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Synthesis, characterization and anticancer studies of some morpholine derived Schiff bases and their metal complexes

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ABSTRACT

This paper reported series of complexes and their modes of coordination. The series consist of *N,N',O*-donor Schiff base formed by condensation reaction of 2-hydroxyacetophenone with 4-(2-aminoethyl)morpholine. The ligand and complexes were characterized by elemental analysis, FT-IR, NMR and UV/Visible spectroscopy. The complexes showed moderate cytotoxicity mediated on MCF-7 breast cancer cell line and were selective to some extent when compared to the WRL68 normal liver cell line.

INTRODUCTION

Schiff base compounds derived from morpholine are completely stable in biological systems, allowing rigorous long-term applications as they constitute a radical re-design of DNA (Summerton, 2007) these important factors are considered in designing this morpholine derived ligands and their metal complexes for their potential anticancer applications. First row transition metals play major roles in various biological activities because of the exceptionally wide range of reactivity available and have been particularly attractive (Petrovic *et. al.*, 1996). It is also known that the existence of metal ions bonded to biologically active compounds may enhance their biological activities, such as antibacterial (Prakash, 2010), anticonvulsant (Sridhar, 2002), antifungal (Bharti *et. al.*, 2010), anti-HIV (Pandeya *et. al.*, 1999), antiviral and anticancer (Creaven *et. al.*, 2010, Garoufis *et. al.*, 2009, Raman *et. al.*, 2010, Shakir *et. al.*, 2011, Zhang *et. al.*, 2009) and antimicrobial (Mandal *et. al.*, 2011, Yusnita *et. al.*, 2009, Pignatello *et. al.*, 1994, Nair *et. al.*, 2001, Tajudeen, 2009, Xue *et. al.*, 2011), DNA binding and DNA cleavage activities (Shahabadi, 2010) and many other biological activities (Mladenova *et. al.*, 2002, Bagihalli, 2008, El-Sherif, 2011, Creaven *et. al.*, 2010, Wang *et. al.*, 2005). Varieties of metal complexes have been used as drugs and are well known to increase their activity or when administered as metal complexes show higher activity towards specific targets (Moriuchi, 1999, Moriuchi *et. al.*, 2000, Bauer, 1999).

In this study, metal complexes of some newly synthesized *N'N''O* donor Schiff base ligands from the reaction of 4-(2-aminoethyl)morpholine with 2-hydroxyacetophenone (scheme 1), were examined for potential anti-cancer applications.

EXPERIMENTAL SECTION

Materials and methods

Chemical and reagents

4-(2-aminoethyl)morpholine, 2-hydroxyacetophenone, copper(II) chloride, manganese(II) chloride, nickel(II) chloride, zinc(II) chloride, glacial acetic acid, triethylamine, absolute ethanol (99.8 %), ethanol (95 %), dimethylsulphoxide and Deuterated dimethylsulphoxide were purchased from the Aldrich–Sigma Company. 95 % Ethanol was distilled prior to use.

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Melting Point Determination

Melting points were determined using a MEL-TEMP II melting point instrument. All samples are placed in the micro haemotocrit tube (soda lime glass). The melting points of the sample were recorded after they have completely melted.

Carbon, Hydrogen and Nitrogen (CHN) Analyses

Microanalyses for carbon, hydrogen and nitrogen in the compounds were carried out on a Perkin-Elmer 2400 elemental analyzer. All compounds (1.75-2.00 mg) were weighted in aluminium foil capsules. The instrument was calibrated with sulfamethinezine.

Infra Red (IR) Spectroscopy

The Infrared spectra were recorded on a Perkin Elmer Spectrum 400 ATR-FT-IR spectrometer at the Department of Chemistry, Faculty of science University of Malaya. All the spectra were run in the range of 400-4000 cm^{-1} at room temperature.

Nuclear Magnetic Resonance (NMR) Spectroscopy

The ^1H and ^{13}C NMR spectra of the Schiff bases were recorded using a Bruker Apex 600MHz; FT-NMR spectrometers chemical shifts are given in δ values (ppm) using TMS as the internal standard. Deuterated dimethylsulphoxide (DMSO) was used as solvent.

