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Synthesis, characterization and anti-bacterial activity of mix ligand complexes of copper with isonicotinic acid and different N-donor ligands

Devang N. Mokariya, Rasik M. Tejani, Juvansinh J. Jadeja and **Manish K. Shah***

Chemical Research Laboratory, Department of Chemistry, Saurashtra University, Rajkot, Gujarat, India

*E-mail address: drmks2000@hotmail.com

ABSTRACT

Metal complexes of copper with isonicotinic acid and different N-donor ligands like N-Ethyl Piperazine, N-Methyl Piperazine and 4-Methyl Pyridine are synthesized. Complexes are characterized by different techniques like Elemental analysis, IR Spectroscopy, MASS Spectroscopy, Conductance and TGA. Complexes are screened for antimicrobial activity.

***Keywords*:** Mix ligand complexes, N-donor ligands, Antibacterial activity

1. INTRODUCTION

Pyridine carboxylic acids are having at least two coordination sites, the structural and chemical properties of their complexes with transition metal ions [1-7] and rare earth ions [8-10] have been the compelling area of research. Copper complexes of various compounds have increased anti-inflammatory effectiveness over the native compounds [11]. Nicotinic acid or vitamin B3 is vital for many biological processes namely for the energy production [12], signal transduction, control of gene expression [13] and involvement in the synthetic route of lipids [14]. Moreover, copper is a necessary nutrient for body, incorporated in the catalytic function

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of many enzymes such as copper-zinc superoxide dismutase (CuZnSOD) [15, 16]. Deficiency of copper has been turn up to cause hematologic disorders, hypopigmentation, defective connective tissue cross-linking and ataxia [17, 18]. Sigman et al have studied that the bis(phen) copper complex acts as an structured nuclease by oxidative cleavage mechanism in the presence of molecular oxygen and a reducing agent [19-22]. By using their redox properties, Palaniandavar et al exemplified the nuclease activity of copper(II) bis complexes of different methyl-substituted 1,10-phenanthrolines [23]. Very recently, mixed ligand copper(II) complexes are found to exhibit prominent anticancer activity by inducing apoptosis, and interestingly they are found to strongly bind and cleave DNA [24-28]. Lanthanide complexes of three derivatives of pyridine carboxylic acid; nicotinic acid, isonicotinic acid and picolinic acid, have been progressively investigated [29-31]. Also Ln^{3+} complexes are the area of great interest due to their properties and applications in the fields of magnetic functional materials, catalysis and luminescent probes in biological systems [32-36]. Moreover, the isonicotinate anions are convenient moieties in forming an extended structure because they are unsymmetrical divergent ligands with a nitrogen atom at one end and two oxygen atoms from the carboxylic acid group at the other one [37-38].

In present work we have successfully synthesised copper mix ligand complex in good percentage yield. All complexes contain isonicotinic acid as ligand and second ligand is different pyridine derivative (like N-Ethyl Piperazine, N-Methyl Piperazine and 4-Methyl Pyridine). Complexes are studied with different techniques. IR and MASS Spectroscopy are used for characterization long with elemental analysis, conductance and thermo gravimetric analysis. Complexes are screened for antibacterial activity and compared with standard drugs.

2. MATERIALS AND METHODS

All chemicals are of analytical grade. Chemicals are used as such without further purification. Infrared spectroscopy was carried with Shimadzu IR Affinity-1S FTIR spectrometer. Elemental data was recorded by Carlo Erba EA 1108 elemental analyser. Mass Spectroscopy was carried out with LC-MS spectrometer Model Q-ToF Micro Waters. Conductance was measured with Equiptronics Digital Conductivity Meter.

3. EXPERIMENTAL

Synthesis of metal complexes was carried out for copper metal with isonicotinic acid and different types of N- donor ligands (Complexes: 1-3)

3. 1. Synthesis of Complex-1

Solution of metal chloride made by dissolving 0.39 gm. (1mmol) of copper chloride ($CuCl_2 \cdot 6H_2O$) in 10 ml distilled water. To another beaker solution of sodium salt of isonicotinic acid prepared by adding equivalent amount of sodium carbonate to 0.56 gm. (2 mmol) isonicotinic acid in 10 ml water. Now both prepared solutions are mixed together with stirring followed by addition of solution of 0.52 gm. (2 mmol) of N-Ethyl Piperazine in 10 ml methanol drop wise and further stirred for one hour in water bath. Complex precipitated, filtered and washed by distilled water, air dried.

3. 2. Synthesis of Complex-2

Solution of metal chloride made by dissolving 0.39 gm. (1 mmol) of copper chloride ($CuCl_2 \cdot 6H_2O$) in 10 ml distilled water. To another beaker solution of sodium salt of isonicotinic acid prepared by adding equivalent amount of sodium carbonate to 0.56 gm. (2 mmol) isonicotinic acid in 10 ml water. Now both prepared solutions are mixed together with stirring followed by addition of solution of 0.45 gm. (2 mmol) of N-Methyl Piperazine in 10 ml methanol drop wise and further stirred for one hour in water bath. Complex precipitated, filtered and washed by distilled water, air dried.

3. 3. Synthesis of Complex-3

Solution of metal chloride made by dissolving 0.39 gm. (1 mmol) of copper chloride ($CuCl_2 \cdot 6H_2O$) in 10 ml distilled water. To another beaker solution of sodium salt of isonicotinic acid prepared by adding equivalent amount of sodium carbonate to 0.56 gm. (2 mmol) isonicotinic acid in 10 ml water. Now both prepared solutions are mixed together with stirring followed by addition of solution of 0.43 gm. (2 mmol) of 4-Methyl Pyridine in 10 ml methanol drop wise and further stirred for one hour in water bath. Complex precipitated, filtered and washed by distilled water, air dried.

4. CHARACTERIZATION

Complexes are studied with various analysis techniques. All synthesised complexes are coloured. They are having melting point higher than of the ligand moieties. C, H, N estimation data is obtained with elemental analyser which is shown in analytical data table.

