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Synthesis and antimicrobial properties of N-substituted derivatives of (*E*)-2′,3″-thiazachalcones

Abstract: N-alkyl substituted 2′,3″-thiazachalcones {3-[(1*E*)-3-(4-methylthiophene-2-yl)-3-oxoprop-1-en-1-yl]-1-alkyl ($C_{5–12,14}$) pyridinium bromides} were synthesized by a two-step reaction. The newly synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, elemental analysis and mass spectral studies. The synthesized compounds were tested for antibacterial activities and found to be more active against Gram-positive as compared to Gram-negative bacteria.

Keywords: antimicrobial activity; azachalcone; N-alkyl azachalconium bromide.

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1 Introduction

Chalcones, 1,3-diphenylprop-2-enone, are common structures in numerous natural products contained in the flavonoid family [1]. These compounds are reported to show a wide variety of biological activities [2–7]. They found numerous applications as pesticides, photoprotectors in plastics, solar creams and food additives [7, 8]. Azachalcones contain an annular N-atom in the phenyl ring, giving rise to a pyridyl moiety. In past years, the synthesis of azachalcones and their N-alkyl substituted derivatives has been studied. These compounds have been reported to possess several biological activities, such as cytotoxic, antimalarial, antileishmanial, antiinflammatory, anti-HIV, antifungal [9–17]. Further, the preparation of furan and thiophene analogues of azachalcones has been described, and some of them have been found to possess a wide variety of biological activities, including antituberculosis, antimicrobial, antioxidant, antiinflammatory and antibacterial properties [15–24].

In our previous work, novel substituted (*E*)-3-, and 4-azachalcones, and their N-alkyl derivatives were synthesized and exhibited very good antimicrobial activities, especially against Gram-positive bacteria [16, 17]. In view of continuing interest in new antimicrobial agents, other N-alkyl ($C_{5–12,\ 14}$) substituted 2′,3″-thiazachalconium bromides have been synthesized with the aim of determining the influence of the length of the carbon chain in the N-alkyl substituent on the antimicrobial activity.

The present work deals with the synthesis, spectral characterization and antimicrobial activity of one already known [16] and eight new N-alkyl substituted 2′,3″-thiazachalcones **(1a**–**1i)** (Figure 1).

2 Results and discussion

2.1 Synthesis of N-alkyl 2′,3″-thiazachalcones

N-alkyl derivatives of 2′,3″-thiazachalcones were synthesized from the corresponding azachalcones with *n*-bromoalkanes (1-bromopentane, 1-bromohexane, 1-bromoheptane, 1-bromooctane, 1-bromononane, 1-bromodecane, 1-bromoundecane, 1-bromododecane, 1-bromotetradecane) in acetonitrile solution under reflux. The known compound **1** was prepared according to the literature [16] (Figure 1).

The spatial relation of the olefinic H-atoms of (*E*)-N-alkyl-3-azachalconium bromides **(1a**–**1i)** was also *E* based on their ^3J values ($^3J_{H\alpha\text{-}H\beta}$ =15.6–16.0 Hz). In the ^{1}H NMR spectrum of **1a**–**1i**, the characteristic –CH_2- signal of N-alkyl groups was exhibited at δ5.03–5.08 ppm (2H, t, *J*=6.6–7.2 Hz) due to the pyridinium salt [9–17].

All synthesized compounds (**1a**–**1i**) were characterized based on the analysis of spectral data (^{1}H NMR, ^{13}C NMR, APT, ^{1}H-^{1}H COSY NMR, ACD NMR, FTIR, LC-MS/MS) and elemental analysis, which were in agreement with the proposed structures (Tables 1–3). The LC mass

