Egyptian Journal of Chemistry
http://ejchem.journals.ekb.eg/

Preparation, Determination and Study Toxicity Effects of new Mixed ligands Complexes Derivative from 8- Hydroxy Quinoline with Pd(II)

Afaq Jaber Kadhium*[a], Bilal Sadiq Abdulmahdi [b], Fatima Jabbar Ali [c]

[a] *Department of Chemistry, Faculty of Education for girls, University of Kufa, Iraq*
b Department of Chemistry, Faculty of Education for girls, University of Kufa, Iraq
[c] *Inorganic Chemistry, Lecturer, Najaf, Iraq*

Abstract
This academic research consists of mixed ligands 8-hydroxy quinolone and new azo ligand [(E)-2-((4-methoxyphenyl) diazenyl)-4-methyl-1H-imidazole](PMI) both of them coordinated with (Cu ,Ni and Pd)(II) , the mole ratio was (1:1:1) . the suggestion geometrical structures of mixed ligands and its complexes have been studied by (FT.IR, UV-Visible, 1H-NMR, Mass and elementary analysis (C.H.N)) In addition, an electrical molar conductivity and magnetic susceptibility used for complexes . The results of analytical studies evidence an Octahedral geometries of (Cu, Ni) (II) complexes while , Square planer of Pd(II) complex .It seems to be there is noticeable inhibition of cancerous cells of human Thyroid cancer (FTC133) compared to normal cells , which mentions to the cytotoxicity of Pd(II) complex ., this results gave good information about including good inhibition against some types of tumor like thyroid cancer and it gave decreasing in size of tumor.
Keywords: imidazole derivatives ,mixed ligands , cytotoxicity compounds

1. Introduction

Recently, the chemistry of chelating complexes has widespread applications [1], especially in pharmaceutical and medical aspects [2]. Among them, 8-hydroxyquinoline complexes are favorable for anticancer[3] antimicrobial[4,5] anti-inflammatory and anti-diabetic agents [6,7]. The coordination between 8-HQ and metals via the nitrogen atom and oxygen atom of the hydroxyl group may effect on human body because of 8-HQ and its complexes can be avoid formation of neurotoxic reactive of Alzheimer's disease [8,9] . in addition, mixed ligands complexes which derivative from 8-HQ have noteworthy role in luminescence field [10,11] because it is highly colored and more stabled , farther more, some of 8-hydroxyquinoline complexes used as antioxidant which have noticeable influenced on reduced mortality assay in the brine shrimp[12]. all these observations engaged number of scientist to synthesis ligands derivative from 8-HQ and study the uses of its complexes.

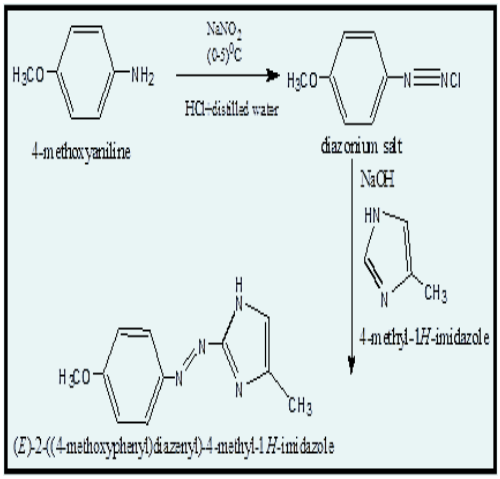
2. Experimental:

Many equipment has been used in this search , melting point measurements recorded by stuart Melting Point (SPM10),FTIR studied by Shimadzu FTIR 8400 Spectrophotometer(4000-400)cm^{-1} those spectra were carried out in pharmacy college – Lab-center for measurements , UV-Visible acquired by Shimadzu-UV-Vis.1700double beam Spectrophotometer (200-1100) nm, NMR spectrophotometer measured by Bruker Bio Spin GmbH300MHZ by DMSO-d6 were carried out in Kashan University in Iran , Mass spectra by Agilent Technology (HP)5973 at 230 ^{0}C were carried out in Kashan University in Iran , Metal percentage and C.H.N by GmbH, Shimadzu AA-66300 Atomic Absorption/flame, Molar Conductivity by 470WTWapparatus.

