

Some bivalent metal complexes of Schiff bases containing N and S donor atoms[†]

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(Received 1 February 2006; accepted 2 May 2006)

Abstract

Schiff bases have been synthesized by the reaction of *p*-nitrobenzaldehyde, *o*-nitrobenzaldehyde and *p*-toluyaldehyde with 4-amino-5-mercapto-1,2,4-triazole. The ligands react with Co(II), Ni(II) and Zn(II) metals to yield (1:1) and (1:2) [metal:ligand] complexes. Elemental analyses, IR, ¹H NMR, electronic spectral data, magnetic susceptibility measurements, molar conductivity measurements and thermal studies have investigated the structure of the ligands and their metal complexes. The electronic spectral data suggests octahedral geometry for Co(II), Ni(II) and Zn(II). The antibacterial activities of the ligands and their metal complexes have been screened *in vitro* against three Gram-positive (*Staphylococcus aureus*, *Staphylococcus epidermidis* and *Bacillus subtilis*) and two Gram-negative (*Salmonella typhi* and *Pseudomonas aeruginosa*) organisms. The coordination of the metal ion had a pronounced effect on the microbial activities of the ligands and the metal complexes have higher antimicrobial effect than the free ligands.

Keywords: Antibacterial activity, divalent metal complexes, Schiff bases

Abbreviations: AMT, 4-amino-5-mercapto-s-triazole; B. subtilis, *Bacillus subtilis*; CFU, Colony Forming Unit; DMSO, Dimethyl Sulfoxide; MIC, Minimum Inhibitory Concentration; MTCC, Microbial Type Culture Collection and Gene Bank; P. aeruginosa, *Pseudomonas aeruginosa*; SCDA, Soyabean Casein Digest Agar; S. typhi, *Salmonella typhi*; S. aureus, *Staphylococcus aureus*; S. epidermidis, *Staphylococcus epidermidis*

Introduction

Schiff base complexes with transition metals have played a prominent role in the development of coordination chemistry [1–2]. Several Schiff base metal complexes have been studied because of their industrial and biological applications [3–6]. Metal complexes of N and S chelating ligands have attracted considerable attention [7] because of their interesting physicochemical properties, pronounced biological activities and as models of the metalloenzyme active sites. It is well known that N and S atoms play a key role

in the coordination of metals at the active sites of numerous metallobiomolecules. Triazoles derivatives [8–11] are known to possess antitubercular, antibacterial, fungicidal, hypotensive and hypothermic-activities. Metallo-organic chemistry is becoming an emerging area of research due to the demand for new metal-based antibacterial compounds [12,13]. The serious medical problem [13–16] of bacterial resistance and the rate at which it develops has led to increasing levels of resistance to classical antibiotics. The discovery and development of effective antibacterial drugs with

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[†]The paper was presented at 92nd Session of the Indian Science Congress, Ahmedabad, No. 13, 2005.

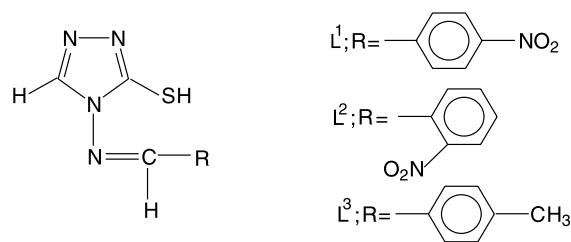


Figure 1. Structure of the Schiff bases.

novel mechanism of action have become an urgent task for infectious diseases research programs [17].

The present investigation aims at a study of Co(II), Ni(II) and Zn(II) complexes of some bioactive ligands/Schiff bases (Figure 1) derived from *p*-nitrobenzaldehyde, *o*-nitrobenzaldehyde and *p*-toluylaldehyde with *s*-triazole and their antibacterial properties against various pathogenic bacterial strains of *Staphylococcus aureus* (MTCC 3160), *Staphylococcus epidermidis* (MTCC 2639), *Bacillus subtilis* (MTCC 121), *Salmonella typhi* (MTCC 733) and *Pseudomonas aeruginosa* (MTCC 3541) using the minimum inhibitory concentration method [18].

