B A R S
Bulletin of Applied and Research Science
ISSN: 1800-556X
Bars journal
Volume 4, Number 2, 2014
Online ISSN 1800-556X
Journal's URL:http://www. barsjournal.net

Synthesis and anti-bacterial activity of new *bis*-chalcones

Sogol Motallebi Tala-Tapeh[*1], Nosrat O. Mahmoodi[2], Ali Vaziri[3]

[1]M.Sc Student, Department of Chemical Engineering, Science and Research Branch, Islamic Azad university, Tehran, Iran, E-mail: sogol.motallebi@yahoo.com

[2]Professor, Department of Chemistry, Faculty of Sciences, University of Guilan, Rasht, Guilan, Iran, E-mail: mahmoodi@guilan.ac.ir:

[3]Assistant Professore, Department of Chemical Engineering, Science and Research Branch, Islamic Azad University, Tehran, Iran, E-mail: a.vaziri@srbiau.ac.ir

Abstract: Some new derivatives of bis-chalcones were synthesized by Claisen-Schmidt condensation of prepared bis-aldehyde and different ketones in basic media. Compounds were characterized by IR, 1H NMR, 13C NMR and EI-Mass spectra. The antibacterial activity and also minimum inhibitory concentration (MIC) of bis-chalcones were evaluated against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa and Bacillus subtilis. Some products exhibit promising activities.

Keywords: bis-chalcones, bis-aldehyde, trioxane, antibacterial

Introduction

Chalcones (1,3-diaryl-2-propen-1-ones) are abundant in nature and have been synthesized during years possessing a variety of biological activities such as antibacterial (Pereira-Ávila et al. 2008; Zangade et al. 2010), antifungal (Sivakumar et al. 2009; Abonia et al. 2012; Lahtchev et al. 2008; Tavares et al. 2011), anti-tubercular (Lin et al. 2002; Qian et al. 2010), anti-inflammatory (Ballesteros et al. 1995; Won et al. 2005; Zhang et al. 2010), antimalarial (Parmer et al. 2003; Awasthi et al. 2009), antitumor (Park et al. 1998; Kumar et al. 2003), antioxidant behavior (Vogel et al. 2008; Sivakumar et al. 2011), inhibition of key enzymes (Rao et al. 2009), cytotoxicity (Tsuchiya et al. 1994; Kumar et al. 2010; Chiaradia et al. 2008; Reddy et al. 2012), antiplatelet (Zhao et al. 2005), antiviral (Biradar et al. 2010), antileishmanial (Miranda et al. 2000; Aponte et al. 2010), inhibitor of colon cancer cell growth (Mizuno et al. 2010), radical-scavenging (Nabi et al. 2011), antidyslipidemic (Shukla et al. 2011), anti-diabetic (Hsieh et al. 2012), vasorelaxant (Dong et al. 2010), antiprotozoal activites (Hayat et al. 2011).

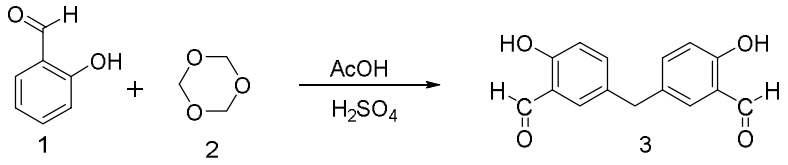
Chalcones are important and useful intermediates in synthesis of many heterocyclic compounds such as pyrimidine (Giles et al. 2012), pyrazole (Bonesi et al. 2010), pyrazoline (Wanare et al. 2010), flavonoids (Shin et al. 2011), flavan (Mazimba et al. 2011), pyridine (Feng et al. 2012), xanthenes (Lu et al. 2012), isoxazolidine (Piotrowska et al. 2011), N-phenylpyrazole (Rashad et al. 2010).

Discussion

Chemistry

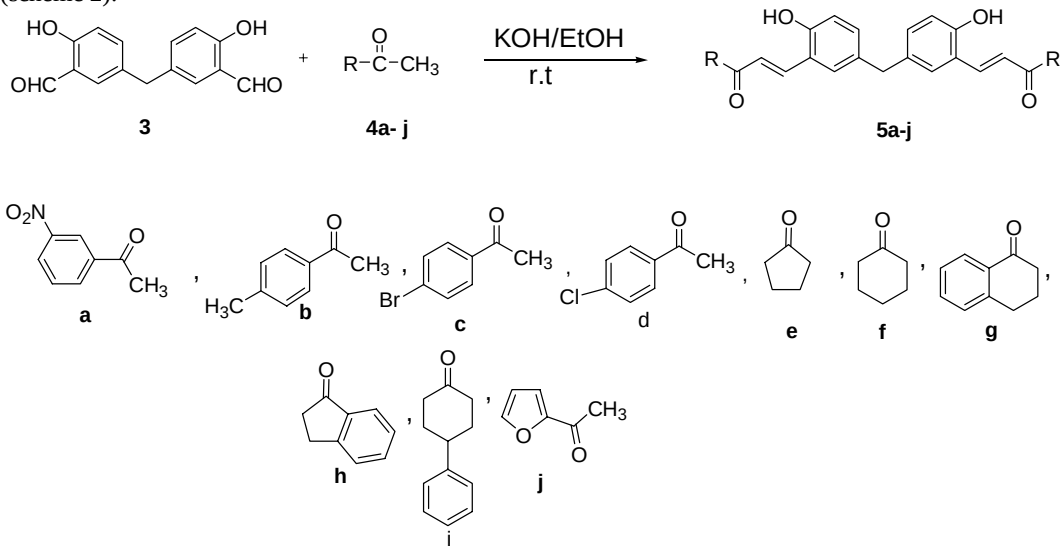
In continuation to our previous works in synthesis of bis- and tris- compounds (Ghavidast et al. 2010; Khodaee et al. 2013; Kiyani et al. 2009a; Kiyani et al. 2009b; Mahmoodi et al. 2012; Mahmoodi et al. 2013), herein we report synthesis of new derivatives of bis-chalcones possessing anti-bacterial activity.

