Journal of Xi'an Shiyou University, Natural Science Edition **ISSN: 1673-064X**

Metal Complexes of 4-aminoAntipyrine: Synthesis, Spectral Characterization, antioxidant and antidiabetic studies

Zarqa Nawaz[1], Samina Aslam[1*] , Muhammad Naeem[2], Amna Bano[3], Aroog Fatima,[1] Ansa Madeeha Zafar[4], Sajjad Hussain,[5] and Taniya Iqbal,[6]

[1]Department of Chemistry, The Women University Multan, Multan

[2]Department of pharmacy, Shah Abdul Latif university Khairpur sindh.

[3]Department of Chemistry, University of Balochistan, Quetta.

[4]Department of Chemistry, Government Sadiq Women University, Bahawalpur, Bahawalpur, Pakistan

[5]Department of Zoology, The Islamia university of Bahawalpur

[6]Institute of chemical sciences, BZU multan

Corresponding https://orcid.org/0000-0001-8902-9376

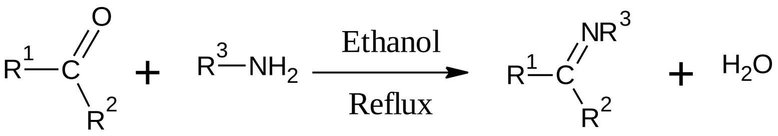
Abstract:

The noval series of the chelates with the transition metals such as Zinc (II), Manganese (II), Nickel (II), Cobalt (II) and Copper (II) have been synthesize in ethanol media at 70 °C temperature from the synthesized Schiff base ligands that have been derived from 4-aminoantipyrine, ortho-phenylenediamine and different aldehydes._The synthesized ligands and their metal complexes were purified by TLC technique, and characterized by different analytical techniques i.e FTIR, NMR, Mass spectra and checked for antioxidant and antidiabetic activities and showed excellent results.

Keywords: ortho-phenylenediamine, 4-aminoantipyrine, Schiff base, metal complexes, 5-Arylfuran-2-carbaldehydes

Introduction

Hugo Schiff was the German chemist who in the 19th century first reported the synthesis of Schiff base in 1864 under azeotropic distillation by the condensation process of a carbonyl compound and an amine (Ochiai, 1973). Schiff base have been found very straightforward to synthesize, also found as monodentate electron donors with simply tunable steric and electronic effect thus resulted as being versatile (Schiff, 1864; Seitz, Kaiser, Stempfhuber, Zabel, & Reiser, 2004; Yuhki et al., 2008) . Compounds that contain the azomethine group i.e. (–C=N–) in its structure are identified as Schiff bases, that are usually easily synthesized (**Scheme 1**) by the condensation reaction of active carbonyl groups and primary amines (Karthikeyan et al., 2006; Krishnan & Saravan, 2001; Pandeya, Sriram, Nath, & DeClercq, 1999; Panneerselvam, Nair, Vijayalakshmi, Subramanian, & Sridhar, 2005; Satyanarayana, Sivakumar, & Ghosh, 2010; K. Singh, Barwa, & Tyagi, 2006).



Scheme 1: General Scheme for the synthesis of Schiff base

The coordinating characteristics of 4-aminoantipyrine have been adapted to synthesize the new ligands that are prepared by the condensation reaction with different compounds for example aldehydes, thiocarbazides, ketones, and carbazides etc (Raman, Thalamuthu, Dhaveethuraja, Neelakandan, & Banerjee, 2008). It has been concluded from the literature survey that a very fewer work has been done on the preparation of Schiff base ligands and their transition metal chelates that involve the functional group amino group and carbonyl group of 4-aminoantipyrine (Suresh & Prakash, 2011).

The 4-aminoantipyrine derived compounds and its transition metal chelates are attaining extensive interest due to their broad applications such as biological, therapeutic and analytical applications in different fields (El-Sherif, 2009; Joseph, Sreekanth, Suni, & Kurup, 2006; Raja & Ramesh, 2010). Furthermore the 4-aminoantipyrine derived Schiff base ligands and its transition metal complexes are also obtaining diverse interest due to their wide applications in biological field such as anti-inflammatory, antifungal, analgesic, antipyretic, antibacterial and sedative agents (Chandra, Jain, Sharma, & Sharma, 2009; Chandraa, Raizada, MonikaTyagia, & Sharma, 2008; Rosu, Pasculescu, Lazar, Chifiriuc, & Cernat, 2006).

Main purpose of the present research is to synthesize 4-aminoantipyrine derived Schiff base ligands and complexes with enormous applications and characterization because the Schiff bases derived from aliphatic aldehydes are readily polymerizable and are comparatively unstable while those derived from aromatic aldehydes have an efficient conjugation system and are extra stable (Arulmurugan, Kavitha, & Venkatraman, 2010).

Experimental Work :

General

All reagents and solvents were used as obtained from the supplier or recrystallized or redistilled as were found necessary. Thin-layer chromatography was performed using aluminium sheets (Merck) coated with silica gel 60 F_{254}. IR spectra were recorded using an IR Perkin-Elmer Spectrum 1 FTIR spectrophotometer, and peaks are reported max (neat)/cm^{-1}, which refers to the min wave numbers. Proton magnetic resonance spectra were recorded in Deuteriochloroform with Bruker AM 300 spectrometers (Rheinstetten–Forchheim, Germany) operating at 300 MHz, respectively. The ^{13}C NMR spectra were recorded in Deuteriochloroform with Bruker AM 100 spectrometer operating at 100 MHz. Tetramethyl-silane was used as an internal standard. Elemental analysis for C, H, and N was recorded with Perkin-Elmer 2400 Series II CHN Analyzer. Melting points were measured using a Gallen Kamp instrument and are unadjusted. Shimadzu MAT 312 mass spectrometers were used to record the low-resolution EI-MS

General procedure for synthesis of the ligands

The ligands were synthesized in two steps. The first step was to synthesize the solid intermediates followed by the synthesis of the ligands. In round bottom flask 20 mL of an ethanolic solution of 2.03 g/0.01 mol of 4-aminoantipyrene or 1-phenyl 2, 3-dimethyl-4-aminopyrazol-5-one has been added to an ethanolic solution of different aldehydes (0.01 mole) one by one for synthesis of different types of ligands. The resulted solution has been stirred for a while vigorously then resulted solution has been refluxed and progress of reaction was monitored by TLC and after the completion of reaction, it was allowed to cool. The resulted solution has been poured into the crushed ice when precipitates were appeared in the solution. These precipitates were collected and recrystallized from the solvent ethanol. Crystals were formed have been collected. The different colored crystals were formed for each intermediate from different aldehydes have been filtered and then recrystallized from the solvent ethanol. The obtained solid intermediate (0.01 mol) has been added to 20 mL of an ethanolic solution of the *o*-phenylenediamine (0.005 mol). The obtained mixture has been refluxed and progress of reaction was monitored by TLC and after the completion of reaction. After completion of reaction contents have been poured in to the crushed ice. The different colored solids product i.e. Ligands were formed. The obtained solid product i.e. Ligands has been filtered and recrystallized from the solvent ethanol. The yield of each ligand was about 85-89%. Each ligand has different colored crystals and different melting points.

