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Anti-cancer activity of novel Schiff base copper (II) complex: synthesis and characterization

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A novel thiosemicarbazone substituted schiff base ligand and its Cu(II) complex have been prepared and characterized. Schiff bases are considered as an important pro ligand in coordination chemistry because they easily form stable complexes with biologically active transition metal ions. Such as Cu^{2+}, Zn^{2+}, Ni^{2+} etc. In this paper, novel Cu (II) complexes of thiosemicarbazone ligands were synthesised by refluxing thiosemicarbazone substituted pro ligands with copper salts in 1:1 molar ratio in absolute ethanol under thermal condition at 80°c for 5-6 hour. The resulting brown coloured copper complexes were filtered and recrystallized from petroleum ether. In this synthesis, we use absolute ethanol as a polar environment for the synthesis of copper complexes from schiff base ligands because the use of polar solvent medium in synthesis plays a very important role in reducing minimum possibilities of side reactions which hinders the proper conversion of ligands into copper complexes and also reducing the reaction time. All synthesized compounds were characterized through various spectroscopic and pharmacological techniques. FT-IR, UV-Vis, NMR, Mass, TGA-DTA, XRD spectra techniques were used to confirm the structures of copper complexes and ligands. All compounds are thermal stable up to 350°c. The good results of pharmacological activities of compounds like in-vitro anti -oxidant and anti - cancer activity against DPPH and cisplatin drug, explained the presence of biologically active functional groups are present in ligands as well as their copper complexes. Results found that the copper complexes were more active than the ligands. The synthesis of copper complexes from thiosemicarbazone schiff base ligands in proper stoichiometic ratio is an excellent method of preparing pharmacological active compounds which can be considered as good anti -cancer drug candidate for the treatment of cancer.

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Keywords: Schiff base ligands, Thiosemicarbazone, Copper complexes, DPPH, Cisplatin, Spectroscopic characterization

1. Introduction

The continuous increase in the numerous diseases poses a challenge for modern chemistry in the search for new pharmacologically active substances that will allow to treat these diseases and increase the duration and quality of life (1-6). The number of various cancers continues to increase (7).Therefore a great attention is paid to synthesis of new anticancer compounds [8,9] but these compounds showed general organotoxicity and reduced solubility so overcome these drawbacks, a special attention should be paid to the synthesis of selective anti-proliferative activity and cytotoxicities of these substances. The expansion of the weaponry of such substances will allow in the future to select the active substance for the treatment of cancer, which should increase the effectiveness of cancer treatment (10). Thiosemicarbazones and biologically active transition metal complexes with them represent one of the classes of compounds that are widely studied in this direction for future aspects in modern medicinal chemists. [11-15]. Thiosemicarbazones of aliphatic [16-18], aromatic [19-21], hetero aromatic aldehydes and ketones (22-24), various derivatives of hetero aromatic carbonyl compounds, generally exhibit the most pronounced pharmacological activities [25-26]. N-substituted thiosemicarbazone of aromatic carbonyl compounds acts as tridentate ligands with NNS set of donor atoms due to the central position of

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nitrogen atom the ligand [27]. Generally, the insertion of various substituents in the fourth position of the thiosemicarbazide moiety leads to a significant increase in pharmacological properties in molecules [28] which is confirmed by their increased anti -cancer and anti-tumor efficacy [29,30,31].Copper complexes from thiosemicarbazone ligands have shown satisfactorily results in the view of biological activity of broad spectrum.[32-35].

Copper metal is considered as the most abundant and biologically important transition metal present in the human body because it play a very important role in the conduction of all biological processes in a body. It functions as co-factors of various metalloenzymes. Copper in the divalent state is considered as the most stable form and can form different geometries with various ligands such as thiosemicarbazone, semicarbazones, Thiourea and ethylene diammine..[36, 37, 38]. Due to our interests in the evaluation of biological activities of novel metallic complexes of thiosemicarbazone ligands.[39,40], here we report the Anti –Cancer activity of Novel Schiff base Copper (II) Complex: Synthesis & Characterization and also discussed their supra molecular arrangements and molecular docking studies in details.

2. Experimental

2.1. Materials and methods

All reagents and solvents were obtained from commercial sources. Thiosemicarbazone ligands were prepared as described in the related literature.[41 – 42] Ethanol, DMSO, Petroleum ether were obtained from Merck Private Limited India and used as received without further purification. Triple distilled water was used for all chemical reactions, spectroscopic analysis and biological analysis of samples

2.2. Characterization

UV-Visible absorption spectra of compounds were recorded on a Perkin Elmer UV-Vis Lambda 25 UV-Visible spectrophotometer (PC Ray Research Centre, ITM University, Gwalior) using a 1 cm path length cuvette and used dichloromethane solvent for dissolution of all compounds . The Fourier – transform infrared spectra were recorded on Perkin Elmer FT-IR spectrophotometer (KBr Pellets) (PC Ray Research Centre, ITM University, Gwalior) with the wave length range from 400 to 4000 cm^{-1}. Melting points of compounds were obtained by an electro thermal melting point apparatus via open capillary method and were not corrected. The elemental analysis was conducted using C,H,N analyser, Thermo- Flash EA – 112 Series at the upper temperature up to 900-1000^{o}c. In this analysis, vanadium pentaoxide (V_2O_5) was used as an oxidizer was used as an oxidizer to prevent oxidation caused by the presence of sulfur element in copper complexes of thiosemicarbazone schiff base ligands, Thin Layer chromatography was performed using a normal hexane and ethyl acetate in 1:3 ratio as an eluent. X-ray measurements of compounds were performed at room temperature using Bruker axis D_8 using Cu K $\propto$ radiations. Molar conductance of copper complexes were measured on the ELICO (CM82T) digital conductivity meter in chemistry lab of ITM University, Gwalior. Chemical naming, calculation of molecular weights of new compounds was performed by Chem Bio Draw 12 squares.

2.3. Synthesis of Schiff base ligand

Synthesis of Schiff base ligand was divided into 3 steps:

Step-1 Synthesis of Ester (Precursor -1)

For the synthesis of an ester, 2.14 gr of paratoludiene and 3.2 ml of diethylmalonate were taken in a round bottom flask. The reaction mixture was kept on refluxing for 30 minutes at 30^{o}c on heating mental fitted with an air condensor (18”) so that an ethanol formed in the reaction can escape. After cooling at room temp, a solid substance was appeared in the round bottom flask and add 30 ml ethanol in a round bottom flask and stirred the solution mechanically for 15 minutes and pour this solution into 100g ice and stirrer the solution continuously for half an hour, then kept the flask for overnight to settle down the precipitate . After 24 hours of ageing process, a white crystalline precipitate was appeared in a flask. Precipitate was filtered and washed with hot

ethanol, recrystallized from petroleum ether and dried over P_4O_{10} in an vaccum dessicator Yield- 75%, melting Point = 110°c, Soluble in ethanol, Colour- white, Molecular weight – 197g/mole.

