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Antifungal Cobalt(II), Copper(II), Nickel(II) and Zinc(II) Complexes of Furanyl-,Thiophenyl-, Pyrrolyl-, Salicylyl- and Pyridyl-derived Cephalexins

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Some novel cephalexin-derived furanyl, thiophenyl, pyrrolyl, salicylyl and pyridyl Schiff's bases and their cobalt (II), copper (II), nickel (II) and zinc (II) complexes have been synthesized and studied for their antifungal properties against *Trichophyton longifusus*, *Candida albicans*, *Aspergillus flavus*, *Microsporum canis*, *Fusarium solani* and *Candida glaberata*. The presence of metal ions in the investigated Schiff's base complexes reported here lead to significant antifungal activity, whereas the parent ligands were generally less active.

Keywords: Cephalexin; Schiff's bases; Transition metal complexes; Antifungal activity

INTRODUCTION

Antibacterial, antifungal and/or antiviral drug resistance is becoming globally a medical problem.[1,2] The process of chelating *via* coordination of transition metal ions has highlighted the use of such metal-based compounds as potential candidates to alleviate this problem.[3–5] In an effort to explore the role of metal-based drugs as potentially useful antibacterials, we have commenced[6–14] an extensive program to synthesize novel antibacterial compounds and to study their therapeutic potentials upon coordination with transition metal ions. We would like to extend these studies to metal-based antifungals and have chosen cephalexin; a clinically well-known and important antibacterial/antifungal drug. The free amino group of cephalexin was initially condensed with heteroaromatic/aromatic aldehydes such as, furan-2-, thiophene-2-, pyrrole-2-, pyridine-2-aldehydes and salicylaldehyde to afford the Schiff's bases ($\mathbf{L^1}$–$\mathbf{L^5}$, Scheme 1) and then complexed with four transition metals *i.e.* cobalt (Co), copper (Cu) nickel and Zinc (Zn). The structures of the newly synthesized ligands and their respective complexes with all four metals were determined using different spectroscopic and microanalytical techniques. Molecular models of the newly synthesized compound ($\mathbf{L^1}$–$\mathbf{L^5}$) indicate that their structures contain potential donor sites suitable for coordination with the metal ions. All the newly synthesized metal complexes along with ligand ($\mathbf{L^1}$–$\mathbf{L^5}$) were screened against *Trichophyton longifusus*, *Candida albicans*, *Aspergillus flavas*, *Microsporum canis*, *Fusarium solani* and *Candida glaberata*. These studies would significantly introduce a new class of metal-based antifungal.

MATERIALS AND METHODS

Cephalexin sodium was obtained from Pharmagen Beximco Ltd, Pakistan. Solvents used were analytical grade. All metal (II) were used as their chloride salts. IR spectra were recorded on a Philips Analytical PU 9800 FTIR spectrophotometer. UV-Visible

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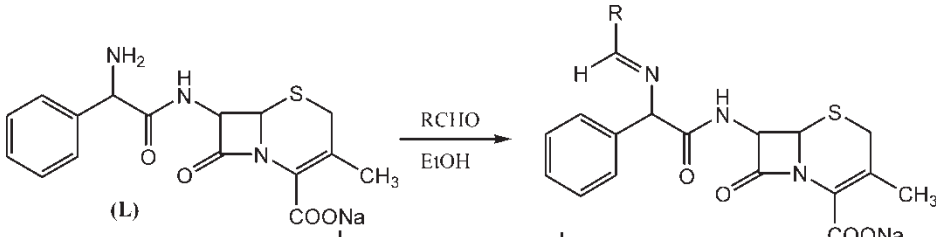
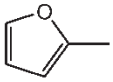
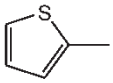
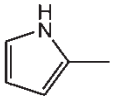
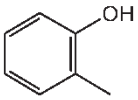
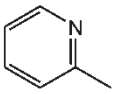


Compound	R	Yields %
L^1		67
L^2		65
L^3		62
L^4		68
L^5		65

SCHEME 1 The Cephalexin Schiff bases studied.

spectra were obtained in DMF on a Hitachi U-2000 double-beam spectrophotometer. Butterworth Laboratories Ltd (U.K.) carried out the C, H and N analyses. Conductance of the metal complexes was determined in DMF on a Hitachi (Japan) YSI-32 model conductometer. Magnetic measurements were carried out on solid complexes using the Gouy's method. Melting points were recorded on a Gallenkamp (U.K.) apparatus and are uncorrected.

