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SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL STUDIES OF CIPROFLOXACI-IMINES AND THEIR COMPLEXES WITH OXOZIRCONIUM(IV), DIOXOMOLYBDENUM(VI), AND DIOXOTUNGSTEN(VI)

Amaal Y. Al-Assafe[1*] and Rana A.S. Al-Quaba[2]

[1] Chemistry Department, College of Education for Pure Science, University of Mosul, Iraq
[2]Chemistry Department, College of Science, University of Mosul, Iraq

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ABSTRACT. We synthesized and characterized ciprofloxacin-imine complexes, generated from ciprofloxacin and either 4-nitro-1,2-phenylenediamine (NO_2PD) or 1,3-propanediamine (PD), in conjunction with zirconyl nitrate dihydrate, sodium molybdate dihydrate, and sodium tungstate dihydrate. Characterization involved numerous analytical methods, containing melting point determination, conductance dimensions, elemental analysis (CHN), metal content determination (%), infrared, electronic spectra, nuclear magnetic resonance, and mass spectrometry. Our findings reveal that the ligand as functions a tetra-dentate chelate binding to metal ions via azomethine and deprotonated carboxylate group. Additionally, the complexes and ligands were tested in contradiction of two types of bacteria (*Staphylococcus aureus*, *Bacillus subtilis*) and all prepared compounds showed good spectrum activity.

KEY WORDS: 4-Nitro-1,2-phenylenediamine, Ciprofloxacin-imine, In-vitro antimicrobial activity, Zr complexes

INTRODUCTION

Schiff bases belong to the most common organic chemicals, play multifaceted roles in various domains. They function as stabilizers in polymers, catalysts in chemical reactions, and contribute to the vibrant world of dyes and pigments [1]. Moreover, Schiff bases show a diverse array of biological actions, encompassing antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic possessions [2]. They have even played a pivotal role in the improvement of chemotherapy agents for combating cancer [3]. Imines or azomethine groups, found in numerous natural, naturally derived, and synthetic complexes, have been shown to be indispensable for the biological actions of these substances [4-6]. Schiff bases are versatile, interact with several metals and are stable in a wide range of oxidation states. Consequently, Schiff-base complexes serve as invaluable models for studying biological systems and catalysts in catalytic reactions [7]. In the realms of industrial, medicinal, and agricultural chemistry, metal complexes hold significant importance [8]. Additionally, aromatic Schiff bases and their metal compounds have demonstrated catalytic prowess in processes such as, biological oxygen carrier systems, hydrolysis, electro-reduction, and decomposition [9]. Notably tetra-dentate ligands containing donor atom (N_2O_2) have attracted considerable attention for their ability to interact with different metal ions. Several works have investigated the fluoroquinolone drug Schiff base. [10-12].

In this work, our primary objectives revolve around preparation and characterization of six novel complexes, featuring a new ciprofloxacin-imine, denoted as CIP-NO_2PD or CIP-PD. Our aim is to explore how these compounds impact antibacterial activity in comparison to free ciprofloxacin. To achieve this, we utilized a comprehensive set of analytical methods, such as molar conductance measurements, elemental analyzes, IR and UV-Vis spectroscopy, as well as ^{1}H, ^{13}C NMR, and mass spectroscopy. Subsequently, we employed Gram-positive bacterial species like *Staphylococcus aurous* and Gram-negative *Bacillus subtilis* to evaluate the

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*Corresponding authors. E-mail: amaalyounis62@uomosul.edu.iq antibacterial action of the investigated compounds. In summary, this study focus on the preparation and characterization of new compounds and their impact on antibacterial properties, using ciprofloxacin-imine as a key player.

EXPERIMENTAL

Materials

High purity chemicals have been, so that, they did not need to be purified. Pure (generic) ciprofloxacin was sourced from Sammra Drug Company in Iraq. Zirconium nitrate hydrate ($ZrO(NO_3)_2.2H_2O$), sodium molybdate dihydrate ($Na_2MoO_4.2H_2O$), sodium tungstate dihydrate ($Na_2WO_4.2H_2O$), 4-nitro-*o*-phenylenediamine (NO_2PD), and 1,3-propanediamine (PD) were acquired from Chemical Company (Aldrich).

Instrumentation

FT-IR spectra were measured using a "Shimadzu FT-IR84005 Spectrophotometer", Japan, at Education for Pure Sciences College, University of Tikrit, at wave number 400-4000 cm^{-1}. (KBr disc). The ^1H NMR and ^{13}C NMR tests were carried out at College of Sciences University of Basra using Bruker-DRX system at 400 MHz, (TMS) as standard in DMSO-d_6."Shimadzu UV-Visible spectrophotometer Ultra Violet-1800 Spectrophotometer," was used for electronic spectra measurements at 10^{-3} M of ligands and their complexes in DMF at 25 ^oC at wave range 190-1100 nm. The GCMSQp2010 Ultra Gas Ghramatography Mass spectroscopy, Shimadzu measurement device was used to determine their molecular weight at center laboratory of Samarra University. Element microanalyses were carried out using a Leco 932 USA Elemental Analyzer (CHN). Molar conductivity of the synthesized complexes have been measured at 25 ^oC using a HANNA EC214 conductivity meter for 10^{-3} M solution in dimethylformamide (DMF). The metal content of complexes was evaluated spectrophotometrically utilizing atomic absorption spectroscopy Analytik Jena GmbH-novAA350.