4. 1. Physical data

Compound	Compound	Molecular weight	Color	M.P. (°C)	Yield (%)
Complex-1	[Cu(Isonicotinic acid)$_2$(N-Ethyl piperazine)$_2$]·2H_2O	570	Bluish green	218	93
Complex-2	[Cu(Isonicotinic acid)$_2$(N-Methyl piperazine)$_2$]·2H_2O	542	Bluish green	219	94
Complex-3	[Cu(Isonicotinic acid)$_2$(4-Methyl pyridine)$_2$]·2H_2O	530	Dark Blue	224	90

4. 2. Analytical data

Compound	Molecular Formula	% C		% H		% N		Λm µs
		Calcd	Found	Calcd	Found	Calcd	Found	
Complex-1	$C_{24}H_{38}CuN_6O_6$	50.56	50.13	6.72	6.79	14.74	14.65	74
Complex-2	$C_{22}H_{34}CuN_6O_6$	48.74	48.70	6.32	6.49	15.50	15.38	68
Complex-3	$C_{24}H_{26}CuN_4O_6$	54.39	54.99	4.94	5.01	10.57	10.77	77

4. 3. IR Spectra

The metal carboxylate complexes can be studied by the use of vibrational spectroscopy. Complexes shows several sharp signals in the mid IR region most of which are also observed in the free carboxylic acid, indicating the presence of the organic moiety in the synthesized complexes.

In case of complex 1 there is signal at 1616 cm^{-1} for C=O stretching, 1379 cm^{-1} for tertiary amine, Hydroxyl stretching in region of 2700-2500 cm^{-1} is lowered shows bonding of metal with oxygen of carboxylic acid and hydroxyl bending at 1415 cm^{-1}, there is a stretching due to secondary amine around 3475 cm^{-1}. This signal shows the presence of acid and amine moiety in the complex.

Same way in case of complex-2 we can observe C=O stretching at 1616 cm^{-1}, 1379 cm^{-1} for tertiary amine, hydroxyl bending at 1413 cm^{-1} and there is a stretching due to secondary amine around 3473 cm^{-1}. In complex-3 C=O stretching is observed at 1610 cm^{-1}, hydroxyl bending at 1417 cm^{-1} and signal around 1360 cm^{-1} for tertiary amine.

4. 4. Mass Spectra

Electrospray ionization-mass spectrometry (ESI-MS) is used to study metal complexes. Mass peaks can be seen in spectra of complex-1 and complex-2. Also the peaks for fragmentation of ligands are well observed in the spectra.

In mass spectra of complex-1 there is a $[M+H]^+$ peak at 571 m/z. We can attribute the ligand fragmentations peaks of complex-1 at 124 m/z and 85 m/z for isonicotinic acid and N-Ethyl piperazine fragments respectively.

Same way in mass spectra of complex-3 there is a $[M+H]^+$ peak for complex-3 at 531 m/z. Ligand fragmentation peaks are 124 m/z and 94 m/z for isonicotinic acid and 4-Methyl pyridine respectively.

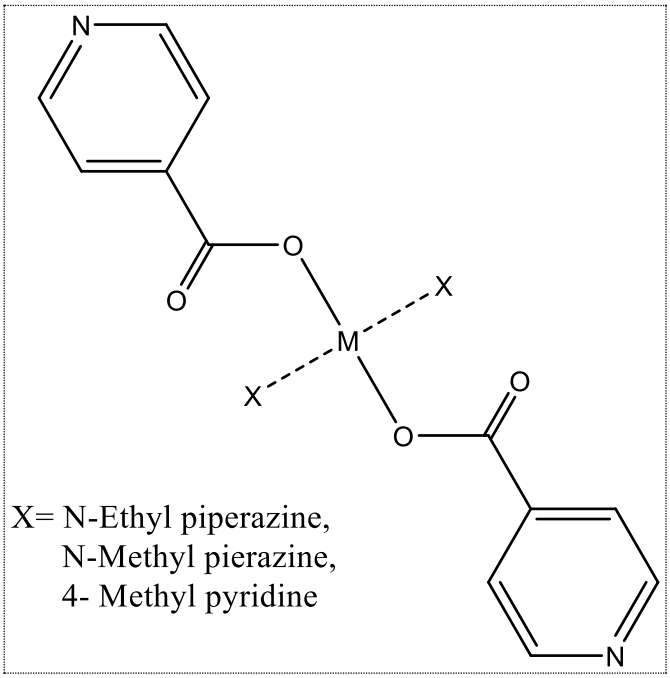
4. 5. Conductance

Solubility range of metal complexes is not higher than the organic moiety but still gives the idea of the electrolyte property of the synthesised complex in solution system. The molar conductivity values of the complexes in DMSO solvent (1.0×10^{-3} mol) were measured in the electrolytic range of (106-311 μs). Conductivity measurements give the structural information of complexes within the range of their solubility limits. Here values are shown in analytical data table. It is clear from data that solutions are not seemed to be electrolytes.

4. 6. Thermogravimetric analysis

TGA data of the complexes is studied. TGA data of complex-3 is shown in figure. It shows several thermal events. There are three weight loss events can be seen. First event can be attributed to the loss of water molecules and the second and third are for the ligand moiety. Complex is almost stable till 80^oC as there is no weight loss and above this temperature there is a weight loss due to removal of water molecules. On further heating around 230^oC and 280^oC there is a weight loss due to removal of ligands.

4. 7. Proposed structure



5. ANTIBACTERIAL ACTIVITY

For evaluation of Antibacterial activity we have used Staphylococcus Aureus and Streptococcus Pyogenes from Gram Positive group of bacteria and Escherichia Coli and Pseudomonas Aeruginosa from Gram Negative group of bacteria. Broth Dilution Method is used to evaluate the antibacterial activity. It is one of the non-automated in vitro bacterial susceptibility tests. This classic method yields a quantitative result for the amount of antimicrobial agents that is needed to inhibit growth of specific microorganisms. DMSO was used as diluents / vehicle to get desired concentration of drugs to test upon standard bacterial strains.