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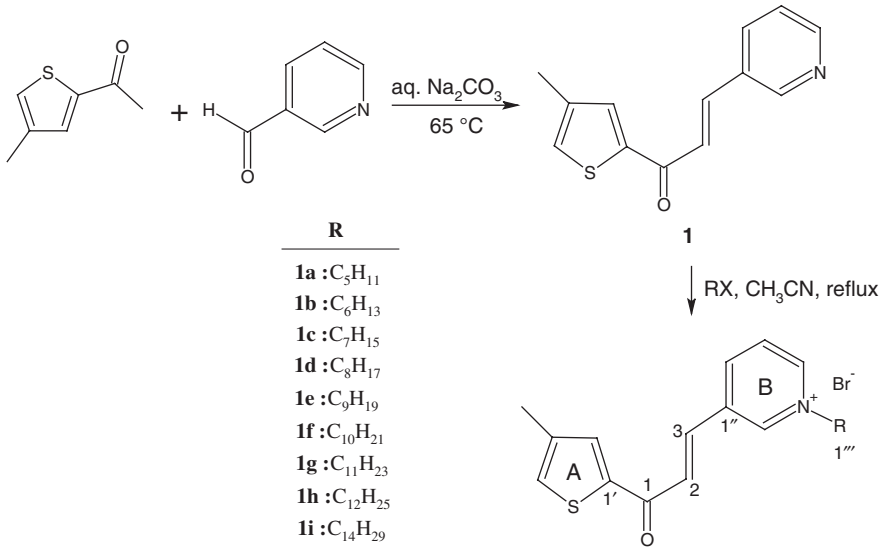

Figure 1: Synthetic pathway for the preparation of compounds **1a–1i.**

Table 1: Physical and analytical data of 3-[(1*E*)-3-(4-methylthiophene-2-yl)-3-oxoprop-1-en-1- yl]-1-alkyl ($C_{5\text{-}12,\,14}$) pyridinium bromides, **(1a–1i).**

Compound	Yield (%)	TLC[a] (R_f)	Mp, °C	Formula	Elemental analysis (%) Calcd/found			
					C	H	N	S
1a	75	0.38	118–120	$C_{18}H_{22}BrNOS$	56.84	5.79	3.68	8.42
					56.71	5.69	3.58	8.53
1b	70	0.41	112–114	$C_{19}H_{24}BrNOS$	57.87	6.09	3.55	8.12
					57.98	6.20	3.67	8.24
1c	80	0.44	81–83	$C_{20}H_{26}BrNOS$	58.82	6.37	3.43	7.84
					58.95	6.27	3.54	7.90
1d	82	0.48	120–122	$C_{21}H_{28}BrNOS$	59.72	6.64	3.32	7.58
					59.61	6.59	3.43	7.47
1e	84	0.52	113–115	$C_{22}H_{30}BrNOS$	60.55	6.88	3.21	7.34
					60.68	6.95	3.28	7.40
1f	77	0.18	60–62	$C_{23}H_{32}BrNOS$	61.33	7.11	3.11	7.12
					61.19	7.21	3.24	7.39
1g	70	0.53	121–123	$C_{24}H_{34}BrNOS$	62.07	7.33	3.02	6.90
					61.96	7.23	3.13	6.80
1h	78	0.54	113–115	$C_{25}H_{36}BrNOS$	62.76	7.53	2.93	6.69
					62.63	7.54	2.83	6.61
1i	85	0.56	129–131	$C_{27}H_{40}BrNOS$	64.03	7.91	2.77	6.32
					64.16	7.93	2.69	6.22

[a]Ethyl acetate-methanol (3:1, v/v).

spectra of **1a**–**1i** exhibited molecular ion peaks for $[M(^{79}Br)]^+$ and $[M(^{81}Br)]^+$. Based on the above observations, the complete chemical shift assignments for **1a**–**1i** were deduced to be those of 3-[(1*E*)-3-(4-methylthiophene-2-yl)-3-oxoprop-1-en-1-yl]-1-alkyl ($C_{5\text{–}12,\,14}$) pyridinium bromides **(1a**–**1i)**.

2.2 Antibacterial activity

The antibacterial effects of these chalcones have been related to the ability of the α,β-unsaturated ketone to undergo a conjugated addition to a nucleophilic group, like a thiol group of proteins. The presence of donor and

Table 2: Spectral data of compounds **1a–1i**.