Ultraviolet-Visible (UV-Vis) Spectroscopy

The spectra (solid) were obtained from reflectance electronic technique by using UV-3600 Shimadzu UV-Vis-NIR Spectrophotometer and were scan from 200-1000, while the spectra (DMSO) were recorded in quartz cuvettes on a Shimadzu 1601 spectrophotometer in the region of 200-1000 nm.

Cell Lines

Human cell lines will be obtained from the American Type Culture Collection ATCC, USA.

SYNTHESIS OF THE COMPOUNDS

2-(1-(2-morpholinoethylimino)ethyl) phenol (L1)

The ligand was obtained from the condensation reaction of 2-hydroxyacetophenone with 4-(2-aminoethyl)morpholine in the presence of few drops of glacial acetic acid to adjust the pH. The product is oily orange solution was formed, which became orange colored hygroscopic solid after 12 hours at 55°C in an oven. The solid product was dissolved in methanol and heated to 60 °C. After evaporating from the solvent under reduced pressure, an orange colored solid was formed. This ligand was characterized by using melting point, elemental analysis, IR, NMR and UV/Vis-spectroscopy. Yield: 55.2%. Molecular formula: $C_{14}H_{20}N_2O_2$, Molecular Weight: 248.15. ^1H-NMR (600 MHz, δ, DMSO-d_6): 11.50 (1H-Phenolic), 7.50-6.98 (4H, CH-Ar), 3.98-3.66 (CH_2-Morph), 3.10-2.80 (NCH_2-CH_2N), 1.24 (CH_3). ^{13}C-NMR (600 MHz, δ, DMSO-d_6): 166.54 (C=N, Schiff) 146.46 (C-aromatic), 138.41 (CH-aromatic), 125.97 (CH-aromatic), 121.81 (CH-aromatic), 63.20, 61.45 (2C, CH_2-aliphatic), 50.67 (2C, CH_2-morpholine), 42.21 (1C, CH_2-morpholine), 33.83 (2C, CH_2-morpholine), 13.82 (CH_3-Methyl).

COORDINATED COMPLEXES FOR L1

A series of copper(II), manganese(II), nickel(II) and zinc(II) complexes of **L1** Schiff base were prepared *in situ* by mixing 2-hydroxyacetophenone (0.20 g, 1.65 mmol) and 4-(2-aminoethyl)morpholine (0.21 g, 1.65 mmol) in ethanol (20 ml) and refluxed. After 2 hr an ethanolic solution containing metal(II) halides was then added and the mixtures were refluxed for 2-5 hours (Scheme 1). The resultant precipitates were filtered off, washed with cold ethanol and dried under vacuum. Physical properties of the synthesized compounds summarized can be found in (Table 1). The obtained compounds were further characterized by using CHN, FT-IR, UV-Visible and FT-NMR. The parameters are summarized in (Tables 1-3). The crystals structure for some of the complex was reported (Hisham, 2011). ^1H-NMR [Zn(L1)Cl] (600 MHz, δ, DMSO-d_6): 8.30-7.85 (4H, aromatic protons), 3.98-3.69 (8H, CH_2 morpholine), 2.75-2.55 (4H, NCH_2-CH_2N ethylenediamine protons), 2.30 (3H, CH_3 methyl ketone protons). ^{13}C-NMR (600 MHz, δ, DMSO-d_6): 168.00 (C aromatic carbon), 158.01 (CH aromatic carbon), 156.64 (CH aromatic carbon), 149.50 (CH aromatic carbon), 137.22 (CH aromatic carbon), 134.40 (CH aromatic carbon), 65.60 (2C, $2CH_2$ ethylenediamine carbons), 56.45 (2C, $2CH_2$ morpholine carbons), 46.00 (1C, CH_2 morpholine carbon), 42.67 (1C, CH_2 morpholine carbon), 18.90 (1C, CH_3 methyl ketone carbon). ^1H-NMR [Zn(L1)Br] (600 MHz, δ, DMSO-d_6): 7.50-6.98 (4H, aromatic protons), 3.98-3.66 (CH_2 morpholine), 3.10-2.80 (2H, NCH_2-CH_2N), 2.24 (3H, $CH_{3,}$ methyl ketone protons). ^{13}C-NMR (600 MHz, δ, DMSO-d_6): 167.52 (1C, C=N), 149.46 (C aromatic carbon), 146.60 (CH aromatic carbon), 141.40 (CH aromatic carbon), 126.90 (CH aromatic carbon), 120.80 (CH aromatic carbon), 60.40 (2C, $2CH_2$ ethylenediamine carbons), 53.09 (2C, $2CH_2$ morpholine carbons), 51.67 (1C, CH_2 morpholine carbon), 43.22 (1C, CH_2 morpholine carbon), 15.81 (1C, CH_3 methyl ketone carbon).

