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Metal complexes of 4-aminopyridine Schiff bases: Potent molecules in the design of anti-tuberculosis agents

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Abstract: *Tuberculosis (TB) has remained a serious public health challenge and one of the most prevalent causes of death regarding infectious diseases, despite decades of relentless drug development research. The resurgence of TB is due to its prevalence in synergy with the AIDS epidemic and the rise of multidrug-resistant (MDR) TB. Therefore, finding new, effective bioactive agents to manage and treat the disease is a top priority. To discover a new and effective chemotherapeutic agent for the treatment of TB, Cu(II), Ni(II) and Co(II) complexes of 4-aminopyridine-based Schiff bases have been synthesized, characterized based on melting point, elemental analyses, FT-IR, NMR, UV-vis and molar conductance. The spectra revealed that the Schiff base ligands act as a bidentate ligand through the azomethine nitrogen atom and a phenolic oxygen atom. The molar conductance measurements of the complexes in DMF correspond to non-electrolytic nature. The antituberculosis activity of the compounds using the proportion method revealed that the nitro-containing Cu(II) and Co(II) complexes exhibited enhanced in vitro antituberculosis activity compared with the ligands and reference compound (INH) at 0.1 μg/ml.*

Keywords*: Schiff base, metal complexes, 4-aminopyridine, Antituberculosis activity*

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1.0 Introduction

Mycobacterium tuberculosis (MTB) is the airborne pathogen that causes tuberculosis (TB), a lung infection that typically results in severe coughing, fever, and chest pains. TB is one of the most significant and age-long public health challenges (Fogel, 2015).

After COVID-19, TB is the second most fatal infectious illness in the world, killing 1.6 million people globally in 2021, including 187 000 people living with HIV. 10.6 million cases of tuberculosis (TB) were documented worldwide in 2021 (WHO, 2023). Drugs, such as isoniazid, rifampicin, ethambutol, etc. are available to treat TB. Recently the US FDA in August 2019 approved pretomanid as an anti-TB drug (US FDA, 2019). Despite these developments, fears that tuberculosis could be eradicated using these drugs have been shattered by the rise of drug-resistant M.TB strains and the co-morbidity of TB with HIV/AIDS (Hu *et al*., 2017).

The increased incidence of TB has generated the demand for therapy regimens that are more effective and have fewer adverse effects. New promising drugs with enhanced activity and lower or no risk of resistance are preferable. The main focus of research in this area is on the modification of currently available medications (Dueke-Eze *et al*., 2020) or the development of novel, potentially therapeutic compounds that are active against (MTB) utilizing a metal-based strategy (More *et al*., 2018). The bioactive metal complexes necessary for the metal-based approach depend on the kind of ligand that surrounds the metal ion. The ligand that surrounds a metal ion has a significant impact on the metal complex's characteristics. It can change the metal ion's physical and chemical characteristics as well as its oral and systemic bioavailability, which can help it target particular organs or enzymes (Thompson and Orvig, 2006). The Schiff base ligand is of particular interest.

Schiff bases (SBs) are chemical compounds that function as interesting biological scaffolds because they have a carbon-nitrogen double bond (C=N) in their structure. They are produced through the condensation reaction between an aldehyde and a primary amine. Schiff bases have shown a variety of biological properties such as antituberculosis (Salve *et al*., 2017; Venugopala *et al*., 2020), anticancer (Jain *et al*., 2022), anti-inflammatory (Hamid and Salih, 2021) and antimicrobial (Shukla *et al*., 2017). Based on the aforementioned, compounds that include Schiff bases as an essential component of their structure have been demonstrated to exhibit distinctive biological activity that has been reported to improve upon complexion with transition metal ions (Dueke-Eze *et al*., 2018; Yadav *et al*., 2021; El-Gammal *et al*., 2021).

2.0 Materials and Methods

Sigma-Aldrich Chemicals Ltd. supplied all the analytical grade chemicals that were used, and they were all used without further purification. On pre-coated Merck TLC silica gel 60 F254 plates, thin layer chromatography (TLC) was performed and the results were observed under UV light (254/365nm). A Stuart SMP3 melting point equipment was used for the melting point tests and the results were unaltered. An FTS 7000 series Digilab Win-IR Pro spectrometer with the ATR- (attenuated total reflectance) Diamond Selenium attachment was used to record infrared spectra using the thin-film technique as instructed in the user guide. The spectra were recorded in the region 4000-400 cm^{-1}. Deuterated chloroform (CDCl3) was used as the solvent for the 1H and 13C NMR spectra, with tetramethylsilane (TMS) serving as the internal reference, using a Varian 300 MHz spectrometer. The chemical shifts are referenced relative to the solvent peaks and were all recorded at room temperature in the spectra. Using a Perkin-Elmer 2400 CHNS/O analyzer, elemental analyses were carried out. After making the solutions, the electronic spectra of the compounds were instantly captured in DMF solution using a 1 cm quartz cell and a Cecil Super Aquarius 9000 series UV-Vis spectrophotometer at room temperature. A conductivity cell with a cell constant of 1.0 was used to measure the molar conductance on a Syntronics digital direct reading conductivity meter. At the Nigeria Institute of Medical Research in Yaba, Lagos, the antituberculosis screening was conducted.