Compound	IR ν, cm^{-1} (C=O)	MS (m/e) $[M(^{79}Br)]^+$	MS (m/e) $[M(^{81}Br)]^+$	^1H NMR ($CDCl_3$) δ (ppm)[a]
1a	1653	380(35)	382(18)	0.8 (3H, t, *J*=6.8 Hz, C(5‴)-H), 1.3 (4H, series of m, C(3‴)-H to C(4‴)-H), 2.0 (2H, m, C(2‴)-H), 2.3 (3H, s, -CH_3), 5.1 (2H, t, *J*=7.2 Hz, N-CH_2-), 7.3 (1H, bs, C(3′)-H), 7.6 (AB, ^3J=15.6 Hz, C(2)-H), 8.0 (1H, m, C(5″)-H), 8.5 (1H, bs, C(5′)-H), 8.6 (AB, ^3J=15.6 Hz, C(3)-H), 8.7 (1H, d, *J*=7.6 Hz, C(6″)-H), 8.9 (1H, d, *J*=5.2 Hz, C(4″)-H), 10.7 (1H, bs, C(2″)-H)
1b	1653	394(40)	396(18)	0.8 (3H, t, *J*=7.2 Hz, C(6‴)-H), 1.3 (6H, series of m, C(3‴)-H to C(5‴)-H), 2.1 (2H, m, C(2‴)-H), 2.3 (3H, s, -CH_3), 5.1 (2H, t, *J*=7.2 Hz, N-CH_2-), 7.3 (1H, bs, C(3′)-H), 7.7 (AB, ^3J=15.8 Hz, C(2)-H), 8.1 (1H, m, C(5″)-H), 8.5 (1H, bs, C(5′)-H), 8.5 (AB, ^3J=15.8 Hz, C(3)-H), 8.7 (1H, d, *J*=7.6 Hz, C(6″)-H), 9.1 (1H, d, *J*=5.6 Hz, C(4″)-H), 10.6 (1H, bs, C(2″)-H)
1c	1651	408(39)	410(18)	0.8 (3H, t, *J*=6.2 Hz, C(7‴)-H), 1.3 (8H, series of m, C(3‴)-H to C(6‴)-H), 2.1 (2H, m, C(2‴)-H), 2.3 (3H, s, -CH_3), 5.1 (2H, t, *J*=7.2 Hz, N-CH_2-), 7.3 (1H, bs, C(3′)-H), 7.7 (AB, ^3J=15.6 Hz, C(2)-H), 8.1 (1H, m, C(5″)-H), 8.5 (1H, bs, C(5′)-H), 8.5 (AB, ^3J=15.6 Hz, C(3)-H), 8.8 (1H, d, *J*=7.8 Hz, C(6″)-H), 9.2 (1H, d, *J*=5.8 Hz, C(4″)-H), 10.6 (1H, bs, C(2″)-H)
1d	1650	422(40)	424(19)	0.8 (3H, t, *J*=6.6 Hz, C(8‴)-H), 1.3 (10H, series of m, C(3‴)-H to C(7‴)-H), 2.1 (2H, m, C(2‴)-H), 2.3 (3H, s, -CH_3), 5.1 (2H, t, *J*=7.2 Hz, N-CH_2-), 7.3 (1H, bs, C(3′)-H), 7.7 (AB, ^3J=15.9 Hz, C(2)-H), 8.2 (1H, m, C(5″)-H), 8.5 (1H, bs, C(5′)-H), 8.5 (AB, ^3J=15.9 Hz, C(3)-H), 8.8 (1H, d, *J*=8.2 Hz, C(6″)-H), 9.3 (1H, d, *J*=5.8 Hz, C(4″)-H), 10.6 (1H, bs, C(2″)-H)
