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Research article

CefotaximeDithiocarbamate as Metalloantibiotic with binuclear Ni^{II}, Pd^{II}, Pt^{IV} Complexes Synthesis, Characterisation, Kinetic and Biological Activity Studies

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Abstract

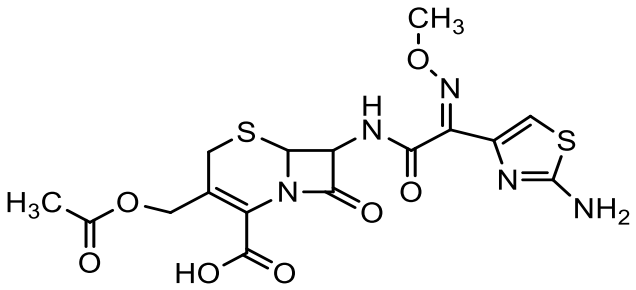
The synthesis of cefotaxime complexes was carried out through multi steps, the first one included the reaction of tolidine as spacer with chloroacetyle chloride to obtain the bridge compound, the second step contain the cefotaxime reaction with the resulted compound, while the third step established by the addition reaction of carbondisulfide to step two compound fo form the dithiocarbamate, the complexes formation with divalent Ni, Pd and tetravalent Pt ions. The prepared compounds was characterized by FT-IR, UV-Vis and NMR spectroscopies, the physical properties (Solubility and Melting point), the kinetic study carried out by HPLC technique and biological activity examined, the spectral studies suggested the geometry around the metal ions are square planer.

Keywords: Cefotaxime, metalloantibiotic, dtc, Ni, Pd, Pt complexes

Introduction

Cefotaxime may be a third-generation cephalosporin anti-microbia .Like other third-generation cephalosporins, cefotaxime need. An expansive range about movement against Gram-positive Furthermore. Gram-negative microscopic organisms[1]. Those soundness of the β-lactamases. Expands

the movement from claiming cefotaxime against Overall. Safe Gram-negative organic entities[2,3]. Cefotaxime may be utilized. To treat infections of the respiratory tract, skin, bones, joints[4]. Urogenital system, meningitis and septicemia. Cefotaxime may be. Dynamic against penicillin-safe strains from claiming streptococcus. Pneumoniae What's more need humble action against those anaerobic. Microscopic organisms bacteroides fragilis. Cefotaxime, like different b-lactam. Antibiotics[5-8], pieces those division about microscopic organisms (counting. Cyanobacteria), the division about cyanelles (the photosynthetic. Organelles of the glaucophytes) and the division of chloroplasts. To bryophytes[9]. The metal complexes with dithiocarbamate as macrocyclic complexes can be use the DTC as receptor to accommodate species in their gaps, considerably of the type of spacers[10]. Dithiocarbamate complexes with a variety of cavities can be achieved; these DTC macrocyclic complexes receptors have the ability to bind various cationic, anionic, ion-pair recognition and neutral bidentate guest's species[11-15].



CEFOTAXIME

Experimental Section

Reagents were purchased from Fluka and BDH Chemical Company. IR spectra were recorded as KBr discs using a Shimadzu 8300 FTIR spectrophotometer in range (4000-400) cm-1. Electronic spectra of the prepared compounds were measured in the region (200-800) nm for 10-3 M solution in DMSO at 25 °C using Shimadzu 160 spectrophotometer, with 1.000 ± 0.001 cm matched quartz cell. The NMR spectroscopy recorded in [JEOL- JNM-ES-400] using DMSO-d^6 solvent. HPLC examined using Scimadzu LC-2010AHT –Japan, λ=254 nm, mobile phase 20% acetonitrile and 80% methanol, with flow rate 1mL/min.

The preparation of precursor 1

In the round bottomed flask 100mL in size, putted 1gm of tolidine dissolved in 20mL dichloromethane (DCM) as a solvent, the choroacytylchoride 0.94 mL was added dropwise. The mixture let to stirring for half an hour. Then refluxed for two hours, gradually to become brown color. The solvent released under vacuum with rotary evaporator the brownish red precipitate obtained with 1.17gm (yield 68%) . mp= 314 ^{0}C.

