



Synthesis, characterization and antimicrobial studies of some Mannich bases derived from phenylethyl amine and their transition metal complexes

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ABSTRACT

In the present study, an attempt has been made to synthesize Mannich bases (**L1** to **L4**) using 2-phenylethylamine, benzaldehyde and amide moieties such as semicarbazide, thiosemicarbazide, urea and thiourea are employed as compound containing active hydrogen atom. Mannich bases thus formed were characterized by physical methods such as TLC, elemental analysis and melting point. Metal complexes of $[MCl_2(L1)_2]$, $[M(L1)_2(H_2O)_2]Cl_2$ [$M=Co(II)$, $Ni(II)$, $Cu(II)$ and $Zn(II)$] of ligand (**L1**) were also prepared. The structures of newly synthesized compounds, complexes, mode of binding and overall geometry were characterized through electronic, IR, ¹H NMR, ¹³C NMR and Mass spectral studies. Elemental analysis, conductance measurements, TGA and DTA studies have been characterized to establish the structure of complexes. In vitro antimicrobial studies of **L1** ligand and its transition metal complexes and all other Mannich bases **L2** to **L4** were recorded against certain pathogenic Gram positive bacteria such as *S. aureus*, *S. faecalis* and certain pathogenic Gram negative bacteria such as *E. Coli*, *P. aeruginosa*, along with antifungal activity against *C. albicans*.

Keywords: Metal complexes of Mannich base, Multicomponent reaction, NO donors 2-phenylethylamine, Antimicrobial activities

INTRODUCTION

The Mannich reaction is a powerful C-C bond formation process has wide applications for the synthesis of various aminoalkyl derivatives¹. The designing and studying of complexes derived from Mannich base as ligands is an interesting area of research both inorganic and bioorganic chemists.^{2,3} Organic chelating ligands containing amide moiety as a functional group have a strong ability to form metal complexes and exhibit a wide range of biological activities.⁴ From the literature it has been observed that 2-phenylethylamine is used as cytotoxic agent⁵ and considerable amount of cytotoxic 2-phenylethylamine Mannich bases were synthesized and reported in the

reputed research papers. B. Testa *et al*⁶ and T.S. Rao *et al*⁷ reported that a Prodrug approach for CNS activity of 2-phenylethylamine (PEA) is found to be higher in the brain of selected rats when compared with free drugs such as *N,N*-dipropargyl-2-phenylethylamine and *N*-propargyl-2-phenylethylamine. Glen B Baker *et al*⁸ also suggest that, *N*-(2-cyanoethyl)-2-phenylethylamine and *N*-(3-chloropropyl)-2-phenylethylamine also caused sustained elevations of CNS in rat brain. From these literature it has been observed that very few research work has been published on the synthesis of metal complexes of 2-phenylethyl amine.^{9,10} Based on the above facts, an attempt has been made to synthesis new class of metal complexes of Mannich bases derived from 2-phenylmethylaniline as ligand in the present study. Further an attempt has been made to study the antimicrobial activity of the synthesized compounds and complexes.¹¹

