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Feature article

Spectral, XRD, SEM and biological properties of new mononuclear Schiff base transition metal complexes



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ABSTRACT

Six new transition metal complexes derived from the reaction of 4(4-(dimethylamino) benzylideneamino) benzoic acid and Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) cations, were prepared, isolated and characterized by a range of spectral and analytical methods including UV/Vis, FT IR, NMR, MS, powder XRD, TGA and SEM. The complexes were formed with the deprotonation of the ligand and presented typical six-coordinated octahedral geometry. In addition, the biological activity was evaluated by conducting in vitro anti-bacterial, anti-fungal and anti-leishmanial screenings. All the complexes were found more active than the ligand, while complex 7 revealed biological significance.

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Introduction. Schiff bases produced by condensation reaction of aromatic amines and aromatic aldehydes; which are versatile ligands furnishing imine N and other donor sites are responsible for a wide range of biological and chemical applications [1-7]. Past several decades have seen a great number of reports describing the synthesis of Schiff bases with interesting structural aspects and their biological perspective as well [8]. Transition metal ions enhance the biological activity of different ligands, and in some cases the activity has been solely attributed to metal ions only [9]. N,O-donor Schiff bases containing carboxylic group have been used extensively in coordination chemistry because of their versatile modes of attachment to metal centers via monodentate, bidentate, chelate or bridging [10-12]. In literature, several reports linked the significance of biological activity of metal complexes with the metal ion rather than with the ligands [13]. Schiff base transition metal complexes 4-dimethylaminobenzaldehyde (Ehrlich's Reagent) are reported in the literature; while little is known

about the synthesis and biological study of 4-(4-(dimethylamino) benzylideneamino) benzoic acid (Fig. 1) and its transition metal complexes [14]. This report is a continuation of the previous work on biologically active coordination compounds, describing the structures and in vitro anti-bacterial, anti-fungal and anti-leishmanial screenings of 4-(4-(dimethylamino) benzylideneamino) benzoic acid and its divalent Mn, Fe, Co, Ni, Cu and Zn transition metal complexes [15,16]. Ligand and complexes were screened in vitro for their anti-bacterial (Pseudomonas aeruginosa, Bacillus subtilis, Methicillin-resistant staphylococcus aureus (MRSA), Klebsiella pneumoniae, and Escherichia coli); anti-fungal (Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger and Fusarium solani) and anti-leishmanial (Leishmania major (MHOM/PK/88/DESTO), Leishmania tropica (K27) and Leishmania donovani (H43)) potential.

Experimental. Ethanolic solutions of 4-aminobenzoic acid (1.02 g, 7.4453 mmol in 30 ml) of 4-(dimethylamino)benzaldehyde (1.12 g, 7.4453 mmol, 30 ml) were mixed together at room temperature. The resulting mixture was stirred at room temperature, and after 5 min the color of the reaction mixture gave a yellowish appearance; the reaction mixture was stirred for 2 h. Ethanol was evaporated at room



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Fig. 1. 4-(4-dimethylamino)benzylideneamino)benzoic acid.

temperature and the solid obtained was washed twice with ether (15 ml) and recrystallized from 90% ethanol.

 $NH_2C_6H_4COOH + OHCC_6H_4N(CH_3)_2 \rightarrow N(CH_3)_2C_6H_4CHNC_6H_4COOH + H_2OH_3C_6H_4COOH + H_2OH_3C_6H_4COOH_3C_6H_3C_6H_4COOH_3C_6H$

All the complexes were synthesized by the same methodology, briefly an ethanolic solution of the freshly prepared ligand was added in portions to the corresponding metal salt solution in the same solvent in 2:1 molar ratio. Instantly, precipitation occurred; colors of the precipitates depended upon the metals. The precipitate was filtered and washed with excess of distilled water, then ethanol and in the end with diethyl ether to remove unreacted ligand and impurities. Instrumentation and acquisition of other spectral data, *in vitro* biological activity protocols were conducted as reported earlier [15–19].