Material and methods

All the chemicals and solvents used were of AnalaR grade. All metal(II) were used as their acetate salts. Melting points were determined in open capillaries in electrical melting point apparatus. IR Spectra were recorded on a Beckman IR-20 spectrophotometer in the region 4000–250 cm^{-1} . Proton NMR spectra were recorded in DMSO- d_6 on a Bruker ACF 300 spectrometer at 300 MHz with reference to Me_4Si (0.0 ppm). Electronic spectra of metal complexes were recorded in the region 1100–200 nm on a Hitachi U-2000 spectrophotometer. Conductance of the metal complexes was determined in dry DMF on a Systronics-306 Conductivity meter. Magnetic measurements were carried out at the Institute Instrumentation Center, IITR, Roorkee on a Vibrating Sample Magnetometer (model 155). The metal complexes were analyzed for their metal content using standard methods [19]. Thermal analyses of metal complexes were carried out in atmospheric air using a Perkin Elmer (Pyris Diamond) Instrument with reference to Alumina Powder at IITR, Roorkee.

Synthesis of ligands

4-amino-5-mercapto-*s*-triazole (AMT) was prepared by the reported procedure [20]. Schiff bases namely, 5-mercapto-4-(*p*-nitrobenzalideneamino)-*s*-triazole (MNBT), 5-mercapto-4-(*o*-nitrobenzalideneamino)-*s*-triazole (MN'BT) and 5-mercapto-4-(*p*-toluylideneamino)-*s*-triazole (MTT), were prepared by refluxing a mixture of equimolar quantities

of the *s*-triazole (AMT) and the corresponding aldehydes, namely, *p*-nitrobenzaldehyde, *o*-nitrobenzaldehyde and *p*-toluylaldehyde, for 5–6 h, respectively, in absolute ethanol. The reaction mixture was then kept at room temperature overnight and the products were filtered and recrystallized from the same solvent.

Synthesis of metal(II) complexes

Aqueous ethanolic solutions of metal acetates of Co(II), Ni(II) and Zn (II), respectively, were added to the hot ethanolic solution of the ligands in (1:1) and (1:2) molar ratios, which resulted in the precipitation of the metal derivatives. The product formed were filtered, washed with warm water, ethanol and finally with acetone and dried on a water bath.

In vitro antibacterial assay

Antibacterial assay of 9 synthesized compounds viz. MNBT, MNBT-Ni(1:1), MNBT-Ni(1:2), MN'BT, MN'BT-Zn(1:1), MN'BT-Zn(1:2), MTT, MTT-Co(1:1) and MTT-Co(1:2) were done *in vitro* by the using minimum inhibitory concentration (MIC) method. MIC is the lowest concentration of the antimicrobial agents that prevents the development of visible growth after overnight incubation [18]. The MIC of chemically synthesized compounds against test bacteria namely *S. aureus* (MTCC 3160), *S. epidermidis* (MTCC 2639), *B. subtilis* (MTCC 121), *S. typhi* (MTCC 733) and *P. aeruginosa* (MTCC 3541) was determined by reported methods [21]. All the test cultures were streaked on SCDA and incubated overnight at 37°C. Turbidity of all the bacterial cultures was adjusted to 0.5 McFarland standard [22] by preparing bacterial suspension of 3–5 well-isolated colonies of same morphological type selected from a SCDA plate culture. The cultures were further diluted 10-fold to get an inoculum size of 1.2×10^7 CFU/ml. A stock solution of 4 mg/mL of each compound was prepared in DMSO and was appropriately diluted to give final concentrations of 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25, 0.12, 0.06, 0.03 $\mu\text{g/mL}$. Standard antibiotics (linezolid and cefuroxime axetial) were also diluted in a similar manner. 320 μl of each dilution was added to 20 mL molten and cooled MHA (separate flasks were taken for each dilution). After thorough mixing, the medium was poured into sterilized petri plates. The test bacterial cultures were spotted in a predefined pattern by aseptically transferring 5 μL of each bacterial culture on the surface of solidified agar-agar plates and the plate incubated at 35°C for 24 h.

Results and discussion

Chemistry

The ligands (Table I) were soluble in ethanol and methanol. All the metal(II) complexes (Table II) were

Table I. Spectral and analytical data of Schiff bases.