Bis-aldehyde 3, 5,5´-methylenbis(2-hydroxybenzaldehyde), was prepared via the reaction of 2-hydroxy benzaldehyde 1 and trioxane 2 in presence of acetic acid under reflux and N2 atmosphere (Marvel et al. 1957) (scheme 1).



Scheme 1. Preparation of 5,5´-methylenbis(2-hydroxybenzaldehyde) 3

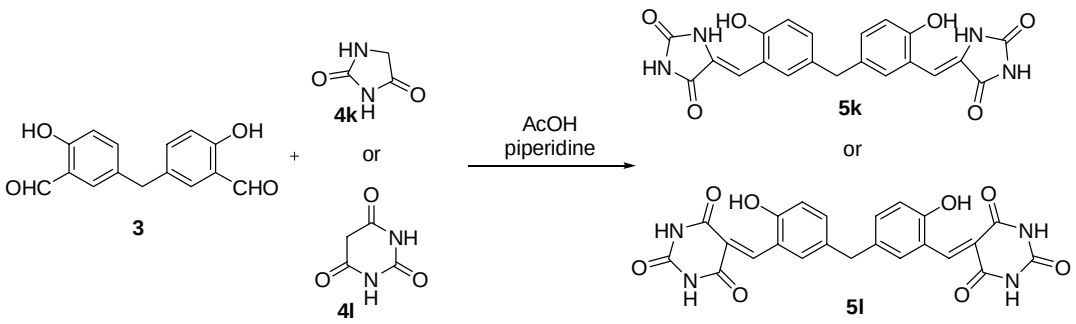
Bis-chalcones 5a-d and 5e-i were synthesized by Claisen-Schmidt reaction of 1 mmol bis-aldehyde 3 and 2.2 mmol of ketones 4a-i such as 3-nitro acetophenone, 4-methyl acetophenone, 4-bromo acetophenone, 4-chloro acetophenone, cyclopentanone, cyclohexanone, tetralone, indanone 4-phenylcyclohexanone, and 1-(fyryl-2-yl)ethanone in the presence of KOH 60% at room temperature (scheme 2).



Scheme 2. Synthesis of bis-chalcones 5a-j

In the first attempt the reaction of 1 mmol of bis-aldehyde and 2 mmol of 2-furyl methyl ketone was accomplished as a model, after completion of the reaction TLC showed small amount of bis-aldehyde beside final product, increasing amount of ketone to 2.2 mmol yielded only final product.

Bis-chalcones 5k-l, 5,5´-((methylenebis(6-hydroxy-3,1-phenylene))bis(methanylylidene))bis (imidazolidine-2,4-dione) and 5,5´-((methylenebis(6-hydroxy-3,1-phenylene))bis(methanylylidene)) bis(pyrimidine-2,4,6(1H,3H,5H)-trione), were synthesized via the reaction of bis-aldehyde and hydantoin 4k or barbituric acid 4l in EtOH under reflux, respectively (scheme 3).



Scheme 3. Synthesis of *bis*-chalcones 5k-l

All products were obtained as pure colored solid in high yield. The structure of compounds were established by IR, 1H NMR, 13C NMR and mass spectroscopy. Due to the low solubility of 5a, 5e-f and 5k-l in DMSO it was impracticable to record their NMR spectrum accordingly their mass spectrum and CHN was recorded as an alternative. The 1H NMR spectra of bis-chalcones 5b, 5c, 5d, 5g, 5h, 5i, and 5h showed singlet at 10.24-9.3 ppm due to phenolic OH, protons of α,β–unsaturated part appeared in aromatic region and CH2 group appeared in 3.93-3.66 ppm. In the 13C NMR spectra of bis-chalcones 5b, 5i, 5j, 5k, and 5l C=O appeared in 193.3-177.0 ppm and CH2 appeared around 40 ppm, in most cases CH2 peak combined with DMSO-d6. EI-Mass spectra of 2,2′-(methylenebis(6-hydroxy-3,1-phenylene))bis(methanylylidene))bis(cyclohexan-1-one) (5f) and 5,5′-((methylenebis(6-hydroxy-3,1-phenylene))bis(methanylylidene))bis(imidazolidine-2,4-dione) (5k) revealed exact mass while, mass spectra of 3,3′-(methylenebis(6-hydroxy-3,1-phenylene))bis(1-(3-nitrophenyl)prop-2-ene-1-one) (5a), 2,2′-(methylenebis(6-hydroxy-3,1-phenylene))bis(methanylylidene))bis(cyclopentan-1-one) (5e) and 5,5′-((methylenebis(6-hydroxy-3,1-phenylene))bis(methanylylidene))bis(pyrimidine-2,4,6(1H,3H,5H)-trione) (5l) revealed [M+2], [M-4] and [M+2], respectively.