*Corresponding author e-mail afaqk@gmail.com .; (Afaq Jaber Kadhium).
Receive Date: 24 April 2021, Revise Date: 03 May 2021, Accept Date: 05 May 2021
DOI: 10.21608/EJCHEM.2021.73861.3652

2.1. Synthesis of new Azo ligand (MPI) (E)-2-((4-methoxyphenyl)diazenyl)-4-methyl-1H-imidazole

This new ligand is synthesized by dissolving (1.231g,0.01 mole) of 4- methoxy aniline in diluted acidic solution of 18%HCl at (0-5)^{0}C , Then it is dropped by solution of $NaNO_2$(0.78g,0.01mole) in 10ml D.W with stirring for 15 minutes. The diazonium salt solution is formed which added slowly with stirring to 10% basic alcoholic solution of (0.83g,0.01mole) imidazole derivative at the same temp. Reddish- Orange precipitation was noticed it kept overnight, then it acidified by dil. HCl at P^H=(6-7) , Following that, it filtered ,washed with D.W , dried . Lastly , it recrystallized with hot ethanol.



Scheme.1:synthesis of new Azo ligand (MPI)

2.2. Synthesis of mixed ligands *complexes*:

Complexes of Cu(II), Ni(II) and Pd(II) were formed by adding ethanolic solution of mixed ligands (MPI + 8HQ) to aqueous solution of Cu(II) and Ni(II) and (CH_3CN) solution of Pd(II) in mole ratio (L:M:L)(1:1:1) with heating and stirring 30 min. the colored precipitations dried and recrystallized with hot ethanol.

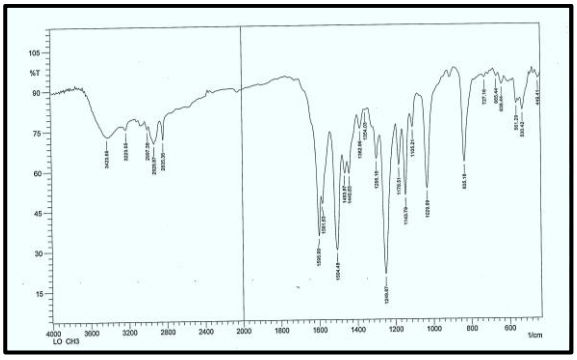
2.3. Cells Cytotoxic Activity

This study focused on the cytotoxic effect of [Pd(PMI)(8HQ)]Cl_2 on human thyroid cancer cells(FTC133) by using number of concentrations of Pd(II)complex started from (25-400) µg/ml , the same concentrations have been studied for healthy cells (WRL-68) , the result appears that 25µg/ml of Pd(II) complex is the best concentration to inhibit the growth of cancerous cells , while it has less effect on healthy cells , which is suggested that Pd(II) complex may be used to treat thyroid cancer .

3. Results and Discussion :

3.1. FT-IR Spectra:

The IR Spectrum shows OH group in the ligand of (8HQ) at 3410 Cm^{-1} , which is disappeared in all complexes because of the coordination [13]. In addition, the spectrum emerges band at 3471 Cm^{-1} for Cu(II) complex and another band at 3437 Cm^{-1} for Ni(II) complex , which is proposed that water is coordinated with both central metals ions [14] . the spectra of all complexes presented new weak bands may be attributed to vibration (M-O) and (M-N) that is evidenced of the bonding with Oxygen and Nitrogen [15].



Fig(1) FT-IR Spectrum of (PMI) ligand

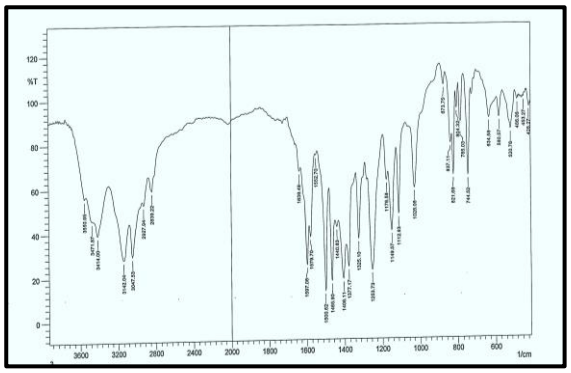
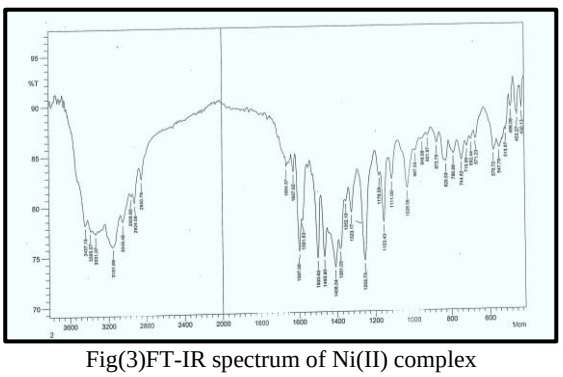
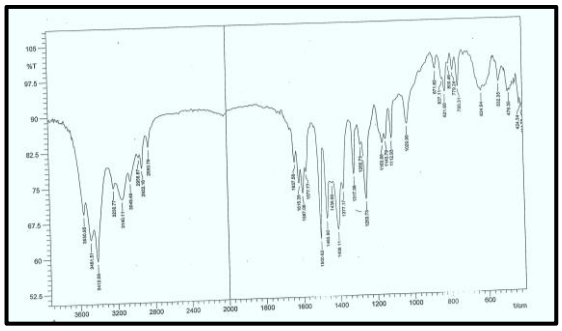