MATERIALS AND METHODS

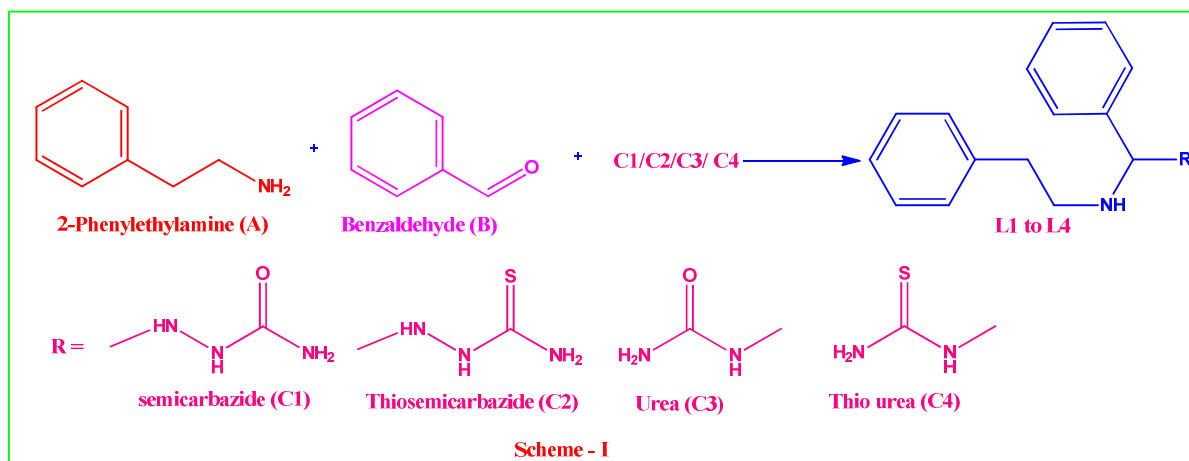
All reagents were commercially available and used without further purification. Solvents were distilled from appropriate drying agents immediately prior to use. Melting points were determined in open capillary tube using melting point apparatus and are uncorrected. The purities of the compounds were checked by TLC on SiO₂ gel coated glass plates using chloroform:ethylacetate (1:1 v/v) as eluting agent and visualized by iodine vapour. C, H and N analysis were performed using Varian EL III C, H, N and S analyzer available at Sophisticated Test and Instrumentation Centre (STIC), Cochin. FTIR spectra were recorded by dispersing the compounds in KBr pellets on a Shimadzu – IR affinity-I at Jamal Mohamed College, Tiruchirappalli. ¹H NMR and ¹³C NMR spectra were recorded in DMSO-d₆ solution using Bruker 400 MHz and JEOL-8X 102 with tetramethylsilane (TMS) as an internal standard. The mass spectra were recorded in Shimadzu GC-MSQP5050 at Madurai Kamaraj University, Madurai. Molar conductance of complexes in DMF at a concentration of 10⁻³ M solution was measured at room temperature using Conductivity Bridge with a tip type cell having a cell constant of 1.03. Gouy's method was employed for getting magnetic measurement values. TGA analyses of complexes were done in nitrogen atmosphere on Perkin-Elmer thermal analyzer instrument at the STIC-Coachin in the temperature range of 0-800°C at heating range of 10°C/min. The EPR spectra of complexes were graphed in JEOL-DPS-2000 at Central University, Pondicherry. The antimicrobial activities for the synthesized compounds and complexes were tested using disc diffusion technique at Periyar College of Pharmacy, Tiruchirappalli.

RESULTS AND DISCUSSION

Mannich bases (**L1** to **L4**) were synthesized (scheme-I) by reacting 2-phenylethylamine and benzaldehyde and amide moieties such as Semicarbazide (**L1**), Thiosemicarbazide (**L2**), Urea (**L3**) and Thiourea (**L4**) are employed as compounds containing active hydrogen atom. Co(II), Ni(II), Cu(II) and Zn(II) complexes were also been prepared (Scheme-II) using **L1** as ligand and characterized by Physical and chemical methods. Elemental analysis values shown in Table-I indicate 1:2 (metal:ligand) stoichiometry for all complexes. The lower conductivity values (2.1 and 8.2 Ω⁻¹cm²mol⁻¹) indicates the non-electrolytic nature of Co(II) and Ni(II) complexes. The molar conductance values of Cu(II) and Zn(II) complexes are found to be in the range 80-100 Ω⁻¹cm²mol⁻¹ indicating the (1:2 type) electrolytic nature.¹² The results of *in vitro* study of antimicrobial activity of Ligand **L1** to **L4** and metal complexes of **L1** against each of two gram positive (*S. aureus* and *B. Substilis*), gram negative (*E.Coli*, *P.aeruginosa*) and a fungi (*C.albicans*) are reported in Table-II.

