Egypt. J. Chem. **Vol. 66**, No. 10 pp. 1 - 7 (2023)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Preparation, Characterization and Antibacterial Activities of Metal complexes with Tyrosine Ligands

Mabrouk M. Salama[1], Sana. F. Moussa[2], Hamad.M.Adress.Hasan[3]

[1]Department of chemistry, faculty of Science, university of Benghazi, Benghazi, Libya
[2]Department of chemistry, Faculty of Science, University of Tobruk, Tobruk, Libya
[3]Department of chemistry, Faculty of Science, University of Omar al-Mukhtar Al Bayda, Libya

Abstract

A series of metal complexes of Cd(II), Co(II), and Cu(II), with tyrosine ligand have been prepared. The tyrosine ligand and its metal complexes have been characterized on various physicochemical studies as infrared spectroscopy (IR), , thermal analysis (TGA) , electrical conductivity , and measurement of the melting point of these complexes, The identification of the prepared complexes by I.R gave clear linkage between the ligand and the selected metals , where the bands of M-O, COOH , NH_2 , gave interesting values comparing with the free ligand and the complexes. The TGA curves show the main decomposition of complexes, as a major loss attributed to decomposition of the amino acid at THE range 220 ^{o}C– 390 ^{o}C. The molar ratio which carried out by U.V calculations gave the ratio of 1:1 (Metal: Ligand) linkage. Their biological activities were investigated by in vitro using spectral of ultraviolet light for molar ratios calculations with items by using the different series of concentrations and Ligand. Study of the effect of complexes prepared on some bacteria (Escherichia coli and Bacillus Subtitles) has improved the two types of bacteria with the complexes prepared on each species of microbial laboratory. Some of the prepared complexes gave anti-bacterial activities on the species of bacteria which used in this study.

Keywords: Tyrosine ligand, spectroscopy investigation, metal complexes, anti-bacterial activities

1. Introduction

Transition metals are essential components of biological systems, playing diverse roles including cofactors in the enzyme oxidation process, controlling the geometry of the enzymic active sites, and activating enzymatic reactions [1,2]. Moreover, they are present in vitamins such as Co(II) in B_{12}. Copper is essential for nervous system development and it exists in many enzymes and proteins with a range of functions such as in energy metabolism [2]. Zinc is the most abundant transition metal in the human body playing several important roles including immunity and metabolism, and is crucial for the function of more than 300 enzymes [2].

The interaction of transition metal complexes with DNA has long been a subject of intensive investigation with the perspective of development of newer materials for application in biotechnology and medicine. These investigations have resulted in the synthesis of many new metal complexes, which bind to DNA by non-covalent interactions such as electrostatic binding, groove binding and intercalative binding [3,4]. Hence, the current growing interest in small molecules that is capable of binding and cleaving DNA is related to their utility in the design and development of synthetic restriction enzymes, new drugs, DNA foot-printing agents, etc., and also to their ability to probe the structure of DNA itself [4].

Transition metal amino acid complexes are a large family of coordination complexes containing the conjugate bases of the amino acids, the 2-aminocarboxylates. Amino acids are prevalent in nature, and all of them function as ligands toward the transition metals [4,5]. Complex combinations of metal ions with amino acids are important because of their biological applications. The L- α- amino acids and their compounds are used in biology, pharmacy, laboratory reagents and industry, Metal amino acid (M-AA) complexes are similar to these compounds

*Corresponding author e-mail: mabrouk.salama@uob.edu.ly; (Mabrouk M. Salama).
EJCHEM use only: Received date 28 March 2023; revised date 20 May 2023; accepted date 07 June 2023
DOI: 10.21608EJCHEM.2023.202542.7787

