Med Chem Res (2012) 21:1811–1816
DOI 10.1007/s00044-011-9696-z

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, characterization and antimicrobial activities of some novel bis-chalcones

Akbar Mobinikhaledi · Mehdi Kalhor · Hossein Jamalifar

Received: 19 May 2010 / Accepted: 8 June 2011 / Published online: 25 June 2011

Abstract A series of novel bis-chalcones **3a–n** were synthesized in excellent yields by condensation reaction of 1,4-diacetylbenzene with various aldehydes in ethanol 96% and aqueous NaOH at room temperature. All compounds were characterized by IR, ^{1}H and ^{13}C NMR, UV spectroscopy and elemental analysis. The antimicrobial activities of synthesized compounds were also evaluated. The most of these compounds exhibited a good activity against *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans* microorganisms. Some of them showed significant activities.

Keywords Bis-chalcones · Microorganisms · Antimicrobial activities

Introduction

Despite recent advances in our understanding of the biological processes leading to the development of microbial diseases, there is still a need for new and effective agents to help bring these diseases under control. Among the currently identified antimicrobial agents, chalcones are widely distributed in nature and considered as the precursors for flavonoid synthesis in plants. They also with proper substitution have recently been isolated from *Broussonetia papyrifera*, known to selectively inhibit enzymes like protein tyrosine phosphatase 1B (PTP1B) (Chan *et al.*, 2002) and aldose reductase (Severi *et al.*, 1998). Chemically, chalcones consist of an open chain in which the two aromatic rings are joined by a three-carbon unsaturated carbonyl system. Chalcones can be easily obtained through the Claisen–Schmidt condensation of benzaldehyde and acetophenone using either basic or acidic catalysts (Davey and Tivey, 1958; Lyle and Paradis, 1955). These compounds are not only a segment of biologically important but also a versatile intermediate for the synthesis of heterocyclic compounds (Nagaraj and Reddy, 2008; Bhat *et al.*, 2009). Compounds with a chalcone-based structure have shown an impressive array of pharmacological activities including anticancer (Ducki *et al.*, 1998; Modzelewska *et al.*, 2006), antiinflammatory (Hsieh *et al.*, 2000), antimalarial (Li *et al.*, 1995; Bhattacharya *et al.*, 2009) and anti-protozoal (Li *et al.*, 1995; Liu *et al.*, 2001) activities. Furthermore, many of chalcones exhibit beneficial biological activities, such as antimicrobial (Nowakowska, 2007), anti-HIV (Artico *et al.*, 1998), antibacterial (Selvakumar *et al.*, 2007), antitumor (Gschwendt *et al.*, 1984) and antioxidant (Bhat *et al.*, 2009; Vaya *et al.*, 1997) activities.

In view of these observations and also due to our interests in synthesis of biologically active heterocycles (Tehranchian *et al.*, 2005; Mobinikhaledi *et al.*, 2010), we report synthesis of some novel biological active bis-chalcones.

A. Mobinikhaledi (✉) · M. Kalhor · H. Jamalifar
Department of Chemistry, Arak University, Arak 38156-879, Iran
e-mail: akbar_mobini@yahoo.com

A. Mobinikhaledi · M. Kalhor · H. Jamalifar
Department of Chemistry, Payame Noor University, Tehran 19395-4697, Islamic Republic of Iran

A. Mobinikhaledi · M. Kalhor · H. Jamalifar
Department of Drug and Food Control Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

Results and discussion

Synthesis

The general synthetic strategy employed to prepare the bis-chalcone derivatives is based on the Claisen–Schmidt condensation (Davey and Tivey, 1958; Lyle and Paradis, 1955). Firstly, the reaction between benzaldehyde and 1,4-diacetylbenzene in the presence of NaOH as a base using various solvents including water, which known as an attractive medium for many organic reactions, was considered at room temperature. The results indicated that the reaction is accomplishable in water with the yield of 65% and the highest yield obtained for EtOH with 94% in 18 min time. The results for compound **3a** are comparable with those reported by pervious method (Hasegawa *et al.*, 1985).

