Volume 07, Issue 05 (September-October 2024), PP 102-117 www.ijmsdr.org
ISSN: 2581-902X

International Journal of Medical Science and Dental Research

Transition Metal Complexes of New Schiff Base Derived from Trimethoprim with 2-Hydroxy-1-Naphthaldehyde: Synthesis, Characterization and Antioxidant Activities

MAY JODA KAREEM ,
PhD. Ministry of Education, Baghdad, Iraq,
https://orcid.org/0009-0005-7957-4721,

Abstract: In the present study, the new Schiff base ligand (HL) was prepared by condensing 2,4- diamine (Trimethoxybenzyl 3,4,5)-5 pyrimidine and 2-hydroxy-1-naphthaldehyde. In turn, the transition metal complexes were prepared. The ligand and its metal complexes Co(II), Ni(II) , Cu(II) and Zn(II) have been characterized by elemental analysis, metal content, chloride containing, molar conductance, FT-IR spectra , ^{1}H-NMR, UV-Vis spectra, magnetic susceptibility and mass spectra. Antioxidant efficiencies of compounds were estimated versus 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical. Then, they were compared to L-ascorbic acid used as a phenolic reference to investigate the antioxidant activity. The selected ligand and complexes were tested for the antioxidant property.

Key words: Antioxidant, Complexes, Mass spectra, Schiff bases

I. Introduction

Schiff bases were discovered by a German chemist, the Nobel Prize winner Hugo Schiff, in 1864 [1]. Schiff bases were derived from an amino and carbonyl compound and comprise an important class of ligands that coordinate with metal ions via azomethine nitrogen and have been investigated extensively. In azomethine derivatives, the C=N linkage is essential for biological activity [2]. Schiff bases play an important role in the biological system, such as anticancer, antibacterial, antiviral, antifungal and other biological properties. These have been extensively used as ligands in coordination chemistry because of their excellent donor abilities as a chelating agent [3-6]. Schiff bases of aliphatic aldehydes are relatively unstable and are readily polymerizable, while those of aromatic aldehydes, having an effective conjugation system, are more stable [7]. Schiff base-transition metal complexes have gained considerable attention in recent years due to their stability, ease of modification and enormous biological properties [8, 9].

Trimethoprim is a chemotherapeutic agent known as dihydrofolate reductase inhibitors. It is used in prophylaxis treatment and urinary tract infections [10]. Aroylhydrazones can act as an N4 chelator forming redox efficient complexes, generate reactive oxygen species, inhibit metalloproteins, relate with DNA and grant disorder of intracellular homeostasis [11]. Trimethoprim and its derivatives comprise a broad spectrum of antimicrobial agents with anti-parasitic activity and were first described by Roth et al. [12].

Antioxidants play an important role in the anti-cancer and anti-inflammatory mechanism of action. They protect the cells against their toxic effects, also have a role in slowing the aging process and preventing a heart disease and stroke [13-15]. The body has various mechanisms to lower oxidative stress by producing either endogenous or exogenous antioxidants [16]. Dietary antioxidants play an important role in the neutralization of free radicals (Figure-1, Action of antioxidants) [17, 18].

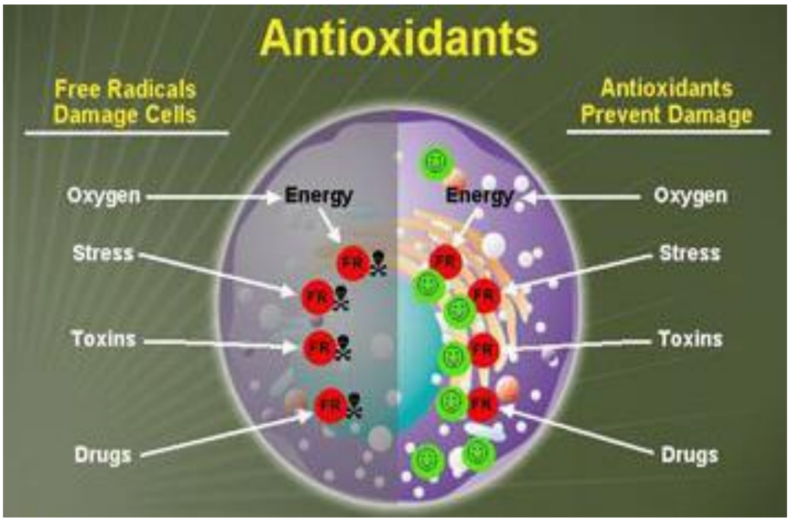


Figure 1: Action of antioxidants

II. Experiment

2. 1. Materials and measurements

All the chemicals and reagents were acquired from the commercial sources (Sigma-Aldrich, Merck, *etc*.) and used without further purification. [1]H-NMR spectra were prepared using Bruker Ultra Sheild 300 MHz NMR, and Elemental microanalysis (C.H.N) were was conducted on Eurovector EA 3000A, Al al-Bayt University (Jordan). The content of metal ions was calculated gravimetrically as metal oxides. The molar conductance measurements of metal complexes of the ligand were obtained using Conductometer WTW, at 25˚C and concentration of 1 x10^{-3}M. Magnetic measurements were made using the Balance of Johnson mattey catalytic system division at 25 °C, England. The UV vis spectra were examined using UV.-Vis. spectrophotometer, UV-1800 Shimadzu by cell quartz 1.0cm of wavelength (200-1100 nm), using 1 cm quartz cell. Fourier Transform Infrared (FT-IR) spectra were measured using SHIMADZU FT-IR 8400S Fourier transforms, within the wavenumber region of 4000-200 cm-1 using KBr disc and CsI disc, Department of chemistry, College of Science, University of Baghdad. Mass spectra were measured using the following instruments: GC MS –QP 2010 VLTRA, Department of chemistry, College of Science, AL- Mustansiriyah University.

2.2. Synthesis of ligand (HL): (*E*)-1-((4-amino-5-(3,4,5-trimethoxybenzyl) pyrimidin-2-ylimino)methyl)naphthalen-2-ol)

This ligand was prepared using the reaction of 3.4 mmol, 1g of 2,4- diamine Trimethoxybenzyl 3,4,5-5 pyrimidine and 3.4 mmol, 0.6 g of 2-hydroxy-1-naphthaldehyde with a pure alcoholic medium of 30 ml with the addition of 2-3 drops of hydrochloric acid (HCl) to the solution. The mixture was left to reflux for 4 hours. Then, it was raised to filter and wash with ethanol and water. The product was recrystallized from ethanol–ether (1:1). It was collected and dried over anhydrous $CaCl_2$ in vacuum. The melting point was measured for the ligand (235-238ºC), M.wt [1]HNMR of ligand HL in DMSO-d6 showed peaks at δ (2.328-2.882) ppm. These were assigned to the solvent DMSO. The peaks observed at δ (3.235) (2H) s , (CH_2), δ (3.535-4.327) (9H) m, (OCH_3), δ (6.646-7.412) (9H) m arom , δ(8.295) (2H) s, (NH_2), 9.211 (1H) s were assigned to the azomethine group (N=C-H), and the peak signal located at δ (12.255) ppm was assigned to the proton (OH) phenolic ring [19].

