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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

SYNTHESIS, ANALYTICAL AND BIOLOGICAL STUDY OF TRANSITION METAL COMPLEXES OF SOME NITROGEN AND SULPHUR-CONTAINING HETEROCYCLIC COMPOUNDS

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Field of science:	Chemistry
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GENERAL CHARACTERISTICS OF THE WORK

Relevance and degree of development of the topic. In recent years, the synthesis of new urea and thiourea derivatives and the study of their analytical capabilities and biological properties have occupied a special place in the field of refined organic synthesis. It is possible to find many scientific studies in this field in the world literature. However, in the literature there is limited information on the synthesis, transformations, and detailed study of them as organic reagents and the biological activities of this group cheating compounds by comparative methods.

Thioureas have a wide range of applications in analytical chemistry as organic reagents. They have the ability to form stable complex compounds with specific metal ions, which allows them to be selectively separated from mixtures. These compounds are used in the selective extraction of copper from ores in the presence of other metals, and in the separation of gold, silver, platinum, and other precious metals from spent catalysts and other sources. Thioureas are used to separate nickel and cobalt ions from laterite (a polymetallic ore containing, in addition to iron and aluminum, valuable elements such as nickel, cobalt, and manganese) ores.

This class of reagents have particular importance in the photometric and extraction photometric determination of a number of metals.

Various derivatives of thioureas also play a very important role in the activity of living organisms. Aryl- and heteroaryl ureas are found in the composition of drugs recommended for atherosclerosis, asthma, and other respiratory tract infections. Some urea and thiourea derivatives are also used in the treatment of eye diseases and the prevention of pathological processes, and in the treatment of oncological diseases.

The use of thiourea derivatives in the determination and concentration of metals, as well as their synthesis and application of them since they have important bioactivity are of the interest. Therefore, the development of a method for the determination and concentration of metals based on thioureas and the determination of the biological activity of their complexes is of relevance.

Object and subject of the study. The object of the study is thiourea and its N-substituted derivatives, which are used as synthons in the field of refined organic synthesis. In order to demonstrate the prospective importance of these reagents in organic and analytical chemistry, some transition metal complexes were obtained on their basis, and their application possibilities were investigated. As a subject of the study, highly selective photometric and extraction photometric determination methods were developed based on these complexes. At the same time, the possibility of using these organic compounds to increase the sorption capacity of synthetic sorbents was determined. The study of the structures of the compounds and some of their complexes by quantum chemical calculations and X-ray structural analysis, also investigation of the antioxidant, physiological activities and especially analytical properties of this class of substances and the finding of a certain relationship between their structures and properties, have provided additional advantages to the subject of the research.

Goals and objectives of the research. The main goal of the research work is to obtain some transition metal complexes based on thiourea and its derivatives, as well as other nitrogenous heterocyclic compounds, to study their structures and individual functional properties in detail, to develop and prepare different determination methods selected by analytical parameters for their determination in natural and industrial objects, and to study various application possibilities.

To achieve the set goal, the following issues were solved:

- synthesis of the studied ligands and their transition metal complexes;
- study of the structures of the synthesized ligands and their complexes with some metals;
- spectrophotometric study of colored complexes formed by the studied ligands with a number of metals: study of optimal conditions, molar absorption coefficient, concentration interval subject to Beer's law, ratio of components in the composition of the complexes;
- modification of the studied sorbents with N,N'-diisopropyl

(R_5) reagent in order to increase the sorption capacity;

- development of highly selective photometric and extraction photometric determination methods for copper (II), nickel (II) and silver (I), and their application for determination in natural and industrial objects;

- study of the biological and antioxidant additive properties of synthesized complex compounds.

Research methods. In carrying out the research work, X-ray Structural Analysis (RSA), X-ray Phase Analysis, Nuclear Magnetic Resonance (NMR), Infrared Spectroscopy (IR), quantum chemical calculations, thermal and spectrophotometric analysis methods were used.

The main provisions of the defense:

- new complex compounds were synthesized based on the ligands taken as the object of research, the probable structures of the complexes formed by 1-[1-methyl-2-(methylamino) ethyl] thiourea with Cu (II) and Ni (II) were determined by quantum chemical calculations based on functional density theory, amongside , during the study of the X-ray structure of the copper complex of 4-((2,4-dioxopentan-3-yl) diazenyl) benzoic acid, it was found that there are several intramolecular and intermolecular interactions that contribute to the stability of the crystal structure with a detailed analysis of hydrogen bonding;

- the binary and multi-ligand complexes formed by the ligands with Ag(I), Ni(II) and Cu(II) were studied and their main spectrophotometric properties were characterized, and the effect of foreign ions and scavengers on the complex formation reactions of these transition metals was determined;

- among the methods developed for the photometric and extraction photometric determination of the mentioned metals, methods with high selectivity were selected and considered appropriate for their application for determination in natural and industrial objects.

Scientific novelty of the research:

- 8 new complex compounds unknown in the literature were synthesized based on the reagents studied.

- Based on the functional density theory, the theoretical parameters of 1-[1-methyl-2-(methylamino) ethyl] thiourea, as well as its complex with copper and zinc, were calculated and their probable structures were determined.
- The crystal structure of the complex ($C_{26}H_{34}CuN_6O_{10}$) formed by copper 4-((2,4-dioxopentan-3-yl) diazenyl) benzoic acid in the presence of ethylenediamine was studied by X-ray structure analysis and it was determined that during the crystallization of the complex compound, one molecule of ethylenediamine and two molecules of water coordinate around the complexing agent. The nitrogen atoms of the ethylenediamine molecules form chemical bonds with two different copper atoms, resulting in the formation of a one-dimensional polymer structure located along the "a" axis. Then, one-dimensional polymer molecules are transformed into a three-dimensional geometric shape due to hydrogen bonds formed with water molecules.
- Spectrophotometric indicators that characterizing the main analytical parameters of the binary complexes formed by silver, copper and nickel with different reagents and complex compounds with various ligands obtained in the presence of surfactants have been found.
- Based on the results obtained from the determination of the physical and chemical indicators of complex compounds, it has been confirmed that complex compounds with various ligands have high analytical properties for the spectrophotometric determination.
- The extraction capabilities of the complex compound formed by nickel with 1-(2-anilino-1-methylethyl) thiourea in various solvents have been studied and it has been determined that when the complex of nickel is dissolved in 1-butanol, it has a higher extraction yield.
- Photometric and extraction photometric determination methods of copper (II), nickel (II) and silver (I) have been developed.
- Previously synthesized sorbents were modified with N,N'-diisopropyl thiourea, which increased their sorption properties.
- A convenient method was developed for the determination of silver, copper and nickel ions compared to the methods known in the

literature.