which allow the metal to be carried in with the amino acids during absorption and can be used to build proteins or provide energy[6]. Complexes of Cu (II) with amino acids can be used as models to study the pharmacodynamics effects of drugs or for increasing the biocompatibility and minimize toxic effects of some metal .Metalloid therapy is a very unique therapeutic method to treat many diseases. Several metal ions and their complexes exhibit anti-diabetic effects[6]. Amino acid coordinates to metals it confirms structural liability, and also have applicability in enzyme inhibition. These complexes have a vast area in pharmacological and toxicological properties that has drawn lot of current attention [7]. Transition metals amino acids complexes have received much attention because they proved to be useful antibacterial agents applied against Staphylococcus aurous, Escherichia coli, nutritive supplies for humans and animals [8]. The importance and applications of transition metal-ligand complexes are widespread from synthetic chemistry to material science and biochemistry. These metals have been used for drug design and delivery [8]. Hemoglobin is most important oxygen transport metalloproteinase which contain utmost, the iron in body. Transferrin and ferritin proteins also contain iron which transports it from one part of the body to another and provided storage respectively. The diets containing iron from amino acids complexes have better metabolism, absorption as well placental and mammary iron transfer than any other form. Ferrous bis-glycinate complex nutritionally meets all the requirements [9,10].The tyrosine ligand with metal complexes have been studies for the first time using nickel (II)[11]. In the present work, we report the preparations, spectroscopic characterization and thermal studies of novel Cd(II), Co(II) and, (Cu(II,I) complexes with tyrosine ligand. These complexes have been characterized by various physicochemical techniques. The antibacterial activities of the ligand and the selected metal complexes were investigated.

2. Materials and Methods

The materials were commercially obtained from Aldrich co. and used without further purification. These include Cadmium (II) chloride anhydrous ($CdCl_2$), cobalt (II) chloride hexahydrate ($CoCl_2.6H_2O$), copper (II) chloride dehydrate ($CuCl_2.2H_2O$), distilled H_2O, and ammonia). The ligand Tyrosine ($C_9H_{11}NO_2$) was obtained from Aldrich Co. All reactions were carried out under normal atmospheric conditions.

Table1
Shows chemicals used in this work

Chemical Materials	Formula
Cadmium(II) Chloride	$CdCl_2$
Cobalt(II) Chloride -6-hydrate	$CoCl_2.6H_2O$
Copper(II) Chloride -2-hydrate	$CuCl_2.2H_2O$
Ammonia	NH_3
Distilled water	H_2O
Tyrosine	$C_9H_{11}NO_3$

Solutions

Tyrosine is the amino acid which used as ligand in the concentrations of (0.2M).

Synthesis of the metal complexes

Synthesis of Tyrosine metal complexes

0.01 mole of metal chloride in 50 ml ammonia was added with stirring to 0.01 mole of Tyrosine ligand in 50 ml distilled water. The reaction mixture was refluxed for 3 hoursand then left overnight. The precipitated solid complexes were separated out by filtration, then washed with water and dried at room temperature.

Characterization of the synthesized complexes

Melting Point measurement

The melting points of both ligands and their complexes were measured using a device (Stuart Melting Point Apparatus).

Determination of conductivity

The conductivity of the solutions of the complexes was measured using conductivity meter (Type HANA).

Infrared spectroscopy

The FT-IR spectra of the metal complexes were recorded for potassium bromide (KBr) discs over the range (400-4000 cm^{-1}), on the basis of the reported infrared spectra of amino acids, L-Tyrosine and their metal complexes [4]. An instrument based on the fundamental principles of molecular spectroscopy was utilized in order to identify the presence of certain functional groups in the synthesized compounds.

Thermal gravimetric Analysis

The Thermo-gravimetric analysis (TGA) of the amino acids complexes which contain water molecules was achieved by using thermal technique model TGA-H50 shimadzu (Japan). The weight loss of sample was measured from room temperature up to (1000 °C) in rate of 10 °C per min. The temperature is most often programmed to increase linearly [11].

Determination of the molar ratio of the metal ions to the ligands spectrophotometrically

The spectrophotometric method was used in this investigation to determine the stoichiometry of the complexes. Spectrophotometric method can be carried out by molar-ratio method. In this method, 10 volumetric flasks (10 ml) were cleaned, 2 ml of $3x10^{-3}$M of the ligand was transferred inside each flask, the flasks were numbered from 1 to 10, then 0.4 ml of $1x10^{-3}$M metal salt aqueous solution was added to the first flask, 0.8 ml to the second, 1.2 ml to the third, each flask has 0.4 ml of metal solution more than the previous one, and so on until 4.0 ml was added to the tenth flask. The volume in each flask was made up to the mark (10 ml). A series of [L]/[M] ratios were obtained. Using UV spectrophotometer, the absorption of each solution was measured at maximum wave length (λmax) of the expected complex. The absorbance values were plotted against [L]/[M] ratios. The result curves are composed of straight lines with inflection points, [L]/[M] ratio corresponding to the infection point indicates to the actual stoichiometry of the complex. This procedure was repeated for each complex, all of the investigated ligands were titrated with the metal ions (Cd, Co and Cu).

