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RESEARCH ARTICLE

Synthesis, Characterization And Antitubercular Activities Of Novel Metal Complexes Derived From Quinoline Based Schiff Base Ligand.

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ABSTRACT

The present work is aimed at synthesis of novel quinoline moiety Schiff base has been made through various steps and their metal complex with Cu^{II}, Ni^{II}, Co^{II} Zn^{II} & Cd^{II} in 1:1 ratio (1L:1M). Structure of prepared Schiff base and their metal complexes are characterized by ^{1}H NMR, ^{13}C NMR, FT-IR, HRMS, XRD and Electronic absorption spectral analysis. In addition to this, all the synthesized compounds were evaluated for their *in vitro* antimycobacterial activity against *M. tuberculosis H37Ra* (*MTB)* and *M. Bovis BCG* strains. Schiff's base Ligand and its complexes showed good in antitubercular activity against *MTB* and *M. Bovis* strains with MIC values 0.061-1.5 and 0.54-2.2 µg/mL, respectively. All compounds were found nontoxic against MCF-7, A549, HCT 116 and THP-1 cell lines. Therefore, all the prepared compounds are useful for the further development of antitubercular, antibacterial agents.

Keywords: Schiff base, Quinoline moiety, Antitubercular, Antimycobacterial activity.

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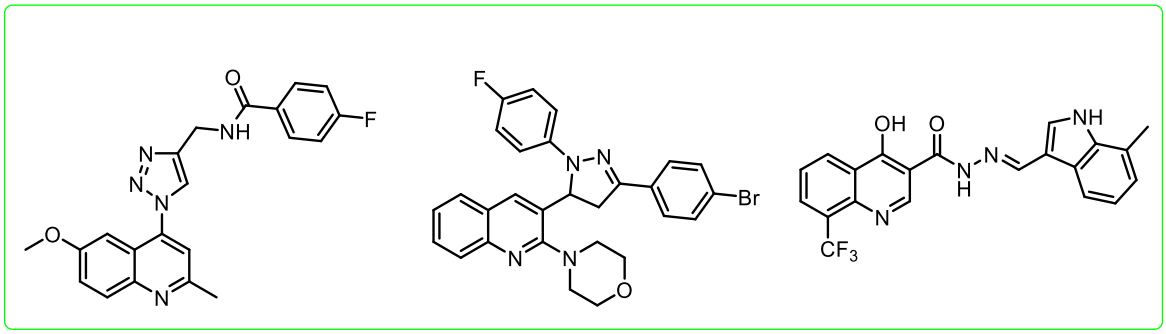
INTRODUCTION

Tuberculosis (TB), caused by the pathogen *Mycobacterium tuberculosis* (*MTB*) is one of the most infectious causes of mortality worldwide [1]. Bacillus Calmette-Guerin (BCG) is an attenuated derivative of a virulent strain of *Mycobacterium bovis* which has been used as a vaccine against *MTB*, as a recombinant vehicle for multivalent vaccines against other infectious diseases and as cancer immunotherapy [2]. Therefore, the ability to identify BCG is clinically important both rapidly and specifically. In addition to this, totally drug-resistant TB (TDR-TB) has recently arisen which is resistant to all clinical drugs [3]. Delamanid (OPC-67683) and Bedaquiline (TMC207) are the two drugs recommended by the US FDA for multi-drug-resistant tuberculosis (MDR-TB) treatment [4]. Therefore, need for safe and effective antimycobacterial drugs will be used efficiently to treat XDR and MDR tuberculosis. Quinolines derivatives are naturally occurring compounds with a broad spectrum of biological activities including antibacterial [5], antimalarial [6], antihypertensive [7], antibiotic [8], anticancer [9], anti-HIV [10]. A highly substituted quinoline derivatives [11] were displayed potent antimycobacterial activity. The fusion of quinoline to the tetrazole ring is known to increase the biological activity. The tetrazole group which is considered as analogues of carboxylic group as a pharmacophore possesses wide range of biological activities such as anticancer [12], antibacterial [13], antitubercular agents [14]. The Schiff bases of quinoline and their metal complexes are widely used in many areas such as dye in solar cells [15], catalyst in olefin polymerization [16], cytotoxic [17], antimicrobial [18], antioxidant [19] and anticancer agents [20]. Schiff-bases complexes derived from 2-oxo-quinoline-carbaldehyde can bind to DNA by intercalation [21]. Experimental investigations of pharmaceutical chemistry and pharmacology particularly highlight the potential biological activity of sulfonyl-hydrazine derivatives. Thus, antimicrobial, anticancer [22], analgesic, anti-inflammatory, and antipyretic properties were already reported in the literature. Some of the known antitubercular compounds bearing quinoline moiety are shown below.



Quinoline based antitubercular agents

The multifarious role of quinoline compounds in biological activity have been continuous efforts based on the design, synthesis and biological evaluation of heterocyclic derivatives. We synthesized metal complexes based on novel quinoline by assembling in a single molecular framework quinoline units, with an aim to obtain prominent antimycobacterial activity with minimal side effects.

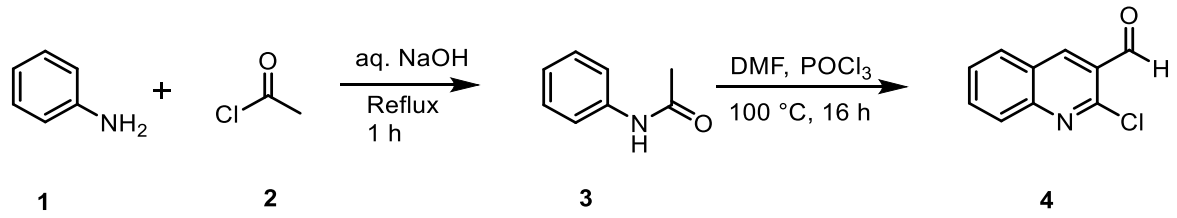
MATERIALS & METHODS

All chemicals and solvents were purchased from Sigma-Aldrich with high purities AR grade and used without further purification and metal salts were purchased from Molychem chemicals. The progress of the reaction was monitored by thin layer chromatography (using silica gel 60 F-254 plates). The products were visualized with a 254 nm UV lamp. Melting points were determined by open capillary methods and are uncorrect. Products were purified by column chromatography on 100-200 mesh silica gel. FT-IR spectra were recorded on Perkin Elmer System 2000 using KBr disc. ^{1}H NMR & ^{13}C NMR spectra were recorded on Bruker Avance NEO 400 spectrometer as solvent DMSO-d_6 by using tetramethylsilane (TMS) as an internal standard at 400 MHz and 100 MHz, respectively. The ^{1}H NMR & ^{13}C NMR spectra chemical shifts were reported in parts per million (d) relative to tetramethylsilane (TMS) as an internal standard. Coupling constant (J) values were reported in hertz (Hz). The splitting patterns of the proton are described as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), and m (multiplet) in ^{1}H NMR spectroscopic analysis. The products were confirmed by ^{1}H and ^{13}C NMR spectroscopy analysis. High-resolution mass spectra (HRMS) were obtained using Agilent 6520 (QTOF) ESI-HRMS model.

Synthesis of Ligand and Metal Complexes:

Synthesis of 2-chloro-3-formylquinolines

The required starting material, quinoline aldehyde **4** was prepared [23] from corresponding aniline by acylation followed by Vilsmeier-Haack formylation at 100 ºC for 16 h as shown in **Scheme 1**.



