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Fluorescence and anti-TB study of chiral schiff bases of (1*R*, 2*R*)-(+)-1,2-diphenylethane-1,2-diamine and their transition metal complexes

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ABSTRACT

Transition metal complexes with Schiff bases derived from (1R,2R)-(+)-1,2-diphenylethylene-1,2-diamine and 5-R-salicylaldehyde (R= H, Br, Cl) have been synthesized and characterized by NMR, MASS, IR and UV-visible Spectroscopies. The fluorescence spectra of the chiral ligands and their related complexes have also been measured. The absorption spectra of the metal complexes in the visible region are consistent with near square planar coordination geometries. Trends in absorption spectra over the series of complexes can be correlated with electronic effects of the substituents at position 5 of the salicylaldehyde. Schiff base ligands and their metal complexes have been screened for anti-tuberculosis activity.

Keywords: chiral schiff base ligands, metal complexes, anti-TB, fluorescence.

INTRODUCTION

Schiff-base macrocycles have been of great importance in macrocyclic and supramolecular chemistry. In coordination chemistry the functionally substituted Schiff bases bearing additional donor groups represent the most important class of heteropolydentate ligands capable of forming mono-, bi-, and polynuclear complexes with transition and non-transition metals. They were among the first artificial metal macrocyclic complexes to be synthesized. Interest in exploring metal ion complexes with macrocyclic ligands has been continuously increasing owing to the recognition of the role played by these structures in metalloproteins. Chiral Schiff bases transition metal complexes, so-called salen-type ligands, are one of the most studied chiral catalysts in asymmetric synthesis because of their ability to act as chiral catalysts or as co-catalysts [1-7]. Moreover, their transition metals complexes have gained importance from the viewpoint of special interest in photophysical and magnetic properties. [8-9]. Schiff-base ligands derived from salicylaldehyde and chiral amines have been widely applied in enantioselective cyclopropanation of styrenes [10], asymmetric aziridination of olefins [11], enantioselective epoxidation [12,13], enantioselective ring opening of epoxides [14], borohydride reduction of aromatic ketones , asymmetric oxidation of methyl phenyl sulfide [15], enantioselective oxidation of silyl enol and trimethylsilylcyanation of benzaldehydes [17]. In particular the Merck company has successfully developed a process for the industrial manufacture of antibacterial drug Cilastatin using chiral copper (II) Schiff-base complexes derived from salicylaldehyde and chiral amine [17].

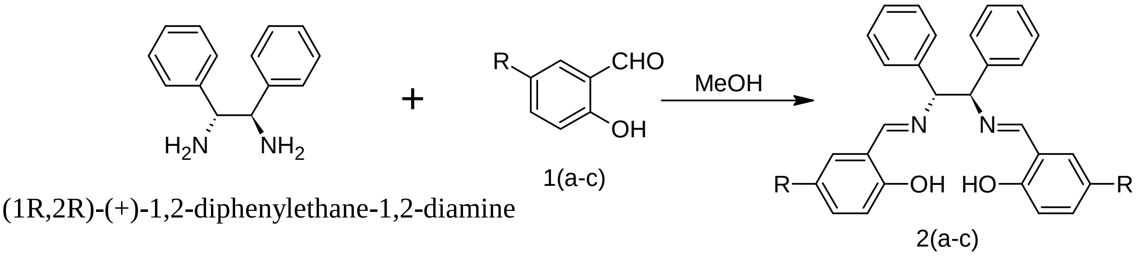
There are numerous publications covering the use of Schiff bases in therapeutic or biological applications either as potential drug candidates or diagnostic probes and analytical tools [18-20]. Moreover, Schiff bases are present in the form of various natural as well as synthetic compounds and have been demonstrated to be essential for their biological activities [21-22].

EXPERIMENTAL SECTION

All chemicals and solvents were of reagent grade quality and were purchased from Sigma Aldrich Chemical Company and used as received without further purification

2.1 SYNTHESIS OF SCHIFF BASES [2(a-c)]

(1*R*,2*R*)-(+)-1,2-diphenylethane-1,2-diamine (0.01mol) and substituted salicylaldehyde [1(a-c)] (0.01mol) taken in round bottom flax containing 5 cm^3 of methanol. Reaction mixture was refluxed for 30 min. Completion of reaction is checked with TLC. Upon cooling the reaction mixture a solid product precipitated out which was filtered, dried and purified by recrystallization from methanol.

