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Synthesis and antimicrobial studies of structurally-related Schiff bases and their metal complexes

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ABSTRACT

Schiff bases were obtained from the reaction between 2-aminopyridine and 4-ethoxybenzaldehyde and the reaction of 4-ethoxyaniline and 2-pyridinecarboxaldehyde using the reflux method in ethanol for 2 hours producing 88.2% and 83.5% yield respectively. The 2-aminopyridine-4-ethoxybenzaldehyde Schiff base was dark yellow crystals with a melting point of 95 – 97 °C, while the 4-ethoxyaniline-2-pyridinecarboxaldehyde compound was dark brown crystals with a melting point of 118 – 120 °C. The IR spectrum showed the absorption band at 1681cm^{-1} (C=N, imino), ^{13}C NMR spectrum showed chemical shift at 158.48 ppm (C=N, imino) while ^{1}H NMR spectrum gave a 1 hydrogen singlet peak at 9.71 ppm, (HC=N-) for the 2-aminopyridine-4-ethoxybenzaldehyde Schiff base. Conversely, the IR spectrum of 4-ethoxyaniline-2-pyridinecarboxaldehyde Schiff base presented an absorption band at 1625 cm^{-1} for the imino (C=N) group, while the ^{13}C NMR and ^{1}H NMR showed peaks at chemical shift 158.68 ppm and 8.69 ppm for the imino carbon and imino proton respectively. Furthermore, the zinc and chromium complexes of the Schiff bases were synthesized using the same method but for 3 hours giving yields above 50%. The IR data for the metal complexes showed shifts in the absorption bands when compared to the ligands and with a specific interest in the imino group absorption, it showed that the chelation occurred at the imino nitrogen for all metal complex. In addition, only the chromium complex of 4-ethoxyaniline-2-pyridinecarboxaldehyde showed antifungal activity against *Saccharomyces cerevisiae* with a zone of inhibition of 15 mm and 11 mm. All other compounds were inactive against all the strains of pathogens tested.

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***Keywords*:** *C. albicans, S. cerevisiae, S. aureus, B. subtilis, E. coli,* Schiff bases, 2-aminopyridine, 4-ethoxybenzaldehyde, 4-ethoxyaniline, 2-pyridinecarboxaldehyde

1. INTRODUCTION

Schiff bases are a subclass of imines. Imines are organic compounds that have the imino functional group (HC=N-) (Li *et al*, 2001). Schiff base synthesis can be done using a variety of methods including microwave irradiation (Narain *et al*, 2010; Hardik *et al*., 2020), reflux method (Naeimi *et al*., 2013) stirring at room temperature (Narain *et al*, 2010; Shipra *et al*., 2021), ultrasonication (Li *et al*, 2001, Bendale *et al*., 2011), and grinding/ direct fusion method (Narain *et al*, 2010; Abood, 2014; Ashok, 2015; Surbhi, 2020).

This synthesis is usually achieved in acid or alkaline medium (Aliyu and Isyaku, 2010; Qin *et al*., 2013). In addition, a variety of solvents like dichloromethane (Mishra *et al*., 2012), methanol (Essa *et al*., 2012), benzene (Yang and Sun, 2006), N,N-dimethyl formamide (Tomma *et al*., 2014), water (Wang *et al*., 2005; Rao *et al*., 2010), ethanol (Sachdeva *et al*., 2014; Endale and Desalegn, 2018) and an ethanol-water mixture (Aliyu and Isyaku, 2010; Umofia *et al*., 2018) have been used for the synthesis of these compounds.

Schiff bases have a wide range of applications in the pharmaceutical industry (Saini *et al*., 2011; Chaturvedi and Kamboj, 2016) because they are known to possess biological properties which make them useful as antimalarial (Harpstrite *et al*., 2008), antifungal, antibacterial (Sachdeva *et al*., 2012), antiviral (Sriram *et al*., 2006), anti-inflammatory (Murtaza *et al*., 2017), antitumor (Hu *et al*., 2012) agents or drugs, to mention a few. Their numerous biological properties are related to the imino functional group they possess, as the imino nitrogen is observed to serve as a binding site in drug activity (Chaturvedi and Kamboj, 2016). In addition, these compounds have been chelated with a variety of transition metals like copper, iron, cobalt, manganese, zinc, chromium, nickel, cadmium, etc., with the purpose of investigating the effect of the complexation on their bioactivity. (Guo 2008; Jamuna 2011; Lovely and Christudhas, 2013). This research focuses on the synthesis of two new structurally-related Schiff bases containing the pyridine moiety and the ethoxy group, and their zinc and chromium complexes using the reflux method in an ecofriendly solvent, then antimicrobial studies of these compounds using certain strains of bacteria and fungi.

2. EXPERIMENTAL

2. 1. Materials

The chemicals used for this research were synthesis grade chemicals purchased from Sigma-Aldrich. The melting point was determined with a melting point apparatus and was uncorrected. Thin Layer Chromatography (TLC) was carried out using a Merck pre-coated silica gel plate (10 × 10 cm), the Rf value obtained using ethyl acetate as the mobile phase and the spot located and visualized using an ultraviolet lamp at 256 nm. The IR spectrum of the sample was recorded on a Fourier Transform Infrared spectrometer, Carry 630 Agilent Technologies in the range of 650-4000 cm^{-1}. ^{1}H NMR and ^{13}C NMR spectrum of the sample was recorded on a JEOL Eclipse 400 NMR spectrophotometer by JEOL (Pleasanton, USA) using DMSO-d_6. (Joshi, 2021; Dhineshkumar, 2020; Chinonso, 2021).

2. 2. Preparation of Schiff bases

The aldehyde and amine were dissolved separately in 20 ml ethanol in a 50 ml beaker. The amine was poured into a 150 ml flat bottom flask followed by the aldehyde. The reaction mixture was stirred under reflux at 80 °C for 1 hr followed by the addition of a few drops of concentrated hydrochloric acid (HCl). The reaction mixture was then stirred for one more hour. The reaction was monitored to completion using thin layer chromatography (TLC) with ethyl acetate as the mobile phase.

2. 3. Preparation of Schiff bases metal complexes (1a, 1b, 2a & 2b)

All metal complexes were reacted in a 1:1 mole ratio of ligand and metal salt. With the aid of a dropping funnel, 20 ml of a hot ethanolic solution of the metal salt was dispensed drop-wise to a 20 ml hot ethanolic mixture of the ligand stirring in a 150 ml flat-bottom flask immersed in a water-bath. The mixture stirred under reflux for 3 hours and the progress of the reaction monitored using TLC (mobile phase: ethyl acetate for Zn complex and chloroform-methanol 1:1 v/v for Cr complex).

Synthesis of 2-aminopyridine-4-ethoxybenzaldehyde Schiff base (1):

2-aminopyridine (0.01 mol, 0.94 g) and 4-ethoxybenzaldehyde (0.01 mol, 1.50 g, 1.39 ml) were reacted. The dark yellow mixture was extracted using water and dichloromethane to give dark yellow crystals after standing overnight. The solid product was recrystallized using ethanol and hexane filtered and air-dried. Rf: 0.53, m.p: 95-97 °C, yield: 88.2%. IR (KBr): 1681 cm^{-1} (C=N), 1595 cm^{-1} (aromatic C=C stretch), 2981 cm^{-1} (aromatic C-H stretch), 1509 cm^{-1} (aromatic C=N stretch), 1155cm^{-1} (aliphatic C-C stretch), 1036 (aromatic C-O stretch), 2825 (aliphatic C-H stretch). ^{13}C NMR (δppm); 158.48 (C=N, imino), 154.98 and 150.18 (C-N of aromatic pyridine moiety), 121.44 – 137.53 (aromatic carbons), 158.68 (aromatic C-O), 63.88 (aliphatic C-O), 15.22 (aliphatic C). ^{1}H (δppm) 7.06-7.91, m (8H) (Ar-H), 9.71, s (1H) (HC=N-), 4.10, q (2H) and 1.32, t (3H) (OCH_2CH_3).