2.1 Typical procedure for the preparation of Schiff bases (DL1-DL3)

A degassed mixture of 4-aminopyridine (0.80 mmol.), aldehyde (0.80 mmol.), and *p*-toluene sulfonic acid monohydrate (10 mg) in dry toluene (100 ml) was refluxed in a nitrogen atmosphere under Dean-Stark condition for 24 h. The solvent was removed under reduced pressure and the residue recrystallized from toluene and dried in a desiccator.

2.2 N-(2-hydroxybenzylidene)pyridine-4-amine (DL1)

Deep yellow solid, yield: 12.80 mg (81%); mp: 77–78^{0}C; R_f : 0.55. IR (cm^{-1}): 3324, 1587, 1557, 1398, 1339, 1271, 1214, 1148, 1121, 1056, 930, 845, 801, 730, 679; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.95–7.05 (m, 2H), 7.14 (d, *J* 6.6 Hz, 2H), 7.46 (t, *J* 15.6 Hz, 2H), 8.61 (s, 1H), 8.65 (d, *J* 5.4 Hz, 2H), 12.57 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 116.10, 151.15, 155.46, 117.50, 118.64, 119.45, 132.92, 134.37, 161.29, 165.68. Anal. calcd.: $C_{12}H_{10}N_2O$: C, 72.71, H, 5.08, N, 14.10. Found: C, 72.62, H, 5.02, N, 13.96.

2.3 N-(5-nitro-2-hydroxybenzylidene)pyridine-4-amine (DL2)

Yellow solid, yield: 14.60 mg (75%); mp: 193–194^{0}C; R_f : 0.32. IR (cm^{-1}): 1652, 1584, 1524, 1471, 1354, 1280, 1228, 1173, 1081, 947, 888, 820, 751, 718, 639; ^{1}HNMR (300 MHz, $CDCl_3$) δ_H: 7.09–7.22 (m, 3H), 8.30–8.44 (m, 2H), 8.56 (s, 1H), 8.717 (t, *J* 8.4Hz, 2H), 10.01; ^{13}CNMR (75 MHz, $CDCl_3$) δ_C: 115.94, 118.58, 119.04, 128.95, 129.30, 129.67, 131.63, 151.44, 164.14, 166.39. Anal. calcd.: $C_{12}H_9N_3O_3$: C, 59.26, H, 3.77, N, 17.28. Found: C, 58.96, H, 3.63, N, 17.06.

2.4 N-(5-bromo-2-hydroxybenzylidene)pyridine-4-amine (DL3)

Orange crystals. Yield: 18.60 mg (84%); mp: 139–141^{0}C; R_f : 0.42. IR (cm^{-1}): 1615, 1582, 1550, 1472, 1411, 1354, 1328, 274, 1183, 1078, 985, 916, 867, 804, 781, 738, 689; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 6.96 (d, *J* 8.7 Hz, 2H), 7.13 (d, *J* 5.4Hz, 2H), 7.48–7.54 (m, 2H), 8.54 (s, 1H), 8.66 (s, 2H), 12.57 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 110.88, 116.05, 119.53, 119.97, 134.80, 136.93, 151.26, 154.93, 160.27, 164.38. Anal. calcd.: $C_{12}H_9BrN_2O$: C, 52.01, H, 3.27, N, 10.11. Found: C, 52.16, H, 3.18, N, 9.82.

2.5 Typical procedure for the preparation of Schiff metal complexes (Cu-DL1-Co-DL3)

A solution of each chloride metal salt (0.5 mmol) dissolved in either water or ethanol was gradually added to a stirred ethanolic solution (10 ml) of the ligands (1.1 mmol). The mixture was refluxed for 4-6 h and the solid product obtained on cooling was filtered and washed severally with ethanol: water (1:1) mixture. The product was dried over silica gel in a desiccator.

2.6 Copper (II) complexes of the Schiff bases

2.6.1 Cu-N-(2-hydroxybenzylidene) pyridine-4-amine (Cu-DL1)

Yield: 2.07 mg (60 %); mp: 244 ^{o}C (dec.). IR (cm^{-1}): 3464, 1594, 1581, 1527, 1438, 1372, 1147, 1058, 1027, 902, 869, 748, 655, 528, 489. Anal. calcd.: $C_{12}H_{11}ClCuN_2O_2$: C, 45.87, H, 3.53, N, 8.92, Cu, 20.22. Found: C, 46.32, H, 3.00, N, 8.40, Cu, 20.74.

