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Synthesis, Characterization and Antibacterial Evaluations of the Schiff Base 2-(1-(2-(Piperazin-1-yl)ethylimino)ethyl)Phenol and its Complexes of Mn(II), Ni(II) and Zn(II)

Salga, M. S., Sada, I. and Abdullahi, A.
Department of Pure and Industrial Chemistry, Umaru Musa 'Yar Adua University, Katsina
Email: salgamohd@yahoo.com

ABSTRACT

Schiff base 2-(1-(2-(piperazin-1-yl)ethylimino)ethyl)phenol and its complexes of Mn(II), Ni(II) and Zn(II) were synthesized and characterized by molar conductance, FTIR, NMR, UV-Visible and elemental analysis. The complexes showed 1:1 metal to ligand (M:L) ratio according to the result obtained from Job's method analysis. Elemental analysis and IR spectral data are in good agreement with the proposed structure of the ligand and the complexes. Both the ligand and its complexes were screened for in-vitro antibacterial activity against two gram negative (*Escherichia coli* and *Klebsella*) and two gram positive (*Staphylococcus aureus and Streptococcus pyrogenes*) bacterial strains. The result of antibacterial activity showed that both the ligand and its complexes have activity more than the referenced drug and that the complexes are more active than free ligand.

Keywords: Antibacterial studies, Characterization, Continuous variation, Synthesis

INTRODUCTION

Piperazine derivatives have wide range of biological activities *viz* antihilmentics (Khyrul Islam *et al.*, 2006), antimicrobial (Narendra *et al.*, 2006), antipsychotic (Alka *et al.*, 2010), anti-PAF, anti-HIV (Wafa *et al*, 2006), anti-cancer (Can-Cheng *et al*, 2004), anti-obesity (Ming *et al*, 2010), for the treatment of Alzeimer's disease (Sadashiva *et al*, 2006), potent MC4-receptor (Dai *et al*, 2007), drug designer with serotnergic properties (Roland *et al*, 2004), potent dopamine uptake inhibitors (Makoto *et al*, 2004), etc. Piperazine derivatives of 1-(2-aminoethyl)piperazine were evaluated for antibacterial activities in this study. Of the various classes of Schiff bases obtained from the condensation of amines and carbonyl compounds, there is little or no report on the biological activities of this amine (Narendra *et al*, 2006). Despite their ability to form very interesting ligands due to their good bridging ability, piperazine derivatives were also found to have antibacterial activity.

Such wide spectrum of biological applications of piperazine compounds aroused our research interest to synthesize novel Schiff base derived from condensation of 1-(2-aminoethyl)piperazine and 2-hydroxyacetophenone and its transition metal complexes. The study also evaluate the antimicrobial activities of the Schiff base and its Mn(II), Ni(II) and Zn(II).

