Synthesis, spectroscopic characterization, analgesic, and antimicrobial activities of Co(II), Ni(II), and Cu(II) complexes of 2-[N,N-bis-(3,5-dimethyl-pyrazolyl-1-methyl)]aminothiazole

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Synthesis, spectroscopic characterization, analgesic, and antimicrobial activities of Co(II), Ni(II), and Cu(II) complexes of 2-[*N*,*N*-bis-(3,5-dimethyl-pyrazolyl-1- methyl)]aminothiazole

M. Kalanithi · M. Rajarajan · P. Tharmaraj ·
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Abstract Synthesis of new series of Cu(II), Co(II), and Ni(II) from the ligand 2-[*N*,*N*-bis-(3,5-dimethyl-pyrazolyl-1-methyl)]aminothiazole is described. The ligand and its complexes were characterized by various techniques such as elemental analysis, FT-IR, UV–Visible, ^{1}H and ^{13}C NMR spectra, mass spectrum, and conductometry. The electronic absorption spectra and magnetic susceptibility measurements suggest a square planar geometry for Cu(II) complex and distorted tetrahedral geometry for the other metal(II) complexes. The EPR spectrum of Cu(II) complex recorded at 77°K confirms the distorted square planar geometry. The antimicrobial activities of the ligand and metal complexes against the bacterial species such as *Xanthomonas maltophilia*, *Chromobacterium violaceum*, *Acinetobacter, Staphylococci, Streptococci,* and the fungus *Candida albicans* are carried out and the results indicated that all compounds exhibit more antibacterial activity than the standard drug. The synthesized compounds were investigated for analgesic activity and they act as potent analgesic drugs.

Keywords 2-Aminothiazole · 3¸5-Dimethyl-1-(hydroxymethyl)-pyrazole · Analgesic activity · Transition metal(II) complexes

Introduction

Heterocyclic compounds with five, six, and seven membered rings comprise a fundamental class of organic compounds that continue to be at the forefront of research efforts in catalysts, pharmaceuticals, and photoluminescence. Microbial infections often produce pain and inflammation. Chemotherapeutic, analgesic, and anti-inflammatory drugs are prescribed simultaneously in normal practice. The compound possessing all three activities is not common. It has been known that pyrazoline possesses analgesic, anti-inflammatory, and antimicrobial activities. Moreover, the chelating nature and properties of pyrazole-based ligands have received considerable interest in the field of coordination chemistry (Mukherjee, 2000). The core pyrazole structure in general has attracted widespread attention because of the diversity of biological activity such as antitubercular (Gupta and Kaskhedikar, 2013) and anticancer (Koca *et al.*, 2013) activities shown by derivatives of this nucleus. Naturally occurring and synthetic thiazole derivatives find applications as antioxidants (De *et al.*, 2008), antibacterial drugs (Yao *et al.*, 2013), and fungicidal compounds (Cukurovali *et al.*, 2006). Aminothiazole compounds are able to block cartilage destruction during the inflammatory process and thus are a promising class of anti-inflammatory compounds (Panico

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M. Kalanithi
Department of Chemistry, Jayaraj Annapackiam College for Women, Periyakulam 625601, India

M. Rajarajan (✉)
Department of Chemistry, Cardamom Planters' Association College, Bodinayakkanur 625513, India
e-mail: rajarajan1962@yahoo.com

P. Tharmaraj (✉)
Department of Chemistry, Thiagarajar College, Madurai 625009, India
e-mail: sheelatharmaraj@gmail.com

S. Johnson Raja
Department of Chemistry, P.S.R. Engineering College, Sivakasi 626140, India

et al., 2003). 2-Aminothiazole derivatives of 4-hydroxychromene-2-one were found (Vukovic *et al.*, 2008) to possess antimicrobial properties. The use of 2-aminothiazole derivatives as inhibitors of human breast cancer (Gorczynski *et al.*, 2004) and Alzheimer's disease (Helal *et al.*, 2004) was studied and developed. Designing of medical devices and bio-fabrication using thiazole Schiff bases to combat the bio-film forming pathogenic organism has been explored (More *et al.*, 2013).

