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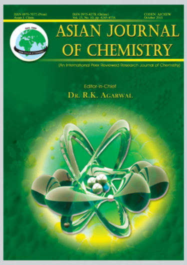

Synthesis, Structural and Biochemical Activity Studies of Symmetrical and Unsymmetrical Pyrroles and their Mononuclear Cu(II), Ni(II) and Co(II) Complexes

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Monomeric copper(II), nickel(II) and Co(II) complexes of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)aniline, (dmpyph) and 1,1'-(1,2-phenylene)-*bis*(2,5-dimethyl-1*H*-pyrrole) (tmpyph) were prepared and characterized by elemental analyses, magnetic moments, ^{1}H NMR and ^{13}C NMR, IR, mass spectral studies. The mononuclear metal complexes of dmpyph and tmpyph were found to have a 1:2 metal:ligand ratio. Elemental analyses, stoichiometric and spectroscopic data of metal complexes indicated that the metal ions were coordinated to the -NH_2 and C=N group nitrogen atoms (C=N). All of the data obtained from spectral studies supported the structural properties of ligands and their metal complexes. The free ligands and their metal complexes showed antimicrobial activity against only *S. aureus*, but no antifungal activity was observed against yeast like fungi. Among them, copper complexes and free ligands showed a narrow range of inhibitory activity against *Mycobacterium smegmatis*. Free ligands (**1, 2**), were found to have activity against *Saccharomyces cerevisiae* (Sc).

Key Words: Pyrrole, Aniline, Metal complexes, Antimicrobial activity.

INTRODUCTION

Pyrrole derivatives represent a class of compounds of great importance in heterocyclic chemistry. These compounds can have intrinsic biological activity and also constitute the structural feature of many biologically active compounds[1]. These compounds have also been found broadly in application materials chemistry[2]. The synthesis of pyrrole derivatives is an important area of heterocyclic chemistry due to the fact that many pyrrole derivatives are subunits of natural products, pharmaceutical agents such as antiinflammatory, analgesic and antirheumatic drugs, dyes and polymers[3]. They have been proven to display antibacterial, antiviral, antiinflammatory and antioxidant activities and to inhibit cytokine-mediated diseases[4]. Despite their importance from a pharmacological, industrial and synthetic point of view, comparatively few methods for their synthesis have been reported[5]. Such as Hantzsch[6], Knorr[7] and aza-Witting reactions[8], the Paal-Knorr[9] reaction is one of the simplest methods for the synthesis of *N*-substituted pyrroles. Many catalysts have been used to promote the Paal-Knorr reaction such as Ti(OiPr$_4$)[10], Al_2O_3[11], Bi(NO_3)$_3$[12], Bi(OTf)$_3$[13], Sc(OTf)$_3$[14] *etc.*[15].

In addition, there was a continuing interest in metal complexes of Schiff bases. Because of the presence of both hard nitrogen or oxygen and soft sulphur donor atoms in the backbones of these ligands, they readily coordinated with a wide range of transition metal ions yielding stable and intensely coloured metal complexes[16,17]. Schiff base complexes have been employed as a catalysts for many reactions and as biomolecules models in understanding the structure of biomolecules and biological process[18]. Transition metal complexes of Schiff bases are important, some of which were shown to exhibit interesting physical and chemical properties[16,17]. Transition metal complex having oxygen and nitrogen donor Schiff bases possess unusual configuration, structural ability and are sensitive to molecular environment. The environment around the metal center "as coordination ligands and their donor groups" is the key factor for metalloproteins to carry out specific physiological functions[19]. Many reports were available for the preparation and properties of model copper complexes which mimicked copper-containing metalloproteins such as hemocyanine and tyrosinase[20,21].

In the present paper, novel metal complexes derived from 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)aniline, (dmpyph) and 1,1'-(1,2-phenylene)-*bis*(2,5-dimethyl-1H-pyrrole) (tmpyph) were reported. Copper(II), nickel(II) and Co(III) complexes were prepared and characterized by elemental analyses, magnetic susceptibilities, IR, UV-VIS, mass spectral studies. The free ligand and metal complexes were tested for bacteria and the free ligands and copper(II) complexes had antibacterial activity against *S. aureus* and *M. smegmatise* was observed.

