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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimicrobial activities of novel bisacridine-1,8-dione derivatives

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Abstract A series of bisacridine-1,8-dione derivatives were synthesized by one-pot reaction of aromatic dialdehydes, dimedone or cyclohexane-1,3-dione and primer aromatic amines in acetonitrile to utilizing Amberlyst-15 as a heterogeneous catalyst. The structures of compounds were characterized by FT-IR, NMR, and elemental analysis. Antimicrobial activities of these compounds were determined by using the disc diffusion method against to these gram-positive and gram-negative bacteria and yeast. The results were compared with reference discs.

Keywords Bisacridine-1,8-diones · Antimicrobial activity · Antibiotics

Introduction

Acridine and acridine-1,8-dione derivatives are important compounds because these compounds have pharmaceutical properties such as antitumor (Mikata *et al.*, 1998), cytotoxic (Antonini *et al.*, 1999), anticancer (Gamega *et al.*, 1999), antimicrobial (Ngadi *et al.*, 1990; Wainwright, 2001), fungicidal (Wainwright, 2001; Srivastava and Nizamuddin, 2004), anti-multidrug-resistant (Gallo *et al.*, 2003), and widely prescribed as calcium β-blockers (Bossert and Vater, 1971, 1989; Berkan *et al.*, 2002). They have similarities in structure to the biologically important compounds NADH and NADPH (Singh *et al.*, 1982; Odabasoglu *et al.*, 2007; Srividya *et al.*, 1996).

As for the preparation of acridine-1,8-dione derivatives, generally similar methods have been employed under traditional heating condition including a two-step procedure and complex operation (Murugan and Ramakrishnan, 1997, 2001; Shanmugasundaram *et al.*, 1997; Kaya *et al.*, 2009). In addition, synthesis of only very few bisacridine-1,8-dione derivatives reported in the literature for microwave-heating synthesis in solid phase (Hua *et al.*, 2005). Each of these methods have their own advantages but also suffer from one or more disadvantages such as long reaction time, complex processes, low yield, and hazardous reaction conditions. Recently, heterogeneous catalysts have been used widely as organic transformations in organic reactions (Sirivinas and Das, 2003; Ramesh *et al.*, 2003; Das *et al.*, 2004a, b; 2006). These methods have advantages process clean, safe, high-yielding, and inexpensive. Due to these advantages, we have used to efficient method as reported in literature for the synthesis of acridine-1,8-diones (Das *et al.*, 2006). In this method using Amberlsyt-15 catalyst has some properties such as easily run, inexpensiveness, non-toxicity, removable easily from reaction medium, and utility several times. In this study, bisacridine-1,8-diones were synthesized via one-pot reaction of dimedone, aromatic dialdehydes, and primer amines. Amberlyst-15 (in acetonitrile) was used as catalyst in these syntheses. As a result, we have performed the synthesis of bisacridine-1,8-dione derivatives in high yields using Amberlyst-15 as a heterogeneous solid acid.

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The newly synthesized bisacridine-1,8-dione compounds **4a–o** were evaluated for their antimicrobial activity against *Shigella sonnei, Salmonella* 21.3*, Bacillus subtilis*, *B. cereus, Staphylococcus aureus, Escherichia coli*, *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Saccharomyces cerevisiae*. These compounds were active on both Gram-positive (*Bacillus subtilis*, *B. cereus*, *Staphylococcus aureus*, *Staphylococcus epidermidis*) and Gram-negative (*Shigella sonnei*, *Salmonella*, *Escherichia coli*, *Pseudomonas aeruginosa*) bacteria.

Result and discussion

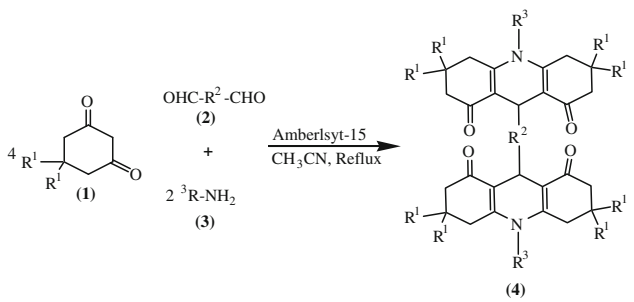
Chemistry

In this study, 15 bisacridine-1,8-dione derivatives were prepared via one-pot reaction in acetonitrile to utilizing Amberlyst-15 as a heterogeneous catalyst. The structures of the synthesized bisacridinedione derivatives, **4a–o**, were confirmed by IR, ^{1}H NMR spectra, and elemental analysis data.