1e	1651	436(38)	438(15)	0.8 (3H, t, *J*=6.8 Hz, C(9‴)-H), 1.3 (12H, series of m, C(3‴)-H to C(8‴)-H), 2.1 (2H, m, C(2‴)-H), 2.3 (3H, s, -CH_3), 5.1 (2H, t, *J*=7.0 Hz, N-CH_2-), 7.3 (1H, bs, C(3′)-H), 7.7 (AB, ^3J=16.0 Hz, C(2)-H), 8.2 (1H, m, C(5″)-H), 8.5 (1H, bs, C(5′)-H), 8.5 (AB, ^3J=16.0 Hz, C(3)-H), 8.8 (1H, d, *J*=7.8 Hz, C(6″)-H), 9.3 (1H, d, *J*=5.6 Hz, C(4″)-H), 10.6 (1H, bs, C(2″)-H)
1f	1651	450(48)	452(22)	0.84 (t, *J*=6.4, C(10‴)-H), 1.3 (14H, series of m, C(3‴)-H to C(9‴)-H), 2.1 (2H, m, C(2‴)-H), 2.3 (3H, s, -CH_3), 5.1 (2H, t, *J*=7.0 Hz, N-CH_2-), 7.3 (1H, d, *J*=1.0 Hz, C(3′)-H), 7.7 (AB, ^3J=15.6 Hz, C(2)-H), 8.1 (1H, dd, *J*=8.2, 6.2 Hz, C(5″)-H), 8.5 (1H, d, *J*=1.0 Hz, C(5′)-H), 8.5 (AB, ^3J=15,6 Hz, C(3)-H), 8.8 (1H, d, *J*=8.2 Hz, C(6″)-H), 9.2 (1H, d, *J*=6.2 Hz, C(4″)-H), 10.5 (1H, bs, C(2″)-H)
1g	1650	464(54)	466(28)	0.9 (3H, t, *J*=6.6 Hz, C(11‴)-H), 1.3 (16H, series of m, C(3‴)-H to C(10‴)-H), 2.1 (2H, m, C(2‴)-H), 2.3 (3H, s, -CH_3), 5.1 (2H, t, *J*=7.0 Hz, N-CH_2-), 7.4 (1H, bs, C(3′)-H), 7.7 (AB, ^3J=15.7 Hz, C(2)-H), 8.2 (1H, m, C(5″)-H), 8.5 (1H, bs, C(5′)-H), 8.5 (AB, ^3J=15.7 Hz, C(3)-H), 8.8 (1H, d, *J*=7.4 Hz, C(6″)-H), 9.3 (1H, d, *J*=5.2 Hz, C(4″)-H), 10.6 (1H, bs, C(2″)-H)
1h	1650	478(35)	480(13)	0.8 (3H, t, *J*=6.8 Hz, C(12‴)-H), 1.3 (18H, series of m, C(3‴)-H to C(11‴)-H), 2.1 (2H, m, C(2‴)-H), 2.3 (3H, s, -CH_3), 5.0 (2H, t, *J* = 7.2 Hz, N-CH_2-), 7.3 (1H, bs, C(3′)-H), 7.7 (AB, ^3J=15.6 Hz, C(2)-H), 8.1 (1H, m, C(5″)-H), 8.4 (1H, bs, C(5′)-H), 8.4 (AB, ^3J=15.6 Hz, C(3)-H), 8.8 (1H, d, *J*=7.2 Hz, C(6″)-H), 9.2 (1H, bs, C(4″)-H), 10.5 (1H, bs, C(2″)-H)
1i	1651	506(35)	508(15)	0.9 (3H, t, *J*=6.6 Hz, C(14‴)-H), 1.3 (20H, series of m, C(3‴)-H to C(13‴)-H), 2.0 (2H, m, C(2‴)-H), 2.3 (3H, s, -CH_3), 5.1 (2H, t, *J*=6.6 Hz, N-CH_2-), 7.3 (1H, bs, C(3′)-H), 7.7 (AB, ^3J=15.9 Hz, C(2)-H), 8.0 (1H, m, C(5″)-H), 8.6 (1H, bs, C(5′)-H), 8.6 (AB, ^3J=15.9 Hz, C(3)-H), 8.7 (1H, d, *J*=8.6 Hz, C(6″)-H), 9.0 (1H, d, *J*=6.4 Hz, C(4″)-H), 10.7 (1H, bs, C(2″)-H)