Anti-bacterial activity

The in vitro antibacterial activity of bis-chalcones were screened against Staphylococcus aureus (S. aureus) ATCC 29213 and Bacillus subtilis (MTCC 121) as gram-positive and Escherichia coli (E. coli) ATCC 25922 and Pseudomonas aeruginosa ATCC 27853 as gram-negative bacteria. Gentamycin was used as standard.

According to table 1. all bis-chalcones were inactive against Escherichia coli. Compounds 5c, 5d, 5j, 5k and 5l showed antibacterial activity against Bacillus subtilis and compounds 5c, 5d, 5l had good antibacterial activity. Compounds 5c-d and 5k had good antibacterial activity against Staphylococcus aureus and compound 5i had remarkable activity against Staphylococcus aureus. Compounds 5c-d and 5f showed good antibacterial activity against Pseudomonas aeruginosa.

Table 1. Antimicrobial activity of compounds 5a-l

entry	compound	Antimicrobial activity (zone of inhibition in mm)			
		Staphylococcus aureus	*Escherichia coli*	*Pseudomonas aeruginosa*	*Bacillus subtilis*
1	5a	18	-	-	-
2	5b	-	-	-	-
3	5c	23	-	18	20
4	5d	23	-	18	20
5	5e	-	-	10	-
6	5f	10	-	14	-
7	5g	9	-	10	-
8	5h	-	-	-	-

9	5i	-	-	-	-
10	5j	17	-	8	8
11	5k	20	-	9	10
12	5l	17	-	-	20
13	DMSO	-	-	-	-
14	Gentamycin	23	22	21	20

Minimum inhibition concentration (MIC) was evaluated for compounds 5a, 5c-f and 5j-l against Staphylococcus aureus, Bacillus subtilis and Pseudomonas aeruginosa. Compound 5a, 5c-d and 5k-l were active against Staphylococcus aureus in minimum concentration of 32-33 μg/mL (table 2).

Table 2. MIC of compounds 5a, 5c-d and 5k-l

entry	compound	minimum inhibition concentration(μg/mL)		
		Staphylococcus aureus	*Pseudomonas aeruginosa*	*Bacillus subtilis*
1	5a	32	-	-
2	5c	33	-	90
3	5d	33	-	96
4	5f	-	512	-
5	5j	128	-	-
6	5k	32	-	-
7	5l	32	-	128

Experimental

Chemistry

Chemicals were purchased from Merck. IR absorption band maxima were measured with a Shimadzu UV-2100 spectrophotometer. Melting points are uncorrected and determined using a Mettler Fp5 melting point apparatus. All NMR data were recorded in DMSO-d6 using a Bruker Avance 400-MHz spectrometer. Chemical shifts are reported in ppm (δ) using deuterated solvents as internal references. EI-Mass spectra were recorded on 5973 Network Mass Selective Detector. Elemental analyses were achieved on a Perkin-Elmer 240 CHN elemental analyzer.

Synthesis of 5,5´-methylenbis(2-hydroxybenzaldehyde) 3

To a two-necked flask was added a well dissolved mixture of trioxane (0.3 g), AcOH (1 mL) and H2SO4 (0.02 mL, 4 drops), then 2-hydroxybenzaldehyde (30 mmol, 3 mL) and AcOH (5 mL) was added to this mixture and refluxed at 85 ˚C under N2 for 22 hours. A pink solution was formed during the reaction. After completion of the reaction, the mixture was poured into an ice-water mixture and kept at refrigerator for one night. The formed pink solid was filtered off, dried and recrystallized from ethanol.

Yield 60%, pink solid, m.p= 138-140°C, FT-IR (KBr cm-1): 3492 (O-H, Stretch), 2923, 1847 (C-H aliphatic, Stretch), 1651 (C=O, Stretch), 1480, 1440 (C=C, Stretch).

General procedure for synthesis of bis-chalcones (5a-j)

bis-aldehyde 3 (1 mmol) and ketone 4a-j (2.2 mmol) were dissolved in EtOH (4 mL). Then, KOH 60% (4 mL) was added dropwise to this mixture at 4-5 ˚C. After completion of the reaction monitored by TLC (petroleum ether : EtOAc 6:3), the mixture was acidified by HCl 5%, the final product precipitate during acidifying. Solid was filtered off, dried and washed with acetone.

