SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL 2-ARYLIDEN-HYDRAZONE-THIAZOLES

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Abstract

A new series of 2-aryliden-hydrazone-thiazoles **3a-l** was synthesized starting from aryliden-thiosemicarbazones by the Hantzsch condensations with different α (or γ)-halocarbonyl compounds. The newly synthesized compounds were screened for their antimicrobial activity against 4 bacterial strains: *Staphylococcus aureus (ATCC 29213), Bacillus subtilis (ATCC 60511), Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 10145)* and one fungal strain: *Candida albicans (ATCC 10231).* The compounds **3i** and **3j** demonstrated a good inhibitory activity against *E. coli*. The results of the antifungal screening showed that the compounds **3a-d** and **3f-j** presented an excellent activity against *Candida albicans*.

Rezumat

A fost sintetizată o nouă serie de 2-ariliden-hidrazon-tiazoli **3a-l** pornind de la ariliden-tiosemicarbazone prin condensări Hantzsch cu diferiţi compuşi α (sau γ)-halocarbonilici. Noii compuşi sintetizaţi au fost evaluaţi privind activitatea antimicrobiană asupra a 4 tulpini bacteriene: *Staphylococcus aureus (ATCC 29213), Bacillus subtilis (ATCC 60511), Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 10145)* şi asupra unei tulpini fungice: *Candida albicans (ATCC 10231).* Compuşii **3i** şi **3j** au demonstrat o bună activitate inhibitorie asupra *E. coli*. Rezultatele *screeningului* antifungic au arătat că, compuşii **3a-d** şi **3f-j** prezintă o excelentă activitate asupra *Candida albicans.*

Keywords: hydrazone-thiazoles, aryliden-thiosemicarbazones, antibacterial, antifungal

Introduction

The twentieth century has been characterized by a drastic reduction in the mortality caused by infectious diseases. Nevertheless, microorganisms still represent a dreadful menace to men's health and therefore, or a more efficient control, require the steady development of novel and more powerful drugs [1,2].

Thiazoles and their derivatives are found to be associated with various biological activities such as antibacterial, antifungal and anti-inflammatory activities [3,4]. On the other hand, compounds containing azomethine group (–CH=N–) in the structure, known as Schiff bases, have gained importance because of physiological and pharmacological activities associated with them, such as antibacterial and antifungal properties [2,5]. Supplementary, the chromone derivatives are gaining importance as medicinal agents, such as antibacterial and antifungal [4]. Also, it has been reported that the introduction of a hydrazone group in position 2 of thiazole enhances the antimicrobial activity [6].

Prompted by these reports [7,8], we decided to synthesize some new compounds containing thiazole nucleus linked to chromone or arylidene rings by a hydrazone fragment.

Our aim was also to study their antimicrobial activity against 4 bacterial strains: *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and one fungal strain: *Candida albicans*.

Materials and Methods

The melting points were registered using an Electrothermal melting point meter and were uncorrected. The ^{1}H NMR spectra were recorded at room temperature on a Bruker Avance NMR spectrometer operating at 500 MHz. Chemical shift values were reported relative to tetramethylsilane (TMS) as internal standard. The samples were prepared by dissolving the compounds in DMSO-d_6 (δH= 2.51ppm) as solvent and the spectra were recorded using a single excitation pulse of 12 μs. GC-MS analyses were performed on an Agilent gas chromatograph 6890 equipped with an apolar Macherey Nagel Permabond SE 52 capillary column. FT-IR spectra were recorded on a Nicolet 210 FT-IR spectrometer using potassium bromide. Elemental analysis was performed using a Vario El CHNS instrument. All compounds gave satisfactory CHNS quantitative elemental analysis results. The purity of the synthesized compounds was verified by thin layer chromatography (TLC) and was carried out on precoated Silica Gel 60F254

sheets using heptan – ethyl-acetate 1:3 system and UV light for visualization 3-formyl-6-methyl-chromone **1c** is a Merck product.