General procedure for synthesis of the metal complexes

The one by one each Ligand (/0.002 mol) was dissolved in 50mL hot ethanol. The hot ethanolic solution of the ligand was slowly added to a hot 1:1 aqueous ethanolic solution of the metal salts e.g. Copper Nitrate Trihydrate, Manganese Chloride Dihydrate, Cobalt Chloride Hexahydrate, Zinc Nitrate Hexa Hydrate, Nickel Chloride Hexahydrate, Iron Sulphate Heptahydrate. The resulting solution was refluxed for 5 hours on a water bath. The solution was reduced to one third on a water bath and cooled at room temperature. The precipitates were separated by filtration process. The solid precipitates were washed several times with distilled water and hot ethanol to purify these precipitates. The yield of each metal complex was good. Each metal complex has different colored precipitates and different melting points.

4-((5-(2-Chlorophenyl)furan-2-yl)methylene)amino)-1,5-diethyl-2-phenyl-1H-pyrazol-3-(2H)-one (1)

Yield: 59% M.P: 217^0C **FTIR:** 3853.29 (substituted pyrazole) 2359.81 (C=N), 1645.01 (C=O), 1298.59 (C-O) , 1023.46 (C-N), 762.41 (Cl-Aromatic) 703.45 (tri-substituted benzene) **^{1}HNMR** (CDCl3,300MHz) δppm(J,Hz) 6.98 ,7.27 [2H furan] 7.24,7.35,7.37 [Ar-H, d=0.02], 3.18 [N-CH$_3$], 2.54[Ar-CH$_3$],7.53,7.497.43 ,7.39 [Ar-H], **^{13}CNMR (CDCl$_3$)δppm:** 111.53,115.43[Furan-C],122.15,122.07,125.09,127.03,129.15[Ar-C],35.22[N-**C**H3],22.15[Ar-**C**H$_3$],10.12 [-**C**H$_3$]**Mass spectrum** (EI, 70 eV, I_{rel} %): 391 [M^+] (10), 356[M^+- Cl](15) 280 [M^+- Ph] (7),214 [M^+-furyl] , 187 [M+-N=C](100) , 110 [M^+-Ph] (90)

(N^1-(1,5-dimethyl-4-(((5-(2-chlorophenyl)furan-2-yl)methylene)amino)-2-phenyl-1H-pyrazol-3(2H)-ylidene)-N^2-(1,5-dimethyl-4-((Z)-((5-(2-chlorophenyl)furan-2-yl)methylene)amino)-2-phenyl-1H-pyrazol-3(2H)-ylidene)benzene-1,2diamine (2)

Yield: 77% M.P: 298^0C **FTIR:**3853.33 (substituted pyrazol),3735.06 and3648.90(o-phenylenediamine),2363.53 (C=N) 1647.24 (C=O) 1541.44 and 1456.80 (Asymmetric and symmetric of NO$_2$)1418.79(C-O), 1023.27 (C=N),745.76 (tri-substituted benzene) **^{1}HNMR** (CDCl3,300MHz) δppm(J,Hz) 6.32 ,7.25 [2H furan] 7.26,7.25 [8Ar-H, d=0.02], 3.18 [N-CH$_3$], 2.54[Ar-CH$_3$],8.08 [14Ar-H] **^{13}CNMR (CdCl$_3$)`** 45.22(**N**-CH3),10.16(-**C**H3), 144.74(**C**=NH),132.29,131.39,129.25,129.24,129.17,128.08, 128.04,127.30,124.82,123.12 (Ar-C) **Mass spectrum** (EI, 70 eV, *I*_{rel} %): 886 [M^+](35), 816[M^+-2Cl] (20),662[M^+-2Ph] (25),530[M^+-2furyl groups] (30),478 [M^+-2N=CH] (10),324 [M^+-2Ph] (25),142 [M^+-0-phenylenediamine ring] (20),82[M^+-4CH_3](10)

N^1-(1,5-dimethyl-4-(((5-(2-chlorophenyl)furan-2-yl)methylene)amino)-2-phenyl-1H-pyrazol-3(2H)-ylidene)-N^2-(1,5-dimethyl-4-((Z)-((5-(2-chlorophenyl)furan-2-yl)methylene)amino)-2-phenyl-1H-pyrazol-3(2H)-ylidene)benzene-1,2diamine Cu (IV) (3)

Yield: 83% M.P: 281^{0}C**FTIR:** 3735.00(substituted pyrazol), 3648.79(o-phenylendiamine), 1489.36(C=N stretching), 1023.64(C-O), 745.67(Substituted Ar ring), 587.46(Cu) **^{1}HNMR:** (CDCl3,300MHz) δppm(J,Hz)2.26 (-CH_3), 3.11 (N-CH_3), 7.07and 6.56 (d=0.02, 2H of Furan)7.37,7.35, 7.27,7.25(Ar-4H),7.52,7.48,7.45,7.41(Ar-4H) 8.13,8.09,7.72,7.07(Ar-4H) **C^{13}NMR ($CDCl_3$ 75MHz**) δppm164.05 [C=N], 133.73, 133.53, 130.59 [Aromatic Cof o-phenylenediamine], 115.27, 123.26, 125.86 [Aromatic C], 114.26,125.88,127.86, 129.46[Aromatic ring attached with pyrazole ring] , 35.61 [N-CH3], 10.26 [CH3] **Mass spectrum** (EI, 70 eV, *I*_{rel} %): 950 [M^+](10),886 [M^+-Cu](20), 816[M^+-2Cl](25),662[M^+-2Ph](35),530[M^+-2furyl groups](47),478 [M^+-2N=CH](25),324 [M^+-2Ph](20),142 [M^+-0-phenylenediamine ring](15),82[M^+-4CH_3](10)

N^1-(1,5-dimethyl-4-(((5-(2-chlorophenyl)furan-2-yl)methylene)amino)-2-phennyl-1H-pyrazol-3(2H)-ylidene)-N^2-(1,5-dimethyl-4-((Z)-((5-(2-chlorophenyl)furan-2-yl)methylene)amino)-2-phenyl-1H-pyrazol-3(2H)-ylidene)benzene-1,2diamineMn (IV) (4)