1 2 3 4

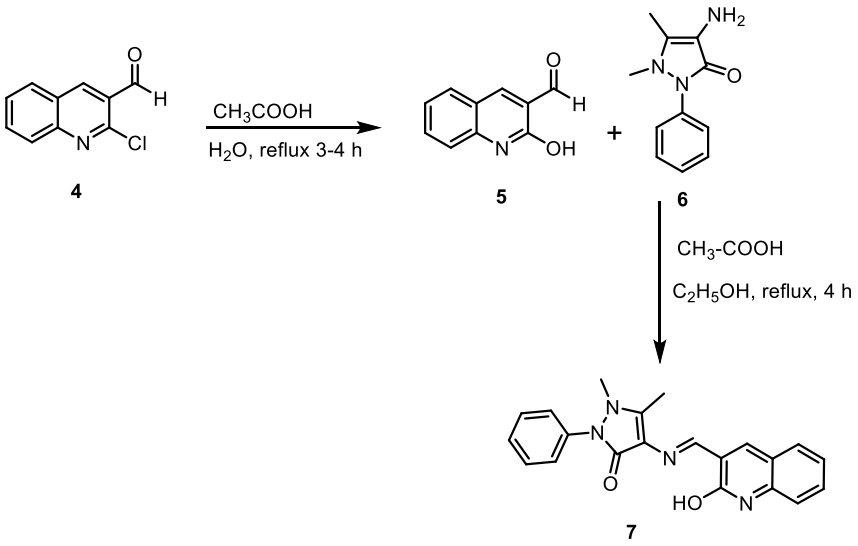
Scheme1. Synthesis of 2-chloro-3-formylquinolines (4)

*Synthesis of 2-hydroxyquinoline-3-carbaldehyde (**5**)*

A reaction of 2-chloroquinoline-3-carbaldehyde (**4**) (10 mmol) and H_2O (1 mL) was dissolved acetic acid (2 mL). The reaction mass was refluxed for 4 h. The progress of reaction was monitored by using TLC. After 4h, the reaction mass was poured into ice cold water. The obtained solid was filtered and washed with water. The crude solid was crystallized in ethanol to afford the corresponding pure product 2-hydroxyquinoline-3-carbaldehyde intermediate (**5**) and used for the further reaction without purification.

*Synthesis of (E)-4-(((2-hydroxyquinoline-3-yl)methylene)amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (**7**)*

The mixture of appropriate 2-hydroxyquinoline-3-carbaldehyde intermediate (**5**) (1mmol), 4-amino-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (**6**) (1 mmol) and acetic acid (5-10 drops) in ethanol (15 mL) was placed in a round bottom flask. The mixture was refluxed at 70 °C for an appropriate time until the completion of the reaction. The progress of the reaction was monitored by TLC using ethyl acetate : hexane as a solvent system. The reaction mixture was quenched with crushed ice and extracted with ethyl acetate (2 × 15 mL). The organic extracts were washed with brine solution (2 × 15 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to afford the corresponding crude compounds **7.** The obtained crude compound was recrystallized using ethanol.



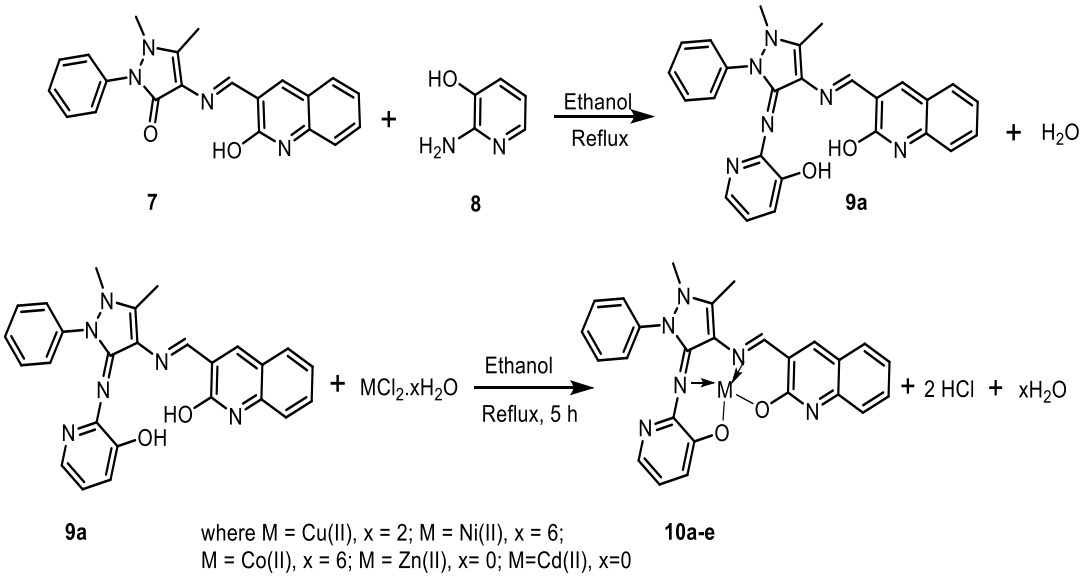
4 5 6 7

Scheme 2. Synthesis of *(E)-4-(((2-hydroxyquinoline-3-yl)methylene)amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one* (7).

Synthesis of novel quinoline based metal complex **(10a-e)**

Schiff's base was prepared by refluxing equimolar mixture of compound **7** (1 mmol) and 2-amino 3-hydroxy pyridine **8** (1 mmol) in 25 mL ethanol was taken in a round bottomed flask. The reaction was refluxed for 5 h on 1 RML Rotamantle. On cooling the reaction mixture was poured in to ice-cold water, the corresponding Schiff's base was obtained, solid product was washed by hot ethanol, recrystallise from ethanol and dried in air.

Metal complexes were prepared by adding 25 mL hot ethanolic metal salt (1 mmol) solution to the 30 mL hot ethanolic HL solution (1 mmol) in 1:1 ratio for Cu^{II}, Ni^{II}, Co^{II} Zn^{II} and Cd^{II}. The reaction mixture was stirred for 30 min, then addition of few drops of 10% alcoholic NH_3 solution to maintain basic PH around 7- 8 of the reaction mixture. The reaction mixture was reflux for about 2 h to give a coloured respective metal solid precipitate. Obtained solid precipitated was filtered off and dried in an oven for about 90 min for 80 ^oC temperature results formation of pure corresponding metal complexes **(10a-e)**



Scheme 3. Synthesis of novel quinoline based metal complex (10a-e).

3-((1E)-((3-((3-hydroxypyridin-2-yl)imino)-1,5-dimethyl-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)imino)methyl)quinolin-2-ol (**9a**)

Yield: 82%; White solid; MP: 236-238 °C; FTIR (KBr, ν_{max}, cm^{-1}):3600-3300 (s, broad, -OH), 3050 (w, Ar-H), 2960 (w, $-CH_3$), 2000-1665 (w, Ar overtone bands), 1670-1620 (s, Ar C=C), 1610 (m, -C=N-), 1190 (m, O-C), 740, 690 (s, Ar mono); ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 9.78 (s, 1H, OH), 8.39 (s, 1H, C=C-H), 8.09-8.07 (m, 1H, Ar–H), 8.01 (s, 1H, OH), 8.00-7.91 (m, 1H, Ar–H), 7.42-7.40 (m, 1H, Ar–H), 7.35-7.33 (m, 5H, Ar–H), 7.15-7.13 (m, 2H, Ar–H), 6.87-6.85 (m, 2H, Ar–H), 6.78-6.75 (m, 1H, Ar–H), 2.73 (s, 3H, $-CH_3$) and 2.12 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 165.35, 148.56, 144.14, 139.80, 136.55, 133.90, 133.86, 130.28, 129.90, 128.17, 127.69, 126.28, 123.96, 123.31, 123.23, 122.94, 122.86, 118.74, 37.46 and 15.71; HRMS (ESI-qTOF): Calcd for $C_{26}H_{23}N_6O_2$ [M+H]+, 451.3550: found: 451.3577.