2.3. General procedure for the synthesis of metal complexes

It was prepared by dissolving Schiff base ligand HL in an ethanolic solution (2mol) (30 ml) around a beaker. Then, NaOH + water was added and stirred. Next, metal salt (1mol) was added that dissolved in ethanol– water (1:1) (20 ml). The mixture was heated under reflux for 2 h and was stirred. It was precipitated and the solution was filtered when it was hot. The product was washed by ethanol and recrystallized in ethanol and diethyl ether. Then, the product was collected and dried over anhydrous $CaCl_2$ in vacuum. Scheme-1.b was the proposed structure of metal complexes.

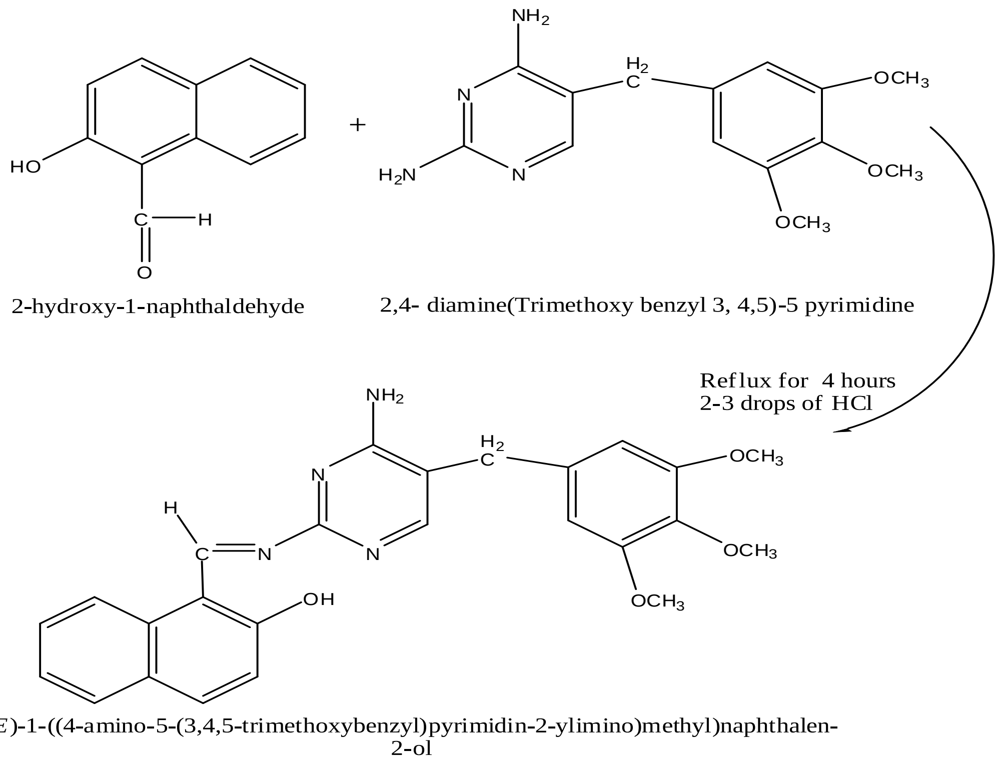
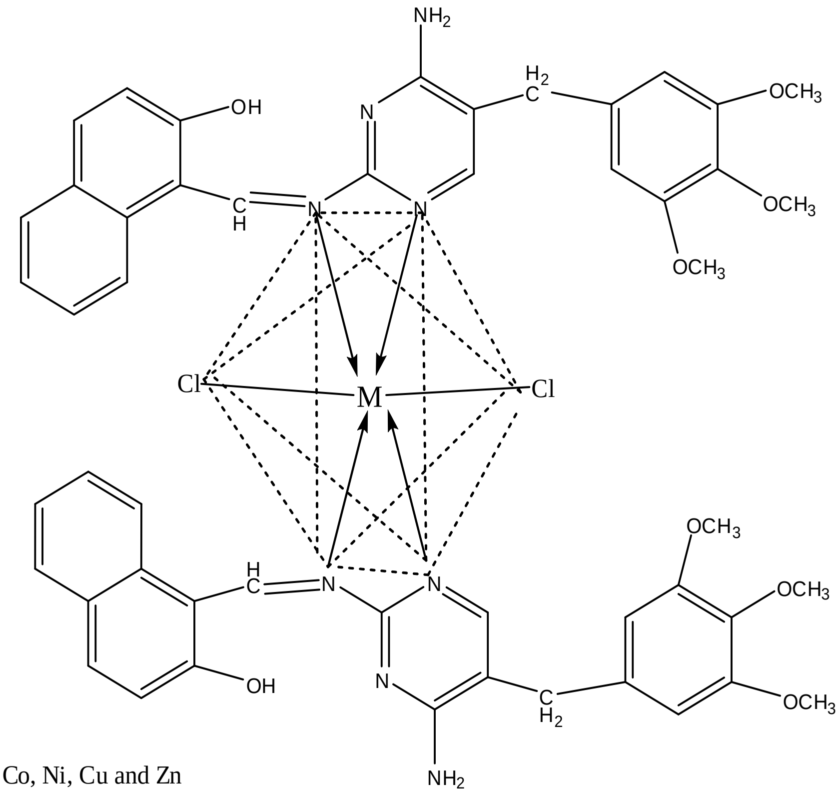


Figure-1: a- Synthesis route of the ligand HL



M(II)= Co, Ni, Cu and Zn

Figure -1: b- Proposed structure of metal complexes

2.4. Measurement of antioxidant efficacy through DPPH manner

To assess the antioxidant efficacy of ligand and metal complexes, L-ascorbic acid was used as a phenolic reference. A chain of standards was prepared for L-ascorbic acid. Five normal solutions were prepared at various condensations (0.2, 0.4, 0.6, 0.8, and 1 mmol1^{-1} of a 10 mmol l^{-1} solution of L-ascorbic acid. Ethanol was used as the diluent. A 6 ml of 45 µg ml^{-1} DPPH solution was added to 100 µL of each normal solution for L-ascorbic acid. The mixture has been brood at room temperature of 30 minutes at darkness, and thereafter, the absorbance of the reacted mixture was read as 517 nm. The new Schiff base (HL) ligand as well the metal complexes were dissolved in DMSO as well as ethanol to get a condensation of 10 mmol l^{-1}. Stock solutions were then diluted as 0.2, 0.4, 0.6, 0.8 and 1 mmol.l^{-1}. For the L-ascorbic acid like standard, the percentage of DPPH root scavenger was calculated via Equation 20. (Figure -2 Method of assessing free radical scavenging activity).

$$\text{DPPH scavenging ability (\%)} = \frac{\textbf{\textit{Abs control}} - \textbf{\textit{Abs sample}}}{\textbf{\textit{Abs control}}} \times 100$$