The IR spectra of the compounds were showed the sharp peaks for the carbonyl groups in region between 1720 and 1633 cm^{-1}. The compounds **4a**, **b**, **h**, **i** were measured peaks belong to CN group in the range 2233–2229 cm^{-1}. Besides, in the IR spectra of the compounds, aliphatic C–H stretching bands at 2962–2942 cm^{-1} and aromatic C–H stretching bands at 3065–3021 cm^{-1} were observed.

The ^{1}H NMR spectra of these compounds were showed singlet peaks belong to protons of the methyl groups in positions 3 and 6 at 0.66 and 0.94 ppm. In the ^{1}H NMR spectra, multiple peaks were showed in the range 1.65–2.96 ppm for the CH_2 group protons of the cyclohexane rings. The signals for the CH protons at 4.53–5.41 ppm and signals for the aromatic protons in the range 6.32–8.30 ppm were observed. Acid protons of compounds **4f**, **g**, **l**, **m** gave broad signals at 12.27, 12.33, 12.40, and 12.62 ppm, respectively.

The yield, melting points, and elemental analyses values of compounds **4a–o** are given in Table 1.



Scheme 1 Synthesis scheme of novel bisacridine-1,8-dione derivatives

Antimicrobial activity

As seen in Table 2, all the compounds except compound **4e** showed antibacterial and antifungal activity against test microorganisms. Compounds **4a**, **b**, **c**, **h**, **i**, **n**, and **4o** were not active against *B. subtilis* and *B. cereus.* Also compound **4a** was not active against *S. epidermidis*. Compound **4f** had no inhibition effect against *B. cereus* and *S. cerevisiae* while compound **4g** was not active against *Shigella sonnei* and *S. aureus*. Compound **4j** showed activity against only *S. sonnei*, *B. cereus*, *E. coli*, and *P. aeruginosa* while compound **4k** showed activity against all the test microorganisms. Compound **4l** had no inhibition effect against *S. aureus*, *P. aeruginosa* and **4m** only was not active against *S. epidermidis*. From antifungal assay, it was observed that all the compounds show significant activity against *C. albicans* and *S. cerevisiae*. Table 2 showed that most of compounds show more inhibition effect against tested bacteria and yeast and these activities could reach the effectiveness of the conventional reference antibiotics.

Acridines are known to be biologically versatile compounds possessing several pharmacological activities, including antimicrobial (Wainwright, 2001; Ngadi *et al.*,1990). Some researchers reported that all of the synthesized acridine derivatives exhibited moderate antibacterial and antifungal activity (Patel *et al.* 2006).

Experimental

Chemistry

The chemicals used in the synthesis of the novel bisacridine-1,8-dione compounds were purchased from Aldrich Chemical Company. All chemicals and solvents used for the synthesis were spectroscopic reagent grade. Melting points were measured on a Bibby Stuart Scientific apparatus. FT-IR spectra were recorded from Bruker Optics, Vertex 70 FT-IR spectrometer using ATR diamond crystal. ^{1}H NMR spectra were recorded on a Bruker DPX-400 FT-NMR instrument with chloroform-d ($CDCl_3$) and dimethyl sulfoxide (DMSO-d_6) as solvent with trimethylsilane as the internal reference. Chemical shifts are expressed in δ units (ppm). The elemental analyses (C, H, N) were recorded on an Elemental Analyzer LECO CHNS-932.

