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Original article

Synthesis and antimicrobial activity of some novel derivatives of benzofuran: Part 2. The synthesis and antimicrobial activity of some novel 1-(1-benzofuran-2-yl)-2-mesitylethanone derivatives

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Abstract

The reaction of salicylaldehyde with 1-chloro-3-mesitylacetone (**2**) and potassium carbonate was used to prepare 1-(1-benzofuran-2-yl)-2-mesitylethanone (**4**) for the starting reagent purposes. 1-(1-Benzofuran-2-yl)-2-mesitylethanoneoxime (**5**) was synthesized by the reaction of the compound (**4**) with hydroxylamine. New derivative of 1-(1-benzofuran-2-yl)-2-mesitylethanoneoxime (**5**) as 1-(1-benzofuran-2-yl)-2-mesitylethanonesemicarbazone (**7**) was obtained in very high yields. Alkyl substituted *N*-oxime ethers (**8a–d**) were obtained by the reaction compound **5** and various halogen contained compounds. The compounds **9a–d** were synthesized by the reaction of the compound (**5**) and four different acyl chlorides. Some of the synthesized compounds were tested for antimicrobial activity against *Staphylococcus aureus* ATCC 6538, *Escherichia coli* ATCC 25922 and *Candida albicans* ATCC 10231. Among the synthesized compounds (*E*)-1-(1-benzofuran-2-yl)-2-mesitylethanone-*O*-benzoyloxime (**9b**) was found the most active derivative against *S. aureus* ATCC 6538 and *E. coli* ATCC 25922. The other compounds exhibited moderate activity against the other test microorganisms.

Keywords: Antimicrobial activity; Mesitylene; Benzofuran; Ketoxime

1. Introduction

Benzofuran derivatives are an important class of heterocyclic compounds that are known to possess important biological properties. Substituted benzofurans find application such as of fluorescent sensor [1], oxidant [2], antioxidants, brightening agents, a variety of drugs and in other field of chemistry and agriculture [3].

Benzofurans occur in a great number of natural products. Many of the natural benzofurans have physiological, pharmacological and toxic properties. The most recognized of the benzofurans are *amiodarone*, *angelicin xanthotoxin*, *bergapten*, *nodekenetin* and usnic acid compounds (Fig. 1). The benzofuran ring system is the basic skeleton of numerous compounds possessing cardiovascular activities [4]. *Amiodarone*, an iodinated lipophilic benzofuran derivative, is widely used in the treatment of ventricular tachyarrhythmia and atrial fibrillation [5,6]. Initially marketed as an antianginal agent, *amiodarone* possesses coronary and peripheral vasodilator effects and exerts a negative chronotropic and dromo-tropic influence on the sinoatrial and atrioventricular nodes, respectively [7].

Benzofuran containing structures have been found among naturally occurring furocoumarins, such as psoralen and methoxalen isolated from the seed of *Ammi majus* L. and used for the treatment of psoriasis and other dermal diseases [8,9]. Psoralen is structurally related to coumarin by the addition of

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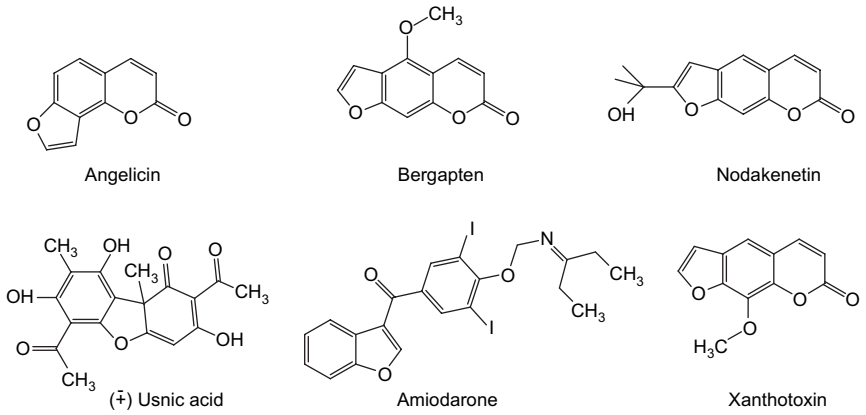


Fig. 1. Benzofuran containing some biological molecules.

a fused furan ring, and may be considered as a derivative of umbelliferone. Some important psoralen derivatives are *imperatorin*, *xanthotoxin*, *bergapten* and *nodekenetin*. One of the most important applications of psoralen is in the field of photo chemotherapy, where psoralens are capable of undergoing photo addition with thymine units present in DNA [10].

Usnic acid is one of the most common and abundant lichen metabolites, well known as an antibiotic, but also endowed with several other interesting properties. Both the (+) and (−) enantiomers of usnic acid are effective against a large variety of Gram-positive bacterial strains, including strains from clinical isolates, irrespective of their resistant phenotype. Of particular relevance is the inhibition of growth of multi-resistant strains of *Staphylococcus aureus*, enterococci and mycobacteria. The (+)-usnic acid enantiomer appears to be selective against *Streptococcus mutans* without inducing perturbing side effects on the oral saprophyte flora [11]. This compound inhibits bacterial as well as eukaryotic cell proliferation *in vitro*. Its antimitotic and antiproliferative action was shown in a variety of biological systems including higher plant cells. Also, the pharmacological potential of usnic acid has been evaluated in the control of tumor proliferation [12].

The spread of multi drug-resistant strains of fungus and bacteria the reduced number of drugs available, makes it necessary to discover new classes of antifungal and antibacterial compounds that inhibit these resistant mechanisms. This has led to a search for therapeutic alternatives, particularly among medicinal plants and compounds isolated from them, used for their empirically antimicrobial properties.