Schiff base	M.P. (°C)	IR (cm ⁻¹)	¹ H NMR (DMSO-d ₆) (ppm)	Calc.(Found) %			Yield (%)
				C	H	N	
L ¹ (MNBT) C ₉ H ₇ N ₅ O ₂ S [249.2]	238	3119, 2625, 1587, 1104	14.0 (s,1H,SH), 8.1–8.4 (m,4H,Aromatic-H), 4.3 (s,1H,Triazole-H), 9.0 (s,1H,-CH=N)	43.4(43.6)	2.8(2.5)	28.1(27.7)	74
L ² (MN ¹ BT) C ₉ H ₇ N ₅ O ₂ S [249.2]	175	3113, 2639, 1610, 1121	13.8 (s,1H,SH), 7.8–8.2 (m,4H,Aromatic-H), 4.3 (s,1H,Triazole-H), 8.9 (s,1H,-CH=N)	43.4(43.8)	2.8(2.6)	28.1(28.0)	78
L ³ (MTT) C ₁₀ H ₁₀ N ₄ S [218.3]	162	3119, 2673, 1606, 1137	14.0 (s,1H,SH), 7.4–7.8 (m,4H,Aromatic-H), 4.3 (s,1H,Triazole-H), 8.9 (s,1H,-CH=N), 2.1 (s,3H,Aromatic-CH ₃)	55.1(55.3)	4.6(4.4)	25.7(25.8)	80

Table II. Physical and analytical data of the metal(II) complexes.

No.	Metal Chelate/Mol. Formula	Mol. Weight	M.P. (°C)(d)	B. M. (μ _{eff})	Calc. (Found)%				Yield
					C	H	N	M	
1	Co(MNBT)OAc.3H ₂ O C ₁₁ H ₁₅ N ₅ CoO ₇ S	[420.3]	>278	4.3	31.4(31.5)	3.6(3.8)	16.7(16.9)	14.1(14.4)	72
2	Ni(MNBT)OAc.3H ₂ O C ₁₁ H ₁₅ N ₅ NiO ₇ S	[420.1]	>268	3.0	31.5(31.4)	3.7(3.9)	16.8(16.7)	14.0(14.3)	64
3	Zn(MNBT)OAc.3H ₂ O C ₁₁ H ₁₅ N ₅ ZnO ₇ S	[426.7]	225	–	31.0(31.4)	3.5(3.9)	16.4(16.6)	15.4(15.8)	67
4	Co(MNBT) ₂ .2H ₂ O C ₁₈ H ₁₆ N ₁₀ CoO ₆ S ₂	[591.4]	>280	4.6	36.6(36.9)	2.7(2.5)	23.7(23.6)	10.0(10.2)	85
5	Ni(MNBT) ₂ .2H ₂ O C ₁₈ H ₁₆ N ₁₀ NiO ₆ S ₂	[591.2]	>292	2.9	36.7(36.9)	2.7(2.8)	23.7(23.8)	9.9(9.5)	71
6	Zn(MNBT) ₂ .2H ₂ O C ₁₈ H ₁₆ N ₁₀ ZnO ₆ S ₂	[597.9]	>276	–	36.2(36.4)	2.6(2.3)	23.5(23.7)	10.9(10.4)	71
7	Co(MN ¹ BT)OAc.3H ₂ O C ₁₁ H ₁₅ N ₅ CoO ₇ S	[420.3]	>280	4.4	31.4(31.2)	3.6(3.8)	16.7(16.9)	14.1(13.7)	73
8	Ni(MN ¹ BT)OAc.3H ₂ O C ₁₁ H ₁₅ N ₅ NiO ₇ S	[420.1]	>272	3.1	31.5(31.9)	3.7(3.8)	16.8(17.0)	14.0(13.7)	80
9	Zn(MN ¹ BT)OAc.3H ₂ O C ₁₁ H ₁₅ N ₅ ZnO ₇ S	[426.7]	232	–	31.0(31.3)	3.5(3.3)	16.4(16.2)	15.4(15.6)	76
10	Co(MN ¹ BT) ₂ .2H ₂ O C ₁₈ H ₁₆ N ₁₀ CoO ₆ S ₂	[591.4]	>284	4.6	36.6(36.8)	2.7(2.5)	23.7(23.4)	10.0(10.4)	82
11	Ni(MN ¹ BT) ₂ .2H ₂ O C ₁₈ H ₁₆ N ₁₀ NiO ₆ S ₂	[591.2]	>296	3.3	36.7(36.4)	2.7(2.9)	23.7(23.3)	9.9(9.8)	72
12	Zn(MN ¹ BT) ₂ .2H ₂ O C ₁₈ H ₁₆ N ₁₀ ZnO ₆ S ₂	[597.9]	230	–	36.2(36.5)	2.6(2.7)	23.5(23.6)	10.9(10.6)	81
13	Co(MTT)OAc.2H ₂ O C ₁₂ H ₁₈ N ₄ CoO ₅ S	[389.3]	>272	4.5	37.0(37.4)	4.6(4.5)	14.4(14.6)	15.1(15.4)	79
14	Ni(MTT)OAc.2H ₂ O C ₁₂ H ₁₈ N ₄ NiO ₅ S	[389.1]	>298	2.8	37.1(37.0)	4.6(4.6)	14.5(14.3)	15.1(15.3)	79
15	Zn(MTT)OAc.2H ₂ O C ₁₂ H ₁₈ N ₄ ZnO ₅ S	[395.7]	>300	–	36.5(36.6)	4.5(4.8)	14.1(14.5)	16.6(16.4)	76
16	Co(MTT) ₂ .2H ₂ O C ₂₀ H ₂₂ N ₈ CoO ₂ S ₂	[529.5]	>280	4.7	45.4(45.8)	4.2(4.5)	21.2(21.5)	11.2(11.4)	87
17	Ni(MTT) ₂ .2H ₂ O C ₂₀ H ₂₂ N ₈ NiO ₂ S ₂	[529.3]	>290	3.5	45.5(45.6)	4.2(4.0)	21.2(21.5)	11.2(11.4)	87
18	Zn(MTT) ₂ .2H ₂ O C ₂₀ H ₂₂ N ₈ ZnO ₂ S ₂	[535.9]	>285	–	44.9(44.7)	4.1(4.4)	20.9(20.5)	12.2(12.5)	78