Results and discussion. In the free ligand, the band at 1650 cm⁻¹ is assigned to $\nu(C=N)$ frequency; after complexation, this band is shifted to lower frequency. Shifting of the ν (C=N) vibration to lower frequency (1612–1581 cm⁻¹) is due to C=N \rightarrow M coordination [20]. Characteristic broad band in the range of $3300-3500 \text{ cm}^{-1}$ is assigned to carboxylic group in the ligand's spectrum that disappeared after complexation which proved deprotonation of the ligand; similarly presence of coordinated water is confirmed by the presence of another broad band at 3160–3550 cm⁻¹ [21]. Coordinated water molecule is also seen as a weak band at 840 cm^{-1} due to rocking mode while band at 605–660 cm⁻¹ indicated the presence of water of crystallization [21]. Difference of symmetric and asymmetric vibrations of the carbonyl group *i.e.* Δv (C=O_{asym} – C=O_{sym}) provided valuable information about the coordination mode of COOH group in the complexes (2-7). The values of Δv less than 200 cm⁻¹ indicate the monodentate coordination mode of carboxylic group [21]. In free ligand, sharp dips were observed at 1685 cm⁻¹ and 1472 cm⁻¹ ($\Delta \nu$: 213 cm⁻¹) for C=O_{asym} and C=O_{sym} respectively, while in complexes these shifted to lower frequencies and the magnitude of Δv also went below 200 cm⁻¹; briefly 190, 181, 183, 183, 182 and 193 cm⁻¹ for complexes **2–7** respectively. This indicated the involvement of monodentate approach of COOH group of the ligand with the central metal cations [22,23]. New bands appeared in the spectra of the complexes at 534–577 cm^{-1} , corresponding to $0 \rightarrow M$ and 425–468 cm⁻¹ due to the N $\rightarrow M$ vibrations which support the involvement of N and O atoms in complexation with metal ions under investigation [24]. Characteristic strong band at 1332 cm⁻¹ is assignable to the stretching vibration of aromatic C–N group that remained unchanged after complexation which confirmed the non-coordination of dimethylamino moiety [25]. All this discussion indicates that the ligand is bidentate coordinating via O,N in octahedral geometry (Fig. 2) and also proves 1:2 metal to ligand stoichiometry [26].

The electronic spectrum gives information on the electronic environment of the metal; the electronic absorption spectra are determined in DMSO in the range of 200–1000 nm *i.e.* 50,000–10,000 cm⁻¹. Pure ligand showed three intensive bands at 42,194 cm⁻¹, 37,037 cm⁻¹ and 29,850 cm⁻¹ suggesting the presence of π – π * and n– π * transitions [27]. The π – π * transition in the complexes (**2–7**) is shifted to a longer wavelength as a consequence of coordination to the metal, confirming the formation of Schiff base metal complexes. Fe(II) complex display maximum absorption bands centered at 30,211–28,490 cm⁻¹; ascribed to an intramolecular charge transfer transition in the complexed ligand. In addition, a band is seen at 23,809–21,276 cm⁻¹ that can be attributed to charge transfer from ligand to metal (L \rightarrow M). Furthermore,



Fig. 2. Octahedral geometry of complexes 2–7 and NMR numbering scheme where $M = Mn^{II}$, Fe^{II}, Co^{II}, Ni^{II}, Cu^{II} and Zn^{II}.

the L \rightarrow MCT band is followed by a long broad tail at 18,868 cm⁻¹ which is due to a $d \rightarrow d$ transition in an octahedral arrangement [28]. Co(II) complex furnished two bands at 16,452 cm^{-1} and 18,530 cm^{-1} respectively for ${}^{4}T_{1}(F) \rightarrow {}^{4}A_{2}(F)$ and ${}^{4}T_{1}(F) \rightarrow {}^{4}T_{1}(P)$ transitions; Cu(II) complex displayed four bands at 37,037-35,714 cm⁻¹, 25,641–25,316 cm⁻¹, 22,222–21,739 cm⁻¹ due to π - π * within organic molecule and 16,393–16,129 cm⁻¹ attributable to π - π * of C = N group $(L \rightarrow Cu^{2+})$ charge transfer after complex formation; while the last band can be assigned to ${}^{2}B_{1g} \rightarrow {}^{2}E_{g}$ transition of the Cu(II) ion in tetragonal elongation of octahedral geometry [29]. Similarly, Ni(II) complex also exhibited two additional bands with 18,868-18,519 cm⁻¹ and 13,514–13,333 cm⁻¹ due to the ${}^{3}A_{2g} \rightarrow {}^{3}T_{1g}(\nu_{1})$ and ${}^{3}A_{2g} \rightarrow {}^{3}T_{1g}(F)(\nu_{2})$ transitions. This indicated octahedral geometry around the Ni(II) ion and is further supported by a v_2/v_1 ratio of (1.4, 1.39), which corresponds to an octahedral geometry [29]. Mn(II) complex exhibited electronic spectral bands at 18,868 cm^{-1} and 25,316 cm⁻¹ corresponding to ${}^{6}A_{1g} \rightarrow {}^{4}T_{1g}(P) (\nu_{3})$ transition, typical of octahedral Mn(II) complex [30].