- Four of the synthesized complex compounds were found to exhibit high biological activity and antioxidant properties. When investigating the physiological activity of new compounds containing nitrogen in their molecules on acetylcholinesterase and butyrylcholinesterase enzymes, it was found that these substances are target compounds with high potential for the creation of new drugs or biological additives in the treatment of some global diseases, including neurological diseases. Among them, especially N-substituted thiourea derivatives can play the role of the most active inhibitor of the cholinesterase enzyme in the treatment of Alzheimer's disease.

Theoretical and practical significance of the study. Comparative analyses from simple to complex were conducted regarding the analytical properties and bioactivity of individual ligands and their metal complexes depending on their structure, and it was determined which functional groups and fragments exhibit potential effects.

The analytical, biological and antioxidant properties of the synthesized complex compounds were studied and their potential use in industry and medicine was investigated. The developed new methods can be used for the separation and determination of nickel from natural and wastewater samples.

Approbation and implementation. 11 theses, 5 articles and 1 patent related to the topic of the dissertation were published. The materials of the dissertation were reported and discussed at the following conferences:

- VIII Republican Scientific Conference dedicated to the 85th anniversary of the Department of “Analytical Chemistry” (Baku, 2020).
- XIV International Scientific Conference of Doctoral Students, Masters and Young Researchers “Current Problems of Chemistry” dedicated to the 98th anniversary of the National Leader H. Aliyev (Baku, 2021).
- Republican Scientific Conference on “Various Purpose Organic Substances and Compositional Materials” dedicated to the 110th anniversary of Academician Ali Musa oglu Guliyev (Baku, 2022).

- III Republican Scientific Conference “Ecology and Soil Sciences in the XXI Century” dedicated to the 99th anniversary of the birth of National Leader Heydar Aliyev (Baku, 2022).
- International Scientific Conference of “Modern Problems of Theoretical and Experimental Chemistry” dedicated to the 90th anniversary of Academician Rafiga Aliyeva (Baku, 2022).
- XIX International Scientific Conference of the “Spectroscopy of Coordination Compounds” (Krasnodar, 2022).
- International Scientific Conference on “Current Problems of Modern Natural and Economic Sciences” dedicated to the 101st anniversary of the birth of the national leader Heydar Aliyev (Ganja, 2024).
- III Republican Scientific Conference on “Chemistry and Chemical Technology” dedicated to the 101st anniversary of the birth of the national leader H. Aliyev (Baku, 2024).
- International Scientific Conference of the “Modern Problems of Macromolecular Compounds Technology” dedicated to the 60th anniversary of the Department of Technology of Organic and High-Molecular Compounds (Baku, 2024).
- XX International Scientific Conference of the “Spectroscopy of Coordination Compounds” (Krasnodar, 2024).

The name of the organization where the dissertation work was performed. The dissertation work was mainly performed at the department of Analytical Chemistry, Faculty of Chemistry, Baku State University.

The applicant's personal contribution to the research conducted. The applicant directly participated in the implementation of the research work. He collected and analyzed the latest literature data on the topic, made generalizations, carried out the synthesis of new complexes based on thiourea derivatives, spectrophotometric studies of Ag (I), Cu (II), Ni (II) complexes. He put forward his arguments in the articles related to the research work.

The total volume of the dissertation is indicated by the mark, with the volume of the structural sections of the dissertation separately indicated.

The dissertation consists of an introduction, four chapters, conclusion and references, written in A4 format, 201 pages. The dissertation work consists of 177652 characters. The results of the research are presented in 63 figures and 36 tables.

The first chapter (513376 characters) presents the literature data of recent years and their analysis.

The second chapter (44016 characters) presents the preparation of metals, devices, synthesis of reagents and complexes, their study by physicochemical and quantum chemical analysis methods.

The third chapter (41113 characters) presents the study of complex compounds formed by N-substituted thioureas with a number of metals.

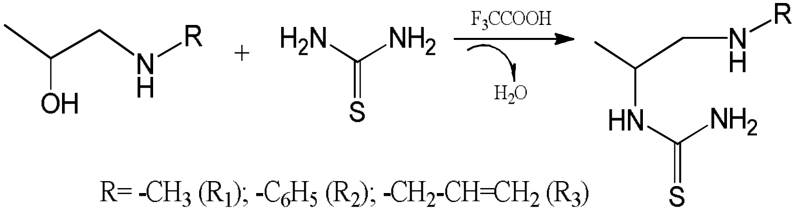
The fourth chapter (25404 characters) presents the development of methods for the determination of silver (I) and nickel (II) using binary and mixed ligand complexes with N-substituted thioureas, and the results of the analysis of the antioxidant and biological activities of reagents and their metal complexes.

SUMMARY

Synthesis of ligands

Five ligands containing a thiourea fragment in the molecule were synthesized using a method known from the literature. These are 1-[1-methyl-2-(methylamino) ethyl] thiourea (R_1), 1-(2-anilino-1-methylethyl) thiourea (R_2), 1-[2-(allylamino)-1-methylethyl] thiourea (R_3), 2,6-Bis(phenyl)hexahydro-1,3,5-triazine-4-thione (R_4), N,N'-diisopropyl thiourea (R_5).

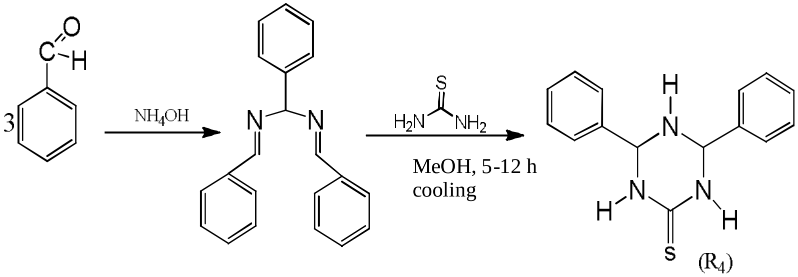
First of all, N-substituted thioureas - 1-[1-Methyl-2-(methylamino)ethyl]thiourea, 1-(2-anilino-1-methylethyl)thiourea and 1-[2-(allylamino)-1-methylethyl]thiourea) are obtained from the interaction of thiourea with amino alcohols (Scheme 1):



R= -CH_3 (R_1); -C_6H_5 (R_2); -CH_2-CH=CH_2 (R_3)

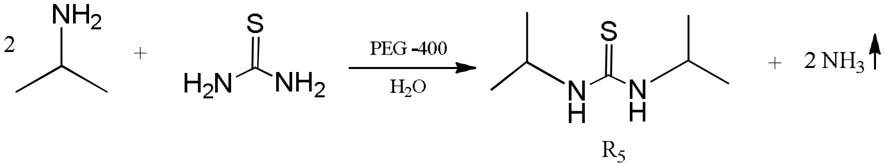
Scheme 1. *Synthesis of N-substituted thioureas (R_1-R_3).*

