

Regular Article

Design, Synthesis, Characterization and Antimicrobial Evaluation of Some Heterocyclic Condensed Systems with Bridgehead Nitrogen from Thiazolotriazole Class

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In the present study, a series of new heterocyclic condensed systems with bridgehead nitrogen from the thiazolo[3,2-*b*][1,2,4]triazoles class was synthesized starting from some 4-(4-*X*-phenylsulfonyl)phenyl)-4*H*-1,2,4-triazole-3-thioles 1a–c (*X*=H, Cl, Br). The intermediates of *S*-alkylated 1,2,4-triazoles, 2-(5-(4-*X*-phenylsulfonyl)phenyl)-2*H*-1,2,4-triazol-3-ylthio)-1-(4-fluorophenyl)ethanones 2a–c, were obtained by treatment of triazoles 1a–c with 2-bromo-4'-fluoroacetophenone. The 2-(4-(4-*X*-phenylsulfonyl)phenyl)-6-(4-fluorophenyl)thiazolo[3,2-*b*][1,2,4]triazoles 3a–c were obtained by cyclization of *S*-alkylated 1,2,4-triazoles 2a–c in sulfuric acid media, at 0°C. For the synthesis of 2-(4-(4-*X*-phenylsulfonyl)phenyl)-5-(4-fluorobenzylidene)-thiazolo[3,2-*b*][1,2,4]triazol-6(5*H*)-ones 4a–c, the triazoles 1a–c were treated with 4-fluorobenzaldehyde, chloroacetic acid and anhydrous sodium acetate, in the presence of acetic acid and acetic anhydride. The structures of the newly synthesized compounds have been confirmed by elemental analysis and spectral methods (IR, ¹H-NMR, ¹³C-NMR, MS). The antimicrobial activity of all new compounds has been screened against some bacteria and yeasts.

Key words thiazolo[3,2-*b*][1,2,4]triazole; 1,2,4-triazole-3-thiole; alkylation; antimicrobial activity

The chemistry of 1,2,4-triazoles and their heterocyclic condensed systems containing both nitrogen and sulfur atoms, has attracted increasing attention of researchers due to their wide-ranging biological importance. From these fused heterocyclic compounds, thiazolotriazoles obtained by fusion of 1,2,4-triazole and 1,3-thiazole ring together, have received considerable attention owing to their synthetic and biological properties. Both triazole and thiazole rings are known that possess various biological properties, being present in composition of numerous drugs, especially with antimicrobial activity.^{1,2)} Among of the antimicrobial drugs are distinguished *Itraconazole*, *Fluconazole*, *Voriconazole* (drugs with 1,2,4-triazole ring), *Sulfathiazole* and *Abafungin* (drugs with thiazole ring). The fusion of triazole and thiazole rings can lead to thiazolotriazoles with superior biological properties due to mutual influence of the pharmacophores centers present in the molecule. Thus, literature data indicate that numerous thiazolo[3,2-*b*][1,2,4]triazoles derivatives have been reported to possess antibacterial,^{3–9)} antifungal,^{3,6–9)} anti-inflammatory,^{3,10,11)} analgesic,^{3,10)} antiproliferative,¹²⁾ anticonvulsant¹³⁾ properties. Also, thiazolo[3,2-*b*][1,2,4]triazol-ones have been studied for their properties with respect to their biological activities including anti-inflammatory,^{14–17)} analgesic,^{15,17)} anticancer,^{18–20)} antibacterial,²¹⁾ antifungal²¹⁾ and anticonvulsant.²²⁾

Another interesting class are diarylsulfones which are important intermediates in organic synthesis because of their chemical properties and biological activities being known especially as antibacterial agents.^{23,24)}

The importance of fluorine atom in medicinal chemistry has been demonstrated by a great number of fluorinated compounds. Introduction of this atom into a molecule of organic compounds, may lead to significant changes in biological and physical properties of these because of their higher metabolic stability, often increased lipophilicity and membrane permeability.²⁵⁾

Knowing that infectious microbial diseases are pressing problems worldwide caused by the resistance of microorganisms to existing antimicrobial agents, there is a vital need to discover new antimicrobial agents.

Inspired by the aforesaid findings and keeping in mind our studies on different heterocycles with biological potential,^{26–32)} we designed the synthesis of new heterocyclic compounds which contain in the same molecule the thiazolotriazole condensed system, diarylsulfone and 4-fluorophenyl fragments, in order to obtain new compounds with potential antimicrobial activity.

Thus, in this paper we synthesized, characterized and evaluated for their antimicrobial activity a series of new heterocyclic condensed systems with bridgehead nitrogen from thiazolo[3,2-*b*][1,2,4]triazole and thiazolo[3,2-*b*][1,2,4]triazol-6(5*H*)-one class containing diarylsulfone and 4-fluorophenyl fragments.

Results and Discussion

Chemistry The synthesis pathway leading to the thiazolotriazoles is given in Chart 1.

