RESEARCH PAPER

Synthesis of Benzo[d]imidazol-2-amine incorporated ligands, novel metal complexes and their bioevaluation

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Abstract
This work is deals with synthesis of novel Schiff base through a various steps and their metal complex with Cu^{II}, Ni^{II}, Co^{II} and Zn^{II} in 2:1 ratio (2L:M1). Structure of prepared Schiff base and their metal complexes are characterized by ^{1}H NMR, ^{13}C NMR, FT-IR, HRMS, Electronic absorption spectra and ESR 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. The compounds **7a**, **8a**, **8b**, **8c** and **8d** showed good in antitubercular activity against MTB and M. Bovis strains with MIC values 0.40-0.90 and 0.10-0.20 µg/mL, respectively. The compounds **7a**, **8a**, **8b**, **8c** and **8d** are found non toxic against MCF-7, A549, HCT 116 and THP-1 cell lines. All the prepared compounds were confirmed by ^{1}H NMR, ^{13}C NMR, HRMS, FTIR and XRD analysis.

Keywords: Green Synthesis, Benzo[d]imidazol-2-amine, Schiff Base Metal Complexes, Antitubercular Activity, Mycobacterium tuberculosis, Quinoline Derivatives, Bio evaluation

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Introduction

Tuberculosis (TB), an infectious disease that usually attacks the lungs, is frighteningly on the rise. TB is a complex disease caused by bacteria Mycobacterium tuberculosis (MTB) which has evolved with highly successful mechanisms to equivocate host defenses and existing classes of antibiotics. Decades after the discovery of MTB, TB remains a major cause of morbidity and mortality in many developing countries. The World Health Organization (WHO) reported that, more than one-third of the world's population is infected with TB and that resulted in an estimated 1.5 million deaths worldwide in 2016.[1] Out of which, 0.36 million peoples were infected with both human immunodeficiency virus (HIV) and TB. Multi-drug-resistant (MDR) strains of this pathogen, emerging in association with HIV, have added a frightening dimension to the problem. The long duration of therapy generally results in noncompliance of the treatment and results in MDR-TB and extensively drug-resistant tuberculosis (XDR-TB), which are highly lethal, extremely expensive and complicated to treat, posing new challenges for the prevention, treatment and control of TB.[2] Despite abundant research on MTB diagnostics, vaccinations and treatments, this disease poses a considerable risk in many developed countries. MTB is very virulent, but there has been no simple answer found yet for what makes MTB so virulent. Historically, MTB H37Ra is the avirulent counterpart of the virulent strain MTB H37Rv and both strains were derived from their virulent parent strain H37 discovered by William Steenken through a process of aging and dissociation from in vitro culture.[3] These strains are phenotypically and genotypically different from each other, but the virulence power is different among these strains, which could probably be owing to a difference in protein expression.

Owing to the advancement of bioinformatics and the genome sequencing project, whole genome and proteome sequences of both the strains are available in the public domain. Current evidence suggest that as a species, MTB exhibits very little genomic sequence diversity.[4] MTB H37Rv is virulent and susceptible to most of the antituberculous drugs, while MTB H37Ra is an avirulent strain and MTB KZN (KwaZulu-Natal, South Africa) strain is resistant to different drugs like isoniazid, pyrazinamide, ofloxacin, kanamycin, rifampicin and ethambutol (**Figure 1**).[5] This may be due to a genetic mutation resulting in the generation of mutated proteins. Therefore, there is a need for genomic as well as proteomic analysis among different strains of MTB to understand the variation among them. Many tools have also been developed for the complete determination of the genome sequence of a large number of bacteria, but still, their proteomes remain relatively poorly defined.

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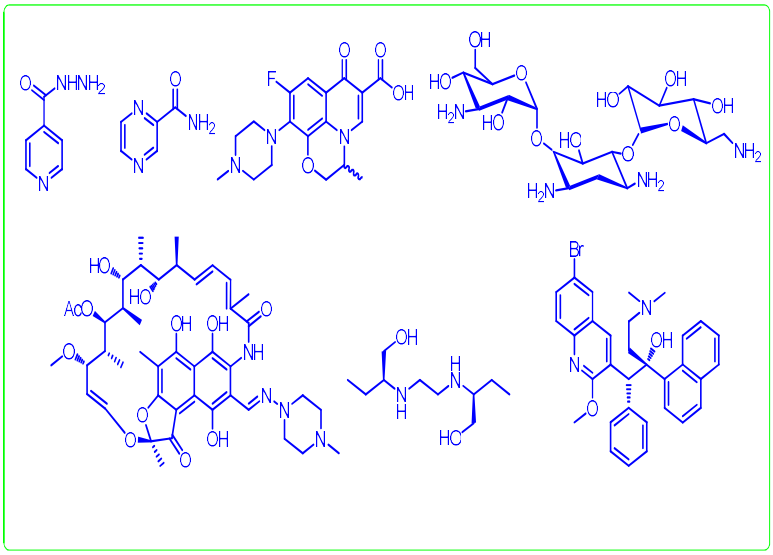