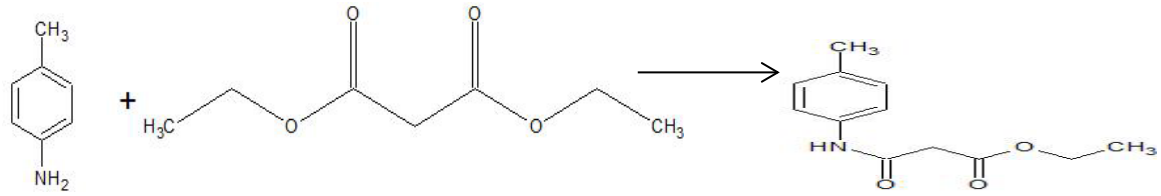

Fig. 1. Synthesis of Precursor–I.

Step II—Synthesis of substituted acid hydrazide (Precursor -2)

For synthesis of substituted acid hydride, dissolved 4g of purified ester in 10 ml absolute ethanol in a round bottom flask and add 6g of 2, 4 dinitrophenylhydrazine and reflux the reaction mixture at 25°c with constant stirring for 8 hours. After 8 hours of refluxing , an orange coloured precipitate was obtained which was filtered, washed three times with absolute ethanol and recrystallized from petroleum ether and dried over P_4O_{10} in an vaccum desiccator.

Yield -72%, Melting point – 160^{0}C, Molecular weight -374 g/mole, Colour –Orange Solubility –soluble in DMSO solvent.

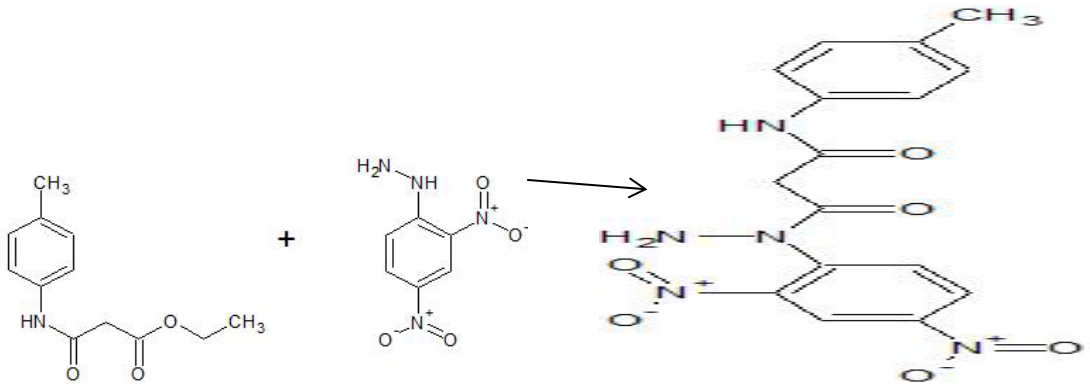

Fig. 2. Synthesis of Precursor –II.

Step III -Synthesis of Substituted acid hydrazone from acid hydrazides (Schiff base ligand)

For synthesis of schiff base ligand, dissolve 6.35g of substituted acid hydrazide in 50 ml absolute ethanol and add 3 ml of cinnamaldehyde in a round bottom flask and reflux the reaction mixture for 4 hours at 70°c. After 4 hours of refluxing, a red colour crystalline precipitate was obtained which was filtered and recrystallized from absolute ethanol and dried over P_4O_{10} in vaccum desiccator at room temperature.

Yield- 70%, Melting Point. – 190°c, Molecular weight- 487g/mole , Colour- Red, Solubility- Soluble in DMSO Solvent.

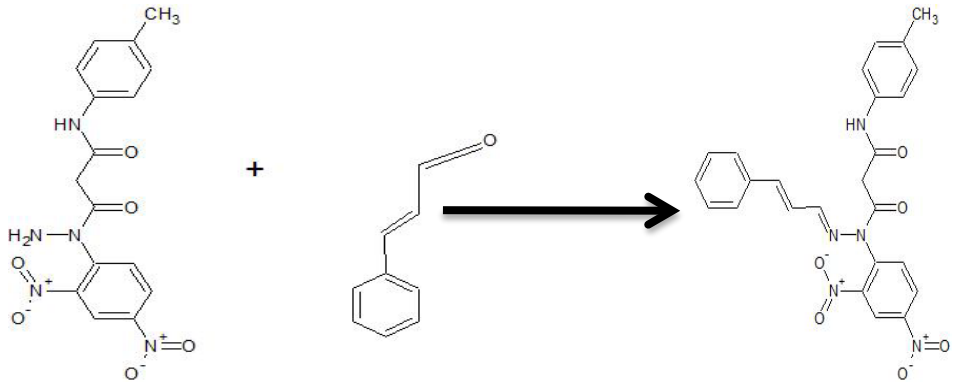

Fig. 3 Synthesis of Schiff Base ligand from precursor –II.

2.4. Step –IV Synthesis of Copper (II) Complex from Schiff base ligand

For Synthesis of Copper Complex from synthesised schiff base ligand, dissolved 0.749g of ligand in 10 ml ethanol, then add 0.14g of thiosemicarbazide hydrochloride and 0.13g of copper chloride in ethanolic solution of ligand and reflux the reaction mixture for 8 hours on a heating mental. After 8 hour of refluxing Process, a brown coloured solid crystalline precipitate was obtained which was filtered and recrystallized from hot ethanol and dried over P_4O_{10} at room temperature.

Yield- 69%, Melting Point. – 200ºc, Molecular Weight – 1194g / mole, Colour – brown, Solubility – Soluble in DMSO Solvent.