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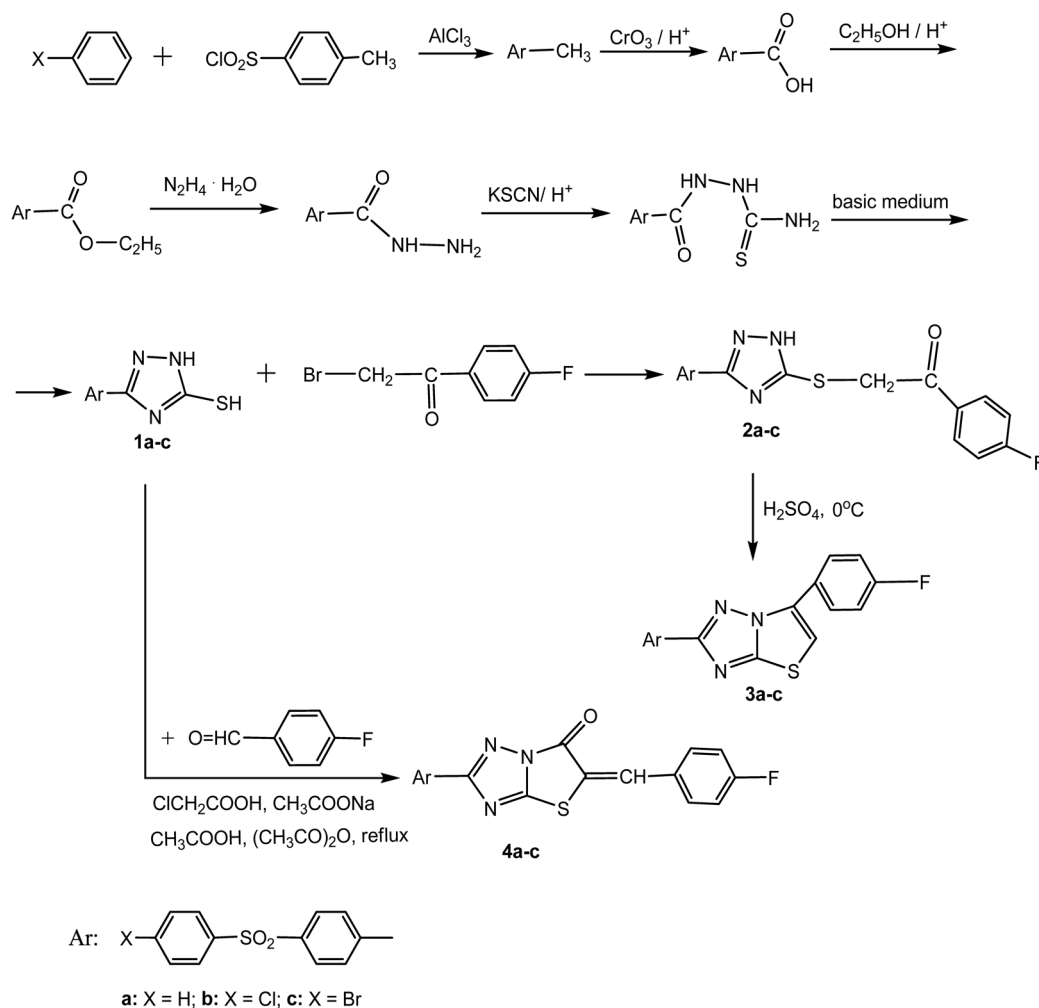


Chart 1.

Synthesis of the compounds **2a-c**~**4a-c** has been achieved starting from the 5-(4-(4-X-phenylsulfonyl)phenyl)-4*H*-1,2,4-triazole-3-thioles **1a-c** known in the literature.³³⁾ The 1,2,4-triazoles intermediates were obtained by cyclization of the corresponding acylthiosemicarbazides according to literature data.³³⁾ Thus, the acylthiosemicarbazides were synthesized starting from Friedel–Crafts reaction of benzene or halobenzene with *p*-tosyl chloride, followed by oxidation at the corresponding acids, esterification and hydrazinolysis. Finally, the acylthiosemicarbazides were obtained by treatment of corresponding hydrazides with potassium thiocyanate in acid media.³³⁾

In order to obtain condensed heterocyclic compounds **3a-c**, in a first stage, new intermediates *S*-alkylates 1,2,4-triazole **2a-c** were synthesized by the reaction of triazoles **1a-c** with 2-bromo-4'-fluoroacetophenone. 2-(4-(4-*X*-Phenylsulfonyl)phenyl)-6-(4-fluorophenyl)thiazolo[3,2-*b*][1,2,4]triazoles **3a-c** were synthesized from *S*-alkylated 1,2,4-triazoles **2a-c**, by cyclization in sulfuric acid medium. 2-(4-(4-*X*-Phenylsulfonyl)phenyl)-5-(4-fluorobenzylidene)thiazolo[3,2-*b*][1,2,4]triazol-6(5*H*)-one **4a-c** were obtained by reaction of triazoles **1a-c** with 4-fluorobenzaldehyde, chloroacetic acid and anhydrous sodium acetate, in the presence of acetic acid and acetic anhydride.

The alkylation reaction of 1,2,4-triazoles **1a-c** with

2-bromo-4'-fluoroacetophenone was confirmed in the IR spectra of compounds **2a-c** by the presence of a new absorption band corresponding to the stretching vibration of the carbonyl group, which occurs in the range 1680–1685 cm⁻¹. The absence of νC=S and νSH absorption bands from 1,2,4-triazoles **1a-c**³³⁾ in the IR spectra of derivatives **2a-c** indicated that alkylation took place at sulfur atom and not at nitrogen atom. In the ¹H-NMR spectra of these *S*-alkylated compounds, the presence of a new singlet signal at a chemical shift δ=4.93 ppm, characteristic to protons from methylene group, confirmed alkylation reaction. The singlet signal of NH heterocyclic group appeared at 3.50 ppm. In the ¹³C-NMR spectra characteristic is the carbon atom signal from carbonyl group which appeared at 191.94–192.24 ppm and the carbon atom signal from methylene group at 39.60–39.70 ppm.

The main proof that the cyclization of intermediates **2a-c** took place is represented by the disappearance of absorption bands and of signals characteristic to carbonyl and methylene groups from the IR and NMR spectra of compounds **3a-c**. In the ¹H-NMR spectra of compounds **3a-c** has appeared a new singlet signal corresponding to the protons of methine group from the thiazole ring which occurs at the chemical shift δ=7.96–7.97 ppm.^{3,8,11)} In the ¹³C-NMR spectra appeared two new characteristic signals. Thus, the methine carbon signal appeared at 111.49–111.51 ppm and the thiazole carbon signal,

adjacent to the methine carbon (which is linked by the 4-fluorophenyl fragment), occurred at 130.61–130.62 ppm.

The condensation reaction of the triazoles **1a–c** with 4-fluorobenzaldehyde and chloroacetic acid is confirmed in the IR spectra of the new compounds **4a–c** by the presence of a new absorption band, of high intensity, in the range 1733–1738 cm⁻¹ characteristic to the stretching vibration of the carbonyl group. The ¹H-NMR spectra revealed a new singlet signal corresponding to methine proton which resonated at 8.32–8.36 ppm.^{15,16,18)} On the other hand, the ¹³C-NMR spectra confirmed the thiazolo[3,2-*b*][1,2,4]triazol-6-one structure by the presence of new signals characteristic to the carbon of the carbonyl group and to the carbon of the methine group that appeared at 167.05–167.29 ppm and 142.82–143.74 ppm, respectively.

Another proof for the obtaining of all new compounds is the characteristic signals of protons in the ¹H-NMR spectra and of carbon atoms in the ¹³C-NMR spectra from 4-fluorophenyl moiety. Also, the signals of the protons and carbon atoms of the arylsulfonylphenyl moiety are found in the corresponding regions (Experimental).

