journal homepage: *http://bsuj.bsu.edu.az/en*
https://doi.org/10.30546/209501.201.2025.2.004.019

SYNTHESIS AND PROPERTIES OF AMINOMETHOXY DERIVATIVES WITH CYCLOHEXANE FRAGMENTS

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Received: 21 October 2025
Accepted: 29 December 2025
Published: 30 December 2025

The presented work is dedicated to the synthesis of cyclohexane fragment containing aminomethoxy derivatives based on the three-component Mannich reaction involving cyclohexanole, formaldehyde, and secondary aliphatic amines (diethyl, dipropyl, dibutyl, dihexyl), as well as the study of their properties. The reaction is carried out by mixing the starting materials in equimolar amounts in a benzene medium at 78-80°C for 4–5 hours. During the reaction, CuCl was employed as a catalyst, leading to a high yield of the synthesized products. The yields of the compounds 83–91%.

The synthesized new aminomethoxy derivatives' physicochemical properties were determined. These substances are yellowish liquids with a distinctive odor. They are insoluble in water but dissolve in organic solvents (such as ethanol, acetone, benzene, chloroform, CCl_4 and others). The composition and structures of N,N-diethylaminomethoxycyclohexane, N,N-dipropylaminomethoxycyclohexane, N,N-dibutylaminomethoxycyclohexane and N,N-dihexylaminomethoxy cyclohexane were confirmed by elemental analysis, IR and NMR spectroscopy methods. As a result of the synthesis of new aminomethoxy derivatives containing a cyclohexane fragment, compounds with high biological activity have been obtained.

The antimicrobial activity of the synthesized compounds was studied using the serial dilution method against various microorganisms. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of the synthesized aminomethoxy derivatives of cyclohexanol were determined against bacteria and fungi (*S.aureus, E.coli, C.albicans*).

Keywords: cyclohexanol, secondary aliphatic amines, CuCl, biological activity

INTRODUCTION

Among reagents with high antimicrobial activity, Mannich bases occupy a special place. The strong bactericidal and fungicidal effects of these compounds enhance their effectiveness[1–6]. Today, many highly effective pharmaceuticals, additives with antimicrobial and antioxidant properties for oils and fuels, organic compounds used in agriculture, and inhibitor-bactericides consist of molecules that contain nitrogen and various functional groups. Although research in this area has been ongoing for a long time, it still remains scientifically and practically relevant. Many leading laboratories around the world continue to actively study the synthesis and properties of nitrogen-containing, functionally substituted organic

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compounds [7–11]. Among these studies, the synthesis of a new generation of functionally substituted amines using readily available components in a convenient manner holds particular importance. The Mannich reaction is one of the key and promising methods for obtaining such compounds. With the help of this reaction, it is possible to synthesize polyfunctional biologically active compounds with high regio-, stereo-, and enantioselectivity. The synthesis and investigation of the biological properties of Mannich bases containing a biologically active cyclohexane fragment is of great theoretical and practical significance [12–16].

The present study focuses on the synthesis of aminomethoxy derivatives of cyclohexanol and the investigation of their physicochemical and biological properties. The primary aim is to develop novel biologically active compounds through a simple, eco-friendly, and waste-free synthetic approach. These compounds are characterized by high antimicrobial activity, multifunctionality, and protective efficiency at low concentrations. Additionally, they are derived from readily available raw materials and offer economic feasibility. The expansion of the structural diversity of such compounds is also a key objective, with the ultimate goal of contributing to the development of effective agents for pharmaceutical, agricultural, and industrial applications[16–20].

EXPERIMENTAL

Aminomethoxy derivatives of cyclohexanol (7–10) were synthesized by the Mannich reaction in equimolar ratios of the starting components in benzene solution. Formaldehyde and 20 ml of benzene were added to a three-neck round-bottom flask equipped with a stirrer, Dean-Stark apparatus, reflux condenser, and thermometer. A mixture of secondary amines and 20 ml of benzene, followed by a mixture of cyclohexanol and 20 ml of benzene, was added dropwise to the flask using a dropping funnel. And 1 gram of CuCl is added as a catalyst. The reaction was carried out at 78–80°C with continuous stirring for 4–5 hours, accompanied by the removal of water. The resulting product was washed with ammonia and then with distilled water, followed by drying over $CaCl_2$. Benzene was first removed from the obtained mixture by simple distillation, and subsequently, the substances were distilled under vacuum. The obtained compounds (7–10) are clear, yellowish liquids with a characteristic odor. They are insoluble in water but dissolve well in organic solvents such as ethanol, acetone, benzene, CCl_4, etc. The structure and composition of the synthesized compounds were confirmed by elemental analysis, IR, ^1H, and ^{13}C NMR spectroscopy methods. The NMR spectra of the synthesized compounds were recorded on a Bruker WP-300 spectrometer operating at 300 MHz frequency in $CDCl_3$ solution using TMS as the internal standard. IR spectra were recorded on a BRUKER ALPHA FURYE spectrometer in the wavelength range of 4000–400 cm^{-1}. The refractive indices were measured using an IRF-22 №700060 refractometer and densities were determined according to GOST 3900-2000.

