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Synthesis, characterization and antimicrobial activity of novel benzofuran- and thiophene-containing diketoxime derivatives

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Abstract: The aim of this study was the preparation of 1,1′-(2,5-thiophene-diyl)bis[1-(2-benzofuranyl)methanone] (**2**), the corresponding diketoxime (**3**), and the ether and ester derivatives (**4a**–**e**) of the diketoxime. These compounds were prepared in good yields. Minimum inhibitory concentrations (*MIC*) of the synthesized compounds **1**–**4** were determined against Salmonella enterica subsp. enterica serovar Typhimurium, *Escherichia coli* and *Staphylococcus aureus*. Among the synthesized compounds, **1** and **4e** showed good activity against *E. coli*, *S. enterica* and *S. aureus*.

Keywords: bisbenzofuran; thiophene; diketoxime; antimicrobial activity.

INTRODUCTION

Benzofuran derivatives are an interesting class of heterocyclic compounds. Many benzofuran derivatives find application in several fields, including as anti-oxidants, brightening agents, a fluorescent sensor[1] and other fields of chemistry.[2] Benzofuran derivatives form a number of natural products, such as bergapten, nodakenetin, xanthotoxin and khellin (Fig. 1).

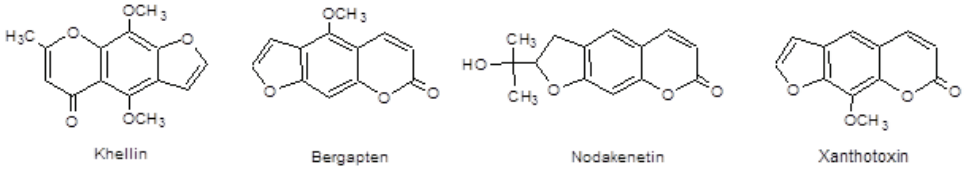

Fig. 1. Several benzofuran derivatives: a) khellin; b) bergapten; c) nodakenetin; d) xanthotoxin.

Thiophene and its derivatives exhibit interesting biological activities and considerable electroluminescent properties.[3,4] These compounds have been used

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as fluorescent markers and sensors in energy transfer and light-harvesting systems.[5]

The diketoxime derivatives are very important model systems in applied chemistry. In general, they are used in medicine, photography, agriculture, textiles, dye chemistry and the manufacture of semiconductors. Furthermore, they are also used as biological model compounds (*i.e.*, vitamin B12).[6–12]

Accordingly, the antibacterial and antifungal activities of oxime derivatives have been well explored.[13–20] Various heterocyclic-substituted oxime ethers were extensively studied due to their diverse biological properties.[21]

Oxime ethers are used as anti-inflammatory drugs,[22,23] β-adrenergics,[24] mild inhibitory active compounds in poultry science[25] and as various materials with steroidal effects.[26] The biological activities of the oxime ether pharmacophore –C=N–O–R is also well documented.[27] However, studies in the literature concerning bisbenzofuran-containing oxime compounds are limited.

Due to the applications of benzofuran, thiophene and diketoxime derivatives mentioned above, it was decided to design new benzofuran- and thiophene-based systems consisting of functionalized diketoxime.

The aim of this study was the synthesis of 1,1′-(2,5-thiophenediyl)bis[1-(2--benzofuranyl)methanone], its dioxime derivative, and new reaction products of the dioxime derivative with various acyl and alkyl halides. In addition, the antimicrobial behavior of all the synthesized compounds was investigated.

EXPERIMENTAL

All the chemicals were supplied from Sigma–Aldrich and used without further purification. Melting points were measured using a differential scanning calorimeter (Shimadzu DSC-50) and are uncorrected. The NMR spectra were determined on a Bruker AC 400 (400 MHz) spectrometer, with tetramethylsilane (TMS) as the internal standard in DMSO-d_6 or $CDCl_3$ as solvents. The FT-IR spectra were recorded as KBr pellets on a Perkin–Elmer Spectrum One FTIR spectrometer.

The synthesis scheme to compounds **1**–**4** is presented in Fig. 2, whereas analytical and spectral data are given in Supplementary material to this paper.