General Methods of preparation of Ligands

An alcoholic solution of 2-phenylethyl amine (A) (0.01 mole) was taken in a 100 ml round-bottomed flask was placed on a magnetic stirrer. The content of the flask was cooled in an ice-bath. Amide moieties such as C1 to C4 in water (0.01 mole) was added dropwise to the reaction mixture followed by Benzaldehyde (B) (0.01 mole) was added and stirring was continued for 30 minutes. A viscous liquid formed initially which on further stirring yields a coloured solid after 2 h. The product obtained was washed with water and crystallized from ethyl acetate.



2-((phenethylamino)(phenyl)methyl)hydrazinecarboxamide (L1)

Yield: 65%; **M.F:** C₁₆H₂₀N₄O; **IR (KBr) cm⁻¹:** 3460 (N-H str), 1648 (C=O), 1140 C-N-C (str), 1598 [C=C (Str)]. **¹H NMR (DMSO) δppm:** 7.08 (m, 6H Ar-proton), 6.21 (s, 2H, Ali-proton), 5.85 (s, 1H, NH-amide), 1.43 (s, H, CH), 2.42 (s, H, NH). **¹³C NMR (DMSO) δppm:** 178 (C=O), 139 (Ar CH), 35 (CH). **Mass Spectra (LC-MS):** Parent ion peak at *m/z*: 283.32 corresponding to M⁺ with Relative Index = 18%.

2-((phenethylamino)(phenyl)methyl)hydrazinecarbothioamide (L2)

Yield: 70%; **M.F:** C₁₆H₂₀N₄S; **IR (KBr) cm⁻¹:** 3457 (N-H str), 1637 (C=S), 1145 C-N-C (str), 1603 [C=C (Str)]. **¹H NMR (DMSO) δppm:** 7.20 (m, 6H Ar-proton), 6.72 (s, 2H, Ali-proton), 5.86 (s, 1H, NH-amide), 1.24 (s, H, CH), 2.21 (s, H, NH). **¹³C NMR (DMSO) δppm:** 185 (C=S), 139 (Ar CH), 33 (CH). **Mass Spectra (LC-MS):** Parent ion peak at *m/z*: 298.14 corresponding to M⁺ with Relative Index = 21%.

1-((phenethylamino)(phenyl)methyl)urea (L3)

Yield: 85%; **M.F:** C₁₆H₁₉N₃O; **IR (KBr) cm⁻¹:** 3465 (N-H str), 1644 (C=O), 1147 C-N-C (str), 1598 [C=C (Str)]. **¹H NMR (DMSO) δppm:** 8.08 (m, 6H Ar-proton), 6.73 (s, 2H, Ali-proton), 5.72 (s, 1H, NH-amide), 1.20 (s, H, CH), 2.23 (s, H, NH). **¹³C NMR (DMSO) δppm:** 175 (C=O), 139 (Ar CH), 32 (CH). **Mass Spectra (LC-MS):** Parent ion peak at *m/z*: 258.23 corresponding to M⁺ with Relative Index = 19%.