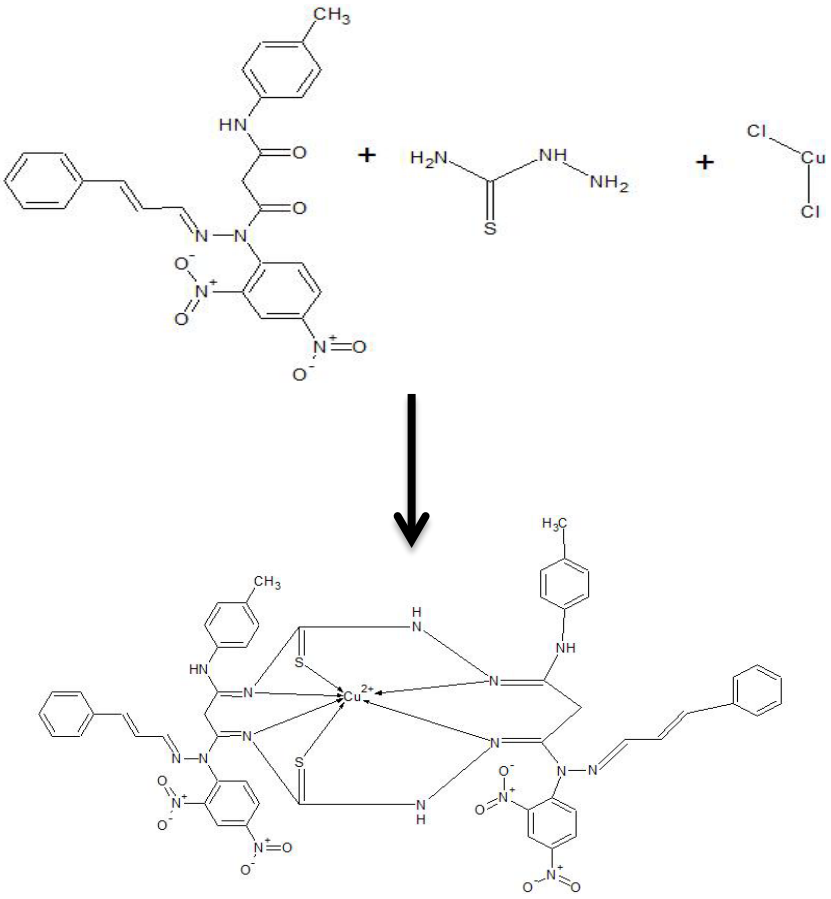

Fig. 4. Synthesis of Copper (II) Complex from Schiff base ligand.

Fig. 5. Pictures of all synthesised compounds.

2.5. Evaluation of antioxidant activities of compounds

2.5.1. DPPH radical scavenging activity

The free radical scavenging activity of ligand and its Cu (II) complex were determined by using DPPH free radical scavenging method according to the literature. Compounds were dissolved in DMSO (1mg/ml) and used as stock solutions. From the stock solutions, 0.01ml of each compound solution with different concentration (2500- 7.8 µg/ml for 1, 3, 4 compounds) and (1000-62.5µg/ml) for 2 compound were added to 0.2 ml of methanolic solution of DPPH. All the tubes were incubated at 37ºC for 30 minutes. After incubation 0.1ml of reaction mixture was pipette out to micro litre plate. Absorbance was measured at 490nm using micro litre reader. Same procedure was repeated for standard by replacing test samples with standard test and control was performed in triplicate and test blank and control blank were conducted in singlet. The percentage of scavenging activity of DPPH free radical was measured by using the following formula

$$\text{Scavenging activity (\%)} = \frac{Ao - Ai}{A0}$$

where A_o is the absorbance of the control and A_i is the absorbance of the sample.

2.6. Evaluation of anticancer activities of compounds

MCF- 7 Cell lines (human breast cancer cell line) were obtained from National Centre for Cell Science (NCCS), Pune, India. The cell line were cultured in Dulbecoo's Modified Eagle medium (DMEM) supplemented with 10% fetal bovine serum (FBS), Amphotericin(µg/ml), Gentamycin(µg/ml), streptomycin (250µg/ml) and penicillin (250unit/ ml) in a CO_2 incubator at 5% CO_2. About 700 cells/ well were seeded in 96 well plate using culture medium. The viability of the cells was tested using trypan blue dye with the help of haemocytometer and 95% of viability was confirmed. After 24 hour, the new medium with compounds in the concentration of 125µg/ml to 3.1µg/ml was added at respective wells and kept in incubation for 48 hr. After incubation the following assay was performed.

2.6.1. MTT ASSAY

After 48 hours of the compounds treatment , the medium was changed again for all compounds and 10µg of MTT(5mg/ml stock solution) was added and the plates were incubated for an additional 4 hr. the medium was discarded and the formazonblue, which was formed in the cells, was dissolved with 50µl of DMSO. The optical density was measured at 570nm. Cisplatin was used as a standard. The percentage of toxicity was calculated by using the following formula

$$\text{Cytotoxicity} = 1 - \frac{O.D\ of\ treated\ cells}{O.D\ of\ untreated\ cells}$$

The IC_{50} (concentration of drug required to inhibit growth of 50% of the cancer cells) values of all the compounds were calculated using graph pad prism software tool.

3. Results and discussion

This research work reports the Synthesis, Spectroscopic Characterization and Biological applications of Novel Schiff base Copper (II) complex, using template method'' which was free from any impurity and requires continuous stirring of reaction mixture. After 24 hours of aging process, formation of brown coloured precipitate indicates the formation of copper complex from schiff base ligand. Ligand and its copper complex were stable at room temperature and had high melting points. Elements of all compounds were present within $\pm$ 0.5% of C, H, N, and S elements within a range. The physical and analytical data of compounds are depicted in Table 1. Ligand and its Copper complex were coloured and soluble in non- polar solvents like DMF and DMSO. Analytical data confirmed the metal to ligand ratio in Copper complex it is 1:2 molar ratio. The molar conductance measurement of complex was recorded in DMF ($1x10^{-3}$M) and results indicates the non-electrolytic nature of complex (Table 1).

The nitrogen content in complex was determined using Kjeldahl's method. The copper content in complex was determined by EDTA method.

Table 1. The physical and analytical data of Schiff ligand and its Cu (II) complex.

S.N.	Compound	Molecular weight (g/mol)	Color	Yield %	Elemental analysis					Molecular conductivity $mho^{-1}mol^{-1}cm^2\lambda$
					C	H	N	S	Cu	
1.	**Schiff base** $[C_{52}H_{44}N_{16}O_8S_2]$	**487**	**Orange**	**69**	**60.6(61.3)**	**3.46(3.400**	**4.47(450)**	**-**	**-**	**-**
2.	$[Cu_{52}H_{44}N_{16}O_8S_2]$	**1194**	**Red**	**79.2%**	**64.1 (64.38)**	**3.53 (3.49)**	**4.49 (4.63)**	**10.28 (10.30)**	**10.12 (9.63)**	**34.1**

3.1. Stability of copper (II) complex

The stability of copper complex has an effect on the anticancer activity therefore the hydrophobic stabilities of Cu (II) complex of thiosemicarbazone ligand was investigated using UV- Vis spectroscopic technique. The UV-Visible absorption of spectra of ligand and its copper complex in solution (TBS, P^4 7.4, 1% DMSO solvent) at different time intervals (0, 24, and 48 hrs) were determined. The UV-Vis spectra of Complex do not differenciate significantly from those observed even after 48 hours at laboratory conditions, which indicated the synthesis copper complex from schiff base ligand was stable in TBS buffer complexes within 48 hours.

