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Synthesis, Characterization and Antibacterial Activities of Manganese(II), Nickel(II), Copper(II) and Zinc(II) Complexes of the Hydrazone Compounds Derived from 1-Phenyl-3-methyl-4-acyl-pyrazole and Benzoyl Hydrazine

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Manganese(II), nickel(II), copper(II) and zinc(II) complexes were prepared by the reactions of the correspondence metal acetate and the hydrazone ligands (L_1-L_3) derived from 1-phenyl-3-methyl-4-acyl-pyrazole and benzoyl hydrazine. The ligands (L_1-L_3) and metal complexes were characterized by elemental analysis and spectroscopic techniques such as ^{1}H NMR and IR. Antimicrobial activity studies of (L_1-L_3) and the metal complexes against *Escherichia coli* and *Bacillus subtilis* were carried out by using disc diffusion method. The results indicate that the free ligands are more or less inactive against the two bacteria, the antibacterial abilities of the ligands become more pronounced when they are coordinated to the metal ions. The copper(II) complex of the benzoic acid [1-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)ethylidene]hydrazide (L_1) shows a signiûcant inhibition to the growth of the two tested bacteria.

Key Words: Synthesis, Characterization, Complex, Antibacterial activity.

INTRODUCTION

Besides the good insecticidal activity and phytocidal activity, aryl pyrazole derivatives have strong inhibition to the activities of the atpase and mitochondrial enzyme in the process of the life[1]. Some aryl pyrazole derivatives such as antipyrine, aminopyrine and analgin, have been widely used in human and livestock medicine to treat headache, fever, rheumatalgia *etc*.[2]. Derivatives of 1-phenyl-3-methyl-4-acyl-pyrazole have been found extensive application in coordination chemistry[3] and in antibacterial activation[4,5]. Hydrazones derived from the condensation reactions of hydrazides with aldehydes or ketones show excellent biological properties, such as antimicrobial[6], anticancer[7] and antimalarial[8] activities. The possible properties and using of hydrazones and the 1-phenyl-3-methyl-4-acyl-pyrazole derivatives make it attractive to study these compounds. The present work deals with the synthesis and antimicrobial activities of the complexes and the hydrazone ligands (L_1-L_3) derived from 1-phenyl-3-methyl-4-acyl-pyrazole and benzoyl hydrazine (Fig. 1).

EXPERIMENTAL

All chemicals and solvents were of analytical grade. Compound 1-phenyl-3-methyl-4-acetyl-5-pyrazolone (**a**) and 1-phenyl-3-methyl-4-(2-thenoyl)pyrazolone (**c**) were synthesized according to the literature[9]. Compound 4-formacyl-5-methyl-3-chloro-2-phenyl-2*H*-pyrazole (**b**) was synthesized according to the literature[10]. IR spectra were recorded (KBr disks) on a Perkin–Elmer FTIR spectrometer. ^{1}H NMR spectra were obtained on a Bruker 200 MHz spectrometer. A Carlo-Erba 1106 Elemental Analyser was utilized for elemental analysis.

Synthesis of the ligands (L_1-L_3): The ligands (L_1-L_3) were synthesized by refluxing the mixture of 1-phenyl-3- methyl-4-acetyl-5-pyrazolone (**a**)/4-formacyl-5-methyl-3-chloro-2-phenyl-2*H*-pyrazole (**b**)/1-phenyl-3-methyl-4-(2-thenoyl)-pyrazolone (**c**) (30 m mol) and benzoyl hydrazine (30 m mol) in ethanol (150 mL) over a steam bath for 6 h, then the solution was cooled down to room temperature. After 7 days, crystal was obtained and recrystallized from ethanol, finally dried in a vacuum desiccator.

2-Methyl-penta-2,4-dienoic acid [1-(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)ethylidene]hydrazide (L_1): White, yield: 83 %, m.p. 247 ± 1 ºC. H NMR (200 MHz, DMF): 7.75 (s, 1H, O=C-NH), 7.14-7.74 (m, 10H, phenyl), 2.49 (m, 1H, pyrazol-NH), 1.72 (d, 3H, pyrazol-CH_3), 0.93 (s, 3H, CH_3-C=N).

