Turk J Chem
33 (2009) , 375 – 384.

doi:10.3906/kim-0801-23

Synthesis and Antimicrobial Activity of Dinaphtho[2,1-*b*]furan-2-yl-methanone and Their Oxime Derivatives

Cumhur KIRILMIŞ[1,*], Murat KOCA[1], Süleyman SERVİ[2] and Seher GÜR[3]
[1]*Adıyaman University, Faculty Science-Art, Department of Chemistry, 02040, Adıyaman-TURKEY*
e-mailaddress: ckirilmis@gmail.com
[2]*Fırat University, Faculty Science-Art, Department of Chemistry, 23169, Elazığ-TURKEY*
[3]*Fırat University, Faculty Science-Art, Department of Biology, 23169, Elazığ-TURKEY*

Received 24.01.2008

The reaction of 2-hydroxy-1-naphthaldehyde with 1,3-dichloroacetone and potassium carbonate was used to prepare dinaphtho[2,1-*b*]furan-2-yl-methanone (**1**) as starting reagents. In order to obtain dinaphtho[2,1-*b*]furan-2-yl-methanole (**2**), compound **1** was reduced with $NaBH_4$. *N*-oxime derivative of this compound (**3**) was synthesized by the reaction of the compound **1** with hydroxylamine. Alkyl and acyl substituted *N*-oxime ethers (**4-11**) were obtained by the reaction compound **3** with various halogen containing compounds. Compound **12** was obtained by reflux of the compound **11** with hydrazine monohydrate in ethanol. Compound **13** was synthesized by the reaction of the compound **11** with NaOH. The synthesized compounds were tested for antimicrobial activity against *Salmonella typhimurium*, *Escherichia coli*, *Bacillus subtilis*, *Candida globrata,* and *Candida tropicalis*. All of the selected compounds showed weak antimicrobial activity against test microorganisms (128- 512 μg/mL).

Key Words: Antimicrobial activity; Naphtho[2,1-*b*]furan; Benzofuran; Ketoxime.

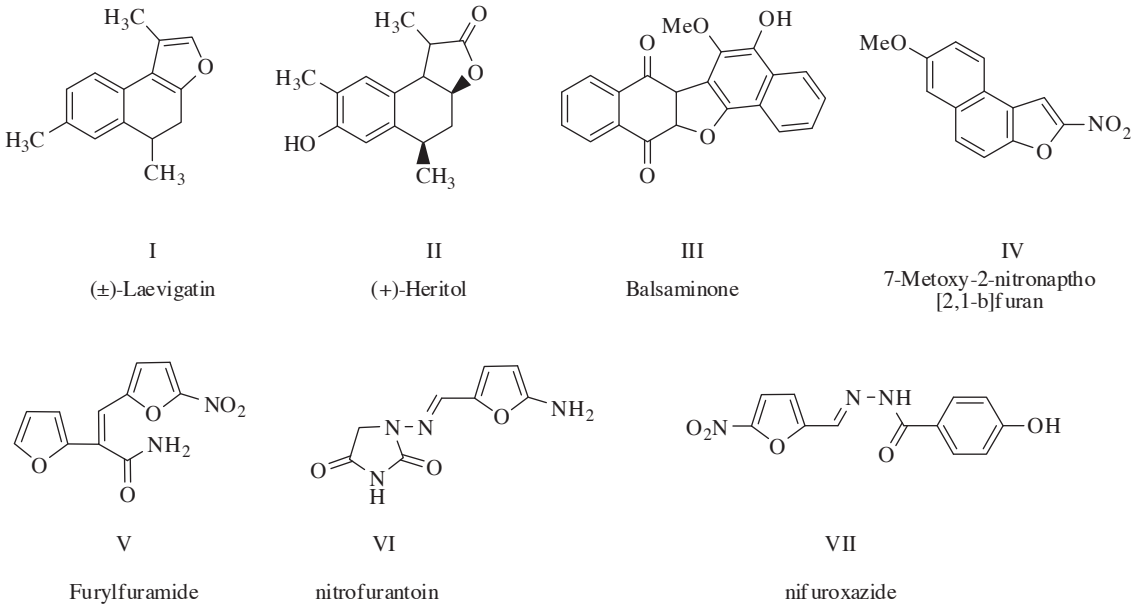
Introduction

Oxygen- and nitrogen-containing polycyclic compounds have attracted considerable attention as a result of their biological activities and their presence in a variety of natural and unnatural products. For example, naphthofuran analogues, which have been isolated from various natural sources such as *Fusarium oxysporum*[1] and *Gossypium barbadense,*[2] are known to exhibit antitumor, antifertility, mutagenic, growth inhibitory, and oestrogenic activities.[3,4]

*Corresponding author

Benzofuran derivatives are nowadays an important class of organic compounds that occur in a great number of natural products,[5] and used in cosmetics[6] and as synthetic pharmaceuticals.[7,8] Moreover, benzo[b]furans build blocks for fluorescent sensors,[9] and are used as optical brighteners. Many of the natural benzo[b]furans have physiological, pharmacological, and toxic properties, and therefore there is continuing interest in their chemical synthesis.[10]

Benzofuran and naphthofuran nuclei are key structural motifs found in a large number of biologically important natural products, mainly belonging to the sesquiterpene and arylquinone classes.[11] Many of the natural naphthofurans, such as (±)-laevigatin,[12,13] (+)-heritol,[14–16] and balsaminone A,[17] possess interesting pharmacological and cytotoxic properties (**Scheme 1**). Several synthetic compounds containing this ring skeleton are associated with diverse biological activities, such as antifungal, antibacterial, [18] antiviral, [19] antitumor, [20] and anthelmintics.[21,22]



Scheme 1. Benzofuran containing some biological molecules.