Figure 1. Stuctures of antitubercular drugs

Quinolines derivatives are naturally occurring compounds[6] with a broad spectrum of biological activities including antibacterial,[7] anti-inflammatory,[8] antimalarial,[9] antihypertensive,[10] antibiotic,[11] anticancer,[12] anti-HIV,[13] histamine H3 receptor antagonist[14] and tyrosine kinase inhibitors.[15] A highly substituted quinoline derivatives[16] were displays 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,[17] antibacterial,[18] antifungal,[19] antitubercular agents[20] and antioxidant.[21] Some of the representive antitubercular compounds bearing quinoline moiety as shown in **Figure 2**.

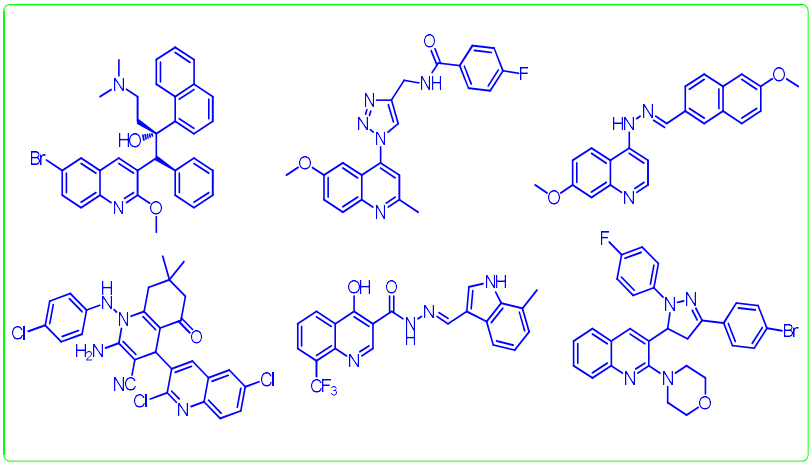
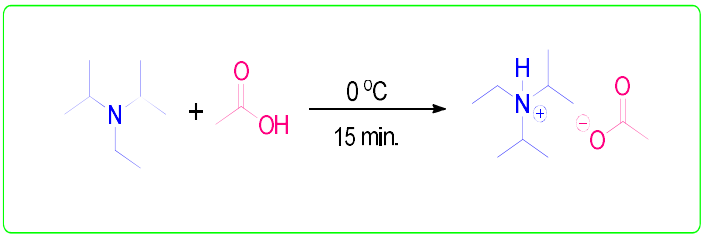


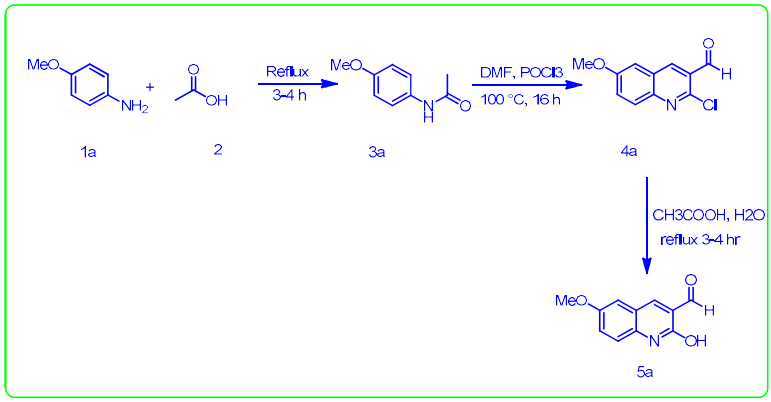
Figure 2. Quinoline based antitubercular agents

Room-temperature ionic liquids (RTILs) have taken the attention of the chemical community all over the globe as a green alternative option to traditional ecofriendly media for catalysis, synthesis, separation, and other several chemical tasks.[22-23] RTILs include numerous exclusive properties, such as extensive liquid range, nonvolatility, low toxicity, high thermal stability, noncombustible, excellent solubility, and recyclability.[24] RTILs act as “neoteric solvents” for a wide range of industrial and chemical processes. In recent times, RTILs have been originating to be valuable as environmental friendly media for countless organic revolutions.[25-27] Thus, the introduction of a dynamic, inexpensive, mild, and environmental friendly catalyst for significant cyclization reaction superior to analogues of pharmaceutical and biological prominence is in demand. As per the pharmacological applications of the reported quinoline derivatives and we have designed and prepared novel quinoline based metal complexes by assembling in a single molecular framework, 2-amino benzimidazole and 2-hydroxy quinoline aldehyde units to obtain promising tubercular activity. In this paper, we have validated DIPEAc as ionic liquid (**Schemes 1**)

