

Transition metal based coordination compounds of Schiff base derived from drug molecules: Synthesis, spectroscopic and *in vitro* biological screening

Prashant Gajera^{*a}, Milan Vadodaria^b & Rahul Parmar^c

^a Atmiya University, Rajkot 360 005, Gujarat, India

^b Chemical Research Laboratory, Shri M. and N. Virani Science College, Rajkot 360 005, Gujarat, India

^c Department of Chemistry, Faculty of Science, Monark University, Ahmedabad 382 330, Gujarat, India

E-mail: ps9601477204@gmail.com

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In order to create novel transition metal-based coordination compounds, Schiff bases (SB) based on the therapeutic molecules ambroxol and imitinib amine have been reacted with 5-methyl-2-furaldehyde. We investigated the antibacterial and spectroscopic characteristics of all the synthesised SB ligands and its coordination compounds. The SB ligand coordination compounds have been validated by IR and FAB mass spectroscopic analysis and the ligand structures have been established by ¹H NMR, IR, mass and elemental analysis. All SB ligands and coordination compounds have been tested *in vitro* on both Gram-positive (*Staphylococcus epidermidis*, *Bacillus subtilis*) and Gram-negative (*Escherichia coli*, *Salmonella enterica*) bacteria. The outcomes show how promising transition metal-based coordination compounds are and how crucial it is to conduct more studies on them.

Keywords: Ambroxol base, Imitinib amine, Transition metal coordination compounds, Antimicrobial studies, Spectroscopic studies

Hugo Schiff initially described Schiff bases (SB) in 1864. These compounds have an azomethine group (-HC=N-), which is created when an active carbonyl compound condenses with a primary amine. This process may generally be catalysed by an acid, base or heat^{1,2}. They have been shown to possess pharmacological actions for example anti-malarial³, anti-cancer⁴, antibacterial, antifungal⁵, anti-tubercular⁶ and anti-inflammatory⁷. Their extensive diversity of biotic activity and industrial applicability make them valuable chemicals. Investigations have been conducted on sulphonamide products and a range of those derivatives are created and applied in several pharmacological and biological domains. Sulphonamide products, which have been utilized to many biological applications are the source of Schiff bases^{8,9}.

The simple synthesis, inexpensive availability and electrical characteristics of transition metals have made coordination chemistry of SBs with these metals a fascinating field of research in current years. The coordination chemistry of SBs has drawn significant attention recently because of its many uses, including thermal investigations¹⁰. Catalytic toxicity^{11,12}, optically active material¹³, agriculture^{14,15}, antibacterial activity¹⁶⁻¹⁸, antifungal activity¹⁹, anticancer activity²⁰, antiviral

activity²¹ and DNA binding²² are among the other factors. The C=N (Imine) moiety in this family of chemicals is crucial for biological action. We propose the transition metal based Heterochelates of Schiff base derived from drug molecules: synthesis, spectroscopic and *in vitro* biological screening motivated by the implications of transition metal-based coordination compounds and our interest in the science of drug-based Schiff base complexes.

Materials and Methods

Materials

As each component used was analytically sound, no additional purification was required. The 5-Methyl-2-furaldehyde was supplied by Sigma Ltd. (India). Ambroxol and Imitinib amine were acquired from Almon Industries in Ahmadabad, Gujarat, India and were utilized devoid of distillation.

Finding techniques

A Perkin-Elmer model 2400 elemental analyzer was used for elemental analysis (C, H, and N). ¹H NMR ranges were obtained using the Advance 400 Bruker FT-NMR device in DMSO-*d*₆ solvent. FT-IR spectra were noted using a Nicolet-400D

spectrophotometer as KBr pellets. The FAB-mass band of the coordination compounds was measured with a JEOL SX-102/DA-6000 mass spectrometer.