*Typical procedure for preparation of bisacridine-1, 8-diones (**4a–o**)*

A mixture of aromatic dialdehydes (1.0 mmol), cyclohexane-1,3-dione or dimedone (4.0 mmol), aromatic amines (2 mmol), and Amberlyst-15 (400 mg) in acetonitrile (20 mL) were stirred at reflux for 4 h. The progress of the

Table 1 Preparation of **4a–o** promoted by Amberlyst-15 in CH_3CN and elemental analyses of compounds **4a–o**

Entry	R^1	OHC–R^2–CHO	R^3	Yield (%)	m.p. (°C)	Elemental analyses (%) Calc./Found		
						C	H	N
4a	H	1,3-$(OHC)_2C_6H_4$	3-CNC_6H_4	81	180[a]	77.73/77.56	5.39/5.36	7.88/7.81
4b	H	1,3-$(OHC)_2C_6H_4$	2-CNC_6H_4	74	153[a]	77.73/77.63	5.39/5.42	7.88/7.82
4c	H	1,3-$(OHC)_2C_6H_4$	6-CH_3Prydine	80	216[a]	76.50/76.42	6.13/6.09	8.11/8.08
4d	H	1,3-$(OHC)_2C_6H_4$	3-$CH_3OC_6H_4$	72	167[a]	76.64/76.41	6.15/6.12	3.89/3.87
4e	H	1,3-$(OHC)_2C_6H_4$	2-$CH_3OC_6H_4$	77	260[a]	76.64/76.49	6.15/6.10	3.89/3.85
4f	H	1,3-$(OHC)_2C_6H_4$	4-$HOOCC_6H_4$	76	327[a]	73.78/73.61	5.38/5.34	3.74/3.76
4g	H	1,3-$(OHC)_2C_6H_4$	3-$HOOCC_6H_4$	73	298[a]	73.78/73.59	5.38/5.33	3.74/3.70
4h	CH_3	1,3-$(OHC)_2C_6H_4$	3-CNC_6H_4	79	290–291	78.80/78.63	6.61/6.57	6.81/6.75
4i	CH_3	1,3-$(OHC)_2C_6H_4$	2-CNC_6H_4	80	221	78.80/78.60	6.61/6.59	6.81/6.76
4j	CH_3	1,3-$(OHC)_2C_6H_4$	3-$CH_3OC_6H_4$	71	228	77.85/77.70	7.26/7.21	3.36/3.38
4k	CH_3	1,3-$(OHC)_2C_6H_4$	2-$CH_3OC_6H_4$	78	265	77.85/77.75	7.26/7.22	3.36/3.33
4l	CH_3	1,3-$(OHC)_2C_6H_4$	4-$HOOCC_6H_4$	77	320[a]	75.33/75.49	6.56/6.53	3.25/3.23
4m	CH_3	1,3-$(OHC)_2C_6H_4$	3-$HOOCC_6H_4$	75	256[a]	75.33/75.17	6.56/6.58	3.25/3.22
4n	CH_3	1,4-$(OHC)_2C_6H_4$	4-ClC_6H_4	82	282[a]	74.18/74.03	6.46/6.41	3.33/3.30
4o	CH_3	1,4-$(OHC)_2C_6H_4$	4-BrC_6H_4	84	210[a]	67.10/67.01	5.85/5.80	3.01/2.97

[a] Decomposition

reaction was monitored by TLC. After completion of the reactions, the mixture was filtered and cooled to room temperature. The crude products were purified by recrystallization from ethyl acetate–methanol. Data all of the compounds are shown below.

3,3′-(9,9′-(1,3-phenylene)bis(1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridine-10,9(9H)-diyl))dibenzonitrile (**4a**): IR (KBr) *v*: 3062 (aromatic CH), 2946 (aliphatic CH), 2232 (CN), 1634 (C=O), 1576 (aromatic C=C), 1229 (CN) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.82–1.96 (m, 6H, 3 × CH_2), 2.03–2.10 (m, 6H, 3 × CH_2), 2.20–2.41 (m, 8H, CH_2), 2.54–2.60 (m, 2H, CH_2), 2.69–2.75 (m, 2H, CH_2), 4.79 and 5.36 (2 × d, 2H, $J = 10.4$ Hz, CH), 6.91 (m, 1H, ArH), 7.02–7.19 (m, 3H, ArH), 7.20–7.25 (m, 2H, ArH), 7.40–7.75 (m, 4H, ArH), 7.83 (t, 2H, $J = 6.1$ Hz, ArH).