The reaction of benzaldehyde with ammonia solution followed by thiourea gave 2,6-*bis*(phenyl)hexahydro-1,3,5-triazine-4-thione (R_4) in high yield (85%). (Scheme 2):



Scheme 2. *Synthesis of 2,6-Bis(phenyl)hexahydro-1,3,5-triazine-4-thione (R_4)*

The synthesis of N,N'-diisopropyl thiourea (R_5) was also carried out according to a known method. Thus, using PEG-400 (polyethylene glycol 400) catalyst, a reaction was carried out between thiourea and diisopropylamine in a 2:1 ratio for 36 hours. Then the obtained solid mass was washed, filtered and dried. The reaction scheme is as follows (Scheme 3):



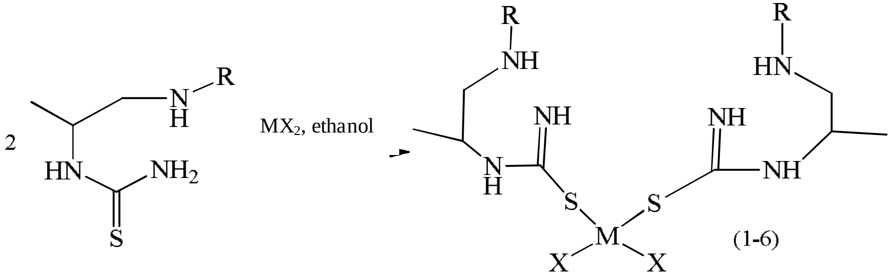
Scheme 3. *Synthesis of N,N'-diisopropyl thiourea (R_5)*

The structures of these ligands were analyzed using IR, NMR spectral analysis methods and their spectral data were confirmed to be in agreement with literature data.

As another nitrogen-containing ligand, 4-((2,4-dioxopentan-3-yl) diazenyl) benzoic acid (R_6) was taken as a ready reagent.

Synthesis of transition metal complexes

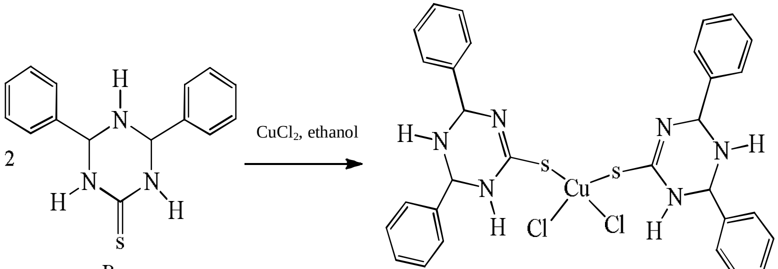
New complexes of N-substituted thioureas with a number of transition metals have been obtained (Scheme 4):



R= $-CH_3$ (R_1); $-C_6H_5$ (R_2); $-CH_2-CH=CH_2$ (R_3)
M= Cu(II), Co (II), Ni (II), Zn (II);
X=Cl
Complex: CuR_1(1); CuR_3 (2); CoR_1 (3); CoR_3 (4); NiR_1 (5); ZnR_3(6)

Scheme 4. *Synthesis of new complexes of N-substituted thioureas with a number of transition metals*

The synthesis reaction of 2,6-Bis(phenyl)hexahydro-1,3,5-triazine-4-thione (R_4) with a copper complex is reflected in the following scheme (Scheme 5):



R_4

Complex: CuR_4 (7)

Scheme 5. *Synthesis of the copper complex of 2,6-Bis(phenyl)hexahydro-1,3,5-triazine-4-thione*

To obtain clear information about their structure, new complexes were studied using IR spectral analysis, X-ray phase analysis, and also temperature stability thermogravimetric analysis. According to the results of IR spectral analysis, the main characteristic frequencies are given in Table 1:

Table 1. Main characteristic frequencies observed in infrared spectral analysis of synthesized complexes

Groups		Literature (sm^{-1})	Complexes (sm^{-1})					
			CoR_1	NiR_1	CuR_1	CoR_3	ZnR_3	CuR_3
			1	**2**	**3**	**4**	**5**	**6**
Defamation	ν NH_2	1650-1580 900-650	646 739 846 878	647 708 741 846 878	665 672 722	692 720 749 828 809 855	697 721 753 808 829 889	692 746 790
	ν R_2NH	1650-1550	1560	1556		1587	1586	1592
Valence	ν R_2N-H	3500-3300				3419	3429	
ν CH_2		2940-2915 2870-2845 1480-1440	2932 1459	2931 1458	1463	1459	1459	1463
ν C=S		1400-1100	1127 1164 1242 1311 1365	1128 1165 1240 1312 1364	1156 1377	1153 1168 1272 1294 1313 1377	1150 1231 1275 1297 1316 1376	1154 1377
ν CH_3		2975-2950 2885-2860 1470-1435 1385-1370	1459 2973	1458 2874 2972	2853 1377	1463 1377 2968	1459 1376 2965	1463 1377

The purpose of X-ray spectral analysis, which is a polycrystalline analysis method, is to confirm the formation of the complex and also to give a certain idea about the crystal structure formed. Although the degree of crystal formation in the synthesized metal complexes varies, it has been found that crystals are formed in most cases. It has been proven as a result of the analysis that crystals with a low degree of symmetry, which is characteristic of this type of compounds, are obtained.

According to the results of X-ray phase analysis, these compounds are individual crystalline substances. The appearance of intense peaks at a small angle indicates that this compound has a low syngony.

These synthesized complex compounds were also studied by the thermal analysis method. As a result of the analysis, it was found that the decomposition proceeds in 2 stages. In the initial stage, after the separation of the thiourea molecule, the second stage of the decomposition that continues corresponds to the separation of chlorine. The final product of the decomposition was metal oxide. The decomposition of other complexes also occurs in two stages: the first stage corresponds to the release of the reactant, and the second stage corresponds to the release of chlorine. In all cases, the final product of the decomposition is metal oxide.