Chelation causes drastic change in the biological properties of the ligands and also the metal moiety. The biological activity of the heterocyclic moieties is mainly dependent on their molecular structures (Elzahamy *et al.*, 2008). Study of wide range of metal complexes of Schiff bases has been the continuing interest of both chemists and biologists. The metal complexes find applications in catalytic activity, (Gupta and Sutar, 2008) DNA cleavage, (Anbu *et al.*, 2009), and antimicrobial activities (Chittilappilly and Yusuff, 2008). The antitumor activities of Cu(II) complexes with pyrazole derivatives (Ruan *et al.*, 2012) and aminothiazole acetate (Alexandru *et al.*, 2010) derivative have been reported. The study on metal(II) complexes of condensation product derived from 2-aminothiazole and 3,5-dimethyl-1-(hydroxymethyl)-pyrazole has not been done so far. The work is carried out to know the enhancement in the biological activity of the synthesized compounds. In line with the above aspects, we are presenting the studies on metal(II) complexes of the ligand 2-[*N*,*N*-bis-(3,5-dimethyl-pyrazolyl-1-methyl)]aminothiazole(BMPMAT). The literature studies on the analgesic activity of pyrazole derivatives (Sahu *et al.*, 2008) initiated us to investigate the analgesic activities of the ligand and its complexes.

Materials and methods

Materials

Acetyl acetone, hydrazine hydrate, 2-aminothiazole, Cu(II)Cl_2.$2H_2O$, Co(II)Cl_2.$6H_2O$, and Ni(II)Cl_2.$6H_2O$ were purchased from Sigma Aldrich. The solvents acetonitrile, ethanol, petroleum ether (60–80 °C), chloroform, dichloromethane, DMF, and DMSO were used after purification by the standard method described in the literature (Perrin *et al*. 1981).

Synthesis of 2-[N,N-bis-(3,5-dimethyl-pyrazolyl-1-methyl)]aminothiazole (BMPMAT)

This compound was prepared by refluxing 2.06 g (20 mmol) of 2-aminothiazole and 5.04 g (40 mmol) of 3,5-dimethyl-1-(hydroxymethyl)-pyrazole (HMDMPZ) (Driessen, 1982) in 35 mL of dichloroethane (DCE) with stirring for 4–5 h at 60–70 °C. The completion of the reaction was confirmed by TLC. After the reaction was over, the solvent was removed by rotavapor. The product was obtained as a cream colored solid. Yield : 80 %; mp: 120–122 °C; UV($CHCl_3$) λmax(log ε) 303(1.5) nm; 270(3.3) nm; IR(KBr) ν_{max} 1595, 1294, 1617, 2960, 761 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz); $\delta = 2.37$ (s, 12H, $J = 2.6$ Hz, CH_3), 5.51(s, 4H, $J = 5.6$ Hz N–CH_2), 6.56 (s, 2H, $J = 7.8$ Hz, pyrazole H), 7.03–7.33(d, 2H, $J = 7.5$ Hz, aminothiazole); ^{13}C NMR ($CDCl_3$, 75 MHz); $\delta = 10.53$–13.14(–CH_3, C–4,4′5,5′) 56.48(N–C=CH, C-7,7′), 62.15(N–C=CH, C-8,8′), 70.32(C=C–C, C-6,6′), 105(S-CH,C-1), 107(N–CH,C-2), 140.3(N–CH_2, C-3), 140.3(C-3,3′) 168.48(C-9); EIMS *m/z* 315.8$[M]^+$ (25), 207(25), 94(100), $C_{15}H_{20}N_6$ S (Calcd, 316.42) Anal.calcd for $C_{15}H_{20}N_6$ S: C 56.94; H 6.37; N 26.56; S 10.13;Found C 56.90; H 6.32; N 26.54; S 10.10; The synthesis of the ligand with the numbering of carbon atoms is depicted in Fig. 1.

Synthesis of metal(II) complexes

Metal complexes were prepared by stirring 0.632 g (2 mmol) of 2-[*N*,*N*-bis-(3,5-dimethyl-pyrazolyl-1-methyl)]aminothiazole and 2 mmol of MCl_2 (M = Cu(II), Co(II), and Ni(II)) in 20 mL dichloromethane for 3 h and the precipitated colored complexes were filtered and washed with dichloromethane and dried.