2,2′-(9,9′-(1,3-phenylene)bis(1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridine-10,9(9H)-diyl))dibenzonitrile (**4b**): IR (KBr) *v*: 3059 (aromatic CH), 2947 (aliphatic CH), 2230 (CN), 1636 (C=O), 1575 (aromatic C=C), 1230 (CN) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.76–2.05 (m, 10H, 5 × CH_2), 2.25–2.40 (m, 10H, 5 × CH_2), 2.53–2.56 (d × t, 2H, CH_2), 2.66–2.70 (d × t, 2H, CH_2), 4.73 and 5.32 (2 × d, 2H, $J = 12.8$ Hz, CH), 6.87 (d, 1H, $J = 7.8$ Hz, ArH), 7.01–7.11 (m, 2H, ArH), 7.21–7.35 (m, 3H, ArH), 7.60–7.66 (m, 2H, ArH), 7.83–7.93 (m, 4H, ArH).

9,9′-(1,3-phenylene)bis(10-(6-methylpyridin-2-yl)-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione) (**4c**): IR (KBr) *v*: 3056 (aromatic CH), 2945 (aliphatic CH), 1668 and 1636 (C=O), 1562 (aromatic C=C), 1175 (CN) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.84–1.87 (m, 4H, 2 × CH_2), 1.95–2.00 (m, 4H, 2 × CH_2), 2.21–2.35 (m, 12H, 6 × CH_2), 2.48–2.58 (m, 4H, 2 × CH_2), 2.59 (s, 3H, CH_3), 4.72 and 5.35 (2 × d, 2H, $J = 18.0$ Hz, CH), 6.85 (m, 2H, ArH), 6.95–7.15 (m, 3H, ArH), 7.25–7.32 (m, 2H, ArH), 7.41–7.48 (m, 1H, ArH), 7.78–7.38 (m, 2H, ArH).

9,9′-(1,3-phenylene)bis(10-(3-methoxyphenyl)-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione) (**4d**): IR (KBr) *v*: 3055 (aromatic CH), 2942 (aliphatic CH), 1634 (C=O), 1571 (aromatic C=C), 1229 (CN) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.74–1.92 (m, 4H, 2 × CH_2), 1.95–2.10 (m, 4H, 2 × CH_2), 2.22–2.40 (m, 12H, 6 × CH_2), 2.49–2.58 (m, 2H, CH_2), 2.70–2.76 (m, 2H, CH_2), 3.88 (s, 6H, 2 × OCH_3), 4.80 and 5.38 (2 × d, 2H, $J = 18.8$ Hz, CH), 6.71–6.83 (m, 4H, ArH), 7.03–7.25 (m, 6H, ArH), 7.41–7.55 (m, 2H, ArH).

9,9′-(1,3-phenylene)bis(10-(2-methoxyphenyl)-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione) (**4e**): IR (KBr) *v*: 3060 (aromatic CH), 2944 (aliphatic CH), 1634 (C=O), 1574 (aromatic C=C), 1229 (CN) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.65–1.99 (m, 8H, 4 × CH_2), 2.07–2.31 (m, 12H, 6 × CH_2), 2.50–2.52 (m, 2H, CH_2), 2.64–2.69 (m, 2H, CH_2), 3.91 (s, 6H, 2 × OCH_3), 4.56 and 5.14 (2 × d, 2H, $J = 15.6$ Hz, CH), 6.53–6.78 (m, 2H, ArH), 6.93–7.14 (m, 5H, ArH), 7.23–7.56 (m, 5H, ArH).

4,4′-(9,9′-(1,3-phenylene)bis(1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridine-10,9(9H)-diyl))dibenzoic acid (**4f**): IR (KBr) *v*: 3365 (COOH), 2952 (aliphatic CH), 1717 and 1640 (C=O), 1596 (aromatic C=C), 1235 (CN) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 1.66–1.71 (m, 2H, CH_2),

Table 2 Inhibition zones diameters of compounds and against to the test microorganisms