MTT - CULTURE OF CELLS AND CYTOTOXICITY ASSAY

The MCF-7 cells (human breast cancer cells) were seeded into 96 well plates at an initial cell density of approximately $5x10^5$ cells cm^{-3}. After 24 hours incubation for cell attachment and growth, the medium was removed and replaced with fresh medium containing varying concentrations of the compounds. The compounds added were first dissolved in DMSO at the required concentration. Subsequent 6 desirable concentrations was prepared using growth medium. Control wells received only DMSO. Each concentration of the compound under study was assayed in six replicates. The assay was terminated after

48 hours incubation period. Again, the medium was removed and cell viability was determined after further 4 hours with 5 mg cm^{-3} MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium] bromide; also named thiazol blue. DMSO was then added per well and the dissolving formazan precipitate was read by using elisa plate reader, Dynatech MR5000 at 570 nm. And comparison was made with positive control cisplatin.

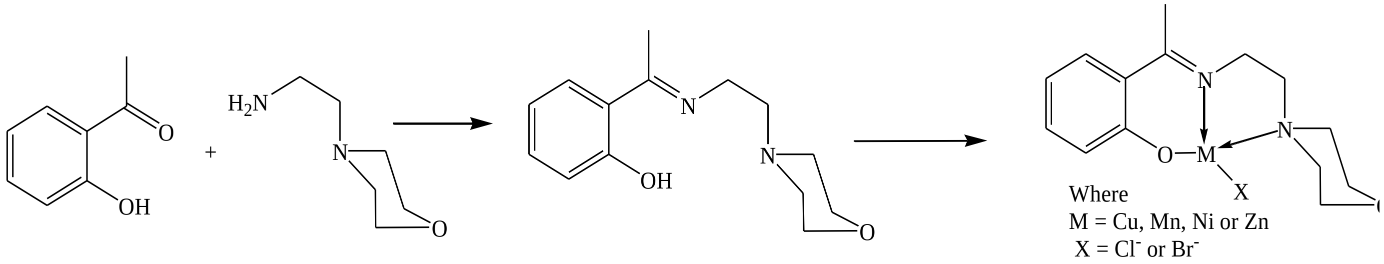
RESULTS AND DISCUSSION

Synthesis and characterization

The reaction of 4-(2-aminoethyl)morpholine with 2-hydroxyacetophenone resulted in the formation of corresponding Schiff base ligand; 2-(1-(2-morpholinoethylimino)ethyl) phenol (**L1**) The prepared Schiff bases further reacted copper(II), manganese(II), nickel(II) and zinc(II) giving rise to different coordination complexes (Scheme 1). The compounds exhibited NMR, IR and UV-Visible spectra consistent with the proposed structures which allowed the synthesized complexes to be recognized as Chlorido(2-{1-[(2-morpholinoethyl)-imino]ethyl} phenolato-κ^3*N,N’,O*)-copper(II) **[Cu(L1)Cl]**, Bromido(2-{1-[(2-morpholinoethyl)-imino]ethyl} phenolato-κ^3*N,N’,O*)- copper(II) [**Cu(L1)Br**], Chlorido(2-{1-[(2-morpholinoethyl)-imino]ethyl} phenolato-κ^3*N,N’,O*)-zinc(II) [**Zn(L1)Cl**], Bromido(2-{1-[(2-morpholinoethyl)- imino]ethyl} phenolato- κ^3*N,N’,O*)-zinc(II) [**Zn(L1)Br**], Chlorido(2-{1-[(2-morpholinoethyl) -imino]ethyl} phenolato-κ^3*N,N’,O*)-nickel(II) [**Ni(L1)Cl**], Bromido(2-{1-[(2-morpholinoethyl)- imino]ethyl}phenolato-κ^3*N,N’,O*)- nickel(II) [**Ni(L1)Br**], 2-(1-(2-morpholinoethylimino)ethyl)-phenoxy)-manganese(II)chloride [**Mn(L1)Cl**], 2-(1-(2-morpholinoethylimino)ethyl)-phenoxy)-manganese(II)bromide [**Mn(L1)Br.** In this context, we would like to compare the structures of some earlier prepared complexes with the present ones. There are two reported complexes of nickel(II) perchlorate with the similar donor-Schiff base ligand (Chiumia *et al.*, 1999 and Bhowmik *et al.*, 2010). Elemental analysis data and physical properties of ligand and complexes are summarized in (Table 1); ligand was obtained in a liquid form. The reaction of ligands with transition metals produced a series of metal complexes with different colors. The data obtained from the melting point apparatus showed that the complexes’ melting point were higher than 300 ºC. The percentages of C, H and N obtained are in agreement with calculated values. The IR spectra of transition metal complexes were carried out in 4000–400 cm^{-1} range. The characteristic IR stretching frequencies of the metal complexes along with their proposed assignments are summarized in (Table 2). There are similarities in the IR spectrum of the metal complexes to each other, except