WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 7, Issue 03, 1602-1610. Research Article ISSN 2277–7105

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITIES OF CO(II), NI(II) AND CU(II) METAL COMPLEXES OF THE PYRAZOLE DERIVATIVES AS LIGANDS

Ambika Bhusanage[1] and Nirdosh Patil[*]

[1]Godutai Engineering College for Women, Vidya Nagar, Kalaburagi, Karanataka, India.
[*]Appa Institute of Engineering and Technology, Vidya Nagar, Kalaburagi, Karanataka, India.

Article Received on
20 Dec. 2017,
Revised on 10 Jan. 2018,
Accepted on 31 Jan. 2018
DOI: 10.20959/wjpr20183-10991

***Corresponding Author**
Dr. Nirdosh Patil
Appa Institute of Engineering and Technology, Vidya Nagar, Kalaburagi, Karanataka, India.

ABSTRACT

The Co(II), Ni(II) and Cu(II) metal complexes has synthesized by 2-(4, 5dihydro-1, 5-diphenyl-1H-pyrazol-3-yl) phenol (HL_1), 2-(4, 5-dihydro-5-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl) phenol(HL_2) and 2-(5-(4-chlorophenyl)-4, 5-dihydro-1-phenyl-1H-pyrazol-3-yl) phenol (HL_3). These complexes were characterized by elemental analyses, conductance measurement, magnetic susceptibility measurement, IR, ^{1}HNMR, ESR, and electronic spectral studies. On the basis of elemental analyses, magnetic and spectral studies octahedral geometry was assigned for these complexes. The complexes have been screened in vitro for their possible antimicrobial activity.

KEYWORDS: Complexes, conductance, magnetic, antimicrobial, pyrazoline.

INTRODUCTION

Pyrazoles have received a considerable interest in the field of drug discovery and therefore pyrazole ring constitutes a relevant synthetic target in pharmaceutical industry.[1-2] Celecoxib use in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms, and to reduce numbers of colon and rectum polyps in patients with familial adenomatous polyposis.[3,4] Lonazolac is a non-steroidal antiinflammatory drug.[5-7] Tepoxalin is a non-steroidal antiinflammatory drug approved for veterinary use in the United States and the European Union.[8-10] The literature survey revealed that numerous N-substituted pyrazoles have been synthesized and exhibited wide biological activities. N-aryl pyrazoles with withdrawing electron groups can be effectively utilized as insecticides[11]

antiinflammatory[12] analgesic[13] and cannabinoid type-1 (CB1) receptor ligands.[14] On the basis of literature survey, author has synthesized, characterized and microbial activity study of Co(II), Ni(II) and Cu(II) metal complexes with 2-(4, 5dihydro-1, 5-diphenyl-1H-pyrazol-3-yl) phenol (HL_1), 2-(4, 5-dihydro-5-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl) phenol(HL_2) and 2-(5-(4-chlorophenyl)-4, 5-dihydro-1-phenyl-1H-pyrazol-3-yl) phenol (HL_3) was carried out.

MATERIALS AND METHODS

All the chemicals and solvents used were of AR grade, were obtained from Sisco-chem. Industries. The metal salts were purchased from commercial sources. Metal contents were estimated using standard methods.[15] IR spectra of the compounds were recorded on a Beckman IR-20 spectrophotometer in the region 4000-250cm^{-1} ^1H NMR spectra were recorded on a Perkin-Elmer 90 MHz spectrometer. The electronic spectra were recorded on an Elico SL 159 spectrophotometer in the 200-1000nm ranges in DMF solution (10^{-3}). Elemental analyses were obtained HERAEUS C, H, N-O rapid analyzer. E.S.R measurements were carried out on a VARAN E-109 GHz. The experiment was carried by taking DPPH as the reference with the field set at 3200 Gauss. Magnetic susceptibilities were determined by the faraday method using a Model 300 Lewis Coil Force Magnetometer of one Tesla field strength at room temperature. The instrument being calibrated with Hg [Co $(SCN)_4$].[16-17] The medium was prepared as per the instructions of the manufacturer of dry Mueller Hinton agar powder (Hi-Media). The test ligand and their metal complexes were dissolved in dimethylsulphoxide (DMSO) at a concentration of 100µg/ml. Ciproflaxacin (100µg/ml) in DMSO was used as reference standard for antibacterial and flucanozole (100µg/ml) in DMSO was used as reference standard for antifungal activity.

