Synthesis and *In vitro* Antibacterial Activity of Some 1,2,4-triazoles and 1,3,4-oxadiazoles Derivatives

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*A new series of the 2-amino-1,3,4-oxadiazoles **6a-c** and 1,2,4-triazoles **8a-c** substituted with 5H-dibenzo[a,d][7]annulene moiety were synthesised following the reaction sequences depicted in Scheme 1 and evaluated for antibacterial activity against Gram-positive and Gram-negative bacteria. All the newly synthesized compounds were characterized by their spectral data IR-, UV-, ^{1}H-NMR and ^{13}C-NMR spectroscopy and elemental analysis.*

Keywords: 5H-dibenzo[a,d][7]annulene, 2-amino-1,3,4-oxadiazole, S-akyl-1,2,4-triazole, antibacterial activity

Bacteria that develop resistance to antibiotics are one of society greatest future threats and are having a major impact on our ability to use various medical treatments. The spread of resistance is no longer a local problem in hospitals, antibiotic-resistant bacteria are also spreading to and throughout the environment. The rising incidence of bacterial infections, along with the emergence of resistance to conventionally-utilized antibiotics has added considerable urgency to the pursuit of safe and effective therapies in the last decade. So, the increasing clinical importance of drug resistant microbial pathogens has additional urgency in microbiological and antifungal research. A wide variety of heterocyclic systems have been explored for developing the new antimicrobial agents.

The 1,3,4-oxadiazole derivatives have been found to exhibit diverse biological activities such as antimicrobial, anti-tubercular, anti-malarial, anti-inflammatory, anticonvulsant, and antitumor, anti HIV, muscle relaxant, antimitotic, diuretic, hypnotic, sedative etc [1-14].

Furthermore, it is well documented that 1,2,4-triazol derivatives posses antimicrobial, antifungal, analgesic, tuberculostatic, carbonic anhydrase inhibitors activities [15-20].

The 5H-dibenzo[a,d][7]annulene ring is incorporated in many biologically active compounds used in therapeutics as antimicrobial, anticonvulsive, anticholinergic, miorelaxant, antihistaminic, antifungal, analgesic agents, carbonic anhydrase inhibitors, but mostly they are used as antidepressant drugs [21-29].

For that reason we report in the present investigation the synthesis, characterization and antibacterial testing of the new 1,3,4-oxadiazole and 1,2,4-triazole derivatives.

Experimental part

All reagents were purchased from the Merck, Sigma-Aldrich and Fluka Companies. Melting points were determined on a Böetius apparatus and were uncorrected. The UV spectra were determined on a SPECORD 40 Analytik Jena spectrophotometer, using methanolic solutions ($2.5.10^{-5}$ M). The IR spectra were recorded in KBr discs on a Vertex 70 Bruker spectrometer. The ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini 300BB spectrometer (300 MHz for H and 75 MHz for C), using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. The content of C, H, and N was assayed using a ECS-40-10-Costeh microdosimeter.

Synthesis of compounds

2-(5*H*-Dibenzo[a,d][7]annulen-5-yl)acetohydrazide **3** is the starting material for the synthesis of all derivatives (Scheme 1) and was prepared according to the reported method [28]. By treatment of hydrazide (**3**) with various alkyl isothiocyanates gave hydrazinecarbothioamides 4a-c [28, 30].

For the synthesis of 1,3,4-oxadiazoles **6a-c,** two methods were used: first method consists in the cyclization of hydrazinecarbothioamides **4a-c** in the presence of mercury oxide in methanol and the second method consists in the treatment of the compounds **4a-c** with methyl iodide in the presence of potassium hydroxide. The reaction probably takes place with the intermediate formation of **5a-c** compounds which we could not isolate in a pure form.

Hydrazinecarbothioamides **4a-c** were cyclized in alkaline conditions to 1,2,4-triazol-3-thioles **7a-c** [28-32]. The thioethers **8a-c** were prepared by alkylation of **7a-c** with ethyl bromide [23, 28, 31].