3.2. Structural and morphological characterization of compounds

Synthesised compounds were Collected and characterized by various spectroscopic, structural, vibrational and morphological Characterization techniques like UV-Vis, FT- IR, H^1-NMR, XRD, TGA etc. The structure and particle size of copper complex was characterized by a Bruker axis D8 Phase X- ray diffractometer (XRD) using Cu K $\propto$ radeation ($\lambda = 1.54A°$) in the 2θ ranging from 20 to 80°.

3.2.1 FT-IR spectral studies

The FT-IR spectral data of Compounds with relevant vibrational bands are listed in table 2. The ligand showed a band in the range of 1615 – 1680 cm^{-1} which is due to the presence of C=O group of the hydrazone moiety, this band was shifted to lower wave number region 5-75 cm^{-1} in its copper complex, indicating the coordination of azomethine nitrogen of the ligand with Cu^{2+} ion & participation of C=S functional group in coordination with Cu^{2+} ion. The FT-IR spectra of ligand appear at 780 cm^{-1} which is shifted to the lower frequency by 40 cm^{-1} in case of copper complex. Further, the coordination of Cu^{2+}ion with azomethine nitrogen was supported by the appearance of

a non-ligand band at 600-400 cm^{-1} region due to the stretching of Cu-N bond. From the above spectral data it was concluded that ligand acts a monobasic tridentate ligand with NNS donor sites.

Table 2. The FT-IR Spectral data of ligand and its copper complex.

Sr. No.	Compound	ν (C = N)	ν (C -S)	ν (Cu - N)
1.	Ligand $[C_{52}H_{44}N_{16}O_8S_2]$	1613	780	600
2.	$[Cu_{52}H_{44}N_{16}O_8S_2]$	1622	786	616

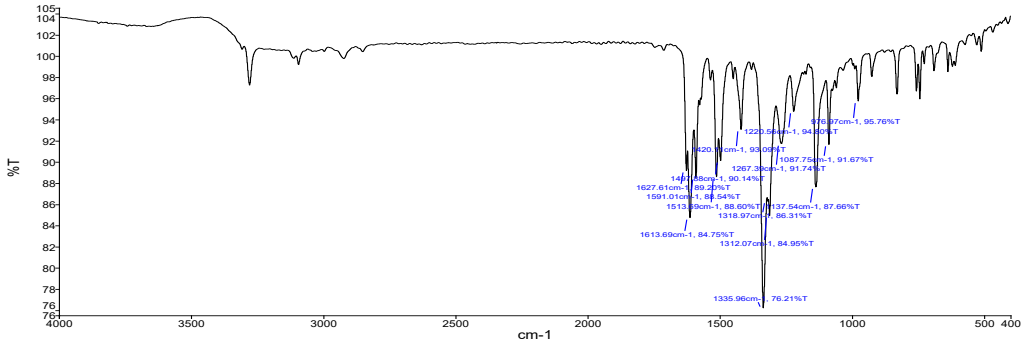

Fig. 6. FT-IR spectra of Schiff base ligand.

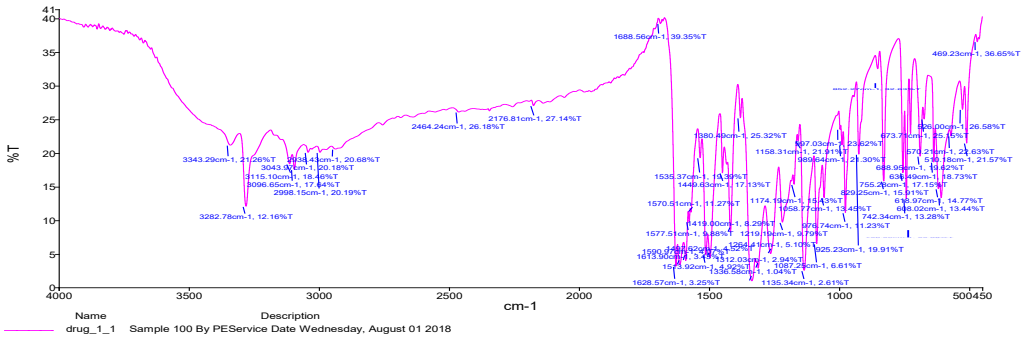

Fig. 7. FT-IR spectra of copper(II) complex of Schiff base ligand.

3.2.2. H [1] NMR spectral studies

The H [1]NMR spectra of copper complex was determined in $CDCl_3$ Solvent. The H [1] NMR spectra of copper complex showed some different NMR peaks as compared to ligand. A broad H [1] NMR signal appear at 11.62 ppm and a signal appear at 11.30 ppm of ligand are assigned to the N-H bonding of azomethine functional group which appear due to reaction between hydrazones and thiosemicarbazide hydrochloride and presence of aliphatic protons in ligand. The presence of two H [1] NMR signals in ligand indicates that ligand present in keto form. This statement in also supported by the FT-IR spectra of ligand in which vibrational frequencies ν (N-H) at 3260 and 1640 cm^{-1} were present. In the proton – NMR spectra of complex, NMR signals at 11.82 and 11.45 PPM were disappeared after coordination with Cu^{2+}ions which indicates that the ligand coordinate with copper (II) ions via nitrogen and sulfur atoms. In H NMR spectra of Cu (II) Complex in $CDCl_3$ solution was shown in figure 8. The following signals are exhibited by the schiff base; phenolic -OH group at 11.59δ, phenyl as multiplet at 7.94- 7.65δ, -N- CH_3 at 3.45, =C-CH_3 at 2.50δ. In copper complex, all the peaks were slightly shifted to downfield region due to metal-coordination.

