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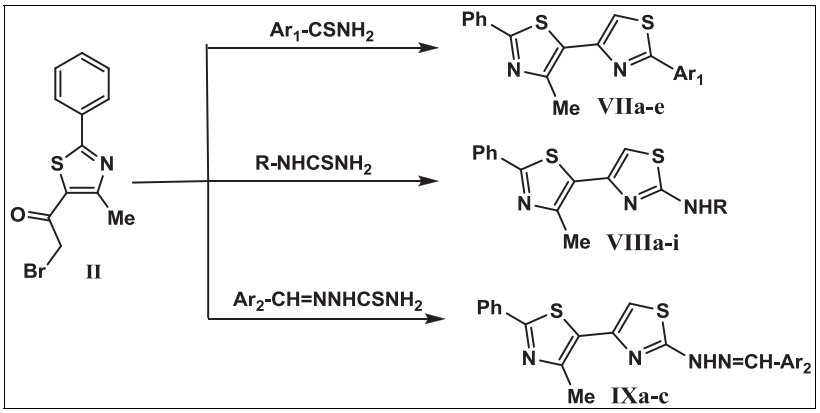


Thiazole and bisthiazole derivatives represent a prevalent scaffold in the antimicrobial drug discovery. Therefore, we have decided to synthesize some new series of 4,5′-bisthiazoles. A total of 17 compounds were synthesized, their structural elucidation being based on elemental analysis (C,H,N,S) and spectroscopic data (MS and ^{1}H NMR). Their *in vitro* antimicrobial activities were assessed against several Gram-positive and Gram-negative bacteria strains and also against one fungal strain (*Candida albicans*) using the difusimetric method. Some of the compounds showed modest to good antibacterial activity against Gram-negative *Escherichia coli* and *Salmonella typhimurium* and Gram-positive *Staphylococcus aureus* and *Bacillus cereus* bacterial strains. All of the synthesized compounds showed moderate to very good antifungal activity against *C. albicans*.

INTRODUCTION

In the current context of increasing resistance of microorganisms to antibiotics, particularly pathogenic bacteria and fungi, development of new antibacterial and antifungal agents is an important issue. Although the anti-infective therapeutic arsenal may be considered rich by the number of molecules existing in therapy, the emergence of the so-called "super bacteria," whose main characteristic is the high level of resistance to antibiotics, currently creates big problems to physicians.

Thiazoles and their derivatives have attracted continuing interest over the years due to their different biological activities [1–8]. For example, the coenzyme of vitamin B_1, which contains a thiazolium ring, is important for the decarboxylation of alpha-ketoacids [9]. This heterocyclic system has found broad application in drug development for the treatment of inflammation [10], convulsion [11], tumors [12–15], hypertension [16], bacterial [17], fungal [18], and HIV infections [19]. Some thiazole derivatives also exhibit herbicidal, insecticidal, schistosomicidal, and anthelmintic activities [20]. More recently, thiazole compounds have been found to possess analgesic [21] and fibrinogen receptor antagonism [22], they being considered also new inhibitors of bacterial DNA gyrase B [23]. In addition, thiazoles are common substructures in numerous biologically active compounds. Thus, the thiazole nucleus has been much studied in the field of organic and medicinal chemistry.

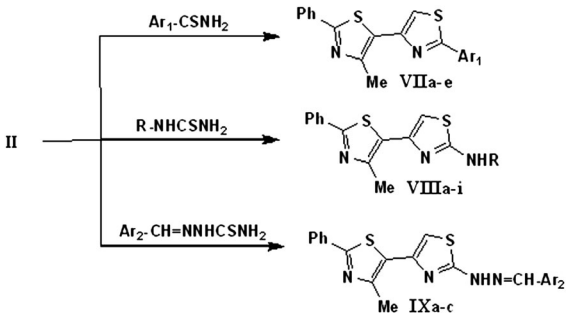
The treatment of bacterial and fungal infectious diseases remains a challenging problem because of the increasing number of multi-drug resistant microbial pathogens. Nowadays, the design of new compounds, capable to deal with resistant bacteria, having new structures and new targets of action, has become one of the most important areas in the antibacterial and antifungal research purpose. Prompted by these findings and as a part of our efforts to discover potentially active new antimicrobial agents, we report in the present work the synthesis of 17 variously substituted 4,5′-bisthiazoles and the evaluation of their antibacterial and antifungal activities.

RESULTS AND DISCUSSION

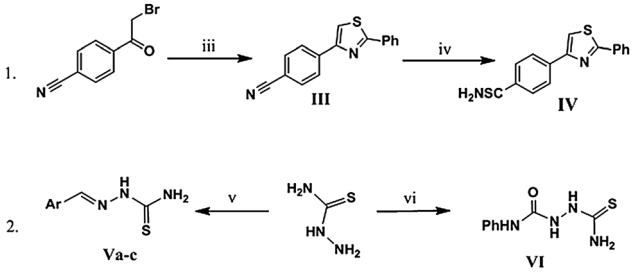
Chemistry. The target molecules (Scheme 1) were obtained via the classical Hantzsch thiazole synthesis through the condensation of bromoketone **II** with various thioamides (Scheme 2), in anhydrous acetone. The synthesis of bromoketone **II** was achieved starting from the corresponding ketone **I** by bromination with molecular bromine. Ketone **I** was easily obtained by the Hantzsch condensation of thiobenzamide with 3-chloroacetylacetone in 96% EtOH at reflux (Scheme 3).