*Synthesis of 2-(aminoalkyl)-5-[5H-dibenzo[a,d][7] annulen-5-ylmethyl]-1,3,4-oxadiazoles **6a-c***

a1) For 0.001 mol hydrazinecarbothioamide in methanol, 0.002 mol of HgO are added, and was refluxed for 3h. The resulted product is filtered in order to remove the HgS, and after cooling the solution, the corresponding 1,3,4-oxadiazoles precipitate.

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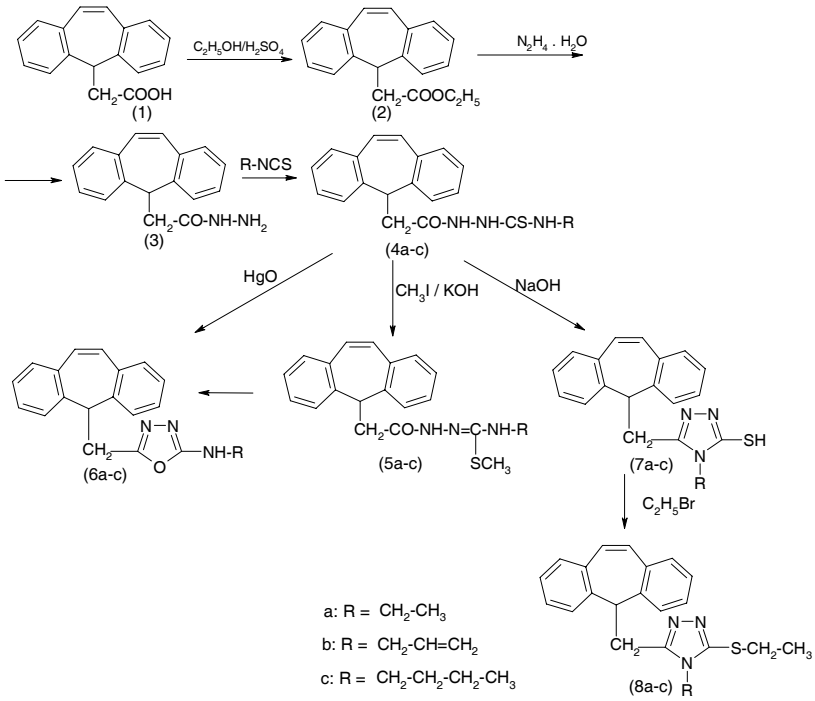


Scheme 1. Synthesis of the new compounds

a2) 0.002 mol KOH and 0.001 mol methyl iodide are added at 0^0C to 0.001 mol of each hydrazine-carbothioamides **4a-c** solved in ethanol. The solution is magnetically stirred at room temperature for 12 h. The solid compound, that was obtained, is filtered, washed with water and boiled in ethanol for 6 h, to result the corresponding 1,3,4-oxadiazole.

2-(Aminoethyl)-5-[5H-dibenzo[a,d][7]annulen-5-ylmethyl]-1,3,4-oxadiazole ***6a***