Table III. Spectral data of metal(II) complexes.

No.	IR (cm ⁻¹)	λ_{\max} (cm ⁻¹)	¹ H NMR (DMSO-d ₆) (ppm)
1	3600–3000,1714,1595,849,746,719,505,344	9794, 20,492	–
2	3600–3000,1730,1595,848,771,705,483,362	10,905, 16,583, 27,100	–
3	3600–3200,1730,1591,846,747,715,519,372	–	8.0–8.3(m,4H,Aromatic-H), 9.27(s,1H,-CH=N),4.3(s,1H,Triazole-H)
4	3600–3200,1593,849,748,717,527,351	9814, 20,619	–
5	3600–2900,1595,848,770,706,491,359	10,941, 16,584, 26,492	–
6	3600–3100,1596,848,767,718,498,375	–	8.1–8.2(m,4H,Aromatic-H), 9.34(s,1H,-CH=N),4.3(s,1H,Triazole-H)
7	3600–3200,1733,1611,851,783,715,514,364	9814, 20,661	–
8	3600–3200,1743,1608,857,737,709,531,333	10,952, 16,585, 27,100	–
9	3600–3100,1743,1618,852,781,711,486,379	–	7.9–8.3(m,4H,Aromatic-H), 9.22(s,1H,-CH=N),4.3(s,1H,Triazole-H)
10	3600–3200,1609,837,756,717,511,357	9850, 18,939	–
11	3600–3100,1608,842,779,712,539,342	10,964, 16,584, 26,954	–
12	3600–3100,1618,852,781,714,496,365	–	7.9–8.3(m,4H,Aromatic-H), 9.31(s,1H,-CH=N),4.3(s,1H,Triazole-H)
13	3600–2800,1725,1609,815,749,720,533,358	9960, 20,542	–
14	3600–3100,1719,1608,817,754,714,488,362	10,952, 16,583, 27,248	–
15	3600–3100,1727,1607,815,736,708,537,371	–	7.4–7.8(m,4H,Aromatic-H), 9.12(s,1H,-CH=N),4.3(s,1H,Triazole-H), 2.1(s,3H,Aromatic-CH ₃)
16	3600–2800,1608,814,752,717,538,363	9921, 18,762	–
17	3600–3200,1606,814,748,712,483,369	10,952, 16,585, 27,027	–
18	3600–3200,1608,815,734,710,542,378	–	7.4–7.8(m,4H,Aromatic-H), 9.26(s,1H,-CH=N),4.3(s,1H,Triazole-H), 2.1(s,3H,Aromatic-CH ₃).