Yield: 87% M.P: 281^{0}C**FTIR:** 3853.25(substituted pyrazol), 3749.65(o-phenylendiamine),, 1489.33(C=N stretching), 1023.41(C-O), 750.60(substituted Ar ring), 594.62(Mn) **^{1}HNMR:** (CDCl3,300MHz) δppm(J,Hz)2.53 (-CH_3), 3.25 (N-CH_3), 7.10 and 6.96 (d=0.02, 2H of Furan)7.39,7.37, 7.29,7.23(Ar-4H),7.50,7.46,7.43,7.39(Ar-4H) 8.11,8.07,9.72(Ar-4H) **C^{13}NMR ($CDCl_3$ 75MHz**) δppm143.05 [C=N], 131.73, 131.53, 129.59 [Aromatic Cof o-phenylenediamine], 114.27, 121.26, 123.86 [Aromatic C], 112.26,123.88,126.86, 127.56[Aromatic ring attached with pyrazole ring] , 33.61 [N-CH3], 12.26 [CH3] **Mass spectrum** (EI, 70 eV, *I*_{rel} %): 941 [M^+](10),886 [M^+-Mn], 816(20)[M^+-2Cl],662[M^+-2Ph](30),530[M^+-2furyl groups],478 (75)[M^+-2N=CH],324 [M^+-2Ph](20),142 [M^+-0-phenylenediamine ring],(15),82[M^+-4CH_3](10)

N^1-(1,5-dimethyl-4-(((5-(2-chlorophenyl)furan-2-yl)methylene)amino)-2-phennyl-1H-pyrazol-3(2H)-ylidene)-N^2-(1,5-dimethyl-4-((Z)-((5-(2-chlorophenyl)furan-2-yl)methylene)amino)-2-phenyl-1H-pyrazol-3(2H)-ylidene)benzene-1,2diamine Co (IV) (5) Yield: 67% M.P: 219^0C**FTIR:** 3853.50(substituted pyrazol),, 3675.48(o-phenylendiamine), 1023.89(C-O),750.12(Substituted Ar ring),696.17)C-Cl),583.31(Co) **^{1}HNMR:** (CDCl3,300MHz) δppm(J,Hz)2.51 (-CH_3), 3.24 (N-CH_3), 7.09 and 6.94 (d=0.02, 2H of Furan)7.38,7.36, 7.28,7.22(Ar-4H),7.49,7.45,7.41,7.38(Ar-4H) 8.01,8.06,9.70(Ar-4H) **C^{13}NMR (CDCl$_3$ 75MHz**) δppm145.05 [C=N], 130.73, 130.53, 12.59 [Aromatic Cof o-phenylenediamine], 115.27, 122.26, 124.86 [Aromatic C], 113.26,124.88,127.86, 128.56[Aromatic ring attached with pyrazole ring] , 35.61 [N-CH3], 10.26 [CH3] **Mass spectrum** (EI, 70 eV, I_{rel} %): 945 [M^+](10),886 [M^+-Co](4), 816[M^+-2Cl](5),662[M^+-2Ph](20),530[M^+-2furyl groups](15),478 [M^+-2N=CH](25),324 [M^+-2Ph](30),142 [M^+-0-phenylenediamine ring],(18),82[M^+-4CH_3]

N^1-(1,5-dimethyl-4-(((5-(2-chlorophenyl)furan-2-yl)methylene)amino)-2-phennyl-1H-pyrazol-3(2H)-ylidene)-N^2-(1,5-dimethyl-4-((Z)-((5-(2-chlorophenyl)furan-2-yl)methylene)amino)-2-phenyl-1H-pyrazol-3(2H)-ylidene)benzene-1,2diamine) Zn (IV) (6) Yield: 71% M.P: 213^0C,**FTIR:** 3853.10(substituted pyrazol),,, 3648.65(o-phenylendiamine),1456.72, (C=N stretching)1023.50(C-O),744.87(substituted Ar ring),696.56(C-Cl)**^{1}HNMR:** (CDCl3,300MHz) δppm(J,Hz)2.92 (-CH_3), 3.26 (N-CH_3), 7.26 and 6.96 (d=0.02, 2H of Furan)7.37,7.34, 6.86,7.17(Ar-4H),7.49,7.46,7.44,7.40(Ar-4H) 8.06,8.05,8.04 (Ar-4H)**C^{13}NMR (CDCl$_3$ 75MHz**) δppm145.03 [C=N], 130.75, 129.44, 128.59 [Aromatic Cof o-phenylenediamine], 115.90, 124.72, 126.92 [Aromatic C], 113.35,124.01,127.24, 128.48[Aromatic ring attached with pyrazole ring] , 35.69 [N-CH3], 10.26 [CH_3]**Mass spectrum** (EI, 70 eV, I_{rel} %): 951 [M^+](10),886 [M^+-Zn](4), 816[M^+-2Cl](5),662[M^+-2Ph](20),530[M^+-2furyl groups](15),478 [M^+-2N=CH](25),324 [M^+-2Ph](30),142 [M^+-0-phenylenediamine ring],(18),82[M^+-4CH_3]

N^1-(1,5-dimethyl-4-(((5-(2-chlorophenyl)furan-2-yl)methylene)amino)-2-phennyl-1H-pyrazol-3(2H)-ylidene)-N^2-(1,5-dimethyl-4-((Z)-((5-(2-chlorophenyl)furan-2-yl)methylene)amino)-2-phenyl-1H-pyrazol-3(2H)-ylidene)benzene-1,2diamine)Ni (IV) (7) Yield: 73% M.P: 231^0C,**FTIR:** .3454.56((substituted pyrazol),3735.23(O-phenylendiamine ring),1508.19,1314.46(Asymmetric and symmetric of NO_2)),1029.72(C-O),794.12 (Substituted Ar ring),585.93(Ni)^1**HNMR:** (CDCl3,300MHz) δppm(J,Hz)2.95 (-CH$_3$), 3.28 (N-CH$_3$), 7.28 and 6.98 (d=0.02, 2H of Furan)7.39,7.36, 6.88,7.19(Ar-4H),7.51,7.48,7.46,7.42(Ar-4H) 8.08,8.07,8.06 (Ar-4H)**C^{13}NMR (CDCl$_3$ 75MHz**) δppm 145.48 [C=N], 130.86, 130.74, 129.23 [Aromatic Cof o-phenylenediamine], 115.93, 124.66, 126.92 [Aromatic C], 127.17,128.23,128.80, 128.58[Aromatic ring attached with pyrazole ring] , 35.73 [N-CH3], 10.27 [CH3]**Mass spectrum** (EI, 70 eV, I_{rel} %): 944 [M$^+$](10),886 [M$^+$-Ni](4), 816[M$^+$-2Cl](5),662[M$^+$-2Ph](20),530[M$^+$-2furyl groups](15),478 [M$^+$-2N=CH](25),324 [M$^+$-2Ph](30),142 [M$^+$-0-phenylenediamine ring],(18),82[M$^+$-4CH$_3$]

