Afyon Kocatepe Üniversitesi Fen ve Mühendislik Bilimleri Dergisi
Afyon Kocatepe University Journal of Science and Engineering

AKÜ FEMÜBİD **18** (2018) **011201** (451-457) AKU J. Sci.Eng.**18** (2018) **011201** (451-457)
DOİ: 10.5578/fmbd.66922

ARAŞTIRMA MAKALESİ

Synthesis and Antimicrobial Evaluation of Novel 5,8-Dibromo-2-O/S-substituted-1,4-naphthoquinone Derivatives

Kıymet BERKİL AKAR*[1], Hasan KILINÇ[1]
[1]*Gaziosmanpaşa University, Faculty of Engineeringand Natural Science, Department of GeneticandBioengineering, 60240, Tokat*

e-posta: kiymet.berkilakar@gop.edu.tr

Geliş Tarihi:07.11.2017 ; Kabul Tarihi: 25.07.2018

Keywords
1,4-Naphthoquinone, Nucleophilic substitution, Antimicrobial activity

Abstract

Novel bromo- and O/S-substituted-1,4-naphthoquninones (**3a**-**3i**) were synthesized *via* nucleophilic substitution reactions from 2,5,8-tribromo-1,4-naphthoquinone (**1**). Antimicrobial evaluation of the newly synthesized derivatives was performed using agar spot method. Compounds **3a**, **3b,** and **3c** exhibited the greatest activity with MIC value of 61,25 µg/mL against *P. vulgaris*, *B. cereus* and *B.subutilis,* and *B.cereus*, respectively. Results revealed that compound **3c** has notable activity against all tested microorganisms.

Yeni 5,8-Dibromo-2-O/S-sübstitüe-1,4-naftakinon Türevlerinin Sentezi ve Antimikrobiyal Aktivitelerinin Değerlendirilmesi

Anahtar kelimeler
1,4-Naftakinon, Nükleofilik yerdeğiştirme, Antimikrobiyal aktivite

Özet

2,5,8-Tribromo-l,4-naftokinon'dan (**1**) nükleofilik sübstitüsyon reaksiyonları ile yeni bromo- ve O/S-sübstitüe-1,4-naftokininon (**3a-3i**) türevleri sentezlendi. Yeni sentezlenen türevlerin antimikrobiyal olarak incelenmesi agar spot yöntemi kullanılarak gerçekleştirildi. Bileşik **3a**, **3b** ve **3c** sırasıyla *P. vulgaris*, *B. cereus* ve *B.subutilis,* ve *B.cereus'a* karşı 61,25 ug/mL'lik MIC değeri ile en büyük aktivite sergiledi. Sonuçlar, bileşik **3c**'nin test edilen tüm mikroorganizmalara karşı belirgin etkinliğe sahip olduğunu ortaya koymuştur.

1. Introduction

Quinone and naphthoquinone structures are common in various bioactive molecules as the main skeletal structure. These compounds are used extensively as pharmaceuticals, pesticides, paints, and raw materials in industrial production of functional chemicals and particularly play an important role as electron carriers in plant, and animal cells (Ambrogi et al., 1970).

Naphthoquinones are very active compounds, especially the presence of a substitute group at the 2-position in the naphthoquinone provides extremely important biological activities to the naphthoquinone core. Many natural and synthetic compounds of this type are available in literature (Aeken et al., 2011). Many derivatives of 1,4-naphthoquinone compound have been synthesized to diversify biological activity because of the their therapeutic properties. The derivatives of 1,4-naphthoquinone have many biological responses such as cytotoxic, anticancer, antiviral, molluscidal, anti-inflammatory, antiplatelet, antiallergic, antimalarial, antileishmanial, antimicrobial, and antifungal (Lien et al., 1997; Tandon et al., 2009). The presence of heteroatoms in the structure generated interesting biological activity profiles (Tandon et al., 2004). The studies were concentrated on the synthesis of 1,4-

naphthoquinone derivatives including S, O, and N atoms since they are the most abundant atoms in biologically active natural naphthoquinones (Anderson, 2005).