General procedure for preparation of 2-(4, 5dihydro-1, 5-diaryl-1H-pyrazol-3-yl) phenol derivatives HL_1, HL_2, and HL_3

To a solution of 2'-hydroxy chalcones 18 (0.02mol) in 30 ml of methanol was added phenyl hydrazine (0.021mol) and refluxed for 6-9 h. After cooling of mixture of reaction, the product was precipitated and filtered. The crud product was crystallized from methanol. The products obtained are 2-(4, 5dihydro-1, 5-diphenyl-1H-pyrazol-3-yl) phenol (HL_1), 2-(4, 5-dihydro-5-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl) phenol (HL_2) and 2-(5-(4-chlorophenyl)-4, 5-dihydro-1-phenyl-1H-pyrazol-3-yl) phenol (HL_3).

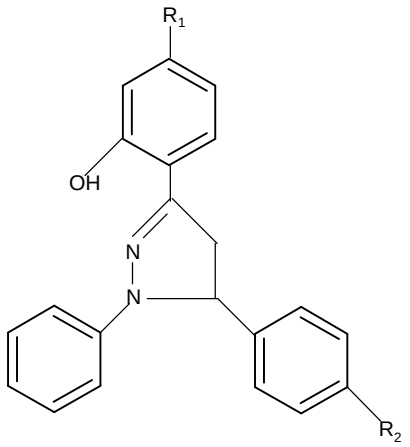


Fig 1: Structure of ligand derivatives.

Table-I: Physico-chemical data of 2-(4, 5-dihydro-1, 5-diaryl-1H-pyrazol-3-yl) phenol Derivatives.

Ligands	R_1	R_2	m.p ^{0}C	Yield (%)
HL_1	H	H	162-163	68
HL_2	H	OMe	167-168	68
HL_3	H	Cl	152-153	69

PREPARATION OF COMPLEXES

A warm ethanolic solution of metal salts (0.01M) were added to ethanolic solution 2-(4, 5dihydro-1, 5-diphenyl-1H-pyrazol-3-yl) phenol (HL_1), / 2-(4, 5-dihydro-5-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl) phenol(HL_2) / 2-(5-(4-chlorophenyl)-4, 5-dihydro-1-phenyl-1H-pyrazol-3-yl) phenol (HL_3) of (0.02 M) in about 25ml of ethanol. The resulting solution was refluxed for about 6-8 hour. The complexes thus formed were suction filtered and washed with alcohol and dried in vacuum over fused $CaCl_2$.

RESULTS AND DISCUSSION

The analytical and physical data of the complexes and their ligands are given in Table-2. The results of elemental analyses of the complexes correspond to stoichiometry for metal:ligand in 1:2 molar ratios. Molar conductance measurements of these complexes in DMF correspond to non electrolytes. IR spectra of ligand show a broad medium intensity band in the region 3236-3132cm^{-1} due to phenolic-OH[17-18], in complexes these bands were not observed due to the coordination through O via deprotonation of phenolic-OH. The band in the region 1601-1596cm^{-1}is assigned to C=N group of pyrazoline ring, the band due to $\nu_{(C=N)}$ appears in the region of 1615-1609cm^{-1} as a high intensity band in the complexes, indicating that the C=N group is involved in coordination of metal ions through nitrogen. In all the complexes, a

broad absorption band appears due to $\nu_{(H2O)}$ in the region 2930-2910 cm^{-1}, this indicates us involvement of water molecules in the complexes. The ^1H NMR spectra of the 2-(4, 5dihydro-1, 5-diphenyl-1H-pyrazol-3-yl) phenol (HL_1), / 2-(4, 5-dihydro-5-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-3-yl) phenol(HL_2) / 2-(5-(4-chlorophenyl)-4, 5-dihydro-1-phenyl-1H-pyrazol-3-yl) phenol (HL_3) provide additional support to the structure of ligands.

