CHEMISTRY AND MATERIALS SCIENCE

DOI 10.51582/interconf.7-8.04.2021.061

Parfenova Irina Vladimirovna
1st year Master Student
Tyumen State University, Russian Federation

Trefilina Daria Alexandrovna
1st year Master Student
National Research University ITMO, Russian Federation

Maltseva Elizaveta Sergeevna
1st year Master Student
National Research University ITMO, Russian Federation

COORDINATION COMPOUNDS OF CYCLIC THIOUREAS WITH COPPER(I) CHLORIDE

Abstract. *Cyclic thioureas, which are represented by 4-thioxo [1,3,5] oxadiazocines and pyrimidine-2-thiones, are the objects of intensive research in scientific groups around the world. Coordination compounds based on them are still poorly studied, despite the intriguing variety of their biological properties. In this work, copper(I) chloride was chosen as the starting salt for the preparation of the target coordination compounds 4-thioxo [1,3,5] oxadiazocines and pyrimidine-2-thiones.*

Keywords: *cyclic thioureas; copper(i) chloride; coordination compounds;*

Cyclic thioureas, which are represented by 4-thioxo [1,3,5] oxadiazocines and pyrimidine-2-thiones, are the objects of intensive research in scientific groups around the world. Coordination compounds based on them are still poorly studied, despite the intriguing variety of their biological properties. In this work, copper(I) chloride was chosen as the starting salt for the preparation of the target coordination compounds 4-thioxo[1,3,5]oxadiazocines and pyrimidine-2-thiones.

Cyclic thioureas obtained by the Biginelli reaction [1] exhibit antitumor, antiviral, antihypertensive, antibacterial, antifungal, analgesic, antiarrhythmic and many other types of biological activity [2-4]. Due to such a wide range of biological properties manifested by these compounds, interest in them does not subside, but only increases.

The most common synthesis method is the classic variation of the reactants and Biginelli reaction conditions, but new possibilities have appeared. For example, with microwave radiation, the reaction proceeds much faster, but problems arise with the release of the target product, and the decomposition of thiourea also occurs [5].

Particularly successful is the direction of obtaining compounds using ultrasonic radiation. The products obtained in this way rarely need additional purification, the reaction time is reduced by almost 40 times, and the probability of the formation of by-products is practically zero, while the yield of the target molecule is 90–95% [6].

Methods for the synthesis of compounds that correspond to the postulates of "green chemistry" are always of particular importance. Often the reaction began to be carried out without solvents and catalysts, although nevertheless the reaction is catalyzed by environmentally friendly compounds, which are quite easy to handle, provide medium or high yields of the target products [7].

It was also found that the Biginelli reaction can be carried out in the complete absence of solvents and catalysts, that is, in a mixture of pure reagents. This achieves medium or high yields [8].

In the article [9], the author writes that, depending on the temperature, in the presence of a trichloroacetic acid catalyst (CCl_3COOH), two different compounds can be obtained. The choice of copper as a complexing agent was based on the biological activity of its compounds [10, 11]. Copper plays an important role in the human body and many other living organisms, being an essential trace element. Over time, medicine began to develop rapidly, and copper compounds became a promising direction of its development. The number of publications concerning the potential medical use of copper compounds has reached tens of thousands. Most inorganic copper salts are toxic. Nevertheless, copper, as a transition metal with an unsaturated d-shell, forms many coordination compounds. Complexation radically changes the

biological properties of copper compounds. Copper complexes can be used to selectively deliver it to diseased tissue sites or to alter the pharmacokinetics and/or pharmacodynamics of ligands. Such complexes are safer than complexes of many other transition metals (Zn, Cd, Hg), since when they are destroyed, copper can be absorbed by the body, and other elements can lead to accumulation and toxic effects.

Copper, both in its metallic form and in many chemical compounds, has antimicrobial activity. Copper ions exhibit nonspecific biocidal activity, although they are weaker than silver. Electrolytic ionization systems for copper and silver are used in many hospitals to reduce the amount of Legionella (the causative agent of Legionnaires' disease) in hot water pipes. Metals and alloys used in orthopedic implants can be alloyed with copper ions to reduce the risk of infection after prosthetics.

Due to the nonspecific toxicity of copper, as an antibacterial therapeutic agent, the metal should be administered in the form of complex compounds and not in the form of simple inorganic salts. The nature of the chelating agent, however, plays a very important role since there can be no simple correlation between antibacterial activity and complex stability [12]. It was reported that complexes of Cu(II) with various ligands have antibacterial and antifungal activity [12-13].

The widespread success of cisplatin (cis-$[Pt(NH_3)_2Cl_2]$) in the clinical management of various types of neoplasias has brought the coordination chemistry of metal-based drugs to the fore in the fight against cancer. Despite the high effectiveness of treatment of various types of cancer, treatment with cisplatin is limited by side effects, hereditary and acquired phenomena of resistance. These problems have prompted chemists to develop alternative compounds based on different metals with improved pharmacological properties. In this area, copper complexes have shown encouraging results. Copper-based complexes have been investigated on the assumption that endogenous metals may be less toxic to normal cells than cancerous ones. However, copper can also be toxic due to its redox activity and affinity for the binding sites where other metals must be present. The altered metabolism of cancer cells and the differentiated response of normal and tumor cells

to copper are the basis for the development of copper complexes with antitumor properties [14].