The preparation of cefotaxime derivative with precursor 1

0.5 gm of precursor no. 1 (tolidine with chloroacytylchloride) was putted in 100mL in round flask then dissolved in 20mL dichloromethane (DCM) with stirring for half an hour without heated , 1.246gm of

cefotaxime was added with continuous stirring for one hour on heating source at 400C , the color of solution was changed to became pale yellow color . yield (87.5%) 0.983 gm, m.p = 294^{0}C.

The synthesis of L^1

In the round bottomed flask 100 mL in size, putted 0.25gm of(tolidine with choroayctylchoride with cefotaxime dissolved in 25mL in dichloromethane (1M) then adding 0.044 g from KOH dissolved in 5mL methanol with ice water bath for Reaction and let the solution for stirring, then adding the CS_2 0.2 mL , let the solution for stirring for two hours. The color of the solution was changed gradually to become very pale yellow, the solvent released under vacuum with rotary evaporator weight is 0.204 yield (74.72%) m.p= 310 ^{0}C .

The synthesis of complexes

Pt^{IV} complex with L^1

The Pt^{+4} complex was carried out via the dissolving (0.25 g, 0.00018 mol.) from the ligand in 25mL of absolute methanol with stirring in round bottomed flask tell completely dissolve. In the other dropper funnel dissolved (0.12 g, 0.00036 mol.) from $PtCl_4$ in 10 mL methanol. Was added as dropwise with stirring let the mixture stirred and refluxed for two hours. The colour of solution was changed to yellow and the precipitate was obtained, filtered the solution, washed and recrystallized with n-hexane and toluene to form a deep yellow precipitate 0.12 g, yield 55 % mp (215 ^{0}C).

Pd^{II} complex with L^1

The solution of 0.097g , 0.00028moL of $PdCl_2$ in 10 ml of HCl and 10 ml of D.W was dissolved in dropper funnel, then added to the ligand solution as dropwise after that the mixture stirred and refluxed for two hours, through this process the colour of solution was changed to the dark yello colour and the precipitate was formed , then recrystallized with n-hexane and toluene, gave yield 71% (0.69g) m.p= 570 ^{0}C.

Ni^{II} complex with L^1

The divalent nickel (II) chloride complex prepared by putted (0.085g , 0.00036 moL.) from L1 dissolved in the 25mL of absolute methanol with stirring in two neck round bottomed flask . the solution of (0.085g, 0.00036 mol) of $NiCl_2$ in 10 ml HCl and 10 ml D.W was dropper funnel, then added to the ligand solutions dropwise, after that the mixture stirred and refluxed for two hours, through this process the colour was changed to pale brown colour and precipitate was formed, the result coumpound filtered and dryed, then recrystallized with n-hexane, gave yield 70%(0.89 g), m,p= 820 ^{0} C.

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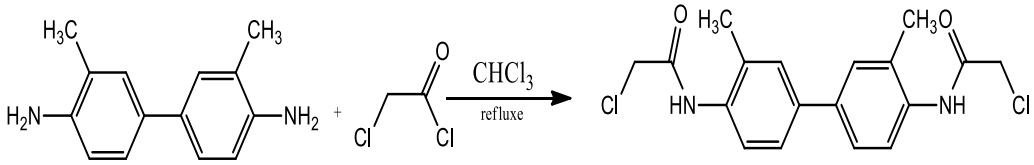
Results and discussion