Synthesis of 4-ethoxyaniline-2-pyridinecarboxaldehyde Schiff base (2)

4-ethoxyaniline (0.01 mol, 1.37 g, 1.29 ml) and 2-pyridinecarboxaldehyde (0.01 mol, 1.07 g, 0.95 ml) were reacted. A dark-brown oil was obtained after extraction using water and dichloromethane. The oil was triturated using diethyl ether to give dark-brown crystals. The solid product was recrystallized using ethanol and hexane, filtered and air-dried. Rf: 0.73, m.p: 118 – 120 °C, yield: 83.5%. IR (KBr, cm^{-1}): 1625 (C=N), 1584 (aromatic C=C stretch), 2981 (aromatic C-H stretch), 1505 (aromatic C=N stretch), 1114 (aliphatic C-C stretch), 1021 (aromatic C-O stretch), 2825 (aliphatic C-H stretch). ^{1}H (δppm) 6.98-8.62, m (8H) (Ar-H), 8.69, s (1H) (HC=N-), 4.05, q (2H) and 1.34, t (3H) (OCH_2CH_3). ^{13}C NMR (δppm); 158.68 (C=N, imino), 154.98 and 150.18 (C-N of aromatic pyridine moiety), 121.44 – 137.53 (aromatic carbons), 158.48 (aromatic C-O), 63.88 (aliphatic C-O), 15.22 (aliphatic C).

Synthesis of 2-aminopyridine-4-ethoxybenzaldehyde-Zn complex (1a)

The ligand 2-aminopyridine-4-ethoxybenzaldehyde (2.26 g) and $ZnCl_2$ (1.36 g) were reacted. After cooling, excess water was added to the mixture and a red-brown precipitate instantly formed. The precipitate was filtered, recrystallized with ethanol and water, and then air-dried.

R_f : 0.42, yield: 54.7%, IR (cm^{-1}): 1640 (C=N), 1595 (aromatic C=C stretch), 2981 (aromatic C-H stretch), 1509 (aromatic C=N stretch), 1155 (aliphatic C-C stretch), 1036 (aromatic C-O stretch), 2825 (aliphatic C-H stretch).

Synthesis of 2-aminopyridine-4-ethoxybenzaldehyde-Cr complex (1b)

The ligand 2-aminopyridine-4-ethoxybenzaldehyde (2.26 g) and the metal salt $CrCl_3.6H_2O$ (2.66 g) were reacted. The mixture was allowed to stand for a month and a reddish-green oil was observed. R_f: 0.38, yield: 62.8%, IR (cm^{-1}): 1666 (C=N), 1625 (aromatic C=C stretch), 1162 (aliphatic C-C stretch), 1039 (aromatic C-O stretch), 3317 (OH stretch).

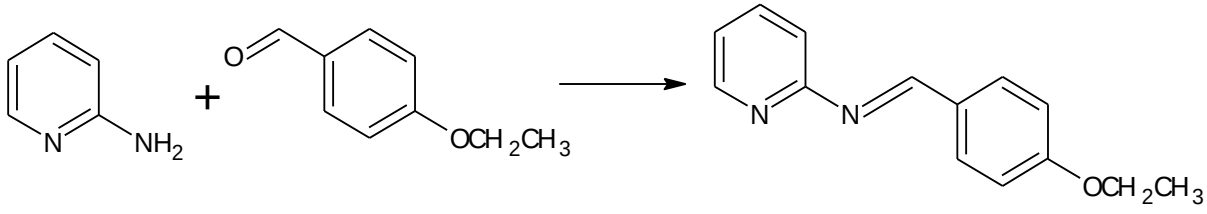
Synthesis of 4-ethoxyaniline-2-pyridinecarboxaldehyde-Zn complex (2a)

The ligand 4-ethoxyaniline-2-pyridinecarboxaldehyde (2.26 g) and $ZnCl_2$ (1.36 g) were reacted. The lemon-yellow precipitate that resulted was collected through filtration, recrystallized using ethanol and water, and then air-dried. R_f : 0.51, M.p: 126-128 °C, yield: 57.0%, IR (cm^{-1}): 1599 (C=N), 1558 (Ar C=C stretch), 2978 (aromatic C-H stretch), 1505 (Ar C=N stretch), 1174 (aliphatic C-C stretch), 1039 (aromatic C-O stretch), 2892 (aliphatic C-H stretch).

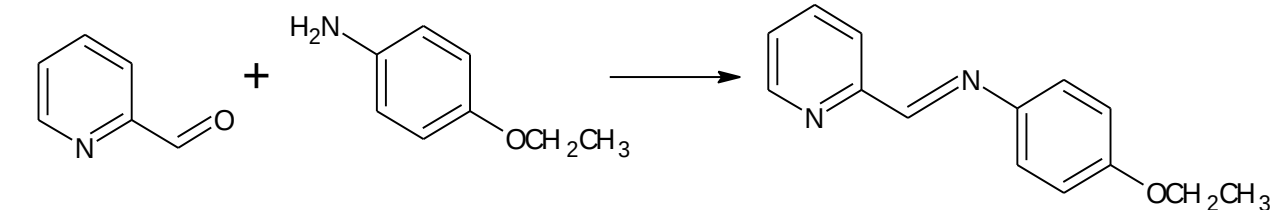
Synthesis of 4-ethoxyaniline-2-pyridinecarboxaldehyde-Cr complex (2b)

The ligand 4-ethoxyaniline-2-pyridinecarboxaldehyde (2.26 g) and $CrCl_3.6H_2O$ (2.66 g) were reacted. The dark-green oil was left to stand for a month. No further change was noticed. R_f:: 0.40, yield: 63.0%, IR (cm^{-1}): 1610 (C=N), 1513 (ArH C=N stretch), 1110 (aliphatic C-C stretch), 1039 (aromatic C-O stretch), 3324 (O-H stretch).

The general reaction equation for the synthesis of the Schiff bases (**1** and **2**) are illustrated in Scheme 1 below.



2-Aminopyridine 4-Ethoxybenzaldehyde 2-aminopyridine-4-ethoxybenzaldehyde Schiff base **(1)**



2-pyridinecarboxaldehyde 4-Ethoxyaniline 4-ethoxyaniline-2-pyridinecarboxaldehyde Schiff base **(2)**

Scheme 1. General reaction equation for the synthesis of Schiff base 1 and 2.

3. BIOLOGICAL ACTIVITY

The antimicrobial test of the Schiff bases were done using the agar diffusion method (Bauer *et al*., 1966). The compounds were tested against gram-positive bacteria, *Staphylococcus aureus* and *Bacillus subtilis*, gram-negative bacteria, *Escherichia coli, Klebsiella pneumoniae*, and *Pseudomonas aureginosa*, and fungi, *Saccharomyces cerevisiae* and *Candida albicans.* The purity and viability of the isolates was confirmed using selective media, mannitol salt, eosine methylene blue agar (for bacteria) and potato dextrose agar (for fungi). The Petri dishes were incubated at 37 °C for 24 hours. Slants were prepared using nutrient agar medium for bacteria and potato dextrose agar for fungi and incubated again to ensure growth and purity of the organisms.