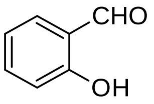
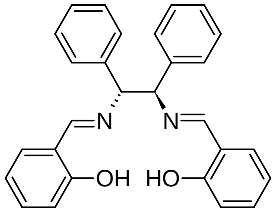
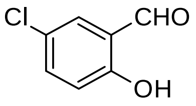
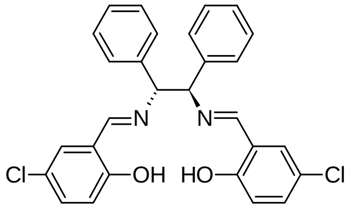
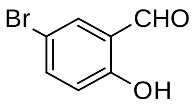
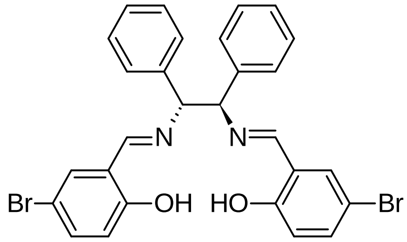


(1R,2R)-(+)-1,2-diphenylethane-1,2-diamine

1(a-c)

2(a-c)

Table No. 01: Structures of synthesized Schiff bases 2(a-c).

Sr. No.	Aldehyde (1)		Schiff Base(2)		Yield	Colour
01	 	**1a**	 	**2a**	90%	Bright yellow
02	 	**1b**	 	**2b**	87%	yellow
03	 	**1c**	 	**2c**	92%	Dark yellow

2.1.1 2,2'-{[(1*R*,2*R*)-1,2-diphenylethane-1,2-diyl]bis[nitrilo(*E*)methylylidene]}diphenol [2a]

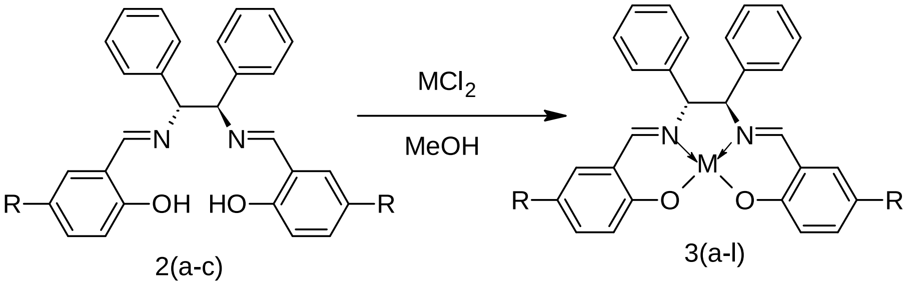
M.P.:153^{0}C, **^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ ppm:** 5.07(s, 2H), 6.79-6.85(m, 4H), 7.15-7.31(m, 14H), 8.51(s, 2H), 13.28(s, 2H). **FTIR (KBr) (cm^{-1}):** 3064, 3031, 2884, 1631, 1583, 1498, 1450, 1276, 1058, 755,717,696. **MASS SPECTRA:** [M+2] 452.29

2.1.2 2,2'-{[(1*R*,2*R*)-1,2-diphenylethane-1,2-diyl]bis[nitrilo(*E*)methylylidene]}bis(4-chlorophenol) [2b]
M.P.: 77^0C, **^{1}H NMR (300 MHz, DMSO-d_6) δ ppm:** 5.09(s,2H), 6.89-6.92(m, 2H), 7.18-7.34(m, 12H), 8.51(s, 2H), **FTIR (KBr) (cm^{-1}):** 3062, 3031, 2877, 1631, 1573, 1479, 1454, 1373, 1274, 1180, 821, 771, 698.**MASS SPECTRA:** [M+] 489.54

2.1.3 2,2'-{[(1*R*,2*R*)-1,2-diphenylethane-1,2-diyl]bis[nitrilo(*E*)methylylidene]}bis(4-bromophenol) [2c]
M.P.: 93^0C, **^{1}H NMR (300 MHz, DMSO-d_6) δ ppm:** 5.09(s, 2H), 6.84-6.87(m, 2H), 7.17-7.32(m, 10H), 7.32-7.43(m, 2H), 7,57(s, 2H), 8.02(s, 2H), 13.28(s, 2H). **FTIR (KBr) (cm^{-1}):** 3062, 3027, 2877, 1629, 1571, 1475, 1452, 1452, 1371, 1274, 1178, 1027, 819, 700. **MASS SPECTRA:** [M+]578.29