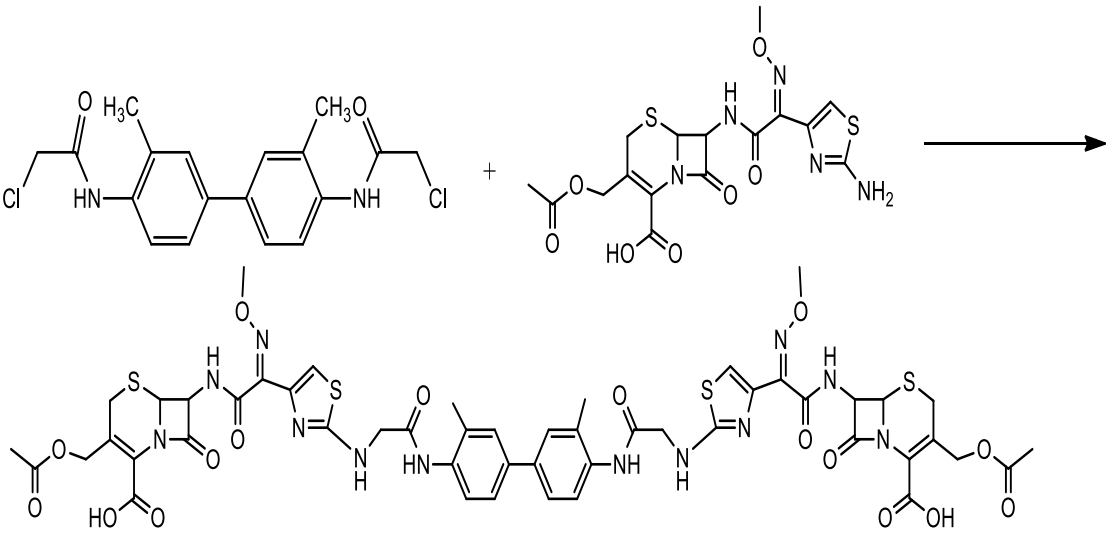
Synthesis of ligand L^1

The reaction carried out through the addition of chloroacetylchloride to the tolidine in presence chloroform as solvent and refluxed the precursor was formed and collected as fine powder the synthesis route was summarized in Scheme 1



Scheme 1 synthesis rout of compound 1

The cefotaxime was added to the prepared compound to obtain the cefotaxime derivative the reaction step shows in Scheme 2



7,7'-(((2Z,2'Z)-2,2'-(2,2'-((((3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl))bis(azanediyl))bis(thiazole-4,2-diyl))bis(2-(methoxyimino)acetyl))bis(azanediyl))bis(3-(acetoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid)

Scheme 2 preparation of cefotaxime derivative

The synthesis of the ligand L1 take places via the reaction between the cefotaxime derivative and carbon disulfide in presence potassium hydroxide the synthesis summarized in Scheme 3.

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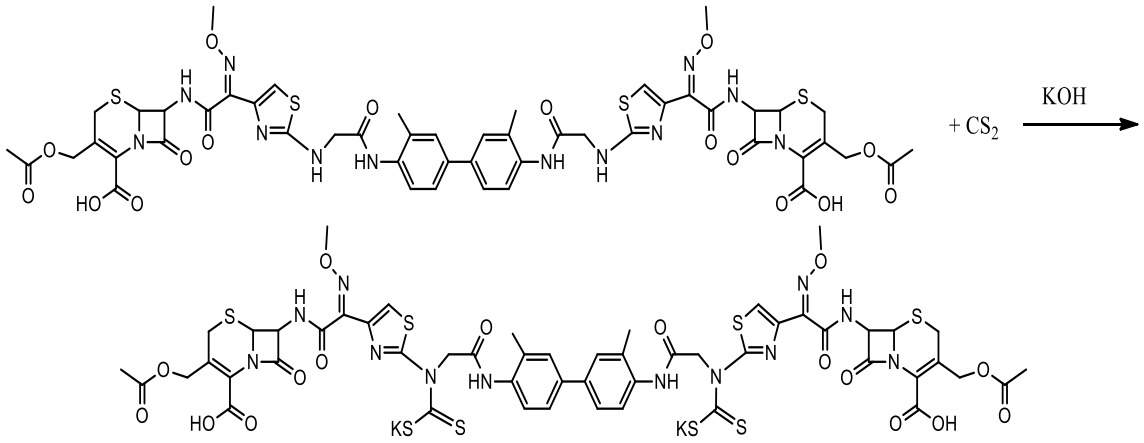
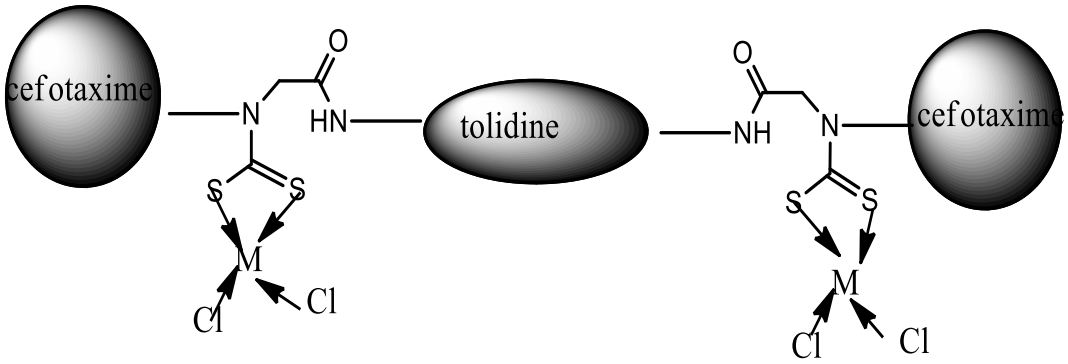


potassium (((3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl))bis((4-((*Z*)-2-((3-(acetoxymethyl)-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-7-yl)amino)-1-(methoxyimino)-2-oxoethyl)thiazol-2-yl)carbamodithioate)