Chemistry

*Synthesis of 2-((6-methyl-4-oxo-4H-chromen-3-yl)methylene) hydrazine-carbothioamide (**2c**)*

In a flask equipped with a reflux condenser, a mixture of **1c** (50 mmol) and thiosemicarbazide (50 mmol) reacted in 100 mL ethanol in the presence of a catalytic amount of acetic acid. The reaction mixture was heated under reflux 3h, where upon the solid product partially crystallized out. The solution was left to cool and the separated solid product was filtered off, washed with water, dried, and recrystallized from ethanol. Yellow crystals; Yield 85%; mp: 202^{0}C. Anal. Calcd. (%) for $C_{12}H_{11}N_3O_2S$ (261.30): C 55.16; H 4.24; N 16.08; S 12.27. Found: C 55.32; H 4.25; N 16.15; S 12.31. MS: m/z = 261 (M^+), 186, 172.

*Synthesis of thiazoles **3a-l** (General procedure)*

0.005 mol of **2a-c** was dissolved in 30 mL acetone and 0.0055 mol halocarbonyl compound (2-chlor-ethylacetoacetate for **3a** and **3j**, 1,3-dichlor-acetone for **3b** and **3i**, 2-chlor-acetophenone for **3c** and **3f**, 1-chlor-propanone for **3g**, 4-chlor-ethylacetoacetate for **3e**, **3h** and **3l**, 3-chlor-acetylacetone for **3d** and **3k**) was added. The mixture was stirred 2 hours at room temperature, cooled at –40 ^{0}C for 1 hour, after which the resulted precipitates were filtered, washed with ether and after that with water, in order to transform the chlorhydrates in the correspondent bases. The resulted compounds were recrystallized from ethanol.

Ethyl 2-(2-cyclopentylidenehydrazinyl)-4-methylthiazole-5-carboxylate (***3a***)

Yellow powder, Yield 81%; mp: 137-139 ^{0}C. IR(KBr): υ/cm^{-1}=3229 (NH), 1744 (C=O ester). ^{1}H NMR (DMSO-*d*$_6$): δ_{ppm} = 1.25 (t, 3H, $CH_2C\underline{H}_3$), 1.70 (dd, 4H, C_3, $C_{3'}$ cyclopentyl), 2.38 (s, 3H, CH_3-4-thiazole), 2.53 (dd, 4H, C_2, $C_{2'}$ cyclopentyl), 4.12 (q, 2H, $C\underline{H}_2CH_3$), 11.77 (s, 1H, NH). MS: m/z = 267 (M^+). Anal. Calcd. (%) for $C_{12}H_{17}N_3O_2S$ (267.35): C 53.91; H 6.41; N 15.72; S 11.99. Found: C 53.82; H 6.43; N 15.67; S 11.94.

4-(chloromethyl)-2-(2-cyclopentylidenehydrazinyl)thiazole (***3b***)

White powder, Yield 80%; mp: 160-163 ^{0}C. IR(KBr): υ/cm^{-1}=3242 (NH). ^{1}H NMR (DMSO-*d*$_6$): δ_{ppm} = 1.77 (dd, 4H, C_3, $C_{3'}$ cyclopentyl), 2.56 (dd, 4H, C_2, $C_{2'}$ cyclopentyl), 2.87 (s, 2H, CH_2-Cl), 7.56 (s, 1H, thiazole C5-H), 11.81 (s, 1H, NH). MS: m/z = 230 (M^+). Anal. Calcd. (%) for $C_9H_{12}ClN_3S$ (229.73): C 47.05; H 5.27; N 18.29; S 13.96. Found: C 47.19; H 5.29; N 18.32; S 13.9.