(2E,2'E)-3,3´-(methylenebis(6-hydroxy-3,1-phenylene))bis(1-(3-nitrophenyl)prop-2-ene-1-one) (5a)

Yield 78%, brown solid m.p= 189-192 °C. IR (KBr, cm-1): 3400 (O-H, Stretch), 1620 (C=O, Stretch), 1560 (NO2, asymmetric Stretch), 1489 (C=C, Stretch), 1350 (NO2, Symmetric Stretch), 1260 (C-O, Stretch). Mass (m/z): C31H22N2O8, 552 (M++2) (14%), 109 (100%).

(2E,2'E)-3,3´-(methylene bis(6-hydroxy-3,1-phenylene))bis(1-(p-tolyl)prop-2-ene-1-one) (5b)

Yield 80%, yellow solid m.p= 149-152 °C. IR (KBr, cm-1): 3200 (O-H, Stretch), 2800 (C=H aliphatic, Stretch), 1640 (C=O, Stretch), 1600 (C=C alkene, Stretch), 1580, 1500 (C=C aromatic, Stretch), 1280 (C-O, Stretch). 1H NMR (400 MHz, DMSO-d6): δ; 10.1 (s,2H,OH), 8.05-8.01 (m, 6H), 7.88-7.84 (m, 4H), 7.34 (d, J=8 Hz, 4H), 7.14 (dd, J=8.4, 1.6 Hz, 2H) , 6.86 (d, J=8.4 Hz, 2H), 3.83 (s, 2H, CH2), 2.41 (s, 6H, CH3) ppm. 13C NMR (100 MHz, DMSO-d6): δ; 188.7 (C=O), 155.4, 143.4, 139.1, 135.3, 132.5, 132.3, 129.3, 128.4, 128.2, 121.0, 120.5, 116.3 (12 C aromatic and olefinic) ~39.8 (CH2), 21.1 (CH3) ppm.

Synthesis of (2E,2'E)-3,3'-(methylenebis(6-hydroxy-3,1-phenylene))bis(1-(4-bromophenyl)prop-2-en-1-one) (3c)

Yield 92%, Yellow solid recrystallized benzene: MeOH (3:2). m.p.: 161-162 ºC; IR (KBr, cm-1): 3445 (O-H, Stretch), 3056 (C-H, Aromatic Stretch), 1640 (C=O, Stretch), 1571(C=C, Stretch) , 1482, 1224(C-O, Stretch). 1H NMR (400, DMSO-d6): 9.24 (s, 2H), 8.06 (d, J = 9.0 Hz, 4H), 7.83-8.19 (m, 6H), 7.71 (d, J = 16.3 Hz, 2H), 7.189 (d, J = 9.0 Hz, 4H), 6.85 (d, J = 16.3 Hz, 2H), 3.84 (s, 2H). MS: m/z 616 (M+). Anal. Calcd. for C31H22Br2O4: C, 60.22; H, 3.59; Br, 25.85. Found: C, 60.19; H, 3.56; Br, 25.60.

Synthesis of (2E,2'E)-3,3'-(methylenebis(6-hydroxy-3,1-phenylene))bis(1-(4-chlorophenyl)prop-2-en-1-one) (3d)

Yield 87%, Brown solid recrystallized benzene: MeOH (3:2). m.p.: 156-157 ºC; IR (KBr, cm-1): 3400 (O-H, Stretch), 3050 (C-H, Aromatic Stretch), 1647 (C=O, Stretch), 1569 (C=C, Stretch) , 1480, 1222(C-O, Stretch). 1H NMR (400, DMSO-d6): 1H NMR (DMSO-d6): 9.19 (s, 2H), 7.91 (d, J = 9.0 Hz, 4H), 7.80-8.16 (m, 6H), 7.69 (d, J = 16.0 Hz, 2H), 7.16 (d, J = 9.0 Hz, 4H), 6.84 (d, J = 16.0 Hz, 2H), 3.83 (s, 2H). MS: m/z 528 (M+). Anal. Calcd. for C31H22Cl2O4: C, 70.33; H, 4.19; Cl, 13.39;. Found: C, 70.29; H, 4.08; Br, 13.48.

2,2´-(methylenebis(6-hydroxy-3,1-phenylene))bis(methanylylidene))bis(cyclopentan-1-one) (5e)

Yield 70%, brown solid m.p= 141-145 °C. IR (KBr, cm-1): 3400 (O-H, Stretch), 1670 (C=H, Stretch), 1600 (C=O, Stretch). Mass (m/z): C25H24O4, 384 (M-4) (4.9%), 147 (100%). Elemental Analysis: C, 77.30; H, 6.23; found C, 77.38; H, 6.33.