EXPERIMENTAL

^1H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer. $CDCl_3$ and DMSO-D_6 were used as solvent. Chemical shifts (δ) were reported in ppm relative to tetramethylsilane, using the solvent signal as an internal reference. Elemental analyses (C, H, N and S contents) were performed on a Costech 4010 CHNS elemental analyzer and metal contents were estimated spectrophotometrically. IR spectra were recorded on an ATI Unicam Matson 1000 Model FTIR spectrophotometer and UV/VIS spectra on an ATI Unicam UV2 Model UV/VIS spectrophotometer. Mass spectra [ESI] were recorded on micromass quanto LC-MS/MS spectrophotometer. Room temperature magnetic susceptibility measurements were done on a PAR model 155 vibrating sample magnetometer. All chemicals were of the highest quality available, obtained from local suppliers and used as received.

General Procedure for the unsymmetrical and symmetrical pyrroles (1, 2): Here, the synthesized materials are in a simple way by us as below and for the preparation of metal complexes were synthesized. 1,2-Phenylenediamine (1 mmol) and 2,5-hexandione (1 mmol for unsymmetrical pyrroles or 2 mmol for symmetrical pyrroles) were dissolved in 50 mL MeOH, then five drops of conc. HCl were added into the round bottom flask equipped with a magnetic stirrer and the mixture was refluxed under nitrogen atmosphere, for 24 h with vigorous stirring. After the reaction, the methanol was evaporated. Then, the oily residue was dissolved in diethyl ether (50 mL) and filtered and ether solution was left for crystallization under room temperature. The crystallized pale brown solid in diethyl ether were filtered and dried over P_4O_{10}.

Anal. calc. for $C_{12}H_{14}N_2$ (dmpyph): C, 77.40; H, 7.60; N, 15.04; found C, 77.55; H, 7.65; N, 15.10. Yield 55 %, m.p. = 75 ºC. (Sub. decomp.) Ms: (ESI) m/z = 184 $[M-2]^+$ selected IR; ν_{max}/cm^{-1} $\nu(NH_2)$: 3468-3366; $\nu(C-H_{arom})$: 3038; $\nu(C-H_{alkyl})$: 2919; $\nu(C=N)$: 1616; $\nu(C-N)$: 1399.

Anal. calcd. for $C_{18}H_{20}N_2$ (tmpyph): C, 81.78; H, 7.63; N, 10.60; found C, 81.70; H, 7.65; N, 10.54. Yield 60 %, m.p. = 132 ºC. Ms: (ESI) m/z = 263 $[M-1]^+$, 264 $[M]^+$, 265 $[M+1]^+$. Selected IR: ν_{max}/cm^{-1} $\nu(C-H_{arom})$; $\nu(C-H_{alkyl})$: 3109, 2920; $\nu(C=N)$: 1623; $\nu(C-N)$: 1393.

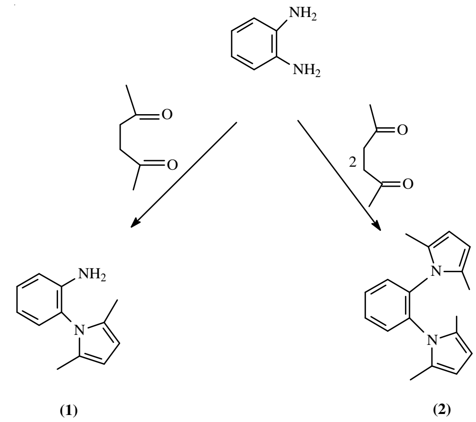
Synthesis of the complexes: Methanolic solution (20 mL) of $M(ClO_4)_2.6H_2O$ (here, M = Cu, Ni and Co, 1 mmol) was added to the solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-aniline (dmpyph) and/or 1,1'-(1,2-phenylene)-*bis*(2,5-dimethyl-1*H*-pyrrole) (tmpyph) (2 mmol) in 20 mL with constant stirring for 2 h then refluxed for 4 h. The precipitate was collected and filtered off, washed with ethanol and then dried diethyl ether and dried over fused calcium chloride *in vacuo*.