Scheme 3 synthesis rout of ligand L^1

The metal complexes of Pt^{+4} , Pd^{+2}, Ni^{+2} ions was obtained through the reaction of ligand with metal salts in methanol Scheme 4. Illustrate the formation of complexes



M= Pt, Pd, Ni

Scheme 4 synthesis rout of complexes

^{1}HNMR spectra

^{1}HNMRspectra for compound 1

The HNMR spectrum of compound(1) in DMSO-d^6, Fig.1 shows the signal at (δ= 10.8) assigned to the OH proton, the signals at(δ=9.8)(9.6ppm) can be attributed to the NH-C=O and NH protons, the benzene ring protons appears at the range between(δ= 6.8-7.9ppm) the signal at (δ= 5.75, 5.60 ,4.65, 4.40 ppm) attributed to the protons if the β-lactam ring, the protons of carbon neighboring to the oxygen atom appears at (δ= 4.10 ppm), the chemical shift at (δ= 3.85) attributed to the methyl group attached to the O=N while the methyl group attached to the esteric group appears at (δ= 2.00 ppm).

^{13}CNMR spectrum for compound 1

The CNMR spectrum of compound 1 In DMSO-d^6, Fig. 2 shows the signal at (δ= 171 ppm) attributed to C=S, and the signal at (δ= 169 ppm) due to amidic C=O, (δ= 166 ppm) attributed to the C=O of β-lactam ring while the signals (δ= 167.6, 163.0, 162.0 ppm) assigned to carboxylic and esteric carbon atoms respectively, the signals at (δ= 149.0, 143.6,143.1,136.0,128 ppm) attributed to the C-C for the aromatic benzene rings and the signals at (δ= 120, 112, 109 ppm) due to the carbon atoms of thiazole rings, the chemical shift($\delta = 64.9,62.3,58.6,57.8,25,21\,ppm$ δ= 64.9, 62.3, 58.6, 57.8, 25.21) for the methylen and methyl groups carbon atoms respectively.

IR spectra

The FT-IR spectrum of compound 1 fig. 3 displays the absence of hand wlich that appeared at (3450, 3330cm^{-1}) due to the $\nu(NH_2)$ in the tolidine and new band shows at (3265cm^{-1}) assigned to the $\nu(NH)$ stretching. The carbonyl group of chloroacetyl chloride shows the shifting and appeared at(1650cm^{-1}) indicating the bounding between the carbonyl group and amine group spacer.

The IR spectrm of cefotaxime derivative Fig. 4 displays the characteristicband at(3215, 3115cm^{-1}) attributed to $\nu(C-H)$ stretching this group showed as two bands refers the groups lies in two differentenvironments and different neighboring groups, the band at(3034cm^{-1}) assigned to the $\nu(C-H)$ stretching of aromaticbenzene ring, the band at(1680cm^{-1})(1587cm^{-1}) assigned to the amide carbonyl groups indicating the different position of these groups. FT-IR spectrum of ligand L^{1}Fig. 5 displays the absence of $\nu(NH)$ in the cefotaxime derivativein addition the shifting of other band was observed, the new band at(1406, 1330cm^{-1}) attributed to the $\nu(C=S)$ and $\nu(C-S)$ stretching respectively.The complexes spectra of Pt^{+4}, Pd^{+2} and Ni^{+2} Figs. (6-8) shows the shifting in the C=S and C-S band as well as the new bands appears to the coordination between the metal ions and sulfur atoms.

UV-Vis spectra

The UV-Vis spectra for L^1 and their complexes. Figs. (9-12) exhibts the absorbed broad peak at (274 nm)(36496cm^{-1}) (εmax= 1495Lcm^{-1}mol^{-1}) assigned to the π→π*and n→π* transitions the n→π* not appear clearly due to the broadness of peak of π→π* , the with pt^{+4}, Pd^{+2}, Ni^{+2} displays the peaks at(283nm)(35335cm^{-1})(εmax=1215 Lcm^{-1} mol^{-1}) and(284nm)(35211cm^{-1})(εma=2692 Lmol^{-1} cm^{-1})

For pt^{+4}, pd^{+2}, Ni^{+2} respectively assigned to charge transfer and ligand field.

