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Synthesis, characterization, biological studies, and molecular modeling of mixed ligand bivalent metal complexes of Schiff bases based on *N*-aminopyrimidine-2-one/2-thione

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Abstract: New mixed Schiff bases, Cu(II), Co(II), Ni(II), and Mn(II) complexes, were synthesized derived from 5-chloro-2-hydroxyacethophenone and 1-amino-5-benzoyl-4-phenyl-1H-pyrimidine-2-one/thione. These complexes were characterized by elemental analysis, magnetic measurements, molar conductivity, IR, electronic, NMR, and mass spectral studies. All the complexes showed nonelectrolytic behavior. Moreover, the newly synthesized mixed ligand complexes were evaluated for their in vitro antimicrobial efficiency against bacteria and yeast. The compound named Co(L_1L) had good antifungal activity against *Candida* species, but no profound antibacterial effect against bacterial strains. In addition, the ground state geometries of the complexes were optimized using a semi-empirical method at PM6 level, which is a suitable and effective basis set for organometallic and large structures to obtain information about their 3D geometries and electronic structures.

Key words: Mixed ligand, Schiff bases, metal complexes, biological activity, molecular modeling, PM6

1. Introduction

Mixed ligand metal complexes are known to play a significant role in biological systems such as galactose oxidase (GO), chlorophyll, vitamin B_{12}, laccases, and hemoglobin.[1] Pyrimidine, which is an integral part of DNA and RNA, imparts diverse pharmacological properties as an effective bactericide and fungicide.[2–4] Many pyrimidine derivatives are known to exhibit analgesic,[5] antihypertensive,[6] antitumor,[7] antimalarial,[8] antioxidant,[9] antimitotic,[10] and anti-HIV activities.[11] The increasing studies on Schiff bases mixed ligand and the various properties examined in studies done on this subject (anticancer[12], antimicrobial[13] etc.) encouraged us to study in this area. Mixed ligand complexes are biologically more active than their constituting ligands for the corresponding homoligated bis-complexes.[14] The electronic and magnetic properties of Schiff bases can also be widely modulated via changes in their chemical structure, using different transition metals that formed different geometrical structures in the cavity of the macro cycle such as mixed ligand metal complex.

In the present study, Schiff base mixed ligand complexes were synthesized from the reaction of substituted *N*-amino pyrimidine-2-on and substituted *N*-amino pyrimidine-2-thione with transition metal salts [Cu(II), Co(II), Ni(II), Mn(II)]. The characterization of Schiff base mixed ligand complexes was achieved by elemental,

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magnetic susceptibility, and electronic, infrared, and mass spectral analysis. All the complexes encouraged us to study their antimicrobial activities against gram-positive and gram-negative bacteria and fungi to give an insight into the steric and electronic effects on the biological activities of ligands with various substituents in the aromatic ring and their complexes. We report theoretical calculations of the Schiff bases mixed ligand complexes as well as their experimental data.

2. Results and discussion

The general view of HL_1 is shown in Figure 1. HL_1 was prepared by the condensation of one mole of 5-chloro-2-hydroxyacethophenone with one mole N-aminopyrimidine-2-on in like manner to the preparation of the ligand HL in the literature.[15] The ligands are soluble in MeOH, acetonitrile, and THF. The elemental analysis results for the mixed ligand metal complexes match calculated values to exhibit that the complexes have a 1:1:1 (HL_1:Metal:HL) metal–ligand ratio (Figure 2). The addition of Cu(II), Co(II), Ni(II), and Mn(II) acetate dissolved in methanol to a THF solution of the ligand gave colored complexes. The newly synthesized mixed ligand complexes are very stable at room temperature in the solid state. While all the mixed ligand metal complexes are insoluble in organic solvents like diethylether, they are soluble in methanol, THF, and DMF. We have estimated from the elemental analysis results that the mixed ligand general formula is $[ML_1L]\cdot nH_2O$, where L_1 or L is the anion of HL_1 or HL. The colors, melting points, yields, IR, and magnetic susceptibility data of the compounds are presented in the Experimental section. The molar conductance measured for 10^{-3} M solutions in DMF of these complexes fall in the range 2.46–4.51 μS/cm, indicating their nonelectrolytic behavior.[16]

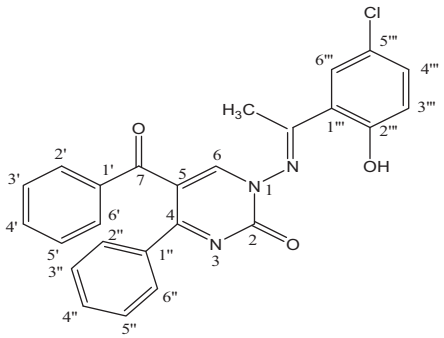

Figure 1. Structure of the Schiff base ligand (HL_1).

2.1. IR spectra

Previously it was reported that a broad band in the range of 3205–3125 cm^{-1} free v(OH) stretching frequencies was observed in the spectra of HL_1 and HL, respectively, but in the newly synthesized mixed ligand metal complexes these bands were not observed. The infrared spectra of the ligands HL_1 and HL display a sharp band around 1609 cm^{-1}, which was assigned to v(C=N) stretching.[17] Actually, this band was shifted to lower (9–11 cm^{-1}) wavenumbers in the mixed ligand Co(II) and Mn(II) complexes, indicating the participation of azomethine nitrogen in the coordination to metal ion.[18] The ν(C=S) at 1208 and 737 cm^{-1} in the free ligand shifts to higher frequency after complexation, due to coordination with the sulfur atom of the thione group for all the complexes (Figure 2a). However, the ν(C=N) imine band in the spectra of Ni(II) and Cu(II) complexes remains at almost 1607 cm^{-1}, suggesting that the imine group does not take part in complexation (Figure

2b). In the spectra of all the mixed ligand complexes, the phenolic band v(C–O) is shifted to lower and higher frequencies (5–16 cm^{-1}).[19] Moreover, the absorption due to v(C=S) of the ligand at 1208 cm^{-1} is shifted to 1204–1216 cm^{-1} in complexes, indicating that the other coordination is through the sulfur atom belonging to pyrimidine rings.[20]