Common process for synthesis of ligands (L₁–L₂)

Double-necked curved end flasks containing a 1:1 molar methanolic solution of ambroxol base (0.001mol) and imitinib amine were spun for several minutes at reflux temperature. In order to finish the reaction, 5-Methyl-2-furaldehyde (0.001 mol) was added drop by drop to the previously described solution and heated for 4 hours at 60°C while moving continuously. TLC analysis was then performed. The compound was left to remain at normal temperature for the whole night-time once the reaction was finished. After employing methanol to crystallise the solid product, diethyl ether was used to wash the material to get solid form.

L₁: M.F-C₂₂H₁₉N₅O. Yield 89%. m.p. 198°C; M.W. 370.2 Dark Brown powder; FT-IR (KBr,cm⁻¹): 3030 ν(N–H), 1230 ν(C–O) ether, 1627 ν(C=N); ¹H NMR (400 MHz,DMSO-d₆): δ (ppm) = 2.21 (3H,s,-CH₃); 2.25 (3H,s,-CH₃); 3.48 (1H,s,-NH); 6.17-9.51 (11H,c,Ar-H), Elemental analysis found (%) C, 71.59; H, 5.22; N, 19.00; calculated for C₂₂H₁₉N₅O: C, 71.53; H, 5.18; N, 18.96.

L₂: M.F-C₁₉H₂₂Br₂N₂O₂. Yield 81%. m.p. 207°C; M.W. 470.95 Cream white powder; FT-IR (KBr,cm⁻¹): 2935 ν(N–H), 1070 ν(C–O) ether, 1591 ν(C=N);

¹H NMR (400 MHz,DMSO-d₆): δ (ppm) = 2.29 (3H,s,-CH₃); 1.52 (1H,b,-NH); 1.21-1.96 (10H,m,-C₆H₁₀); 4.84-7.43 (4H,c,Ar-H), Elemental analysis found (%) C, 48.56; H, 4.75; N, 6.01 calculated for C₁₉H₂₂Br₂N₂O₂: C, 48.53; H, 4.72; N, 5.96.

Common process for the synthesis of coordination compounds (ML₁– ML₂)

All heterochelates may now be created and isolated using a general method. Drop by drop, and with constant stirring, a warm methanolic metal (II) acetate salt (0.001mol) solution was added to the equivalent ligand solution (0.001mol) in 1:1 molar ratios. After heating at 70°C for four hours, the mixture was permitted to cool overnight. After being soaked by methanol and water, the densely coloured product was allowed to dry in desiccators. Reaction scheme for the synthesis of ligands and its transition metal based heterochelates is shown in Fig. 1.

Physical and Spectral data of coordination compounds

[Mn(L₁)(CH₃COO)₂(H₂O)]: Mol. Wt. 559. Color: Brown. Yield 88%. FT-IR (KBr): 1570 (C=N), 1203 (C=O) Ether, 1670 (C=O) Acetate. Anal. Calcd Found (%): C, 55.86% (55.82%); H, 4.73% (4.68%); N, 12.55% (12.52%); Mn, 9.89% (9.82%).

[Ni(L₁)(CH₃COO)₂(H₂O)]: Mol. Wt. 562. Color: Black. Yield 70%. FT-IR (KBr): 1572 (C=N), 1201 (C=O) Ether, 1663 (C=O) Acetate. Anal. Calcd Found