Fig.(2):FT-IR spectrum of Cu(II) complex



Fig(3)FT-IR spectrum of Ni(II) complex



Fig(4):FT-IR spectrum Pd(II) complex

3.2. Electronic spectra and magnetic measurements:

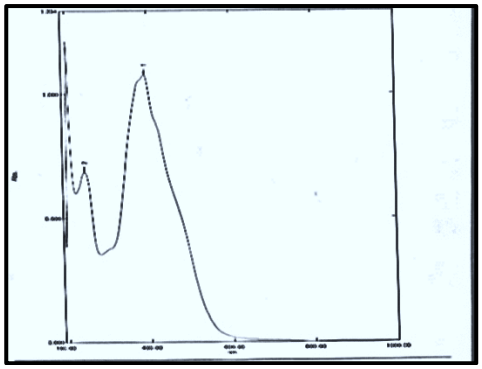
The result of this research appears three main bands of the ligand (PMI) , the first one at (202)nm due to electronic transition (π→π*) of imidazole ring [16], the second band at (244)nm refers to electronic transition (n→π*) of Azo group (N=N) ,which shifted to higher wavelength because of coordination with transition ions[17].the third band at (392)nm mentions to electronic transition (π→π*) of benzene ring that is conjugated with imidazole ring [18]. The Cu (II) complex exhibits band at (548)nm which assigned to $Eg \rightarrow T_2g$ [15], the magnetic moment existed at (1.76)B.M., which indicated that an Octahedral geometry [19], the spectrum of Ni(II) complex displayed two bands at (556)nm and (372)nm due to $^3A_2g_{(F)} \rightarrow {}^3T_1g_{(p)}$ and (M.L.C.T.)[15] , the magnetic moment rate at (2.8)B.M., which may be taken as evidence for Octahedral geometry [20]. In addition, the spectrum of Pd(II) complex illustrated broad band at (536)nm refers to $^1A_1g \rightarrow {}^1B_1g$ transition [15], this complex is diamagnetic moment , which suggested as a square planar geometry [14].

3.3. Molar conductivity measurements:

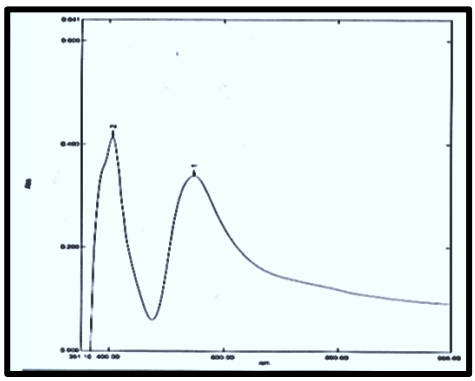
The molar conductivity values of all prepared complexes have been done in DMSO solvent at a concentration of (10^{-3})M in room temperature as listed in table(4) , all results indicated that Cu(II) and Ni(II) complexes are non- electrolytes, while Pd(II) which is electrolytic nature.