[Cu(BMPMAT)Cl_2] Green colored product, Yield:65 %; mp 153–155 °C; UV($CHCl_3$) λmax(log ε) 414(1.43) nm; 710(1.8) nm; IR(KBr) ν_{max} 1585, 1280, 1617, 2960, 761, 478 cm^{-1} EIMS *m/z* 451$[M]^+$ (20), 251(15), 95(100), $C_{15}H_{20}N_6SCuCl_2$(Calcd,450.88) Anal.calcd for $C_{15}H_{20}N_6$ $SCuCl_2$: Cu 14.09; C 39.96; H 4.47; N 18.64; S 7.11; Found Cu 14.06; C 39.94; H 4.44; N 18.62; S 7.08;

[Co(BMPMAT)Cl_2] Blue colored product, Yield:60 %; mp 218–221 °C; UV($CHCl_3$) λmax(log ε) 659(0.24) nm; 1080(0.19) nm; IR(KBr) νmax 1575, 1282, 1617, 2960, 761, 480 cm^{-1} EIMS *m/z* 446.5$[M]^+$ (15), 251(20), 95(100), $C_{15}H_{20}N_6SCoCl_2$(Calcd,446.26) Anal.calcd for $C_{15}H_{20}N_6SCoCl_2$: Co 13.21; C 40.37; H 4.52; N 18.83; S 7.19; Found Co 13.17; C 40.32; H 4.47; N 18.80; S 7.15;

[Ni(BMPMAT)Cl_2] Pale green colored product, Yield:75 %; mp 198–201 °C; UV($CHCl_3$) λmax(log ε) 670(0.18) nm; IR(KBr) νmax 1581, 1274, 1617, 2960, 761, 460 cm^{-1} EIMS *m/z* 445.68$[M]^+$ (23), 251(20), 206(19), 95(100), $C_{15}H_{20}N_6SNiCl_2$(Calcd,446.26) Anal.calcd for $C_{15}H_{20}N_6$ $SNiCl_2$: Ni 13.16; C 40.39; H 4.52; N 18.84; S 7.19; Found Ni 13.14; C 40.34; H 4.48; N 18.80; S 7.16; The elemental analyses, melting point and conductance data of the ligand and its complexes are given in Table 1.

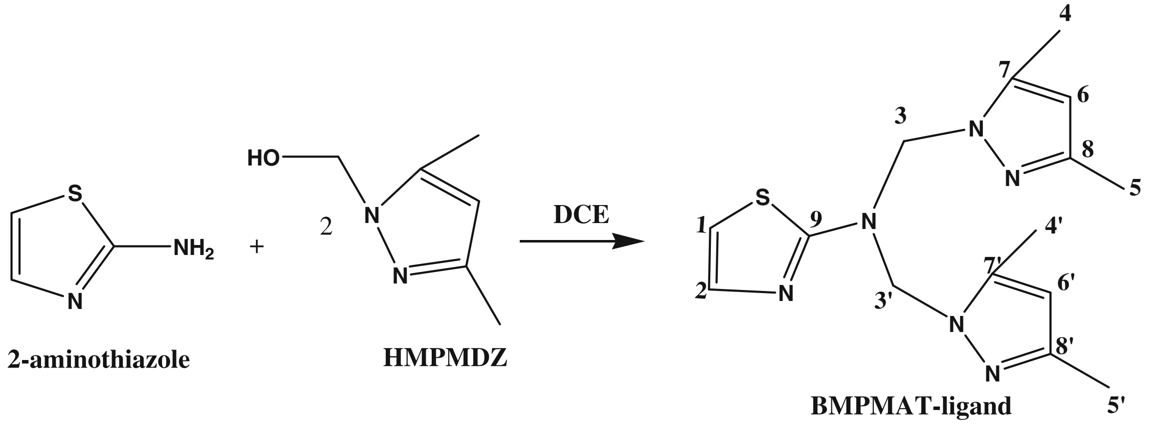

Fig. 1 Synthesis of ligand (BMPMAT)

Table 1 Physical characterization, analytical, molar conductance data, Λ_M of the ligand and its metal (II) complexes

Compounds	FW g/mol	Color	Found (Calcd) (%)					Λ_M (mho cm^2 mol^{-1})	m.p. °C
			M	C	H	N	S		
$C_{15}H_{20}N_6$ S (BMPMAT)	316.42	Cream	–	56.85 (56.94)	6.22 (6.37)	26.46 (26.56)	10.02 (10.13)	–	120–122
[Cu(BMPMAT)Cl_2]	450.88	Green	14.00 (14.09)	39.84 (39.96)	4.34 (4.47)	18.52 (18.64)	7.01 (7.11)	04	153–155
[Co(BMPMAT)Cl_2]	446.26	Blue	13.11 (13.21)	40.28 (40.37)	4.41 (4.52)	18.70 (18.83)	7.15 (7.19)	06	218–221
[Ni(BMPMAT)Cl_2]	446.02	Pale Green	13.04 (13.16)	40.24 (40.39)	4.40 (4.52)	18.73 (18.84)	7.06 (7.19)	07	198–201

