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Synthesis of new derivatives of hydrazinecarbothioamides and 1,2,4-triazoles, and an evaluation of their antimicrobial activities

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Abstract: A new series of hydrazinecarbothioamides **6**–**9** bearing a 5*H*-dibenzo[*a*,*d*][7]annulene moiety were synthesized. Cyclization of **6**–**9** in NaOH solution produced the corresponding 4*H*-1,2,4-triazole-3-thiols **10**–**13**, which proved to be axial isomers. The thioethers **14**–**17** were prepared by alkylation of **10**–**13** with methyl iodide. All new compounds were characterized by elemental analysis, and IR, UV, ^{1}H-NMR and ^{13}C-NMR spectroscopy. An evaluation for antimicrobial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Bacillus subtilis*, *Salmonella enterica* subsp. *enterica* serovar Typhimurium, *Shigella flexneri* and *Candida albicans* was performed.

Keywords: acylhydrazinecarbothioamide; 1,2,4-triazole-3-thiol; dibenzo[*a*,*d*]-[7]annulene; antimicrobial activity.

INTRODUCTION

Bacterial infection remains a serious threat to human lives because of their capacity to develop resistance to existing antibiotics, which is an increasing public health problem. For this reason, obtaining new types of antibacterial agents is a very important task.

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The tricyclic framework of 5*H*-dibenzo[*a*,*d*][7]annulene constitutes an integral part of the structure of molecules that are known to be effective for the treatment of depressive disorders.[1,2] Analogs of 5*H*-dibenzo[*a*,*d*][7]annulene, such as protriptyline and demexiptiline, are well known tricyclic antidepressants, which are used in the treatment of migraines, tension headaches, anxiety, psychosis, aggression and violent behavior. The anti-allergic drug cyproheptadine (Cyp) is known to have inhibitory activity for L-type calcium channels in addition to histamine and serotonin receptors.[3]

Recently, studies that were trying to detect other possible pharmacological actions of already known tricyclic antidepressants have received increasing interest.[4–13]

Dibenzo[*a*,*d*][7]annulene moieties are incorporated in biologically active compounds that exhibit muscarinic receptor antagonist properties and are useful in the treatment of Parkinson's disease, tardive dyskinesia and motion sickness.[4]

Dibenzo[*a*,*d*][7]annulene derivatives exhibit antidiabetic,[5] antiparasitic,[6] metalloprotease inhibitory[7] and antimicrobial activity.[8–13] Munoz-Bellido *et al.* realized an extensive study that demonstrated the intense antibacterial activities presented by some antidepressant from the group of serotonin recapture inhibitors, such as clomipramine and sertraline.[11] Similarly some psychiatric agents, such as protriptyline or cyclobenzaprine, are associated with some chemotherapy agents (sulfathiazole) that enhance the antibacterial activity of the latter and reduce the *MIC* up to 50 %.[11]

1,2,4-Triazole derivatives are known to show biological properties including antimicrobial,[14–19] anticancer,[20] anti-inflammatory,[21,22] anticonvulsant,[23] antiviral,[24,25] antitubercular,[25] hypolipidemic,[26] antioxidant activities[27,28] and others.

Several compounds containing 1,2,4-triazole rings are used in therapy. For example, fluconazole, terconazole and itraconazole are used as antimicrobial drugs, while vorozole, letrozole and anastrozole are non-steroidal drugs used for the treatment of cancer.[29] Other examples are ribavirin (antiviral agent), rizatriptan (antimigraine agent) and alprazolam (anxiolytic agent),[30] beside others.