2,2´-(methylenebis(6-hydroxy-3,1-phenylene))bis(methanylylidene))bis(cyclohexan-1-one) (5f)

Yield 75%, brown solid dec=290 °C. IR (KBr, cm-1): 3400 (O-H, Stretch), 1650 (C=O, Stretch), 1600 (C=C, Stretch), 1260, 1040 (C-O, Stretch). Mass (m/z): C27H28O4, 416 (M+) (6%), 125(100%). Elemental Analysis: C, 77.86; H, 6.78; found C, 77.94; H, 6.84.

2,2´-((methylenebis(6-hydroxy-3,1-phenylene))bis(methanylylidene))bis(3,4-dihydronaphthalen-1(2H)one) (5g)

Yield 82%, brown solid dec= 313 °C. IR (KBr, cm-1): 3400 (O-H, Stretch), 1640 (C=O, Stretch), 1590, 1480 (C=C, Stretch), 1290, 1230 (C=O, Stretch). 1H NMR (400 MHz, DMSO-d6): δ; 10.2 (s, 2H, OH), 7.95 (d, J = 7.6 Hz, 1H), 7.83 (s, 1H), 7.55 (d, J= 6.8, 2H), 7.42-7.29 (m, 7H), 7.17 (s, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.89 (d, J=8Hz, 2H), 3.79 (s,2 H, CH2), 2.97-2.95 (s, 4H, CH2), 2.88-2.86 (s, 4H, CH2) ppm. 13C NMR (100 MHz, DMSO-d6): δ; 186.7 (C=O), 155.0, 143.2, 133.9, 133.3, 132.9, 132.4, 131.7, 130.5, 129.7, 128.4, 127.3, 126.9, 121.9, 115.7, (14C aromatic and olefinic), ~40.04 (CH2), 28.0, 27.0 (C aliphatic) ppm.

2,2´-((methylenebis(6-hydroxy-3,1-phenylene))bis(methanylylidene))bis(2,3-dihydro-1H-inden-1-one) (5h)

Yield 78%, orange solid, m.p= 109-111 °C. IR (KBr, cm-1): 3400 (O-H, Stretch), 1670 (C=O, Stretch), 1600, 1490 (C=C, Stretch), 1250, (C-O, Stretch). 1H NMR (400 MHz, DMSO-d6): δ; 10.1 (s,OH), 7.95 (s,1H), 7.78-7.56 (m, 8H), 7.46 (T, J= 7.4 Hz, 2H), 7.19 (dd, J=8.4, 2Hz, 2H), 6.94 (d, J=8.4Hz, 2H), 4.08, 4.02 (s, 4H), 3.93 (s, 2H,CH2) ppm. 13C NMR (100 MHz, DMSO-d6): δ; 193.3 (C=O), 156.0, 149.8, 137.4, 134.5, 133.2, 132.3, 131.8, 129.4, 127.5, 123.5, 121.5, 116.0 (13 C aromatic and olefinic) ~40.09 (CH2), 31.9 (CH3) ppm.

2,2′-((methylenebis(6-hydroxy-3,1-phenylene))bis(methanylylidene))bis(4-phenylcyclohexan-1-one) (5i)

Yield 70%, brown solid, m.p= 105-107 °C. IR (KBr, cm-1): 3400 (O-H, Stretch), 2800 (C-H, Stretch), 1600, 1690 (C=O, Stretch), 1600, 1480 (C=C, Stretch). 1H NMR (400 MHz, DMSO-d6): δ; 9.80 (s, 2H, OH), 7.32-6.75 (m, 18H) 3.66(s, 2H), tt (3.05, J=12, 3.4 Hz, 4H) 2.6 (dd, J=16, 6Hz, 2H), 2.53 (dd, J=12, 6Hz, 2H), 1.91 (dd, J=16, 4Hz, 2H), 1.85 (dd, J=13, 4Hz, 2H)

(2E,2'E)-3,3′-(methylenebis(6-hydroxy-3,1-phenylen))bis-(1-(furan-2-yl)prop-2-en-1-one) (5j)

Yield 88%, orange solid, m.p= 175-184 °C. IR (KBr, cm-1): 3400 (O-H, Stretch), 1640 (C=O, Stretch), 1580 (C=C, Stretch), 1260, (C-O, Stretch). 1H NMR (400 MHz, DMSO-d6): δ; 10.24 (s, OH), 8.04-6.55 (m, 16H), 3.92 (s, 2H, CH2) ppm. 13C NMR (100 MHz, DMSO-d6): δ; 177.0 (C=O), 155.8, 153.1, 148.0, 147.6, 136.7, 128.0, 120.5, 118.7, 118.7, 116.3, 112.6, 42.0 (CH2) ppm.

General procedure for synthesis of bis-chalcones (5k-l)

To solution of bis-aldehyde 3 (1 mmol) and ketone 4k-l (2.2 mmol) dissolved in EtOH (7 mL) was added AcOH (4 drops) and piperidine (0.1 mL) then refluxed for 12 hours. Progress of the reaction was controlled by TLC (petroleum ether : EtOAc 6:3), after completion of the reaction the solid was filtered off, dried and washed with ethanol.