General Method for the Preparation of (L^1–L^5) and Metal(II) Complexes (1–20)

To a stirred solution of cephalexin sodium (4.5 g, 0.01 mmol) in warm ethanol (20 mL) was added furan-2-carboxaldehyde (0.97 g, 0.01 mmol) in ethanol (10 mL). The mixture was refluxed for 2 h and completion of reaction was monitored through TLC. After completion of the reaction, it was cooled to afford a solid product. The solid residue was filtered, washed with ethanol, then with ether and dried. Crystallization from hot ethanol gave $\mathbf{L^1}$.

The same method was applied for the preparation of $\mathbf{L^2}$–$\mathbf{L^5}$ by using the respective reagents in the same molar ratio.

A solution (30 mL) of the respective ligand (0.02 mmol) in hot ethanol was added to a stirred solution of metal (II) chloride (0.01 mmol) in ethanol (25 mL). The mixture was refluxed for 1 h then cooled to room temperature, when it solidified on cooling. The solid was filtered, washed with ethanol, then with ether and dried in air. Crystallization from aqueous/ethanol (30:70) gave the desired metal complexes. The same method was used for the preparation of all other complexes by using their respective metal (II) salts.

Biological Activity

All the synthesized drug ligands and their respective metal (II) chelates were screened for *in vitro* antifungal activity against *T. longifusus*, *C. albicans*, *A. flavus*, *M. canis*, *F. solani* and *C. glaberata* using the agar well method.[15–17] Two to eight hours old fungal inoculums containing approximately 10^4–10^6 colony forming units (CFU)/ml were used. These were poured into nutrient agar plate and allowed to solidify. The wells were dug in the media with the help of a sterile metallic borer with centers of at least 24 mm. Different concentrations (100 μl) of the test sample (1 mg/ml in DMSO) was introduced into the respective wells. Other wells were supplemented with DMSO and reference antifungal drugs serving as negative and positive controls, respectively. The plates were incubated immediately at 37°C for 20 h. Activity was determined by measuring the diameter of zones showing complete inhibition (mm). Miconazole and Amphotericin B were used as standard drugs.

TABLE I Physical, Spectral and Analytical Data Ligands L^1–L^5

Ligand	M.P (°C)	IR (cm^{-1})	C, H, N; Calc. (Found) %	Yield (%)
L^1 ($C_{21}H_{18}N_3O_5NaS$)	197	3520, 1760, 1725, 1660, 1640, 1620,1600, 1565, 1110, 945	56.4(56.7), 4.0(3.3), 9.4(9.2)	67
L^2 ($C_{21}H_{18}N_3O_4NaS_2$)	188	3515, 1760, 1725, 1660,1635, 1620, 1600, 1565, 1115, 950	54.4 (54.6), 3.9 (3.2), 9.1 (8.8)	65
L^3 ($C_{21}H_{19}N_4O_4NaS$)	190	3525, 1760, 1725, 1660,1640, 1620, 1600, 1565, 1115, 950	56.5 (56.9), 4.3 (4.0), 12.6 (12.8)	62
L^4 ($C_{23}H_{20}N_3O_5NaS$)	195	3575, 3520, 1760, 1725,1660, 1640, 1620, 1600, 1565, 1115	58.4 (58.8), 4.2 (3.9), 8.9 (9.3)	68
L^5 ($C_{22}H_{19}N_4O_4NaS$)	193	3518, 1760, 1725, 1660, 1640, 1620, 1560, 1115, 940	57.6 (57.4), 4.1 (4.5), 12.2 (12.6)	65

