwave irradiation in solvent free environment, with improved yields and short reaction time.

## RESULTS AND DISCUSSION

### *Chemistry*

Chalcone derivatives were synthesized by the reaction of 1-(2,5-dimethyl-furan-3-yl)-ethanone and corresponding active aldehyde (Scheme and Table 1). The purified products was characterized by EI-MS *m/z* values (rel. int. %), FT-IR, $^1$H NMR, $^{13}$C NMR, and elemental analysis. The IR spectra of compounds (**1**–**8**) show the characteristic band: the ν(C=O) peak of Act-furan observed at 1668 cm$^{-1}$ shifts to a lower frequency of 1636–1655 cm$^{-1}$ in chalcones. This is due to the conjugation of the π-electrons of the benzene moiety with those of the ethylene moiety in the

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**Table 1.** Physicochemical data on the synthesized compounds (**1**–**8**)

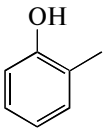
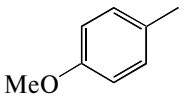
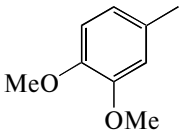
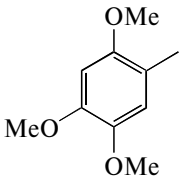
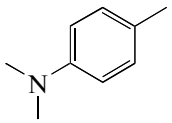
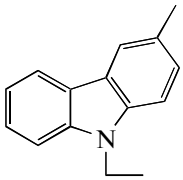
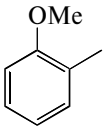
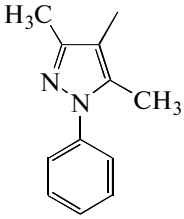
| Compound no. | Ar | Molecular formula | Crystallization | % Yield | Reaction time, microwave |
|---|---|---|---|---|---|
| **1** |  | $C_{15}H_{14}O_3$ | $CHCl_3$ | 87.8 | 35 s |
| **2** |  | $C_{16}H_{16}O_3$ | $CH_2Cl_2$ | 89.5 | 42 s |
| **3** |  | $C_{17}H_{18}O_4$ | $CH_2Cl_2$ | 87.8 | 46 s |
| **4** |  | $C_{18}H_{20}O_5$ | $CHCl_3$ | 88.5 | 52 s |
| **5** |  | $C_{17}H_{19}NO_2$ | $CHCl_3$ | 86.8 | 45 s |
| **6** |  | $C_{23}H_{21}NO_2$ | $CH_2Cl_2$ | 87.5 | 42 s |
| **7** |  | $C_{16}H_{16}O_3$ | $CHCl_3$ | 90.0 | 40 s |
| **8** |  | $C_{20}H_{20}N_2O_2$ | $CHCl_3$ | 88.6 | 46 s |

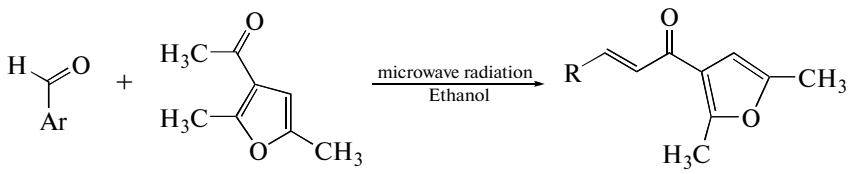
**Table 2.** Antibacterial activity of chalcones measured by the halo zone (mm) test; positive control, chloramphenicol (Chlor.) and negative control, DMSO

| Compounds | Corresponding effect on microorganisms | | | |
|---|---|---|---|---|
| | *S. aureus* | *S. pyogenes* | *S. typhimurium* | *E. coli* |
| **1** | 9.8 ± 0.3 | 9.6 ± 0.2 | 9.0 ± 0.3 | 9.2 ± 0.4 |
| **2** | 10.2 ± 0.2 | 11.2 ± 0.4 | 10.8 ± 0.3 | 11.6 ± 0.2 |
| **3** | 11.2 ± 0.3 | 11.4 ± 0.4 | 10.6 ± 0.4 | 11.4 ± 0.4 |
| **4** | 9.6 ± 0.3 | 9.2 ± 0.5 | 11.9 ± 0.4 | 12.2 ± 0.1 |
| **5** | 10.6 ± 0.2 | 12.2 ± 0.3 | 11.8 ± 0.4 | 12.2 ± 0.4 |
| **6** | 10.8 ± 0.4 | 10.6 ± 0.4 | 12.8 ± 0.5 | 12.6 ± 0.5 |
| **7** | 11.8 ± 0.3 | 12.2 ± 0.5 | 12.6 ± 0.2 | 13.6 ± 0.5 |
| **8** | 18.0 ± 0.4 | 18.2 ± 0.5 | 19.4 ± 0.4 | 21.2 ± 0.5 |
| Chlor. | 17.0 ± 0.5 | 18.2 ± 0.4 | 17.2 ± 0.8 | 20.0 ± 0.2 |
| DMSO | – | – | – | – |