In the last decade, several authors have reported copper(II) complexes with potential anti-inflammatory properties. For the treatment of rheumatoid arthritis, chelating agents have been investigated that can facilitate the transport of Cu(II) ions to sites of inflammation. In the article [15], an attempt was made to design linear polyamine ligands that can activate copper in the body. Complexes cannot be too stable because they are quickly excreted in the urine unchanged. The ligands formed neutral complexes only at a pH above 7.0 and were too labile for systemic administration. Complexes with an additional nitrogen atom were significantly more stable, complexes were more lipophilic, but the stability was still optimal [15]. Promising results for dermally absorbed copper complexes have been achieved for several ligands. The compounds show selectivity for copper ions, good stability at physiological pH, low renal clearance, which indicates possible skin absorption. An important feature of compounds (9) and (10) is that they form more labile complexes with Ca^{2+} and Zn^{2+} ions [16]. It is also reported [16, 17] about skin-absorbed copper complexes. The compounds showed an approximately 24 hour biological half-life that is desirable for potential anti-inflammatory drugs. Modeling the behavior of the complexes in blood plasma showed that the concentration of Ca^{2+} and Zn^{2+} ions is sufficient to compete with Cu^{2+}, even if the ligand is more selective with respect to copper ions. Therefore, the ligand can promote the transport of copper through the skin and then release Cu^{2+} ions in the blood.

The aim of this work is to synthesize, and study new coordination compounds based on 4-thioxo[1,3,5]oxadiazocines and pyrimidine-2-thiones with copper(I) chloride.

The composition and structure of the isolated ligands and the corresponding complexes were confirmed using IR, UV, and NMR spectroscopy. The structure of one of the complexes has been proved by the method of X-ray structural analysis. The rest of the coordination compounds can be considered isostructural based on general regularities in the corresponding spectra. The biological activity of the

complexes of 4-thioxo[1,3,5]oxadiazocines in relation to the fluorescent strain of *Escherichia coli* was revealed.

References:

1. P. Biginelli. (1891). Ueber Aldehyduramidedes Acetessigathers. *Chem. Ber.*, 24, 1317-1319.
2. Pecorari P. et al. (1991). Synthesis and biological activity of pyrimido[2,1-b][1,3]thiazine, [1,3]thiazino[3,2-a]purine and [1,2,3]triazolo[4,5-d][1,3]thiazino[3,2-a]pyrimidine derivatives and thiazole analogues. *Farmaco (Societa chimica italiana*, 46, 899-911.
3. Dave C. G. et al. (1986). Pyridopyrimidines: part III – synthesis and analgesic activity of 4-aminopyrido[2, 3-d]pyrimidines. *Indian Journal of Pharmaceutical Sciences,* 48.
4. Kappe C. et al. (2004). The Biginelli dihydropyrimidine synthesis. *Org React*., 63, 1–7.
5. Stadler A. (2000). Microwave-mediated Biginelli reactions revisited. On the nature of rate and yield enhancements. *Journal of the Chemical Society, Perkin Transactions, 2*, 7, 1363-1368.
6. Zhidovinova M.S. (2003). *Izv. RAS. Ser. Chem,* 11, 2389.
7. Lin H. et al. (2000). An efficient synthesis of 5-alkoxycarbonyl-4-aryl-3, 4-dihydropyrimidin-2 (1H)-ones catalyzed by KSF montmorillonite. *Molecule*, 5, 12, 1240-1243.
8. Wang C. et al. (2006). Synthesis of (E)-alkenes via hydroindation of CC in $InCl_3$–$NaBH_4$ system. *Tetrahedron,* 62, 33, 7712-7717.
9. Taslimi P. et al. (2017). Synthesis of new cyclic thioureas and evaluation of their metal-chelating activity, acetylcholinesterase, butyrylcholinesterase, and carbonic anhydrase inhibition profiles. *Journal of biochemical and molecular toxicology*, 31, 7, 21897.
10. Hosty´nek J. (2006). Human stratum corneum penetration by copper: in vivo study after occlusive and semi-occlusive application of the metal as powder. *Food Chem. Toxicol.* 44, 1539–1543.
11. Azenha M. (1995). Organic ligands reduce copper toxicity in Pseudomonas syringae. *Environ. Toxicol. Chem*, 14, 369–373.
12. Golcu¨ A. (2005). Synthesis of Binuclear Copper(II) Complex of the Antihypertensive Drug Pindolol. *KSU J. Sci. Eng.*, 8, 4–9.
13. Shakir M. (2006). Synthesis, characterization of complexes of Co(II), Ni(II), Cu(II) and Zn(II) with 12-membered Schiff base tetraazamacrocyclic ligand and the study of their antimicrobial and reducing power. *Spectrochim. Acta. A,* 65, 490–496.
14. Singh B.K. (2008). Copper(II) complexes with bioactive carboxyamide: synthesis, characterization and biological activity. *Spectrochim. Acta. A*, 70, 758–765.

15. Zvimba J.N. (2007). Copper chelating anti-inflam-matory agents; N1-(2-aminoethyl)-N2-(pyridin-2-ylme-thyl)-ethane-1,2-diamine and N-(2-(2-aminoethylamino)ethyl)picolinamide: an in vitro and in vivo study. *J. Inorg. Biochem. 101*, 148–158.
16. Odisitse S. (2009). In vitro and in vivo studies of thedermally absorbed Cu(II) complexes of N_5O_2 donorligands – Potential anti-inflammatory drugs. *Inorg. Chim. Acta.,* 362, 125–135.
17. Azenha M. (1995). Organic ligands reduce copper toxicity in Pseudomonas syringae. *Environ. Toxicol. Chem.*, 14, 369–373.