Thioamide **IV**, with a thiazole nucleus in its structure, was obtained via a two-step synthesis involving a Hantzsch reaction and a nitrile to thioamide transformation using hydrogen sulfide gas. Thioamides **Va–c**, which have a simple thiosemicarbazone structure, were obtained from thiosemicarbazide and various aldehydes or cyclohexanone in refluxing ethanol. Thioamide **VI** was synthesized from thiosemicarbazide and phenylisocyanate in ethanol at reflux.

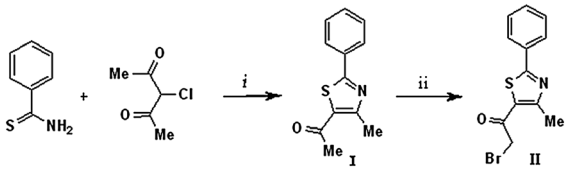
Scheme 1. Synthesis of bisthiazoles VIIa–e, VIIa–i, IXa–c; anhydrous acetone, RT, 24 h.



Scheme 2. Synthesis of some of the thiomide components. iii: $PhCSN_2$, EtOH, reflux, 3 h; iv: H_2S, EtOH, TEA, 48 h, v. ArCHO, EtOH, AcOH cc, reflux 2 h; vi. PhNCO, EtOH, TEA, reflux, 2 h.



Scheme 3. Synthesis of bromoketone II; i: EtOH, reflux, 4 h; ii: Br_2/CCl_4, HCl cc. (cat.), reflux, 2 h.



All newly synthesized compounds were characterized by melting point, elemental analysis, and spectroscopic data (^{1}H NMR and MS). All of them gave very good C,H,N,S quantitative elemental analysis results. All spectral data were in accordance with the assumed structures. The physical data, the yields, and the spectral characterizations of the synthesized compounds are presented in the Experimental section, along with the details of the synthetic procedures.

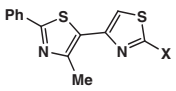
The mass spectra of the synthesized compounds gave idea about the fragmentation of the final compounds, with their corresponding mass, and showed the correct molecular ions (M^+ or M+1), as suggested by their molecular formulas. The structures of the final compounds are presented in Table 1.

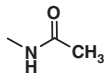
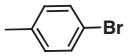
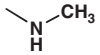
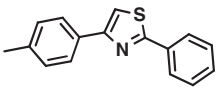
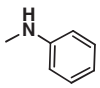
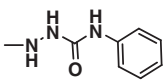
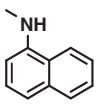
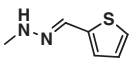
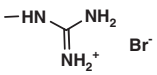
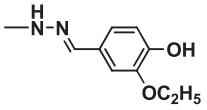
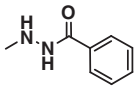
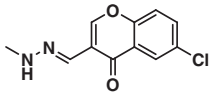
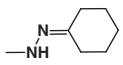
Antimicrobial activity. The *in vitro* antimicrobial activities were evaluated by the agar disk diffusion method according to the National Committee for Clinical Laboratory Standards guidelines. The antibacterial activities of the synthesized bisthiazoles were evaluated against various pathogenic Gram-negative (*Salmonella typhimurium* ATCC 13311 and *Escherichia coli* ATCC 25922) and Gram-positive (*Listeria monocytogenes* ATCC 35152, *Staphylococcus aureus* ATCC 25923, and *Bacillus cereus* ATCC 13061) strains. The antifungal activities of the previously mentioned compounds were evaluated against a strain of *Candida albicans* (ATCC 90028).

For the antibacterial assay, Mueller-Hinton agar medium was used. For the antifungal assay, this medium was supplemented with 2% glucose (providing adequate growth of yeasts) and 0.5 mg/mL methylene blue (providing a better definition of the inhibition zone). 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 a 0.5 McFarland standard by measuring the absorbance with a spectrophotometer at a wavelength of 530 nm and adding sterile distilled water as required (corresponding to a population of $1–5 \times 10^6$ CFU/mL). Six-millimeter diameter wells were cut from the agar using a sterile cork-borer, and a predetermined volume of each compound solution was delivered into the wells. 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 ([A-Za-z0-9,10–15 min, the 6 mm diameter wells were inoculated with 50 µL from 1 mg/mL solution in dimethyl sulfoxide (DMSO) (Merck, Germany) of each compound (50 µL/well). Ciprofloxacin (50 µL/well) and Fluconazole (50 µL/well) were used as standard drugs. The plates were incubated at 35°C. The diameters of the zone of inhibition were measured to the nearest whole millimeter at a point in which there will be no visible growth after 24–48 h. DMSO, the solvent used for the preparation of the newly synthesized compound solutions, did not show any inhibition against the tested bacterial and fungal strains. The assays were executed in duplicate.

Table 1

The structures of the synthesized bisthiazoles.



Compound	X	Compound	X
VIIa		VIIIe	
VIIb		VIIIf	
VIIc		VIIIg	
VIId		VIIIh	
VIIe		VIIIi	
VIIIa		IXb	
VIIIb		IXc	
VIIIc		IXa	
VIIId			

The results of the antifungal and antibacterial activities of the compounds are presented in Table 2, in comparison with ciprofloxacin and fluconazole, the reference drugs.

RESULTS

All of the bisthiazoles showed good antifungal activities, representative for the three series being **VIId**, **VIIIg**, and **IXc**. This is consistent with the fact that compounds with a bulky substituent in position 2 of the bisthiazole (*4-(2-phenylthiazol-5-yl)phenyl* and *6-chlorochromenyl*) have an increased activity against *C. albicans*. Compound **VIIIg**, with methylamino in position 2 of the heterocyclic system, showed superior antifungal activity compared with fluconazole. Against *B. cereus* compounds **VIIb**, **VIIIa**, **VIIIb**, **VIIIh**, **IXb**, and **IXc** showed higher activity than the standard ciprofloxacin. Therefore, we could assume that the activity against this strain in series **VIII** is increased

Table 2

Antimicrobial evaluation (diameter of inhibition zone/mm).

