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OBTAINING A NEW SOLUBLE BETAIN DERIVATIVE OF CHITOSAN

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This work reported, that in microwave irradiation in an aqueous solution, thiol derivatives of chitosan and propargyl ether of betaine in a 1:1 molar ratio are subjected to selective thioline addition with the formation of new betaine chitosan cationic derivatives. The completeness of the conversion was controlled by the ^{1}H NMR spectroscopy.

Keywords. chitosan, thioline, p-merkaptobenzoic acid, betaine, nuclear magnetic resonance

INTRODUCTION

Chitosan, thanks to the wealth of raw materials, biocompatibility, low toxicity and biodegradability, is experiencing considerable pharmaceutical and medical interest [1]. Its cationic derivatives show transfectional and antibacterial activity, however, ways to obtain them can make changes to the polymer chain of chitosan itself, which is undesirable for these areas [2-4].

EXPERIMENTAL

For the introduction of a thiol fragment into a chitosan chain, the so-called preclick modifications was used by the processing of chitosan with p-merkaptobenzoic acid in the presence of EDC (1-ethyl-3- (3-deimethylaminopropil) of carbotiamide) and NHS (n-hydroxyccinimide) (Scheme 1).

The degree of replacement of the resulting products depends on the molar ratio of reagents. When using the molar ratio of chitosan:thiosalicylic acid 1:1, the degree of substitution of the resulting derivatives was 0.15. With molar ratio of chitosan:thiosalicylic acid 1:4 or 1:10, derivatives with a replacement degree of about 0.4 and 0.6 are formed, respectively.

The resulting chitosan derivatives having a thiol functional group were used as reagents for ultrasonic-promoted thioline addition as a thiol component. Propargyl ester of betaine was used as the alkyne component (Scheme 1).

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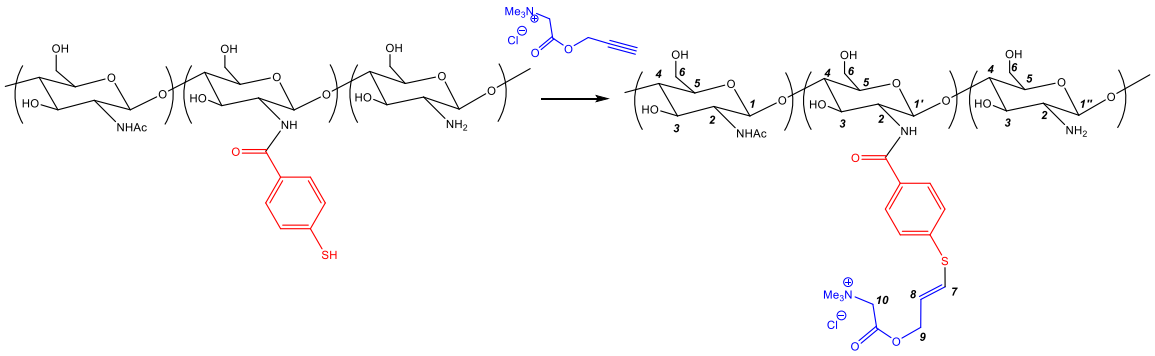

Scheme 1. Synthesis of chitosan derivatives

RESULTS AND DISCUSSION

In microwave irradiation in aqueous solution, thiol derivatives of chitosan and propargyl ether of betaine in a 1:1 molar ratio are subjected to selective thioline addition with the formation of new betaine chitosan cationic derivatives. The completeness of the conversion was controlled by the ^{1}H NMR spectroscopy. The conversion was considered complete when the degree of replacement of the formed betaine derivative of chitosan was the same as the degree of replacement of the initial thiol derivative of chitosan.

The resulting derivatives were characterized using spectroscopy of the ^{1}H NMR. The signals of aromatic protons are in the area of 7.44 and 7.21 ppm. while the signals of protons 7 and 8 are located at 7.72 ppm. and 6.94 ppm. Their presence in the spectrum confirms the transformation of the alkine function into the corresponding CH = CH fragment as a result of the click-reaction of thioline addition. Protons signals 1', 1'' and 1 are localized at 5.27, 5.12 and 4.83 ppm. respectively. In the spectrum there are proton signals 2–6, 9, 10 and NMe_3 signals at 4.60–3.40 ppm. The signal of the NHAc methyl protons is observed at 2.28 ppm. The numbering of protons is presented in the scheme 1. The degree of replacement was calculated according to the formula C3 = I (7) = I (8), provided that I (1'', 1', 1) = 1.

The results of the studies indicate that the antibacterial activity of the betaine derivatives of chitosan has a pronounced dependence on both the molecular mass of the polymer and the degree of replacement.

An increase in the degree of substitution leads to an increase in antibacterial activity both in relation to *S. aureus* and in relation to *E. coli* in polymers of all studied molecular masses. At the same time, the most effective were derivatives with the average molecular mass in comparison with the derivatives of high and low molecular masses. An increase in antibacterial activity with an increase in the degree of substitution can be explained by the following factors:

(1) an increase in the cationic density of the polymer, caused both by an increase in the proportion of secondary amino groups in the macromolecule of the derivative, and by a symbat increase in the number of quaternized positively charged nitrogen atoms;

(2) an increase in the increase in the degree of replacement of the share of hydrophobic fragments in the macromolecular, which is responsible for hydrophobic interaction with the surface of the bacterial cell.