The thermogram curve of the complex of thiourea with copper metal is given in the graph below (Figure 1):

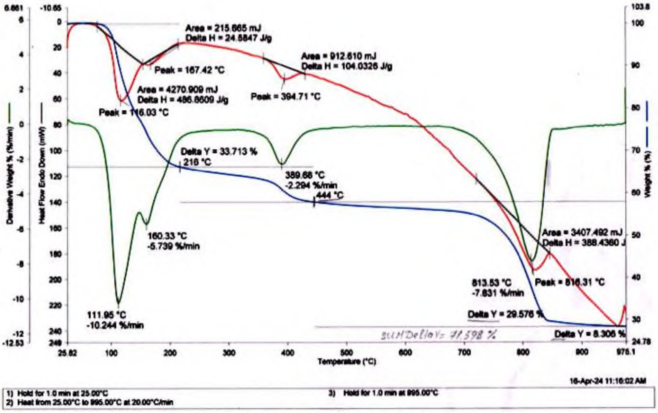


Figure 1. Thermogram of the $Cu(C_5H_{13}N_3S)Cl_2$ complex

Molecular structure analysis of the copper complex of 4-((2,4-Dioxopentan-3-yl) diazenyl) benzoic acid

The synthesis of the ethylenediamine copper complex of 4-((2,4-Dioxopentan-3-yl) diazenyl) benzoic acid is shown in the following scheme (Scheme 6):

$$2C_{11}H_{12}O_4N_2 + (CH_3COO)_2Cu \times H_2O + C_2H_6N_2 \longrightarrow C_{26}H_{34}CuN_6O_{10}$$

Scheme 6. *Synthesis of the copper complex of 4-((2,4-Dioxopentan-3-yl)diazenyl)benzoic acid*

The synthesis method is also simple and convenient. Thus, the ligand (4-((2,4-dioxopentan-3-yl) diazenyl) benzoic acid) and the metal salt ($(CH_3COO)_2Cu$) were taken from the same concentration solutions in a ratio of 1:2 and mixed with a magnetic stirrer for 30 minutes, then a solution of 2 mol of ethylenediamine in alcohol was added to it and stirred for 1 hour in a heater equipped with a reflux condenser.

After the synthesis, the colored solution obtained was poured into a beaker and stored. After 48 hours, needle-shaped crystals were formed at the bottom of the container.

Crystal structure analysis - The crystal structure analysis of the $C_{26}H_{34}CuN_6O_{10}$ compound was carried out using a transparent, light green, prism-shaped crystal with dimensions of $0.10\times0.04\times0.03$ mm^3. The analysis was performed at a constant temperature (111 K) using an XtaLAB AFC11 diffractometer and a MoKα-radiation monochromator, ω scanning radiation ($\lambda = 1.54184$ Å).

The ShelXT program was used to solve the structure. Hydrogen atoms were geometrically calculated and their positions were refined using a sliding model, and the positions of selected hydrogen atoms were freely refined.

Analysis of crystallographic parameters shows that $C_{26}H_{34}CuN_6O_{10}$ belongs to the P-1 (№2) space group and crystallizes in the triclinic syngony. The dimensions of the elementary lattice: a = 7.3645(3) Å, b = 14.2102(8) Å, c = 15.2334(9) Å, α = 110.626(6)°, β = 96.088(4)°, γ = 99.886(4)°, Volume (V) = 1445.67(15) $Å^3$.

The density of the crystal is 1.503 g/cm^3, and the absorption coefficient (μ) is 1.647 mm^{-1}. The degree of correspondence of the analyzed crystal to the true structure is R= 0.0603, which indicates that the structure is accurately determined.

During the crystallization of the complex compound, in addition to two molecules of $C_{12}H_{13}O_4N_2$, one molecule of ethylenediamine and two molecules of water are coordinated around the complexing agent. In this case, the composition of the elementary lattice is as follows: $C_{26}H_{34}CuN_6O_{10}$.

Note that each copper atom forms a bond with two nitrogen atoms of two ethylenediamine molecules, two oxygen atoms of the -COOH group of two $C_{12}H_{13}N_2O_4$ molecules, and one oxygen atom of a water molecule. Thus, the coordination number of each copper atom is five, and the coordination polyhedron has the shape of a tetragonal pyramid. The base of this pyramid is close to a slightly deformed square, and here the Cu-N and Cu-O distances are in the range of 1.98-2.01 Å. The distance from the oxygen of the water molecules located at the top of the coordination pyramid to the copper is larger and is 2.29 Å. The nitrogen atoms of the ethylenediamine molecules combine with two different copper atoms, resulting in a one-dimensional polymer structure located along the "a" axis (Figure 2).

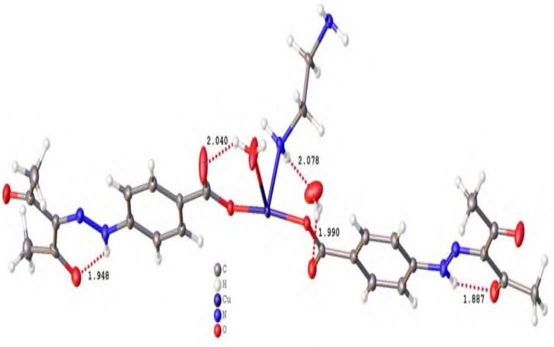


Figure 2. Molecular structure$C_{26}H_{34}CuN_6O_{10}$

As it turns out, one more water of crystallization molecule was required to stabilize the crystal structure, in which the main molecules interact with hydrogen bonds. The complex is characterized by three intramolecular hydrogen bonds: N(1) - H...O(3), N(3) - H...O(8) and N(3) - H...O(8), O(9) - H...O(5).

Indeed, the coordination forms a hydrogen bond with the oxygen of the neighboring molecule (O9-H...O4). The water of crystallization molecule (O10) forms hydrogen bonds with the oxygen atoms of the main O1 and N5 molecules: O10-H...O1 and O10-H...N5. Thus, the one-dimensional polymer molecules mentioned above are combined into a three-dimensional framework due to hydrogen bonds formed with water molecules. The significant bond lengths are Cu1–O2 = 1.993(3) Å; Cu1–O6 = 1.980(3) Å; Cu1–N6 = 2.005(3) Å; Cu1–N5 = 2.011(4) Å and Cu1–O9 = 2.286(4) Å.

The variation of the bond angles around Cu1 between 87.15(13)° and 168.56(12)° clearly indicates that these angles deviate slightly from the binary state. This geometric distortion can be explained by the Jahn–Teller effect, which is common to copper (II) complexes.

Hydrogen bonding analysis revealed the presence of several intramolecular and intermolecular interactions that contribute to the stability of the crystal structure. The main interactions include hydrogen bonds (O-H and N-H) involving oxygen and nitrogen atoms with distances between 0.82 and 1.24 Å (Figure 3).

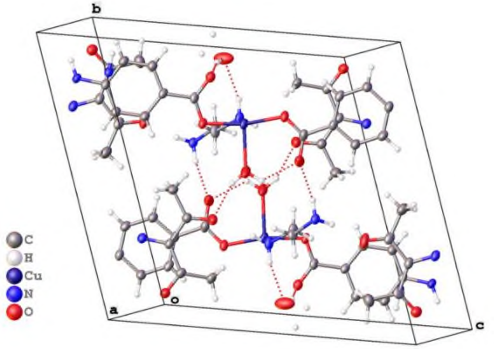


Figure 3. Crystal structure of $C_{26}H_{34}CuN_6O_{10}$

The isotropic displacement parameters (Ueq) for non-hydrogen atoms were moderate, indicating a stable and robust molecular lattice at low temperatures. The largest thermal displacement parameters were observed for peripheral oxygen and hydrogen atoms.