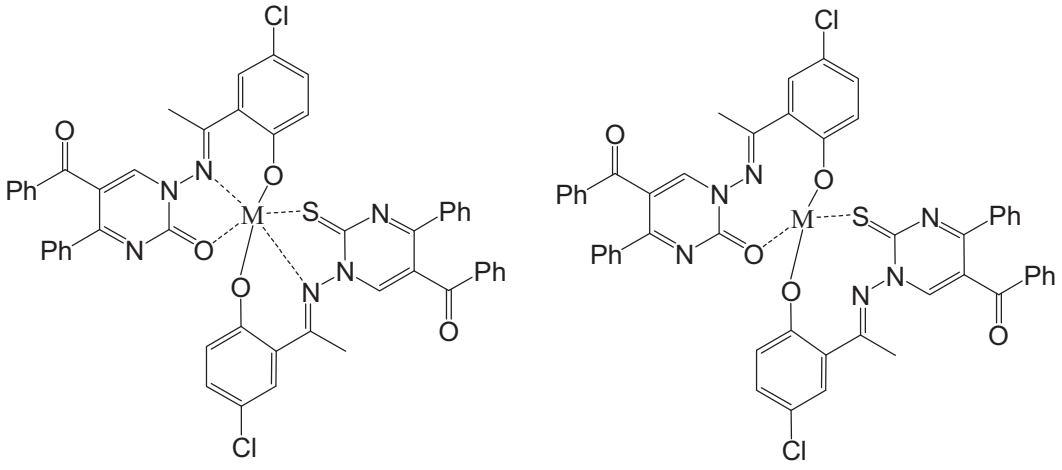

Figure 2. General structure of mixed ligand complexes.

2.2. Mass spectra

In the mass spectra of the mixed ligand metal complexes, peaks were attributable to the molecular ions: m/z: 966.1[Cu+L_1+L+1], m/z: 977 [Co + L_1+L+H_2O]$^+$, m/z: 977 [Ni + L_1+L+H_2O]$^+$, m/z: 956 [Mn + L_1+L]. The spectra of the mixed ligand complexes Cu(II), Mn(II), Ni(II), and Co(II) are shown in Figures 3–6, respectively.

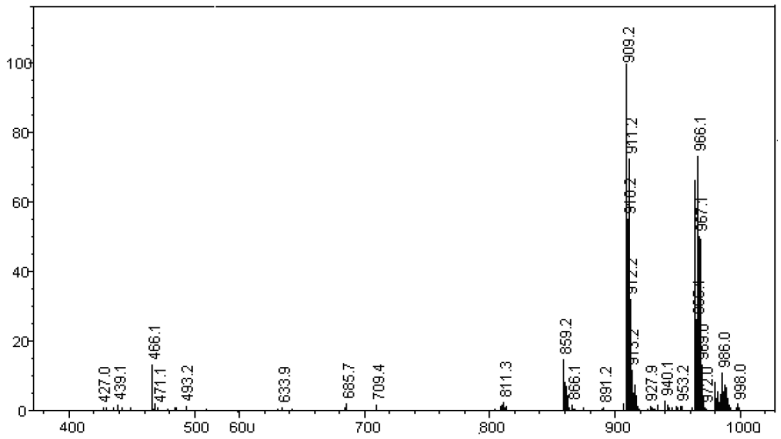

Figure 3. Mass spectrum of Cu(II) complex.

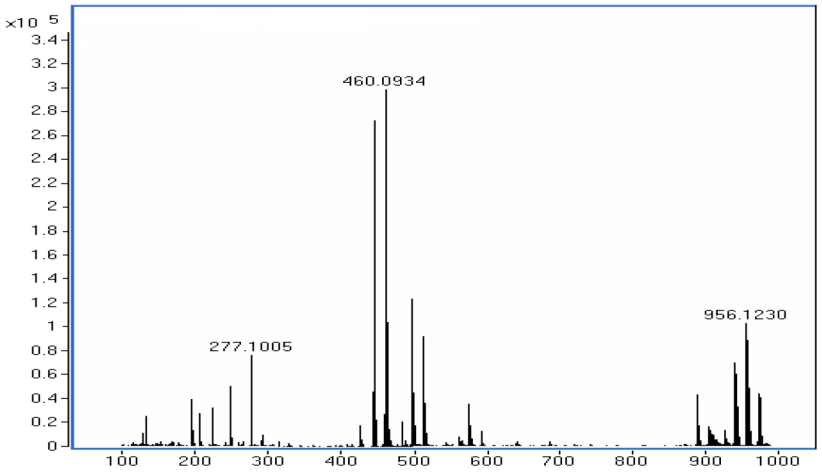

Figure 4. Mass spectrum of Mn(II) complex.

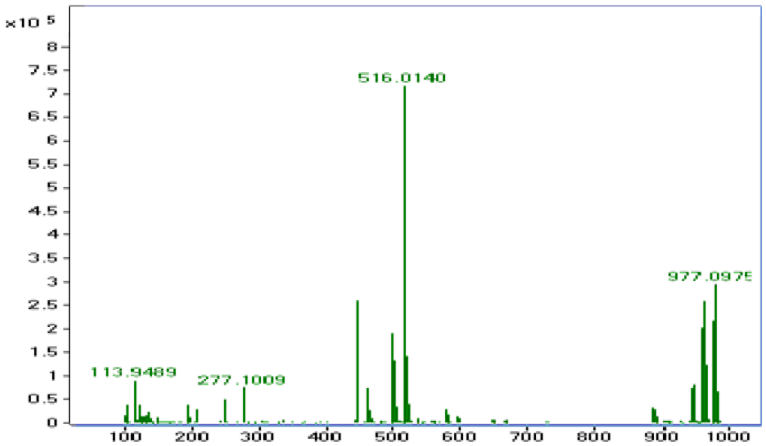

Figure 5. Mass spectrum of Ni(II) complex.

