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ORIGINAL RESEARCH

Synthesis and antimicrobial activity of bischalcone derivatives

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Abstract Several bischalcones (**2a–h** and **5a–e**) and flavones (**3a–f**) were synthesized and evaluated for their antimicrobial actions. Bischalcones were prepared by condensing 1,1′-(4,6-dimethyl-1,3-phenylene)diethanone (**1**) or 1-(5-acetyl-2,4-dimethoxyphenyl)-1-ethanone (**4**) with arylaldehydes. Bischalcones were cyclized in presence of iodine to give corresponding flavones (**3a–f**). An alternative route to synthesize the flavones consisted in preparing the diester derivatives (**6a–f**) of (**1**) with different aromatic acids, which could be converted to β-diketones followed by cyclization to give the corresponding flavones. However, all the attempts in this direction were unsuccessful and it could not be possible to proceed beyond diester stage; six diester derivatives (**6a–f**) were synthesized. The structures of the synthesized compounds were assigned on the basis of ^{1}H NMR, mass spectral data and microanalyses results. The antimicrobial screening was performed at a concentration of 100 μg/mL by cup plate method; the compounds inhibiting growth of one or more of the microorganisms were further tested for their minimum inhibitory concentration (MIC) by turbidity method. Preliminary antimicrobial results revealed that the compounds **2a–h** and **3a–f** were significant in their antibacterial and antifungal activities. MICs results showed that the compound **2f** exhibited very good activity against *E. coli*, *P. aeruginosa*, and *C. albicans* with MIC-12.5 μg/mL. Similar type of activity was shown the compound **3a** against *S. aureus* and *C. albicans* with MIC-12.5 μg/mL. Another compound, **3f**, was active against *P. aeruginosa* and *C. albicans* with MIC-12.5 μg/mL. Methylation of the two chelated hydroxyls (**5a–e**) significantly reduced the activity. However, oxidative cyclization of bischalcones resulted in compounds (**3a–f**) which were found to be considerably active. Diesters (**6a–f**) were insignificant in their antimicrobial activities.

Keywords Bischalcones · Flavone · Antibacterial · Antifungal

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Introduction

Over the past decades, the incidence of systemic bacterial and fungal infections has been increasing dramatically due to an increase in the number of immuno-compromised hosts (Davies, 1996). Immunosuppression due to malignancy, immunosuppressive therapies, HIV-infection, broad-spectrum antimicrobial treatment and age, as well as invasive procedures and mucosal barriers places patients at risk for microbial infections. The increasing incidence of resistance to a large number of antibacterial agents is becoming a major concern (Chu *et al.*, 1996). Currently, a small number of antifungal agents are available, and all have some drawbacks regarding their spectrum, toxicity, tissue distribution, and high cost (Dupont *et al.*, 2002; Baddley and Moser, 2004).

These observations place new emphasis on the need of as well as search for alternative new and more effective

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antimicrobial agents with a broad-spectrum activity (Alvarez *et al.*, 2008). Among a wide variety of compounds that have been explored for developing pharmaceutically important antimicrobial agents, Flavonoidal derivatives—chalcones and bischalcones, flavanones and flavones have played an important role (Cushnie and Lamb, 2005; Nowakowska, 2007; Lin *et al.*, 2002; Batovska and Todorova, 2010; Sharma *et al.*, 2009; Oganesyan *et al.*, 1988). Flavonoids have attracted considerable attention due to their marked physiological activity and distinct functions. Flavonoids form a large group of naturally occurring organic compounds and possess wide range of pharmacological actions including antimicrobial action (Casano *et al.*, 2010; Liu *et al.*, 2010; Mojzis *et al.*, 2008; Alvim *et al.*, 2010; Boumendiel *et al.*, 2009; Alcaraz *et al.*, 2000, pp. 5–15). Moreover, flavonoidal derivatives acquire a special place in natural chemistry and in heterocyclic chemistry because this system is a frequently encountered structural motif in many pharmacologically relevant compounds (Gatto *et al.*, 2002; Sherif *et al.*, 2008; Ashok and Sarma, 1987, pp. 15–19).

Resorcinol is a simple and important aromatic chemical (1,3-benzenediol) that has been chemically incorporated into various compounds to enhance their pharmacological profile (Soliman *et al.*, 2005; Khan *et al.*, 2002, 2010). In view of these points it was considered worthwhile to study some flavonoidal derivatives for their antimicrobial actions.

Materials and methods

Chemistry

All the solvents were of LR grade and were obtained from Merck (Mumbai, India), S.D. fine (Mumbai, India) and CDH (New Delhi, India). Melting points are uncorrected and were recorded in liquid paraffin bath using open end capillaries. ^{1}H NMR spectra were recorded on Bruker spectropsin DPX-300 MHz in $CDCl_3$; chemical shift (δ) values are reported in parts per million (ppm). The splitting pattern abbreviations are as follows: s, singlet; d, doublet; dd, double doublet; m, multiplet. Mass spectroscopic analyses for compounds were performed on a JEOL JMS-D 300 instrument. Elemental analyses were performed on a Perkin-Elmer 240 analyzer and were in range of ±0.4 % for each element analyzed (C, H, N). Thin-layer chromatography (TLC) was carried out to monitor the reactions using silica gel G (Merck) as stationary phase in the solvent system-Toluene: Ethyl acetate: Formic acid (5:4:1, v/v/v); iodine chamber, and UV lamp were used for visualization of TLC spots.