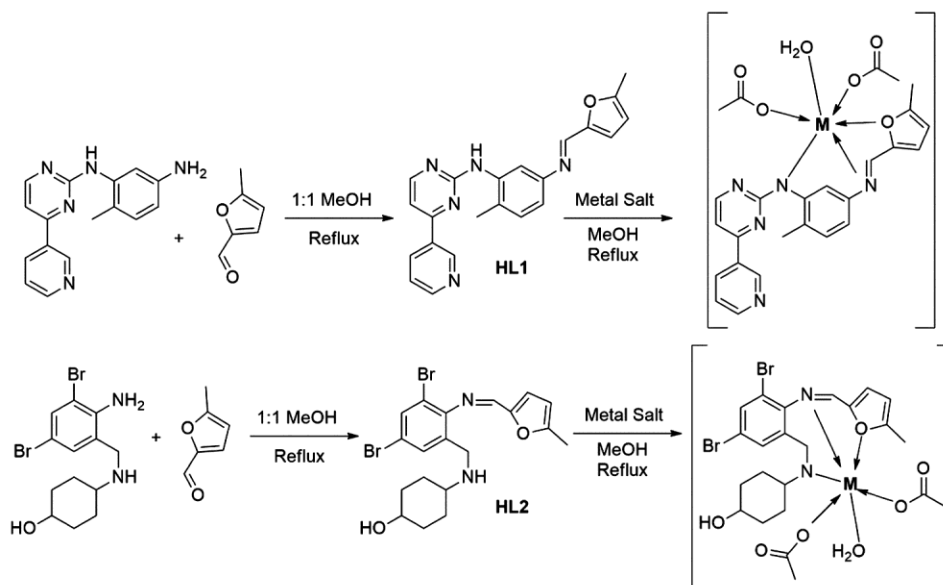


Fig. 1 — Reaction Scheme for the synthesis of ligands and it's coordination compounds

(%): C, 55.50% (55.45%); H, 4.68% (4.65%); N, 12.47% (12.43%); Ni, 10.44% (10.42%).

[Cu(L₁)(CH₃COO)₂(H₂O)]: Mol. Wt. 567. Color: Dark Green. Yield 85%. FT-IR (KBr): 1573 (C=N), 1197 (C=O) Ether, 1672 (C=O) Acetate. Anal. Calcd Found (%): C, 55.01% (54.97%); H, 4.64% (4.61%); N, 12.36% (12.33%); Cu, 11.23% (11.19%).

[Zn(L₁)(CH₃COO)₂(H₂O)]: Mol. Wt. 568. Color: Brown. Yield 83%. FT-IR (KBr): 1575 (C=N), 1203 (C=O) Ether, 1674 (C=O) Acetate. Anal. Calcd Found (%): C, 54.83% (54.80%); H, 4.64% (4.60%); N, 12.31% (12.29%); Zn, 11.50% (11.47%).

[Mn(L₂)(CH₃COO)₂(H₂O)]: Mol. Wt. 660. Color: Grey. Yield 70%. FT-IR (KBr): 1562 (C=N), 1051 (C=O) Ether, 1691 (C=O) Acetate. Anal. Calcd Found (%): C, 41.87% (41.84%); H, 4.44% (4.43%); N, 4.27% (4.24%); Mn, 8.36% (8.32%).

[Ni(L₂)(CH₃COO)₂(H₂O)]: Mol. Wt. 664. Color: Light Green. Yield 67%. FT-IR (KBr): 1560 (C=N), 1053 (C=O) Ether, 1635 (C=O) Acetate. Anal. Calcd Found (%): C, 41.63% (41.60%); H, 4.44% (4.40%); N, 4.26% (4.22%); Ni, 8.88% (8.84%).

[Cu(L₂)(CH₃COO)₂(H₂O)]: Mol. Wt. 669. Color: Dark Green. Yield 65 FT-IR (KBr): 1560 (C=N), 1053 (C=O) Ether, 1670 (C=O) Acetate. Anal. Calcd Found (%): C, 41.33% (41.30%); H, 4.40% (4.37%); N, 4.21% (4.19%); Cu, 9.56% (9.50%).

[Zn(L₂)(CH₃COO)₂(H₂O)]: Mol. Wt. 671. Color: Buff Colour. Yield 63%. FT-IR (KBr): 1561 (C=N), 1051 (C=O) Ether, 1701 (C=O) Acetate. Anal. Calcd Found (%): C, 41.23% (41.19%); H, 4.38% (4.36%); N, 4.23% (4.18%); Zn, 9.79% (9.75%).