Compound	I	II	III	IV	V	VI
VIIa	13	10	12	8	10	15
VIIb	10	12	10	12	16	12
VIIc	12	8	12	10	12	12
VIId	12	8	15	6	10	20
VIIe	12	8	12	16	14	16
VIIIa	16	10	15	16	24	14
VIIIb	14	22	18	14	26	25
VIIIc	10	6	10	10	10	10
VIIId	10	6	10	8	10	22
VIIIe	12	16	14	10	10	22
VIIIf	12	15	10	8	10	15
VIIIg	12	20	14	12	14	30
VIIIh	16	16	18	14	26	14
VIIIi	14	14	12	10	16	12
IXa	12	8	12	6	8	12
IXb	12	10	14	12	24	12
IXc	16	12	15	16	24	20
C	26	12	16	26	14	-
F	-	-	-	-	-	28

-, Agar diffusion technique, diameter of inhibition (mm). Solutions of compounds: 1 mg/mL (DMSO) (50 µL/well). Microbial strains **I** = *Salmonella typhimurium* ATCC 13311; **II** = *Staphylococcus aureus* ATCC 25923; **III** = *Listeria monocytogenes* ATCC 35152; **IV** = *Escherichia coli*; ATCC 25922; **V** = *Bacillus cereus* ATCC 13061; **VI** = *Candida albicans* ATCC 90028.

when the radical **R** from the –**NHR** substituent is aromatic (*phenyl*, *α-naphthyl*) or *amidino*. The most active compounds from series **IX** were those with a bulky substituent in position 2 (*6-chlorochromenyl* and *ethylvanilyl*). Compounds **VIIIb** and **VIIIh** also showed high activities against *L. monocytogenes*, which were slightly higher than the activity of the standard antibiotic. All compounds showed modest activity against *E. coli*, lower than that of ciprofloxacin. *S. aureus* showed a good sensitivity toward compounds **VIIIb** and **VIIIg**, which were more active compared with the standard. The compounds from series **VIII** were also the most active against *S. typhimurium* from all the synthesized compounds.

The newly synthesized 4,5′-bisthiazoles showed an interesting antifungal activity as well as very good antibacterial activity against *B. cereus* and two of them (**VIIIb** and **VIIIg**) also against *S. aureus*. The most promising compounds were found to be those from series **VIII**, respectively the aminobisthiazoles with an –**NHR** type of substituent in position 2 of the heterocyclic system.

CONCLUSIONS

In conclusion, a series of 17 new 4,5′-bisthiazoles were synthesized, with promising antimicrobial activities. The formation of the second thiazole nucleus in this type of compounds has occurred very easily in mild condition reactions, respectively in anhydrous acetone at room temperature. All compounds were characterized with the help of analytical techniques: ^{1}H NMR, mass, and elemental analysis. They were evaluated for their *in vitro* antibacterial and antifungal activities, and some structure-activity relationships have been made. The best activity has been found against *C. albicans* and Gram-positive bacteria (*B. cereus*, *S. aureus*, and *L. monocytogenes*). These classes of compounds, especially those belonging to series **VIII**, may constitute potential antimicrobial agents against certain drug-resistant strains.

EXPERIMENTAL

Chemistry. The melting points were taken with an Electrothermal melting point meter (Hamburg, Germany) and were uncorrected. Analytical thin layer chromatography (TLC) was used to monitor the reaction progress and to confirm the purity of the compounds being carried out on precoated Silica Gel 60F_{254} sheets (Darmstadt, Germany). We used heptane–ethyl-acetate (3:7) as mobile phase and UV absorbtion for visualization. Yields were not optimized. The ^{1}H NMR spectra were recorded at room temperature on a Bruker Avance NMR spectrometer (Karlsruhe, Germany) operating at 500 MHz and were in accordance with the assigned structures. Chemical shift values were reported relative to tetramethylsilane (TMS) as internal standard. 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). Elemental analysis was registered with a Vario El CHNS instrument (Hanau, Germany).

Reagents and solvents were purchased from Sigma-Aldrich (St. Louis, MO) and used without further purification.

1-(4-Methyl-2-phenylthiazol-5-yl)ethanone (I). The synthesis was performed according to literature [24,25]. Thiobenzamide (3.425 g, 25 mmol) was dissolved in 96% EtOH (40 mL); and after total dissolution by refluxing for 5 min, 3-chloroacetylacetone was

added (3.625 g, 27.5 mmol) and refluxed for 4 h. After cooling, the precipitated ketone hydrochloride was suction-filtered. The product was dissolved in distilled water/ice (30 mL) and neutralized with a 10% Na_2CO_3 solution to pH 9–10. The product was recrystallized from 96% ethanol. Yield (77%, 4.18 g), white solid, mp 66–67°C.

2-Bromo-1-(4-methyl-2-phenylthiazol-5-yl)ethanone (II). The synthesis was performed according to literature [24,25], with a slight modification, in order to improve the yield and to shorten the reaction time. 1-(4-methyl-2-phenylthiazol-5-yl)ethanone (4.34 g, 20 mmol) was dissolved in dry carbon tetrachloride (20 mL), and a few drops of concentrated hydrochloric acid were added. A 10% solution of bromine in CCl_4 (10 mL) was gradually added while stirring at 0°C for 30 min. The mixture was refluxed for 2 h, with continued stirring. At the end of the reaction, the solvent was evaporated under vacuo and the obtained residue was recrystallized from absolute ethanol. The product was washed with a cold (0°C) 10% solution of $NaHCO_3$ for neutralization, until no bromide ions could be detected in the filtrate and then with cold distilled water until neutral pH. Yield (80%, 4.80 g), beige crystalline solid, mp: 108–110°C.