Synthesis of the compounds

*Synthesis of 1-(5-acetyl-2,4-dimethoxyphenyl)-1-ethanone (**4**)* A mixture of 1,1′-(4,6-dimethyl-1,3-phenylene)-diethanone (1). (2.5 mmol), dimethylsulphate (5 mmol) and anhydrous potassium carbonate (11.25 g) in dry acetone (100 mL) was refluxed for 6 h. The contents were then filtered, concentrated to a small volume and poured onto crushed ice. A solid mass separated out which was filtered, washed with water, dried and then crystallized from methanol: dichloromethane mixture to give shiny needles of 4. Yield 74 %; m.p. 164–166 °C; R_f 0.76; ^{1}H NMR ($CDCl_3$) δ ppm: 2.61 (s, 6H, 2× –$COCH_3$), 3.93 (s, 6H, 2× –OCH_3), 6.34 (s, 1H, H-2), 8.37 (s, 1H, H-5); MS: *m/z* 222 (M^+), 207, 177, 175, 149; $C_{12}H_{14}O_4$; Calc. C 64.85, H 6.35; Found C 64.71, H, 6.22.

*Synthesis of Bischalcones (**2a–i** and **5a–e**) (Dhar, 1981) general procedure* A mixture of 1/4 (5 mmol) in ethanol (20 mL), aromatic aldehyde (10 mmol) and a solution of potassium hydroxide (3 g) in distilled water (5 mL) was stirred for 2 h at room temperature and then left overnight. It was poured into cold water and acidified with HCl, a solid mass separated out which was filtered, washed with water, sodium bicarbonate solution (2 % w/v in water) and again with water. It was crystallized from methanol to give **2a–i** (it gave a violet colour with alcoholic ferric chloride solution and a red colour with conc. sulphuric acid) and **5a–e** (It gave a red colour with conc. sulphuric acid and no colour with alcoholic ferric chloride solution).

*3-(4-Chlorophenyl)-1-{5-[3-(4-chlorophenyl)-2-propenoyl]-2,4-dihydroxyphenyl}-2-propen-1-one (**2a**)*: Yield 61 %; m.p. 210–212 °C; R_f 0.72; ^{1}H NMR ($CDCl_3$) δ ppm: 6.62 (s, 1H, H-3′), 7.08 (d, 4H, $J = 8.1$ Hz, 2× H-3,5), 7.39 (d, 2H, $J = 15.6$ Hz, 2× H-α), 7.71 (d, 4H, $J = 8.1$ Hz, 2× H-2,6), 8.04 (d, 2H, $J = 15.6$ Hz, 2× H-β), 8.66 (s, 1H, H-6′), 13.53 (s, 2H, OH); MS: *m/z* 439 (M^+), 327, 163, 137; $C_{24}H_{16}Cl_2O_4$; Calc. C 65.62, H 3.67; Found: C 65.44, H 3.72.

*3-(3-Chlorophenyl)-1-{5-[3-(3-chlorophenyl)-2-propenoyl]-2,4-dihydroxyphenyl}-2-propen-1-one (**2b**)*: Yield 58 %; m.p. 184–186 °C; R_f 0.70; ^{1}H NMR ($CDCl_3$) δ ppm: 6.57 (s, 1H, H-3′), 7.21–7.84 (m, 8H, 2× H-2, 4,5,6), 7.96 (d, 2H, $J = 15.6$ Hz, 2× H-α), 8.35 (d, 2H, $J = 15.6$ Hz, 2× H-β), 8.61 (s, 1H, H-6′), 13.58 (s, 2H, OH); MS: *m/z* 439 (M^+), 163, 137, 77; $C_{24}H_{16}Cl_2O_4$; Calc. C 65.62, H 3.67; Found C 65.41, H 3.73.

*1-{2,4-Dihydroxy-5-[3-(3,4,5-trimethoxyphenyl)-2-propenoyl]phenyl}-3-(3,4,5-trimethoxyphenyl) -2-propen-1-one (**2c**)*: Yield 64 %; m.p. 190–192 °C; R_f 0.73; ^{1}H NMR ($CDCl_3$) δ ppm: 3.97–4.01(broad s, 18H, 6× –OCH_3), 6.21 (s, 2H, OH), 6.54 (s, 1H, H-3′), 7.66–7.71 (m, 4H, 2× H-2,6), 7.83 (d, 2H, $J = 15.3$ Hz, 2× H-α), 8.27 (d, 2H,

J = 15.6 Hz, 2× H-β), 8.56 (s, 1H, H-6′), 13.64 (s, 2H, OH); MS: m/z 550 (M^+), 326, 164, 77; $C_2H_1Cl_2O_4$; Calc. C 65.45, H 5.49; Found C 65.37; H 5.41.

1-*{2,4-Dihydroxy-5-[3-(2-methylphenyl)-2-propenoyl] phenyl}-3-(2-methylphenyl)-2-propen-1-one* (***2d***): Yield 60 %; m.p. 209–211 °C; R_f 0.71; ^{1}H NMR ($CDCl_3$) δ ppm: 2.44 (s, 6H, 2× –CH_3), 6.31 (s, 2H, OH), 6.51 (s, 1H, H-3′), 7.08 (m, 4H, 2× H-3,5), 7.54 (m, 4H, 2× H-4,6), 7.76 (d, 2H, J = 15.3 Hz, 2× H-α), 8.23 (d, 2H, J = 15.3 Hz, 2× H-β), 8.57 (s, 1H, H-6′), 13.61 (s, 2H, OH); MS: m/z 398 (M^+), 307, 280, 118; $C_{26}H_{22}O_4$; C 78.37, H 5.56; Found C 78.26; H 5.38.

1-{2,4-Dihydroxy-5-[3-(3-methoxyphenyl)-2-propenoyl] phenyl}-3-(3-methoxyphenyl)-2-propen-1-one (***2e***): Yield 63 %; m.p. 192–194 °C; R_f 0.73; ^{1}H NMR ($CDCl_3$) δ ppm: 3.92 (s, 6H each, 4× –OCH_3), 6.53 (s, 1H, H-3′), 7.32–7.78 (m, 8H, 2× H-2,4,5,6), 7.80 (d, 2H, J = 15.3 Hz, 2× H-α), 8.07 (dd, 2H, J = 8.1 Hz, 1.8 Hz, 2× H-6), 8.23 (d, 2H, J = 15.3 Hz, 2× H-β), 8.31 (s, 1H, H-6′), 13.59 (s, 2H, OH); MS: m/z 430 (M^+), 296, 163, 134, 104; $C_{26}H_{22}O_6$; Calc. C 72.55, H 5.15; Found C 72.40, H 5.21.