Comp.	Inhibition zone (mm)									
	Shigella sonnei RSKK 877	*Salmonella* 21.3	*B. subtilis* RSKK 240	*B. cereus* RSKK 863	*S. aureus ATCC* 25923	*E. coli ATCC* 35218	*S. epidermidis* Mu 30	*P. aeruginosa* ATCC 27853	*C. albicans* ATCC 16231	*S. cerevisiae* TP (3–2)
4a	12	10	–	–	9	8	–	10	27	17
4b	10	11	–	–	10	8	10	14	13	20
4c	9	9	–	–	18	12	8	9	14	17
4d	10	12	11	–	16	14	11	9	12	11
4e	–	–	–	–	–	–	–	–	–	–
4f	9	8	8	–	11	9	12	10	10	–
4g	–	11	9	8	–	12	–	9	14	11
4h	9	10	–	–	10	13	8	8	16	14
4i	10	9	–	–	12	12	9	9	14	14
4j	12	–	–	13	–	10	–	7	–	–
4k	12	8	8	13	9	14	13	10	15	14
4l	11	9	11	9	–	10	11	–	12	13
4m	10	11	9	8	10	9	–	9	16	16
4n	10	12	–	–	9	12	7	9	10	14
4o	12	10	–	–	12	10	10	10	11	16
Amphisiline	22	23	24	20	24	27	–	–	–	–
Gentamycine	11	10	–	–	–	15	–	20	–	–
Ketoconazole									21	24

1.84–1.98 (m, 8H, 4 × CH_2), 2.21–2.34 (m, 10H, 5 × CH_2), 2.49–2.51 (m, 2H, CH_2), 2.61–2.65 (m, 2H, CH_2), 4.55 and 5.15 (2 × d, 2H, J = 19.2 Hz, CH), 6.55 (d, 1H, J = 8.5 Hz, ArH), 6.92–7.29 (m, 3H, ArH), 7.61 (d, 4H, J = 8.7 Hz, ArH), 8.10 (d, 4H, J = 8.7 Hz, ArH), 12.27 (br, 2H, COOH).

3,3′-(9,9′-(1,3-phenylene)bis(1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridine-10,9(9H)-diyl))dibenzoic acid (**4g**): IR (KBr) *v*: 3050 (aromatic CH), 2948 (aliphatic CH), 1718 and 1633 (C=O), 1586 (aromatic C=C), 1231 (CN) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$ and DMSO-d_6) δ: 1.73–2.00 (m, 8H, 4 × CH_2), 2.19–2.25 (m, 8H, 4 × CH_2), 2.50–2.61 (m, 4H, 2 × CH_2), 2.78–2.90 (m, 4H, 2 × CH_2), 4.56 and 5.19 (2 × d, 2H, J = 18.8 Hz, CH), 6.88–7.06 (m, 4H, ArH), 7.39–7.68 (m, 4H, ArH), 7.85–7.90 (m, 2H, ArH), 8.07 (d, 2H, J = 7.55, ArH), 12.40 (br, 2H, COOH).

3,3′-(9,9′-(1,3-phenylene)bis(3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridine-10,9(9H)-diyl))dibenzonitrile (**4h**): IR (KBr) *v*: 3051(aromatic CH), 2959 (aliphatic CH), 2233 (CN), 1640 (C=O), 1580 (aromatic C=C), 1219 (CN) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.71 (s, 9H, 3 × CH_3), 0.85 (s, 12H, 4 × CH_3), 0.98 (s, 3H, CH_3), 1.68 (t, 4H, J = 17.0 Hz, 2 × CH_2), 1.94–2.12 (m, 10H, 5 × CH_2), 2.36 (q, 2H, J = 8.4 Hz, CH_2), 4.59 and 5.15 (2 × d, 2H, J = 11.6 Hz, 2 × CH), 6.68 (d, 1H, J = 7.8 Hz, ArH), 6.99 (t, 1H, J = 6.2 Hz, ArH), 7.03–7.12 (s, 2H, ArH), 7.20 (m, 1H, ArH), 7.34 (m, 1H, ArH), 7.41–7.46 (m, 2H, ArH), 7.67–7.52 (m, 4H, ArH).