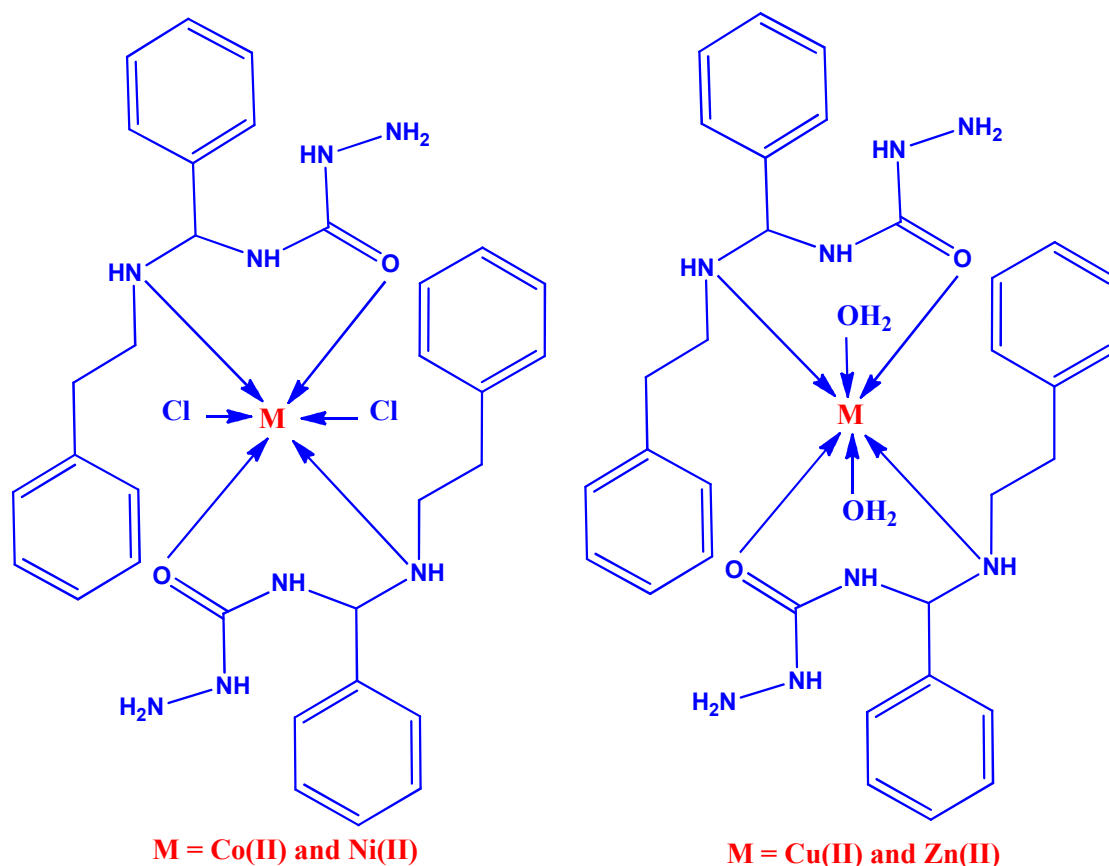
1-((phenethylamino)(phenyl)methyl)thiourea (L4)

Yield: 75%; **M.F:** C₁₆H₁₉N₃S; **IR (KBr) cm⁻¹:** 3468 (N-H str), 1642 (C=S), 1136 C-N-C (str), 1613 [C=C (Str)]. **¹H NMR (DMSO) δppm:** 7.82 (m, Ar-proton), 7.23 (s, Ali-proton), 5.71 (s, 1H, NH-amide), 1.64 (s, H, CH), 2.52 (s, H, NH). **¹³C NMR (DMSO) δppm:** 188 (C=S), 139 (Ar CH), 31 (CH). **Mass Spectra (LC-MS):** Parent ion peak at *m/z*: 310.25 corresponding to M⁺ with Relative Index = 18%.

Preparation of metal complexes

To a methanolic solution of L1, metal chloride [Co(II)] dissolved in a mixture of CHCl₃:CH₃OH (1:2) v/v was added. The resulting mixture was stirred for 2 h during which a solid complex

appeared, was collected by filtration, washed with mixture of methanol, diethyl ether and dried in *vacuo*. The same procedure was employed for all the complexes.



Scheme - II

FT-IR Spectra

Comparison of the IR spectra of the **L1** ligand and its transition metal complexes, it is observed that bands appearing at 1648 cm^{-1} due to $\nu_{(\text{C}=\text{O})}$ in the **L1** spectrum is shifted to lower side by $10\text{-}40\text{ cm}^{-1}$ in the spectra of the complexes confirms the coordination of carbonyl oxygen towards central metal ion. The band at 3240 cm^{-1} due to $\nu_{[\text{NH}(\text{str})]}$ of **L1** is found shifted to lower frequency by $10\text{-}20\text{ cm}^{-1}$ in the spectra of complexes confirm the participation of N-atom of amine in coordination with the metal ion. The presence of coordinated water molecule in Cu(II) and Zn(II) complexes have been confirmed by the appearance of bands at $3450\text{-}3550\text{ cm}^{-1}$ and a peak at 873 cm^{-1} assignable to stretching and rocking mode of water molecule. These bands are not observed in the IR spectra of Co(II) and Ni(II) complexes, confirm the absence of water molecule in complexes¹³. This is further supported by thermal analysis.