3-*(2-Furyl)-1-{5-[3-(2-furyl)-2-propenoyl]-2,4-dihydroxyphenyl}-2-propen-1-one* (***2f***): Yield 61 %; m.p. 224 °C; R_f 0.69; ^{1}H NMR ($CDCl_3$) δ ppm: 6.51 (s, 1H, H-3′), 7.24–7.67 (m, 6H, 2× furyl H), 7.65 (d, 2H, J = 15.3 Hz, 2× H-α), 8.22 (d, 2H, J = 15.3 Hz, 2× H-β), 8.38 (s, 1H, H-6′), 13.51 (s, 2H, OH); MS: m/z 350 (M^+), 272, 163, 102, 91; $C_{20}H_{14}O_6$; Calc. C 68.57, H 4.03; Found C 68.52, H 4.15.

3-(4-Dimethylaminophenyl)-1-{5-[3-(4-dimethylaminophenyl)-2-propenoyl]-2,4-dihydroxyphenyl}-2-propen-1-one (***2g***): Yield 52 %; m.p. 232-234 °C; R_f 0.71; ^{1}H NMR ($CDCl_3$) δ ppm: 2.42 (broad s, 12H, 4× –CH_3), 6.64 (s, 1H, H-3′), 7.26 (d, 4H, J = 7.8 Hz, 2× H-3,5), 7.39 (d, 2H, J = 15.3 Hz, 2× H-α), 7.57 (d, 4H, J = 7.6 Hz, 2× H-2,6), 7.98 (d, 2H, J = 15.6 Hz, 2× H-β), 8.56 (s, 1H, H-6′), 13.57 (s, 2H, OH); MS: m/z 456 (M^+), 310, 146, 134, 91; $C_{28}H_{28}N_2O_4$; Calc. C 73.66, H 6.18, N 6.14; Found C 73.58, H 5.96, N 6.21.

3-(4-Diethylaminophenyl)-1-{5-[3-(4-diethylaminophenyl)-2-propenoyl]-2,4-dihydroxyphenyl}-2-propen-1-one (***2h***): Yield 50 %; m.p. 220-222 °C; R_f 0.68; ^{1}H NMR ($CDCl_3$) δ ppm: 1.56-1.61 (m, 12H, 4× –CH_3), 4.08-4.13 (m, 8H, 4× –CH_2–), 6.57 (s, 1H, H-3′), 7.23 (d, 4H, J = 7.8 Hz, 2× H-3,5), 7.37 (d, 2H, J = 15.3 Hz, 2× H-α), 7.61 (d, 4H, J = 7.6 Hz, 2× H-2,6), 7.88 (d, 2H, J = 15.6 Hz, 2× H-β), 8.48 (s, 1H, H-6′), 13.55 (s, 2H, OH); MS: m/z 512 (M^+), 338, 174, 163; $C_{32}H_{36}N_2O_4$; Calc. C 74.97, H 7.08, N 5.46; Found C 75.11, H 6.95, N 5.65.

1-{2,4-Dimethoxy-5-[3-(3-methoxyphenyl)-2-propenoyl] phenyl}-3-(3-methoxyphenyl)-2-propen-1-one (***5a***): Yield 62 %; m.p. 210–212 °C; R_f 0.67; ^{1}H NMR ($CDCl_3$) δ ppm: 3.86 & 4.02 (s each, 12H, 4× –OCH_3), 6.58 (s, 1H, H-3′), 6.92–7.48 (m, 8H, 2× H-2,4,5,6), 7.54 (d, 2H, J = 15.3 Hz, 2× H-α), 8.05 (d, 2H, J = 15.3 Hz, 2× H-β), 8.19 (s, 1H, H-6′); MS: m/z 458 (M^+), 327, 161, 121; $C_{28}H_{26}O_6$; C 73.35, H 5.72; Found C 73.23, H 5.81.

1-{2,4-Dimethoxy-5-[3-(3,4-dimethoxyphenyl)-2-propenoyl]phenyl}-3-(3,4-dimethoxyphenyl)-2-propen-1-one (***5b***): Yield 65 %; m.p. 208–210 °C; R_f 0.66; ^{1}H NMR ($CDCl_3$) δ ppm: 3.79 (s, 6H, 2× –OCH_3), 4.16 (broad s, 12H, 4× –OCH_3), 6.55 (s, 1H, H-3′), 6.82 (d, 2H, J = 7.6 Hz, 2× H-5), 7.14–7.22 (m, 4H, 2× H-2,6), 7.26 (d, 2H, J = 15.6 Hz, 2× H-α), 7.71 (d, 2H, J = 15.6 Hz, 2× H-β), 8.08 (s, 1H, H-6′); MS: m/z 518 (M^+), 357, 162, 77; $C_{30}H_{30}O_8$; C 69.49, H 5.83; Found C 69.43, H 5.75.

3-(2-Furyl)-1-{5-[3-(2-furyl)-2-propenoyl]-2,4-dimethoxyphenyl}-2-propen-1-one (***5c***): Yield 70 %; m.p. 216–218 °C; R_f 0.64; ^{1}H NMR ($CDCl_3$) δ ppm: 3.95 (s, 6H, 2× –OCH_3), 6.33 (s, 1H, H-3′), 6.86–7.59 (m, 8H, 2 × furyl hydrogens + 2H-α), 7.78 (d, 2H, J = 15.3 Hz, 2× H-β), 8.12 (s, 1H, H-6′); MS: m/z 378 (M^+), 301, 137; $C_{22}H_{18}O_6$; C 69.84, H 4.79; Found C 69.56, H 4.75.

