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Synthesis and Antibacterial Activity of (*N*-1-Methylglucosaminocarbonothioyl)-4-bromobenzamide Chelate Complex with Copper(II) Sulfate

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Abstract—Reactions of (*N*-1-methylglucosaminocarbonothioyl)-4-bromobenzamide with copper(II) sulfate in the ratios 1:1 and 2:1 affords the corresponding chelate complexes of the metal. Their structure was proved by high resolution mass spectrometry. The complex of (*N*-1-methylglucosaminocarbonothioyl)-4-bromobenzamide with copper(II) sulfate (ratio 1:1) exhibits pronounced antibacterial activity.

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It is known that one of the main methods for obtaining new medicines on the basis of existing drugs is the synthesis of their metal complexes, which not only lead to an increase in water solubility and reduced toxicity, but also to an increase in biological activity. For example, isoniazid complexes with transition metals and iron have higher activity and are less toxic than the original izoniazid [1]. Many metal complexes, in particular, the copper complexes with thiosemicarbazone manifest high antibacterial and antitumor activities [2–4].

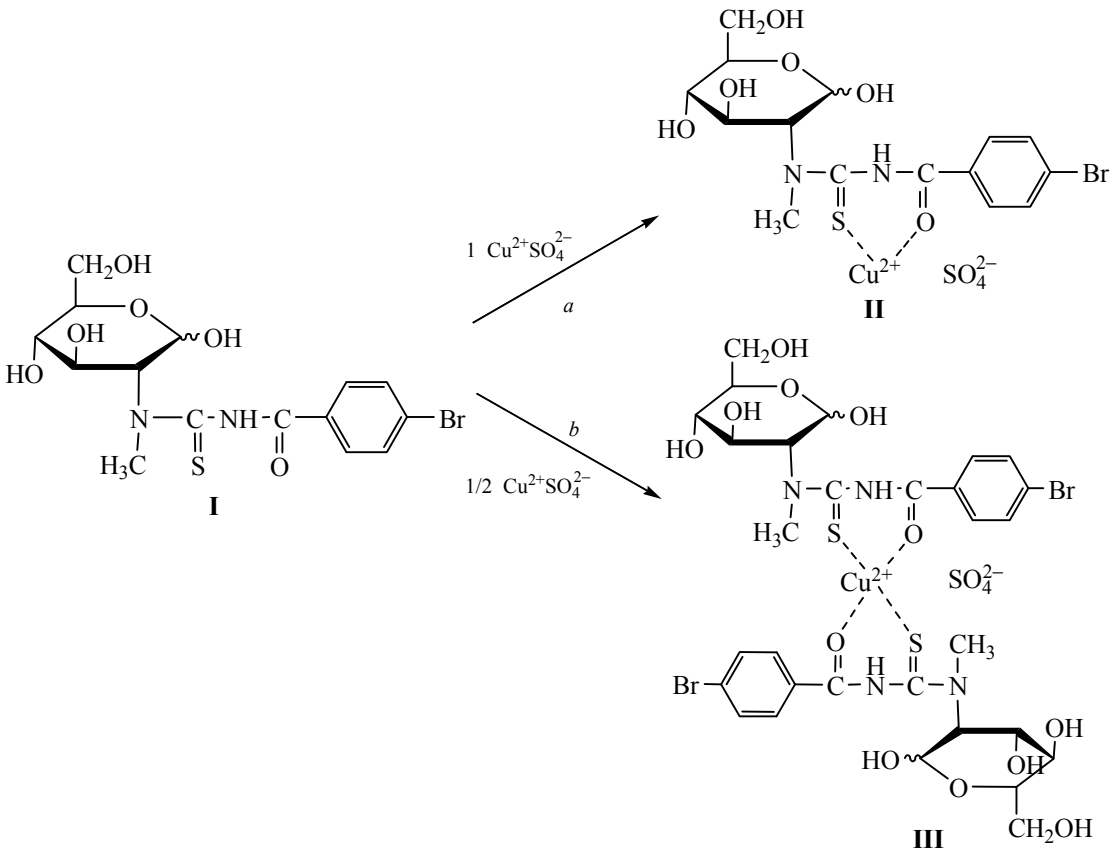
N-(Methylglucosamino-1-carbonothioyl)benzamides are very promising for the possible creation of new effective and low toxic drugs. The synthesis of these compounds via the nucleophilic addition of *N*-methylglucosamine to the appropriate benzoylisothiocyanates have been described [5]. The biological screening showed the moderately expressed antimicrobial activity of one of the synthesized derivatives **I** with a broad spectrum of activity against Gram-positive strains (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram-negative strain *Escherichia coli*. Since the synthesized *N*-(1-methylglucosaminocarbonothioyl)-4-bromobenzamide **I** [5] contained in its structure several electron-acceptor groups (thioamide and benzamide) with the potential chelating ability, we were interested in obtaining metal complexes with copper(II) sulfate on its basis.