Table 1: Analytical data of the Ligand and its metal (II) complexes

Compound	Yield %	m.w.	Elemental Analysis %: Calcd. (found)				
			C	H	N	O	M
$C_{26}H_{22}N_6O_2$-L	82	451.3577	69.32 (69.30)	4.92 (4.89)	18.66 (18.63)	7.10 (7.08)	-
$C_{26}H_{22}N_6O_2$-Cu	70	512.3112	60.99 (60.98)	3.94 (3.91)	16.41 (16.40)	6.25 (6.22)	12.41 (12.40)
$C_{26}H_{22}N_6O_2$-Ni	67	507.2635	61.57 (61.55)	3.97 (3.94)	16.57 (16.53)	6.31 (6.30)	11.57 (11.54)
$C_{26}H_{22}N_6O_2$-Co	72	507.4233	61.54 (61.52)	3.97 (3.95)	16.56 (16.54)	6.31 (6.28)	11.61 (11.58)
$C_{26}H_{22}N_6O_2$-Zn	65	514.3297	60.77 (60.73)	3.92 (3.90)	16.35 (16.34)	6.23 (6.21)	12.72 (12.69)
$C_{26}H_{22}N_6O_2$-Cd	64	562.0713	55.68 (55.66)	3.59 (3.58)	14.98 (14.96)	5.70 (5.68)	20.04 (20.01)

Electronic absorption spectra

The UV spectra are conveniently measured in the range absorption bands at 39,720-11280 cm^{-1}. The spectra of the ligand and its Co(II), Ni(II) and Cu(II) complex are shown in **Fig. 1**.

IR spectra

Ligand such as C=O, C=N and -OH group on the complex formation, The IR spectrum of the ligand shows a weak broad band in the region 3600-3300 cm-1 assignable to intra-molecular hydrogen bonded -OH groups. The absence of this band, noted in the spectra of the complexes, indicates the deprotonation of the -OH groups on complexation. The -C=N bands of salicylidene-4-aminoantipyrinyl moiety appearing in the region 1612-1600 cm^{-1} for the free ligand are also shifted to lower frequencies in the spectra of the complexes (1585-1565 cm^{-1}) on coordination. The band in the ligand spectrum at 1565 cm^{-1} is ascribed to C=N of pyridine ring, but there is no appreciable change in the spectra of the complexes which indicates that pyridine nitrogen does not involve in the coordination. IR spectra of the metal chelates also shows some new bands in the region 465-455 cm-1 and 410-390 cm^{-1} which are probably due to the formation of M-O and M-N bonds respectively. IR spectra of the Schiff base ligand and its metal complex such as Co(II), Ni(II), Cu(II) and Zn(II) complex are shown in **Fig. 2a-e** in supporting information.

Powder X-ray diffraction study

As single crystals of synthesized compounds were not obtained, The powder XRD diffractograms of synthesized Co(II), Ni(II), Cu(II) and Zn(II) metal ligand complexes were performed to find out the nature of all compounds by taking 2θ scale in the range of 2–90° degrees. From the results, all the compounds showed sharp peaks which indicates their crystallinity in nature. XRD spectra of metal complexes shown in **Fig. 5**

ESR spectra

The ESR spectrum of the present Cu(II) complex at 77 K is shown in **Fig. 6.** And the interaction of the Cu(II) odd electron with nitrogen atoms. The magnetic susceptibility value reveals that the Cu(II) complex has a magnetic moment, 1.75 B.M., corresponding to one unpaired electron, indicating that the complex is mononuclear. This fact was also evident from the absence of a half field signal, expected in the spectrum at 1600 G due to the ms = ±2 transitions, ruling out any Cu-Cu interaction.

RESULT AND DISCUSSION

Antitubercular activity screening

The newly synthesized quinoline based metal complex (**10a-e**) were screened for *in vitro* antitubercular activity against *MTB H37Ra* (ATCC 25177) and *M. Bovis BCG* (ATCC 35743) in liquid medium [24]. We explored the eminent XTT Reduction Menadione assay (XRMA) of the anti-mycobacterial

screening protocol employing first-line anti-mycobacterial rifampicin drug as a standard reference and the IC_{50} and MIC values are presented in **Table 2**.

The Schiff base **9a** and novel quinoline based metal complex **10a, 10b, 10c, 10d** and **10e** exhibited excellent antitubercular activities with MIC values ranging from 0.061-1.5 and 0.54 - 2.2 µg/mL. They are found to be most active against *MTB H37Ra* and *M. bovis BCG* strain, respectively.

Firstly, we will elaborate the antitubercular activity of novel quinoline based metal complex against *MTB* strain. From the novel quinoline based metal complex **(10a-e)**, compound **10a** in which Cu metal present exhibits excellent activity against *MTB* strain with MIC = 0.12 µg/mL and the results are presented in **Table 2**. Compounds **10b** in which (Metal = *Ni*) are active against *MTB* strain with MIC = 1.5 µg/mL. When the installation of the *Co metal* in compound **10c** (Metal = Co) showed excellent activity against *MTB* strain with MIC= 0.18 µg/mL. When a *Zn* metal present in compound **10d** (Metal = Zn) exhibits prominent antimycobacterial activity against *MTB* strain with MIC= 0.10 µg/mL. When a Cd metal present in compound **10e** (Metal = Cd) results excellent activity against *MTB* strain with MIC with MIC = 0.061 µg/mL. Compound **9a** exhibits excellent antitubercular activity against *MTB* strain with MIC = 0.24 µg/mL. Hence, among all the synthesized Schiff base and novel quinoline based metal complex, compounds **9a, 10a, 10b, 10c, 10d** and **10e** are found highly potent against *MTB* and the details are disclosed in **Table 2**.

Further, all the compounds also tested for antitubercular activity against the *M. Bovis BCG* strain. From the novel quinoline based metal complex **(10a-e)**, compound **10a** in which Cu metal present shows promising antitubercular activity against *M. Bovis BCG* strain with MIC = 0.02 µg/mL and the results are presented in **Table 2**. Compounds **10b** in which (Metal = *Ni*) are active against *M. Bovis BCG* strain with MIC = 2.2 µg/mL. When the introduction of the *Co metal* in compound **10c** (Metal = Co) showed prominent activity against *M. Bovis BCG* strain with MIC= 1.32 µg/mL. When a *Zn* metal present in compound **10d** (Metal = Zn) exhibits excellent antimycobacterial activity against *M. Bovis BCG* strain with MIC= 0.84 µg/mL. When a Cd metal present in compound **10e** (Metal = Cd) results excellent activity against *M. Bovis BCG* strain with MIC = 0.54 µg/mL. Compounds **9a** exhibits excellent antitubercular activity against *M. Bovis BCG* strain with MIC = 0.70 µg/mL. Hence, among all the synthesized Schiff base and novel quinoline based metal complex, compounds **9a, 10a, 10b, 10c, 10d** and **10e** are found highly potent against *M. Bovis BCG* and the details are disclosed in **Table 2**.