Then a series of the bis-chalcones **3a**–**n** were prepared by condensing aromatic aldehydes and 1,4-diacetylbenzene to form the expected compounds using aqueous sodium hydroxide as a catalyst in ethanol at room temperature (Scheme 1). The products were isolated after addition of aqueous sodium hydroxide to the well stirred mixture of aldehyde and 1,4-diacetylbenzene as the unsaturated bisketones, which yielded the *trans*-alkene as a major isomer (*E*-form, $J = 15.3$–15.8 Hz) as judged by ^{1}H NMR spectroscopy.

The ^{1}H NMR data of compounds **3b**, **3e**, **3h** and **3n**, show that these compounds exist either as *Z*-form or *Z*/*E*-form ($J = 9.1$–9.3 Hz) (Yoshizawa and Shioiri, 2006). These compounds are insoluble in water and also have low solubility in the most common organic solvents.

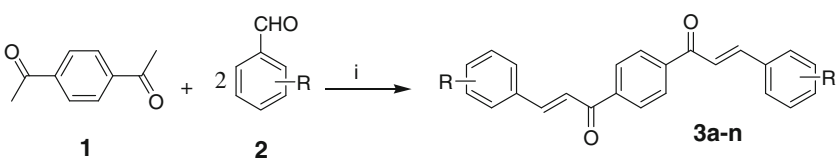
The structure of synthesized compounds was established by means of their IR, UV, ^{1}H NMR, ^{13}C NMR spectra and elemental analyses. The assignment of selected characteristic IR bands provides significant indications for the formation of the bis-chalcones **3a**–**n**. The appearance of a strong absorption band between 1655 and 1666 cm^{-1} region is due to stretching vibration of the carbonyl group at adjacent unsaturated bond. The UV spectra of the bis-chalcone analogues in methanol, exhibited three absorption bands at 377–306 nm, 280–234 nm and 261–220 nm assigned to $n \rightarrow \pi\bigstar$, $\pi \rightarrow \pi\bigstar$ and $n \rightarrow \sigma\bigstar$ transitions, respectively. The band at 377–306 nm was assigned to the transition involving the carbonyl portions (C=O) of chalcone group. The two other absorption bands were due to transitions of aryl rings. In ^{1}H NMR spectra of compounds **3a**–**n**, the aromatic protons resonate as a multiple at 6.86–8.31 ppm depending on the substituent on the Ar group. The appearance of singlet signals at the region between 8.07–8.36 ppm is attributed to the resonance of the 1,4-phenylene ring protons. The presence of doublet signals at the regions between 7.18–7.85 and 7.75–8.18 ppm are due to the resonance of the double bond protons of the adjacent carbonyl group. The ^{13}C NMR spectra of compounds **3a**–**n** showed signals between 111.1–161.9 ppm due to the resonance of aryl and unsaturated carbons. The appearance of signals at the region between 189.3–190.8 ppm attributed to the carbon resonance of the C=O group is in support of the expected structures.

Antimicrobial activity

The results of the bioassay are given in Table 1. A cursory view of the data indicates that most of the compounds exhibit a moderate to good activity against the Gram negative strain. Compounds **3f**, **3i** do not exert a significant effect against the three microorganisms. It is noteworthy that compounds **3a**, **3b**, **3d**, and especially **3e** have moderate to potent bactericidal effects on three microorganisms.

Although compounds **3k**–**n** have the most antibacterial effect on the gram negative *Escherichia coli*, they do not show any antifungal activity. Perhaps, presence of the nitro and methoxy groups on the 4-position of the phenyl ring is the reason why these two compounds show the most fungicidal activity. The same way, probably, compound **3e** has the potential to be a good antimicrobial candidate should it acquire methoxy, nitro or chloro groups on 4-position of the phenyl group that the research is ongoing in this regard. In addition, investigation of the minimum inhibitory concentration (MIC) values of the potent derivatives against

Scheme 1 Synthesis route of compounds **3a**–**n**



i: NaOH/ EtOH/RT

R		R	
3a	H	**3h**	2-OMe
3b	2-Cl	**3i**	3-OMe
3c	3-Cl	**3j**	4-OMe
3d	4-Cl	**3k**	3,4-OMe
3e	2-NO_2	**3l**	3-Br
3f	3-NO_2	**3m**	4-Br
3g	4-NO_2	**3n**	2-OH

Table 1 Antimicrobial activities of bis-chalcones **3a–n** (zone of inhibition in mm)