MATERIALS AND METHODS

Materials

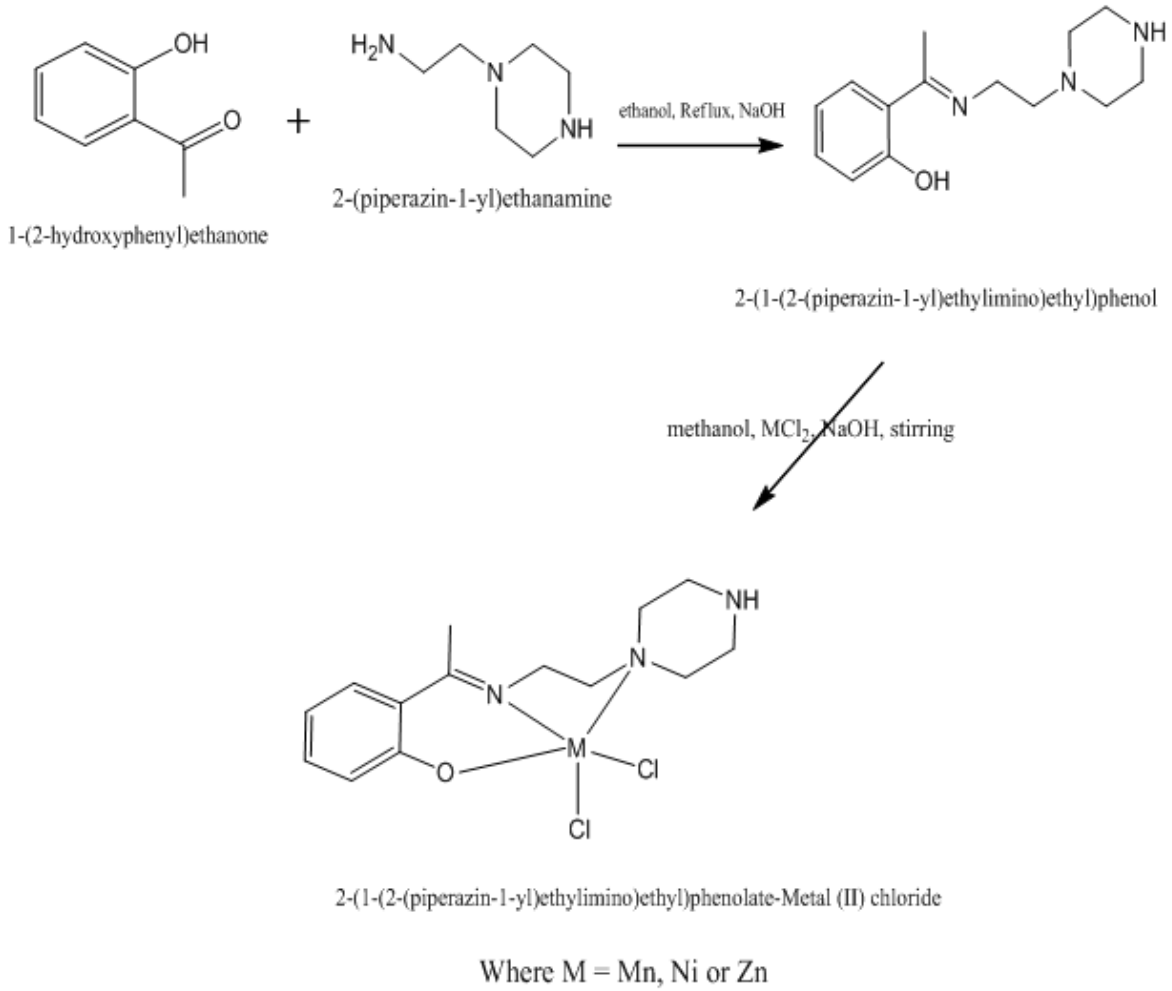
The percentages of C, H and N were obtained from Perkin elmer CHNS-932 elemental analyzer. The ^{1}H-NMR spectra were recorded from ECA-400 high performance FT-NMR spectrophotometer (with $SiMe_4$ as standard). Infrared spectra in the region of 4000-400cm^{-1} were obtained from KBr-pellets with a Perkin elmer PE-1600 FT-IR spectrometer. Thermogravimetric measurements were obtained from Perkin elmer TG4000 thermoanalyzer while the UV-visible spectra were recorded on Perkin Elmer PC-650 UV-visible spectrophotometer. The 1-(2-aminoethyl) piperazine, 1-(2-hydroxyphenyl) ethanone, solvents (ethanol, methanol and DMSO-d_6) and the metal salts used were of analytical grade, purchased from Sigma-Aldrich company and used without further purifications.

Synthesis of the ligand:

To a stirred ethanolic solution of 1-(2-aminoethyl)piperazine (0.13g, 10mmol) was added drop-wise to the equimolar quantity ethanolic solution of 1-(2-hydroxyphenyl) ethanone (0.14g, 10mmol) at room temperature and then refluxed for 2hrs at 60^{0}C, the solution was cooled down and the solvent evaporated using rotary evaporator to give golden yellow oil (Salga *et al*, 2013).

Synthesis of the complexes:

To the methanolic solution of the Schiff base ligand (0.25g, 10mmol) an equimolar methanolic solution of $ZnCl_2$ (0.14g, 10mmol) was added with stirring at room temperature. Pale yellow solution was formed which after stirring for 2 minutes generates a white precipitate, the precipitate was filtered, washed with ethanol and dried in the vacuum. The precipitate was washed with water-ethanol mixture (50:50) and dried in the vacuum. Same procedure was followed for the preparation of Mn(II) and Ni(II) complexes (Salga *et al*, 2013). Yield: (Mn: 0.24g, 64.5%), (Ni: 0.29g, 77.3%), (Zn: 0.27g,70%). Anal.Calcd: $C_{14}H_{20}Cl_2MnN_3O$: C, 45.1; H, 5.4; N, 19.1. Found: C, 39.8; H, 4.4; N, 16.8. $C_{14}H_{20}Cl_2N_3NiO$: calcd: C, 44.7; H, 5.4; N, 11.2. Found: C, 41; H, 4.8; N, 9.6. $C_{14}H_{20}Cl_2N_3OZn$: calcd: C, 43.9; H, 5.3; N, 10.98. Found: C, 40; H, 3.9; N, 9.2. Conductance: 5.58µscm^{-1} (65^{o}C), 6.04µscm^{-1}(72^{o}C), 6.22 µscm^{-1}(78^{o}C) and 9.8 µscm^{-1} (81^{o}C) (no charge). Job method: n = 1 (M:L = 1:1). IR (KBr disk cm^{-1}): ν(N-H), (3388, 3417,3404,3494cm^{-1}); ν(C=N), (1609,1593,1606, 1584cm^{-1}), C-O/phenolate, (1494,1372,1241,1267cm^{-1}). NMR (DMSO-d6): NH, 2.0ppm; C=N, 1.81ppm; phenyl ring, 7.02; O-H, 13.19ppm (ligand only). Uv-visible (DMSO): λmax for L, Mn, Ni and Zn, (262, 285,277, 267nm).



1-(2-hydroxyphenyl)ethanone

2-(piperazin-1-yl)ethanamine

2-(1-(2-(piperazin-1-yl)ethylimino)ethyl)phenol

2-(1-(2-(piperazin-1-yl)ethylimino)ethyl)phenolate-Metal (II) chloride

Scheme 1: Reaction pathway for the synthesis of ligand and the complex

Antimicrobial study

The compounds were assayed for antimicrobial activity by well-diffusion method (Iffet *et al,* 2004). Each compound was dissolved in DMSO at concentration of (100µl) 1mg/mL and placed in the respective wells. Other wells were supplemented with DMSO and referenced antibacterial drug, amoxicillin served as negative and positive controls, respectively. 1cm^3 of 24h broth culture containing10^{6}CFU/cm^3 was placed in sterile Petri dishes. Molten nutrient agar (15cm^3) maintained at ca 45^{o}C was poured into the Petri dishes and allowed to solidify. Holes of 6mm were formed in the agar and filled with the test solutions. The plates were incubated for 24h at 36^{o}C. The tests were carried out in triplicate. Growth inhibition was compared with the standard drug. In order to clarify any participating role of DMSO in screening activity of the compounds, separate studies were carried out with DMSO alone and no activity was found against any of the bacterial strains.

Results and Discussion

The infrared spectra of the Schiff base and its complexes shows prominent absorptions at 3388, 3417, 3404 and 3494cm^{-1} respectively which can be attributed to secondary amines of the piperazine ring changing from (R_2NH) cyclohexane form in the free ligand to ($R_2NH_2^+$) chair conformations in the complexes, at 1609, 1593, 1606, 1584cm^{-1} regions ν(C=N) was observed which shows some shifts from 1609cm^{-1} in the ligand spectra down to 1584cm^{-1} in the spectra of the complexes indicating complexation of the metal ions with the Schiff base.