Table 2: Anti-mycobacterial activity[a]

Entry	Structures	*MTB H37Ra*		*M. Bovis BCG*	
		IC_{50}	MIC	IC_{50}	MIC
9a	**Schiff base**	0.08	0.24	0.50	0.70
10a	**Cu**	0.05	0.12	0.22	0.02
10b	**Ni**	0.45	1.5	0.60	2.2
10c	**Co**	0.38	0.18	0.34	1.32
10d	**Zn**	0.38	0.10	0.14	0.84
10e	**Cd**	0.55	0.061	0.08	0.54
[b]RP	-	0.0043± 0.00030	0.0173± 0.040	0.0019± 0.00028	0.020± 0.0026

[a]IC_{50}/MIC in µg/mL. Anti-mycobacterial activity of each agent was determined by serial dose dependent dilutions.
[b]Rifampicin as a standard reference antitubercular drugs and positive controls.

Cytotoxicity Activity

The highly active Schiff base **9a** and novel quinoline based metal complex **10a, 10b, 10c, 10d** and **10e** were tested for cytotoxicity activity against three human cancer cell lines MCF-7, HCT 116, and A549 using the well-established MTT protocol [25]. The cytotoxicity results of these compounds indicate they are highly potent and are specific inhibitors against *MTB H37Ra* and *M. Bovis BCG* strain with GI_{50}/GI_{90} (>100 µg/mL). Thus, all the most active compounds were relatively non-toxic against MCF-7, HCT 116 and A549 cell lines with (GI_{50}/GI_{90}) of >100 and the results are incorporated in **Table 3**.

Table 3: *In vitro* cytotoxicity of Schiff base and novel quinoline based metal complex

Entry	MCF-7 (Breast) Cell line		HCT116(Colorectal) Cell line		A549 (Lung) Cell line	
	GI_{50} (µg/mL)	GI_{90} (µg/mL)	GI_{50} (µg/mL)	GI_{90} (µg/mL)	GI_{50} (µg/mL)	GI_{90} (µg/mL)
9a	>100	>100	>100	>100	>100	>100
10a	>100	>100	>100	>100	>100	>100
10b	>100	>100	>100	>100	>100	>100
10c	>100	>100	>100	>100	>100	>100
10d	>100	>100	>100	>100	>100	>100
10e	>100	>100	>100	>100	>100	>100
Paclitaxel	0.0048	0.075	0.1279	5.715	0.0035	0.0706
Rifampicin	>100	>100	>100	>100	>100	>100

Selectivity index (SI)

The selectivity index indicates that a highly potent compound is only active against *mycobacteria* but it is non-toxic against host human cell lines. According to a study on the drug susceptibility of TB, antitubercular activity was considered to be specific when the selectivity index was >10 [26]. This study suggested that, compounds **9a, 10a, 10b, 10c, 10d** and **10e** display the highest selectivity index >10, suggesting that these compounds act as highly potent antimycobacterial agents and should be modified for the next level. The selectivity index study results are incorporated in **Table 4.**

Table 4. Selectivity index against dormant *MTBH37Ra* and *M. bovis BCG*

Entry	MCF-7		HCT 116		A549	
	MTB H37Ra	***M. Bovis BCG***	***MTB H37Ra***	***M. Bovis BCG***	***MTB H37Ra***	***M. Bovis BCG***
9a	140	482	140	482	140	482
10a	92	810	92	810	92	810
10b	64	20	64	20	64	20
10c	22	580	22	580	22	580
10d	146	658	146	658	146	658
10e	232	16	232	16	232	16
Rifampicin	>5000	1758.4	>5000	1758.4	>5000	1758.4

Antibacterial Activity

To determine the specificity of the most potent compounds **9a, 10a, 10b, 10c, 10d** and **10e** were evaluated for their antibacterial activity against Gram-negative bacteria (*P. flurescense* ATCC 13525), (*E. coli* ATCC 25292) and Gram-positive bacteria (*B. subtillus* ATCC 23857), (*S. aureus* ATCC 29213). The antibacterial activity protocol suggests that all the active compounds were much less active towards bacterial strains. All the most active compounds exhibited higher specificity towards antibacterial activity (**Table 5**).

Table 5: Antibacterial activity MIC (µg/mL).

Entry	*P. flurescense*	*E. coli*	*B.subtillus*	*S.aureus*
9a	>100	>100	>100	>100
10a	>100	>100	>100	>100
10b	>100	>100	>100	>100
10c	>100	>100	>100	>100
10d	>100	>100	>100	>100
10e	>100	>100	>100	>100
Ampicillin	4.40	1.50	10.40	1
Kanamycin	0.50	1.66	1.38	>30

Antitubercular assay

All the synthetic compounds were screened for their *in vitro* activity against MTB (ATCC 25177) and *M. bovis* BCG (ATCC 35743) using two folds dilution technique, in order to determine the actual minimum inhibitory concentration (MIC). Activity against MTB was determined through the XTT reduction menadione assay (XRMA) reading absorbance at 470 nm. The nitrate reductase (NR) assay was performed to estimate inhibition of *M. bovis* BCG by compounds [27]. Absorbance for the NR assay was measured at 540 nm. *In vitro* activity against MTB and *M. bovis* BCG at active (8 days) and dormant (12 days) stages was performed using the XRMA and NR assay, respectively, as described above. Percentage inhibition was calculated using the following formula:

$$\% \text{ inhibition} = [(\text{control} - \text{CMP}) / (\text{control} - \text{blank})] \times 100$$

Where 'control' is the activity of mycobacteria without compounds, 'CMP' is the activity of mycobacteria in the presence of compounds and 'blank' is the activity of the culture medium without mycobacteria.

Cytotoxicity assay

2-chloro quinoline incorporated xanthene derivatives were assayed for their cytotoxic effects in four different cell lines, MCF-7, HCT-116 and A549 using MTT assay [28]**.** The cell lines were maintained under standard cell culture conditions under 5% CO_2 at 37°C in 95% air humidified environment. Each concentration was tested in duplicates in a single experiment. GI_{50}/GI_{90} values were calculated using OriginPro Software.

Selectivity Index

The selectivity index was calculated by dividing the 50% growth inhibition concentration (GI_{50}) for cell lines (MCF-7, HCT 116 and A549) by the MIC_{90} for *in vitro* activity against dormant MTB and BCG [29].

Anti-Bacterial activity

All bacterial cultures were first grown in LB media at 37 ^{0}C at 180 RPM. Once the culture reaches 1 O.D, it is used for anti-bacterial assay. Bacterial strains *E. coli* (NCIM 2688- ATCC 25292), *P. flurescense* (NCIM 2036-ATCC 13525) as gram-negative and B. subtillis (NCIM 2079-ATCC 23857), *S. aureus* (NCIM 2010- ATCC 29213) as gram-positive are used. The assay was performed in 96 well plates after 8 h. and 12 h for Gram negative and Gram-positive bacteria, respectively. 0.1 % of 1 O.D. culture at 620 nm was used for screening [30], 0.1 % inoculated culture was added in to each well of 96 well plate containing the compounds to be tested.