The nitro derivatives of naphtho[2,1-*b*]furans have been extensively studied for their mutagenic activities, for example 7-methoxy-2-nitronaphtho[2,1-*b*]furan (R7000) is one of the strongest mutagens described for mammalian. 5-Nitrofuran derivatives possess broad-spectrum antimicrobial properties and are used as veterinary and human drugs.[23] Unfortunately, most of them are mutagenic in bacteria suggesting that their use could constitute a risk for human health. The genotoxic properties of a 5-nitrofuran derivative, 7-methoxy-2-nitronaphtho[2,1-*b*]furan (**Scheme 1**) have been extensively studied in bacteria. This compound ranks among the most potent mutagens known in the *Salmonella* microsome assay.[24–26] It is also a very efficient inducer of the SOS chromotest, a bacterial test for detecting DNA-damaging agents, functions in *E. coli.*[27] 5-Nitrofurans have been widely used as antibacterial and ant parasitic agents, as well as food and feed additives. The fact that most of them are mutagens and some are carcinogens has reduced their usage. For example, furylfuramide (AF2) which was found to be mutagenic in bacterial tests and carcinogenic in animals was banned as a food additive in Japan in the 1970s (Scheme 1). However, some compounds of the series, such as nitrofurantoin and

nifuroxazide, are still used as antibacterial agents in human.[28] (Scheme 1).

The wide pharmacological potential of these bioactive molecules has attracted many organic and medicinal chemists to develop efficient routes for their syntheses.

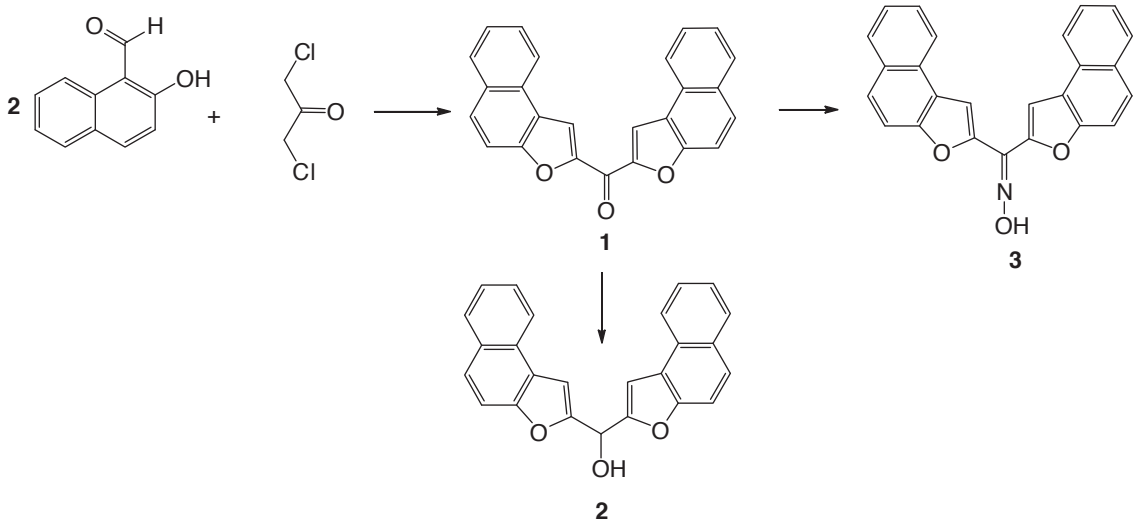
In previous studies, our group reported the synthesis and antimicrobial activity of some bis-(benzofuran-2-yl) methanone, cyclobutane and mesitilen substituted benzofuran derivatives.[29–33] Bis-(Benzofuran-2-yl)methanone exhibited activity towards all the microorganisms studied, but its derivatives generally showed moderate activity at the higher concentrations towards many of the bacteria and the fungus tested but cyclobutane substituted benzofuran derivatives exhibited very strong antimicrobial effect against *C. albicans* and (benzofuran-2-yl)(3-phenyl-3-methylcyclobutyl)-*O*-[2-hydroxy-3-(methylpiperazino)]propyl ketoxime was found to be the most active derivative against *Staphylococcus aureus.*[31] In another study, we also found (E)-1-(1-benzofuran-2-yl)-2-mesitylethanone-*O*-benzoyloxime the most active derivative against *S. aureus* and *E. coli.*[33]

Encouraged by the good results obtained from that work, we planned to prepare di(naphtofuran-2-yl) methanone and its derivatives (**1-13**) and perform antimicrobial activity tests. In this study, as the starting material, dinaphtho[2,1-*b*]furan-2-yl-methanone (**1**) was synthesized according to cited references.[30–33] This compound was obtained by reaction of 2-hydroxy-1-naphthaldehyde with 1,3-dichloroacetone in presence of potassium carbonate. Dinaphtho[2,1-*b*]furan-2-yl-methanone oxime (**3**) was obtained from the reaction of the compound (**1**) with hydroxylamine hydrochloride. By using the compound **3** its derivatives were synthesized in good yields. All of these compounds were synthesized for the first time and characterized on the present study. The synthetic route is depicted in Scheme 2.