stable at room temperature, non-hygroscopic, insoluble in water and many common organic solvents, infusible at high temperature, and all of were thought to be polymeric in nature. Molar conductance values of 10⁻³M solutions of the metal complexes in dry DMF lie in the range 5–16 $\Omega^{-1}\text{cm}^2\text{mol}^{-1}$, indicating their non-electrolytic nature [23]. Structures of the Schiff bases were assigned with the aid of IR, ¹H NMR and analytical data (Figure 1).

IR spectra. The IR spectra of the ligands show characteristic bands (Table I) due to $\nu(\text{N-H})$ and $\nu(\text{S-H})$ at ~ 3100 and $\sim 2600\text{ cm}^{-1}$, respectively [24]. Another band at $\sim 1105\text{ cm}^{-1}$ is assigned to $\nu(\text{C=S})$ [24]. The deprotonation of the thiol group is indicated by the absence of a band in the metal complexes at $\sim 2600\text{ cm}^{-1}$, which appears due to $\nu(\text{S-H})$ in the spectra of the ligands indicating thereby complexation through sulphur. A new band appears at $734\text{--}783\text{ cm}^{-1}$ which is assigned to $\nu(\text{C-S})$ and it further confirms coordination through the sulphur atom. Metal-sulphur bond formation is further confirmed by a band in the region $333\text{--}379\text{ cm}^{-1}$ in the far IR-spectra (Table III).

The presence of coordinated water in the complexes [24] is indicated by a broad trough band in the region $2800\text{--}3600\text{ cm}^{-1}$ and two weaker bands in the region $814\text{--}857\text{ cm}^{-1}$ and $705\text{--}720\text{ cm}^{-1}$ due to $\nu(\text{-OH})$ rocking and wagging mode of vibrations, respectively

[25]. A strong band in the region $1714\text{--}1743\text{ cm}^{-1}$ has been assigned to $\nu(\text{OOCCH}_3)$ in (1:1) (metal: ligand) complexes.

A strong band in the region $1587\text{--}1610\text{ cm}^{-1}$ in the free ligands assigned to $\nu(\text{N=CH})$ exhibits $\pm 5\text{--}10\text{ cm}^{-1}$ shift [26–30] in the spectra of complexes indicating coordination through the azomethine nitrogen of Schiff bases and shifting of $\nu(\text{N=CH})$ in the complexes as compared to the ligands, is due to reduction of double bond character of the carbon-nitrogen bond of the azomethine group. Formation of a metal-nitrogen bond is further supported by the presence of a band in the region $483\text{--}542\text{ cm}^{-1}$ in the far-IR spectra.

Thus the IR spectral data provide strong evidences for the complexation of the potentially multidentate ligands.

Electronic spectra and magnetic measurements. The cobalt complexes generally exhibited two distinct bands in the region $9794\text{--}9960$ and $18,939\text{--}20,661\text{ cm}^{-1}$ which may be assigned to ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{T}_{2g}(\text{F})(\nu_1)$ and ${}^4\text{T}_{1g}(\text{F}) \rightarrow {}^4\text{T}_{1g}(\text{P})(\nu_3)$ transitions, respectively, and are suggestive of octahedral geometry around the cobalt ions [31–32]. The electronic spectra of Ni(II) complexes showed d-d bands in the region $10,905\text{--}10,964$, $16,583\text{--}16,585$ and $20,492\text{--}27,248\text{ cm}^{-1}$. These are assigned [31] to the transitions ${}^3\text{A}_{2g}(\text{F}) \rightarrow {}^3\text{T}_{2g}(\text{F})(\nu_1)$;