The main advantage of the Broth Dilution Method for MIC determination lies in the fact that it can readily be converted to determine the MIC as well. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic is immediately sub cultured [before inoculation] by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 ^{0}C overnight. The tubes are then incubated overnight. The MIC of the control organism is read to check the accuracy of the drug concentrations.

The lowest concentration inhibiting growth of the organism is recorded as the MIC. The amount of growth from the control tube before incubation [which represents the original inoculum] is compared. Activity data is shown in following table along with Standard drugs minimum inhibition concentration.

ANTIBACTERIAL ACTIVITY TABLE					
MINIMUM INHIBITION CONCENTRATION					
SR. NO	COMPOUND	*E. COLI*	*P. AERUGINOSA*	*S. AUREUS*	*S. PYOGENUS*
		MTCC 443	MTCC 1688	MTCC 96	MTCC 442
1	COMPLEX-1	500	100	25	62.5
2	COMPLEX-2	100	62.5	250	250
3	COMPLEX-3	100	200	500	500
4	GENTAMYCIN	0.05	1	0.25	0.5
5	AMPICILLIN	100	--	250	100
6	CHLORAMPHENICOL	50	50	50	50
7	CIPROFLOXACIN	25	25	50	50
8	NORFLOXACIN	10	10	10	10

6. CONCLUSIONS

Mix Ligand complexes of copper are found to be stable under normal temperature. Stability is higher than that of the ligands used. Complexes are generally coloured. Solubility is higher in polar solvents and insoluble in most of non-polar solvents such as benzene, toluene and ether etc.

C, H, N estimation is in good orientation with calculated data. Complexes are having melting point higher than 200 ºC. Complexes are synthesized in good percentage yield. Infrared Spectroscopy and Mass Spectroscopy data gives fair resolution to structure of complexes. IR data shows the existence of functional groups in ligands co-ordinated in the complexes. Mass Spectroscopy confirms the presence and fragmentation of co-ordinated ligand moieties. TGA data suggests the presence of water molecules in complex. Conductance of all complexes attributed to the non-electrolyte nature of complexes in solution.

Bioactivity data shows the comparable minimum inhibition concentration for the synthesised complexes. Concentration values are compared with standard drugs, some of the complexes shows fair inhibition concentration.

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References

[1] Kh. Kh. Khakimov, M. A. Azizov and A. L. Kats, *Zh. Neorg. Khim.* 15, 2173 (1970)

[2] M. K. Alyaviya, R. S. Rysopaeva and A. L. Kats, *Zh. Neorg. Khim.* 17, 957 (1972)

[3] M. K. Alyaviya and Z. M. Teplyakova, *Zh. Neorg. Khim.* 15, 958 (1970)

[4] Kleinstein and G. A. Webb, *J. lnorg. Nucl, Chem.* 33, 405 (1971)

[5] Anagnostopoulos, M. G. B. Drew and R. A. Walton, *Chem.Commun.* 1241 (1969).

[6] G. C. Marina, D. Paolo, G. Carlo, M. Amos and N. Mario, *Gazz. Chim. Lt al.* 101, 455, 815 (1971)

[7] Anagnostopoulos, R. W. Matthew and R. A. Walton, *Can.J. Chem.* 50, 1307 (1972)

[8] R. H. Chopakhina and V. V. Serebrennikov, *Zh. Neorg. Khim.*8, 1284 (1963)

[9] J. Moore, M. D. Glick and W. A. Baker, *J. Am. Chem.* 94, 1858 (1972)

[10] J. Kay, J. Moore and M. D. Glick, *Inorg. Chem.* 11, 2818 (1972)

[11] Mcgahan MC. Copper and aspirin treatment increase the antioxidant activity of plasma. *Agents Actions* 1990; 31: 59064

[12] Depeint, F.; Bruce, W.R.; Shangari, N.; Mehta, R.; O'Brien, P.J. Mitochondrial function and toxicity: role of the B vitamin family on mitochondrial energy metabolism. *Chem. Biol. Interact.* 2006, 163, 94-112

[13] Hageman, G.J.; Stierum, R.H. Niacin, poly(ADP-ribose) polymerase-1 and genomic stability. *Mutat. Res.* 2001, 475, 45-56

[14] Carlson, L.A. Nicotinic acid: the broad-spectrum lipid drug. A 50th anniversary review. *J. Intern.Med.* 2005, 258, 94-114

[15] Bo, S.; Durazzo, M.; Gambino, R.; Berutti, C.; Milanesio, N.; Caropreso, A.; Gentile, L.; Cassader, M.; Cavallo-Perin, P.; Pagano, G. Associations of dietary and serum copper with inflammation, oxidative stress, and metabolic variables in adults. *J. Nutr.* 2008, 138, 305-310

[16] Olivares, M.; Uauy, R. Copper as an essential nutrient. *Am. J. Clin. Nutr.* 1996, 63, 791S-796

[17] Koca, E.; Buyukasik, Y.; Cetiner, D.; Yilmaz, R.; Sayinalp, N.; Yasavul, U.; Uner, A. Copper deficiency with increased hematogones mimicking refractory anemia with excess blasts. *Leuk. Res.* 2008, 32, 495-499

[18] Twomey, P.J.; Reynolds, T.M.; Wierzbicki, A.S.; Viljoen, A. The relationship between serum copper and ceruloplasmin in routine clinical practice. *Int. J. Clin. Pract.* 2008, 62, 485-487

[19] Sigman DS, Graham DR, Aurora VD, Stern AM. Oxygendependent cleavage of DNA by the 1,10-phenanthroline cuprous complex. Inhibition of Escherichia coli DNA polymerase I. *J Biol Chem.* 1979; 254: 12269-12272

[20] Spassky A, Sigman DS. Nuclease activity of 1,10-phenanthroline-copper ion. Conformational analysis and footprinting of the lac operon. *Biochemistry* 1985; 24: 8050-8056

[21] Sigman DS. Nuclease activity of 1,10-phenanthrolineecopper ion. *Acc Chem Res.* 1986; 19: 180-186