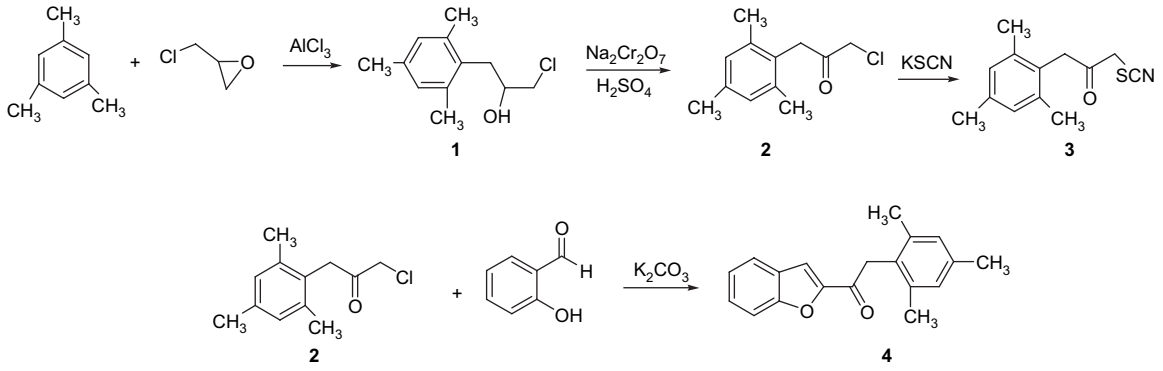
Previously, our group reported the synthesis and antimicrobial activity of some bis-(benzofuran-2-yl)methanone and cyclobutane substituted benzofuran derivatives. Bis-(benzofuran-2-yl)methanone exhibited activity towards all the microorganisms studied, but its derivatives generally showed moderate activity at the higher concentrations towards many of the bacteria and the fungus tested [13,14], but cyclobutane substituted benzofuran derivatives exhibited very strong antimicrobial effect against *Candida albicans* and (benzofuran-2-yl)(3-phenyl-3-methylcyclobutyl)-*O*-[2-hydroxy-3-(*N*-methylpiperazino)]propylketoxime was found to be the most active derivative against *S. aureus* [15]. Encouraged by the good results obtained from that work, we planned to prepare 1-(1-benzofuran-2-yl)-2-mesitylethanone derivatives (**5**–**11**) and perform antimicrobial activity tests.

In this study, the starting material, 1-chloro-3-mesitylpropane-2-ol (**1**) was synthesized from the reaction of mesitylene and 1-chloro-2,3-epoxypropane according to cited Ref. [16] and it was characterized by using spectroscopic methods. 1-(1-Benzofuran-2-yl)-2-mesitylethanone (**4**) was obtained by the reaction of salicylaldehyde with 1-chloro-3-mesitylacetone (**2**) in presence of potassium carbonate. (*E*,*Z*)-1-(1-Benzofuran-2-yl)-2-mesitylethanoneoxime (**5**) was synthesized from the reaction of the compound (**4**) with hydroxylamine hydrochloride. The derivatives of compound **5**, such as, **8a**–**d**, **9a**–**d**, **10** and **11** were obtained in good yields and these compounds were synthesized for the first time and characterized in the present study. Some of the synthesized compounds were tested *in vitro* for their antimicrobial activities. Melting points and yields of the obtained compounds are given in Section 4.

2. Chemistry

In the first part of the study, 1-chloro-3-mesitylpropane-2-ol (**1**) was synthesized from Friedel–Crafts alkylation reaction with mesitylene and epichlorohydrine by using $AlCl_3$ as catalyst at −5 °C [16]. 1-Chloro-3-mesitylacetone (**2**) was prepared by oxidation reaction of the compound **1** and Jones reagent at room temperature. 3-Mesityl-1-thiocyanateacetone (**3**) was obtained from the S_N reaction of 1-chloro-3-mesitylacetone (**2**) and SCN^-.

1-(1-Benzofuran-2-yl)-2-mesitylethanone (**4**) was synthesized from the reaction of the compound **2** and salicylaldehyde with K_2CO_3 in acetone. Structure of this compound was characterized by using FT-IR, ^{1}H NMR, ^{13}C NMR and X-ray data [17]. In order to improve yields of this compound, many reactions were performed with various bases (NaH, KOH, Na_2CO_3 and K_2CO_3, etc.) and solvents (acetonitrile, acetone, ethanol, benzene and THF, etc.) at various temperatures. When K_2CO_3 and acetone were used for the synthesis of 1-(1-benzofuran-2-yl)-2-mesitylethanone (**4**), maximum yield was obtained. The



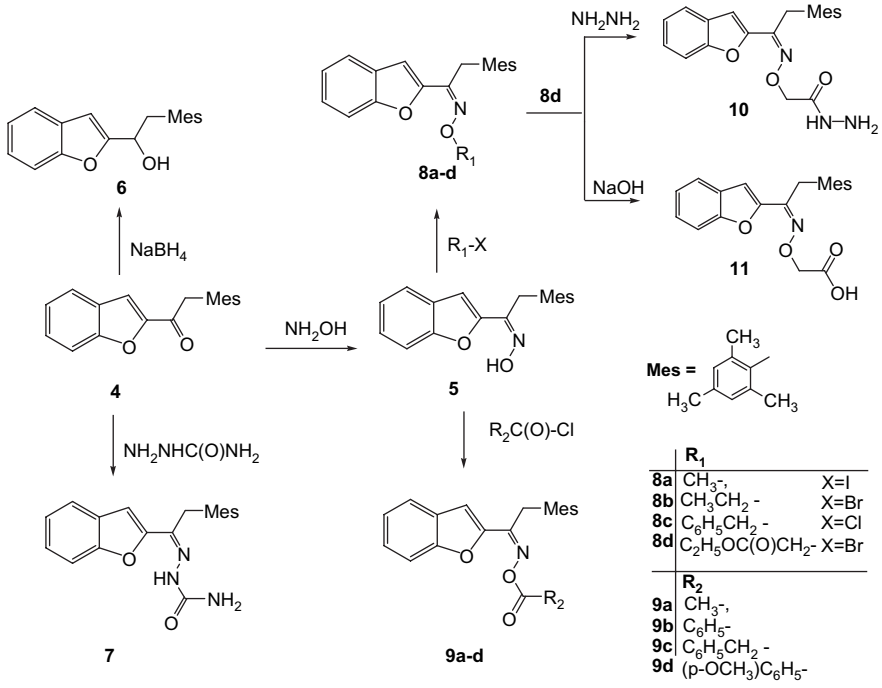
Scheme 1. Synthesis of 3-mesityl-1-thiocyanateacetone (**3**) and 1-(1-benzofuran-2-yl)-2-mesitylethanone (**4**).

most relevant temperatures were determined as boiling points of the solvents [15]. The synthesis of compounds **1**–**11** is presented in Schemes 1 and 2.