Table II: Analytical, magnetic and conductance data of Co(II), Ni(II) and Cu(II) complexes with ligands HL_1, HL_2, and HL_3

Complexes / Abbreviations	Found / (Calculated) %					μ_{eff} (BM)	Molar Cond λ_m
	M	C	H	N	Cl		mho cm^2 mol^{-1}
HL_1 $C_{21}H_{17}N_2O$	--	80.22 (80.25)	5.46 (5.41)	8.85 (8.90)	--	--	--
Co($C_{21}H_{16}N_2O)_2$ $Co(HL_1)_2$	8.66 (8.60)	73.65 (73.58)	4.70 (4.67)	8.22 (8.17)	--	4.95	34.90
Ni($C_{21}H_{16}N_2O)_2$ $Ni(HL_1)_2$	8.62 (8.57)	73.55 (73.61)	4.62 (4.67)	8.21 (8.18)	--	3.15	29.40
Cu($C_{21}H_{16}N_2O)_2$ $Cu(HL_1)_2$	9.27 (9.21)	73.15 (73.09)	4.60 (4.64)	8.08 (8.12)		1.90	25.00
HL_2 $C_{22}H_{19}N_2O_2$	--	75.90 (75.86)	6.22 (6.28)	8.10 (8.04)	--	--	--
Co($C_{22}H_{19}N_2O_2)_2$ $Co(HL_2)_2$	7.95 (7.91)	70.92 (70.87)	5.05 (5.10)	7.55 (7.51)	--	4.98	28.00
Ni($C_{22}H_{19}N_2O_2)_2$ $Ni(HL_2)_2$	7.94 (7.88)	70.85 (70.90)	5.16 (5.10)	7.56 (7.52)	--	3.28	27.00
Cu($C_{22}H_{19}N_2O_2)_2$ $Cu(HL_2)_2$	8.55 (8.47)	70.38 (70.44)	5.11 (5.07)	7.52 (7.47)	--	1.93	28.90
HL_3 $C_{21}H_{16}N_2OCl$	--	80.31 (80.25)	4.72 (4.65)	8.10 (8.04)	18.15 (10.20)	--	--
Co($C_{21}H_{15}N_2OCl)_2$ $Co(HL_3)_2$	7.86 (7.82)	66.97 (66.93)	34.02 (3.98)	7.50 (7.44)	9.38 (9.43)	5.15	33.20
Ni($C_{21}H_{15}N_2OCl)_2$ $Ni(HL_3)_2$	7.85 (7.79)	66.90 (66.95)	4.05 (3.99)	7.36 (7.43)	9.45 (9.43)	3.40	29.32
Cu($C_{21}H_{15}N_2OCl)_2$ $Cu(HL_3)_2$	8.42 (8.38)	66.57 (66.53)	4.03 (3.96)	7.43 (7.39)	9.32 (9.37)	2.07	35.55