The antimicrobial activity of the synthesized compounds (7–10) was studied using the serial dilution method against various microorganisms. Meat-peptone agar with a pH of 7.2–7.4 was used as the nutrient medium for bacteria, and Sabouraud medium was used for fungi. The incubation period in the thermostat was 18–24 hours at 37°C for bacteria and 1–10 days at 28°C for fungi. The dilution levels of the compounds were 1:100, 1:200, 1:400, and 1:800 respectively. Inoculations were made after 5, 15, 30, 45, and 60 minutes of exposure time. For comparison, the control drug (ethanol) and reference drugs (rivanol, furacilin, carbolic acid, chloramine) were studied at the same dilutions. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of the synthesized aminomethoxy derivatives of cyclohexanol were determined against bacteria and fungi (*S.aureus, E.coli, C.albicans*). Meat-peptone broth was used as the nutrient medium for bacteria, and sweet broth was used for fungi. The dilution method was applied, and the incubation time was 24 hours.

RESULTS AND DISCUSSION

The reaction was carried out at a temperature of 78–80°C for 4–5 hours in a benzene solution, using an equimolar ratio of the starting components. The yield of the compounds ranged from 83% to 91%, with the highest yield obtained when diethylamine was used. The target compounds are liquids with a characteristic odor, insoluble in water but highly soluble in organic solvents. The composition and structure of compounds 7–10 were determined based on elemental analysis, IR, ^{1}H and ^{13}C NMR spectroscopy, as well as mass spectrometry.

The antibacterial activity of compounds 7–10 was studied in comparison with medicinal preparations used in medical practice: rivanol, furacilin, carbolic acid (phenol), and chloramine. To investigate the antimicrobial activity of the synthesized compounds, the serial dilution method was used. For this purpose, a 1% alcoholic solution of the test substance was diluted in physiological solution to various concentrations (1:100; 1:200; 1:400; 1:800). Then, 0.1 ml of the test culture was inoculated into each test tube containing the substance. Gram-positive and gram-negative bacteria: *S. aureus, E. coli, P. aeruginosa, K. Pneumoniae* as well as yeast-like fungi of the genus *Candida* were used as test cultures.

The results of the antimicrobial activity tests of the synthesized compounds are presented in Table 1. Compounds 7–10 exhibit high antibacterial and antifungal activity against the microorganisms listed above. All compounds 7–10 showed a 100% lethal effect on *C.albicans*. Compounds 9, 10, and 16 inhibited the growth of K. pneumoniae and *P.aeruginosa* in 100% of cases after just 10 minutes of exposure. Compounds 7–9 inhibited the growth of *P. aeruginosa*, and compound 10 inhibited the growth of *E.coli* at low concentrations after 20 minutes of exposure. Compounds 7–9 inhibited the growth of *K.pneumoniae*, compounds 7, 8, and 10 inhibited the growth of *S.aureus*, and compound 10 inhibited the growth of *E.coli* at low concentrations after 40 minutes of exposure.

A comparison of the antimicrobial activity of the synthesized compounds 10–16 with control agents (rivanol, furacilin, carbolic acid, chloramine) showed that the antimicrobial activity of the obtained compounds was higher than that of the reference drugs against the tested microorganisms.

The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of compounds 7–10 were determined against some of the above microorganisms (*Staphylococcus aureus, Pseudomonas aeruginosa, Candida fungi*). It has been established that at very low concentrations these compounds inhibit the development of bacteria and fungi. The research results allow us to recommend the synthesized compounds 7–10 for use as potential antimicrobial agents. Thus, as a result of the study carried out, new aminomethoxy derivatives of cyclohexanol were synthesized and characterized via the Mannich reaction, and these compounds exhibit high antimicrobial activity.

CONCLUSION

New aminomethoxy derivatives of cyclohexanol were synthesized and characterized via the Mannich condensation, and they exhibit pronounced antimicrobial activity. The synthesized aminomethoxy compounds showed higher results than the control preparations.

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