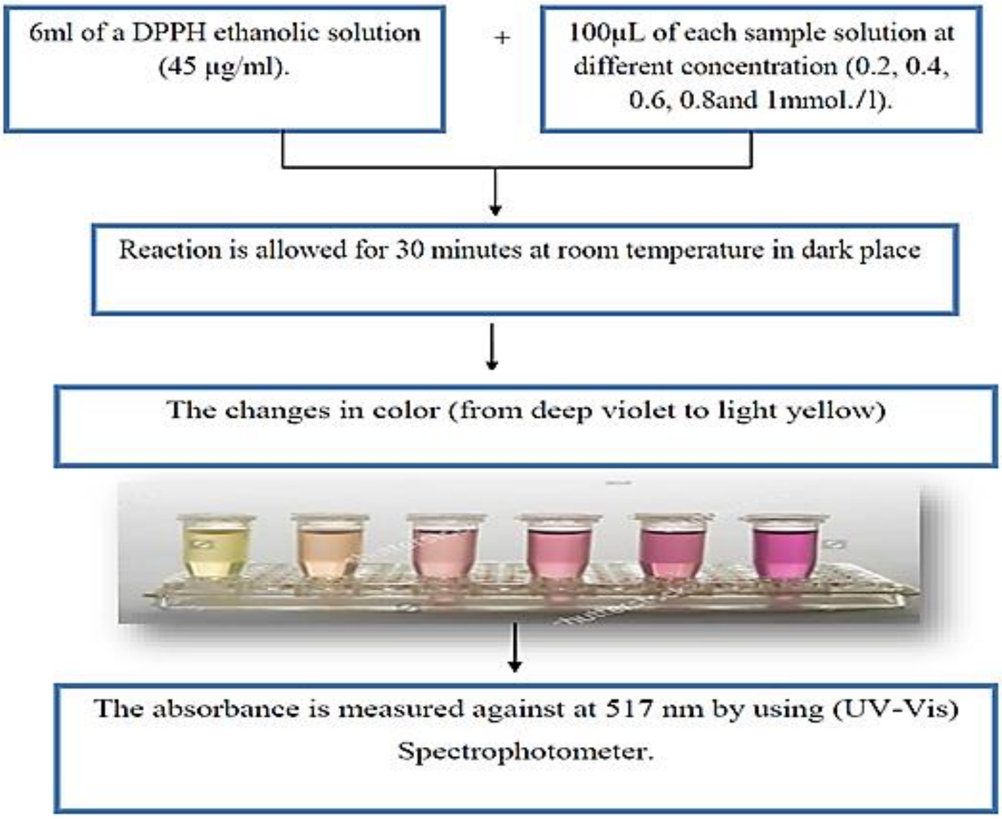


Figure -2: Method of assessing free radical scavenging activity

III. Results and discussions

The physical properties and elemental results of C.H.N. analyses, chloride content and metal content of the prepared compounds are described in (Table -1).

Table -1:- Elemental microanalysis results and some physical properties of ligand HL and metal complexes

Compound	Formula	M.Wt	Elemental Analysis Cal (Found)%				
			C	H	N	M	Cl
HL	$C_{25}H_{24}N_4O_4$	444.18	(66.14) 67.56	(5.23) 5.40	(12.07) 12.61	-	-
[Co (HL)$_2$Cl$_2$]	$C_{50}H_{48}N_8O_8CoCl_2$	1017.93	(58.20) 58.94	(5.11) 4.71	(10.83) 11.00	(5.21) 5.78	(7.01) 6.97
[Ni (HL)$_2$Cl$_2$]	$C_{50}H_{48}N_8O_8NiCl_2$	1017.69	(57.70) 58.95	(5.02) 4.71	(10.92) 11.00	(5.83) 5.76	(7.22) 6.97
[Cu (HL)$_2$Cl$_2$]	$C_{50}H_{48}N_8O_8CuCl_2$	1022.54	(58.45) 58.67	(5.21) 4.69	(11.15) 10.95	(6.43) 6.21	(7.03) 6.94
[Zn (HL)$_2$Cl$_2$]	$C_{50}H_{48}N_8O_8ZnCl_2$	1024.38	(57.30) 58.57	(4.80) 4.68	(9.67) 10.93	(5.95) 6.38	(6.56) 6.93

3.1 Mass spectrum

The mass spectra of the new ligand were obtained using the electron impact of fragmentation [21, 22]. The electron impact mass spectrum of ligand HL is shown in Figure -2. The estimated molecular weight of this ligand is (444.18) g/mol. The spectrum exhibited a peak at (444) m/z corresponding to the Schiff base moiety [$C_{25}H_{24}N_4O_4$] which was assigned to $[M]^{+\cdot}$. Other characteristic observed at 277, 167, 143 and 134 m/z may be assigned to various fragments. Their intensity gives an idea of the stability of fragments. The suggested fragmentation pathways and structural assignments of fragments are described in Figure-3.