The synthesis of 2,5,8-tribromo-1,4-naphthoquinone (**1**) was described in our previous study starting from 1-bromonaphthalene (**2**) (Çakmak et al., 2012). In this study, the reactions of 2,5,8-tribromo-1,4-naphthoquinone (**1**) with oxygen, and sulphur nucleophiles were carried out, and the obtained substituted naphthoquinones were then characterized *via* spectral methods. The antimicrobial activities of the compounds **3a**-**3i** were evaluated against *C.albicans, C.utulis, B.subtilis, P.vulgaris, E.aerogenes, B.cereus,* and *St.pyogenes.*

2. Materials and Methods

2.1. Chemistry

2.1.1. General experimental procedures

2,5,8-Tribromo-1,4-naphthoquinone (**1**) was synthesized using known procedures (Çakmak et al., 2012). Melting points recorded by an Electrothermal (IA9100) melting point apparatus. Infrared spectra were recorded on a Jasco FT/IR 430 apparatus. Mass spectrometer was an Agilent 6210 TOF LC/MS and GC-MS Perkin Elmer Clarus 500 using electron impact (EI) conditions. ^{1}H and ^{13}C NMR spectra were recorded on 400 (100) MHz Bruker spectrometer, and 600 (150) MHz Agilent spectrometer. Merck 60 (70-230 Mesh) silica was used in column chromatography.

2.1.2. Reactions of 2,5,8-tribromo-1,4-naphthoquinone (1) with nucleophiles

To a stirred solution of 2,5,8-tribromo-1,4-naphthoquinone (**1**) (0.4 to 1.52 mmol) in the appropriate solvent (7 to 90 mL), and at the desired temperature was added appropriate base (K_2CO_3 or TEA) (0.57 to 3.8 mmol), and the nucleophile (0.41 to 1.52 mmol). Upon completion the reaction (TLC), the reaction mixture was diluted with water (50 mL), and extracted with dichloromethane (3×50). The organic layer was washed with water (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum. The resulting residue was purified on SiO_2 column chromatography (%10 ethyl acetate in hexane), and crystallized from the appropriate solvent to give compounds **3a-3i**.

5,8-Dibromo-2-methoxy-1,4-naphthoquinone (3a): Light yellow needle crystals, yield 91%, 480 mg, mp 196-197 °C, R_f= 0.14 (1:9 ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (A part of the AB system, *J*= 8.6 Hz, 1H, H_6), 7.76 (B part of the AB system, *J*= 8.6 Hz, 1H, H_7), 6.19 (s, 1H, H_3), 3.92 (s, 3H, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 181.9, 178.0, 159.4, 141.0, 140.0, 131.6, 131.1, 122.2, 121.3, 109.7, 56.6; IR (ν_{max}, cm^{-1}) 3100, 3060, 2954, 2923, 2852, 1729, 1685, 1654, 1631, 1542, 1454, 1428, 1357, 1313, 1268, 1253, 1209, 1132, 1089, 1045, 877, 831, 727, 511, 410; HPLC-TOF/MS m/z 344.8141$[M+H]^+$, 366.7923 $[M+Na]^+$; Anal. Calcd. For $C_{11}H_6Br_2O_3$: C, 38.19; H, 1.75. Found: C, 38.02; H, 1.75.

5,8-Dibromo-2-ethoxy-1,4-naphthoquinone (3b): Dark red needle crystals, yield 95%, 350 mg, mp 219-220 °C, R_f = 0.19 (1:9 ethyl acetate/hexane). ^{1}H NMR (400 MHz, ppm) δ 7.78 (A part of the AB system, $J_{6,7}$=8.8 Hz, 1H, H_6), 7.75 (B part of the AB system, $J_{6,7}$=8.8 Hz, 1H, H_7), 6.16 (s, 1H, H_3), 4.10 (q, $J_{6,7}$= 7.2 Hz, 2H, CH_2), 1.55 (t, *J*= 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.1, 178.2, 158.8, 140.9, 140.0, 131.6, 131.2, 122.2, 121.2, 110.1, 65.1, 13.9; IR (ν_{max}, cm^{-1}) 3100, 3064, 2977, 1683, 1654, 1631, 1542, 1430, 1407, 1375, 1353, 1315, 1257, 1213, 1133, 1093, 1043, 906, 879, 821, 736, 624, 580, 516, 480, 458, 441, 418, 404; HRMS (HPLC-TOF/MS) m/z 358.9205 $[M+H]^+$, 380.9029 $[M+Na]^+$; Anal. Calcd. For $C_{12}H_8Br_2O_3$: C, 40.04; H, 2.24. Found: C, 40.18; H, 2.26.