2-(2-cyclopentylidenehydrazinyl)-4-phenylthiazole (***3c***)
White powder, Yield 78%; mp: 160 ^{0}C. IR(KBr): υ/cm^{-1}=3244 (NH). ^{1}H NMR (DMSO-d_6): δ_{ppm}= 1.75 (dd, 4H, C_3, $C_{3'}$ cyclopentyl), 2.54 (dd, 4H, C_2, $C_{2'}$ cyclopentyl), 7.33-7.41 (m, 5H, C_6H_5-4-thiazole), 7.55 (s, 1H, thiazole C5-H), 11.80 (s, 1H, NH). MS: m/z = 257 (M^+). Anal. Calcd. (%) for $C_{14}H_{15}N_3S$ (257.35): C 65.34; H 5.87; N 16.33; S 12.46. Found: C 65.45; H 5.86; N 16.34; S 12.46.

1-(2-(2-cyclopentylidenehydrazinyl)-4-methylthiazol-5-yl)ethanone (***3d***)
White-yellow powder, Yield 74%; mp: 190 ^{0}C. IR(KBr): υ/cm^{-1}=3239 (NH), 1720 (C=O ketone). ^{1}H NMR (DMSO-d_6): δ_{ppm}= 1.39 (s, 3H, COC$\underline{H}_3$), 1.71 (dd, 4H, C_3, $C_{3'}$ cyclopentyl), 2.35 (s, 3H, CH_3-4-thiazole), 2.53 (dd, 4H, C_2, $C_{2'}$ cyclopentyl), 11.77 (s, 1H, NH). MS: m/z = 237 (M^+). Anal. Calcd. (%) for $C_{11}H_{15}N_3OS$ (237.32): C 55.67; H 6.37; N 17.71; S 13.51. Found: C 55.49; H 6.41; N 17.65; S 13.54.

Ethyl 2-(2-(2-cyclopentylidenehydrazinyl)thiazol-4-yl)acetate (***3e***)
White-yellow powder, Yield 81%; mp: 88-89 ^{0}C. IR(KBr): υ/cm^{-1}=3242 (NH), 1729 (C=O ester). ^{1}H NMR (DMSO-d_6): δ_{ppm}= 1.25 (t, 3H, $CH_2C\underline{H}_3$), 1.79 (dd, 4H, C_3, $C_{3'}$ cyclopentyl), 2.55 (dd, 4H, C_2, $C_{2'}$ cyclopentyl), 3.52 (s, 2H, 4-thiazolyl-CH_2-), 4.23 (q, 2H, $C\underline{H}_2CH_3$), 7.66 (s, 1H, thiazole C5-H), 11.65 (s, 1H, NH). MS: m/z = 267 (M^+). Anal. Calcd. (%) for $C_{12}H_{17}N_3O_2S$ (267.35): C 53.91; H 6.41; N 15.72; S 11.99. Found: C 53.82; H 6.46; N 15.77; S 11.96.

2-(2-cyclohexylidenehydrazinyl)-4-phenylthiazole (***3f***)
White-yellow powder, Yield 80%; mp: 179 ^{0}C. IR(KBr): υ/cm^{-1}=3240 (NH). ^{1}H NMR (DMSO-d_6): δ_{ppm}= 1.57-1.66 (m, 6H, cyclohexyl), 2.56 (dd, 4H, C_2, $C_{2'}$ cyclohexyl), 7.33-7.51 (m, 5H, C_6H_5-4-thiazole), 7.57 (s, 1H, thiazole C5-H), 11.69 (s, 1H, NH). MS: m/z = 271 (M^+). Anal. Calcd. (%) for $C_{15}H_{17}N_3S$ (271.38): C 66.39; H 6.31; N 15.48; S 11.82. Found: C 66.47; H 6.33; N 15.54; S 11.79.