No.	Compound	*S. aureus*	*E. coli*	*C. albicans*
1	**3a**	10	13	17
2	**3b**	10	27	12
3	**3c**	NA	13	12
4	**3d**	10	23	12
5	**3e**	15	21	15
6	**3f**	NA	NA	NA
7	**3g**	10	13	25
8	**3h**	NA	NA	9
9	**3i**	NA	NA	NA
10	**3j**	NA	NA	22
11	**3k**	11	30	NA
12	**3l**	10	30	NA
13	**3m**	9	30	NA
14	**3n**	13	30	NA
15	Gentamicin	23	24	NT
16	Amphotricin B	NT	NT	21

Dimethyl sulfoxide (DMSO) only, control for compounds and references

NA Not active, *NT* not tested

three microorganisms indicates that compounds **3g** and **3l–n** have the highest bactericidal activity (50 μg/ml) against the *E. coli* and compound **3e** has a high activity (100 μg/ml) against all three microorganisms (Table 2). Additionally, compound **3g** has the highest antifungal activity relative to other compounds (50 μg/ml) on *C. albicans* fungus.

Table 2 Minimum inhibitory concentration (MIC) of the selected compounds against certain microbial strains (μg/ml)

Compound	*C. albicans*	*E. coli*	*S. aureus*
3a	200	200	200
3b	100	100	200
3c	NT	300	300
3d	200	100	200
3e	100	100	100
3g	200	50	50
3h	NT	NT	300
3j	NT	NT	300
3k	200	100	NT
3l	200	50	NT
3m	200	50	NT
3n	100	50	NT

Disc diffusion method used to determine the MICs (Chand *et al.*, 1994). DMSO only, control for compounds

NT not tested

From a chemical perspective, these compounds have low solubility in common solvents such as water, EtOH and MeOH. So it is possible that if their solubility is improved, these compounds would demonstrate a more potent anti-microbial effect. Research on this aspect is ongoing.

Experimental

All the used chemicals were purchased from Merck or Fluka Company. Melting points were determined using an electro thermal digital apparatus and are uncorrected. Elemental analyses were performed on a Vario EL III elemental analyzer. IR spectra were performed on a Galaxy series FTIR 5000 spectrometer using KBr discs. NMR spectra were recorded on a Bruker (300 MHz) spectrometer. Chemical shifts (ppm) were referenced in the internal standard tetramethylsilane (TMS). UV spectra were recorded on a Diod Array UV–Vis Hp 8450 spectrometer. The reactions were monitored by thin layer chromatography (TLC).

General procedure for the synthesis of bis-chalcones (**3a–n**) (Scheme 1)

A solution of diacetylbenzene (0.1 g, 0.6 mmol) and the corresponding aromatic aldehyde (1.2 mmol) in 15 ml of ethanol was treated with 2 ml of NaOH (0.048 g, 1.2 mmol) at 5–10°C. The reaction mixture was stirred at room temperature for desired time. After completion of the reaction, it was diluted with water (5 ml). The aqueous solution was acidified with dilute HCl. The obtained solid was filtered, washed thoroughly with water and dried. The crude product was purified by recrystallization from appropriate solvent.

*1,1′-(1,4-Phenylene)bis(3-phenylprop-2-en-1-one) (**3a**)*

Yellowish solid, reaction time: 18 min, m.p. 210°C, 94% yield, recrystallization solvent: benzene/MeOH; IR (KBr): υ 3053 (w), 1655 (s, C=O), 1599 (s), 1448 (m), 1332 (s), 1226 (s), 1035 (m), 983 (m), 837 (m), 754 (s), 682 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 7.45–7.47 (m, 6H, H–ph), 7.53 (d, 2H, $J = 15.7$ Hz, CO–CH), 7.67 (m, 4H, H–ph), 7.84 (d, 2H, $J = 15.7$ Hz, C=CH), 8.14 (s, 4H, C_6H_4) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 121.8, 128.6, 128.7, 129.0, 130.9, 134.6, 141.3, 145.8, 190.1 (C=O) ppm; Anal. Calcd. for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36; found: C, 84.92; H, 5.33%; UV/vis λ_{max} (MeOH) 264, 274, 320 nm.