5,8-Dibromo-2-phenoxy-1,4-naphthoquinone (3c): Dark yellow plate crystals, yield 99%, 306 mg, mp 122-124 °C, R_f= 0.37 (1:9 ethyl acetate/hexane). ^{1}H NMR (400 MHz, ppm) δ 7.80 (s, 2H, H_6 and H_7), 7.49 (m, 2H, H_b), 7.35 (m, 1H, H_c), 7.15 (m, 2H, H_a), 5.97

(s, 1H, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.1, 177.8, 159.3, 152.5, 141.1, 140.2, 131.6, 131.0, 130.5 (2C), 126.8, 122.4, 121.4, 121.0 (2C), 113.1; IR (ν_{max}, cm^{-1}) 3091, 3064, 2954, 2923, 2854, 1741, 1691, 1648, 1633, 1585, 1542, 1486, 1454, 1432, 1349, 1309, 1261, 1205, 1159, 1122, 1087, 1018, 993, 871, 848, 819, 804, 771, 725; HPLC-TOF/MS m/z 408.8205 $[M+H]^+$, 430.7985 $[M+Na]^+$; Anal. Calcd. For $C_{16}H_8Br_2O_3$: C, 47.10; H, 1.98. Found: C, 47.17; H, 1.99.

5,8-Dibromo-2-(*4*-tolyloxy)-1,4-naphthoquinone (3d): Yellow powder, yield 99%, 212 mg, mp 150-152 °C, R_f= 0.61 (2:8 ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 2H, H_6 and H_7), 7.27 (A part of the AB system, $J_{a,b}$=8 Hz, 2H, H_a), 7.02 (B part of the AB system, $J_{a,b}$=8 Hz, 2H, H_b), 5.97 (s, 1H, H_3), 2.41 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.1, 177.9, 159.5, 150.3, 141.1, 140.2, 136.6, 131.7, 131.1, 130.9 (2C), 130.0, 122.4, 121.4, 120.6 (2C), 115.1, 113.0, 20.9 (CH_3); IR (ν_{max}, cm^{-1}) 3102, 3058, 3029, 2958, 2921, 2856, 1681, 1635, 1542, 1504, 1430, 1351, 1311, 1265, 1216, 1205, 1160, 1122, 1087, 730, 482; HPLC-TOF/MS m/z 420.9378 $[M+H]^+$, 442.9209 $[M+Na]^+$; Anal. Calcd. For $C_{17}H_{10}Br_2O_3$: C, 48.38; H, 3.39. Found: C, 48.55; H, 2.40.

5,8-Dibromo-2-(4-bromophenoxy)-1,4-naphthoquinone (3e): Yellow powder, yield 75%, 180 mg, mp 167-169 °C, R_f= 0.35 (1:9 ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 2H, H_6 and H_7), 7.61 (A part of the AB system, $J_{a,b}$=8.8 Hz, 2H, H_b), 7.05 (B part of the AB system, $J_{a,b}$=8.8 Hz, 2H, H_a), 5.99 (s, 1H, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.8, 177.5, 158.7, 151.6, 141.2, 140.3, 133.6 (2C), 131.6, 131.0, 122.7 (2C), 122.5, 121.5, 119.9, 113.5; IR (ν_{max}, cm^{-1}) 3063, 2956, 2918, 2850, 1733, 1684, 1635, 1578, 1541, 1482, 1456, 1431, 1351, 1310, 1213, 1123, 1086, 1007, 862, 827; HPLC-TOF/MS m/z 425.2471 [M-Br+H_2O+H]; Anal. Calcd. For $C_{16}H_7Br_3O_3$: C, 39.47; H, 1.45. Found: C, 39.61; H,1.47.

5,8-Dibromo-2-(4-chlorophenoxy)-1,4-naphthoquinone (3f): Dark yellow powder, yield 99%, 435 mg, mp 176-177 °C, R_f =0.38 (1:9 ethyl acetate/hexane). ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.79 (s, 2H, H_6 and H_7), 7.45 (A part of the AB system, $J_{a,b}$=8.8 Hz, 2H, H_b), 7.10 (B part of the AB system, $J_{a,b}$=8.8 Hz, 2H, H_a), 5.97 (s, 1H, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.85, 177.50, 158.82, 151.02, 141.17, 140.30, 132.26, 130.61, 129.44, 122.45, 122.32, 121.50, 116.70, 113.39; IR (ν_{max}, cm^{-1}) 3090, 3077, 3041, 1683, 1649, 1637, 1543, 1485, 1428, 1353, 1304, 1262, 1213, 1159, 1123, 1085, 1013, 997, 868, 860, 833, 740, 698, 575, 536, 493, 418; HPLC-TOF/MS m/z 444.8124 $[M+H]^+$; Anal. Calcd. For $C_{16}H_7Br_2ClO_3$: C, 43.43; H, 1.59. Found: C, 43.56; H, 1.59.

