Schiff Bases of Hydroxyacetophenones and their Copper(II) and Nickel(II) Complexes: Synthesis, Antioxidant Activity and Theoretical Study

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The synthesis of a series of Schiff base ligands derived from tryptamine and 5-methoxy-2-hydoxyacetophenone, 5-methyl-2-hydroxyacetophenone and 2-hydoxyacetophenone together with their copper(II) and nickel(II) complexes is presented. The ligands and complexes were characterized by elemental analysis, IR, ^{1}H and ^{13}C NMR, UV-visible spectroscopy as well as magnetic measurements. Semi empirical quantum mechanical calculations and DFT calculations were performed to model the structures of the compounds. The complexes were found to have the general formula $[M(L)_2]$. Spectral studies reveal that these Schiff bases act as bidentate ligands and coordinate to the metal center through deprotonated phenolate oxygen and azomethine nitrogen atoms. Nickel(II) complexes establish square planar geometry around the central metal, whereas distorted tetrahedral geometry is proposed for copper(II) complexes. Electronic energy, molecular orbitals energy, HOMO-LUMO gap, ionization potentials, heat of formation and dipole moments were also optimized. The compounds are screened for their antioxidant activity using 2,2-diphenyl-1-picrylhydrazyl free radical (DPPH$^•$) and ferric-reducing antioxidant power (FRAP) assays in which butylated hydroxytoluene (BHT) is used as a reference. The investigations reveal that the ligands appear to be more effective antioxidants, but also copper(II) complexes show good activity. Methoxy-substituted ligand shows an enhanced activity over BHT in the FRAP assay.

Keywords: Tryptamine, Hyroxyacetophenones, Metal complexes, Antioxidant activity, PM6 & DFT study.

INTRODUCTION

There is a significant research efforts to overcome the deleterious effects of free radicals in human body [1]. Free radicals are species contain unpaired electrons such as superoxide (O_2^-) and hydroxyl radicals (OH$^•$), that produced as a result of normal or pathological metabolitic reactions [2,3]. Overproduction of such free radicals lead to dangerous consequences affecting biological molecules such as lipids, proteins, enzymes, DNA and RNA, changing their structures, altering their functions, or promote an extended oxidative cell damage [4]. Elimination of such free radicals becomes one of the major aims of current research by designing suitable antioxidant drugs to be administered [5]. Of course many naturally occurring antioxidants are present, but their uses are limited by different factors including difficulty of separation and purification from their natural resources and in many cases they cannot be used in their original form owing to unknown disasters that may originate from other associated ingredients. This justifies the search for effective synthetic antioxidants that are capable to get over the toxic and side effects arising from natural ones [6].

Schiff bases, as an important class of organic compounds, show a wide spectrum of biological activities. Many studies have been reported regarding the biological activities of Schiff bases, including their anticancer [7], antibacterial [8], antifungal and herbicidal activities [9,10]. Developing new chemotherapeutic Schiff bases and their metal complexes is now attracting the attention of medicinal chemists [6].

In this study, we are encouraged to synthesize new Schiff bases containing hydroxyl groups attached to the aromatic ring stemmed from indole derivative, tryptamine, coupled with hyroxyacetophenones, with their copper(II) and nickel(II) complexes for comparing their function. The novel compounds were characterized on the bases of elemental analysis, IR, ^{1}H and ^{13}C NMR spectroscopy, UV-visible, magnetic measurements as well as semi-empirical PM6 and DFT quantum mechanical calculations with a view to gain more insight about their electronic structure and activity. Further investigations were carried to evaluate the radical scavenging abilities of these novel compounds using the DPPH$^•$ and FRAP methods.

EXPERIMENTAL

Chemicals were purchased from Sigma-Aldrich and used without further purification, ethanol was redistilled before use. Dry dimethyl sulfoxide, ethyl acetate and dimethyl formamide were utilized for recrystallization purposes.