Characterisation

The UV–Visible spectra of the ligand and metal complexes were recorded using a JASCO V-530 spectrophotometer. The IR spectra in KBr disks were recorded on a SHIMADZU FT-IR 8400 S spectrophotometer. Cyclic voltammetry measurements were carried out at room temperature in DMSO (CH Instruments, USA, voltammograph) using a three electrode cell containing a reference Ag/AgCl electrode, Pt wire auxiliary electrode, and glassy carbon working electrode with tetrabutylammonium perchlorate (TBAP) as supporting electrolyte. Elemental analyses were performed at SAIF, CDRI-Lucknow. The metal contents of the complexes were estimated by incinerating them to oxides (Angellici, 1969). NMR spectrum was recorded using a Bruker DRX-300 MHz NMR spectrometer. EI mass was recorded by JEOL-GC MATE-2 at IIT, Madras-Chennai. EPR spectrum was recorded by Varian E-112 spectrometer at X-band, using TCNE with 100 kHz modulation frequency and 9.1 GHz microwave frequency at SAIF, IIT Bombay, India. Magnetic susceptibility of the complexes was measured by MSB mark 1 Sherwood U.K at Thiagarajar College, Madurai. Effective magnetic moments were calculated using the formula $\mu_{eff} = (2.828 \times \chi_M \times T)^{1/2}$, where χ_M is the corrected molar susceptibility. The diamagnetic corrections were made by Pascal's constant and $Hg[Co(SCN)_4]$ was used as a calibrant. Molar conductance of the complexes (10^{-3} M) was measured in DMF at room temperature using a Systronic conductivity bridge type. The antimicrobial and analgesic activity studies are carried out at Kaleeswari Pharmaceutical College, Sivakasi.

Pharmacology

Analgesic activity

The analgesic effect of the ligand (BMPMAT) and its complexes was tested by tail-flick method in mice (Kar *et al*., 2003). The mice were weighed, marked, and divided into control and test group. First each mouse in the control and test group was placed one by one in the analgesiometer at 1 Ampere current for heating coil of the analgesiometer (Besto). The basal reaction time was measured by placing tip of the tail on the radiant heat source. The point was the tail withdrawal from the heat (flickering response). Basal reaction time for each mouse was noted at a gap of 5 min to confirm normal behavior of the animal. The dosage of 5 mg/10 ml aqueous solution of the drug was given orally to the test group of mice. The mice were allowed to stand

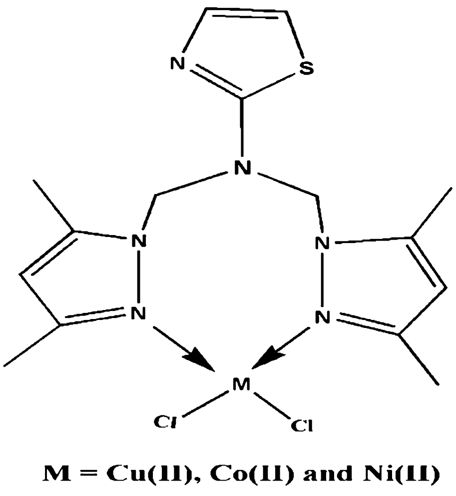

Fig. 2 Proposed structure of the complexes

some time for the drug distribution. After the drug treatment, reaction time was noted at a gap of 15, 30, 60, 90, and 120 min. Values of test group compared with normal group.

Antimicrobial activity

The in vitro antibacterial and antifungal activity tests were performed through the well diffusion method (Chandra *et al.*, 2009) using Amikacin and ketoconazole as positive control for bacteria and fungus, respectively. The bacteria used were *Xanthomonas maltophilia*, *Chromobacterium violaceum*, *Acientobacter* (Gram negative), and *Staphylococci, Streptococci* (Gram positive). The fungus used was *Candida albicans.* Stock solution (0.001 mol) was prepared by dissolving the compounds in DMSO. The diameter of the inhibition zones was measured in millimeters. Antimicrobial activities were performed in triplicate and the average was taken as the final reading.