The mass spectra of the new thiazolotriazoles **3a–c** and **4a–c** and of the *S*-alkylated 1,2,4-triazole intermediates **2a–c** have confirmed the proposed structures through the presence of the molecular ion corresponding to molecular weight. In case of compounds containing chlorine or bromine atom there was observed the molecular ion corresponding to the halogens isotopes (³⁵Cl/³⁷Cl and ⁷⁹Br/⁸¹Br). The main fragments obtained through the fragmentation of the molecular ion are given in Experimental.

The thiazolotriazoles can exist in two isomer forms: thiazolo[3,2-*b*][1,2,4]triazole and thiazolo[2,3-*c*][1,2,4]triazole. The IR and NMR spectra of these isomers are similar and can not be differentiated based on these data.^{11,34)} Correct assignment of the structure of the compounds **3a–c** type of thiazolo[3,2-*b*][1,2,4]triazoles was made by the mass spectrometry. The absence of the fragment [M–28]⁺ corresponding to the loss of nitrogen molecule (this type of cleavage took place easier in case of [2,3-*c*] isomer) is a proof of the obtaining of isomers type of [3,2-*b*].^{11,34)}

Antimicrobial Activity Evaluation The antimicrobial activity of the investigated compounds was tested against

some reference bacterial and fungal strains belonging to the following species: Gram-positive strains (*Staphylococcus aureus* ATCC 29213 and *Bacillus cereus* ATCC 13061), Gram-negative strains (*Escherichia coli* ATCC 25922, *Enterobacter cloacae* ATCC 49141, *Acinetobacter baumannii* ATCC 19606, *Pseudomonas aeruginosa* ATCC 27853) and yeast strains (*Candida albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, *Candida glabrata* ATCC 15126 and *Candida tropicalis* 13803), using the broth microdilution method.

The results of the antimicrobial activity screening of newly synthesized compounds are presented in the Table 1.

The aim of this study was to assess the antimicrobial activity and how this activity of new compounds synthesized is modified by:

- the replacement of a hydrogen atom from 4 position of diphenylsulfone fragment with a chlorine or bromine atom.
- creation of a new nucleus, thiazole, in condensed system, type of thiazolo[3,2-*b*][1,2,4]triazole, by cyclization of *S*-alkylated 1,2,4-triazoles **2a–c** to compounds **3a–c**.
- grafting on the condensed heterocyclic system of two exocyclic double bonds, C=O and C=C through the 4-fluorobenzylidene fragment in compounds **4a–c**.

The results obtained by the screening of the antibacterial activity against Gram-positive bacteria *S. aureus* and *B. cereus* indicated that all compounds tested had a better activity against *B. cereus* bacterium. The presence of the chlorine or bromine atom on the diphenylsulfone fragment in case of all tested compounds against the *B. cereus* strain produces a significant improvement of the antibacterial activity (minimum inhibitory concentration (MIC)=8 μg/mL or MIC=16 μg/mL). The studies on the same *B. cereus* strain indicated that the presence of the carbonyl group type of acyclic ketone in compounds **2a–c** or type cyclic ketone in compounds **4a–c** beside of the chlorine or bromine atoms in *para*-position on the diphenylsulfone had as result the obtaining of the best values of MIC.

The antibacterial screening of compounds on Gram-negative bacteria indicated that the best activity was obtained against *A. baumannii* strain (MIC=16 μg/mL) in case of compounds **2b** and **4b**, both having the chlorine atom in the *para*-position from diphenylsulfone fragment and the carbonyl group type of ketone. From structural point of view, in these compounds **2b**

Table 1. Antimicrobial Activities of Compounds **2a–c**~**4a–c** as MIC Values (μg/mL)

Compd	Gram-positive bacteria ^{a)}		Gram-negative bacteria ^{b)}				Yeasts ^{c)}			
	<i>Sa</i>	<i>Bc</i>	<i>Ec</i>	<i>Ecl</i>	<i>Ab</i>	<i>Pa</i>	<i>Ca</i>	<i>Cp</i>	<i>Cg</i>	<i>Ct</i>
2a	128	32	128	64	32	128	64	256	64	256
2b	128	8	128	128	16	128	128	128	64	128
2c	256	8	128	128	64	128	256	256	256	256
3a	128	64	128	128	64	128	128	128	64	128
3b	128	16	128	128	32	128	256	256	256	256
3c	512	16	256	256	64	>512	128	256	128	256
4a	512	16	128	128	64	128	128	256	128	256
4b	128	8	64	64	16	64	256	256	64	256
4c	>512	8	128	64	32	128	128	256	128	256
Control (AM)	2	—	2	—	—	2	—	—	—	—
Control (FL)	—	—	—	—	—	—	—	2	—	—

Note: a) *Sa* (*Staphylococcus aureus* ATCC 29213); *Bc* (*Bacillus cereus* ATCC 13061) b) *Ec* (*Escherichia coli* ATCC 25922); *Ecl* (*Enterobacter cloacae* ATCC 49141); *Ab* (*Acinetobacter baumannii* ATCC 19606); *Pa* (*Pseudomonas aeruginosa* ATCC 27853) c) *Ca* (*Candida albicans* ATCC 90028); *Cp* (*Candida parapsilosis* ATCC 22019); *Cg* (*Candida glabrata* ATCC 15126); *Ct* (*Candida tropicalis* ATCC 13803) Control: AM=amikacin; FL=fluconazole.

and **4b**, the π electrons of double bond permitted conjugation with π electrons of *p*-fluorophenyl fragment or with exocyclic double bond=CH-C₆H₄-F (*p*). Compounds **2a**, **3b**, **4c** also had a good activity against the same strain (MIC=32 μ g/mL).

The results of the antifungal screening indicated insignificant behaviors between these classes of the tested compounds. The presence of the chlorine atom on the diphenylsulfone fragment determined the best antifungal activity against *C. glabrata* fungus for compounds **2b** and **4b** (MIC=64 μ g/mL). Compound **2a** had the same MIC value against the same strain and against *C. albicans*.

The study of both the synthesis condition and structural and biological properties will be interesting both for ongoing and further researches on these heterocyclic classes.

The promising results obtained for compounds **2b**, **c** and **4b**, **c** (MIC=8 μ g/mL) against *B. cereus* strain needs further researches referring to the design of another structural models.