2.6.2 Cu-N-(5-nitro-2-hydroxybenzylidene)pyridine-4-amine (Cu-DL2)

Yield: 1.67 mg (39%); mp: >349 ^{o}C. IR (cm^{-1}): 3212, 1597, 1508, 1424, 1373, 1246, 1101, 1087, 1003, 850, 826, 720, 622, 508, 482, 444. Anal. calcd.: $C_{12}H_{10}ClCuN_3O_4$: C, 40.12, H, 2.81, N, 11.70, Cu, 17.69. Found: C, 40.07, H, 2.61, N, 10.78, Cu, 18.19.

2.6.3 Cu-N-(5-bromo-2-hydroxybenzylidene)pyridine-4-amine (Cu-DL3)

Yield: 2.33 mg (59%); mp: 248 ^{o}C (dec.). IR (cm^{-1}): 2359, 1739, 1598, 1517, 1452, 1391, 1333, 1316, 1279, 1168, 1028, 933, 874, 700, 626, 563, 464, 439. Anal. Calcd: $C_{12}H_{10}BrClCuN_2O_2$: C, 36.66, H, 2.56, N, 7.13, Cu, 16.16. Found: C, 38.49, H, 2.17, N, 6.63, Cu, 16.00.

2.7 Nickel (II) complexes of the Schiff bases

2.7.1 Ni-N-(2-hydroxybenzylidene)pyridine-4-amine (Ni-DL1)

Yield: 2.39 mg (49%); mp: 265 ^{o}C (dec.). IR (cm^{-1}): 1591, 1521, 1490, 1448, 1390, 1357, 1319, 1173, 1143, 1054, 1014, 982, 926, 867, 752, 734, 541, 529, 485. Anal. calcd.: $C_{24}H_{22}N_4NiO_4$: C, 58.93, H, 4.53, N, 11.45, Ni, 12.00. Found: C, 59.31, H, 3.88, N, 11.11, Ni, 13.54.

2.7.2`Ni-N-(5-nitro-2-hydroxybenzylidene) pyridine-4-amine (Ni-DL2)

Yield: 3.15 mg (52%); mp: 296-299 ^{o}C. IR (cm^{-1}): 1735, 1651, 1542, 1415, 1397, 1367, 1291, 1202, 1137, 1082, 923, 833, 799, 753, 728, 693, 667, 507, 461. Anal. calcd.: $C_{24}H_{26}N_6NiO_8$: C, 53.07, H, 2.97, N, 15.47, Ni, 10.81. Found: C, 54.93, H, 3.02, N, 14.76, Ni, 10.23.

2.7.3 Ni-N-(5-bromo-2-hydroxybenzy-lidene)pyridine-4-amine (Ni-DL3)

Yield: 3.43 mg (63%); mp: 300-303 ^{o}C. IR (cm^{-1}): 1596, 1511, 1490, 1459, 1416, 1387, 1319, 1205, 1132, 1079, 1060, 981, 841, 820, 695, 453, 428. Anal. calcd.: $C_{24}H_{16}Br_2N_4NiO_2$: C, 47.18, H, 2.64, N, 9.17, Ni, 9.61. Found: C, 46.49, H, 2.67, N, 8.48, Ni, 9.80.

2.8 Cobalt (II) complexes of the Schiff bases

2.8.1 Co-N-(2-hydroxybenzylidene) pyridine-4-amine (Co-DL1)

Yield: 3.33 mg (54 %); mp: 298-303 ^{o}C. IR (cm^{-1}): 1590, 1524, 1491, 1462, 1444, 1387, 1351, 1319, 1174, 1124, 1056, 1027, 980, 866, 834, 753, 735, 445, 414.Anal. calcd.: $C_{24}H_{22}CoN_4O_4$: C, 58.90, H, 4.53, N, 11.45, Co, 12.04. Found: C, 60.64, H, 4.02, N, 10.81, Co, 13.17.

2.8.2 Co-N-(5-nitro-2-hydroxybenzylidene) pyridine-4-amine (Co-DL2)

Yield: 4.93 mg (58%); mp: 248-251 ^{o}C. IR (cm^{-1}): 3421, 1597, 1574, 1507, 1456, 1395, 1369, 1335, 1216, 1196, 1160, 1084, 1055, 922, 855, 804, 696, 490, 428. Anal. Calcd: $C_{24}H_{20}CoN_6O_8$: C, 49.75, H, 3.48, N, 14.51, Co, 10.17. Found: C, 50.26, H, 3.02, N, 15.8,5 Co, 9.71.