***In Vitro* biological screening**

Zone of Inhibition

All ligands and coordination compounds were tested for antimicrobial activity using the Cup Borar method, with Penicillin acting as the standard. The chemical was liquefied in the least quantity of DMSO and diluted with binary distilled water to form a standard solution of 10 mgmL⁻¹. One liter of distilled water was used to melt twenty grams of bacteriological agar and twenty grams of Luria broth (SRL, India) to create the medium. The mixture was

put onto sterile petri plates, permitted to coagulate and then utilized for inoculation after being autoclaved for 15 minutes at 120°C. Each target microbe culture was created distinctly in 15 mL of liquid Luria broth standard in order to be activated. A micropipette with sterile tips was used to inoculate. Next, an agar plate was evenly covered with 100 µL of active strain using a sterile, twisted glass rod. Next, two 10-mm-diameter bores were prepared in each plate using a germ-free borer. Using discs Agar plates that had previously been inoculated were filled with wells containing disinfected standard solutions (10 mg mL⁻¹). The discs were placed and incubated at 30°C (Gram +ve) and 37°C (Gram -ve) for duration of 24 hours. Next, the area of inhibition surrounding the disc shown in Fig. 2 was measured (in millimeters). The region of inhibition was calculated (in mm) in accordance with Table 2 and the control tests were achieved using just the relevant bulk of solvents and devoid of the addition of any test chemicals^{23,24}.

Results and Discussion

The structure of synthesised SB ligands and coordination compounds were identified by elements analysis, ¹H NMR, FAB-Mass bands and infrared bands. The experimental part contains the ¹H NMR data for Schiff's base ligands. The systematic and somatic characteristics of coordination compounds are displayed in experimental section. The coordination compounds were very faintly soluble in methanol, but fully soluble in DMSO and DMF. For a short time, none of the heterochelates moved during the airborne phase.

¹H NMR

Fig. 3 and Fig. 4 display the ¹H NMR spectra of ligands L₁ and L₂, respectively. The methyl group proton (-CH₃) is responsible for the two singlet peaks in the ligand L₁'s 1H NMR spectra, which are located

