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Synthesis and antimicrobial activity of some new *N*-(aryloxoalkyl)-5-arylidene-thiazolidine-2,4-diones

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Abstract: A series of new 5-(2,6-dichlorobenzylidene)thiazolidine-2,4-dione and 5-(4-methoxybenzylidene)thiazolidine-2,4-dione derivatives (**3a–h** and **5a–h**, respectively) were synthesized starting from 5-arylidenethiazolidine--2,4-dione and *α*-halo-ketones. The structural elucidation of the newly synthesized compounds was based on elemental analysis and spectroscopic data (MS, ^{1}H-NMR and ^{13}C-NMR). The synthesized compounds were screened *in vitro* for their antimicrobial activities against several pathogenic strains of Gram-positive and Gram-negative bacteria and one fungal strain (*Candida albicans*), as growth inhibition diameters. Some of the compounds displayed better inhibitory activities than that of the reference drug against the Gram--positive *Staphylococcus aureus*, *Bacillus cereus* and *Listeria monocytogenes* bacterial strains, and showed good antifungal activity against *C. albicans*, while the antibacterial activity against the Gram-negative *Escherichia coli* and *Salmonella typhimurium* bacterial strains was moderate.

Keywords: 5-arylidenethiazolidine-2,4-dione; *α*-haloketone; antibacterial; antifungal.

INTRODUCTION

Heterocyclic compounds have long been recognized in the field of synthetic organic chemistry as a very important class. Nitrogen-, oxygen- and sulphur--containing heterocyclic compounds are known to exhibit a large variety of biological activities and are used in various fields of pharmacy.[1]

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Especially great attention has been given to thiazolidine-2,4-dione derivatives as they posses a diverse array of pharmacological activities, such as antidiabetic,[2] antioxidant, analgesic, anti-arthritic,[3] anti-inflammatory,[4] anticancer,[5] antibacterial and antifungal.[6] Besides showing a remarkable antidiabetic activity by binding with PPARγ, heterocyclic compounds bearing thiazolidine-2,4-dione moiety with substitution at the fifth position can reduce oxidative stress and inhibit intracellular free radical overproduction.[7] They also have inhibitory effects on monocyte/macrophage activation, the expression of inflammatory molecules[8] and tyrosinase activity.[9] It was reported that 5-arylidene-2,4-thiazolidinediones can act as potentially promising 15-hydroxyprostaglandin dehydrogenase inhibitors,[10] inhibitors of MurD ligase[11] and antimicrobial agents.[12–14]

The search for new high-effective antimicrobial drugs is a very important issue because of the appearance of a large group of antibiotic and antifungal resistant strains.[15]

In view of these facts and in continuation of efforts to discover potentially active new antimicrobial agents,[16] the synthesis of two series of various N-substituted 5-arylidene-thiazolidine-2,4-diones and an evaluation of their antibacterial and antifungal activities are reported herein.

RESULTS AND DISCUSSION

Chemistry

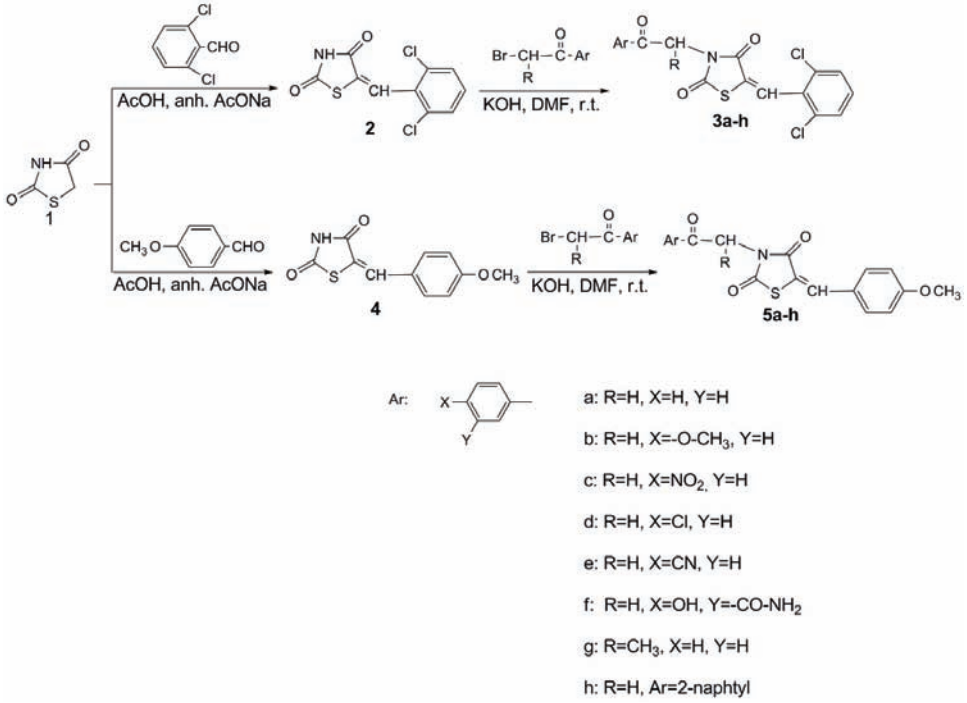
The synthetic strategy for the target compounds, *N*-(aryloxoalkyl)-5-(2,6-dichlorobenzylidene)thiazolidine-2,4-diones (**3a**–**h**) and *N*-(aryloxoalkyl)-5-(4-methoxybenzylidene)thiazolidine-2,4-diones (**5a**–**h**) is illustrated in Scheme 1.