3.4. ^{1}HNMR-Spectrum:

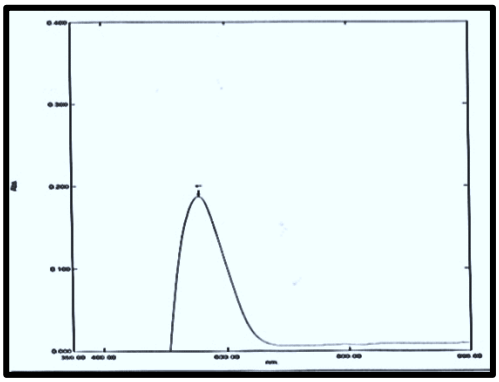
The main signals of the ligand(PMI) in the 1HNMR-Spectrum are shown in figure(9) by using d^6- DMSO solvent and TMS as an internal reference . the spectrum gives the characteristic multiples signals at (7.2-8)ppm due to protons of aromatic rings [21]. A singlet at (2.4)ppm attributed to (CH3)group in imidazole ring [16], and a single signal at (3.6)ppm mentions to (OCH3) group in aromatic ring[22], and at (13.4)ppm for (NH) imidazole ring [14].



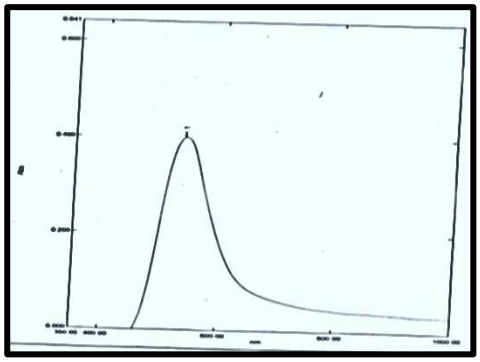
Fig(5 UV-Visible Spectrum(PMI) ligand



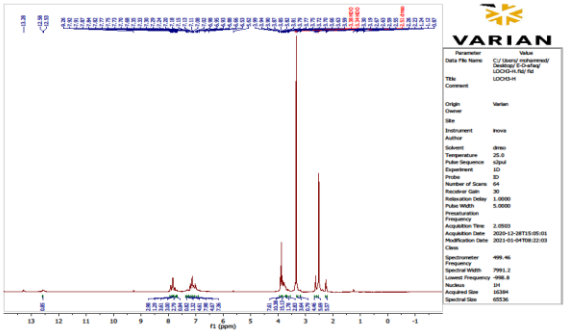
Fig(6):UV-Visible spectrum Cu(II) complex



Fig(7)UV-Visible spectrum Ni(II) complex



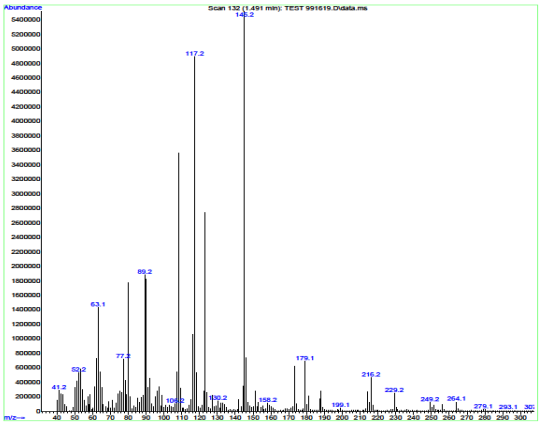
Fig(8)UV-Visible spectrum Pd(II) complex



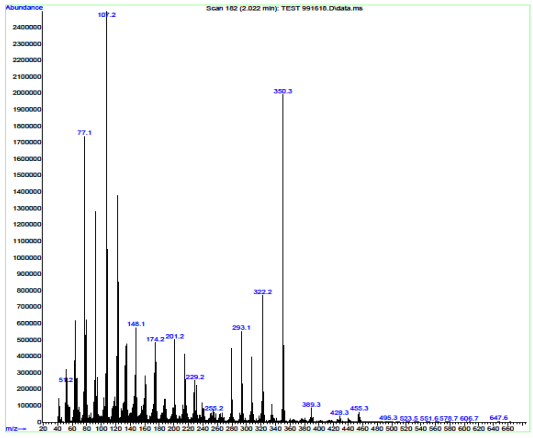
Fig(9)1HNMR-Spectrum(PMI) ligand

3.5. Mass Spectra :

Mass Spectra of new Azo ligand (PMI) and Cu(II) complex are shown in fig.(10)and (11) . while, the suggested mass spectral fragmentations of both ligand and Cu(II) complex are presented in spectra , the mass spectra of both ligand and Cu(II) complex display base peaks at m/z+= 216.2 , 477.3 ,which are agreement their formula .