Quantum chemical calculations

Quantum chemical calculations are one of the most attractive methods for the design of new molecules and the study of their structural, molecular, and reactivity properties. Thiourea and its $CuCl_2$ complex were studied by DFT using the hybrid potential B3LYP with the Gaussian09 software package. A broad basis set of 6–31++G(d,p) with polarization and diffusion functions was used for the calculations. The optimized structures of the studied compounds, molecular electrostatic potential (MEP) maps, highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) contours were visualized in GaussView.

Quantum chemical study of the $CuCl_2$ complex of 1-[1-Methyl-2-(methylamino)ethyl] thiourea

The optimized structures of the complex formed by 1-[1-Methyl-2-(methylamino)ethyl]thiourea with $CuCl_2$ are shown below (Figure 4):

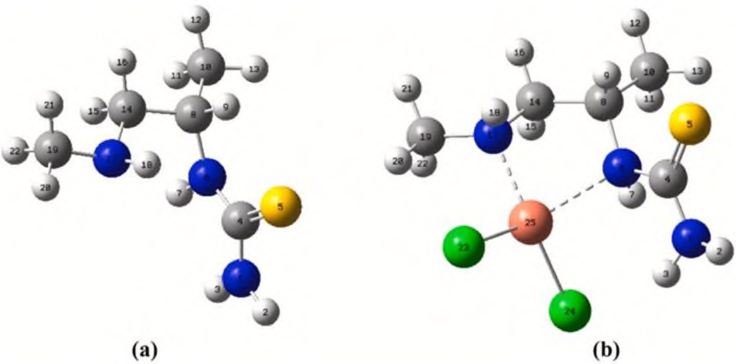


Figure 4. Optimized structures of [1-Methyl-2-(methylamino)ethyl]thiourea (a) and its complex with $CuCl_2$ (b)

As can be seen from the presented data, the Cu25 – N6 and Cu25-N17 coordination bonds take the values of 2.2978 and 2.0471 Å, respectively; they differ from each other by only 0.25 Å. It was found that the optimization of the complex leads to the formation of a five-membered ring, as a result of which there are noticeable changes in the values of the dihedral angles C4N6C8C10 and C4N6C8C14 by

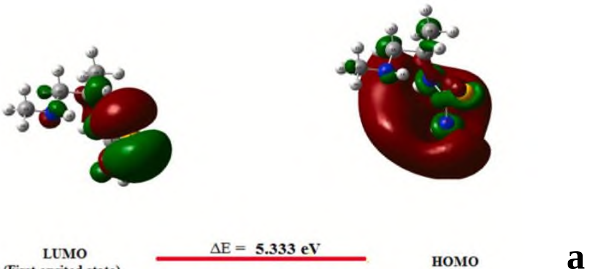
48◦, S5C4N6C8 by 25.1◦, N1C4N6C8 by 23◦, H3N1C4N6 by 18.5◦, H2N1C4N6 and C8C14N17C19 by 8◦. As a result of the deformation of the indicated angles, the S5 atom, together with the C4 and N6 atoms, leaves the initial plane formed by this atom and changes its position in space, approaching the atoms forming the five-membered ring.

Atomic charges

In this study, Mulliken population analysis was performed on atomic charges. It was found that as a result of the formation of the complex, there is a decrease in the charge of C4 (0.038059e), N6 (0.345071e), C14 (0.031575e), N17 (0.293518e) atoms and an increase in the charge of N1 (0.084948 e), H3 (0.026185e), S5 (0.127656 e), H7 (0.096239 e), C8 (0.173059 e) atoms, which leads to an increase in the dipole moment values of 3.578 Debye and polarizability of 60.374 eV in the complex compared to thiourea.

HOMO and LUMO analysis

HOMO-LUMO analysis was performed to explain the charge transfer in the molecule. The HOMO is an orbital that acts primarily as an electron donor, while the LUMO is an orbital that acts primarily as an electron acceptor. The frontier molecular orbitals for the thiourea complex $CuCl_2$ have been calculated and their schematic representation and corresponding positive and negative regions are shown below (Figure 5).



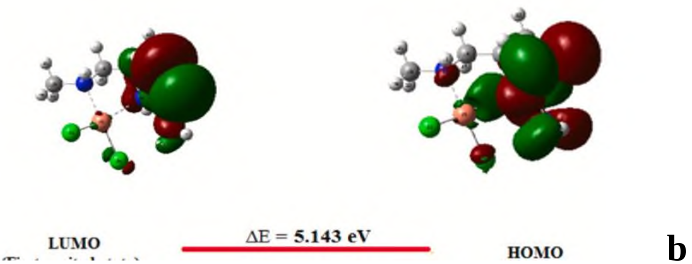


Figure 5. Frontier molecular orbitals for 1-[1-Methyl-2-(methylamino)ethyl]thiourea (a) and its complex with $CuCl_2$ (b)

For both compounds, the HOMO and LUMO are located on most of the methyl groups and, in the case of thiourea, on the N17-C19, C14-C8 bonds, and in the case of the complex, on the N17 atom and the CH_2 group atoms. For the complex, the HOMO is also located towards the N6 - Cu25 coordination bond. As can be seen from the presented data, the areas occupied by the frontier molecular orbitals in the complex are significantly narrowed compared to the thiourea molecule.

Study of molecular electrostatic potential

The molecular electrostatic potential surface shows the shape, size and charge distribution in the molecule. Each molecular electrostatic potential surface has a color scale indicating negative and positive values, which allows us to determine the location of the positive and negative electrostatic potential in the molecule. Molecular electrostatic potential maps for thiourea and its complex with $CuCl_2$ are shown in the figures below (Figure 6).

In the molecular electrostatic potential map of thiourea, the regions with negative potential values are concentrated on the nitrogen atoms of the NH and NH_2 groups, and the region with the highest negative potential, with a lowest value of −6.807e-2, is located on the S5 atom. The regions with positive potential are concentrated on the hydrogen atoms of the NH_2, CH_2, CH_3 groups, and the region with the highest positive potential, with a value of 6.807e-2, is located on the hydrogens of the NH groups, H7 and H18.