1-{2,4-Dimethoxy-5-[3-(3,4,5-trimethoxyphenyl)-2-propenoyl]phenyl}-3-(3,4,5-trimethoxyphenyl)-2-propen-1-one (***5d***): Yield 62 %; m.p. 196–198 °C; R_f 0.67; ^{1}H NMR ($CDCl_3$) δ ppm: 3.89 (s, 6H, 2× –OCH_3), 4.08 (broad s, 18H, 6 × –OCH_3), 6.51 (s, 1H, H-3′), 7.24–7.78 (m, 8H, 2× H-2,6 + 2H-α + 2H-β), 8.12 (s, 1H, H-6′); MS: m/z 578 (M^+), 191, 146, 134; $C_{32}H_{34}O_{10}$; C 66.43, H 5.92; Found C 66.50, H 4.78.

3-(4-Diethylaminophenyl)-1-{5-[3-(4-diethylaminophenyl)-2-propenoyl]-2,4-dimethoxyphenyl}-2-propen-1-one (***5e***): Yield 64 %; m.p. 218–220 °C; R_f 0.66; ^{1}H NMR ($CDCl_3$) δ ppm: 1.52-1.58 (m, 12H, 4× –CH_3), 3.87 (s, 6H, 2× –OCH_3), 4.04-4.11 (m, 8H, 4× –CH_2–), 6.38 (s, 1H, H-3′), 6.62 (d, 4H, J = 7.8 Hz, 2× H-3,5), 7.26 (d, 2H, J = 15.3 Hz, 2× H-α), 7.44 (d, 4H, J = 7.6 Hz, 2× H-2,6), 7.68 (d, 2H, J = 15.6 Hz, 2× H-β), 8.19 (s, 1H, H-6′); MS: m/z 540 (M^+), 338, 174, 134; $C_{34}H_{40}O_8$; C 75.53, H 7.46, N 5.18; Found C 75.45, H 7.28, N 5.30.

Synthesis of flavones (***3a–c***) *(Doshi et al., 1986) General procedure* To a solution of compound **2a** (200 mg) in dimethylsulphoxide (5 mL), 2 crystals of iodine were added. The contents were refluxed for 30 min, cooled to room temperature and poured into ice cold water. A solid mass separated out which was filtered, washed with water, sodium thiosulphate solution (2 %w/v in water) and again with water. After drying it was crystallized from methanol:dichloromethane mixture to give TLC pure **3a–c** (It did not give colour with ethanolic ferric chloride solution).

2,8-Bis(4-Chlorophenyl)-4H,6H-pyrano[3,2-g]chromene-4, 6-dione (***3a***): Yield 36 %, m.p. 226–228 °C; R_f 0.56; ^{1}H NMR ($CDCl_3$) δ ppm: 6.97 (s, 2H, 2× H-3), 7.39 (s, 1H, H-8), 7.52-7.76 (m, 8H, *p*-chlorophenyl), 9.37 (s, 1H, H-5); MS: m/z 435

(M^+), 298, 207, 136; $C_{24}H_{12}Cl_2O_4$; C 66.23, H 2.78; Found C 66.05, H 2.74.

*2,8-Bis(3-chlorophenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (**3b**)*: Yield 32 %, m.p. 220–222 °C; R_f 0.54; ^{1}H NMR ($CDCl_3$) δ ppm: 7.03 (s, 2H, 2× H-3), 7.48 (s, 1H, H-8), 7.46-7.82 (m, 8H, 2× *m*-chlorophenyl), 9.46 (s, 1H, H-5); MS: *m/z* 435 (M^+), 298, 235, 136; $C_{24}H_{12}Cl_2O_4$; C 66.23, H 2.78; Found C 66.18, H 2.66.

*2,8-Bis(3,4,5-Trimethoxylphenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (**3c**)*: Yield 41 %; m.p. 236–238 °C; R_f 0.58; ^{1}H NMR ($CDCl_3$) δ ppm: 3.91 (broad s, 18H, 6× $-OCH_3$), 6.94 (s, 2H, 2 ×H-3), 7.46 (s, 1H, H-8), 7.33–7.78 (m, 4H, 2× trimethoxyphenyl), 9.39 (s, 1H, H-5); MS: *m/z* 546 (M^+), 326, 267, 135, 91, 77; $C_{30}H_{26}O_{10}$; C 65.93, H 4.80; Found C 65.68, H 4.92.

*2,8-Bis(2-Methylphenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (**3d**)*: Yield 62 %; m.p. 212–214 °C; R_f 0.53; ^{1}H NMR ($CDCl_3$) δ ppm: 2.42 (s, 6H, 2× $-CH_3$), 6.83 (s, 2H, 2× H-3), 7.32 (s, 1H, H-8), 7.38–7.81 (m, 8H, 2× *o*-tolyl), 9.19 (s, 1H, H-5); MS: *m/z* 394 (M^+), 236, 208, 91; $C_{26}H_{18}O_4$; C 79.17, H 4.60; Found C 78.94, H 4.78.

*2,8-Bis(3-Methoxylphenyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (**3e**)*: Yield 47 %; m.p. 226–228 °C; R_f 0.55; ^{1}H NMR ($CDCl_3$) δ ppm: 3.87 (s, 6H, 2× $-OCH_3$), 6.85 (s, 2H, 2× H-3), 7.38 (s, 1H, H-8), 7.41–7.84 (m, 8H, 2× *m*-methoxyphenyl), 9.37 (s, 1H, H-5); MS: *m/z* 426 (M^+), 296, 134, 77; $C_{26}H_{18}O_6$; C 73.23, H 4.25; Found C 73.05, H 4.14.

*2,8-Bis(2-furyl)-4H,6H-pyrano[3,2-g]chromene-4,6-dione (**3f**)*: Yield 47 %; m.p. 242-244 °C; R_f 0.52; ^{1}H NMR ($CDCl_3$) δ ppm: 6.88 (s, 2H, 2× H-3), 7.34 (s, 1H, H-8), 7.36-7.71 (m, 6H, 2× furyl H), 9.39 (s, 1H, H-5); MS: *m/z* 346 (M^+), 98, 35, 16; $C_{20}H_{10}O_6$; C, 69.37; H, 2.91; Found C 69.12, H 2.76.