*1,1′-(1,4-Phenylene)bis(3-(2-chlorophenyl)prop-2-en-1-one) (**3b**)*

Yellowish solid, reaction time: 14 min, m.p. 248–250°C, 85% yield, recrystallization solvent: DMF; IR (KBr): υ 3078 (w), 1655 (s, C=O), 1591 (s), 1442 (m), 1371 (s), 1272 (s), 1226 (s),1035 (s), 1008 (s), 754 (s, C–Cl), 682 (m) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ_H 7.47–7.51 (m, 4H, H–Ar), 7.58-7.61 (d, 2H, $J = 9.3$ Hz, CO–CH), 8.07 (d, 4H, $J = 3.12$, H–Ar), 8.25–8.28 (d, 2H, $J = 9.3$, C=CH), 8.33 (s, 4H, C_6H_4) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ_C 125.2, 128.2, 129.2, 129.5, 130.5, 132.6, 132.7, 134.9, 139.7, 140.9, 189.3 (C=O) ppm; Anal. Calcd. for $C_{24}H_{16}Cl_2O_2$: C, 70.77; H, 3.96; found: C, 71.08; H, 3.94%; UV/vis λ_{max} (MeOH) 262, 315 nm.

*1,1′-(1,4-Phenylene)bis(3-(3-chlorophenyl)prop-2-en-1-one) (**3c**)*

Yellowish solid, reaction time: 12 min, m.p. 185–186°C, 88% yield, recrystallization solvent: DMF; IR (KBr): υ 3041 (w), 1656 (s, C=O), 1606 (s), 1562 (m), 1415 (w), 1309 (m), 1224 (s), 1035 (w), 976 (m), 800 (m, C–Cl), 673 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 7.36–7.44 (m, 4H, H–Ar), 7.50–7.57 (m, 4H, H–Ar, CO–CH), 7.67 (s, 2H, H–Ar), 7.76 (d, 2H, $J = 15.7$ Hz, C=CH), 8.15 (s, 4H, C_6H_4) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 122.9, 126.9, 128.0, 128.8, 130.3, 130.7, 135.1, 136.4, 141.1, 144.1, 189.5 (C=O) ppm; Anal. Calcd. for $C_{24}H_{16}Cl_2O_2$: C, 70.77; H, 3.96; found: C, 70.50; H, 3.94%; UV/vis λ_{max} (MeOH) 265, 314 nm.

*1,1′-(1,4-Phenylene)bis(3-(4-chlorophenyl)prop-2-en-1-one) (**3d**)*

Yellow solid, reaction time: 10 min, m.p. 284–285°C, 91% yield, recrystallization solvent: DMF/H_2O; IR (KBr): *v* 3059 (w), 1656 (s, C=O), 1599 (s), 1489 (m), 1406 (m), 1327 (s), 1224 (s), 1091 (m), 1010 (s), 812 (s, C–Cl), 503 (w) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ_H 7.55 (d, 4H, $J = 7.56$, H–Ar), 7.82 (d, 2H, $J = 15.7$, CO–CH), 7.95–7.98 (m, 6H, H–Ar, C=CH), 8.31 (s, 4H, C_6H_4) ppm; Anal. Calcd. for $C_{24}H_{16}Cl_2O_2$: C, 70.77; H, 3.96; found: C, 70.43; H, 3.95%; UV/vis λ_{max} (MeOH) 266, 324 nm.

*1,1′-(1,4-Phenylene)bis(3-(2-nitrophenyl)prop-2-en-1-one) (**3e**)*

Brown solid, reaction time: 15 min, m.p. 254–256°C, 88% yield, recrystallization solvent: DMF; IR (KBr) *v* 3109, 3063 (w), 1660 (s, C=O), 1595, 1344 (s, NO_2), 1518 (s), 1411 (m), 1221 (s), 1109 (m), 985 (m), 827 (s), 750 (s), 540 (m) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ_H 7.75–8.11 (m, 10H, H–Ar, CO–CH and C=CH), 8.28 ((s, 4H, C_6H_4), 8.31 (d, 2H, $J = 7.6$ Hz, H–Ar) ppm; Anal. Calcd. for $C_{24}H_{16}N_2O_6$: C, 67.29; H, 3.76; N, 6.54; found: C, 67.62; H, 3.75; N, 6.51%; UV/vis λ_{max} (MeOH) 264, 277, 318 nm.