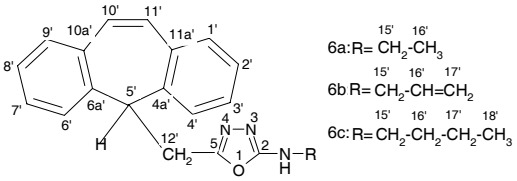
m.p. 157-159°C; yield: 29% (using CH_3I), 62.5% (using HgO); elemental analysis: anal. calcd. for (317.39 g/mol): C, 75.69; H, 6.03; N, 13.24; found: C, 75.66; H, 6.05; N, 13.26 UV (methanol, λ_{max}, nm): 213.2; 227.3; 292.5 IR (KBr, cm^{-1}): 3331 (N–H stretching), 3042, 3022 (C–H stretching of aromatic ring), 2976, 2874 (CH_3 stretching), 2932 (CH_2 stretching), 1635, 1586, 1490, (C=C stretching, C=N stretching); ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 7.20-7.35 (*m*, $H^{1'-4'}$, $H^{6'-9'}$); 6.95 (*s*, $H^{10'}$, $H^{11'}$); 4.80 (*s*, NH); 4.49 (*t*, *J*=8.0 Hz, $H^{5'}$); 3.17 (q, *J*=7.1 Hz, $H^{15'}$); 3.12 (*d*, *J*=8.0 Hz, $H^{12'}$); 1.13 (*t*, *J*=7.1 Hz, $H^{16'}$); ^{13}C-NMR (75 MHz, $CDCl_3$, δ / ppm): 163.46 (C^2); 159.33 (C^5); 139.09 ($C^{4a'}$, $C^{6a'}$); 134.08 ($C^{10a'}$, $C^{11a'}$); 131.11 ($C^{10'}$, $C^{11'}$); 130.07 ($C^{1'}$, $C^{9'}$); 129.65 ($C^{2'}$, $C^{8'}$); 129.07 ($C^{4'}$, $C^{6'}$); 127.05 ($C^{3'}$, $C^{7'}$); 52.75 ($C^{5'}$); 38.44 ($C^{15'}$); 26.53 ($C^{12'}$); 15.21 ($C^{16'}$);

2-(Aminoallyl)-5-[5H-dibenzo[a,d][7]annulen-5-ylmethyl]-1,3,4-oxadiazole ***6b***

m.p. 101-103°C; yield: 40% (using CH_3I), 65% (using HgO); elemental analysis: anal. calcd. for (329.41 g/mol): C, 76.57; H, 5.81; N, 12.76; found: C, 76.53; H, 5.80; N, 12.75; UV(methanol, λ_{max}, nm): 220.3 ; 292.5; IR (KBr, cm^{-1}): 3438 (N–H stretching), 3058, 3016 3020 (C–H stretching of aromatic ring), 2924, 2845 (CH_2 stretching), 1605, 1582, 1491, 1456 (C=C stretching, C=N stretching); ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 7.15-7.40 (*m*, $H^{1'-4'}$, $H^{6'-9'}$); 6.98 (*s*, $H^{10'}$, $H^{11'}$); 5.82 (*ddt*, *J*=5.4;17.2;10.3 Hz, $H^{16'}$); 5.12 (*m*, $H^{17'}$); 4.90 (*s*, NH); 4.49 (*t*, *J*=8.1 Hz, $H^{5'}$); 3.77 (*dl*, *J*=5.4 Hz, $H^{15'}$); 3.13 (*d*, *J*=8.1 Hz, $H^{12'}$); ^{13}C-NMR (75 MHz, $CDCl_3$, δ / ppm): 163.21 (C^2); 158.26 (C^5); 138.84 ($C^{4a'}$, $C^{6a'}$); 133.68 ($C^{10a'}$, $C^{11a'}$); 133.48 ($C^{16'}$); 130.91 ($C^{10'}$, $C^{11'}$); 129.90 ($C^{1'}$, $C^{9'}$); 129.45 ($C^{2'}$, $C^{8'}$); 128.88 ($C^{4'}$, $C^{6'}$); 126.88 ($C^{3'}$, $C^{7'}$); 116.65 ($C^{17'}$); 52.55 ($C^{5'}$); 45.60 ($C^{15'}$); 26.33 ($C^{12'}$);