*Synthesis of compounds **1**–**3***

The required starting material 2-acetylbenzofuran was obtained by cyclocondensation reaction. Currently, several general methods are known for the preparation of 2-acetylbenzofuran.[28]

1-(Benzofuran-2-yl)-2-bromoethanone was obtained by reaction of 2-acetylbenzofuran with bromine in acetic acid, according to the general procedure described in the literature,[29] with slight modifications.

The new diketo sulfide (**1**) and its 2,5-diacylthiophene derivative (**2**) were prepared according to the procedure described by Miyahara.[30]

*Synthesis of 2,2'-thiobis[1-(1-benzofuranyl)ethanone] (**1**).* A solution of sodium sulfide nonahydrate (4.80 g, 20 mmol) in 12 mL of water was added dropwise to a stirred solution of 1-(benzofuran-2-yl)-2-bromo ethanone (9.56 g, 40 mmol) in 100 mL of acetone cooled in an ice bath. Reaction mixture was stirred at room temperature for 2 h. The yellow residue was

filtered and washed with water and methanol. The compound **1** was then recrystallized from benzene–methanol (1:3 volume ratio).

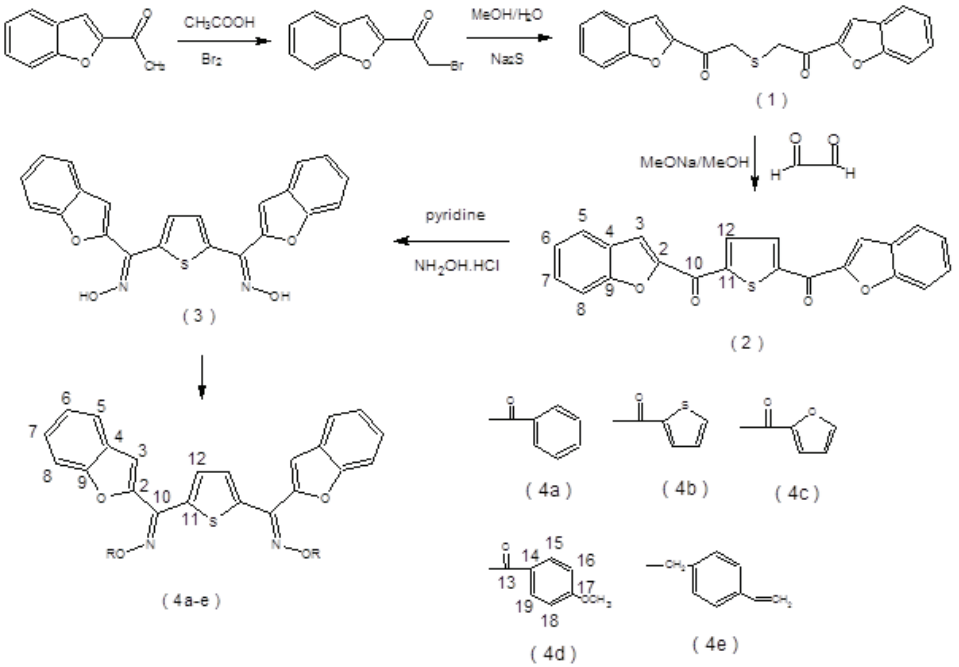

Fig. 2. Synthesis to the benzofuran- and thiophene-substituted diketoxime derivatives.

*Synthesis of 1,1′-(2,5-thiophenediyl)bis[1-(2-benzofuranyl)methanone] (**2**)*. A solution of glyoxal was prepared by refluxing a mixture of 0.34 g (1.60 mmol) glyoxal trimer dihydrate and 10 mL of methanol and 30 mL of dioxane for 1 h under magnetic stirring. The keto sulfide (1.40 g, 4 mmol) was dissolved in the solution. A solution of sodium methoxide (0.10 g of sodium dissolved in 10 mL of methanol) was added dropwise to this solution at 40 °C. A precipitate then began to form. The mixture was stirred for 30 min. The formed solid was filtered, washed with methanol and dried.

*Synthesis of 1,1′-(2,5-thiophenediyl)bis[1-(2-benzofuranyl)methanone], 1,1′-dioxime (**3**)*. Compound **2** (1.00 g, 2.69 mmol), hydroxylamine hydrochloride (0.37 g, 5.38 mmol) and pyridine (50 mL) were mixed and refluxed for 24 h. After cooling to room temperature, the mixture was poured into water and the crude **3** that separated was filtered, washed with water several times and crystallized from ethanol.