2.8.3 Co-N-(5-bromo-2-hydroxybenzylidene)pyridine-4-amine (Co-DL3)

Yield: 4.78 mg (66 %); mp: >349 ^{o}C. IR (cm^{-1}): 3060, 1597, 1554, 1470, 1334, 1279, 1211, 1170, 1081, 987, 913, 870, 848, 818, 781, 628, 529, 523, 429. Anal. calcd.: $C_{24}H_{24}Br_2CoN_4O_6$: C, 42.19, H, 3.54, N, 8.20, Co, 8.63. Found: C, 41.54, H, 2.79, N, 7.56, Co, 8.51.

2.9 Antituberculosis activity

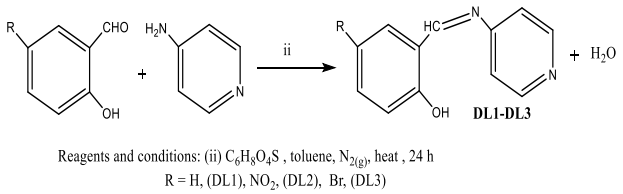
The antituberculosis test was performed at the tuberculosis unit, Nigeria Institute of Medical Research, Yaba, Lagos using a standard method (Dueke-Eze *et al.*, 2018). Freshly laid chicken eggs, mineral salt, and 2% malachite green were blended to afford the Lowenstein-Jensen (LJ) medium. A 0.04 mg/mL stock solution of the test substance in DMF was made, filtered through a 0.22 g pore membrane, and then diluted to 0.4, 0.2, and 0.1 µg/mL. Each solution (7–10 mL) was placed into a sterile, all-purpose container and congealed for 45 min at 85 °C (LJ slope). The LJ slopes were cultured at 37 °C for 28 days with standard M. TB H37RV inoculations of 10^{-2} and 10^{-4} CFU/ml, respectively. The active substances were then cultured for a further 14 days. INH was employed as a reference substance, and the assay was carried out in duplicates.

3.0 Results and Discussion

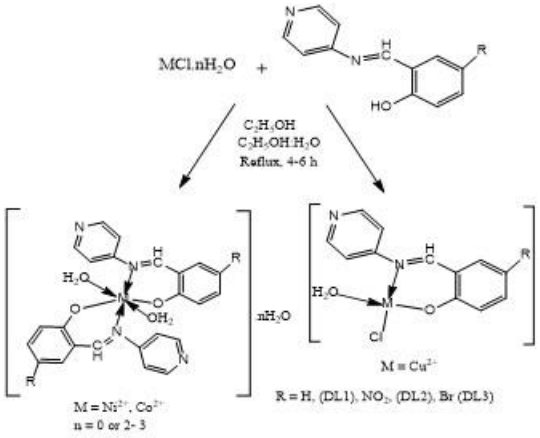
3.1 Synthesis

The ligands DL1, DL2 and DL3 were synthesized by the direct condensation reaction of 4-aminopyridine with 2-hydroxybenzaldehyde (DL1), 5-nitro-2-hydroxybenzaldehyde (DL2) and 5-bromo-2-hydroxybenzaldehyde (DL3) (Scheme 1). Table 1 shows the analytical and physical data of the compounds. The compounds were

produced in good yields, and the elemental analysis is consistent with the molecular formulas proposed for each Schiff base. It is suggested that the metal complexes formed because the melting points of the metal complexes and their corresponding ligands varied. Each of the metal complexes had elemental constituents that supported the molecular formula.



Scheme 1: Synthetic route to the Schiff bases formation



Scheme 2: Synthetic route to Schiff base metal complex formation

Table 1: Physical and analytical data of DL1-DL3

Ligand code	Molecular Wt. (M.wt. (g/mol))	mp:(°C)	Yield (%)	Microanalysis: %Calculated (Found)			
				C	H	N	M
	$C_{12}H_{10}N_2O$	77-78	81	72.71	5.08	14.10	
DL1	(198)			(72.62)	(5.02)	(13.96)	
Cu-DL1	$C_{12}H_{11}ClCuN_2O_2$	244	60	45.87	3.53	8.92	20.22
	(314)	(dec.)		(46.32)	(3.00)	(8.40)	(20.74)
Ni-DL1	$C_{24}H_{22}N_4NiO_4$	265	49	58.93	4.53	11.45	12.00
	(488)	(dec.)		(59.31)	(3.88)	(11.11)	(13.54)
Co-DL1	$C_{24}H_{22}CoN_4O_4$	298-303	54	58.90	4.53	11.45	12.04
	(489)			(60.64)	(4.02)	(10.81)	(13.17)
	$C_{12}H_9N_3O_3$	193-194	75	59.26	3.77	17.28	
DL2	(243)			(58.96)	(3.63)	(17.06)	
Cu-DL2	$C_{12}H_{10}ClCuN_3O_4$	>349	39	40.12	2.81	11.70	17.69
	(359)			(40.07)	(2.61)	(10.78)	(18.19)
Ni-DL2	$C_{24}H_{26}N_6NiO_8$	296-299	52	53.07	2.97	15.47	10.81
	(542)			(54.93)	(3.02)	(14.76)	(10.23)
Co-DL2	$C_{24}H_{20}CoN_6O_8$	248-251	58	49.75	3.48	14.51	10.17
	(579)			(50.26)	(3.02)	(15.15)	(9.71)
	$C_{12}H_9BrN_2O$ (277)	139-141	84	52.01	3.27	10.11	
DL3				(52.16)	(3.18)	(9.82)	