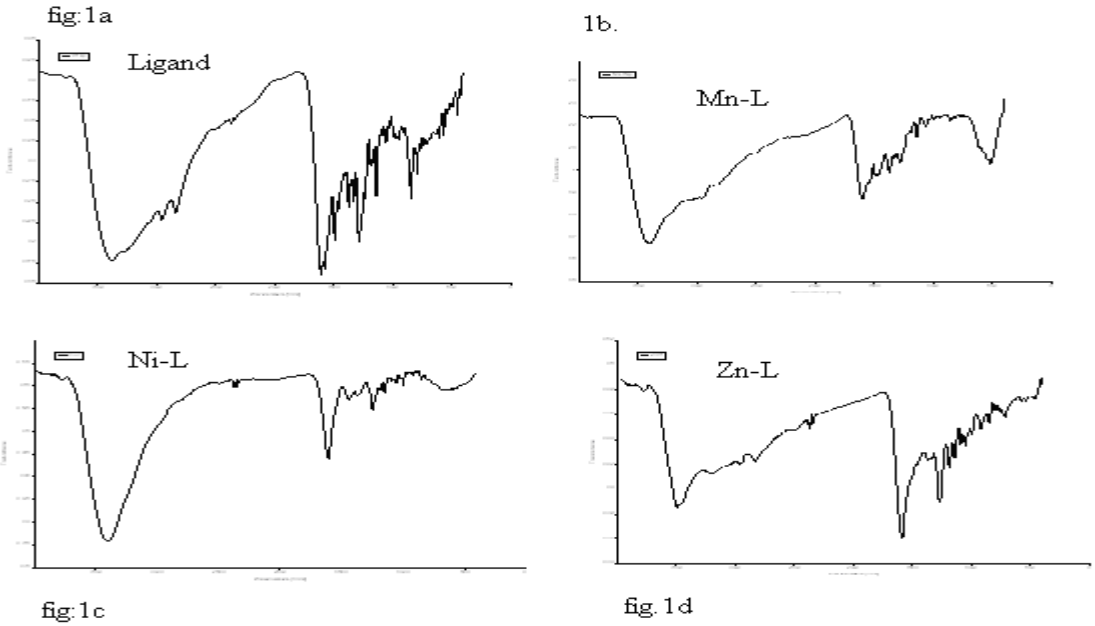


Figure 1: FTIR spectra for the ligand and its complexes

Stretching mode of C-O/phenolate for the ligand and its complexes were observed at 1494, 1372, 1241, 1267cm^{-1} which further confirmed the participation of phenol group in the ligand in bonding with the metal ion by shifting from 1494cm^{-1} in the ligand down to 1241cm^{-1} in the spectra of the complexes (Mukhopadhyay *et al*, 2003) (Figure 1) as proposed in the scheme of the reaction. NMR spectra of all the complexes shows same signal being derived from same Schiff base.

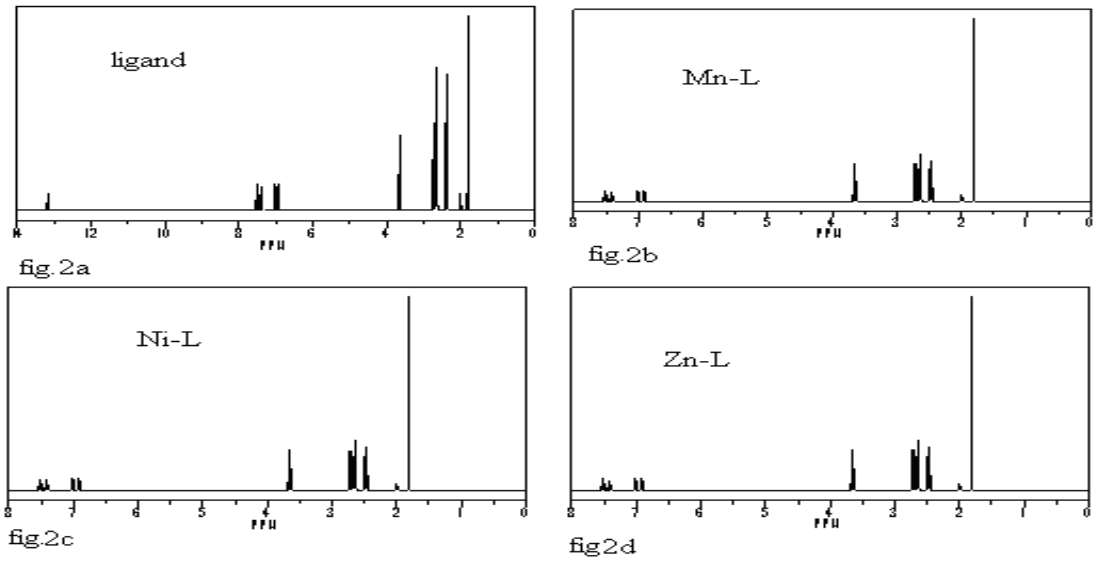


Figure 2: ^{1}H-NMR spectra for the ligand and its complexes

The chemical shifts at 2.0ppm, 1.81ppm and 7.02ppm can be assignable to N-H, C=N, and phenyl ring respectively as appeared in the proton nmr spectra of both the Schiff base and its Zn complex as manifested in Table 2 and Figure 2.