4-(2-Phenylthiazol-4-yl)benzonitrile (III). The 4-(2-bromoacetyl)benzonitrile (4.48 g, 20 mmol) was introduced into a round-bottom flask, absolute ethanol (20 mL) was added and the mixture was brought to reflux. Thiobenzamide was then gradually added (2.74 g, 20 mmol) and refluxing was continued for 3 h. The mixture was then cooled, and the precipitate was suction-filtered. The product was washed with a cold 10% solution of Na_2CO_3 for neutralization, until no bromide ions could be detected in the filtrate and then with cold distilled water until neutral pH. The product was recrystallized from 96% ethanol. Yield (92.5%, 4.85 g), white powder, mp: 137–139°C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 7.68–7.72 (m, 4H, Ar–H), 7.61 (s, 1H, Thiazole-CH), 7.25–7.41 (m, 5H, Ar–H); MS (EI, 70 eV) *m/z* (%): 263 (M + 1) *Anal*. Calcd. (%) for $C_{16}H_{10}N_2S$: C, 73.26; H, 3.84; N, 10.68; S, 12.22 Found: C, 73.22; H, 3.88; N, 10.72; S, 12.25.

4-(2-Phenylthiazol-4-yl)benzothioamide (IV). Compound **III** (2.62 g, 10 mmol) was added in a round bottomed flask and was suspended in absolute EtOH (30 mL). Triethylamine (TEA, 2 mL) was added, and the flask was introduced into an ice cold water bath. Hydrogen sulfide gas (44.8 L, 2000 mmol) was slowly passed through the suspension for 48 h. The precipitated product was suction-filtered and recrystallized from absolute ethanol. Hydrogen sulfide was generated from iron (II) sulfide and concentrated hydrochloric acid, using a Kipp apparatus. Yield (80%, 2.37 g), yellow crystalline powder, mp: 178–179°C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 8.06–8.09 (m, 2H, Ar–H), 7.62–7.64 (m, 2H, Ar–H), 7.58 (s, 1H, Thiazole-CH), 7.39–7.42 (m, 1H, Ar–H), 7.32–7.34 (m, 2H, Ar–H), 7.31 (s, 2H, –$CSNH_2$), 7.24–7.28 (m, 2H, Ar–H); MS (EI, 70 eV) *m/z* (%): 297 (M + 1) *Anal*. Calcd. (%) for $C_{16}H_{12}N_2S_2$: C, 64.83; H, 4.08; N, 9.45; S, 21.64 Found: C, 64.79; H, 4.05; N, 9.49; S, 21.67.

2-(3-Ethoxy-4-hydroxybenzylidene)hydrazinecarbothioamide (Va). Thiosemicarbazide (0.455 g, 5 mmol) was suspended in absolute EtOH (10 mL). The mixture was brought to reflux for 5 min, then ethylvaniline (0.831 g, 5 mmol) and three drops of glacial AcOH were added. Refluxing was continued for an additional 4 h. After cooling, the white crystalline precipitate was suction-filtered and recrystallized from absolute ethanol. Yield (82%, 0.98 g), white crystals, mp: 198–200°C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 8.24 (m, 1H, =CH), 7.16 (m, 1H, Ar–H), 6.88–6.92 (m, 1H, Ar–H), 6.78 (s, 4H, –OH, –NH, –NH_2), 6.75–6.78 (m, 1H, Ar–H), 3.98–4.06 (q, 2H, –CH_2), 1.47–1.50 (t, 2H, –CH_3); MS (EI, 70 eV) *m/z* (%): 240 (M + 1) *Anal*. Calcd. (%) for $C_{10}H_{13}N_3O_2S$: C, 50.19; H, 5.48; N, 17.56; S, 13.40 Found: C, 50.17; H, 5.52; N, 17.53; S, 13.44.

2-((6-Chloro-4-oxo-4H-chromen-3-yl)methylene)hydrazinecarbothioamide (Vb). The 6-chloro-4-oxo-4H-chromene-3-carbaldehyde (0.417 g, 2 mmol) was suspended in absolute ethanol (10 mL) and brought to reflux for 5 min. Thiosemicarbazide (0.182 g, 2 mmol) and three drops of glacial AcOH were added, and reflux was continued for 2 h. After cooling, the product was suction-filtered and recrystallized from absolute ethanol. Yield (73%, 0.41 g), yellow microcrystalline powder, mp: 193–195°C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 8.15 (d, 1H, Chromene-H), 8.04 (d, 1H, CH), 7.59–7.61 (dd, 1H, Chromene-H), 7.51–7.53 (dd, 1H, Chromene-H), 6.47 (s, 3H, NH, NH_2); MS (EI, 70 eV) *m/z* (%): 282 (M + 1) *Anal*. Calcd. (%) for $C_{11}H_8ClN_3O_2S$: C, 46.90; H, 2.86; N, 14.92; S, 11.38 Found: C, 46.88; H, 2.89; N, 14.87; S, 11.41.

2-(Thiophen-2-ylmethylene)hydrazinecarbothioamide (Vc). This compound has been previously reported [26,27]. Yield (83%, 0.77 g), white microcrystalline powder, mp: 192–194°C.

2-Carbamothioyl-N-phenylhydrazinecarboxamide (VI). This compound has been previously reported [28]. Yield (45%, 0.283 g), white microcrystalline powder, mp: 195–196°C.