5,8-Dibromo-2-(4-methoxyphenoxy)-1,4-naphthoquinone (3g): Dark yellow powder, yield 90%, 199 mg, mp 150-151 °C, R_f= 0.29 (1:9 ethyl acetate/hexane). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (s, 2H, H_6 and H_7), 7.04 (A part of the AB system, $J_{a,b}$=7.8 Hz, 2H, H_b), 6.95 (B part of the AB system, $J_{a,b}$=7.8 Hz, 2H, H_a), 5.94 (s, 1H, H_3), 3.83 (s, 3H, OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 182.0, 177.8, 159.7, 158.0, 145.8, 141.0, 140.1, 131.7, 131.0, 122.3, 121.8 (2C), 121.3, 115.4 (2C), 112.8, 55.7; IR (ν_{max}, cm^{-1}) 3104, 3053, 2922, 2841, 1683, 1655, 1625, 1541, 1505, 1469, 1349, 1306, 1255, 1200, 1117, 1087, 1022, 991, 890, 827, 731, 503, 427; HPLC-TOF/MS m/z 436.9348 $[M+H]^+$, 458.9167 $[M+Na]^+$; Anal. Calcd. For $C_{17}H_{10}Br_2O_4$: C, 46.61; H, 2.30. Found: C, 46.41; H, 2.28.

5,8-Dibromo-2-(phenylthio)-1,4-naphthoquinone (3h): Orange needle crystals, yield 98%, 215 mg, mp 197-198 °C, R_f= 0.41 (1:9 ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 2H, H_6 and H_7), 7.54-7.50 (m, 5H, PhH), 7.51-6.09 (s, 1H, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 179.4, 156.2, 140.9, 140.0, 135.7 (2C), 131.9, 131.6, 130.7, 130.4 (2C), 128.2, 127.2, 122.3, 121.7; IR (ν_{max}, cm^{-1}) 3098, 3054, 2922, 2851, 1741, 1669, 1643, 1585, 1540, 1471, 1436, 1369, 1303, 1258, 1212, 1068, 872, 827, 783, 748, 706, 687, 641, 536, 517, 427; MS (GCMS) m/z 421.96/424.05/426.00 $[M^+]$, 344.94/346.89/348.77 $[M^+ - C_6H_5]$, 314.93, 300.94, 259.99/261.94/263.96, 236.14, 208.17, 180.20, 153.00, 109.23, 85.14, 74.13, 51.01, 44.02; Anal.

Calcd. For $C_{16}H_8Br_2O_2S$: C, 45.31; H, 1.90; S, 7.56. Found: C, 45.32; H, 1.88; S, 7.59.

5,8-Dibromo-2,3-bis(butylthio)-1,4-naphthoquinone (3i): Dark red needle crystals, yield 99%, 202 mg, mp 92-93 °C, R_f= 0.8 (1:9 ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 2H, H_6 and H_7), 3.16 (t, $J_{6,7}$=7.2 Hz 4H, H_a), 1.57 (m, 4H, H_b), 1.45 (m, 4H, H_c), 0.92 (t, $J_{6,7}$=7.2 Hz, 6H, H_d); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3 (2C), 146.9 (2C), 138.9 (2C), 134.4 (2C), 120.2 (2C), 33.2 (2C), 32.9 (2C), 21.9 (2C), 13.6 (2C); IR (ν_{max}, cm^{-1}) 3091, 3064, 2923, 2854, 1947, 1886, 1799, 1741, 1691, 1648, 1633, 1585, 1542, 1486, 1454, 1432, 1349, 1309, 1261, 1205, 1159, 1122, 1087, 1018, 993, 871, 848, 835, 819, 804, 788, 771, 725, 692, 588, 553, 489, 443; HPLC-TOF/MS m/z 490.9602 $[M+H]^+$; Anal. Calcd. For $C_{18}H_{20}Br_2O_2S_2$: C, 43.92; H, 4.09; S, 13.03. Found: C, 44.19; H, 4.07; S, 13.86.