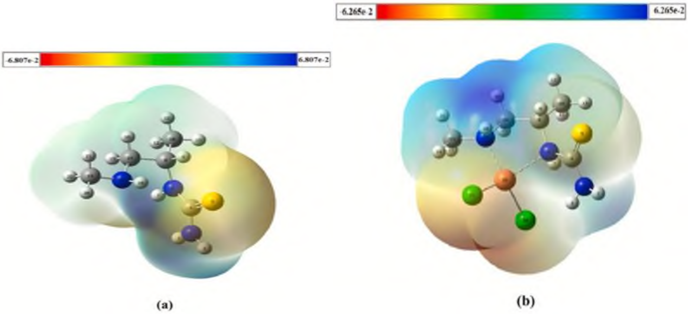


Figure 6. Molecular electrostatic potential map for 1-[1-Methyl-2-(methylamino)ethyl]thiourea (a) and its complex with $CuCl_2$ (b)

The formation of the thiourea complex with $CuCl_2$ transfers the highest negative potential to the chlorine atoms Cl23 and Cl24, with a lowest value of −6.265e-2, and the highest positive potential, with a highest value of 6.265e-2, to the hydrogens of the methylene group H15, H16, H20, H21, H22. The mentioned sites of the complex play an important role in the interactions of electrostatic and hydrogen bonds.

Thus, with the formation of coordination bonds, the geometric, energy and charge differences between thiourea and its complex increase significantly. It was found that new non-valent, electrostatic and hydrogen bonding interactions were formed in the complex. These changes make weak forces stronger and create a more stable structure for the thiourea – $CuCl_2$ complex.

Analytical application of reagents

The ions formed by reagents (R1-R6) with copper (II), nickel (II) and silver (I) ions were studied spectrophotometrically. The optimal conditions of the complexation reaction were determined, and the dependence of the complexation on pH, wavelength, reagent concentration, temperature and time was studied.

In order to increase the analytical parameters of the complexation reaction, the effect of hydrophobic amines phenanthrene, α,α′-dipyridine, diphenylguanidine, triphenylguanidine on the binary complex was studied. As a result of the study, it was found that a complex compound with different ligands is formed under the influence of third components. As can be seen from the table, certain changes occur in the optimal conditions for the formation of complexes with different ligands formed under the influence of the hydrophobic amines used (Table 2).

Table 2. Main spectrophotometric characteristics of the studied complex compounds

Reagents	pH_{opt}	λ_{opt}	$\varepsilon x10^4$	Ratio of the components (M:R)	Obey of the Beer's law mkq/ml
1	**2**	**3**	**4**	**5**	**6**
Ag (I) -R_1	5.5	460	1.82	1:2	0.234-2.31
Ag (I) -R_1-fen	4.5	476	2.53	1:2:2	0.168-2.242
Ag (I) -R_1-α,α′-dip	4.5	473	2.38	1:2:2	0.176-2.32
Ag (I) -R_2	4.5-5.3	457	1.53	1:2	0.234-2.31
Ag (I) -R_2-fen	4.2-5.2	471	2.4	1:2:1	0.164-2.24
Ag (I) -R_2-fen- α,α′-dip	4.0-5.3	474	2.45	1:2:1	0.164-2.24
Ag (I) -R_2-triton	4.0-5.0	470	1.98	1:2:1	1.64-2.24
Ni (II) -R_2	4.7-5.8	469	1.8	1:2	0.5-4.0
Ni (II) -R_2-DFQ	4.4-5.2	480	2.5	1:2:2	0.1-2.8
Ni (II) -R_2-TFQ	4.4-5.2	489	2.7	1:2:2	0.1-2.8
Ni (II) -R_3	4.8-5.8	460	1.75	1:2	0.5-4.0
Ni (II) -R_3-DFQ	4.3-5.2	475	2.35	1:2:2	0.1-2.8
Ni (II) -R_3 – TFQ	4.4-5.2	488	2.65	1:2:2	0.1-2.8
Cu (II) -R_1-fen	4.3-5.4	435	2.52	1:2:1	0.18-2.45
Cu (II) -R_1-α,α′-dip	4.2-5.4	440	2.43	1:2:1	0.18-2.45

Cu (II) -R3	4.9-6.2	415	1.95	1:2	0.25-2.07
Cu (II) -R$_3$-fen	4.2-5.6	437	2.94	1:2:1	0.12-2.56
Cu (II) -R$_3$-α,α′-dip	4.2-5.6	443	2.81	1:2:1	0.18-2.45
Cu (II)-R$_6$-ED	5.3-5.6	440	1.45	1:2:2	0.25-2.45

Due to the influence of the third component, a bathochromic shift is observed at the maximum wavelength towards the optimal pH acidic environment. The molar absorption coefficient was also calculated. In all cases, the molar absorption coefficient value is higher in complexes with different ligands than in binary complexes.

The ratio of components in the composition of binary and complex compounds with different ligands was studied using isomolar series, Starik-Barbanel and equilibrium shift methods. The ratio of components in the binary complex is 1:2, and in complexes with different ligands it is 1:2:2 and 1:2:1. The complexation reactions with the highest molar absorption coefficient are Cu-R3 - α,α′-dip Cu-R$_3$ - α,α′-dip $e = 2.81 \times 10^4$, Cu-R$_3$ - phen $e = 2.94 \times 10^4$.

Therefore, smaller amounts of substance can be determined by different ligand reactions.

Effect of N,N'-diisopropyl thiourea on the sorption capacity of nickel by maleic anhydride styrene copolymer and 4-amino-N-2-thiazolylbenzenesulfanilamide synthetic sorbent (S1)

In the dissertation work, the adsorption of Ni (II) ions by a synthetic adsorbent (S1) modified with thiourea based on maleic anhydride with styrene and 4-amino-N-2-thiazolylbenzenesulfanilamide was also studied. In the course of the work, various parameters affecting the adsorption process were studied, including the effect of pH, time dependence, ionic strength and layering of metal ions.

The effect of pH on Ni (II) sorption was studied. As a result of the measurement, it was found that the highest percentage of Ni (II) ions was captured from the solution at pH 3. Therefore, all subsequent experiments were carried out at this pH value.

The effect of pH on the sorption process was also studied after the sorbent was modified with N,N'-diisopropyl thiourea, and it was determined that the maximum absorption was at pH 3.

The effect of time on the sorption of metal ions was determined.

It was found that after 60 minutes, the sorption had already stabilized and reached an equilibrium state. After this period, it can be said that the metal ion was not captured from the solution. The same situation was observed in the sorbent modified with N,N'-diisopropyl thiourea sorbent. That is, after 60 minutes, the sorption reaches a maximum value.

In the course of this work, the effect of ionic strength on the rate of Ni(II) ion capture was also studied. For these purposes, a 2 mol/l potassium chloride (KCl) solution was used. Studies have shown that the presence of K^+ and Cl^- ions in the range of µ=(0.2-1.4) mol/l has a slight effect on the sorption of metal ions.