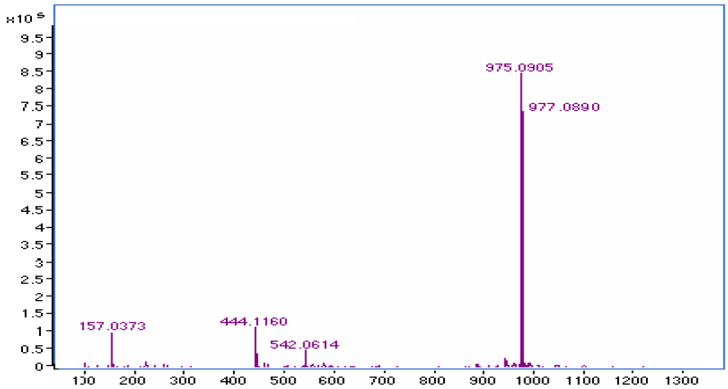

Figure 6. Mass spectrum of Co(II) complex.

2.3. Electronic spectra and magnetic measurements

$[Cu(L_1L)]$, $[Co(L_1L)]\cdot 4H_2O$, $[Ni(L_1L)]\cdot 4H_2O$, and $[Mn(L_1L)]$ mixed complexes exhibit green, brown, dark yellow, and yellow colors in DMF or aqueous solutions, respectively. The electronic spectra of the metal

complexes displayed strong bands in the range of 350–381 nm, which can be assigned to n$\rightarrow \pi^*$, and a charge transfer LMCT band was exhibited in the range of 400–410 nm. On the other hand, the spectra of metal complexes displayed bands in the visible region observed at 422–468 nm, which are assigned to d–d electronic transition. The room temperature magnetic moment of the mixed ligand mononuclear complex of Cu(II) = 1.72–1.80 B.M. almost agrees with the spin-only value of 1.77 B.M. for S = 0.5, as mostly seen for Cu(II) complexes.[21,22] The measured magnetic moment value (3.69 B.M.) of the Co(II) complex was much the same as the spin-only value (3.87 B.M.) and this value complies with values reported for octahedral complexes.[23,24] The Mn(II) complex has a magnetic moment of 5.44 B.M., as expected for high spin distorted octahedral geometry around the central metal ion.[25] The magnetic moment value of 0.52 B.M. for the Ni(II) complex suggests a square planar environment of the structure.[26]

2.4. Proton and carbon nuclear magnetic resonance spectra

DMSO was used as a deuterated solvent to measure the ^{1}H NMR and ^{13}C NMR spectra of the ligand (HL_1). A sharp singlet was observed at about δ 10.68 ppm due to the phenolic proton of the ligand (HL_1).[27] The singlet at δ 9.97 ppm is the proton of the pyrimidine ring. In the spectrum of the Schiff base aromatic protons appeared as a multiplet band between δ 7.01 and 7.61 ppm. The ^{13}C NMR spectrum of HL_1 indicated a signal at 156 ppm, which may be attributed to the C=N group.[28] The spectrum of HL_1 indicated signals in the region 110–147 ppm, due to aromatic carbons. The spectrum of the ligand indicated signals at 195 ppm and 158 ppm, which may be attributed to the C(7)=O and C(2)=O groups, respectively.

2.5. Biological results

Biological activity of the newly prepared ligand and 4 mixed ligand complexes [Ni(L_1L), Mn(L_1L), Cu(L_1L), and Co(L_1L)] was determined toward 4 gram-positive (*S. aureus* ATCC 6538, *S. aureus* ATCC 25923, *B. cereus* ATCC 7064, and *M. luteus* ATCC 9345) and 1 gram-negative (*E. coli* ATCC 4230) bacteria and against 3 yeast species (*C. albicans* ATCC 14053, *C. krusei* ATCC 6258, and *C. parapsilosis* ATCC 22019) by using microdilution. The obtained antimicrobial findings against the tested microorganisms are presented in Tables 1 and 2. The biological activity of HL ligand and its metal complexes has been discussed in a previous manuscript.[15]

Table 1. The MICs* of the (HL) and (HL_1) ligand and mixed ligand complexes against bacterial strains.

Compounds	*Bacillus cereus* ATCC 7064	*Staphylococcus aureus* ATCC 6538	*Staphylococcus aureus* ATCC 25923	*Escherichia coli* ATCC 4230	*Micrococcus luteus* ATCC 9345
(HL)	80	80	80	160	40
(HL_1)	640	640	640	-	640
[Ni(L_1L)]·4H_2O	320	640	640	640	640
[Mn(L_1L)]	320	640	640	320	640
[Cu(L_1L)]	320	640	640	320	640
[Co(L_1L)]·4H_2O	80	160	160	320	80
Ampicillin	5	5	10	20	10

*The MICs values were determined as μg mL^{-1} active compounds in medium.
- No activity.

Table 2. The MICs* of the (HL) and (HL_1) ligand and mixed ligand complexes against fungal strains.

Compounds	*Candida albicans* ATCC 14053	*Candida parapsilosis* ATCC 22019	*Candida krusei* ATCC 6258
(HL)	640	640	640
(HL_1)	640	320	320
[Ni(L_1L)]·4H_2O	320	640	640
[Mn(L_1L)]	320	640	640
[Cu(L_1L)]	160	640	640
[Co(L_1L)]·4H_2O	40	20	20
Fluconazole	5	5	10

* The MICs values were determined as μg mL^{-1} active compounds in medium.

The biological results showed that all tested chemicals prevented the growth of bacteria with MICs between 80 and 640 μg mL^{-1}, also exhibiting antifungal activity with MIC values in the range of 20–640 μg mL^{-1}.

Our results demonstrated that the substance called Co(L_1L) had medium-level antibacterial efficacy against *B. cereus* ATCC 7064 and *M. luteus* ATCC 9345, with a MIC value of 80 μg mL^{-1}. On the other hand, the rest of the tested compounds presented low antibacterial activity against bacteria, with MIC values in the range of 160–640 μg mL^{-1}.

Antiyeast activity values of HL_1 ligand and mixed ligand complexes [Ni(L_1L), Mn(L_1L), Cu(L_1L), and Co(L_1L)] toward 3 *Candida* species are given in Table 2. The results of the antifungal assay exhibited that merely Co(L_1L) complex had high antifungal activity against 3 *Candida* strains (MICs 20–40 μg mL^{-1}). However, some compounds showed low antiyeast activity, with MICs between 160 and 640 μg mL^{-1}.

As a result, the antimicrobial results suggested that Co(L_1L) compound had good antifungal activity against the tested *Candida* species but did not have good antibacterial activity against bacterial strains.