The complexation was performed by mixing hot alcohol solutions of *N*-(methylglucosamino-1-carbonothioyl)benzamide **I** and $CuSO_4$ in the ratios 1:1 and 2:1 by two presumed reaction schemes (*a* and *b*).

Depending on the ratio and order of addition of the reactants, the reaction of **I** with $CuSO_4$ affords two colored complex: yellow (**II**) and dark green (**III**) distinguished by the melting points and solubility in organic solvents. The structure of the obtained metal complexes **II** and **III** was determined by the spectroscopic methods.

In the ^{1}H NMR spectrum of complex **III** the proton signals are not clear, owing apparently to its poor solubility. The ^{1}H NMR spectrum of the complex **II** contains broad signals of the aromatic protons of 4-bromophenyl moiety and broad signal at 3.2–4.4 ppm belonging to the hydroxy proton and to the protons of pyranose ring of the carbohydrate fragment.

The high resolution mass spectrometry (HRMS) with the electrospray chemical ionization and positive ions registration was more informative for the study of the structure of metal complex **II.** The HRMS spectrum of the metal complex **II** contains the



molecular ions with *m*/*z* 593.9033 $[M + H]^+$ and 595.9013 $[M + H]^+$ with relative intensity (*I*, %) of 30 and 40%, respectively (Fig. 1). In addition, the spectrum recorded with a chemical ionization contains molecular ions with *m*/*z* 615.8853 $[M + Na]^+$ and 617.8833 $[M + Na]^+$ with the relative intensity (*I*, %) 30 and 40%, respectively (Fig. 2).

The presence of multiple peaks of molecular ions with a difference of 2 units is due to the presence of the bromine atom, which is known to contain two isotopes: ^{79}Br and ^{81}Br, in the ratio of about 1:1. In addition, the mass spectrum of **II** contains the ion fragments of the starting *N*-(methylglucosamino-1-carbonothioyl)benzamide **I**: 457.0039 $[M + Na]^+$ and 459.0019 $[M + Na]^+$. Consequently, the metal complex of *N*-(methylglucosamino-1-carbonothioyl)benzamide **I** with copper(II) sulfate forms the more stable complex with a ratio of 1:1.

Since the parent compound **I** showed a moderately expressed antimicrobial activity [5], we were also interested in testing antibacterial properties of the synthesized complex **II**. The study of the antimicrobial activity was performed by *in vitro* experiments relative to the museum strains of *Staphylococcus aureus* ATCC 6538-P B-RKM 0039 and *Bacillus subtilis* ATCC 6633 B-RKM 0065 from the Republican Collection of Microorganisms (Astana). The susceptibility of bacteria to the above-mentioned chemical complex **II** was evaluated using the methods of successive (serial) diluting in the broth at a concentration from 500 to 0.063 μg ml^{-1} [6, 7].

According to the investigation results, the complex **II** has the expressed antimicrobial activity relative to the museum strains. Thus, the minimal inhibitory concentration (MIC) of compound **II** against *Staphylococcus aureus* is 31 μg ml^{-1}, and in respect of *Bacillus subtilis*, 8 μg ml^{-1}.