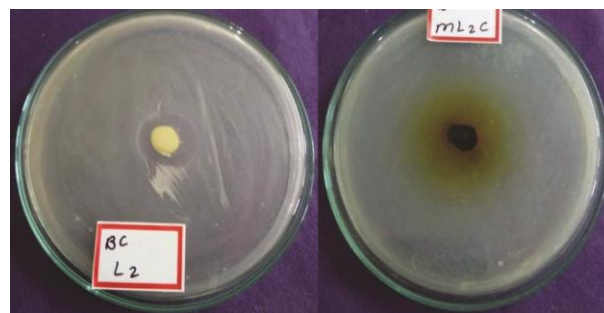
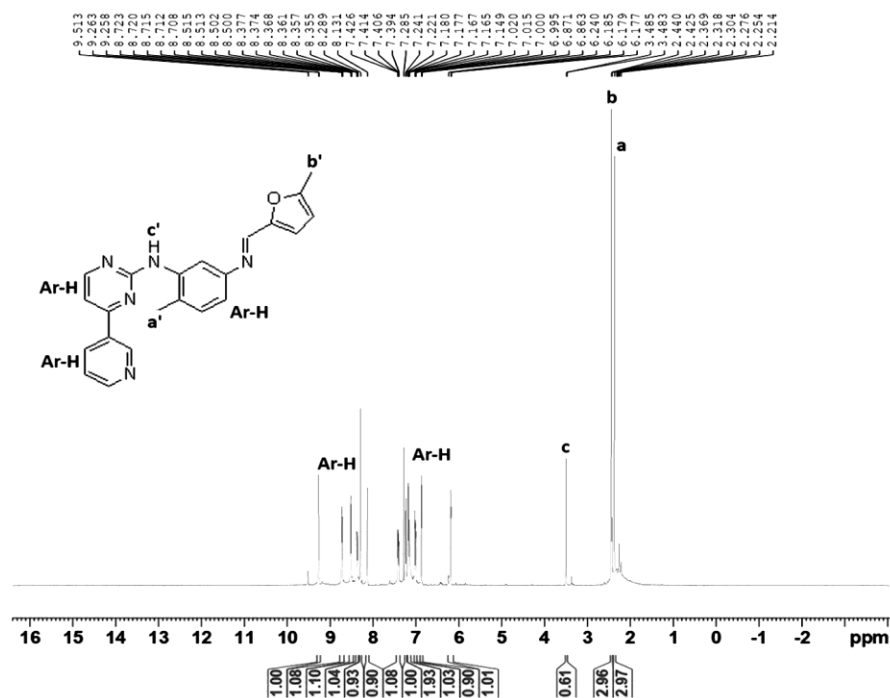
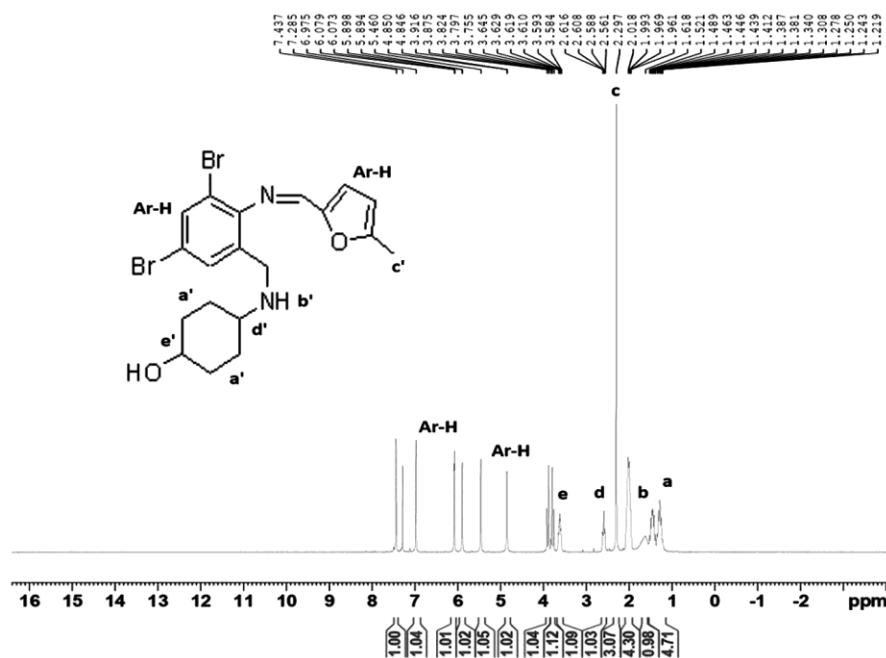


Fig. 2 — Region of reserve (mm) of Ligand and its coordination compounds

Fig. 3 — ¹H NMR spectrum of Ligand L₁Fig. 4 — ¹H NMR spectrum of Ligand L₂

at 2.21 and 2.25 δ ppm. The 1H singlet peak observed at 3.48 δ ppm may be attributed to aromatic 11H and –NH protons found in the range of 6.17–9.51 δ ppm. A singlet for three protons at 2.29 δ ppm is seen in the ¹H NMR spectra of ligand L₂, showing the presence of a –CH₃ group. The range in which the ligands

create aromatic protons is 4.84–7.43 δ ppm. The ligand L₂ displays a wide peak at 1.52 δ ppm for –NH protons and a range of 1.21–1.96 δ ppm for 10H multiplets of substituted cyclohexyl ring. It could be challenging to distinguish between the –NH proton signal if it combines in the higher region. The molecule's

chemical formula and the number of protons match exactly. Additionally, the mass spectra of each ligand validates it.

IR (Infrared Spectra)

The comparison for IR data of the transition metal coordination compounds with SB ligands (L_1 and L_2) are displayed in Table 1. To determine the ligands' metal binding modes, the infrared (IR) data of the coordination compounds and the ligands were compared. The acyclic azomethine group's $\nu(\text{C}=\text{N})$ is clearly seen in a prominent band between 1590 and 1630 cm^{-1} for the SB ligands L_1 and L_2 . This band arises between 1560 and 1575 cm^{-1} in the coordination compounds; its reported lower energy shift suggests azomethine nitrogen coordination^{25,27}. In the range of 1050 to 1230 cm^{-1} , ligands and coordination compounds exhibit the $\nu(\text{C}-\text{O})$ ether band in their spectra. The remarkable negative motion of 15-20 cm^{-1} seen in the IR bands of coordination compounds indicates direction through the oxygen of the ligand. But the $\text{C}=\text{O}$ acetate band that looked in the 1630–1700 cm^{-1} range and the lack of an acetate group band in ligands showed that the acetate group was attached to the metal in coordination compounds^{28,29}.