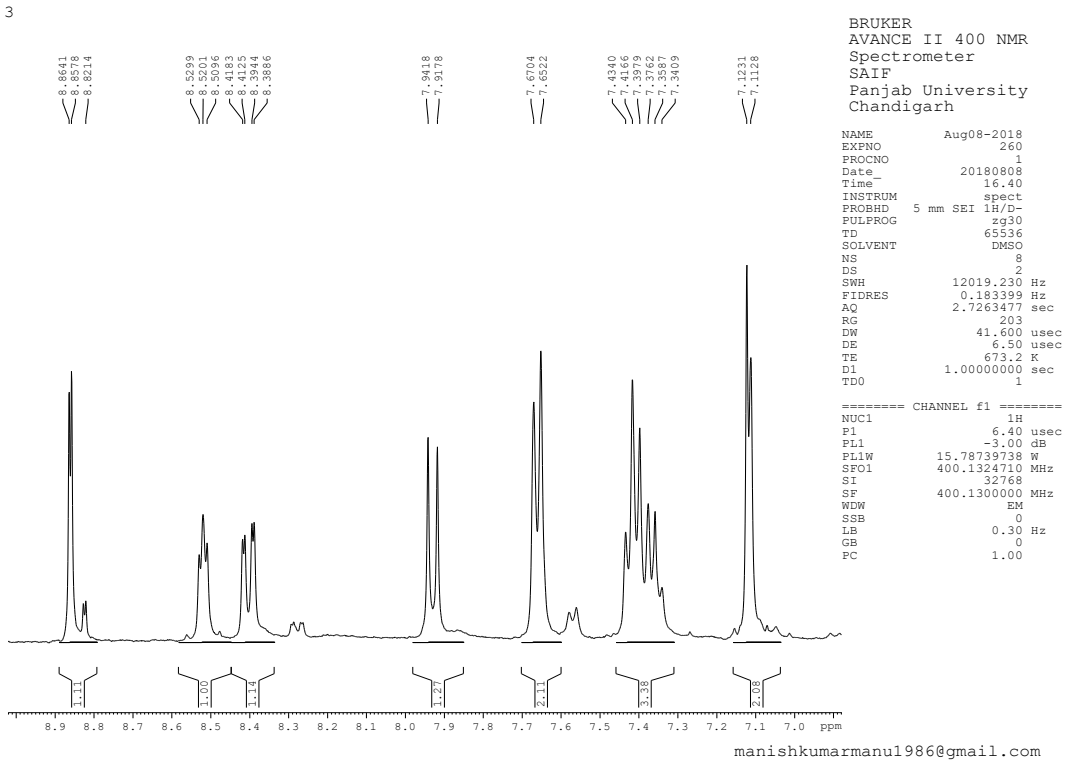

Fig. 8 NMR spectra of copper (II) complex of schiff base ligand.

3.2.3. Electronic spectral studies

The UV- Visible Spectra of ligand and its copper complex were recorded in CH_3CN solution at 300K. Ligand shows two peaks at 32054 and 24866 cm^{-1} due to intra ligand change transfer (INCT) transition. Copper complex showed a band at 19884 cm^{-1} and another strong broad band at 12568 cm^{-1} which are assignable to $^2B_{2g} - {}^2B_{1g}$ and, $^2B_{2g} - {}^2A_{1g}$ transitions which were appeared at 32847 and 24938 cm^{-1} region. In addition two INCT bands revealed that the copper complex has distorted octahedral geometry.

3.2.4 XRD studies

The X-ray diffraction pattern of copper complex is shown in fig -. Single Crystal of copper complex could not be isolated from any solvent. The powdered XRD of copper complex showed sharp crystalline peaks indicating its crystalline nature. Some additional XRD peaks were also appeared in XRD spectrum due to formation of coordinate bonds between ligand and Cu^{2+}ions.Highest intensity peak is observed at 26.528º in copper complex. All peaks are fairly sharpened in complex is due to the quantum confinement of ligand with cu^{2+} ion. X-ray diffraction pattern of copper complex indicates that the size of complex is decreased due to formation of strong coordinate bonds between ligand and cu^{2+}ion. As a result of decrease in size of copper complex, the value of full width half maximum (FWHM) increases simultaneously. The crystalline size of complex was calculated by prominent peaks appeared in X-ray diffraction spectra, by using Debye – Scherrer's formula.

$$D = \frac{0.94\,\lambda}{\beta . Cos\,\theta}$$

where $\lambda =$ wave langht of $X -$ ray radiations

$\beta =$ Full width at half maximum of diffraction lines.

$\theta =$ diffraction angle.

Using the FWHM maximum intensities of X- ray spectra pattern, the average size of particle of copper complex is 26.52 A °.

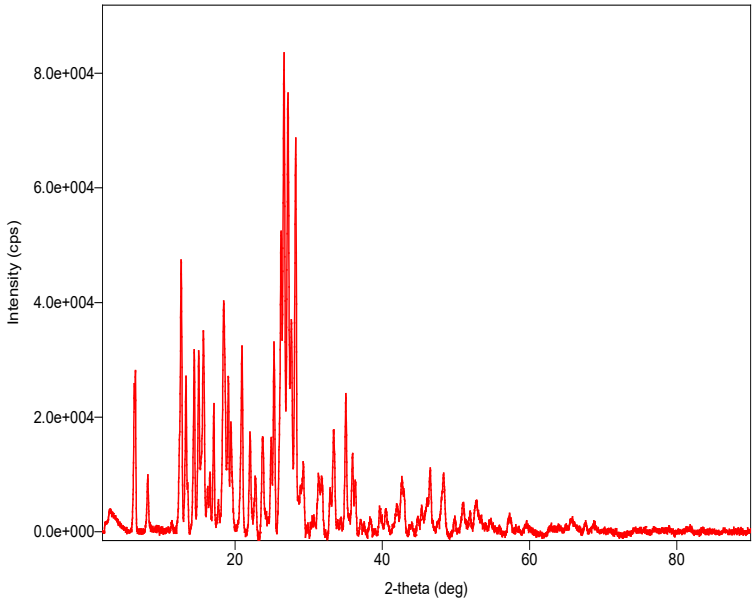

Fig. 9. Powder XRD pattern of [Cu($C_{52}O_8H_{44}N_{16}S_2$)].2H_2O.

3.2.5. Thermogravimetric analysis of compounds

Thermogravimetric weight loss curves and the corresponding differential thermogravimetric (DTG) curves for the schiff base ligand and its Cu(II) complex are shown in figure 10 & 11. The Schiff base ligand showed two well defined steps at 133.69 – 326.26 (73.31%). The loss in weight its Cu(II) complex is 142 .18 – 313 .49 (10.034 %).This large weight drop can be explained by considering that the residue as a 1:1 mixture of Cu_2O and Cu O residues.

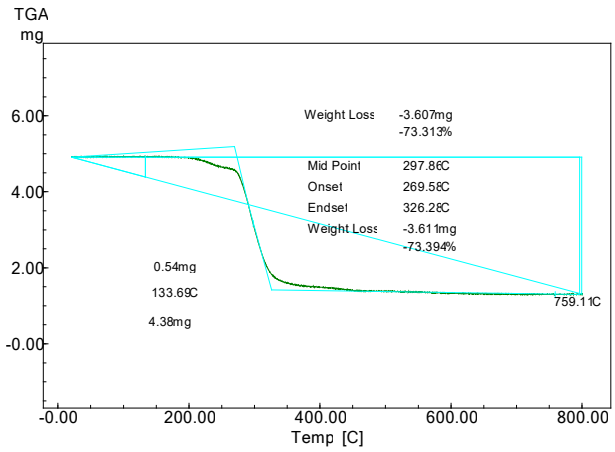

Fig. 10. TGA Spectra of Schiff base ligand.