**Table 3.** Minimum inhibition concentration (MIC) of chalcones (**1**–**8**), positive control, chloramphenicol

| Bacterial strain | MIC, μg mL$^{-1}$ compound | | | | | | | | Positive control |
|---|---|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | |
| *S. aureus* | 512 | 512 | 256 | 512 | 256 | 128 | 128 | 16 | 32 |
| *S. pyogenes* | 512 | 256 | 128 | 512 | 128 | 128 | 64 | 32 | 32 |
| *S. typhimurium* | 512 | 512 | 256 | 128 | 128 | 64 | 64 | 16 | 32 |
| *E. coli* | 512 | 256 | 128 | 128 | 128 | 64 | 64 | 16 | 32 |

enone linkage. $^1$H NMR spectra is a proved diagnostic tool for the positional elucidation of the proton. Assignments of the signals are based on chemical shift and intensity pattern. The $^1$H NMR spectra of all the compounds (**1**–**8**) measured at room temperature show two doublets at 7.60–8.01 ppm ($J$ = 15.6) and 6.07–7.25 ppm ($J$ = 15.6 Hz) indicating that the ethylene moiety in the enone linkage is in the *trans*-configuration which confirms the formation of chalcones.




**Scheme.**

$^{13}$C NMR ($CDCl_3$) spectra of chalcones (**1**–**8**) were recorded in $CDCl_3$ and the spectra are in good agreement with the theoretic structure $^{13}$C NMR spectra proposed for all compounds.

Characteristic peaks were observed in the EI mass spectra of compounds **1**–**8**, which followed common molecular ion peak and fragmentation patterns.

### *Antimicrobial Activity*

The compounds (**1**–**8**) were tested for their antibacterial activities by disc-diffusion method [16]. The Gram-positive bacteria and Gram-negative bacteria utilized in this study included *S. aureus, S. pyogenes, S. typhimurium*, and *E. coli*. The results (see Tables 2 and 3) show that the nitrogen-containing heterocyclic chalcones exhibited increased antibacterial activity. Among the entire eight compounds, pyrazol-containing chalcone (**8**) exerted antibacterial activity against *S. aureus* and *S. pyogenes* higher than that of the reference drug chloramphenicol.

## EXPERIMENTAL

### *General Method for the Synthesis of Chalcones*

To a solution of 1-(2,5-dimethyl-furan-3-yl)-ethanone (0.34 g, 2.5 mmol) and corresponding active aldehyde (2.5 mmol) in dry ethanol (20 mL) taken in a beaker (100 mL), a catalytic quantity of sodium hydroxide (0.05 g, 1.25 mmol) was added and the reaction mixture was heated inside a microwave oven for 35–52 s (at 210 W, i.e. ~30% microwave power) [15]. The reactions were monitored through TLC using solvent system ethyl acetate : benzene (2 : 8), When the reaction was complete the reaction mixture was cooled in an ice bath and the product thus formed was filtered, washed with ethanol followed by washing with water till the washings were neutral and recrystallized from distilled ethanol and chloroform.