2-[N2-(5-Chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-ylmethylene)-hydrazino]-1-phenyl-ethanone (L_2): Yellow, yield: 93 %, m.p. 176 ± 1 ºC. H NMR (200 MHz, DMF): 8.06

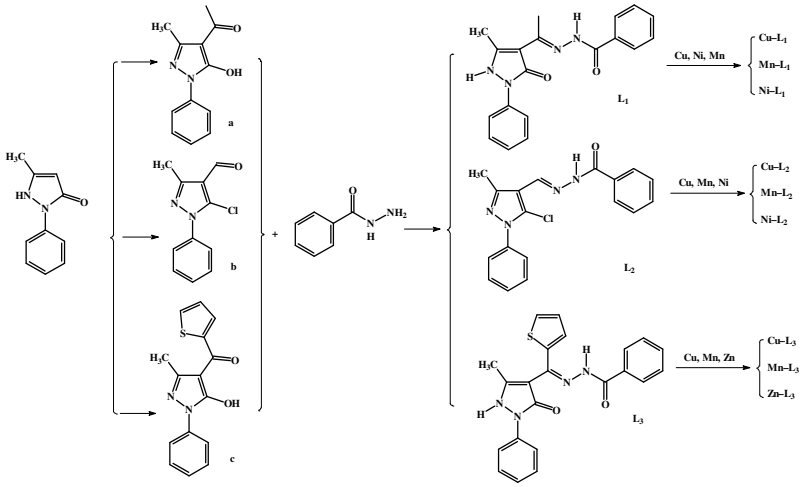

Fig. 1. Main synthesis route of the ligands and the metal complexes

(s, 1H, O=C-NH), 7.21-7.96 (m, 10H, phenyl), 5.12 (s, 1H, H-C=N),1.83 (d, 3H, pyrazol-CH_3).

Benzoic acid [(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-yl)thiophen-2-yl-methylene]hydrazide (L_3): Pale yellow, yield: 90 %, m.p. 224 ± 1 ºC. H NMR (200 MHz, DMF): 8.02-8.07(m, 3H, thiophen ring), 7.77 (s, 1H, O=C-NH), 7.24-7.76 (m, 10H, phenyl), 3.57 (m, 1H, pyrazol- NH), 1.83 (d, 3H, pyrazol-CH_3).

Synthesis of the metal complexes: 25 mL ethanol solution containing 1 mmol $M(Ac)_2$ (M = Cu, Mn, Ni, Zn) was dropped in the solution of 2 mmol ligand (L_1-L_3) with 30 mL ethanol. The mixture was stirred and refluxed for about 4 h. After 4 h, the solution was cooled down to room temperature and the precipitate was filtered off. The precipitate was washed with ethanol and then dried in vacuum. All the complexes were prepared by the same method and isolated as powder material. Though all the four metal complexes of each ligand were tried to prepared, only three of them were obtained.

Antimicrobial activities: The antibacterial activity tests of the ligand and the metal complexes at different concentrations against *Escherichia coli* and *Bacillus subtilis* were performed using disc diffusion method. Each compound was dissolved in DMF and was made into quantificational medicine sensitive pieces at different concentration, then the medicine sensitive pieces were put into the culture dish with equal culture medium and *Bacterial inoculum*, The bacteria were incubated in constant temperature incubator at 37 ºC for 24 h. All experiments were performed three times parallelly. The diameter data of inhibition zone of the ligands and complexes was measured and averaged.

RESULTS AND DISCUSSION

The ligands (L_1-L_3) (Fig. 1) were synthesized in a two-step process in which the 1-phenyl-3-methyl-4-acyl-pyrazole (**a-c**) were firstly synthesized according to the literature. In the second step, the ligands were obtained by reaction of benzoyl hydrazine with an appropriate 1-phenyl-3-methyl-4-acyl-pyrazole (**a-c**) by refluxing in absolute ethanol. The ligands (L_1-L_3) and their metal complexes were characterized by infrared spectra, ^{1}H NMR and elemental analyses. The newly synthesized ligands and their metal complexes are stable at room temperature in the solid state. The ligands and its metal complexes are generally soluble in EtOH, DMF and DMSO. Physical properties, element analysis data are reported in Table-1. The analytical data of all the synthesized complexes shows that the complexes are composed by the 2:1 rate of ligand and metal iron.