Furthermore, a number of substituted hydrazinecarbothioamide were found to exhibit antifungal,[12,31–36] tuberculostatic,[36] cytostatic,[37] anticonvulsant,[38] antiviral[39] and antioxidant activities.[28,40]

Considering the above data, in continuation of ongoing research on biologically active compounds, the synthesis of new hydrazinecarbothioamides and 1,2,4--triazoles bearing the 5*H*-dibenzo[*a*,*d*][7]annulene moiety and their antimicrobial activities were considered.[41,42]

EXPERIMENTAL

Chemistry

All reactants and solvents of the highest purity were obtained commercially and used without further purification. Melting points were determined on a Boetius apparatus and are

uncorrected. The UV–Vis spectra were recorded on a SPECORD 40 Analytik Jena spectrometer, in methanol (2.5×10^{-5} M) in the wavelength range 200–600 nm. The IR spectra were recorded in KBr pellets using a Vertex 70 Bruker spectrometer. Elemental analyses were performed on an ECS-40-10-Costeh micro-dosimeter (and the values were within ±0.4 % of the theoretical ones). The NMR spectra were recorded on a Varian Gemini 300 BB instrument operating at 300 MHz for ^{1}H- and 75 MHz for ^{13}C-NMR, using DMSO-d_6 as solvent for the hydrazinecarbothioamides and $CDCl_3$ for the 1,2,4-triazole compounds. Chemical shifts (δ in ppm) were assigned according to the internal standard signal of tetramethylsilane in DMSO-d_6 (δ = 0 ppm). Coupling constants, J, are expressed in Hz.

Analytical and spectral data of the synthesized compounds are given in the Supplementary material to this paper.

General procedure for the preparation of N-*substituted 2-(5*H-*dibenzo[*a,d*][7]annulen-5-ylacetyl)-hydrazinecarbothioamides (**6**–**9**)*

A mixture of 2-(5*H*-dibenzo[*a*,*d*][7]annulen-5-yl)acetohydrazide (**1**, 4 mmol) and the required isothiocyanate **2**–**5** (4 mmol) in absolute ethanol (30–50 mL) was refluxed for 6–12 h. On cooling the reaction mixture to room temperature, a precipitate appeared. This was filtered off and recrystallized from ethanol to obtain the desired compound.

*General procedure for the preparation of 4-substituted 5-(5*H-*dibenzo[*a,d*][7]annulen-5-ylmethyl)-4*H-*1,2,4-triazole-3-thiols (**10**–**13**)*

A solution of the required hydrazinecarbothioamide (**6**–**9**, 1 mmol) in 8 mL of 8 % NaOH solution was refluxed for 3–9 h and then filtered. After cooling, the filtrate was neutralized with acetic acid. The obtained white precipitate was filtered and recrystallized from $CHCl_3$:petroleum ether (1:2, *V*:*V*, boiling range: 60–80 °C).

*General procedure for the preparation of 4-substituted 3-(5*H-*dibenzo[*a,d*][7]annulen-5-ylmethyl)-5-(methylsulfanyl)-4*H-*1,2,4-triazoles (**14**–**17**)*

To a solution of sodium ethoxide (1mmol of sodium in 10 mL of absolute ethanol) was added the required triazole **10**–**13** (1 mmol). The reaction mixture was stirred at room temperature until a solution was obtained. To this solution, methyl iodide (1 mmol) was added and stirring continued for 10 h. The reaction mixture was poured into ice water and the precipitate was filtered off, washed with water and recrystallized from ethanol.

Antimicrobial activity

The antibacterial and antifungal activities of the compounds were investigated by the broth microdilution method, in 96 flat-bottomed wells microplates (Nunc, Denmark). Dimethyl sulfoxide was used as the solvent for the preparation of stock solutions of the compounds, to obtain a concentration of 2048 μg mL^{-1}. The antimicrobial actions of the newly-synthesized compounds were tested against 6 reference bacterial strains, *i.e*., *Staphylococcus aureus* ATCC 25923, *Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922, *Bacillus subtilis* ATCC 6633, *Salmonella enterica* subsp. *enterica* serovar Typhimurium ATCC 14028, *Shigella flexneri* ATCC 12022, and one reference yeast strain, *i.e*., *Candida albicans* ATCC 90028. Gentamicin was used as a positive control for *S. aureus*, *P. aeruginosa* and *E. coli*, and fluconazole for *C. albicans*. Bacterial susceptibility testing was performed according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) M100-S16 and European Committee on Antimicrobial Susceptibility Testing (EUCAST).[43,44]