While the d-d transitions appeared in the visible region as weak peaks because these transition are not allowed according to the selection roles of multiplicity and laporte laws but appears due to the

hybridization and the mixing between the d and s or p orbital's.The pt complex show the peak at(456nm)(21978cm^{-1}) (εmax= 20 Lmol^{-1}cm^{-1}) pd complex shows the peak at(480cm)(20833cm^{-1})(εmax= 44Lmol^{-1} cm^{-1}) assigned to the d-d transition type $^1A_1g \rightarrow {}^1B_2g$ corresponding with the squareplanar geometry of these type complexes.

Kinetic studies

The stability of prepared compounds was examined compared with the standard compound cefotaxime Fig. 13 since shows three peaks at ret. time (2.4, 2.8, 3.5 min), the ligand L^1 Fig.14 appears at ret. time (3.0, 3.3, 4.3 min), while the Pt, Pd, Ni complexes ion Fig. 15-17 displays four peaks at ret. time (2.2,3.1,4.0,4.9), (2.2,3.1,4.0,5.1), (2.4,3.1,4.0,5.1) respectively. Refer to the stability of the ligand and their complexes at room temperature.

Biological studies

In medicinal chemistry, dithiocarbamate derivatives and complexes have been very well known for their therapeutic applications. Many dithiocarbamate derivatives have been developed as chemotherapeutic agents and are widely used. Dithiocarbamate nucleus is one of the most important thiol compounds exhibiting remarkable pharmacological activities. The biological activity of prepared compounds were tested using *E-Coli, pseudomonas, bacillus and staphylococcus aureus bacteria* , the results show the ligand displays inhibition activity more than the control, while the complexes appears inhibition with Pt^{+4} complex for the four bacteria types, since the Pd ion complex displayed inhibition except the *E-Coli*, the nickel ion complex didn't appear any inhibition activity with the bacteria used in test. Table 1 showed the details of biological activity.

Table 1: The biological activity of prepared compounds

compound	E-coli	pseudomonas	bacillus	staphylococcus aurous
control	24	20	12	29
ligand	30	23	13	31
Pt complex	33	34	21	34
Pd complex	-	28	14	34
Ni complex	-	-	10	18

References

[1] El-Shaboury, S.R., Saleh, G.A., Mohamed, F.A., Rageh, A.H., J. Pharm. Biomed. Anal.45(1), (2007)

[2] Sweetman, S.: Martindale, The Extra Pharmacopoeia, 33rd edn. Royal Pharmaceutical Society, London (2002)

[3] Dollery, C.: Therapeutic Drugs, vol. I, 2nd edn,.Churchill Livingstone, Edinburgh (1999)

[4] Britta, K., Ralf, R., J. Plant Physiol. 150, (1997)

[5] Williams JD. Classification of cephalosporins. Drugs ; 34 (1987):

[6] Fried JS, Hinthorn DR. The cephalosporins. Dis Mon 1985; 31.

[7] J. R. Anacona and C. Patiˇno, Journal of Coordination Chemistry, vol. 62, no. 4, 2009

[8] S. Joshi, V. Pawar, and V. Uma, Research Journal of Pharmaceutical, Biological and Chemical Sciences, vol. 2, no. 1, 2011.

[9] K. Singh, Y. Kumar, P. Puri, and G. Singh, Bioinorganic Chemistry and Applications, vol. 2012, 2012.

[10] M. R. Karekal, V. Biradar, and M. B. H. Mathada, Bioinorganic Chemistry and Applications, vol. 2013 , 2013.

[11] K. M. Khan, M. Khan, M. Ali et al., Journal of Chemical Society of Pakistan, vol. 35, no. 3, 2013.

[12] A.K. Mishra and N.K. Kaushik, Spectrochim. Acta Part A 69 (2008) .

[13] C. Pellerito, L. Nagy, L. Pellerito and A. Szorcsik, J. Organomet. Chem. 691 (2006).