2.6. Molecular modeling results

It is known that geometry optimized structures and Mulliken atomic charge distribution are very important for the present complexes, as given in Figure 7 and Table 3. The complexes that include Ni(II) and Cu(II) metals were computed to have square planar geometry at heterocyclic moieties of ligands (Figures 7A and 7B, respectively), based on the results of electronic spectra and magnetic measurements. The Schiff bases ligand HL was oriented perpendicular to the ligand HL_1. The Co(II) and Mn(II) heterocyclic mixed ligand complexes were found to have six coordinated octahedral and distorted octahedral geometry at the phenyl and pyrimidine moieties of both ligands, respectively (Figures 7C and 7D). In the meantime, Table 3 exhibits the importance of a representative charge distribution in the complexes. Figure 8 also summarizes the charge distribution of the different metal complexes. As seen in Figure 8, the net charges on Ni, Cu, Co, and Mn are about 0.731, –0.0364, 1.932, and 0.730, being lower than the formal charge +2. These cases are a consequence of charge donation from coordinating sulfur, oxygen, and nitrogen atoms. A prominent point of these data is that the Cu compound shows a different trend, when we compare the Ni, Co, and Mn compounds. This arises from the diamagnetic property of Cu metal in the complex.

3. Experimental

3.1. Physical measurements

Elemental analyses (C, H, N, S) were performed using a Thermo Scientific Flash 2000 elemental analyzer. UV-Vis spectra were recorded on a PG Instruments T80+UV/Vis spectrometer. The samples were dissolved in

DMF and the spectra were recorded in the 190–1100 nm range. The magnetic moments of the complexes were measured by the Gouy method on a Sherwood Scientific model instrument. The IR spectra were recorded in the range 4000–400 cm^{-1} on a Shimadzu FTIR (8000) model spectrometer. Molar conductances of the mixed Schiff base ligand metal complexes were determined in DMF at room temperature by using a Thermo Scientific conductivity meter.

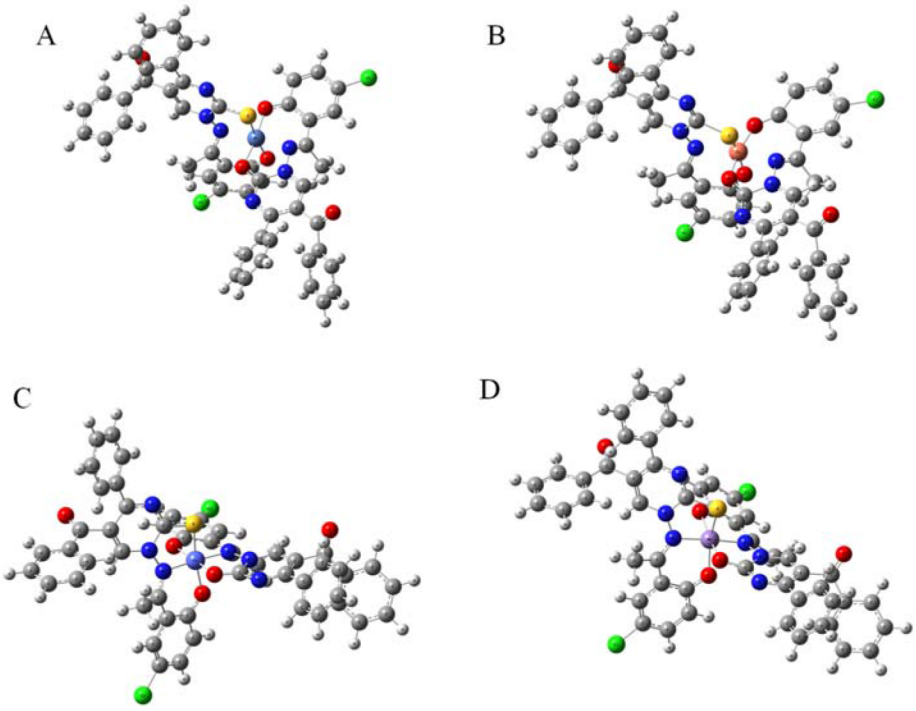

Figure 7. Geometry optimized structures of the complexes.

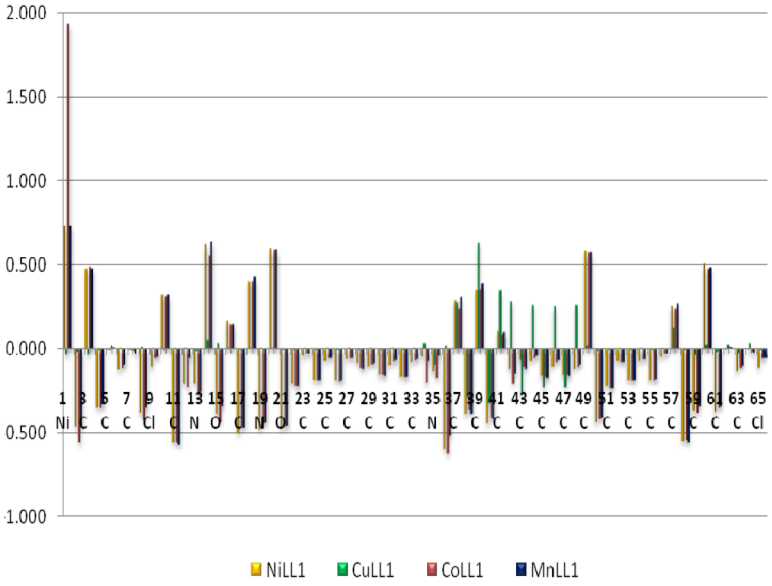

Figure 8. Mulliken atomic charges of the complexes.

Table 3. Mulliken atomic charges of each ligand and complex.

