

SYNTHESIS AND PHYSICO-CHEMICAL CHARACTERIZATION OF SOME QUATERNARY AMMONIUM SALTS OF 2-ARYL THIAZOLE DERIVATIVES

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Abstract

New quaternary ammonium compounds, having at the basis the 2-aryl-thiazole system diversely substituted at the 2, 4, and 5 positions, have been synthesized.

The basic component is represented by tertiary amines in which the nitrogen is included either into an aromatic heterocycle (pyridine, quinoline), or into a tertiary cyclic amine (N-methyl-piperidine, N-methyl-morpholine).

The benzenic ring in the 2 position can be substituted or not. The selected substituents are electron-donating (methyl), or electron-attracting (chlorine).

In order to elucidate the structure of the synthesized compounds, UV, IR, Raman, Mass and ¹H-NMR spectroscopy were performed.

The bactericide activity of the new compounds has been evaluated against two strains of germs: *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

Rezumat

Au fost sintetizați noi compuși cuaternari de amoniu care au la bază sistemul 2-aril-tiazolic, divers substituit în pozițiile 2,4,5.

Componenta bazică este reprezentată de amine terțiare, în care azotul este fie inclus într-un heterociclu aromatic (piridina, chinolina), fie este o amină terțiară ciclică (N-metil-piperidina, N-metil-morfolina). Nucleul benzenic din poziția 2 poate să fie substituit sau nu. Substituenți aleși sunt electrono-donori (metil) sau electrono-atrăgători (clor).

În vederea elucidării structurii compușilor sintetizați s-au efectuat determinări spectrale UV, IR, Ramman, spectroscopie de masă și ¹H-RMN.

S-a testat activitatea bactericidă a noilor compuși pe două tulpini de germeni: *Staphylococcus aureus* și *Pseudomonas aeruginosa*.

Keywords: quaternary ammonium compounds; 2-aryl-thiazole system; bactericide activity

Introduction

Drugs-resistant germs represent a challenging issue in the anti-infectious therapy. With the view to counteract the increasing prevalence of this phenomenon, a large number of research studies have been focussed on the development of new molecules with antibacterial and/or fungicidal properties [1, 2, 4, 5, 6, 7, 9, 14, 16].

In this context, our research has been focused on the synthesis of new quaternary ammonium salts based on the 2-aryl-thiazole system diversely substituted at the 2, 4, and 5 positions. Moreover, this study was prompted by our previous data which revealed the favourable effects of the thiazole ring associated within the same molecule with a quaternary ammonium group [8, 10, 11, 12, 13, 17].

Materials and methods

The synthesis of these compounds was performed by alkylation of some nitrogen heterocycles, with halogen compounds that have in their structure the 2-aryl-thiazole system. The 2-aryl-halogenomethyl-thiazole derivatives were obtained according to the methods elaborated in our laboratory [10, 15]. We started from diversely substituted thioamides.

In order to enhance the molecular lipophilicity, the compounds substituted with bromine at the position 5 of the thiazole were synthesized.

Chlorine and iodine derivatives (1-5) treated with N-nucleophiles (Nu) in chloroform were transformed into their corresponding ammonium salts (6-17). The basic component is represented by the tertiary nitrogen included into an aromatic (pyridine, quinoline) or non-aromatic heterocycle (N-methyl-pyridine, N-methyl-morpholine) (Fig. 1):

