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BIS-CHALCONES AND FLAVONES: SYNTHESIS AND ANTIMICROBIAL ACTIVITY

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Abstract: A series of bis-chalcones (**3a**-**g**) and their flavones derivatives (**4a**-**g**) were synthesized and evaluated for their antimicrobial activity. Bis-chalcones were prepared by condensing 1,1´-(4,6-dihydroxy-1,3-phenylene)diethanone (**2**) with appropriate aryl aldehydes following Claisen-Schmidt reaction conditions. Oxidative cyclization of bis-chalcones (**3a**-**g**) in DMSO in the presence of iodine furnished flavones (**4a**-**g**). The synthesized compounds were evaluated for their antibacterial and antifungal actions against some selected microbes. The results of antimicrobial evaluation showed that some of the synthesized compounds were good in their antibacterial and antifungal actions.

Keywords: bis-chalcones, flavone, antibacterial, antifungal

During the recent years, the incidence of bacterial and fungal infections has been increasing dramatically due to an increase in the number of immuno-compromised hosts (1). Immunosuppression due to HIV-infection, malignancy, immunosuppressive therapies, broad-spectrum antimicrobial treatment and age, as well as invasive procedures and mucosal barriers places patients at high risk for microbial infections. The increasing incidence of resistance to a large number of antibacterial agents is becoming another major concern (2). Currently, a small number of antifungal agents are available, and all have some drawbacks regarding their spectrum, toxicity, tissue distribution, and high cost (3, 4). These observations clearly indicate the need of as well as search for alternative new and more effective antimicrobial agents with a broad spectrum of activity.

Among a number of compounds that have been researched for developing pharmaceutically important antimicrobial agents, flavonoidal derivatives chalcones, flavanones and flavones have played an important role (5-9). Flavonoids have attracted wide attention due to their important physiological activities and distinct functions. Flavonoids form a large group of naturally occurring organic compounds and possess wide range of pharmacological actions including potential antimicrobial actions (5-14). 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 (15-18).

Resorcinol (1,3-benzenediol) is a simple and important chemical which has been chemically incorporated into various compounds to enhance their pharmacological profile (19-21). In view of these points it was considered worthwhile to study some newer flavonoidal derivatives of 1,3-benzenediol for their antimicrobial actions.

EXPERIMENTAL

Melting points were recorded in liquid paraffin bath using open end capillaries and are uncorrected. ^{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) downfield from tetramethylsilane (TMS), which was used as internal standard. The splitting pattern abbreviations are as follows: s, singlet; d, doublet; m, multiplet. Mass spectra were recorded on a JEOL JMS-D

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300 instrument fitted with a JMS 2000 data system at 70 eV. Elemental analyses were performed on a Perkin-Elmer 240 analyzer and the values were found within ± 0.4% of theoretical values. Thin-layer chromatography was carried out to monitor the reactions using silica gel G as stationary phase.

1,1´-(4,6-Dihydroxy-1,3-phenylene)diethanone (2)

It was prepared from resorcinol (**1**) following literature method (19). Yield 72%; m.p. 184-186°C. ^{1}H NMR ($CDCl_3$, δ, ppm): 2.65 (s, 6H, 2× -$COCH_3$), 6.65 (s, 1H, H-2), 8.15 (s, 1H, H-5).

General method for the synthesis of bis-chalcones 3a-g (22)

A mixture of **2** (5 mmol) in ethanol (20 mL), arylaldehyde (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 was filtered, washed with water, sodium bicarbonate solution (2% w/v in water) and again with water. It was crystallized to give **3a-g**. It gave a violet color with alcoholic ferric chloride solution and a red color with conc. sulfuric acid.