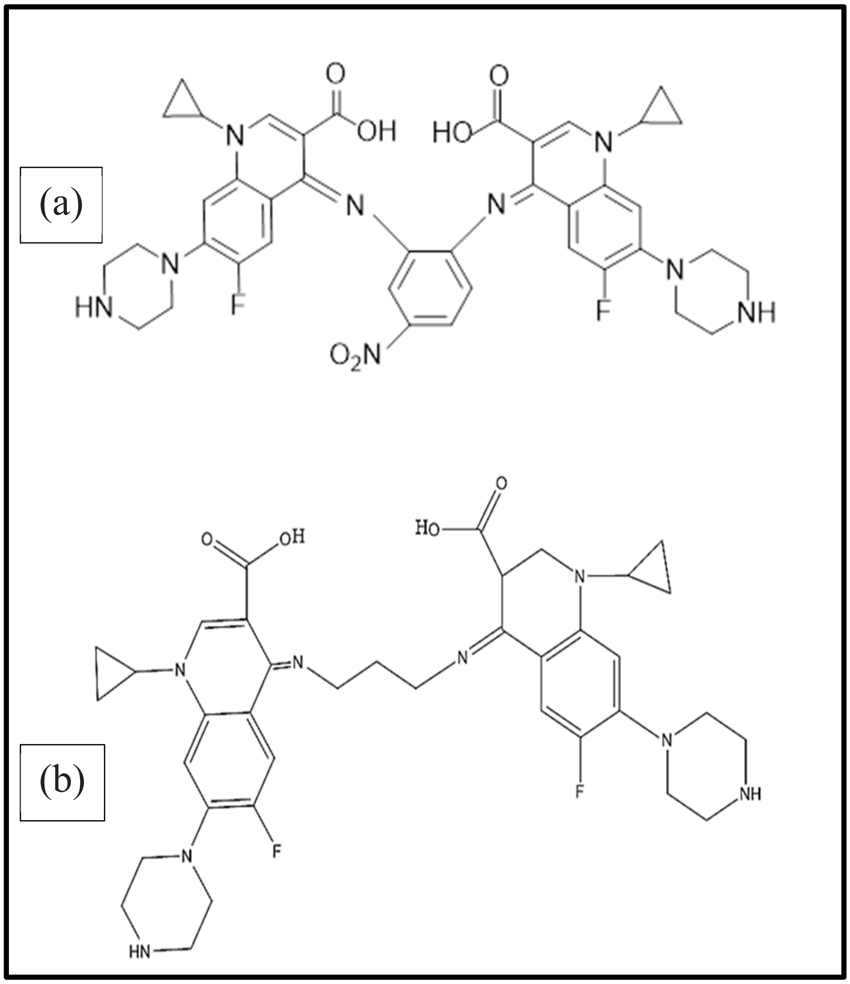
Synthesis

Synthesis of ciprofloxacin-imines

The Schiff- base ligand, denoted as HL_1 and HL_2, was synthesized following a modified version of established literature procedures [13, 14]. In separate reactions, ciprofloxacin (2 mmol, 0.662 g), (10 mL) ethanolic solution was mixed in either 4-nitro-1,2-phenylenediamine (NO_2PD) (1 mmol, 0.153 g) or 1,3-propanediamine (PD) (1 mmol, 0.074 g). These mixtures were subjected to reflux conditions in presence of glacial CH_3COOH for a duration of 4 hours. Subsequently, the resulting solutions were concentrated to a final volume (8 mL) and allowed to cool. Colored solid precipitates were obtained, filtered, thoroughly wash away with cold ethanol, and finally dried Scheme 1.

Preparation of metal compounds

Solid compounds were set by the gradual addition of 1 mmol each of $ZrO(NO_3)_2{\cdot}2H_2O$, $Na_2MoO_4{\cdot}2H_2O$, and $Na_2WO_4{\cdot}2H_2O$ to a vigorously stirred suspension containing 2 mmol of (cip-4-NO_2Phdn/cip-PD) in ethanol (20 mL). The reaction was maintained under continuous stirring and reflux conditions for 4 h. After the end of the reaction, the product was left to cool, then filtered, followed by washing with ethanol and subsequent drying.



Scheme 1. (a). Molecuer structure of cip-4-NO_2Phdn = (Z)-4-((4-nitro-o-aminophenyl)imino)-bis-1-cyclo-6-fluoro-7-(piperazine-1-yl)-1-4-dihydroquinoline-3-carboxylic acid ligand (H_2L_1). (b) Molecuer structure of cip-PD = (Z)-4-(3-aminopropyl)imino)-bis-1-cyclo-6-fluoro-7-(piperazine-1-yl)-1-4-dihydroquinoline-3-carboxylic acid ligand (H_2L_2)" .

Bacterial activity of the synthesized compounds

Verification the bacterial activity of the synthesized compounds involved the preparation and utilization of Hinton Mueller agar culture medium following the protocols established by an Indian reference. This process commenced with the dissolution of 38 g of agar in one liter of boiling purified water. The resulting solution was carefully modified to achieve the desired pH level and subsequently placed in an autoclave operating at 121 °C and 150 pound/inch for a duration of 15 min.