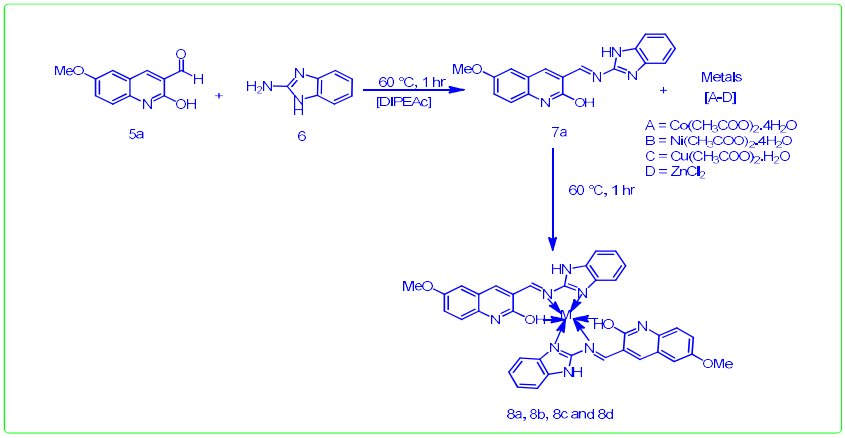
catalyzed the efficient synthesis of quinoline based schiff base under ecofriendly reaction conditions (**Schemes 2 and 3**).



Scheme 1. Synthesis of Diisopropylethylammonium Acetate (DIPEAc)



Scheme 2. Synthesis of 2-chloro-3-formylquinolines and 2-hydroxy-3-formylquinolines.



Scheme 3. Synthesis of metal complexes using imidazole incorporated quinoline derivatives

All the newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and HRMS techniques. The ^{1}H NMR spectrum of compound **7a**, N=CH-Ar proton appeared as a singlet at δ 8.39 ppm due to formation of imine bond. The carbonyl group observed at 165.35, 148.56 ppm due to the =C-OH and C=N bonds respectively in the ^{13}C NMR spectrum of compound **7a**.

Experimental procedures and spectra of quinoline based ligand are given in the supplementary materials.

Experimental section

Chemistry

All chemicals and solvents were purchased from sigma aldrich with high purities and used without further purification. Whereas metal salts are 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 uncorrected. Products were purified by column chromatography on 100-200 mesh silica gel. The ^{1}H NMR spectra were recorded on 400 spectrometers using tetramethylsilane (TMS) as an internal standard. The ^{13}C NMR spectra were recorded at 100 MHz and 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.

Preparation of DIPEAc

General Procedure for the Synthesis of DIPEAc ionic liquid

Reaction of acetic acid (3 mmol) and N,N-diisopropylethylamine (3 mmol) was stirred at 0-10 °C for 20 min to form DIPEAc as a viscous liquid.

Synthesis of 2-chloro-6-methoxyquinoline-3-carbaldehyde

The 2-chloro-6-methoxyquinoline-3-carbaldehyde was synthesized from starting material Para anisidine by acylation followed by Vilsmeier Haack reaction as reported method.

Typical Experimental Procedure for the Synthesis of 2-hydroxy-6-methoxyquinoline-3-carbaldehyde intermediate (**5**)

A reaction of 2-chloro-6-methoxyquinoline-3-carbaldehyde (**4**) (10 mmol)and H_2O(1 ML) was dissolved acetic acid in (2 mL). The reaction mass was refluxed for 4 h.The progress of the 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 hydroxy-6-methoxyquinoline-3-carbaldehyde intermediate (**5**) and used for the next step.

Synthesis of Schiff base

The appropriate mixture of 2-hydroxy-6-methoxyquinoline-3-carbaldehyde (5) (1 mmol), (6) (1 mmol) and DIPEAc (5 ml) was placed in a round bottom flask. The reaction mixture was heated at 60°C for 1 hr and progress of the reaction was checked by TLC using solvent system as ethyl acetate: n-hexane. After completion of reaction mixture was poured on crushed ice and extracted with ethyl acetate (2 × 15 mL). The organic product was washed with brine solution (2 × 15 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to obtain the corresponding crude Schiff base (7a). The obtained crude product was recrystallized using ethanol and dried under vacuum. Details of the reaction are represented in Scheme 1 and 2.

Typical Experimental Procedure for the Synthesis of ((E)-3-(((1H-benzo[d]imidazol-2-yl)imino)methyl)-6-methoxyquinolin-2-ol (**7a**)

The mixture of appropriate hydroxy-6-methylquinoline-3-carbaldehyde (**5a**) (1mmol), 1H-benzo[d]imidazol-2-amine (**6**) (1 mmol) and acetic acid (5-10 drops) in ethanol (5 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 compounds were recrystallized using ethanol.