*General procedure for the synthesis of **4a–d***

Triethylamine (0.07 mL, 0.5 mmol) was added to a stirred solution of **3** (0.10 g, 0.25 mmol) in 5 mL of tetrahydrofuran. The mixture was stirred at room temperature for 10 min. The appropriate acyl chloride (0.5 mmol) was added dropwise at 0 °C and the reaction mixture was stirred at room temperature for 24 h. The mixture was poured into water and the formed precipitate was filtered, dried in air and recrystallized from ethanol.

*Synthesis of 1,1′-(2,5-thiophenediyl)bis[1-(2-benzofuranyl)methanone], 1,1′-bis[O-(4-ethenylphenyl)methyloxime] (**4e**)*. Compound **3** (0.10 g, 0.25 mmol), K_2CO_3 (0.076 g, 0.55

mmol) and the appropriate alkyl chloride (0.5 mmol) were mixed in absolute acetone and the mixture was refluxed for 5 h. After cooling to room temperature, the mixture was poured into water. The formed solid was filtered, washed with water and recrystallized from ethanol.

Antibacterial assays

Bacterial cultures were obtained in Mueller–Hinton broth (Difco) for *Escherichia coli* (ATCC 25922) Salmonella *enterica* subsp. *enterica* serovar Typhimurium (NRRL 4420) and *Staphylococcus aureus* (ATCC 6538) after 24 h of incubation at 37±0.1 °C. Testing for the bacteria was realized in Mueller–Hinton broth. The final inoculum size for all bacteria was 10^5 CFU mL^{-1}. The test compounds were dissolved in DMSO at an initial concentration of 1024 μg mL^{-1} and then serially diluted to 1 μg mL^{-1} in culture medium. A set of tubes containing only inoculated broth served as the control. Antibacterial activity was determined after incubation for 24 h at 37 °C. The minimum inhibitory concentration (*MIC*) and defined as the lowest concentration of the compounds that inhibited the visible growth of a microorganism. All experiments were replicated two times to define the *MIC* values.

RESULTS AND DISCUSSION

First, 2-acetylbenzofuran was obtained in the reaction of 2-hydroxybenzaldehyde and 1-chloroacetone. 1-(Benzofuran-2-yl)-2-bromoethanone, which was the starting material, was synthesized by bromination of 2-acetylbenzofuran with bromine in acetic acid. Treatment of this compound with hydroxylamine hydrochloride in pyridine gave **3**.

Reaction of **3** with appropriate acyl chlorides in THF in the presence of triethylamine gave the oxime ester compounds **4a**–**d**. Furthermore, reaction of compound **3** with the appropriate alkyl chloride in acetone in the presence of K_2CO_3, gave the oxime ether derivative **4e**.

All new compounds were characterized by ^{1}H-NMR, ^{13}C-NMR and FT-IR spectroscopy and elemental analysis. These data are given in the Supplementary material to this paper.

In FT-IR spectrum, the most important evidence of the formation **1** was the observation of two stretching vibrations at about 1663 and 1680 cm^{-1}, belonging to the two C=O groups. Additionally, in the ^{1}H-NMR spectrum, a signal at 4.1 ppm as a singlet belonging to $–SCH_2–$ protons and in the ^{13}C-NMR spectrum, a signal at 185.48 ppm belonging to the C=O group proved the formation of compound **1**.

In the FTIR spectrum of compound **2**, the C=O stretching vibration was observed at 1618 cm^{-1}. Due to conjugation, this stretching vibration shifted to a lower wave number. In the ^{1}H-NMR spectrum of this compound, the disappearance of the singlet signal at 4.1 ppm, belonging to $–SCH_2$ protons, was evidence for the formation of compound **2**.