The general method known as the Knoevenagel condensation was used to synthesize the *N*-unsubstituted 5-arylidene-thiazolidine-2,4-diones (**2** and **4**) in good yields (94–95 %). 5-(2,6-Dichlorobenzylidene)thiazolidine-2,4-dione (**2**) and 5-(4-methoxybenzylidene)thiazolidine-2,4-dione (**4**) were prepared by the condensation of thiazolidine-2,4-dione with the appropriate arylaldehyde, according to procedures reported in the literature.[17,18]

In order to accomplish *N*-substitution, the 5-arylidenethiazolidine-2,4-diones (**2** and **4**) were first converted into potassium salts at the nitrogen atom of the thiazolidine-2,4-dione ring with the help of anhydrous potassium hydroxide in dimethylformamide (DMF) under continuous stirring at room temperature. The treatment of the obtained potassium salts with various α-halo-ketones in DMF under continuous stirring at room temperature afforded the target compounds, *N*-(aryloxoalkyl)-5-arylidene-thiazolidine-2,4-diones (**3a**–**h** and **5a–h**, respectively) in 45–95 % yields.

The newly synthesized *N*-substituted 5-arylidenethiazolidine-2,4-diones (**3a**–**h** and **5a–h**) were characterized by melting point, elemental analysis and spectro-

scopic data (^{1}H-NMR, ^{13}C-NMR and MS). All compounds gave good CHNS quantitative elemental analysis results, in agreement with the calculated values**.** All spectral and analytical data were consistent with the assumed structures. Details of the synthetic procedures and the yields are presented in the Experimental while the physical, analytical and spectral data for the synthesized compounds are given in the Supplementary material to this paper.



Scheme 1. General synthetic route for the synthesis of the compounds **3a**–**h** and **5a**–**h**.

The IR spectra of the synthesized compounds **3a**–**h** and **5a**–**h** displayed three strong absorption peaks at 1749–1731 cm^{-1}, 1705–1692 cm^{-1} and 1687–1668 cm^{-1} due to C=O stretching of the thiazolidine-2,4-dione ring and the arylalkylketone, respectively. The absence of absorption bands corresponding to the –NO group of the thiazolidine-2,4-dione moiety in the IR spectra of all the newly synthesized compounds confirmed the formation of *N*-substituted derivatives. Compounds **3b** and **5a**–**h** give two strong bands at 1043–1031 cm^{-1} and 1258––1248 cm^{-1} due to the presence of phenyl methyl ether group. The absorption bands at 1521–1517 cm^{-1} and 1331–1324 cm^{-1} in the IR spectra of compounds **3c** and **5c** are due to the asymmetric and symmetric stretch of the –NO_2 group. The IR spectra of compounds **3e** and **5e** exhibited one sharp absorption at 2235––2231 cm^{-1} due to the –C≡N stretch. In the IR spectra of compounds **3f** and **5f**,

the C=O stretch of the amide group appeared at 1635–1628 cm^{-1} and the phenol group presented an absorption band at 1233–1231 cm^{-1} due to the C–O stretching vibration and an absorption band at 3417–3411 cm^{-1} due to the intramolecular hydrogen-bonded OH stretch.