4′-Methyl-2′-phenyl-2-(pyridin-3-yl)-4,5′-bisthiazole (VIIa). **II** (0.296 g, 1 mmol) was dissolved in 96% EtOH (4 mL), and then pyridine-3-carbothioamide (0.138 g, 1 mmol) was added, and the mixture was refluxed for 2 h. After cooling, the mixture was poured into ice-cold water (20 mL) and the formed precipitate was suction-filtered. The product was neutralized with a 10% solution of Na_2CO_3 and then washed with distilled water until neutral pH. The product was recrystallized from 96% ethanol. Yield (45%, 0.150 g), brown powder, mp: 114°C.

VIIa was also prepared according to the general procedure in anhydrous acetone, as described for **VIIId**, using pyridine-3-carbothioamide (1 mmol) as a thioamide component. The product was recrystallized from 96% ethanol. Yield (38%, 0.127 g), brown powder, mp: 114°C. ^{1}H NMR (DMSO-*d*6, 500 MHz) δ ppm: 9.19 (m, 1H, Ar–H), 8.71–8.73 (m, 1H, Ar–H), 8.35–8.38 (m, 1H, Ar–H), 8.08 (s, 1H, Thiazole-CH), 7.97–7.99 (m, 2H, Ar–H), 7.58–7.61 (m, 1H, Ar–H), 7.51–7.52 (m, 3H, Ar–H), 2.71 (s, 3H, CH_3); MS (EI, 70 eV) *m/z* (%): 336 (M + 1) *Anal*. Calcd (%) for $C_{18}H_{13}N_3S_2$: C, 64.45; H, 3.91; N, 12.53; S, 19.12 Found: C, 64.49; H, 3.86; N, 12.46; S, 19.17.

4′-Methyl-2′-phenyl-2-(pyridin-4-yl)-4,5′-bisthiazole (VIIb). The synthesis was performed in 96% EtOH at reflux according to the first procedure described for **VIIa**. The product was recrystallized from 96% ethanol. Yield (60%, 0.200 g), gray powder, mp: 175–176°C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 8.52–8.54 (m, 2H, Ar–H), 7.83–7.85 (m, 2H, Ar–H), 7.49 (s, 1H, Thiazole-CH), 7.39–7.42 (m, 1H, Ar–H), 7.29–7.31 (m, 2H, Ar–H), 7.23–7.26 (m, 2H, Ar–H), 2.72 (s, 3H, CH_3); MS (EI, 70 eV) *m/z* (%): 336 (M + 1) *Anal*. Calcd. (%) for $C_{18}H_{13}N_3S_2$: C, 64.45; H, 3.91; N, 12.53; S, 19.12 Found: C, 64.48; H, 4.00; N, 12.50; S, 19.16.

2-(4-Bromophenyl)-4′-methyl-2′-phenyl-4,5′-bisthiazole (VIIc). The synthesis was performed according to the general procedure described for **VIIId** by using 4-bromobenzothioamide (0.108 g, 0.5 mmol) as a thioamide component. The product was recrystallized from 96% ethanol. Yield (70%, 0.143 g), beige

powder, mp: 152–153°C. ^{1}H NMR (DMSO-d_6, 500MHz) δ ppm: 7.39–7.42 (m, 2H, Ar–H), 7.83 (Thiazole-CH), 7.28–7.31 (m, 4H, Ar–H), 7.22–7.26 (m, 2H, Ar–H), 7.06–7.08 (m, 2H, Ar–H), 2.49 (s, 3H, CH_3); MS (EI, 70 eV) *m/z* (%): 413 (M + 1), 415 (M + 1) —corresponding to the two isotopes of bromine. *Anal*. Calcd. (%) for $C_{19}H_{13}BrN_2S_2$: C, 55.21; H, 3.17; N, 6.78; S, 15.51 Found: C, 55.25; H, 3.14; N, 6.74; S, 15.56.

4′-Methyl-2′-phenyl-2-(4-(2-phenylthiazol-5-yl)phenyl)-4,5′-bisthiazole (VIId). The synthesis was performed according to the general procedure described for **VIIId**. The product was recrystallized from absolute ethanol. Yield (77.5%, 0.38 g), yellow powder, mp: 221–223°C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 8.37 (s, 1H, Thiazole-CH), 8.22–8.24 (m, 2H, Ar–H), 8.10–8.12 (m, 2H, Ar–H), 8.06–8.08 (m, 2H, Ar–H), 8.02 (s, 1H, Thiazole-C_7-H), 7.99–8.00 (m, 2H, Ar–H), 7.52–7.54 (m, 6H, Ar–CH), 2.72 (s, 3H, –CH_3); MS (EI, 70 eV) *m/z* (%): 494 (M + 1). *Anal*. Calcd. (%) for $C_{28}H_{19}N_3S_3$: C, 68.12; H, 3.88; N, 8.51; S, 19.49. Found: C, 68.15; H, 3.82; N, 8.47; S, 19.50.

2-(4′-Methyl-2′-phenyl-4,5′-bisthiazol-2-yl)phenol (VIIe). The synthesis was performed according to the general procedure described for **VIIId** by using **II** (0.148 g, 0.5 mmol) and 2-hydroxybenzothioamide (0.077 g, 0.5 mmol) as the thioamide component. The product was recrystallized from 96% ethanol. Yield (16%, 0.028 g), light beige powder, mp: 170–172°C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm): 7.60 (s, 1H, Thiazole-CH), 7.47–7.49 (m, 1H, Ar–H), 7.39–7.42 (m, 1H, Ar–H), 7.29–7.31 (m, 2H, Ar–H), 7.22–7.26 (m, 2H, Ar–H), 7.13–7.16 (m, 1H, Ar–H), 6.83–6.86 (m, 1H, Ar–H), 6.66–6.68 (m, 1H, Ar–H), 4.39 (s, 1H, –OH), 2.53 (s, 3H, –CH_3); MS (EI, 70 eV) *m/z* (%): 352 (M + 1) *Anal*. Calcd. for $C_{19}H_{14}N_2OS_2$: C, 65.12; H, 4.03; N, 7.99; O, 4.57; S, 18.30 Found: C, 65.07; H, 4.05; N, 7.94; S, 18.33.