*1,1′-(1,4-Phenylene)bis(3-(3-nitrophenyl)prop-2-en-1-one) (**3f**)*

Light brown solid, reaction time: 12 min, m.p. 270–271°C, 94% yield, recrystallization solvent: DMF/H_2O; IR (KBr): *v* 3086 (w), 1666 (s, C=O), 1608 (s), 1523, 1340 (s, –NO_2), 1402 (w), 1330 (s), 1275 (m), 1221 (s), 1099 (w), 979 (m), 798 (m), 736 (s) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ_H 7.77 (d, 2H, $J = 8.0$ Hz, H–Ar),7.89 (d, 2H, $J = 15.7$ Hz, CO–CH), 8.18–8.30 (m, 4H, H–Ar, C=CH), 8.36 (s, 4H, C_6H_4), 8.80 (s, 2H, H–Ar) ppm; Anal. Calcd. for $C_{24}H_{16}N_2O_6$: C, 67.29; H, 3.76; N, 6.54; found: C, 67.65; H, 3.79; N, 6.51%; UV/vis λ_{max} (MeOH) 261, 272, 306 nm.

*1,1′-(1,4-Phenylene)bis(3-(4-nitrophenyl)prop-2-en-1-one) (**3g**)*

Brown crystalline solid, reaction time: 12 min, m.p. 305–307°C, 92% yield, recrystallization solvent: DMF; IR (KBr): *v* 3109 (w), 1656 (s, C=O), 1593 (s), 1535, 1346 (s, –NO_2), 1413 (m), 1224 (s), 1109 (m), 1030 (m), 974 (m), 825 (s), 748 (s) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ_H 7.85–7.95 (m, 4H, H–Ar, CO–CH), 8.14–8.36 (m, 12H, H–Ar, C=CH, C_6H_4) ppm; Anal. Calcd. for $C_{24}H_{16}N_2O_6$: C, 67.29; H, 3.76; N, 6.54; found: C, 66.98; H, 3.75; N, 6.52%; UV/vis λ_{max} (MeOH) 277, 307 nm.

*1,1′-(1,4-Phenylene)bis(3-(2-methoxyphenyl)prop-2-en-1-one) (**3h**)*

Dark yellow solid, reaction time: 18 min, m.p. 159–161°C, 81% yield, recrystallization solvent: EtOH/H_2O; IR (KBr): *v* 3059 (w), 2947, 2839 (w, OCH_3), 1657 (s, C=O), 1599 (s), 1491 (s), 1308 (m), 1248 (s), 1182 (s, C–OCH_3), 748 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 3.93 (s, 6H, 2OCH_3), 6.95–7.05 (m, 4H, H–Ar), 7.38 (t, 2H, $J = 8.2$ Hz, H–Ar), 7.58–7.67 (m, 4H, H–Ar, CO–CH), 8.06–8.18 (m, 6H, C=CH, C_6H_4) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 55.6 (OCH_3), 111.3, 120.8, 122.7, 123.6, 128.3, 128.7, 129.4, 132.1, 141.3, 158.9 (C–OCH_3), 190.8 (C=O) ppm; Anal. Calcd. for $C_{26}H_{22}O_4$: C, 78.37; H, 5.57; found: C, 78.66; H, 5.60%; UV/vis λ_{max} (MeOH) 261, 280, 307, 362 nm.

*1,1′-(1,4-Phenylene)bis(3-(3-methoxyphenyl)prop-2-en-1-one) (**3i**)*

Yellow solid, reaction time: 18 min, m.p. 165°C, 88% yield, recrystallization solvent: DMF/H_2O; IR (KBr): *v*

3011 (w), 2941 (w, OCH_3), 1656 (s, C=O), 1599 (s), 1493 (m), 1325 (m), 1255 (s, C–OCH_3), 1168 (m), 1035 (s), 985 (s), 831 (m), 788 (s), 678 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 3.88 (s, 6H, $2OCH_3$), 6.99 (d, 2H, $J = 8.0$ Hz, H–Ar), 7.18 (s, 2H, H–Ar), 7.26 (d, 2H, $J = 7.3$ Hz, H–Ar), 7.37 (t, 2H, $J = 8.0$ Hz, H–Ar), 7.49 (d, 2H, $J = 15.7$ Hz, CO–CH), 7.84 (d, 2H, $J = 15.7$ Hz, C=CH), 8.13 (s, 4H, C_6H_4) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 55.4 (OCH_3), 113.5, 116.6, 121.2, 122.1, 128.7, 130.0, 135.9, 141.2, 145.7, 160.0 (C–OCH_3), 190.1 (C=O) ppm; Anal. Calcd. for $C_{26}H_{22}O_4$: C, 78.37; H, 5.57; found: C, 78.08; H, 5.58%; UV/vis λ_{max} (MeOH) 261, 274, 314 nm.