[22] Sigman DS, Mazumder A, Perrin DM. Chemical nucleases. *Chem Rev.* 1993; 93: 2295-2316

[23] Mahadevan S, Palaniandavar M. Spectroscopic and voltammetric studies on copper complexes of 2,9-dimethyl-1,10-phenanthrolines bound to calf thymus DNA. *Inorg Chem*. 1998, 37: 693-700

[24] Ng, C. H.; Kong, K. C.; Von, S. T.; Balraj, P.; Jensen, P.; Thirthagiri, E.; Hamada, H.; Chikira, M. *Dalton Trans.* 2008, 447-454

[25] Barve, A.; Kumbhar, A.; Bhat, M.; Joshi, B.; Butcher, R.; Sonawane, U.; Joshi, R. *Inorg. Chem.* 2009, 48, 9120-9132

[26] Zhang, S.; Zhu, Y.; Tu, C.; Wei, H.; Yang, Z.; Lin, L.; Ding, J.; Zhang, J.; Guo, Z. *J. Inorg. Biochem.* 2004, 98, 2099

[27]) (a) Rajendiran, V.; Karthik, R.; Palaniandavar, M.; Evans, H. S.; Periasamay, V. S.; Akbarsha, M. A.; Srinag, B. S.; Krishnamurthy, H. Inorg. Chem. 2007, 46, 8208. (b) Rajendiran, V.; Palaniandavar, M.; Swaminathan, P.; Uma, L. *Inorg. Chem.* (Commun) 2007, 46, 8208

[28] Ramakrishnan, S.; Rajendiran, V.; Palaniandavar, M.; Periasamay, V. S.; Akbarsha, M. A.; Srinag, B. S.; Krishnamurthy, H. *Inorg. Chem.* 2009, 48, 1309

[29] P. Starynowicz, Acta Crystallogr. C 47 (1991) 294

[30] J.-F. Ma, Z.-S. Jin, J.-Z. Ni, *Polyhedron* 14 (1995) 563

[31] J.-F. Ma, Z.-S. Jin, J.-Z. Ni, *Polyhedron* 15 (1996) 1797

[32] K. Binnemans, *Chem. Rev.* 2009, 109, 4283-4374

[33] Y. Gao, G. F. Xu, L. Zhao, J. Tang, Z. Liu, Inorg. Chem. 2009, 48, 11495–11497.

[34] H. Ke, P. Gamez, L. Zhao, G. F. Xu, S. Xue, J. Tang, *Inorg. Chem.* 2010, 49, 7549-7557

[35] G. Mezei, C. M. Zaleski, V. L. Pecoraro, Chem. Rev. 2007, 107, 4933-5003

[36] B. Biswas, P. Raghavaiah, N. Aliaga-Alcalde, J. D. Chen, R. Ghosh, *Polyhedron* 2010, 29, 2716-2721

[37] Q. Yang, J. P. Zhao, B. W. Hu, X. F. Zhang, X. H. Bu, *Inorg. Chem.* 2010, 49, 3746-3751

[38] M. E. Chapman, P. Ayyappan, B. M. Foxman, G. T. Yee, W. Lin. *Cryst. Growth Des.* 2001, 1, 159-163