Mulliken atomic charges											
	HL		HL1		NiLL1		CuLL1		CoLL1		MnLL1
				1 Ni	0.73149	**1 Cu**	–0.03645	**1 Co**	1.93208	**1 Mn**	0.73041
1 O	–0.65896	**1 O**	–0.63793	**2 O**	–0.46173	**2 O**	–0.01971	**2 O**	–0.55732	**2 O**	–0.46085
2 C	0.33014	**2 C**	0.30503	**3 C**	0.47586	**3 C**	–0.03541	**3 C**	0.48883	**3 C**	0.47751
3 C	–0.15898	**3 C**	–0.18781	**4 C**	–0.35142	**4 C**	–0.00732	**4 C**	–0.35236	**4 C**	–0.33339
4 C	–0.12568	**4 C**	–0.12677	**5 C**	–0.00669	**5 C**	–0.00445	**5 C**	0.01845	**5 C**	0.00615
5 C	–0.07710	**5 C**	–0.07126	**6 C**	–0.12799	**6 C**	0.00626	**6 C**	–0.11492	**6 C**	–0.09413
6 C	–0.17983	**6 C**	–0.16454	**7 C**	–0.00351	**7 C**	–0.00612	**7 C**	–0.01000	**7 C**	–0.03296
7 C	0.06632	**7 C**	0.07641	**8 C**	–0.38391	**8 C**	0.01052	**8 C**	–0.42606	**8 C**	–0.35242
8 Cl	–0.02849	**8 Cl**	–0.01745	**9 Cl**	–0.10785	**9 Cl**	0.00003	**9 Cl**	–0.05449	**9 Cl**	–0.05050
9 C	0.24087	**9 C**	0.32841	**10 C**	0.31917	**10 C**	–0.00387	**10 C**	0.31271	**10 C**	0.31765
10 C	–0.51482	**10 C**	–0.50783	**11 C**	–0.55368	**11 C**	0.00039	**11 C**	–0.55914	**11 C**	–0.57048
11 N	–0.28109	**11 N**	–0.30469	**12 N**	–0.20680	**12 N**	0.00402	**12 N**	–0.23281	**12 N**	–0.05698
12 N	–0.36967	**12 N**	–0.32800	**13 N**	–0.20825	**13 N**	–0.01251	**13 N**	–0.27798	**13 N**	–0.25373
13 C	0.73940	**13 C**	0.28833	**14 C**	0.61851	**14 C**	0.04771	**14 C**	0.55743	**14 C**	0.62857
14 O	–0.53706	**14 S**	–0.23159	**15 O**	–0.39058	**15 O**	0.02782	**15 O**	–0.43514	**15 O**	–0.34111
15 C	0.11198	**15 C**	0.08720	**16 C**	0.16557	**16 C**	0.00332	**16 C**	0.14292	**16 C**	0.14290
16 C	–0.02523	**16 C**	–0.02500	**17 C**	–0.50475	**17 C**	–0.00382	**17 C**	–0.46438	**17 C**	–0.46837
17 C	0.22206	**17 C**	0.23199	**18 C**	0.40103	**18 C**	0.00613	**18 C**	0.40248	**18 C**	0.42385
18 N	–0.53707	**18 N**	–0.47377	**19 N**	–0.48052	**19 N**	0.00802	**19 N**	–0.44180	**19 N**	–0.44071
19 C	0.29783	**19 C**	0.31738	**20 C**	0.59394	**20 C**	0.00031	**20 C**	0.58464	**20 C**	0.58488
20 O	–0.47399	**20 O**	–0.45252	**21 O**	–0.47532	**21 O**	–0.00023	**21 O**	–0.46075	**21 O**	–0.45978
21 C	0.09487	**21 C**	0.06892	**22 C**	–0.20926	**22 C**	–0.00006	**22 C**	–0.22764	**22 C**	–0.22674
22 C	–0.15367	**22 C**	–0.15121	**23 C**	–0.04688	**23 C**	0.00007	**23 C**	–0.03297	**23 C**	–0.03424
23 C	–0.13437	**23 C**	–0.13414	**24 C**	–0.18955	**24 C**	–0.00006	**24 C**	–0.18975	**24 C**	–0.18888
24 C	–0.11723	**24 C**	–0.11801	**25 C**	–0.07512	**25 C**	0.00006	**25 C**	–0.05521	**25 C**	–0.05638
25 C	–0.13492	**25 C**	–0.13392	**26 C**	–0.18808	**26 C**	–0.00006	**26 C**	–0.19202	**26 C**	–0.19037
26 C	–0.16665	**26 C**	–0.18286	**27 C**	–0.06105	**27 C**	0.00007	**27 C**	–0.05540	**27 C**	–0.05736
27 C	0.10481	**27 C**	0.13149	**28 C**	–0.08519	**28 C**	–0.00441	**28 C**	–0.11328	**28 C**	–0.12120
28 C	–0.17514	**28 C**	–0.15571	**29 C**	–0.10697	**29 C**	0.00529	**29 C**	–0.09299	**29 C**	–0.08723
29 C	–0.13462	**29 C**	–0.13853	**30 C**	–0.15783	**30 C**	–0.00487	**30 C**	–0.15815	**30 C**	–0.16157
30 C	–0.11770	**30 C**	–0.11790	**31 C**	–0.09977	**31 C**	0.00523	**31 C**	–0.07707	**31 C**	–0.07221
31 C	–0.13618	**31 C**	–0.13696	**32 C**	–0.16644	**32 C**	–0.00490	**32 C**	–0.16872	**32 C**	–0.17141
32 C	–0.14630	**32 C**	–0.14890	**33 C**	–0.07951	**33 C**	0.00528	**33 C**	–0.06974	**33 C**	–0.06243
33 H	0.15690	**33 H**	0.13659	**34 S**	–0.04803	**34 S**	0.03326	**34 S**	–0.20346	**34 S**	–0.07776
34 H	0.15985	**34 H**	0.16436	**35 N**	–0.14004	**35 N**	–0.09335	**35 N**	–0.17379	**35 N**	–0.04228
35 H	0.15445	**35 H**	0.17864	**36 O**	–0.59205	**36 O**	0.02027	**36 O**	–0.62525	**36 O**	–0.51805
36 H	0.18189	**36 H**	0.17081	**37 C**	0.28639	**37 C**	0.27758	**37 C**	0.23531	**37 C**	0.30858
37 H	0.16942	**37 H**	0.16880	**38 N**	–0.39076	**38 N**	–0.28997	**38 N**	–0.36559	**38 N**	–0.38541
38 H	0.21705	**38 H**	0.22801	**39 C**	0.35103	**39 C**	0.62669	**39 C**	0.35767	**39 C**	0.38730
39 H	0.21212	**39 H**	0.20087	**40 C**	–0.44310	**40 C**	–0.32563	**40 C**	–0.40955	**40 C**	–0.41620
40 H	0.16316	**40 H**	0.16751	**41 C**	0.10408	**41 C**	0.34336	**41 C**	0.08726	**41 C**	0.09672
41 H	0.14128	**41 H**	0.14363	**42 N**	–0.12134	**42 N**	0.28061	**42 N**	–0.20511	**42 N**	–0.14725
42 H	0.14105	**42 H**	0.14214	**43 C**	–0.07042	**43 C**	–0.27289	**43 C**	–0.10381	**43 C**	–0.12117
43 H	0.14024	**43 H**	0.13996	**44 C**	–0.07344	**44 C**	0.26089	**44 C**	–0.05968	**44 C**	–0.04572
44 H	0.14076	**44 H**	0.14067	**45 C**	–0.16338	**45 C**	–0.23006	**45 C**	–0.16846	**45 C**	–0.17689
45 H	0.15817	**45 H**	0.13228	**46 C**	–0.10397	**46 C**	0.24876	**46 C**	–0.07931	**46 C**	–0.06759
46 H	0.14035	**46 H**	0.13437	**47 C**	–0.15473	**47 C**	–0.23051	**47 C**	–0.15776	**47 C**	–0.16463
47 H	0.13864	**47 H**	0.13472	**48 C**	–0.11935	**48 C**	0.26031	**48 C**	–0.10787	**48 C**	–0.09524
48 H	0.13977	**48 H**	0.13779	**49 C**	0.58154	**49 C**	0.01858	**49 C**	0.57220	**49 C**	0.57292
49 H	0.16115	**49 H**	0.17241	**50 O**	–0.43556	**50 O**	–0.01225	**50 O**	–0.41978	**50 O**	–0.41505