for some slight variations in the shifts and intensities of few vibration peaks caused by different metal (II) ions, indicating that the metal complexes had similar structure. However, there were no significant differences between the metal(II) halides complexes as expected. The IR spectra of all the complexes possess very strong characteristic absorption bands in the region of 1670.00-1650.00cm^{-1} which is attributed to the C=N stretching vibration of the Schiff base imino functional group (Raman, 2011, Khan *et. al.*, 2011, Nakamoto, 1978, Inamur *et. al.*, 2001, Banerjee *et. al.*, 2005). The spectra for the complex showed M–N bands at a lower wavelength in the range of 477-575 cm^{-1} (Raman, 2011 and Khan, 2011). The electronic spectra for the free ligands were obtained and showed absorption band in three distinct regions.

The first region ranging from 270 to approximately 290 nm, is characteristic for the electronic inter-ligand $\pi\rightarrow\pi^*$ transitions (Mohamed *et. al*., 2009), while the second characteristic wavelength in the region of 320 nm to approximately 450 nm is the second inter ligand $n\rightarrow\pi$ transition of the C=C and C=N chromophores (Yusnita *et. al*., 2009). The third distinct region in the complexes ranging from 450 nm to approximately 500 nm is the characteristic for the ligand to metal charge transfer (LMCT) from the nitrogen atom to the transition metal centre (Yusnita *et. al*., 2009). The last distinct region ranging from 600 nm to approximately 780 nm is the characteristic for inter metal $d\rightarrow d^*$ transition (Yusnita *et. al*., 2009). The Cu (II) ion with its d^9 configuration in tetrahedral environment is highly susceptible to Jahn-Teller distortion. The spectrum of Cu(II) complexes Cu(L1)Cl and Cu(L1)Br showed three bands in the visible region at 594, 726, 744 nm and 403, 596, 778 respectively. These are assigned to the transitions $^1A_{1g}\rightarrow{}^1B_{1g}$, $^1A_{1g}\rightarrow{}^1A_{2g}$ and $^1A_{1g}\rightarrow{}^1E_g$ respectively consistent with distorted square planar geometry (Shayma, 2010). Nickel(II), which has a *d*^{8} configuration, commonly exhibits octahedral, square planar and tetrahedral coordination geometries. The electronic spectra of Ni(II) complexes Ni(L1)Cl and Ni(L1)Br showed d-d transitions in the region of 574, 845 and, 372, 597, 778 respectively. These are assigned to the transitions $^3T_{1(F)} \rightarrow {}^3A_{2(F),}$ $^3T_{1(F)} \rightarrow {}^3T_{1(P)}$ and $^3T_{1(F)} \rightarrow {}^3T_{2(F)}$ consistent with distorted square planar geometry (Shaker, 2010, Cotton, 1998, Selbin, 1983). The electronic spectra of Mn^{2+} *d*^{5} complexes Mn(L1)Cl and Mn(L1)Br indicate that they have tetrahedral geometries. The $^6A_1 \rightarrow {}^4E(D)$ and $^6A_1 \rightarrow {}^4T_2(D)$ can attributed to the band at 307, 628, 745 and 229, 307, 712 nm respectively (Shayma, 2009). Lastly the electronic spectra for Zn(II) and Cd(II) complexes with an electronic configuration of *d*^{10} the absorption bands observed were due to charge transfer transitions which suffered from blue shift with hyper chromic effect (Ceyhan, 2011). All these absorptions for the free ligands and their corresponding metal complexes have been fully assigned in (Table 3). Fourier transforms nuclear magnetic resonance (FT-NMR) for the coordinated complexes have been summarized in the experimental part.