The effect of the initial concentration of metal ions on the degree of adsorption by the synthesized sorbent was studied. For this purpose, the concentration range of Ni (II) ions from $2\cdot10^{-4}$ mol/l to $8\cdot10^{-3}$ mol/l was used.

During the study, the desorption process was also studied. For this purpose, various inorganic acids of the same concentration were used, in particular, 0.5 mol/l solutions of HNO_3, HCl, H_2SO_4 and CH_3COOH acids. The results of the study showed that the maximum desorption capacity on Ni(II) ions is 0.5 mol/l HNO_3 solution.

In order to better understand the adsorption process, the appropriate adsorption equilibrium should be used in the study. The nature of the adsorbate-adsorbent interaction is described by the adsorption equilibrium. In this study, equilibrium data were analyzed using Langmuir, Freundlich, and Dubinin-Radushkevich isotherms.

The Langmuir equation is often used to describe sorption equilibrium. In this isotherm, it is assumed that all surface areas of the sorbent are homogeneous and its main characteristic can be represented by the so-called equilibrium parameter (R), which has the following form:

$$R_L = \frac{1}{1+bC_0}$$

Here b is the Langmuir constant (L/mmol), C0 is the initial concentration (mmol/L). The R_L value indicates the type of isotherm. A value between 0 and 1 indicates a favorable adsorption process. As a result of the calculation, it was determined that both before and after modification, R_L is between 0 and 1 and is equal to 0.99, which indicates that adsorption is favorable under the experimental conditions determined by the Langmuir model.

The Freundlich isotherm model determines the degree of heterogeneity of the adsorbent surface. Each of the adsorption centers consists of small heterogeneous adsorption sites, each of which is homogeneous. According to this model, more favorable adsorption is observed at a value of the Freundlich constant between 1 and 10. A larger value of n, a smaller value of 1/n, indicates a stronger interaction between the adsorbent and the adsorbate, while a value of 1/n equal to 1 indicates linear adsorption, which is characterized by the same adsorption energies for all sorption points. Our calculations show that in the usual case 1/n=0.5674 and after functionalization it is equal to 1.602. Thus, both cases indicate normal adsorption.

The Temkin model was used to explain whether the sorption process proceeds by a physical or chemical mechanism. According to this model, when the Temkin constant B_T<8 kJ/mol, physical sorption occurs, and B_T>8 kJ, chemical sorption occurs. The values for B_T are 5.5688 for the original sorbent and 8.2229 after modification.

The Dubinin-Raduškevich (D-R) isotherm model was applied to evaluate porosity, free energy, and sorption properties. The parameter E is used to determine whether the sorption process is physical or chemical.

$$E = \frac{1}{\sqrt{2K_{D-R}}}$$

The value of E is equal to 3.5 kJ/mol. According to this model, if E is less than 8 kJ/mol, it indicates that physical adsorption is taking place.

Application of synthetic sorbents modified with thiourea derivatives for the determination of Ni (II) in oil field wastewater

For the purpose of analysis, a water sample was taken from the oil field of Pirallahi Island. The amount of Ni (II) ions in water samples was calculated based on the previously established calibration curve. The results were compared with AAS and are given below (Table 3).

Table 3. Determination of Ni (II) in oil field wastewater

Object	Adsorbent	Reagent	$\bar{X} \pm \frac{t_{p.f.} \cdot S}{\sqrt{n}}, \frac{mg}{L}$	S_r
Water	S	R	$(0.357 \pm 0.015) \times 10^{-3}$	0.02
		AAS	$(0.364 \pm 0.016) \times 10^{-3}$	0.04

Methodology for the determination of Ag (I) in synthetic mixtures.

The Ag (I)-1-[2-(allylamino)-1-methylethyl] thiourea-α,α′-dipyridine system has been successfully applied for the determination of Ag (I) in a series of synthetic mixtures with different compositions. Thus, the amount of silver was accurately determined using this method in several samples of synthetic mixtures containing Ag (I) and known concentrations of various ions using EDTA as a masking agent. It was determined that the results of the spectrophotometric analysis of synthetic mixtures were in perfect agreement with the results obtained by ICP-OES. The analysis results are given in Table 4.

Table 4. Determination of Ag(I) in synthetic mixtures

Sample	Composition of the mixture (mkq/ml)	Added Ag(I) mkq/ml	Ag(I) mkq/ml Found (Proposed methodology)	Ag(I) mkq/ml Found (ICP-OES)
1	**2**	**3**	**4**	**5**
A	Ag+	1.5 2.0	1.51 2.02	1.50 2.01
B	Ag+ + Cu2+(25) + Fe3+(25)	1.5 2.0	1.52 2.04	1.51 2.02

D	C + Cr3+(25) + Ca2+(25)	1.5 2.0	1.48 2.02	1.49 2.01
E	D + K+(25) + Hg22+(25)	1.5 2.0	1.49 2.02	1.495 2.025

Enzyme inhibitory activity and molecular docking study of some thiourea compounds

Taking into account the medical importance of N-replaceable Thioureas (R_1-R_5), which are bifunctional compounds, their physiological activity has been explored. Thus, in the molecule, the inhibition of inhibitors and inhibitors in different enzymes and isoensims with the participation of these compounds with several reactionary centers have been studied in the molecule.

Initially, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes were used to determine the enzyme inhibition properties of N-substituted thiourea derivatives. Thiourea derivatives (R_1-R_5) have been identified in nanomolar concentration levels and have an effective ACHE and BCHE inhibitor with a standard takrin combination of values.

According to the results, the ICE Formerian N-substituted Thiourea derivatives (R1-R5) IC50 are determined to be 51.13 Nm from 51.13 Nm. Interestingly, all compounds have a stronger impact on the standard takes (that: 115.70 ± 10.40).

Similarly, the IC50 inhibition values of N-replacement of N-substituted TIIs (R1-R5) were found in 184,41 Nm with 184.41 Nm. In vitro studies show Thiourea derivatives (R_1-R_5) Intensive Ache and BCHE inhibitor. In particular, R_3 and R_5 combinations demonstrate more effective inbaliated properties compared to the standard takes. These compounds can play the role of the most active inhibitor of the cholinesterase enzyme in an approach to Alzeymer's disease.