Results and discussion

The synthesized ligand 2-[*N*,*N*-bis-(3,5-dimethyl-pyrazolyl-1-ethyl)]aminothiazole (BMPMAT) forms stable complexes with Co(II), Ni(II), and Cu(II). The complexes have been characterized by IR, UV–Vis, ^{1}H and ^{13}C NMR, Mass, EPR spectrum, magnetic susceptibility measurements, and conductance studies. The analytical data of the ligand and the complexes together with their physical properties are given in Table 1. The complexes are partially soluble in ethanol, chloroform, acetonitrile, but completely soluble in polar coordinating solvents such as DMF and DMSO. The molar conductance of complexes in 10^{-3} molar DMF solution is in the range of 4-7 Ω^{-1} cm^{2}mol^{-1} indicating that these chelates are non-electrolytes(Geary, 1971). The elemental analyses data of the complexes are in good agreement with the calculated data for the 1:1 (M:L) ratio. Elemental analysis, spectral, mass, and conductance data suggest the molecular formula [ML.Cl$_2$.] for all metal(II) complexes. The proposed structure of the complexes is given in Fig. 2.

NMR spectra

The ^{1}H NMR (300 MHz) spectrum of 2-[*N*,*N*-bis-(3,5-dimethyl-pyrazolyl-1-methyl)]aminothiazole(BMPMAT) was recorded in CDCl$_3$. The spectrum of the free ligand showed a singlet at 2.37 δ (s, $\mathbf{CH_3}$, 12H) due to four methyl groups at 3, 5-positions on the pyrazole rings. Pyrazole ring protons appeared as singlet at 7.8 δ and a singlet at 5.51 δ due to methylene proton (s, 2 N–$\mathbf{CH_2}$-N, 4H), the aminothiazole ring protons are obtained as doublet at 7.03–7.33 δ (d, 2H). The spectrum is given in supplementary material (Fig. S1).

The ^{13}C NMR spectrum for 2-[*N*,*N*-bis-(3,5-dimethyl-pyrazolyl-1-methyl)]aminothiazole(BMPMAT) was also recorded in CDCl$_3$. The peaks are assigned as follows: ^{13}C NMR(CDCl$_3$, 75 MHz); $\delta = 10.53–13.14$(–CH$_3$,C-4,4′5,5′) 56.48(N–C=CH, C-7,7′), 62.15(N–C=CH, C-8,8′),70.32(C=C–C,C-6,6′), 105(S-CH,C-1), 107(N-CH, C-2), 140.3(N-CH$_2$,C-3), 140.3(C-3,3′), 168.48(C-9). The spectrum is given in supplementary material (Fig. S2).

Infrared spectra

The band at 1595 cm^{-1} is assigned to ν(C=N) of the pyrazole group in the ligand. Also the ligand shows a band at 1617 cm^{-1} which is attributed to ν(CH=N) of the thiazole ring. The stretching vibration appears at 761 cm^{-1} is due to ν(C–S) of the thiazole ring (Chandra *et al.*, 2009).

After complexation the stretching vibration of ν(C=N) (1595 cm^{-1}) is shifted to lower frequency($\sim$14–20 cm^{-1}) in the complexes indicating the coordination of pyrazole ring nitrogen(N2) to the metal ion (Kalanithi *et al.*, 2011)]. The stretching band at 1294 cm^{-1} due to ν(N–N) is shifted to lower frequency (15–20 cm^{-1}) in the complexes confirming the coordination of ring nitrogen(N2) to the metal ion(Tharmaraj *et al.*, 2009). The shift in ν(N–N) can be attributed to the reduction of lone pair-lone pair repulsion in N–N bond. In all the complexes (1–3), the ν(C=N) and ν(C–S) of thiazole ring remain unchanged suggesting that the endocyclic nitrogen and sulfur do not take part in coordination. The ligand as well as its coordinating complexes show peak at 2960 cm^{-1} due to C–H stretching in CH$_2$ group bonded to pyrazole nucleus. In the far IR spectra of complexes, the weak non-ligand bands appeared at 480-460 cm^{-1} regions which are assigned to ν(M–N) (Mohamed *et al.*, 2009).