Experimental

All reagents were obtained from commercial sources. Solvents were dried and purified with known conventional methods. Melting points (uncorrected) were determined with a Gallenkamp apparatus. Elemental analyses were determined on a LECO CHNS-90 auto elemental analysis apparatus. The IR spectra were measured with Mattson 1000 FT-IR spectrophotometer (potassium bromide disks). The ^{1}H-NMR spectra were recorded on a Varian-Gemini 200 MHz spectrometer and reported at ppm (δ) relative to tetramethylsilane (TMS) as the internal standard and ^{13}C-NMR (50.34 MHz) is referenced to chloroform-d ($CDCl_3$). The purity of all compounds was checked with Thin Layer Chromatography (TLC) using on recoated 0.2 mm Merck Kieselgel 60 F_{254} plates.

Synthesis of Dinaphtho[2,1-b]furan-2-yl-methanone (1). 2-Hydroxy-1-naphth aldehyde (14.97 g, 87 mmol), K_2CO_3 (18.03 g, 131 mmol), and dry acetone (350 mL) were stirred at room temperature for 3 h. To the mixture, 1,3-dichloroacetone (5.53 g, 44 mmol dissolved in 20 mL dry acetone) was added drop wise and refluxed for 4 h. The reaction mixture was cooled, and then water added. The resulting solid was filtrated off and dried, and the compound (1) was recrystallized from ethanol. IR (KBr) (υ, cm^{-1}), 3057-3124 (aromatic C-H stretching), 1621 (C=O stretching); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ (ppm), 7.53-8.48 (m, 14H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ: 114.74 (2C), 103.29 (2C), 125.16 (2C), 125.50 (2C), 127.67 (2C), 129.54 (2C), 130.22 (2C), 131.11 (2C), 132.30 (2C), 143.88 (2C), 153.47 (2C), 156.44 (2C), 203.36. Yield 75%. M.p.: 214-215 °C. Anal. Calcd. For $C_{25}H_{14}O_3$: C 82.86, H 3.89. Found: C 82.91, H 3.90.



Scheme 2. Synthesis of Dinaphtho[2,1-*b*]furan-2-yl-methanone **(1)** and its derivatives.

Synthesis of Dinaphtho[2,1-b]furan-2-yl-methanole (2). Compound **1** (1.0 g, 2.75 mmol) and $NaBH_4$ (0.10 g, 2.77 mmol) in 1.4-dioxane (25 mL) were stirred at room temperature for 3 h and then refluxed for 1 h. The mixture was poured in cold water. The resulting solid was filtrated and dried, and the compound **3** was recrystallized from ethanol. IR (KBr) (υ, cm^{-1}), 3426 (O-H stretching), 992 (C-O stretching); ^{1}H-NMR (DMSO-d_6, 200 MHz) δ (ppm), 6.37 (s, 1H, CH-OH); 6.90 (s, 1H, OH); 7.46-8.58 (m, 14H, aromatic protons); ^{13}C NMR (DMSO-d_6) δ: 65.53, 105.29 (2C), 114.17 (2C), 124.79 (2C), 125.39 (2C), 126.47 (2C), 129.96 (2C), 128.29 (2C), 129.07 (2C), 130.39 (2C), 1331.70 (2C), 153.52 (2C), 158.44 (2C). Yield 45%. M.p.: 195-196 °C. Anal. Calcd. For $C_{25}H_{16}O_3$: C 82.40, H 4.43. Found: C 82.36, H 4.45.

Synthesis of Dinaphtho[2,1-b]furan-2-yl-methanone oxime (3). A mixture of compound **1** (8.0 g, 22 mmol), $NH_2OH.HCl$ (1.59 g, 23 mmol), and pyridine (25 mL) were refluxed for 1 h. The mixture was cooled, and then poured in cold water. The solid was filtrated off and dried, and the compound **3** was recrystallized from acetone. IR (KBr) (υ, cm^{-1}), 3390 (O-H stretching), 1040 (N-O stretching); ^{1}H-NMR (DMSO-d_6, 200 MHz) δ (ppm), 7.56-8.57 (m, 14H, aromatic protons), 9.83 (s, 1H, N-OH); ^{13}C NMR (DMSO-d_6) δ: 114.11 (2C), 114.47 (2C), 125.60 (2C), 128.33 (2C), 128.54 (2C), 128.89 (2C), 129.10 (2C), 129.17 (2C), 129.32 (2C), 130.52 (2C), 130.60 (2C), 131.84 (2C), 153.70. Yield 97%. M.p.: 258-260 °C. Anal. Calcd. For $C_{25}H_{15}NO_3$: C 79.56, H 4.01, N 3.71. Found: C 79.55, H 3.98, N 3.67.

General Method for the synthesis of the compounds 4-7 A mixture of compound **3** (1.0 g, 2.64 mmol) and acetone (50 mL) was cooled to -5 °C and then corresponding acyl chlorides (2.7 mmol), such as acetyl chloride (for 5), chloroacetyl chloride(for 6), phenylacetylchloride (for 7), and benzoyl chloride (for 8), were added dropwise. The reaction was maintained at room temperature for 2 h, then poured into water and neutralized with diluted NH_3. The formed precipitate was filtrated and washed with water. Compounds **4-7** were recrystallized from ethanol.