Following sterilization, it was permitted to cool to 50 °C. Subsequently, the microbial liquid was aseptically poured into Petri dishes, each with a uniform 2 mm thickness, and left undisturbed until precipitation occurred. The prepared Petri dishes were then transferred to an incubator and maintained at 37 °C for a 24-hour period to ensure the absence of any potential contamination. Solvent (DMSO) was added to the compounds to prepare a solution with 10 µg/ml concentration.

RESULTS AND DISCUSSION

Elemental analysis and molar conductivity

Ciprofloxacin-imine complexes denoted as H_2L_1 and H_2L_2, were synthesized in solid form with Zr(IV), Mo(VI), and W(VI) ions. These complexes exhibited distinct colors corresponding to the respective metal ions. Table 1 provides a summary of the CHN, metal content, melting points, molar conductance of prepared complexes.

The data obtained from this study revealed that all isolated complexes were formed from respective metal salts and H_2L_1 or H_2L_2 reaction in molar ratio (1:1). Additionally, these complexes remained stable as solids when stored at room temperature. Elemental analysis supported the proposed formulas for the complex structures, showing good agreement among the experimental and theoretical values of CHN (%) and metal content (%). This alignment in quantitative analysis substantiated the correctness of the synthesized complexes molecular formulas. Furthermore, conductance measurements for isolated complexes in (10^{-3}M solution) DMF as solvent indicated that none of them acted as electrolytes [13], as detailed in Table 1.

Table 1. Physico-chemical and elemental analyses data for CIP-4-NO_2phdn, CIP-PD and its metal complexes.

No.	Compound	Color	M.P. C°	Yield %	M.Wt. $g.mol^{-1}$	Elemental analysis% found/(calc.) C	H	N	Metal% found/ (calc.)	Λ (DMF) cm^2 ohm^{-1} mol^{-1}
L_1	$H_2L_1(C_{40}H_{39}N_9O_6F_2)$	Orange	155-158	90	779	60.98 (61.61)	4.74 (5.00)	16.01 (16.17)	--	--
L_2	$H_2L_2(C_{37}H_{42}N_8O_4F_2)$	White	105-107	92	700	63.23 (63.42)	5.87 (6.00)	15.56 (16.00)	--	--
1	$[ZrO(Cip-NO_2PD)(H_2O)]).3H_2O$	Orange red	194-196	53	902.024	52.99 (53.21)	4.76 (4.98)	13.23 (13.96)	9.98 (10.11)	15
2	$[MoO_2(Cip-NO_2PD)]$	Dark yellow	190-192	55	904.95	52.68 (53.04)	3.94 (4.08)	13.21 (13.92)	10.36 (10.60)	30
3	$[WO_2(Cip-NO_2PD)]$	Dark orange	145-147	57	992.84	48.10 (48.34)	2.87 (3.72)	12.41 (12.69)	17.27 (18.51)	32
4	$[ZrO(Cip-PD)(H_2O)].3H_2O$	Off white	215-217	50	823.22	51.45 (52.04)	5.05 (5.10)	12.71 (13.60)	10.89 (11.08)	16
5	$[MoO_2(Cip-PD)]$	White	173-175	53	825.95	53.31 (53.75)	4.31 (4.84)	13.15 (13.56)	11.27 (11.61)	40
6	$[WO_2(Cip-PD)]$	White	236-238	55	913.84	48.18 (48.58)	3.98 (4.37)	11.97 (12.25)	19.89 (20.11)	35

Infrared spectroscopy

The infrared spectra of both ciprofloxacin imine and their compounds meticulously prepared, and then measured using KBr discs, have been meticulously presented in Table 2. A detailed analysis was conducted, comparing the FT-IR spectra of Schiff base to the synthesized compounds, with the primary objective of discerning the binding mechanism of these freshly crafted compounds.

Notably, alterations in peak positions and intensities were observed as a consequence of the complexation process.

The infrared spectra of the CIP-imine reveal absence of peaks associated with ν(NH_2) group which found in 4-nitro phenylenediamine or 1,3-propanamide [14, 15]. In contrast, two prominent bands at (1703, 1787, 1625, 1631) cm^{-1}, because of the extending vibrations of carbonyl and isomethine groups, respectively [16].

Peaks at (1703, 1787) cm^{-1} assignable to the carboxyclic group of cip-imine were absent in the metal complexes, coupled with the characteristic azomethine band shifting from (1625, 1631 cm^{-1}) in the CIP-imine to lower wavenumbers for all complexes, reveales that nitrogen azomethine group and oxygen carboxylate group of Schiff base coordination to metal ions with deprotonated carboxylic group [17].

The antisymmetric and symmetric (COO) stretches have been displaced to anew frequencies (higher or lower) in monodentate carboxylate ligand with an average $\Delta\nu > 200$. For our metal cip-Schiff base complexes the presence of peak at 1625-1641 cm^{-1}in the infrared spectra indicated the presence of the asymmetric stretching vibration of the connected carboxylate set, while the other vibrations that occurs at 1471-1488 cm^{-1} with $\Delta\nu > 200$ cm^{-1} showed that the carboxylate groups acts as mono-dentate through one oxygen atom [18, 19] .