Typical Experimental Procedure for the Synthesis of novel quinoline based metal complex **(8a-d)**

Metal complex were prepared by adding 25 mL hot ethanolic metal salt (0.0015 mol) solution to the 30 mL hot ethanolic HL solution (0.0030 mol) in 1:2 ratio for Co^{II}, Ni^{II}, Cu^{II} and Zn^{II}. The reaction mixture was stirred for 60 min then addition of few drops of 5% NaOH solution to maintain basic PH 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 oven for about 90 min for 80 ºC temperature results formation of pure corresponding metal complexes **(8a-d).**

(E)-3-(((1H-benzo[d]imidazol-2-yl)imino)methyl)-6-methoxyquinolin-2-ol **(7a)**

Compound **7a** was obtained from the condensation reaction between **5a, 6** and DIPEAc for 1 h. White solid; MP: 226-228 °C; Yield: 90%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.24 (d, J = 1.4 Hz, 1H), 8.20 (s, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.67 (dt, J = 10.0, 5.1 Hz, 2H), 7.47 (dd, J = 7.5, 1.4 Hz, 1H), 7.35 (pd, J = 7.5, 1.8 Hz, 2H), 7.02 (t, J = 1.5 Hz, 1H), 6.78 (s, 1H), 3.92 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 55.8 ppm (O-CH_3) . HRMS (ESI-qTOF): Calcd for $C_{18}H_{15}N_4O_2$ $[M+H]^+$, 319.1860: found: 319.1852.

HRMS spectra for Co(II) metal complex

HRMS (ESI-qTOF): Calcd for $C_{36}H_{29}CoN_8O4$ [M+H], 695.5174: found: 695.5135

HRMS spectra for Ni(II) metal complex

HRMS (ESI-qTOF): Calcd for **$C_{36}H_{29}N_8NiO_4$** [M+H]+, 694.2650: found: 694.4186

HRMS spectra for Cu(II) metal complex

HRMS (ESI-qTOF): Calcd for **$C_{36}H_{29}N_8CuO_4$** [M+H]+, 699.4130: found: 699.5377

HRMS spectra for Zn(II) metal complex

HRMS (ESI-qTOF): Calcd for **$C_{36}H_{28}N_8O_4Zn$** [M+H]+,700.5845: found: 700.5825

Table 1. Analytical data of the Schiff base ligand and its metal (II) complexes

Compound	Yield%	MW	Elemental Analysis %: Calcd. (found)				
			C	H	N	O	M

$C_{18}H_{14}N_4O_2$-L	91	318.1120	68.50	4.38	18.02	9.09	-
			(67.91)	(4.43)	(17.60)	(10.05	-
$C_{36}H_{28}CoN_8O_4$	85	695.1566	61.90	4.00	16.50	9.10	8.50
			(62.16)	(4.06)	(16.11)	(9.20)	(8.47)
$C_{36}H_{28}N_8NiO_4$	87	694.1587	62.03	4.10	16.25	9.25	8.37
			(62.18)	(4.06)	(16.11)	(9.20)	(8.44)
$C_{36}H_{28}N_8CuO_4$	86	699.1530	62.00	4.10	16.10	9.21	8.59
			(61.75)	(4.03)	(16.00)	(9.14)	(9.08)
$C_{36}H_{28}N_8O_4Zn$	88	700.1525	61.80	4.09	16.10	9.50	8.51
			(61.59)	(4.02)	(15.96)	(9.12)	(9.31)

IR spectra

Schiff base ligand such as C=N and -OH group on the complex formation. In the FT-IR spectrum of the ligand the broad peak observed at 3600-3250 cm^{-1} due to presence of –OH group via intra-molecular hydrogen bonding. Synthesis of metal complex results vanish this –OH bonds prove that deprotonation of the -OH groups on complexation. The -C=N bands of 1H-benzo[d]imidazol-2-amine moiety appearing in the region 1630-1600 cm^{-1} for the free ligand are also shifted to 1585-1560 cm^{-1} lower frequencies in the metal ligand coordination. The C=N bond observed at 1575 cm^{-1} due to imidazole ring. The IR spectra of metal complexes observed at 465-450 cm-1 and 430-400 cm^{-1} due to the presence of M-O and M-N bonds, respectively.

Powder X-ray diffraction study

The powder XRD difractograms of prepared 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. The sharp peaks observed due to crystallinity in nature. XRD spectra of schiff base and metal complexes shown in **Fig. 3a-d**

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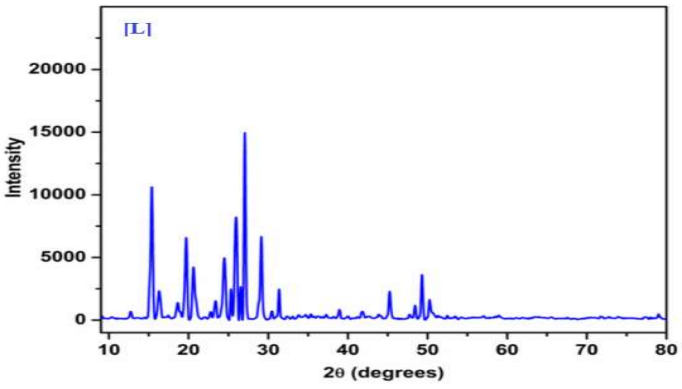