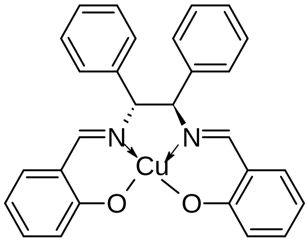
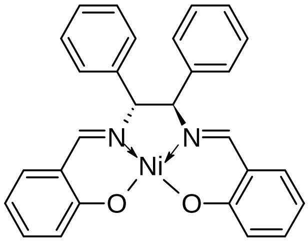
2.2 SYNTHESIS OF METAL COMPLEXES

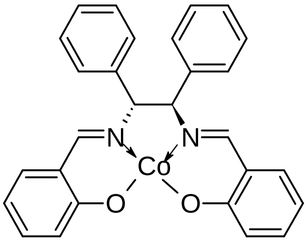
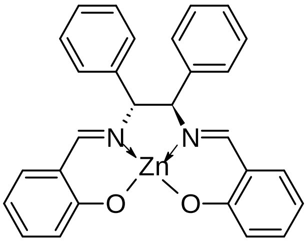
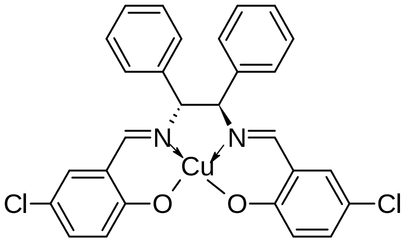
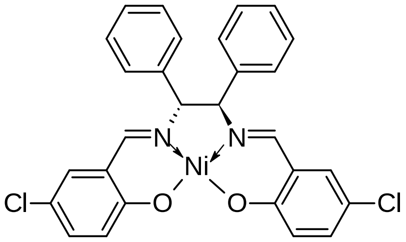
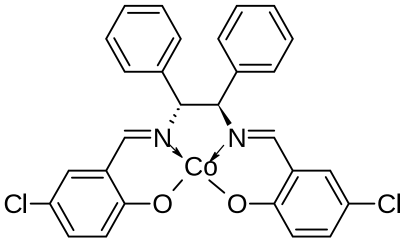
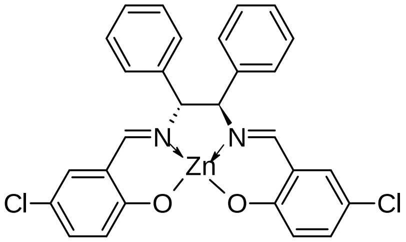
Schiff base (0.050 mmol) was dissolved in 10 ml of methanol in round bottom flask fitted with reflux condenser and calcium chloride guard tube. Corresponding metal salt ($CuCl_2$, $NiCl_2$, $CoCl_2$, $ZnCl_2$) (0.050 mmol) was added and stirred the reaction mixture, finally Potassium hydroxide (0.050 mmol) was added and reaction mixture was refluxed for 3-5 hours in water bath. It was cooled and filtered the solid separated and dried in oven at 70-80°C.

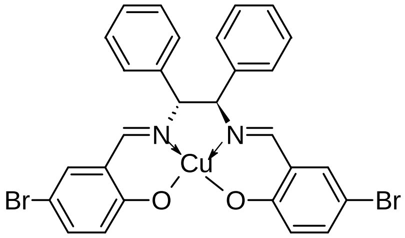
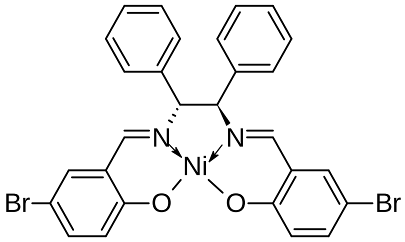
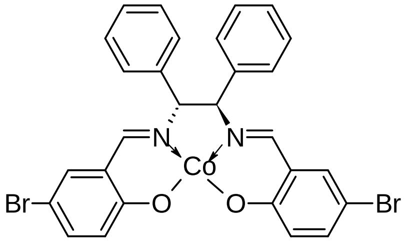
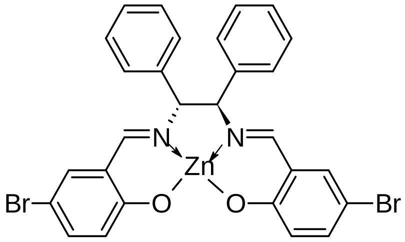


Where M= Cu(II), Ni(II), Co(II) and Zn(II)

Table 02: Structures of synthesized metal complexes 3(a-l)

No.	Complex	Yield	Colour
3a		**92%**	Dark blue
3b		**90%**	Shiny brown

3c		**93%**	faint green
3d		**88%**	faint yellow
3e		**92%**	Dark blue
3f		**90%**	Faint yellow
3g		**87%**	Brown
3h		**89%**	Faint yellow