3-(4-Bromophenyl)-1-{5-[3-(4-bomophenyl)-2-propenoyl]-2,4-dihydroxyphenyl}-2-propen-1-one (3a)

Yield 63%; m.p. 218-220°C. ^{1}H NMR ($CDCl_3$, δ, ppm): 6.65 (s, 1H, H-3'), 7.06 (d, 4H, *J* = 8.1 Hz, 2× H-3,5), 7.43 (d, 2H, *J*= 15.6 Hz, 2× H-α), 7.68 (d, 4H, *J* = 8.1 Hz, 2× H-2,6), 8.08 (d, 2H, *J*= 15.9 Hz, 2× H-β), 8.63 (s, 1H, H-6'). MS (*m*/*z*): 528 (M^+), 375, 346, 163, 131. Analysis: for $C_{24}H_{16}Br_2O_4$ calcd.: C 54.58; H 3.05%; found: C 54.32, H 3.11%.

3-(3-Nitrophenyl)-1-{5-[3-(3-nitrophenyl)-2-propenoyl]-2,4-dihydroxyphenyl}-2-propen-1-one (3b)

Yield 68%; m.p. 197-199°C. ^{1}H NMR ($CDCl_3$, δ, ppm): 6.59 (s, 1H, H-3'), 7.16-7.78 (m, 8H, 2× H-2,4,5,6), 7.92 (d, 2H, *J* = 15.6 Hz, 2× H-α), 8.24 (d, 2H, *J* = 15.6 Hz, 2× H-β), 8.57 (s, 1H, H-6'). MS (*m*/*z*): 460 (M^+), 312, 163, 177, 148, 91. Analysis: for $C_{24}H_{16}N_2O_8$ calcd.: C 62.61; H 3.50, N 6.08%; found: C 62.44, H 3.43, N 5.89%.

1-{2,4-Dihydroxy-5-[3-(2,6-dichlorophenyl)-2-propenoyl]phenyl}-3-(2,6-dichlorophenyl)-2-propen-1-one (3c)

Yield 56%; m.p. 219-221°C. ^{1}H NMR ($CDCl_3$, δ, ppm): 6.55 (s, 1H, H-3'), 7.43-7.72 (m, 6H, 2× H-3,4,5), 7.84 (d, 2H, *J* = 15.6 Hz, 2× H-α), 8.26 (d, 2H, *J* = 15.6 Hz, 2× H-β), 8.49 (s, 1H, H-6'). MS (*m*/*z*): 506 (M^+), 301, 163, 139, 77. Analysis: for $C_{24}H_{14}Cl_4O_4$ calcd.: C 56.72, H 2.78%; found: C 56.34, H 2.96%.

1-{2,4-Dihydroxy-5-[3-(2-hydroxyphenyl)-2-propenoyl]phenyl}-3-(2-hydroxyphenyl)-2-propen-1-one (3d)

Yield 60%; m.p. 219-221°C. ^{1}H NMR ($CDCl_3$, δ, ppm): 6.53 (s, 1H, H-3'), 7.18 (m, 4H, 2× H-3,5), 7.43 (m, 4H, 2× H-4,6), 7.77 (d, 2H, *J* = 15.3 Hz, 2× H-α), 8.25 (d, 2H, *J* = 15.6 Hz, 2× H-β), 8.51 (s, 1H, H-6'). MS (*m*/*z*): 402 (M^+), 384, 282, 163, 102. Analysis: for $C_{24}H_{18}O_6$ calcd.: C 71.64, H 4.51%; found: C 71.38, H 4.46%.

1-{2,4-Dihydroxy-5-[3-(3-methylphenyl)-2-propenoyl]phenyl}-3-(3-methylphenyl)-2-propen-1-one (3e)

Yield 63%; m.p. 197-199°C. ^{1}H NMR ($CDCl_3$, δ, ppm): 2.42 (s, 6H each, 2× -CH_3), 6.55 (s, 1H, H-3'), 7.32-7.76 (m, 8H, 2× H-2,4,5,6), 7.89 (d, 2H, *J* = 15.0 Hz, 2× H-α), 8.03 (dd, 2H, *J* = 8.1, 1.8 Hz, 2× H-6), 8.22 (d, 2H, *J* = 15.3 Hz, 2× H-β), 8.36 (s, 1H, H-6'). MS (*m*/*z*): 398 (M^+), 280, 163, 145, 91. Analysis: for $C_{26}H_{22}O_4$ calcd.: C 78.37, H 5.57%; found: C 78.20, H 5.64%.