UV–Visible spectroscopy

The absorption spectrum of the ligand in chloroform shows strong peaks at 303 nm (33,003 cm^{-1}) 270 nm (37,037 cm^{-1}), which are attributed to π-π* and n-π* transitions, respectively. The Cu(II) complex shows a broad band at 710 nm (14,084 cm^{-1}) with high molar intensity (1453 L cm^{-1} mol^{-1}) assignable to the transition $^2B_{1g} \rightarrow {}^2A_{1g}$ characteristic of square planar geometry with tetrahedral distortion(Kasumov and Koksal, 2004). An additional band appears at 414 nm (24,154 cm $^{-1}$) which may be due to metal–ligand charge transfer(MLCT). The molar absorption coefficient (1,870 L cm^{-1} mol^{-1}) of charge transfer transition is higher than the d–d transition. The electronic spectrum of Co(II) complex shows peaks at 659 nm (15,174 cm^{-1}), and 1,080 nm (9269 cm^{-1}) may be assigned to $^4A_2(F) \rightarrow {}^4T_1(P)$ and $^4A_2(F) \rightarrow {}^4T_1(F)$ suggesting distorted tetrahedral environment around Co(II) (Dhanaraja and Nair, 2009). The molar intensities of the absorptions are in the order of 10^2 L cm^{-1} mol^{-1}. Ni(II) complex under investigation exhibits absorption band at 670 nm (14,925 cm^{-1}) assignable to $^3T_1(F) \rightarrow {}^3T_1(P)$ transition indicating the tetrahedral geometry of the complex (Arish and Nair, 2010). The molar absorption coefficients of tetrahedral Ni(II) complexes are smaller than the Cobalt(Td) complexes (Lever, 1968).

Magnetic susceptibility

The magnetic susceptibilities of the complexes were determined at room temperature. The obtained magnetic moment data show the presence of paramagnetic behavior of Cu(II), Co(II), and Ni(II). The magnetic moment value of 1.75 B.M for copper complex falls within the range normally observed for square planar Cu(II) complex (Lever, 1968). For Co(II) complex, the magnetic moment is found to be 4.25 B.M. which is an indicative of distorted tetrahedral geometry (Mohamed *et al*., 2009). The Ni(II) complex reported herein is high spin with a room temperature magnetic moment value of 2.90 B.M. suggesting distorted tetrahedral coordination when compared with reported value (El-Tabl *et al*., 2008).

Mass spectra

The EI mass spectrum of ligand (BMPMAT) and complexes of Co(II), Ni(II), and Cu(II) are recorded. The molecular ion peak for the ligand was observed at 316 *m/z*, whereas the same of Cu(II), Co(II), and Ni(II) complexes were observed at 451, 446.5, and 446 *m/z*, respectively, which corresponds to the molecular ion $[M(BMPMAT)Cl_2]^+$. The ligand fragmentation pattern followed the cleavage of C–N, C–C, and C=C bonds. The mass spectral data support the structures of mononuclear transition metal complexes. The fragmentation pattern of the complexes does not show any loss of water or chlorine which is present outside the coordination sphere. The mass spectrum of BMPMAT and the mass spectrum of $[Ni(BMPMAT)Cl_2]$ are given in supplementary material (Fig. S3 and S4).