Attempted synthesis of (**3a**–**c**) via Baker–Venkataraman rearrangement (Jain *et al.*, 1982). This route of synthesis involved three steps namely—(i) synthesis of diester (ii) synthesis of β-diketone from diester and (iii) cyclization of the β-diketone to the corresponding flavone.

*Synthesis of diesters (**6a–f**) General procedure* To a solution of **1** (2 mmol) in dry pyridine (5 mL) was added a solution of aromatic acid (4 mmol) in dry pyridine (5 mL). The contents were stirred for 5 min and $POCl_3$ (0.3 mL) was added dropwise into it. Stirring was continued for another 2 h and then reaction mixture poured into ice cold water containing HCl. A solid mass separated out which was filtered, washed with water and dried. It was crystallized from methanol:dichloromethane mixture to give TLC pure **6a**–**f** (it did not give colour with ethanolic ferric chloride solution).

*4,6-Diacetyl-1,3-di(2-nitrophenyl carbonyloxy)benzene (**6a**)*: Yield 70 %; m.p. 138–140 °C; R_f 0.76; ^{1}H NMR ($CDCl_3$) δ ppm: 2.63 (s, 6H, 2× $-COCH_3$), 7.21 (s, 1H, H-2), 7.44–7.56 (m, 6H, 2× H-3′,4′,5′), 7.92–8.08 (m, 2H, 2× H-6′), 8.21 (s, 1H, H-5); MS: *m/z* 492 (M^+), 344, 104, 77; $C_{24}H_{16}N_2O_{10}$; C 58.54, H 3.28, N 5.69; Found C 58.47, H 3.16, N 5.81.

4,6-Diacetyl-1,3-di(3-nitrophenyl carbonyloxy)benzene (**6b**): Yield 68 %; m.p. 148–150 °C; R_f 0.77; ^{1}H NMR ($CDCl_3$) δ ppm: 2.61 (s, 6H, 2× $-COCH_3$), 7.18 (s, 1H, H-2), 7.21–7.38 (m, 6H, 2× H-4′,5′,6′), 7.49–7.62 (m, 2H, 2× H-2′), 8.45 (s, 1H, H-5); MS: *m/z* 492 (M^+), 150, 104, 77; $C_{24}H_{16}N_2O_{10}$; C 58.54, H 3.28, N 5.69; Found C 58.50, H 3.21, N 5.63.

*4,6-Diacetyl-1,3-di(2-methoxyphenyl carbonyloxy)benzene (**6c**)* Yield 72 %; m.p. 132-134 °C; R_f 0.74; ^{1}H NMR ($CDCl_3$) δ ppm: 2.60 (s, 6H, 2× $-COCH_3$), 3.87 (s, 6H, 2× $-OCH_3$), 7.24 (s, 1H, H-2), 7.32–7.67 (m, 8H, 2× H-3′,4′,5′,6′), 8.18 (s, 1H, H-5); MS: *m/z* 462 (M^+), 328, 135, 105; $C_{26}H_{22}O_8$; C 67.53, H 4.79; Found C 67.45, H 5.06.

*4,6-Diacetyl-1,3-di(3-chlorophenyl carbonyloxy)benzene (**6d**)*: Yield 66 %; m.p. 143–145 °C; R_f 0.75; ^{1}H NMR ($CDCl_3$) δ ppm: 2.44 (s, 6H, 2× $-COCH_3$), 7.13 (d, 2H, $J = 7.6$ Hz, 2× H-5′), 7.21 (s, 1H, H-2), 7.29–7.53 (m, 8H, 2× H-2′,4′,5′,6′), 8.41 (s, 1H, H-5); MS: *m/z* 471 (M^+), 332, 139, 111; $C_{24}H_{16}Cl_2O_6$; C 61.16, H 3.42; Found C 60.91, H 3.63.

*4,6-Diacetyl-1,3-di(4-chlorophenyl carbonyloxy)benzene (**6e**)*: Yield 70 %; m.p. 138–140 °C; R_f 0.76; ^{1}H NMR ($CDCl_3$) δ ppm: 2.29 (s, 6H, 2× $-COCH_3$), 6.96 (s, 1H, H-2), 7.28 (d, 4H, $J = 7.6$ Hz, 2× H-3′,5′), 7.82 (d, 4H, $J = 7.8$ Hz, 2× H-2′,6′), 8.19 (s, 1H, H-5); MS: *m/z* 471 (M^+), 139, 111; $C_{24}H_{16}Cl_2O_6$; C 61.16, H 3.42; Found C 61.04, H 3.58.

*4,6-Diacetyl-1,3-di(2-methylphenyl carbonyloxy)benzene (**6f**)*: Yield 74 %; m.p. 115–117 °C; R_f 0.72; ^{1}H NMR ($CDCl_3$) δ ppm: 2.51 (s, 6H, 2× $-CH_3$), 2.67 (s, 6H, 2× $-COCH_3$), 7.19 (s, 1H, H-2), 7.24–7.43 (m, 6H, 2× H-3′,4′,5′), 7.76–7.82 (m, 2H, 2× H-6′), 8.21 (s, 1H, H-5); MS: *m/z* 430 (M^+), 119, 91, 77; $C_{26}H_{22}O_6$; C 72.55, H 5.15; Found C 72.38, H 5.23.

Attempted synthesis of β-diketones It gave back the starting material (**1**).

Microbiology

The synthesized compounds were evaluated for their antimicrobial activity (Colle *et al.*, 1989; Varma, 1998) against three bacterial strains and three fungal strains at a concentration of 100 µg/mL by cup plate method. Compounds inhibiting growth of one or more of the test microorganisms were further tested for their minimum inhibitory concentration (MIC).