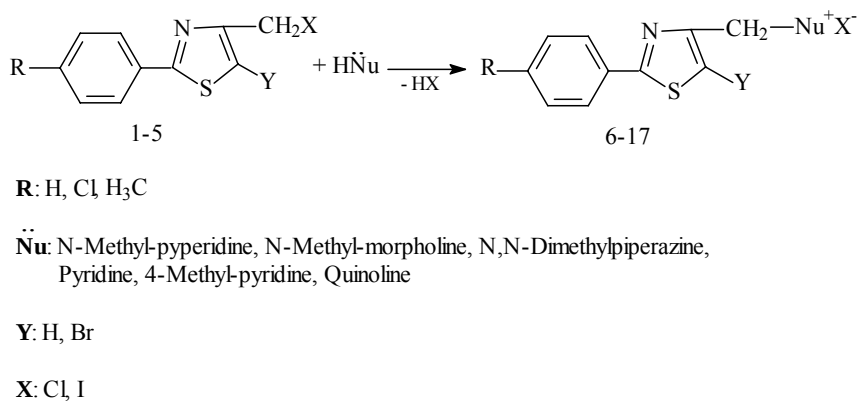
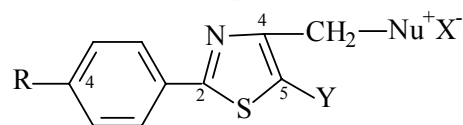


Figure 1

The synthesis of the quaternary ammonium salts

The structures, molecular weights (MW), melting points (Mp) and yields of the obtained compounds are presented in table I.



6-17

Table I
The compounds' characteristics

Comp. no.	R	Y	X	Nu	MW	Mp °C	Yield
6	H	H	Cl	N-Methyl-piperidine	308.5	85-86	43%
7	H	H	I	N-Methyl-piperidine	400	138-141	75%
8	H	Br	I	N-Methyl-piperidine	479	228-229	85%
9	Cl	H	I	N-Methyl-piperidine	434.5	230-232	75%
10	H	H	Cl	N-Methyl-morpholine	310.5	206.7-208	41%
11	H	H	I	N-Methyl-morpholine	402	182-185	88%
12	H	H	I	N,N-dimethyl-piperazine	716	186-188	48%
13	H ₃ C	H	I	Pyridine	394	177.2-178.5	40%
14	Cl	H	I	Pyridine	414.5	187-189	35%
15	H	H	I	4-Methyl-pyridine	394	199-200	75%
16	H	Br	I	Quinoline	509	224-226	30%
17	H ₃ C	H	I	Quinoline	444	198-200	35%

All melting points were determined in open capillaries on Electrothermal IA 9000 apparatus and are uncorrected. The purity of the compounds was routinely checked by thin layer chromatography (TLC) using silica gel with fluorescent indicator 254 nm. Spectroscopic data were recorded on the following instruments: FT-IR/ATR, Bruker Miracle ATR; FT-Raman, Bruker FRA 106/S; ¹H-NMR, Bruker Avance – RMN spectrometer in DMSO-d₆ using tetramethylsilane (TMS) as an internal standard, LC-MSD-Trop-VL mass spectrometer; elemental analyses were performed on Elemental Analysen systeme GmbH VarioEL.

Preparation of N-(2-phenyl-thiazole-4-yl-methyl)-N-methyl-piperidinium chloride (6):

In a flask equipped with a reflux condenser, a mixture of 1 mmol 2-aryl-4-chloromethyl-thiazole and 1 mmol (Nu) was dissolved in 3 ml chloroform. The mixture was heated under reflux for 2 h. The solvent was removed under reduced pressure and the residue was taken again with ether, the solid separated out was filtered and air-dried to give the crude product, which was purified by crystallisation from absolute ethanol to give pure products.

The compounds 7-17 were synthesized in a similar manner.

Results and discussion

The synthesised compounds are white or yellowish-white crystalline powders, soluble in ethanol and in dimethylsulfoxide, less soluble in water, slightly soluble in chloroform and insoluble in ether.

The reactions presented a high yield in case of iodine derivatives, which are more reactive compared to chlorine derivatives. At the same time, the higher nucleophile properties of the N-methyl derivatives induced a higher reaction yield compared to the heteroaromatic tertiary amines.

To elucidate the structures of the resulting compounds the elemental analysis, as well as UV, IR, Raman, MS and $^1\text{H-NMR}$ were performed.