The chemical shift in the region 8.70-7.80 ppm, were observed for complexes respectively and they were assigned to the aromatic ring protons. The other single peaks appeared in the region 2.60 ppm-2.90ppm respectively were attributed to $\delta(CH_3)$ indicating the methyl on the carbonyl group in the complexes. In the ^{13}C NMR spectra of the metal complexes, the signal at region of 165.00 ppm-170.00 can be assigned to the azomethine (C=N) carbon atoms for complexes. Aromatic ring carbon atoms of the ligands were determined in the region of 120.00-160.00 ppm.



Scheme 1: Synthetic pathway for the Schiff base ligand and its metal complexes

Table 1: The physical properties of the ligands and their metal complexes.

Compound	Mol.W. (g/mol)	Color	M.P (°C)	Yield (%)	Elemental Percentage (%) Calculated (Found)		
					C	H	N
L1	248.15	Yellow	-	65	67.71(68.19)	8.12(7.89)	11.28(11.48)
Cu(L1)Cl	346.31	Blue	345-350	83	48.55(48.49)	5.53(5.71)	8.09(8.39)
Cu(L1)Br	390.76	Brown	355-360	78	43.03(43.19)	4.90(4.11)	7.17(7.29)
Zn(L1)Cl	348.16	White	>400	82	48.30(48.48)	5.50(5.79)	8.05(8.98)
Zn(L1)Br	392.61	Milky	345-350	87	42.83(42.94)	4.88(4.88)	7.14(7.24)
Ni(L1)Cl	341.46	Green	360-365	76	49.24(49.25)	5.61(5.63)	8.20(8.50)
Ni(L1)Br	385.91	Greenish	>400	68	43.57(44.00)	4.96(5.01)	7.26(7.28)
Mn(L1)Cl	337.70	Reddish	380-385	73	49.79(48.99)	5.67(5.54)	8.30(8.40)
Mn(L1)Br	382.15	Brown	>400	65	44.00(43.97)	5.01(5.17)	7.33(7.40)

Table 2: The characteristic infrared absorptions of ligands and their metal complexes.

Compound	ν(C-H)	ν(SCN/N$_3$)	ν(C=N)	ν(C-C)	ν(C-N)	ν(M-N)	ν(M-O)
L1	2952	-	1611	1448	-	-	-
Cu(L1)Cl	2972	-	1580	1432	1113	526	493
Cu(L1)Br	3109	-	1664	1428	1113	531	473
Zn(L1)Cl	2984	-	1654	1438	1125	541	453
Zn(L1)Br	3076	-	1654	1438	1115	557	454
Ni(L1)Cl	2943	-	1605	1436	1121	518	474
Ni(L1)Br	2980	-	1597	1441	1102	516	492
Mn(L1)Cl	2974	-	1651	1442	1157	522	461
Mn(L1)Br	2838	-	1650	1464	1165	555	462

Table 3: U.V – visible spectra of free ligands and their metal complexes 10-4 in DMSO and Solid state.