IR spectra were recorded with a Perkin-Elmer FT-IR spectrophotometer model Spectrum 2000 using KBr pellets as support in the range 4000-370 cm^{-1}. ^{1}H NMR spectra were recorded at room temperature on a JEOL ECA-400 spectrometer, operating with a frequency of 400 MHz, using DMSO-d_6 as solvent. Electronic spectra, in DMSO solution, were obtained using a Varian 50 Conc UV-visible spectrophotometer over the wavelength range 200-800 nm. Magnetic susceptibility data were obtained from powdered samples using a Sherwood Scientific magnetic susceptibility balance. The effective magnetic moments were calculated from the expression (μ_{eff} = 2.83$\sqrt{\chi_M T}$) BM, where χ_M is the molar susceptibility corrected using Pascal's constants for diamagnetism of all atoms in the compounds.

Theoretical calculations of copper(II) and nickel(II) complexes were carried out using PM6 semi-empirical methods in MOPAC2007 program, implemented on an Intel Pentium (R) 1.86 GB computer. Initial estimates for the geometries of all the structures were obtained by molecular mechanics program (ACD11) for Widows, followed by full optimization of all geometrical variables (bond lengths, bond angles and dihedral angles), without any symmetry constraints. DFT calculations were performed for the ligands on B3LYP level of theory with the Gaussian 09 software packages [11]. All the structures were fully optimized at Density Functional Study (DFT) level, RB$_3$LYP for neutral ligands and UB3LYP for cation ligands using the high level 6-31g basis set in the gas phase, for the purpose of calculating ionization potentials.

Preparation of 2-{1-[2-(1*H*-Indole-3-yl)ethylimino]-ethyl}phenol (THAP): This ligand is prepared according to the literature method [12]. A solution of tryptamine (0.5 g, 3.12 mmol) in 50 mL of acidified ethanol (pH 4.5) was added to a boiling solution of 2-hydroxyacetophenone (0.426 g, 3.13 mmol) in 50 mL of acidified ethanol (pH 4.5). The mixture was refluxed for 2 h. The solid product was filtered off and recrystallized from ethanol (Yield 79.4 %). The compound was soluble in ethanol, methanol, acetone, THF and DMSO, but insoluble in water. Anal. calcd. for C$_{18}$H$_{18}$N$_2$O: C, 77.67; H, 6.52; N, 10.06 %. Found: C, 77.52; H, 6.25; N, 10.05 %.

Preparation of 2-{1-[2-(1*H*-Indole-3-yl)-ethylimino]-ethyl}-4-methyl phenol (TMeHAP): The above procedure was followed using (0.5 g, 3.12 mmol) of tryptamine and (0.468 g, 3.11 mmol) of 5-methyl-2-hydroxyacetophenone in 50 mL of acidified ethanol. The yield was 70 %. The compound was soluble in most organic solvents, but insoluble in water. It was recrystallized from ethanol [12]. Anal. calcd. for C$_{19}$H$_{20}$N$_2$O: C, 77.90; H, 6.84; N, 9.57 %. Found: C, 77.62; H, 6.62; N, 9.83 %.

Preparation of 2-{1-[2-(1*H*-Indole-3-yl)-ethylimino]-ethyl}-4-methoxy phenol (TOMeHAP): The same above procedure was followed using (1 g, 6.24 mmol) of tryptamine and (1.04 g, 6.25 mmol) of 5-methoxy-2-hydroxyaceto-phenone. (Yield 72.2 %). The product was recrystallized from

ethyl acetate. Anal. calcd. for C$_{19}$H$_{20}$N$_2$O$_2$: C, 74.00; H, 6.54; N, 9.08 %. Found: C, 74.20; H, 6.19; N, 9.13 %.

General method of preparation of the complexes: To solutions of copper(II) acetate monohydrate and nickel(II) acetate tetrahydrate, (1 mmol) in absolute ethanol (50 mL), were added solutions of the appropriate Schiff base (2 mmol) in the same solvent (20 mL), followed by a few drops of triethylamine. The mixtures were heated under reflux for 5 h. The product that had formed was filtered off, washed with absolute ethanol and dried over anhydrous silica gel.

THAP copper(II) complex: Percentage yield (28.4 %). The compound is soluble in THF, DMSO and DMF. Anal. calcd. for C$_{36}$H$_{34}$N$_4$O$_2$Cu: C, 69.87; H, 5.49; N, 9.05 %. Found: C, 70.11; H, 5.77; N, 8.92 %.

THAP nickel(II) complex: Percentage yield (60.0 %). The compound is soluble in THF, DMSO and DMF. Anal. calcd. for C$_{36}$H$_{34}$N$_4$O$_2$Ni: C, 70.43; H, 5.54; N, 9.13 %. Found: C, 70.56; H, 5.20; N, 8.97 %.