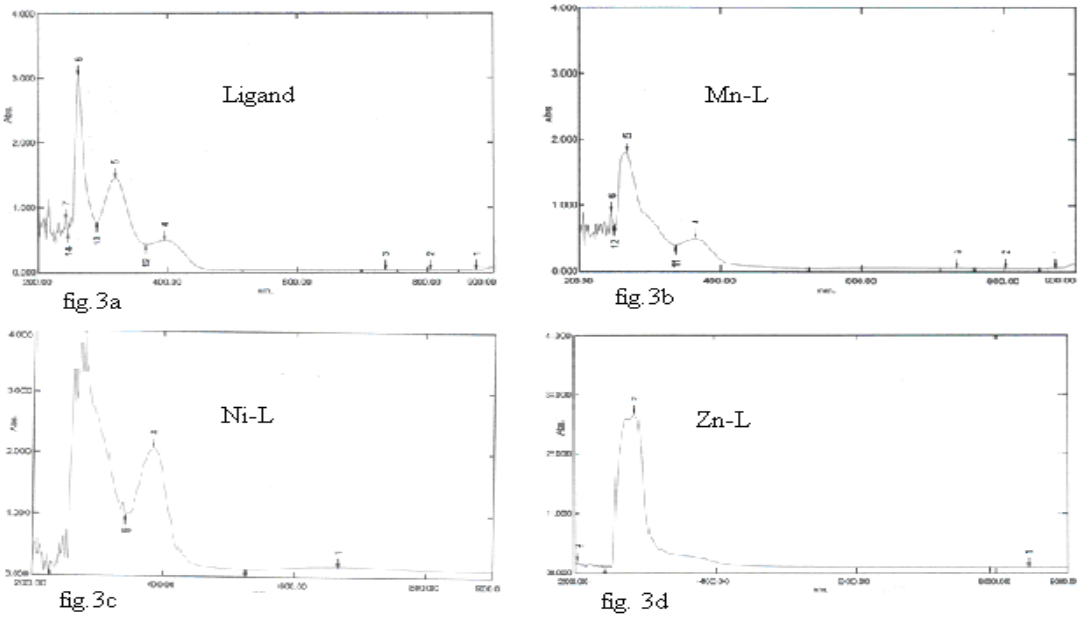


Figure 3: UV-VIS spectra

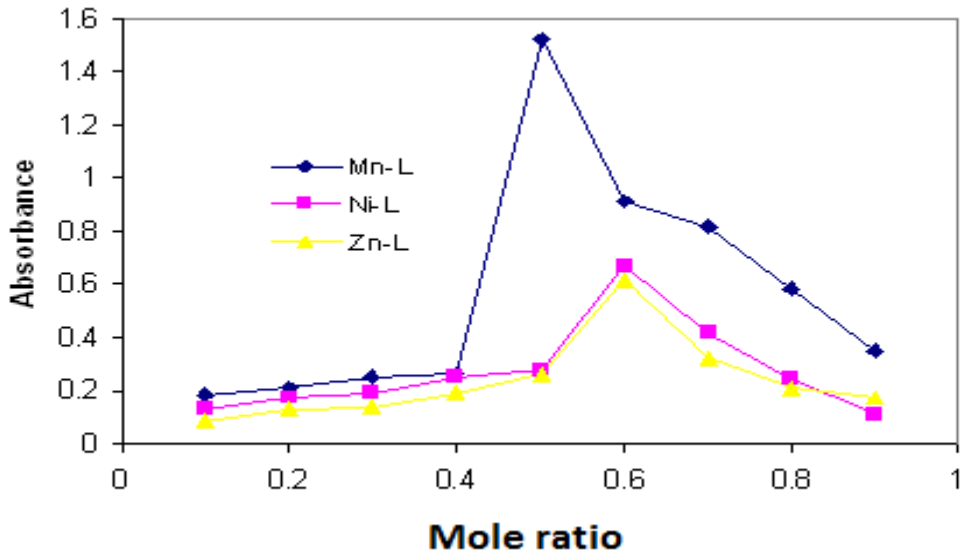


Figure 4: Determination of Metal-ligand ratio using Job's Method

Signal at 13.19ppm representing OH was only observed in the ligand spectra which is absent in the spectra of the complexes, this indicate its participation in bonding (Fig. 2). However, Mn, and Ni complexes did not show clear spectra in the proton nmr. UV-visible spectra shows bathochromic shifts of maximum wavelength from 262nm in the Schiff base to 285nm, 277nm and 267nm in Mn, Ni and Zn complexes respectively, which can be attributed to ligand-metal charge transfer (Pavia *et al*, 1996) in the bonding sites (Fig. 3). Elemental analysis shows values of C, H and N to be in good agreement with the calculated values and the complex was stoichiometrically found to be 1:1 (M:L), from the result of Job's method analysis (Fig. 4) with no charge outside the coordination sphere as revealed by the conductivity measurements in DMSO at various temperatures.

Table: 1 FTIR result for the Ligand and its Complexes of Mn(II), Ni(II) and Zn(II)

Ligand/Complex	OH(cm^{-1})	-C=N- (cm^{-1})	NH/NR_3 (cm^{-1})
Ligand	3394	1609	753
Mn-complex	-	1593	760
Ni- complex	-	1606	756
Zn- complex	-	1584	775

Table 2: ^{1}H-NMR result for the ligand and its complexes of Mn(II), Ni(II) and Zn(II)

Ligand/Complex	NH (ppm)	-C=N- (ppm)
Ligand	2.05	3.65
Zn- complex	2.18	3.50
^{13}C-NMR		
Ligand	14.80	46.50
Zn- complex	19.13	28.10

The Schiff base 2-(1-(2-(piperazin-1-yl)ethylimino)ethyl)phenol and its complexes of Mn(II), Ni(II) and Zn(II) were analyzed in vitro for their ability to inhibit the growth of representative gram positive(*Staphylococcus aureus and Streptococcus pyrogenes*) and gram negative (*Escherichia coli and Klebsiella pneumonia*) bacteria. The susceptibilities of certain strains of bacteria to the Schiff base and its complexes were evaluated by measuring the size of bacteriostatic diameter as shown in Table 3.

Table 3: Results for the Antimicrobial Activity of the Ligand and its Complexes

