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Synthesis and biological evaluation of novel cyanuric acid-tethered tris-pyridinium derivatives

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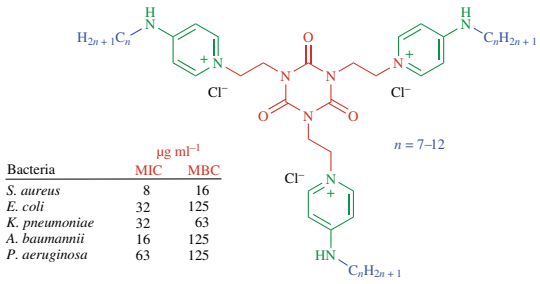
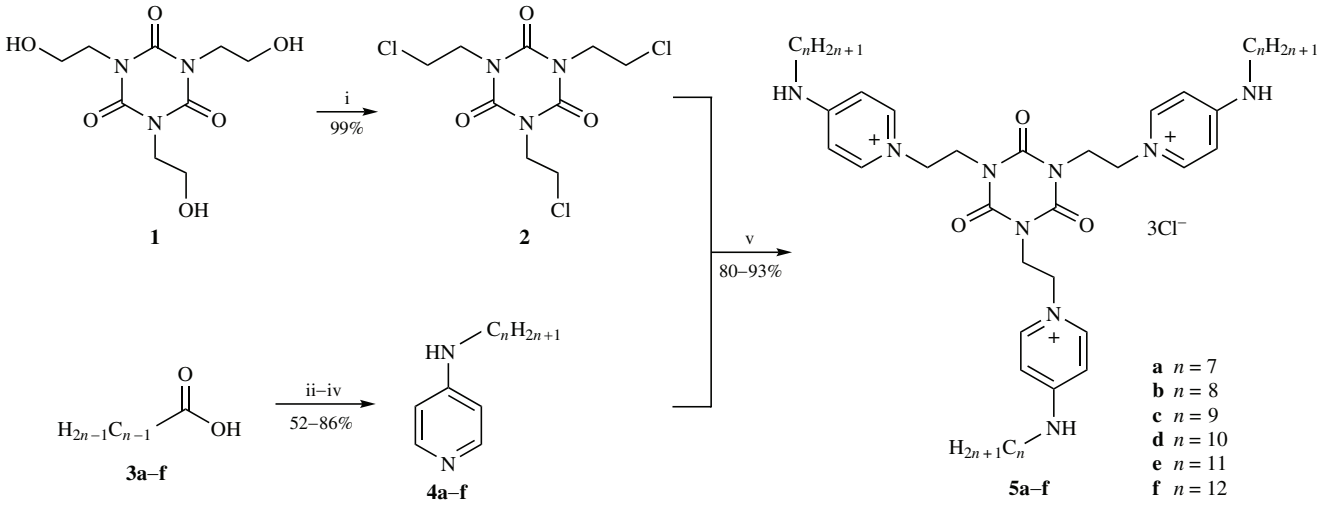
Novel tris(4-alkylaminopyridin-1-ium) trichlorides with alkylcyanuric spacer were synthesized by quaternization of 4-alkylaminopyridines with tris(2-chloroethyl) cyanurate. The obtained compounds were evaluated for microbiological activity against five pathogenic bacterial strains (*Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Acinobacter baumannii*, *Pseudomonas aeruginosa*). The results indicate the presence of pronounced antibacterial properties in this group of compounds.



Keywords: tris-quaternary ammonium compounds, pyridinium salts, biological activity, antibacterial agents.

For many years, quaternary ammonium compounds (QACs) have been included in most antiseptics and disinfectants that are used from household and agricultural to hospital and industrial business.[1] The COVID pandemic that played out in 2020 led to a significant increase in the widespread use of antiseptics, including QACs. Recent studies show that in more than 90% of dust samples analyzed during the pandemic, QACs were detected, and their average concentration has doubled compared to the period before COVID.[2] While the effectiveness of QACs against the viral strains responsible for the spread of this pandemic has not yet been conclusively proven,[3,4] the threat of the spread of bacterial resistance is more urgent than ever, primarily in regard to the main QACs on the pharmaceutical market (see Online Supplementary Materials, Figure S1). The solution to this problem lies in the synthesis of new compounds exhibiting biocidal properties using a structure–activity relationship approach.[5]

Earlier, our research group has reported the synthesis and study of the antibacterial and antifungal activity of bis-QACs based on pyridine with aromatic spacers.[6–10] This work is focused on obtaining trimeric QACs (for examples, see Figure S2). With a