2-(Aminobutyl)-5-[5H-dibenzo[a,d][7]annulen-5-ylmethyl]-1,3,4-oxadiazole ***6c***

m.p. 135-137°C; yield: 33% (using CH_3I), 53.6% (using HgO); elemental analysis: anal. calcd. for (345.45 g/mol): C, 76.49; H, 6.71; N, 12.16; found: C, 76.50; H, 6.70; N, 12.15; UV: (methanol, λ_{max}, nm): 211.0; 226.4; 292.5; IR (KBr, cm^{-1}): 3193 (N–H stretching), 3063, 3019 (C–H stretching of aromatic ring), 2963, 2865 (CH_3 stretching), 2935, 2830 (CH_2 stretching), 1657, 1588, 1493 (C=C stretching, C=N stretching); ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 7.20-7.40 (*m*, $H^{1'-4'}$, $H^{6'-9'}$); 6.99 (*s*, $H^{10'}$, $H^{11'}$); 4.80 (s, NH); 4.50 (*t*, *J*=8.0 Hz, $H^{5'}$); 3.14 (*d*, *J*=8.0 Hz, $H^{12'}$); 3.15-3.19 (*m*, $H^{15'}$); 1.49 (*cv*, *J*=7,4 Hz, $H^{16'}$); 1.31 (*sx*, *J*=7.4 Hz, $H^{17'}$); 0.93 (t, J=7.4 Hz, $H^{18'}$); ^{13}C-NMR (75 MHz, $CDCl_3$, δ / ppm): 163.39 (C^2); 159.07 (C^5); 138.95 ($C^{4a'}$, $C^{6a'}$); 133.93 ($C^{10a'}$, $C^{11a'}$); 130.94 ($C^{10'}$, $C^{11'}$); 129.90 ($C^{1'}$, $C^{9'}$); 129.58 ($C^{4'}$, $C^{6'}$); 129.49 ($C^{2'}$, $C^{8'}$); 126.88 ($C^{3'}$, $C^{7'}$); 45.17 ($C^{15'}$); 52.66 ($C^{5'}$); 31.64 ($C^{16'}$); 26.12 ($C^{12'}$); 19.71 ($C^{17'}$); 13.61 ($C^{18'}$);



b) *Synthesis of 5-(5H-dibenzo[a,d][7]annulen-5-ylmethyl)-3-ethylthio-4-alkyl-4H-1,2,4-triazoles* ***8a-c***

To a 10 mL absolute ethanol add 0.004 mol Na and stir magnetically at room temperature. After obtaining a clear solution add 0.004 mol of the 1,2,4-triazole **7a-c** and continue stirring for 30 min. Then add stoechiometrically ethyl bromide and stir at room temperature for 12 hours. The precipitate is filtered off and washed with water.

5-(5H-dibenzo[a,d][7]annulen-5-ylmethyl)-3-ethylthio-4-ethyl-4H-1,2,4-triazole ***8a***

m.p. 96-98°C; yield: 81.35%; elemental analysis: anal. calcd. for (361.51 g/mol): C, 73.09; H, 6.41; N, 11.62; S, 8.87; found: C, 73.08; H, 6.43; N, 11.62; S, 8.86; UV: (methanol, λ_{max}, nm): 215.0; 293.8; IR (KBr, cm^{-1}): 3044, 3022 (C–H stretching of aromatic ring), 2978, 2869 (CH_3 stretching), 2930, 2823 (CH_2 stretching), 1512, 1493 (C=C stretching); ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 7.20-7.27

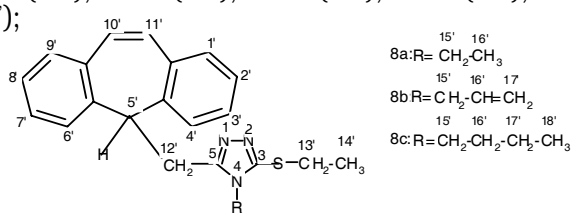
(*m*, $H^{1'-4'}$; $H^{6'-9'}$); 6.99 (*s*, $H^{10'}$; $H^{11'}$); 4.75 (*t*, *J*=7.8 Hz, $H^{5'}$); 3.36 (*q*, *J*=7.3 Hz, $H^{15'}$); 3.13 (*d*, *J*=7.8 Hz $H^{12'}$); 3.04 (*q*, *J*=7.3 Hz, $H^{13'}$); 1.24 (*t*, *J*=7.3 Hz, $H^{14'}$); 0.94 (*t*, *J*=7.3 Hz, $H^{16'}$); ^{13}C-NMR (75 MHz, $CDCl_3$, δ / ppm): 153.85 (C^3); 148.74 (C^5); 130.16 ($C^{10'}$, $C^{11'}$); 139.36 ($C^{4a'}$, $C^{6a'}$); 133.79 ($C^{10a'}$, $C^{11a'}$); 130.95 ($C^{4'}$, $C^{6'}$); 129.72 ($C^{2'}$, $C^{8'}$); 129.12 ($C^{1'}$, $C^{9'}$); 126.87 ($C^{3'}$, $C^{7'}$); 53.60 ($C^{5'}$); 38.00 ($C^{15'}$); 28.04 ($C^{13'}$); 25.74 ($C^{12'}$); 15.10 ($C^{16'}$); 14.85 ($C^{14'}$);