RESULTS AND DISCUSSION

Chemistry

The ligands (L^1–L^5) were prepared by refluxing an appropriate amount of cephalexin sodium with the corresponding furan-, thiophene-, pyrrole, pyridine-2-carboxaldehyde and salicylaldehyde in ethanol in 1:1 molar ratio. The structures of these synthesized drug ligands were established with the help of their IR and microanalytical data (Table I). All metal complexes (**1**–**20**) of these ligands were air and moisture stable and prepared by the stoichiometric reaction of the corresponding metal (II) chloride with the ligand, in a molar ratio M:L of 1:2. These complexes are intensely colored and amorphous solids, which decompose without melting. They are insoluble in common organic solvents and only soluble in water, DMF and DMSO. Molar conductance values of the soluble complexes in DMF show lower values (16–20 $ohm^{-1}\,cm^{-2}\,mol^{-1}$) indicating that they are all non-electrolytic in nature.[18] The elemental analyses data agree well with the proposed formulae for the ligands and also confirmed the ML_2 composition of the metal (II) chelates (Table II). Efforts to grow good crystals of the ligands and their metal chelates for X-ray diffraction studies were unsuccessful due to their poor solubility in common organic solvents.

IR Spectra

The IR spectra of the ligands reported in Table I show the absence of bands at 3420 and 1715 cm^{-1} due to ν (NH_2) and ν (HC═O) stretching vibrations and instead, the appearance of a strong new band at ~1620 cm^{-1} assigned to the azomethine, ν (HC═N) vibration indicated that the starting materials do not exist and have condensed into the corresponding[19] Schiff's base ligands. Comparison of the IR spectra of the ligands with their metal complexes indicated that all the ligands were tridentately coordinated to the cobalt, nickel and zinc and, bidentately to the copper metal ions. In addition, there appears[20] an intense band at ~1760 cm^{-1} attributed to the ν C═O stretching vibration of the β-lactam ring. This band is not shifted with respect to the ligand indicating that the β-lactam ring is not modified in the complexes, and this group does not interact directly with the metal atom. The band assigned to the amide stretching vibration at ~1665 cm^{-1} in the ligand