2.2. In vitro antimicrobial studies of 2-substituted-1,4-naphthoquinones (3a-3i)

The synthesized naphthoquinone derivatives were evaluated for in vitro antimicrobial activity against seven different bacterial strains using spot on lawn method.

Test Microorganisms and Culture Conditions

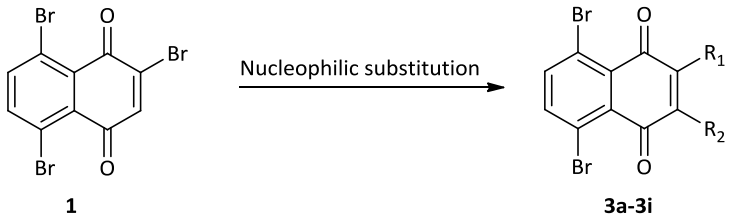
The antimicrobial activity of the compounds was evaluated against three gram (+) bacteria; *Bacillus subtilis* (ATCC6633), *Bacillus cereus* (DSM4312), and *Streptococcus pyogenes* (ATCC176), two gram (-) bacteria: *Proteus vulgaris* (Kuen1329), and *Enterobacter aerogenes;* and two yeasts: *Candida albicans* (ATCC1223), and *Caraipa utilis* (Kuen 1030). The bacterial strains were subcultured aerobically using Brain Heart Infusion (BHI) or Potato Dextrose Agar (PDA) at 36 ± 1°C for 24 h. Test microorganisms were grown overnight and incubated 18 h at 36 ± 1°C. Then bacterial suspension was diluted to about 10^8 cfu/mL with sterile physiological solution (turbidity equivalent to 0.5 McFarland standard) (Andrews, 2001).

Minimum Inhibitory Concentrations (MIC)

Agar spot method (Wiegand et al., 2008) was used to determine the MIC of the synthesis naphthoquinones with minor modifications. Bacteria cultures (100 µL, containing 10^8 cfu/mL of bacteria or 10^6 cfu/mL of yeast) were spread onto Mueller Hinton Agar (MHA) plates. The test concentrations of the naphthoquinone derivatives were made from 15.31–1000 µg/mL in appropriate solutions (water or dimethyl sulfoxide (DMSO)). 10 µL of chemical suspensions were spotted on air-dried MHA plates, and incubated at 36 ± 1°C for 24 h. The MIC values were defined as the lowest concentration of compounds at which there was no visible growth of microorganism of the plate. Each test was repeated three times.

3. Results and Discussion

The aim of this work was to synthesize a new series of 5,8-dibromo-2-O/S-substituted-1,4-naphthoquinones, and to evaluate their antimicrobial properties. As shown in Figure 1, a series of 1,4-naphthoquinones (**3a-3i**) were synthesized in one-step reaction between 2,5,8-tribromonaftalin-1,4-dion (**1**), and one of the following nucleophiles according to known methods with minor modification (Tandon et al., 2009; Bolognesi et al., 2008; Sayıl and Ibis, 2010): methanol, ethanol, phenol, *p*-cresol, *p*-bromophenol, *p*-chlorophenol, *p*-methoxyphenol, thiophenol, and *n*-butanthiol (Figure 1 and Table 1). Structures of these compounds were confirmed by several spectroscopic methods (^{1}H NMR, ^{13}C NMR, mass spectra, IR, and elemental analysis).

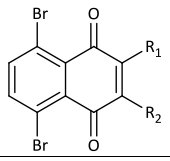


1 **3a-3i**

3a R_1= OCH_3, R_2=H
3b R_1= OCH_2CH_3, R_2=H
3c R_1= OC_6H_5, R_2=H
3d R_1= $OC_6H_4CH_3$, R_2=H
3e R_1= OC_6H_4Br, R_2=H
3f R_1= OC_6H_4Cl, R_2=H
3g R_1= $OC_6H_4OCH_3$, R_2=H
3h R_1= SC_6H_5, R_2=H
3i R_1= $S(CH_2)_3CH_3$, R_2=$S(CH_2)_3CH_3$