N^1-(1,5-dimethyl-4-(((5-(2-chlorophenyl)furan-2-yl)methylene)amino)-2-phennyl-1H-pyrazol-3(2H)-ylidene)-N^2-(1,5-dimethyl-4-((Z)-((5-(2-chlorophenyl)furan-2-yl)methylene)amino)-2-phenyl-1H-pyrazol-3(2H)-ylidene)benzene-1,2diamine) Fe (IV) (8) Yield: 53% M.P: 210^{0}C**FTIR:** 1418.61(C=N), 1340.23(C-O),850.58(1,2-disubstituted ring), 685.03(C-Cl)^1**HNMR (CDCl3,300MHz)** δppm(J,Hz) 9.73,9.63 [4H, o-phenylenediamine ring], 7.61 [8H-Ar], 7.76 [8H-Ar], 7.37,6.88 [4H, J= 0.02 Furayl ring], 3.83 [2CH3 with N], 6.90 [2CH$_3$]^{13} **C^{13}NMR (CDCl$_3$**) δppm 155.2 [C=N], 129.1, 130.5, 130.4 [Aromatic Cof o-phenylenediamine], 145.7, 123.4, 122.5 [Aromatic C], 130.2,121.9,127.2, 120.8[Aromatic ring attached with pyrazole ring] , 37.2 [N-CH3], 10.7 [CH3]**Mass spectrum** (EI, 70 eV, I_{rel} %): 942 [M$^+$](10),886 [M$^+$-Fe](4), 816[M$^+$-2Cl](5),662[M$^+$-2Ph](20),530[M$^+$-2furyl groups](15),478 [M$^+$-2N=CH](25),324 [M$^+$-2Ph](30),142 [M$^+$-0-phenylenediamine ring],(18),82[M$^+$-4CH$_3$]

Antidiabetic Activity

Antidiabetic activity of all the compounds (**2-8**) was screened by following the method reported by Eseyin et al. (Eseyin et al., 2018) with little modification described here (Zarren et al., 2019) . Different concentrations of samples (250µg, 200µg, 150µg, 100µg and 50µg) along with 0.5ml buffered solution of the enzyme were incubated at 37C for 10 minutes. Mixture used for purpose contacting 0.5 ml of each sample concentration. Then poured 1ml of DNSA in mixture to boil at water bathe for 5 minutes, cooled and further diluted with 20 ml distilled water. Negative control was used as a blank sample and acarbose used as standard. The absorbance of the mixture was taken at 540nm using Hitachi U-2900 spectrophotometer. The inhibitory percentage was calculated using the same formula. For comparing results, IC 50 values of each compound were calculated from the plots by performing non-linear regression analysis on GraphPad Prism 8.0.2. Table:1

Antioxidant activity

Garret nitric oxide (NO) scavenging method was used for the determination of antioxidant activity (Garret, 1964). The method is based on the principle that nitrate present in the sample must be reduced to nitrite. The nitric oxide is generated from sodium nitroprusside (SNP) and measured with Griess reagent. SNP produces NO in aqueous solution at pH 7.4 which gives nitrite ions on interacting with oxygen. So NO scavenging activity assay is based on determination of nitrite.

Procedure

In NO scavenging assay, aqueous sodium nitroprusside at physiological pH of 7.4 spontaneously generates NO radicals to produce nitrite ions which are estimated by using Griess reagent(Garret, 1964). First of all, test compound solution (2µL) was added to sodium nitroprusside (20µL) and phosphate buffer (178 µL) in the wells of plate. After incubation for 2 hours at 37 ^{0}C, Griess reagent (20 µL) was added. The mixture was kept at room temperature for 20 min for color development. The absorbance of each of the solution in well was recorded at 490 nm using software Gen5 of ELISA reader. The percentage inhibition was calculated by the following formula

$$\text{Percentage Inhibition} = \frac{(\text{O.D of positive control} - \text{O.D of Sample})}{\text{O.D of positive control}} \times 100$$

Results and Discussion:

In this study, initially we prepared hydrazone (**1**) by reacting 5-Arylfuran-2-carbaldehydes with4-amino Antipyrine and then resulting intermediate was reacted with o-phenylenediamine to get ligands (**2**) which were then coordinated with different transition metals like copper, nickel, manganese, iron, zinc and cobalt to give a series of complexes (**3-8**) by conventional synthetic method under acidic condition (**Scheme 2**). All the compounds were obtained in a yield 43-79%. Hydrazone ligands are soluble in almost all ordinary organic solvents but complexes are only soluble only in DMSO. For structural confirmation of all the synthesized ligands and complexes, FTIR, elemental analysis, EIMS, NMR, were performed and data is presented above. To check the antidiabetic activity, compounds were tested by following the method reported by Eseyin et al. (Eseyin et al., 2018) with little modification described here (Zarren et al., 2019) (**table 1**). Furthermore, total antioxidant activity was checked by NO scavenging method (**table 2)**

All synthesized compounds including ligands and metal complexes are colored, solids and stable. These synthesized compounds were affirmed by elemental analysis, proton and Carbon NMR, mass spectra, FTIR. The data of the complexes suggested, square planar geometry for the metals with primary valency two. The Schiff base behaves as a tetra dentate ligand. The metals, forms 1:1 complexes with the Schiff base ligand as shown in **Scheme 2**.

FTIR analysis of Ligand and metal complexes

The IR spectra provide valuable information regarding the nature of the functional group attached to the metal atom . The frequency corresponding to νC=N nitrogen in the complex participates in coordination to the metal ion . Coordination to the metal through the nitrogen atom is expected to reduce the electron density in the azomethine link and lowers the νC=N. The spectrum of the ligand shows two νC=N bands in the region 1650 cm-1 to 1565 cm-1 which is shifted to lower frequencies in the spectrum of the complex, showing the participation of –C=N nitrogen in the coordination to the metal ion . The ligand acts as a tetra dentate chelating agent, bonded to the metal ion via the four nitrogen –C=N atoms of the Schiff base. The appearance of medium band in the region 570 cm^{-1} to 445.57 cm-1 confirms the presence of M-N coordination in the complex.

NMR analysis of Ligand and metal complexes

The spectral information was obtained from the proton NMR and 13C NMR spectrum of the ligand with respect to TMS and given in the experimental section. Multiplet around δ 7.52 shows the presence of benzylidenium CH group. The peak for the benzene appears as multiplet at δ 7.44, the peaks for C-CH_3 and N-CH_3 Chemical Shift, in the region δ 3.11 and δ 2.44 respectively. The peaks for the benzylidenium hydrogen appear at δ 7.82 and δ 7.75. The C13 NMR spectral analyses shows corresponding peaks for imines, the peak at δ 140.5 corresponds to –N=C bonded to benzene ring through nitrogen. The respected peak confirmed the structure of ligands and metal complexes.

Mass Spectra of Ligands and Metal Complexes

Mass spectra of ligand and their metal complexes given in the experimental section and confirmed the structure of compounds.