### *(2E)-1-(2,5-dimethylfuran-3-yl)-3-(2-hydroxyphenyl)prop-2-en-1-one (**1**)*

Orange solid: mp 137°C; EI-MS *m/z* (rel. int. %): 244 (62) $[M + 1]^+$; IR (KBr) $\nu_{max}$, $cm^{-1}$: 3134 (OH), 2914 (C–H), 1642 (C=O), 1554 (C=C); $^1H$ NMR (600 MHz, $CDCl_3$) δ: 9.74 (s, OH), 7.73 (d, C = CH, $J$ = 15.6 Hz), 7.02 (d, CO=CH, $J$ = 15.6 Hz), 7.51–6.67(m, 6.33 (s, CH), 2.60 (s, $-CH_3$), 2.28 (s, $-CH_3$); $^{13}C$ NMR ($CDCl_3$) δ: 186.23, 157.04, 151.80, 149.70, 143.68, 130.17, 122.80, 122.62, 119.11, 111.78, 105.81, 40.15, 40.15, 14.41, 40.30; Anal. calc. for $C_{15}H_{14}O_3$: C, 74.36, H, 5.82. Found: C, 74.32, H, 5.78.

### *(2E)-1-(2,5-dimethylfuran-3-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (**2**)*

Light-yellow solid: m.p 85.5°C; EI-MS *m/z* (rel. int. %): 258 (65) $[M + 1]^+$; IR (KBr) $\nu_{max}$, $cm^{-1}$: 2922 (C–H), 1654 (C=O), 1564 (C=C); $^1H$ NMR (600 MHz $CDCl_3$) δ: 7.70 (d, C=CH, $J$ = 15.6 Hz), 7.56 (d, CH, $J$ = 8.4 Hz), 6.92 (d, CH, $J$ = 1.8 Hz), 6.32 (s, CH), 6.07 (d, CO=CH, $J$ = 15.6 Hz), 6.34 (s, CH), 3.84 (s, $-OCH_3$), 3.75 (s, $-OCH_3$), 2.60 (s, –CH3), 2.23 (s, $-CH_3$); $^{13}C$ NMR ($CDCl_3$) δ: 186.01, 161.40, 151.61, 149.92, 142.57, 130.03, 127.61, 122.56, 121.86, 114.31, 105.70, 55.38, 14.46, 13.27; Anal. calc. for $C_{16}H_{16}O_3$: C, 74.98, H, 6.29. Found: C, 74.92, H, 6.25.

### *(2E)-3-(3,4-dimethoxyphenyl)-1-(2,5-dimethylfuran-3-yl)prop-2-en-1-one (**3**)*

Yellow solid: mp 140°C; EI-MS *m/z* (rel. int. %): 288 (75) $[M + 1]^+$; IR (KBr) $\nu_{max}$, $cm^{-1}$: 3122 (C–H), 2961 (C–H), 1654 (C=O), 1587 (C=C); $^1H$ NMR (600 MHz, $CDCl_3$) δ: 7.60 (d, C=CH, $J$ = 15.6 Hz), 7.20 (d, CH, $J$ = 1.2 Hz), 7.19 (d, CH, $J$ = 1.8 Hz), 7.11 (s, CH), 6.89 (d, CO=CH, $J$ = 15.6 Hz), 6.34 (s, CH), 2.61 (s, $-OCH_3$), 2.53 (s, $-OCH_3$), 2.29 (s, $-CH_3$), 2.25 (s, $-CH_3$); $^{13}C$ NMR ($CDCl_3$) δ: 186.01, 157.69, 151.12, 149.95, 149.12, 142.91, 127.87, 122.89, 122.15, 111.02, 109.91, 105.69, 55.98, 55.92, 14.45, 13.29; Anal. calc. for $C_{17}H_{18}O_4$: C, 71.31, H, 6.39. Found: C, 71.27, H, 6.35.

### *(2E)-1-(2,5-dimethylfuran-3-yl)-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one (**4**)*

Light-yellow solid: mp 128°C; EI-MS *m/z* (rel. int. %): 318 (68) $[M + 1]^+$; IR (KBr) $\nu_{max}$, $cm^{-1}$: 3129 (C–H), 1652 (C=O), 1581 (C=C); $^1H$ NMR (600 MHz, $CDCl_3$) δ: 8.01 (d, C=CH, $J$ = 15.6 Hz), 7.11 (d, C=CH, $J$ = 15.6 Hz), 7.06 (s, CH), 6.33 (s, CH), 6.51 (s, CH), 2.60 (s, $-OCH_3$), 2.59 (s, $-OCH_3$), 2.29 (s, $-OCH_3$), 2.24 (s, $-CH_3$), 1.75 (s, $CH_3$); $^{13}C$ NMR ($CDCl_3$) δ: 186.59, 157.28, 159.44, 152.13, 149.78, 143.13, 138.12, 122.71, 122.49, 115.44, 111.31, 105.84, 96.78, 56.50, 56.35, 14.43, 13.29. Anal. calc. for $C_{18}H_{20}O_5$: C, 68.34, H, 6.37; Found: C, 68.31, H, 6.32.