TABLE II Physical and Analytical Data of the Metal (II) Complexes of L^1–L^5

No	Metal chelate, Mol. weight, Mol. formula	M.P (°C)	B.M (μ_{eff})	C, H, N; Cal (Found) %	Yield (%)
1	$[Co(L^1)_2]$, [907.0], ($C_{42}H_{36}CoNs_6O_{10}S_2$)	221–223	3.9	55.6 (55.9), 4.0 (3.7), 9.3 (9.7)	56
2	$[Co(L^2)_2]$, [939.0], ($C_{42}H_{36}CoN_6O_8S_4$)	227–229	3.8	53.7 (53.9), 3.8 (4.2), 8.9(8.4)	60
3	$[Co(L^3)_2]$, [905.0], ($C_{42}H_{38}CoN_8O_8S_2$)	220–222	4.1	55.7 (56.1), 4.2 (4.1), 12.4 (12.2)	58
4	$[Co(L^4)_2]$, [959.0], ($C_{46}H_{40}CoN_6O_{10}S_2$)	214–216	4.2	57.6 (57.8), 4.2 (4.0), 8.8 (9.2)	55
5	$[Co(L^5)_2]$, [929.0], ($C_{44}H_{38}CoN_8O_8S_2$)	211–213	3.8	56.8 (56.5), 4.1(4.4), 12.1 (11.8)	59
6	$[Cu(L^1)_2]$, [911.5], ($C_{42}H_{36}CuN_6O_{10}S_2$)	225–227	1.8	55.3 (55.7), 4.0 (3.8), 9.2 (9.3)	61
7	$[Cu(L^2)_2]$, [943.5], ($C_{42}H_{36}CuN_6O_8S_4$)	226–228	1.6	53.4(53.5), 3.8 (3.3), 8.9 (8.6)	58
8	$[Cu(L^3)_2]$, [909.5], ($C_{42}H_{38}CuN_8O_8S_2$)	222–223	1.4	55.4 (55.7), 4.2 (4.0), 12.3 (12.5)	57
9	$[Cu(L^4)_2]$, [963.5], ($C_{46}H_{40}CuN_6O_{10}S_2$)	228–230	1.7	57.3 (57.1), 4.2 (4.5), 8.7 (8.9)	59
10	$[Cu(L^5)_2]$, [933.5], ($C_{44}H_{38}CuN_8O_8S_2$)	217–219	1.6	56.6 (56.8), 4.1 (3.8), 12.0 (12.4)	60
11	$[Ni(L^1)_2]$, [906.7], ($C_{42}H_{36}NiN_6O_{10}S_2$)	220–222	3.1	55.6 (55.9), 4.0 (4.2), 9.3 (9.1)	62
12	$[Ni(L^2)_2]$, [938.7], ($C_{42}H_{36}NiN_6O_8S_4$)	215–218	3.3	53.7 (53 4), 3.8 (4.0), 8.9 (8.5)	58
13	$[Ni(L^3)_2]$, [904.7], ($C_{42}H_{38}NiN_8O_8S_2$)	223–225	3.4	55.7 (55.5), 4.2 (4.6), 12.4 (12.6)	57
14	$[Ni(L^4)_2]$, [958.7], ($C_{46}H_{40}NiN_6O_{10}S_2$)	218–220	3.2	57.6 (57.8), 4.2 (4.4), 8.8 (8.5)	58
15	$[Ni(L^5)_2]$, [928.7], ($C_{44}H_{38}NiN_8O_8S_2$)	220–222	3.3	56.9 (57 3), 4.1 (4.3), 12.1 (12.5)	60
16	$[Zn(L^1)_2]$, [913.4], ($C_{42}H_{36}ZnN_6O_{10}S_2$)	217–218	Dia	55.2 (55.5), 3.9 (4.2), 9.2 (9.5)	56
17	$[Zn(L^2)_2]$, [945.4], ($C_{42}H_{36}ZnN_6O_8S_4$)	222–224	Dia	53.3 (53.5), 3.8 (4.1), 8.9 (9.2)	58
18	$[Zn(L^3)_2]$, [911.4], ($C_{42}H_{38}ZnN_8O_8S_2$)	218–220	Dia	55.3 (55.5), 4.2 (4.5), 12.3 (12.0)	60
19	$[Zn(L^4)_2]$, [965.4], ($C_{46}H_{40}ZnN_6O_{10}S_2$)	215–217	Dia	57.2 (57.0), 4.1 (4.3), 8.7 (8.8)	57
20	$[Zn(L^5)_2]$, [935.4], ($C_{44}H_{38}ZnN_8O_8S_2$)	212–214	Dia	56.4 (56.7), 4.1 (4.0), 12.0 (12.4)	61

is not shifted in the complex indicating that the amido group is not involved in coordination with the metal ion. The band at ~1600 cm^{-1} includes the stretching vibration of ν C═O of the carboxylate group in the ligand. This band shifts to the lower frequency side by 15 cm^{-1} indicating direct participation of the carboxylate oxygen in the bonding linkage with the metallic ion. The band at ~1620 cm^{-1} due to azomethine linkage is also shifted to lower frequency ~1610 cm^{-1} indicating[21] coordination of azomethine nitrogen to the metal atom. However, further conclusive evidence of the coordination of the ligands with the metal atoms was established[22] by the far IR spectra, in which the appearance of new bands at 340–355, 415–430 and 545–560 cm^{-1} assigned to ν M-S, ν M-O and ν M-N in the spectra of the metal complexes were observed, which are not present in the spectra of the corresponding ligands. These new bands were, however, not observed in the copper (II) chelates that clearly revealed no participation of newly incorporated heteroatoms of the ligands to the metal ions. Also, a band at ~3525 cm^{-1} attributed to ν OH in the ligand L^4 disappeared in its metal complexes and instead appearance of a band at 1580 cm^{-1} indicated deprotonation of an OH moiety during coordination.