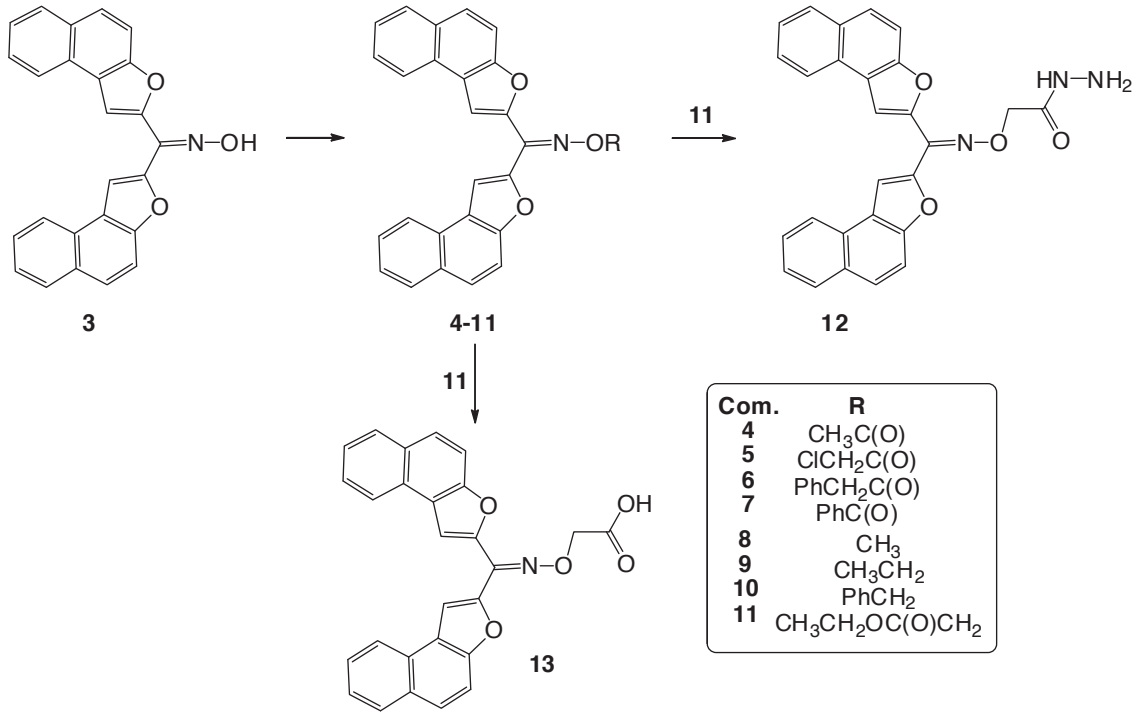
Dinaphtho[2,1-b]furan-2-yl-methanone O-acetyl-oxime (4). IR (KBr) (υ, cm^{-1}), 1779 (C=O stretching), 1001 (N-O stretching); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.85 (s, 3H, C(O)CH_3), 7.50-8.27 (m, 14H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ: 21.88, 114.78 (2C), 114.38 (2C), 117.19 (2C), 125.39 (4C), 127.51 (2C), 128.96 (2C), 130.06 (2C), 130.90 (2C), 130.97 (2C), 131.09 (2C), 132.59 (2C), 154.80, 170.10. Yield

79%. M.p.: 180-181 °C. Anal. Calcd. For $C_{27}H_{17}NO_4$: C 77.32, H 4.09, N 3.34. Found: C 77.33, H 4.00, N 3.40.

Dinaphtho[2,1-b]furan-2-yl-methanone *O*-chloroacethyl-oxime (5). IR (KBr) (υ, cm^{-1}), 1762 (C=O stretching), 1033 (N-O stretching); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ (ppm), 4.49 (s, 2H, Cl-CH_2), 7.52-8.43 (m, 14H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ: 42.15, 114.33 (2C), 114.74 (2C), 118.56 (2C), 125.38 (2C), 127.24 (2C), 127.62 (2C), 129.07 (2C), 129.49 (2C), 130.41 (2C), 131.01 (2C), 131.09 (2C), 131.31 (2C), 154.99, 166.73. Yield 82%. M.p.: 214-216 °C. Anal. Calcd. For $C_{27}H_{16}ClNO_4$: C 71.45, H 3.55, N 3.09. Found: C 71.46, H 3.52, N 3.15.

Dinaphtho[2,1-b]furan-2-yl-methanone *O*-phenylacethyl-oxime (6). IR (KBr) (υ, cm^{-1}), 1762 (C=O stretching), 1030 (N-O stretching); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ (ppm), 4.02 (s, 2H, C(O)CH_2), 7.30-8.40 (m, 19H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ: 42.1, 114.35 (2C), 117.35 (2C), 125.14 (2C), 125.62(2C), 127.13 (2C), 127.48 (2C), 127.96 (2C), 128.96 (2C), 129.73 (2C), 130.87 (2C), 130.87 (4C), 130.94 (2C), 131.04 (2C), 131.49 (2C), 155.66, 170.31. Yield 80%. M.p.: 185-186 °C. Anal. Calcd. For $C_{33}H_{21}NO_4$: C 79.99, H 4.27, N 2.83. Found: C 80.01, H 4.25, N 2.80.

Dinaphtho[2,1-b]furan-2-yl-methanone *O*-benzoyl-oxime (7). IR (KBr) (υ, cm^{-1}), 1745 (C=O stretching), 1013 (N-O stretching); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ (ppm), 7.50-8.26 (m, 19H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ: 114.33 (2C), 125.31 (2C), 125.42 (2C), 127.17 (2C), 127.53 (2C), 129.00 (2C), 129.40 (2C), 130.18 (2C), 130.79 (4C), 130.95 (2C), 131.13 (2C), 132.02 (4C), 135.66 (2C), 155.90. Yield 77%. M.p.: 206-207 °C. Anal. Calcd. For $C_{32}H_{19}NO_4$: C 79.82, H 3.98, N 2.91. Found: C 79.83, H 3.96, N 2.90.