3i		**86%**	Dark blue
3j		**91%**	Yellow
3k		**86%**	Brown
3l		**89%**	Dark yellow

3 Anti-TB Study

The anti mycobacterial activity of compounds were assessed against M. tuberculosis using microplate Alamar Blue assay (MABA). This methodology is non-toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method. Briefly, 200µl of sterile de-ionized water was added to all outer perimeter wells of sterile 96 wells plate to minimized evaporation of medium in the test wells during incubation. The 96 wells plate received 100 µl of the Middlebrook 7H9 broth and serial dilution of compounds were made directly on plate. The final drug concentrations tested were 100 to 0.2 µg/ml. Plates were covered and sealed with parafilm and incubated at 37°C for five days. After this time, 25µl of freshly prepared 1:1 mixture of Almar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 hrs. A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth. The MIC was defined as lowest drug concentration which prevented the color change from blue to pink.

Figure 01: Anti-TB activity using Alamar Blue Dye

Table 03: Anti-TB results

Sr.No.	Samples	100µg/ml	50µg/ml	25µg/ml	12.5µg/ml	6.25g/ml	3.12µg/ml	1.6µg/ml
1.	2a	S	S	R	R	R	R	R
2.	2b	S	S	R	R	R	R	R
3.	2c	S	S	R	R	R	R	R
4.	3a	S	S	R	R	R	R	R
5.	3b	S	S	R	R	R	R	R
6.	3c	S	S	S	R	R	R	R
7.	3d	S	S	R	R	R	R	R
8.	3e	S	S	S	R	R	R	R
9.	3f	S	S	R	R	R	R	R
10.	3g	S	S	R	R	R	R	R
11.	3h	S	S	R	R	R	R	R
12.	3i	S	S	S	R	R	R	R
13.	3j	S	S	S	R	R	R	R
14.	3k	S	S	S	R	R	R	R
15.	3l	S	S	S	R	R	R	R
16.	Pyrazinamide	S	S	S	S	S	S	R
17.	Streptomycin	S	S	S	S	S	R	R
18.	Ciprofloxacin	S	S	S	S	S	S	R
Note: S-Sensitive, R-Resistant								

4 Fluorescence Study

UV–Visible absorption spectra were recorded on UV spectrophotometer Shimadzu UV-1800 and recorded in quartz cells with 1 cm optical path length. Fluorescence spectra were obtained on a Spectrofluorophotometer Shimadzu RF-5301pc and equipped with quartz cuvette of 1 cm path length using DMF as a solvent. Figure 02-05 represents absorption and emission spectra of synthesized compounds. The instrumental results are summarized in table no.04.

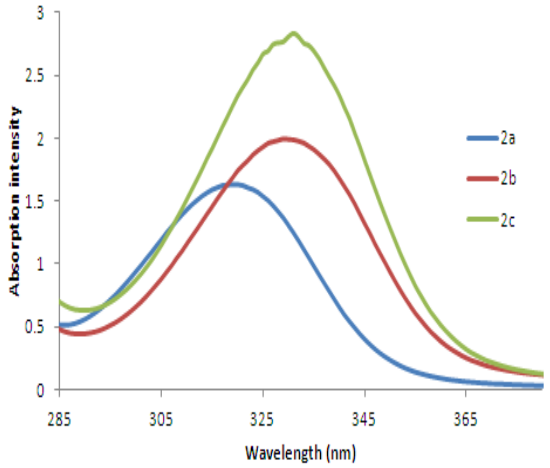


Figure 02: Electronic spectra of Schiff Bases (2a-c)

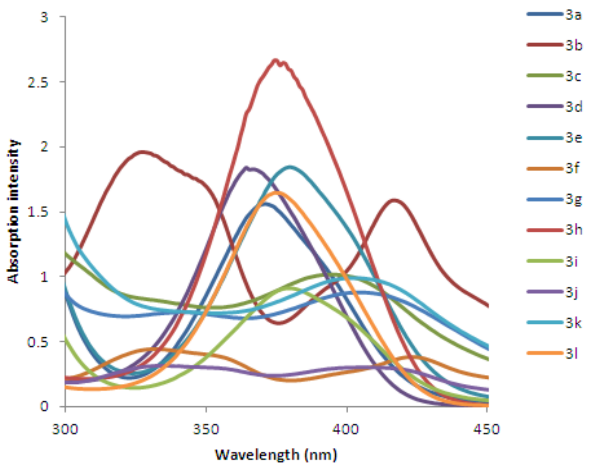


Figure 03: Electronic spectra of Metal Complexes (3a-l)