Ligands/Complex	*S. Aureus (mm)*	*S. pyrogenes (mm)*	E. Coli *(mm)*	K. *Pneumonia (mm)*
Ligand	18	14	18	20
Mn-complex	08	05	07	09
Ni- complex	19	08	04	07
Zn- complex	09	15	10	10
Amoxicillin	00	00	14	15

According to literature report (Koksal *et al*, 2001), the Schiff bases were found to show more activity than their corresponding complexes under identical condition.

In conclusion, similar observation was made in our previous study (Salga *et al*, 2013). However, in this work, the Schiff base shows more activity on *Klebsiella pneumonia* with the nickel complex showing the highest activity on staphylococcus while zinc complex shows highest activity on streptococcus. Manganese complex was found to be active on all the bacterial strains but does not show highest activity in any case. The control drug was found to be completely inactive against the gram positive bacteria as shown in table 3. This manifested the resistant behavior of the bacterial strains (used for this study) to the reference drug (amoxicillin).

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REFERENCES

Alka B, Komal S, Abhishek B, Suman B, Dinesh R, Anant S and Anil K. (2010) Synthesis, evaluation and computational studies on a series of acetophenone based 1-(aryloxypropyl)-4-(chloroaryl) piperazines as potential atypical antipsychotics. *Eur. J. Med.Chem., 45,* 2656-2671.

Can-Cheng, G., Rong-Biao, T. and Ke-Lai, L. (2004) Chloroalkyl piperazine and nitrogen mustard porphyrins: synthesis and anticancer activity. J. *Bioorg. & Med. Chem., 12*, 2469–2475.

Dai N, Taketoshi O, Takaaki I, Kazuaki T, Shigeyuki C, Shigeru O and Atsuro Nakazato. (2007) Novel piperazines: Potent melanocortin-4 receptor antagonists with anxiolytic-like activity. *J. Bioorg. & Med.Chem. , 15*, 2375.

Iffet S., Elif L., Seza A., Nurşen S., Nazmiye S. (2004) Antimicrobial activities of N-(2-hydroxy-1-naphthalidene)-amino acid(glycine, alanine, phenylalanine, histidine, tryptophane) Schiff bases and their manganese(III) complexes. *Biometals, 17*(2), 115-120.