[14] H. van de Bossche, F. Dromer, I. Improvissi, M. Lozane-Chiu, J.H. Hex and D. Sanglard, Med. Mycol. 36 (1998) 119-128.

[15] D.C Menezes, F.T. Viera, G.M. de Lima, A.O. Porto, M.E. Cortes, J.D.

[16] Ardisson and T.E. Albrecht-Schmitt, Eur. J. Med. Chem. 40 (2005).

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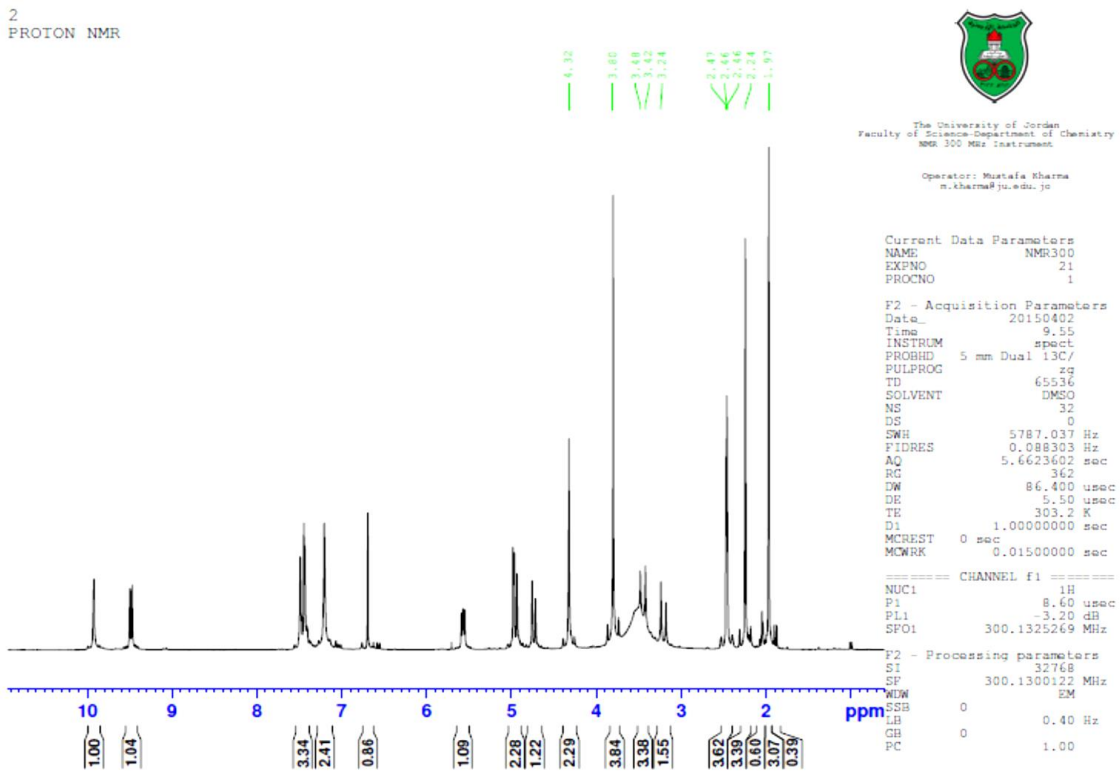