Conclusion

In summary, we synthesized and evaluated for their antimicrobial activity new heterocyclic condensed systems with bridgehead nitrogen from thiazolo[3,2-*b*][1,2,4]triazole and thiazolo[3,2-*b*][1,2,4]triazol-6(*5H*)-one class starting from some 4-(4-*X*-phenylsulfonyl)phenyl)-4*H*-1,2,4-triazole-3-thioles (*X*=H, Cl, Br) key intermediates. The target compounds from thiazolo[3,2-*b*][1,2,4]triazole class were synthesized by cyclization of the *S*-alkylated 1,2,4-triazole intermediates (obtained from triazoles **1** with 2-bromo-4'-fluoroacetophenone) in sulfuric acid media. The thiazolo[3,2-*b*][1,2,4]triazol-ones were obtained by treatment of 1,2,4-triazol-3-thioles with 4-fluorobenzaldehyde, chloroacetic acid and anhydrous sodium acetate, in presence of acetic acid and acetic anhydride. All the new compounds were confirmed by spectral techniques and elemental analysis. The results of the antimicrobial activity of the compounds synthesized indicated that the most active are thiazolo[3,2-*b*][1,2,4]triazol-6(*5H*)-ones **4b**, **c** and *S*-alkylated 1,2,4-triazoles **2b**, **c** against *B. cereus* (MIC=8 μ g/mL).

Experimental

Chemistry All chemicals were of analytical reagent grade. The ¹H-NMR and ¹³C-NMR spectra were recorded with a Varian Gemini 300 BB instrument working at 300 MHz for ¹H and 75 MHz for ¹³C, using dimethyl sulfoxide (DMSO)-*d*₆ or CDCl₃ with trifluoroacetic acid (TFA) as solvents and tetramethylsilane (TMS) as internal standard. Chemical shifts δ are reported in parts per million and coupling constant *J* values are in Hertz (Hz). The following abbreviations are used to explain the multiplicities: s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublets), tt (triplet of triplets), br (broad). Melting points were taken with a Boetius apparatus and were uncorrected. The infrared absorption spectra (IR) were recorded on a Vertex 70 Bruker spectrometer using potassium bromide pellets. Mass spectra were recorded on a triple quadrupole mass spectrometer Varian 1200 LC/MS/MS with electrospray interface (ESI) coupled with a Varian ProStar 240 SDM pump. The sample solution (2 μ g/mL in methanol–0.1% ammonia in water 10:1, v/v) was introduced, at a flow rate of 20 μ L/min, by direct infusion, in the ESI interface. The instrument was operated in positive ions mode and the fragmentation of protonated molecular ion was per-

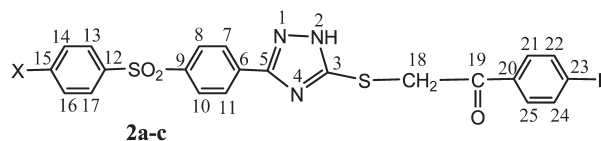


Fig. 1. Structure of Compounds **2a–c**

formed by collision with argon at 1.5 mTorr. The elemental analyses (% C, H, N) of the new compounds were performed with ECS-40-10-Costeh micro-dosimeter.

General Procedure for the Synthesis of 2-(5-(4-(4-*X*-Phenylsulfonyl)phenyl)-2*H*-1,2,4-triazol-3-ylthio)-1-(4-fluorophenyl)ethanone **2a–c** Triazole **1** (5 mmol) was dissolved in 160 mL dimethylsulfoxide and to the solution obtained was added 2-bromo-4'-fluoroacetophenone (5 mmol). The reaction mixture was stirred at room temperature for 10 h, then it was poured onto crushed ice. The precipitate obtained was filtered off, washed with water and finally with ethyl ether. The product was recrystallized from ethanol (Fig. 1).

1-(4-Fluorophenyl)-2-(5-(4-(phenylsulfonyl)phenyl)-2*H*-1,2,4-triazol-3-ylthio)ethanone **2a**

mp=186–187°C; yield=89.8%; IR (KBr) cm^{−1}: 3272 m (NH), 3082 (CH), 2959, 2918 (CH₂), 1680 (C=O), 1598 (C=N), 1507, 1449 (C=C), 1318, 1290, 1155 (SO₂), 1107 (C-F); ¹H-NMR (DMSO-*d*₆) δ : 3.50 (1H, brs, NH); 4.93 (2H, s, H-18); 7.40 (2H, t, *J*=8.8 Hz, H-22, H-24); 7.63 (2H, brt, *J*=7.6 Hz, H-14, H-16); 7.70 (1H, tt, *J*=7.6 Hz, *J*=1.6 Hz, H-15); 7.98 (2H, dd, *J*=7.6 Hz, *J*=1.6 Hz, H-13, H-17); 8.06 (2H, d, *J*=8.5 Hz, H-8, H-10); 8.11 (2H, d, *J*=8.5 Hz, H-7, H-11); 8.13 (2H, dd, *J*=8.8 Hz, *J*=5.5 Hz, H-21, H-25); ¹³C-NMR (DMSO-*d*₆) δ : 39.70 (C-18); 115.86 (d, *J*=22.1 Hz, C-22, C-24); 126.84 (C-8, C-10); 127.38 (C-7, C-11); 128.10 (C-6); 128.17 (C-13, C-17); 129.82 (C-14, C-16); 131.42 (d, *J*=9.4 Hz, C-21, C-25); 132.60 (d, *J*=3.6 Hz, C-20); 133.85 (C-15); 140.84 (C-12); 141.50 (C-9); 153.57 (C-5); 156.92 (C-3); 162.25 (d, *J*=252.5 Hz, C-23); 192.24 (C-19); ESI-MS, *m/z* (%): 454 [M+H]⁺; 436 (1) [M+H–H₂O]⁺; 420 (2) [M+H–H₂O–1/2O₂]⁺; 392 (10) [M+H–HF–1/2O₂–C₂H₂]⁺; 330 (28) [C₆H₅SO₂C₆H₄TriazoleSCH₂]⁺; 317 (35) [C₆H₅SO₂C₆H₄TriazoleSH]⁺; 301 (21) [C₆H₅SO₂C₆H₄TriazoleSH–NH₂]⁺; 244 (33) [C₆H₅SO₂C₆H₄CNH]⁺; 217 (12) [C₆H₅SO₂C₆H₄]⁺; 109 (100, BP) [C₆H₅S]⁺; Anal. Calcd for C₂₂H₁₆FN₃O₃S₂: C, 58.26; H, 3.56; N, 9.25. Found: C, 58.17; H, 3.64; N, 9.16.