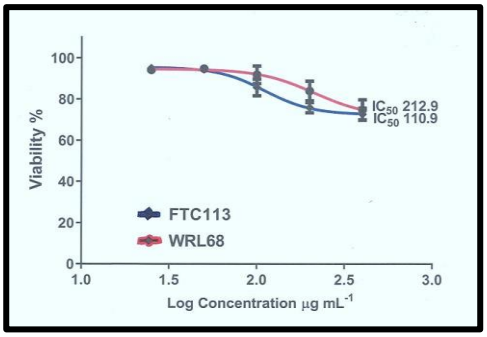
Fig(10)mass spectrum (PMI)ligand



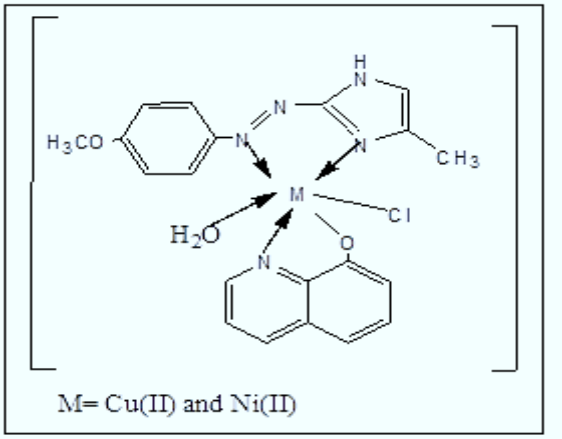
Fig(11)mass spectrum Cu(II) complex

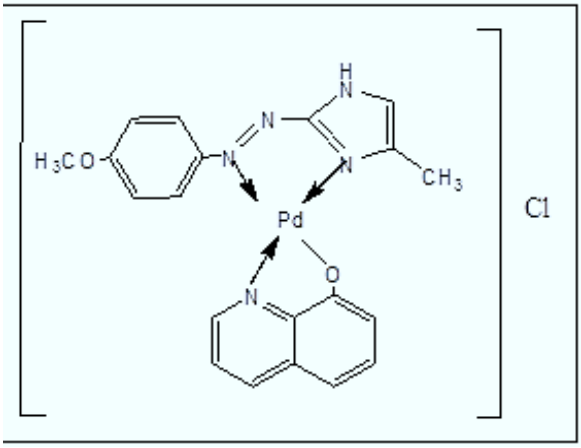
3.6. Cytotoxic Activity of [Pd(PMI)(8HQ)] on cancerous cells :

The result appears that ,IC50= 110.9 for thyroid cancer cells (FTC113), while, IC50=212.9 for healthy cells (WRL-68) which is indicated that , the concentration which kills half of (FTC113) is lower than the concentration to kill half of (WRL-68) this result approves Pd(II) complex may be used as new medicine for inhibition of thyroid cancer cells.



Fig(12) Anticancer activity data of Pd(II) complex against healthy cells





Scheme(4) Suggested geometries of mixed ligands complexes

Table (1)some of physical and analytical data of (PMI),(8HQ) and its mixed complexes

No.	*Compound*	*Formu-la Weight*	*Colour*	*M.p.^{0}c*	*Yield %*	*Found (Calc.)%*			
						%C	*%H*	*%N*	*%M*
1	PMI=$C_{11}H_{12}N_4O$	216.23	Orange	110-113	77	(61.o4) 61.10	(5.54) 5.60	(25.89) 25.88	-----
2	8HQ= C_9H_7NO	145.15	Color-less	76-79	78	(74.40 74.33	(4.82) 4.92	(9.64) 9.78	-----
3	[Ni(PMI)(8HQ)(H_2O)Cl]	472.42	Red-dish-brown	228-232	73	(50.80) 49.73	(4.23) 4.38	(14.81) 14.98	(12.40) 12.38
4	[Cu(PMI)(8HQ)(H_2O)C l]	477.3	Red-dish-brown	164-165	80	(50.28) 50.19	(4.19) 4.22	(14.66) 14.58	(13.30) 13.28
5	[Pd(PMI)(8HQ)] Cl	502.2	Red-dish-Pink	193-195	72	(47.78) 47.60	(3.58) 3.66	(13.93) 13.89	(21.18) 21.09

Table.(2):effect of [Pd(PMI)(8HQ)]Cl_2 on thyroid cancerous cells (FTC133) viability compared with healthy cells (WRL-86) at the same concentrations using 24hrs MTT test at 37 ^{0}C