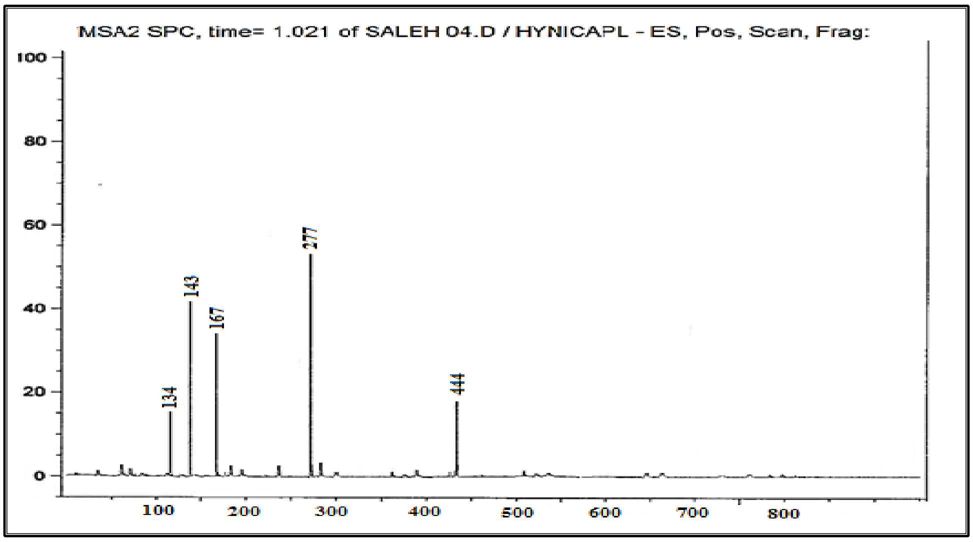


Figure -2: LC-Mass spectrum of ligandHL

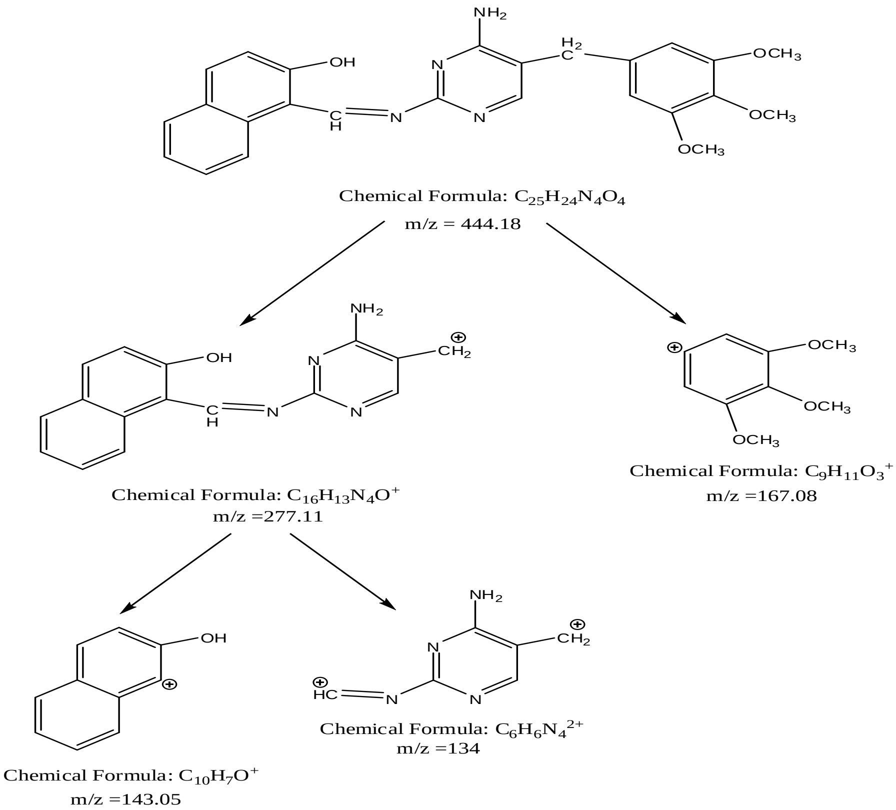


Figure -3: Fragmentation pattern of ligand HL

3.2 Infrared analysis

The important characteristics, the absorption bands of the ligand (HL) and metal complexes are described in Table 2. The IR spectra of all complexes showed ligand bands with appropriate shifts due to a complex formation. All the data suggest that the HL ligand coordinates with metal ion through the nitrogen azomethine groups and the nitrogen pyrimidine ring acting as a bidentate ligand [21, 23-25].

Table -2 :- Infrared spectral data of the ligand (HL) and metal complexes

Sym.	*v*(OH) Ph.	*v*(NH$_2$)	*v*(C-H) Arom.	*v*(C-H) aliph.	*v*(C=N) azome-thine	*v*(C=C) Arom.	*v* (M-N)	*v* (M-Cl)
HL	3421.23	3397.73	3258.17	2934.19	1635.36	1456.61	-	-
[Co(HL)$_2$Cl$_2$]	3443.47	3355.27	3276.22	2959.56	1659.33	1473.85	526.42	488.66
[Ni(HL)$_2$Cl$_2$]	3441.12	3351.22	3278.68	2981.59	1657.57	1478.68	525.28	490.72
[Cu(HL)$_2$Cl$_2$]	3437.43	3353.47	3273.43	2973.46	1667.58	1470.65	527.41	483.63
[Zn(HL)$_2$Cl$_2$]	3440.22	3360.12	3280.27	2977.10	1663.37	1467.22	532.12	478.13

3.3 Electronic spectra and magnetic moment studies

The UV-Vis spectra of ligand HL and their metal complexes are summarized in Table-3 [26-31].

Table -3:- Electronic Spectral Data of Metal Complexes with (HL) Ligand, Molar Conductivity in (DMSO 1×10^{-3}M) and Magnetic Moments

Complex Geometry	λ_{max} (nm)	*v* cm^{-1}	ABS	ε_{max} L mol^{-1}cm^{-1}	Assignment	Λ_m cm^2 Ω^{-1}mol^{-1}	μ_{eff} B.M
HL	272 350	36764.7 28571.4	2.216 1.632	2216 1632	$\pi\rightarrow\pi^*$ $n\rightarrow\pi^*$	-	-
[Co(HL)$_2$Cl$_2$] Octahedral	288 340 526 670 721	34722.2 29411.7 19011.4 14925.3 13869.6	1.756 2.335 0.573 0.337 0.109	1756 2335 573 337 109	L.F C.T $^4T_{1g} \rightarrow {}^4T_{1g\,(P)}$ $^4T_{1g} \rightarrow {}^4A_{2g\,(F)}$ $^4T_{1g} \rightarrow {}^4T_{2g\,(F)}$	9.4	4.35
[Ni(HL)$_2$Cl$_2$] Octahedral	286 335 443 585 645	34965.0 29850.7 22573.3 17094.0 15503.8	1.825 2.213 0.832 0.556 0.328	1825 2213 832 556 328	L.F C.T $^3A_{2g(F)}\rightarrow{}^3T_{1g(P)}$ $^3A_{2g(F)}\rightarrow{}^3T_{1g(F)}$ $^3A_{2g(F)}\rightarrow{}^3T_{2g(F)}$	10.80	2.85
[Cu(HL)$_2$Cl$_2$] Octahedral	285 347 455	35087.7 28818.4 21978.0	1.788 2.186 0.423	1788 2186 423	L.F C.T $^2Eg\rightarrow{}^2T_2g$	12.5	1.85
[Zn(HL)$_2$Cl$_2$] Octahedral	293 480	34129.6 20833.3	2.346 1.850	2346 1850	ligand field C.T	17.02	Dia

3.5 Antioxidant efficacy of ligand HL and metal complexes via DPPH

DPPH reacts with ligand HL and the metal complexes change in color from purple to yellow, as shown in Figure-4. These can be measured, after reduction, by their absorbance at a wavelength of 517 nm using a UV–Vis spectrophotometer [32, 33], shown in Figures 3-7. The order of antioxidant activity is ZnHL > CuHL > HL >NiHL > CoHL. In 30 minutes, the metal complex ZnHL showed more antioxidant activity, as shown in Figures 8-12. Figure 13 shows the antioxidant activity of HL and the metal complexes.