2-(5-(4-(4-Chlorophenylsulfonyl)phenyl)-2*H*-1,2,4-triazol-3-ylthio)-1-(4-fluorophenyl)ethanone **2b**

mp=177–179°C; yield=77.5%; IR (KBr) cm^{−1}: 3274 (NH), 3076 (CH), 2966, 2913 (CH₂), 1685 (C=O), 1598 (C=N), 1507, 1478 (C=C), 1320, 1286, 1160 (SO₂), 1105 (C-F), 768 (C-Cl); ¹H-NMR (DMSO-*d*₆) δ : 3.50 (1H, brs, NH); 4.93 (2H, s, H-18); 7.40 (2H, t, *J*=8.8 Hz, H-22, H-24); 7.70 (2H, d, *J*=8.5 Hz, H-14, H-16); 7.99 (2H, d, *J*=8.5 Hz, H-13, H-17); 8.00–8.20 (6H, m, H-7, H-11, H-8, H-10, H-21, H-25); ¹³C-NMR (DMSO-*d*₆) δ : 39.60 (C-18); 115.57 (d, *J*=21.8 Hz, C-22, C-24); 126.68 (C-8, C-10); 127.56 (C-7, C-11); 128.09 (C-6); 129.30 (C-13, C-17); 131.09 (C-14, C-16); 131.17 (d, *J*=9.8 Hz, C-21, C-25); 131.96 (d, *J*=3.5 Hz, C-20); 138.69 (C-15); 139.36 (C-12); 140.77 (C-9); 156.63 (C-3); 164.96 (d, *J*=252.5 Hz, C-23); 153.27 (C-5); 191.94 (C-19); ESI-MS, *m/z* (%): 488 [M+H]⁺; 490 [M+H]⁺; 454 (21) [M+H–H₂O–1/2O₂]⁺; 456 (23) [M+H–H₂O–1/2O₂]⁺; 364 (54) [ClC₆H₅SO₂C₆H₄TriazoleSCH₂]⁺; 366 (57) [ClC₆H₅SO₂C₆H₄

TriazoleSCH₂)⁺; 351 (18) [ClC₆H₄SO₂C₆H₄TriazoleSH]⁺; 353 (21) [ClC₆H₄SO₂C₆H₄TriazoleSH]⁺; 320 (60) [ClC₆H₄SO₂C₆H₄Triazole+H]⁺; 322 (55) [ClC₆H₄SO₂C₆H₄Triazole+H]⁺; 278 (40) [ClC₆H₅SO₂C₆H₄CNH]⁺; 280 (38) [ClC₆H₅SO₂C₆H₄CNH]⁺; 175 (63) [ClC₆H₅SO₂]⁺; 177 (55) [ClC₆H₅SO₂]⁺; 152 (100) [C₇H₄SO₂]⁺; *Anal.* Calcd for C₂₂H₁₅ClFN₃O₃S₂: C, 54.15; H, 3.10; N, 8.61. Found: C, 54.04; H, 3.01; N, 8.74.

2-(5-(4-(4-Bromophenylsulfonyl)phenyl)-2H-1,2,4-triazol-3-ylthio)-1-(4-fluorophenyl)ethanone **2c**

mp=186–188°C; yield=78.0%; IR (KBr) cm⁻¹: 3268 (NH), 3085 (CH), 2974, 2917 (CH₂), 1684 (C=O), 1598 (C=N), 1573, 1507, 1473 (C=C), 1321, 1288, 1160 (SO₂), 1104 (C-F), 579 (C-Br); ¹H-NMR (DMSO-*d*₆) δ: 3.50 (1H, brs, NH); 4.93 (2H, s, H-18); 7.40 (2H, t, *J*=8.8 Hz, H-22, H-24); 7.84 (2H, d, *J*=8.8 Hz, H-14, H-16); 7.91 (2H, d, *J*=8.8 Hz, H-13, H-17); 8.06 (2H, d, *J*=8.8 Hz, H-8, H-10); 8.12 (2H, d, *J*=8.8 Hz, H-7, H-11); 8.13 (2H, dd, *J*=8.8 Hz, *J*=5.5 Hz, H-21, H-25); ¹³C-NMR (DMSO-*d*₆) δ: 39.68 (C-18); 115.87 (d, *J*=22.0 Hz, C-22, C-24); 126.91 (C-8, C-10); 128.10 (C-15); 128.27 (C-6); 128.40 (C-7, C-11); 129.41 (C-13, C-17); 131.47 (d, *J*=9.5 Hz, C-21, C-25); 132.26 (d, *J*=3.6 Hz, C-20); 132.94 (C-14, C-16); 140.84 (C-12); 140.97 (C-9); 153.59 (C-5); 156.94 (C-3); 165.27 (d, *J*=252.5 Hz, C-23); 192.24 (C-19); ESI-MS, *m/z* (%): 532 [M+H]⁺; 534 [M+H]⁺; 408 (100, BP) [BrC₆H₄SO₂C₆H₄TriazoleSCH₂]⁺; 410 (100, BP) [BrC₆H₄SO₂C₆H₄TriazoleSCH₂]⁺; 395 (31) [BrC₆H₄SO₂C₆H₄TriazoleSH]⁺; 397 (15) [BrC₆H₄SO₂C₆H₄TriazoleSH]⁺; 322 (42) [BrC₆H₄SO₂C₆H₄CNH]⁺; 324 (12) [BrC₆H₄SO₂C₆H₄CNH]⁺; 219 (22) [BrC₆H₄SO₂]⁺; 221 (23) [BrC₆H₄SO₂]⁺; *Anal.* Calcd for C₂₂H₁₅BrFN₃O₃S₂: C, 49.63; H, 2.84; N, 7.89. Found: C, 49.72; H, 2.91; N, 7.80.

General Procedure for the Synthesis of 2-(4-(4-X-Phenylsulfonyl)phenyl)-6-(4-fluorophenyl)thiazolo[3,2-*b*][1,2,4]triazole **3a–c** To 100 mL of concentrated sulfuric acid was added, on ice bath, *S*-alkylated 1,2,4-triazole **2** (2 mmol). The mixture was stirred at 0°C for 3 h and then, at room temperature, for 3 h. The solution obtained was poured onto crushed ice, then precipitated obtained was filtered off, washed with water until pH *ca.* 7 and was recrystallized from ethanol (Fig. 2).