Compound	λ_{max}	ABS	ε_{max} (Lmol^{-1}cm^{-1})	Assignment
L1	321	2.817	5634.00	n→ π*
	396	0.749	1498.00	n→ π*
Cu(L1)Cl	279	1.551	3102.00	C.T. M → L
	358	1.470	2942.00	C.T. M → L
	594	0.231	462.00	$^2B_2g_{(D)} \rightarrow {}^2B_1g_{(D)}$
	726	0.162	324.00	$^2E_2g_{(D)} \rightarrow {}^2B_1g_{(D)}$
	744	0.110	220.00	$^2E_2g_{(D)} \rightarrow {}^2B_1g_{(D)}$
Cu(L1)Br	403	3.215	6430.00	$^1A_{1g} \rightarrow {}^1B_{1g}$
	596	0.734	1468.00	$^1A_{1g} \rightarrow {}^1A_{2g}$
	778	0.090	180.00	$^1A_{1g} \rightarrow {}^1E_g$
Ni(L1)Cl	574	0.374	748.00	$^3T_{1(F)} \rightarrow {}^3T_{1(P)}$
	845	0.224	448.00	$^3T_{1(F)} \rightarrow {}^3T_{2(F)}$
Ni(L1)Br	372	2.635	5270.00	$^3T_{1(F)} \rightarrow {}^3A_{2(F)}$
	597	0.332	664.00	$^3T_{1(F)} \rightarrow {}^3T_{1(P)}$
	778	0.063	126.00	$^3T_{1(F)} \rightarrow {}^3T_{2(F)}$
Mn(L1)Cl	307	1.068	2056.00	$^6A_1 \rightarrow {}^4E_{(D)}$
	628	0.114	228.00	$^6A_1 \rightarrow {}^4T_{2(D)}$
	728	0.126	252.00	
	745	0.078	156.00	
Mn(L1)Br	229	0.241	482.00	$^6A_1 \rightarrow {}^4E_{(D)}$
	307	1.068	2136.00	$^6A_1 \rightarrow {}^4T_{2(D)}$
	712	0.112	224.00	
Zn(L1)Cl	322	0.645	1290.00	C.T. M → L
Zn(L1)Br	307	1.068	2136.00	C.T. M → L

MTT assay

MTT assay was used to determine the metal complexes cytotoxicity against human breast cancer cells MCF-7. This assay served as an index used to determine cytotoxicity of the metal complex to stimulate or inhibit cell viability and growth by detecting the reduction of tetrazolium salt to blue formazan by mitochondrial enzyme activity of succinate dehydrogenase in living cells. MCF-7 cells were treated with varying concentrations of the complexes for 48 h, and the cells viabilities were measured by MTT assay. The metal complexes were found to inhibit the growth of MCF-7 cells in a dose-dependent manner (Table 4). The free ligand MTT assay showed no significant inhibition activities at a concentration even higher than the complex which confirmed that chelation of ligand with metal ions was significance for the activity of this novel compounds.

Table 4: EC50 values in µg/ml of the tested compounds on WRL68 and MCF-7 cell lines.

Cpd.		**EC50 µg/ml**	
		WRL68	**MCF-7**
1	L1	n.d.	n.d.
2	Cu(L1)Cl	41.15	37.58
3	Cu(L1)Br	23.28	4.25
4	Zn(L1)Br	52.26	33.09
5	Zn(L1)Cl	32.69	10.94
6	Ni(L1)Cl	13.05	8.15
7	Ni(L1)Br	64.53	27.64
8	Mn(L1)Cl	44.25	24.54
9	Mn(L1)Br	4.65	5.93
10	Cisplatin	-	2.50

CONCLUSION

In this paper we presented synthesis, characterization and cytotoxicity mediated by synthesized metal complexes on MCF-7 cells. In advanced, the study of mechanism of action (MOA) of the compound is suggested to further expand the knowledge on its target organism and application.

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