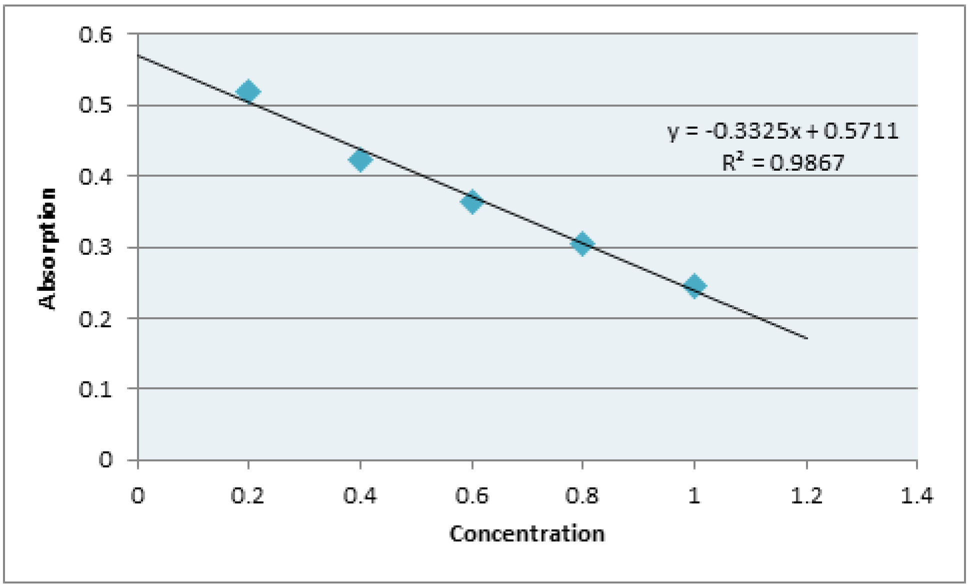


Figure- 3: Standard curve of HL

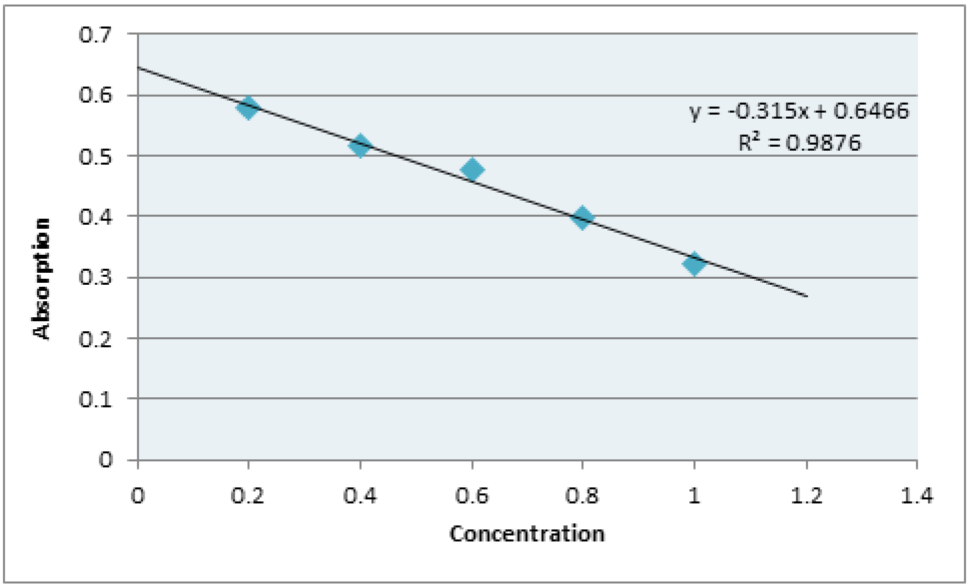


Figure- 4: Standard curve of $Co(HL)_2Cl_2$ complex

Volume 07, Issue 05 (September-October 2024), PP 102-117 www.ijmsdr.org
ISSN: 2581-902X