In the IR spectrum of **3**, while OH band of the oxime was displayed between 3000–3250 cm^{-1}, the C=N stretching band and the N–O stretching band were seen at 1583 and at 1030 cm^{-1}, respectively. As is known, there are three geometrical isomers of the dioximes due to the two oxime groups including the *anti*-(*E*,*E*), *amphi*-(*E*,*Z*) and *syn*-(*Z*,*Z*) forms, which are shown in Fig. 3.[31]

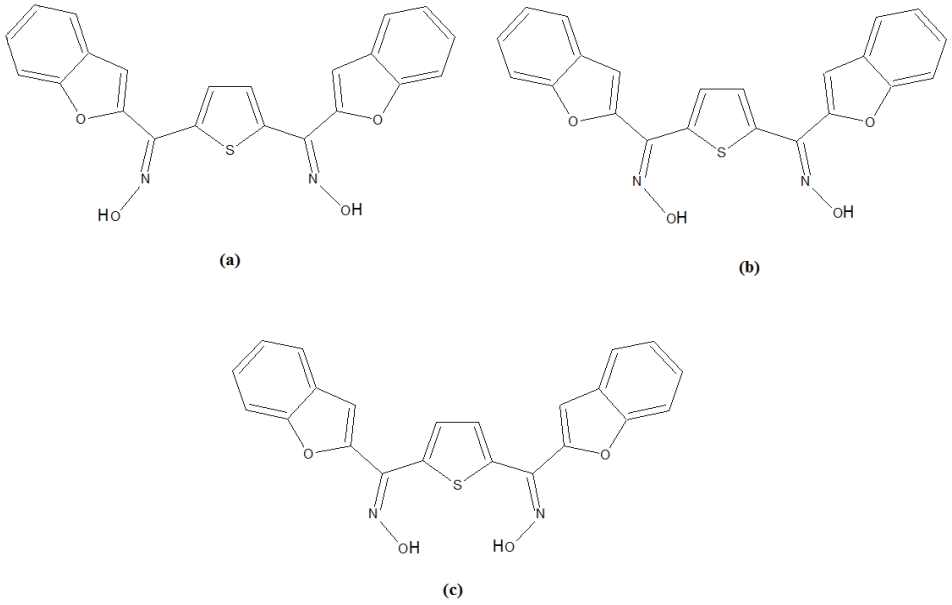

Fig. 3. Geometric isomers of the symmetrically substituted dioxime **3**: a) *anti*-(*E*,*E*), b) *amphi*-(*E*,*Z*) and c) *syn*-(*Z*,*Z*).

It was expected that **3** would show two different isomeric structures. When the ^{1}H-NMR spectrum for compound **3** was investigated, the N–OH resonances appeared as two singlets at 13.1 ppm (for the *E*,*E* isomer) and at 12.8 ppm (for the *Z*,*Z* isomer). The *E* isomer appeared at a higher frequency than the *Z* isomer.[32–36]

In the ^{13}C-NMR spectrum of dioxime **3**, twenty-four carbon signals were seen, supporting a *syn*- and *anti*-isomer mixture of compound **3**. In the ^{13}C-NMR spectrum of compound **3**, the C=N signal was displayed at 153 ppm while the C=O signal had disappeared. Dioxime **3** was not expected to be in the *amphi* form due to different integral values belonging to the N–OH protons at 13.1 and 12.8 ppm. The different integral values belonging to the two N–OH protons confirmed that compound **3** consisted of a *syn*- and *anti*-isomer mixture. Moreover, if the *amphi*-isomer were present in the mixture, more carbon peaks could be expected in the ^{13}C-NMR spectrum. Due to molecular balancing, the molecules in the *amphi*-isomer structure break down.

Additionally, a TLC run of a sample of the crystalline dioxime **3** was performed and doubled spots on the plate were observed. Therefore, it was concluded that the dioxime **3** consisted of a mixture of *EE*/*ZZ* isomers.

Reactions of dioxime **3** with appropriate alkyl and acyl chlorides gave isomer mixtures that consisted of dioxime ether and dioxime ester type compounds, **4a**–**e**. The disappearance of strong broad –OH band in the 3250–3000 cm^{-1}

region in the FT-IR spectrum of **4a**–**d** and the appearance of strong bands at around 1755–1740 and 1250–1050 cm^{-1}, which were due to C=O and C–O stretching vibrations, respectively, indicated the formation of ester products.