The ^{1}H-NMR spectra of the synthesized compounds **3a**–**h** and **5a**–**h** showed one signal for the methylidene proton, as a singlet at 7.879–7.991 ppm, which supported the occurrence of the Knoevenagel condensation between the thiazolidine-2,4-dione and aromatic aldehydes. The absence of a singlet signal corresponding to the NH proton from the thiazolidine-2,4-dione ring in the 12.50–12.52 ppm region[16] in the ^{1}H-NMR spectra of all compounds confirmed the formation of *N*-substituted derivatives. The $-OCH_3$ protons resonated as singlets at 3.822––3.896 ppm and the aromatic protons appeared as characteristic doublets, triplets or multiplets in the 7.043–8.902 ppm region of the ^{1}H-NMR spectra. ^{13}C-NMR spectra of the synthesized compounds were in accordance with the assumed structures.

The mass spectra of the synthesized compounds gave idea about the fragmentation of the final compounds with their corresponding mass and revealed the correct molecular ion peaks (M^+ or M+1), as suggested by their molecular formulas.

Antibacterial/antifungal activity

All compounds were tested for their antibacterial activity against two Gram--negative (*Salmonella typhimurium* ATCC 13311 and *Escherichia coli* ATCC 25922) and three Gram-positive (*Listeria monocytogenes* ATCC 35152, *Staphylococcus aureus* ATCC 25923 and *Bacillus cereus* ATCC 13061) bacterial strains. The antifungal activity of the compounds was evaluated against a strain of *Candida albicans* ATCC 90028.

The results of the antifungal and antibacterial activity of the *N*-(aryloxoalkyl)-5-arylidenethiazolidine-2,4-diones **3a**–**h** and **5a**–**h** in comparison with those of reference drugs are presented in Table I.

All the tested compounds presented modest to good inhibitory activity against the Gram-positive and the Gram-negative bacteria, compared to ciprofloxacin (50 μg $well^{-1}$), employed as a standard drug. All of the synthesized compounds were active and showed moderate activity against *E. coli* and *S. typhimurium* (10–18 mm inhibition zone). The 5-(4-methoxybenzylidene)thiazolidine-2,4-diones (**5a**–**h**) were generally more active than the 5-(2,6-dichlorobenzylidene)thiazolidine-2,4-diones (**3a**–**h**), suggesting that substitution of the thiazolidine-2,4-dione ring with a methoxybenzylidene moiety in the fifth position rather than with a 2,6-dichlorobenzylidene moiety favoured the antibacterial activity of the compounds against Gram-negative bacteria. On the contrary, the 5-(2,6-dichlorobenzylidene)thiazolidine-2,4-diones **3a**–**h** exhibited better anti

-bacterial properties than the 5-(4-methoxybenzylidene)thiazolidine-2,4-diones (**5a**–**h**) did against the Gram-positive bacteria. Compounds **3a,c,e** and **f** and **5a**–**c** displayed similar or better inhibitory activities than that of the reference drug ciprofloxacin against *S. aureus*, while compounds **3e–f** were more active than ciprofloxacine against *L. monocytogenes*, and compound **3f** was more active than the standard against *B. cereus*. The antibacterial activity of compounds **3a, 3c** and **3e**–**f** and **5a**–**c** was generally better than that of the other *N*-(aryloxoalkyl)--5-arylidenethiazolidine-2,4-diones, suggesting that the presence of an electron withdrawing group, such as nitro, nitrile or carbonyl, on the aromatic ring plays an important role in enhancing the antibacterial properties of the titled compounds. Regarding the antifungal activity, most of the synthesized compounds showed moderate to good inhibition (14–24 mm inhibition zone) against *C. albicans*, at the test concentrations.

TABLE I. Antimicrobial activity of the synthesized compounds **3a**–**h** and **5a**–**h**; inhibition zone, mm; (–) no activity

Compound	Gram-positive bacteria			Gram-negative bacteria		Fungi
	S. aureus	*L. monocytogenes*	*B. cereus*	*E. coli*	*S. typhimurium*	*C. albicans*
3a	20	18	20	16	14	14
3b	18	16	12	12	12	18
3c	28	16	18	14	16	16
3d	18	16	16	12	14	18
3e	22	28	20	12	12	22
3f	20	22	24	10	16	22
3g	18	18	16	10	14	24
3h	18	16	14	10	14	18
5a	20	18	14	14	18	18
5b	20	18	14	14	18	18
5c	24	16	12	12	18	16
5d	18	16	12	12	18	16
5e	18	18	12	14	16	14
5f	18	18	14	14	18	14
5g	18	16	12	18	18	16
5h	18	16	12	16	18	16
Ciprofloxacin[a]	20	22	22	24	22	–
Fluconazole[a]	–	–	–	–	–	25