Cu-DL3	$C_{12}H_{10}BrClCuN_2O_2$ (393)	248 (dec)	59	36.66 (38.49)	2.56 (2.17)	7.13 (6.63)	16.16 (16.00)
Ni-DL3	$C_{24}H_{16}Br_2N_4NiO_2$ (607)	300-303	63	47.18 (46.49)	2.64 (2.67)	9.17 (8.48)	9.61 (9.80)
Co-DL3	$C_{24}H_{24}Br_2CoN_4O_6$ (683)	>349	66	42.19 (41.54)	3.54 (2.79)	8.20 (7.56)	8.63 (8.51)

3.2 NMR spectra of DL1-DL3

The ^{1}H NMR spectrum of ligands resonate as a singlet δ_H 8.61 and 12.57 ppm (DL1), δ_H 8.56 and 10.01 ppm (DL2) and δ_H 8.54 and 12.57 ppm (DL3) attributed to the imine (HC=N) and hydroxyl (OH) protons respectively. All the signals for the carbon atoms were accounted for in the ^{13}C NMR spectrum. Hence, the NMR signals support the structure of the ligand.

3.3 IR Spectra

The IR spectra of the complexes and the free ligands were compared in order to ascertain the binding mode of the Schiff bases to the metal ions in the complexes. After complexation, the ligands' distinctive absorption bands, which were at frequencies 1587, 1650, and 1615 cm^{-1} moved by ± 3-6 cm^{-1}, demonstrating the participation of azomethine nitrogen in coordination.

The coordination of the ligand's phenolic oxygen to the metal ion caused the C-O band, which at frequencies of 1271, 1280, and 1274 cm^{-1}, to appear at higher frequencies following complexation. It can be inferred that the Schiff bases are bidentate, coordinating through azomethine nitrogen and phenolic oxygen (Aggoun *et al.*, 2020).

Table 2: Characteristic ^{1}H and ^{13}C NMR bands of DL1-DL3

Ligand code	Chemical shift (ppm)			
	HC=N		C-OH	
	δ_H	δ_C	δ_H	δ_C
DL1	8.61	161.29	12.57	165.68
DL2	8.56	164.14	10.01	166.39
DL3	8.54	160.27	12.57	164.38

Table 3: Characteristic IR (cm^{-1}) bands of DL1-Co-DL3

Compound code	Molecular formula	*v*OH	*v*C=N	*v*C-O	*v*C=N (pyridine)	*v*(H_2O)	*v*(M-O)	*v*(M-N)
DLI	$C_{12}H_{10}N_2O$	3324	1587	1271	1056	-	-	-
Cu-DL1	[CuDL1.Cl.H_2O]		1581	1372	1058	869	528	489
Ni-DL1	[Ni(DL1)$_2$.2H2O]		1591	1319	1054	867	529	485
Co-DL1	[Co(DL1)$_2$.2H2O]		1590	1319	1056	866	445	414
DL2	$C_{12}H_9N_3O_3$		1650	1280	1081	-	-	-
Cu-DL2	[CuDL2.Cl.H2O]		1597	1373	1087	850	482	444
Ni-DL2	[Ni(DL2)2]		1651	1291	1082	-	507	461
Co-DL2	[Co(DL2)2.2H2O]		1597	1335	1084	855	490	428
DL3	$C_{12}H_9BrN_2O$		1615	1274	1078	-	-	-
Cu-DL3	[CuDL3.Cl.H_2O]		1598	1279	1080	874	464	439
Ni-DL3	[Ni(DL3)$_2$]		1596	1319	1079	-	453	428
Co-DL3	[Co(DL3)$_2$.2H2O].2H_2O		1597	1279	1081	870	523	429

The appearance of two additional bands at 414-489 (M-N) and 445-529 (M-O) further supports the coordination of the ligand to the metal ion through azomethine nitrogen and phenolic oxygen (Vidya Rani *et al*., 2020).