The biological activity study for the tyrosine metal complexes

In this study two groups of bacteria were testing, Gram-positive bacteria (Bacillus) and Gram-negative bacteria (Escherichia colli).

3. Results and Discussion

Characterization of the prepared complexes:

Some physicochemical properties such as color, melting point, and molar conductivity of the ligands and the corresponding metal complexes are presented in Table 2. The complexes, ligands and metal salts were mostly insoluble in organic solvents of acetone but all are soluble in ammonia and distilled water, possibly due to its high polarity and donor strength which enhance its ionic interaction with the samples in solution. The ionic nature of the complexes as shown by the conductivity results could be traced to the presence of electropositive metal ions in their structures compared to the parent ligands. The melting points of the complexes are lower when compared to the salts/ligands and the sharpness could imply a good purity of the complexes. The significant changes in the melting points, as well as colors between the ligands and their respective metal complexes, indicate a change in the atomic structures, possibly due to chemical coordination.

Table 2
Shows colors, melting point and the electrical conductivity of the complexes

Parameter / Complex	Color	E.C(μS/cm)	M.P (℃)
Tyr-Cd	White orange	5.26	315-318
Tyr-Co	Dark brown	4.49	>350
Tyr-Cu	Bluish green	5.27	305.5

Infrared spectra studies

The IR spectrum of free ligand is compared with IR spectra of its metal complexes, to investigate the mode of bonding Schiff base ligand to metal ion. The characteristic bands of the IR spectrum of the Schiff base ligand and metal complexes are listed in Table 3 and Fig. 1, Fig. 2 and Fig. 3. The broad band in case of (CdL) at 3203 cm^{-1} is assigned to the (OH) stretching frequency, the band at 3104 , is assigned of (NH_2), where , the band at (1578 cm^{-1}), is assigned of (CO) , and the band at 572 cm^{-1} is assigned to (M-O). The IR spectrum. On complexation, the IR spectra of all complexes display the bands of the imine groups has shifted to lower wave number as compared of free Schiff base ligand. Also the bands of carbonyl group were shifted to lower wavenumber accompanied by a decrease in their intensity, indicating that they are involved in complex formation.

Table 3
Fundamental infrared bands (cm^{-1}) for the prepared tyrosine complexes

Complex	OH (phenolic)	NH_2	C = O	M -O
CdL	3202	3104	1578	577
CoL	-	3277	1584	580
CuL	3201	-	1579	615

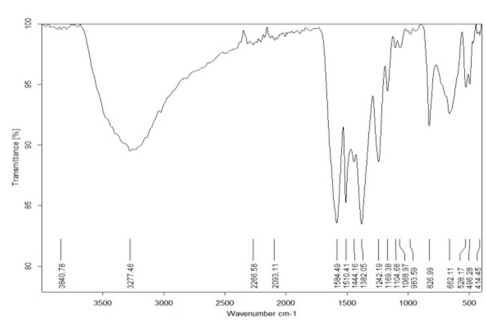

Fig.1: The infrared spectra of complex [Cd-L]

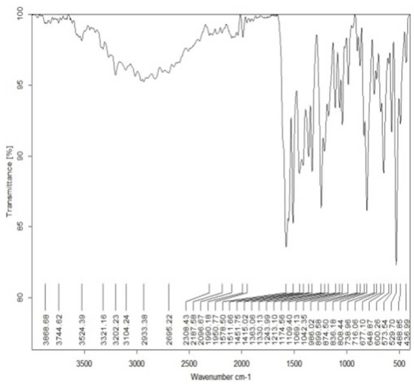

Fig.2: The infrared spectra of complex [Co-L]

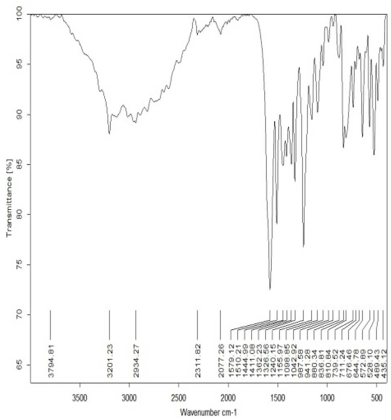

Fig.3: The infrared spectra of complex [Cu-L]

Thermal gravimetric analysis (TGA)

In case of L-tyrosine complex the first step shows a weight loss due to one water molecule in the temperature range ambient to RT- 255 ^{o}C, in case of Cd(II) and Cu(II) complex where in case of Co(II) complex appear at RT-180 ^{o}C, followed by weight loss due to the decomposition of nitrate in the range 220-390 ^{o}C. The final step shows a major weight loss attributed to decomposition of the amino acid.