Electronic Spectra and Magnetic moments measurements

The Co(II) complex of **L1** ligand shows a magnetic moment value of 4.39 Bohr Magneton at room temperature. This is supported by electronic spectra, the absorption bands appear at $476\text{-}526\text{ nm}$ and $830\text{-}1086\text{ nm}$ ($21000\text{-}19000\text{ cm}^{-1}$ and $12048\text{-}92000\text{ cm}^{-1}$) are assigned to ${}^4\text{A}_2(\text{F})\rightarrow{}^4\text{T}_1(\text{P})$ and ${}^4\text{A}_2(\text{F})\rightarrow{}^4\text{T}_1(\text{F})$ transitions respectively suggest Tetrahedral geometry¹⁴. The Ni(II) complex of **L1** ligand exhibits two absorption bands one at $668\text{-}651\text{ nm}$ ($14960\text{-}15350\text{ cm}^{-1}$ and $8400\text{-}9250\text{ cm}^{-1}$)

and another at 1190-1081 nm ($8400-9250\text{ cm}^{-1}$) which are assigned to ${}^3T_1(F)\rightarrow{}^3T_1(P)$ and ${}^3T_1(F)\rightarrow{}^3A_2(F)$ transitions respectively, suggesting distorted Tetrahedral geometry. This is further supported by the magnetic moment value of 3.52 Bohr Magneton.^{15,16} The magnetic moment value of Cu(II) complex of **L1** ligand is 1.69 Bohr Magneton at room temperature which is closely related to spin-allowed value expected for a $S=1/2$ system which indicates distorted octahedral geometry around Cu(II) ion. This has been further supported by electronic spectrum of Cu(II) complex which has a band at 722-757 nm ($13850-13210\text{ cm}^{-1}$) corresponding to ${}^2E_g\rightarrow{}^2T_{2g}$ transition. This transition shows distorted octahedral geometry¹⁷. The diamagnetic Zn(II) complex did not show any d-d bands and its spectrum is subjected only by a charge transfer band due to distribution of electrons between metal and ligands.¹⁸

¹H NMR spectra

The binding mode and the geometry of diamagnetic Zn(II) complex of **L1** ligand was established by getting ¹H NMR spectrum recorded in DMSO-*d*₆. The broad signal of NH proton attached to the amide group shifted to down field from δ 5.8 to 5.9 ppm in a complex and a signal appears due to -NH proton of 2-phenylethylamine also shifted to down field from δ 2.4 to 2.8 ppm in a complex. From the above fact it is observed that, Zn(II) complex of **L1** ligand coordinated through oxygen atom of the carbonyl oxygen and Nitrogen atom of the NH group. These factors corroborating that ligand **L1** acts as neutral bidentate in all the complexes.

EPR Spectra

EPR spectrum of Cu(II) chloro complex of **L1** ligand was recorded in room temperature. The obtained value of $g_{\square} = 2.05$ is less than the value of 2.3 as reported by Kivelson and Neiman¹⁹ indicate the covalent character and unpaired electron is localized on $d_{x^2-y^2}$ orbital. A lesser G value of $2 < 4.0$ also confirmed the strong bonding of metal-ligand.