¹H NMR spectral data of the ligand and its complexes were recorded in DMSO- d_6 for the evaluation of the number & nature of all the protons relative to TMS with chemical shifts given in ppm (DMSO: \approx 2.0 ppm). All the protons resonated at appropriate positions *i.e.* COOH group in the ligand gives a broad singlet at 12.85 ppm, a singlet for azomethine hydrogen (CH=N) at 8.73 ppm, aromatic ring attached to dimethylamino 6.5–7.35 ppm, aromatic protons of benzoic phenyl ring at 7.3–8.0 ppm and singlet at 2.94 ppm for methyl groups. The peak near 11 ppm is absent metal(II) complexes, confirmed the deprotonation of CO–O–H. The azomethine signal is shifted to downfield as well and indicated deshielding of the azomethine proton due to coordination to the metal ion through the azomethine nitrogen atom [31]. ¹³C NMR spectral data corroborated the mode of bonding situation depicted by



Fig. 3. Thermograms of compounds 1-6.



Fig. 4. X-ray diffraction pattern of Zn(II) complex.



Fig. 5. Scanning electron micrographs of (a) ligand, (b) Cu(II) complex and (c) Zn(II) complex.

¹H NMR; carbon attached to the hydroxyl group in the ligand is observed at 158.5 ppm, which after complexation shifted to > 168 ppm, and confirmed the coordination of the ligand through oxygen. The deshielding of the azomethine carbon is also confirmed by a signal at > 173 ppm; which provided support that the azomethine nitrogen is also involved in the complexation ($C=N \rightarrow M$) [32,33].

FAB spectrum of the ligand showed molecular ion peak at m/z 268 equal to its molecular mass. FAB spectrum of Co(II) complex showed a molecular ion peak M⁺ at m/z 629 that is equivalent of its molecular mass, while that of Cu(II) at m/z 634 and Zn(II) at m/z 635 are attributable to [M + 1] and [M + 2] respectively. Co(II), Cu(II) and Zn(II) complexes lost two water molecules and thereby displayed fragments at m/z 593, 597 and 598. Further, [L + H]⁺ observed at m/z 268 is furnished by all the complexes because of demetallation. Complexes show [M]⁺ peaks in good agreement with the structures proposed by elemental analysis and spectral data and molar stoichiometry [34 – 36]. TGA study was carried out up to 1000 °C; thermograms

(1–7) showed gradual weight loss, indicating decomposition by fragmentation with increase in temperature. For all the complexes, following steps were observed (i) small weight loss in the range of 40–110 °C assignable to the loss of water of crystallization, (ii) maximum weight loss in the range of 130–170 °C which is attributable to the loss of coordinated water (iii) and gradual weight loss in the range of 540–1000 °C that can be assigned to complete decomposition of ligand moiety around the metal ion respectively and finally the complex is converted into its metal oxide [37]. Thermograms of compounds **1–6** are plotted in Fig. 3; showing approximately 80% weight loss up to 1000 °C which is according to the aforementioned three steps.

During powder X-ray diffraction analysis (Fig. 4), only Ni(II) and Zn(II) complexes exhibited sharp peaks, while no peaks were observed for the rest of the complexes indicating their amorphous nature. Line broadening of the crystalline diffraction peak in the Zn(II) complex showed higher crystallinity. Crystalline nature of the complexes was indicated by comparing the diffractograms of the ligand and



Fig. 6. Anti-bacterial and anti-fungal activity of compounds 1-7 and standards at a: 25, b: 50 and c: 100 µg/ml respectively.