The ester derivatives of the dioxime **4b** (Fig. 4) and **4c** (Fig. 5) were obtained as a mixture of *anti*- and *amphi*-forms. In the ^{1}H-NMR spectrum of **4b**, the signals of thiophene ring protons (H_a1 and H_a) in the ester unit of the *amphi*--form of **4b** appeared as two doublets at 7.32 (J = 3.5 and 5.1 Hz) and 7.14 (J = = 3.6 Hz and 5.8 Hz) ppm. In the ^{1}H-NMR spectrum of **4b**, the signals of the thiophene ring protons of the *anti*-form of **4b** are probably among multiple signals at 7.33–8.15 ppm. In the ^{1}H-NMR spectrum of compound **4c**, both resonances of the furan ring proton (H_b) belonging to the *anti*-isomer of **4c** appeared as a singlet signal at 6.87 ppm. Signals of the H_a1 and H_a protons belonging to *amphi*-isomer of **4c** appeared as two singlets at 6.82 and 6.63 ppm. For a symmetrical dioxime in the *anti*-form, only a single peak was expected.[37,38] These three values might correspond to a mixture of *anti*- and *amphi*-forms.[39,40]

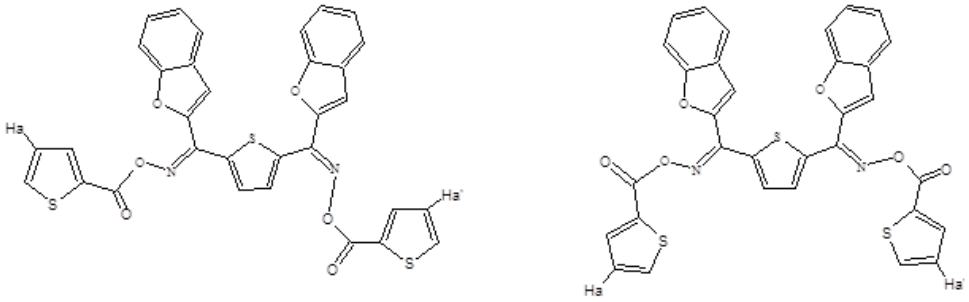

Fig. 4. a) *Amphi*-(*E*,*Z*)- and b) *anti*-(*E*,*E*)-isomers of **4b**.

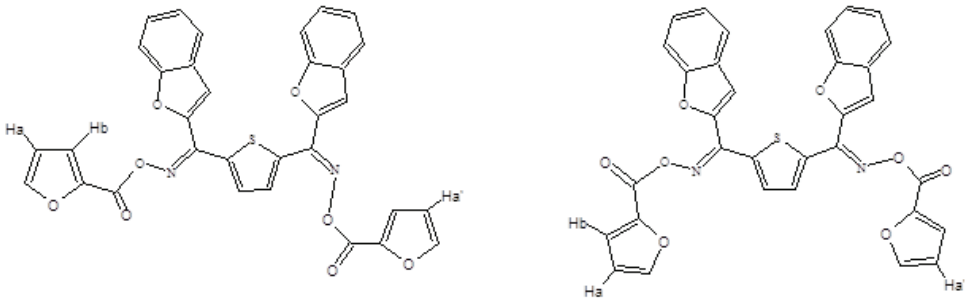

Fig. 5. a) *Amphi*-(*E*,*Z*)- and b) *anti*-(*E*,*E*)-isomers of **4c**.

The amounts of the *syn*-, *anti*- and *amphi*-isomers of **3** and **4c**–**e** were calculated from the integrated heights in the ^{1}H-NMR spectra and these values are given in Table I.

TABLE I. *E*,*E*, *Z*,*Z* and *E*,*Z* amounts, %, of 1,1′-(2,5-thiophenediyl)bis[1-(2-benzofuranyl)methanone], 1,1′-dioxime

Compound	Isomer		
	E,*E*	*Z*,*Z*	*E*,*Z*
3	55	45	–
4c	41	–	59
4d	61	39	–
4e	31	69	–

The ester derivatives of the dioxime **4a, 4d** and **4e** (Fig. 6) were obtained as a mixture of *anti*- and *syn*-forms. In the ^{1}H-NMR spectrum of **4d**, signal of the OCH_3 protons belonging to the *anti*-isomer of **4d** was observed as a singlet signal at 3.87 ppm. In addition, the signal of the OCH_3 protons belonging to the *syn*--isomer of **4d** appeared as a singlet at 3.75 ppm. In the ^{1}H-NMR spectrum of **4e**, signals of the OCH_2 protons belonging to the *anti*- and *syn*-isomer were observed as two singlets at 5.47 and 5.40 ppm, respectively.