Thermal Studies

The thermogram of TGA and DTA of transition metal complexes of **L1** ligand was recorded in nitrogen atmosphere in the heating range of 10°C/min upto 700°C. From the thermogram of the Co(II) and Ni(II) complex of **L1** ligand, a complex is thermally stable upto 240°C. Appearance of two DTA endothermic peak range at 230-240°C and 260-270°C corresponds to decomposition of ligand and chlorides respectively. A weight of final residue indicates the formation of metal oxides. Absence of two coordinated water molecule was confirmed by the absence of characteristic endothermic peak and weight loss. The thermogram of Cu(II) and Zn(II) complex of **L1** ligand is thermally stable upto 250°C. The weight loss of 8% in the temperature range 120-150°C represents the elimination of two coordinated water molecules from the complex. A sharp endothermic peak in the temperature region of 230 and 276°C in DTA curve reports the loss of **L1** ligand and melting of complex and further oxidation of Metal at 350°C.

Table-1
Analytical Data of transition metal complexes

Compound	Colour	M.P (°C)	μ (B.M)	Λ^*	Found (calculated)				
					C	H	N	M	Cl
L1	Yellow	205	-	-	67.51 (67.58)	7.01 (7.09)	19.66 (19.70)	-	-
[CoCl ₂ (L1) ₂]	Green	235	4.39	8.2	55.01 (55.02)	5.72 (5.77)	16.01 (16.04)	8.38 (8.44)	10.10 (10.15)

[NiCl ₂ (L1) ₂]	Brown	240	3.52	2.1	55.02 (55.04)	5.71 (5.77)	16.02 (16.05)	8.37 (8.41)	10.11 (10.15)
[Cu(L1) ₂ (H ₂ O) ₂]Cl ₂	Brown	230	1.69	88.1	51.96 (51.99)	5.98 (6.00)	15.07 (15.16)	8.52 (8.60)	9.55 (9.59)
[Zn(L1) ₂ (H ₂ O) ₂]Cl ₂	White	250	Dia	89.3	51.83 (51.86)	5.94 (5.98)	15.09 (15.12)	8.78 (8.83)	9.52 (9.57)
L2	Yellow	219	-	-	63.92 (63.97)	6.69 (6.71)	18.60 (18.65)	-	-
L3	Yellow	226	-	-	71.31 (71.35)	7.06 (7.11)	15.56 (15.60)	-	-
L4	Yellow	266	-	-	67.29 (67.33)	6.68 (6.71)	14.69 (14.72)	-	-
C=Carbon, H=Hydrogen, N=Nitrogen, M=Metal and Cl= Chlorine									* [Ω ⁻¹ cm ² mol ⁻¹]

Antimicrobial Activity

Antimicrobial activities of **L1** and its complex along with other Mannich bases (**L2** to **L4**) were observed by disc diffusion method using nutrient agar as medium for bacteria and Potato Dextrose Agar (PDA) for fungi. The zone of inhibition²⁰ of all compounds was measured in mm and the activities are compared with Ciprofloxacin 5 µg/disc for bacteria and Fluconazole 100 units/disc for fungi. The zone of inhibition values are tabulated in Table-II. From the zone of inhibition values, this has been found that all the synthesized Mannich bases and their metal complexes possess moderate activities.

Table – II
Antimicrobial activities of the synthesized compounds

Compound	Zone of inhibition (mm)				
	Bacteria				Fungus
	Gram positive		Gram Negative		
	<i>Staphylococcus faecalis</i>	<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	<i>Candida albicans</i>
L1	20	22	18	16	16
[CoCl ₂ (L1) ₂]	22	25	16	18	18
[NiCl ₂ (L1) ₂]	NI	23	18	20	20
[Cu(L1) ₂ (H ₂ O) ₂]Cl ₂	21	22	15	18	22
[Zn(L1) ₂ (H ₂ O) ₂]Cl ₂	23	21	17	NI	16

L2	22	19	16	20	20
L3	24	16	NI	21	18
L4	20	23	19	20	20
Standard	32	30	32	37	35
DMSO (Control)	NI	NI	NI	NI	NI

Standard = Ciprofloxacin 5 µg/disc for bacteria and Fluconazole 100 units/disc for fungi
NI = No Inhibition

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