4′-Methyl-N-(naphthalen-1-yl)-2′-phenyl-4,5′-bisthiazol-2-amine (VIIIa). **II** (0.148 g, 0.5 mmol) was dissolved in the minimum amount of anhydrous acetone, and α-naphthylthiourea (0.101 g, 0.5 mmol) was added. The mixture was stirred for 24 h at room temperature, and the formed precipitate was suction-filtered. The product was refluxed with a mixture of CH_2Cl_2: Acetone 1:1 (10 mL) for 5 min, and the precipitate was rapidly suction-filtered. Finally, it was neutralized with a 10% solution of Na_2CO_3 solution and washed with distilled water until neutral pH. Yield (58%, 0.115 g), gray powder, mp: 213–215°C; ^{1}H NMR (DMSO-d_6, 500MHz) δ (ppm): 10.56 (s, 1H, NH) 7.53–7.55 (m, 1H, Ar–H), 7.39–7.43 (m, 3H, Ar–H), 7.29–7.31 (m, 2H, Ar–H), 7.18–7.28 (Ar–H), 7.24 (s, 1H, Thiazole-CH), 2.67 (s, 3H, CH_3); MS (EI, 70 eV) *m/z* (%): 400 (M + 1); *Anal*. Calcd (%) for $C_{23}H_{17}N_3S_2$: C, 69.14; H, 4.29; N, 10.52; S, 16.05. Found: C, 69.23; H, 4.22; N, 10.61; S, 15.95.

Amino(4′-methyl-2′-phenyl-4,5′-bisthiazol-2-ylamino) methaniminium bromide (VIIIb). **II** (0.296 g, 1 mmol) was dissolved in anhydrous acetone (5 mL), and a solution of 2-imino-4-thiobiuret (0.118 g, 1 mmol) in acetone (5 mL) was gradually added with continuous stirring at 0°C, over 30 min. Stirring was continued for 24 h, and the formed precipitate was suction-filtered and washed with dry diethyl ether (5 mL). The product was recrystallized from absolute ethanol. Yield (59%, 0.234 g), light-yellow crystalline powder, mp: 282–284°C. ^{1}H NMR (DMSO-d_6, 500MHz) δ ppm: 7.39–7.42 (m, 1H, Ar–H), 7.22–7.26 (m, 2H, Ar–H), 7.29–7.31 (m, 2H, Ar–H), 7.84 (s, 1H, Thiazole-CH), 5.60 (s, 5H, guanidino-H), 2.71 (s, 3H, CH_3); MS (EI, 70 eV) *m/z* (%): 316 (M + 1) *Anal*. Calcd. (%) for $C_{14}H_{14}N_5S_2Br$: C, 42.43, H, 3.56, N, 17.67, S, 16.18. Found: C, 42.41, H, 3.52, N, 17.70, S, 16.16.

N′-(4′-Methyl-2′-phenyl-4,5′-bisthiazol-2-yl)benzohydrazide (VIIIc). 2-Benzoylhydrazinecarbothioamide (0.195 g, 1 mmol) and **II** (0.296 g, 1 mmol) were separately dissolved in minimum amounts of anhydrous acetone. The solutions were mixed and stirred at room temperature for 24 h. The precipitate was then filtered, suspended in distilled water, neutralized with a 10% solution of Na_2CO_3 and then washed again with water until neutral pH. The product was recrystallized from 96% ethanol. Yield (71%, 0.236 g), white powder, mp: 211–212°C; ^{1}H NMR (DMSO-d_6, 500MHz) δ ppm: 11.42 (s, 1H, NH), 9.49 (s, 1H, NH), 7.68–7.71 (m, 2H, Ar–H), 7.62–7.65 (m, 2H, Ar–H), 7.56–7.58 (m, 1H, Ar–H), 7.39–7.42 (m, 1H, Ar–H), 7.22–7.26 (m, 2H, Ar–H), 7.29–7.31 (m, 2H, Ar–H), 7.37 (s, 1H, Thiazole-CH), 2.67 (s, 3H, CH_3); MS (EI, 70 eV) *m/z* (%): 393 (M + 1) *Anal*. Calcd. (%) for $C_{20}H_{16}N_4OS_2$: C, 61.20; H, 4.11; N, 14.27; S, 16.34. Found: C, 61.22; H, 4.09; N, 14.30; S, 16.30.

2-(2-Cyclohexylidenehydrazinyl)-4′-methyl-2′-phenyl-4,5′-bisthiazole(VIIId). 2-Cyclohexylidenehydrazinecarbothioamide (0.171 g, 1 mmol) was suspended in anhydrous acetone (10 mL), and then **II** (0.296 g, 1 mmol) was added. The mixture was stirred for 24 h at room temperature. The precipitate was then filtered, washed with dry diethyl ether, and neutralized with a 10% solution of Na_2CO_3. The product was then washed with distilled water until neutral pH and dried overnight at room temperature. The product was recrystallized from absolute ethanol. Yield (80%, 0.298 g), light beige powder, mp: 177–178°C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 11.02 (s, 1H, NH), 7.91–7.93 (m, 2H, Ar–H), 7.48–7.50 (m, 3H, Ar–H), 7.08 (s, 1H, Thiazole-CH), 2.61 (s, 3H, CH_3), 2.44–2.46 (m, 2H, CH_2), 2.25–2.27 (m, 2H, CH_2), 1.58–1.64 (m, 6H, CH_2); MS (EI, 70 eV) *m/z* (%): 369 (M + 1) *Anal*. Calcd. for $C_{19}H_{20}N_4S_2$: C, 61.92; H, 5.47; N, 15.20; S, 17.40. Found: C, 61.89; H, 5.48; N, 15.17; S, 17.45.