Here, we performed molecular docking analysis to evaluate the structural activities of the novel compounds (R_1-R5) with AChE and BChE in real and native conditions. The bound and rearranged control complex for each target is shown in Figure 7:

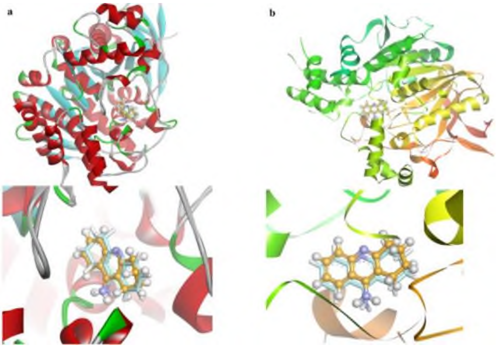


Figure 7. Validation of the docking protocol for both targets a) AChE and b) BChE. Bound ligand tacrine **(orange color, ball and stick shape), re-bound ligand (light blue color, stick shape)**

Our studies in this direction have shown that the chemical structures of thiourea compounds can bind to the active sites of AChE and BChE enzymes and cause their inhibition. The chemical binding energy estimated from the molecular structure of the designed compounds is in good agreement with the activity values.

RESULTS

1. Synthesis methods of Cu (II), Co (II), Ni (II) complexes based on 5 reactants (R_1-R5) containing nitrogen and sulfur atoms in the molecule and four of them (R1-R4) were developed and 8 new complexes were obtained. The synthesized compounds were studied in detail by X-ray diffraction, thermogravimetric and spectral analysis methods. Also, according to quantum chemical calculations, the optimized structure, molecular electrostatic potential map, highest occupied molecular orbital and lowest unoccupied molecular contours of 1-[1-methyl-2-(methylamino) ethyl] thiourea (R_1) and its complexes with Zn and Cu were determined [1].

2. For the first time, a complex of 4-((2,4-dioxopentan-3-yl) diazenyl) benzoic acid (R_6) with copper in the presence of ethylenediamine with various ligands was synthesized, and its structure was studied by X-ray analysis, which revealed that several

intramolecular and intermolecular interactions in this complex ensure the stability of the crystal structure. In particular, during the crystallization of the complex, one molecule of ethylenediamine and two molecules of water coordinate around the complexing agent. The nitrogen atoms of ethylenediamine molecules form chemical bonds with two different copper atoms, and as a result, a one-dimensional polymer structure is formed along the "a" axis. Then, the one-dimensional polymer molecules transform into a three-dimensional geometric shape due to hydrogen bonds formed with water molecules.

3. Binary and various ligand complexes formed by Ag (I), Cu (II), Ni (II) ions with reagents R_1-R_4 were studied by spectrophotometric method. The optimal conditions for complex formation were determined and the main spectrophotometric characteristics of the complexes were calculated [2;3;4].

4. The effect of hydrophobic amines phenanthroline (phen), α,α′-dipyridyl (α,α′-dip), diphenylguanidine (DFQ), triphenyl guanidine (TFQ) on the formation of reagents with copper (II), nickel (II) and silver (II) was studied. It was found that complex compounds with different ligands with high analytical parameters are obtained under the influence of these amines. The conditions for the formation of these complexes were found and the main spectrophotometric characteristics were calculated. Based on the results obtained, it was found that complexes with different ligands have higher analytical properties than complexes with the same ligand.

5. During the study of the complex formed by nickel (II) with the R2 reagent by the spectrophotometric method, various solvents were used for the extraction of the compound. It was found that when 1-butanol was removed from the solvents, the extraction yield of the complex was high. This indicates that the reagent forms a charged complex with nickel ion. The effect of DFQ and TFQ on the extraction yield of complex compounds formed by nickel (II) with R_2 has been shown that under the influence of these hydrophobic amines, the yield increases and the extraction shifts to an acidic medium [4].

6. When studying the effect of foreign ions and masking agents on the formation of complexes of copper (II), nickel (II) and silver with the same and different ligands with the reagents R_1-R_3, it was determined that the analytical properties of the methods developed with the participation of modified forms of the reagents are characterized by higher selectivity compared to the methods known from the literature.

7. The sorption properties of nickel (II) ion were studied using a sorbent based on maleic anhydride-styrene and a sorbent impregnated with thiourea, as well as the influence of various factors on this process. When calculating the sorption capacities of the sorbent, it was found that the sorption capacity of the modified sorbent is 20% higher than that of the original sorbent. During the study of the effect of mineral acids on the desorption process of nickel (II) ion, it was determined that HNO_3 acid desorbs nickel better [5].

8. The synthesized reagents were successfully applied to the determination of silver, copper, nickel in water samples contaminated with various natural and petroleum products, as well as in synthetic mixtures, by photometric and extraction-photometric methods [4].

9. During the study of the inhibitory activities of N-substituted thioureas as ligands on enzymes, it was found that these substances can play the role of the most active inhibitor of the cholinesterase enzyme in the treatment of Alzheimer's disease, which is widespread in the world. During the comparative analysis with molecular docking studies, it was determined that among the studied compounds, R_3 and R_4 compounds demonstrate the highest binding affinities for the AChE enzyme, and R_3 and R_5 compounds for BChE. The most potent molecule against both targets is the R_3 compound.

The main results of the dissertation work are reflected in the following publications.

1. Synthesis, structural analysis, DFT study, antioxidant activity of metal complexes of N-substituted thiourea / Tahir Javadzade, İrada Rzayeva, Svetlana Demukhamedova [et al.] // Polyhedron, Amsterdam, – 2023. – 231, – s.1-16.

2. New simple method for the determination of trace level copper (II) using 1- [2- (allylamino) -1-methylethyl] thiourea in presence of hydrofob amines by molecular absorption spectral method in the UV and visible region / Polad Mammadov, Tahir Javadzade, Afsun Sucayev [et al.] // Azerbaijan Journal of Chemical News, – 2022. v.4, №2, – s. 40-50.
3. New simple spectrophotometric methods for the determination of trace level silver(I) using 1-[2-(allylamino)-1-methylethyl] thiocarbamide / Polad Mammadov, Tahir Javadzade, Afsun Sucayev [et al.] // – Bakı: Bakı Universitetinin Xəbərləri, – 2021. №1, – s. 5-13.
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9. Javadzade, T., Mammadov, P., Sujayev, A., Khalilova, F. New simple spectrophotometric method for the determination of trace level copper (II) using 1-[2- (allylamino)-1-methylethyl] thiourea in presence of hydrofob amines // International Conference Modern Problems of Theoretical and Experimental Chemistry, Devoted to the 90th anniversary of academician Rafiga Alieva, – Bakı: – 2022, – s. 75-76.
10. Javadzade, T., Chiragov, F., Rzayeva, I., Sucayev, A. Combined action of metal complexes of cyclic thiocarbamides as antioxidant additives // Akad. Əli Musa oğlu Quliyevin 110 illik yubileyinə həsr olunmuş “Müxtəlif təyinatlı üzvi maddələr və kompozision materiallar” mövzusunda Respublika elmi konfransı, – Bakı: – 2022, – s. 68.
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