SYNTHESIS AND STRUCTURE OF BIOLOGICALLY ACTIVE 3D-METAL COORDINATION COMPOUNDS WITH 4-ALLYLCHALCOGENSEMICARBAZONES AND THEIR DERIVATIVES

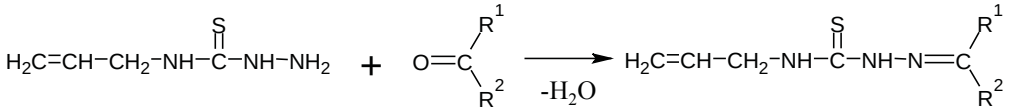
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Despite advances in the sphere of new drug synthesis, the synthesis of new substances with high biological activity remains an actual problem of modern chemistry. In recent years coordination compounds of biometals with thiosemicarbazones have been actively researched for solving this problem.[1]

In the present work a variety of 4-allylthiosemicarbazones of different aldehydes and ketones and their coordination compounds of some 3d-metals were synthesized in order to determine the main factors that have an influence on the biological activity of these substances.

The thiosemicarbazones synthesis may be described by the following reaction scheme:



These syntheses were carried out in hot ethanol solutions with 1:1 molar ratio of the initial substances. In cases of aldehydes ($R^1 \neq H$; $R^2 = H$) the reaction rate was fast enough. The hot reac-

tion mixture was heated for around 1h. After that it was cooled and the crystals of corresponding thiosemicarbazone appeared. After that crystals were collected by filtration, washed with cold ethanol, and dried in vacuo.

In cases of ketones ($R^1 \neq H$; $R^2 \neq H$) the reaction rate was too slow. In order to reduce required time for these syntheses a catalytic amount of anhydrous acetic acid was added to the reaction medium. It reduced the required time of heating to 3-5h.

The synthesized thiosemicarbazones were studied using elemental analyses, NMR spectroscopy, and X-ray analyses in order to determine their composition, structure, and purity. In all cases in ^{1}H-NMR spectra there were characteristic picks for the allyl moiety and the corresponding picks of the carbonyl fragment. The presense of the C=S bond was proved by the presence of a pick at around 177-179ppm in ^{13}C-NMR spectra.

These thiosemicarbazones have a wide range of reactive atoms and can form with metal ions coordination compounds with various composition, structure, and properties.

For 10 synthesized 4-allylthiosemicarbazones their structures were determined using X-ray analysis. X-ray diffraction analysis showed that in most cases the organic molecules have almost planar structure except the allyl moiety.

Synthesized 4-allylthiosemicarbazones react in hot ethanol solutions with 3d-metal salts. For the copper salts the synthesis was carried in most cases 1:1 molar ratio forming green or brawn coordination compounds that precipitate after cooling and were filtered and washed with small amounts of cold ethanol. In case of cobalt, iron, nickel salts the reaction was carried in 1:2 (salt:ligand) molar ratio. Mostly brawn resulting complexes were also filtered and washed with ethanol.

In the coordination compounds the 4-allylthiosemicarbazones in most cases bind to the central ions as tridentate ligands by sulfur atom of the thiosemicarbazide moiety, azomethin nitrogen atom, and one donor atom from the carbonyl moiety (mostly O, N). 4-allylthiosemicarbazones can be deprotonated in the composition of coordination compounds due to presence of some functional groups in the structure of carbonyl moiety that have acid properties or due to tautomerization from the thione form to the thiol form of the thiosemicarbazide moiety.

For 12 coordination compounds of copper, cobalt, iron, and nickel monocrystals were obtained after recrystallization from different organic solvents, such as ethanol, methanol, acetonitrile, DMSO, DMF etc. Their structures were determined using X-ray analysis. In most cases coordination number of copper in these coordination compounds equals to five. Copper complexes have monomeric, dimeric or polymeric structures. Coordination number of cobalt, iron, and nickel equals to six. They form octahedral monomeric coordination compounds.

The magnetochemical research showed that the synthesized coordination compounds of cobalt are diamagnetic. It indicates that ligands form an octahedron around the cobalt ions that are in the oxidation state +3.