6-(4-Fluorophenyl)-2-(4-(phenylsulfonyl)phenyl)thiazolo[3,2-*b*][1,2,4]triazole **3a**

mp=259–261°C; yield=90.0%; IR (KBr) cm⁻¹: 3080, 3062 (CH), 1602 (C=N), 1505, 1464 (C=C), 1322, 1277, 1158 (SO₂), 1101 (C-F); ¹H-NMR (DMSO-*d*₆) δ: 7.44 (2H, t, *J*=8.8 Hz, H-22, H-24); 7.65 (2H, br t, *J*=7.2 Hz, H-16, H-18); 7.72 (1H, tt, *J*=7.2 Hz, *J*=1.7 Hz, H-17); 7.97 (1H, s, H-5); 8.01 (2H, dd, *J*=7.3 Hz, *J*=1.7 Hz, H-15, H-19); 8.07 (2H, d, *J*=8.5 Hz, H-9, H-13); 8.31 (2H, d, *J*=8.5 Hz, H-10, H-12); 8.35 (2H, dd, *J*=8.8 Hz, *J*=5.5 Hz, H-21, H-25); ¹³C-NMR (DMSO-*d*₆) δ: 111.49 (C-5); 116.04 (d, *J*=22.0 Hz, C-22, C-24); 124.12 (d, *J*=3.0 Hz, C-20); 127.32 (C-9, C-13); 128.20 (C-10, C-12); 128.80 (d, *J*=8.3 Hz, C-21, C-25); 128.82 (C-15, C-19); 129.84

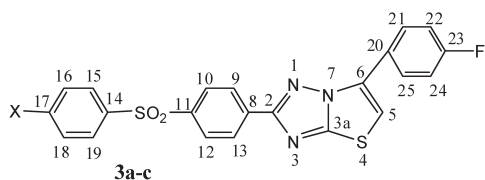


Fig. 2. Structure of Compounds **3a–c**

(C-16, C-18); 130.62 (C-6); 133.88 (C-17); 135.39 (C-8); 140.87 (C-14); 141.78 (C-11); 157.93 (C-2); 162.65 (d, *J*=246.8 Hz, C-23); 163.95 (C-3a); ESI-MS, *m/z* (%): 436 [M+H]⁺; 295 (100) [M+H–C₆H₅SO₂]⁺; 152 (73) [FC₆H₄CHCS]⁺; *Anal.* Calcd for C₂₂H₁₄FN₃O₂S₂: C, 60.67; H, 3.24; N, 9.65. Found: C, 60.56; H, 3.38; N, 9.73.

2-(4-(4-Chlorophenylsulfonyl)phenyl)-6-(4-fluorophenyl)-thiazolo[3,2-*b*][1,2,4]triazole **3b**

mp=239–240°C; yield=88.1%; IR (KBr) cm⁻¹: 3087 (CH), 1604 (C=N), 1505, 1464, (C=C), 1325, 1278, 1159 (SO₂), 1100 (C-F), 1159 (νSO₂), 772 (C-Cl); ¹H-NMR (DMSO-*d*₆) δ: 7.43 (2H, t, *J*=8.8 Hz, H-22, H-24); 7.72 (2H, d, *J*=8.6 Hz, H-16, H-18); 7.96 (1H, s, H-5); 8.02 (2H, d, *J*=8.6 Hz, H-15, H-19); 8.11 (2H, d, *J*=8.5 Hz, H-9, H-13); 8.29 (2H, dd, *J*=8.8 Hz, *J*=5.2 Hz, H-21, H-25); 8.32 (2H, d, *J*=8.5 Hz, H-10, H-12); ¹³C-NMR (DMSO-*d*₆) δ: 111.51 (C-5); 116.02 (d, *J*=21.8 Hz, C-22, C-24); 124.13 (d, *J*=3.2 Hz, C-20); 127.36 (C-9, C-13); 128.26 (C-10, C-12); 128.74 (d, *J*=8.3 Hz, C-21, C-25); 129.38 (C-15, C-19); 130.00 (C-16, C-18); 130.61 (C-6); 135.59 (C-8); 138.99 (C-17); 139.69 (C-14); 141.27 (C-11); 157.93 (C-2); 162.63 (d, *J*=246.8 Hz, C-23); 164.27 (C-3a); ESI-MS, *m/z* (%): 470 [M+H]⁺; 472 [M+H]⁺; 295 (49) [M+H–ClC₆H₄SO₂]⁺; 175 (42) [ClC₆H₄SO₂]⁺; 177 (38) [ClC₆H₅SO₂]⁺; 152 (100, BP) [FC₆H₄CHCS]⁺; *Anal.* Calcd for C₂₂H₁₃ClFN₃O₂S₂: C, 56.23; H, 2.79; N, 8.94. Found: C, 56.34; H, 2.88; N, 9.08.

2-(4-(4-Bromophenylsulfonyl)phenyl)-6-(4-fluorophenyl)-thiazolo[3,2-*b*][1,2,4]triazole **3c**

mp=247–251°C; yield=93.0%; IR (KB) cm⁻¹: 3084 (CH), 1603 (C=N), 1573, 1505, 1463, (C=C), 1325, 1277, 1160 (SO₂), 1099 (C-F), 578 (C-Br); ¹H-NMR (DMSO-*d*₆) δ: 7.44 (2H, t, *J*=8.8 Hz, H-22, H-24); 7.86 (2H, d, *J*=8.5 Hz, H-16, H-18); 7.93 (2H, d, *J*=8.5 Hz, H-15, H-19); 7.97 (1H, s, H-5); 8.12 (2H, d, *J*=8.2 Hz, H-9, H-13); 8.30 (2H, dd, *J*=8.8 Hz, *J*=5.5 Hz, H-21, H-25); 8.33 (2H, d, *J*=8.2 Hz, H-10, H-12); ¹³C-NMR (DMSO-*d*₆) δ: 111.49 (C-5); 116.01 (d, *J*=21.7 Hz, C-22, C-24); 124.12 (d, *J*=3.2 Hz, C-20); 127.37 (C-9, C-13); 128.09 (C-17); 128.26 (C-10, C-12); 128.74 (d, *J*=8.3 Hz, C-21, C-25); 129.40 (C-15, C-19); 130.61 (C-6); 132.94 (C-16, C-18); 135.59 (C-8); 140.11 (C-14); 141.23 (C-11); 157.92 (C-2); 162.63 (d, *J*=246.8 Hz, C-23); 163.87 (C-3a); ESI-MS, *m/z* (%): 514 [M+H]⁺; 516 [M+H]⁺; 295 (100) [M+H–BrC₆H₄SO₂]⁺; 219 (9) [BrC₆H₄SO₂]⁺; 221 (22) [BrC₆H₄SO₂]⁺; 155 (50) [BrC₆H₄]⁺; 157 (62) [BrC₆H₄]⁺; 152 (30) [FC₆H₄CHCS]⁺; *Anal.* Calcd for C₂₂H₁₃BrFN₃O₂S₂: C, 51.37; H, 2.55; N, 8.17. Found: C, 51.22; H, 2.66; N, 8.33.