The UV spectra of these compounds present a maximum absorption between 283 nm and 284.5 nm (which is assigned to the benzene ring), shifting towards higher wavelengths (289 nm to 290 nm) when the benzene ring in the 2 position of thiazole is substituted with methyl or chlorine. If the 5 position of the thiazole ring is substituted with bromine, the maximum absorption becomes visible at 293.5 nm.

The Raman spectra, recorded for the synthesized compounds, revealed the presence of $\text{N}=\text{C}$ endocyclic bonds between $1680\text{--}1500\text{ cm}^{-1}$; the valence vibrations of aromatic C-H bonds are present at the $3100\text{--}3000\text{ cm}^{-1}$, and the valence vibrations corresponding to the aliphatic C-H are present between $2990\text{--}2800\text{ cm}^{-1}$.

As an example, the Raman spectra of N-(2-phenyl-thiazole-4-yl-methyl)-N-methyl-piperidinium iodide is presented. In Raman spectra, an intense band was observed at 1600 cm^{-1} attributed to the $\text{N}=\text{C}$ endocyclic bond in the thiazole system; the bands between 3017 cm^{-1} and 3074 cm^{-1} were attributed to valence vibration induced by aromatic C-H, whilst the bands between 2977 cm^{-1} and 2869 cm^{-1} were ascribed to the aliphatic C-H (Fig. 2).

Table II
The attribution of the signals
for N-(2-phenyl-thiazole-4-yl-methyl)-N-methyl piperidinium chloride

2H (10)	2H (11)	2H (9)	DMSO	3H (13)	4H (8,12)	2H (7)	3H (2,3,4)	2H (1,5)	1H (6)
1.572	1.831	1.952	2.508	3.096	3.434	4.786	7.538	7.972	8.135
1.585	1.851	1.965	3.74		3.443		7.544	7.977	
1.600	1.859		3.395		3.454		7.553	7.986	
			3.420		3.463		7.563	7.995	

The recorded mass spectra have the molecular peaks in accordance to the synthesized compounds. In the mass spectra of 2-(4-methyl-phenyl)-thiazol-4-yl-methyl-quinolinium iodide the molecular peak of the compound without iodide, m/z 317, was obtained. Besides this, other peaks specific to the heterocyclic fragmentation were presented (m/z 188 and 129). With a relative high abundance, the peaks characteristic for the fragmentation of the 2-aryl-thiazolic (m/z 118, 91, 135, 71, 45) were observed (Fig. 4).

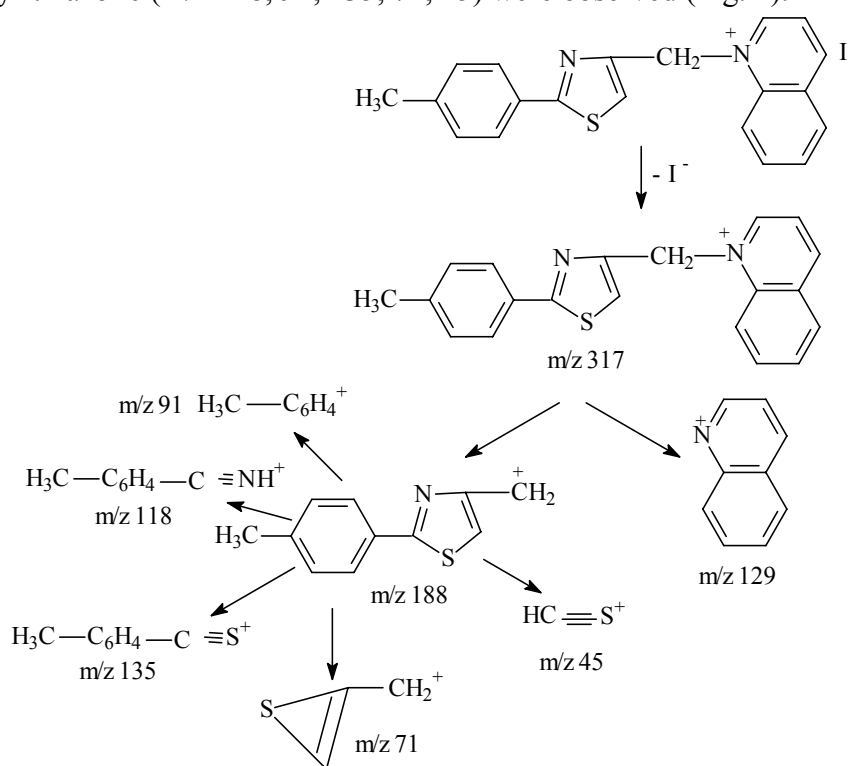
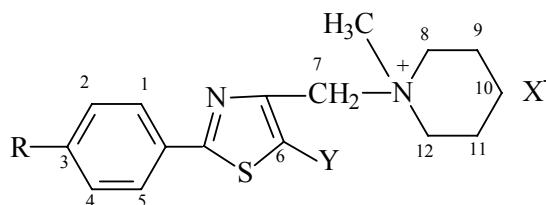