TMeHAP copper(II) complex: Percentage yield (34.6 %). The compound is soluble in THF, DMSO and DMF. Anal. calcd. for C$_{38}$H$_{38}$N$_4$O$_2$Cu: C, 70.55; H, 5.87; N, 8.66 %. Found: C, 70.75; H, 5.57; N, 8.59 %.

TOMeHAP copper(II) complex: Percentage yield (19.1 %). The compound is soluble in THF, DMSO and DMF. Anal. calcd. for C$_{38}$H$_{38}$N$_4$O$_4$Cu: C, 67.22; H, 5.60; N, 8.25 %. Found: C, 67.49; H, 5.90; N, 8.23 %.

TOMeHAP nickel(II) complex: Percentage yield (19.1 %). The compound is soluble in THF, DMSO and DMF. Anal. calcd. for C$_{38}$H$_{38}$N$_4$O$_4$Ni: C, 67.71; H, 5.64; N, 8.31 %. Found: C, 67.54; H, 5.48; N, 8.07 %.

Attempts to prepare TMeHAP nickel(II) complex by the same procedure were unsuccessful.

Antioxidant assays

DPPH• method: The total free radical scavenging capacity of the Schiff bases and complexes was estimated and was compared to BHT as standard.

Freshly prepared DPPH• solution (100 μM) in DMSO was used in the determination. 5 μL of the samples (with a concentration range between 50-250 μM) and standards were added to 195 μL of DPPH reagent to start the reaction. The final concentration was 97.5 μM for DPPH• and varies between 50-250 μM for the test compounds. This has been done to determine the optimum concentration that achieves maximum inhibition of DPPH•. The plate was read at 515 nm for 3 h with 20 min intervals to reach a steady state against DMSO as a blank. The percentage DPPH• quenched was calculated according to the equation:

$$\text{DPPH quenched (\%)} = \frac{\text{Abs. blank} - \text{Abs. sample}}{\text{Abs. blank}} \times 100$$

Ferric reducing antioxidant power assay: Total antioxidant activity is measured by ferric reducing antioxidant power (FRAP) assay of Benzie and Strain [13]. FRAP assay uses antioxidants as reductants in a redox-linked colorimetric method, employing an easily reduced oxidant system present in stoichiometric excess.

The FRAP reagent was prepared by mixing 50 mL of 300 mmol/L sodium acetate buffer (pH 3.6), with 5 mL of 10

mmol/L tripyridyl triazine (TPTZ) in 40 mmol/L HCl and 5 mL of 20 mmol/L $FeCl_3 \cdot 6H_2O$. Samples (10 µL) and standards (BHT) were mixed with 300 µL of the working FRAP reagent and the absorbance at 593 nm was measured at 0 min after mixing and 4 min. Each test was carried out in triplicates.

The FRAP value was calculated as ferrous equivalents which obtained by comparing the absorbance change in the test reaction mixture with those containing known concentrations of ferrous ions (standard).

RESULTS AND DISCUSSION

The title Schiff bases were successfully prepared according to **Scheme-I**. The physical properties of all prepared ligands and complexes have been summarized in Table-1.

Infrared spectroscopy: The IR spectra of the ligands and complexes have been summarized in Table-2. It can be clearly shown that the absence of the characteristic aldehydic carbonyl stretching bands and the appearance of the azomethine –C=N– bands, at 1609, 1605 and 1602 cm^{-1} for THAP, TMeHAP and TOMeHAP, respectively indicates the formation of the Schiff base. The broad band at 3166-3142 cm^{-1} could be attributed to the intramolecular hydrogen-bonded O-H group [14-16]. This

band was absent in the spectra of complexes due to deprotonation upon complexation. The metal ion is coordinated through the oxygen atom of the hydroxyl group. The azomethine –C=N– bands have been shifted to lower frequencies in all complexes due to the withdrawal of electron density from the nitrogen atom owing to coordination [14]. A similar effect was observed in the stretching vibration of the Schiff base phenolic C-O group, with respect to the same group in the complexes where it was shifted to higher frequency, confirming oxygen co-ordination to the metal [17]. The shifts observed for indolic N-H band in the complexes with respect to the ligands suggests an intermolecular interaction between NH group of the indole moiety and the phenolic oxygen of another molecule [12]. New bands in the region 429-421 cm^{-1} and 509-583 cm^{-1} were assigned to vibrations associated with ν(M-N) and ν(M-O) bonds, respectively [18,19].