Antimicrobial activity assessment: All test microorganisms were obtained from the Hifzissihha Institute of Refik Saydam (Ankara, Turkey) and were as follows: *Escherichia coli* ATCC 25922, *Enterobacter aeroginosa* ATCC 13048, *Yersinia pseudotuberculosis* ATCC 911, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Listeria monositogenes* ATCC 43251, *Bacillus cereus* 709 ROMA, *Mycobacterium smegmatis* ATCC607, *Candida albicans* ATCC 60193, *Candida tropicalis* ATCC 13803 and *Saccharomyces cerevisiae* RSKK 251. All the newly synthesized compounds were dissolved in dimethylsulphoxide (DMSO) to prepare chemicals stock solution.

Agar well diffusion method: Simple susceptibility screening test using agar-well diffusion method[22] as adapted earlier[23] was used. Each bacterium was suspended in Mueller Hinton (MH) (Difco, Detroit, MI) broth. The yeast like fungi was suspended in yeast extracts broth. Then the microorganisms were diluted approximately 10^6 colony forming unit (cfu) per mL. For yeast like fungi, Sabouraud Dextrose Agar (SDA) (Difco, Detriot, MI) were used. Middlebrook 7H10 agar medium (Becton, Dickinson Microbiology Systems) was used for *M. smegmatis*. They were "flood-inoculated" onto the surface of MH and SD agars and then dried. Five-millimeter diameter wells were cut from the agar using a sterile cork-borer and 500 µg/50 µL of the extract substances were delivered into the wells. The plates were incubated for 18 h at 35 ºC. The *Mycobacterium smegmatis* was grown for 3 to 5 days on Middlebrook 7H10 agar plates at 35 ºC. Antimicrobial activity was evaluated by measuring the zone of inhibition against the test organism. Ampicillin (10 µg), streptomycine (10 µg) and fluconazole (5 µg) were standard drugs. Dimethyl sulphoxide was used as control solvent.

RESULTS AND DISCUSSION

Mononuclear Cu(II), Ni(II) and Co(II) complexes of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)aniline, (dmpyph) and/or 1,1'-(1,2-phenylene)-*bis*(2,5-dimethyl-1*H*-pyrrole) (tmpyph) was prepared and characterized (**Scheme-I**). Metal complexes were verified by elemental analyses and magnetic moment), UV-VIS and IR data (Tables 1-3). In the proposed structures of the ligands N_2 units were available for the complexation of metal ions. The corresponding metal complexes (**3-8**) have been prepared with a reaction of the ligand-metal perchlorate salts mixture in ethanol.



Scheme-I. Preparation of ligands

NMR spectra: In the ^1H NMR spectra of a $CDCl_3$ solution of compound **1** was seen singlet at 1.98 ppm (CH_3, 6H), singlet at 5.93 ppm (pyrrole, 2H), doublet at 6.81 ppm (phenyl, 2H), multiplet at 7.17 ppm (phenyl, 2H) and broad singlet at 3.45 ppm corresponding to the $-NH_2$ proton resonance, this signal disappeared on deuterium exchange. (Fig. 1). The ^1H NMR spectra of a $CDCl_3$ solution of compound **2** shows singlets at 1.89 ppm (12H), singlets at 5.83 ppm (4H), multiplet at 7.30 ppm (2H), multiplet at 7.45 ppm (2H), corresponding to the

TABLE-1
ANALYTICAL DATA, COLOUR, AND PERCENTAGE YIELD OF THE LIGANDS AND ITS METAL COMPLEXES

Compounds	Colour	Yield (%)	Analysis (%) found (calcd.)			
			C	H	N	M
dmpyph (1)	Pale pink	55	77.55 (77.40)	7.65 (7.60)	15.10 (15.04)	-
tmpyph (2)	Pale brown	60	81.70 (81.78)	7.65 (7.63)	10.54 (10.60)	-
Complex **3**	Black	90	45.35 (45.39)	4.44 (4.41)	8.90 (8.82)	10.05 (10.00)
Complex **4**	Blue	60	45.76 (45.75)	4.42 (4.48)	8.95 (8.90)	9.37 (9.30)
Complex **5**	Fume	50	53.33 (53.25)	5.85 (5.90)	10.05 (9.93)	10.50 (10.45)
Complex **6**	Dark pink	51	60.85 (60.92)	5.95 (5.96)	7.86 (7.90)	9.00 (8.95)
Complex **7**	Cream	55	73.75 (73.61)	6.88 (6.86)	9.50 (9.55)	10.03 (10.00)
Complex **8**	Brown purple	85	73.55 (73.59)	6.83 (6.81)	9.60 (9.54)	10.08 (10.03)