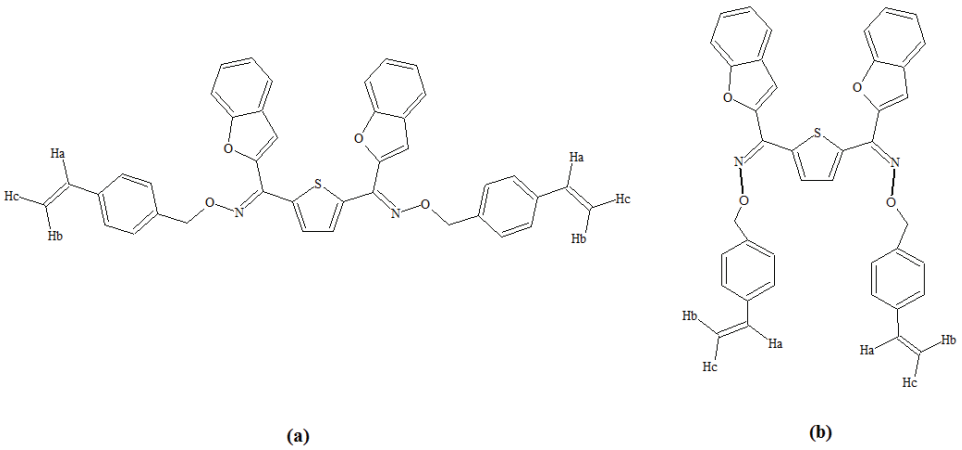

Fig. 6. a) *Anti*-(*E*,*E*)- and b) *syn*-(*Z*,*Z*)-isomers of **4e**.

In the ^{13}C-NMR spectra of **4b** and **4c**, the 48 carbon signals prove that these dioxime derivatives consisted of *anti*- and *amphi*-isomer mixtures. Moreover, in the ^{13}C-NMR spectra of **4a**, **4d** and **4e**, the 34, 38 and 40 carbon signals, respectively, proved that these dioxime derivatives consisted of *anti*- and *syn*-isomer mixtures.

The OCH_3 proton signals at 3.87 ppm (*anti*-isomer) and 3.75 ppm (*syn*-isomer) also have good correlation with the quaternary carbon signal at 162.72 ppm in HMBC spectrum (Fig. S-7c of the Supplementary material). The ^{13}C-signals at 56.17 ppm (*anti*-isomer) and 56.02 ppm (*syn*-isomer) give cross peaks with two OCH_3 protons belonging to the *anti*- and *syn*-isomers at 3.87 and 3.75 ppm, res-

pectively, in the HSQC spectrum (Fig. S-7d of the Supplementary material). It is clear that the signals at 56.17 and 56.02 ppm belong to the aliphatic OCH_3 carbons of *anti*- and *syn*-isomers of **4d**. All these data obtained from HSQC and HMBC spectra showed that the signal at 162.72 ppm is the quaternary carbon (C-17) on the disubstituted phenyl ring. The ^{13}C-signals at 132.59 and 132.35 ppm have a cross peak with the proton resonances around 8.14–8.04 ppm (*anti*--isomer) and 7.94–7.92 ppm (*syn*-isomer) in the HSQC spectrum. These proton signals have good *β*-correlation with the carbon signals at 164.35 and 164.17 ppm in the HMBC spectrum. It is clear that the signals at 164.35 and 164.17 ppm belong to the carbonyl carbon (C-13) of *anti*- and *syn*-isomers of **4d**. In the HSQC spectrum, the signals around 7.83–7.77 ppm have a cross peak with the ^{13}C-signals at 112.38 and 112.31 ppm. In the HMBC spectrum, the same proton signals are in correlation with the quaternary carbon (C-4) signals at 127.54 ppm (*anti*-isomer) and 127.46 ppm (*syn*-isomer). These data show that the signals around 7.83–7.77 ppm belong to the olefinic protons attached to the olefinic carbons (C-3) on benzofuran, which give signals at 112.38 and 112.31 ppm. The correlations in the HMBC spectrum show that the carbons giving the signals at 155.49 and 154.81 ppm, 148.81 and 148.51 ppm and 127.54 and 127.46 ppm belong to C-9, C-2 and C-4 of the *anti*- and *syn*-isomers, respectively. The signals around 7.83–7.94 ppm have cross peaks with the ^{13}C-signals at 123.64 ppm (*anti*-isomer) and 122.99 ppm (*syn*-isomer) in the HSQC spectrum and have *α*-correlation with the quaternary carbon signals at 155.49 and 154.81 ppm and 127.54 and 127.46 ppm in the HMBC spectrum. The protons giving the signals around 7.83–7.94 ppm are attached to C-5, which resonate at 123.64 ppm (*anti*--isomer) and 122.99 ppm (*syn*-isomer). The quaternary carbon signals at 155.49 and 154.81 ppm and 148.81 and 148.51 ppm have *α*-correlation with the signals at 7.65–7.59 ppm in the HMBC spectrum, and these proton signals have cross peak with the ^{13}C-signal at 113.48 ppm (*anti*-isomer) and 113.36 ppm (*syn*-isomer) in the HSQC spectrum. These data show that the signals around 7.65–7.59 ppm are due to the protons attached to C-8.