3-(4-Fluorophenyl)-1-{5-[3-(4-fluorophenyl)-2-propenoyl]-2,4-dihydroxyphenyl}-2-propen-1-one (3f)

Yield 55%; m.p. 172-174°C. ^{1}H NMR ($CDCl_3$, δ, ppm): 6.48 (s, 1H, H-3'), 7.14-7.39 (m, 8H, 2×H-2,3,5,6), 7.57 (d, 2H, *J* = 15.3 Hz, 2× H-α), 7.98 (d, 2H, *J* = 15.3 Hz, 2× H-β), 8.42 (s, 1H, H-6'). MS (*m*/*z*): 406 (M^+), 284, 266, 131, 77. Analysis: for $C_{24}H_{16}F_2O_4$ calcd.: C 70.93, H 3.97%; found: C 70.58, H 3.93%.

3-(4-Nitrophenyl)-1-{5-[3-(4-nitrophenyl)-2-propenoyl]-2,4-dihydroxyphenyl}-2-propen-1-one (3g)

Yield 50%; m.p. 232-234°C. ^{1}H NMR ($CDCl_3$, δ, ppm): 6.53 (s, 1H, H-3'), 7.16 (d, 4H, *J* = 7.8 Hz, 2× H-3,5), 7.39 (d, 2H, *J* = 15.6 Hz, 2× H-α), 7.58 (d, 4H, *J* = 7.6 Hz, 2× H-2,6), 7.94 (d, 2H, *J* = 15.6 Hz, 2× H-β), 8.47 (s, 1H, H-6'). MS (*m*/*z*): 460 (M^+), 312, 266, 131, 91, 77. Analysis: for $C_{24}H_{16}N_2O_8$ calcd.: C 62.61, H 3.50, N 6.08%; found: C 62.53, H 3.65, N 5.92%.

General method for the synthesis of flavones 4a-g (23)

To a solution of compound **3a** (200 mg) in dimethyl sulfoxide (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 was separated out, filtered, washed with water, sodium thiosulfate 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 color with ethanolic ferric chloride solution).

2,8-Bis(4-bromophenyl)-4*H*,6*H*-pyrano[3,2-g]chromene-4,6-dione (**4a**)

Yield 42%; m.p. 211-213°C. ^{1}H NMR ($CDCl_3$, δ, ppm): 6.94 (s, 2H, 2× H-3), 7.37 (s, 1H, H-8), 7.46-7.75 (m, 8H, 2× *p*-bromophenyl), 9.33 (s, 1H, H-5). MS (*m*/*z*): 524 (M^+), 344, 235, 104. Analysis: for $C_{24}H_{12}Br_2O_4$ calcd.: C 54.00, H 2.31%; found: C 53.72, H 2.44%.

2,8-Bis(3-nitrophenyl)-4*H*,6*H*-pyrano[3,2-*g*]chromene-4,6-dione (**4b**)

Yield 45%; m.p. 230-232°C. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.02 (s, 2H, 2× H-3), 7.44 (s, 1H, H-8), 7.37-7.81 (m, 8H, 2× *m*-nitrophenyl), 9.38 (s, 1H, H-5). MS (*m*/*z*): 456 (M^+), 309, 235, 208, 102. Analysis: for $C_{24}H_{12}N_2O_8$ calcd.: C 63.17, H 2.65, N 6.14%; found: C 63.02, H 2.43, N 6.18%.

2,8-Bis(2,6-dichlorophenyl)-4*H*,6*H*-pyrano[3,2-g]chromene-4,6-dione (**4c**)

Yield 56%; m.p. 209-211°C. ^{1}H NMR ($CDCl_3$, δ, ppm): 6.91 (s, 2H, 2× H-3), 7.47 (s, 1H, H-8), 7.38-7.74 (m, 6H, 2× dichlorophenyl), 9.27 (s, 1H, H-5). MS (*m*/*z*): 504 (M^+), 264, 208, 102, 77. Analysis: for $C_{24}H_{10}Cl_4O_4$ calcd.: C 57.18, H 2.00%; found: C, 56.93; H, 2.08%.