Table 3. Continued.

Mulliken atomic charges											
	HL		HL1		NiLL1		CuLL1		CoLL1		MnLL1
				1 Ni	0.73149	**1 Cu**	–0.03645	**1 Co**	1.93208	**1 Mn**	0.73041
50 H	0.46018	**50 H**	0.41857	**51 C**	–0.22322	**51 C**	–0.00561	**51 C**	–0.23537	**51 C**	–0.23854
				52 C	–0.07846	**52 C**	0.00372	**52 C**	–0.08076	**52 C**	–0.08106
				53 C	–0.18867	**53 C**	–0.00364	**53 C**	–0.19017	**53 C**	–0.18901
				54 C	–0.07771	**54 C**	0.00390	**54 C**	–0.06104	**54 C**	–0.05984
				55 C	–0.18676	**55 C**	–0.00372	**55 C**	–0.18512	**55 C**	–0.18468
				56 C	–0.04727	**56 C**	0.00414	**56 C**	–0.03379	**56 C**	–0.03347
				57 C	0.25060	**57 C**	0.12400	**57 C**	0.23892	**57 C**	0.26714
				58 C	–0.54804	**58 C**	–0.00459	**58 C**	–0.54578	**58 C**	–0.55551
				59 C	–0.37103	**59 C**	–0.03527	**59 C**	–0.37973	**59 C**	–0.34699
				60 C	0.50493	**60 C**	0.02313	**60 C**	0.47459	**60 C**	0.48409
				61 C	–0.37714	**61 C**	–0.02117	**61 C**	–0.35077	**61 C**	–0.34242
				62 C	–0.00125	**62 C**	0.02599	**62 C**	0.01052	**62 C**	0.00348
				63 C	–0.13551	**63 C**	–0.02376	**63 C**	–0.11192	**63 C**	–0.10004
				64 C	–0.00293	**64 C**	0.02900	**64 C**	–0.01925	**64 C**	–0.02707
				65 Cl	–0.11117	**65 Cl**	–0.00028	**65 Cl**	–0.05703	**65 Cl**	–0.05813
				66 H	0.18324	**66 H**	0.00013	**66 H**	0.18964	**66 H**	0.19338
				67 H	0.15396	**67 H**	–0.00040	**67 H**	0.16812	**67 H**	0.17142
				68 H	0.14609	**68 H**	0.00026	**68 H**	0.15362	**68 H**	0.15968
				69 H	0.17494	**69 H**	–0.00011	**69 H**	0.19326	**69 H**	0.19731
				70 H	0.18311	**70 H**	–0.00005	**70 H**	0.18391	**70 H**	0.18938
				71 H	0.20294	**71 H**	–0.00003	**71 H**	0.21061	**71 H**	0.21270
				72 H	0.19062	**72 H**	–0.00033	**72 H**	0.18954	**72 H**	0.19400
				73 H	0.16167	**73 H**	0.00000	**73 H**	0.16600	**73 H**	0.16570
				74 H	0.15779	**74 H**	0.00000	**74 H**	0.16707	**74 H**	0.16683
				75 H	0.14697	**75 H**	0.00000	**75 H**	0.15441	**75 H**	0.15445
				76 H	0.15669	**76 H**	0.00000	**76 H**	0.16089	**76 H**	0.16123
				77 H	0.14690	**77 H**	0.00000	**77 H**	0.13883	**77 H**	0.13992
				78 H	0.15904	**78 H**	–0.00018	**78 H**	0.15822	**78 H**	0.15796
				79 H	0.15588	**79 H**	0.00017	**79 H**	0.16458	**79 H**	0.16515
				80 H	0.14903	**80 H**	–0.00018	**80 H**	0.15739	**80 H**	0.15741
				81 H	0.15573	**81 H**	0.00017	**81 H**	0.16343	**81 H**	0.16475
				82 H	0.16213	**82 H**	–0.00018	**82 H**	0.15876	**82 H**	0.16128
				83 H	0.18502	**83 H**	–0.01130	**83 H**	0.18294	**83 H**	0.19082
				84 H	0.16658	**84 H**	–0.00901	**84 H**	0.16368	**84 H**	0.16643
				85 H	0.15590	**85 H**	0.00817	**85 H**	0.16366	**85 H**	0.16589
				86 H	0.14795	**86 H**	–0.00864	**86 H**	0.15606	**86 H**	0.15659
				87 H	0.15250	**87 H**	0.00817	**87 H**	0.16098	**87 H**	0.16322
				88 H	0.14964	**88 H**	–0.00905	**88 H**	0.15209	**88 H**	0.15193
				89 H	0.14884	**89 H**	–0.00003	**89 H**	0.14060	**89 H**	0.14157
				90 H	0.15653	**90 H**	0.00013	**90 H**	0.15999	**90 H**	0.16132
				91 H	0.14855	**91 H**	–0.00014	**91 H**	0.15571	**91 H**	0.15654
				92 H	0.15981	**92 H**	0.00013	**92 H**	0.16840	**92 H**	0.16899
				93 H	0.16556	**93 H**	–0.00014	**93 H**	0.17016	**93 H**	0.16970
				94 H	0.17476	**94 H**	0.00371	**94 H**	0.18904	**94 H**	0.19161
				95 H	0.19873	**95 H**	0.00060	**95 H**	0.20598	**95 H**	0.21147
				96 H	0.18001	**96 H**	0.00157	**96 H**	0.18080	**96 H**	0.18314
				97 H	0.17678	**97 H**	0.00074	**97 H**	0.18328	**97 H**	0.18600
				98 H	0.15114	**98 H**	–0.00090	**98 H**	0.16743	**98 H**	0.16780
				99 H	0.14478	**99 H**	–0.00103	**99 H**	0.15518	**99 H**	0.15770