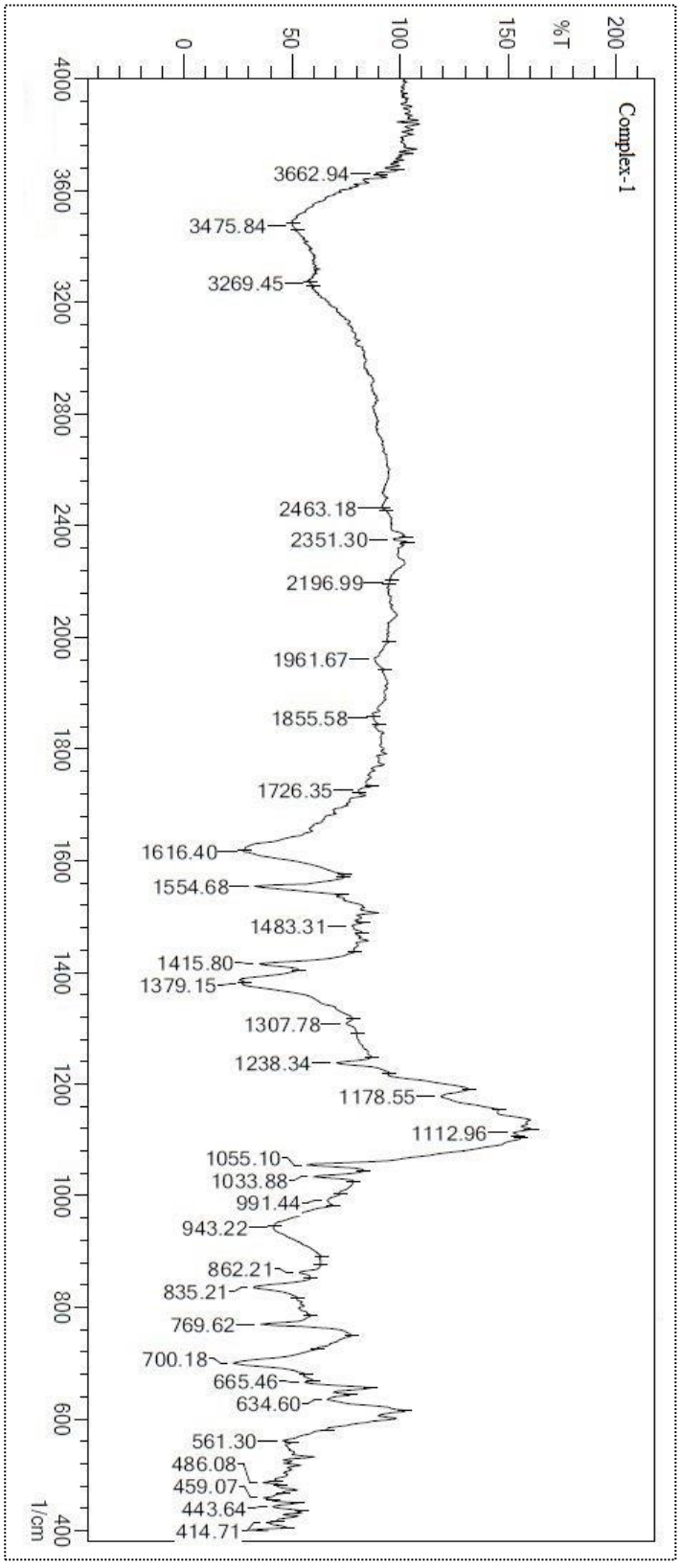

Figure 1. IR Spectra of Complex-1

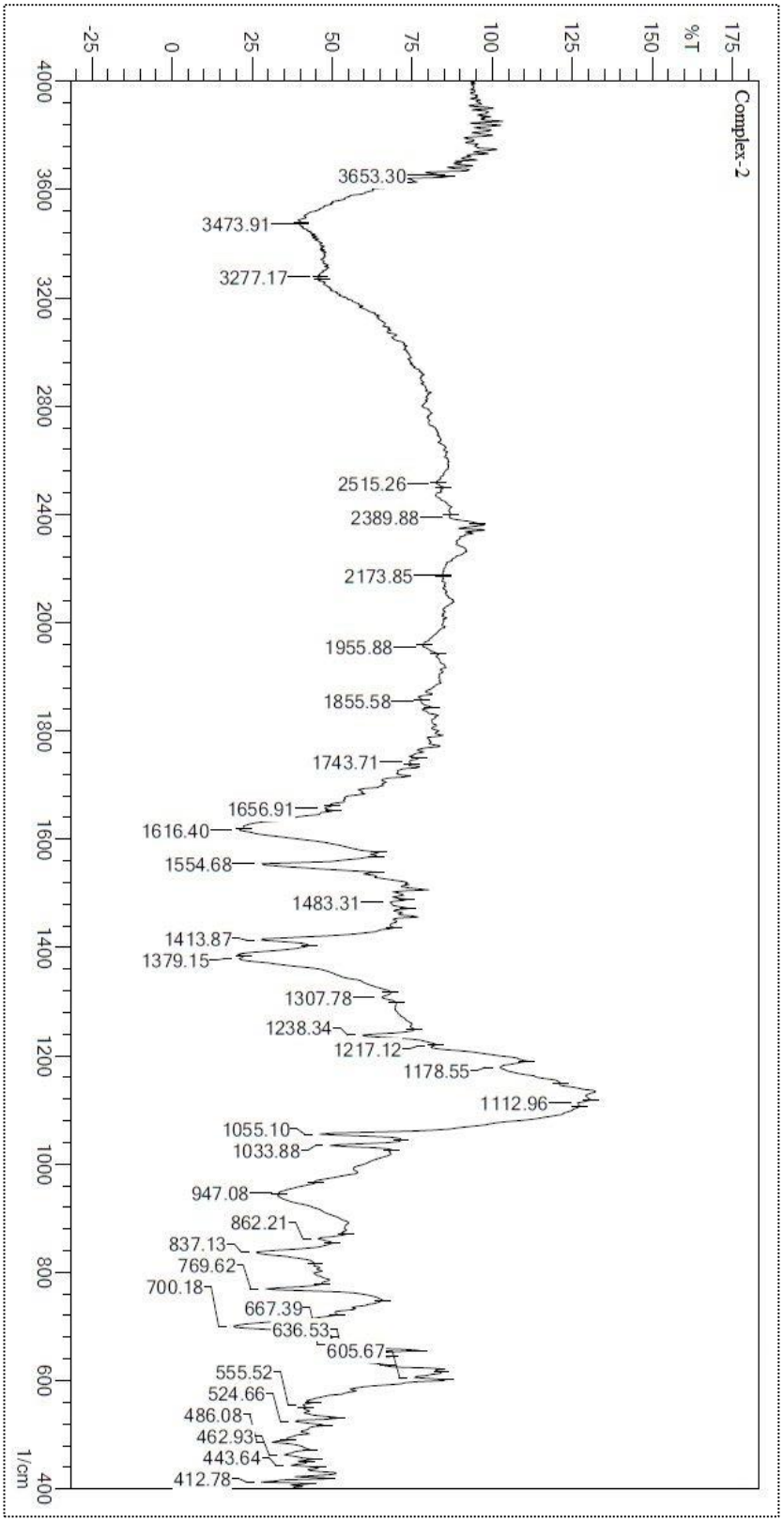