Antibacterial activity

The compounds were screened for their antibacterial activity against *Staphylococcus aureus* (ATCC-25923), *Escherichia coli* (ATCC-25922), and *Pseudomonas aeruginosa* (ATCC-27853) bacterial strains at a concentration of 100 μg/mL by cup plate method (Colle *et al.*, 1989). Ciprofloxacin was used as standard drug for comparison. Freshly prepared liquid agar medium (20 mL/petridish) was poured into each petridishes and the plates were dried by placing in an incubator at 37 °C for 1 h. Then standardized culture of microorganism was spread on each petridishes by L-shaped spreader. Wells (6 mm) were made using an agar punch and, each well was labeled accordingly. A control (solvent) was also included in the test. The test compound and standard drug solutions (100 μg/mL) were made in dimethylsulfoxide (DMSO) and added in each well separately and petridishes kept aseptically for 1 h for diffusion of the sample. After the completion of diffusion, all the petridishes were kept for incubation at 37 °C for 24 h and then diameter of the zone of inhibition was measured in mm (Table 2).

Compounds inhibiting growth of one or more of the test microorganisms were further tested for their MIC by broth dilution technique. A solution of the compounds (100 μg/mL) was prepared in DMSO and a series of doubling dilutions prepared with sterile pipettes. To each of a series of sterile test tubes a standard volume of nutrient broth medium was added. A control tube containing no antimicrobial agent was included. The inoculum consisting of an overnight broth culture of microorganisms was added to separate tubes. The tubes were incubated at 37° for 24 h and examined for turbidity. The highest dilution (lowest concentration) required to stop the growth of bacteria was regarded as MIC.

Antifungal activity

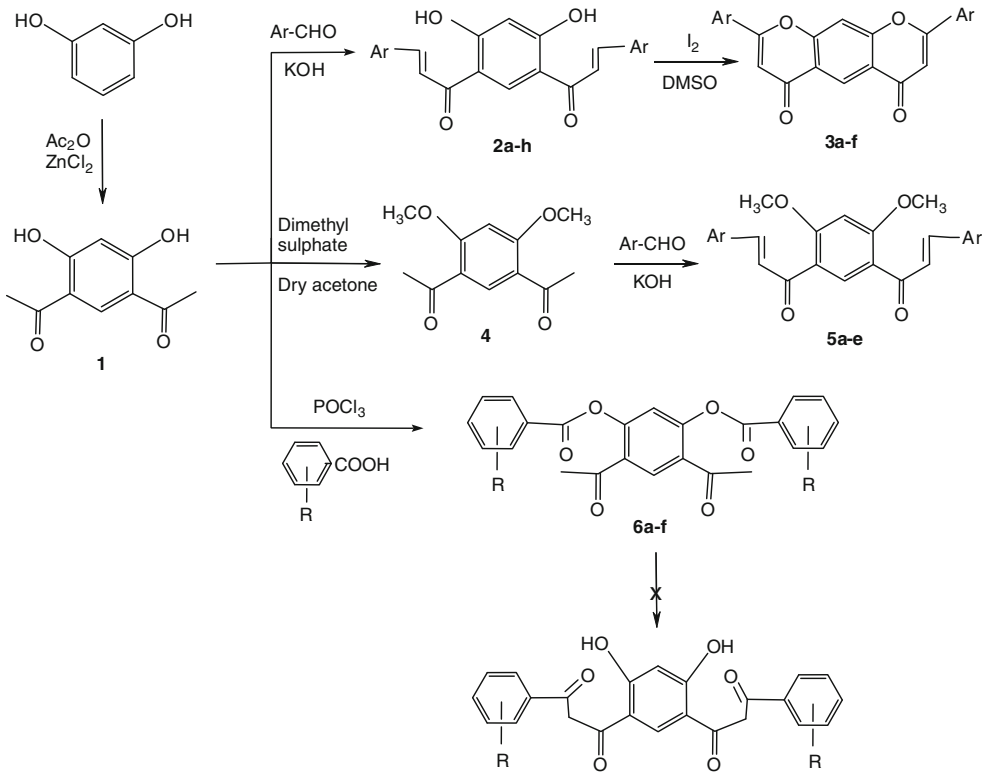
Antifungal activity of the synthesized compounds was determined against *Candida albicans* (ATCC-10231), *Aspergillus niger* (ATCC-16404) and *Rhizopus oryza* (MTCC-262) by agar diffusion method (Varma, 1998). Sabourands agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 mL) and adjusting pH to 5.7. Normal saline was used to make a suspension of spore of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. Agar media (20 mL) was poured into each petridish and the plates were dried by placing in an incubator at 37 °C for 1 h. Wells were made using an agar punch and, each well was labeled accordingly. A control was also prepared in triplicate and maintained at 37 °C for 3–4 days. The test compounds and standard drug (Griseofulvin) solutions (100 μg/mL) were made in DMSO and added in each well separately and petridishes kept aseptically for 1 h for diffusion of the sample. After the completion of diffusion, all the petridishes were kept for incubation at 37 °C for 3–4 days and then diameter of the zone of inhibition was measured in mm (Table 2). Compounds inhibiting growth of one or more of the fungal strains were further tested for their MIC. A solution of the compounds (100 μg/mL) was prepared in DMSO and a series of doubling dilutions prepared with sterile pipettes. To each of a series of sterile test tubes a standard volume of nutrient broth medium was added. A control tube containing no antimicrobial agent was included. The tubes were inoculated with $\sim 1.6 \times 10^4$–6×10^4 c.f.u. mL^{-1} and incubated for 48 h at 37 °C and examined for growth. The lowest concentration (highest dilution) required to arrest the growth of fungus was regarded as MIC.