3.4 Electronic absorption

A compound's molecular structure can be determined from its electronic spectra. In DMF at room temperature, the compounds' electronic absorption spectra were recorded and the results are shown in Table 4. The π-π* transition at 275-278 nm is due to the ligand's aromatic band. The non-bonding electron that is present on the nitrogen of the azomethine causes the band to appear in the 333–369 nm range due to n-π* transition. The electronic spectra of the complexes show an intense absorption band at 401 nm to 742 nm assigned to d-d transition. All the Cu(II) complexes displayed band characteristics of a square planar geometry within the range 401-424 nm (Yusuf *et al*., 2021). While this is true, Ni(II) complexes displayed varied geometry of square planar for DL2 and DL3 and octahedral for DL1 (Ommenya *et al*., 2020). The Co(II) showed a band typical of an octahedral configuration (El-ghamry *et al*., 2022).

Table 4: Electronic absorption bands and molar conductance for the compounds

Compound code	Molecular formula	λ_{max}(nm) (Assignment)	Molar conductance ($ohm^{-1}cm^2mol^{-1}$)	Proposed Geometry
DLI	$C_{12}H_{10}N_2O$	277, 333 (π-π*, n-π*)	-	-
Cu-DL1	[CuDL1.Cl.H_2O]	401 (d-d)	4.24	Square planar
Ni-DL1	[Ni(DL1)$_2$.2H2O]	561,677 (d-d)	1.94	octahedral
Co-DL1	[Co(DL1)$_2$.2H2O]	656 (d-d)	2.20	octahedral
DL2	$C_{12}H_9N_3O_3$	275, 369 (π-π*, n-π*)	-	-
Cu-DL2	[CuDL2.Cl.H2O]	412 (d-d)	3.60	Square planar
Ni-DL2	[Ni(DL2)2]	402 (d-d)	3.83	Square planar
Co-DL2	[Co(DL2)2.2H2O]	558 (d-d)	2.10	octahedral
DL3	$C_{12}H_9BrN_2O$	278, 349 (π-π*, n-π*)	-	-
Cu-DL3	[CuDL3.Cl.H_2O]	424 (d-d)	3.92	Square planar
Ni-DL3	[Ni(DL3)$_2$]	424 (d-d)	1.75	Square planar
Co-DL3	[Co(DL3)$_2$.2H2O].2H_2O	742 (d-d)	2.18	octahedral

3.5 Molar conductance

The molar conductance of the isolated complexes was measured in 10^{-3} M DMF solutions. The molar conductance measurements of the Schiff base complexes ranged from 1.75 to 4.24 $ohm^{-1}cm^2mol^{-1}$,

demonstrating their non-electrolytic nature (Ejidike, 2018).

3.6 Anti-tuberculosis activity

Results of the *in-vitro* anti-TB activity revealed that not all of the compounds are effective against Mycobacterium tuberculosis $H37_{RV}$. These Schiff bases displayed a significant substituent effect on their activity with the -nitro-containing compound (**DL2**) exhibiting comparable activity to the reference compound (**INH**). However, a comparison of the Schiff bases and their metal complexes revealed that several of the complexes had improved anti-tuberculosis efficacy in comparison to the free ligands and the reference drug (INH). This might be a result of the metal complexes' high lipid content relative to the ligand, which enhanced their penetration into the cell membrane of *Mycobacterium tuberculosis (*More *et al*., 2018**)**. The copper and cobalt complexes of the nitro (**Cu-DL2 and Co-DL2**) containing ligands displayed enhanced activity over the reference compound at 0.1 µg/ml. Hence, the nitro-containing complex can be considered as a potential drug candidate in the development of antituberculosis drugs.