Spectroscopic characterization: The ^{1}H NMR data for ligands showed the signals at 7.14-7.74 in the H NMR specta of L_1 were assigned to the ten protons of two phenyl group. The singlet at 7.75 ppm was attributed to the proton of the acylamino group. The signal of the NH proton in the pyrazol ring was observed at 2.49 ppm, there is no obvious signals of OH which showed the ligand of L_1 existed in imine-keto form.

The ^{1}H NMR spectra of L_2 showed a singlet at 5.12 ppm and a singlet at 8. 06 ppm belonging to the proton of H-C=N and O=C-NH group, respectively. The peaks between 7.21 and 7.96 ppm were assigned to the aromatic protons. The double signals at 1.83 belonged to the three protons of the methyl boned to the pyrazol ring.

The signals at 7.24-7.76 ppm in the ^{1}H NMR spectra of L_3 were assigned to the aromatic protons. The signal of the NH proton in the pyrazol ring was observed at 3.57 ppm, there was no obvious signal of OH which showed the ligand of L_3 existed in imine-keto form. The signals at 8.02-8.07 ppm and the singlet at 7. 77 ppm belonged to the proton of thiophene ring and O=C-NH group, respectively.

The IR spectra data of the free ligands and the complexes is given in Table-2. In the spectra of the ligand L_1, bands at 3436, 1666 and 1622 cm^{-1} were attributed to N-H, C=O and C=N, respectively. These bands switched to lower wave number after coordination of the ligand to the metal iron through the atom nitrogen of the C=N, atom nitrogen of the N-H and the atom O of the C=O, the coordination way was also confirmed by the band at 559-529 cm^{-1} assigned to ν(M-O) and the band at 491-439 cm^{-1} assigned to ν(M-N).

In the spectra of the ligand L_2, bands at 3505, 1645 and 1621 cm^{-1} were attributed to N-H, C=O and C=N. Differently, the coordination way of L_2 and iron was that the ligand coordinated with the iron only through the atom O of the C=O and atom nitrogen of the N-H, while the atom nitrogen of the C=N did not take part into coordination. All these could be confirmed by only the band of C=O and N-H switches to lower wave number after coordination, while the band of C=N did not change.

TABLE-1
ANALYTICAL DATA AND PHYSICAL PROPERTIES OF THE LIGANDS AND THE METAL COMPLEXES

Compound	Colour	m.p. (ºC)	Yield (%)	Found (calcd.) %		
				C	H	N
L_1	White	247 ± 1	83	59.54 (59.50)	6.87 (6.86)	21.37 (21.39)
Cu-L_1	Yellow	>360	75	53.06 (53.08)	6.12 (6.10)	19.05 (19.05)
Ni-L_1	Green	>360	68	53.51 (53.49)	6.17 (6.18)	19.21 (19.22)
Mn-L_1	Yellow	>360	43	53.89 (53.84)	6.22 (6.19)	19.34 (19.37)
L_2	Yellow	176 ± 1	93	63.81 (63.80)	4.43 (4.44)	16.54 (16.56)
Cu-L_2	Brown	271 ± 1	87	58.30 (58.29)	4.05 (4.08)	15.11 (15.13)
Mn-L_2	Brown	>360	71	59.02 (58.99)	4.10 (4.12)	15.30 (15.29)
Ni-L_2	Orange	311 ± 1	64	58.70 (58.73)	4.08 (4.06)	15.22 (15.23)
L_3	Yellow	224 ± 1	90	65.12 (65.12)	3.88 (3.87)	14.47 (14.49)
Cu-L_3	Green	324 ± 1	82	60.14 (60.20)	3.58 (3.49)	13.37 (13.28)
Mn-L_3	Yellow	335 ± 1	56	60.80 (60.90)	3.62 (3.72)	13.51 (13.40)
Zn-L_3	Yellow	329 ± 1	62	60.07(60.10)	3.58 (3.44)	13.35 (13.45)