Scheme 3. Synthesis of Dinaphtho[2,1-*b*]furan-2-yl-methanone oxime **(4)** and its derivatives.

General method for the synthesis of the compounds 8-11 A corresponding alkyl halogenide (3.5 mmol) was added to a mixture of compound **4** (3.4 mmol), anhydrous K_2CO_3 (0,48 g, 3.50 mmol), and dry

acetone (150 mL) at room temperature, and refluxed for 8 h. Then, the precipitated compound was filtered and washed with acetone. The obtained crude product was recrystallized from ethanol to yield the desired compound.

Dinaphtho[2,1-b]furan-2-yl-methanone *O*-methyl-oxime (8). IR (KBr) (υ, cm^{-1}), 1016 (N-O stretching); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ (ppm), 4.36 (s, 3H, OCH_3), 7.48-8.29 (m, 14H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ: 65,87, 114.39 (2C), 114.66 (2C), 125.45 (2C), 125.54 (2C), 126.83 (2C), 127.13 (2C), 128.62 (2C), 128.83 (2C), 128.93 (2C), 129.85 (2C), 130.86 (2C), 130.93 (2C), 154.81. Yield 70%. M.p.: 180-182 °C. Anal. Calcd. For $C_{26}H_{17}NO_3$: C 79.78, H 4.38, N 3.58. Found: C 79.75, H 4.39, N 3.63.

Dinaphtho[2,1-b]furan-2-yl-methanone *O*-ethyl-oxime (9). IR (KBr) (υ, cm^{-1}), 1014 (N-O stretching); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.57 (t, 3H, CH_3, J=0.6 and 6.4 Hz), 4.63 (q, 2H, OCH_2, J=0.6 and 6.4 Hz), 7.52-8.32 (m, 14H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ: 16.85, 74.02, 110.95 (2C), 114.43 (2C), 114.70 (2C), 125.47 (2C), 125.52 (2C), 126.80 (2C), 127.10 (2C), 128.57 (2C), 128.89 (2C), 129.74 (2C), 130.86 (2C), 130.94 (2C), 153.69. Yield 81%. M.p.: 173-175 °C. Anal. Calcd. For $C_{27}H_{19}NO_3$: C 79.98, H 4.72, N 3.45. Found: C 80.02, H 4.75, N 3.45.

Dinaphtho[2,1-b]furan-2-yl-methanone *O*-benzyl-oxime (10). IR (KBr) (υ, cm^{-1}), 1009 (N-O stretching); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ (ppm), 5.62 (s, 2H, OCH_2), 7.39-8.31 (m, 19H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ: 80.39, 111.35 (2C), 114.41 (2C), 114.69 (2C), 116.24 (2C), 125.50 (4C), 126.84 (2C), 127.13 (2C), 128.82 (2C), 128.93 (2C), 129.90 (2C), 130.24 (4C), 130.93 (2C), 132.46, 146.05, 154.82. Yield 68%. M.p.: 173-174 °C. Anal. Calcd. For $C_{32}H_{21}NO_3$: C 82.21, H 4.53, N 3.00. Found: C 82.18, H 4.52, N 3.00.

(Dinaphtho[2,1-b]furan-2-yl-methyleneaminooxy)acetic acid ethyl ester (11). IR (KBr) (υ, cm^{-1}), 1733 (C=O stretching), 1029 (N-O stretching); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.37 (t, 3H, CH_3, J= 7.2 Hz), 4.36 (q, 2H, CH_2-CH_3, J= 7.2 Hz), 5.11 (s, 2H, $NOCH_2$), 7.52-8.49 (m, 14H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ: 16.28, 63.27, 74.40, 114.39 (2C), 114.62 (2C), 116.96 (2C), 125.46 (2C), 125.58 (2C), 126.89 (2C), 127.16 (2C), 128.97 (2C), 129.04 (2C), 130.00 (2C), 130.04, 130.91 (2C), 154.91, 171.17. Yield 85%. M.p.: 159-161 °C. Anal. Calcd. For $C_{29}H_{21}NO_5$: C 75.15, H 4.57, N 3.02. Found: C 75.15, H 4.55, N 3.00.

Synthesis of 2-{[(Dinaphtho[2,1-b]furan-2-yl-methylene)amino]oxy}aceto hydrazide (12). A mixture of compound **11** (0.85 g, 1.84 mmol), hydrazine monohydrate (0.97 mL, 2 mmol, d:1.06 g/cm^3, 99%) and absolute ethanol was refluxed for 3 h. The mixture was cooled, and poured into water. The solid yielded was filtrated off and dried, and compound **12** recrystallized from ethanol. IR (KBr) (υ, cm^{-1}), 3459 (NH_2 stretching), 3399 (NH stretching), 1666 (C=O stretching), 1021 (N-O stretching); ^{1}H-NMR (DMSO-d_6, 200 MHz) δ (ppm), 4.46 (s, 2H, NH_2), 4.92 (s, 2H, O-CH_2), 6.39-6.43 (broad, 1H, NH), 7.56-8.6 (m, 14H, aromatic protons); ^{13}C NMR (DMSO-d_6) δ: 75.24, 114.16 (2C), 114.59 (2C), 124.72 (2C), 124.98 (2C), 125.70 (2C), 126.97 (2C), 128.72 (2C), 129.04 (2C), 129.11 (2C), 130.75 (2C), 131.97 (2C), 144.98 (2C), 153.97, 168.94. Yield 73%. M.p.: 203-205 °C. Anal. Calcd. For $C_{27}H_{19}N_3O_4$: C 72.15, H 4.26, N 9.35. Found: C 72.16, H 4.25, N 9.30.