Antibacterial activity

The minimal inhibitory concentration (*MIC*) of the synthesized compounds was determined against *S. aureus, E. coli* and *S. enterica* subsp. *enterica* serovar Typhimurium using a standard broth dilution technique. All the *MIC* results are presented in Table II. The obtained data showed that the compounds were able to inhibit the growth of the selected microorganisms *in vitro* with *MIC* values between 32 and 128 μg mL^{-1}.

Among the synthesized compounds, **4e** exhibited good activity against *S. aureus* and *E. coli* and **1** against *S. enterica* subsp. *enterica* serovar Typhimurium

with an *MIC* value of 32 μg mL^{-1}. The other compounds showed moderate activity against the tested microorganisms.

TABLE II. Minimum inhibitory concentration (*MIC* / μg mL^{-1}) of compounds **1**–**4**; positive control: chloramphenicol

Compound	*E. coli* ATCC 25922	*S. enterica* NRRL 4420	*S. aureus* ATCC 6538
1	64	32	64
2	64	128	64
3	64	64	128
4a	64	128	128
4b	64	128	64
4c	128	128	128
4d	128	128	64
4e	32	64	32
Positive control	32	32	32

CONCLUSIONS

In the present study, 1,1′-(2,5-thiophenediyl)bis[1-(2-benzofuranyl)methanone] (**2**), the corresponding diketoxime (**3**) and the ether and ester derivatives (**4a**–**e**) of the diketoxime were designed and synthesized. The synthesized compounds **3** and **4a**–**e** were mixtures of different isomers, such as *syn*-, *anti*- and *amphi*-isomers. Synthesized compounds were tested for antimicrobial activity against *S. aureus*, *E. coli* and *S. enterica* subsp. *enterica* serovar Typhimurium. Among the synthesized compounds, **1** and **4e** showed good activity against *E. coli* (ATCC 25922), *S. typhimurium* (NRRL 4413) and *S. aureus* (ATCC 6538). The biological effects of **1**–**4** could be helpful in the design of more potent antibacterial agents for therapeutic use.

SUPPLEMENTARY MATERIAL

Analytical and spectral data, as well as the NMR spectra, of the synthesized compounds are available electronically at the pages of journal website: http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА, КАРАКТЕРИЗАЦИЈА И АНТИМИКРОБНА АКТИВНОСТ НОВИХ ДЕРИВАТА ДИКЕТОКСИМА КОЈИ САДРЖЕ БЕНЗОФУРАН И ТИОФЕН

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Описана је синтеза 1,1′-(2,5-тиофендиул)бис[1-(2-бензофуранил)метанона] (**2**), одговарајућих дикетоксима (**3**) и етарских и естарских деривата дикетоксима (**4a**–**e**). Једињења су синтетисана у добром приносу. Одређена је минимална инхибиторна

активност (*MIC*) синтетисаних једињења **1**–**4** према *Salmonella enterica* subsp. *enterica* serovar Typhimurium, *Escherichia coli* и *Staphylococcus aureus*. Од синтетисаних једињења, деривати **1** и **4e** показују добру активност према *E.coli, S. enterica* и *S.aureus*.

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