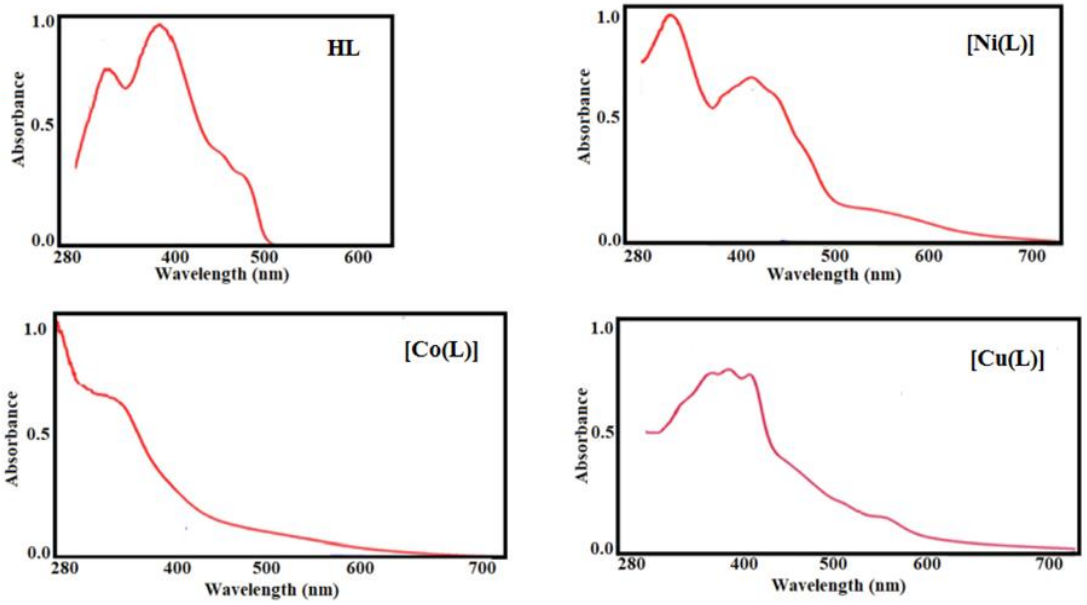


Figure 1: U.V. spectra of the ligand HL, Co(II), Ni(II) and Cu(II) complexes

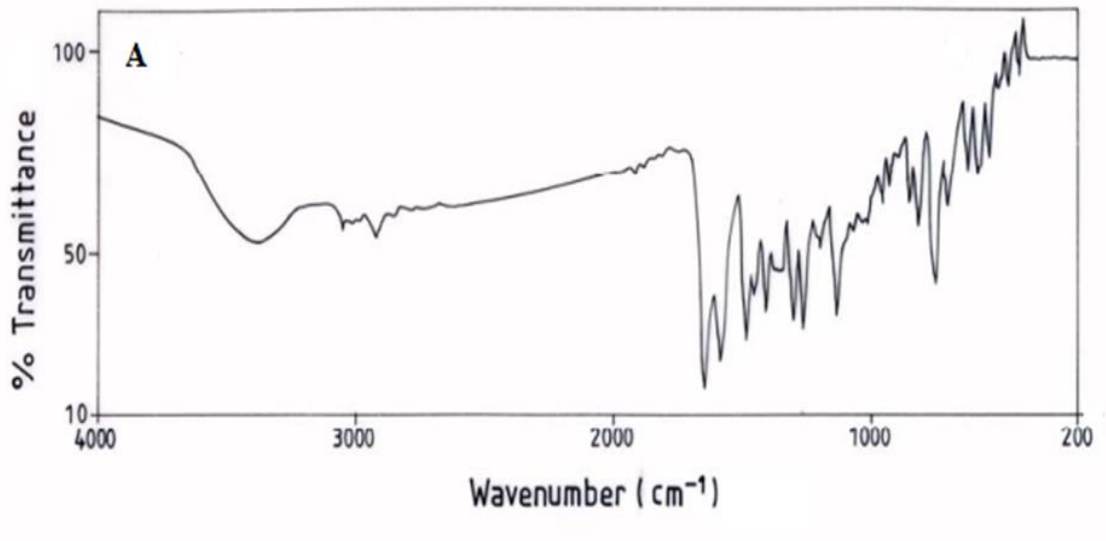


Figure 2a: IR spectra of ligand 9a

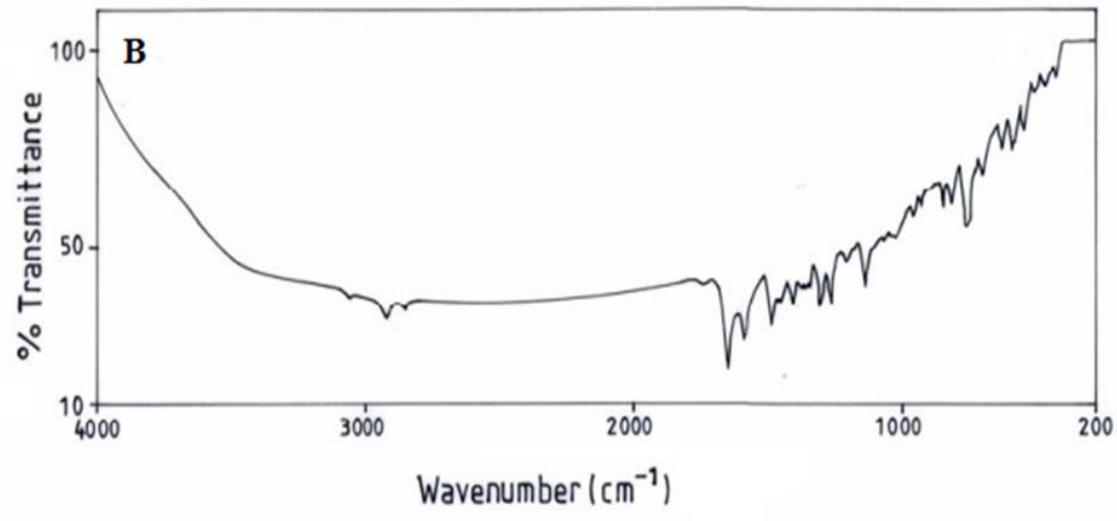