Cip-imine compounds spectra revealed series of peaks at 951-982, 541-621, and 418-464 cm^{-1} with varying intensities that corresponded to νM=O [20], νM-O and νM-N, respectively [16].

Those peaks are absent in the CIP-imine spectrum, signifying the coordination of CIP-imine via nitrogen azomethane and oxygen carboxylic groups [21]. The coordinated water molecues in coordinated zirconium complexes were found in the IR spectra at 3429-3454 cm^{-1}, along with two weaker bands that were identified as the OH stretching at νr(823-883) cm^{-1} and at νw(656-669) cm^{-1} [22]. Notably, the spectra of uncoordinated ligands do not contain any of these vibrations (Figure 1).

Table 2. IR data list of cip-imine and their complexes in cm^{-1}.

No.	Compound	νC=O	νC-O	νC=N	νCOO$^-$	νM-N	νM-O	νM=O	νH_2O
L_1	Cip-4-NO_2Phdn (HL_1)	1703	1282	1631	1508 1481				
L_2	Cip-PD(HL_2)	1787	1255	1625	1571 1486				
1	[ZrO(Cip-4-		1301	1595	1633	464	545	1091	3429
2	[MoO_2(Cip-4-NO_2Phdn)]		1298	1585	1629 1475	457	545	1029 945	
3	[WO_2(Cip-4-NO_2Phdn)]		1303	1598	1641 1473	460	541	1012 943	
4	[ZrO(Cip-PD)(H_2O)].3H_2O		1255	1569	1625 1487	418	621	1035	3454
5	[MoO_2(Cip-PD)]		1259	1568	1631 1488	459	545	1031 941	
6	[WO_2(Cip-PD)]		1253	1579	1631 1487	460	584	1031 997	

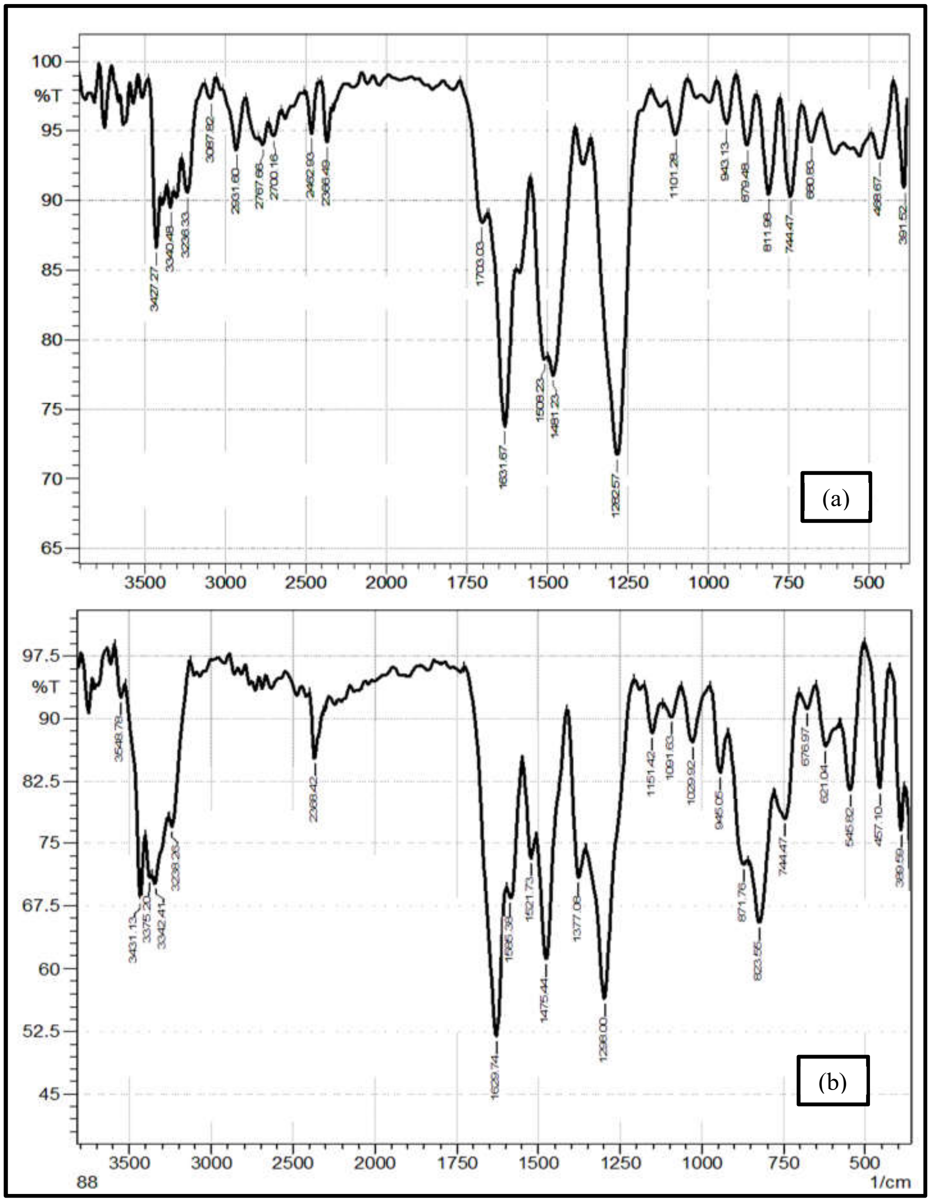


Figure 1. (a) IR spectra of Cip-4-NO_2Phdn (H_2L_1) and (b) IR spectra of [MoO_2(Cip-4-NO_2Phdn).