Proton NMR spectra: ^{1}H NMR spectra of the TOMeHAP ligand was summarized in Table-3 with chemical shifts expressed in ppm down field tetra methylsilane as reference.

The spectral data of the Schiff bases were consistent with the structure proposed (Fig. 1). The singlet observed at 10.82 ppm can be attributed to the indolic N-H proton (H_a). The
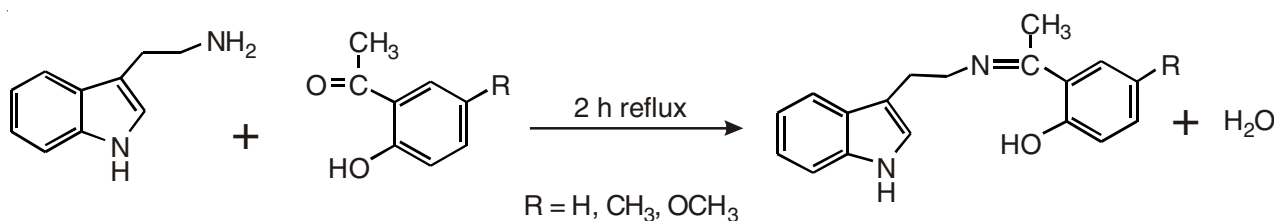
Scheme-I: Synthesis of the Schiff base ligands

TABLE-1
PHYSICAL PROPERTIES OF SCHIFF BASES AND THEIR Cu(II) AND Ni(II) COMPLEXES

Name of the compound	m.f.	Molar mass	Colour	m.p. (°C)	μ_{eff} (BM)
THAP	$C_{18}H_{18}N_2O$	278.35	Yellow	112	–
TMeHAP	$C_{19}H_{20}N_2O$	292.38	Yellow	175	–
TOMeHAP	$C_{19}H_{20}N_2O_2$	308.38	Bright yellow	179	–
(THAP)₂Cu	$C_{36}H_{34}N_4O_2Cu$	618.24	Brown	212 (dec.)	1.78
(THAP)₂Ni	$C_{36}H_{34}N_4O_2Ni$	613.38	Yellowish green	249 (dec.)	Diamagnetic
(TMeHAP)₂Cu	$C_{38}H_{38}N_4O_2Cu$	646.29	Brown	282 (dec.)	2.10
(TOMeHAP)₂Cu	$C_{38}H_{38}N_4O_4Cu$	678.29	Brown	206	2.20
(TOMeHAP)₂Ni	$C_{38}H_{38}N_4O_4Ni$	673.43	Brownish yellow	238 (dec.)	Diamagnetic

TABLE-2
IR SPECTRA OF THE LIGANDS AND COMPLEXES

Compound	ν(N-H)	ν(O-H)	C-H aliphatic	ν(C=N)	C-O	C-H aromatic	ν(M-O)	ν(M-N)
THAP	3433	3142-2875Brd	2926	1609	1265	731	–	–
(THAP)₂Cu	3371	–	2940	1599	1237	738	525	429
(THAP)₂Ni	3409	–	2917	1600	1220	745	583	428
TMeHAP	Superimposed	3167-2915Brd	2915	1605	1280	753	–	–
(TMeHAP)₂Cu	3417	–	2918	1589	1315	740	509	424
TOMeHAP	Superimposed	3166	2913	1602	1222	757	–	–
(TOMeHAP)₂Cu	3413	–	2930	1598	1213	745	531	421
(TOMeHAP)₂Ni	3331	–	2929	1599	1214	745	536	426