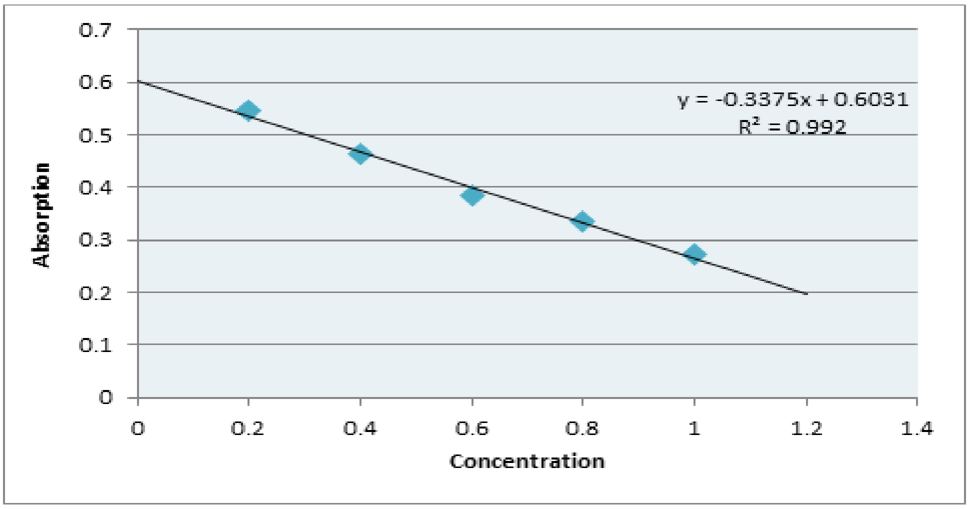


Figure-5: Standard curve of $Ni(HL)_2Cl_2$ complex

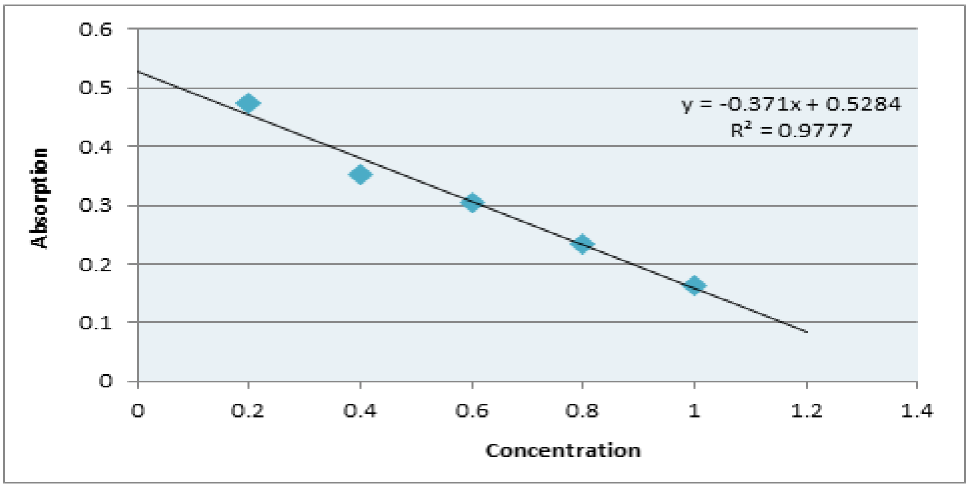


Figure-6: Standard curve of $Cu(HL)_2Cl_2$ complex

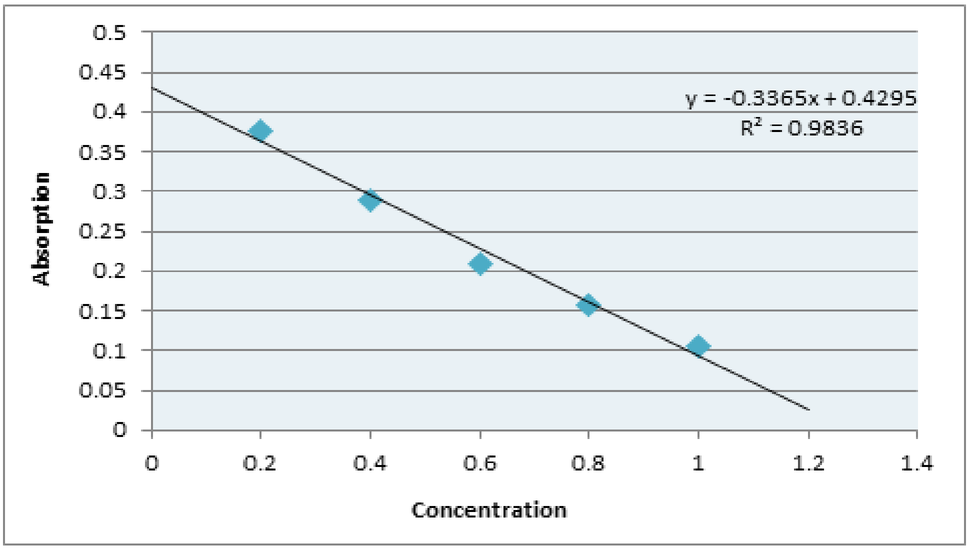


Figure-7: Standard curve of $Zn(HL)_2Cl_2$ complex

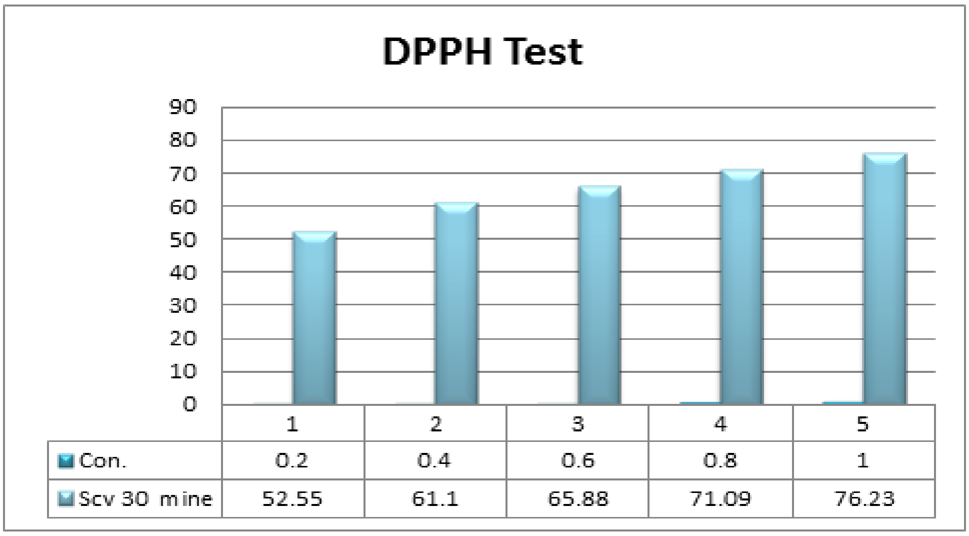


Figure-8: DPPH Test of HL

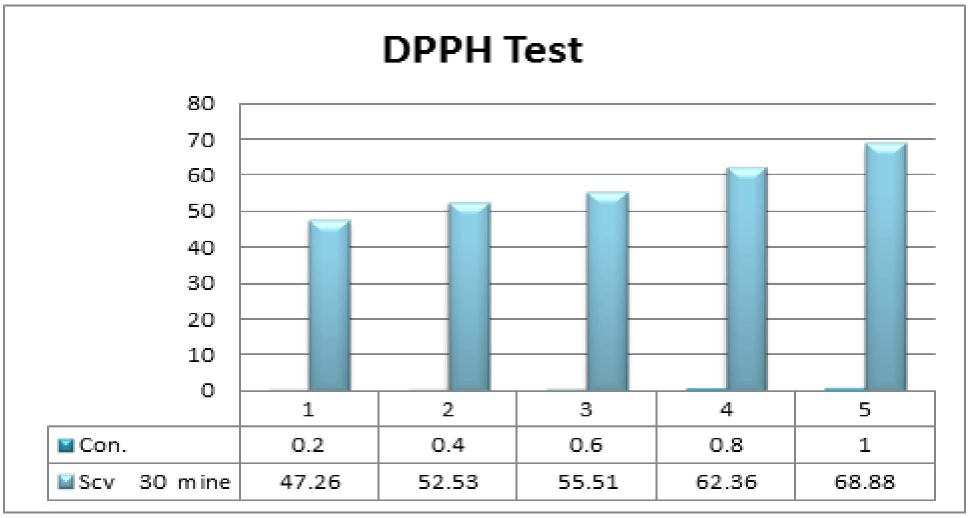


Figure-9: DPPH Test of Co HL

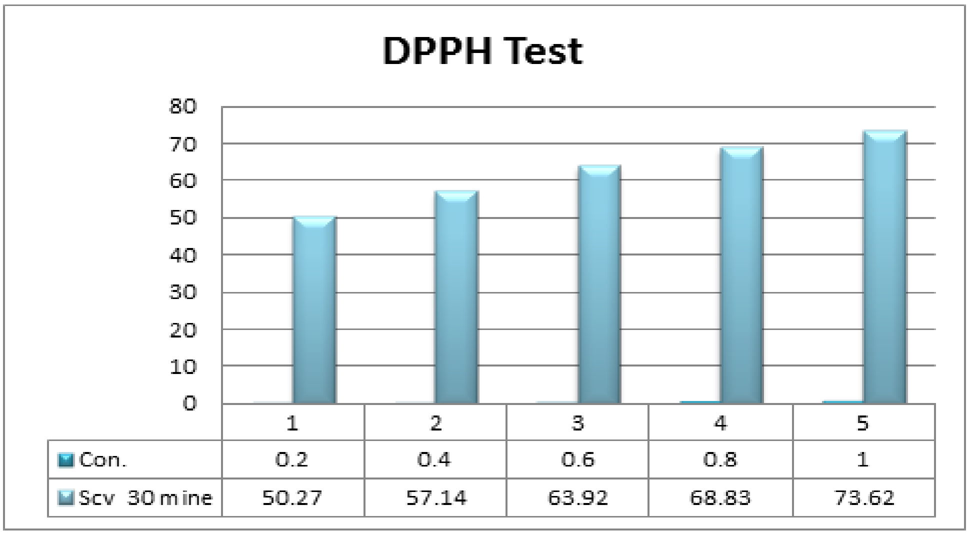


Figure-10: DPPH Test of Ni HL

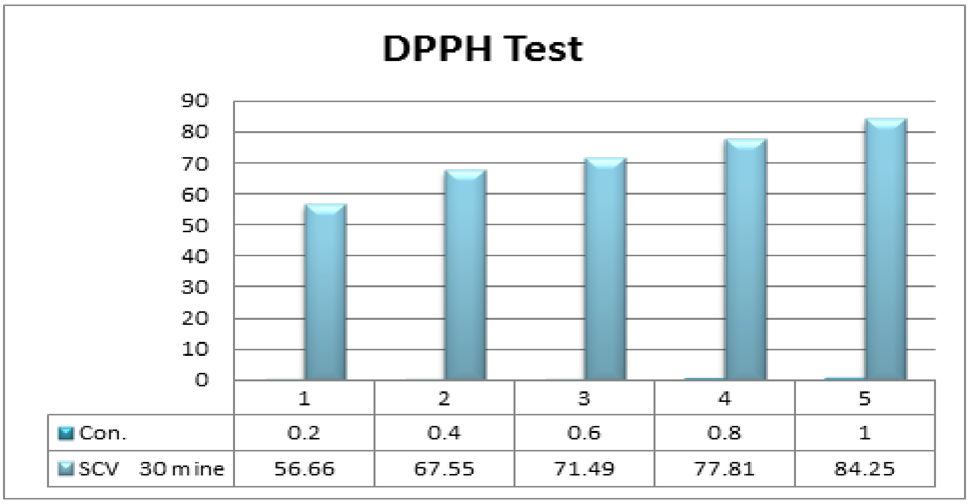


Figure-11: DPPH Test of Cu HL

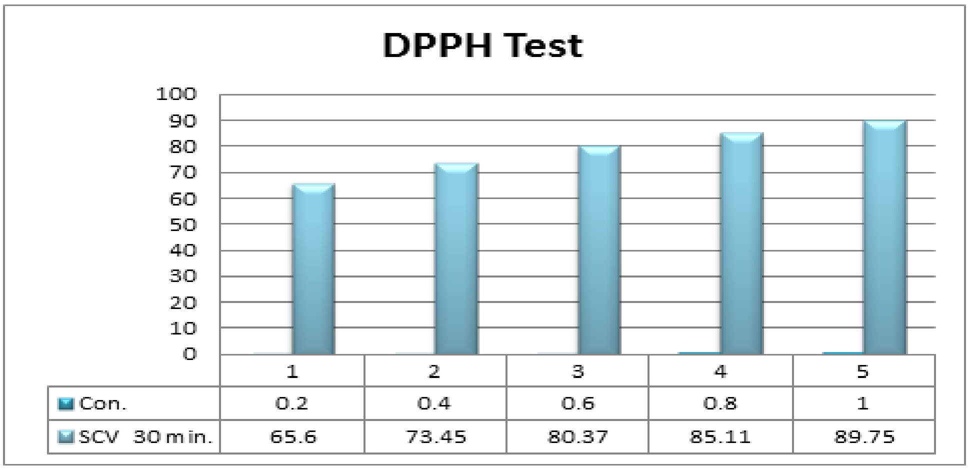
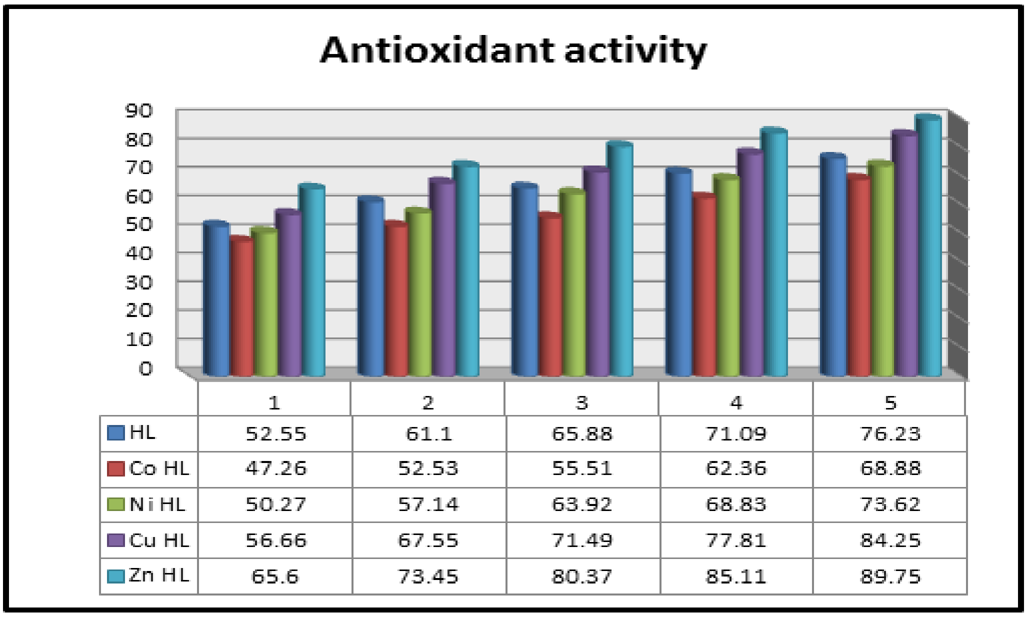


Figure-12: DPPH Test of Zn HL



	1	2	3	4	5
HL	52.55	61.1	65.88	71.09	76.23
Co HL	47.26	52.53	55.51	62.36	68.88
Ni HL	50.27	57.14	63.92	68.83	73.62
Cu HL	56.66	67.55	71.49	77.81	84.25
Zn HL	65.6	73.45	80.37	85.11	89.75

Figure -13: Antioxidant activity of HL and the metal complexes

