SYNTHESIS AND BIOLOGICAL ACTIVITY OF NOVEL ADAMANTANE-BASED DIALKYLAMINOPROPANOL QUATERNARY SALTS

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Topicality. The emergence and spread of multidrug-resistant pathogens leads to a decrease in efficacy of antibiotic therapy, causes the duration of patient’s hospital stay and increases treatment costs. The screening of potential antimicrobial agents among the new classes of chemical compounds is one of the promising methods to overcome the problem of resistance.

Aim. To synthesize and to make screening studies of antimicrobial activity of quaternary salts of adamantane derivatives (3a–3l) with the aim to find of new prospective compound with good activity.

Materials and methods. The synthesis and investigation of physicochemical properties of new adamantane-based dialkylaminopropanol quaternary salts were carried out. The evaluation of antimicrobial action against S. aureus, E. coli and C. albicans strains were performed.

Results and discussion. The results showed that the inhibitory activities of quaternary salts with 1-adamantyl-ethyl radical in their alkoxy group were significantly higher than those of the compounds with 1-adamantyl and 1-adamantyl-ethyl radicals in their alkoxy group.

Conclusions. 3c was the most active compound tested against all strains, with MIC between 1.56 and 3.12 µg/mL, and its antimicrobial activity was similar to that of myramistin.

Key words: adamantane derivatives; dialkylaminopropanol; synthesis; antibacterial activity; antifungal action

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**INTRODUCTION**

Nowadays, the emergence and spread of multidrug-resistant (MDR) pathogens (e.g., methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Enterobacteriaceae* (CRE), fluoroquinolone-resistant *Escherichia coli* or resistant to third-generation cephalosporins *Neisseria gonorrhoeae* isolates) pose a global threat to public health. According to WHO data about antibiotic-resistance (2014), the lethality in patients with MRSA infection is higher on 64 % than with susceptible form of infection [1]. A wide spread of MDR-pathogens leads to a decrease in efficacy of antibiotic therapy, prolongation of the length of patient’s hospital stay and an increase in treatment costs. In addition, patients with MDR-infections often have increased mortality rates.

The screening of potential antimicrobial agents among the new classes of chemical compounds is one of the promising methods to overcome the problem of resistance. In this respect, adamantane-based aminopropanols are attracting attention owing to their broad antibacterial and antifungal activity [2, 3]. The significant antimicrobial action is attributable to high lipophilicity and crystal structure of the adamantine moiety [4].

**The aim** is to carry out synthesis and screening studies of antimicrobial activity of quaternary salts of adamantane derivatives (3a-3l) with the aim to find of new prospective compound with good activity.

**MATERIALS AND METHODS**

The structure of compounds was confirmed by using set of physical and chemical methods such as elemental analysis, IR- and $^1$H NMR-spectrometry. The elemental analyses were detected using a Carlo Erba CHNS-O EA 1106 analyzer. The melting point were determined on a Gallenkamp melting point apparatus MFB-595 in open capillary tube. $^1$H NMR-spectra were acquired on a Varian VXP spectrometer (299.945 MHz). The solvent was DMSO-$_d$6, with tetramethylsilane (TMS) as an internal standard. IR spectra were registered by using UR-20 spectrophotometer with liquid films between KBr plates.

**RESULTS AND DISCUSSION**

**Experimental Chemical Part**

In our work 1-adamantylglycidyl ether, 1-adamantylethoxy- and 1-(2-adamantoxethoxy)-glycidyl ethers were used as initial substances. 1-Adamantylglycidyl ether was obtained according to the method reported previously [6]; 1-adamantylethoxy and 1-(2-adamantoxethoxy) glycidyl ethers were obtained under conditions of the phase-transfer catalysis (50 % NaOH, TEBAC, epichlorohydrin) (Scheme) [7].

The synthesis of the target compounds was carried out according to Scheme 1. Quaternary salts of adamantane-based dialkylaminopropanol (3a-1) were obtained starting from relevant epoxides (1) by treatment with excess amount (double amount, 50 %) of secondary amines in the presence of isopropanol with heating. The excess of reagents (amines and alcohol) was evaporated under reduced pressure. Then these intermediates (2) were converted into quaternary salts (3a-1) by treatment with excess amount (5 %) of alkyl halides (CH$_3$I, C$_2$H$_5$I, C$_3$H$_7$Cl) in the presence acetone or acetonitrile with heating at 10 h.