Figure 2b: IR spectra of Cu^{II} complex 10a

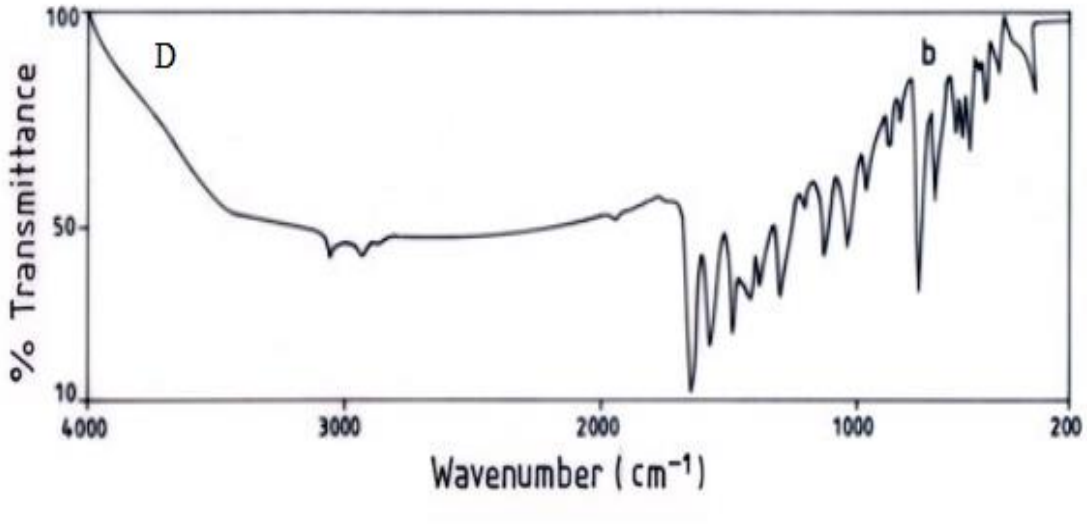


Figure 2c: IR spectra of Ni^{II} complex 10b

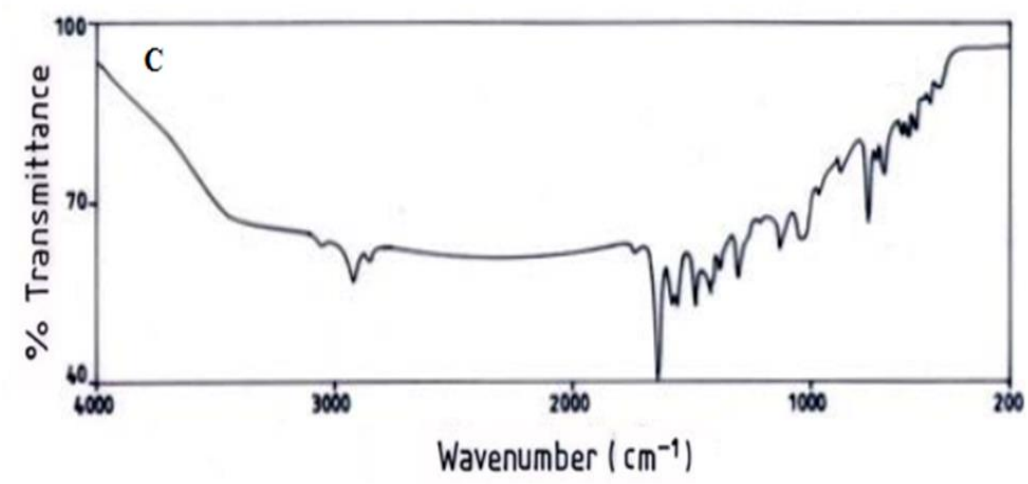


Figure 2d: IR spectra of Co^{II} complex 10c

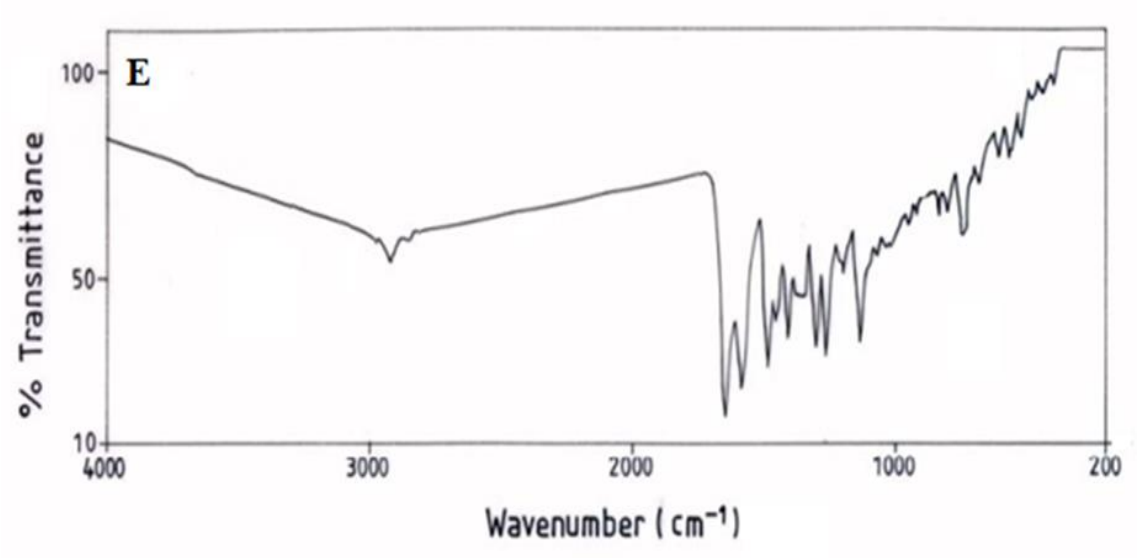