Electronic Spectra

The Co (II) complexes exhibited well-resolved, low-energy bands at 7,635–7,585 cm^{-1} and 17,350–17,450 cm^{-1} and a strong high-energy band at 20,580–20,715 cm^{-1} (Table 3) and are assigned[21] to the transitions $^4T_{1g}(F) \rightarrow {}^4T_{2g}(F)$, $^4T_{1g}(F) \rightarrow {}^4A_{2g}(F)$ and $^4T_{1g}(F) \rightarrow {}^4T_{2g}(P)$ for a high-spin octahedral geometry.[21,22] A high intensity band at 28460–29325 cm^{-1} was assigned to metal to ligand charge transfer. The magnetic susceptibility measurements for the solid Co (II) complexes are also indicative of three unpaired electrons per Co (II) ion suggesting[23] consistency with their octahedral environment.

The electronic spectra of the Cu (II) complexes (Table III) showed two low-energy weak bands at 15,115–15,235 cm^{-1} and 19,420–19,540 cm^{-1} and a strong high-energy band at 30,240–30,425 cm^{-1}. The low-energy bands in this position are typically expected for a square-planar configuration and may be assigned to $^2B_{1g} \rightarrow {}^2A_{1g}$ and $^2B_{1g} \rightarrow {}^2E_g$ transitions, respectively.[24] The strong high-energy band, in turn, is assigned to metal → ligand charge transfer. Also, the magnetic moment values (1.4–1.8 B.M) (Table 2) for the copper (II) are indicative of anti-ferromagnetic spin–spin interaction through molecular association. Hence, the copper (II) complexes appear to be in a square-planar geometry with a $d_x^2 - d_y^2$ ground state.[25]

TABLE III Spectral Data of the Metal Chelates of L^1–L^5

No	IR (cm^{-1})	λ_{max} (cm^{-1})
1	1760, 1665, 1610, 1595,415, 560	28,460, 20,580, 17,350, 7,635
2	1760, 1665, 1615, 1595, 430, 545	29,325, 20,715, 17,350, 7,715
3	1765, 1665, 1610, 1595,415, 555, 355	29,275, 20,645, 17,385, 7,570
4	1760, 1665, 1615, 1595, 1580, 425, 550	28,890, 20,685, 17,450, 7,610
5	1760, 1665, 1610, 1595, 415, 560	28,765, 20,615, 17,415, 7,585
6	1760, 1665, 1610, 1595, 430, 545	30,240, 19,475, 15,115
7	1760, 1665, 1615, 1595,415, 550	30,425, 19,540, 15,235
8	1760, 1665, 1610, 1595,425, 555	30,335, 19,495, 15,170
9	1760, 1665, 1615, 1595,420, 545	30,415, 19,420, 15,225
10	1760, 1665, 1610, 1595,425, 560	30,290, 19,535, 15,185
11	1760, 1665, 1610, 1595, 415, 560	29,885, 26,385, 15,665, 10,260
12	1760, 1665, 1610, 1595, 425, 545, 340	30,210, 26,555, 15,715, 10,315
13	1760, 1665, 1610, 1595, 430, 555	30,215, 26,445, 15,680, 10,285
14	1760, 1665, 1610, 1595,1580, 420, 560	29,995, 26,465, 15,710, 10,310
15	1760, 1665, 1610, 1595, 425, 560	30,190, 26,550, 15,770, 10,275
16	1760, 1665, 1610, 1595, 415, 545	28,350
17	1760, 1665, 1610, 1595,430, 555, 340	29,145
18	1760, 1665, 1610, 1595,425, 550	28,770
19	1760, 1665, 1610, 1595, 1580, 420, 560	28,935
20	1760, 1665, 1610, 1595,420, 545	28,815