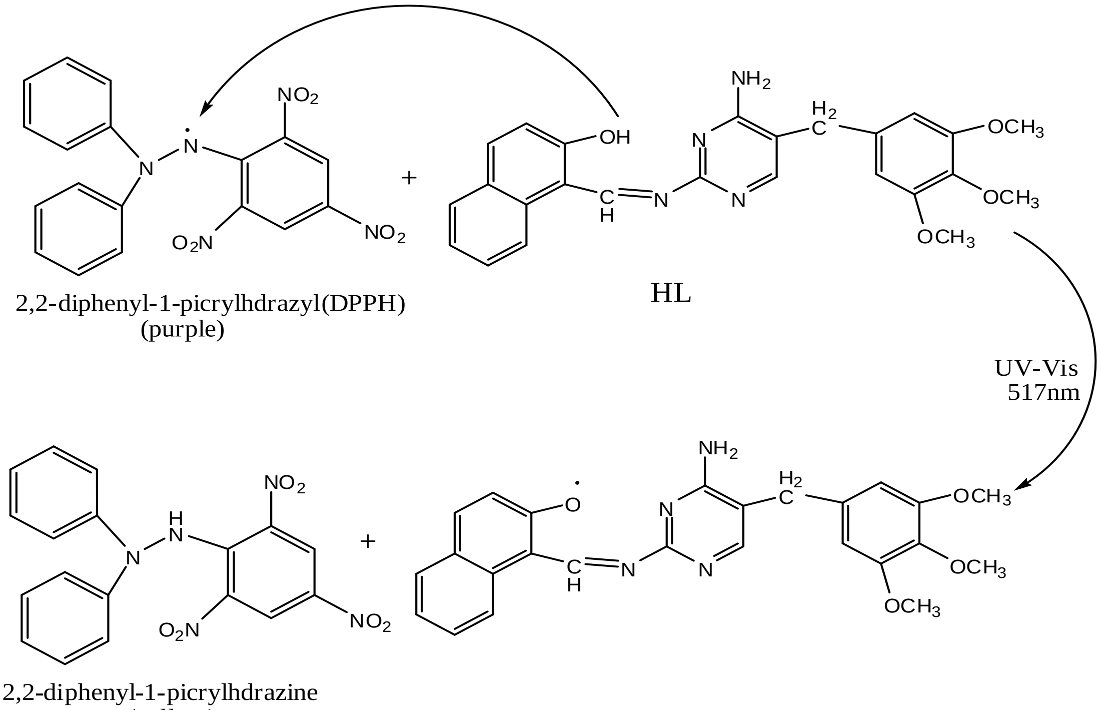


Figure-4: Conversion of DPPH (purple) to the corresponding hydrazine (yellow) by adding Ligand HL compound to DPPH due to proton transfer

IV. Conclusion

In this paper, new Schiff base ligand ((*E*)-1-((4-amino-5-(3,4,5-trimethoxybenzyl) pyrimidin-2-ylimino)methyl)naphthalen-2-ol) and metal complexes were prepared. The bonding mode and overall structure of complexes were determined through physico-chemical and spectroscopic methods. The spectroscopic investigation of all complexes showed that ligand HL is a bidentate ligand and is coordinated with the metal ions through the nitrogen azomethine groups and the nitrogen pyrimidine ring. The structure of complexes based on

Uv-vis, FT-IR spectra suggested that the geometry of all metal complexes is octahedral. The metal complex ZnHL shows more antioxidant activity in 30 minutes. Figure-14 shows the 3D chemical structure of ligand HL.