2-(2-cyclohexylidenehydrazinyl)-4-methylthiazole (***3g***)
White-yellow powder, Yield 78%; mp: 43-44 ^{0}C. IR(KBr): υ/cm^{-1}=3245 (NH). ^{1}H NMR (DMSO-d_6): δ_{ppm}= 1.59-1.68 (m, 6H, cyclohexyl), 2.45 (s, 3H, CH_3), 2.56 (dd, 4H, C_2, $C_{2'}$ cyclohexyl), 7.59 (s, 1H, thiazole C5-H), 11.76 (s, 1H, NH). MS: m/z = 209 (M^+). Anal. Calcd. (%) for $C_{10}H_{15}N_3S$ (209.31): C 57.38; H 7.22; N 20.08; S 15.32. Found: C 57.44; H 7.23; N 20.13; S 15.36.

Ethyl 2-(2-(2-cyclohexylidenehydrazinyl)thiazol-4-yl)acetate(***3h***)
White-yellow powder, Yield 75%; mp: 180 ^{0}C. IR(KBr): υ/cm^{-1}=3244 (NH), 1722 (C=O ester). ^{1}H NMR (DMSO-d_6): δ_{ppm}= 1.27 (t, 3H, $CH_2C\underline{H}_3$), 1.55-1.69 (m, 6H, cyclohexyl), 2.56 (dd, 4H, C_2, $C_{2'}$ cyclohexyl), 3.55 (s,

2H, 4-thiazolyl-CH_2-), 4,24 (q, 2H, $C\underline{H}_2CH_3$), 7.59 (s, 1H, thiazole C5-H), 11.66 (s, 1H, NH). MS: m/z = 281(M^+). Anal. Calcd. (%) for $C_{13}H_{19}N_3O_2S$ (281.37): C 55.49; H 6.81; N 14.93; S 11.40. Found: C 55.29; H 6.84; N 14.87; S 11.38.

4-(chloromethyl)-2-(2-cyclohexylidenehydraziny)thiazole (***3i***)

White powder, Yield 79%; mp: 167-168 ^{0}C. IR(KBr): υ/cm^{-1}=3239 (NH). ^{1}H NMR (DMSO-d_6): δ_{ppm}= 1.59-1.69 (m, 6H, cyclohexyl), 2.65 (dd, 4H, C_2, $C_{2'}$ cyclohexyl), 3.54 (s, 2H, CH_2-Cl), 7.56 (s, 1H, thiazole C5-H), 11.69 (s, 1H, NH). MS: m/z = 244 (M^+). Anal. Calcd. (%) for $C_{10}H_{14}ClN_3S$ (243.76): C 49.27; H 5.79; N 17.24; S 13.15. Found: C 49.41; H 5.77; N 17.29; S 13.23.

Ethyl 2-(2-cyclohexylidenehydrazinyl)-4-methylthiazole-5-carboxylate(***3j***)

White-yellow powder, Yield 83%; mp: 157-158 ^{0}C. IR(KBr): υ/cm^{-1}=3242 (NH), 1722 (C=O ester). ^{1}H NMR (DMSO-d_6): δ_{ppm}= 1.28 (t, 3H, $CH_2C\underline{H}_3$), 1.59-1.67 (m, 6H, cyclohexyl), 2.36 (s, 3H, CH_3-4-thiazole), 2.57 (dd, 4H, C_2, $C_{2'}$ cyclohexyl), 4.17 (q, 2H, $C\underline{H}_2CH_3$), 11.63 (s, 1H, NH). MS: m/z = 281 (M^+). Anal. Calcd. (%) for $C_{13}H_{19}N_3O_2S$ (281.37): C 55.49; H 6.81; N 14.93; S 11.40. Found: C 55.33; H 6.83; N 14.89; S 11.36.