2,2′-(9,9′-(1,3-phenylene)bis(3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridine-10,9(9H)-diyl))dibenzonitrile (**4i**): IR (KBr) *v*: 3053 (aromatic CH), 2959 (aliphatic CH), 2229 (CN), 1639 (C=O), 1579 (aromatic C=C), 1220 (CN) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.75 (s, 9H, 3 × CH_3), 0.87 (s, 12H, 4 × CH_3), 0.98 (s, 3H, CH_3), 1.60–1.77 (m, 4H, 2 × CH_2), 1.96–2.19 (m, 8H, 4 × CH_2), 2.32–2.45 (m, 4H, 2 × CH_2), 4.62 and 5.14 (2 × d, 2H, J = 10.0 Hz, 2 × CH), 6.73 (d, 1H, J = 7.8 Hz, ArH), 6.97–7.08 (m, 2H, ArH), 7.10–7.19 (s, 1H, ArH), 7.22–7.31 (m, 2H, ArH), 7.58–7.64 (m, 2H, ArH), 7.79–7.86 (m, 3H, ArH), 8.20 (d, 1H, J = 7.7 Hz, ArH).

9,9′-(1,3-phenylene)bis(10-(3-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione) (**4j**): IR (KBr) *v*: 3043 (aromatic CH), 2956 (aliphatic CH), 1664 (C=O), 1572 (aromatic C=C), 1224 (CN) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$ and DMSO-d_6) δ: 0.88 (s, 9H, 3 × CH_3), 0.94 (s, 12H, 4 × CH_3), 0.99 (s, 3H, CH_3), 1.91–2.02 (m, 10H, 5 × CH_2), 2.21–2.34 (m, 4H, 2 × CH_2), 2.41–2.43 (m, 2H, CH_2), 3.62 (s, 6H, 2 × OCH_3), 4.92 and 5.41 (2 × d, 2H, J = 12.4 Hz, 2 × CH), 6.32–6.77 (m, 8H, ArH), 6.87–6.92 (m, 2H, ArH), 7.02–7.07 (m, 2H, ArH).

9,9′-(1,3-phenylene)bis(10-(2-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione) (**4k**): IR (KBr) *v*: 3045 (aromatic CH), 2957 (aliphatic CH), 1636 (C=O), 1585 (aromatic C=C), 1221(CN) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.75 (s, 9H, 3 × CH_3), 0.87 (s, 12H, 4 × CH_3), 1.01 (s, 3H, CH_3), 1.78–1.82 (m, 4H, 2 × CH_2), 2.03–2.16 (m, 8H, 4 × CH_2), 2.33–2.48 (m, 4H, 2 × CH_2), 3.57 (s, 6H, 2 × OCH_3), 4.64 and 5.19 (2 × d, 2H, J = 12.4 Hz, 2 × CH), 6.77–7.07 (m, 4H, ArH), 7.35–7.64 (m, 4H, ArH), 7.78–7.98 (m, 2H, ArH), 8.12–8.30 (m, 2H, ArH).

4,4′-(9,9′-(1,3-phenylene)bis(3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridine-10,9(9H)-diyl))dibenzoic acid (**4l**): IR (KBr) *v*: 3048 (aromatic CH), 2961(aliphatic CH), 1720 and 1638 (C=O), 1603 (aromatic C=C), 1221 (CN) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$ and DMSO-d_6) δ: 0.70 (s, 9H, 3 × CH_3), 0.84 (s, 12H, 4 × CH_3), 1.00 (s, 3H, CH_3), 1.76–1.82 (m, 4H, 2 × CH_2), 1.93–2.11 (m, 8H, 4 × CH_2), 2.49–2.51 (m, 4H, 2 × CH_2), 4.60 and 5.08 (2 × d, 2H, J = 10.0 Hz, 2 × CH), 6.74 (d, 1H, J = 7.9 Hz, ArH), 6.96–7.14 (m, 2H, ArH), 7.32–7.48 (m, 5H, ArH), 8.16 (d, 4H, J = 8.0 Hz, ArH), 12.62 (br, 2H, COOH).