2,8- Bis(2-hydroxyphenyl)-4*H*,6*H*-pyrano[3,2-g]chromene-4,6-dione (**4d**)

Yield 44%; m.p. 192-193°C. ^{1}H NMR ($CDCl_3$, δ, ppm): 6.88 (s, 2H, 2× H-3), 7.32 (s, 1H, H-8), 7.35-7.68 (m, 8H, 2× *o*-hydroxyphenyl), 9.24 (s, 1H, H-5). MS (*m*/*z*): 398 (M^+), 380, 235, 118. Analysis: for $C_{24}H_{14}O_6$ calcd.: C 72.36, H 3.54%; found: C 72.32, H 3.36%.

2,8-Bis(3-methylphenyl)-4*H*,6*H*-pyrano[3,2-g]chromene-4,6-dione (**4e**)

Yield 60%; m.p. 210-212°C. ^{1}H NMR ($CDCl_3$, δ, ppm): 2.43 (s, 6H, 2×-CH_3), 6.82 (s, 2H, 2×H-3), 7.29 (s, 1H, H-8), 7.33-7.68 (m, 8H, 2×for*m*-tolyl), 9.17 (s, 1H, H-5). MS (*m*/*z*): 394 (M^+), 278, 235, 104, 91. Analysis: for $C_{26}H_{18}O_4$ calcd.: C 79.17, H 4.60%; found: C 78.92, H 4.41%.

2,8-Bis(4-fluorophenyl)-4*H*,6*H*-pyrano[3,2-g]chromene-4,6-dione (**4f**)

Yield 56%; m.p. 186-187°C. ^{1}H NMR ($CDCl_3$, δ, ppm): 6.85 (s, 2H, 2× H-3), 7.36 (s, 1H, H-8), 7.44-7.71 (m, 8H, 2× *p*-fluorophenyl), 9.33 (s, 1H, H-5). MS (*m*/*z*): 402 (M^+), 264, 235, 208, 104. Analysis: for $C_{24}H_{12}F_2O_4$ calcd.: C 71.64, H 3.01%; found: C 71.62, H 3.08%.

2,8-Bis(4-nitrophenyl)-4*H*,6*H*-pyrano[3,2-g]chromene-4,6-dione (**4g**)

Yield 48%; m.p. 238-240°C. ^{1}H NMR ($CDCl_3$, δ, ppm): 6.99 (s, 2H, 2× H-3), 7.41 (s, 1H, H-8), 7.43-7.84 (m, 8H, 2× *p*-nitrophenyl), 9.36 (s, 1H, H-5). MS (*m*/*z*): 456 (M^+), 309, 235, 102. Analysis: for $C_{24}H_{12}N_2O_8$ calcd.: C 63.17, H 2.65, N 6.14%; found: C 63.10, H 2.58, N 6.06%.