(*E*,*Z*)-1-(1-Benzofuran-2-yl)-2-mesitylethanoneoxime (**5**) was synthesized by reflux of compound **4** with $NH_2OH \cdot HCl$ and natrium acetate in ethanol. 1-(1-Benzofuran-2-yl)-2-mesitylethanole (**6**) was prepared from the reaction of compound **4** and $NaBH_4$. 1-(1-Benzofuran-2-yl)-2-mesitylethanonesemicarbazone (**7**) was synthesized from the reaction of compound **4** and semicarbazide hydrochloride.

The synthesis of compounds **8a**–**d** was carried out by the S_N reaction of compound **5** and different alkyl halogens with potassium carbonate in acetone. Compounds **9a**–**d** were synthesized by *O*-acylation reaction of compound **5** and four different acyl chlorides such as, acetyl chloride, benzoyl chloride, 4-methoxybenzoyl chloride and phenyl acetyl chloride, after neutralizing the reaction mixture with 5% ammonia solutions. (*E*,*Z*)-[1-(1-Benzofuran-2-yl)-2-mesityl-ethylideneaminooxy] acetic acid hydrazide (**10**) was obtained by reflux of the compound **8d** with hydrazine monohydrate (99%) in ethanol. The synthesis of (*E*,*Z*)-[1-(1-benzofuran-2-yl)-2-mesityl-ethylideneaminooxy]acetic acid (**11**) was performed with NaOH and the compound **8d**, after the reaction mixture neutralized with dilute HCl.

Compounds **3**–**7**, **8a**–**d**, **9a**–**d**, **10** and **11** were first time synthesized and characterized in this study. For compounds **8a**–**d** and **9b**, only the *E* isomer was isolated, whereas the compounds **9a**, **9c**, **9d**, **10** and **11** were obtained as the mixture of *E* and Z isomers. The isomer rates were calculated by the ^1H NMR integrals and these values are shown in Table 1. Some of the synthesized compounds were tested *in vitro* for their antimicrobial activities.



Scheme 2. Synthesis of 1-(1-benzofuran-2-yl)-2-mesitylethanone (**4**), 1-(1-benzofuran-2-yl)-2-mesitylethanoneoxime (**5**) and their derivatives.

Table 1
E and *Z* isomer rates of 1-(1-benzofuran-2-yl)-2-mesitylethanoneoxime (**5**) and its derivatives

Compound no.	*E* isomers (%)	*Z* isomer (%)
5	65	35
8a	100	–
8b	100	–
8c	100	–
8d	100	–
9a	50	50
9b	100	–
9c	64	36
9d	62	38
10	62	38
11	34	66

3. Result and discussion

The structures of the synthesized compounds were verified by using ^{1}H, ^{13}C NMR and FT-IR spectroscopic methods. Melting points and yields of the compounds are given in Section 4.

In the IR spectra of (*E*,*Z*)-1-(1-benzofuran-2-yl)-2-mesitylethanoneoxime (**5**) was displayed broad OH absorption peak between 3429 and 3199 cm^{-1} and N–O (stretching) absorption peak at 995 cm^{-1}. As is known, oxime can be found in two different isomeric structures namely, the *syn* (*Z*) and *anti* (*E*) configurations [18,19]. It was expected that 1-(1-benzofuran-2-yl)-2-mesitylethanoneoxime (**5**) shows two different isomeric structures. When the ^{1}H NMR spectra were investigated for the compound **5** and its derivatives (**9a**, **9c**, **9d**, **10** and **11**) two different proton signals were observed for *E* and *Z* isomers, whereas only *E* isomer was isolated for compounds **8a–d** and **9b**. It might be as a result of the crystallization technique [15]. When the *E* and *Z* isomers were separately isolated, *E* isomer was appeared at lower frequency than *Z* isomer [20–24]. In spite of our all efforts, *E* and *Z* isomers belonging to compounds **5**, **9a**, **9c**, **9d**, **10** and **11** could not be separated by using column chromatography. *E* and *Z* isomer rates of these compounds were calculated from integrated height in the ^{1}H NMR spectra and these values are given in Table 1.

In the ^{1}H NMR spectra (*E*,*Z*)-1-(1-benzofuran-2-yl)-2-mesitylethanoneoxime (**5**) signals belonging to =N–OH appeared at 8.69 (for *Z* isomer) and 9.88 (for *E* isomer) ppm. In the ^{13}C NMR spectra of compound **5**, C=N signal was displayed at δ 156 ppm while the C=O signal disappeared.

3.1. Biological evaluation

We have designed and synthesized novel compounds of mesitylene substituted benzofuran class, in order to investigate antimicrobial activity. The compounds (**1–7**, **8a**, **8d**, **9b**, **9c** and **10**) were tested for antimicrobial activity against *S. aureus*, *Escherichia coli* and *C. albicans*.

The minimal inhibitory concentration (MIC) of the synthesized compounds was determined against *S. aureus*, *E. coli* and *C. albicans* using a standard broth dilution technique. All the MIC results are presented in Table 2. The obtained data reported that compounds were able to inhibit the growth of the selected microorganisms *in vitro* showing MIC values between 4 and 256 μg/ml.