Note: The values shown in the parenthesis are calculated one

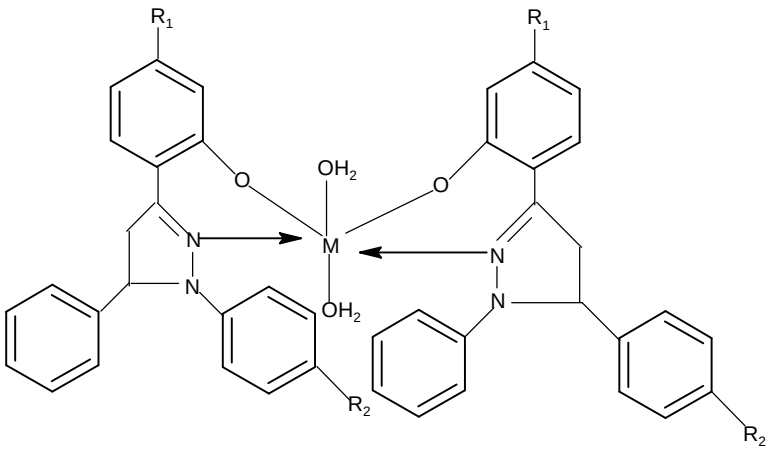
The 1H NMR spectra of pyrazole chalcones revealed doublets at δ 7.50 and 8.10 ppm assigned to the H-6 and H-7 protons respectively (for 9d), with J = 15.6 Hz in agreement with E configuration (trans configuration). The phenolic proton (2'-OH) was observed as singlet at δ 10–12.85 ppm, while other aromatic and aliphatic protons were showed at expected

regions. In the complexes, the multiplates observed between 6.55-7.92δ(ppm) due to aromatic protons. The proton signal at δ 10–12.85 ppm, due to phenolic-OH has disappeared in the complexes, suggesting that the –OH (phenolic) has deprotoneted on complexation, because of coordination through oxygen of phenolic-OH and nitrogen of (C=N) group of pyrazole ring to the metal ions respectively. In the present investigation the observed magnetic moment values for Co(II) complexes fall in the range 4.95-5.15 BM which are representing the octahedral geometry for the present Co(II) complexes. These values lie in the range expected for μ_s and μ_{S+L}. This is due to the partial quenching of orbital contribution to the magnetic moment since Co(II) ion posses $^4T_{1g}$ ground state in its octahedral environment. The magnetic moment values for Ni(II) complexes fall in the range 3.15-3.40 BM which are well within the expected range for octahedral geometry around the central metal ion. Hiremath et. Al[19] have reported the magnetic moment values in the region 2.01 BM for Cu(II) complexes of distorted octahedral geometry, and Cu(II) complexes with magnetic moment values falling in the range 1.90-2.07 BM for distorted octahedral geometry. In the present work the observed values of magnetic moments are in the range 1.85-2.20 BM. These values suggest the distorted octahedral geometry around Cu(II) ion.

The electrnic spectra of cobalt(II) complexes show the bands around 9,000, 16800 and 20,000 cm^{-1} which are assigned to the transitions $^4T_{1g}(F) \rightarrow {}^4T_{2g}$, $^4T_{1g}(F) \rightarrow {}^4A_{2g}$ and $^4T_{1g}(F) \rightarrow {}^4T_{1g}(P)$ respectively. A strong charge transfer band is observed at 25000 cm^{-1}, these data suggest an octahedral geometry. The electronic spectra of the Ni(II) complexes around 10400, 16800 and 26000cm^{-1} due to $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$, $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ and $^3A_{2g}(P) \rightarrow {}^3T_{1g}(P)$, respectively, in an octahedral geometry. The calculated values of ligand field parameters Dq=1042cm^{-1}, B^1 = 734.33 cm^{-1}, β = 0.706, β% = 27.40%, λ = 154.26, ν_2/ν_1 = 1.52 and L.F.S.E. = 14.973 kJ mol^{-1} are in agreement with octahedral geometry. The nephelauxetic parameter, β is readily obtained using the relation β=B(complex)/B(free ion), indicate that complex under study have appreciable covalent character. In the present study three absorption bands at 12885, 16940 and 26028 cm^{-1} corresponding to $^2B_{1g} \rightarrow {}^2A_{2g}$ (ν_1), $^2B_{1g} \rightarrow {}^2B_{2g}$ (ν_2) and $^2B_{1g} \rightarrow {}^2E_{1g}$ (ν_3) transitions respectively, for all copper complexes, indication of an octahedral geometry around Cu(II) ion. The ESR spectra of the copper complex $Cu(HL_2)_2$ as polycrystalline sample have been recorded at room temperature, (ESR chart was calibrated with DPPH). The observed g values of the $Cu(HL_2)_2$ complex as follows $g_{\|}$ =2.09, $g_{\perp}$ =2.04, g_e =2.0036 and G = 2.25. The isotropic g values have been calculated Kneubuhl`s