3-((2-(5-acetyl-4-methylthiazol-2-yl)hydrazono)methyl)-6-methyl-4H-chromen-4-one (***3k***)

White-yellow powder, yield 56%; mp: 259-260 ^{0}C. IR(KBr): υ/cm^{-1}=3238 (NH), 1732 (C=O chromone), 1722 (C=O ketone). ^{1}H NMR (DMSO-d_6): δ_{ppm}= 1.43 (s, 3H, $COC\underline{H}_3$), 2.41 (s, 3H, CH_3-4-thiazole), 2.46 (s, 3H, $C_{6\text{-chromone}}$-CH_3), 7.45 (s, 1H, $C_{2\text{-chromone}}$-H), 7.47 (s, 1H, $C_{5\text{-chromone}}$-H), 7.52 (d, 1H, $C_{8\text{-chromone}}$-H), 7.56 (d, 1H, $C_{7\text{-chromone}}$-H), 8.26 (s, 1H, CH=N), 9.12 (s, 1H, NH). MS: m/z = 341 (M^+). Anal. Calcd. (%) for $C_{17}H_{15}N_3O_3S$ (341.38): C 59.81; H 4.43; N 12.31; S 9.39. Found: C 59.69; H 4..42; N 12.33; S 9.38.

Ethyl 2-(2-(2-((6-methyl-4-oxo-4H-chromen-3-yl)methylene)hydrazinyl) thiazol-4-yl)acetate (***3l***)

White-yellow powder, yield 63%; mp: 198-200 ^{0}C. IR(KBr): υ/cm^{-1}=3243 (NH), 1733 (C=O chromone), 1722 (C=O ester). ^{1}H NMR (DMSO-d_6): δ_{ppm}= 1.27 (t, 3H, $CH_2C\underline{H}_3$), 2.45 (s, 3H, $C_{6\text{-chromone}}$-CH_3), 3.52 (s, 2H, 4-thiazolyl-CH_2-), 4.24 (q, 2H, $C\underline{H}_2CH_3$), 7.47 (s, 1H, $C_{2\text{-chromone}}$-H), 7.49 (s, 1H, $C_{5\text{-chromone}}$-H), 7.53 (d, 1H, $C_{8\text{-chromone}}$-H), 7.61 (d, 1H, $C_{7\text{-chromone}}$-H), 8.29 (s, 1H, CH=N), 9.15 (s, 1H, NH). MS: m/z = 371 (M^+). Anal. Calcd. (%) for $C_{18}H_{17}N_3O_4S$ (371.41): C 58.21; H 4.61; N 11.31; S 8.63. Found: C 58.36; H 4.69; N 11.29; S 8.62.

Experimental procedures for antimicrobial activity

Disk diffusion method

The antimicrobial activity of the newly synthesized compounds was evaluated according to the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS, 1997) using the agar disk diffusion method [9]. Ciprofloxacin and Fluconazole were purchased from Romanian market and used as reference for antibacterial and antifungal activity, respectively. Petri plates containing 20 mL of Mueller Hinton Agar were used for all the bacteria tested. *Candida albicans* strain was cultivated in Sabouraud's dextrose agar. The *inoculum* was spread on the surface of the solidified media. Solutions of the tested compounds were prepared in dimethylsulfoxide (DMSO) at a concentration of 5 mg/0.5 mL. Sterile Whatman no. 1 filter paper disks (6 mm in diameter) impregnated with the solution in DMSO of the test compounds (20µL solution corresponding to 200 µg compound/disk) were placed on the Petri plates. Ciprofloxacin (200 µg/disc) was used as positive control for bacteria. Fluconazole (200 µg/disc) was used as positive control for *Candida albicans*. A paper disk impregnated with DMSO was used as negative control. Plates inoculated with bacteria were incubated for 24h at 37^0C and the fungal culture was incubated for 72h at 25^0C. The inhibition zone diameters were measured in millimeters. All the tests were performed in duplicate and the average was taken as final reading.

Determination of MIC

The MIC (µg/mL) were determined by binary microdilution method in 96 multi-well microtitre plates. Solutions of the test compounds, Ciprofloxacin and Fluconazole were prepared in DMSO at a concentration of 100 µg/mL. From these stock solutions, serial dilutions of the compounds (50, 25, 12.5, 6.25, 3.12 and 1.56 µg/mL) were prepared under aseptic conditions in a final volume of 200 µl of nutrient medium. 50 µL of microbial inoculums were added to all tubes, which were incubated at 37^0C for 24 h. The MIC were recorded in each case as the minimum concentration of the compound which inhibited the visible growth of the tested microorganism. All determinations were performed in duplicate and the average was taken as final reading. 50 µL of DMSO were used as a negative control.