Table 2
Antimicrobial activities of compounds (**1–7**, **8a**, **8d**, **9b**, **9c** and **10**) against *S. aureus*, *E. coli* and *C. albicans*

Compound no.	MIC values (μg/ml)		
	S.a.	E.c.	C.a.
1	128	64	32
2	16	64	16
3	256	256	32
5	128	128	128
6	128	128	64
7	128	64	64
8a	256	128	64
8d	256	256	256
9b	4	32	64
9c	256	128	128
10	256	64	32
Meropenem	1	0.125	–
Fluconazole	–	–	0.25

S.a., *Staphylococcus aureus* ATCC 6538; E.c., *Escherichia coli* ATCC 25922; C.a. *Candida albicans* ATCC 10231.

Because the compounds (**5**, **9a**, **9c**, **9d** and **10**) weren't able to purified with chromatographic and crystallographic methods, these compounds were obtained as *E* and *Z* isomer mixture (Table 1) and their antimicrobial activity results are given as isomer mixture in Table 2.

Among the synthesized compounds, (*E*)-1-(1-benzofuran-2-yl)-2-mesitylethanone-*O*-benzoyloxime (**9b**) was found to be the most active derivative against *S. aureus* and *E. coli* at MIC values of 4 and 32 μg/ml, respectively. Compound **2** showed the best activity against *C. albicans* (16 μg/ml) but the compounds **1**, **3** and **10** also showed a good activity with MICs of 32 μg/ml. Also, the other compounds exhibited moderate activity against the other test microorganisms.

4. Experimental

4.1. Chemistry

All of the reagents were obtained from commercial sources. Solvents were dried and purified with known conventional methods. Melting points (uncorrected) were determined on a Gallenkamp apparatus. The IR spectra were measured on a Mattson 1000 FT-IR spectrophotometer (potassium bromide disks). The ^{1}H NMR spectra were recorded on a Varian-Gemini 200 MHz spectrometer and are reported in ppm (δ) relative to tetramethyl silane (TMS) as the internal standard and ^{13}C NMR (50.34 MHz) is referenced to deutero-chloroform ($CDCl_3$). Elemental analyses were determined by a LECO CHNSO-932 auto elemental analysis apparatus. Analyses (TLC) were performed on recoated 0.2 mm Merck Kieselgel 60 F254 plates. Column chromatography was performed using Merck silica gel, 70–230 mesh.

4.1.1. Synthesis of 1-chloro-3-mesitylpropane-2-ol (*1*)

Mesitylene (1700 mL, *d*: 0.864 g/cm^3, 12.21 mol) and dry $AlCl_3$ (305.2 g, 2.29 mol) were placed in a 5 L two-necked

flask. Epichlorohydrine (175 mL, *d*: 1.18 g/cm^3, 2.23 mol) was added drop wise at 15 °C and the reaction mixture was stirred at room temperature for 2 h. The mixture was hydrolyzed with 15% HCl solution and then neutralized with a 5% solution of NaOH. The residue was extracted with diethyl ether and the ether phase dried over $MgSO_4$. After the residue was distillated in vacuum at 145–148 °C (5 mmHg), the following product was obtained.

*4.1.1.1. 1-Chloro-3-mesitylpropane-2-ol (**1**).* IR (KBr) (ν, cm^{-1}), 3593–3284 (O–H stretching), 1028 (C–O stretching), 852 (C–Cl stretching); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.38 and 2.44 (s, 9H, $3CH_3$), 2.97 (d, $J = 6.0$ Hz, 2H, $-CH_2-$CH–), 3.62–3.76 (m, 3H, $-CH_2-CH-CH_2-$Cl), 4.06–4.08 (broad, 1H, O*H*), 6.98 (s, 2H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ: 22.51 (2C), 22.95, 36.12, 51.84, 73.77 (*C*H–OH), 131.38 (2C), 133.36, 138.04, 139.14 (2C). Anal. Calcd. for $C_{12}H_{17}ClO$: C, 67.76; H, 8.06. Found: C, 67.25; H, 7.96. Yield %: 64.21.

*4.1.2. Synthesis of 1-chloro-3-mesitylacetone (**2**)*

Compound **1** (9.5 g, 8.04 mmol), $Na_2Cr_2O_7$ (7.0 g, 26.71 mmol) and H_2O (7.3 mL) were placed in a 100 mL two-necked flask with a reflux condenser. H_2SO_4/H_2O (7.5/3.0 mL) solution was added drop wise to the reaction mixture at 27 °C for 8 h. The mixture was extracted with diethyl ether and ether phase dried with $MgSO_4$. After filtration and removal of the solvent under reduced pressure, the compound **2** was recrystallized from ethanol. The following product was obtained.

*4.1.2.1. 1-Chloro-3-mesitylacetone (**2**).* IR (KBr) (ν, cm^{-1}), 1727 (C=O stretching), 750 (C–Cl stretching); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.24 and 2.30 (s, 9H, $3CH_3$), 3.95 (s, 2H, Ar-C*H*$_2$–), 4.13 (s, 2H, C(O)–C*H*$_2$–Cl), 7.28 (s, 2H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ: 22.33 (2C), 22.88, 43.13, 49.84, 129.62, 131.17 (2C), 138.76 (2C), 138.95, 202.04 (*C*=O). Anal. Calcd. for $C_{12}H_{15}ClO$: C, 68.40; H, 7.18. Found: C, 67.20; H, 6.98. Yield %: 69.75. M.p. 69–70 °C.

*4.1.3. Synthesis of 3-mesityl-1-thiocyanateacetone (**3**)*

The compound **2** (2.1 g, 10 mmol), KSCN (0.19 g, 2 mmol) and absolute ethanol (50 mL) were placed in a 100 mL flask with a reflux condenser. The reaction mixture was refluxed for 12 h. After the mixture was cooled, water was added drop wise. The solid was filtrated off, dried and the compound **3** was recrystallized from ethanol. The following product was obtained.