5-(5H-dibenzo[a,d][7]annulen-5-ylmethyl)-3-ethylhthio-4-allyl-4H-1,2,4-triazole ***8b***

m.p. 121-123°C; yield: 79.2%; elemental analysis: anal. calcd. for (373.52 g/mol): C, 73.96; H, 6.21; N, 11.25; S, 8.58; found: C, 73.96; H, 6.22; N, 11.22; S, 8.59; UV: (methanol, λ_{max}, nm): 216.3; 293.8; IR (KBr,cm^{-1}): 3063, 3024 (C–H stretching of aromatic ring), 2967, 2868 (CH_3 stretching), 2926, 2834 (CH_2 stretching), 1511, 1492 (C=C stretching); ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 7.15-7.40 (*m*, $H^{1'-4'}$; $H^{6'-9'}$); 6.99 (*s*, $H^{10'}$, $H^{11'}$); 5.51 (*ddt*, *J*=5.0;17.0;10.3 Hz, $H^{16'}$); 5.05 (*d*, *J*=10.3 Hz, $H^{17'}$; 4.75 (*t*, *J*=7.8 Hz, $H^{5'}$); 4.67 (*d*, *J*=17.0 Hz, $H^{17'}$); 3.94 (*dl*, *J*=5.0 Hz, $H^{15'}$); 3.13 (*d*, *J*=7.8 Hz, $H^{12'}$); 3.02 (*q*, *J*=7.3 Hz, $H^{13'}$); 1.24 (*t*, *J*=7.3 Hz, $H^{14'}$); ^{13}C-NMR (75 MHz, $CDCl_3$, δ / ppm): 154.47 (C^3); 149.29 (C^5); 139.38 ($C^{4a'}$, $C^{6a'}$); 133.88 ($C^{10a'}$, $C^{11a'}$); 130.96 ($C^{10'}$, $C^{11'}$); 130.15 ($C^{1'}$, $C^{9'}$); 130.10 ($C^{16'}$); 129.77 ($C^{2'}$, $C^{8'}$); 129.15 ($C^{4'}$, $C^{6'}$); 126,92 ($C^{3'}$, $C^{7'}$); 117.60 ($C^{17'}$); 55.65 ($C^{5'}$); 44.95 ($C^{15'}$); 28.30 ($C^{13'}$); 25.98 ($C^{12'}$); 14.85 ($C^{14'}$);

5-(5H-dibenzo[a,d][7]annulen-5-ylmethyl)-3-ethylthio-4-butyl-4H-1,2,4-triazole ***8c***