Figure 2e: IR spectra of Zn^{II} complex 10d

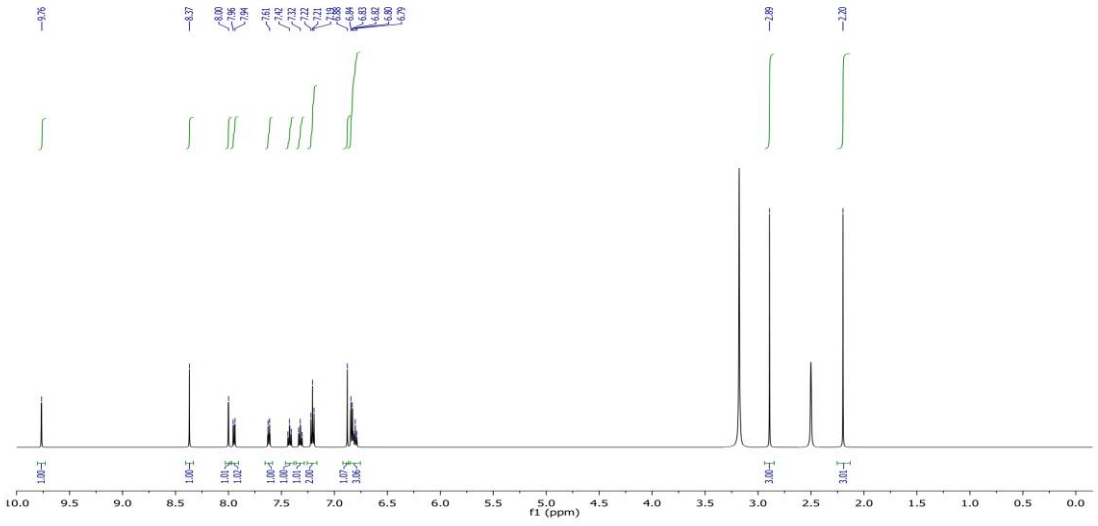


Figure 9a: ^{1}H NMR, 400 MHz, DMSO-d_6

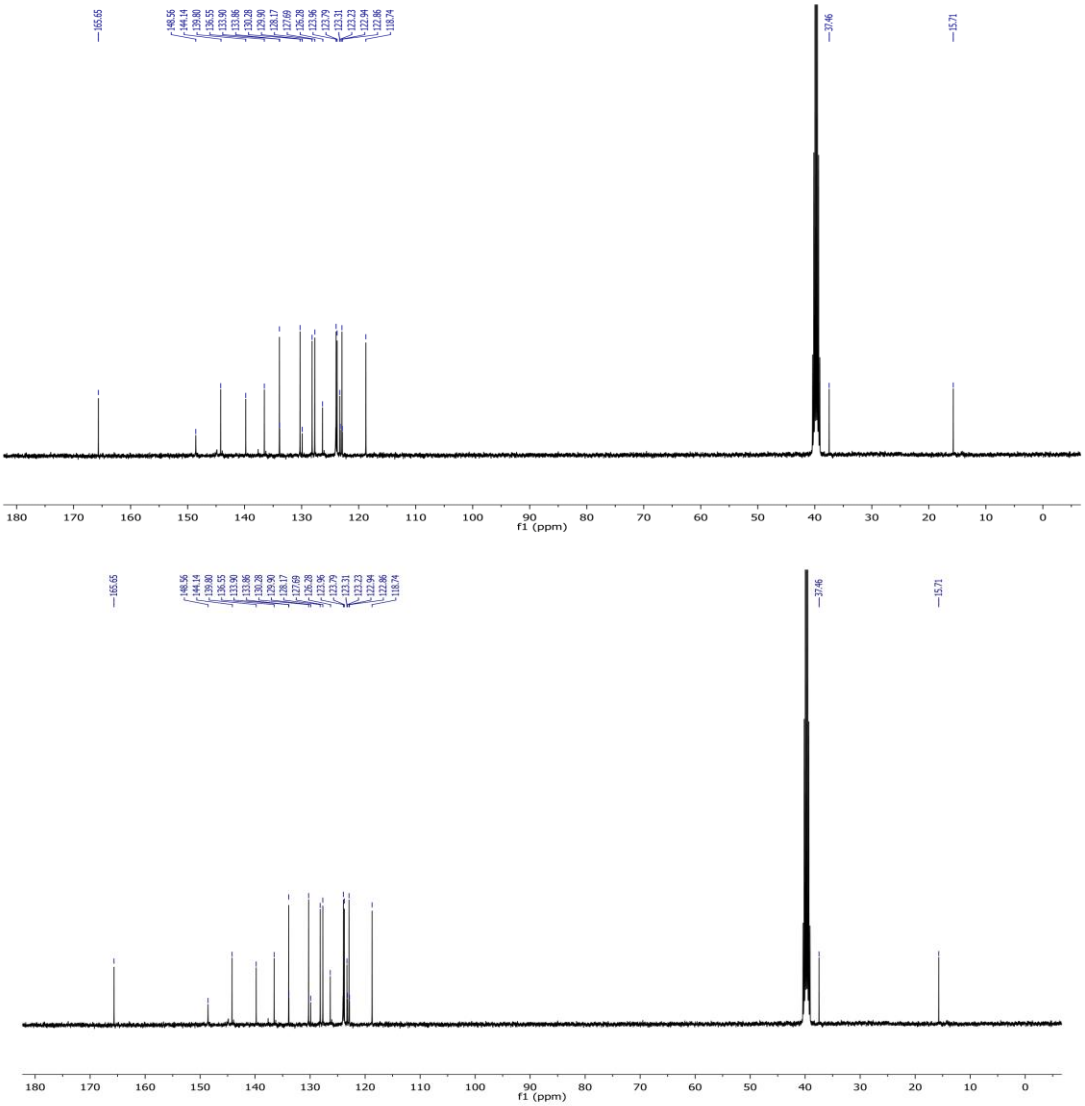
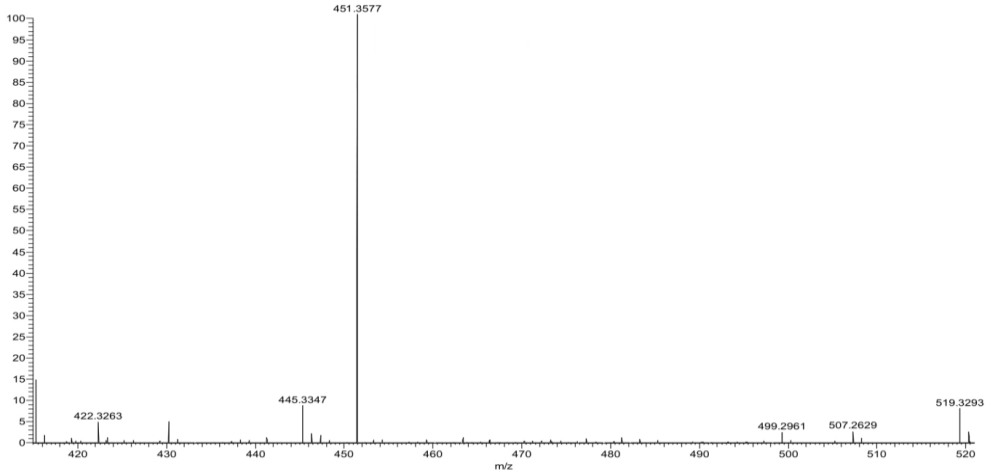
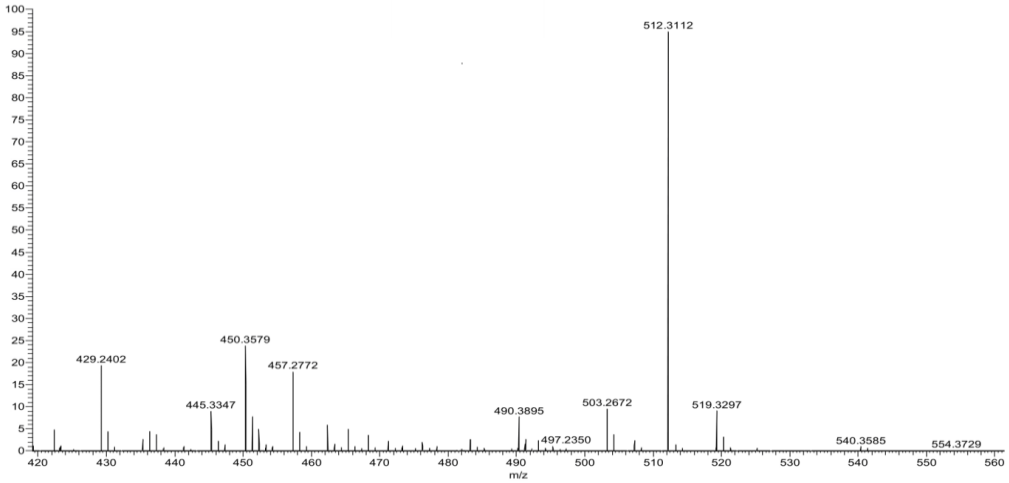