Fig. 7. Zones of inhibition by compounds 6 and 7 against *Pseudomonas aeruginosa* and *Bacillus subtilis*.



Fig. 9. Anti-fungal activity of 1 and 4 against A. flavus, A. fumigatus, A. niger and F. solani.

complexes. Based on literature, this may be due to the incorporation of water molecules into the coordination sphere [38]. Although single crystal X-ray crystallography is the most precise source of information regarding the structure of a complex, the difficulty of obtaining suitable crystals in proper symmetric form has rendered this method unsuitable for such a study.

The SEM analysis was here carried out to check the surface morphology of the selected complexes and the micrographs obtained are given in Fig. 5. The micrograph of the Schiff base ligand is given in Fig. 5(a); it can be seen that it gave a rock like appearance with a numerous territorial patches. These facts revealed the amorphous nature of the ligand with complicated interpretation due to unclear appearance. On the other hand, the micrographs of copper and nickel complexes Fig. 5(b & c) indicated that the presence of well defined crystals free from any shadow of the metal ion on their external surface had a twisted fiber and grass like morphology. It is evident from the SEM study that in all the synthesized metal complexes, crystals were found to grow up from just a single molecule to several molecules in an aggregate distribution with particle sizes starting from a few nanometers to several hundred. In addition, different characteristic shapes of metal Schiff base complexes were identified and these SEM images were quite different from that of Schiff base. The difference in the shape of the Schiff base metal complex crystal aggregates deposited on the thin films was mainly dependent on the metal ions.

The experimental data obtained from elemental analysis are in good agreement to support 1:2 metal to ligand stoichiometry. The molar conductance measurements suggested the absence of ionic character of the monovalent anions of the ligand coordinated to metal ion. Molar conductance values in DMSO solutions of the complexes that fell in the range of $17-19 \ \Omega^{-1} \ cm^2 \ mol^{-1} \ proved$ that the complexes were non-electrolytes ($1 \times 10^{-3} \ mol \ dm^{-3}$). The coordinated water analysis of the complexes indicated two water molecules per molecule.

Effectiveness of an antimicrobial agent is based on the zones of inhibition; based on their respective zones of inhibition, the data obtained showed that the synthesized complexes have got the capacity to inhibit the metabolic growth of the investigated bacteria (Fig. 6). All the complexes displayed increased activity compared to that of the ligand; while among the complexes, Zn(II) complex furnished significant activity under identical experimental conditions (Figs. 7 and 8). The possible mode of increased toxicity of the complexes may be explained by Tweedy's chelation theory, which states that chelation reduces the polarity of the central metal atom because of partial sharing of its positive charge with the ligand which favors the permeation of the complexes through the lipid layer of cell membranes [39]. Furthermore, hydrogen bonding may affect the mode of action of compound probably through the azomethine (C==N) group and the active centers of cell constituents resulting in the interference with normal cell processes [39-41]. In vitro anti-fungal activity of all the synthesized compounds was carried out against A. flavus, A. fumigatus, A. niger and F. solani by agar tube dilution method using Miconazole as reference and significant activity results were observed at 25, 50 and 100 μg ml⁻¹ concentrations. Significant improvement in ligand's anti-fungal effect upon complexation was observed; the increase in anti-fungal activity is due to the structural changes after coordination which can be seen in Figs. 9 and 10. The increase in activity with the increase in concentration of the test compound, and the variation in the effectiveness of the different compounds against different organisms is due to the impermeability of the microbial cells or ribosomal difference in the microbial cells [42–44]. Anti-leishmanial activity findings are depicted in Fig. 11; it was clearly evident from the plotted data that all the complexes showed excellent activity in comparison to the ligand and the standard drug. This enhancement in activity may be attributed to the structural changes taking place in vitro during the assaying and it is suggested that the metal-ligand interactions are a major deciding factor responsible for the increase in anti-leishmanial activity.

Conclusions. Condensation reaction of 4-dimethylaminobenzaldehyde and 4-aminobenzoic acid resulted in the production of Schiff base ligand in excellent yield. The ligand coordinates in 2:1 ligand to metal ratio as a monobasic bidentate (ON) donor in all the complexes. The analytical, thermal, molar conductance, vibrational, resonance, mass and electronic spectral study suggested the structures shown in Fig. 2 in octahedral



Fig. 8. Zone of inhibition by compounds 6 and 7 against *Escherichia coli* and *Methicillin*resistant Staphylococcus aureus (MRSA).