*1,1′-(1,4-Phenylene)bis(3-(4-methoxyphenyl)prop-2-en-1-one) (**3j**)*

Yellow solid, reaction time: 15 min, m.p. 217°C, 91% yield, recrystallization solvent: benzene/MeOH; IR (KBr): *v* 3067 (w), 2972, 2841 (w, OCH_3), 1656 (s, C=O), 1593 (s), 1512 (s), 1425 (m), 1292 (s), 1235 (s), 1182 (s, C–OCH_3), 1031 (s), 987 (m), 810 (s), 563 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 3.88 (s, 6H, $2OCH_3$), 6.96 (d, 4H, $J = 7.4$ Hz, H–Ar), 7.40 (d, 2H, $J = 15.5$ Hz, CO–CH), 7.63 (d, 4H, $J = 7.3$ Hz, H–Ar), 7.80 (d, 2H, $J = 15.3$ Hz, C=CH), 8.12 (s, 4H, C_6H_4) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 55.4 (OCH_3), 114.5, 119.6, 127.4, 128.6, 130.4, 141.5, 145.6, 161.9 (C–OCH_3), 190.1 (C=O) ppm; Anal. Calcd. for $C_{26}H_{22}O_4$: C, 78.37; H, 5.57; found: C, 78.66; H, 5.55%; UV/vis λ_{max} (MeOH) 277, 357 nm.

*1,1′-(1,4-Phenylene)bis(3-(3,4-dimethoxyphenyl)prop-2-en-1-one) (**3k**)*

Yellow solid, reaction time: 15 min, m.p. 183–185°C, 85% yield, recrystallization solvent: DMF/H_2O; IR (KBr): *v* 3092 (w), 2935, 2837 (w, OCH_3), 1662 (s, C=O), 1591 (s), 1516 (s), 1425 (m), 1265 (s, C–OCH_3), 1141 (m), 1028 (m), 810 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 3.83 (s, 6H, $2OCH_3$), 3.95 (s, 6H, $2OCH_3$), 6.91–6.94 (m, 4H, H–Ar), 7.18 (d, 2H, $J = 17.7$ Hz, CO–CH), 7.71 (m, 2H, H–Ar), 7.76 (d, 2H, $J = 15.7$ Hz, C=CH), 8.07 (s, 4H, C_6H_4) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 55.8 (OCH_3), 56.0 (OCH_3), 111.1, 119.7, 123.6, 127.5, 128.3, 128.6, 146.0, 147.8, 148.9, 149.2, 190.1 (C=O) ppm; Anal. Calcd. for $C_{28}H_{26}O_6$: C, 73.35; H, 5.72; found: C, 73.05; H, 5.70%; UV/vis λ_{max} (MeOH) 274, 377 nm.

*1,1′-(1,4-Phenylene)bis(3-(3-bromophenyl)prop-2-en-1-one) (**3l**)*

Yellow solid, reaction time: 15 min, m.p. 221°C, 85% yield, recrystallization solvent: DMF/H_2O; IR (KBr): *v* 3059 (w), 1655 (s, C=O), 1604 (s), 1554 (s), 1475 (w), 1411 (m), 1325 (m). 1222 (s), 1035 (m), 976 (s), 835 (m), 798 (s, C–Br), 669 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ_H 7.33 (t, 2H, $J = 7.8$ Hz, H–Ar), 7.51 (d, 2H, $J = 15.8$ Hz, CO–CH), 7.57 (d, 4H, $J = 8.2$ Hz, H–Ar), 7.75 (d, 2H, $J = 15.7$ Hz, C=CH), 7.80 (d, 2H, $J = 9.1$ Hz, H–Ar), 8.15 (s, 4H, C_6H_4) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 122.9, 123.2, 127.3, 128.8, 130.5, 130.9, 133.6, 136.7, 141.1, 144.0, 189.5 (C=O) ppm; Anal. Calcd. for $C_{24}H_{16}Br_2O_2$: C, 58.09; H, 3.25; found: C, 58.38; H, 3.27%; UV/vis λ_{max} (MeOH) 262, 315 nm.