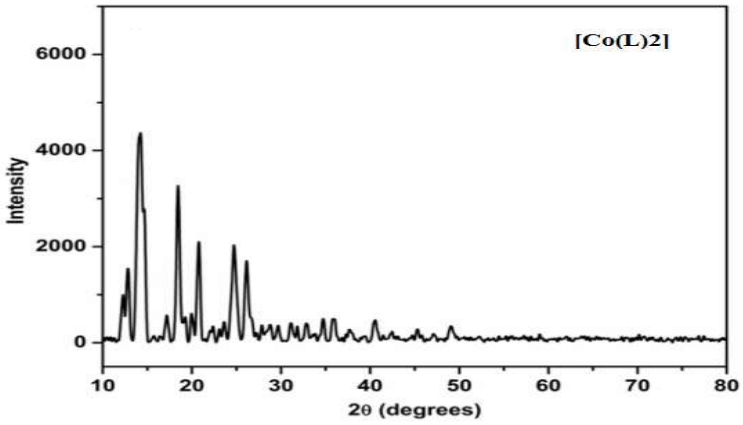
[Co(L)2]
Intensity
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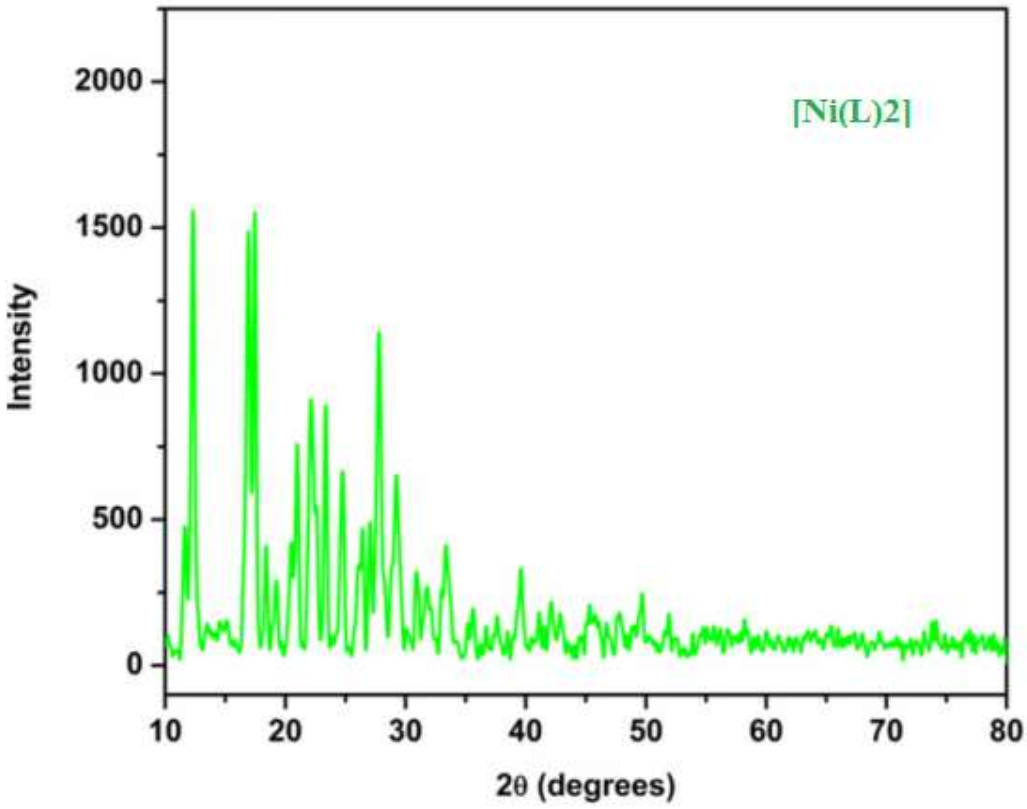
4000
2000
0
10
20
30
40
50
60
70
80
2θ (degrees)


[Ni(L)2]
Intensity
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1500
1000
500
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10
20
30
40
50
60
70
80
2θ (degrees)