TABLE-3
^{1}H NMR SPECTRA OF THE LIGANDS, s = SINGLET, t = TRIPLET, m = MULTIPLET

Compound	H_a	H_b	H_c	H_d	H_e	H_R	$H_{aromatic}$
TOMeHAP	10.82(s)	3.07(t)	3.84(t)	2.26(s)	16.81(s)	3.74(s)	6.69-7.58(m)

ethyleneic protons (H$_b$) and (H$_c$) resonate at 3.07 and 3.84 ppm as triplets, respectively. The methyl protons (H$_d$) resonates at 2.26 ppm as a singlet. Integration line confirms that 3 protons are responsible for the signal. The signals between 6.69 and 7.58 ppm are due to 8 aromatic protons as the integration implies. The methoxy protons resonate further down field at 3.74 ppm. This is because of the effect exerted by the electronegative oxygen atom directly attached. ^{1}H NMR spectra for the other two ligands were described in the literature [12]. No clear spectra were recorded for metal complexes due to paramagnetic effects in solution.
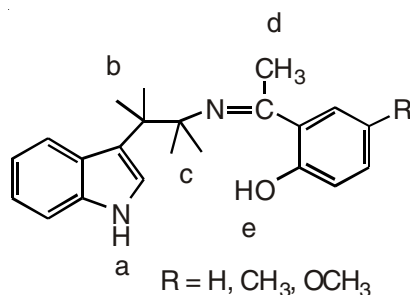

Fig. 1. Proposed framework structure of the ligands

^{13}C NMR spectra: Table-4 summarizes the key ^{13}C spectral data together with their assignments. Further support to the proposed structure of the ligands can be obtained from their ^{13}C NMR spectra. All aromatic carbon atoms lie in the chemical shift range 111.4-172.1 ppm. The most down field peaks at about 172.42 ppm could be assigned to the phenolic carbon atoms C-OH. The peaks at the range 157-165 ppm can be attributed to azomethine carbon atoms. Ethylenic carbons appear in the range 25.9-49.1 ppm. Acetophenone methyl group in all ligands appears at 14.5 ppm, whereas the signals at 20.2 and 55.7 ppm were ascribed to substituted methyl and methoxy groups, respectively.

TABLE-4
^{13}C NMR SPECTRA OF THE LIGANDS

Chemical shift range (ppm)	Assignment
26.0-49.2	Ethylenic carbons -CH$_2$-CH$_2$-
111.4-172.1	Aromatic
157.0-165.0	Azomethine -C=N-
171.0-172.0	Phenolic -C-OH
20.2	5-methyl -CH$_3$
55.7	5-methoxy -OCH$_3$
14.5	Acetophenone CH$_3$ group

UV-visible spectroscopy and magnetic measurements: The electronic spectra of all compounds in DMSO with their assignments are given in Table-5. The spectra of THAP exhibit bands at 395, 317, 291 and 276 nm, which are well consistent with reported data by Zarza *et al.* [12] in chloroform.

For the rest of the compounds bands in the region 260-346 were associated with π-π* transitions within the aromatic rings. Those bands undergo either hypsochromaic or bathochromic shifts upon complex formation. n-π* transitions in complexes were usually obscured by the near intense charge transfer bands. For nickel(II) complexes, weak intensity bands at 572 nm could be assigned to *d-d* transitions. Those bands indicate that nickel(II) complexes undergo geometrical changes in solution since they are diamagnetic in the solid state as it is usual for square planar *d*^{8} complexes [20]. Copper complex of the methyl-substituted ligand has a magnetic moment of 2.1 BM at room temperature. This behaviour is in agreement with analogous copper(II) complexes with pseudo tetrahedral geometry around the copper ion [21,22].

Computational study: The chemical structures of the compounds under investigation are presented in Fig. 2. The optimized molecular structure of (TOMeHAP)$_2$Cu using PM6 semi-empirical methods is shown in Fig. 3. The calculated quantum chemical indices E$_{HOMO}$, E$_{LUMO}$, ΔE (E$_H$-E$_L$), heat of formation, ionization potential, electronic energy, total energies