m.p. 75-77°C; yield: 57%; elemental analysis: anal. calcd. for (389.57 g/mol): C, 74.00; H, 6.99; N, 10.79; S, 8.23; found: C, 74.02; H, 6.96; N, 10.79; S, 8.22; UV: (methanol, λ_{max} nm): 222.6; 294.3; IR (KBr, cm^{-1}): 3067, 3020 (C–H stretching of aromatic ring), 2962, 2872 (CH_3 stretching), 2932 (CH_2 stretching), 1615, 1457 (C=C stretching); ^{1}H-NMR (300 MHz, $CDCl_3$, δ / ppm): 7.20-7.35 (*m*, $H^{1'-4'}$; $H^{6'-9'}$); 6.99 (*s*, $H^{10'}$, $H^{11'}$); 4.73 (*t*, *J*=7.8 Hz, $H^{5'}$); 3.26 (*t*, *J*=7.3 Hz, $H^{15'}$); 3.13 (*d*, *J*=7.8 Hz, $H^{12'}$); 3.04 (*q*, *J*=7.3 Hz, $H^{13'}$); 1.23 (*t*, *J*=7.3 Hz, $H^{14'}$); 1.05-1.38 (*m*, $H^{16'}$, $H^{17'}$); 0.85 (*t*, *J*=7.3 Hz, $H^{18'}$); ^{13}C-NMR (75 MHz, $CDCl_3$, δ/ ppm): 154.11 (C^3); 148.30 (C^5); 139.36 ($C^{4a'}$, $C^{6a'}$); 133.81 ($C^{10a'}$, $C^{11a'}$); 130.93 ($C^{4'}$, $C^{6'}$); 130.16 ($C^{10'}$, $C^{11'}$); 129.71 ($C^{2'}$, $C^{8'}$); 129.13 ($C^{1'}$, $C^{9'}$); 126.88 ($C^{3'}$, $C^{7'}$), 53.78 ($C^{5'}$); 42.84 ($C^{15'}$); 31.85 ($C^{16'}$); 28.11 ($C^{13'}$); 25.86 ($C^{12'}$); 19.70 ($C^{17'}$); 14.84 ($C^{14'}$); 13.46 ($C^{18'}$);



8a:R= CH_2-CH_3

8b R= CH_2-CH=CH_2

8c: R= CH_2-CH_2-CH_2-CH_3

Antibacterial activity

The *in vitro* activities of new compunds **6a-c** and **8a-c** were determined for a collection of the most frequently isolated bacterial pathogens from St. Pantelimon Emergency Hospital from patients with acute peritonitis, different abscesses, and phlegmons.

The tested compounds were solved in DMSO. To determine the antibacterial activity, we tested the inhibitory activity of the new compounds on the pathogenic bacterial strains of *Bacillus Proteus, Staphylococcus aureus, Pseudomonas Aeruginosa, Escherichia coli* and *Klebsiella pneumoniae in vitro*, using the Mueller-Hinton plates. To determine the MIC (minimum inhibitory concentration), the dilution method was used in liquid environment [32]. The observed MIC for the respective microorganisms is listed in the table 1.

Results and discussions

Chemistry

For the synthesis of new 1,3,4-oxadiazoles **6a-c,** two methods were used: first method consists in the cyclization of hydrazinecarbothioamides **4a-c** in the presence of mercury oxide in methanol. The best yields in 1,3,4-oxadiazoles were obtained by the first method. The losses recorded for the second method is due to the secondary reaction product which have not been isolated in pure form.

The 1,2,4-triazoles **7a-c** were converted to their corresponding thioethers **8a-c** by the reaction of their salts with the ethyl bromide (scheme 1).

The UV spectrum of 1,3,4-oxadiazoles **6a-c** is characterized by two or three absorbtion peaks at 211 and 292 nm.

The absence of carbonyl absorption in the IR spectra of the 1,3,4-oxadiazole as compared to corresponding hydrazinecarbothioamide and the appearing of a new band generated by the stretching vibration of a C=N group (1605-1657 cm^{-1}), indicated that cyclization reaction had occurred.