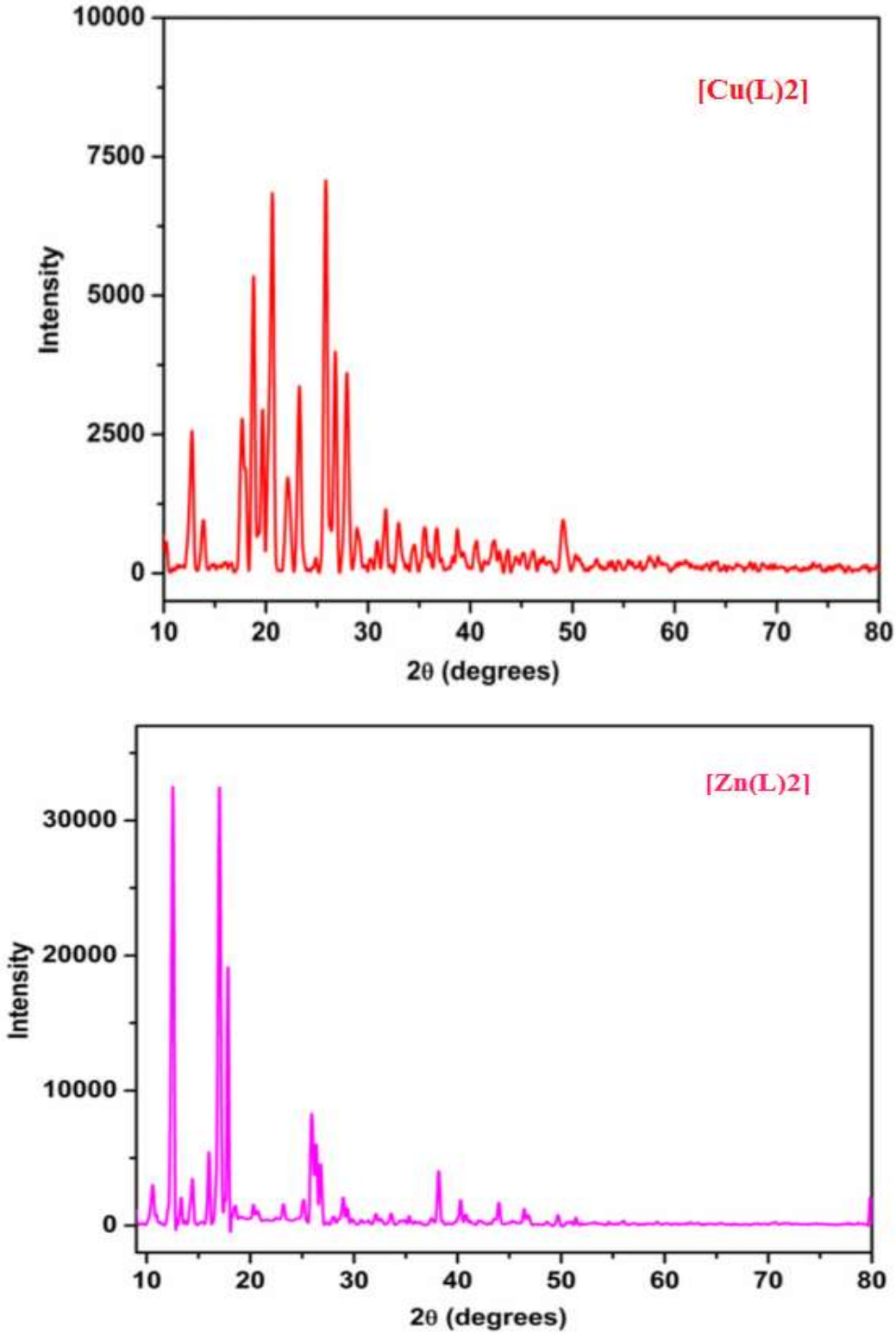

Fig. 3. Powder XRD patterns of ligand, metal ligand Co(II), Ni(II), Cu(II) and Zn(II) complexes

ESR spectra

The ESR spectrum of the present Cu^{II} complex are shown **Fig. 4** 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, 1.78 B.M., corresponding to one unpaired electron, indicating that the complex is mononuclear.