5,5′-((methylenebis(6-hydroxy-3,1-phenylene))bis(methanylylidene))bis(imidazolidine-2,4-dione) (5k)

Yield 83%, brown solid, m.p= 208-210 °C. IR (KBr, cm-1): 3500, 3400, 3100 (2N-H, OH, Stretch), 2850 (C-H, Stretch), 1700, 1660 (C=O, Stretch), 1580, 1530, 1490 (C=C, Stretch), 1280 (C-O, Stretch). Mass (m/z): C21H16N4O6, 420 (M+) (1.5%), 276 (100%). Elemental Analysis: C, 60.00; H, 3.84; N, 13.33; found C, 60.11; H, 3.93; N, 13.41.

5,5′-((methylenebis(6-hydroxy-3,1-phenylene))bis(methanylylidene))bis(pyrimidine-2,4,6(1H,3H,5H)-trione) (5l)

Yield 87%, yellow solid, m.p= 101-104 °C. IR (KBr, cm-1): 3400 (O-H, stretch), 1670 (C=O, Stretch), 1600, 1490 (C=C, Stretch), 1250 (C-O, Stretch). Mass (m/z): C23H16N4O8, 478 (M+2) (2.187), 262 (100%). Elemental Analysis: C, 57.99; H, 3.39; N, 11.76; found C, 58.89; H, 3.31; N, 11.68

Determination of antimicrobial activity

The antibacterial activity of compounds was assayed biologically using the Agar well-diffusion method. Then Mueller–Hinton agar (Merck) plates were prepared according to manufacturers' instructions in order to evaluate the antibacterial activities of compounds. The sterile Mueller–Hinton agar plates were inoculated with the bacteria.0.001 g of test samples was dissolved in 1 mL dimethyl sulfoxide (DMSO) to obtain a stock solution. 0.1 mL of each sample was dropped into each labeled well aseptically. The inculcated plates were then incubated for 24 h at 37 ˚C. Gentamycin was used as a positive control and DMSO as a negative control. After incubation time, antimicrobial activity was evaluated by measuring the zone of inhibition against the test organisms and compared with that of the standard. The results of our tests were presented as the inhibition zones, given in millimeters (mm). The experiment was carried out in duplicate and the average zone of inhibition was calculated.

References

1. Abonia R, Insuasty D, Castillo J, Insuasty B, Quiroga J, Nogueras M, Cobo J (2012) Synthesis of novel quinoline-2-one based chalcones of potential anti-tumor activity. Eur J Med Chem 57:29-40.
2. Aponte JC, Castillo D, Estevez Y, Gonzalez G, Arevalo J, Hammonda GB, Sauvain M (2010) In vitro and in vivo anti-Leishmania activity of polysubstituted synthetic chalcones. Bioorg Med Chem Lett 20:100–103.
3. Awasthi SK, Mishra N, Kumar B, Sharma M, Bhattacharya A, Mishra LC, Bhasin VK (2009) Potent antimalarial activity of newly synthesized substituted chalcone analogs in vitro. Med Chem Res 18:407–420.