*1,1′-(1,4-Phenylene)bis(3-(4-bromophenyl)prop-2-en-1-one) (**3m**)*

Yellowish crystalline solid, reaction time: 10 min, m.p. 287–288°C, 94% yield, recrystallization solvent: DMF; IR (KBr): *v* 3041 (w), 1656 (s, C=O), 1604 (s), 1487 (m), 1404 (m), 1224 (m), 1035 (m), 981 (m), 815 (s, C–Br), 497 (w) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ_H 7.70 (m, 4H, H–Ar), 7.78–8.10 (m, 8H, H–Ar, CO–CH and C=CH), 8.31 (s, 4H, C_6H_4) ppm; Anal. Calcd. for $C_{24}H_{16}Br_2O_2$: C, 58.09; H, 3.25; found: C, 58.47; H, 3.24%; UV/vis λ_{max} (MeOH) 220, 234, 319 nm.

*1,1′-(1,4-Phenylene)bis(3-(2-hydroxyphenyl)prop-2-en-1-one) (**3n**)*

Yellow solid, reaction time: 25 min, m.p. 155–156°C, 94% yield, recrystallization solvent: EtOH/H_2O; IR (KBr): *v* 3254 (s, OH), 3041 (w), 1662 (s, C=O), 1575 (s), 1422 (m), 1334 (m), 1267 (s), 1211 (m), 991 (m), 758 (m), 594 (w) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ_H 6.85–6.97 (m, 4H, H–Ar), 7.26 (t, 2H, $J = 7.2$ Hz, H–Ar), 7.87–7.91 (m, 4H, H–Ar, CO–CH), 8.08 (d, 2H, $J = 15.5$ Hz, C=CH), 8.23 (s, 4H, C_6H_4), 10.38 (s, 2H, OH) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ_C 116.7, 119.9, 121.3, 121.7, 129.1, 129.3, 132.8, 140.8, 141.4, 157.9 (C–OH), 189.7 (C=O) ppm; Anal. Calcd. for $C_{24}H_{18}O_4$: C, 77.82; H, 4.90; found: C, 77.52; H, 4.89%; UV/vis λ_{max} (MeOH) 306, 361 nm.

Biological screening

Preliminary experiments were carried out to determine the antimicrobial activity in vitro of all compounds **3a**–**n** by using cup–plate agar method (Barry, 1976) at a concentration of 400 μg/ml against *staphylococcus aureus* ATCC 29737, *Escherichia coli* ATCC 35218 and *Candida albicans* ATCC 10231. The compounds were diluted in DMSO for bioassay. The solvent control was included, although no antibacterial and antifungal activity has been noted. All

samples were tested in triplicate and the average results were recorded. The plates were incubated at 37°C for 24 h to bacteria and incubated at 25°C for 48 h to fungus.

In addition, determination of the minimum inhibitory concentration (MICs) values for the potent bis-chalcone derivatives against three microorganisms using disc diffusion method (Chand *et al.*, 1994) was evaluated. In this method, concentrations of 400, 200, 100, 50 and 25 μg/ml used in per disc and incubated the same up conditions for bacteria and fungus.

Acknowledgments We are indebted to the Chemistry Department of Arak University for providing of financial supports and also thank the research council of Tehran University of Medical Sciences for the evaluating of biological activities.

References

Artico M, Santo RD, Costi R, Novellino E, Greco G, Massa S, Tramontano E, Marongiu ME, Montis AD, Colla PL (1998) Geometrically and conformationally restrained cinnamoyl compounds as inhibitors of HIV-1 integrase: synthesis, biological evaluation, and molecular modeling. J Med Chem 41:3948–3960

Barry AL (1976) The antimicrobial susceptibility test: principle and practices. Illus Lea and Febiger, Philadelphia, p 180

Bhat AR, Athar F, Azam A (2009) Bis-pyrazolines: synthesis, characterization and antiamoebic activity as inhibitors of growth of Entamoeba histolytica. Eur J Med Chem 44:426–431

Bhattacharya A, Mishra LC, Sharma M, Awasthi SK, Bhasin VK (2009) Antimalarial pharmacodynamics of chalcone derivatives in combination with artemisinin against *Plasmodium falciparum* in vitro. Eur J Med Chem 44:3388–3393