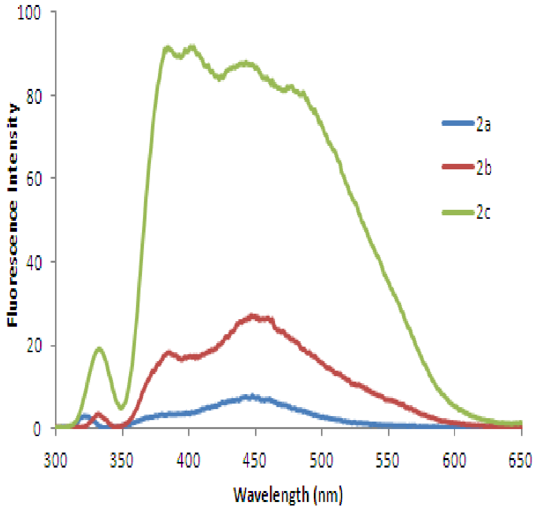


Figure04: Fluorescence spectra of Schiff Bases (2a-c)

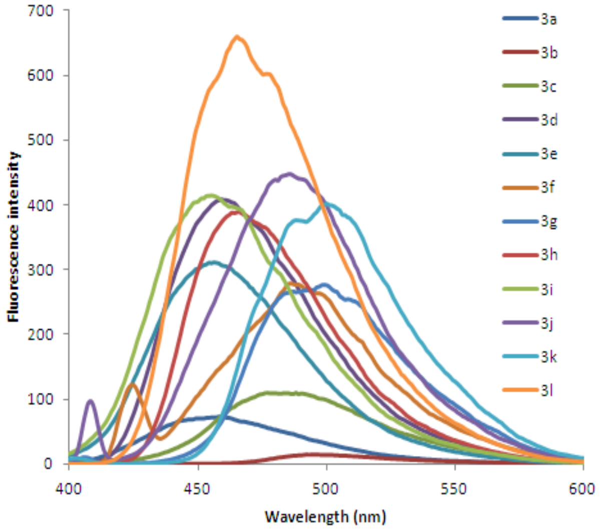


Figure05: Fluorescence spectra of Metal Complexes(3a-l)

Table No. 04: The Absorption and Emission wavelength with intensity

Compound	Absorption λ_{max} (Intensity)	Emission λ_{max} (Intensity)
2a	319 (1.639)	447(7.791)
2b	329(2.003)	446(27.085)
2c	331(2.839)	383(91.394)
3a	370(1.563)	458(72.704)
3b	417(1.591)	496(15.572)
3c	394(1.022)	488(109.678)
3d	364(1.846)	459(408.306)
3e	380(1.846)	456(311.337)
3f	423(0.385)	486(277.917)
3g	404(0.880)	499(276.350)
3h	374(2.671)	466(387.897)
3i	379(0.914)	455(415.269)
3j	406(0.301)	485(446.254)
3k	402(0.993)	500(401.611)
3l	374(1.651)	465(658.786)

RESULTS AND DISCUSSION

Chiral Schiff bases have been synthesized by condensation of (1*R*,2*R*)-(+)-1,2-diphenylethane-1,2-diamine and different salicylaldehyde derivatives. Further these chiral Schiff base ligands were complexed with Cu(II), Ni(II), Co(II) and Zn(II) metal ions. All synthesized Schiff bases and their metal complexes have been thoroughly characterized by various spectroscopic methods.

The IR spectra of the ligands show a broad band of weak intensity around 3062-3064 cm^{-1}. This band can be ascribed to O-H stretching vibration. Very sharp bands at 1274-1276 cm^{-1} were assigned to in plane bending (O-H) vibration of the ligands. Peak in the range of 1629-1631 cm^{-1} confirms the formation of imine (C=N) bond. The NMR spectra of ligands show signal at 8.02-8.51 ppm responsible for azomethine proton. Mass Spectral evaluation predicts the molecular weights of the desired Schiff base compounds.

The spectral data of the Schiff base ligands and their metal complexes in DMF solutions are presented in table no.04 and figure no.02-05. An apparent bathochromic shift of the $\pi\rightarrow\pi^*$ ligand transition is observed upon metal complex formation (table no.04). All the spectra of the metal complexes exhibit a d-d band in the visible region whose maximum of emission lies in the wavelength region 455-500 nm.

In this paper, we have described the antimycobacterial properties of series of Schiff bases 2a-c and their metal complexes 3a-l. Out of all these target compounds 3i, 3j, 3k and 3l showed promising activity against M. tuberculosis (H37 RV strain).

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