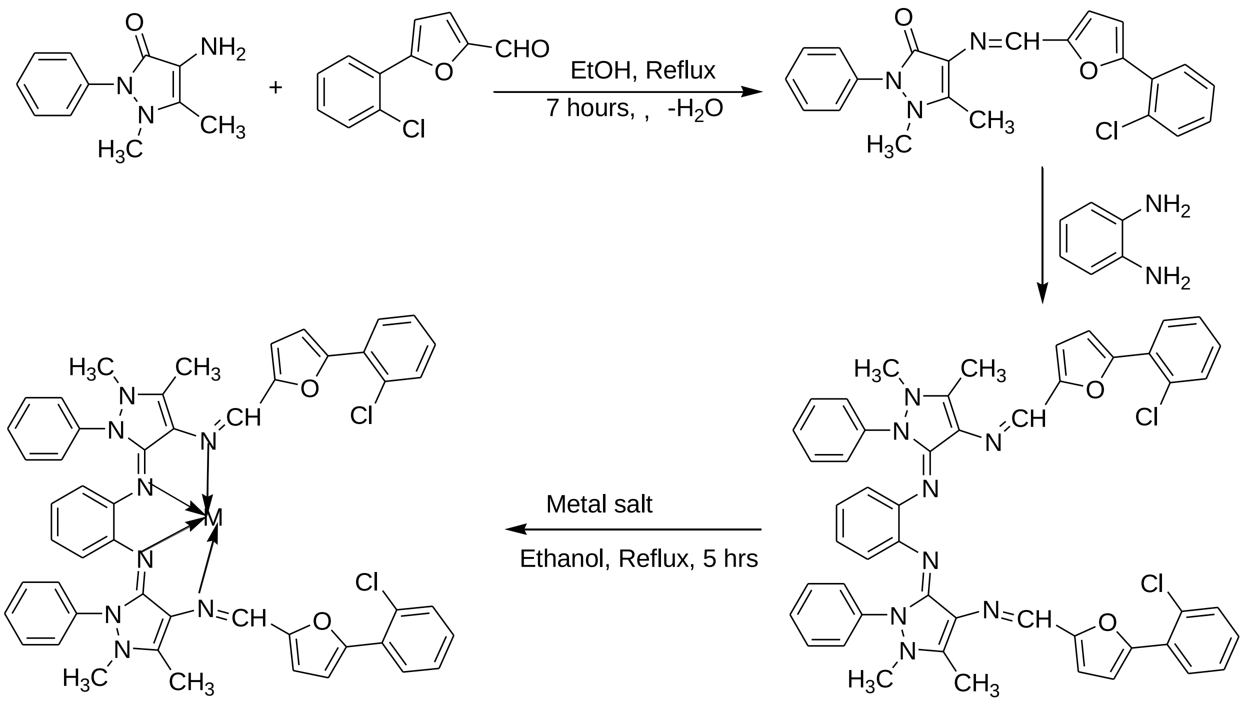
Antidiabetic Activity

The disease of high blood glucose levels is characterized as diabetes, which becomes a serious problem nowadays. So, the main goal of the scientist is to develop treatment or medication that can effectively treat diabetes by controlling the levels of blood sugar. In this modern age, there is a great development in the field of medication or treatment which can treat diabetes with hyperglycemia and hypoglycemia agents [55, 56]. Despite these developments, all the treatment modes and medications are still related to some side effects which opens up the ways for further investigation. In this study, we have checked the antidiabetic activity of newly synthesized ligand and metal complexes (**3-8**) by in vitro alpha-amylase analysis. In vitro antidiabetic activity of all the synthesized compounds have shown the results summarized in Table 1. Acarbose was used as a standard. The inhibitory effects of each synthesized compound were evaluated with the calculation of IC50 which interprets the concentration of the inhibitor that is required to inhibit 50% of its targeted enzyme. The lower IC50 values indicate the greater antidiabetic activity of compounds. In comparison to the overall result, compound **7** have shown a significant inhibitory activity with the IC_{50} value of 40.84µg/ml . The overall difference showed in the results may be attributed to the structural differences of a compound.

Antioxidant Activity

The compound **3-8** were tested for their antioxidant activity in concentrations of 10µM and 100µM. The %age antioxidant activity is given in **tables 2** .Unfortunately none of the compounds has shown significant activity. However metal complexes especially iron and copper metal complexes of synthesized ligands showed good activity as compared to their parent ligands.

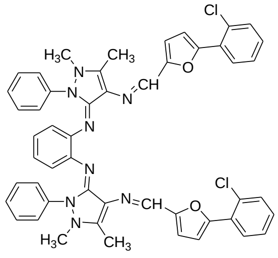
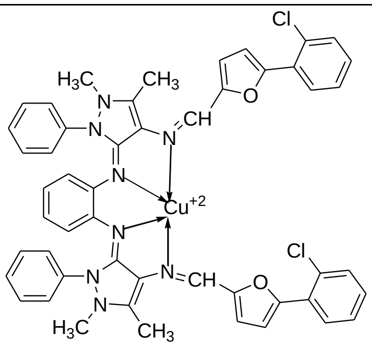
General Scheme for the synthesis of the Metal complexes

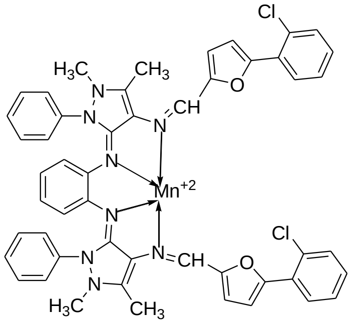
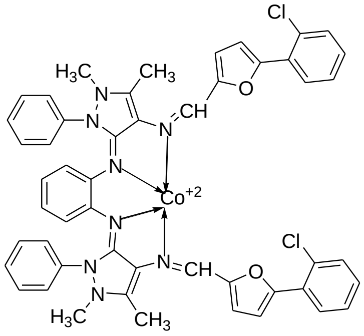
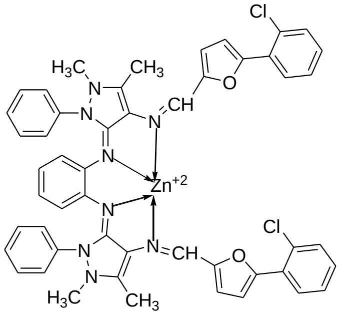
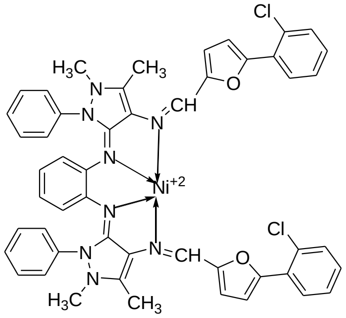