All 96 wells of the microplate were filled in with 100 μL of Müller–Hinton broth (cation-adjusted) when testing compounds against bacteria and Sabouraud broth when testing against

the yeast. Series of two-fold dilutions of the newly-obtained compounds were performed in Műller–Hinton or Sabouraud broth. In the case of the reference bacterial strains, the inoculum was prepared by suspending 5 distinct colonies from a 24 h culture obtained on Columbia Blood Agar (BioMérieux, France), in a tube with Brain Heart Infusion broth (BHI broth). After vortex mixing and adjusting the density to the turbidity of the 0.5 McFarland standard, the bacterial suspension was diluted 1:100 in BHI broth, in order to obtain the working inoculum. Afterwards, each well of the microdilution plates containing 100 µL of Müller––Hinton broth with compound was inoculated within 15 min with 100 µL of the bacterial inoculum, including the growth control wells, but not the sterility control wells that were filled with 200 µL of compound-free Müller–Hinton broth.

In the case of the reference yeast strains, the inoculum was prepared by suspending 5 distinct colonies from a 24 h culture obtained on Sabouraud dextrose agar, in a tube with 5 mL of sterile distilled water. After vortex mixing and adjusting the density to the turbidity of the 0.5 McFarland standard, the fungal suspension was diluted in sterile distilled water in order to obtain a working inoculum. Each well of the microdilution plates containing 100 µL of Sabouraud broth with compound was inoculated with 100 µl yeast inoculum within 15 min, including the growth control wells, but not the sterility control wells, which were filled only with 200 µL compound-free Sabouraud broth. After performing the inoculum controls from the growth control wells, the microplates were incubated at 37 °C for 24 h.[48-50]

The lowest concentration of each compound able to inhibit visible microbial growth was considered the minimum inhibitory concentration (*MIC*) value.

RESULTS AND DISCUSSION

Chemistry

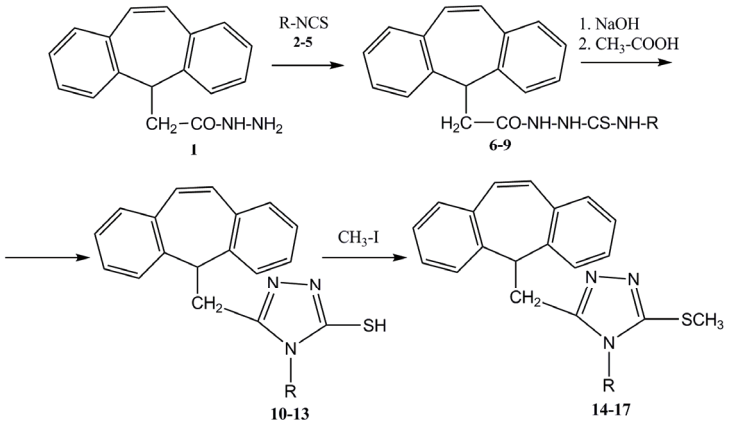
The reaction sequences employed for the syntheses of the title compounds are shown in Scheme 1. In the present work, *N*-aryl-2-(5*H*-dibenzo[*a*,*d*][7]-annulen-5-ylacetyl)hydrazinecarbothioamides **6**–**9** were synthesized by nucleophilic addition of 2-(5*H*-dibenzo[*a*,*d*][7]annulen-5-yl)acetohydrazide (**1**) to the aryl isothiocyanates **2**–**5**, in absolute ethanol under reflux. 2-(5*H*-Dibenzo[*a*,*d*]-[7]annulen-5-yl)acetohydrazide (**1**) was prepared starting from dibenzosuberenone, according to a literature method.[42,43,46]

Synthesis of the new 4-alkyl/aryl-5-(5*H*-dibenzo[*a*,*d*][7]annulen-5-yl-methyl)-4*H*-1,2,4-triazole-3-thiols **10**–**13** (that exist in equilibrium with their thione tautomer) consisted in intramolecular cyclization of acylhydrazine-carbothioamides **6**–**9** in 8 % sodium hydroxide solution under reflux.[41,46,47]

The treatment of 1,2,4-triazoles **10**–**13** with methyl iodide in basic media yielded the 4-substituted 3-(5*H*-dibenzo[*a*,*d*][7]annulen-5-ylmethyl)-5-(methylsulfanyl)-4*H*-1,2,4-triazoles **14**–**17** and not the *N*-methylated derivatives.