Results and Discussion

Chemistry

The synthetic strategies adopted to obtain the targeted compounds are outlined in Figure 1. Thiosemicarbazones **2a-b** were synthesized in accordance with the literature data [10]. Thiosemicarbazone **2c** was obtained

starting from 3-formyl-6-methyl-chromone by condensing with thiosemicarbazide in refluxing ethanol.

In order to obtain 2-hydrazone-thiazoles **3a-l**, variously substituted in positions 4 and 5 of thiazole, we applied the Hantzsch condensation between thiosemicarbazones **2a-c** and chlorocarbonyl compounds (Figure 1), in acetone, at room temperature.

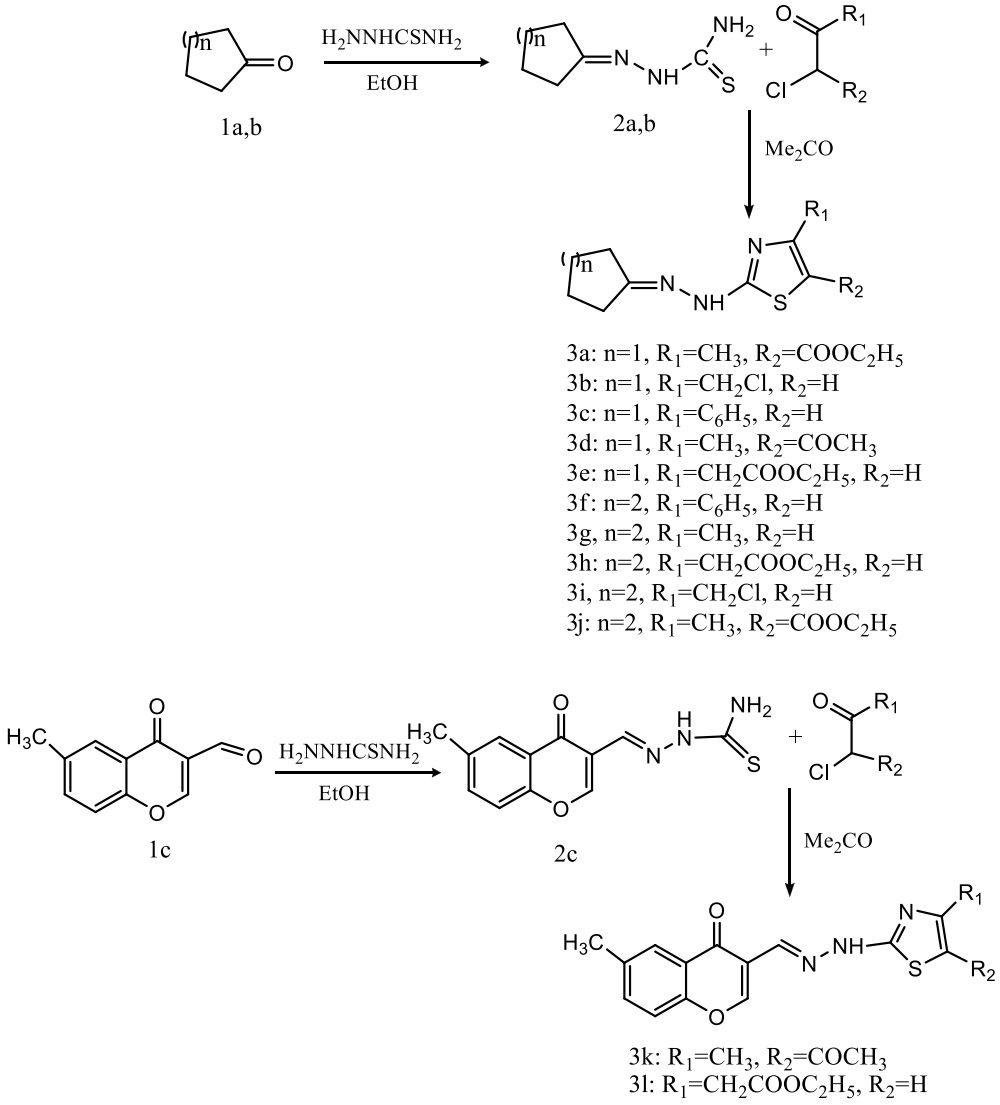

Figure 1
Synthesis of aryliden-hydrazone-thiazoles **3a-l**

The structures of thiazole derivatives were confirmed by ^{1}H NMR and mass spectroscopy. ^{1}H NMR spectra showed a singlet corresponding to the NH proton in the 11.65-11.85 ppm area. A singlet at 6.90-7.66 ppm was attributed to the C-5 proton of the thiazole ring for the compounds unsubstituted in position 5.

Mass spectra of the synthesized compounds showed that the most important fragmentation is that of N-N bond.

Antimicrobial evaluation

The newly synthesized compounds were screened for their antimicrobial activity against 4 bacterial strains: *Staphylococcus aureus (ATCC 29213)*, *Bacillus subtilis (ATCC 60511), Escherichia coli (ATCC 25922), Pseudomonas aeruginosa (ATCC 10145)* and one fungal strain: *Candida albicans ATCC 10231*, by the agar diffusion technique and MIC (minimal inhibitory concentration) determination. The organisms were obtained from the Microbiological Laboratory of University of Medicine and Pharmacy Cluj-Napoca, Romania. The results of the antimicrobial evaluation are summarized in Table I.