[a]Ciprofloxacin and fluconazole (50 μg well^{-1}) were used as standard drugs

EXPERIMENTAL

Chemistry

All chemicals and reagents were obtained from commercial sources and were used as supplied, without further purification. Compounds **2** and **4** were previously reported in the literature.[16-18]

Melting points were determined with an electrothermal melting point meter in open glass capillary method and are uncorrected. The reaction progress and purity of the synthesized

compounds were monitored by analytical thin layer chromatography (TLC) using Merck pre-coated Silica Gel $60F_{254}$ sheets (Darmstadt, Germany), a heptane–ethyl acetate 3:7 elution system and UV light for visualization. The IR spectra were recorded on a JASCO FT-IR-4100 spectrometer (Cremella, Italy) using the ATR technique (Attenuated Total Reflectance). The nuclear magnetic resonance (^{1}H-NMR) spectra were recorded at room temperature on Bruker Avance NMR spectrometer (Karlsruhe, Germany) operating at 500 and 125 MHz for ^{1}H- and ^{13}C-NMR, respectively, using tetramethylsilane (TMS) as an internal standard (chemical shifts, δ, in ppm). The spectra were in accordance with the assigned structures. The samples were prepared by dissolving the compounds in DMSO-d_6 (δ_H = 2.51 ppm) as solvent and the spectra were recorded using a single excitation pulse of 12 μs (^{1}H-NMR). Spin multiplets are given as *s* (singlet), *d* (doublet), *t* (triplet) and *m* (multiplet). The ^{13}C-NMR spectra were recorded on a Bruker Avance NMR spectrometer (Karlsruhe, Germany) operating at 125 MHz in DMSO-d_6, using a waltz-16 decoupling scheme. The MS analyses were performed at 70 eV with an Agilent gas chromatograph 6890 (Darmstadt, Germany) equipped with an apolar Macherey Nagel Permabond SE 52 capillary column (Dueren, Germany) and with an LCMS--2020 Shimadzu mass spectrometer (Shimadzu Corporation, North America). Elemental analyses were realized using a Vario El CHNS instrument (Hanau, Germany). Physical, analytical and spectral data of the prepared compounds are given in Supplementary material to this paper.

*5-(2,6-Dichlorobenzylidene)-3-(2-oxo-2-phenylethyl)thiazolidine-2,4-dione (**3a**)*. 1 mmol (273 mg) of **2** was dissolved in dimethylformamide (DMF) (3.5 mL) and finely dispersed anhydrous potassium hydroxide (84 mg, 1.5 mmol) was added. The mixture was stirred for 30 min at room temperature to give the potassium salt of 5-(2,6-dichlorobenzylidene)thiazolidine-2,4-dione. To the resulting suspension was added 2-bromo-1-phenylethanone (199 mg, 1 mmol) for *N*-substitution. The mixture was stirred at room temperature for 8 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mass was poured into ice-cold water. The resulting precipitate was filtered, washed with water and ethanol, dried and then recrystallized from absolute ethanol. Yellow solid; yield: 85 %.

*5-(2,6-Dichlorobenzylidene)-3-[2-(4-methoxyphenyl)-2-oxoethyl]thiazolidine-2,4-dione (**3b**)*. Using 2-bromo-1-(4-methoxyphenyl)ethanone (229 mg, 1 mmol), the compound was prepared according to the procedure described for **3a**. White solid; yield: 93 %.

*5-(2,6-Dichlorobenzylidene)-3-[2-(4-nitrophenyl)-2-oxoethyl]thiazolidine-2,4-dione (**3c**)*. The compound was prepared according to the procedure for **3a** using 2-bromo-1-(4--nitrophenyl)ethanone (244 mg, 1 mmol). Dark brown solid; yield: 69 %.

*3-[2-(4-Chlorophenyl)-2-oxoethyl]-5-(2,6-dichlorobenzylidene)thiazolidine-2,4-dione (**3d**)*. The title compound was prepared according to the procedure described for **3a** using 2-bromo--1-(4-chlorophenyl)ethanone (233.5 mg, 1 mmol). Brown solid; yield: 74 %.