Analytical and spectral data of the newly synthesized compounds

All the synthesized compounds were analyzed by IR, UV–Vis, ^{1}H-NMR and ^{13}C-NMR spectroscopy. The analytical and spectral data of the new compounds are given in the Supplementary material to this paper.



R= p-C_6H_4-Cl : 2, 6, 10, 14
R= p-C_6H_4-Br : 3, 7, 11, 15
R= p-C_6H_4-I : 4, 8, 12, 16
R= -CH_2-CH_2-C_6H_5 : 5, 9, 13, 17

Scheme 1. Synthetic route to the title compounds.

Infrared spectra of new hydrazinecarbothioamides **6**–**9** showed a new band at 1249–1258 cm^{-1} due to the stretching vibration of the C=S groups. This fact confirmed the addition of the 2-(5*H*-dibenzo[*a*,*d*][7]annulen-5-yl)acetohydrazides to different isothiocyanates. The C=O and N–H stretching bands were present at 1673–1699 and 3141–3359 cm^{-1}, respectively.

The hydrazinecarbothioamides **6**–**9** were present as two conformational isomers, 5′-axial and 5′-equatorial in about 3:1 ratio, interconvertible by inversion of the middle ring, which was confirmed by their ^{1}H-NMR spectra.[42] In **6**–**9**-axial isomers, the H-5′(eq) is deshielded, manifested as a triplet at 4.62–4.65 ppm (*J* in range 7.0–7.3 Hz), whereas the CH_2-12′ protons are shielded by the double bond, showing a doublet at 2.57–2.60 ppm (Scheme S-1 of the Supplementary material to this paper). Double bonds shield H-5′ axial, while aromatic rings deshield H-5′ equatorial, because of the current cycle. The H-5′(eq) appeared at δ = 4.62–4.65 ppm (triplet) and H-5′(ax) appeared at δ 3.74–3.76 ppm (triplet).[42]

The signals of NH protons appeared as singlets between 9.53–10.12 ppm and the double bond protons H-10′ and H-11′ appeared as a singlet at 7.02–7.03 ppm.

The ^{13}C-NMR spectrum of compounds **6**–**9** showed a narrow δ domain (123–140 ppm) with C-10′ and C-11′ easily recognizable at δ 130–131 ppm, corresponding to the dibenzo[*a*,*d*][7]annulene moiety. C=S carbon atom could be responsible for the appearance of a signal at $\delta \approx 181$ ppm.

Cyclization of **6**–**9** to **10**–**13** was proved by the IR spectra that showed the disappearance of the $\nu_{C=O}$ band. It appears that in KBr pellets, the 1,2,4-triazole-3-thiols **10**–**13** exist in their thionic tautomeric form.[41]

The presence of a single conformational isomer (the axial one) of the triazoles **10**–**13** was confirmed by their ^{1}H-NMR spectra. Cyclization of **6**–**9** to **10**––**13** and the subsequent reactions produced the loss of the minor equatorial isomer, probably due to an increased solubility in acidic water. H-5′(eq) appears at δ 4.35–4.45 ppm (triplet, J = 7.9 Hz) and the CH_2-12′ protons manifest as doublets at 2.67–2.93 ppm in **10**–**13**. The NH signals of **6**–**9** totally disappeared, and were replaced by singlets at δ 11.44–11.90 ppm, attributable to the SH proton. Thus, in solution, the above equilibrium was shifted towards the thiolic form.