Electronic spectra

The electronic spectra of H_2L_1 and H_2L_2 along compounds at 200-1100 nm are listed in Table 3. Notably, distinctive peaks emerge wavelengths at 37363-37735 cm^{-1} may be signified to ($\pi \rightarrow \pi^*$) transition and at 34982, 35211 cm^{-1} are assigned to ($n \rightarrow \pi^*$) transition in cip–imine [23]. Such transitions typically manifest in unsaturated hydrocarbons that incorporate ketone or azomethine groups [19]. It is noteworthy that upon comparison with their respective complexes (Table 3), these bands exhibit a discernible shift towards higher wavelengths. This phenomenon, known as a bathochromic shift, is indicative of complex formation. Furthermore, the reflectance spectrum of the complexes displays appearance peaks at 29946-33000 cm^{-1}. These newly emerged bands are likely related to charge-transfer transitions [24, 25].

Table 3. Electronic spectral data on metal complexes and (H_2L_1, H_2L_2) ligands, in (DMF 10^{-3} M).

No.	Compounds	Absorption cm^{-1}	Assignment
L_1	H_2L_1	37735	$\pi \rightarrow \pi^*$
		35211	$n \rightarrow \pi^*$
L_2	H_2L_2	37363	$\pi \rightarrow \pi^*$
		34982	$n \rightarrow \pi^*$
1	[ZrO(Cip-4-NO_2Phdn)(H_2O)]).3H_2O	36363	$\pi \rightarrow \pi^*$
		34246	$n \rightarrow \pi^*$
		29946	C.T
2	[MoO_2(Cip-4-NO_2Phdn)]	36303	$\pi \rightarrow \pi^*$
		34567	$n \rightarrow \pi^*$
		30120	C.T
3	[WO_2(Cip-4-NO_2Phdn)	36349	$\pi \rightarrow \pi^*$
		34130	$n \rightarrow \pi^*$
		30769	C.T
4	[ZrO(Cip-PD)(H_2O)].3H_2O	36343	$\pi \rightarrow \pi^*$
		34227	$n \rightarrow \pi^*$
		32557	C.T
5	[MoO_2(Cip-PD)]	36370	$\pi \rightarrow \pi^*$
		34119	C.T
		30674	
6	[WO_2(Cip-PD)]	36206	$\pi \rightarrow \pi^*$
		34075	$n \rightarrow \pi^*$
		33000	C.T

NMR spectra

To verify the suggested structure of the prepared compounds we conducted ^{1}H-NMR spectroscopy using DMSO-d_6 (Table 4). Upon comparing the prominent peaks of the Schiff base ligands and their compounds, we noticed that all signals from the ligand were retained in complex spectrum, indicating chemical shifts following the coordinating of Schiff base with metal ion (Figure 2) [26, 27].

Table 4. ^{1}H-NMR, ^{13}C-NMR spectral data of TMP and some complexes.

Compounds	^{1}H NMR – spectral data	^{13}C-NMR spectra data
(Cip-4-NO_2-Phdn)HL_1	δ_H (400 MHz, DMSO-d_6) 8.68 (1 H, s), 7.95 (2 H, d, *J* 13.1 Hz), 7.60 (2 H, d, *J* 7.4 Hz), 7.42 (1 H, d, *J* 2.6 Hz), 7.39 (1 H, dd, *J* 6.7, 2.6 Hz), 3.90 – 3.82 (2 H, t, *J* 5.1 Hz), 3.55 (2 H, t, *J* 4.9 Hz), 3.42 (1 H, p, *J* 9.3 Hz), 3.36 – 3.28 (4 H, m), 1.86 (1 H, s), 1.32 (2 H, q, *J* 6.5 Hz), 1.22 – 1.16 (2 H, m).	δ_C (101 MHz, DMSO-d_6) 176.4, 165.9, 148.2, 143.4, 139.0, 136.8, 134.0, 115.6, 111.4, 108.0, 106.9, 46.3, 42.5, 36.0,7.6.
Cip-PD(HL_2)	δ_H (400 MHz, DMSO-d_6) 8.55 (1 H, s), 7.82 (1 H, d, *J* 13.6 Hz), 7.46 (1 H, d, *J* 7.4 Hz), 4.33 – 3.61 (2H, m), 3.18 (4 H, m), 2.88 (1 H, p), 2.83 (4 H, td, *J* 5.1, 1.7 Hz), 2.68 (2H, m), 1.88 (1 H, s), 1.56 (2 H, dt, *J* 13.4, 6.6 Hz), 1.73 (2 H, s),1.28 (2 H, m), 1.09 (2 H, m).	
[ZrO(Cip-4-NO_2Phdn)(H_2O)]).3H_2O	δ_H (400 MHz, DMSO-d6) 8.68 (2 H, s), 7.96 (1 H, d, J 13.1 Hz), 7.48 (1 H, d, J 7.5 Hz), 7.14 (2 H, dd, J 10.0, 7.9 Hz), 6.52 (2 H, d, J 8.6 Hz), 3.59 (4 H, t, *J* 5.1), 3.43 (4 H, t, *J* 5.0), 3.07 (2 H, p, *J* 9.1), 2.83 (8 H, td, *J* 5.1, 1.3), 1.83 (2 H, s), 1.06 (4 H, m), 1.02 (4 H, m).	δ_C (101 MHz, DMSO-d_6) 143.4, 136.8, 134.0, 115.6, 111.4, 108.0.