Con. µg/ml	Cell viability FTC133	Cell inhibition (FTC133)	Cell viability WRL-86	Cell inhibition (WRL-86)
	94.17	5.83	95.06	4.94
50	94.83	5.17	94.41	5.59
100	91.84	8.16	85.69	14.31
200	84.01	15.99	75.83	24.17
400	74.81	25.19	72.69	27.31

Table (3) FT-IR data of (PMI) and complexes of mixed ligands (PMI)and (8HQ)

Compounds	NH Imid	OH (water) coordi-nated	C=N	N=N	M-O	M-N
(PMI)	3423	_____	1598	1440	_____	_____
[Cu(PMI)(8HQ)(H_2O)Cl]	3414	3471	1570	1406	580	426
[Ni(PMI)(8HQ)(H_2O)Cl]	3385	3437	1581	1408	576	430
[Pd(PMI)(8HQ)]Cl_2	3412	_____	1577	1406	532	424

Table(4):- Electronic spectra (nm, cm^{-1}) magnetic moments, geometry, hybridization and conductivity.

Compounds	λ_{max} nm	Absorption bands(cm^{-1})	Transitions	μ_{eff} B.M	Geometry	Hybridization	Conduc-tivity $S.mol^{-1}.cm^2$
(PMI)	202 392 244	49504 25510 40983	$\pi \rightarrow \pi^*$ $\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$	----	----	----	----
[Cu(PMI)(8HQ)(H_2O)Cl]	548	18248	$Eg \rightarrow T_2g$	1.76	Octahedral	Sp^3d^2	18
[Ni(PMI)(8HQ)(H_2O)Cl]	556 372	17985 26881	$^3A_2g_{(F)} \rightarrow {}^3T_1g_{(P)}$ C.T.	2.8	Octahedral	Sp^3d^2	15
[Pd(PMI)(8HQ)]Cl_2	536	18656	$^1A_1g \rightarrow {}^1B_1g$	Dia	Square planer	dsp^2	72

4. Conclusion

This search contains new mixed ligands and their complexes were prepared and characterized by many spectral equipment , the results explain an Octahedral geometry of Cu(II),Ni(II) complexes .However, Pd(II) complex is Square planner . High cytotoxicity od Pd(II) complex suggests the probability of using as new thyroid anticancer.

5. References

1- Muna A. H. and Ibtihal K.K., Synthesis and characterization of some Transition Metal Complexes with New Azo-Schiff Base Ligand 3,4- bis(((1E,2E)2-((2-((4-((Z)-(3-Hydroxyphenyl) Diazenyl)Naphthalen -1-yl)amino)ethyl)imino)-1,2-Diphenylethyli-dene)Amino)phenyl)phenyl)Methanone, Egypt .J. Chem. , 63(1),301-313,(2020).

2- Ivana M.S. and Ivan M.S. , Drug design strategies with metal-hydroxyquinoline complexes , Expert Opinion on Drug Discovery, https://doi.org/10.1080 /17460441.2020.1702964.

3- Chan-On W., Huyen NTB, Songtawee N., et al., Quinoline –based clioquinol and nitroxoline exhibit anticancer activity inducing FoxM1 inhibition in cholangiocarcinoma cells , Drug Des Dev Ther., 9, 2033-2047, (2015).

4- Cherdtrakulkiat R., Lawung R., Nabu S., et al., Nitroxoline : a potent antimicrobial agent against multidrug resistant enterobacteriaceae., Excli J. , 18, 445-453, (2019).

5- Lawung R., Cherdtrakulkiat R., Nabu S., et al., Repositioning of 8-hydroxyquinoline derivatives as a new promising candidate for combating multidrug resistant Neissria gonorroeae., Excli. J., 17, 840-846, (2018).

6- Krishna P., Chemoselective synthesis of 5- amino-7-bromoquinolin-8-yl sulfonate derivative and their antimicrobial evaluation., Phosphorus Sulfur silicon Relat Elem., 193, 685-690, (2018).

7- Krawczyk M., Pastuch –Gawolek G., Mrozek –Wilczkiewicz A., et al., Synthesis of 8-hydroxyquinoline glycoconjugates and preliminary assay of their B1,4-GaIT inhibitory and anti-cancer properties ., Bioorg Chem., 84, 326-338,(2019).