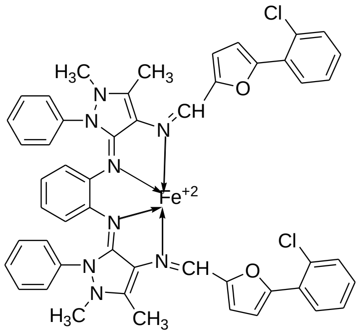
M= Cu, Zn, Co, Mn, Ni,Fe

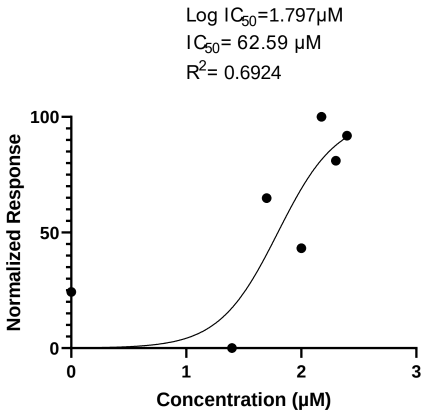
Scheme: 2

Table 1: Antidiabetic activity of synthesized Ligands and Metal Complexes

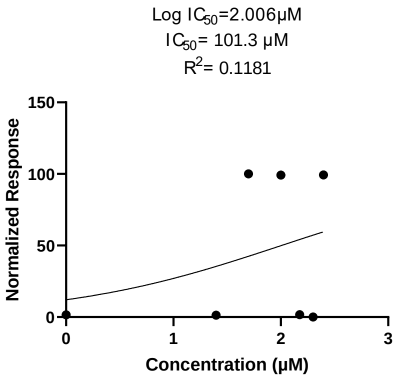
S.no	Structure	IC 50 µM	logIC50 µM
2		62.59	1.797
3		101.3	2.006

4		134.1	2.128
5		40.84	1.611
6		144.7	2.160
7		79.19	1.899

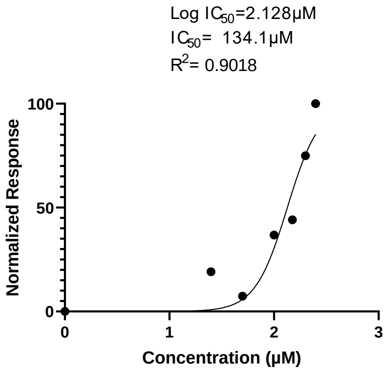
8		570.0	2.756



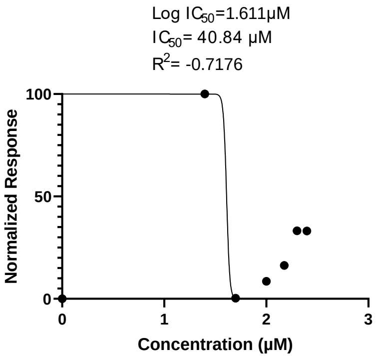
2



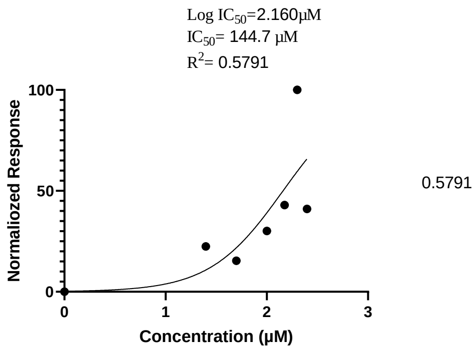
3



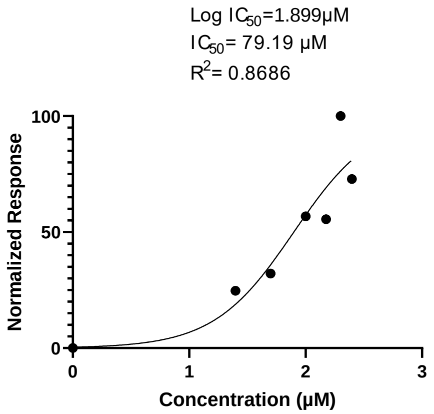
4



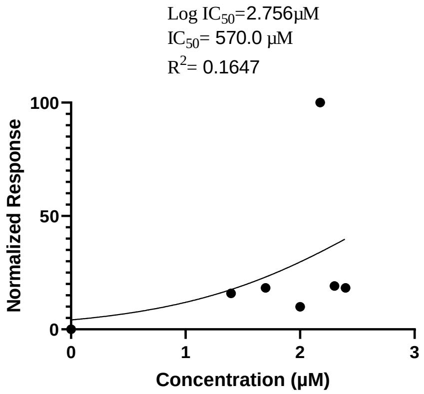
5



6



7



8

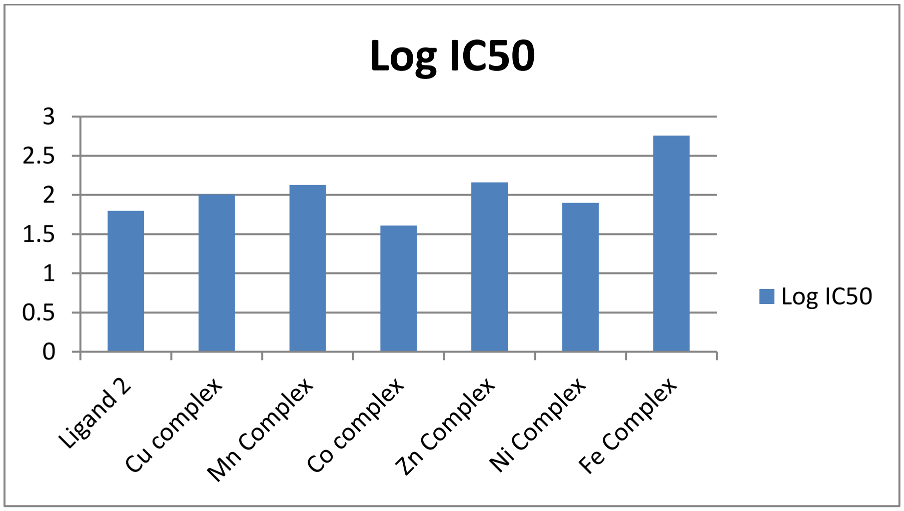
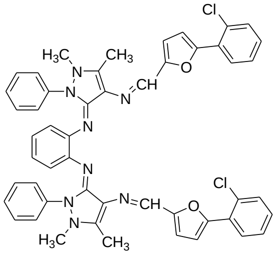
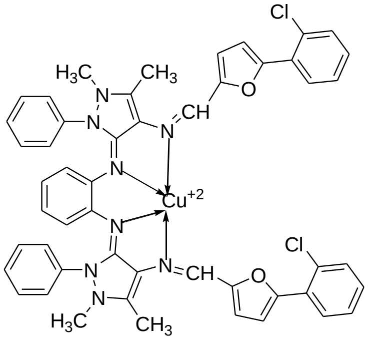
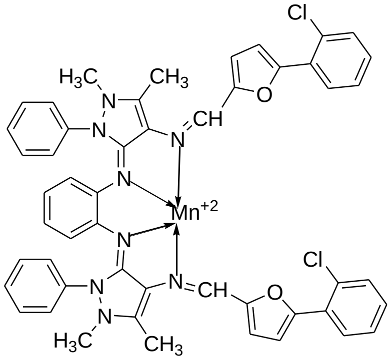
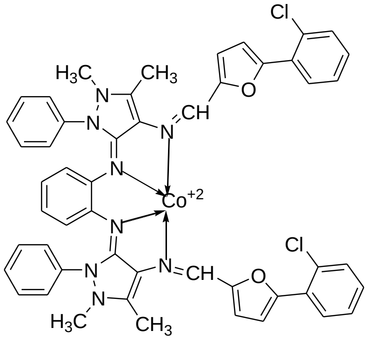
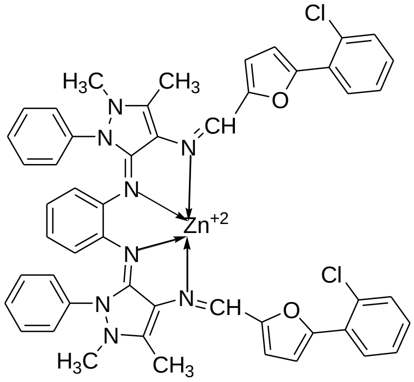
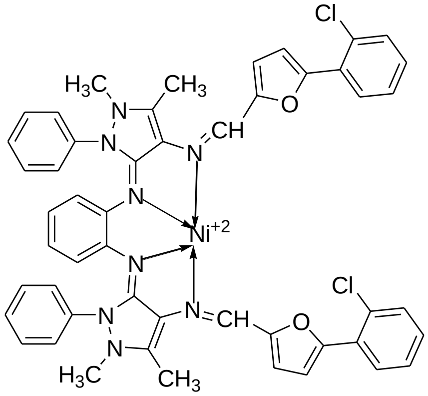
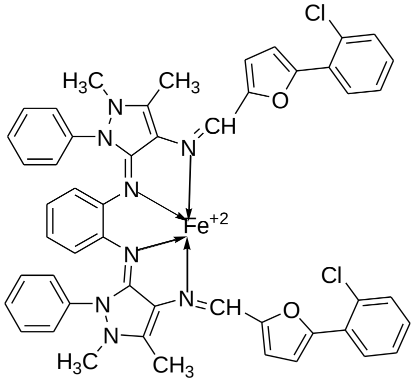