TABLE-2
SELECTED INFRARED SPECTRAL DATA OF THE LIGANDS AND THE COMPLEXES (cm^{-1})

Compound	ν(C=N)	ν(N-H)	ν(C=O)	ν(M-N)	ν(M-O)
L_1	1622	3436	1666	–	–
Cu-L_1	1621	3427	1644	550	466
Ni-L_1	1604	3415	1638	559	439
Mn-L_1	1612	3425	1639	529	491
L_2	1621	3505	1645	–	–
Cu-L_2	1621	3417	1630	548	450
Mn-L_2	1621	3424	1644	529	500
Zn-L_2	1621	3425	1639	599	498
L_3	1623	3412	1647	–	–
Cu-L_3	1603	3410	–	577	422
Mn-L_3	1605	3350	–	548	469
Zn-L_3	1619	3359	–	551	471

The IR spectrum of the ligand L_3 exhibited a strong and sharp band at 1647 cm^{-1} assigned to ν(C=O), while this band was absent in the spectra of the complexes indicated that the coordination of the metal ion was through the carbonyl oxygen of pyrazolone as well as the atom nitrogen of the C=N and atom nitrogen of the N-H. This was also supported by the presence of the band at 577-548 cm^{-1} assigned to ν(M-O) and the band at 471-422 cm^{-1} assigned to ν(M-N).

Antimicrobial activity: The average diameter data of inhibition zone of the ligands and complexes against *Escherichia coli* and *Bacillus subtilis* are listed in Table-3. The free ligands are more or less inactive against the two bacteria, the antibacterial activity of the ligands become more pronounced when it is coordinated to the metal ions. The biological activities of the all the complexes against *E. coli* follow the order: Cu-L_1 > Mn-L_1 > Ni-L_1 > CuL_2 > L_1 > amoxicillin > Mn-L_3 > Cu-L_3 > Mn-L_2 > Zn-L_2 > Zn-L_3 > L_2 > L_3. The biological activities of the all the complexes against *Bacillus subtilis* follow the order: Cu-L_1 > Cu-L_2 > amoxycillin > Mn-L_3 > Ni-L_1 > Mn-L_1 > L_1 > L_3 > L_2 > Zn-L_3 > Cu-L_3 > Zn-L_2 > Mn-L_2. All the data showed that *E. coli* and *Bacillus subtilis* were inhibited to a greater degree by the Cu(II)-L_1 complex, even greater than the contrasted amoxycillin.

Conclusion

In this study, we have presented the synthesis and characterization of three new ligands and their Ni(II), Cu(II), Mn(II) and Zn(II) complexes. The antibacterial properties of these compounds were also investigated.

TABLE-3
AVERAGE DIAMETER DATA OF INHIBITION ZONE OF THE LIGANDS AND METAL COMPLEXES

Compound	Average diameter (cm) (concentration: 5.00, 2.50, 1.25 mg/mL)	
	Escherichia coli	*Bacillus subtilis*
L_1	1.15/1.03/1.05	–/1.03/1.00
Cu-L_1	1.50/1.38/1.35	1.97/1.40/1.00
Mn-L_1	1.28/1.12/0.98	1.18/–/–
Ni-L_1	1.12/1.35/1.33	1.25/0.93/1.53
L_2	0.87/0.83/0.90	–/0.85/1.05
Cu-L_2	1.23/1.22/1.12	1.43/1.40/1.15
Mn-L_2	0.95/1.08/0.72	–/–/0.83
Zn-L_2	–/1.08/–	–/0.90/–
L_3	0.89/0.82/0.81	1.06/0.96/0.85
Cu-L_3	1.04/0.96/1.06	0.81/0.92/0.83
Mn-L_3	1.12/0.83/0.81	1.29/1.14/0.83
Zn-L_3	1.09/0.83/0.92	0.91/0.98/0.88
Amoxycillin	1.10/1.00/1.10	1.40/1.25/1.35

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