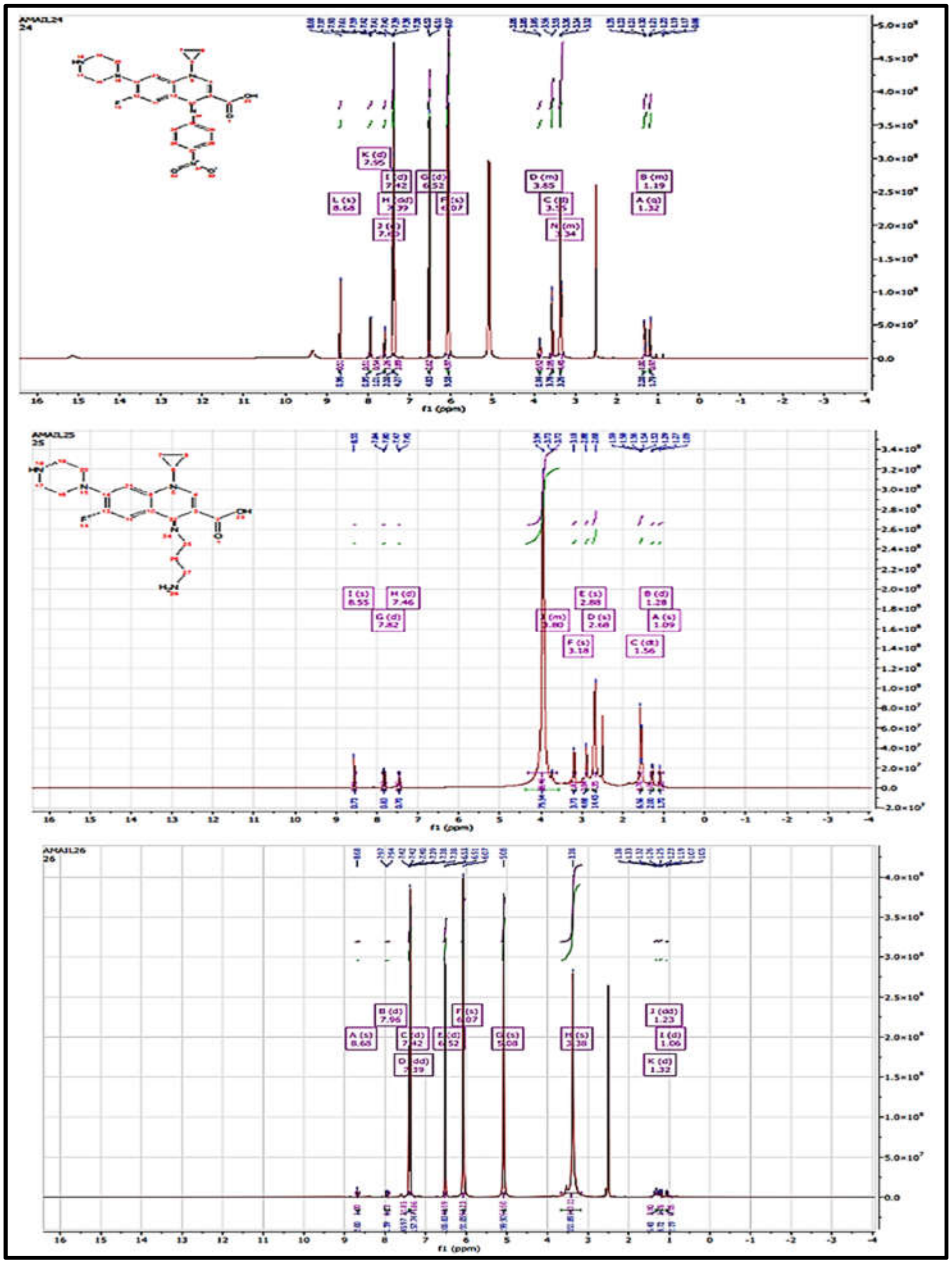


Figure 2. ^{1}H-NMR spectra of (a) Schiff base (Cip-4-NO_2Phdn)(H_2L_1), (b) Schiff base (cip-PD)(H_2L_2) and (c) [ZrO(Cip-4-NO_2Phdn)(H_2O)]).3H_2O complex.

Mass spectra

A mass spectrometer operates on the fundamental principle of segregating ion segments according to their mass-to-charge ratio (m/z). The mass spectra for both CIP-4-NO_2-phdn and cip-PD, when compared to the proposed structure (Figure 3) exhibit a high degree of concordance. Notably, the mass spectrum of the W(VI) complex displays a prominent molecular top at 992, corresponding to the complex's molecular weight (M.Wt.). To elucidate the fragmentation patterns of our investigated complexes, we derived valuable insights from the mass spectra, which were corroborated by-products matching those obtained through elemental and thermogravimetric analyses. The calculated molecular weights were established through qualitative and thermogravimetric assessments, aligning with our experimental findings [14].