[a]Assignment based on ^1H-^1H COSY, and comparison with ACD NMR program.

acceptor groups in such compounds had a direct influence on the charge of this enone group. Such studies have shown that the lipophilic nitrogen in the heterocyclic ring B, together with the hydrophobic functionality at ring A, enhances the biological activity [7, 25].

The data obtained for compounds (**1a–1i**) indicated that the effects on Gram-positive cocci and aerobic bacilli were stronger than those on Gram-negative rods. Compounds **1a–1i** did not exhibit any activity against *Pseudomonas aeruginosa*. Similarly, except **1f**, compounds **1a–1i** were inactive against the yeast *Candida albicans*. The antimicrobial activity increased as the length of the alkyl substituent increased from five to 10. The highest activity is related to the presence of 10 carbon atoms in the bromoalkyl chain of **1f**. The results obtained for these compounds are shown in Table 4.

In conclusion, all synthesized compounds showed differential effects against the tested bacteria. N-alkylated compounds (**1a–1i**) were better antimicrobials than compounds with the unsubstituted N atom of the pyridinyl ring [16]. Most compounds exhibited significant antimicrobial activities that were higher than those observed for some previously studied congeners lacking the thiophenyl ring [26].

Table 3: ^{13}C NMR (δ_C ppm) data of compounds **1a–1i** in $CDCl_3$.

Carbon no.	Compounds								
	1a	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**	**1h**	**1i**
1	180.95	181.27	180.85	180.76	180.80	180.80	180.71	180.94	180.88
2	138.30	138.11	137.77	137.63	137.68	137.70	137.54	137.78	138.16
3	133.51	133.95	133.73	133.76	133.74	133.70	133.74	133.88	133.30
1′	144.40	144.40	144.00	143.96	144.00	144.00	143.91	144.17	144.15
3′	130.90	130.54	129.88	129.63	129.75	129.70	129.57	129.97	130.53
4′	140.43	140.20	139.92	139.81	139.86	139.00	139.77	140.02	140.18
5′	131.90	131.92	131.67	131.60	131.62	131.70	131.53	131.69	131.80
-CH_3	15.45	15.70	15.54	15.47	15.51	15.50	15.42	15.61	15.65
1″	135.90	136.40	135.94	135.79	135.85	135.80	135.73	136.02	136.31
2″	144.85	144.90	144.30	144.12	144.22	144.20	144.15	144.43	144.51
4″	143.19	144.38	143.50	143.65	143.63	143.60	143.63	143.78	142.96
5″	128.15	128.46	128.20	128.19	128.20	128.20	128.17	128.34	127.89
6″	144.50	144.80	144.15	144.08	144.09	144.10	144.01	144.22	144.28
1‴	62.36	62.26	61.84	61.75	61.80	61.90	61.70	62.01	62.09
2‴	32.30	32.01	32.04	31.96	32.02	32.00	31.93	32.10	32.16
$(CH_2)_n$‴	31.32	31.76	31.36	31.46	31.58	31.70	31.60	31.85	31.88
	22.54	28.30	28.60	28.82	29.15	29.30	29.28	29.55	29.61
		22.35	25.90	25.89	28.99	29.20	29.14	29.50	29.49
			22.36	22.34	25.94	29.10	29.02	29.40	29.33
					22.43	29.00	28.88	29.36	29.06
						26.00	25.87	29.28	26.10
						22.50	22.39	29.10	22.67
								26.11	
								22.63	
-CH_3	14.08	14.00	13.90	13.87	13.94	13.90	13.88	14.07	14.11

Table 4: Screening for antimicrobial activity of compounds **1a–1i**.

Comp. No	Microorganisms and minimal inhibitory concentration, µg/mL							
	Ec	**Yp**	**Pa**	**Li**	**Ef**	**Sa**	**Bc**	**Ca**
1a	21.2	85	n.a.	2.7	2.7	2.7	2.7	170
1b	535	535	n.a.	8.4	16.7	8.4	33.5	267
1c	40	80	n.a.	1.3	5	2.5	5	80
1d	5.6	21.5	n.a.	0.7	0.7	0.7	0.7	90
1e	2.4	4.8	n.a.	2.4	2.4	2.4	1.2	77.5
1f	2.0	4.0	n.a.	0.1	0.3	0.6	0.3	64
1g	5.8	23.1	n.a.	1.4	1.4	1.4	0.7	92.5
1h	2.2	4.4	n.a.	0.6	0.6	0.6	0.6	70
1i	150	150	n.a.	18.7	18.7	18.7	18.7	75
Amp.	10	18	18	10	10	35	15	
Flu.								<8
DMSO	n.a.	n.a.	n.a	n.a.	n.a.	n.a.	n.a.	n.a.

Amp., Ampicillin; Bc, *Bacillus cereus*; Ca, *Candida albicans*; Ec, *Escherichia coli*; Ef, *Enterococcus faecalis*; Flu., fluconazole; Li, *Listeria monocytogenes*; n.a., no activity, Pa, *Pseudomonas aeruginosa*, Sa, *Staphylococcus aureus*, Str., streptomycin, Yp, *Yersinia pseudotuberculosis*; <, lower values.