Synthesis of 2-{[(Dinaphtho[2,1-b]furan-2-yl-methylene)amino]oxy}acetic acid (13). Compound **11** (0.85 g, 1.84 mmol) and powder NaOH (0.11 g, 2.76 mmol) in ethanol were refluxed for 1 h. The mixture poured into water and was neutralized with dilute HCl. The obtained solid was filtrated and dried,

and compound **13** was recrystallized from ethanol. IR (KBr) (υ, cm^{-1}), 3450 (OH stretching), 1738 (C=O stretching), 1037 (N-O stretching); ^{1}H-NMR (DMSO-d_6, 200 MHz) δ (ppm), 4.60 (brs, 1H, OH), 4.97 (s, 2H, $NOCH_2$), 7.54-8.71 (m, 14H, aromatic protons); ^{13}C NMR (DMSO-d_6) δ: 75.32, 114.12 (2C), 114.55 (2C), 124.73 (2C), 125.01 (2C), 125.66 (2C), 128.63 (2C), 128.80 (2C), 128.92 (2C), 129.10 (2C), 130.69 (2C), 131.86 (2C), 131.95 (2C), 153.88, 175.00. Yield 90%. M.p.: 220-221 °C. Anal. Calcd. For $C_{27}H_{17}NO_5$: C 74.48, H 3.94, N 3.22. Found: C 74.50, H 3.98, N 3.22.

Microbiology

For determining both antibacterial and antifungal activity, the synthesized compounds and the control drugs were dissolved in absolute dimethylsulfoxide (DMSO). Further dilutions were prepared at the required quantities of 1024, 512, 256, 128, 64, 32, 16, 8, 4, 2, and 1 μg mL^{-1} on the microorganisms at the concentrations studied. The stock solutions were prepared in DMSO and DMSO had no effect on the microorganisms in the concentrations studied. Antimicrobial activities of compounds were determined using the broth dilution method proposed by the National Committee for Clinical Laboratory Standards (CLSI). MIC, which is the lowest concentration of a compound that completely inhibits microbial growth, was determined by a standard broth dilution technique adapted from the CLSI.[35,36] As quality control strains 1 gram-positive bacterium, 1 Gram-negative bacterium, and 2 yeast-like fungi were used. Tested microorganisms were gram-positive *B. subtilis* ATCC 6633, gram-negative *E. coli* ATTC 25922, *S. typhimurium* NRRL B 4420, and the yeast like fungi; *C. globrata* ATCC 66032 and *C. tropicalis* ATCC 13803. Ampicillin (Mustafa Nevzat) and Fluconazole (Pfizer) were used as antibiotic reference for bacteria and yeast, respectively (obtained from Department of Biology, Fırat University, Turkey).

Antibacterial and antifungal assays

Bacterial cultures were obtained in Mueller–Hinton broth (Difco) for all the bacterial strains after 24 h of incubation at 37 ± 0.1 °C. The yeasts were propagated in Sabouraud dextrose broth (Difco) after incubation for 24 h at 25 ± 0.1 °C.[32] Testing was carried out in Mueller–Hinton broth and Sabouraud dextrose broth at pH 7.4 for bacteria and yeast, respectively. The final inoculum size for bacteria and fungi was 10^5 CFU mL^{-1}. Test compounds were dissolved in DMSO at an initial concentration of 1024 μg mL^{-1} and then were serially diluted in culture medium to 1 μg mL^{-1}. A set of tubes containing only inoculated broth was kept as control. Antibacterial activity was determined after incubation for 24 h at 37 °C for bacteria and after incubation for 48 h at 25 °C for the yeasts. MIC was defined as the lowest concentration of the compounds that inhibited the visible growth of a microorganism. Every experiment in the antibacterial and antifungal assays was replicated twice to define the MIC values.

Result and discussion

Dinaphtho[2,1-*b*]furan-2-yl-methanone (**1**) was prepared from the reaction of 2-hydroxy-1-naphthaldehyde with 1,3-dichloroacetone and K_2CO_3 in acetone according to the cited references.[29–33] In order to obtain dinaphtho[2,1-*b*]furan-2-yl-methanole (**2**), compound **1** was reduced with $NaBH_4$. Dinaphtho[2,1-*b*]furan-2-yl-methanone

oxime (**3**) was synthesized by reflux of compound **1** with $NH_2OH.HCl$ and sodium acetate in ethanol.

Compounds **4-7** were obtained by reflux of compound **3** with various acyl chlorides in dry acetone. The synthesis of compounds **8-11** was carried out by the reaction of compound **3** with various alkyl halogenides and K_2CO_3 in acetone. Compound **12** was obtained by reflux of compound **11** with hydrazine monohydrate (99%) in ethanol. Compound **13** was synthesized by the reaction of compound **11** with NaOH; this compound was isolated after the reaction mixture was neutralized with dilute HCl.