Figure 2. IR Spectra of Complex-2

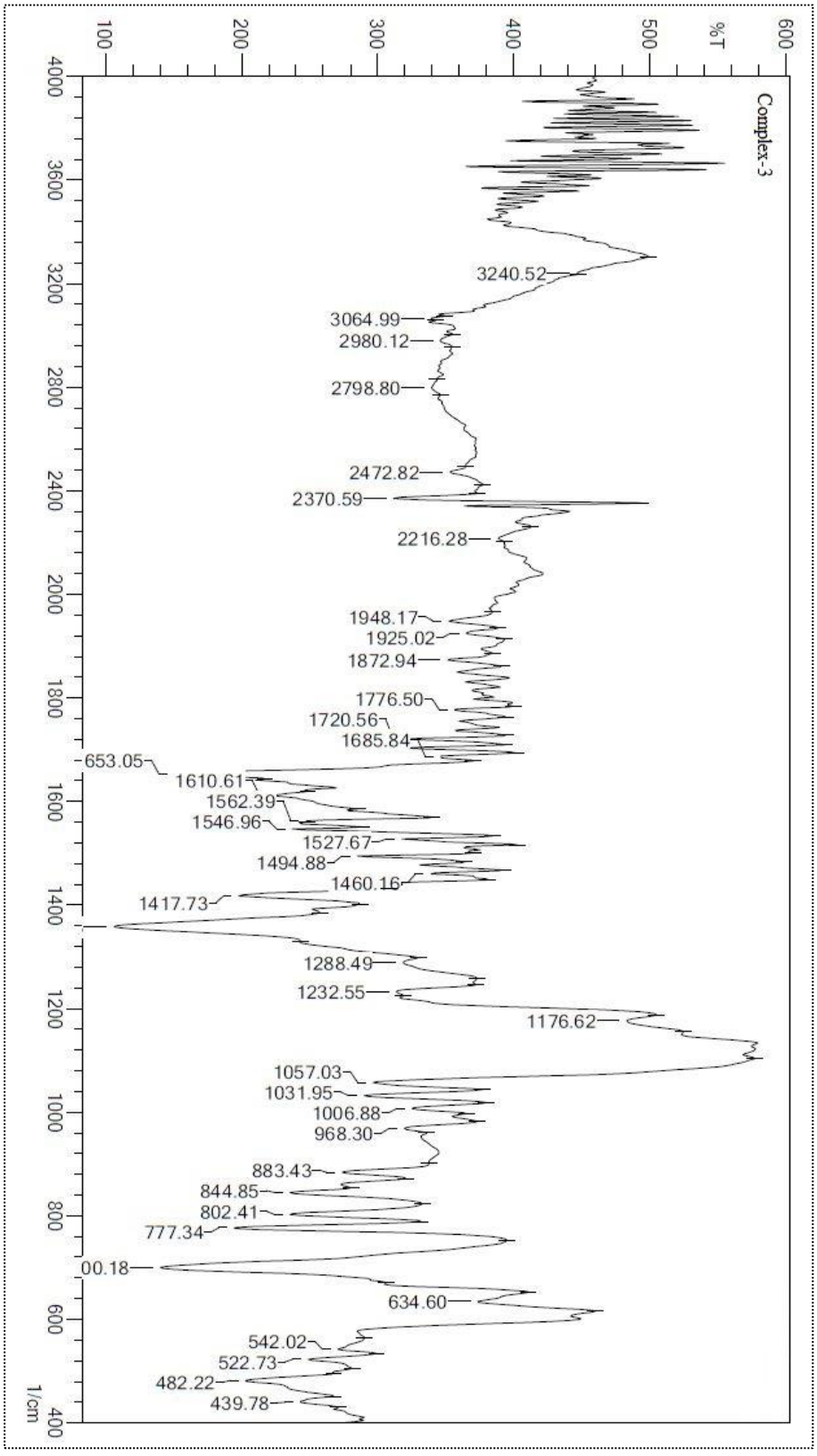

Figure 3. IR Spectra of Complex-3

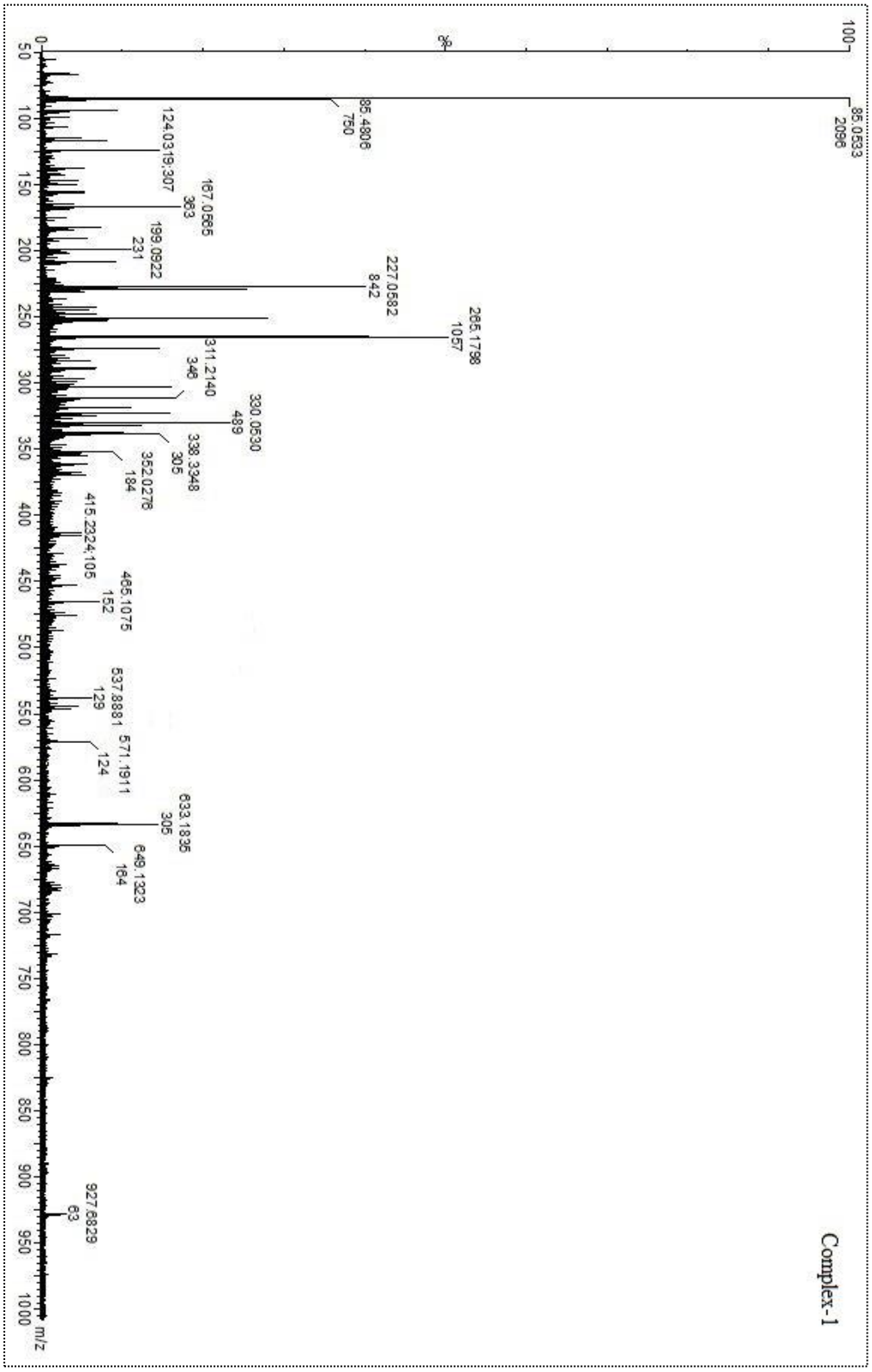