Antimicrobial activity

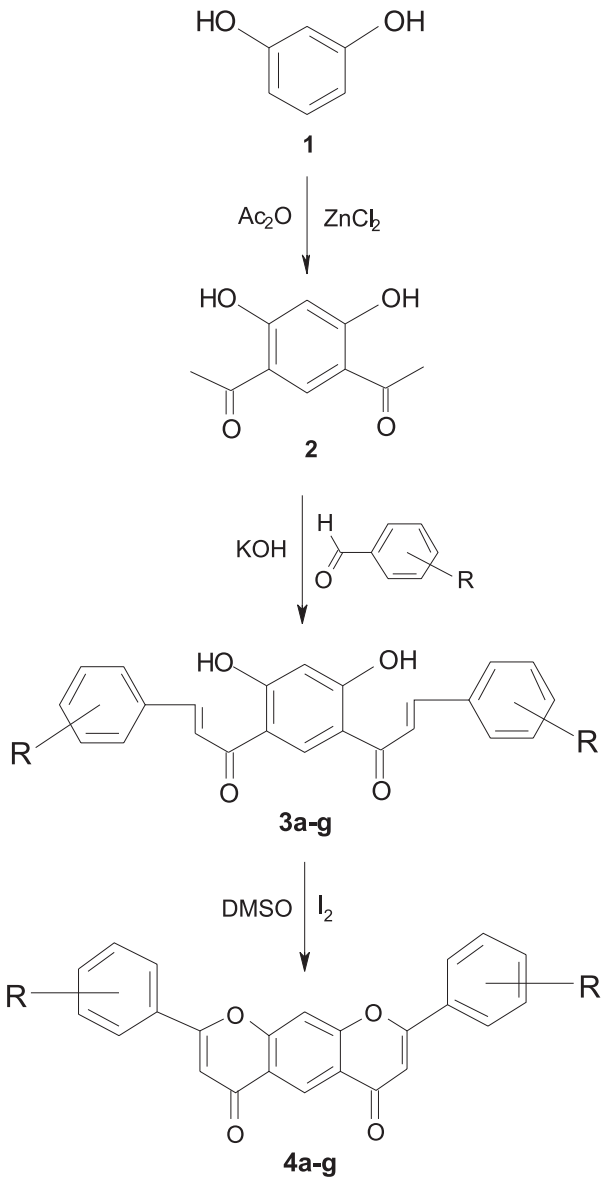
The synthesized compounds were evaluated for their antimicrobial activity (24, 25) against three bacterial strains and two fungal strains.

Antibacterial activity

The compounds were screened for their antibacterial activity against *Staphylococcus aureus* (ATCC-29737), *Escherichia coli* (ATCC-25922), and *Pseudomonas aeruginosa* (ATCC-27853) bacterial strains at a concentration of 100 µg/mL by cup plate method (24). Compounds inhibiting growth of one or more of the above microorganisms were again tested for their minimum inhibitory concentration values (MIC). Ciprofloxacin was used as a standard drug for comparison. The MIC values were determined by broth dilution technique. A solution of the compounds was prepared in dimethylformamide (DMF) and a series of doubling dilutions was prepared. 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 also 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) and *Aspergillus niger* (ATCC-16404) by agar diffusion method (25). Sabourauds agar medium was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled



Scheme 1. Synthesis of title compounds

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 medium (20 mL) was poured into each Petri dish. Excess of suspension was decanted 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 antifungal activity of the compounds was compared with the standard drug: griseofulvin. The nutrient broth, which contained logarithmic serially twofold diluted amount of test compound and controls was inoculated with approximately 1.6×10^4 - 6×10^4 c.f.u./mL. The cultures were incubated for 48 h at 37°C and the growth was monitored. The lowest concentration (highest dilution) required to arrest the growth of fungus was regarded as minimum inhibitory concentration..

RESULTS AND DISCUSSION

Chemistry

The protocol for synthesis of title compounds is presented in Scheme 1. The starting material, resorcinol (**1**), was treated (19) with acetic anhydride in the presence of anhydrous zinc chloride to get 1,1´-(4,6-dihydroxy-1,3-phenylene)diethanone (**2**). Compound **2** was then condensed with different aryl aldehydes in the presence of potassium hydroxide following Claisen-Schmidt reaction conditions (22) to give 7-bis-chalcones (**3a**-**g**). Bis-chalcones were cyclized in the presence of iodine (23) to get the corresponding flavones (**4a**-**g**). The structures assigned to the compounds were supported by ^{1}H NMR, mass spectral and microanalysis data.