Conversion of hydrazinecarbothioamides **6**–**9** to the triazoles **10**–**13** was also confirmed by the ^{13}C-NMR spectra. A new quaternary carbon signal (for C-3) appeared at δ 166.57–167.97 ppm (Scheme S-2 of the Supplementary material) simultaneously with the disappearance of the C=S signal of **6**–**9** (δ = 181 ppm). Furthermore, a new signal for C-5 of **10**–**13** appeared at $\delta \approx$ 155.5 ppm, instead of the C=O signal from **6**–**9** at δ 169–170 ppm.

A new band in 2929–2983 cm^{-1} region, due to presence of methyl group (ν_{CH_3}) in the IR spectra confirmed the structures of compounds **14**–**17**, obtained by alkylation of the triazoles **10**–**13** with methyl iodide. Proof of *S*-alkylation that led to the formation of compounds **14**–**17** was given by the disappearance of the C=S stretching band in the IR spectra.

The presence of new signals at 14.8 ppm corresponding to CH_3 group in the ^{13}C-NMR spectra of compounds **14**–**17** was the most significant proof of alkylation of triazoles **10**–**13** with methyl iodide. Heterocyclic carbons C-3 and C-5 from these methylated compounds resonated at 154.82–155.11 ppm (more shielded than the C-3 heterocyclic carbon from the 1,2,4-triazoles **10**–**13**) and δ 151.28––151.54 ppm, respectively.

^{1}H-NMR spectra of the 3-(methylsulfonyl)-1,2,4-triazoles indicated the presence of a single conformational isomer, the axial one, except for triazole **15**, which exists as two isomers, 5′-axial and 5′-equatorial in about 1:1 ratio.

Antimicrobial activity

The antimicrobial activities of all products were investigated *in vitro* against *S. aureus*, *P. aeruginosa*, *E. coli*, *B. subtilis*, *S. enterica* subsp. *enterica* serovar Typhimurium, *S. flexneri* and *C. albicans* by the dilution method. The *MIC* values were determined using the dilution method with dimethyl sulfoxide as solvent.

Dimethyl sulfoxide showed no antimicrobial activity against the tested strains. The *MIC* values (μg mL^{-1}) for the new compounds against the strains are presented in Table I.

The investigation of the antimicrobial activity of the compounds was performed in duplicate. As control, *S. aureus*, *E. coli* and *P. aeruginosa* were tested against gentamicin, and *C. albicans* against fluconazole by the broth micro-

dilution method.[44,45,49–51] The *MIC* value of gentamicin was 2 μg mL^{-1} for all tested strains and the *MIC* value of fluconazole was 2 μg mL^{-1} for the reference strain.

TABLE I. *In vitro* antimicrobial activity of compounds **6–17** as *MIC* values (μg mL^{-1})

Compd.	Bacterial strains						Yeast
	S. aureus	*P. aeruginosa*	*E. coli*	*B. subtilis*	*S. enterica* subsp. *enterica* serovar Typhimurium	*S. flexneri*	*C. albicans*
6	256	16	512	>1024	256	1024	>1024
7	512	256	>1024	>1024	256	256	>1024
8	>1024	1024	512	>1024	1024	512	>1024
9	512	256	512	>1024	512	512	>1024
10	512	>1024	64	128	64	512	>1024
11	256	128	512	128	>1024	1024	>1024
12	256	512	512	128	>1024	512	>1024
13	512	64	>1024	>1024	512	512	>1024
14	256	128	512	128	>1024	512	128
15	256	128	512	128	512	512	128
16	256	256	512	256	128	512	128
17	512	512	512	256	256	512	256
Gentamicin	2	2	2	–	–	–	–
Fluconazole	–	–	–	–	–	–	2

The antimicrobial screening data revealed that all the newly synthesized compounds exhibited weaker antimicrobial activities compared to those of the control drugs.