Figure 4

MS fragmentation of 2-(4-Methyl-phenyl)-thiazol-4-yl-methyl-quinolinium iodide

The obtained physico-chemical data provide strong evidences, which are in accordance with the attributed structures.

N-(2-phenyl-thiazole-4-yl-methyl)-N-methyl pyperidinium chloride (iodide) (6, 7)



^1H NMR (500 MHz, DMSO- d_6) δ (ppm): 1.57-1.60 (2H, t, C₁₀ pyperidine), 1.83-1.86 (2H, t, C₁₁ pyperidine), 1.95-1.96 (2H, d, C₉ pyperidine), 3.09 (3H, s, CH₃), 3.44-3.46 (4H, 2d, C_{8,12} pyperidine), 4.78 (2H, s, C₇ methylene), 7.53-7.55 (3H, t, C_{2,3,4} phenyl), 7.97-7.99 (2H, 2d, C_{1,5} phenyl), 8.13 (1H, s, C₆ thiazole);

For C₁₆H₂₁ClN₂S calculated: 62.24% C, 6.81% H, 9.08% N, 10.37% S; found 62.28% C, 6.80% H, 9.04% N, 10.39% S; MS: m/z: 273 [M-M_{Cl}].

For C₁₆H₂₁IN₂S calculated: 48.01% C, 5.25% H, 7.00% N, 8.00% S; found 48.00% C, 5.27% H, 7.03% N, 7.98% S; MS: m/z: 273 [M-M_I], Ramman ν_{max} (cm⁻¹): 1600 (N=C endocyclic), 2863-2918 (C-H aliphatic), 3005-3012 (C=H aromatic).

N-(5-Bromo-2-phenyl-thiazole-4-yl-methyl)-N-methyl-pyperidinium iodide (8)

^1H NMR (500 MHz, DMSO- d_6) δ (ppm): 1.59-1.60 (2H, t, C₁₀ pyperidine), 1.88-1.89 (2H, t, C₁₁ pyperidine), 1.94-1.95 (2H, d, C₉ pyperidine), 3.11 (3H, s, CH₃), 3.55-3.57 (4H, 2d, C_{8,12} pyperidine), 4.68 (2H, s, C₇ methylene), 7.55-7.57 (3H, q, C_{2,3,4} phenyl), 7.93-7.95 (2H, 2d, C_{1,5} phenyl);

For C₁₆H₂₀BrIN₂S calculated: 40.08% C, 4.18% H, 5.85% N, 6.68% S; found 40.00% C, 4.20% H, 5.95% N, 6.65% S; MS: m/z: 352 [M-M_I]; Ramman ν_{max} (cm⁻¹): 1600 (N=C endocyclic), 2863-2918 (C-H aliphatic), 3000-3010 (C=H aromatic).