Results and discussion

Synthesis

The protocol for synthesis of title compounds is presented in Scheme 1. The starting material, 1,1′-(4,6-dimethyl-1,3-phenylene)diethanone (**1**), was condensed with different arylaldehydes in presence of potassium hydroxide following Claisen-Schmidt reaction conditions (Dhar, 1981) to give 8 bischalcones (**2a**–**h**). Bischalcones were cyclized in presence of traces of iodine in dimethylsulphoxide to give 6 flavones (**3a**–**f**) (Doshi *et al.*, 1986). An alternative route to synthesize the flavones consisted in preparing the diester derivatives of (**1**) with different aryl acids in presence of phosphorous oxychloride, which could be converted to β-diketones through Baker–Venkataraman rearrangement (Jain *et al.*, 1982) followed by cyclization to give the corresponding flavones. However, this route of flavone synthesis was unsuccessful and it was not possible to go beyond diester stage; 6 diester derivatives (**6a**–**f**) were prepared. The dimethyl ether derivative (**4**) was synthesized by reacting compound (1) with dimethylsulphate in the presence of potassium carbonate. This compound (**4**) was condensed with different arylaldehydes to give 5 bischalcones (**5a**–**e**). The structures were established on the basis of ^{1}H NMR, Mass spectral data and elemental analysis results.

In general, the ^{1}H NMR spectra of bischalcones (**2a**–**h** and **5a**–**e**) explained the presence of two –CH=CH– groups from the presence of two doublets at δ 7.5 and δ 8.2 as two doublets integrating for two CH-α and two CH-β protons, respectively. Chalcone ring protons H-3′ & H-6′ appeared as singlet at δ 6.6 and δ 8.1, respectively. Other



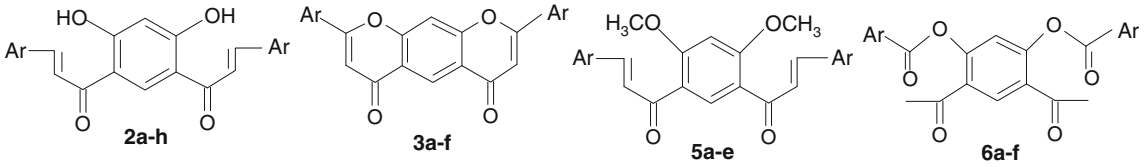
Scheme 1 Protocol for synthesis of title compounds

signals were observed at appropriate δ values integrating for the protons of two phenyl rings. In addition to these peaks, one more peak was observed as a singlet at δ 3.8 in the case of chalcones **5a**–**e** integrating for two methoxy groups. They (**5a**–**e**) did not show the presence of hydroxyl group as evident from the negative ferric chloride test, while chalcones **2a**–**h** gave positive ferric chloride test showing the presence of hydroxyl group. Mass spectral of bischalcones showed the presence of molecular ion peaks in reasonable intensities. Cyclization of bischalcones 2 into flavones **3a**–**f** was carried out using DMSO/I_2 reagent. The formation of flavones was supported by spectral data and elemental analysis. A negative ferric chloride test also indicated the absence of hydroxyl group. In ^{1}H NMR spectra of flavones **3a**–**f**, there located three singlet at δ 6.9, δ 7.4, and δ 9.3 integrating for 2× H-3, H-8 and H-5 of flavones ring, respectively. The spectral data together with negative ferric chloride test confirmed the cyclization of bischalcones to flavones. Another route was tried for synthesis of flavones 3 via Baker–Venkataraman rearrangement. For this, first diesters **6a**–**f** were synthesized in order to prepare β-diketones, which in turn would be cyclized to get the desired flavones. However, diesters could not be converted into β-diketones and this route found unsuccessful. In ^{1}H NMR spectral data, presence of a singlet at δ 2.6 integrating for 2× $COCH_3$ protons together with negative ferric chloride test indicated the formation of diesters. Mass spectral data of diesters **3a**–**f** showed the presence of molecular ion peaks in reasonable intensities. In case of compounds having phenyl rings with chloro-substituents (**2a**, **2b**, **3a**, **3b**, **6d** and **6e**), the molecular ion peak or their fragments having chloro-group appeared as cluster of peaks.

Antibacterial and antifungal activity

The newly prepared compounds were screened for their antibacterial activity against *S. aureus* (ATCC-25923), *E. coli* (ATCC-25922) and *P. aeruginosa* (ATCC-27853) bacterial species, and antifungal activity against *Candida albicans* (ATCC-10231), *Aspergillus niger* (ATCC-16404) and *Rhizopus oryza* (MTCC-262). The initial test was performed at a concentration of 100 μg/mL and the compounds found active were further tested for their MIC. The preliminary antimicrobial results (Table 2) indicated that the compounds **2a**–**h** and **3a**–**f** showed significant antibacterial and antifungal activities. The MIC data showed that compound **2f** exhibited very good activity against *E. coli*, *P. aeruginosa*, and *C. albicans* with MIC-12.5 μg/mL. Similar type of activity was shown the compound **3a** against *S. aureus* and *C. albicans* with MIC-12.5 μg/mL. Another compound, compound **3f** was active

Table 1 Antibacterial and antifungal activities (MIC, μg/mL) of the title compounds



Compounds	Ar	Antibacterial activity			Antifungal activity		
		S. aureus	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*	*R. oryza*
2a	4-Chlorophenyl	50	50	25	50	50	50
2b	3-Chlorophenyl	>100	–	50	50	>100	50
2c	3,4,5-Trimethoxyphenyl	50	50	>100	25	50	50
2d	2-Methylphenyl	>100	–	>100	>100	–	–
2e	3-Methoxyphenyl	50	50	50	25	50	25
2f	2-Furyl	25	12.5	12.5	12.5	25	50
2g	4-Dimethylaminophenyl	50	25	50	50	>100	50
2h	4-Diethylaminophenyl	50	50	>100	50	>100	>100
3a	4-Chlorophenyl	12.5	25	25	12.5	50	25
3b	3-Chlorophenyl	25	50	25	50	25	50
3c	3,4,5-Trimethoxyphenyl	>100	50	>100	50	50	50
3d	2-Methylphenyl	50	>100	50	50	>100	>100
3e	3-Methoxyphenyl	50	>100	50	25	25	25
3f	2-Furyl	25	25	12.5	12.5	50	>100
5a	3-Methoxyphenyl	–	>100	–	>100	–	–
5b	3,4-Dimethoxyphenyl	>100	50	–	>100	>100	–
5c	2-Furyl	50	–	–	50	50	>100
5d	3,4,5-Trimethoxyphenyl	>100	50	>100	>100	–	–
5e	4-Diethylaminophenyl	–	–	>100	–	>100	–
6a	2-Nitrophenyl	50	>100	–	–	–	–
6b	3-Nitrophenyl	>100	–	–	>100	–	–
6c	2-Methoxyphenyl	–	–	>100	–	>100	–
6d	3-Chlorophenyl	>100	–	–	–	–	–
6e	4-Chlorophenyl	>100	>100	–	>100	–	>100
6f	2-Methylphenyl	–	–	–	–	–	–
Standard-1[a]		6.25	6.25	6.25	nt	nt	nt
Standard-2[a]		nt	nt	nt	6.25	6.25	6.25
Standard-3[b]		>100	>100	nt	>100	nt	nt