4. Ballesteros JF, Sanz MJ, Ubeda A, Miranda MA, Iborra S, Paya M, Alcarz MJ (1995) Synthesis and Pharmacological Evaluation of 2'-Hydroxychalcones and Flavones as Inhibitors of Inflammatory Mediators Generation. J Med Chem 38: 2794-2797.
5. Biradar JS, Sasidhar BS, Parveen R (2010) Synthesis, antioxidant and DNA cleavage activities of novel indole derivatives. Eur J Med Chem 45:4074–4078.
6. Bonesi M, Loizzo MR, Statti GA, Michel S, Tillequin F, Menichini F (2010) The synthesis and Angiotensin Converting Enzyme (ACE) inhibitory activity of chalcones and their pyrazole derivatives. Bioorg Med Chem Lett 20: 1990–1993.
7. Chiaradia LD, Mascarello A, Purificacao M, Vernal J, Cordeiro MNS, Zenteno ME, Villarino A, Nunes RJ, Yunes RA, Terenzi H (2008) Synthetic chalcones as efficient inhibitors of Mycobacterium tuberculosis protein tyrosine phosphatase PtpA. Bioorg Med Chem Lett 18:6227-6230.
8. Domínguez JN, Leon C, Rodrigues J, Domínguez NG, Gut J, Philip J, Rosenthal PJ (2005) Synthesis and antimalarial activity of sulfonamide chalcone derivatives. II Farmaco 60:307-311.
9. Dong X, Du L, Pan Z, Liu T, Yang B, Hua Y (2010) Synthesis and biological evaluation of novel hybrid chalcone derivatives as vasorelaxant agents . Eur J Med Chem 45:3986-3992.
10. Feng H, Li Y, Van der Eycken EV, Peng Y, Song G (2012) Synthesis of polysubstituted pyridines under combined microwave and ultrasound irradiation: K2CO3-promoted tandem addition/cyclization/hydrogen shift process. Tetrahedron Lett 53:1160–1162.
11. Ghavidast A, Mahmoodi NO, Tabatabaeian K (2010) Synthesis and photochromic behavior of mono-, and biphotochromic system linked by *p*-phenylene bridge. Chin Chem Lett 21:1199–1202.
12. Giles D, Roopa K, Sheeba FR, Gurubasavarajaswamy PM, Divakar G, Vidhya T (2012) Synthesis pharmacological evaluation and docking studies of pyrimidine derivatives. Eur J Med Chem 58:478-484.
13. Hayat F, Moseley E, Salahuddin A, Van Zyl RL, Azam A (2011) Antiprotozoal activity of chloroquinoline based chalcones. Eur J Med Chem 46:1897-1905.
14. Hsieh CT, HsiehTJ, El-Shazly M, Chuang DW, Tsai YH, Yen CT, Wua SF, Wua YC, FR Chang (2012) Synthesis of chalcone derivatives as potential anti-diabetic agents. Bioorg Med Chem Lett 22:3912–3915.
15. Khodaee Z, Yahyazadeh A, Mahmoodi NO (2013) One-pot synthesis and characterization of some new types of 5,5′-disubstituted bis(imidazolidine-2,4-diones). J Hetrocyclic Chem 50:288–292.
16. Kiyani H, Mahmoodi NO, Tabatabaeian K, Zanjanchi MA (2009a) Photochromic behavior of several new synthesized bis-1,3-diazabicyclo[3.1.0]hex-3-enes. J Phys Org Chem 22:559–567.
17. Kiyani H, Mahmoodi NO, Tabatabaeian K, Zanjanchi MA (2009b) Synthesis and photochromism of 1,3-diazabicyclo[3.1.0]hex-3-ene phenol rings. Mendeleev Commun 19:203–205.
18. Kumar R, Mohanakrishnan D, Sharma A, Kaushik NK, Kalia K, Sinha AK, Sahal D (2010) Reinvestigation of structure–activity relationship of methoxylated chalcones as antimalarials: Synthesis and evaluation of 2,4,5-trimethoxy substituted patterns as lead candidates derived from abundantly available natural β-asarone. Eur J Med Chem 45:5292-5301.
19. Kumar SK, Erin H, Catherine P, Halluru G, Davidson NE, Khan SRJ (2003) Design, Synthesis, and Evaluation of Novel Boronic-Chalcone Derivatives as Antitumor Agents. J Med Chem 46:2813-2815.
20. Lahtchev KL, Batovska DI, Parushev SP, Ubiyvovk VM, Sibirny AA (2008) Antifungal activity of chalcones: A mechanistic study using various yeast strains. Eur J Med Chem 43:2220-2228.
21. Lin YM, Zhou Y, Flavin MT, Zhou IM, Nie W, Chen FC (2002) Chalcones and flavonoids as anti-Tuberculosis agents. Bioorg Med Chem 10:2795-2802.
22. Lin, C. H., Feng, Y. R., Dai, K. H., Chang, H C, Juang, T. Y. (2013) Synthesis of a benzoxazine with precisely two phenolic OH linkages and the properties of its high-performance copolymers. Polymer scince & Technology General 51:1612-1620.
23. Lu C, Dubrovskiy AV, Larock RC (2012) Synthesis of 9-substituted xanthenes by the condensation of arynes with ortho-hydroxychalcones. Tetrahedron Lett 53:2202–2205.
24. Mahmoodi NO, Kiyani H, Tabatabaeian K (2012) Two 1,3-diazabicyclo[3.1.0]hex-3-enes with a 'Tripod' core. Helv Chim Acta 95:536–542.