Table 5: *In vitro* anti-tuberculosis activity of the compounds on *M.TB* H37Rv

Compd code	Molecular formula	0.4(µg/mL)		0.2(µg/mL)		0.1(µg/mL)	
		10^{-2} CFU/ml(std)	10^{-4} CFU/ml(std)	10^{-2} CFU/ml (std)	10^{-4} CFU/ml (std)	10^{-2} CFU/ml(std)	10^{-4} CFU/ml (std)
DLI	$C_{12}H_{10}N_2O$	25 ± 0.37	7 ± 0.17	37± 0.40	13± 0.22	42 ± 0.42	17 ± 0.34
Cu-DL1	[CuDL1.Cl.H_2O]	14± 0.28	0 ± 0.00	19 ± 0.33	9± 0.19	30± 0.39	13± 0.24
Ni-DL1	[Ni(DL1)$_2$.2H2O]	20 ± 0.36	7± 0.16	28 ± 0.37	14± 0.27	29 ± 0.37	19 ± 0.36
Co-DL1	[Co(DL1)$_2$.2H2O]	0 ± 0.00	0± 0.00	12 ± 0.09	0 ± 0.00	17 ± 0.35	11 ± 0.32
DL2	$C_{12}H_9N_3O_3$	0 ± 0.00	0 ± 0.00	20 ± 0.67	0 ± 0.00	25 ± 0.71	3 ± 0.01
Cu-DL2	[CuDL2.Cl.H2O]	0 ± 0.00	0 ± 0.00	14 ± 0.36	0 ± 0.00	17 ± 0.42	0 ± 0.00
Ni-DL2	[Ni(DL2)2]	0 ± 0.00	0 ± 0.00	20 ± 0.64	0 ± 0.00	20 ± 0.68	5 ± 0.09
Co-DL2	[Co(DL2)2.2H2O]	0 ± 0.00	0 ± 0.00	18 ± 0.45	0 ± 0.00	20 ± 0.67	0 ± 0.00
DL3	$C_{12}H_9BrN_2O$	0 ± 0.00	0 ± 0.00	37 ± 1.21	4 ± 0.01	42 ± 1.41	7 0±0.4
Cu-DL3	[CuDL3.Cl.H_2O]	0 ± 0.00	0 ± 0.00	29 ± 0.45	20 ±0.21	36 ± 1.21	24 ± 0.36
Ni-DL3	[Ni(DL3)$_2$]	0 ± 0.00	0 ± 0.00	30 ± 0.67	0 ± 0.00	42 ± 1.37	2± 0.01
Co-DL3	[Co(DL3)$_2$.2H2O]. $2H_2O$	0 ± 0.00	0 ± 0.00	26 ± 0.38	0 ± 0.00	32 ± 0.98	32 ± 0.87
INH	INH	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	12 ± 0.47	8 ± 0.16

***CFU (colony forming unit); std (standard Deviation)**

4.0 Conclusion

Schiff base-metal complexes are an interesting and active field of research due to their easy and affordable method of synthesis. Nine Cu(II) Ni(II) and Co(II) complexes were synthesized in this study using salicyl diene-4-aminopyridine derivatives as ligands. Comparing the complexes to INH, a first-line antituberculosis drug and the corresponding Schiff base ligands, the complexes demonstrated improved inhibitory in-vitro antituberculosis action on Mycobacterium tuberculosis $H37_{RV}$. The Schiff base ligand (DL2) with the nitro group was discovered to be a superior anti-mycobacterium agent compared to INH based on this study. Further research would be done on this compound in order to develop it into a potential TB drug candidate.

5.0 References

Aggoun, D., Fernández-García, M., López, D., Bouzerafa, B., Ouennoughi, Setifi, F. & Ourari,

A. (2020). New nickel (II) and copper (II) bidentate Schiff base complexes, derived from dihalogenated salicylaldehyde and alkylamine: Synthesis, spectroscopic, thermogravimetry, crystallographic determination and electrochemical studies, *Polyhedron*, 187, 114640, doi:10.1016/j.poly.2020.114640

Dueke-Eze, **C. U**., Fasina, T. M., Oluwalana, A. E., Familoni, O. B., Mphalele, J. M. & Onubuogu, C. (2020). Synthesis and biological evaluation of copper and cobalt complexes of (5-substituted-salicylidene) isonicotinichydrazide derivatives as antitubercular agents, *Scientific African*, **9**, e00522. https://doi.org/10.1016 -/j.sciaf.2020.e00522

Dueke-Eze, C. U., Fasina, T. M., Familoni, O. B., Coker, A. O. & Onubogu, C. C. (2018). Synthesis and anti-tuberculosis activity of some copper(II) and cobalt(II) complexes of substituted methylene isonicotinoyl hydrazide Schiff Bases, *Journal of Chemical Society of Nigeria*, 43, 1, pp. 24-30.

Ejidike, I. P. (2018). Cu(II) Complexes of 4-[(1*E*)-*N*-{2-[(*Z*)-Benzylidene-amino]ethyl}ethanimidoyl]benzene-1,3-diol Schiff Base: Synthesis, Spectroscopic, In-Vitro Antioxidant, Antifungal and Antibacterial Studies, *Molecules*, 23, 7, 1581. doi: 10.3390/molecules23071581.