FAB Mass

The molecular ion peak for the coordination compound $[\text{Mn}(L_1)(\text{CH}_3\text{COO})_2(\text{H}_2\text{O})]$ and the validated

Table 1 — IR data of ligands and its metal coordination compounds

Compd	N	N	$\nu(\text{C}-\text{O})$	$\nu(\text{C}=\text{O})$
	(C=N)	(N-H)	Ether	Acetate
L_1	1627	3030	1230	—
$[\text{Mn}(L_1)(\text{CH}_3\text{COO})_2(\text{H}_2\text{O})]$	1570	—	1203	1670
$[\text{Ni}(L_1)(\text{CH}_3\text{COO})_2(\text{H}_2\text{O})]$	1572	—	1201	1663
$[\text{Cu}(L_1)(\text{CH}_3\text{COO})_2(\text{H}_2\text{O})]$	1573	—	1197	1672
$[\text{Zn}(L_1)(\text{CH}_3\text{COO})_2(\text{H}_2\text{O})]$	1575	—	1203	1674
L_2	1591	2935	1070	—
$[\text{Mn}(L_2)(\text{CH}_3\text{COO})_2(\text{H}_2\text{O})]$	1562	—	1051	1691
$[\text{Ni}(L_2)(\text{CH}_3\text{COO})_2(\text{H}_2\text{O})]$	1560	—	1053	1635
$[\text{Cu}(L_2)(\text{CH}_3\text{COO})_2(\text{H}_2\text{O})]$	1560	—	1053	1670
$[\text{Zn}(L_2)(\text{CH}_3\text{COO})_2(\text{H}_2\text{O})]$	1561	—	1051	1701

mass spectra (Fig. 5) were utilized to approve the molecular prescription for the proposed coordination compound. Fig. 6 shows the strategic disintegration pattern. The compound's molecular ion peak is the initial signal at $m/z=560$. Fig. 6 shows the conceivable disintegration path for the compound under investigation. The coordination compounds principal fragmentation is caused by the loss of two CH_3COO molecules and one H_2O molecule from species (a). This leads to species (b), which has a signal at $m/z=424$ as its base signal of highest intensity. Additional disintegration gives species (c), which loses a portion of the ligand molecule $\text{C}_5\text{H}_5\text{O}$. Species (c) disintegrate further to a stable species (d), may be due to the loss of the remaining ligand molecule and MnO . The computed molecular weights for all indicated degradation processes were precisely the same as the expected values^{30,31}.