The study of biological activity of synthesized compounds showed that many of them have bacteriostatic, bactericidal, and antitumor activity.

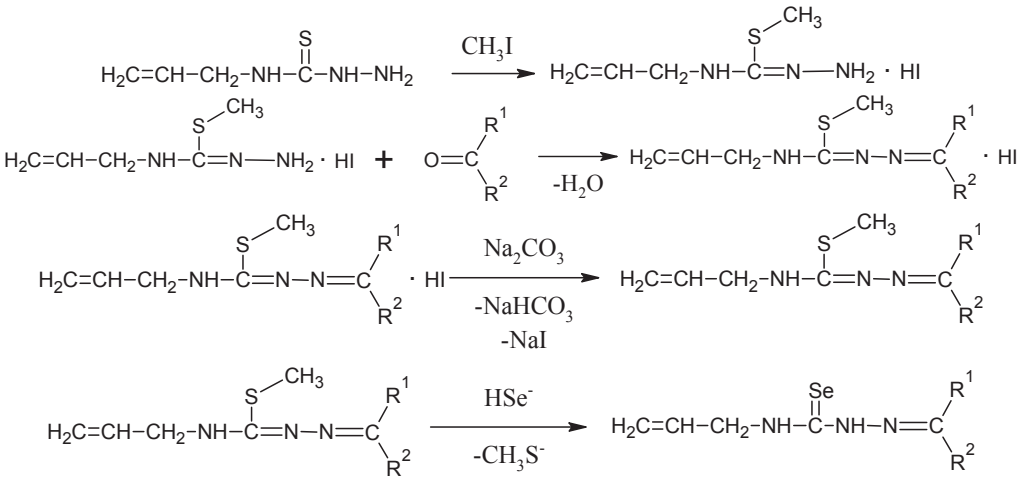
Antimicrobial activity was tested on a series of standard strains of gram-positive, gram-negative microorganisms and fungi. It was studied *in vitro* using the method of two-fold serial dilutions in liquid nutrient medium (meat infusion broth, pH = 7.0). The substances were dissolved in DMSO in such amounts that the solutions of concentration 10 mg/mL were obtained. The next dilutions were made using meat infusion broth.

In many cases coordination compounds of copper have lower values of the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) than the corresponding thiosemicarbazone. For the coordination compounds of other studied metals values of MIC and MBC are near the values for the free ligand. Usually 4-allylthiosemicarbazones with

electron-seeking substituents in the carbonyl moiety have better antimicrobial activity compared to whose with electron donating substituents. The change of an aldehyde to a ketone in the reaction of thiosemicarbazone synthesis in some cases also leads to the growth of antimicrobial activity. Thiosemicarbazones with heterocyclic carbonyl moiety usually have lower values of MIC and MBC. The acid residue also has an effect on the antimicrobial activity of the synthesized compounds. The activity usually decreases in the following way: $Cl^- > Br^- > NO_3^-$. These series of compounds is more active for the gram-positive microorganism and fungi than for the gram-negative microorganisms.

The antitumor activity of these 4-allylthiosemicarbazones and coordination compounds was tested on a series of tumor cells. As for the antimicrobial activity the antitumor activity of copper complexes in most cases is much higher than of the corresponding 4-allylthiosemicarbazone. Other metals in the composition of coordination compound lead to a much lower enhance of antitumor activity. The most active compounds of these series are active at the lower concentrations than substances currently used for treating these diseases.

From the literature source it is known that in many cases enhancement of biological activity is observed when going from thiosemicarbazones to the corresponding selenosemicarbazones. [2] Therefore, in the continuation of this work the 4-allylthiosemicarbazone was transformed into the 4-allylselenosemicarbazone. This process was carried out through a series of reactions that can be described by the following schemes:



The 4-allylselenosemicarbazone was obtained by the substitution of CH_3S^- group by the HSe^- from the sodium hydrogen selenide. [3] The primary screening of 4-allylselenosemicarbazone biological activity showed that it is more active than the corresponding 4-allylthiosemicarbazone. The received data indicates that the further research in this field is promising for searching new substances with high biological activity.

References

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