Fig 2: Graphical representation of anti-diabetic activity (2-8) and estimation of IC_{50} value by non-linear regression analysis in GraphPad Prism

Table 2: Antioxidant activity of synthesized Ligands and Metal Complexes

S.no	Structure	Conc.(µmoles)	% inhibition
3		100 10	20.36±0. 520 13.98±0.309
5		100 10	16.25±0.445 3.89±0.643
6		100 10	4.11±1.156 1.56±0.390
7		100 10	35.01±0.332 2.97±0.453

8		100 10	18.76±0.198 4.76±0.659
9		100 10	28.60±0.665 13.23±0.251
10		100 10	9.15±0.167 3.87±0.235

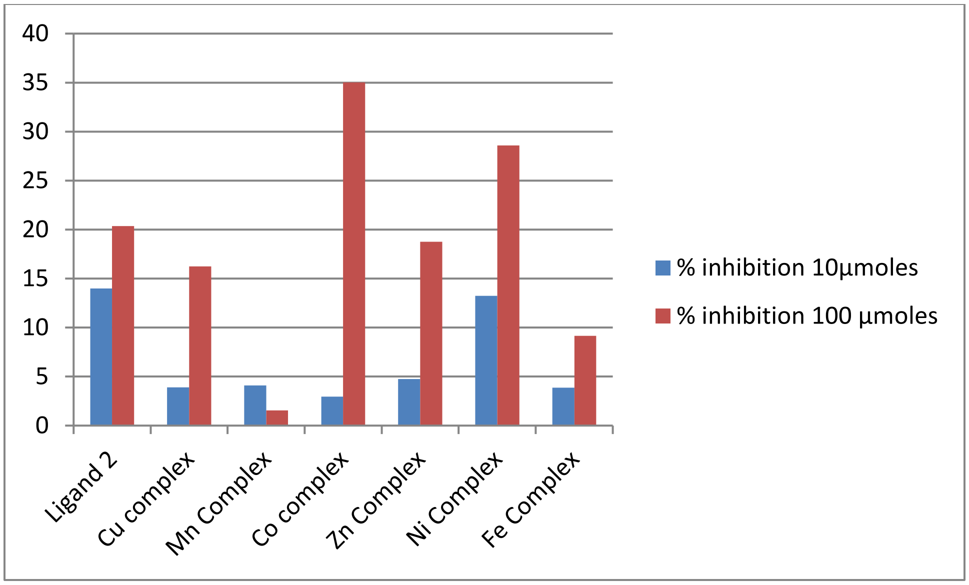


Fig 3: Graphical representation of anti-oxident activity (2-8) and estimation of IC$_{50}$ value by non-linear regression analysis in GraphPad Prism

Conclusion:

This work describes a simple and effective technique for the synthesis of metal complexes **(5-16)** by reacting various ligand **(3,4)** with metallic salts in acidic environments. These ligands were prepared from the reaction of 4-amino antipyrine, o-phenylenediamine with 5-Arylfuran-2-carbaldehydes. These prepared metal complexes were tested for their antidiabetic and antioxidant activity and it may act as potential lead molecules in the drug discovery program.

Acknowledgments

The author (SA) would like to acknowledge the financial support by PHEC, Govt. of Pakistan, for Postdoctoral fellowship.

Conflict of interest:

There is no conflict of interest.

References:

Alaghaz, A. N., Bayoumi, H., Ammar, Y. A., & Aldhlmani, S. A. (2013). Synthesis, characterization, and antipathogenic studies of some transition metal complexes with N,O-chelating Schiff's base ligand incorporating azo and sulfonamide Moieties. *Journal of Molecular Structure, 1035*, 383-399.

Anitha, C., Sheela, C. D., Tharmaraj, P., & Raja, S. J. (2012). Synthesis and characterization of VO (II), Co (II), Ni (II), Cu (II) and Zn (II) complexes of chromone based azo-linked Schiff base ligand. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 98,* 35-42.

Arulmurugan, S., Kavitha, P. H., & Venkatraman, B. R. (2010). Biological Activities of Schiff Base and its Complexex: A Review. *Rasayan Journal of Chemistry, 03,* 385-410.

Chandra, S., Jain, D., Sharma, A. K., & Sharma, P. (2009). Coordination Modes of a Schiff Base Pentadentate Derivative of 4-Aminoantipyrine with Cobalt(II), Nickel(II) and Copper(II) Metal Ions: Synthesis, Spectroscopic and Antimicrobial Studies. *Molecules, 14*, 174-190.

Chandraa, S., Raizada, S., MonikaTyagia, & Sharma, P. K. (2008). Spectroscopic and biological approach of Ni(II) and Cu(II) complexes of 2-pyridinecarboxaldehyde thiosemicarbazone. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 69*, 816-821.

El-Sherif, A. A. (2009). Synthesis, spectroscopic characterization and biological activity on newly synthesized copper(II) and nickel(II) complexes incorporating bidentate oxygen–nitrogen hydrazone ligands. *Inorganica Chimica Acta, 362*, 4991-5000.