Table 4
Shows the thermo-gravimetric analysis data for tyrosine complexes

Decomposition / Complex	H_2O Temp. rang	CO_2 Temp.	MO_2 Temp.
Tyr - Cd	RT-255	380	550
Tyr - Co	RT-180	350	470
Tyr - Cu	RT-255	285	305

In general, the steps of the investigated complexes may be occurred as:

[ML.nH_2O].nH_2O → [ML.nH_2O]
[ML.nH2O] → [ML]
[ML] → Intermediate
(unstable) Intermediate → Metal oxide MO_2
Intermediate (decomposition of organic ligand).

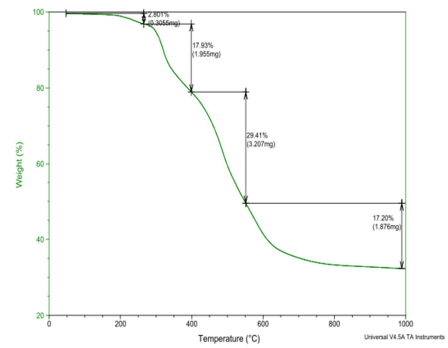

Fig.4: The TGA curve of Cd complex

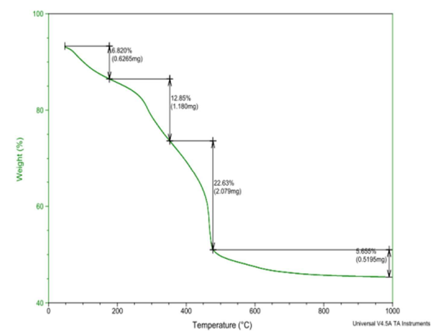

Fig.5: The TGA curve of Co complex

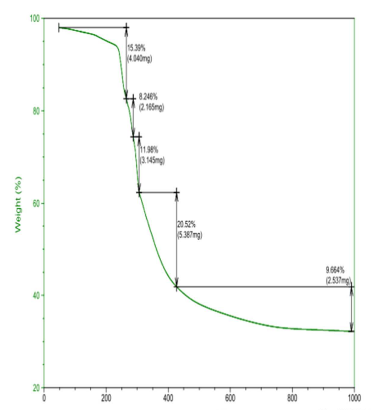

Fig.6: The TGA curve of Cu complex

Spectrophotometric Studies

In this investigation, the concentrations of the metal ions were varied and the ligand concentration were maintained constant, so, a series of metal-ligand aqueous solutions were prepared with different [L]/[M] ratios. The absorptions of these solutions were measured using UV spectrophotometer at λ_{max} of the expected complex MLx. Absorbance versus [L]/[M] curves were drawn for all complexes. It was observed that the absorption increase linearly as the metal ion concentration increases, because of the formation of the complex, until the solution reaches the actual molar ratio of the investigated complex. At this point, all of the added materials were completely reacted, and the absorption observed is the absorption of the investigated complex alone. After this point, the excess amount of the added metal ion causes an inflection in the straight line that is because the metal ion has an absorption value differ from that of the complex at λ_{max} of the complex. [L]/[M] ratio corresponding to the inflection point in (ABS - [L]/[M] curve) indicates to the actual [L]/[M] ratio of the investigated complex, Referring to the Figure7, it was found that of the Tyrosine complexes in this investigation are able to be stable in the form ML.