N-2-(4-Chloro-phenyl)-thiazole-4-yl-methyl-N-methyl-pyperidinium iodide (9)

^1H NMR (500 MHz, DMSO- d_6) δ (ppm): 1.57-1.60 (2H, t, C₁₀ pyperidine), 1.83-1.86 (2H, t, C₁₁ pyperidine), 1.95-1.96 (2H, d, C₉ pyperidine), 3.09 (3H, s, CH₃), 3.44-3.46 (4H, t, C_{8,12} pyperidine), 6.05 (2H, s, C₇ methylene), 7.77-7.96 (2H, 2d, C_{1,5} phenyl), 7.32-7.55 (2H, t, C_{2,4} phenyl), 7.97 (1H, s, C₆ thiazole);

For C₁₆H₂₀ClIN₂S calculated: 44.19% C, 4.60% H, 6.44% N, 7.36% S; found 44.25% C, 4.53% H, 6.60% N, 7.25% S; MS: m/z: 307.5 [M-M_I]; Ramman ν_{max} (cm⁻¹): 1602 (N=C endocyclic), 2863-2918 (C-H aliphatic), 3050-3075 (C=H aromatic).

N-2-Phenyl-thiazole-4-yl-methyl-N-methyl-morpholinium chloride (iodide) (10, 11)

$^1\text{HNMR}$ (500 MHz, DMSO- d_6) δ (ppm): 3.21 (3H, s, CH_3), 3.46-3.52 (2H, d, C_{11} morpholine), 3.64-3.71 (2H, t, C_9 morpholine), 3.99-4.01 (2H, t, C_{12} morpholine), 4.08-4.05 (2H, d, C_8 morpholine), 5.00 (2H, s, C_7 methylene), 7.53-7.55 (3H, t, $\text{C}_{2,3,4}$ phenyl), 7.97-7.99 (2H, 2d, $\text{C}_{1,5}$ phenyl), 8.22 (1H, s, C_6 thiazole);

For $\text{C}_{15}\text{H}_{19}\text{ClON}_2\text{S}$ calculated: 57.97% C, 6.12% H, 9.02% N, 10.31% S; found 57.89% C, 6.14% H, 9.10% N, 10.30% S. m/z : 275 [$\text{M}-\text{M}_{\text{Cl}}$].

For $\text{C}_{15}\text{H}_{19}\text{ION}_2\text{S}$ calculated: 44.78% C, 4.73% H, 6.97% N, 7.96% S; found 44.79% C, 4.70% H, 6.94% N, 7.93% S; MS: m/z : 275 [$\text{M}-\text{M}_{\text{I}}$];

Ramman ν_{max} (cm^{-1}): 1596 (N=C endocyclic), 2950-2963 (C-H aliphatic), 3052-3059 (C=H aromatic).

N,N-(2-Phenyl-thiazole-4-yl-methyl)-N,N-dimethyl-piperazinium iodide (12)

$^1\text{HNMR}$ (500 MHz, DMSO- d_6) δ (ppm): 2.31 (6H, s, 2 CH_3), 2.65-2.72 (2H, t, C_{12} piperazine), 2.85-2.9 (2H, d, C_{10} piperazine), 3.38-3.50 (2H, t, C_9 piperazine), 3.49-3.60 (2H, t, C_8 piperazine), 4.83 (4H, s, C_7 methylene), 7.55-7.57 (6H, t, $\text{C}_{2,3,4}$ phenyl), 7.97-8.00 (4H, 2d, $\text{C}_{1,5}$ phenyl), 8.13 (2H, s, C_6 thiazole);

For $\text{C}_{26}\text{H}_{30}\text{I}_2\text{N}_4\text{S}_2$ calculated: 43.58% C, 4.19% H, 7.82 % N, 8.94% S; found 43.71% C, 4.02% H, 7.62 % N, 9.00% S; MS: m/z : 462 [$\text{M}-\text{M}_{2\text{I}}$];

Ramman ν_{max} (cm^{-1}): 1595 (N=C endocyclic), 2939-2970 (C-H aliphatic), 3026-3059 (C=H aromatic).