*4.1.3.1. 3-Mesityl-1-thiocyanateacetone (**3**).* IR (KBr) (ν, cm^{-1}), 2153 (C≡N stretching), 1708 (C=O stretching); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.23 and 2.29 (s, 9H, $3CH_3$), 3.87 (s, 2H, Ar-CH_2–), 3.96 (s, 2H, C(O)–CH_2–SCN), 6.91 (s, 2H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ: 22.38 (2C), 22.91, 44.94, 45.58, 113.39 (S–*C*≡N), 128.95, 131.51 (2C), 138.66 (2C), 139.52, 201.54. Anal. Calcd. for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00; S, 13.74. Found: C, 65.28; H, 5.69; N, 6.33; S, 13.54. Yield %: 85.55. M.p. 125–126 °C.

*4.1.4. Synthesis of 1-(1-benzofuran-2-yl)-2-mesitylethanone (**4**)*

Salicylaldehyde (82.5 mL, *d*: 1.146 g/cm^3, 24 mmol), dry K_2CO_3 (4.91 g, 35.6 mmol) and dry acetone (200 mL) were placed in a 500 mL flask with a reflux condenser. The mixture was stirred at room temperature for 1 h. To the mixture, compound **2** (23.73 mmol, 5.0 g) was added and refluxed for 3 h. The reaction mixture was cooled, and then water was added. The solid filtrated off, dried and the compound (**4**) was recrystallized from ethanol. The following product was obtained.

*4.1.4.1. 1-(1-Benzofuran-2-yl)-2-mesitylethanone (**4**).* IR (KBr) (ν, cm^{-1}), 1680 (C=O stretching), 1161 (C–O–C stretching), 1059 and 758 (=CH benzofuran out of plane ring bending); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.23 and 2.29 (s, 9H, $3CH_3$), 4.38 (s, 2H, Ar-CH_2–), 6.95 (s, 2H, mesitylene ring protons), 7.57 (s, 1H, furan ring), 7.28–7.78 (m, 4H, benzofuran ring protons); ^{13}C NMR ($CDCl_3$) δ: 22.36 (2C), 22.95, 41.83, 114.47 (2C), 125.30, 125.92, 129.14, 130.18, 130.39, 130.92 (2C), 138.60, 139.05 (2C), 154.65, 157.55, 190.92 (*C*=O). Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 81.23; H, 6.58. Yield %: 69.84. M.p. 172–173 °C.

*4.1.5. Synthesis of 1-(benzofuran-2-yl)-2-mesitylethanoneoxime (**5**)*

Compound **4** (3.0 g, 10.77 mmol), $NH_2OH{\cdot}HCl$ (0.83 g, 12.0 mmol) and 25 mL pyridine were placed in a 100 mL flask with a reflux condenser. The reaction mixture was refluxed for 2 h. The mixture was cooled, and water was added drop wise. The solid was filtrated off, dried and the compound **5** was recrystallized from acetone. The following product was obtained.

*4.1.5.1. (E,Z)-1-(1-Benzofuran-2-yl)-2-mesitylethanoneoxime (**5**).* IR (KBr) (ν, cm^{-1}), 3429–3199 (O–H stretching), 1613 (C=N stretching), 1169 (C–O–C stretching), 1065 (=CH benzofuran out of plane ring bending), 995 (N–O stretching); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.34 and 2.37 (s, 9H, $3CH_3$), 4.22 (s, 2H, Ar-CH_2–), 6.23 for *Z* isomer and 6.95 for *E* isomer (s, 1H, furan ring), 7.01 (s, 2H, mesitylene ring protons), 7.21–7.78 (m, 4H, benzofuran ring protons), 8.69 for *Z* isomer and 9.88 for *E* isomer (s, 1H, N–OH); ^{13}C NMR ($CDCl_3$) δ: 22.03 (2C), 22.31, 33.23, 113.35, 115.84, 124.35, 125.29, 128.19, 130.94 (2C), 131.21, 132.25, 139.00 (2C), 146.93, 151.56, 155.49, 156.41 (*C*=N–OH). Anal. Calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 76.60; H, 6.99; N, 4.54. Yield %: 97.91. M.p. 189–191 °C.

*4.1.6. Synthesis of 1-(1-benzofuran-2-yl)-2-mesitylethanole (**6**)*

Compound **4** (1.0 g, 3.59 mmol) and $NaBH_4$ (0.14 g, 3.70 mmol) in 1,4-dioxane (50 mL) were placed in a 100 mL

flask. The reaction mixture was stirred at room temperature for 24 h and then to the mixture, water was added drop wise. The solid was filtrated, dried and the compound **6** was recrystallized from ethanol. The following product was obtained.

*4.1.6.1. 1-(1-Benzofuran-2-yl)-2-mesitylethanole (**6**).* IR (KBr) (ν, cm^{-1}), 3375 (O–H stretching), 1072 and 1027 (C–O–C stretching); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.28 and 2.33 (s, 9H, $3CH_3$), 3.29 (d, $J = 5.7$ Hz, 2H, –CH–CH_2–), 5.01 (t, $J = 3.1$ Hz, 1H, –CH_2–C*H*–O), 6.64 (s, 1H, furan ring), 6.89 (s, 2H, mesitylene ring protons), 7.26–7.53 (m, 4H, benzofuran ring protons); ^{13}C NMR ($CDCl_3$) δ: 22.26 (2C), 22.83, 37.69, 70.41 (*C*H–OH), 104.50, 113.26, 123.02, 124.78, 126.13, 130.20, 131.22 (2C), 133.02, 138.10, 139.37 (2C), 156.80, 161.03. Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 80.21; H, 6.41. Yield %: 90.45. M.p. 75–76 °C.