3,3′-(9,9′-(1,3-phenylene)bis(3,3,6,6-tetramethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridine-10,9(9H)-diyl))dibenzoic acid (**4m**): IR (KBr) *v*: 3041 (aromatic CH), 2958 (aliphatic CH), 1717 and 1637 (C=O), 1585 (aromatic C=C), 1220 (CN) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.66 (s, 9H, 3 × CH_3), 0.79 (s, 12H, 4 × CH_3), 0.95 (s, 3H, CH_3), 1.71 (d, 4H, J = 17.0 Hz, 2 × CH_2), 1.94–2.07 (m, 8H, 4 × CH_2), 2.24–2.50 (m, 4H, 2 × CH_2), 4.53 and 5.04 (2 × d, 2H, J = 11.2 Hz, 2 × CH), 6.72 (d, 1H, J = 7.8 Hz, ArH), 6.90–7.08 (m, 4H, ArH), 7.42–7.56 (m, 3H, ArH), 7.71–7.98 (m, 2H, ArH), 8.07 (d, 2H, J = 7.7 Hz, ArH), 12.33 (br, 2H, COOH).

9,9′-(1,4-phenylene)bis(10-(4-chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione) (**4n**): IR (KBr) *v*: 3021(aromatic CH), 2960 (aliphatic CH), 1637 (C=O), 1579 (aromatic C=C), 1220 (CN) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.81 (s, 12H, 4 × CH_3), 0.92 (s, 12H, 4 × CH_3), 1.78–2.15 (m, 14H, 7 × CH_2), 2.87–2.96 (m, 2H, CH_2), 5.27 (s, 2H, 2 × CH), 7.13–7.24 (m, 8H, ArH), 7.70 (d, 4H, J = 8.1 Hz, ArH).

9,9′-(1,4-phenylene)bis(10-(4-bromophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione) (**4o**): IR (KBr) *v*: 3023 (aromatic CH), 2962 (aliphatic CH), 1637 (C=O), 1578 (aromatic C=C), 1221(CN) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.83 (s, 12H, 4 × CH_3), 0.95 (s, 12H, 4 × CH_3), 1.79 (d, 4H, 2 × CH_2), 1.91–2.22 (m, 12H, 6 × CH_2), 5.31 (s, 2H, 2 × CH), 7.12–7.23 (m, 8H, ArH), 7.77 (d, 4H, J = 7.9 Hz, ArH).

Biology

Test microorganisms

The bacterial subcultures for *Shigella sonnei* RSKK 877, *Salmonella* 21.3, *Bacillus subtilis* RSKK 240, *B. cereus* RSKK 863, *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 35218, *Staphylococcus epidermidis* Mu 30, *Pseudomonas aeruginosa* ATCC 27853, *Candida albicans* 16231, and *Saccharomyces cerevisiae* TP (3–2) were obtained from Gazi University, Biology Department. Bacterial strains were cultured overnight at 37°C in Nutrient Broth and the yeast were cultured overnight at 30°C in Sabouraud Dextrose Broth for antibacterial and antifungal activity tests. These stock cultures were stored in the dark at 4°C during the survey.

Biological screening

Antibacterial activities of the compounds were determined by using the disc diffusion method (NCCLS 1997). The antimicrobial screening was performed using Mueller–Hinton Agar for bacteria and Sabouraud Dextrose Agar for yeast. The culture suspensions were prepared and adjusted by comparing against 0.5 Mc Farland turbidity standard tubes. Mueller–Hinton Agar (20 ml) was poured into each sterile Petri dish after injecting cultures (100 µl) of microorganisms and distributing medium in Petri dish homogeneously. Compounds were filtered with a pore size of 0.45 µm. Compounds **4a**, **b**, **c**, **d** were dissolved in $CHCl_3$ of 5 mg ml^{-1}. All of the other compounds were dissolved in DMSO of 5 mg ml^{-1} (Katırcıoğlu *et al.*, 2007; Loğoğlu *et al.*, 2007; Ünlüsoy *et al.*, 2007). Empty sterilized discs of 6 mm (Whatman No: 1) were each impregnated with 20 µl of compounds. Discs were placed on agar plates, and the plates were incubated at 37°C for 24 h. Inhibition zones formed on the medium were evaluated in millimeters. Studies performed in duplicate and the inhibition zones were compared with those of reference discs. The solvents control ($CHCl_3$, DMSO) did not show any antimicrobial activity.

Conclusion

In this study, 15 novel bisacridine-1,8-dione derivatives were synthesized using Amberlyst-15 as a heterogeneous catalyst and their antimicrobial activities evaluated. All the compounds except compound **4e** showed antibacterial and antifungal activity against test microorganisms.

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