Fig. 10. Anti-fungal activity of 6 and 7 against A. flavus, A. fumigatus, A. niger and F. solani.



Fig. 11. Anti-leishmanial activity of compounds 1-8 and standard.

arrangement. TGA showed that the complexes are thermally more stable than the ligand. The biological activity results solely depend upon the coordination sphere of the central metal ion and the role of the ligand is vital in facilitating the transportation to the target sight.

Appendix A. Supplementary material

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.inoche.2013.06.014.

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- [17] Ligand 1: Yield: 1.35 g, 70%. MP: 265–267 °C; Ω (S·cm²·mol⁻¹): 11.21. ¹H NMR (400 MHz, DMSO- d_6): CH, $\delta = 9.65$ ppm (s, 1-H); CH, $\delta = 7.68$ ppm (d, 3-H, J: (400 min, bino a_0), c.i., s. 11, r. 12, k.i., CH, $\delta = 8.47$ ppm (s, 6-H); CH, \delta = 8.47 ppm (s, 6-H); CH, $\delta = 8.47$ ppm (s, 6-H); CH, \delta = 8.47 ppm (s, 6-H); CH, \delta = 8.47 ppm (s, 6-H); CH, \delta = 8.47 ppm (s, 8-H); CH, \delta = 8.47 ppm (s, 8-H); 8.8 Hz); CH, $\delta = 0.79$ ppin (d, 4-ri, J. 8.0 Hz); CH, $\delta = 0.74$ ppin (d, 0-ri), Ci, $\delta = 7.61$ ppm (d, 8-H, J: 8.8 Hz); CH, $\delta = 6.54$ ppm (d, 9-H, J: 8.8 Hz); CH3, $\delta = 3.03$ ppm (s, 11-H). ¹³C NMR (100 MHz, DMSO-*d*₆): COOH, $\delta = 189.72$ ppm; C=C (aromatic), $\delta = 110.12-155.42$ ppm; C=N, $\delta = 160$ ppm; CH₃, $\delta = 38.86$. Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.58; H, 5.88: N. 1022. FT IR: 3391 (COOH), 1650 (C=N), 1472 (C=O)sym, 1687 (C=O)asym, 1601 (C=C) cm⁻¹. MS: 268. [2] Yield: 54%. MP: 210–220 °C; Ω (S.cm2.mol⁻¹): 11.21. ¹H NMR (400 MHz, DMSO- d_6): CH (azomethine), $\delta = 9.73$ ppm (s, 1-H); CH (aromatic), $\delta = 6.55 - 8.42 \text{ ppm}.^{13} \text{CNMR} (100 \text{ MHz}, \text{DMSO-}d_6): \text{COO}, \delta = 182.18 \text{ ppm}; \text{C=C} (\text{ar-})^{13} \text{CNMR} (100 \text{ MHz}, \text{DMSO-}d_6): \text{COO}, \delta = 182.18 \text{ ppm}; \text{C} = 100 \text{ cm}$ omatic), $\delta = 114.55-159.12$ ppm; C=N, $\delta = 162.31$ ppm; CH₃, $\delta = 39.47$. Anal. Calcd. for C32H34MnN4O6: C, 61.44; H, 5.48; N, 8.96; Mn, 8.78. Found: C, 61.12; H, 5.11; N, 8.66; Mn, 8.52. FT IR: 1600 (C=N), 1465 (C=O)sym, 1655 (C=O)asym, 1600 (C=C), 548 (O → M), 436 (C=N → M) cm⁻¹. MS: 625. [3] Yield: 76%. MP: 252–254 °C; Ω (S·cm²·mol⁻¹): 17.11. ¹H NMR (400 MHz, DMSO- d_{o}): CH (azomethine), δ = 9.69 