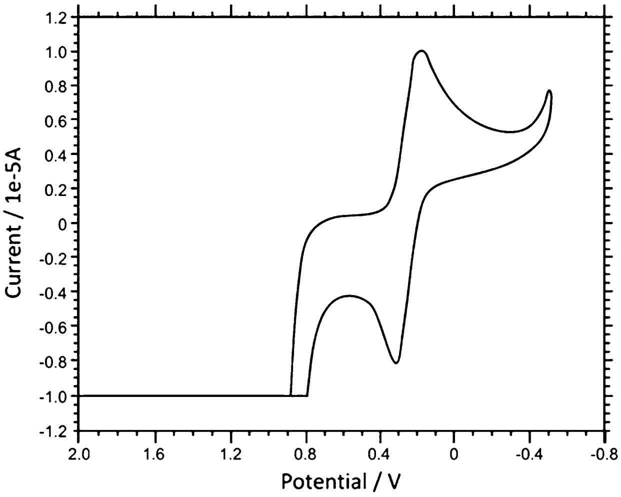

Fig. 3 Cyclic voltammogram of $[Cu(BMPMAT)Cl_2]$ in DMSO

Electrochemical behavior

In this work, cyclic voltammetric studies of the Cu(II) complex were performed in DMSO solution at room temperature with TBAP as supporting electrolyte, glassy carbon as working electrode, Pt wire as auxiliary electrode, Ag/AgCl as reference electrode, and scan rate 100 mVs^{-1} (−0.8–2.0 V). The free ligand does not show oxidation or reduction peak values. The copper complex shows a quasi reversible peak in anodic direction at $E_{pa} = 0.172$ V. In cathode direction, the direct reduction takes place at $E_{pc} = 0.315$ V which is due to Cu(II)/Cu(I) couple of complex and it was unaffected by varying the scan rate ranging from 50 to 250 mV with peak potential. The difference $\Delta E_p = E_{pa} - E_{pc}$ exceed the nernstain requirement of 59/n mV (n = no of electron involved in oxidation reaction) which suggests the quasi reversible character of the complex. The copper complex shows large separation between anodic and cathodic peak (0.143 V) indicating the quasi reversible character (Tas *et al*., 2004). The ratio of cathodic and anodic peak current ($I_{pc}/I_{pa} \sim 1$) shows a one electron process as shown in Fig. 3.

Electron paramagnetic resonance spectrum

A powder EPR spectrum of Cu(II) complex was recorded at room temperature and at LNT using tetracyano ethylene(TCNE) as a reference standard. The spectrum is characterized by an axial g tensor. Hyperfine splitting features are observed both in 300 and 77 K due to copper ($S = 1/2$ and $I = 3/2$). The spectrum shows rhombic spectral features with $g_{||} = 2.275$ and $g_{\perp} = 2.189$ suggesting a tetrahedral distortion around the Cu(II) ion corresponding to elongation along the four-fold symmetry Z-axis (Chandra and Kuar, 2005). The $g_{||}$ value (2.275) for the complex is less than 2.3 suggesting a covalent character of the metal ligand bond. The calculated values of $g_{||}$ and $g_{\perp}$ for the complex show the order as $g_{||} > g_{\perp} > g_e$ (2.0027) which is in consistent with the $d_{x2\text{-}y2}$ ground state (Kivelson and neiman, 1961). The odd electron may be located in the B_{1g} antibonding orbital. The geometric parameter G is estimated from the expression $G = (g_{||}\text{-}2.0027)/(g_{\perp}\text{-}2.0027)$.

If $G > 4.0$ their local axes are said to be aligned parallel or only slightly misaligned. If $G < 4.0$, significant exchange coupling is present and the misalignment is appreciable. The observed value (1.46) for the exchange interaction parameter for the Cu(II) complex **(1)** ($G < 4$) suggests that significant exchange coupling is present and the misalignment is appreciable. The hyperfine parameters ($A_{||}$ and $A_{\perp}$) have been calculated using the expression

$$A_{||} = P - (4\alpha^2/7) - K + (g_{||} - 2.0027) + 3/7(g_{\perp} + 2.0027)$$

$$A_{\perp} = P + (2\alpha^2/7) - K + (11/14)(g_{\perp} - 2.0027)$$

where $P = 0.036$ and $K = 0.30$ are the spin–orbit interaction factor and Fermi contact term, respectively. The ratio $g_{||}/A_{||}$ for a square planar geometry is 103–135 cm (Kasumov *et al.*, 2006). The ratio($g_{||}/A_{||}$) for the Cu(II) complex is 110 cm indicating a negligible distortion from the square planar geometry. The EPR parameters $g_{||}$, $g_{\perp}$, $A_{||}$ and the energies of d–d transition were used to evaluate the bonding parameters α^2, β^2 which may be regarded as measures of the covalency of the in-plane σ bonds and in-plane π bonds.

$$\alpha^2_{Cu} = A_{||}/p + \left(g_{||} - 2.0027\right) + 3/7(g_{\perp} - 2.0027) + 0.04$$

$$\beta^2_{Cu} = \left(g_{||} - 2.0027\right)E / -8\lambda\alpha^2$$

$\alpha^2 = 0.5$ indicates complete covalent bonding and $\alpha^2 = 1$ suggests complete ionic bonding. The observed value of α^2 of the complex is greater than 0.5 ($\alpha^2 = 0.9760$) which indicates the slight ionic character of the in-plane σ bonds.