nt not tested; *MIC* minimum inhibitory concentration

–, Insignificant activity; [a] Standard-1 = Ciprofloxacin, Standard-2 Griseofulvin; [b] Standard-3 = Quercetin (a natural antimicrobial flavonoid, data from literature; Gatto *et al.*, 2002)

against *P. aeruginosa* and *C. albicans* with MIC-12.5 μg/mL. Compound **3e** showed significant activity against *C. albicans, A. niger* and *R. oryza* at 25 μg/mL concentration. Compound **3b** also exhibited significant activity against *S. aureus, P. aeruginosa* and *A. niger* with 25 μg/mL concentration. Compound **2e** was significant in its action against *C. albicans* and *R. oryza* at 25 μg/mL concentration. Results are presented in Table 1.

An analysis of results revealed that the compounds **2a–h** and **3a–f** showed a good antibacterial and antifungal activity. Methylation of the two chelated hydroxyls (**5a–e**) was done in order to see the change in antimicrobial action of bischalcones, and this resulted in significant decrease in antimicrobial activity. However, oxidative cyclization of bischalcones resulted in flavones (**3a–f**) which were found to be considerably active. Bischalcones were

Table 2 Preliminary antibacterial and antifungal activities of the title compounds

Compounds	Antibacterial activity[a]			Antifungal activity[a]		
	S. aureus	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*	*R. oryza*
2a	++	++	+++	++	++	++
2b	+	–	++	++	+	++
2c	++	++	+	+++	++	++
2d	+	–	+	+	–	–
2e	++	++	++	+++	++	+++
2f	+++	+++	+++	+++	+++	++
2g	++	+++	++	++	+	++
2h	++	++	+	++	+	+
3a	+++	+++	+++	+++	++	+++
3b	+++	++	+++	++	+++	++
3c	+	++	+	++	++	++
3d	++	+	++	++	+	+
3e	++	+	++	+++	+++	+++
3f	+++	+++	+++	+++	++	+
5a	–	+	–	+	–	–
5b	+	++	–	+	+	–
5c	++	–	–	++	++	+
5d	+	++	+	+	–	–
5e	–	–	+	–	+	–
6a	++	+	–	–	–	–
6b	+	–	–	+	–	–
6c	–	–	+	–	+	–
6d	+	–	–	–	–	–
6e	+	+	–	+	–	+
6f	–	–	–	–	–	–
Standard-1[b]	++++	++++	++++	nt	nt	nt
Standard-2[b]	nt	nt	nt	++++	++++	++++

nt not tested

[a] Zone of inhibition: –, <5 mm (insignificant or no activity); +, 5–9 mm (weak activity); ++, 10–14 mm (moderate activity); +++, 15–20 mm (strong activity); ++++, >20 mm

[b] Standard-1, Ciprofloxacin; Standard-2, Griseofulvin

almost having equal antibacterial and antifungal actions. Flavones were slightly more active as antibacterial than as antifungal. Diesters (**6a–f**) were insignificant in their antimicrobial activities.

Structure activity relationship (SAR)

The following points could be drawn after analyzing the antimicrobial results:

- Flavones (**3a–f**) were found to have better antimicrobial activity than those of Bischalcones (**2a–h** and **5a–e**).
- Among Bischalcones (**2a–h** and **5a–e**), the compounds having free hydroxyls (**2a–h**) were more active than those of the compounds having methoxy groups (**5a–e**). In other words, methylation of the two hydroxyls (**5a–e**) resulted in decreased antimicrobial activity.
- The antimicrobial activity was found improved due to presence of electron withdrawing groups like chloro on *ortho*, *meta* or *para* position(s) of the two aryl rings. *para*-Substituted derivatives were more active than *meta* or *ortho* substituted derivatives.
- On the other hand the electron releasing groups like methyl, methoxy, hydroxyl group attached with the two phenyl rings decreased the antimicrobial activity. *meta*-Substituted derivatives were more active than *para* or *ortho* substituted derivatives.
- Diesters (**6a–f**) were least active among all the synthesized compounds

Conclusion

Two series of bischalcones (**2a–h** and **5a–e**) and a series of flavones (**3a–f**) were synthesized successfully. Two routes were applied for the synthesis of flavones; first route of synthesis of flavones via oxidative cyclization of bischalcones gave six flavones (**3a–f**), the other route for preparation of flavones via Baker–Venkataraman was unsuccessful. Among the synthesized compounds, three compounds, 3-(2-furyl)-1-{5-[3-(2-furyl)-2-propenoyl]-2,4-dihydroxyphenyl}-2-propen-1-one 2f, 2,8-bis(4-chlorophenyl)-4*H*,6*H*-pyrano[3,2-*g*]chromene-4,6-dione 3a and 2,8-bis(2-furyl)-4*H*,6*H*-pyrano[3,2-*g*]chromene-4,6-dione **3f** emerged as lead compounds. These compounds showed good antibacterial and antifungal activities with MIC 12.5 μg/mL. After analyzing the results, it is conceivable that the derivatives showing significant antimicrobial activity can be further modified to exhibit better potency than the standard drugs.

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