TABLE-5
UV-VISIBLE SPECTRA OF LIGANDS AND COMPLEXES

| Compound	Concentration (mol/L)	ε (mol^{-1} L cm^{-1})	λ$_{max}$ (nm)	Assignment
THAP	9.88×10^{-5}	1.56×10^3	395	n-π*
		3.67×10^3	317	π-π* chelate ring
		6.94×10^3	291	–
		7.78×10^3	276	π-π* indole group
		9.42×10^3	260	π-π* indole group
(THAP)$_2$Ni	7.33×10^{-5}	–	572	*d-d* transition
		5.06×10^3	388	CT, n-π*
		2.34×10^4	263	π-π* indole group
(THAP)$_2$Cu	6.47×10^{-5}	7.86×10^3	358	CT, n-π*
		2.13×10^4	273	π-π* ligand
TMeHAP	1.54×10^{-4}	3.77×10^3	338	π-π* chelate ring
		8.08×10^3	282	π-π* indole group
(TMeHAP)$_2$Cu	6.57×10^{-5}	9.71×10^3	358	CT, n-π*
		2.40×10^4	272	π-π* ligand
TOMeHAP	1.13×10^{-4}	3.98×10^3	346	π-π* chelate ring
		7.94×10^3	281	π-π* indole group
(TOMeHAP)$_2$Ni	1.48×10^{-4}	364.86	572	*d-d* transition
		4.03×10^3	412	CT, n-π* transition
(TOMeHAP)$_2$Cu	1.91×10^{-4}	6.45×10^3	386	CT, n-π*
		1.80×10^4	268	π-π* ligand

R = H, CH₃, OCH₃;   M = Cu, Ni
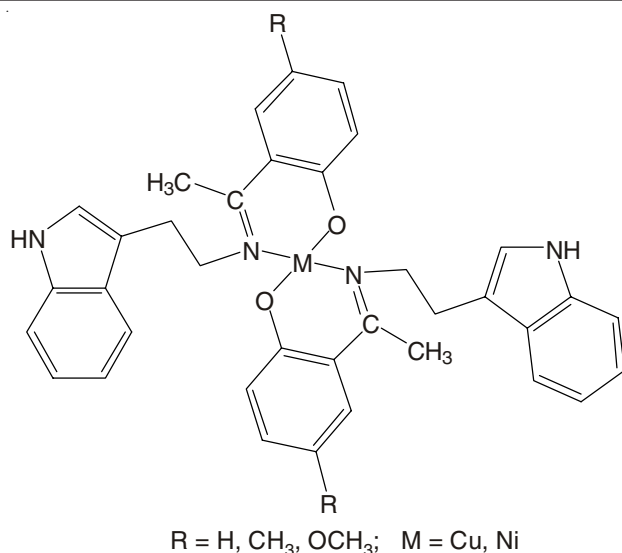
Fig. 2. Proposed molecular structure of Cu(II) and Ni(II) complexes

and dipole moments, are given in Table-6. The concept of HOMO-LUMO energy gap is used to develop theoretical models, which are capable of explaining the structure and conformation barriers in many molecular systems qualitatively [23]. According to the data in Table-6, there is a good correlation in HOMO-LUMO energy gap calculated in the gas phase for studied complexes. Copper(II) complexes have smallest HOMO-LUMO gaps (0.064 eV), (0.044 eV) and (0.043 eV) for (THAP)₂Cu, (TMeHAP)₂Cu and (TOMeHAP)₂Cu, respectively, compared to nickel(II) complexes, which have higher HOMO-LUMO gaps *i.e.* (1.30 eV) and (1.219 eV) for (THAP)₂Ni and (TOMeHAP)₂Ni, respectively. Moreover, the heat of formation and the total energy of copper(II) complexes is less
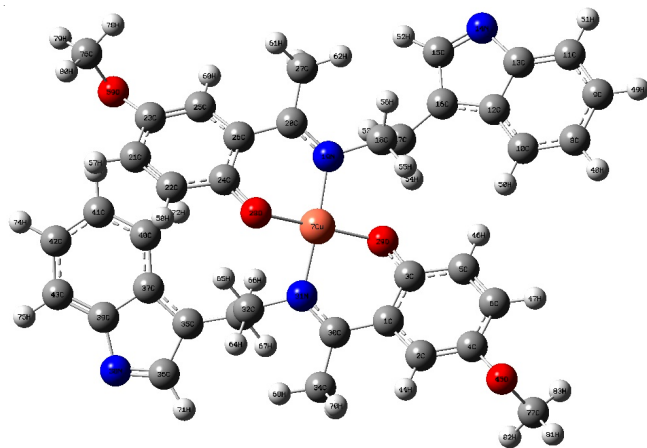
Fig. 3. Optimized structure of (TOMeHAP)₂Cu complex

than that of nickel(II) complexes. This indicates that copper(II) complexes are more stable than nickel(II) complexes. The heats of formation of copper(II) complexes are 124.311, 107.987 and 51.662 kcal/mol for (THAP)₂Cu, (TMeHAP)₂Cu and (TOMeHAP)₂Cu, respectively, whereas for nickel(II) complexes are 164.637 and 94.247 kcal/mol for (THAP)₂Ni and (TOMeHAP)₂Ni, respectively.