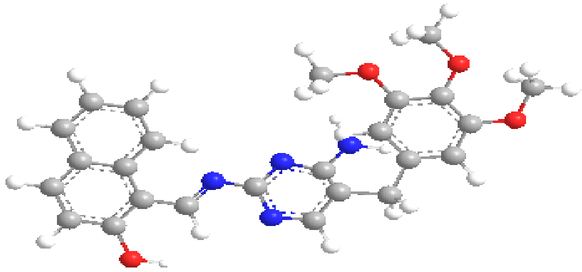


Figure -14: The 3D chemical structure of ligand HL

References:

[1] Sidambaram R. R., Jisha J and Mary N.L . Antibacterial studies of Schiff base complexes and polymer supported Schiff base complexes. International Journal of Institutional Pharmacy and Life Sciences , 2011, 1(2); 49-56.

[2] Anant P., Devjani A. Application of Schiff bases and their metal complexes-A Review. Int.J. ChemTech Res.2011; 3 (4); 1891-1896

[3] Tonelli M, Simone M, Tasso B , Novelli F, Boido V. Antiviral activity of benzimidazole derivatives Antiviral activity of 2-phenyibenzimidazole derivatives. Bioorganic & Medicinal Chemistry. 2010.18; 2937–2953.

[4] Jawaharmal S , Narwal S , Singh G , Saini D. R , Kaur A, Narwal S. Synthesis of novel imidazoles as potent antimicrobial agents. Indo Global Journal of Pharmaceutical Sciences . 2012. 2(3), 305-312.

[5] Kapoor V. K, Chadha R, Venisetty P. K, and Prasanth S. Medicinal significance of nitroimidazoles: Some recent advances. 2003. J Sci Ind Res (India). 62, 659–665.

[6] Rudrapal M and Bipab D. Chemistry and biological importance of heterocyclic Schiff's bases. International Research Journal of Pure & Applied Chemistry. 2013, 3(3): 232-249.

[7] Elgellal AA, Alshadly AM. Preparation Characterization and Biological Evaluation of Schiff-Base of Some Drug Substances. Journal of Medical and Bioengineering Vol. 2014 Sep;3(3).

[8] Shalini AS, Amaladasan M, Prasannabalaji N, Revathi J, Muralitharan G. Synthesis, characterization and antimicrobial studies on 13-membered-N6-macrocyclic transition metal complexes containing trimethoprim. Arabian Journal of Chemistry. 2019 Nov 1;12(7):1176-85.

[9] Ndahi NP, Garba H, Waziri I, Osunlaja AA, Putaya HA. Complexes of Mn (II) and Fe (III) with Schiff bases Derived from Trimethoprim with Salicyldehyde and Benzaldehyde as Potential Antimicrobial Agents. Nigerian Journal of Pharmaceutical and Biomedical Research. 2018 Apr;3(1).

[10] Al-Sahib SA. Preparation and identification of some a new derivative for Trimethoprim drug. Journal of university of Anbar for Pure science. 2009; 3(3).

[11] Zaidan BA, Majeed NM, Al-Shemary RK, Numan AT. Synthesis of some Schiff base metal complexes involving trimethoprim and 2'-amino-4-chlorobenzophenone: Spectral, thermal, DNA Cleavage

antimicrobial, antifungal and Cytotoxic activity studies. Journal of Pharmaceutical Sciences and Research. 2019 Feb 1;11(2):618-26.

[12] Deepak KV, Gar GS. Synthesis, Spectral and Biological Studies of Some Salicylidene-Trimethoprim Schiff Base Complexes of Aryltellurium (IV). Chemical Science. 2017;6(3):437-47.

[13] Arman MS, Al Mahmud A, Mahmud HR, Reza AA. Free radical, oxidative stress and diabetes mellitus: A mini review. Discovery Phytomedicine. 2019;6(3):99-101.

[14] Jayathilake C, Rizliya V, Liyanage R. Antioxidant and free radical scavenging capacity of extensively used medicinal plants in Sri Lanka. Procedia food science. 2016 Jan 1; 6:123-126.

[15] Sarma AD, Mallick AR, Ghosh AK. Free radicals and their role in different clinical conditions: an overview. International Journal of Pharma Sciences and Research. 2010 Apr;1(3):185-192.

[16] Kumar S. Free radicals and antioxidants: human and food system. Adv Appl Sci Res. 2011 Feb;2(1):129-135.

[17] Pham-Huy LA, He H, Pham-Huy C. Free radicals, antioxidants in disease and health. International journal of biomedical science: IJBS. 2008 Jun;4(2):89.

[18] Yadav A, Kumari R, Yadav A, Mishra JP, Srivatva S, Prabha S. Antioxidants and its functions in human body-A Review. Res. Environ. Life Sci. 2016 Nov;9(11):1328-1331.

[19] Attia AM, Abdallah EK, Alzahawy HM. Synthesis and identification Of Four Membered Rings Heterocyclic Compounds Derived From Trimethoprim. kirkuk university journal for scientific studies. 2016;11(3).

[20] Kedareand S. B, Singh R. P. Genesis and development of DPPH methodof antioxidant assay , 2011,J. Food Sci. Technol, 48(4):412–422.

[21] Silverstein R. M , Webster E. X, Kiley D. J . Spectrometric identification of organic compounds 7th ed , John Wilye and SonsS. INC. 2005, 1-550.

[22] Chen BH, Liu JT, Chen HM, Chen WX, Lin CH. Comparison of the characteristic mass fragmentations of phenethylamines and tryptamines by electron ionization gas chromatography mass spectrometry, electrospray and matrix-assisted laser desorption ionization mass spectrometry. Applied Sciences. 2018 Jul;8(7):1022.

[23] Prakash A , Adhikari D. Application of Schiff bases and their metal complexes-A Review. Int.J. ChemTech Res . 2011, 3(4)1891-1896.

[24] Figgis BN. Ligand field theory. Comprehensive Coordination Chemistry. 1987;1:213-79.

[25] Abu-Dief AM, Mohamed IM. A review on versatile applications of transition metal complexes incorporating Schiff bases. Beni-suef university journal of basic and applied sciences. 2015 Jun 1;4(2):119-33.

[26] Lever AB. Inorganic Electronic Spectroscopy .Elsevier Publishing Company, Amsterdam, Londen. 1968.

[27] Lever AB. Electronic spectra of some transition metal complexes. Journal of Chemical Education. 1968 Nov;45(11):711.

[28] Figgis BN. Introduction to ligand fields. Inter science publishers; 1966.

[29] Jisha MJ, Sobana Raj C. Isac. Synthesis and characterization of Schiff base complexes of Cu (II), Ni (II), Co (II) complexes of Schiff base derived from furan 3-carboxaldehyde and 3-amino pyridine. International Journal of Scientific and Research Publications. 2017;7(10):10-19.

[30] Gaikwad VK, Yadav UM. Metal Complexes of Schiff Bases. SRJIS.2016; 3: 2225-34.

[31] Sani S, Hussain S.Y.A Convenient Method to Synthesis and Characterization of Ni(II) and Zn(II) Schiff Base Complexes. International Journal of Innovative Research & Development. 2017;6(12):1-6.

[32] Dehariya R, Dixit AK. A review on different methods of determination of antioxidant activity assay of herbai plants. Life science informatics publications, 2018. 4 (6);708.

[33] Kedare SB, Singh RP. Genesis and development of DPPH method of antioxidant assay. Journal of food science and technology. 2011 Aug 1;48(4):412-422.