The compounds (1, 1a, 1b, 2, 2a and 2b) were dissolved in 30% dimethyl sulphoxide (DMSO) to achieve 0.50 mg/ml, 0.25 mg/ml and 0.17 mg/ml. They were stored overnight in a refrigerator at 15 ^{o}C (Akujobi *et al*., 2004). Mueller-Hinton agar medium and Potato Dextrose Agar medium was used for the bacteria and fungi respectively. From an overnight broth culture, a 1 x 10^8 cell/ml McFarland standard was prepared and 0.1 ml of the isolates were aseptically transferred to sterile Petri dishes before adding 20 ml of the prepared molten agar.

The content was thoroughly mixed and allowed to solidify. Three 5.0 mm holes were made in each plate using a sterile cup-borer and 0.2 ml of the different compound concentrations dispensed to each hole aseptically using a syringe. Pre-diffusion was allowed for 1 hour prior to incubation at 37 °C for 24 hours for bacteria and 48 hours for fungi. Similar Petri dishes were prepared for standard drugs, Ciprofloxacin and Ketoconazole, for bacteria and fungi respectively and for DMSO to serve as the control for bacteria and fungi. The zones of growth inhibition were measured and recorded in millimetres. The compound activities at all concentrations are presented in the Table 1 – 3 below.

4. RESULTS AND DISCUSSION

The synthesis of the Schiff base and their Zn and Cr complexes were achieved using the reflux method with ethanol as a solvent. The yield obtained for the ligands were relatively high, 88.2% for compound **1** and 83.5% for compound **2** respectively. The physicochemical and spectral studies proved that the Schiff bases formed as expected. The results obtained from the spectral analyses proved that the structure of the compounds were as anticipated. With respect to spectral studies, the IR absorption bands observed at 1681cm^{-1} and 1625 cm^{-1} for compound **1** and **2** respectively proved the presence of the imino functional group (C=N). Moreover, the single peaks observed in the ^{1}H NMR and the ^{13}C NMR spectrum at 9.71 ppm (imino proton) and 158.48 ppm (imino carbon) for compound **1** and at 8.69 ppm (imino proton) and 158.68 ppm (imino carbon) for compound **2** further revealed that the structures were as expected. In addition, the shift in IR absorption bands in the metal complexes (**1a**, **1b**, **2a** and **2b**) when compared to the ligands (**1** and **2**), especially for the imino absorption band, showed that the ligand-metal complexation was successful and involved the imino nitrogen atom (MacAleese and Maitre, 2007; Świderski *et al*., 2018).

Furthermore, the results from the susceptibility tests of all the compounds showed that not all Schiff bases and metal complexes are active against some pathogens or show a broad spectrum activity and hence may be pathogen-selective. The only active compound was the

chromium complex of compound **2** (**2b**) and this showed only antifungal properties against only *S.cerevisiae*, hence showing that complexation with chromium increased the ability of the ligand to be bioactive.

Table 1. Susceptibility Test on Gram-positive bacteria.

ORGANISM	**Zone of Inhibition (mm)**					
	S. aureus			*B. subtilis*		
	CONCENTRATION (mg/ml)					
COMPOUND	**0.50**	**0.25**	**0.17**	**0.50**	**0.25**	**0.17**
1	-	-	-	-	-	-
1a	-	-	-	-	-	-
1b	-	-	-	-	-	-
2	-	-	-	-	-	-
2a	-	-	-	-	-	-
2b	-	-	-	-	-	-
DMSO	-	-	-	-	-	-
Ciprofloxacin	**20**	**20**	**20**	**30**	**30**	**30**

- : No activity

Table 2. Susceptibility Test on Gram-negative bacteria.

ORGANISM	**Zone of Inhibition (mm)**								
	E. coli			*K. pneumoniae*			*P. aureginosa*		
	CONCENTRATION (mg/ml)								
COMPOUND	0.50	0.25	0.17	0.50	0.25	0.17	0.50	0.25	0.17
1	-	-	-	-	-	-	-	-	-
1a	-	-	-	-	-	-	-	-	-

1b	-	-	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-	-	-
2a	-	-	-	-	-	-	-	-	-
2b	-	-	-	-	-	-	-	-	-
DMSO	-	-	-	-	-	-	-	-	-
Ciprofloxacin	**16**	**16**	**12**	-	-	-	**48**	**48**	**40**

- : No activity

Table 3. Susceptibility Test on Fungi.

ORGANISM	**Zone of Inhibition (mm)**					
	C. albicans			*S. cerevisiae*		
	CONCENTRATION (mg/ml)					
COMPOUND	0.50	0.25	0.17	0.50	0.25	0.17
1	-	-	-	-	-	-
1a	-	-	-	-	-	-
1b	-	-	-	-	-	-
2	-	-	-	-	-	-
2a	-	-	-	-	-	-
2b	-	-	-	**15**	**11**	-
DMSO	-	-	-	-	-	-
Ketoconazole	**30**	**28**	**24**	**20**	**16**	**14**