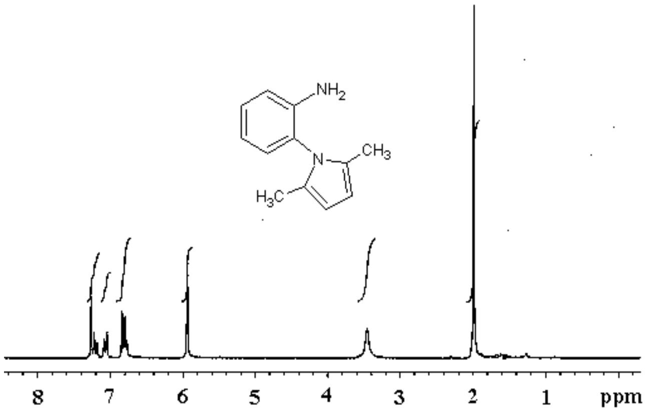
TABLE-2
CHARACTERISTIC IR BANDS (cm^{-1}) OF THE LIGAND AND ITS METAL COMPLEXES

Compounds	ν(N-H)	ν(C-H)$_{ar}$	ν(C=N)	ν(M-N)	ν(M-H$_2$O)	(ClO$_4^-$)
dmpyph (1)	3468-3366(d)	3038	1616	-	-	-
tmpyph (2)		3109	1623	-	-	-
Complex **3**	3420-3368	3066	1618	450	-	1087, 1020
Complex **4**	3445, 3368	3038	1617	430	-	1088, 1021
Complex **5**	3467, 3413	3025	1617	445	3410, 520	1150, 1120, 1080, 1030, 624
Complex **6**	-	3107	1622	460	3406, 556	1146, 1113, 1083, 1023, 636
Complex **7**	-	3054	1623	475	-	1144, 1120, 627
Complex **8**	-	3099	1619	455	-	1140, 1120, 624

CH$_3$, pyrrole, phenyl and phenyl proton resonances, respectively. (Fig. 1). The ^{13}C NMR spectrum of dmpyph and tmpyph show nine and/or six different signal, respectivelly. In the ^{13}C NMR spectra, resonances were observed as expected which was also consistent with the formula. In the ^{1}H NMR spectra, integrated data are consistent with the formula of proposed compounds. The ^{1}H- and ^{13}C-NMR spectral data supports the proposed structure the pyrroles (**1** and **2**).

TABLE-3
MAGNETIC MOMENTS AND ELECTRONIC SPECTRAL BANDS OF THE METAL COMPLEXES (DMSO)

Compounds	μ_{eff} (B.M.)	Electronic bands (nm)
dmpyph (1)	-	270, 305
tmphph (2)	-	260, 275, 291, 304
Complex **3**	1.83	270, 340, 466, 626, 677
Complex **4**	2.80	260, 292, 325, 414, 626, 690
Complex **5**	4.65	275, 350, 441, 624, 685
Complex **6**	1.76	253, 363, 379, 499, 630
Complex **7**	2.70	284, 299, 345, 440, 479
Complex **8**	4.20	284, 305, 330, 467, 520