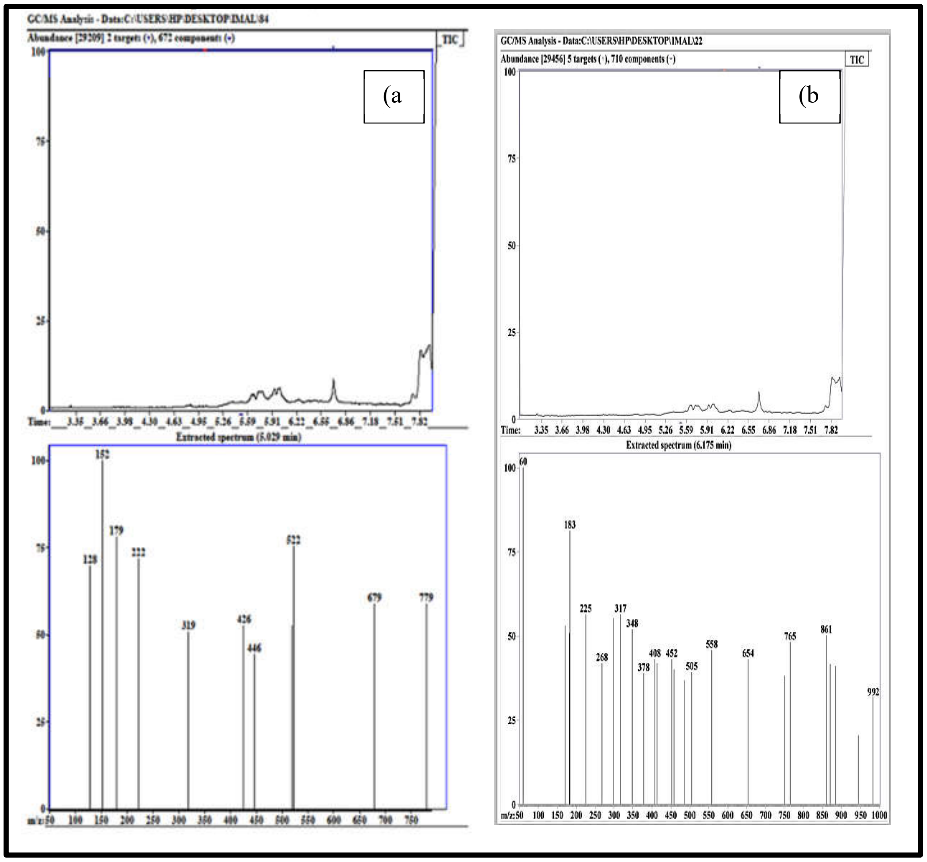
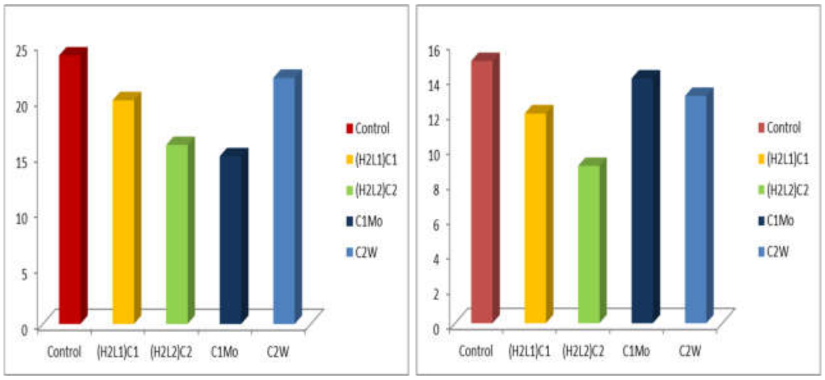


Figure 3. Mass spectrum of (a) [(Cip-4-NO_2Phdn)] and (b) [WO_2(Cip-4-NO_2Phdn)].

Application of bacterial efficacy

In our research, we examined the effectiveness of Schiff bases and their respective complexes against various bacterial strains. This study involved evaluating their impact on a selection of bacterial species that were identified through chemical and microscopic analysis in our laboratory.

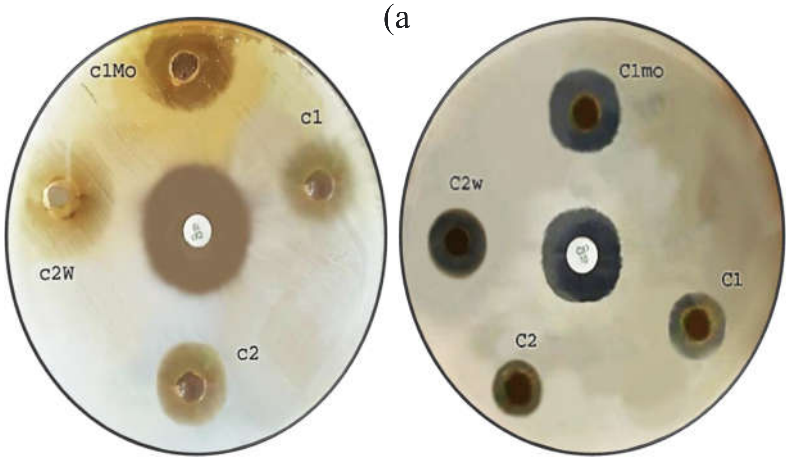
These microorganisms are known to be responsible for many human illnesses. The bacteria were categorized into two groups: gram-negative bacteria, represented by *Bacillus subtilis*, and gram-positive bacteria, represented by *Staphylococcus aureus*. Figure 4 provides a comparison of the compounds' effectiveness in inhibiting bacterial growth and visually illustrate the areas of bacterial evolution inhibition around the discs.