In the ^{1}H-NMR spectrum of the 1,3,4-oxadiazoles, the 5-H-dibenzo[a,d][7]annulene system is identified through a singlet at 6.95-6.99 ppm for to the $H^{10'}$ and $H^{11'}$ protons. The signals of the $H^{1'-4'}$ and $H^{6'-9'}$ protons appear as a multiplet between 7.15-7.40 ppm. The signal of the H^5 proton appears as a triplet at 4.49-4.50 ppm, and the signal of the methylen protons ($H^{12'}$) appear as a dublet at 3.12-3.14 ppm. The 2-amino-1,3,4-oxadiazoles **6a-c** structure is confirmed by the presence in the ^{1}H-NMR spectrum of a one singlet for to the NH group at 4.8-4.9 ppm.

Thereby, the ^{13}C-NMR spectrum is characterized by the appearance of a signal for to a quaternary carbon C^2 at 163 ppm, simultaneously with the disappearing of a signal at 181 ppm for to a thionic hydrazinecarbothioamide group.

Compound	*B. Proteus*	*S. aureus*	*B. Aeruginosa*	*E. Coli*	*Klebsiella pneumoniae*
6a	>1024	128	64	>1024	>1024
6b	64	128	>1024	>1024	>1024
6c	>1024	>1024	>1024	>1024	>1024
8a	64	>1024	>1024	>1024	>1024
8b	>1024	32	>1024	>1024	>1024
8c	>1024	>1024	>1024	>1024	>1024

Tabel 1
ANTIBACTERIAL SCREENING RESULTS OF COMPOUNDS (MIC-μg/mL)

Instead of the signal of the amidic >C=O group at 170 ppm, we noticed the presence of a signal at 158-159 ppm, which belongs to a C^5 carbon from the oxadiazole nucleus.

The new synthesized 1,2,4-triazole derivatives **8a-c**, have similar UV spectra, showing two absorbtion peaks, one at 215-222 nm and the other between 291-294 nm.

The IR spectrum of the alkylated 1,2,4-triazoles **8a-c** is characterized by the disappearing of the band characteristic to a thionic group, which appeared at 1233-1256 cm^{-1} in the case of unalkylated 1,2,4-triazoles **7a-c**.

In the ^{1}H-NMR spectrum of the new compounds, the 5-H-dibenzo[a,d][7]annulene system is easy to recognize [1]. The ^{1}H-NMR spectrum is characterized by the presence of the signals belonging to the alkyl groups bound to a sulfur atom: a quartet at 3.04 ppm and a triplet at 1.24 ppm.

In the ^{13}C-NMR spectrum of **8a-c** compounds, the signal of the quaternary C^3 carbon at 154 ppm and of the quaternary C^5 carbon at 148-149 ppm.

Antibacterial activity

The experimental results showed that the antibacterial activity of the new compounds is negligible, the compound **6a**, **6b** and **8b** present weak inhibitory activity over the *Staphylococcus aureus*, the compounds **6b** and **8a** over *Proteus bacilli* and the compound **6a** over the *Pseudomonas aeruginosa bacilli*.

To note that the presence of 1,3,4-oxadiazole **6b** and also of 1,2,4-triazole **8b** determine a moderate antibacterial action upon *Bacillus Proteus,* and *Staphylococcus aureus*. In the case of *Staphylococcus aureus* strain the value of MIC of 32 μg/mL presented by the **8b** compound is to be considered for further research. Presentation of the ethyl radical in the case of 1,2,4-triazole **8a** and of 1,3,4-oxadiazole **6a** determines an increase of the antibacterial activity upon *Staphylococcus aureus* and *Pseudomonas Aeruginosa,* for **8a** and *Bacillus Proteus* for **6a**. None of the tested compounds has antibacterial activity upon *Escherichia coli* and *Klebsiella pneumoniae*.

Conclusions

This study reports the synthesis, characterization and antibacterial activity of six new compounds: three 1,3,4-oxadiazoles and three 1,2,4-triazoles with 5H-dibenzo [a,d][7]annulene nucleus. The chemical structure was determined by elemental analysis and spectral methods. The antimicrobial activity of these compounds on gram-positive and gram-negative bacterial strains was tested *in vitro*, and demonstrated that some of them possess a weak antibacterial activity.

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