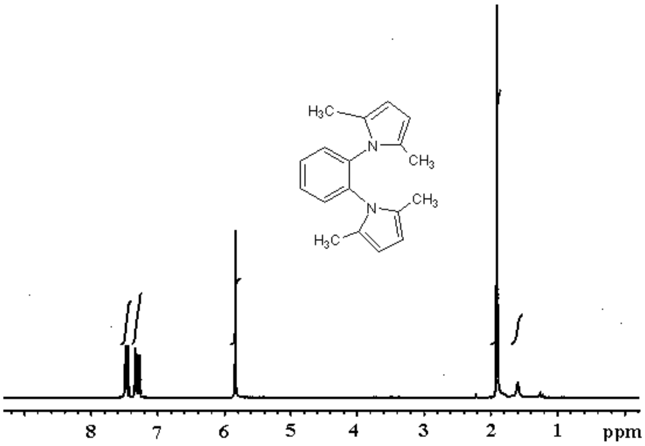
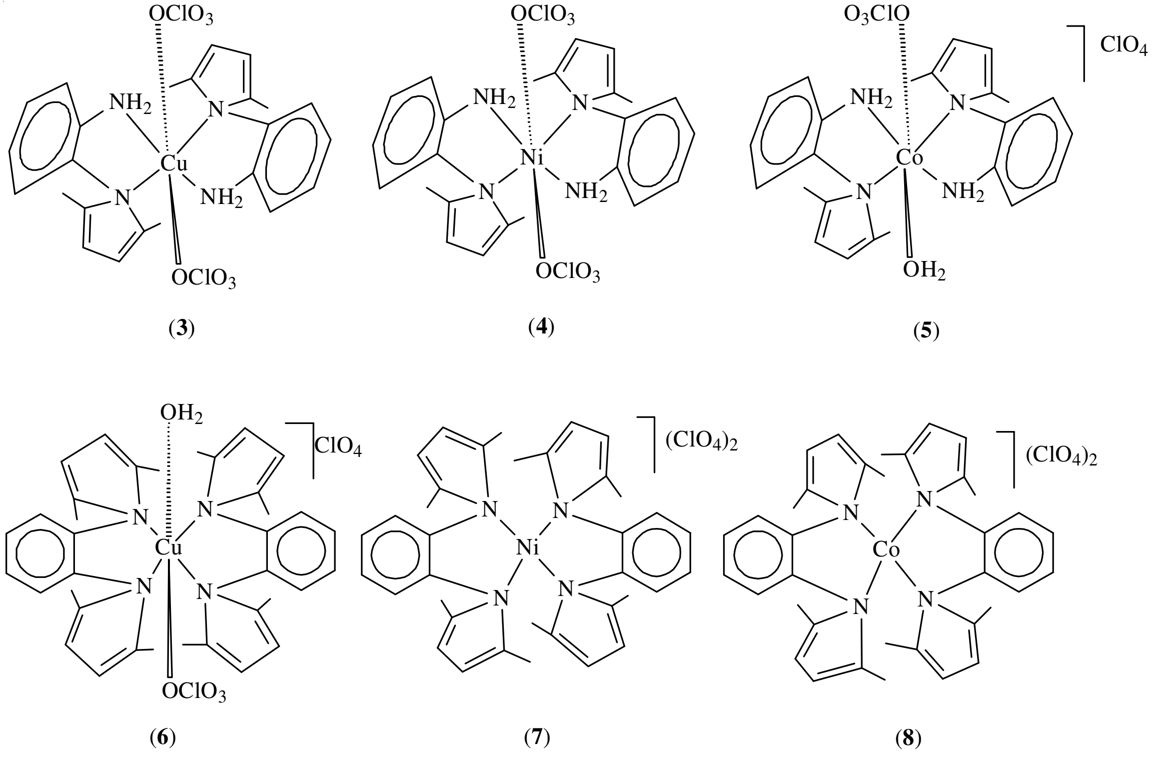


Fig. 1. ^{1}H NMR spectra of the compounds **1** and **2**, in CDCl$_3$

Mass spectra: The mass spectra of compounds **1** and **2** exhibit molecular ion peaks at m/z = 184 [M-2]$^+$ and/or 264 M$^+$ indicating formation of the **1-2** respectively. The molecular ion peak appeared (m/z, ESI) at 636.6 [M+2]$^+$ for the [Cu(dmpyph)$_2$(ClO$_4$)$_2$], at 629 [M]$^+$ for [Ni(dmpyph)$_2$(ClO$_4$)$_2$], at 567 [M+4]$^+$ for the [Co(dmpyph)$_2$(ClO$_4$)(H$_2$O)], at 711 [M+1]$^+$ for the [Cu(tmpyph)$_2$(ClO$_4$) (H$_2$O)], at 585 [M-H$^+$]$^+$ for [Ni(tmpyph)$_2$], at 587 [M-H$^+$]$^+$ for the [Co(tmpyph)$_2$]. The mass spectra of the compounds showed the formation of the metal complexes.