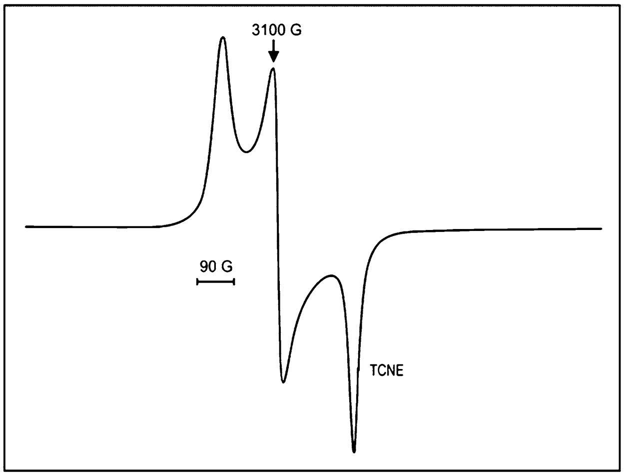

Fig. 4 EPR spectrum of [Cu(BMPMAT)Cl$_2$] at 300 K

The orbital reduction factors $K_{||}$ and $K_{\perp}$ were calculated using the expressions reported (Hathaway, 1973). Likewise, according to Hathaway, for pure σ bonding $K_{||}(0.7535) \approx K_{\perp}$ (0.6255) ≈ 0.77, for in-plane π bonding $K_{||} < K_{\perp}$, and for out-of-plane π bonding $K_{||} > K_{\perp}$. The $K_{||}$, $K_{\perp}$ values in complex **1** evidence the presence of out-of-plane π bonding. The EPR spectrum is shown in Fig. 4.

Pharmacology study

Analgesic activity

The analgesic activity is found to be almost same up to 60 min of basal reaction time. At the reaction time of 90 min, the analgesic activity of the Ni(II) complex is greater than the ligand. The same trend is observed for other complexes also. It is interesting to note that the ligand and its complexes exhibit better activity than the standard drug Aspirin. The analgesic activity of the compounds decreases when the treatment time increases to 120 min. This decrease is due to decrease in maximum effective concentration of the drug in the plasma level.

Antimicrobial activity

It is well known that Schiff bases find potential applications as antimicrobial agents (Rehman *et al.*, 2012). The present study reveals that the mannich base from 2-aminothiazole and a pyrazole derivative and its metal(II) complexes possess antimicrobial activities. The results exhibited markedly an enhancement in activity on coordination with the metal ions against five bacterial and one

Table 2 Antimicrobial activity of ligand (BMPMAT) and its metal (II) complexes (zone of inhibition in mm*)

Compounds	*X.maltophilia*	*C.violaceum*	*A. bacter*	*Staph. cocci*	*S. cocci*	*C. albicans*
BMPMAT	14	27	20	19	20	16
[Cu(BMPMAT)Cl_2]	16	28	22	20	23	17
[Co(BMPMAT)Cl_2]	17	31	20	22	22	17
[Ni(BMPMAT)Cl_2]	18	30	21	22	21	18
Amikacin	18	19	17	18	18	–
Ketoconazole	–	–	–	–	–	18
DMSO	–	–	–	–	–	–

* Each value observed is within the error limits of ±2

fungal strain. Chelation reduces the polarity (Chohan, 2006) of the metal ion mainly because of the partial sharing of its positive charge with the donor groups and possibly the π-electron delocalization within the whole chelate ring system, thus formed during coordination. This process of chelation thus increases the lipophilic nature of the central metal atom, which in turn favors its permeation through the lipid layer of the membrane. This in turn is responsible for increasing the hydrophobic character and liposolubility of the molecule in crossing cell membrane of the microorganism, and hence enhances the biological utilization ratio and activity of the testing drug/compound. All the complexes are found to have more activity against the all bacterial species except *Xanthomonas maltophilia* compared with the standard drugs. The data of inhibition zones in mm after incubation are shown in Table 2. The photographs of inhibition zones are given in supplementary material (Fig. S5).

Conclusion

Complexes of 2-[*N*,*N*-bis-(3,5-dimethyl-pyrazolyl-1-methyl)] aminothiazole with Cu(II), Co(II), and Ni(II) were synthesized and characterized by various analytical techniques. The ligand acts as bidentate(NN) ligand and Cu(II) complex shows distorted square planar and other complexes possess distorted tetrahedral geometry. EPR studies of copper complex confirm the covalent character of the metal ligand linkage.

The ligand and the metal complexes exhibit enhanced antimicrobial activity in relation with standard drugs. The activity was found to be higher than the standard drugs particularly for *Chromobacterium violaceum*. The data for analgesic activity studies by tail-flick method reveal a promising activity for the system. The antimicrobial and analgesic activity investigations could be helpful in designing more potent antimicrobial and analgesic agents for therapeutic use.

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