Chan RM, Hu LH, An TY, Li J, Shen Q (2002) Natural PTP1B inhibitors from *Broussonetia papyrifera*. Bioorg Med Chem Lett 12:3387–3390

Chand S, Lusunzi I, Veal DA, Williams LR (1994) Rapid screening of the antimicrobial activity of extracts and natural products. J Antibiot 47:1295–1304

Davey W, Tivey DJ (1958) Chalcones and related compounds. Part IV. Addition of hydrogen cyanide to chalcones. J Chem Soc 1230–1236

Ducki S, Forrest R, Hadfield JA, Kendall A, Lawrence NJ, Mcgown AT, Rennison D (1998) Potent antimitotic and cell growth inhibitory properties of substituted chalcones. Bioorg Med Chem Lett 8:1051–1056

Gschwendt M, Kisttstein W, Furstenberg G, Mark F (1984) The mouse ear edema: a quantitatively evaluable assay for tumor promoting compounds and for inhibitors of tumor promotion. Cancer Lett 25:177–185

Hasegawa M, Saigo K, Mori T, Uno H, Nohara M, Nakanishi H (1985) Topochemical "double" photocyclodimerization of the 1,4-dicinnamoylbenzene crystal. J Am Chem Soc 107: 2788–2793

Hsieh HK, Tsao LT, Wang JP, Lin CN (2000) Synthesis and anti-inflammatory effect of chalcones. J Pharm Pharmacol 52:163–171

Li R, Kenyon GL, Cohen FE, Chen X, Gong B, Dominguez JN, Davidson E, Kurzban G, Miller RE, Nuzum EO, Rosenthal PJ, McKerrow JH (1995) In vitro antimalarial activity of chalcones and their derivatives. J Med Chem 38:5031–5037

Liu M, Wilairat P, Go M-L (2001) Antimalarial alkoxylated and hydroxylated chalones: structure–activity relationship analysis. J Med Chem 44:4443–4452

Lyle RE, Paradis LP (1955) Acid-catalyzed condensations. II. The condensation of benzaldehyde with substituted acetophenones. J Am Chem Soc 77:6667–6668

Mobinikhaledi A, Foroughifar N, Kalhor M, Mirabolfathy M (2010) Synthesis and antifungal activity of novel 2-benzimidazolylimino-5-arylidene-4-thiazolidinones. J Heterocycl Chem 47:77–80

Modzelewska A, Pettit C, Achanta G, Davidson NE, Huangb P, Khana SR (2006) Anticancer activities of novel chalcone and bis-chalcone derivatives. Bioorg Med Chem 14:3491–3495

Nagaraj A, Reddy CS (2008) Synthesis and biological study of novel bis-chalcones, bis-thiazines and bispyrimidines. J Iran Chem Soc 5:262–267

Nowakowska Z (2007) A review of anti-infective and anti-inflammatory chalcones. Eur J Med Chem 42:125–137

Selvakumar N, Kumar GS, Azhagan AM, Rajulu GG, Sharma S, Kumar MS, Das J, Iqbal J, Trehan S (2007) Synthesis, SAR and antibacterial studies on novel chalcone oxazolidinone hybrids. Eur J Med Chem 42:538–543

Severi F, Benvenuti S, Constantino LC, Vampa G, Antolini L (1998) Synthesis and activity of a new series of chalcones as aldose reductase inhibitors. Eur J Med Chem 3:859–866

Tehranchian S, Akbarzadeh T, Fazeli MR, Jamalifar H, Shafiee A (2005) Synthesis and antibacterial activity of 1-[1,2,4-triazol-3-yl] and 1-[1,3,4-thiadiazol-2-yl]-3-methylthio-6,7-dihydrobenzo[c] thiophen-4(5H)ones. Bioorg Med Chem Lett 15:1023–1025

Vaya J, Belinky PA, Aviram M (1997) Antioxidant constituents from licorice roots: isolation, structure elucidation and antioxidative capacity toward LDL oxidation. Free Radic Biol Med 23: 302–313

Yoshizawa K, Shioiri T (2006) Convenient stereoselective synthesis of (Z)-chalcone derivatives from 1,3-diaryl-2-propynyl silyl ethers. Tetrahedron Lett 47:4943–4945