2-(4-Methyl)-phenyl-thiazole-4-yl-methyl-pyridinium iodide (13)

$^1\text{HNMR}$ (500 MHz, DMSO- d_6) δ (ppm): 2.34 (3H, s, CH_3), 6.02 (2H, s, C_7 methylene), 7.31-7.32 (2H, d, $\text{C}_{2,4}$ phenyl), 7.77-7.79 (2H, 2d, $\text{C}_{1,5}$ phenyl), 7.97 (H, s, C_6 thiazole), 8.20-8.24 (2H, t, $\text{C}_{9,11}$ pyridine), 8.64-8.68 (H, t, C_{10} pyridine) 9.23-9.25 (2H, d, C_8 , C_{12} pyridine);

For $\text{C}_{16}\text{H}_{15}\text{IN}_2\text{S}$ calculated: C 48.73%, H, 3.81% N, 7.11% S 8.12%; found 48.70% C, 3.84% H, 7.08 % N, 8.09% S; MS: m/z : 267 [$\text{M}-\text{M}_{\text{I}}$]; Ramman ν_{max} (cm^{-1}): 1600 (N=C endocyclic), 3050-3080 (C=H aromatic).

2-(4-Cloro)-phenyl-thiazole-4-yl-methyl-pyridinium iodide (14)

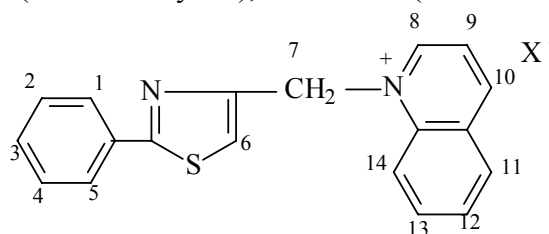
$^1\text{HNMR}$ (500 MHz, DMSO- d_6) δ (ppm): 6.02 (2H, s, C_7 methylene), 7.30-7.32 (2H, d, $\text{C}_{2,4}$ phenyl), 7.77-7.79 (2H, d, $\text{C}_{1,5}$ phenyl), 7.97 (H, s, C_6 thiazole), 8.20-8.24 (2H, t, C_9 , C_{11} pyridine), 8.47-8.68 (H, t; C_{10} pyridine), 9.23-9.25 (2H, d, C_8 , C_{12} pyridine),

For $C_{15}H_{12}ClIN_2S$ calculated: 43.42% C, 2.89% H, 6.76% N, 7.72% S; found 43.50% C, 2.91% H, 6.60% N, 7.75% S; MS: m/z : 287.50 $[M-M_I]$; Ramman ν_{max} (cm^{-1}): 1602 (N=C endocyclic), 3020-3065 (C=H aromatic).

2-Phenyl-thiazole-4-yl-methyl-(4-methyl)-pyridinium iodide (15)

1H NMR (500 MHz, DMSO- d_6) δ (ppm): 2.62 (3H, s, CH_3), 5.97 (2H, s, C_7 methylene), 7.50-7.51 (3H, t, $C_{2,3,4}$ phenyl), 7.89-7.90 (2H, 2d, $C_{1,5}$ phenyl), 8.01 (H, s, C_6 thiazole), 8.04-8.03 (2H, d, C_9 , C_{11} pyridine), 9.10-9.09 (2H, d, C_8 , C_{12} pyridine);

For $C_{16}H_{15}IN_2S$ calculated: C 48.73%, H, 3.81% N, 7.11% S 8.12%; found 48.75% C, 3.79% H, 7.13 % N, 8.10% S; MS: m/z : 267 $[M-M_I]$, Ramman ν_{max} (cm^{-1}): 1598 (N=C endocyclic), 3000-3070 (C=H aromatic).