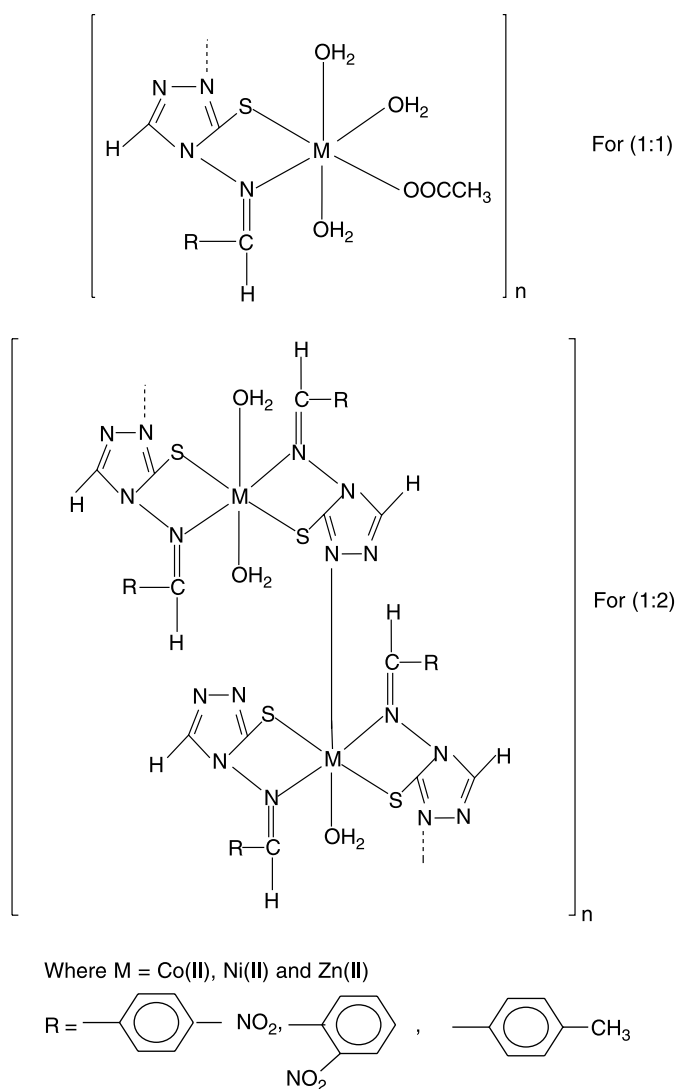


Figure 2. Structures of metal complexes.

${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)(\nu_2)$ and ${}^3A_{2g}(F) \rightarrow {}^3T_{1g}(P)(\nu_3)$, respectively, consistent with their well defined octahedral configuration [31–32] (Figure 2).

The magnetic measurements for Co(II) and Ni(II) complexes showed three and two unpaired electrons and the magnetic moment values (4.3–5.2 BM) and (2.8–3.5 BM), respectively, for Co(II) and Ni(II) ion suggesting [33] consistency with their octahedral environment.

NMR spectra. In the NMR spectra of complexes we observed a shift of electron density from the ligands to metal. The signal of azomethine protons deshielded in the spectra of metal complexes was found to occur in the range (9.12–9.34) ppm, as compared to its Schiff bases (8.9–9.0) ppm after complexations to the metal ion inferring co-ordination through the azomethine nitrogen atom [34] of the ligands. Disappearance of –SH protons in the spectra of

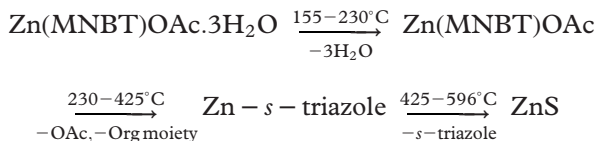
complexes supported the deprotonation of the thiol group (Tables I and III).