For the reference bacterial strains, the *MIC* values of the compounds ranged between: 16–1024 μg mL^{-1} for the hydrazinecarbothoamides **6**–**9**, 64–1024 μg mL^{-1} for the 1,2,4-triazole-3-thiols **10**–**13** and 128–512 μg mL^{-1} for the methylsulfamyl-1,2,4-triazoles **14**–**17**.

Hydrazinecarbothioamide **6** with a chlorine atom presented the strongest action against *P. aeruginosa* (*MIC* 16 μg mL^{-1}). 1,2,4-Triazole-3-thiol **13** with a 4-(2-phenylethyl) fragment presented the strongest action against *P. aeruginosa* (MIC 64 μg mL^{-1}).

Comparing the results of this study, it was observed: a) compounds containing 4-chlorophenyl group had moderate antibacterial activity, hydrazinecarbothioamides against *S. aureus*, *S. enterica* subsp. *enterica* serovar Typhimurium and *P. aeruginosa*, 1,2,4-triazole-3-thiol against *E. coli* and *S. enterica* subsp. *enterica* serovar Typhimurium, and methylsulfanyl-1,2,4-triazole against *P. aeruginosa*; b) hydrazinecarbothioamides containing 4-chlorophenyl or 4-bromophenyl had better action compared to derivatives containing 4-iodophenyl or 4-(2-phenylethyl); c) the presence of methylsulfanyl-1,2,4-triazole ring in the structures **14**–**17** were favorable for the activity against the bacterial strains; d)

hydrazinecarbothioamides **6**–**9** and 1,2,4-triazole-3-thiols **10**–**13** were almost inactive against *C. albicans* but methylsulfanyl-1,2,4- triazole showed moderate activity against fungus strain.

CONCLUSIONS

In this paper, the synthesis and characterization of four new acyl hydrazinecarbothioamides, four 4*H*-1,2,4-triazole-3-thiol derivatives and four methylsulfanyl-1,2,4-triazoles containing the 5*H*-dibenzo[*a*,*d*]annulene moiety were presented. The structures of new compounds were confirmed by spectral data (IR, UV, ^{1}H-NMR and ^{13}C-NMR) and elemental analysis. All the compounds were investigated for their antimicrobial activity against *S. aureus*, *P. aeruginosa*, *E. coli*, *B. subtilis*, *S. enterica* subsp. *enterica* serovar Typhimurium, *S. flexneri* and *C. albicans*.

The antibacterial screening data are given for all the tested compounds. The data indicated weak antibacterial activity, except for compound **6** (which presented good action against *P. aeruginosa*), **10** (which presented moderate action on *S. enterica* subsp. *enterica* serovar Typhimurium and *E. coli*) and **13** (which presented a moderate action on *P. aeruginosa*). Based on the *MIC* values presented by the tested compounds, it could be concluded that, in general, the derivatives containing a chlorine or bromine atom had better antibacterial activity against the tested strains.

SUPPLEMENTARY MATERIAL

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

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ИЗВОД

СИНТЕЗА НОВИХ ДЕРИВАТА ХИДРАЗИНКАРБОТИОАМИДА И 1,2,4-ТРИАЗОЛА И ЊИХОВА АНТИМИКРОБНА АКТИВНОСТ

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Синтетисана је серија деривата хидразинкарботиоамида **6**–**9** који садрже 5*H*-дибензо[*a*,*d*][7]ануленски део. Циклизација деривата **6**–**9** у раствору NaOH даје одговарајуће аксијалне изомере 4*H*-1,2,4-триазол-3-тиола **10**–**13**. Тиоетри **14**–**17** су добијени алкиловањем деривата **10**–**13** јодметаном. Сва нова једињења окарактерисана су елементалном

анализом, IR, UV, ^{1}H-NMR и ^{13}C-NMR спектроскопијом. Извршено је испитивање антимикробне активности према *Staphylococcus aureus* ATCC 25923, *Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922, *Bacillus subtilis* ATCC 6633, *Salmonella enterica* subsp. *enterica* serovar Typhimurium ATCC 14028, *Shigella flexneri* ATCC 12022 и *Candida albicans* ATCC 90028.

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