None of the compounds inhibited the growth of *Pseudomonas aeruginosa* and *Bacillus subtilis*. Also, the activity against *S. aureus* is modest. The compounds **3i** and **3j** have an interesting activity against *E. coli*. The results of the antifungal screening showed that the synthesized compounds (except **3e**, **3k** and **3l**) presented high activity against *C. albicans*. The most active compounds against *C. albicans* were **3b**, **3c**, **3f, 3g** and **3j**. The results of our study revealed that the presence of the chromone ring in the structures canceled the antimicrobial activity.

Table I

Antimicrobial activity of the compounds **3a-l**

Compounds	Zone of inhibition (MIC[a] values)				
	S.aureus	*E.coli*	*B.subtilis*	*P.aeruginosa*	*C.albicans*
3a	-	-	-	-	20 (6.25)
3b	-	-	-	-	40(3.12)
3c	-	-	-	-	40(3.12)
3d	-	-	-	-	20(6.25)
3e	-	-	-	-	-
3f	-	-	-	-	40(3.12)
3g	-	-	-	-	30(3.12)
3h	-	-	-	-	20(6.25)
3i	-	20(6.25)	-	-	20(6.25)
3j	-	20(6.25)	-	-	40(3.12)
3k	-	-	-	-	-
3l	-	-	-	-	-
Ciprofloxacin	20 (6.25)	20 (3.12)	20 (3.12)	20 (6.25)	-
Fluconazole	-	-	-		25 (3.12)
DMSO	-	-	-		-

[a]The MIC values were determined only for the active compounds with zones of inhibition > 10 mm. The MIC values were evaluated in the range 1.56-50 μg/mL.

Conclusions

In this paper, we have presented the synthesis of some novel 2-aryliden-hydrazones by Hantzsch condensation of aryliden-thiosemicarbazones and different α (or γ)-halocarbonyl compounds. The structures of the newly synthesized compounds were confirmed by elemental analysis and spectroscopic methods. The therapeutic potential of the new molecules was investigated by screening their antimicrobial activity against four bacterial strains and one fungal strain. The compounds **3i** and **3j** demonstrated a good inhibitory activity against *E. coli*, while compounds **3a-d** and **3f-j** presented an excellent activity against *Candida albicans*.

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