Thermal studies. The thermal behavior of all the complexes is almost the same. Hence only two complexes namely Zn(MNBT)OAc.3H₂O and Co(MTT)₂.2H₂O are discussed in detail:

The DTG Curve of Zn(MNBT)OAc.3H₂O showed that the three water molecules were lost at 155, 220 and 230°C corresponding to the mass loss of 3.98% (calc. 4.22%), 7.97% (calc. 8.44%) and 12.02% (calc. 12.66%) on the TG curve. After 230°C, the organic part starts decomposing, giving metal-triazole at 425° with a mass loss of 57.85% on the TG curve [35–36] (calc. 58.16%), as indicated by the DTA curve. In the temperature range 425–596°C, all the triazole part decomposed, with the mass loss of 76.85% (calc. 77.16%) and, finally, formation of ZnS took place at 596°C.

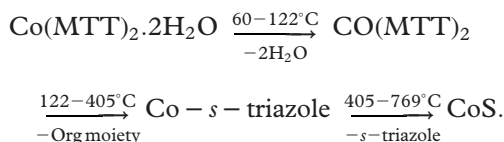
The sequence for thermal degradation of the complex

Zn(MNBT)OAc.3H₂O are given below:



The complex Co(MTT)₂.2H₂O lost its two water molecules at 60° and 122°C with the mass loss of 3.14%(calc. 3.40%) and 6.59%(calc. 6.80%) on the TG curve [35–36]. At higher temperature, the organic part decomposed. The DTG curve indicated the formation of Co-s-triazole, which was further supported by the DTA curve at 405°C and a mass loss of 45.68%(calc. 46.12%) on the TG curve. The first part of triazole was lost at 431°C with a mass loss of 60.92%(calc. 61.44%) and the decomposition of the second part of the triazole, left behind CoS at 769°C with a mass loss of 76.82%(calc. 76.75%).

The sequence of thermal degradation of the complex Co(MTT)₂.2H₂O are given below:



Biological results and discussion

The antibacterial activity results presented in Table IV show clearly that the newly synthesized compounds and their metal complexes containing Co(II), Ni(II) and Zn(II) possess good biological activity [37]. Nine chemically synthesized compounds viz. L¹, L², L³, 2, 5, 9, 12, 13, 16 were tested *in vitro* for their

Table IV. Minimum inhibitory concentration (mic) of nine compounds against test microorganisms using the agar dilution assay technique.

Compounds	Sa*	Se	Bs	St	Pa
L ¹	16	2	4	32	16
2	4	2	2	32	16
5	32	2	4	16	8
L ²	2	2	2	1	4
9	0.25	1	0.5	2	4
12	16	8	8	64	32
L ³	4	4	8	16	32
13	2	2	0.5	16	16
16	2	2	1	8	4
Linezolid	2	8	16	32	32
Cef. Axetial	32	16	32	16	32

Sa*-*S. aureus* (MTCC 3160), Se-*S. epidermidis* (MTCC 2639), Bs-*Bacillus subtilis* (MTCC 121), St-*S. typhi* (MTCC 733), and Pa-*Pseudomonas aeruginosa* (MTCC 3541).

antibacterial activity against *S. aureus*, *S. epidermidis*, *B. subtilis*, *S. typhi* and *P. aeruginosa* at different concentrations in DMSO solution using MIC. The antibacterial studies suggested that all the Schiff bases/ligands were found to be biologically active and their metal(II) complexes showed significantly enhanced antibacterial activity against one or more bacterial species in comparison to the free ligands. It is, however, known [38–39], that chelation tends to make the ligands act as more powerful and potent bacteriostatic agents, thus inhibiting the growth of bacteria more than the parent ligands do. It is suspected that factors such as solubility, conductivity, dipole moment and cell permeability mechanism (influenced by the presence of metal ions) may be the possible reasons for the increase in activity. The minimum inhibitory concentration 0.25 µg/mL was shown by compound 9 against *S. aureus* and 0.5 µg/mL was shown by compounds 9 and 13 against *B. subtilis*, respectively. Compound, L², 9 and 16 showed MIC 1 µg/mL against *S. typhi*, *S. epidermidis* and *B. subtilis*, respectively. In all other cases, the compounds exhibited MICs ranging from 2 µg-32 µg/mL against all the bacterial strains (Table IV). The antibacterial activity of these compounds also compared well with two commercial antibiotics namely, linezolid and cefuroxime axetial.

Acknowledgements

This investigation received financial support from University Grant Commission (UGC); New Delhi provided a project fellowship to one of the authors (M.S.B.).

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