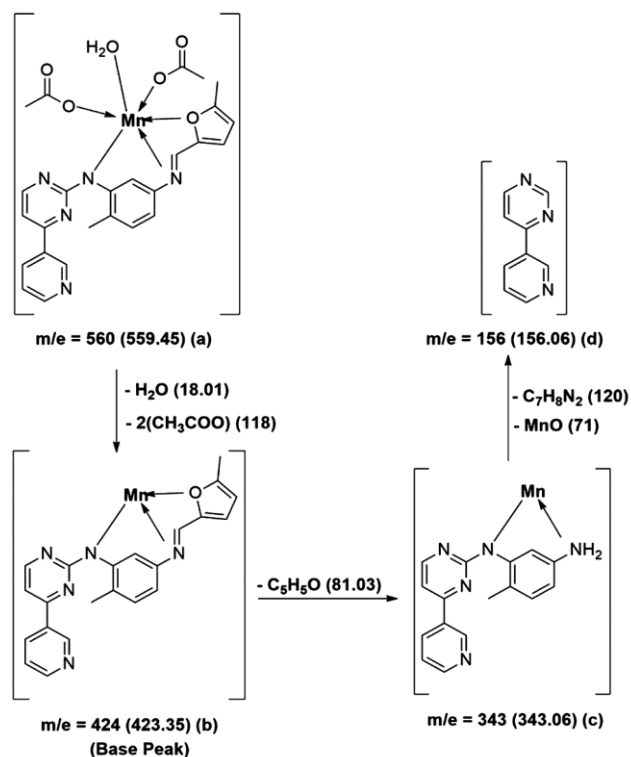


Fig. 6 — Proposed mass disintegration pattern for coordination compounds $[\text{Mn}(L_1)(\text{CH}_3\text{COO})_2(\text{H}_2\text{O})]$

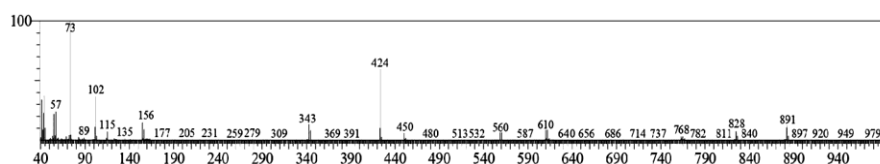


Fig. 5 — FAB Mass spectrum of coordination compound $[\text{Mn}(L_1)(\text{CH}_3\text{COO})_2(\text{H}_2\text{O})]$

Table 2 — Antimicrobial properties of the ligands and its coordination compounds

Sr. No.	Compd	Gram +Ve (mm)		Gram -Ve (mm)	
		<i>B. subtilis</i>	<i>S. Aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>
Ref. Drug	Penicillin	25	22	23	21
1	L ₁	9	7	5	8
2	[Mn(L ₁)(CH ₃ COO) ₂ (H ₂ O)]	12	16	15	12
3	[Ni(L ₁)(CH ₃ COO) ₂ (H ₂ O)]	14	11	13	15
4	[Cu(L ₁)(CH ₃ COO) ₂ (H ₂ O)]	18	15	18	14
5	[Zn(L ₁)(CH ₃ COO) ₂ (H ₂ O)]	11	9	10	13
6	L ₂	14	14	13	10
7	[Mn(L ₂)(CH ₃ COO) ₂ (H ₂ O)]	13	12	14	11
8	[Ni(L ₂)(CH ₃ COO) ₂ (H ₂ O)]	12	13	16	15
9	[Cu(L ₂)(CH ₃ COO) ₂ (H ₂ O)]	12	13	18	15
10	[Zn(L ₂)(CH ₃ COO) ₂ (H ₂ O)]	15	14	12	13

Biological Screening

The synthesised Schiff's base ligands, L₁–L₂, together with their heterochelates based on transition metals (Mn, Ni, Cu and Zn), were all tested against various gram +ve and –ve bacterial strains. When compared to parent Schiff's base ligands, heterochelates have greater inhibitory effects, according to the antimicrobial screening results (Table 2). The heterochelates [Cu(L₁)(CH₃COO)₂(H₂O)] are considerably effective bactericides against *B. subtilis* and *E. coli*, respectively. However, compound [Cu(L₂)(CH₃COO)₂(H₂O)] was only shown to be highly vigorous against *E. coli*. The overtone notion^{32,33} and chelation theory³⁴ can be utilized to describe why the coordination compounds have higher activity than ligands.

Conclusion

We are currently developing novel SB ligands based on ambroxol and imitinib amine based drug molecules and their transition metal coordination compounds. ¹H NMR, IR and mass spectrometry were used to verify and characterise all of the synthesised ligands and coordination compounds. We checked each synthesised compounds for the existence of antibacterial properties. The coordination compound show strong antibacterial action against Gram positive (*Staphylococcus epidermidis*, *Bacillus subtilis*) and Gram negative (*Escherichia coli*, *Salmonella enterica*) pathogens when compared to their respective ligands. The compounds' extraordinary efficacy against one or more microbes opens the door to future research on a potential type of transition metal-based bactericidal medicines.

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