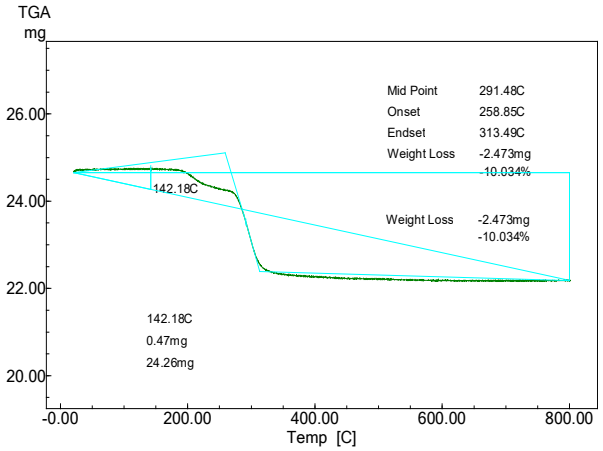

Fig. 11. TGA spectra of copper complex of Schiff base ligand.

Table 3. TGA data of ligand and its copper(II) complex.

S.No.	Compounds	Temperature range (°C)	Mass loss found (% calculated)	Assignment
1.	**[($C_{52}O_8H_{44}N_{16}S_2$)] Schiff base ligand**	133.69 – 326.26	73.31	Loss of thiosemicarbazone group
2.	**[Cu($C_{52}O_8H_{44}N_{16}S_2$)].$2H_2O$**	142 .18 – 313 .49	10.34	Formation of Cu O residue

3.2.6. Evaluation of in vitro antioxidant activities of compounds

In DPPH method, free radical scavenging activity, antioxidants are reacting with the stable free radical 1,1 di phenyl-2-picrylhydrazyl (DPPH) forming a colourless 1,1 di-phenyl-2-picryl hydrazine,, When DPPH compound receives an election or hydrogen radical from compounds it becomes more stable, and its absorption decreases simultaneously . The DPPH antioxidant activity was expressed as IC_{50} values, whose concentration is sufficient to obtain 50% of maximum scavenging activity. The IC_{50} Values of ligand and its copper complex is depicted in table 3. In this experiment, ascorbic acid was used as a standard substance. The results of DPPH activity of compounds explained the influence of copper complex on the initiation of free radical activity. The results of antioxidant activities of compounds clearly indicate that copper complex showed good antioxidant activity as compared to schiff base ligand. The free radical scavenging activity of compounds depends upon the structural features, geometries of complexes and presence of different election withdrawing or election releasing functional groups in the compounds.

Table 4. In vitro antioxidant activities of compounds.

Sr. No.	Compound	IC_{50} $\mu g/ml$
1.	[$C_{52}H_{44}O_8N_{16}S_2$] Ligand	260.95 ± 0.66
2.	[Cu($C_{52}O_8H_{44}N_{16}S_2$)] Copper complex	130.52±3.76

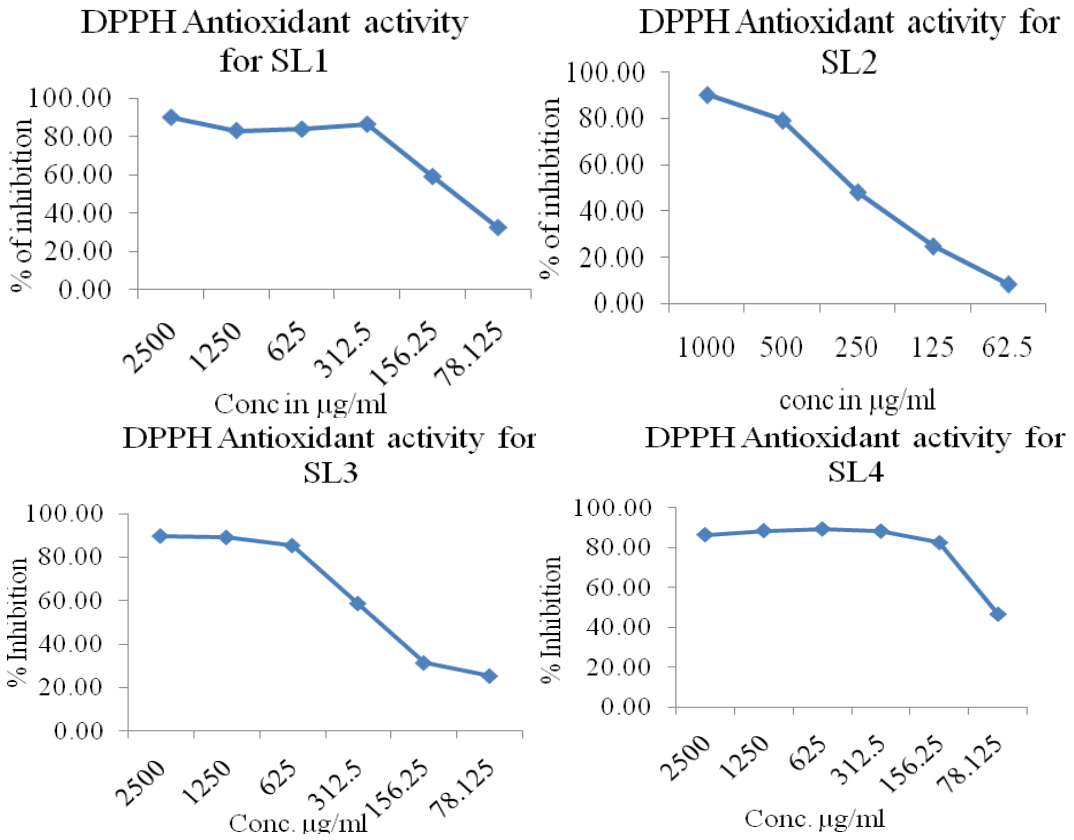

Fig. 12. DPPH antioxidant activities of compounds.