General Procedure for Synthesis of 2-(4-(4-X-Phenylsulfonyl)phenyl)-5-(4-fluorobenzylidene)thiazolo[3,2-*b*][1,2,4]triazol-6(5H)-one **4a–c** A mixture of triazole **1** (3 mmol), 4-fluorobenzaldehyde (3 mmol), chloroacetic acid (4.5 mmol), anhydrous sodium acetate (0.4 g) in 8 mL glacial acetic acid and 6 mL acetic anhydride was refluxed for 9 h. The excess solvent evaporated under reduced pressure and a residue was obtained. Petroleum ether was added to the residue and

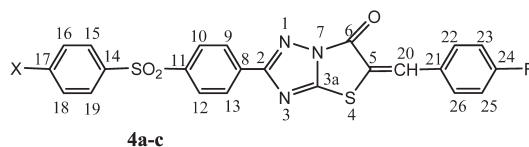


Fig. 3. Structure of Compounds **4a–c**

the obtained solid was filtered and washed with water. The product was purified from CH_2Cl_2 –petroleum ether (1 : 1, v/v) (Fig. 3).

5-(4-Fluorobenzylidene)-2-(4-(phenylsulfonyl)phenyl)-thiazolo[3,2-*b*][1,2,4]triazol-6(5*H*)-one **4a**

mp=269–272°C; yield=76.1%; IR (KBr) cm^{-1} : 3098, 3059 (CH), 1733 (C=O), 1612 (C=N), 1598, 1510 (C=C), 1311, 1279, 1159 (SO_2), 1105 (C-F); $^1\text{H-NMR}$ (CDCl_3 +TFA) δ : 7.29 (2H, t, J =8.5 Hz, H-23, H-25); 7.59 (2H, brt, J =7.5 Hz, H-16, H-18); 7.68 (1H, brt, J =7.5 Hz, H-17); 7.72 (2H, dd, J =8.5 Hz, J =5.2 Hz, H-22, H-26); 8.00 (2H, brd, J =7.5 Hz, H-15, H-19); 8.11 (2H, d, J =8.5 Hz, H-9, H-13); 8.25 (2H, d, J =8.5 Hz, H-10, H-12); 8.36 (1H, s, H-20); $^{13}\text{C-NMR}$ (CDCl_3 +TFA) δ : 117.65 (d, J =22.3 Hz, C-23, C-25); 121.46 (C-8); 127.96 (C-15, C-19); 128.63 (C-9, C-13); 128.81 (C-10, C-12); 128.27 (d, J =3.4 Hz, C-21); 130.04 (C-16, C-18); 134.06 (d, J =9.8 Hz, C-22, C-26); 134.73 (C-17); 139.44 (C-14); 143.46 (C-11); 143.74 (C-20); 143.84 (C-5); 156.87 (C-2); 165.58 (d, J =257.3 Hz, C-24); 166.92 (C-3a); 167.29 (C-6); ESI-MS, m/z (%): 464 $[\text{M}+\text{H}]^+$; 436 (25) $[\text{M}+\text{H}-\text{CO}]^+$; 323 (25) $[\text{M}+\text{H}-\text{FC}_6\text{H}_4\text{CHSH}]^+$; 244 (38) $[\text{C}_6\text{H}_5\text{SO}_2\text{C}_6\text{H}_4\text{CN}+\text{H}]^+$; 152 (100) $[\text{FC}_6\text{H}_4\text{CHCS}]^+$; Anal. Calcd for $\text{C}_{23}\text{H}_{14}\text{FN}_3\text{O}_3\text{S}_2$: C, 59.60; H, 3.04; N, 9.07. Found: C, 59.94; H, 2.86; N, 8.80.

2-(4-(4-Chlorophenylsulfonyl)phenyl)-5-(4-fluorobenzylidene)-thiazolo[3,2-*b*][1,2,4]triazol-6(5*H*)-one **4b**

mp=266–269°C; yield=77.8%; IR (KBr) cm^{-1} : 3084, 3073 (CH), 1736 (C=O), 1614 (C=N), 1597, 1507, 1496 (C=C), 1315, 1280, 1159 (SO_2), 1106 (C-F), 771 (C-Cl); $^1\text{H-NMR}$ (CDCl_3 +TFA) δ : 7.29 (2H, t, J =8.2 Hz, H-23, H-25); 7.54 (2H, d, J =8.5 Hz, H-16, H-18); 7.70 (2H, dd, J =8.2 Hz, J =5.2 Hz, H-22, H-26); 7.93 (2H, d, J =8.5 Hz, H-15, H-19); 8.09 (2H, d, J =8.5 Hz, H-9, H-13); 8.26 (2H, d, J =8.5 Hz, H-10, H-12); 8.32 (1H, s, H-20); $^{13}\text{C-NMR}$ (CDCl_3 +TFA) δ : 117.56 (d, J =22.3 Hz, C-23, C-25); 121.81 (C-8); 128.27 (d, J =3.3 Hz, C-21); 128.54 (C-9, C-13); 128.72 (C-10, C-12); 129.40 (C-15, C-19); 138.55 (C-14); 132.93 (C-16, C-18); 133.82 (d, J =9.7 Hz, C-22, C-26); 140.82 (C-17); 141.26 (C-5); 142.82 (C-20); 143.30 (C-11); 156.52 (C-2); 165.32 (d, J =261.8 Hz, C-24); 166.90 (C-3a); 167.05 (C-6); ESI-MS, m/z (%): 498 $[\text{M}+\text{H}]^+$; 500 $[\text{M}+\text{H}]^+$; 470 (38) $[\text{M}+\text{H}-\text{CO}]^+$; 472 (24) $[\text{M}+\text{H}-\text{CO}]^+$; 152 (100) $[\text{FC}_6\text{H}_4\text{CHCS}]^+$; Anal. Calcd for $\text{C}_{23}\text{H}_{13}\text{ClFN}_3\text{O}_3\text{S}_2$: C, 55.48; H, 2.63; N, 8.44. Found: C, 55.16; H, 2.77; N, 8.24.