The order of stability is therefore: copper(II) complexes > nickel(II) complexes and the methoxy-substituted ones are the most stable.

The gas-phase ionization potentials (IP) of the ligands were calculated to compare their antioxidant activities and gain more understanding of the mechanisms involved. The total electronic energies of neutral ligands and cations are illustrated in Table-7 and the ionization potentials were calculated according to the relation:

Ionization potential (IP) = Electronic energy of cation –
Electronic energy of neutral ligand

It follows that the order of ease of ionization is:

TOMeHAP > TMeHAP > THAP

TABLE-7
TOTAL ELECTRONIC ENERGY AND IONIZATION
POTENTIALS OF THE LIGANDS CALCULATED BY
DFT B3LYP/6-31g IN a.u. (ATOMIC UNIT)

Ligands	Total electronic energy (a.u.)	Ionization potential (a.u.)	Ionization potential (eV)
THAP-neutral	-881.25851110	0.25322009	6.89062
THAP-cation	-881.00529191		
TMeHAP-neutral	-920.56359766	0.24861614	6.76534
TMeHAP-cation	-920.31498152		
TOMeHAP-neutral	-995.72743754	0.24569433	6.68583
TOMeHAP-cation	-995.48174321		

Antioxidant activity

DPPH• assay: The antioxidant activity of the ligands and its complexes were measured in terms of their hydrogen donating or radical scavenging ability by UV-visible spectrophotometer using the stable 2,2-diphenyl-1-picrylhydrazyl free radical (DPPH•).

In general, the ligands show better scavenging activity against DPPH• radical than do their corresponding complexes especially at higher concentrations (Fig. 4). The higher antioxidant activity of the ligands is related to the significant contribution of the hydroxyl group that facilitates hydrogen transfer reactions to DPPH• radical and stabilizing the system by a combination of hydrogen bonding and electronic effects

TABLE-6
CALCULATED ELECTRONIC PROPERTIES OF THE STUDY COMPLEXES USING SEMI EMPIRICAL PM6 METHOD

Complex	E HOMO (eV)	E LUMO (eV)	ΔE (H-L) (eV)	Heat of formation (kcal/mol)	Total energy (eV)	Electronic energy (eV)	Ionization potential (eV)	Dipole moment (Debye)
(THAP)₂Cu	-8.501	-8.437	0.064	124.3110	-6799.724	-72900.095	8.3410	1.287
(TMeHAP)₂Cu	-8.218	-8.174	0.044	107.9870	-7099.681	-78789.049	8.1210	1.391
(TOMeHAP)₂Cu	-8.363	-8.320	0.043	51.6624	-7681.544	-85938.716	8.2691	1.187
(THAP)₂Ni	-6.112	-4.812	1.300	164.6370	-6627.504	-72066.146	6.1110	2.536
(TOMeHAP)₂Ni	-6.140	-4.921	1.219	94.2470	-7509.226	-84087.213	6.1400	2.189

[24]. This is reflected in their lower ionization potentials calculated theoretically. The ionization potential values for TOMeHAP, TMeHAP and THAP are 6.686, 6.765 and 6.890 eV, respectively. It is obvious that TOMeHAP has lower ionization potential indicating stronger donating ability, which may result in stabilization of DPPH• radical through electron donation and hence higher antioxidant activity. Moreover, it is reported that methoxy substituents influence the scavenging effects of free radicals [5,25]. Nevertheless, the title compounds do not act as efficient radical scavengers in any way comparable to butylated hydroxytoluene (BHT).