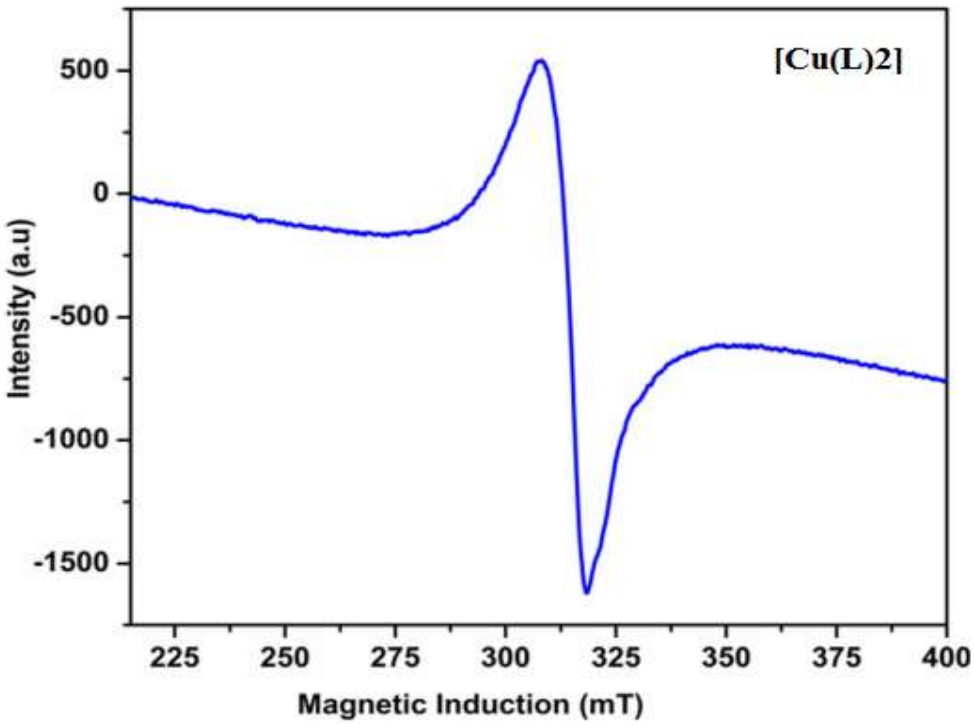

Fig. 4. ESR spectrum of Cu^{II} complex

Thermal study

Thermogravimetric analysis of all metal complexes (**8a-8d**) was carried out to determine the thermal stability over a temperature range from 100-1200 °C. The analysis was accomplished at an increased heating rate of 10 °C per minute under the nitrogen environment. **Fig. 5** and represents the thermogravimetric curves of Co^{II}, Ni^{II}, Cu^{II} and Zn^{II} complexes.

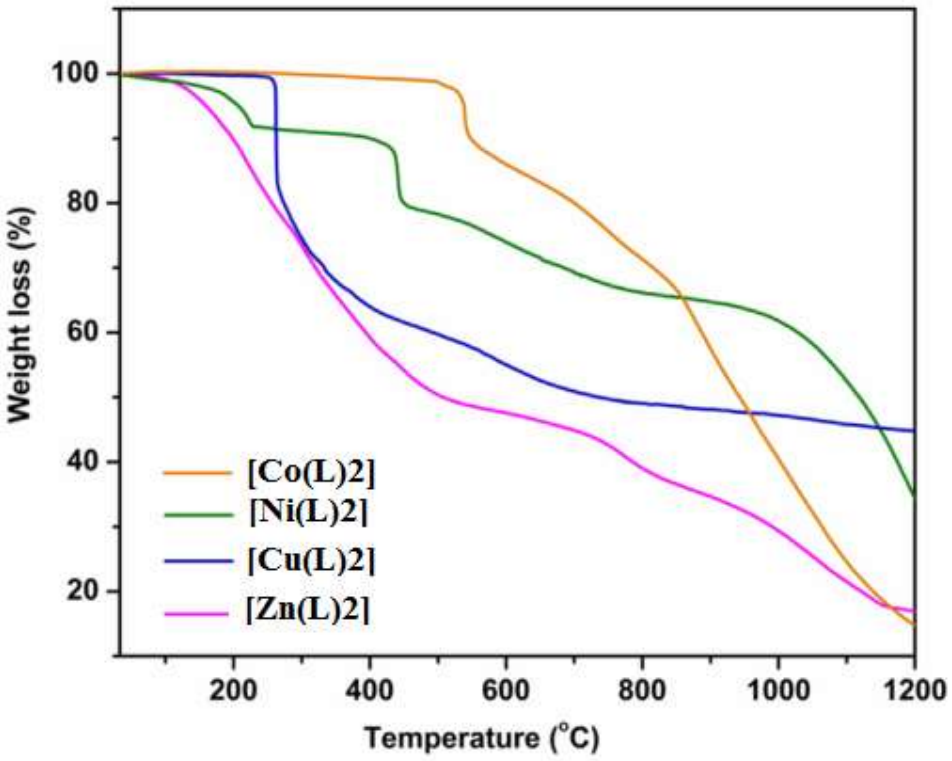

Fig. 5. Thermogravimetric analysis of all metal complexes (**8a-8d**)

Anti-mycobacterial activity

The newly synthesized Benzo[d]imidazol-2-amine hybrids (**7a, 8a-d**) were screened for in vitro antitubercular activity against M. Bovis BCG (ATCC 35743) and MTB H37Ra (ATCC 25177) in liquid medium. We have explored the eminent XTT Reduction Menadione assay (XRMA) of anti-mycobacterial screening protocol employing first-line anti-mycobacterial rifampicin drug as a standard reference and the IC_{50} and IC_{90} values are presented in **Table 1**.