Eseyin.O.A, E. Edem, E. Johnson, A. Ahmad, S. Afzal, Synthesis and in vitro antidiabetic activity of some alkyl carbazole compounds, Tropical Journal of Pharmaceutical Research 17(3) (2018) 537-541

Garret, D. C. (1964). *Quantitative analysis of drugs* (Vol. 3). Japan: Champan and Hall.

Gul Zarren , Nusrat Shafiq , Uzma Arshad , Naila Rafiq ,Shagufta Parveen , Zaheer Ahmad , Copper-catalyzed one-pot relay synthesis of anthraquinone based pyrimidine derivative as a probe for antioxidant and antidiabetic activity, *Journal of Molecular Structure* (2020), doi: https://doi.org/10.1016/j.molstruc.2020.129668

Henry, P. M., Lange, G. L., & Patai, S. (1977). The chemistry of double bonded functional groups. *Interscience, New York, supplies, 02*, 1067-1069.

Joseph, M., Sreekanth, A., Suni, V., & Kurup, M. R. P. (2006). Spectral characterization of iron(III) complexes of 2-benzoylpyridine N(4)-substituted thiosemicarbazones. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 64*, 637-641.

Kakanejadifard, A., ashari, F. E., Hashemi, P., & Zabardasti, A. (2013). Synthesis and characterization of an azo dibenzoic acid Schiff base and its Ni(II), Pb(II), Zn(II) and Cd(II) complexes. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 106*, 80-85.

Karthikeyan, M. S., Prasad, D. J., Poojary, B., Bhat, K. S., Holla, B. S., & Kumari, N. S. (2006). Synthesis and biological activity of Schiff and Mannich bases bearing 2, 4-dichloro-5-fluorophenyl moiety. *Bioorganic & medicinal chemistry, 14*, 7482-7489.

Kaspady, M., Narayanaswamy, V. K., Raju, M., & Rao, G. K. (2009). *Lett. Drug Design Discov., 6*, 21.

Krishnan, S. S., & Saravan, M. (2001). Ultrasonic Assisted Synthesis of Naphthalene Substituted Schiff Base Derivatives and Their Antioxidant Activity Studies. *European Journal of Medicinal Chemistry, 36*, 615-619.

Lakhe, D., & Mangaonkar, V. K. (2013). Synthesis, Characterization and Antimicrobial activity ofMixed Ligand Complexes of Ni(II), Cu(II) and Fe(III) ionswith [phenol-2-[(3-methylphenyl)imino]methyl-4-nitro-] and[phenol-2-[(3-chlorophenyl)imino]methyl-4-nitro-]. *International Journal of ChemTech Research, 05*, 293-298.

Ochiai, E. I. I. (1973). A laboratory program for bioinorganic chemistry. *Journal of Chemical Education, 50*, 610-611.

Pandeya, S. N., Sriram, D., Nath, G., & DeClercq, E. (1999). Synthesis, antibacterial, antifungal and anti-HIV activities of Schiff and Mannich bases derived from isatin derivatives and N-[4-(4'-chlorophenyl)thiazol-2-yl] thiosemicarbazide. *European Journal of Pharmaceutical Sciences, 09*, 25-31.

Panneerselvam, P., Nair, R. R., Vijayalakshmi, G., Subramanian, E. H., & Sridhar, S. K. (2005). Synthesis of Schiff bases of 4-(4-aminophenyl)-morpholine as potential antimicrobial agents. *European Journal of Medicinal Chemistry, 40*, 225-229.

Patel, K. A., Patel, R. J., Patel, K. H., & Patel, R. M. (2009). *J. Chil. Chem. Soc.*, *54*, 228.

Pham-Huy, L. A., He, H., & Pham-Huy, C. (2008). *J. Biomed. Sci.*, *4*, 89.

Raja, N., & Ramesh, R. (2010). Mononuclear ruthenium(III) complexes containing chelating thiosemicarbazones: Synthesis, characterization and catalytic property. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 75*, 713-718.

Raman, N., Thalamuthu, S., Dhaveethuraja, J., Neelakandan, M. A., & Banerjee, S. S. (2008). DNA Cleavage and Antimicrobial Activity Studies on Transition Metal(II) Complexes of 4-Aminoantioyrine Derivative. *Journal of the Chilean Chemical Society, 53*, 1-9.

Rosu, T., Pasculescu, S., Lazar, V., Chifiriuc, C., & Cernat, R. (2006). Copper(II) Complexes with Ligands Derived from 4-Amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one: Synthesis and Biological Activity. *Molecules, 11*, 904-914.

Satyanarayana, V. S. V., Sivakumar, A., & Ghosh, A. R. (2010). Ultrasonic Assisted Synthesis of Naphthalene Substituted Schiff Base Derivatives and Their Antioxidant Activity Studies. *Journal of Pharmacy Research, 03* 2327-2329.

Schiff, H. (1864). The syntheses and characterization of Schiff base. *Annual chemical pharmaceutical suppliers*, *3*, 343-370.

Seitz, M., Kaiser, A., Stempfhuber, S., Zabel, M., & Reiser, O. (2004). Helical, nonracemic inorganic-organic hybrid polymers of cadmium halides with pentadentate bis(oxazoline) ligands. *Journal of American Chemical Society, 126*, 11426-11427.

Singh, K., Barwa, M. S., & Tyagi, P. (2006). Synthesis, characterization and biological studies of Co(II), Ni(II), Cu(II) and Zn(II) complexes with bidentate Schiff bases derived by heterocyclic ketone. *European Journal of Medicinal Chemistry, 41*, 147-153.

Singh, K. B., & Adhikari, D. (2012). Complexation Behaviour of Schiff Base Ligands with Transition Metal Ions. *International Journal of Basic and Applied Chemical Sciences, 02*, 84-107.

Suresh, M. S., & Prakash, V. (2011). Preparation Characterization and Antibacterial Studies of Chelates of Schiff Base Derived from 4-Aminoantipyrine, Furfural and o-Phenylenediamine. *E-Journal of Chemistry, 08*, 1408-1416.

Terao, J., & Piskula, M. K. (1997). Flavonoids as inhibbitors of lipid peroxidation in membraces. In C. A. Rice-Evans & L. Packer (Eds.), *Flavonoids in health and diseases* (pp. 277). New York: Marcel Dekker.

Yazıcı, A., & Akgün, F. (2006). Synthesis and Characterization of Two New Schiff Base Ligands and their Complexes with Cobalt(II), Nickel(II) and Copper(II). *Transition Metal Chemistry, 31*, 152-156.

Yuhki, S., Keiko, N., Mitsuru, K., Sachie, Y., Kenji, M., Fumio, U., & Hiroyuki, K. (2008). The Copper(II) Complex with Two Didentate Schiff Base Ligands. The Unique Rearrangment that Proceeds under Alcohol Vapor in the Solid State to Construct Noninclusion Structure. *The Chemical Society of Japan, 37*, 78-79.