The structures of the synthesized compounds were verified by using ^{1}H, ^{13}C-NMR, and FT-IR spectroscopic methods. Melting points, yields, and elemental analyses of the compounds are given in the experimental section. The synthesis of compounds **1-13** are presented in **Schemes 2** and **3**. The synthesized compounds were tested in vitro for their antimicrobial activity.

The IR spectrum of dinaphtho[2,1-*b*]furan-2-yl-methanone (**1**) showed C=O absorption (stretching), which is adjacent to benzofuran ring, at 1621 cm^{-1} and the signals belonging to furan ring absorption were observed at 1549 and 1226 cm^{-1}. In the ^{13}C-NMR spectrum of this compound, the signal belonging to C=O group appeared at δ 203.6 ppm. The IR spectra of dinaphtho[2,1-*b*]furan-2-yl-methanole (**2**) displayed no signal belonging to C=O group; instead, OH stretching appeared between 3426 and 3385 cm^{-1}. In the ^{1}H-NMR spectrum of compound **2**, the signal belonging to CH, which is between naphthyl groups, were observed at 6.37 ppm as a singlet. In the^{13}C-NMR spectrum of this compound CH signal appeared at 65.5 ppm. In the IR spectrum of this dinaphtho[2,1-*b*]furan-2-yl-methanone oxime (**3**) displayed a broad OH absorption between 3390 and 3180 cm^{-1} and N-O (stretching) absorption at 1040 cm^{-1}. In the ^{13}C-NMR spectrum of this compound C=O signal appeared at δ 198 ppm.

In the IR spectra of compounds **4-7,** C=O absorption of ester was observed at 1779, 1762, 1762, and 1745 cm^{-1}, respectively. In the ^{1}H-NMR spectra compounds **5** and **6** the signal belonging to CH_2 were observed at δ 4.49 ppm and δ 4.02 ppm as a singlet, respectively. The signal due to CH_3 protons was recorded at δ 1.85 ppm as a singlet for compound **5**. In the ^{13}C NMR spectra of compounds **4-7**, the C=O signals were observed between 156 and 170 ppm.

In the NMR spectrum of compound **8**, OCH_3 protons were observed at δ 4.36 ppm as a singlet, whereas CH_3 protons of compounds **9** and **11** appeared at δ 1.57 and 1.37 ppm as triplets, respectively. Moreover, CH_2 protons of these compounds were observed at δ 4.63 and δ 4.36 ppm as quartet, respectively. The signal originated from benzylic CH_2 protons of compound **10** appeared at 5.62 ppm as a singlet in the ^{1}H-NMR spectrum.

Biological evaluation

We have designed and synthesized novel dinaphtofuran-2-yl) methanone (**1**) and its novel derivatives (**2-13**) in order to investigate antimicrobial activities. The compounds (**1-13**) were tested for their antimicrobial activity against *Salmonella typhimurium*, *Escherichia coli*, *Bacillus subtilis*, *Candida globrata,* and *Candida tropicalis.*

The minimal inhibitory concentration (MIC) of the synthesized compounds was determined against *S. typhimurium*, *E. coli*, *B. subtilis*, *C. globrata,* and *C. tropicalis* using a standard broth dilution technique. All the MIC results are presented in **Table 1**. The obtained data showed that the tested compounds were able to inhibit the growth of the selected microorganism in vitro showing MIC values between 128 and 512 μg/mL.

Table 1. Antimicrobial activity (MIC values in μg/mL) of synthesized compounds and the standard drugs used in the study.

Sample	MIC Values in μg/mL				
	S.t.	E.c.	B.s.	C.g.	C.t.
1	128	128	128	256	256
2	256	256	128	256	128
3	256	256	256	256	256
4	512	512	512	512	512
5	256	256	256	256	256
6	256	256	256	256	256
7	256	256	256	256	256
9	256	256	256	256	256
10	256	256	256	256	256
11	128	128	128	128	256
12	256	256	128	256	256
13	256	256	256	256	256
Ampicilin	2	2	2		
Fluconazole				8	8

S.t. *Salmonella typhimurium* NRRL B 4420, E.c. *Escherichia coli* ATCC 25922, B.s. *Bacillus subtilis* ATCC 6633, C.g. *Candida globrata* ATCC 66032 and C.t. *Candida tropicalis* ATCC13803.

Acknowledgments

We are indebted to the Scientific and Technological Research Council of Turkey (Project No DPT-2003K120440-2) for financial support of this work.

References

1. Stipanovic, R. D.; Bell, A. A.; Howell, C. R. *Phytochemistry* **1975**, *14*, 1809-1811.
2. Tatum, J. H.; Baker, R. A.; Berry, R. E. *Phytochemistry* **1987**, *26*, 2499-2500.
3. Weillthevenet, N.; Buisson, J. P.; Royer, R.; Hofnung, M. *Mut. Res.* **1982**, *104*, 1-8.
4. Ribeirorodrigues, R.; Dossantos, W. G.; Oliveira, A. B.; Snieckus, V.; Zani, C. L.; Romanha, A. J. *Bioorg & Med. Chem. Let.* **1995**, *5*, 1509-1512.
5. Simpson, T.J. Aromatic Compounds. In: R.H. Thomson, Editor, *The Chem. of Nat. Prod.,* Blackie, London 1985.
6. Leung, A. Y.; Foster, S. *Encyclopedia of Common Natural Ingredients Used in Food, Drugs, and Cosmetics,* Wiley, New York 1996.