The Benzo[d]imidazol-2-amine derivatives **7a, 8a**, **8b**, **8c** and **8d** are exhibited excellent antitubercular activities with IC_{90} value ranging from 0.10-0.20 and 0.40-0.90 µg/mL were found to be most active against M. bovis BCG and MTB H37Ra and 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 **(8a-d)**, compound 8**a** in which Cu metal present exhibits excellent activity against MTB strain with MIC = 0.62 µg/mL and the results are presented in **Table 1**. Compounds 8**b** in which (Metal = Ni) are active against MTB strain with MIC = 0.90 µg/mL. When the installation of the Co metal in compound 8**c** (Metal = Co) showed excellent activity against MTB strain with MIC= 0.65 µg/mL. When a Zn metal present in compound 8**d** (Metal = Zn) exhibits prominent antimycobacterial activity against MTB strain with MIC= 0.40 µg/mL. Further, we also check the antitubercular activity of schiff base complex **10a.** Compounds 7a exhibits excellent antitubercular activity against MTB strain with MIC = 0.60 µg/mL. Hence, among all the synthesized Schiff base and novel quinoline based metal complex, compounds **7a, 8a**, **8b**, **8c** and **8d** are found highly potent against MTB and the details are disclosed in **Table 1**.

Further, all the compounds also tested for antitubercular activity against the M. Bovis BCG strain. From the novel quinoline based metal complex **(7a, 8a-d)**, compound 8**a** in which Cu metal present shows promising antitubercular activity against M. Bovis BCG strain with MIC = 0.10 µg/mL and the results are presented in **Table 1**. Compounds 8**b** in which (Metal = Ni) are active against M. Bovis BCG strain with MIC = 0.14 µg/mL. When the introduction of the Co metal in compound 8**c** (Metal = Co) showed prominent activity against M. Bovis BCG strain with MIC= 0.13 µg/mL. When a Zn metal present in compound 8**d** (Metal = Zn) exhibits excellent antimycobacterial activity against M. Bovis BCG strain with MIC= 0.16 µg/mL. Compounds 7**a** exhibits excellent antitubercular activity against M. Bovis BCG strain with MIC = 0.20 µg/mL. Hence, among all the synthesized Schiff base and novel quinoline based metal complex, compounds **7a, 8a**, **8b**, **8c** and **8d** are found highly potent against M. Bovis BCG and the details are disclosed in **Table 1**.

Table 1. Anti-mycobacterial activitiy

Entry	Structures	M. Bovis BCG		MTB H37Ra	
		IC_{50}	IC_{90}	IC_{50}	IC_{90}
7a	**Schiff base**	0.03	0.20	0.50	0.60
8a	**Cu**	0.02	0.10	0.10	0.62
8b	**Ni**	0.20	0.14	0.14	0.90
8c	**Co**	0.022	0.13	0.10	0.65
8d	**Zn**	0.016	0.16	0.012	0.40
[b]**RP**	-	0.0043± 0.00028	0.0173± 0.039	0.0019± 0.00022	0.020± 0.0021

[a]IC_{50}/IC_{90} 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.

2.2. Cytotoxicity

The highly active **7a, 8a**, **8b**, **8c** and **8d** were tested for cytotoxicity activity against three human cancer cell lines such as MCF-7, HCT 116 and A549 using well established MTT protocol. The cytotoxicity results of these compounds indicates that these compounds are highly potent and specific inhibitors against M. Bovis BCG and MTB H37Ra 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.

Table 2. In vitro cytotoxicity of selected quinoline derivatives.

Entry	MCF-7 (Breast) Cell line		HCT 116 (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)
7a	>100	>100	>100	>100	>100	>100
8a	>100	>100	>100	>100	>100	>100
8b	>100	>100	>100	>100	>100	>100
8c	>100	>100	>100	>100	>100	>100
8d	>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

2.3. Antibacterial activity

To determine the specificity of most potent compounds **7a, 8a, 8b**, **8c** and **8d** 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 very less active towards bacterial strains. All the most active compounds exhibited higher specificity towards M. Bovis BCG and MTB H37Ra strains and detailed study are described in **Table 3**.

Table 3. Antibacterial activity IC_{90} (µg/mL).

Entry	P. flurescense	E. coli	B.subtillus	S.aureus
7a	>100	>100	>100	>100
8a	>100	>100	>100	>100
8b	>100	>100	>100	>100
8c	>100	>100	>100	>100
8d	>100	>100	>100	>100
Ampicillin	4.36	1.46	10.32	1
Kanamycin	0.49	1.62	1.35	>30

Conclusions

The present protocol reports convenient and eco-friendly approach for the synthesis of schiff base and

Benzo[d]imidazol-2-amine derivatives. All the compounds were evaluated first time for the antitubercular activity against the MTB H37Ra and M. bovis BCG strain. From our initial screening studies, it was found that the Benzo[d]imidazol-2-amine **7a, 8a**, **8b**, **8c** and **8d** exhibited significant activity against Mycobacterium tuberculosis H37Ra with MIC range (0.40-0.90 µg/mL) and also Mycobacterium bovis BCG MIC range (0.10-0.20µg/mL). Further, the active antitubercular compounds were evaluated for their cytotoxic effect against cancer cell lines MCF-7, A549 and HCT116. The cytotoxic study revealed that the compounds **7a, 8a**, **8b**, **8c** and **8d** does not showed any cytotoxicity against all the cell lines at the maximum concentration evaluated.

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