Also, one of the possible factors that increase antibacterial activity could be its own high antibacterial activity introduced into the chitosan chain of a pharmacophore fragment.

However, the results of the study of in vitro antibacterial activity of the compound of the compound NH_2- CH_2-C_6H_4-S-CH=CH-CH_2-O-C(O)-CH2-$N^+(CH_3)_3Cl^-$ showed its effectiveness close to betaine, although also it's a little exceeding the activity.

The obtained cationic derivatives of chitosan were compared according to the degrees of replacement in terms of the ability to damage the bacterial cell membrane. As expected, the greatest damage to the bacterial cells *E. coli* and *S. aureus* cause a high degree of replacement. In addition, the value of the optical density of the A_{260} for the most active highly developed chitosan derivatives is much higher than for any of the most active derivatives of the above group (Fig. 1 and 2).

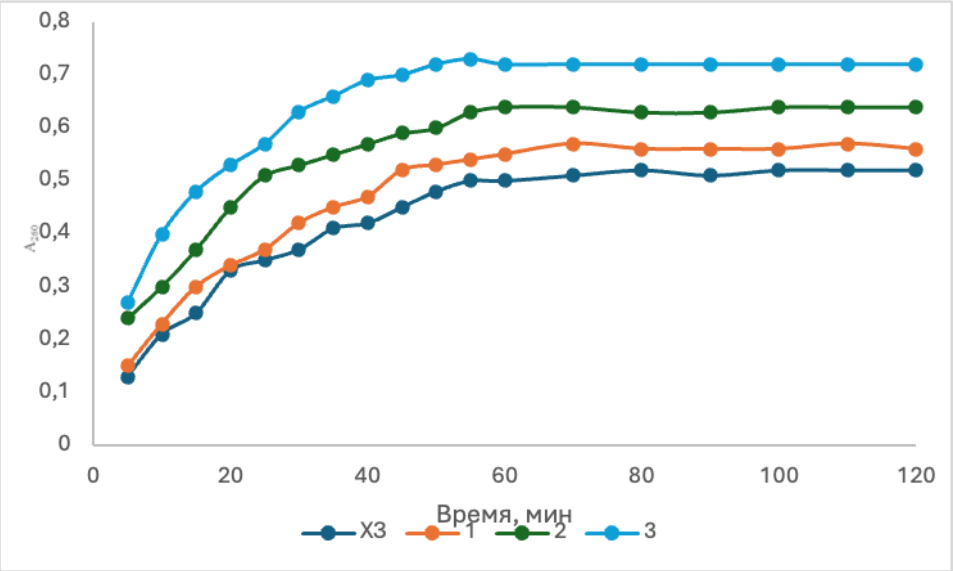

Figure 1. The release of the contents of bacterial cells that absorbs at 260 nm from *E. coli* during the treatment of a bacterial suspension 0.15% aqueous solution of chitosan (X3) or its betaine derivatives (1 - low C3, 2 - average C3, 3- high C3).

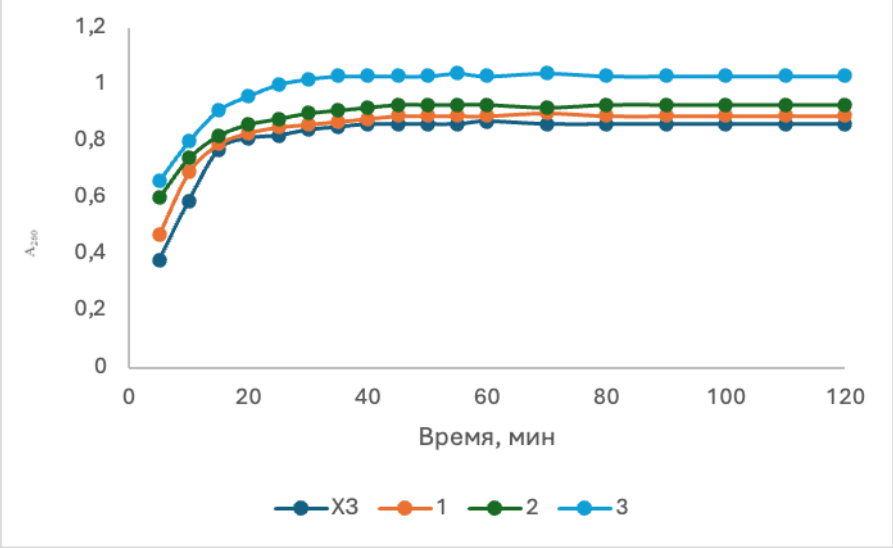

Figure 2. The release of the contents of bacterial cells that absorbs at 260 nm from *S. aureus* during the processing of a bacterial suspension 0.15% aqueous solution of chitosan (X3) or its betaine derivatives (1 - low C3, 2 - average C3, 3- high C3).

CONCLUSIONS

Thus, as a result of the study, antibacterial derivatives of chitosan were obtained and their ability to damage the membrane of bacterial cells was shown.

ACKNOWLEDGMENTS

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