7. Nagahara, T.; Yokoyama, Y.; Inamura, K.; Katakura, S.; Komoriya S.; Yamaguchi, H.; Hara, T.; Iwamoto, M. *J. Med. Chem.* **1994**, *37*, 1200-1207.
8. Gubin, J.; Devogelaer, H.; Inion, H.; Houben, C.; Lucchetti, J.; Mahaux, J.; Rosseels, G.; Peiren, M.; Clinet, M.; Polster, P.; Chatelain, P. *J. Med. Chem.* **1993**, *36*, 1425-1433.
9. Oter, Ö.; Ertekin, K.; Kirilmis, C.; Koca, M.; Ahmedzade, M. *Sens. and Act. B: Chem.* **2007**, *122*, 450-456.
10. Katrizky, A. R.; Fali, C. N.; Li, J. Q. *J. Org. Chem.* **1997**, *62*, 8205-8209.
11. Goel, A.; Dixit, M. *Tetrahedron Lett.* **2004**, *45*, 8819-8821.
12. Bohlmann, F.; Zdero, C. *Chemische Berichte-Recueil* **1977**, *110*, 487–490.
13. Bragadeoliveira, A.; Deoliveira, G.G.; Carazza, F.; Filho, R. B.; Bacha, C.T.M.; Bauer, L.; Silva, G.A.D.; Siqueira Laevigatin, N.C.S. *Tetrahedron Lett.* **1978**, *30*, 2653-2654.
14. Miles, D.H.; Lho, D.S. *J. Org. Chem.* **1987**, *52*, 2930-2932.
15. Zubaidha, P.K.; Chavan, S.P.; Racherla, U.S.; Ayyangar, N.R. *Tetrahedron* **1991**, *47*, 5759–5768.
16. Irie, H.; Matsumoto, R.; Nishimura, M.; Zhang, Y. *Chem. Pharm. Bul.* **1990**, *38*, 1852-1856.
17. Ishiguro, K.; Ohira, Y.; Oku, H. *J. Nat. Prod.* **1998**, *61*, 1126-1129.
18. Einhorn, J.; Demerseman, P.; Royer, R.; Cavier, R.; Gayral, P. *Eur. J. Med. Chem.***1984**, *19*, 405-410.
19. Giovanni, G.; Cavrini, V.; Chiarini, A.; Garuti L.; Manninip, A. *Farmaco-Edizione Scientifica* **1974**, *24*, 375-385.
20. Hranjec, M.; Grdisa, M.; Pavelic, K.; Boykin, D.W.; Karminski-Zamola, G. *Il Farmaco* **2003**, *58*, 1319-1324.
21. Mahadevan, K.M.; Padmashali, B.; Vaidya, V.P. *Indian J. Het. Chem.* **2001**, *11*, 15-20.
22. Mahadevan, K.M.; Vaidya V.P. *Indian J. Pharm. Sci.* **2003**, *65*, 128-134.
23. IARC monographs on the evaluation of carcinogenic risks to humans, *Pharm. Drugs,* Vol. 50, WHO Publications, IARC Lyon France, 195-221, 1990.
24. Weillthevenet, N.; Buisson, J.P.; Royer, R.; Hofnung, M. *Mut. Res.* **1981**, *88*, 355-362.
25. Weillthevenet, N.; Buisson, J.P.; Royer, R.; Hofnung, M. *Mut. Res.* **1982**, *104*, 1-8.
26. Arnaise, S.; Boeuf, H.; Buisson, J.P.; Cantat, N.; Demerseman, P.; Einhorn, J.; Lamotte, G.; Lemelin, M.; Brimer, P.A.; Perdue, S.W.; Hsie, A.W.; Royer, R.; Kelly, F.; Hofnung, M. *Mutagenesis* **1986**, *1*, 217-229.
27. Quillardet, P.; Huisman, O.; Dari, R.; Hofnung, M. *Bio. Sci.* **1982**, *79*, 5971-5975.
28. Hofnung, M.; Quillardet, P.; Michel, V.; Touati, E. *Res. Microbiol.,* **2002**, *153*, 427-434.
29. Karatas, F.; Koca, M.; Kara, H.; Servi, S. *Eur. J. Med. Chem.* **2006**, *41*, 664-669.
30. Koca, M.; Servi, S.; Kirilmis, C.; Ahmedzade, M.; Kazaz, C.; Özbek, B.; Ötük, G. *J. Med. Chem.* **2005**, *40*, 1351-1358.
31. Koca, M.; Ahmedzade, M.; Cukurovali, A.; Kazaz, C. *Molecules* **2005**, *10*, 747-754.
32. Kirilmis, C.; Koca, M.; Cukurovali, A.; Ahmedzade, M.; Kazaz, C. *Molecules* **2005**,*10*, 1399-1408.
33. Kirilmis, C.; Ahmedzade, M.; Servi, S.; Koca, M.; Kizirgil A.; Kazaz, C. *J. Med. Chem.* **2008**, *43*, 300-308.
34. Oter, Ö.; Ertekin, K.; Kirilmis, C.; Koca, M. *Anal. Chim. Acta* **2007**, *584*, 308-314.
35. Yildiz-Oren, I.; Yalcın, I.; Aki-Sener, E.; Ucarturk, N. *J. Med. Chem.* **2004**, *39*, 291-298.
36. Clinical and Laboratory Standards Institute: Performance Standards for Antimicrobial Suspectibility Testing, 16^{th} Informational Supplement. CLSI M100-S16, 940 West Valley Road, Wayne, Pennsylvania, USA, 2006.