The electronic spectra of the Ni (II) complexes showed d-d bands in the region 26,385–26,555, 15,665–15,770 and 10,260–10,315 cm^{-1}. These are assigned[26] to the transitions $^3A_{2g}(F) \rightarrow {}^3T_{2g}(F)$, $^3A_{2g}(F) \rightarrow {}^3T_{1g}(F)$ and $^3A_{2g}(F) \rightarrow {}^3T_{2g}(P)$, respectively, consistent with their well-defined octahedral configuration. The band at 29,885–30,210 cm^{-1} was assigned to metal → ligand charge transfer. The magnetic measurements (3.1–3.4 B.M) showed two unpaired electrons per Ni (II) ion suggesting[27] also an octahedral geometry for the Ni (II) complexes. The electronic spectra of the Zn (II) complexes exhibited only a high-intensity band at 28,350–29,145 cm^{-1} and are assigned[28] to a ligand-metal charge transfer.

Biological Activity

The antifungal activity results shown in Table IV indicate a clear picture of all the newly synthesized compounds (L^1–L^5) and their metal complexes

TABLE IV Antifungal Activity Data for **L**, $\mathbf{L^1}$–$\mathbf{L^5}$

	Fungus					
Ligand/Complex	(a)	(b)	(c)	(d)	(e)	(f)*
L	15	17	18	18	17	18
$\mathbf{L_1}$	20	22	20	20	20	20
$\mathbf{L_2}$	18	20	19	19	19	20
$\mathbf{L_3}$	21	18	22	20	21	21
$\mathbf{L_4}$	22	24	24	23	23	22
$\mathbf{L_5}$	20	25	24	24	24	25
1	23	26	27	27	29	28
2	25	27	25	28	28	29
3	23	28	29	29	30	31
4	26	29	30	31	30	30
5	27	30	28	29	29	30
6	28	28	29	30	31	28
7	26	29	30	31	30	30
8	27	31	29	30	29	30
9	30	30	28	29	28	29
10	29	28	30	30	30	31
11	28	29	31	30	31	30
12	27	31	30	30	30	30
13	30	30	30	30	29	30
14	29	30	31	29	30	31
15	30	31	29	31	30	30
16	28	29	30	30	31	29
17	28	30	30	29	31	30
18	29	30	28	28	29	30
19	30	28	31	31	30	29
20	30	31	29	30	30	30

(a) = *Trichophyton longifusus* (b) = *Aspergillus flavas* (c) = *Candida albicans* (d) = *Microsporum canis* (e) = *Fusarium solani* (f) = *Candida glabeata*
*Significant 18–25, Moderate 10–17, Weak <10

(**1**–**20**). The new derivatives ($\mathbf{L^1}$–$\mathbf{L^5}$) derived from cephalexin sodium (**L**), screened for their antifungal effect against *T. longifusus*, *C. albicans*, *A. flavas*, *M. canis*, *F. solani* and *C. glaberata*, ligands ($\mathbf{L^1}$–$\mathbf{L^5}$) exhibited a marked enhancement in activities against all the tested fungal strains compared to the parent uncomplexed cephalexin sodium (**L**) and complexation of these ligands with metals (II) as target molecules also increased activity. This enhancement in the activity of derivatives ($\mathbf{L^1}$–$\mathbf{L^5}$) may be rationalized on the basis of their structures. The ligands, $\mathbf{L^1}$–$\mathbf{L^5}$ have an additional C=N bond with a heterocyclic or aromatic ring. On the basis of the electron flow in cephalexin sodium and the newly synthesized ligands ($\mathbf{L^1}$–$\mathbf{L^5}$), we can conclude that the C=N bond definitely disturbs the electronic density of the entire parent molecule, which may be responsible for the diffusion or interaction of the molecule into the fungal cell. Metals play a critical role in achieving activity which may be due to it's transition properties from electropositive to electronegative, which also causes shuffling of the electronic charge density within the targeted metal complexes and seemingly aids lethal penetration of the pathogens. Another supporting opinion in this regard is that chelation reduces the polarity[29,30] of the metal ion because of the partial sharing of its positive charge with the donor groups and possibly the π-electron delocalization[31,32] within the whole chelate ring system. The process of chelation thus increases the lipophilic nature of the central metal atom, which in turn, favors its permeation through the lipoid layer of the membrane.[33–37]

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