Thus, according to the guidelines for experimental study of the new pharmacological substances [6], compound **II** is very promising for further research.

EXPERIMENTAL

^1H NMR spectrum was recorded on a Bruker DRX500 spectrometer (500 MHz) in DMSO-d_6, internal reference TMS. The high resolution mass

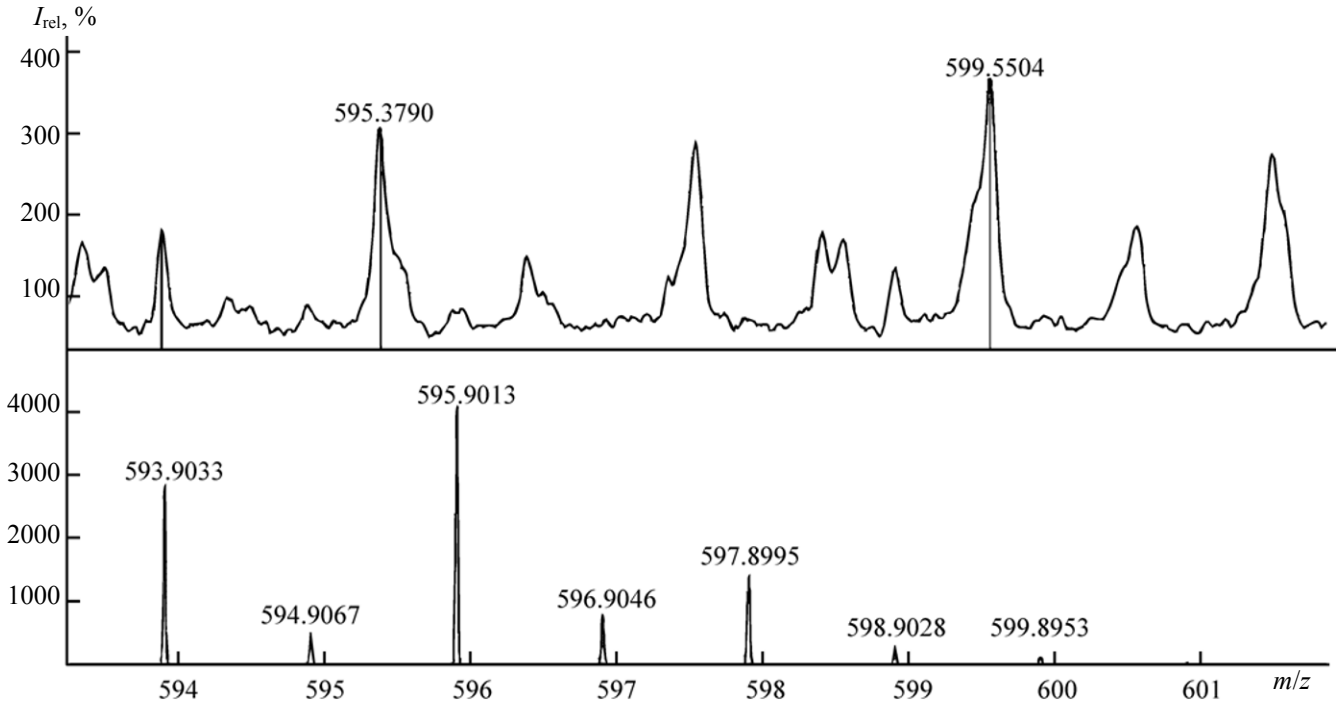


Fig. 1. HRMS spectrum of the metal complex **II** (ionization with H^+ ions).