- : No activity

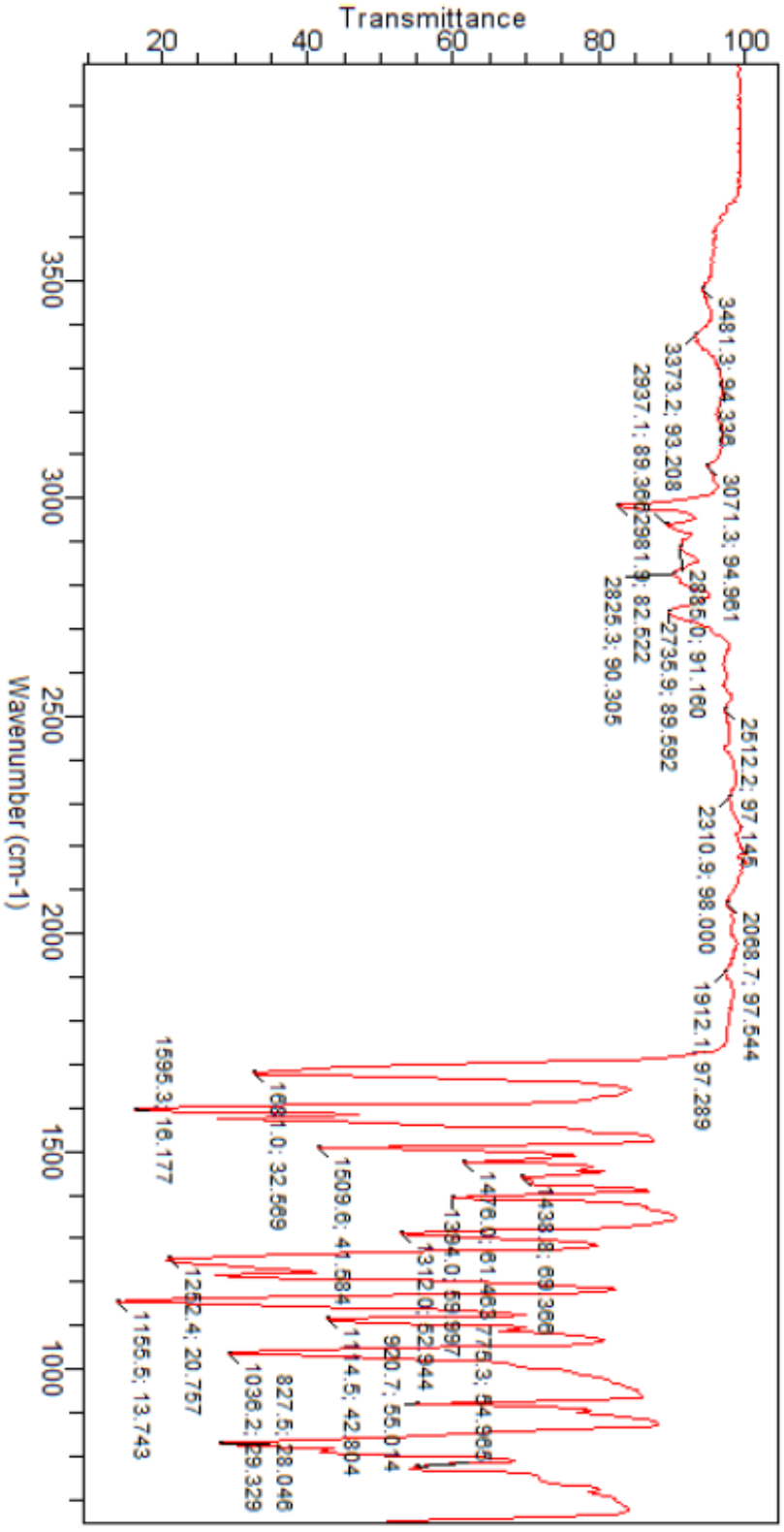


Figure 1. IR Spectrum of Schiff base 1

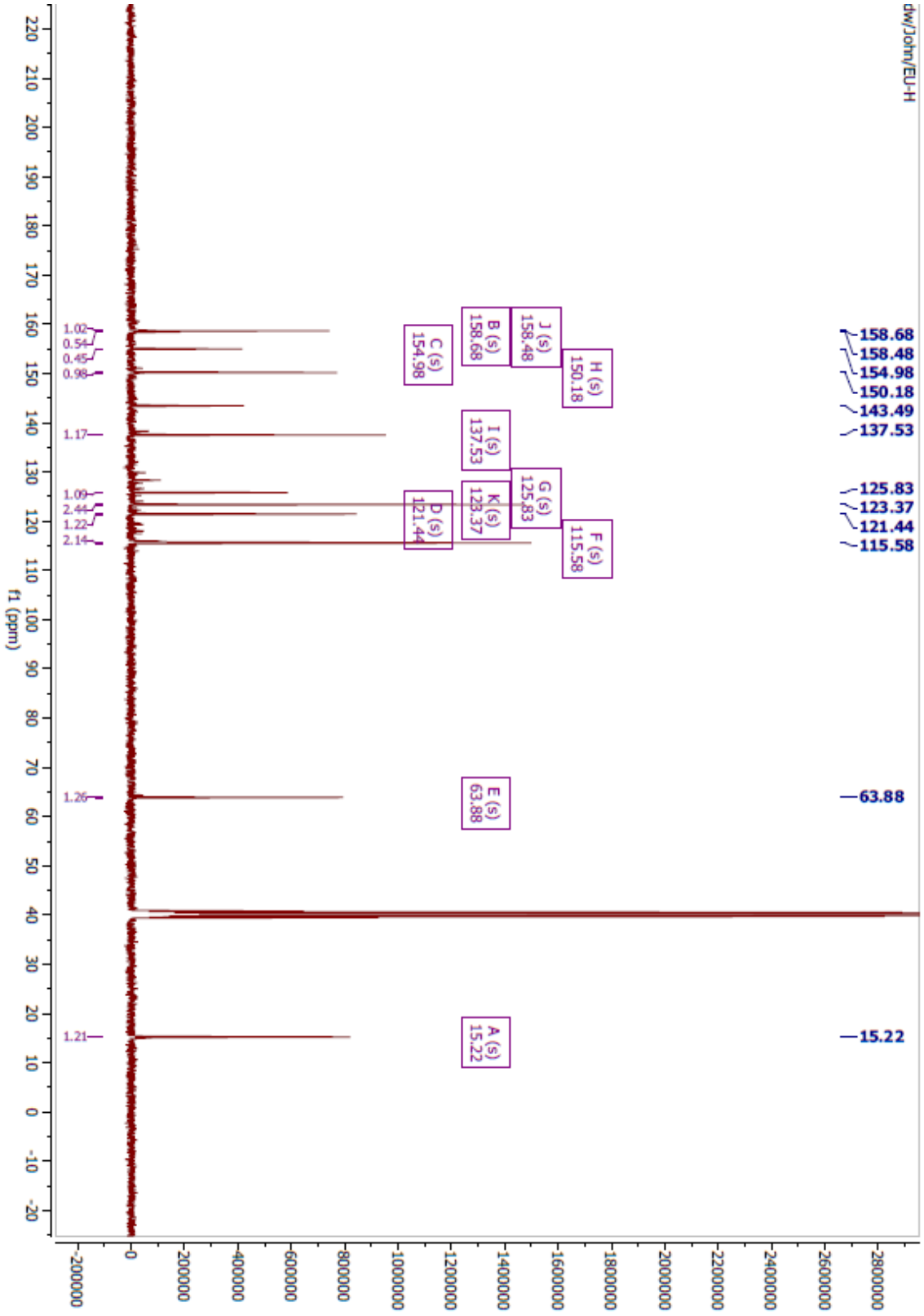


Figure 2. ^{13}C NMR Spectrum of Schiff base 1

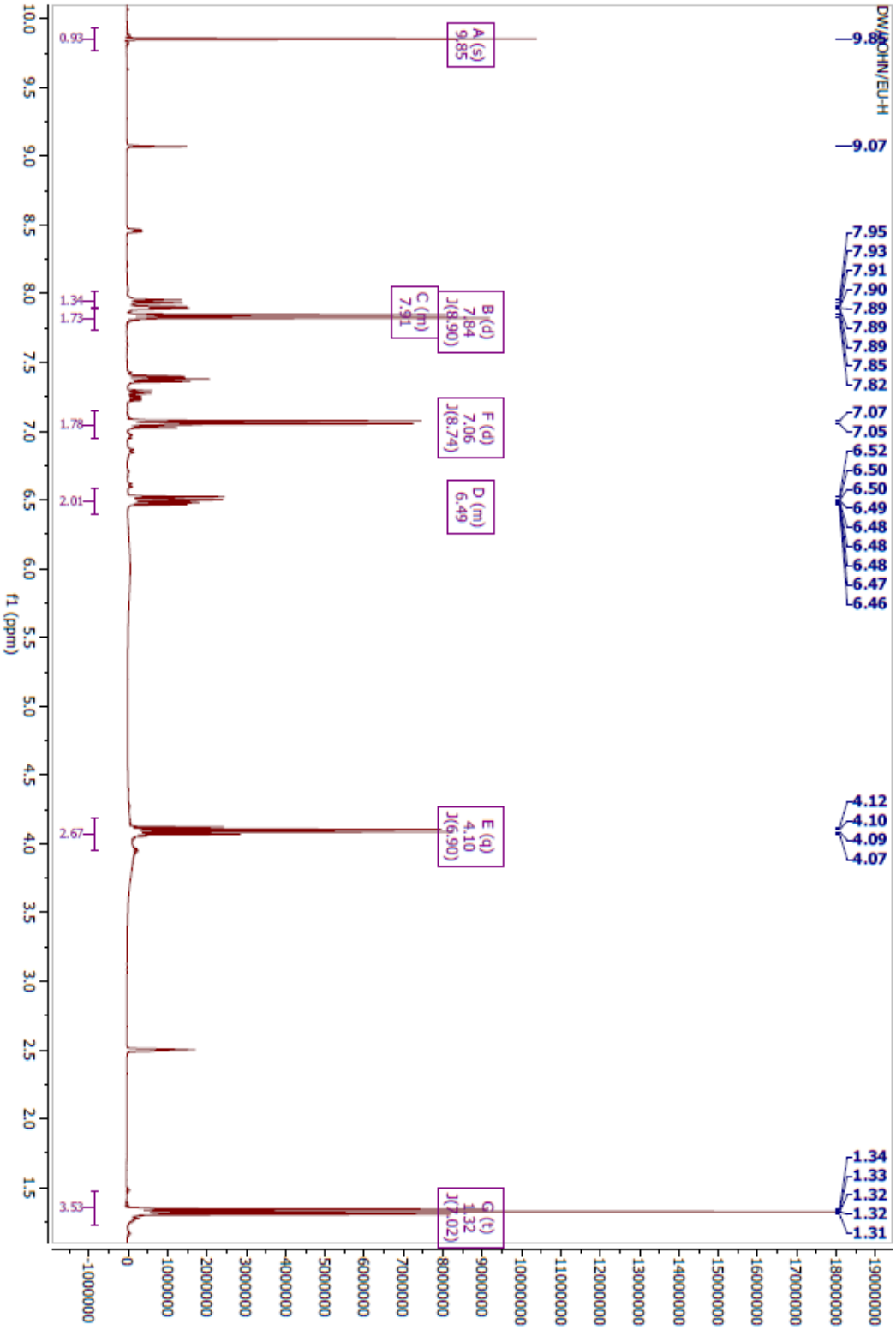


Figure 3. ^{1}H NMR Spectrum of Schiff base 1

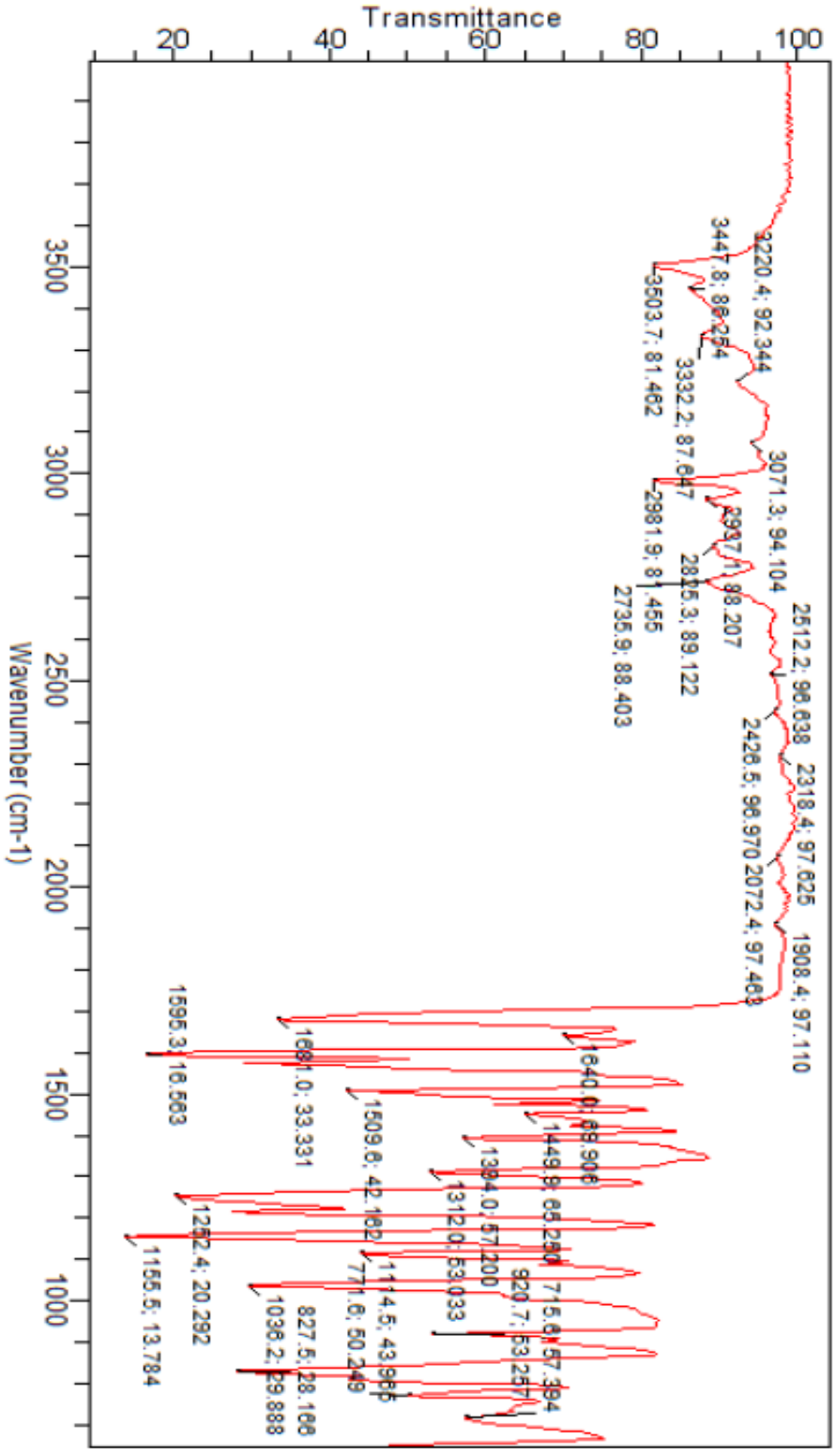