**Scheme.** The synthesis of quaternary salts of adamantane-based dialkylaminopropanols (3a-1)
During our synthetic work, 12 new compounds of adamantane-based dialkylaminopropanol quaternary salts were obtained. Compounds are colorless or light yellow substances, soluble in water and in organic solvents (DMSO, ethanol).

The melting point, elemental analysis and yield of compounds (3a-3l) are shown in Table 1. The data obtained from the calculation of elemental analysis (C, N, H) are corresponded to experimental data.

In the IR-spectra of synthesized compounds the adsorption bands due to the OH-group are present in the range of 3500-3200 cm⁻¹, the adsorption bands of CH₃, CH₂-groups are in 2975-2840 cm⁻¹ region. They also show absorptions near 1150-1100 cm⁻¹ due to stretching of ether linkage.

All ¹H NMR-spectra of compounds contain the signals of protons of adamantane ring at 1.50-2.10 ppm; the CH₂ group of benzyl radical gives the resonance peaks at 4.75-5.15 ppm as a doublet of doublets. The protons in the benzene ring resonate in the region of 7.40-7.65 ppm, the ethyl group displays a triplet at 3.75-4.11 ppm. The CH₃ and CH₂-O groups are in 2975-2840 cm⁻¹ region. They also show adsorptions near 1150-1100 cm⁻¹ due to stretching of ether linkage.

All ¹H NMR data of compounds are given in Table 2. The data obtained from the calculation of theoretical analysis (C, N, H) are corresponded to experimental data.

### Table 1

| Compound | M. p., °C | Yield, % | Found, % | Mol. Formula | Calc, % |
|----------|-----------|----------|----------|--------------|---------|
|          | C         | H        | N        | C, H, N, O   | C       |
| 3a       | 97-99     | 51       | 55.34    | 8.44         | 2.93    |
| 3b       | 172-173   | 57       | 51.06    | 8.09         | 3.30    |
| 3c       | 167-168   | 64       | 50.61    | 8.40         | 3.43    |
| 3d       | 128-131   | 73       | 53.45    | 8.07         | 3.11    |
| 3e       | 130-131   | 67       | 51.90    | 8.28         | 3.22    |
| 3f       | 123-125   | 52       | 72.77    | 9.59         | 3.02    |
| 3g       | 138-141   | 63       | 51.31    | 7.65         | 3.32    |
| 3h       | 157-159   | 68       | 52.41    | 7.87         | 3.21    |
| 3i       | 174-175   | 70       | 50.12    | 7.42         | 3.43    |
| 3j       | 172-174   | 60       | 69.54    | 9.01         | 3.68    |
| 3k       | 95-97     | 70,5     | 50.36    | 5.63         | 3.26    |
| 3l       | 75-77     | 59       | 69.63    | 6.81         | 3.38    |

### Table 2

| Compound | Chemical shift, δ, ppm. (¹H NMR DMSO-d₆, δ, ppm) |
|----------|-------------------------------------------------|
|          | Ad                                              |
|          | OH                                              |
|          | Ar                                              |
|          | Other groups                                   |