5-Bromo-2-phenyl-thiazole-4-yl-methyl-quinolinium iodide (16)

1H NMR (500 MHz, DMSO- d_6) δ (ppm): 6.40 (2H, s, C_7 methylene), 7.47-7.45 (3H, 2d, $C_{2,3,4}$ phenyl), 7.80 -7.78 (2H, 2d, protons $C_{1,5}$ phenyl), 8.04-8.07 (1H, t, proton C_9 quinoline), 8.30-8.27 (1H, t, proton C_{12} quinoline), 8.35-8.32 (1H, 2d, C_{13} quinoline), 8.52-8.51 (1H, d, C_{11} quinoline), 8.81-8.79 (1H, d, C_8 quinoline), 9.40-9.38 (1H, d, C_{10} quinoline), 9.86-9.85 (1H, d, C_{14} quinoline);

For $C_{19}H_{14}BrIN_2S$ calculated: 44.79% C, 2.75% H, 5.50% N 6.29% S; found 44.85% C, 2.82% H, 5.60% N, 6.31 % S; MS: m/z : 382 $[M-M_I]$, Ramman ν_{max} (cm^{-1}): 1631 (N=C endocyclic), 3000-3025 (C=H aromatic).

2-(4-Methyl)-phenyl-thiazole-4-yl-methyl-quinolinium iodide (17)

1H NMR (500 MHz, DMSO- d_6) δ (ppm): 2.3 (3H, s, CH_3), 6.40 (2H, s, C_7 methylene), 7.25-7.27 (2H, d, $C_{2,4}$ phenyl), 7.67 -7.69 (2H, 2d, $C_{1,5}$ phenyl), 8.03-8.07 (1H, 2d, C_{13} quinoline), 8.06 (1H, s, C_6 thiazole), 8.27-8.31 (1H, t, C_9 quinoline), 8.32-8.34 (1H, t, C_{12} quinoline), 8.50-8.52 (1H, d, C_{11} quinoline), 8.77-8.79 (1H, d, C_8 quinoline), 9.37-9.39 (1H, d, C_{10} quinoline), 9.81-9.82 (1H, d, C_{14} quinoline);

For $C_{20}H_{17}IN_2S$ calculated: 54.05% C, 3.83% H, 6.31% N, 7.21 % S; found 54.25% C, 3.66% H, 6.48% N, 7.03% S; MS: m/z : 317 $[M-M_I]$; Ramman ν_{max} (cm^{-1}): 1625 (N=C endocyclic), 3025-3075 (C=H aromatic).

Some compounds were assessed for their bactericide activity on *Pseudomonas aeruginosa* ATCC15442 and *Staphylococcus aureus* ATCC6538. In order to be considered a molecule with bactericidal activity, these compounds have to demonstrate at least a 5 decimal log reduction of at least two test microorganisms *Pseudomonas aeruginosa* ATCC 15442 (1) and *Staphylococcus aureus* ATCC 6538 (2), at 20°C, after 5 minutes contact time, if the basic limits of the method are accomplished [3, 17, 18, 19, 20]. Initially, the number of the germs was 4×10^8 for *Pseudomonas aeruginosa* and 8×10^8 for *Staphylococcus aureus*. The obtained data are presented in table III. Only the compounds 8, 11 and 16 have presented a low bactericide activity.

Table III

The bactericide activity of the obtained compounds

No. comp.	(1)	(2)
6, 7, 9, 10, 12-14, 15, 17	countless	countless
8	<4000	<3500
11	<4000	<4000
16	<4000	<3500

Conclusions

New quaternary ammonium compounds that have in their structure the 2-aryl-thiazole system were synthesized.

In order to ascertain the structure of resulting compounds IR, Raman, MS and $^1\text{H-NMR}$ spectroscopy were performed.

Some compounds were assessed for their bactericide action on *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The compounds 8, 11 and 16 have presented a low bactericide action.

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