8- Rabab Mahdi Ubaid Mahmood, Rajaa Abdul Ameer Ghafil., Synthesis and Characterization some Imidazolidine Derivatives and Study the Biological Activity ,Annals of R.S.C.B., ISSN: 1583-6258, Vol. 25, Issue 3, 2021,Pages. 569 - 584 .

9- Suwanjang W., Prachayasittikul S., Prachayasittikul V. Effect of 8-hydroxyquinoline and derivatives on human neuroblastoma SH-SY5Y cells under high glucose peer J., 4:e 2389, (2016).

10- Gurnule W.B., Kiran S.V., Mankar R.V. and Kohad C.G., Photoluminescence studies of copolymer metal complexes with 8- hydroxyquinoline , hexamethylenediamine and formaldehde , Material Today : Proceedings , http://doi.org/10.1016/j.matpr.2020.04.175 .

11- Nagham Mahmood Aljamali, Asmaa Kefah Mahdi., Synthesis, Identification and Anticancer Studying of Heterocyclic- Mefenamic Drug via Thiosemicarbazide., Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 8521 – 8537.

12- Vladimir C., Franz H., Gert B., Wolfram W. and Lenka K., Antioxident properties and the Formation of Iron coordination compleses of 8-hydroxyquinoline, Int. J. Mol. Sci., 19, 3917, (2018).

13- Layla A.M., Afaq J.K. and Nadia H.A. , Synthesis and characterization of new Schiff base ligand with its some complexes derived from 4- amino antipyrine , sulphadiazine and acetoacetanilide , Acta Chem.Pharm. Indica: 3(2), (2013).

14- Hasaneen Kudhair Abdullabass, Aseel Mahmood Jawad ,Nagham Mahmood Aljamali. Synthesis of drugs derivatives as inhibitors of cancerous cells., Biochem. Cell. Arch, Vol. 20 (2) – October 2020., DocID: https://connectjournals.com/03896.2020.20.5315.

15- Afaq J.K. , Saad M.M. and Faiz HA., synthesis and characterization of new Chalcone –Azo ligands and its transition metal mixed ligands complexes with A Cytotoxic Activity study of Pd(II) complex, Int. J. Pharm. Research, 11(4),(2019).

16- Rajaa Abdul Ameer Ghafil, Nour A Alrazzakb, Nagham Mahmood Aljamali., Synthesis of Triazole Derivatives via Multi Components Reaction and Studying of (Organic Characterization, Chromatographic Behavior, Chem-Physical Properties)., Egypt. J. Chem. Vol. 63, No. 11, pp. 4163 - 4174 (2020). DOI: 10.21608/EJCHEM.2020.23541.2399 .

17- Mithaq S.M. and Husain S. M., Preparation ,characterization and Biological study of some new Transition Metal complexes Derived from Imidazole and Thiazole, Int. J. Pharm. Research, 12(4) ,(2020).

18- Mohamad M., Some transition metal complexes with new Schiff base ligand hexa dentate, Acta chimica .Pharm.Indica., 3(2), (2013).

19- Salih HK.,Ibtihal QA and Thikra JH., Synthesis and characteristic study of Co(II),Ni(II) and Cu(II) complexes of new Schiff base Derived from 4-Amino Antipyrine , Int. J.Chem.Sci., 1(5),(2017).

20- Harisha S., Jathi K., Sameer RP and Maliyappa MR , Synthesis , characterization and Anti-bacterial Activity of new disperse Azo dyes derived from 2- amino-6-methoxy Benzothiazole , Asian J. of Bio. and Pharm. Research , 3(9),(2015).

21- Munna A.H., Mithaq S.M. and Afaq J.K., Synthesis , characterization and spectral studies and Biological screening study of Transition Metal complexes with new Heterocyclic Ligand Derived from pyridoxal Hydrochloride, Sys .Rev. Pharm., 12(1),(2021).

22- Rabab Mahdi Ubaid Mahmood, Synthesis, Spectral Investigation and Microbial Studying of Pyridine-Heterocyclic Compounds.,European Journal of Molecular & Clinical Medicine, 2020, Volume 7, Issue 11, Pages 4444-4453.

23- Loznskyi M., Zimenkovsky B., Nektegayev I. and Lesyk R., Arylidene pyruvic acids motif in the synthesis of new thiopyrano [2,3-d]thiazoles as potential biologically active compounds,Heterocyclic communications,21(1), (2015).