2-(4-(4-Bromophenylsulfonyl)phenyl)-5-(4-fluorobenzylidene)-thiazolo[3,2-*b*][1,2,4]triazol-6(5*H*)-one **4c**

mp=272–274°C; yield=78.3%; IR (KBr) cm^{-1} : 3083 (CH), 1738 (C=O), 1614 (C=N), 1598, 1507, 1497 (C=C), 1315, 1280, 1160 (SO_2), 1103 (C-F), 584 (C-Br); $^1\text{H-NMR}$ (CDCl_3 +TFA) δ : 7.30 (2H, t, J =8.4 Hz, H-23, H-25); 7.71 (2H, dd, J =8.4 Hz, J =5.3 Hz, H-22, H-26); 7.73 (2H, d, J =8.6 Hz, H-16, H-18); 7.86 (2H, d, J =8.6 Hz, H-15, H-19); 8.10 (2H, d, J =8.4 Hz, H-9, H-13); 8.26 (2H, d, J =8.4 Hz, H-10, H-12); 8.36 (1H, s, H-20); $^{13}\text{C-NMR}$ (CDCl_3 +TFA) δ : 117.65 (d, J =22.6 Hz, C-23, C-25); 128.21 (C-17); 121.46 (C-8); 128.31 (d, J =3.3 Hz, C-21); 128.63 (C-9, C-13); 128.87 (C-10, C-12); 129.42 (C-15, C-19); 133.96 (C-16, C-18); 134.02 (d, J =9.2 Hz, C-22, C-26); 138.70 (C-14); 143.16 (C-11); 143.63 (C-20); 143.73 (C-5); 156.82 (C-2); 165.54 (d, J =257.3 Hz, C-24); 166.29 (C-3a); 167.25 (C-6); ESI-MS, m/z (%): 542 $[\text{M}+\text{H}]^+$; 544 $[\text{M}+\text{H}]^+$; 514 (13) $[\text{M}+\text{H}-\text{CO}]^+$; 516 (9) $[\text{M}+\text{H}-\text{CO}]^+$; 152 (100) $[\text{FC}_6\text{H}_4\text{CHCS}]^+$; Anal. Calcd for $\text{C}_{23}\text{H}_{13}\text{BrFN}_3\text{O}_3\text{S}_2$: C, 50.93; H, 2.42; N, 7.75. Found: C, 51.32; H, 2.63; N, 7.43.

Antimicrobial Assay The testing of antimicrobial activity for the compounds synthesized was performed *in vitro* using the broth microdilution method for detecting the MICs. For preparing the stock solutions, the compounds were dissolved in DMSO, at 2048 $\mu\text{g/mL}$. The solvent has shown no antimicrobial activity against the tested microbial strains. Series of binary dilutions of the tested compounds, from 1 : 2 to 1 : 1024, were performed in Mueller–Hinton broth, in 96-well plates (Nunc, Denmark), in volume of 50 μL broth per well.

The protocol used for antimicrobial screening is accordingly with other protocol presented by us previously.²⁷⁾ For testing the antibacterial activity, the initial inoculum of each bacterial strain was adjusted at 0.5 McFarland turbidity and afterwards diluted to 1/100 in Mueller–Hinton broth. From this diluted inoculum, 50 μL were added in every well which contained the tested compounds and in the wells with the positive growth control, the last ones containing already 50 μL of compound-free broth. The wells containing the negative growth control (the sterility control) were filled in only with compound-free Mueller–Hinton broth (100 μL). Then, the 96-well plates were sealed with sterile adhesive sheet, covered by a proper lid and incubated at 37°C for 24 h. The MICs of the tested compounds were read after 20 h by naked-eye examination of the aspect of the growth controls and of the wells containing the compounds. The MIC was considered the lowest concentration of the tested compounds which was able to inhibit the bacterial growth, which was the concentration of the compound in the last well (in each dilution series) showing no turbidity.

For the antifungal testing, the initial inoculum of each yeast strain was adjusted at 0.5 McFarland turbidity. Afterwards, it was diluted in Sabouraud broth in order to obtain an inoculum with a microbial density of 1×10^5 colony forming units (CFU)/mL of which 50 μL were added in every well containing the tested compounds and in the wells with the positive growth control, the last ones containing already 50 μL of compound-free broth. The wells containing the negative growth control (the sterility control) were filled in only with compound-free Sabouraud broth (100 μL). Then, the 96-well plates were sealed with sterile adhesive sheet, covered by a proper lid and incubated at 37°C for 24 h. The MICs of the tested compounds were read after 24 h by naked-eye examination of the aspect of the growth controls and of the wells containing the compounds. The MIC was considered the lowest concentration of the tested compounds which was able to inhibit the yeast growth, which was the concentration of the compound in the last well (in each dilution series) showing no turbidity.

In addition, for all 10 microbial strains, an inoculum control was performed by removing 10 μL from the positive growth control wells (just after they had been inoculated), which were further diluted into 10 mL of Mueller–Hinton broth when controlling the bacterial inoculum and of Sabouraud broth when controlling the yeast inoculum. After vortexing, 100 μL of this dilution were spread onto a Columbia blood agar plate or onto a Sabouraud agar plate, respectively, that were afterwards incubated for 24 h, followed by counting the total number of CFU/mL.

The following reference strains: *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853 and *S. aureus* ATCC 25923 were tested against amikacin (for quality control) and *C. parapsilosis* ATCC 22019 was tested against fluconazole (as quality

control) by the same microdilution broth method. The MIC value of amikacin was 2 µg/mL for the 3 tested bacterial strains and the MIC value of fluconazole was also 2 µg/mL, for the yeast reference strain. The investigation of the antimicrobial activity of the compounds was done in duplicate.

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Conflict of Interest The authors declare no conflict of interest.

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