3 Experimental

3.1 General

NMR spectra were recorded on a Varian Mercury NMR (Darmstadt, Germany) at 200 MHz in $CDCl_3$. NMR data assignment was based on ^1H, ^{13}C, APT, ^1H-^1H COSY NMR and ACD NMR software (Toronto, Canada). The mass spectral analyses were carried out on a Micromass Quattro LC-MS/MS spectrometer (Braunschweig, Germany). The elemental analyses were performed on a Costech 4010 CHNS instrument (Valencia, CA, USA). IR spectra were obtained with a Perkin-Elmer 100 FTIR (4000–400 cm^{-1}) spectrophotometer (Waltham, MA, USA). Melting points were determined using a Thermo-var apparatus (Braunschweig, Germany) fitted with a microscope and are uncorrected. UV-Vis spectral analyses were performed on a Shimadzu UV 1601 (Kyoto, Japan) spectrophotometer at 25 °C. Thin-layer chromatography (TLC) was carried out on Merck (Darmstadt, Germany) precoated 60 Kieselgel F_{254} analytical aluminum plates, and silica gel was used in column chromatography.

3.2 Materials

2-Acetyl-4-methylthiophene and 3-pyridinecarboxaldehyde were purchased from Fluka-Merck (Darmstadt, Germany) and used without

further purification. The solvents used were either of analytical grade or bulk solvents distilled before use. Compound **1** was synthesized according to the published method [16].

3.3 General procedure for synthesis of compounds (1a–1i)

2′,3″-Thiazachalcone (**1**) (0.02 mol) and *n*-bromoalkanes (1-bromopentane, 1-bromohexane, 1-bromoheptane, 1-bromooctane, 1-bromononane, 1-bromodecane, 1-bromoundecane, 1-bromododecane, 1-bromotetradecane) (0.05 mol each) in acetonitrile (30 mL) were refluxed. After the reactions were completed, the acetonitrile was removed by rotary evaporation, and the residues were purified by column chromatography (eluent: ethyl acetate/methanol=60/40 v/v) on silica gel (30×2 cm, ~25 g each, Merck, 230–400 mesh) The desired light-brown amorphous solids **(1a–1i)** were obtained from fractions 7–15 (yields given in Table 1).

3.3.1 3-[(1E)-3-(4-methylthiophene-2-yl)-3-oxoprop-1-en-1-yl]-1-alkyl ($C_{5–12, 14}$) pyridinium bromides, (1a–1i): See the physicochemical and spectral data (^{1}H NMR, ^{13}C NMR, IR and MS) of compounds **1a**–**1i** in Tables 1–3.

3.3.2 Microbial strains and antimicrobial activity: The compounds were tested individually against eight microbial species, four Gram-positive and three Gram-negative bacteria, and one yeast-like fungus. All test microorganisms were obtained from the Hıfzısıhha Institute of Refik Saydam (Ankara, Turkey) and were as follows: *Escherichia coli* (ATCC 25922), *Yersinia pseudotuberculosis* (ATCC 911), *P. aeruginosa* (ATCC 10145), *Listeria monocytogenes* (ATCC 43251), *Staphylococcus aureus* (ATCC 25923), *Enterococcus faecalis* (ATCC 29212), *Bacillus cereus* 709 Roma and *Candida tropicalis* (ATCC 60193). All newly synthesized compounds were dissolved in dimethyl sulfoxide (DMSO) to prepare stock solutions of 2600–21,400 μg/mL.

3.3.3 Determination of minimal inhibitory concentration: The antimicrobial effects of the substances were tested quantitatively in the respective media by serial double dilution, and the minimal inhibitory concentrations (MIC) (μg/mL) were determined [27]. The antibacterial and antifungal assays were performed in Mueller-Hinton broth (MH) (Difco, Detroit, MI, USA) at pH 7.3 and buffered Yeast Nitrogen Base (YNB) (Difco) at pH 7.0, respectively. Solutions of chemicals to be tested were prepared in 0.1 mL of sterile MH and YNB broth to give concentrations ranging from 21,400 μg/mL to 2600 μg/mL. All chemicals were prepared by serial (as 1/2) dilution of at least 14 with the respective medium in the wells of an ELISA plate. After preparation of suspensions of the test microorganisms in MH and YNB broth (approximately 10^6 microorganisms/mL), one drop of suspension (0.02 mL) was added to each well. The plates were incubated for 18–24 h at 35 °C. At the end of incubation, the effect of the compounds on the growth of the microorganisms was determined. Ampicillin (10 μg/mL) and fluconazole (5 μg/mL) were used as standard antibacterial and antifungal drugs, respectively. DMSO with dilution of 1:2 was used as solvent control.

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