Figure 4. MASS Spectra of Complex-1

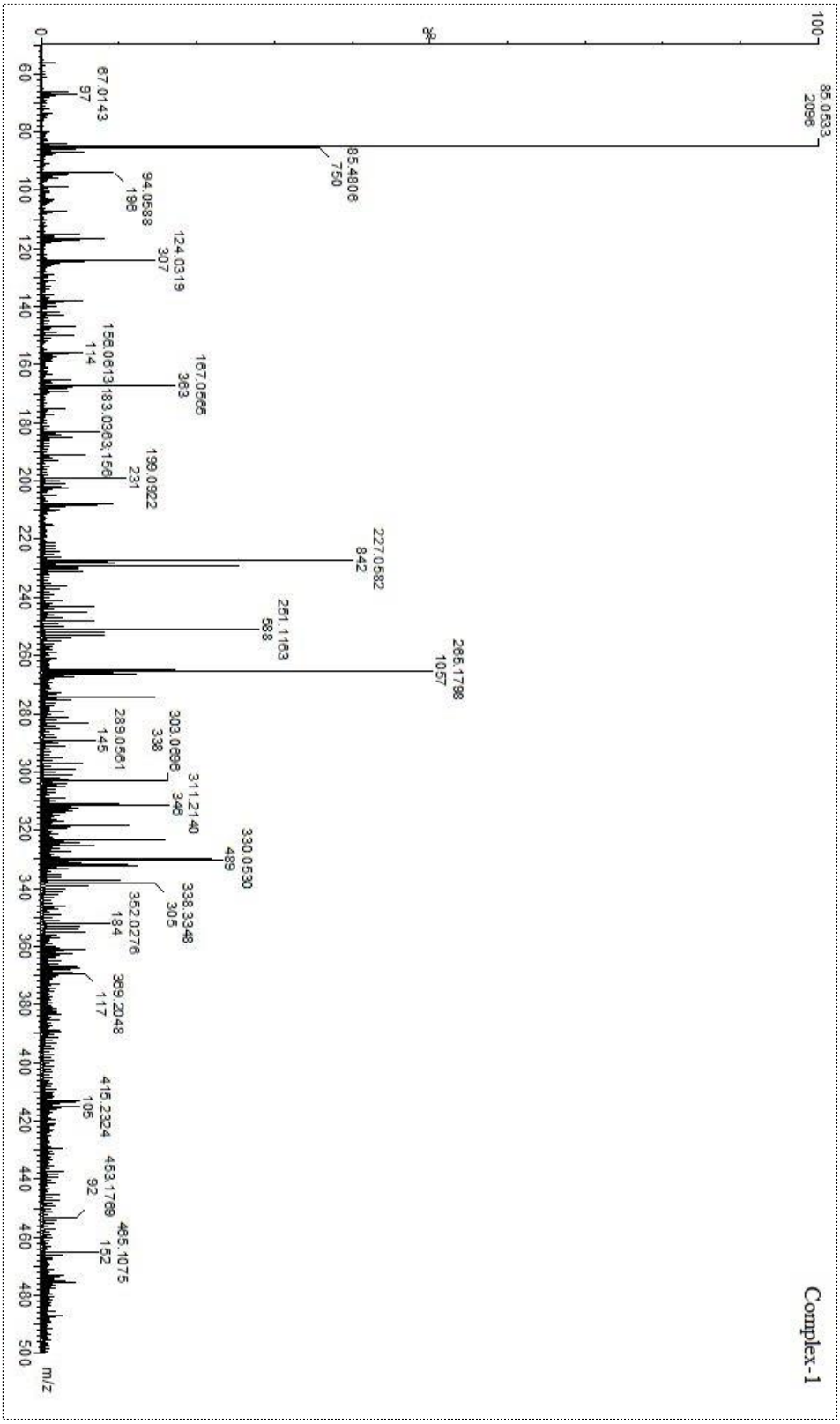

Figure 5. MASS Spectra of Complex-1(a)