In general, the ^{1}H NMR spectra of bis-chalcones (**3a**-**g**) revealed the presence of two -CH=CH- groups from the appearance of two doublets at δ 7.5 and 8.2 ppm as two doublets integrating for two CH-α and two CH-β protons, respectively. Chalcone ring protons H-3' and H-6'

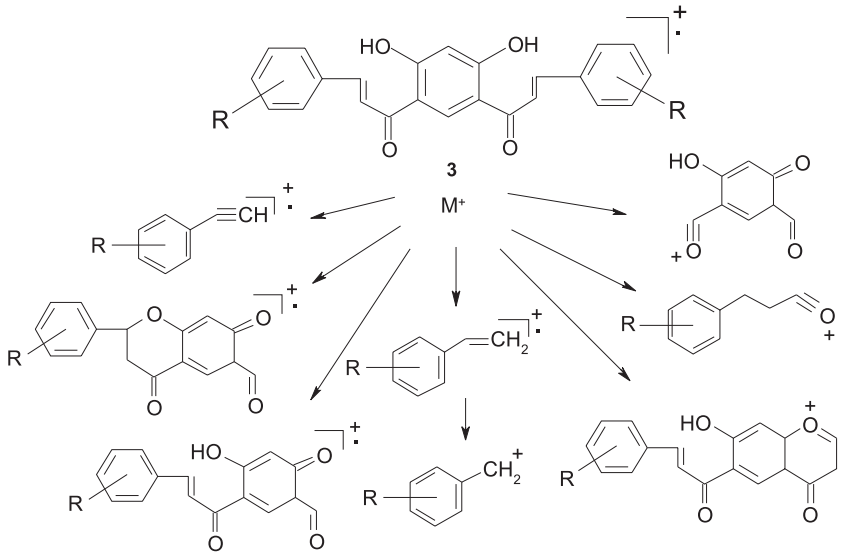


Figure 1. Mass fragmentation pattern of compounds **3**

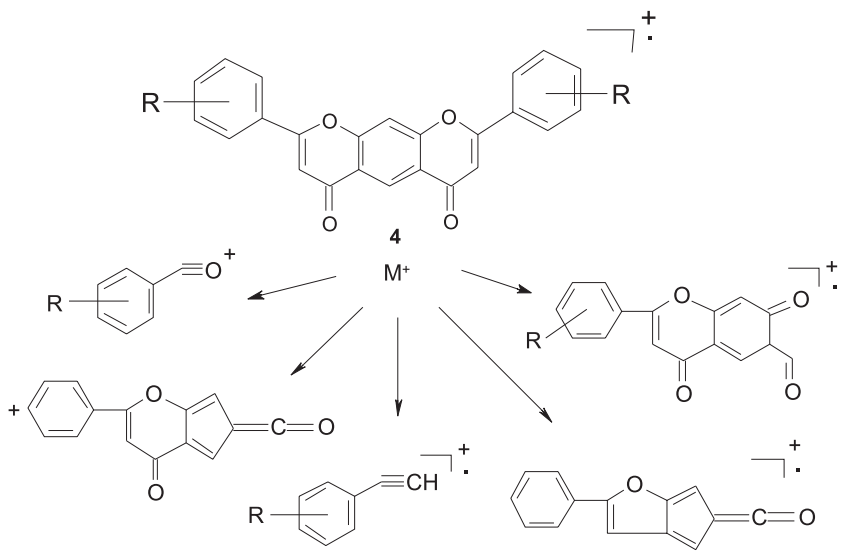
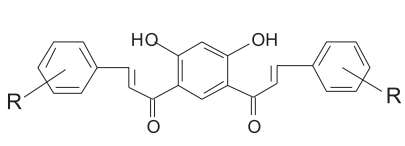
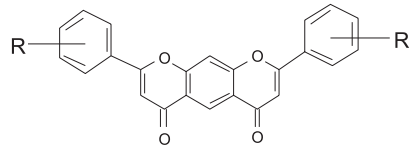


Figure 2. Mass fragmentation pattern of compounds **4**

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



(Bischalcones; 3a-g)



(Flavones; 4a-g)