*4-{2-[5-(2,6-Dichlorobenzylidene)-2,4-dioxothiazolidin-3-yl]acetyl}benzonitrile (**3e**)*. The title compound was prepared following the procedure presented for **3a** using 4-(2-bromo-acetyl)benzonitrile (224 mg, 1 mmol) and was recrystallized from absolute ethanol. Yellow solid; yield: 51 %.

*5-{2-[5-(2,6-Dichlorobenzylidene)-2,4-dioxothiazolidin-3-yl]acetyl}-2-hydroxybenzamide (**3f**)*. The compound was prepared using 5-(2-bromoacetyl)-2-hydroxybenzamide (258 mg, 1 mmol) following the synthetic procedure described for **3a**. Brown solid; yield: 53 %.

*5-(2,6-Dichlorobenzylidene)-3-(1-methyl-2-oxo-2-phenylethyl)thiazolidine-2,4-dione (**3g**)*. The title compound was prepared following the procedure presented for **3a** using 2-bromo-1-phenylpropan-1-one (213 mg, 1 mmol). Yellow liquid; yield: 45 %.

*5-(2,6-Dichlorobenzylidene)-3-[2-(naphthalen-2-yl)-2-oxoethyl]thiazolidine-2,4-dione (**3h**)*. The title compound was prepared using 2-bromo-1-(naphthalen-2-yl)ethanone (249 mg, 1 mmol) according to the procedure described for **3a**. White solid; yield: 78 %.

*5-(4-Methoxybenzylidene)-3-(2-oxo-2-phenylethyl)thiazolidine-2,4-dione (**5a**)*. To a solution of **4** (235 mg, 1 mmol) in DMF (3.5 mL) was added finely dispersed anhydrous potassium hydroxide (84 mg, 1.5 mmol). The mixture was stirred for 30 min at room temperature to give the potassium salt of 5-(4-methoxybenzylidene)thiazolidine-2,4-dione. To the resulting suspension was added 2-bromo-1-phenylethanone (199 mg, 1 mmol) and then the reaction mixture was stirred at room temperature for 8 h. TLC was used to monitor the reaction progress. After completion of the reaction, the mass was poured into ice-cold water under continuous stirring. The resulting compound was washed with water and ethanol, dried and then recrystallized from absolute ethanol. White solid; yield: 79 %.

*5-(4-Methoxybenzylidene)-3-(2-(4-methoxyphenyl)-2-oxoethyl)thiazolidine-2,4-dione (**5b**)*. Using 2-bromo-1-(4-methoxyphenyl)ethanone (229 mg, 1 mmol), the title compound was prepared according to the procedure described for **5a**. White solid; yield: 95 %.

*5-(4-Methoxybenzylidene)-3-[2-(4-nitrophenyl)-2-oxoethyl]thiazolidine-2,4-dione (**5c**)*. The title compound was prepared according to the procedure for **5a** but using 2-bromo-1-(4--nitrophenyl)ethanone (244 mg, 1 mmol). Pale yellow solid; yield: 92 %.

*3-[2-(4-Chlorophenyl)-2-oxoethyl]-5-(4-methoxybenzylidene)thiazolidine-2,4-dione (**5d**)*. The title compound was prepared according to the procedure described for **5a** but using 2-bromo-1-(4-chlorophenyl)ethanone (233.5 mg, 1 mmol). White solid; yield: 78 %.

*4-{2-[5-(4-methoxybenzylidene)-2,4-dioxothiazolidin-3-yl]acetyl}benzonitrile (**5e**)*. Following the procedure presented for **5a**, the title compound was prepared using 4-(2-bromoacetyl)benzonitrile (224 mg, 1 mmol) and was recrystallized from absolute ethanol. Light brown solid; yield: 53 %;

*2-Hydroxy-5-{2-[5-(4-methoxybenzylidene)-2,4-dioxothiazolidin-3-yl]acetyl}benzamide (**5f**)*. The compound was prepared using 5-(2-bromoacetyl)-2-hydroxybenzamide (258 mg, 1 mmol) according to the synthetic procedure described for **5a**. Yellow solid; yield: 62 %.

*5-(4-Methoxybenzylidene)-3-(1-methyl-2-oxo-2-phenylethyl)thiazolidine-2,4-dione (**5g**)*. Following the procedure presented for **5a** but using 2-bromo-1-phenylpropan-1-one (213 mg, 1 mmol), the title compound was prepared. White solid; yield: 64 %.