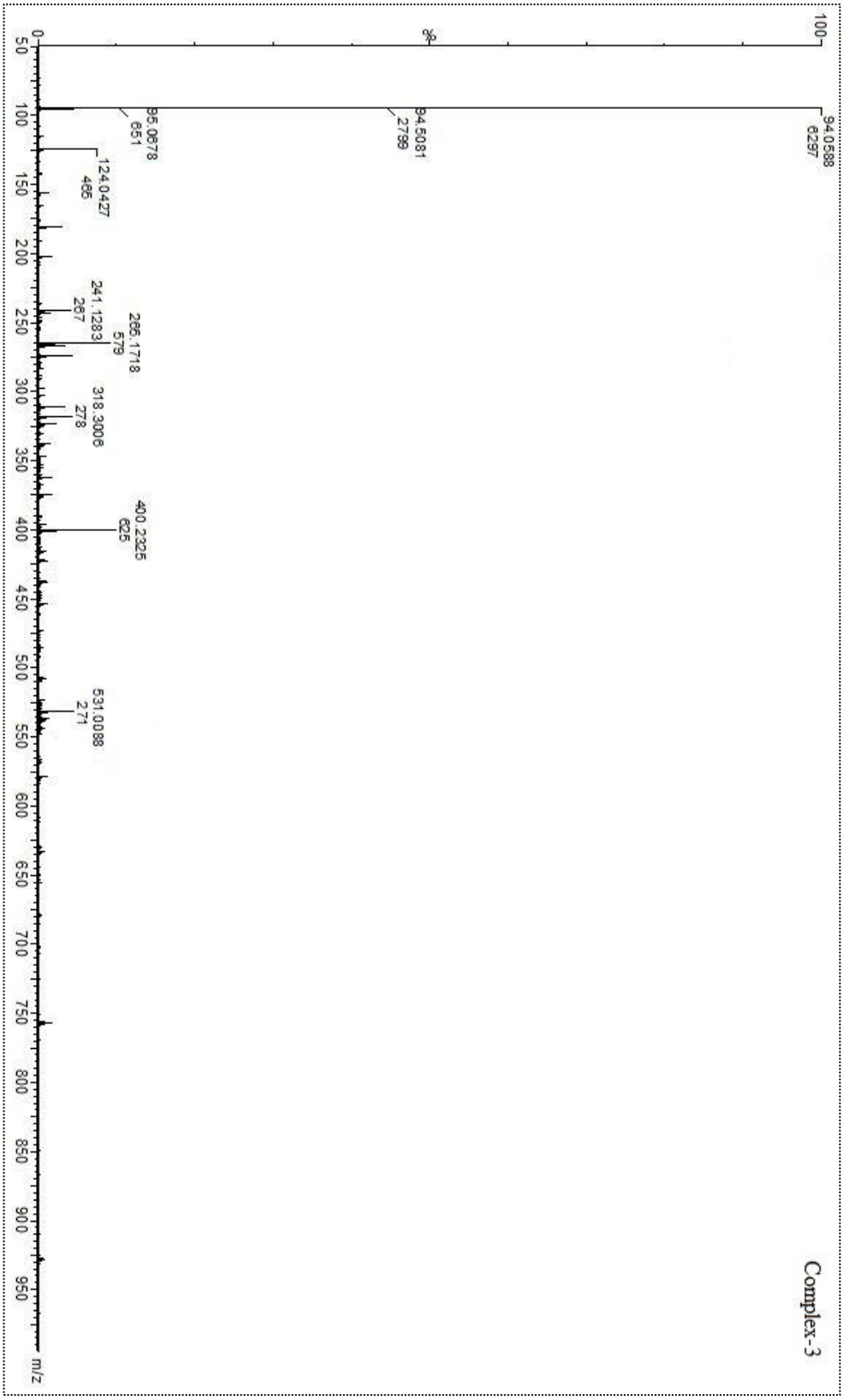

Figure 6. MASS Spectra of Complex-3

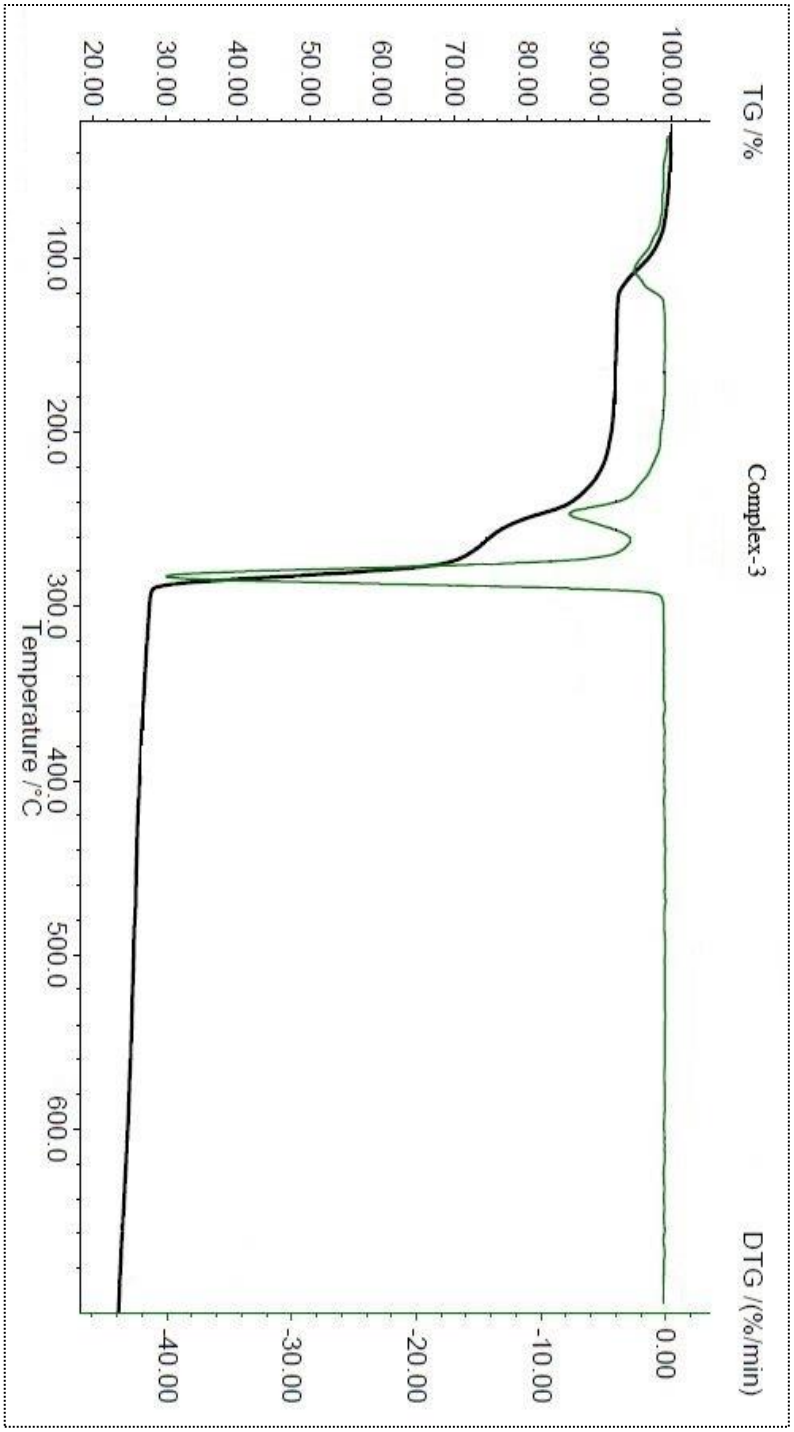

Figure 7. TGA Graph of Complex-3