3.2.7. Evaluation of in vitro anticancer activities of compounds

The synthesised ligand and its Cu (II) complex was evaluated for their effectiveness against the human breast cancer cell lines MCF-7 using MTT assay. For comparison purpose, the cis-platin (an anticancer drug) was used as standard drug under the same experimental conditions. The values of cell Viability were calculated after the tested compounds were incubated for 48 hrs. The CTC_{50} values were calculated using MTT assay as shown in Table 4. Human Breast Carcinoma. MCF-7 cell lines were procured from National Centre for Cell Science were cultured in DMEM Supplement with 10% inactivated FBS (Fetal Bovine Serum, penicillin (100 IU/ml).Streptomycin (100 $\mu g/ml$), and amphotericin – B (5 $\mu g/ml$) in an humidified atmosphere of 5% CO_2 at 37°c until confluent .The cells were dissociated with TPVG Solution (0.2% trypsin,0.02% EDTA, 0.05% glucose in PBS). The stock culture were grown in 25 cm^2 culture flasks and all the experiments were carried out in 96 wells micro titre plates (Tarsons). India, Pvt. Ltd. Kolkata, India.

The schiff base ligand, copper chloride, Cu (II) complex of schiff base ligand and cisplatin were tested cytotoxicities towards the MCF-7 Breast Cancer cell lines in-vitro via MTT assay. The IC_{50} Values obtained are summarized in Table 4.

Table 5. IC_{50} Values of anticancer activity of compounds.

Sr. No.	Compounds	IC50[a] ($\mu g/ml$)
1.	Schiff base ligand $[C_{52}H_{44}N_{16}O_8S_2]$	13.01 ± 0.1
2.	Cu Cl_2 .$2H_2O$.	34.79± 0.3
3.	$[Cu(C_{52}H_{44}N_{16}O_8S_2)]$	7.21± 0.1
4.	Cisplatin(standard anti -cancer drug	1.9

[a] IC_{50} values were presented as the mean SD (standard error of the mean) from five independent experiments.

Results showed that the copper complex has potent inhibition activity towards MCF-7 breast cancer cell lines, with IC_{50} Values in the micro molar range and definitely less than cisplatin. In contrast, the free schiff base ligand and copper salt displayed relatively high cytotoxicity towards MCF-7 cell lines. The enhanced anticancer activity of copper complex of schiff base ligand may be due to synergistic effect of cu ions and schiff base ligand. Apart from the potency, the copper complex was much less toxic towards human normal cells (H1-7702), with IC_{50} Value $7.21\pm0.1(\mu g/ml)$ which was slightly higher than that of IC_{50} Value of cisplatin. The results also showed that the copper complex showed good selectivity between normal cells and cancerous cells, and thus have the potential for application in human breast cancer chemotherapy.

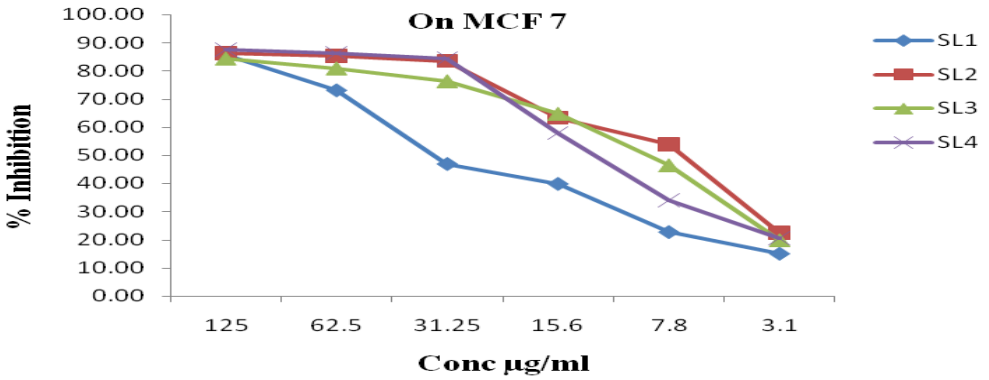

Fig. 13. In vitro anticancer activities of compounds.

4. Conclusion

In the present study, we reported the Anticancer activity of Novel Schiff base Copper (II) Complex: Synthesis & Characterization. All compounds were fully characterized by various spectroscopic methods like FT-IR, H ^{1} NMR, molar conductance and elemental analysis. According to results of spectral studies of compounds, it is concluded that synthesised Cu complex showed distorted octahedral geometry with the ligand having tridentated NNS cheating motif. Cu (II) complex of schiff base ligand showed significant anticancer activity against human breast cancer cell lines. In this study, the use of DMSO plays a very important role in reducing reaction time, reducing minimum possibilities of side reactions and proper conversion of ligand into its copper complex in a very Short Time. This synthetic method has a very strong potential to be utilised for large scale production of metallodrugs. From the results of biological activities of compounds it has been observed that the synthesised copper complex of thiosemicarbazone schiff base ligand may be consider as a good drug candidate for the treatment of various cancers.

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References

[1] E. Pahontu, V. Fala, A. Gulea, D. Poirier, V. Tapcov, T. Rosu, Molecules, vol. 18, no. 8, p. 8812, 2013; https://doi.org/10.3390/molecules18088812

[2] C. Fischer, B. Koenig, Beilstein Journal of Organic Chemistry, vol. 7, no. 1, pp. 59-74, 2011;