### *(2E)-3-[4-(dimethylamino)phenyl]-1-(2,5-dimethylfuran-3-yl)prop-2-en-1-one (**5**)*

Yellow solid: mp 116°C; EI-MS *m/z* (rel. int. %): 271 (62) $[M+1]^+$; IR (KBr) $\nu_{max}$, $cm^{-1}$: 3101(C–H), 1641(C=O), 1604 (C=C), 1167 (C–N); $^1H$ NMR (600 MHz, $CDCl_3$) δ: 7.70 (d, C=CH, $J$ = 15.6 Hz), 6.71 (d, CO=CH, $J$ = 6Hz), 6, $J$ = 15.6 Hz), 7.51 (d, CH, $J$ = 8.4 Hz), 6.71 (d, CH, $J$ = 8.4 Hz), 6.67 (d, CH, $J$. 7.56 (d, CH, $J$ = 6.8 Hz), 6.32 (c, CH), 3.08 (s, $-NCH_3$), 3.03 (s, $-NCH_3$), 2.60 (s, $CH_3$), 2.28 (s, $CH_3$); $^{13}C$ NMR ($CDCl_3$) δ: 157.04, 151.80, 149.70, 143.68, 130.17, 122.80, 122.62, 119.60, 111.78, 105.81, 40.15, 40.13, 40.12, 14.41, 13.30; Anal. calc.

for $C_{17}H_{19}NO_2$: C, 75.81, H, 7.11, N, 5.20. Found: C, 75.76, H, 7.06, N, 5.16.

*(2E)-1-(2,5-dimethylfuran-3-yl)-3-(9-ethyl-9H-carbazol-3-yl)prop-2-en-1-one (**6**)*

Orange yellow solid: m.p. 109°C; EI-MS *m/z* (rel. int. %): 345 (68) $[M + 1]^+$; IR (KBr) $\nu_{max}$, $cm^{-1}$: 3397 (C–H), 2976 (C–H), 1640 (C=O), 1560 (C=C), 1162 (C–N); $^1H$ NMR (600 MHz, $CDCl_3$) δ, ppm: 8.14 (d, CH, $J$ = 8.4 Hz), 8.01 (d, CH, $J$ = 7.8 Hz), 7.94 (d, C=CH, $J$ = 15.6 Hz), 7.75 (d, CH, $J$ = 8.4 Hz), 7.25 (d, CO=CH, $J$ = 15.6 Hz), 7.55 (dd, CH, $J$ = 7.8, 6.6 Hz), 7.33 (dd, CH, $J$ = 7.2, 7.2), 4.41 (q, N–$CH_2$–$CH_3$, $J$ = 7.2 Hz), 2.35 (s, $CH_3$), 2.19 (s, –$CH_3$), 1.47 (t, N–$CH_2$–$CH_3$); $^{13}C$ NMR ($CDCl_3$) δ: 186.66, 157.47, 149.85, 144.35, 141.26, 140.63, 140.39, 127.18, 126.71, 125.89, 123.37, 122.69, 121.40, 120.79, 119.59, 109.13, 108.67, 105.82, 37.90, 37.73, 14.48, 13.84; Anal. calc. for $C_{23}H_{21}NO_2$: C, 80.44, H, 6.16, N, 4.08. Found: C, 80.44, H, 6.16, N, 4.08.

*(2E) 1-(2,5-dimethyl-furan-3-yl)-3-(2-methoxy-phenyl)-propenone (**7**)*

Light-yellow solid: mp 81°C; EI-MS *m/z* (rel. int. %): 258 (58) $[M + 1]^+$; IR (KBr) $\nu_{max}$, $cm^{-1}$: 3016 (Ar–H), 2918 (C–H), 1655 (C=O), 1580 (C=C); $^1H$ NMR (600 MHz, $CDCl_3$) δ, ppm: 8.03 (d, C=CH, $J$ = 15.6 Hz), 7.58 (dd, CH, $J$ = 1.8 Hz), 7.36 (dd, CH, $J$ = 1.2 Hz), 7.26 (d, CH, $J$ = 7.2 Hz), 6.98 (d, CO=CH, $J$ = 15.6 Hz); 6.32 (s, CH), 2.60 (s, $CH_3$), 2.28 (s, $CH_3$); $^{13}C$ NMR ($CDCl_3$) δ: 186.00, 158.64, 157.55, 149.89, 138.35, 131.45, 129.13, 124.98, 123.93, 122.71, 120.67, 111.16, 105.83, 55.44, 14.48, 13.26; Anal. calc. for $C_{16}H_{16}O_3$: C, 74.98, H, 6.29. Found: C, 74.92, H, 6.24.