*4.1.7. Synthesis of 1-(1-benzofuran-2-yl)-2-mesitylethanonesemicarbazone (**7**)*

Compound **4** (7.18 mmol, 2.00 g), semicarbazide hydrochloride (10 mmol, 1.11 g), natrium acetate (10 mmol, 1.36 g) and ethanol/water (80/20 mL) were placed in a 250 mL flask with a reflux condenser. The reaction mixture was refluxed for 12 h. The reaction mixture was cooled, and then water was added drop wise. The solid was filtrated off, dried and the compound **7** was recrystallized from ethanol. The following product was obtained.

*4.1.7.1. 1-(1-Benzofuran-2-yl)-2-mesitylethanonesemicarbazone (**7**).* IR (KBr) (ν, cm^{-1}), 3464–3388 (N–H stretching), 1706 (C=O stretching), 1581 (C–N stretching), 1142–1048 (C–O–C stretching); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.26 and 2.30 (s, 9H, $3CH_3$), 3.96 (s, 2H, Ar-CH_2–), 5.47–5.51 (broad, 2H, C(O)–NH_2), 6.89 (s, 2H, mesitylene ring protons), 7.16 (s, 1H, furan ring), 7.33–7.70 (m, 4H, benzofuran ring protons), 9.85 (s, 1H, N–N*H*–); ^{13}C NMR ($CDCl_3$) δ: 22.09 (2C), 22.60, 35.51, 82.45 (2C), 110.89, 113.83, 124.06, 126.07, 128.63, 128.75, 130.62 (2C), 132.84, 137.94, 151.96, 156.55 (N–*C*O–N), 159.34, 159.41. Anal. Calcd. for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.55; H, 6.12; N, 12.55. Yield %: 78.55. M.p. 206–208 °C.

*4.1.8. General method for the synthesis of compounds (**8a–d**)*

To a solution of compound **5** (1.0 g, 3.4 mmol) in dry acetone (150 mL) was added K_2CO_3 (0.48 g, 3.50 mmol) and was stirred at room temperature for 1 h. Different alkyl halogens (3.5 mmol) were added drop wise to the reaction mixture and were refluxed for 8 h. The reaction mixture was cooled, and then water was added drop wise. The solid was filtrated off, dried and then the compounds **8a–d** were crystallized from acetone/ethanol (3/1). The following products were obtained.

*4.1.8.1. (E)-1-(1-Benzofuran-2-yl)-2-mesitylethanone-O-methyloxime (**8a**).* IR (KBr) (ν, cm^{-1}), 1083 (C–O–C benzofuran ring stretching), 1023 (N–O stretching); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.28 and 2.34 (s, 9H, $3CH_3$), 3.95 (s, 3H, O–CH_3), 4.12 (s, 2H, Ar-CH_2–), 6.86 (s, 2H, mesitylene ring protons), 7.26–7.66 (m, 5H, benzofuran ring protons); ^{13}C NMR ($CDCl_3$) δ: 22.30, 22.88 (2C), 33.66, 64.64 (*C*H_3–), 113.42, 124.60, 124.13, 125.11, 127.94, 130.42, 130.58 (2C), 133.09, 137.52, 139.23 (2C), 146.66, 148.62, 155.29. Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.10; H, 6.75; N, 3.98. Yield %: 74.64. M.p. 86–87 °C.

*4.1.8.2. (E)-1-(1-Benzofuran-2-yl)-2-mesitylethanone-O-ethyloxime (**8b**).* IR (KBr) (ν, cm^{-1}), 1138 (C–O–C benzofuran ring stretching), 977 (N–O stretching); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.29 (t, $J = 7.0$ Hz, 3H, –O–CH_2–C*H*$_3$), 2.28 and 2.34 (s, 9H, CH_3), 4.12 (s, 2H, Ar-CH_2), 4.18 (q, $J = 7.0$ Hz, 2H, O–CH_2–CH_3), 6.86 (s, 2H, mesitylene ring protons), 7.22–7.69 (m, 5H, benzofuran ring protons); ^{13}C NMR ($CDCl_3$) δ: 16.80 (*C*H_3–), 22.28, 22.89 (2C), 33.71, 72.43, 113.41, 115.13, 124.12, 125.08, 127.87, 130.48, 130.55 (2C), 133.20, 137.44, 139.22 (2C), 146.30, 148.83, 155.27. Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.48; H, 7.21; N, 4.36. Found: C, 78.00; H, 7.68; N, 3.52. Yield %: 73.26. M.p. 74–75 °C.

*4.1.8.3. (E)-1-(1-Benzofuran-2-yl)-2-mesitylethanone-O-benzyloxime (**8c**).* IR (KBr) (ν, cm^{-1}), 1170 and 1113 (C–O–C benzofuran ring stretching), 991 (N–O stretching); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.27 and 2.31 (s, 9H, $3CH_3$), 4.12 (s, 2H, Ar-CH_2), 5.16 (s, 2H, Ar-CH_2–O), 6.87 (s, 2H, mesitylene ring protons), 7.22–7.70 (m, 10H, benzofuran and phenyl ring protons); ^{13}C NMR ($CDCl_3$) δ: 22.19 (2C), 22.90, 33.67, 79.08 (Ph–*C*H_2–), 113.42, 115.45, 124.21, 125.12, 127.98, 129.78 (2C), 130.24 (2C), 130.33, 130.47 (3C), 133.06, 137.46, 139.22 (2C), 139.84, 146.95, 148.70, 155.34. Anal. Calcd. for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65. Found: C, 80.95; H, 6.12; N, 3.02. Yield %: 83.07. M.p. 94–95 °C.