Figure 4. IR Spectrum of Zn Complex of Schiff base 1

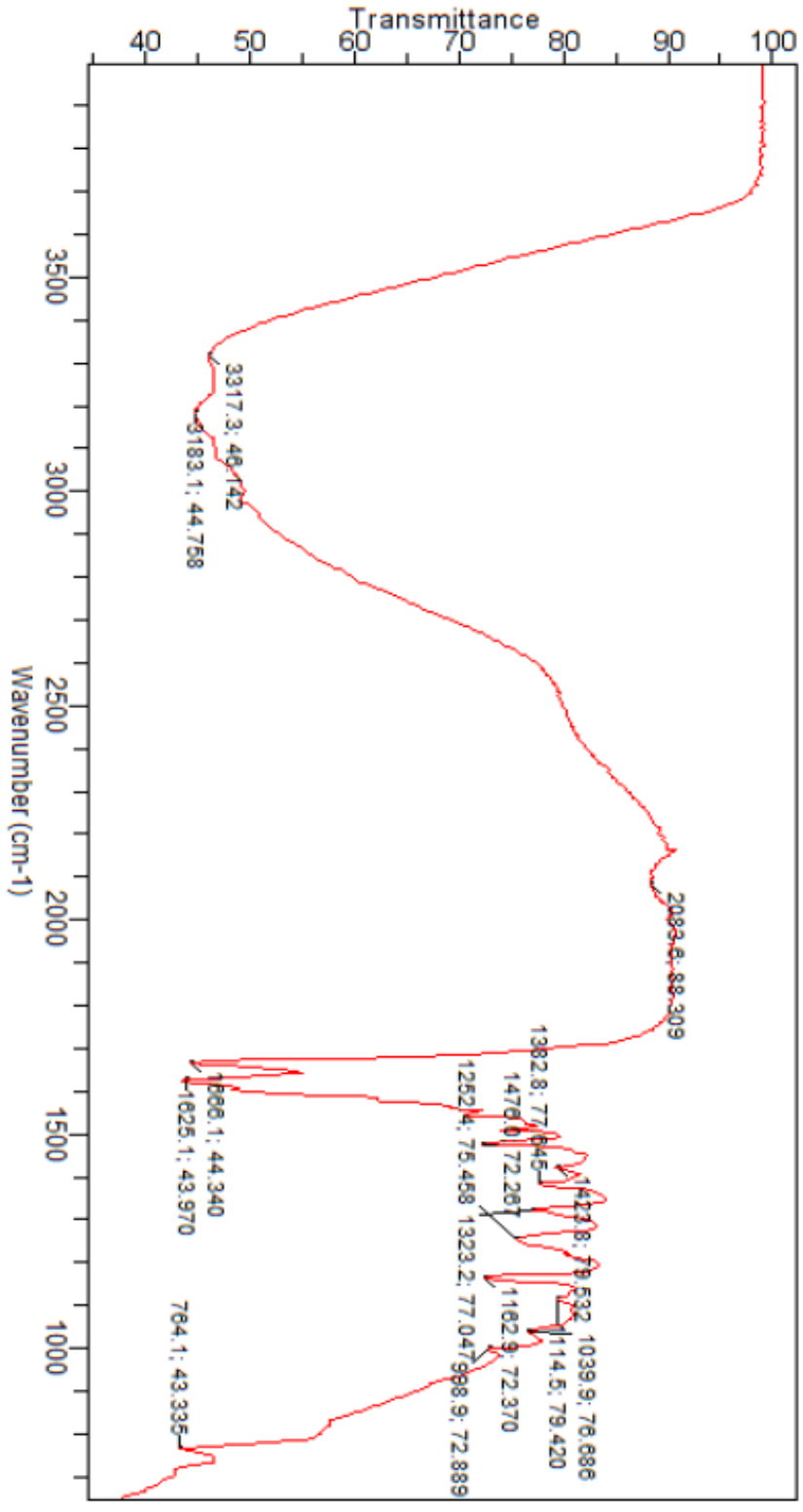


Figure 5. IR Spectrum of Cr Complex of Schiff base 1

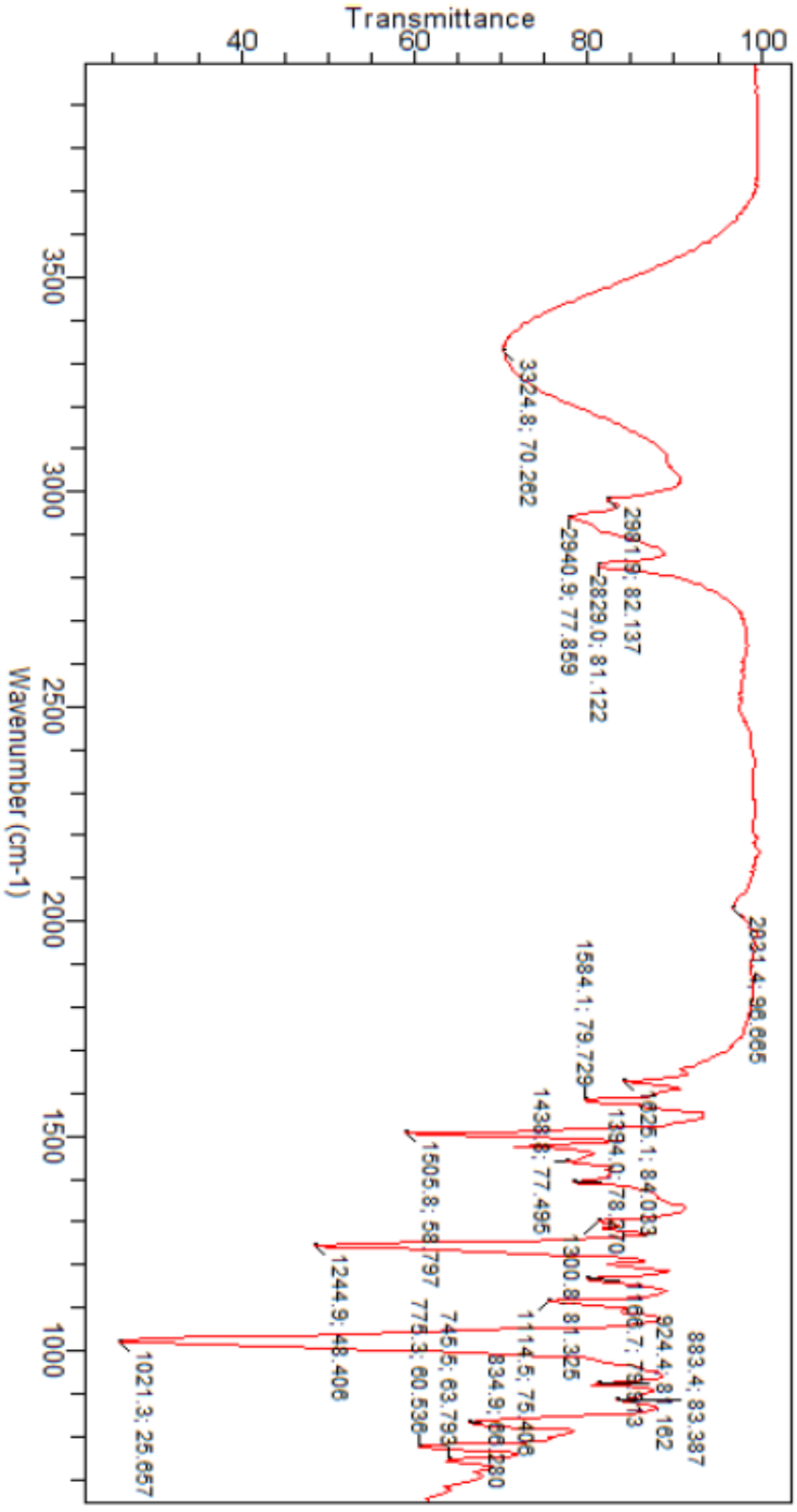


Figure 6. IR Spectrum of Schiff base 2

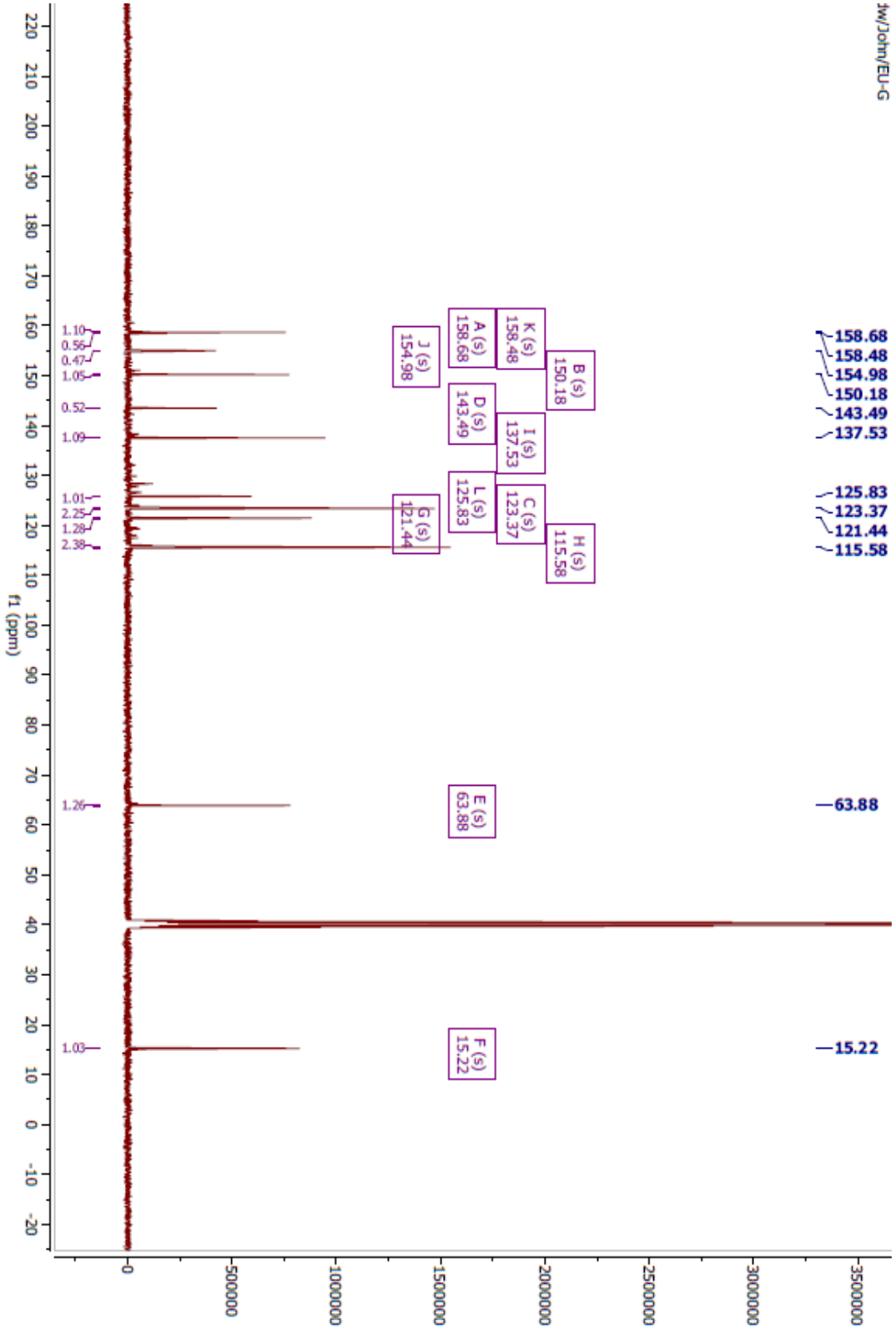


Figure 7. ^{13}C NMR Spectrum of Schiff base 2