25. Mahmoodi NO, Shoja S, Sharifzadeh B, Rassa M (2013) Regioselective synthesis and antibacterial evaluation of novel bis-pyrimidine derivatives via a three-component reaction. Med Chem Res. 23: 1207-1213.
26. Mazimba O, Masesane IB, Majinda RR (2011) An efficient synthesis of flavans from salicylaldehyde and acetophenone derivatives. Tetrahedron Lett 52:6716–6718.
27. Miranda C, Aponso G, Stevens J, Deinzer M, Buhler D (2000) Antioxidant and Prooxidant Actions of Prenylated and Nonprenylated Chalcones and Flavanones in Vitro. J Agric Food Chem 48:3876–3884.
28. Mizuno CS, Paul S, Suh N, Rimando AM (2010) Synthesis and biological evaluation of retinoid-chalcones as inhibitors of colon cancer cell growth. Bioorg Med Chem Lett 20:7385–7387.
29. Nabi G, Liu ZQ (2011) Radical-scavenging properties of ferrocenyl chalcones. Bioorg Med Chem Lett 21:944–946.
30. Park EJ, Park HR, JS Lee, Kim J (1998) Licochalcone A: An Inducer of Cell Differentiation and Cytotoxic Agent from *Pogostemon cabling*. Planta Med 64:464-466.
31. Parmer VS, Sharma NK, Husain M, Watterson AC, Kumar J, Samuelson LA, Ashok LC, Prasad AK, Kumar A, Malhotra S, Kumar N, Jha A, Singh A, Singh Himanshu I, Vats A, Shakil NA, Trikha S, Mukherjee S, Sharma SK, Singh SK, Kumar A, Jha HN, Olsen CE, Stove CP, Bracke ME, Mareel MM (2003) Bioorg Med Chem 11:913.
32. Pereira-Ávila H, Albino-Smânia EdeF, Delle-Monache F, Smânia- Júnior A (2008) Structure–activity relationship of antibacterial chalcones. Bioorg Med Chem 16:9790-9794.
33. Piotrowska DG, Cieslak M, Królewska K, Wróblewski AE (2011) Design, synthesis and cytotoxicity of a new series of isoxazolidines derived from substituted chalcones. Eur J Med Chem 46:1382-1389.
34. Qian Y, GY Ma, Y Yang, K Cheng, QZ Zheng, WJ Mao, L Shi, J Zhao, HL Zhu (2010) Bioorg Med Chem. Bioorg Med Chem 18:4310-4316.
35. Rao YK, Fang SH, Tzeng YM (2009) Synthesis and biological evaluation of 3′,4′,5′-trimethoxychalcone analogues as inhibitors of nitric oxide production and tumor cell proliferation. Bioorg Med Chem 17:7909-7914.
36. Rashad AA, El-Sabbagh OI, Baraka MM, Ibrahim SM, Pannecouque C, Andrei G, Snoeck R, Balzarini J, Mostafa A (2010) Design, synthesis and preliminary antiviral screening of new *N*-phenylpyrazole and dihydroisoxazole derivatives. Med Chem Res 19:1025–1035.
37. Reddy MVB, Shen YC, Ohkoshi E, Bastowd KF, Qian K, Lee KH, Wu TS (2012) Bis-chalcone analogues as potent NO production inhibitors and as cytotoxic agents. Eur J Med Chem 47:97-103.
38. Shin SY, Woob Y, Hyun J, Yong Y, Koh D, Lee YH, Lim Y (2011) Relationship between the structures of flavonoids and their NF-κB-dependent transcriptional activities. Bioorg Med Chem Lett 21:6036–6041.
39. Shukla P, Srivastava SP, Srivastava R, Rawat AK, Srivastava AK, Pratap R (2011) Synthesis and antidyslipidemic activity of chalcone fibrates. Bioorg Med Chem Lett 21:3475–3478.
40. Sivakumar PM, Muthu-Kumar T, Doble M (2009) Antifungal Activity, Mechanism and QSAR Studies on Chalcones. Chem Biol Drug Des 74:68-79.
41. Sivakumar PM, Prabhakar PK, Doble M (2011) Synthesis, antioxidant evaluation, and quantitative structure–activity relationship studies of chalcones. Med Chem Res 20:482–492.
42. Sivakumar PM, Priya S, Doble M (2009) Synthesis, Biological Evaluation, Mechanism of Action and Quantitative Structure–Activity Relationship Studies of Chalcones as Antibacterial Agents. Chem Biol Drug Des 73:403-415.
43. Tavares LC, Johann S, Almeida Alves TM, Guerra JC, Souza-Fagundes EM, Cisalpino PS, Bortoluzzi AJ, Caramori GF, Mattos Piccoli R, Braibante HTS, MEF, Pizzolatti MG (2011) Quinolinyl and quinolinyl N-oxide chalcones: Synthesis, antifungal and cytotoxic activities. Eur J Med Chem 46:4448-4456.
44. Tsuchiya H, Sato M, Akagiri M, Takagi N, Tanaka T, Iinuma M (1994) Anti-Candida activity of synthetic hydroxychalcones.Pharmazie 49:756-758.
45. Vogel S, Ohmayer S, Brunner G, Heillmann J (2008) Natural and non-natural prenylated chalcones: Synthesis, cytotoxicity and anti-oxidative activity. Bioorg Med Chem 16:4286-4293.
46. Wanare G, Aher R, Kawathekar N, Ranjan R, Kumar Kaushik N, Sahal D (2010) Synthesis of novel α-pyranochalcones and pyrazoline derivatives as Plasmodium falciparum growth inhibitors. Bioorg Med Chem Lett 20:4675–4678.

47. Won SJ, Liu CT, Tsao LT, Weng JR, Ko HH, Wang JP, Lin CN (2005) Synthetic chalcones as potential anti-inflammatory and cancer chemopreventive agents. Eur J Med Chem 40:103-112.
48. Zangade SB, Jadhav JD, Vibhute YB, Dawane BS (2010) Synthesis and antimicrobial activity of some new chalcones and flavones containing substituted naphthalene moiety. J Chem Pharm Res 2:310-314.
49. Zhang XW, Zhao DH, Quan YC, Sun LP, Yin XM, Guan LP (2010) Synthesis and evaluation of antiinflammatory activity of substituted chalcone derivatives. Med Chem Res 19:403–412.
50. Zhao L, Jin Sun L, Piao H, Quan Z (2005) Synthesis and evaluation of antiplatelet activity of trihydroxychalcone derivatives. Bioorg Med Chem Lett 15:5027–5029.