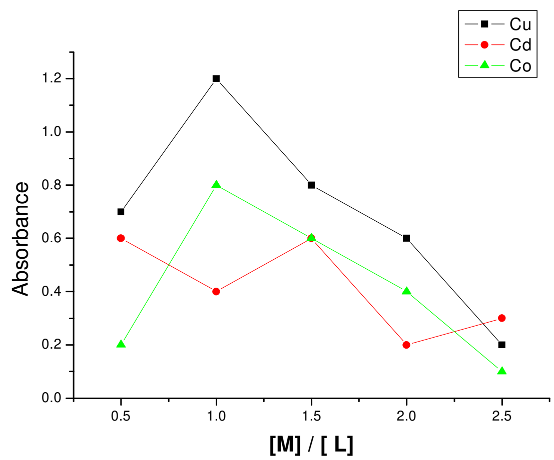

Fig.7: Shows the relationship between molar ratio of ligand- Absorbance of the metal ions of (Cu, Cd and Co)

The biological activity of complexes with bacteria

The results of the antibacterial activity showed that the free ligand and its metal complex are active against Gram positive bacteria (Bacillus subtilis). The results of the antibacterial activity showed that the free ligand and its metal complex are active against Gram positive bacteria (Bacillus subtilis) and gram negative bacteria (Escherichia coli). On the chelation recommendation [13,14,15], we can explain the inhibition zones results., as the metal ion polarity will be decreased after chelation mostly due to of the partial positive charge sharing with the donor groups within the chelate ring system which formed during the coordination as supported by the dipole values ,Table 5,[13,14,15]. A gram positive bacteria such as Bacillus subtitles, and gram negative bacteria such as Escherichia coli were selected to be investigated for the recent study. Table 5 shows that the Cd(II), Co(II), Cu(II) complexes exhibit significant activity against the gram positive and gram negative bacteria. In our biological experiments using cadmium complex. We observed considerable antibacterial activity against gram positive bacteria Bacillus and gram negative bacteria E. coli. The cadmium complex has shown a good activity against gram negative than against gram positive bacteria. It may be concluded that our Cd(II) complex inhibits the growth of bacteria to a good extent but in case of Cu(II) complex show less inhabitation of growth of bacteria either gram positive or gram negative.

Table 5
The inhibition zones in millimeter of the ligands and their Complexes

	Bacillus				*E.colli*			
	Concentration(mglml)							
Complexes	**0.1**	**0.01**	**0.001**	**0.0001**	**0.1**	**0.01**	**0.001**	**0.0001**
[Cd(Tyr)$_2$]	**12**	**10**	**5**	**-**	**13**	**10**	**9**	**5**
[Co(Tyr)$_2$]	**-**	**-**	**-**	**-**	**4**	**2**	**-**	**-**
[Cu(Tyr)$_2$]	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**

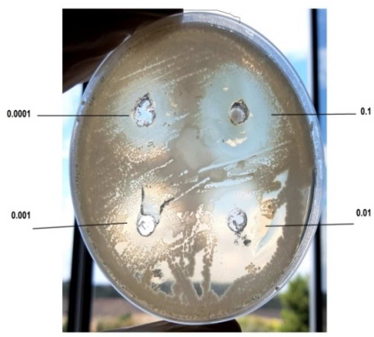

Fig.8: Biological activity of the [Cd(Tyr)] complex with the (Bacillus) bacteria.

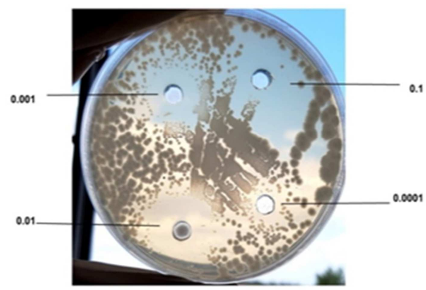

Fig. 9: Biological activity of the [Cd(Tyr)] complex with the (E.Coli) bacteria

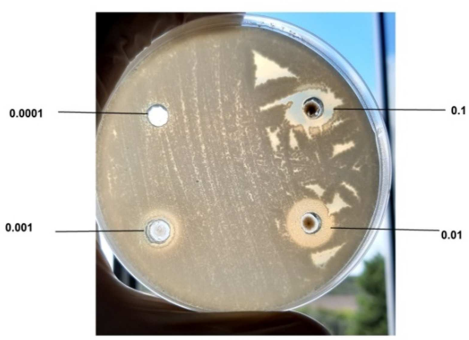

Fig.10: Biological activity of the [Co(Tyr)] complex with the (E.coli) bacteria

4. Conclusion

In this paper, the tyrosine ligand with Cd(II), Co(II), and Cu(II) complexes were synthazed and described. Further characterization of the tyrosine ligand and the metal complexes were achieved through physic-chemical and spectroscopic methods. The effectiveness of the binding of metal complexes are being confirmed, by its Schiff base phenolic OH, and amino acid COOH..The biological applications such as antibacterial of tyrosine ligand and its metal complexes are reported. These complexes exhibit excellent antibacterial ability against E. coli and bacillus. Thus, the study of metal complexes can hopefully become a novel kind of drugs.

5. Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

6. Acknowledgment

Authors would like to thanks university of Omer Al-Mukhtar in general and analysis central laboratory for chemical and biological analysis.

7. References

1. I. Kostava, The Role of Complexes of Biogenic Metals in Living Organisms, Inorganics, 11(2), 56,(2023).
2. W. Kaim, B. Schwederski, A. Klein, *Bioinorganic Chemistry--Inorganic Elements in the Chemistry of Life: An Introduction and Guide*. (John Wiley & Sons, 2013).
3. S Mathur, S.Tabassum,Synthesis and characterization of a new macrocyclic copper(II) complex with an N-glycosidic pendant arm: in vitro cytotoxicity and binding studies with calfthymus DNA Cent. Eur. J. Chem. (2006) 502–522.
4. D. Kannan and M.N. Arumugham, "Synthesis, Characterisation, DNA-Binding Studies and antimicrobial activity of Copper (II) Complex with 1,10 Phenanthroline, L-Tyrosine and Thiosemicarbazide as Ligands ", Elixir Appl. Chem. 74, 27007-27014 (2014).
5. T. Oshio, S. Uehara, Y. Uno, T. Inouse, E. Sasaki and H. Yamazaki, Marmoset cytochrome P450 2B6, a propofol hydroxylase expressed in liver. Xenobiotica, 49, 265-269 (2019).
6. M. Shebl, S. M. E. Khalil and F. S. Al-Gohani, J. Mol. Struct. Preparation, spectral characterization and antimicrobial activity of binary and ternary Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Ce(III) and UO2(VI) complexes of a thiocarbohydrazone ligand, J. Mol. Struct., 78, 980, (2010).
7. A. Binolfi *et al.*, Bioinorganic chemistry of Parkinson's disease: structural determinants for the copper-mediated amyloid formation of alpha-synuclein. *Inorganic chemistry* 49, 10668-10679 (2010).
8. A. Ganesan, J. Dreyer, F. Wang, J. Akola, J. Larrucea, Density functional study of Cu2+-phenylalanine complex under micro-solvation environment. *Journal of Molecular Graphics and Modelling* 45, 180-191 (2013).
9. O. Yamauchi, A. Odani, M. Takani, Metal–amino acid chemistry. Weak interactions and related functions of side chain groups. *Journal of the Chemical Society, Dalton Transactions*, 3411-3421 (2002).
10. S. E. Waisbren *et al.*, Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. *Molecular genetics and metabolism* 92, 63-70 (2007).
11. Md. R.l Islam , S. M. R. Islam , Abu. M. Noman , J. A. Khanam , S. M. M, Ali, S. Alam and M. W. Lee , Biological Screening of a Novel Nickel (II) Tyrosine Complex , Mycobiology 35(1): 25-29 (2007).
12. K. Wei *et al.*, Effects of iron from an amino acid complex on the iron status of neonatal and suckling piglets. *Asian-Australasian Journal of Animal Sciences* 18, 1485-1491 (2005).
13. S. S. Hassan, E. A. Bedir, A. El-Rahman M. Hamza, A. M. Ahmed, N. M. Ibrahim, M. S. Abd El-Ghany, N. N. Khattab, B. M. Emeira, M. M. Salama, E. F. Mohamed, D. B. Fayed, Appl. Organomet. Chem., 2022, 36, 1-19.
14. E. Fares Mohamed, S. S. Hassan, Synthesis, DFT, Antibacterial and Molecular Docking Studies of Novel La(III) Complex of Benzo-Chromen Substituted Thiosemicarbazide Egypt. J. Chem. 2022, 65, 11.
15. S. S. Hassan, R. N. Shallan , M. M. Salama, "Antibacterial and molecular study of thiourea derivative ligand and its Dimethyltin(IV) complex with the superior of its Copper(II) complex as a hepatocellular antitumor drug", Journal of organomettalic chemistry, 2020, 91, 121115.