methods and methods reported earlier. The $g_{||}$ value indicate that the, complex is covalent in nature $g_{||} > g_{\perp}$, it is evident that the unpaired electron lies predominantly in the d_{x2-y2} orbital of Cu(II) ion. The $G = (g_{||}-2)/(g_{\perp}-2)$ which measures the exchange interaction between copper centers in a polycrystalline solid has been calculated. According to the Hathaway[21] if the G value is greater than 4, the exchange interaction is negligible, while a value of G less than 4 indicates a considerable exchange in the solid complexes. Thus G value is 2.25, which less than 4, indicating the exchange interaction of the copper centers.

On the basis of analytical data, electronic spectra, magnetic susceptibility measurements, IR, NMR, ESR, spectral data octahedral geometry has been assigned to Cobalt(II), Nickel(II) and Copper (II) complexes.



M = Co(II), Ni(II) and Cu(II)

Fig2: Structure of complexes.

ANTIMICROBIAL ACTIVITY

The antimicrobial activity of the ligands HL_1 HL_2 and HL_3 and their metal complexes were determined by agar cup-plate method.[22] The antibacterial activity against *Escherichia coli* and *Pseudomonas aeroginosa* and antifungal activity against *Aspergillus niger* and *Candida albicans*, were screened by the ligands and their metal complexes. The solvent control (only DMSO) was also maintained throughout the experiment. The zones of inhibition are reported in Table-III.

Table-III: Antibacterial and antifungal activity data of the ligand and their complexes (Zone of inhibition in mm)

Ligands/ Complexes	Antibacterial		Antifungal	
	E.coli	*P.aeroginosa*	*A.niger*	*C.albicans*
HL_1	12	14	11	09
$Co(HL_1)_2$	14	17	13	12
$Ni(HL_1)_2$	15	18	14	12
$Cu(HL_1)_2$	20	19	21	20
HL_2	13	14	13	12
$Co(HL_2)_2$	15	14	12	13
$Ni(HL_2)_2$	14	12	13	14
$Cu(HL_2)_2$	22	20	22	19
HL_3	14	13	12	14
$Co(HL_3)_2$	13	12	11	13
$Ni(HL_3)_2$	12	13	14	12
$Cu(HL_3)_2$	19	21	22	19
Ciproflaxacin	27	30	__	__
Flucanozole	__	__	24	23
DMSO	00	00	00	00

From the Table-III, it is clear that the ligands HL_1, HL_2 and HL_3 show moderate activity against all the antibacterial and antifungal microorganisms. But all the metal complexes show moderate to high active against all the organisms. Among the complexes, copper complex $Cu(HL_1)_2$, $Cu(HL_2)_2$ and $Cu(HL_3)_2$ was found to be most active against all the microbes tested, as compared to their ligands, which due to the faster diffusion of the Cu(II) complex.[23] Even though the test compounds are less active with reference to the standard drug *ciproflaxacin* and *flucanozole*, the data reported in this article may be a helpful guide for the medicinal chemists who are working in the area.

CONCLUSION

In the present work pyrazole based compartmental ligand and its metal complexes have been studied. The compound behaved as a bidentate ligands coordinating through depronated phenoxo group and nitrogen atom of pyrazole group. The ligand was so designed that it can secure metal ions in the close proximity in the compartmental site of the ligand and coordinated through bridging phenolate ion, nitrogen atom of pyrazole group. -N functions respectively. On the basis of analytical data, electronic spectra, magnetic susceptibility measurements, IR, NMR, ESR, spectral data octahedral geometry has been assigned to Cobalt(II), Nickel(II) and Copper (II) complexes. Among the complexes, copper complex $Cu(HL_1)_2$, $Cu(HL_2)_2$ and $Cu(HL_3)_2$ was found to be most active against all the microbes

tested, as compared to their ligands, which due to the faster diffusion of the Cu(II) complexes. The results of the preliminary antimicrobial and the antifungal activities are shown in Table-III, it is clear that the ligands HL_1, HL_2 and HL_3 show moderate activity against all the antibacterial and antifungal microorganisms. But all the metal complexes show moderate to high active against all the organisms.