Infrared spectra: Characteristic IR bands (cm^{-1}) of the ligands (**1** and **2**) and its metal complexes were given in Table -2. In the IR spectrum compound **1**, the strong band was observed at 1616 cm^{-1} ν(C=N) vibration[22]. In ligands, bands at 2919 cm^{-1} may be assigned to ν(C-H$_{alkyl}$) vibration. The ligand exhibited ν(N-H) of primary amine in the region 3468-3366 cm^{-1}. The -C-H$_{arom}$ stretching bands were observed in the *ca.* 3038 cm^{-1} region. In the IR spectrum compound **2**, the strong band at 1623 cm^{-1} may be assigned to ν(C=N) vibration[24]. In



(**3**) (**4**) (**5**)

(**6**) (**7**) (**8**)

Fig. 2. Proposed structures for the metal complexes

the complexes, ν(C=N), ν(N-H) were shifted to lower or higher frequency by 5-10 cm^{-1}, suggesting coordination of metal *via* nitrogen of pyrrole. The metal complexes (**3-6**) show a doublet at *ca*. 1080-1020 cm^{-1}, due to splitting of the [$\nu(T_2)$] vibration into [$\nu_3(A)$] and [$\nu_3(E)$][25]. The presence of these bands shows that the perchlorate is coordinated in the complexes. In the complexes (**5, 8**) were observed to have bands *ca*. at 1150-1120 and 625 cm^{-1} featuring typical characteristics of uncoordinated perchlorates[26]. The strong and broad bond *ca*. at 3400 cm^{-1} indicate the presence of water molecule associated in the complexes (**5, 6**). In the 475-430 cm^{-1} region, bonds was attributed to ν(M-N). IR data confirm the binding of the copper(II), nickel(II) and cobalt(II) ions by N_2 donor groups for the by N_4 donor groups of ligands also support the tentative structure of the complexes (Fig. 2). The significant shifts in ν(C=N) and ν(N-H) upon complexetion are consistent with complex formation and support the concept of coordination of the ligand through the nitrogen.

Electronic spectra and magnetic moment: Electronic spectra of the complexes were recorded in DMSO (ε in L mol^{-1} cm^{-1}) at room temperature. The UV spectral data of the ligand and its complexes are given in Table-3. The aromatic band of the ligand at 265 -275 nm is attributed to benzene $\pi \rightarrow \pi^*$ transition. The band around 378 nm is due to the $n \rightarrow \pi^*$ transition of the non-bonding electrons present on the nitrogen of the azomethine group in the ligand[27]. Electronic spectra of Cu(II) complex(**3**) show bands at 677 (740), 626 (580) and 466 (350) nm assignable to a $^2E_g \rightarrow {}^2T_{2g}$ transition and charge transfer. Electronic spectral data coupled with detected magnetic moment of 1.83 B.M. suggests octahedral geometry[28]. Ni(II) complex (**4**) displays bands at 690(980), 626(615) and 414(345) nm assignable to $^3A_{2g} \rightarrow {}^3T_{2g}(F)$, $^3A_{2g} \rightarrow {}^3T_{1g}(F)$ and $^3A_{2g} \rightarrow {}^3T_{1g}(P)$, respectively. These electronic transitions along with magnetic moment 2.80 B.M. suggest octahedral geometry for Ni(II) complex[29]. The Co(II) complex (**5**) shows three bands at 685 (880), 624(525) and 441(390) nm assignable to $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$, $^4T_{1g}(F) \rightarrow {}^4A_{2g}$ and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ transitions, respectively. These transitions and observed magnetic moment of 4.65 B.M. indicate high spin octahedral complex[30]. Cu(II) complex (**6**) displays bands at 630(650), 499(530) and 379(370) nm assignable to a $^2E_g \rightarrow {}^2T_{2g}$ transition and charge transfer. Electronic spectral data coupled with detected magnetic moment of 1.76 B.M. suggests octahedral geometry. The nickel(II) and cobalt(II) complexes (**7, 8**) show less intense shoulders at *ca*. 480-520 nm (ε = 140-160 L mol^{-1} cm^{-1}), assigned as *d-d* transitions of the metal ions due to the $^3A_2 \rightarrow {}^3T_2$ (F) for Ni(II) complex transitions, $^4A_2 \rightarrow {}^4T_1$ (P) for Co(II) complex. These electronic transitions along with magnetic moment 2.70- 4.20 B.M. suggest tetrahedral geometry for Ni(II) and Co(II) complex respectively[25]. All the complexes show an intense band at *ca*. 330-380 nm ($\varepsilon = 1.30 - 3.25 \times 10^3$ L mol^{-1} cm^{-1}) assigned to the $n \rightarrow \pi^*$ transition associated with azomethine[27]. The spectra of all the complexes show an intense band at *ca*. 414-467nm ($\varepsilon = 2.1\text{-}2.4 \times 10^3$ L mol^{-1} cm^{-1}), which can be assigned to charge transfer (C-T) transitions[27].