Figure 3: ^{1}H and ^{13}C NMR of ligands

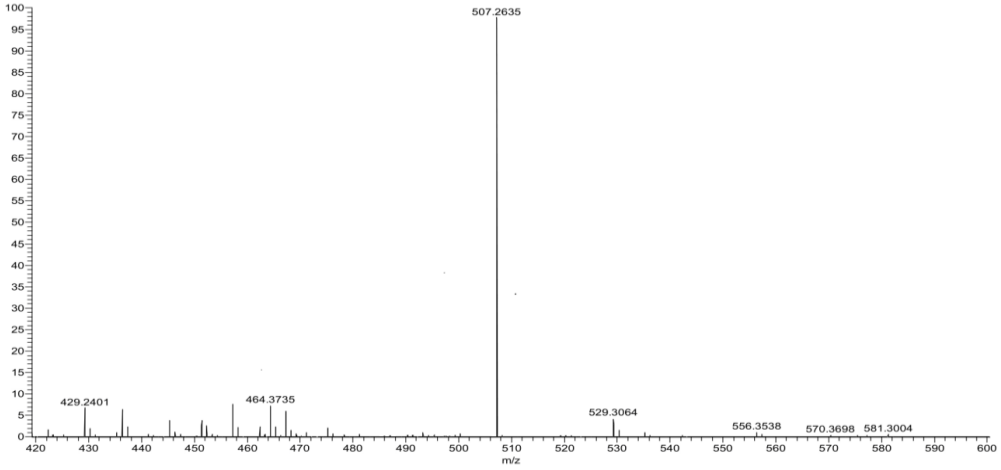
9a. HRMS



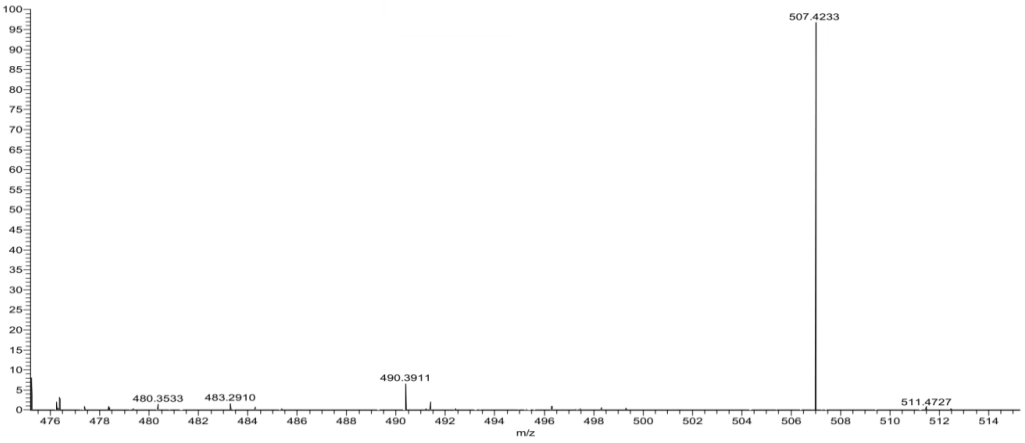
10a. HRMS



10b. HRMS



10c. HRMS



10d. HRMS

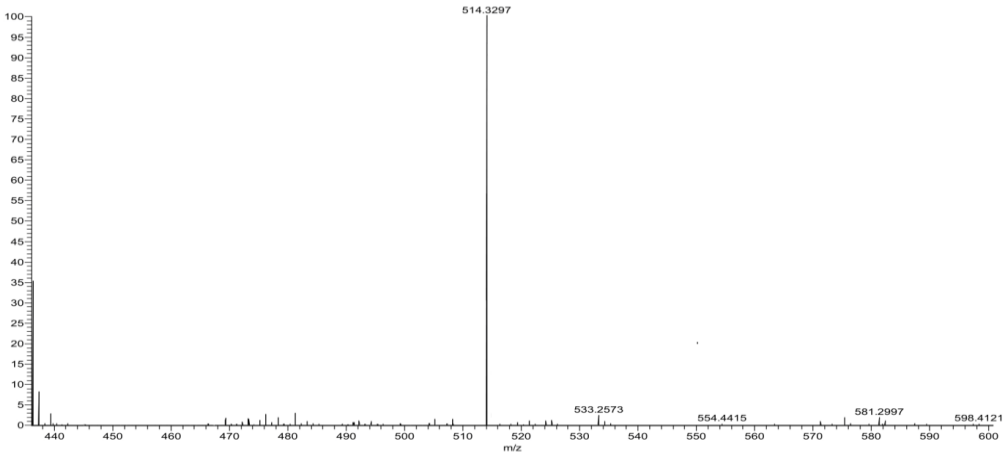
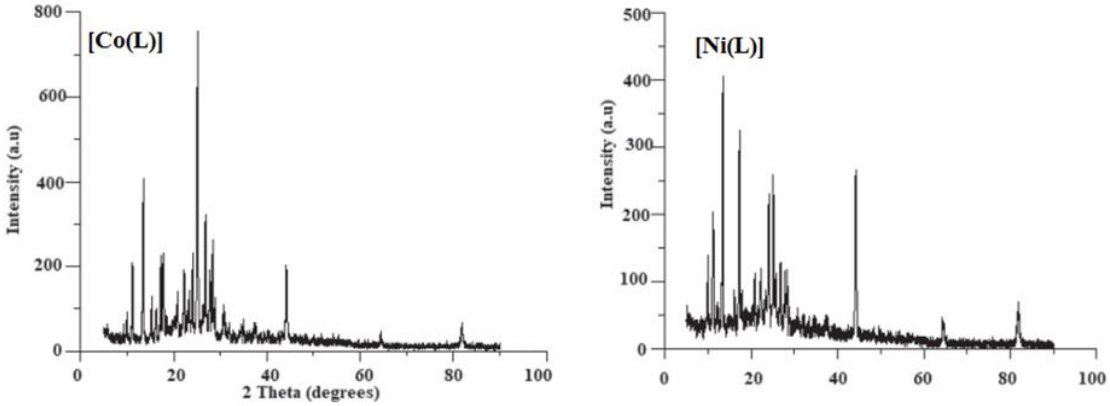
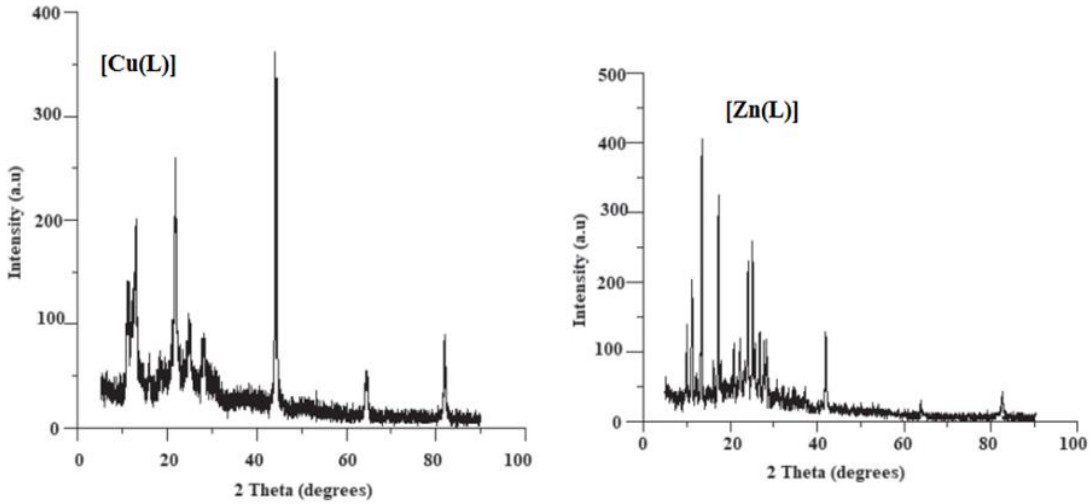


Figure 4: 10a-d HRMS of ligand, Cu(II), Ni(II), Co(II) and Zn(II) metal complexes





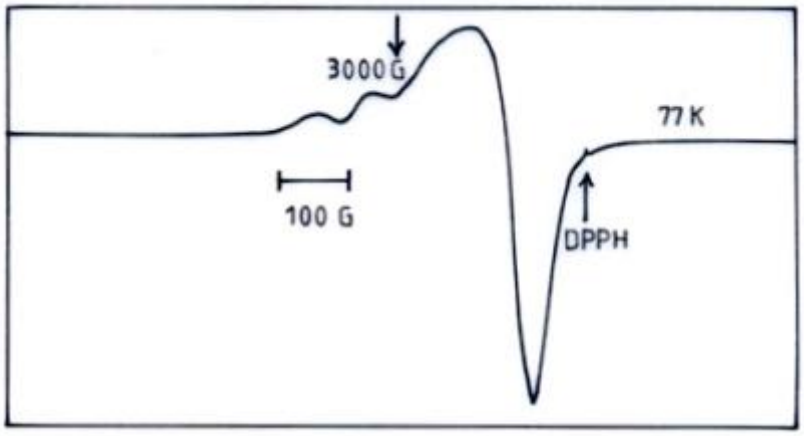


Figure 6:. ESR spectrum of Cu^{II} complex at 77 K

CONCLUSION

In the light of above work, the synthesis of novel quinoline based Schiff base and its metal complex (**9a** and **10a-e**) was carried out and their antitubercular activity against *MTB H37Ra* and *M. Bovis BCG* strains determined. Among all the tested compounds, **9a, 10a, 10b, 10c, 10d** and **10e** were identified as the most active compounds with activity MIC range 0.061-1.5 against *M. bovis BCG* strain and 0.54-2.2 µg/mL against *MTB H37Ra* strain. The most potent compounds displayed lower cytotoxicity and higher selectivity index >10 against MCF-7, HCT 116 and A549 cell line using MTT assay, which indicated that they act as prominent antitubercular agents. Therefore, quinoline based compounds and its complexes shows prominent biological activity, present series of compounds can be further optimized and should be developed as lead molecules.

SUPPLEMENTARY MATERIALS

^{1}H NMR, ^{13}C NMR, HRMS, FTIR, electronic absorption spectra, XRD and ESR spectra of synthesized metal complex.

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Conflict Of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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