N-Allyl-4′-methyl-2′-phenyl-4,5′-bisthiazol-2-amine (VIIIe). The synthesis of this compound has been previously reported by using EtOH as solvent in reflux conditions, although its biological activity has not been determined [29]. **II** (0.148 g, 0.5 mmol) was dissolved in the minimum amount of anhydrous acetone, and allylthiourea (0.058 g, 0.5 mmol) was added. The precipitate was then filtered, washed with dry diethyl ether, and neutralized with a 10% solution of Na_2CO_3. The product was then washed with distilled water until neutral pH and dried overnight at room temperature. The product was recrystallized from absolute methanol. Yield (54.4%, 0.085 g), yellow solid, mp: 112–113°C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 10.60 (s, 1H, NH), 7.41 (m, 1H, Ar–H), 7.29 (m, 2H, Ar–H), 7.22–7.26 (m, 2H, Ar–H), 7.32 (s, 1H, Thiazole-CH), 5.92–6.00 (m, 1H, CH), 5.12–5.17 (m, 1H, CH), 5.02–5.05 (m, 1H, CH), 3.51 (m, 2H, CH_2), 2.68 (s, 3H, CH_3); MS (EI, 70 eV) *m/z* (%): 314 (M + 1) *Anal*. Calcd. (%) for $C_{16}H_{15}N_3S_2$: C, 61.31; H, 4.82; N, 13.41; S, 20.46. Found: C, 61.36; H, 4.79; N,13.34; S, 20.41.

N-(4′-Methyl-2′-phenyl-4,5′-bisthiazol-2-yl)acetamide (VIIIf). The synthesis was performed according to the general procedure described for **VIIId** by using *N*-carbamothioylacetamide (0.118 g, 1 mmol) as a thioamide component. The product was recrystallized from 96% ethanol. Yield (73%, 0.23 g), yellow powder, mp: 269–270°C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 9.47 (s, 1H, NH), 7.39–7.42 (m, 1H, Ar–H), 7.28–7.31 (m, 2H, Ar–H), 7.23–7.26 (m, 2H, Ar–H), 7.22 (s, 1H, Thiazole-CH), 2.40 (s, 3H, –CH_3), 2.70 (s, 3H, CH_3); MS (EI,

70 eV) *m/z* (%): 316 (M + 1) *Anal*. Calcd. (%) for $C_{15}H_{13}N_3OS_2$: C, 57.12; H, 4.15; N, 13.32; S, 20.33. Found: C, 57.14; H, 4.11; N, 13.27; S, 20.29.

N-4′-Dimethyl-2′-phenyl-4,5′-bisthiazol-2-amine (VIIIg). The synthesis was performed according to the general procedure described for **VIIId** by using **II** (0.148 g, 0.5 mmol) and 1-methylthiourea (0.045 g, 0.5 mmol) as a thioamide component. The product was recrystallized from 96% ethanol. Yield (74%, 0.106 g), yellow powder, mp: 153–154°C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm 9.13 (s, 1H, NH), 7.39–7.42 (m, 1H, Ar–H), 7.28–7.31 (m, 2H, Ar–H), 7.23–7.26 (m, 2H, Ar–H), 7.25 (s, 1H, Thiazole-CH), 2.95 (s, 3H, CH_3), 2.50 (s, 3H, –CH_3); MS (EI, 70 eV) *m/z* (%): 288 (M + 1) *Anal*. Calcd. (%) for $C_{14}H_{13}N_3S_2$: C, 58.51; H, 4.56; N, 14.62; S, 22.31. Found: C, 58.49; H, 4.58; N, 14.57; S, 22.36.

4′-Methyl-N,2′-diphenyl-4,5′-bisthiazol-2-amine (VIIIh). The synthesis of this compound has been previously reported, although its biological activity has not been determined [30].

II (0.296 g, 1 mmol) was dissolved in 96% EtOH (5 mL). 1-phenylthiourea (0.152 g, 1 mmol) was added and the mixture was refluxed for 3 h. After cooling, the formed precipitate was suction-filtered, neutralized with a 10% solution of Na_2CO_3, and washed with distilled water until neutral pH. The product was recrystallized from 96% ethanol. Yield (51%, 0.180 g), yellow powder, mp 122–123°C;

VIIIh was also prepared according to the general procedure described for **VIIId** by using **II** (0.296 g, 1 mmol) and 1-phenylthiourea (0.152 g, 1 mmol) as a thioamide component. The product was recrystallized from 96% ethanol. Yield (60%, 0.208 g), yellow powder, mp 122–123°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 10.41 (s, 1H, NH), 7.95–7.97 (m, 2H, Ar–H), 7.68–7.70 (m, 2H, Ar–H), 7.50 (m, 3H, Ar–H), 7.35–7.38 (m, 2H, Ar–H), 7.12 (s, 1H, Thiazole-CH), 2.66 (s, 3H, CH_3); MS (EI, 70 eV) *m/z* (%): 350 (M + 1) *Anal*. Calcd. (%) for $C_{19}H_{15}N_3S_2$: C, 65.30; H, 4.33; N, 12.02; S, 18.35. Found: C, 65.25; H, 4.26; N, 11.96; S, 18.32.