| 3a       | 1.49 s (6H, 3xCH₃) 1.62 q (6H, 3xCH₃) 1.90 s (3H, 3xCH₃) | 5.76 d |
| 3b       | 1.48 s (6H, 3xCH₃) 1.62 q (6H, 3xCH₃) 1.91 s (3H, 3xCH₃) | 5.54 d |
| 3c       | 1.48 s (6H, 3xCH₃) 1.62 q (6H, 3xCH₃) 1.91 s (3H, 3xCH₃) | 6.07 d |
| 3d       | 1.49 s (6H, 3xCH₃) 1.63 q (6H, 3xCH₃) 1.90 s (3H, 3xCH₃) | 5.48 d |
| 3e       | 1.51 s (6H, 3xCH₃) 1.62 q (6H, 3xCH₃) 1.90 s (3H, 3xCH₃) | 6.12 d |
| 3f       | 1.49 s (6H, 3xCH₃) 1.65 q (6H, 3xCH₃) 1.91 s (3H, 3xCH₃) | 6.15 d |
| 3g       | 1.58 s (6H, 3xCH₃) 1.68 q (6H, 3xCH₃) 2.10 s (3H, 3xCH₃) | 5.76 d |
| 3h       | 1.57 s (6H, 3xCH₃) 1.67 q (6H, 3xCH₃) 2.09 s (3H, 3xCH₃) | 5.54 d |
1-(1-adamantylethoxy)-3-(N-methyl hexamethylenamine)-2-propanol iodide (3a). To the mixture of 1-adamantylethyl glycidyl ether (2.36 g/0.01 Mol) in isopropanol (5 ml), hexamethylenamine (1.48 g/0.015 Mol) was added, and the reaction mixture was heated for 8 h. The excess of amine and alcohol was evaporated under reduced pressure. The residue was dissolved in 5 ml of acetonitrile with adding methyl iodide (0.75 g/0.0105 Mol) followed refluxing for 10 h. After cooling to the appropriate temperature, dry diethyl ether (5 ml) was added, then the reactive mixture was left for 6-8 h at +5 °C. The precipitate was filtered out, washed with diethyl ether and dried. Yield – 2.43 g (51 %). M. p. – 97-99 °C.

For compounds 3b-3l all procedures were the same.

Experimental Biological Part

Antibacterial and antifungal activity assay showed that derivatives, containing adamatylethhyl radical in their alkoxy group (3a-3f), possessed significant inhibitory activity (Table 3).

No antimicrobial activity was observed against tested bacterial and fungal strains for compounds, containing 1-adamantyl (3g-3j) and 1-adamantylxoxethyl (3k-3l) fragment in their alkoxy group (except compound 3l with activity against S. aureus, MIC 50.0 μg/mL).

Among the adamantane-based derivatives tested, compounds 3a-f and 3l possessed inhibitory activity against the grampositive bacteria (S. aureus), the MIC values were between 1.25 and 50.0 μg/mL. The most active compounds were 3c and 3e, which inhibited S. aureus as well as myramistin.

Derivatives of adamantane were also active when tested against gramnegative strains. The compounds 3a-c,e,f at concentrations between 3.12 and 50.0 μg/mL inhibited E. coli growth. The MIC value of compound 3c was comparable to that of myramistin.

Antifungal activity results revealed that compounds 3a-f possessed inhibitory action against C. albicans at concentrations less than or equal to 25.0 μg/mL. The compounds 3c and 3f, as well as myramistin, inhibited the yeast growth (MICs 1.56 and 1.25 μg/mL respectively).

In conclusion, this study showed that 3c was the most active compound, and its antimicrobial effect was simi-
lar to that of myramistin. Significant inhibitory activity against \textit{S. aureus} and \textit{C. albicans} was registered for compounds 3e and 3f respectively. So, quaternary salts of dialkylaminopropanol with 1-adamantylethyl radical in their alkoxy group possessed polyvalent action against bacteria and fungi. These compounds are promising class for the research and development of novel antimicrobial agents for treatment of infectious diseases.

**CONCLUSIONS**

1. The effective synthetic methods of 12 novel quaternary salts of adamantine-containing dialkylaminopropanol and their derivatives have been developed.

2. The structure of the compounds obtained has been confirmed with a set of modern physical and chemical methods of analysis, and their individuality has been proven by elemental analysis, IR- and NMR-spectroscopy.

3. It was shown that compounds with 1-adamantylethyl radical in their alkoxy group (3a-3f) possessed narrow (3e and 3f) and broad spectrum (3e) of antimicrobial action against bacteria and fungi.

4. It was found that derivatives with 1-adamantyl (3g-3i) and 1-adamantylsloxyethyl (3k-3l) radical in their alkoxy group had no antimicrobial activity against bacterial and fungal strains.

5. The present results suggest that compound 3c could be a lead for development of antimicrobial agents in the future.

**Conflict of Interests:** authors have no conflict of interests to declare.

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