Figure 1. Synthesis of 2-O/S-substituted-1,4-naphthoquinone derivatives **3a-3i**

Table 1. Nucleophilic substitution reactions of 2,5,8-tribromo-1,4-naphthoquinone (**1**)

						Structure			
									
Entry	**Comp.**	**Nucleophiles**	**Solvent**	**Base**	**Temp**	**R_1**	**R_2**	**Time**	**Isolated yields (%)**
1	**3a**	Methanol	CH_3OH	K_2CO_3	rt	OCH_3	H	1 d	91
2	**3b**	Ethanol	CH_3CH_2OH	K_2CO_3	rt	OCH_2CH_3	H	3 d	95
3	**3c**	Phenol	CH_2Cl_2	K_2CO_3	reflux	OC_6H_5	H	3 d	99
4	**3d**	*p*-Cresol	CH_2Cl_2	K_2CO_3	reflux	$OC_6H_4CH_3$	H	3 h	99
5	**3e**	*p*-Bromophenol	CH_2Cl_2	K_2CO_3	reflux	OC_6H_4Br	H	6 h	75
6	**3f**	*p*-Chlorophenol	CH_2Cl_2	K_2CO_3	rt	OC_6H_4Cl	H	2 h	99
7	**3g**	*p*-Methoxyphenol	CH_2Cl_2	K_2CO_3	rt	$OC_6H_4OCH_3$	H	1 d	90
8	**3h**	Thiophenol	CH_2Cl_2	TEA	reflux	SC_6H_5	H	1 d	98
9	**3i**	*n*-Butanthiol	CH_2Cl_2	TEA	rt	$S(CH_2)_3CH_3$	$S(CH_2)_3CH_3$	1 d	99

2.2. Antimicrobial activity

Agar plate dilution test results shown in Table 2 reveal that all of the compounds (**3a**-**3i**) possessed activity against all of the tested organisms with MIC values between 61.25, and 1000 μg mL^{-1}. In addition, **3a** for *P. vulgaris*, **3b** for *B. Cereus,* and **3c** for *B. Cereus and B. subtilis* were the most potent compounds with MIC 61.25 μg mL^{-1} (Table 2). The results also reveal that compound **3c** was the most active compounds among the synthesized compounds and highly active against gram positive bacteria than gram negative bacteria, and fungi. Even the datas obtained from minimum inhibition concentration of the compounds showed the lowest activity against *C. albicans, E. aerognes,* and *St. pyogens*.

We have found that the displacement of the oxygen atom in the phenol group with sulphur atom results in loss of activity. In addition, when phenol derivatives were examined among themselves, the presence of any group at the para position also reduced activity.

Table 2. Structures and in vitro antimicrobial activities for 2-substituted-1,4-naphthoquinones **3a-3i**

	MIC (μg mL^{-1})						
Comp.	***C. albicans***	***C. utilis***	***P. vulgaris***	***E.aerogenes***	***B. subtilis***	***B.cereus***	***St. pyogenes***
3a	250	125	61.25	1000+	125	1000+	1000+
3b	500	1000+	1000+	1000+	1000+	61.25	500
3c	500	125	500	125	61.25	61.25	125
3d	1000+	125	250	1000+	500	125	1000+
3e	1000+	500	1000+	1000+	250	1000+	1000+
3f	1000+	250	1000+	125	1000	1000+	1000+
3g	1000+	1000+	500	250	500	250	500
3h	1000+	125	500	1000+	250	125	1000+
3i	1000+	125	125	1000+	1000+	125	1000+
DMSO	0	0	0	0	0	0	0

4. Conclusion

In conclusion, with an aim of developing potent antimicrobial agent, a series of new 5,8-dibromo-2-O/S-substituted-1,4-naphthoquinones **3a**-**3i** were synthesized. Antimicrobial activities of the synthesized compounds were investigated against *C.albicans, C.utulis, B.subtilis, P.vulgaris, E.aerogenes, B.cereus,* and *St.pyogenes*. Results revealed that compound **3c** has notable activity against the tested microorganisms. The results also reveal that all of the compounds (**3a**-**3i**) possessed activity against all of the tested organisms with MIC values between 61.25 and 1000 μg mL^{-1}.

Acknowledgment

The authors thank the Department of Genetic and Bioengineering, Gaziosmanpaşa University, for providing the necessary facilities and Barış Eran and Eda Mercan for technical assistance.

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