Compd. No.	Substituent (R)	Antibacterial activity			Antifungal activity	
		S. aureus	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
3a	4-Bromo	50	> 100	50	50	> 100
3b	3-Nitro	> 100	-	50	50	> 100
3c	2,6-Dichloro	12.5	25	25	25	50
3d	2-Hydroxy	50	> 100	> 100	50	-
3e	3-Methyl	-	-	> 100	> 100	-
3f	4-Fluoro	25	25	50	25	50
3g	4-Nitro	50	25	> 100	50	> 100
4a	4-Bromo	50	50	25	50	50
4b	3-Nitro	> 100	> 100	50	25	50
4c	2,6-Dichloro	12.5	25	25	6.25	12.5
4d	2-Hydroxy	> 100	-	> 100	25	> 100
4e	3-Methyl	50	> 100	50	50	-
4f	4-Fluoro	12.5	25	12.5	25	25
4g	4-Nitro	50	50	-	-	> 100
Standard-1†		6.25	6.25	6.25	nt	nt
Standard-2†		nt	nt	nt	6.25	6.25
Standard-3#		> 100	> 100	nt	> 100	nt

- indicates insignificant activity; nt = not tested; †Standard-1 = Ciprofloxacin, Standard-2 = Griseofulvin, #Standard-3 = Quercetin (a natural antimicrobial flavonoid, data from the literature (15); MIC = minimum inhibitory concentration, i.e., the lowest concentration to completely inhibit microbial growth.

appeared as singlets at δ 6.6 and 8.1 ppm, respectively. Other signals were observed at appropriate δ values integrating for the protons of two phenyl rings. These compounds gave positive ferric chloride test showing the presence of hydroxyl group. Mass spectra of bis-chalcones showed the presence of molecular ion peaks of reasonable intensities. The observed fragmentation pattern of bis-chalcones (**3a**-**g**) is presented in Figure 1. Oxidative cyclization of bis-chalcones into flavones **4a**-**g** was carried out using DMSO/I_2 reagent. In ^{1}H NMR spectra of flavones **4a**-**g**, there located three singlet at δ 6.9, 7.4, and 9.3 ppm integrating for 2× H-3, H-8 and H-5 of flavones ring, respectively. Other signals were observed at appropriate δ values integrating for the protons of two phenyl rings. Mass spectra of flavones showed the presence of molecular ion peaks of reasonable intensities. The observed fragmentation pattern of flavones (**4a**-**g**) is presented in Figure 2. The spectral data together with negative ferric chloride test confirmed the cyclization of bis-chalcones to flavones.

Antibacterial and antifungal activity

All the synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* bacterial species, and antifungal activity against *Candida albicans* and *Aspergillus niger*. The antimicrobial screening data showed that compound **4c** exhibited excellent activity against *C. albicans* with MIC 6.25 μg/mL and very good activity against *S.*

aureus and *A. niger* with MIC of 12.5 μg/mL. Similar type of activity was shown by compound **4f** against *S. aureus* and *P. aeruginosa* with MIC 12.5 μg/mL. Another compound, **3c** showed good activity against *S. aureus* with MIC 12.5 μg/mL and significant activity against *E. coli, P. aeruginosa* and *C. albicans* with MIC 25 μg/mL. Compound **3f** showed significant activity against *S. aureus, E. coli* and *C. albicans* at 25 μg/mL concentration. The results are presented in Table 1.

An analysis of results indicated that bis-chalcones **3a**-**g** were good in their antibacterial and antifungal actions. The oxidative cyclization of bis-chalcones resulted in flavones (**4a**-**g**) which were also found to be very good in their antimicrobial activity.

CONCLUSION

Seven new bis-chalcones (**3a**-**g**) and their flavone derivatives (**4a**-**g**) were successfully synthesized. The antimicrobial studies showed that the synthesized compounds were having significant antibacterial and antifungal activities. 2,8-Bis(2,6-dichlorophenyl)-4*H*,6*H*-pyrano[3,2-g]chromene-4,6-dione (**4c**) emerged as a lead compound among the synthesized compounds. The presence of chloro or fluoro substituent(s) increased the antimicrobial activity. 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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