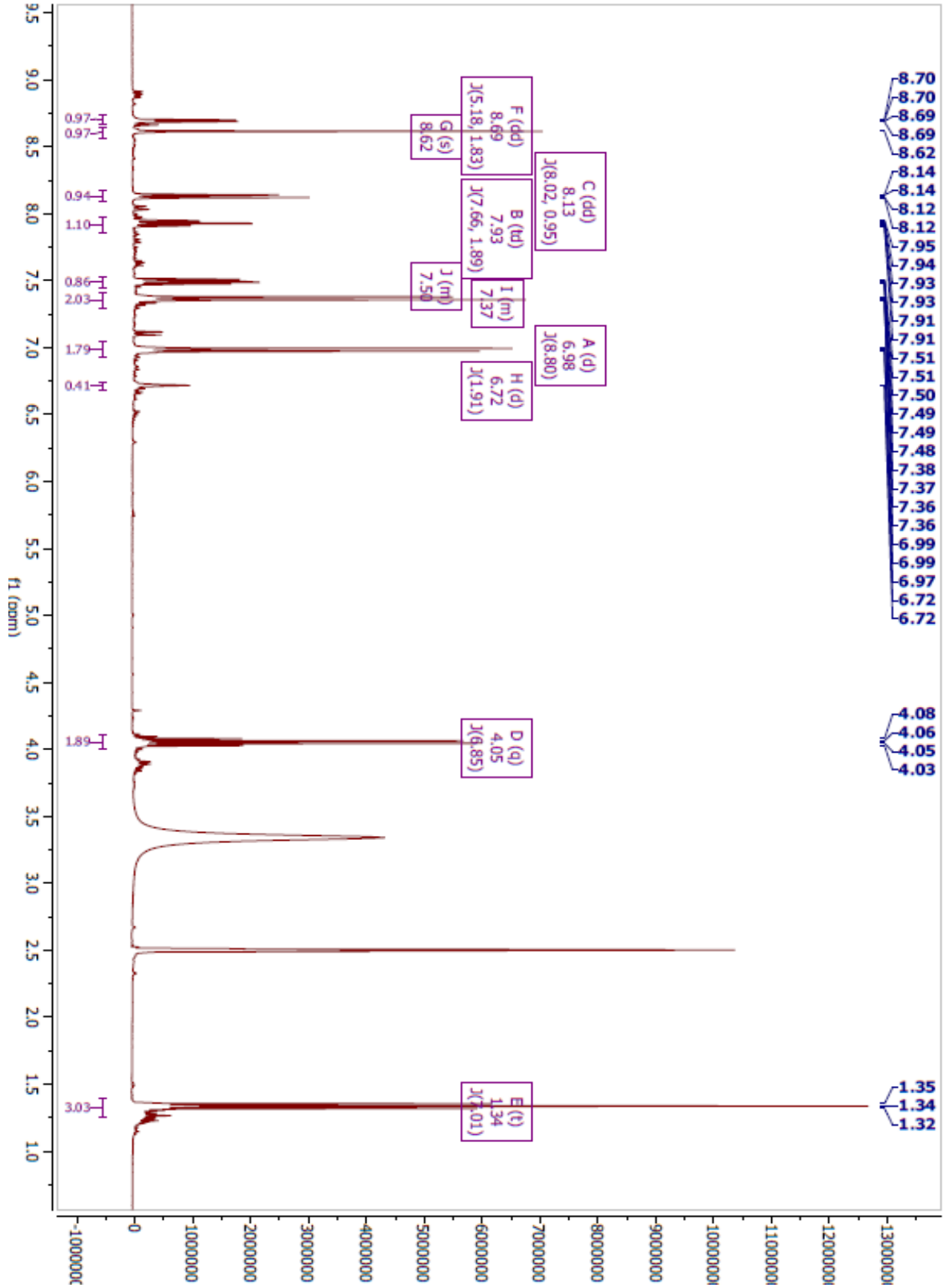


Figure 8. ^{1}H NMR Spectrum of Schiff base 2

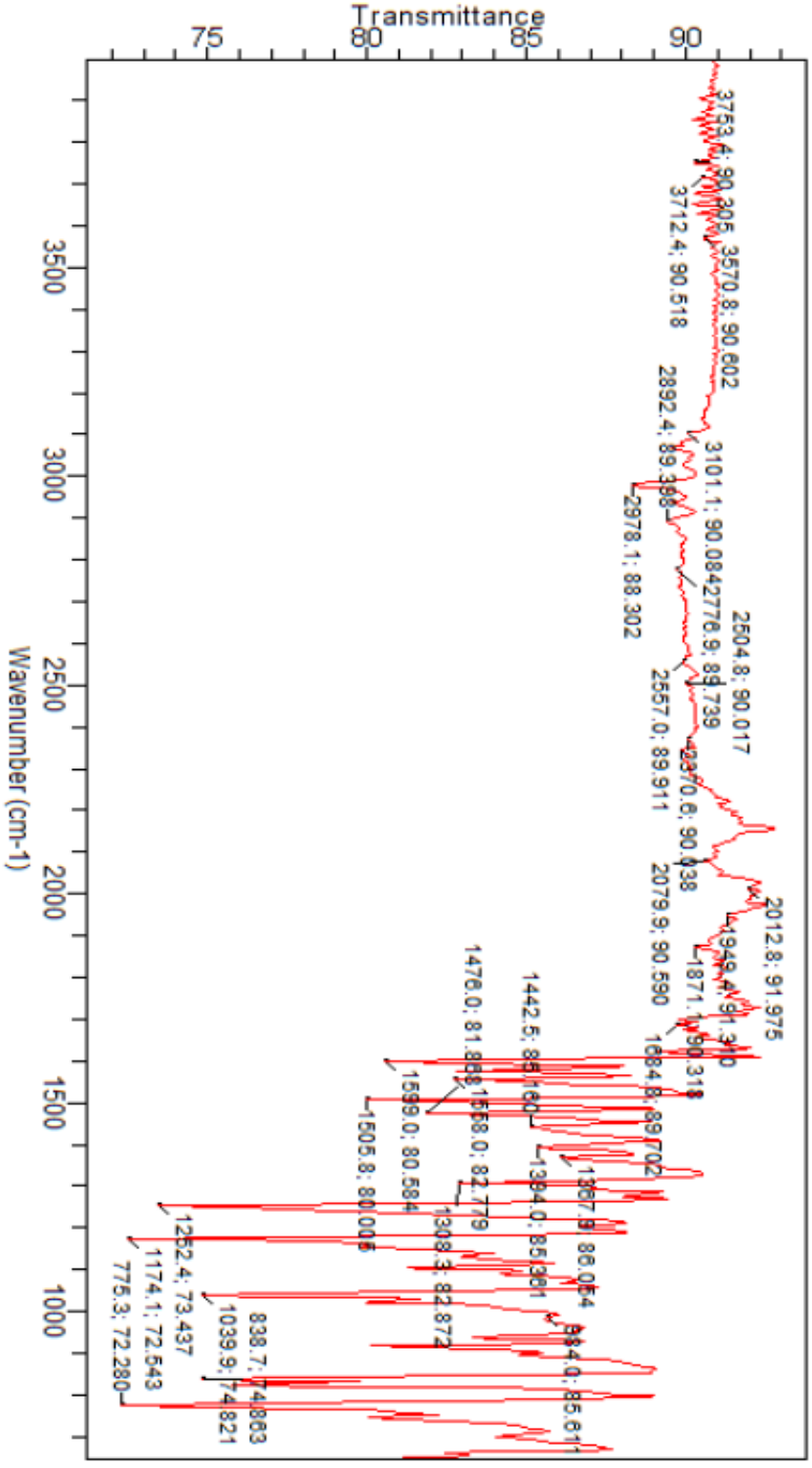


Figure 9. IR Spectrum of Zn Complex of Schiff base 2

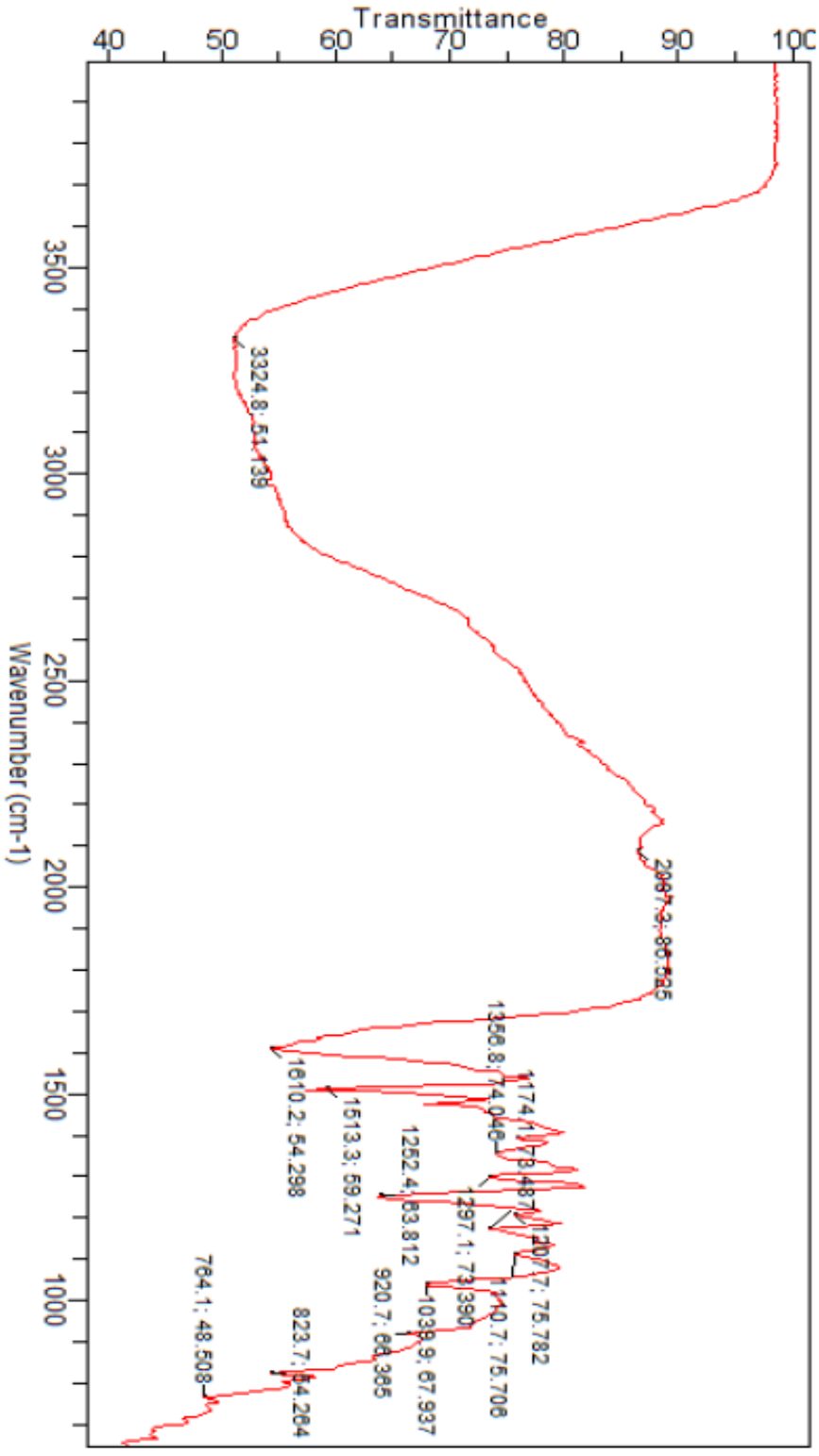


Figure 10. IR Spectrum of Cr Complex of Schiff base 2

5. CONCLUSION

The results obtained from this research proves that the 2-aminopyridine-4-ethoxybenzaldehyde and 4-ethoxyaniline-2-pyridinecarboxaldehyde Schiff base and their Zn and Cr complexes can be synthesized using ecofriendly solvents at relatively high yields.

In addition, from the antimicrobial tests, it was observed that only the chromium complex of the 4-ethoxyaniline-2-pyridinecarboxaldehyde Schiff base showed activity against *S.cerevisiae*, therefore, it is safe to say that not all compounds have biological activities against certain pathogens and metal complexation does not always enhance bioactivity.

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