ppm (s, 1-H); CH (aromatic), δ = 6.59–8.32 ppm. ¹³C NMR (100 MHz, DMSO- d_6): COO, $\delta = 186.21$ ppm; C=C (aromatic), $\delta = 114.43$ -160.04 ppm; C=N, δ = 165.00 ppm; CH₃, δ = 40.02. Anal. Calcd. for C₃₂H₃₄FeN₄O₆: C, 61.35; H, 5.47; N, 8.94; Fe, 8.91. Found: C, 61.03; H, 5.31; N, 8.67; Fe, 8.55. FT IR: 1612 (C=N), 1470 (C=O)sym, 1651 (C=O)asym, 1597 (C=C), 534 (O → M), 425 (C=N → M) cm⁻¹. MS: 626. [4] Yield: 69%. MP: 256 °C; Ω (S·cm²·mol⁻¹): 20.31. ¹H NMR (400 MHz, DMSO- d_6): CH (azomethine), $\delta = 9.62$ ppm (s, 1-H); CH (aromatic), $\delta = 6.50-8.21$ ppm. ¹³C NMR (100 MHz, DMSO- d_6): COO, $\delta = 181.33$ ppm; C=C (aromatic), $\delta = 118.22-167.44$ ppm; C=N, $\delta = 169.07$ ppm; CH3, $\delta = 40.11$. Anal. Calcd. for C₃₂H₃₄CoN₄O₆: C, 61.05; H, 5.44; N, 8.90; Co, 9.36. Found: C, 60.87; H, 5.21; Calculate to (c₃)r₁₃(c)r₄(c)r₄(c)r₆(c)r₆(c)r₇(c) DMSO-*d*₆): COO, δ = 183.0 ppm; C=C (aromatic), δ = 120.1–163.75 ppm; C=N, $\delta = 170.0$ ppm; CH₃, $\delta = 39.69$. Anal. Calcd. for C₃₂H₃₄NiN₄O₆: C, 61.07; H, 5.45; N, 8.90; Ni, 9.33. Found: 59.71; H, 5.18; N, 8.53; Ni, 8.92. FT IR: 1601 (C=N), 1488 (C==O)sym, 1670 (C==O)asym, 1622 (C==C), 555 (O → M), 433 (C==N → M) cm⁻¹. MS: 628. [6] Yield: 53%. >300 °C; Ω (S·cm²·mol⁻¹): 11.48. ¹H NMR (400 MHz, DMSO- d_{0}): CH (azomethine), $\delta = 9.41$ ppm (s, 1-H); CH (aromatic), $\delta = 6.42-7.94$ ppm. ¹³C NMR (100 MHz, DMSO- d_{0}): COO, $\delta = 180.4$ ppm; C=C (aromatic), $\delta = 124.2-165.0$ ppm; C=N, $\delta = 175.2$ ppm; CH₃, $\delta = 40.11$. Anal. Calcd. for C32H34CuN4O6: C, 60.60; H, 5.40; N, 8.83; Cu, 10.02. Found: 60.31; H, 5.22; N, bit C₂₇13₄Cutq₄Q₆, C, 00.00, H, 0.40, H, 0.05, (n, 1002, 1001d, 00.51, H, 522, H, 8.66; Cu, 9.69, FT IR: 1605 (C=N), 1479 (C=O)sym, 1669 (C=O)asym, 1629 (C=C), 549 (O → M), 458 (C=N → M) cm⁻¹. MS: 633. [7] Yield: 51%. >300 °C; Ω (S·cm²·mol⁻¹): 19.96. 1H NMR (400 MHz, DMSO- d_6): CH (azomethine), δ = 9.33 ppm (s, 1-H); CH (aromatic), δ = 6.51–7.82 ppm. ¹³C NMR (100 MHz, 100 DMSO-*d*₆): COO, $\delta = 178.04$ ppm; C=C (aromatic), $\delta = 126.14-167.76$ ppm; C=N, $\delta = 175.87$ ppm; CH₃, $\delta = 40.43$. Anal. Calcd. for C₃₂H₃₄ZnN₄O₆: C, 60.43; H, 5.39; N, 8.81; Zn, 10.28. Found: C, 60.08; H, 5.12; N, 8.61; Zn, 9.88. FT IR: 1581 (C=N), 1482 (C==0)sym, 1675 (C==0)asym, 1626 (C==C), 577 (O \rightarrow M), 468 (C==N \rightarrow M) cm⁻¹. MS: 634
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