Antimicrobial activity: The free ligand and copper(II) and nickel(II) and cobalt(II) complexes (**3-8**) were tested against morphology of bacteria, a series of the gram negative bacilli (*E. coli, E. aeroginosa, Y. pseudotuberculosis, P. aeruginosa*), gram positive coccus (*S. aureus, E. faecalis*), gram positive bacilli (*L. monocytogenes*), gram-positive spore-forming bacteria (*B. cereus*) and *M. smegmatis*, antituberculosis activity. The free ligand and metal complexes were tested for bacteria, only ligand and copper(II) complexes had antibacterial activity against *S. aureus* and *M. smegmatise* observed. The free ligand and metal complexes for antifungal activity against

TABLE-4
SCREENING FOR ANTIMICROBIAL ACTIVITY OF THE COMPOUNDS (100 µL)

Compounds	Stoc. (µg mL)	Microorganisms and inhibition zone (mm)											
		Ec	Ea	Yp	Pa	Sa	Ef	Li	Bc	Ms	Ca	Ct	Sc
dmpyph (1)	40	-	-	-	-	5	-	-	-	9	-	-	20
tmphph (2)	50	-	-	-	-	6	-	-	-	12	-	-	20
Complex **3**	165	-	-	-	-	14	-	-	-	-	-	-	-
Complex **4**	1651	-	-	-	-	8	-	-	-	-	-	-	-
Complex **5**	125	-	-	-	-	8	-	-	-	-	-	-	-
Complex **6**	175	-	-	-	-	12	-	-	-	11	-	-	-
Complex **7**	150	-	-	-	-	10	-	-	-	-	-	-	-
Complex **8**	150	-	-	-	-	9	-	-	-	-	-	-	-
Amp.	-	10	10	18	18	35	10	10	15	-	-	-	-
Str.	-	-	-	-	-	-	-	-	-	35	-	-	-
Flu	-	-	-	-	-	-	-	-	-	-	25	25	>25

Ec*: Escherichia coli* ATCC 25922, Ea: *Enterobacter aeroginosa* ATCC 13048 Yp: *Yersinia pseudotuberculosis* ATCC 911, Pa: *Pseudomonas aeruginosa* ATCC 43288, Sa: *Staphylococcus aureus* ATCC 25923, Ef: *Enterococcus faecalis* ATCC 29212, Li: *Listeria monocytogenes* ATCC 43251, Bc: *Bacillus cereus* 702 Roma, Ms: *Mycobacterium smegmatis* ATCC607, Ca: *Candida albicans* ATCC 60193 Ct: *Candida tropicalis* ATCC 13803, Sc: *Saccharomyces cerevisiae* RSKK 251, Amp.: Ampicillin, Str.: Streptomycin, Flu.: Fluconazole, (—): no activity

C. albicans, C. tropicalis and *S. cerevisiae* were tested, but no antifungal activity had been observed against yeast like fungi. (Table-4). Free ligands (**1, 2**), were found to have activity against *Saccharomyces cerevisiae* (Sc).

Conclusion

In the present study, we demonstrated the preparation of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)aniline (dmpyph, **1**), ligand providing N_2 donor array moiety and their three mononuclear copper(II) nickel(II) and cobalt(II) complexes. Metal complexes were paramagnetic. The metal ion was complexed with nitrogen atoms of ligand, water molecules and/or perchlorate ions. Elemental analyses results were found to be in good agreement(± 0.3 %) with the calculated values. All of the data obtained from spectral data, supported the structural properties of ligands and its Cu(II), Ni(II) and Co(II) metal complexes. The synthesized ligand and metal complexes (**3-8**) showed antibacterial and antifungal properties. In comparison, the copper(II) complex showed more activity against either bacterial or fungal strains, this introducing a novel class of metal-based bactericidal and fungicidal agents. The free ligand and copper(II), nickel(II) and cobalt(II) complexes showed antimicrobial activity against only *S. aureus* but no antifungal activity was observed against yeast like fungi. Among them, copper complex and free ligand showed a narrow range of inhibitory activity against *Mycobacterium smegmatis*. Free ligands (**1, 2**), were found to have activity against *Saccharomyces cerevisiae* (Sc).

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