*4.1.8.4. (E)-[1-(1-Benzofuran-2-yl)-2-mesityl-ethylidineaminooxy]acetic acid ethylester (**8d**).* IR (KBr) (ν, cm^{-1}), 1752 (C=O stretching), 1165 and 1098 (C–O–C benzofuran ring stretching), 1024 (N–O stretching); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm), 1.31 (t, $J = 7.0$ Hz, 3H, –O–CH_2–C*H*$_3$), 2.27 and 2.31 (s, 9H, $3CH_3$), 4.21 (s, 2H, Ar-CH_2), 4.27 (q, $J = 7.0$ Hz, 2H, –O–CH_2–CH_3), 4.88 (s, 2H, N–O–CH_2), 6.19 (s, 1H, furan ring), 6.85 (s, 2H, mesitylene ring protons), 7.09–7.47 (m, 4H, benzofuran ring protons); ^{13}C NMR ($CDCl_3$) δ: 16.18, 22.31 (2C), 22.84, 29.54, 62.94, 73.45, 109.77, 113.46, 123.49, 124.85, 127.51 (3C), 131.10 (3C), 132.52, 138.19, 139.17 (2C), 152.87, 171.52 (*C*=O). Anal. Calcd. for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.50; H, 6.44; N, 3.19. Yield %: 54.26. M.p. 130–132 °C.

*4.1.9. General method for the synthesis of compounds **9a–d***

Compound **5** (1.0 g, 3.40 mmol) and dry acetone (50 mL) were placed in a 100 mL two-necked flask with a reflux

condenser. The mixture was cooled to −5 °C and then acyl chloride (3.5 mmol) was added drop wise and the reaction was maintained at room temperature for 2 h. After the reaction mixture was cooled, it was neutralized with NH_3 solution and the resulting precipitate was filtrated and washed with water. Compounds **5a–c** were recrystallized from ethanol. The following product was obtained.

*4.1.9.1. (E,Z)-1-(1-Benzofuran-2-yl)-2-mesitylethanone-O-acetyloxime (**9a**).* IR (KBr) (ν, cm^{-1}), 1777 (C=O stretching), 1173 (C–O–C benzofuran ring stretching), 1004 (N–O stretching); ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.17 for *Z* isomer and 2.20 for *E* isomer (s, 3H, C(O)–CH_3), 2.26 for *Z* isomer and 2.28 for *E* isomer (s, 3H, CH_3), 2.30 and 2.36 (s, 6H, $2CH_3$), 4.21 for *Z* isomer and 4.26 for *E* isomer (s, 2H, Ar-CH_2), 6.70 (s, 1H, furan ring), 6.87 (s, 2H, mesitylene ring protons), 7.20–7.74 (m, 4H, benzofuran ring protons). Anal. Calcd. for $C_{21}H_{21}NO_3$: C, 78.15; H, 6.89; N, 10.41. Found: C, 76.24; H, 6.47; N, 10.55. Yield %: 80.70. M.p. 89–91 °C.

*4.1.9.2. (E)-1-(1-Benzofuran-2-yl)-2-mesitylethanone-O-benzoyloxime (**9b**).* IR (KBr) (ν, cm^{-1}), 1747 (C=O stretching), 1176 and 1078 (C–O–C benzofuran ring stretching), 1050 (N–O stretching); ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.29 and 2.32 (s, 9H, $3CH_3$), 4.35 (s, 2H, Ar-CH_2), 6.72 (s, 1H, furan ring), 6.88 (s, 2H, mesitylene ring protons), 7.17–7.95 (m, 7H, benzofuran and phenyl ring protons), 8.12 (d, $J = 4.9$ Hz, 2H, phenyl ring protons); ^{13}C NMR ($CDCl_3$) δ: 22.55 (2C), 22.86, 31.27, 112.22, 113.91, 116.70, 123.90, 125.21, 128.44 (2C), 129.62 (2C), 130.48 (2C), 130.72 (2C), 131.04, 131.76, 135.42, 138.85, 139.40, 151.18, 156.91, 159.04, 165.42 (*C*=O). Anal. Calcd. for $C_{26}H_{23}NO_3$: C, 78.57; H, 5.83; N, 3.52. Found: C, 77.48; H, 5.16; N, 3.57. Yield %: 70.37. M.p. 110–112 °C.

*4.1.9.3. (E,Z)-1-(1-Benzofuran-2-yl)-2-mesitylethanone-O-(2-phenylacetyl)oxime (**9c**).* IR (KBr) (ν, cm^{-1}), 1761 (C=O stretching), 1108 (C–O–C benzofuran ring stretching), 939 (N–O stretching); ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.26 and 2.35 (s, 9H, $3CH_3$), 3.73 for *Z* isomer and 3.83 for *E* isomer (s, 2H, C(O)–CH_2), 4.15 for *Z* isomer and 4.25 for *E* isomer (s, 2H, Ar-CH_2), 6.69 (s, 1H, furan ring), 6.88 (s, 2H, mesitylene ring protons), 7.13–7.58 (m, 9H, benzofuran and phenyl ring protons); ^{13}C NMR ($CDCl_3$) δ: 22.33, 22.88, 34.24, 42.24, 113.62, 117.84, 124.67, 125.53, 129.07, 129.27 (2C), 129.84, 130.67 (2C), 130.92 (2C), 131.28 (2C), 131.52, 131.66 (2C), 138.17, 139.25, 146.83, 155.06, 158.75, 171.47 (*C*=O). Yield %: 62.59. M.p. 117–119 °C.

*4.1.9.4. (E,Z)-1-(1-Benzofuran-2-yl)-2-mesitylethanone-O-(4-methoxybenzoyl)oxime (**9d**).* IR (KBr) (ν, cm^{-1}), 1789 and 1747 (C=O stretching), 1164 (C–O–C benzofuran ring stretching), 1040 (N–O stretching); ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.26 for *Z* isomer and 2.31 for *E* isomer (s, 3H, CH_3), 2.45 (s, 6H, 2 CH_3), 3.90 (s, 3H, OCH_3), 4.34 (s, 2H, Ar-CH_2), 6.95 (s, 1H, furan ring), 6.96 (s, 2H, mesitylene ring protons), 7.26–7.93 (m, 6H, benzofuran and phenyl ring protons), 8.06–8.13 (m, 2H, phenyl ring protons). Anal. Calcd. for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.89; N, 3.28. Found: C, 75.10; H, 5.41; N, 3.12. Yield %: 87.58. M.p. 96–98 °C.