3.2. Synthesis of Schiff base ligands and mixed ligand complexes

3.2.1. Synthesis of Schiff base ligand (HL)

1-[[1-(5-Chloro-2-hydroxyphenyl)ethyliden]amino]-4-phenyl-5-benzoyl-pyrimidine-2-thione [HL] was prepared by the reported method.[15]

3.2.2. Synthesis of Schiff base ligand (HL_1)

1-Amino-5-benzoyl-4-phenyl-1H-pyrimidine-2-one/thione (*N*-aminopyrimidine-2-one/*N*-amino pyrimidine-2-thione) was prepared according to the literature.[29,30] The Schiff bases ligand (1-[[1-(5-chloro-2-hydroxyphenyl) ethyliden]amino]-4-phenyl-5-benzoyl-pyrimidine-2-one) (HL_1) was synthesized by a condensation method. *N*-aminopyrimidine-2-one (0.291 g, 0.1 mmol) was dissolved in n-butanol (40 mL) and was added to a solution of 5-chloro-2-hydroxyacethophenone (0.17 g, 0.1 mmol) and sodium acetate catalyst. The mixture was heated to 100 °C and kept at this temperature for 24 h. After cooling to room temperature the residue was filtered and the crude solid product was purified by recrystallization from an acetonitrile–methanol (4:1) mixture. Yield was HL_1: 0.350 g (79%), mp 311–312 °C. IR (ATR) (υ_{max}, cm^{-1}): 3205 (OH), 1686 $(C{=}O)_{benzoyl}$, 1649 $(–C{=}O)_{Pyrimidine}$, 1609 (C=N), 1342 $(C\text{-}O)_{phenolic}$. ^{1}H NMR (400 MHz, d_6-DMSO) δ (ppm); s, singlet; d, doublet; m, multiplet: 10.67 (s, 1H, OH proton), 9.95 (s, 1H, H-6), 7.61 (s, 2H, H-2′, H-6′), 7.47 (s, 2H, H-2″ , H-6″), 7.35 (d_d, 1H, H-6‴); 7.21 (d, 1H, J =7.28 Hz, H-4‴), 7.07–7.17 (m, 6H, Harm). 7.01 (d, 1H, J= 8.8 Hz, H-3‴). ^{13}C NMR (d_6-DMSO, ppm), δ 195.06 $(C{=}O)_{benzoyl}$, 158.24 $(C{=}O)_{pyrimidine\,ring}$, 156.17 (C=N), 147.96 (C6), 147.64 (C5), 139.54 (C4), 133.28 (C2‴), 131.87 (C5‴), 130.42 (C3‴), 129.31 (C4‴), 128.54 (C6‴), 128.27 (C1‴), 128.04 (C1′), 123.57 (C1″), 118.82 (C4′, C4″), 118.35 (C3′, C3″ , C5′, C5″), 109.87 (C2′, C2″ , C6″ , C6″), 58.51 (CH_3–C=N). UV-Vis (DMF) λmax (log ε): 330 (0.377), 303 (0.251) nm. LC-MS, m/z: 444.1 [HL_1+H^+]. Anal. Calc. for $C_{25}H_{18}ClN_3O_3$ (443.88): C, 67.65; H, 4.09; N, 9.47. Found: C, 67.89; H, 4.05; N, 10.04%.

3.2.3. General procedure for the preparation of mixed ligand complexes

First 0.110 g (0.25 mmol) (HL_1) of the ligand and 0.115 g (0.25 mmol) (HL) were solved in 30 mL of THF/MeOH (4:1) mixture, and a solution of 0.25 mmol of the metal salt $Cu(AcO)_2{\cdot}H_2O$, $Co(AcO)_2{\cdot}4H_2O$, $Ni(AcO)_2{\cdot}4H_2O$ or $Mn(AcO)_2{\cdot}2H_2O$ in 10 mL of methanol was added dropwise with continuous stirring. The mixture was stirred further for 30 min at 70 °C. The product separated out solid was filtered, washed with cold methanol, and dried.

[$Cu(L_1L)$]: Dark green compound. Yield: 0.121 g (50%); 239 °C decompose. IR (ATR) (υ_{max}, cm^{-1}): 2970 (Aliphatic C–H); 1738, 1688 (C=O), 1607 (C=N), 1364 $(C–O)_{phenolic}$, 1217 (C=S). UV-Vis (DMF) λmax (log ε): 456 (0.180), 397.91 (0.139), 350.71 (0.296), 328 (0.495), 282 (0.506). μ_{eff}: 1.77 BM. Λ_M (10^{-3} M, in DMF, μS/cm): 4.51. API-ES, m/z: 966.1 [Cu+L_1+L+H]. Anal. Calc. for $C_{50}H_{34}Cl_2CuN_6O_5S$ (965.4): C, 61.82; H, 4.12; N, 8.18; S, 3.10. Found: C, 61.45; H, 3.81; N, 8.19; S, 2.55%.