*5-(4-Methoxybenzylidene)-3-[2-(naphthalen-2-yl)-2-oxoethyl]thiazolidine-2,4-dione (**5h**)*. The title compound was prepared using 2-bromo-1-(naphthalen-2-yl)ethanone (249 mg, 1 mmol) according to the procedure described for **5a**. White solid; yield: 81 %.

Antibacterial/antifungal activity

The *in vitro* antimicrobial activity was determined using the cup-plate agar diffusion method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.[19]

For antibacterial testing, Mueller–Hinton agar medium was used whereas for antifungal testing, Mueller–Hinton medium supplemented with 2 % glucose (providing adequate growth of yeasts) and 0.5 mg mL^{-1} methylene blue (providing a better definition of the inhibition zone diameter) was used. The inoculum was prepared by suspending five representative colonies, obtained from an 18–24 h culture on non-selective nutritive agar medium, in sterile distilled water. The cell density was adjusted to the density of 0.5 McFarland standard by measuring the absorbance in a spectrophotometer at a wavelength of 530 nm and adding sterile distilled water as required (corresponding to a population of $(1–5)\times10^6$ CFU mL^{-1}). A sterile swab was soaked in suspension and then the Mueller–Hinton agar plates were inoculated by streaking the entire surface. After drying for 10–15 min, six mm-diameter wells were cut from the agar

using a sterile cork-borer, and a volume of 10 μL of each compound solution (5 mg mL^{-1} in DMSO) were delivered into the wells (50μg $well^{-1}$). Ciprofloxacin (50 μg $well^{-1}$) and fluconazole (50 μg $well^{-1}$) were used as standard drugs. The controls were performed with only sterile broth, overnight culture and 10 μL DMSO. The plates were incubated at 35 °C. The inhibition zone diameters were measured to the nearest whole millimetre where there was no visible growth after 24–48 h. The results were obtained in triplicate. The solvent used for the preparation of each compound stock solution (5 mg ml^{-1}), DMSO (Merck, Germany) exhibited no inhibitory activity against the tested bacterial and fungal strains.

CONCLUSIONS

In conclusion, a series of new 5-(2,6-dichlorobenzylidene)thiazolidine-2,4--dione and 5-(4-methoxybenzylidene)thiazolidine-2,4-dione derivatives were synthesized by Knoevenagel condensation of thiazolidine-2,4-dione with the required aromatic aldehyde, followed by N_3-substitution with various *α*-halo--ketones. Their structures were confirmed by analytical techniques: ^{1}H-NMR, ^{13}C-NMR, mass and elemental analysis. The synthesized compounds were evaluated for their antibacterial and antifungal activities against several Gram-positive, Gram-negative bacteria and *Candida albicans*. The results of the antimicrobial screening revealed that all of the tested compounds have antibacterial and antifungal properties, while some showed promising antimicrobial activities: compounds **3c**, **3e** and **5c** displayed better inhibitory activities than ciprofloxacin against *S. aureus*, compounds **3e** and **3f** were more active against *L. monocytogenes* and compound **3f** was more active against *B. cereus* than ciprofloxacin.

SUPPLEMENTARY MATERIAL

Physical, analytical and spectral data of the prepared compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

ИЗВОД

СИНТЕЗА И АНТИМИКРОБНА АКТИВНОСТ НОВИХ *N*-(АРИЛОКСОАЛКИЛ)-5--АРИЛИДЕНТИАЗОЛИДИН-2,4-ДИОНА

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Синтетисана је серија нових деривата 5-(2,6-дихлоробензилиден)тиазолидин-2,4--диона и 5-(4-метоксибензилиден)тиазолидин-2,4-диона (**3a**–**h** и **5a**–**h**) полазећи од 5-арилидентиазолидин-2,4-диона и *α*-халоген-кетона. Структура нових једињења одређена је на основу елементалне анализе и спектроскопских података (IR, MS, ^{1}H-NMR и ^{13}C-NMR). Одређена је антимикробна активност синтетисаних једињења према неко-

лико сојева грам-позитивних и грам-негативних бактерија и сoју гљивица (*Candida albicans*). Нека од синтетисаних једињења показују добру активност према *C. albicans*, док је активност према сојевима грам-негативних бактерија *Escherichia coli* и *Salmonella typhimurium* умерена.

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