*4.1.10. Synthesis of (E,Z)-[1-(1-benzofuran-2-yl)-2-mesitylethylideneaminooxy]acetic acid hydrazide (**10**)*

Compound **8d** (0.70 g, 1.84 mmol) and hydrazine monohydrate (0.97 mL, *d*: 1.06 g/cm^3, 2 mmol, 99%) in ethanol (98%) were placed in a 100 mL flask with a reflux condenser. The reaction mixture was refluxed for 3 h. The mixture was cooled, and then water was added drop wise. The solid was filtrated off, dried and compound **10** was crystallized from ethanol. The following product was obtained.

*4.1.10.1. Synthesis of (E,Z)-[1-(1-benzofuran-2-yl)-2-mesitylethylideneaminooxy]acetic acid hydrazide (**10**).* IR (KBr) (ν, cm^{-1}), 3479–3288 (N–H stretching), 1666 (C=O stretching), 1169–1145 (C–O–C benzofuran ring stretching), 1049 (N–O stretching); ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.28 and 2.30 (s, 9H, $3CH_3$), 3.68–3.73 (broad, 2H, –NH–NH_2), 4.09 for *Z* isomer and 4.15 for *E* isomer (s, 2H, Ar-CH_2), 4.75 for *Z* isomer and 4.97 for *E* isomer (s, 2H, O–CH_2), 6.42–6.44 (broad, 1H, –C(O)–N*H*–NH_2), 6.82 (s, 2H, mesitylene ring protons), 6.91 (s, 1H, furan ring), 7.23–7.70 (m, 4H, benzofuran ring protons); ^{13}C NMR ($CDCl_3$) δ: 22.17, 22.89 (2C), 33.75, 75.36, 109.71, 113.63, 123.67, 124.45, 125.55, 128.79, 130.76 (2C), 132.13, 137.97, 138.86 (2C), 149.71, 153.29, 156.59, 172.06 (*C*=O). Yield %: 66.67. M.p. 114–115 °C.

*4.1.11. Synthesis of (E,Z)-[1-(1-benzofuran-2-yl)-2-mesitylethylideneaminooxy]acetic acid (**11**)*

Compound **8d** (0.70 g, 1.84 mmol) and powder NaOH (0.11 g, 2.76 mmol) in ethanol (98%) were placed in a two-necked flask with a condenser. The reaction mixture was refluxed for 1 h. The mixture was cooled and then water was added drop wise and was neutralized with dilute HCl. The solid was filtrated, dried and compound **11** was recrystallized from ethanol. The following product was obtained.

*4.1.11.1. (E,Z)-[1-(1-Benzofuran-2-yl)-2-mesityl-ethylideneaminooxy]acetic acid (**11**).* IR (KBr) (ν, cm^{-1}), 1725 (C=O stretching), 1175–1102 (C–O–C benzofuran ring stretching), 1048 (N–O stretching); ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm), 2.29 and 2.33 (s, 9H, $3CH_3$), 4.18 for *Z* isomer and 4.23 for *E* isomer (s, 2H, Ar-CH_2), 4.75 for *Z* isomer and 4.97 for *E* isomer (s, 2H, N–O–CH_2), 6.20 and 6.88 (s, 2H, mesitylene ring protons), 7.14–7.82 (m, 5H, benzofuran ring protons), 10.21–10.23 (broad, 1H, OH); ^{13}C NMR ($CDCl_3$) δ: 22.37 (2C), 22.92, 29.72, 72.87, 110.22, 113.55, 116.70, 124.49, 128.48, 130.40 (2C), 131.22, 132.40, 138.37, 139.16 (2C), 149.31, 153.53, 156.55, 176.94 (*C*=O). Anal. Calcd. for $C_{21}H_{21}NO_4$:

C, 71.78; H, 6.02; N, 3.99. Found: C, 70.54; H, 5.68; N, 3.57. Yield %: 82.81. M.p. 143–144 °C.

4.2. Microbiology

For determining both antibacterial and antifungal activities, 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 concentrations. The stock solutions were prepared in dimethylsulfoxide (DMSO) and DMSO had no effect on the microorganisms in the concentrations studied. Antimicrobial activities of compounds were determined by using broth microdilution method as described in Refs. [25,26]. After overnight incubation at 35 ± 1 °C, minimal drug concentration which inhibits the visual reproduction was accepted as minimal inhibitory concentration (MIC) value.

One Gram-positive and Gram-negative bacteria and one yeast-like fungi were used as quality control strains. Tested microorganisms were the Gram-positive *S. aureus* ATCC 6538, the Gram-negative *E. coli* ATTC 25922 and the yeast-like fungi, *C. albicans* ATCC 10231. *Meropenem* and *fluconazole* were used as antibiotic reference for bacteria and yeast, respectively (isolates obtained from Firat University at the School of Medicine, Department of Clinical Microbiology, Turkey).

4.2.1. Antibacterial and antifungal assays

Prior to testing bacterial strains were subcultured on blood agar plate (Oxoid), and incubated at 37 ± 1 °C for 24 h. The yeasts were subcultured on Sabouraud dextrose agar plate (Oxoid), and incubated at 35 ± 1 °C for 24 h [27]. Broth microdilution test was carried out using Cation Adjusted Mueller–Hinton broth (BBL) and RPMI 1640 medium buffered with MOPS at pH 7.0 and twofold serial dilution technique was applied. The final size of inoculum was 10^5 CFU/mL for bacteria and 0.5×10^3–2.5×10^3 CFU/mL for yeast.

Test compounds were dissolved in DMSO at an initial concentration of 1024 μg/ml and then were serially diluted in culture medium to 1 μg/ml.

A set of tubes containing only inoculumed broth was kept as control. Antibacterial and antifungal activities were determined after incubation both bacteria and yeasts for 48 h at 35 °C. MIC was defined as the lowest concentrations of the compounds that inhibited visible growth of the microorganism. Every experiment in the antibacterial and antifungal assays was replicated twice to define the MIC values.

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