[$Co(L_1L)$]$\cdot 4H_2O$: Brown compound. Yield: 0.116 g (45%); 258 °C decompose. IR (ATR) (υ_{max}, cm^{-1}): 3027, 2970 (Aliphatic C–H); 1738, 1687 (C=O), 1595 (C=N), 1365 $(C–O)_{phenolic}$, 1216 (C=S). UV-Vis (DMF) λmax (log ε): 422 (0.129), 355.73 (0.249), 328 (0.495), 282 (0.523). μ_{eff}: 3.69 BM. Λ_M (10^{-3} M, in DMF, μS/cm): 2.95. API-ES, m/z: 977 [Co + L_1+L+H_2O]$^+$. Anal. Calc. for $C_{50}H_{42}Cl_2CoN_6O_9S$ (1032.8): C, 58.15; H, 4.10; N, 8.14; S, 3.10. Found: C, 58.21; H, 4.10; N, 8.08; S, 3.50%.

[Ni(L_1L)]·4H_2O: Dark yellow compound. Yield: 0.095 g (37%); 241 °C decompose. IR (ATR) (v_{max}, cm^{-1}): 3061 (Aliphatic C–H); 1733 (C=O), 1606 (C=N), 1327 (C–O)$_{phenolic}$, 1214 (C=S). UV-Vis (DMF) λmax (log ε): 468 (0.094), 352.72 (0.244), 330 (0.301), 276 (0.451), 265 (0.589). μ_{eff}: 0.52 BM. Λ_M (10^{-3} M, in DMF, μS/cm): 2.58. API-ES, m/z: 977 [Ni + L_1+L+H_2O]$^+$. Anal. Calc. for $C_{50}H_{42}Cl_2NiN_6O_9S$ (1032.56): C, 58.16; H, 4.10; N, 8.14; S, 3.11. Found: C, 58.13; H, 3.62; N, 8.16; S, 2.54%.

[Mn(L_1L)]: Yellow compound. Yield: 0.12 g (50%); 265–266 °C. IR (ATR) (v_{max}, cm^{-1}): 3102 (Aliphatic C–H); 1691, 1627 (C=O), 1596 (C=N), 1326 (C–O)$_{phenolic}$, 1218 (C=S). UV-Vis (DMF) λmax (log ε): 445 (0.037), 381.84 (0.244), 336 (0.616), 290 (0.583), 265 (0.865). μ_{eff}: 5.44 BM. Λ_M (10^{-3} M, in DMF, μS/cm): 2.46. API-ES, m/z: 956 [Mn + L_1+L]$^+$. Anal. Calc. for $C_{50}H_{34}Cl_2MnN_6O_5S$ (956.7): C, 62.77; H, 3.58; N, 8.78; S, 3.35. Found: C, 62.52; H, 3.90; N, 8.54; S, 3.69%.

3.3. Biological assay

3.3.1. Compounds

The newly synthesized chemical substances and standard antibiotics were dissolved in DMSO (12.5%) at an initial concentration 1280 μg mL^{-1} and then two-fold serial dilutions of all tested chemicals were prepared in approved broth medium.

3.3.2. Microorganisms

The tested microorganisms using in the study were supplied from the American Types Culture Collection and Refik Saydam Hıfsısıhha Research Institute, Ankara, Turkey.

3.3.3. Antimicrobial procedures

Antibacterial efficiency of all the chemicals was screened toward the tested bacterial strains as summarized by the guidelines in the NCCLS proposed standard document M7-A6 with the conventional microdilution procedure.[31] The tested bacterial strains were *Staphylococcus aureus* ATCC 6538, *S. aureus* ATCC 25923, *Bacillus cereus* ATCC 7064, *Micrococcus luteus* ATCC 9345, and *Escherichia coli* ATCC 4230. The yeast activities of the compounds were also evaluated against 3 *Candida* species (*Candida albicans* ATCC 14053, *C. krusei* ATCC 6258, and *C. parapsilosis* ATCC 22019) as mentioned by the guidelines in the NCCLS recommended standard document M27-A2 with the microdilution procedure.[32] Ampicillin for bacteria and fluconazole for yeasts were chosen as standard drugs. Two-fold serial dilutions of chemicals and standard antibiotics were prepared to reach the final concentrations as follows: 1280, 640, 320, 160, 80, 40, 20, 10, >5 μg mL^{-1}. One noninoculated tube was defined as the negative control, while one inoculated tube with bacterial suspension was selected as the positive control.

Antimicrobial activity assays were carried out in Mueller–Hinton broth (DIFCO) medium at pH 7.2 for bacterial strains and in RPMI 1640 medium (Sigma) at pH 7.0 for yeast with an inoculum of (1–2) × 10^3 cells mL^{-1} according to the modified spectrophotometric method.[33] All serial tube dilutions inoculated with each microorganism were cultivated at 37 °C for 18 h at 150 rpm in an orbital rotary shaker. The minimum inhibitory concentrations (MICs) of all the chemicals were recorded as the lowest concentration of each chemical substance in comparison with negative controls (no turbidity).

3.3.4. Molecular modeling

In an attempt to gain a better insight into the molecular structure of the ligands and their complexes, geometry optimization was carried out using density functional theory at B3LYP/6-31G* level for the ligands and the semiempirical method at PM6 with no symmetry constrains for the complexes as implemented in Gaussian 09.[34]

4. Conclusion

New Ni(II), Cu(II), Co(II), and Mn(II) heterocyclic mixed ligand complexes containing a pyrimidine ring were synthesized and characterized. Analytical data, electronic spectra, and magnetic susceptibility, IR mass spectral, and molecular modeling data reveal square planar and distorted octahedral geometry for the complexes. Various attempts such as crystallization using mixtures of solvents, and low temperature crystallization were unsuccessful to obtain a single crystal for X-ray crystallography. However, the analytical, spectroscopic, and magnetic data enable us to predict the possible structure of the synthesized complexes. The newly prepared HL_1 ligand and mixed ligand complexes were screened for their in vitro antimicrobial properties against some bacteria and yeast. The compound named $[Co(L_1L)].4H_2O$ had good antifungal efficiency towards *Candida* species, with MIC values in the range of 20–40 $\mu g\ mL^{-1}$. Multiple drug resistance or multiresistant microorganisms are a significant public health problem in the medical environment all over the world and therefore there is an urgent need to find new drugs. In conclusion, we hope that the $[CoL_1L].4H_2O$ chemical compound can be effective against fungi.

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