Scheme 1 *Reagents and conditions*: i, $SOCl_2$ (3.3 equiv.), PhH, 80°C, 9 h; ii, $SOCl_2$ (1.3 equiv.), DMF (0.1 equiv.), PhMe, 110°C, 3 h; iii, 4-aminopyridine (0.8 equiv.), Et_3N (1.2 equiv.), CH_2Cl_2, 40°C, 2 h; iv, $LiAlH_4$ (2 equiv.), THF, 66°C, 6 h; v, **2** (1 equiv.), **4a–f** (3.3 equiv.), butan-1-ol, 117°C, 3 days.

Table 1 MIC/MBC values (μg ml^{-1}) for prepared QACs.

Compound	MIC/MBC[a]				
	S. aureus	*E. coli*	*K. pneumoniae*	*A. baumannii*	*P. aeruginosa*
5a, $n = 7$	8/16	16/16	63/250	250/250	63/250
5b, $n = 8$	8/16	32/32	32/125	125/125	63/250
5c, $n = 9$	8/16	32/63	32/125	16/250	63/125
5d, $n = 10$	16/32	32/125	32/125	63/125	125/125
5e, $n = 11$	16/63	500/>500	63/500	63/250	250/250
5f, $n = 12$	32/63	125/250	500/500	125/250	500/500
CPC	4/16	8/8	63/500	16/32	500/500
BAC	125/250	4/8	500/500	>500/>500	>500/>500

[a] Reference strains of microorganisms *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 700603, *Staphylococcus aureus* ATCC 43300, *Acinobacter baumannii* ATCC 15308, *Pseudomonas aeruginosa* ATCC 27853.

large abundance of works on mono- and bis-QACs, it is surprising that multi-QACs (QACs with three or more heads) are studied scarcely (Figure S3).[11–18]

As a starting platform (Scheme 1), we used tris(2-chloroethyl) cyanurate **2**, which is easily obtained by treatment of the corresponding alcohol **1** with thionyl chloride (step i). Compound **2** being a trimeric alkyl chloride looks good as a spacer for our purpose. This compound was further introduced into quaternization of 4-alkylaminopyridines, the reaction having proceeded at the pyridinium nitrogen atom to afford the target products **5a–f** (step v). The head–tail complex is 4-alkylaminopyridines **4a–f** with different alkyl chain lengths. These reactants, in turn, were readily obtained from aliphatic carboxylic acids (steps ii–iv).

The obtained compounds **5a–f** were tested for microbiological activity against five bacterial strains (*Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 700603, *Staphylococcus aureus* ATCC 43300, *Acinobacter baumannii* ATCC 15308, *Pseudomonas aeruginosa* ATCC 27853) at the State Research Center for Applied Microbiology & Biotechnology. Table 1 shows the values of the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of salts **5a–f** and the reference samples CPC and BAC.

According to the results obtained from bacteriostatic study, it can be argued that compounds **5a–f** possess antibacterial activity against all five studied strains. Compound **5f** is less active than **5a–e**, inhibiting growth at higher concentrations. Compound **5c** exhibits the best bacteriostatic properties among all studied compounds on *Klebsiella pneumoniae* strains (together with **5b** and **5d**), *Pseudomonas aeruginosa* (with **5a** and **5b**), *Acinobacter baumannii* and comparative MIC for *Staphylococcus aureus*, yielding to CPC only by one dilution. Bactericidal study showed that compound **5c** has the lowest MBC against *Pseudomonas aeruginosa* (with **5d**), *Klebsiella pneumoniae* (with **5b** and **5d**) and *Staphylococcus aureus* (with **5a** and **5b**). Hence, compound **5c** is the best in the series in both bacteriostatic and bactericidal activity. In general, with elongation of alkyl tails of 4-alkylaminopyridines **4a–f** from seven to nine, the biological activity is growing and then falls on further lengthening the chain. The tested compounds were less active against *Escherichia coli* than the reference samples.

In conclusion, new trimeric pyridinium salts with alkyl-cyanuric spacer have been synthesized. Their MIC and MBC values measured on five bacteria pathogenic for humans confirm that substances **5a–d** exhibit high antibacterial activity compared to reference BAC and CPC. Compound **5c** is the lead one in this series showing the best activity against *Klebsiella pneumoniae*, *Acinobacter baumannii*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. This result provides grounds for further studies of this group of compounds based on cyanuric spacer.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.05.028.

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