https://doi.org/10.3762/bjoc.7.10
[3] T. Rosu, M. Negoiu, S. Pasculescu, E. Pahontu, D. Poirier, A. Gulea, European Journal of Medicinal Chemistry, vol. 45, no. 2, pp. 774-781, 2010; https://doi.org/10.1016/j.ejmech.2009.10.034
[4] S. Ammaji, S. Masthanamma, R. R. Bhandare, S. Annadurai, A. B. Shaik, Arabian Journal of Chemistry, vol. 15, no. 2, Article ID 103581, 2022; https://doi.org/10.1016/j.arabjc.2021.103581
[5] M. Braña, M. Cacho, A. Ramos et al., Organic and Biomolecular Chemistry, vol. 1, no. 4, pp. 648-654, 2003; https://doi.org/10.1039/b209042b
[6] V. Graur, I. Usataia, P. Bourosh et al., Applied OrganometallicChemistry, vol. 35, no. 4, Article ID e6172, 2021; https://doi.org/10.1002/aoc.6172
[7] WHO Report on Cancer: Setting Priorities, Investing Wisely and Providing Care for All, World Health Organization, Geneva, Switzerland, 2020.
[8] T. de Santana, M. de Oliveira Barbosa, P. de Moraes Gomes,A. da Cruz, T. da Silva, A. Leite, European Journal of Medicinal Chemistry, vol. 144, pp. 874- 886, 2018; https://doi.org/10.1016/j.ejmech.2017.12.040
[9] U. P. Yadav, A. J. Ansari, S. Arora et al., Bioorganic Chemistry, vol. 118, Article ID 105464,2022; https://doi.org/10.1016/j.bioorg.2021.105464
[10] B. A. Chabner, T. G. Roberts, Nature Reviews Cancer, vol. 5, no. 1, pp. 65-72,2005; https://doi.org/10.1038/nrc1529
[11] E. Pahontu, F. Julea, T. Rosu et al., Journal of Cellular and Molecular Medicine, vol. 19, no. 4, pp. 865-878, 2015; https://doi.org/10.1111/jcmm.12508
[12] J. Wang, Z.-M. Zhang, M.-X. Li, Inorganica Chimica Acta, vol. 530, Article ID 120671, 2022; https://doi.org/10.1016/j.ica.2021.120671
[13] M. Belicchi Ferrari, F. Bisceglie, G. Pelosi, P. Tarasconi,R. Albertini, S. Pinelli, Journal of Inorganic Biochemistry, vol. 87, no. 3,pp. 137-147, 2001; https://doi.org/10.1016/S0162-0134(01)00321-X
[14] A. Gulea, D. Poirier, J. Roy et al., Journal of Enzyme Inhibition and Medicinal Chemistry, vol. 23, no. 6, pp. 806-818, 2008; https://doi.org/10.1080/14756360701743002
[15] E. Pahont¸u, C. Paraschivescu, D. C. Ilies¸ et al., Molecules, vol. 21, no. 5, p. 674, 2016; https://doi.org/10.3390/molecules21050674
[16] M. Manowitz and G. Walter, Journal of Pharmaceutical Sciences, vol. 54, no. 4, p. 650, 1965; https://doi.org/10.1002/jps.2600540438
[17] B. A. Gingras, G. Colin, and C. H. Bayley, Journal of Pharmaceutical Sciences,vol. 54, no. 11, pp. 1674-1675, 1965; https://doi.org/10.1002/jps.2600541127
[18] F. H. H. Carlsson, A. J. Charlson, E. C. Watton, Carbohydrate Research, vol. 36, no. 2, pp. 359-368, 1974; https://doi.org/10.1016/S0008-6215(00)83057-8
[19] Z. A. Kaplancıklı, M. D. Altıntop, B. Sever, Z. Cant¨urk, A. Ozdemir, Journal of Chemistry, vol. 2016, Article ID 1692540,7 pages, 2016; https://doi.org/10.1155/2016/1692540
[20] A. Karakuçuk-Iyidogan, B. Aydınoz, T. Taskın-Tok, E. E. Oruç-Emre, J. Balzarini, Pharmaceutical Chemistry Journal, vol. 53, no. 2, p. 139, 2019; https://doi.org/10.1007/s11094-019-01968-3
[21] H. R. Fatondji, S. Kpoviessi, J. Bero et al., African Journal of Pure and Applied Chemistry,vol. 5, no. 4, p. 59, 2011; https://doi.org/10.4314/ijbcs.v4i6.64982
[22] F. A. French, E. J. Blanz Jr, Journal of Medicinal Chemistry, vol. 9,no. 4, pp. 585-589, 1966; https://doi.org/10.1021/jm00322a032
[23] B. A. Booth, E. C. Moore, A. C. Sartorelli, Cancer Research, vol. 31, no. 3, p. 228,1971.
[24] J. Easmon, G. Heinisch, W. Holzer, B. Rosenwirth, Arzneimittel Forschung, vol. 39, no. 10, p. 1196,1989; https://doi.org/10.1002/chin.199009203
[25] A. Matesanz, P. Souza, Mini Reviews in Medicinal Chemistry, vol. 9, no. 12, pp. 1389-1396, 2009; https://doi.org/10.2174/138955709789957422
[26] K. C. Agrawal, A. C. Sartorelli, Progress in Medicinal Chemistry, vol. 15, pp. 321-356, 1978;

https://doi.org/10.1016/S0079-6468(08)70259-5
[27] H. Beraldo, D. Gambino, Mini Reviews in Medicinal Chemistry,vol. 4, p. 31, 2004; https://doi.org/10.2174/1389557043487484
[28] D. R. Richardson, D. S. Kalinowski, V. Richardson et al., Journal of Medicinal Chemistry, vol. 52, no. 5, pp. 1459-1470, 2009; https://doi.org/10.1021/jm801585u
[29]. Beraldo H, Gambinob D, 2004 Mini-Rev. Med.Chem. 4 31; https://doi.org/10.2174/1389557043487484
[30] Cavalcanti de Queiroz A, Alves M A, Barreiro E J,Lima L M, Alexandre-Moreira M S 2019 Semicarbazone Derivatives as Promising Therapeutic Alternatives in Leishmaniasis Exp. Parasitol. 201 57; https://doi.org/10.1016/j.exppara.2019.04.003
[31] Casas J S, Garcı'a-Tasende M S, Sordo J 2000 Main Group Metal Complexes of Semicarbazones and Thiosemicarbazones.A Structural Review Coord. Chem. Rev. 209 197; https://doi.org/10.1016/S0010-8545(00)00363-5
[32] Santini C, Pellei M, Gandin V, Porchia M, Tisato F, Marzano C 2014 Advances in Copper Complexes as Anticancer Agents Chem. Rev. 114 815; https://doi.org/10.1021/cr400135x
[33] Qi J, Liang S, Gou Y, Zhang Z, Zhou Z, Yang F, Liang H 2015, Eur. J. Med. Chem. 96 360; https://doi.org/10.1016/j.ejmech.2015.04.031
[34] Venkatachalam T K, Bernhardt P V, Noble C J, Fletcher N, Pierens G K, Thurecht K J, Reutens D C 2016, J. Inorg. Biochem.162 295; https://doi.org/10.1016/j.jinorgbio.2016.04.006
[35] Marzano C, Pellei M, Santini F T 2009, Copper Complexes as Anticancer Agents Anticancer Agents Med. Chem. 9 185; https://doi.org/10.2174/187152009787313837
[36] Tiago F S, Santiago P H O, Amaral M M P, Martins J B L, Gatto C C 2016, J. Coord. Chem. 69 330; https://doi.org/10.1080/00958972.2015.1105367
[37]. Gatto C C, Miguel P M, Almeida C M, Santiago P H O,Paier C R K, Pessoa C 2017, Transit. Met. Chem. 42 503; https://doi.org/10.1007/s11243-017-0154-8
[38] Dziewulska-Kuaczkowska, A., 2010, Thermochim.Acta 421, 151- 159; https://doi.org/10.1016/j.poly.2009.10.017
[41] R. C. Mawya, D.D. Mishra, P.K. Trivedi, A. Gupta, Inorganic Met-org.chem, 24, 17 (1994); https://doi.org/10.1080/00945719408000091
[42]. M.K.M. Nair, P.K. Radhakrishnan, Inorg. Met.-org.chem.,26,529 (1996)