2-(4′-Methyl-2′-phenyl-4,5′-bisthiazol-2-yl)-N-phenylhydrazinecarboxamide (VIIIi). Synthesis was performed according to the general procedure described for **VIIId** by using **II** (0.296 g, 1 mmol) and 2-carbamothioyl-N-phenylhydrazinecarboxamide (0.21 g, 1 mmol) as a thioamide component. The product was recrystallized from absolute ethanol. Yield (86%, 0.349 g), yellow powder, mp 245–246°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 8.80 (s, 1H, –NH), 8.51 (d, 1H, –NH), 7.69 (d, 1H, –NH), 7.37–7.42 (m, 3H, Ar–H), 7.28–7.31 (m, 2H, Ar–H), 7.22–7.26 (m, 2H, Ar–H), 7.17–7.21 (m, 2H, Ar–H), 6.92–6.96 (m, 1H, cAr–H), 6.67 (s, 1H, Thiazole-CH), 2.61 (s, 3H, –CH_3); MS (EI, 70 eV) *m/z* (%): 408 (M + 1); *Anal*. Calcd. for $C_{20}H_{17}N_5OS_2$: C, 58.95; H, 4.20; N 17.19; S, 15.74. Found: C, 59.03; H, 4.17; N, 17.11; S, 15.80.

4′-Methyl-2′-phenyl-2-(2-(thiophen-2-ylmethylene)hydrazinyl)-4,5′-bisthiazole (IXa). The synthesis was performed according to the general procedure described for **VIIId** by using 2-(thiophen-2-ylmethylene)hydrazinecarbothioamide as a thioamide component. The product was recrystallized from absolute ethanol. Yield (79%, 0.300 g), light beige powder, mp: 243–244°C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 12.78 (s, 1H, NH), 7.73 (m, 1H, Ar–H), 7.60 (m, 1H, Thiophene-CH), 7.55 (s, 1H, Thiazole-CH) 7.39–7.42 (m, 1H, Ar–H), 7.28–7.31 (m, 2H, Ar–H), 7.27–7.28 (m, 1H, Thiophene-CH), 7.22–7.26 (m, 2H, Ar–H), 6.93 (m, 1H, Thiophene-CH), 2.70 (s, 3H, CH_3); MS (EI, 70 eV) *m/z* (%): 383 (M + 1) *Anal*. Calcd. (%) for $C_{18}H_{14}N_4S_3$: C, 56.52; H, 3.69; N, 14.65; S, 25.15. Found: C, 56.46; H, 3.73; N, 14.52; S, 25.05.

2-Ethoxy-4-((2-(4′-methyl-2′-phenyl-4,5′-bisthiazol-2-yl) hydrazono)methyl)phenol (IXb). Synthesis was performed according to the general procedure described for **VIIId** by using 2-(3-ethoxy-4-hydroxybenzylidene)hydrazinecarbothioamide (0.119 g, 0.5 mmol) as a thioamide component. The product was recrystallized from absolute ethanol. Yield (80%, 0.180 g), brown-reddish powder, mp; 240–242°C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ ppm: 8.85 (s, 2H, –OH and –NH), 8.17–8.18 (m, 1H, =CH), 7.39–7.42 (m, 1H, Ar–H), 7.29–7.31 (m, 2H, Ar–H), 7.23–7.26 (m, 2H, Ar–H), 6.93–6.95 (m, 1H, Ar–H), 7.20 (s, 1H, Thiazole-CH); 6.74–6.76 (m, 1H, Ar–H); 3.99–4.0 (q, 2H, CH_2); 2.62 (s, 3H, CH_3); 1.47–1.50 (t, 3H, CH_3); MS (EI, 70 eV) *m/z*: 437 (M + 1) *Anal*. Calcd. (%) for $C_{22}H_{20}N_4O_2S_2$: C, 60.53; H, 4.62; N 12.83; S, 14.69. Found: C, 60.55; H, 4.63; N, 12.79; S, 14.84.

***6-Chloro-3-((2-(4′-methyl-2′-phenyl-4,5′-bisthiazol-2-yl) hydrazono)methyl)-4H*-chromen-4-one (IXc).** 2-((6-Chloro-4-oxo-4H-chromen-3-yl)methylene)hydrazinecarbothioamide (0.282 g, 1 mmol) was suspended in anhydrous acetone (20 mL), and **II** (0.296 g, 1 mmol) was added. After stirring for 24 h at room temperature, the product was filtered, washed with diethyl ether (5 mL), and neutralized with a 10% solution of Na_2CO_3. The compound was recrystallized from absolute ethanol. Yield (83%, 0.400 g), white powder, mp: 225–226°C; ^{1}H NMR (DMSO-d_6, 500MHz) δ ppm: 9.70 (s, 1H, –NH–), 7.77 (d, 1H, Ar–H), 7.58–7.59 (dd, 1H, Chromone-CH), 7.50–7.52 (dd, 1H, Chromone-CH), 7.35–7.37 (m, 1H Chromone-CH), 7.39–7.42 (m, 1H, Ar–H), 7.29–7.31 (m, 2H, Ar–H), 7.22–7.26 (m, 2H, Ar–H), 7.16 (s, 1H, Thiazole-CH), 5.72 (d, 1H, Chromone-CH), 2.76 (s, 3H, –CH_3); MS (EI, 70 eV) *m/z* (%): 479 (M + 1), 481 (M + 1)—corresponding to the two isotopes of chlorine. *Anal*. Calcd. (%) for $C_{23}H_{15}ClN_4O_2S_2$: C, 57.67; H, 3.16; N 11.70; S, 13.39. Found: C, 57.59; H, 3.11; N 11.61; S, 13.51.

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