Staphylococcus ureus	Prepared comounds
24	Control
20	(CIP-4-NO2-phdn) H_2L_1(C1)
16	(CIP-PD) H_2L_2(C2)
15	C1Mo
22	C2W

Bacillus subtilis	Prepared comounds
15	Control
12	(CIP-4-NO2-phdn) H_2L_1(C1)
9	(CIP-PD) H_2L_2(C2)
14	C1Mo
13	C2W

(a



Staph. Aureus (b) ***Bacillus***

Figure 4. (a) Effect different concentration of materials on the growth of *Bacillus Subtillis* and *Staph. aureus* and (b) Inhibition zones (mm) of complexes with ligands for two types of bacteria.

As a control, the antibiotic Ciprodar was employed. Our antibacterial investigation shown that both Schiff base (CIP-imine) and its compounds exhibited inhibitory effects on two distinct types of bacteria (as depicted in the Figure 4 and summarized in). Our compounds reveal advanced antibacterial action against both gram -positive and negative bacteria, according to a comparison of ligands and their complexes. Complex of Mo(VI) is very highly significant antibacterial activity aganist *Bacillus subtilis* but W(VI) showed highly significant against *Staphylococcus aureus* comparison to Schiff bases (cip-imine) ligands.

Gram-negative bacteria are less affected, meaning more resistant to antibiotics, and this is due to the presence of the capsule that surrounds the bacterial membrane.

Structure for prepared compounds

According to the results discussed in our paper, compounds can be illustrated as follow:

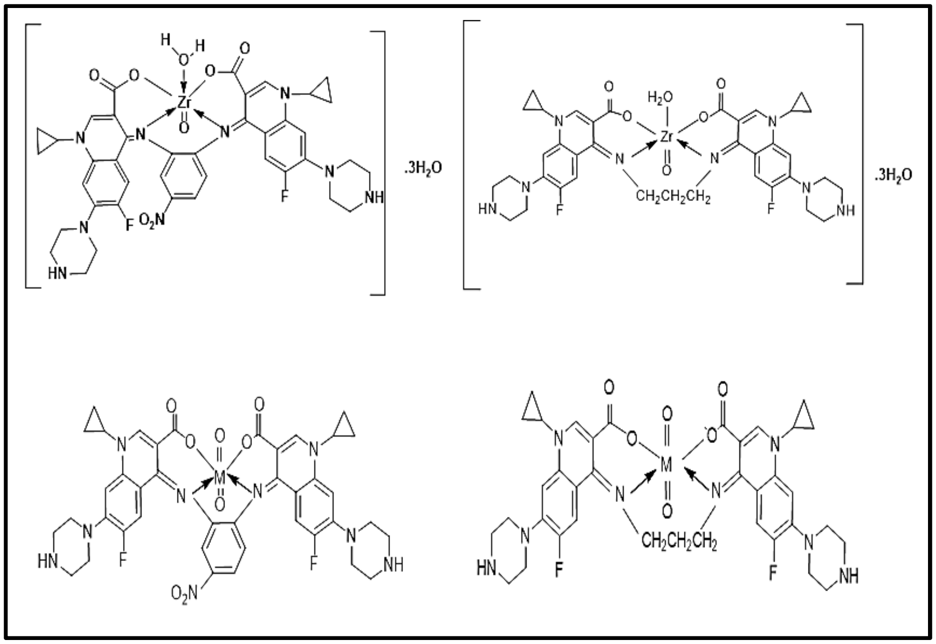


Figure 5. Proposed structure (a) [ZrO(Cip-4-NO_2Phdn)(H_2O)]).3H_2O, (b) ZrO(Cip-PD)(H_2O)].3H_2O, (c) [MO_2(Cip-4-NO_2Phdn)] and (d) [MO_2(Cip-PD)] (M = Mo, W).

CONCLUSION

Transition metals, including zirconium(IV), molybdenum(VI), and tungsten(VI), underwent a unique reaction with Schiff base (CIP-imine). The geometry of formed complexes was confirmed by elemental analyses (CHN), infrared, UV-Visible, ^{1}H-, ^{13}C-NMR and mass spectroscopy studies. Octahedral geometry were all complexes assigned. In all these complexes, Schiff bases (CIP-imine) were found in their deprotonated form and acted as tetra-dentate ligands, connected with metal ions through two oxygen atoms and nitrogen atoms of carboxylate and azomethine sets respectively to present the probable octahedral geometry surrounding each metal ion, with the presence of the oxo group and water molecule in Zr(IV) and the di-oxo group in Mo(VI) and W(VI).

To evaluate their antibacterial properties, antimicrobial studies were conducted against *Staphylococcus aureus* and *Bacillus subtilis*. The results demonstrated an important increase in antibacterial action for prepared compounds compared to Schiff –base ligands.

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