El-Gammal, O. A., Mohamed, F. S., Rezk, G. N. & El-Bindary, A.A. (2021). Synthesis, characterization, catalytic, DNA binding and antibacterial activities of Co(II), Ni(II) and Cu(II) complexes with new Schiff base ligand, *Journal of Molecular Liquids*, 326,115223, doi: 10.1016/j.molliq.2020.115223

El-ghamry, M.A., Elzawawi, F.M., Aziz, A.A.A. *et al*. (2022). New Schiff base ligand and its novel Cr(III), Mn(II), Co(II), Ni(II), Cu(II), Zn(II) complexes: spectral investigation, biological applications, and semiconducting properties, *Scientific Reports*, 12, 17942, https://doi.org/10.1038/s41598-022-22713-z

Fogel, N. (2015). Tuberculosis: A disease without Boundaries, *Tuberculosis*, 1**,** 527e531

Hamid, S. J. & Salih, T. (2022). Design, synthesis and anti-inflammatory activity of some Coumarin Schiff base derivatives:In silico and in vitro study, *Drug Design, Development and Therapy*, 16, 2275, doi: 10.2147/DDDT.S364746,

Hu, Y., Xu, L., He, Y .L, . Pang, Y., Lu, N., Liu, J., Shen, J., Zhu, D.M., Feng, X., & Wang, Y.W. (2017). Prevalence and molecular characterization of second-line drugs resistance among multidrug-resistant Mycobacterium tuberculosis isolates in Southwest of China. *BioMed Research Int*ernational, 4563826. Doi: 10.1155/2017/4563826

Jain, S., Rana, M., Sultana, R., Mehandi, R. & Rahisuddin, (2022). Schiff base metal complexes as antimicrobial and anticancer agents, *Polycyclic Aromatic compounds*, **5**,1-56. Doi: 10.1080/10406638.2022.2117210

More, G., Bootwala, S., Shenoy, S., Mascarenhas, J., & Aruna, K. (2018). Synthesis, Characterization and In vitro Antitubercular and Antimicrobial Activities of new Aminothiophene Schiff Bases and their Co(II), Ni(II), Cu(II) and Zn(II) Metal Complexes, *Oriental Journal Chemistry*, 34, 2, pp. 800-812.

Ommenya, F. K., Nyawade, E. A., Andala, D. M. & Kinyua, J. (2020). Synthesis, Characterization and Antibacterial Activity of Schiff Base, 4-Chloro-2-{(E)-[(4-Fluorophenyl)imino]methyl}phenol Metal (II) Complexe, *Journal of Chemistry*, 8, doi.org/10.1155/2020/1745236

Salve, P. S.,, Alegaon, S. G.and Sriram, D. (2017). Threecomponent, one-pot synthesis of anthranilamide Schiff bases bearing 4-aminoquinoline moiety as Mycobacterium tuberculosis gyrase inhibitors, *Bioorganic Medicinal Chemistry Letter*, 27, 8, pp**.** 1859-1866

Shukla, M., Kulshrashtha, H. & Seth, D. S. (2017). Comparative study of the Schiff bases by conventional and Green method and antimicrobial activity, *International Journal of Material Sciences*, 12(, 1, pp. 71-76

Thompson, K. H. & Orvig, C. (2006). Metal complexes in medicinal Chemistry: New vistas and challenges in drug design. *Journal of Chemical Society Dalton Transactions*, 6, pp. 761-764.

U.S. Food and Drug Administration. FDA *Approves New Drug for Treatment-Resistant*

Forms of Tuberculosis that Affects the Lungs; U.S. Food and Drug Administration: Rockville, MD, USA, 2019. Available online: https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug treatment-resistant-forms-tuberculosis-affects-lungs

Venugopala, K. N., Kandeel, M., Pillay, M., Kishore, P., Abdallah, H. H., Mahomoodally, M. F. & Deepak Chopra, D. (2020). Anti-Tubercular Properties of 4-Amino-5-(4-Fluoro-3- Phenoxyphenyl)-4H-1,2,4-Triazole-3-Thiol and Its Schiff Bases: Computational Input and Molecular Dynamics, *Antibiotics,* 9, 559; doi:10.3390/antibiotics9090559

Vidya Rani, C., Kesavan, M.P., Haseena, S. *et al*. (2020). Bidentate Schiff Base Ligands Appended Metal(II) Complexes as Probes of DNA and Plasma Protein: In Silico Molecular Modelling Studies, *Applied Biochemistry and Biotechnol*ogy, 191, pp. 1515–1532 (2020). https://doi.org/10.1007/s12010-020-03270-5

WHO(2023).https://www.who.int/campaigns/world-tb-day/2023

Yadav, M., Sharma, S. &Devi, J. (2021). Designing, spectroscopic characterization, biological screening and antioxidant activity of mononuclear transition metal complexes of bidentate Schiff base hydrazones, *Journal of Chemical Sciences*, 133, 1, pp. 1-22, doi: 10.1007/s12039-020-01854-6

Yusuf, T. L., Oladipo,S. D., Zamisa, S., Kumalo, H. M., Isiaka A. Lawal, I. A., Lawal, M. M. & Maba, N. (2021). Design of New Schiff-Base Copper(II) Complexes: Synthesis, Crystal Structures, DFT Study, and Binding Potency toward Cytochrome P450 3A4, *American Chemical Society Omega*, *6* , 21, pp. 13704-13718, doi: 10.1021/acsomega.1c00906

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