Furthermore, it can also be drawn from Fig. 4 that free radical scavenging activity increased with increasing concentration from 50 to 250 mM. Copper(II) complexes seem to be more efficient in quenching radicals than their corresponding nickel(II) congeners.
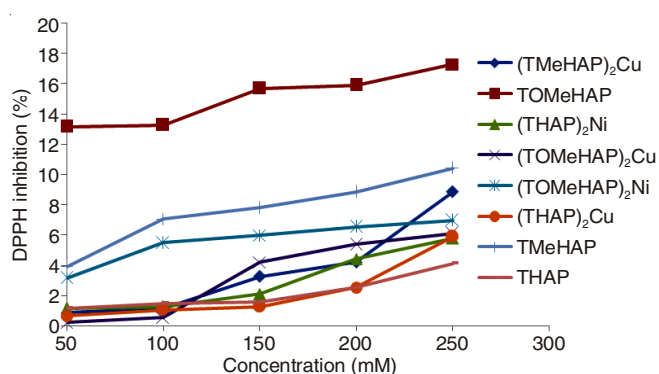

Fig. 4. Dependance of DPPH• scavenging activity of ligands and their metal complexes on concentration evaluated through the absorbance decrease at 515 nm

The different relative scavenging capacity of individual compounds against different radicals may be explained by the different mechanisms involved in the radical-antioxidant reactions. Other factors, such as stereoselectivity of the radicals or the solubility of these compounds in different testing systems, may also affect the capacity of individual compounds to react and quench different radicals [26].

Ferric reducing antioxidant power assay: The column graph in Fig. 5 compares the proportions of ferric reducing abilities of prepared compounds with butylated hydroxytoluene (BHT) as standard. In this series of compounds, the highest reducing ability has been found in TOMeHAP which accounts for 6570 μM ferrous equivalents four times as effective as BHT. This had decreased gradually from nickel(II) to copper(II) complexes, but still better than BHT. Likewise the trend has been observed for the methyl-substituted ligand and its copper complex. In this category the ligand shows a potency of approximately ten-fold of the corresponding copper complex and approaches three times the activity of BHT. The energy of the highest occupied molecular orbital (HOMO) can be taken as a clue for the electron donating ability of a molecule [25]. In contrast to ionization potentials, a higher HOMO reflects a stronger ability to donate electrons and hence act as a reductant. Both (TOMeHAP)$_2$Cu and (TMeHAP)$_2$Cu complexes reveal bigger values of HOMO (-8.363 and -8.218, respectively) than do (THAP)$_2$Cu complex (-8.501) and hence
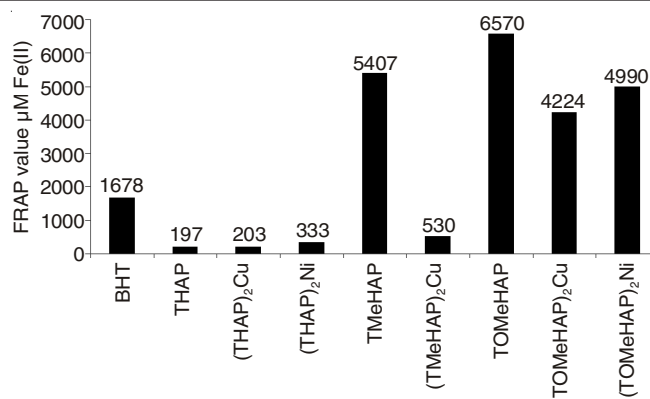

Fig. 5. Coulmn graph showing FRAP values in (μM) Fe(II) equivalents for the different compounds in comparison to BHT

became a better antioxidants in the FRAP assay. Reverse trend has been observed in other related copper complexes in which halo substituent group replaces alkyl and alkoxy substituents [27]. In those compounds the ligand show less potency due to the presence of electronegative atom attached to the hydroxyacetophenone moiety. Complexation may also reduce the oxidation potential, which results in ease of oxidation by free radicals [28].

Conclusion

Schiff base ligands derived from tryptamine and hydroxyacetophenones have been successfully synthesized and characterized. The antioxidant studies of the compounds reveal that the ligands are more effective antioxidants than their metal complexes in concentration-dependant manner. They mainly act as a hydrogen atom transferring antioxidants in an oxidative process. This effect is more remarkably pronounced for TOMeHAP as compared to butylated hydroxytoluene (BHT), which is a commercially available antioxidant drug. However, chelating to the metal ions suppresses this property through coordination to the metal centre, thus hampers hydrogen atom abstraction mechanism through deprotonation.

Theoretical calculations using both PM6 semi-empirical and DFT method supports the experimental results obtained.

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