ACKNOWLEDGEMENTS

The authors are thankful to Poojya Dr. Sharanbasvappa Apaa, President Sharanbasveshwar Vidya vardhak Sangha, Kalaburagi, Prof. Dr. V D. Mytri, Principal, Dr. Anilkumar Bidve, Dean, Appa Institute of Engineering and Technology, Kalaburagi, Karnataka, for encouragement during the process of carrying out this work.

REFERENCES

1. Wiley RH., The Chemistry of Heterocyclic Chemistry: Pyrazoles, Pyrazolines, pyrazolidines, Indazoles and Condensed Ring; Behr LC., Fusco R., Jarboe CH., Interscience Publishers: John Wiley & Sons, 1967; 3-20.
2. Ring Nitrogen and Key Biomolecules E.G. Brown press: Kluwer Academic publishers 1987.
3. Habeeb AG., Rao PNP, Knaus EE ., J. Med. Chem, 2001; 44: 3039.
4. Szabo G. Fischer J., Kis-Varga, A. Gyires KJ., Med. Chem, 2008; 51: 142.
5. Rainer G., Kruger U Klemm K., Arzneimittel-Forschung, 1981; 31: 649.
6. Goertz R., Appelboom, T. Int. Tissue React.i, 1985; 7: 263.
7. Vinge E., Bjorkman SB., Acta Pharmacol. Toxicol, ,1986; 59: 165.
8. Leone S., Ottani A., Bertolini A., Curr. Topics Med. Chem, 2007; 7: 265.
9. Zhou I., Ritchie D., Wang EY., Barbone AG., Argentieri D., Lau CY, J. Immunology, 1994; 153: 5026.
10. Lee DHS., Macintyre JP., Taylor GR.,Wang E., Plante RK., Tam SSC., Pope BL, Lau CY., JPET, 1999; 289: 1465.
11. Sammelson RE., Caboni P, Durkin KA., Casida JE., Bioorg. Med. Chem, 2004; 12; 3345: 133.
12. Sridhar R., Perumal PT., Etti S., Shanmugam G., Ponnuswamy MN., Prabayathy VR., Mathivanan N. Bioorg. Med. Chem. Lett, 2004; 14: 6035.
13. Banoglu E., Sukuroglu M., Caliskan B., Nacak S., Aypar E., Ark M. Turk J. Chem. 2007; 31: 677.

14. Donohue SR., Halldin C., Pike VW. Bioorg. Med. Chem, 2006; 14: 3712.
15. Vogel A I, A Text book of Quantitative Inorganic Chemistry, ELBS and Longmanns Green and Co. Ltd. London 3rd Ed, 1962.
16. Setwood P. W., Magneto Chemistry 2nd Edition Interscience, New York, 1958
17. Nakamoto N., "Infrared and Raman Spectra of Inorg. & Coord. Complexes" John Wiley, New York, 3rd Ed, 1978.
18. Jain A C, S K Mathur and Shashadri T R, J. Sci. Ind. Res, 1962; 21B: 214.
19. Hiremath SP, K.Rudresh and Badami S, Chem, 1998; 163.
20. Thirugnanasambanatham N., Arivundai, Ind. J. Pharma Sciences, 1996; 58; 18-21.
21. Hathaway B J, Procter LM and Nicholls P, J. Chem. Soc., A, 1968; 1678.
22. Kupchan MS, Bauerssimidt, Phytochemistry, 1971; 10: 664.
23. N. Upadhyay, World J. of Pharmaceutical Research, 2017; 6(16): 10268.