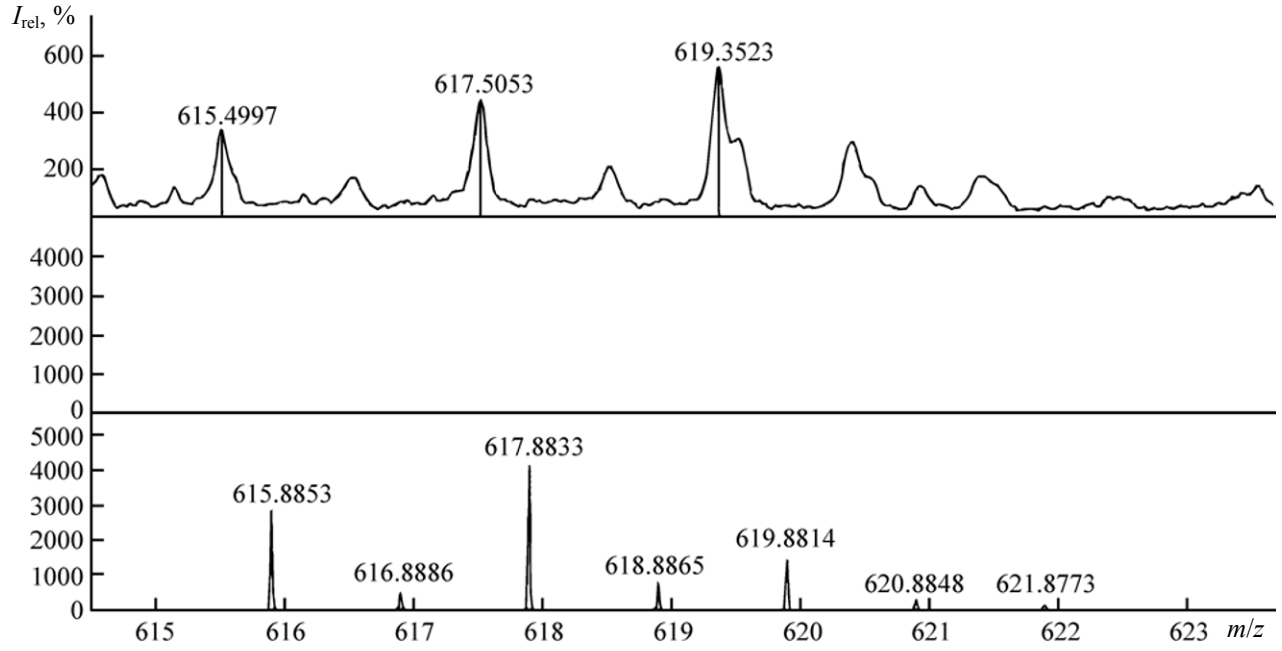


Fig. 2. HRMS spectrum of the metal complex **II** (ionization with Na^+ ions).

spectra were registered on a MicrOTOF II (Bruker Daltonics) instrument by electrospray ionization (solvent acetonitrile). The reaction progress was monitored by thin layer chromatography on Sorbfil plates eluting with a mixture 2-propanol–benzene–25% ammonia (10:5:2).

Chelate of *N*-(methylglucosamino-1-carbonothioyl)benzamide with copper(II) sulfate (1:1) (II). To a warm solution of 0.48 g (3 mmol) of anhydrous $CuSO_4$ in 90% ethanol was added dropwise a solution of 1.3 g (3 mmol) of *N*-(methylglucosamino-1-carbonothioyl)benzamide **I** in 50 ml of hot isopropyl alcohol under stirring. The mixture was kept for 12 h. The yellow precipitate was filtered off, dissolved in 50 ml of hot isopropyl alcohol, and the solution was filtered through a filter paper to separate a small amount of dark residue. Upon cooling, a yellow precipitate formed, which was filtered off, washed with cold isopropyl alcohol, and dried. Yield 0.33 g (56%), mp 127–130ºC.

Chelate of *N*-(methylglucosamino-1-carbonothioyl)benzamide with copper(II) sulfate (2:1) (III). To a warm solution of 0.87 g (2 mmol) *N*-(methylglucosamino-1-carbonothioyl)benzamide **I** in 50 ml of hot isopropyl alcohol was added dropwise with the stirring a solution of 0.16 g (1 mmol) of anhydrous $CuSO_4$ in 90% ethanol. The mixture was kept for 12 h. The dark green precipitate was filtered off, washed with isopropyl alcohol, and dried. Yield 0.71 g (70%), mp 143–146ºC.

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