*(2E)-3-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)-1-(2,5-dimethyl-3-furanyl)prop-2-en-1-one (**8**)*

Light brown; yield: 85%; mp 109–110°C; ESI-MS *m/z* (rel. int. %): 321 (72) $[M + 1]^+$ IR (KBr) $\nu_{max}$, $cm^{-1}$: 3043 (C–H aromatic), 2926 (C–H aliphatic), 1636 (C=O), 1562 (C=C); $^1H$ NMR (600 MHz, $CDCl_3$) δ, ppm: 7.79 (d, 1H, C7, C=CH, $J$ = 15.6 Hz), 6.93 (d, 1H, C8, CO=CH, $J$ = 15.6 Hz), 7.27 (s, 1H, C3, CH, furan), 7.49–6.90 (m, 5H, Ar–H), 2.63 (s, C2, $CH_3$), 2.51 (s, C5, $CH_3$), 2.43 (s, C10, $CH_3$), 2.22 (s, C11, $CH_3$); $^{13}C$ NMR ($CDCl_3$) δ: 185.99, 157.43, 149.92, 149.21, 141.08, 138.92, 134.11, 129.24,128.18, 125.17, 124.28, 122.67, 121.08, 115.25, 114.32, 105.24, 14.51, 14.29, 13.28, 11.60; Anal. calc. for $C_{20}H_{20}N_2O_2$: C, 78.98, H, 6.29, N, 8.74; Found: C, 78.93, H, 6.21, N, 8.72.

*In vitro Screening: Disc Diffusion and Micro Dilution Assays*

Antibacterial activity was evaluated by the disc diffusion method with minor modifications. *S. aureus, S. pyogenes, S. typhimurium*, and *E. coli* were sub-cultured in BHI medium and incubated for 18 h at 37°C, and then the bacterial cells were suspended, according to the McFarland's protocol, in saline solution to produce a suspension of about $10^{-5}$ CFU $mL^{-1}$; 10 μL of this suspension was mixed with 10 mL of sterile nutrient agar at 40°C and poured onto an agar plate under laminar flow. Five paper discs (6.0 mm diameter) were fixed onto nutrient agar plate. One milligram of each test compound was dissolved in 100 μL DMSO to prepare stock solutions of different concentrations: 10, 20, 25, 50, and 100 μg/μL. The compounds at different concentration were poured onto a disc plate. Chloramphenicol (30 μg/disc) was used as standard drug (positive control). DMSO-poured disc was used as negative control. The susceptibility of the bacteria to the test compounds was determined by the formation of an inhibitory zone after 18 h of incubation at 36°C.

The minimum inhibitory concentration (MIC) was evaluated by the macro dilution test using standard inoculums of $10^{-5}$ CFU $mL^{-1}$. Serial dilutions of the test compounds, previously dissolved in DMSO, were prepared at final concentrations of 512, 256, 128, 64, 32, 16, 8, 4, 2 and 1 μg/mL; 100 μL of a 24 h old inoculum was added to each test tube. The MIC, defined as the lowest concentration of the test compound which inhibits visible growth, was determined visually after incubation for 18 h at 37°C. Tests using DMSO and chloramphenicol as negative and positive controls.

## CONCLUSION

A series of chalcones was prepared by the reaction of 1-(2,5-dimethyl-furan-3-yl)-ethanone with corresponding active aldehyde in ethanolic NaOH in microwave oven. The antibacterial activity of these compounds was examined using bacterial cultures and the results show that the nitrogen-containing heterocyclic chalcones possess increased antibacterial activity. Among the eight compounds synthesized, pyrazol-containing chalcone (**8**) demonstrated antibacterial activity against *S. aureus* and *S. pyogenes* better than that of the reference drug chloramphenicol.

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