Khyrul Islam, M., Takeharu, M., Manabu Y., Abdul Alim, M., Xiaohong, H., Maki, M., Naotoshi, T. (2006) Effect of piperazine (diethylenediamine) on the moulting, proteome expression and pyrophosphatase activity of Ascaris suum lung-stage larvae. . *Acta Tropica, 99*, 208-217.

Koksal H, Dolaz M, Tumer M, Serin S. (2001) Copper(II), Cobalt(III), Nickel(II), palladium(II), and zinc(II) complexes of the schiff base ligands derived from 2,6-diacetylpyridine and phthaldialdehyde. *Synth. Reac. Inorg. Met-Org. Chem., 37*(7), 1141-1162.

Makoto K, Tomoko M, Koji Y, Masaki M Nobuo K, Nobuyuki K, Kenichi K, Masato I, Yuji K, Katsuji O and Takayuki N. (2004) Efficient asymmetric syntheses, determination of absolute configurations and biological activities of 1-[4,4-bis(4-fluorophenyl)butyl] -4-[2-hydroxy-3-(phenylamino)propyl] piperazine as a novel potent dopamine uptake inhibitor in the central nervous system. *J. Bioorg. & Med. Chem., 2*, 3069–3078.

Ming Yu, Mike L, Holger B, Richard C, Kang D, Katrin H, Cong Li, Lingming L, Michelle L, Ji M, Alykhan M, Malgorzata W, Alex Z, Leping Li, Julio C. (2010) Identification of piperazine-bisamide GHSR antagonists for the treatment of obesity. *J. Bioorg. & Med. Chem. Lett., 20*, 1758-1762.

Mukhopadhyay, S., D. Mandal, D. Ghosh, I. Goldberg, M. Chaudhury. (2003) Equilibrium studies in solution involving nickel (II) complexes of flexidentate Schiff base ligands: Isolation and structural characterization of the planar red and octahedral green species involved in the equilibrium. *Inorg. Chem., 42*(25), 8439-8445.

Narendra S. Chandra J N, Sadashiva C T, Kavita C V, and Rangappa K S. (2006) Synthesis and in vitro antimicrobial studies of medicinally important novel N-alkyl and N-sulfonyl derivatives of 1-[bis(4-fluorophenyl)-methyl]piperazine. *J. Bioorg. & Med. Chem., 14*, 6621-6636.

Pavia D L, Lampman G. S. (1996) Introduction to spectroscopy, A guide for student of organic chemistry. *2nd ed., Brooks/Cole, 10 Davis drive, Belmone C.A. 94002-3098, Kritz USA.*, 267-293.

Roland F, Staack, Liane D, Paul D, Springer Thomas K, Hans, Maurer H. (2004) Cytochrome P450 dependent metabolism of the new designer drug 1-(3-trifluoromethyl phenyl)piperazine (TFMPP): In vivostudies in Wistar and Dark Agouti rats as well as in vitro studies in human liver microsomes. *J. Biochem. Pharmacol., 67*, 235-244.

Sadashiva, C.T., Narendra Sharath Chandra, J.N., Ponnappa, K.C., Veerabasappa Gowdab T. and Kanchugarakoppal S. R. (2006) Synthesis and efficacy of 1-[bis(4-fluorophenyl)-methyl]piperazine derivatives for acetylcholinesterase inhibition, as a stimulant of central cholinergic neurotransmission in Alzheimer's disease. *J. Bioorg. & Med. Chem. Lett. 16*, 3932–3936.

Salga, M. S., Ali, H. M., Abdulla, M. A., Abdelwahab, S. I., Taha, M. M. E., Yagoub, U. (2013) Synthesis and gastroprotective activities of some zinc (II) complexes derived from (E)-2-(1-(2-(piperazin-1-yl)ethylimino)ethyl)phenol and (E)-4-(1-(2-(piperazin-1-yl) ethylimino)ethyl)benzene-1,3-diol Schiff bases against aspirin induced ulceration. http//dx.doi.org/10.1016/jarabjc.2013.05.028

Wafa S, Nawal S, Nathalie D, Georges D, Pascal C and Francoise H. (2006) Synthesis and biological evaluation of piperazine derivatives with dual anti-PAF and anti-HIV-1 activity. *J. Bioorg. & Med. Chem., 14*, 7999-8013.