Fig. 1: [1]HNMR spectrum of compound1

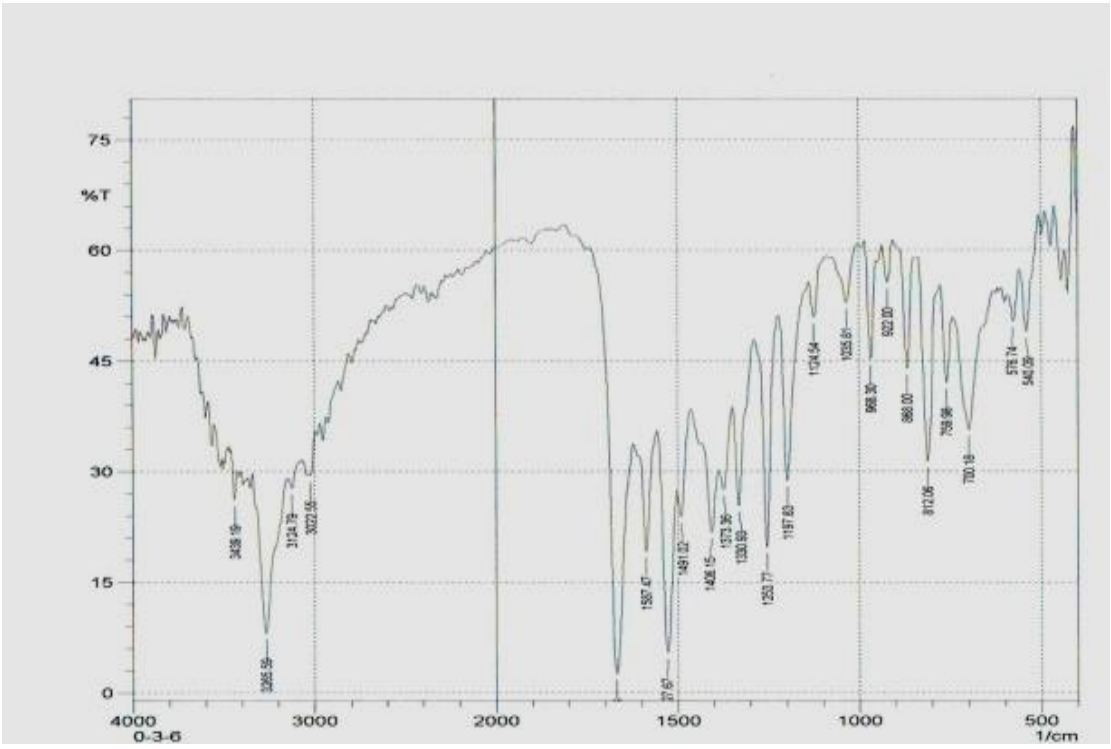

Fig. 2: FTIR spectrum of compound1

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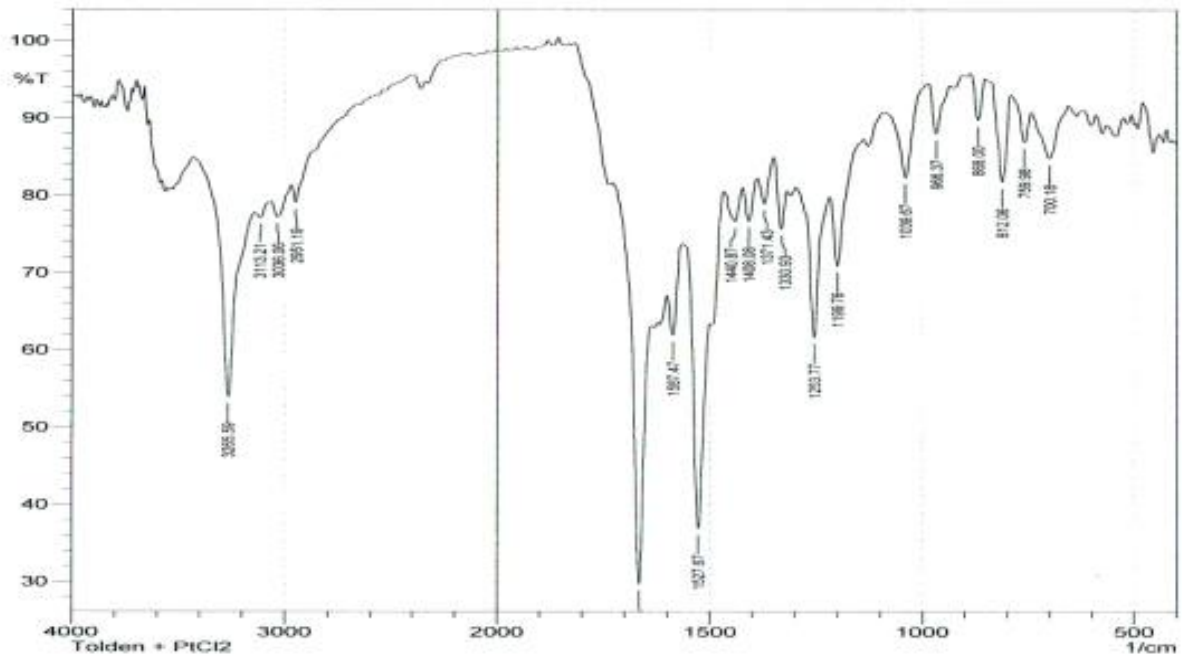

Fig. 3: FTIR spectrum of cefotaxime derivative

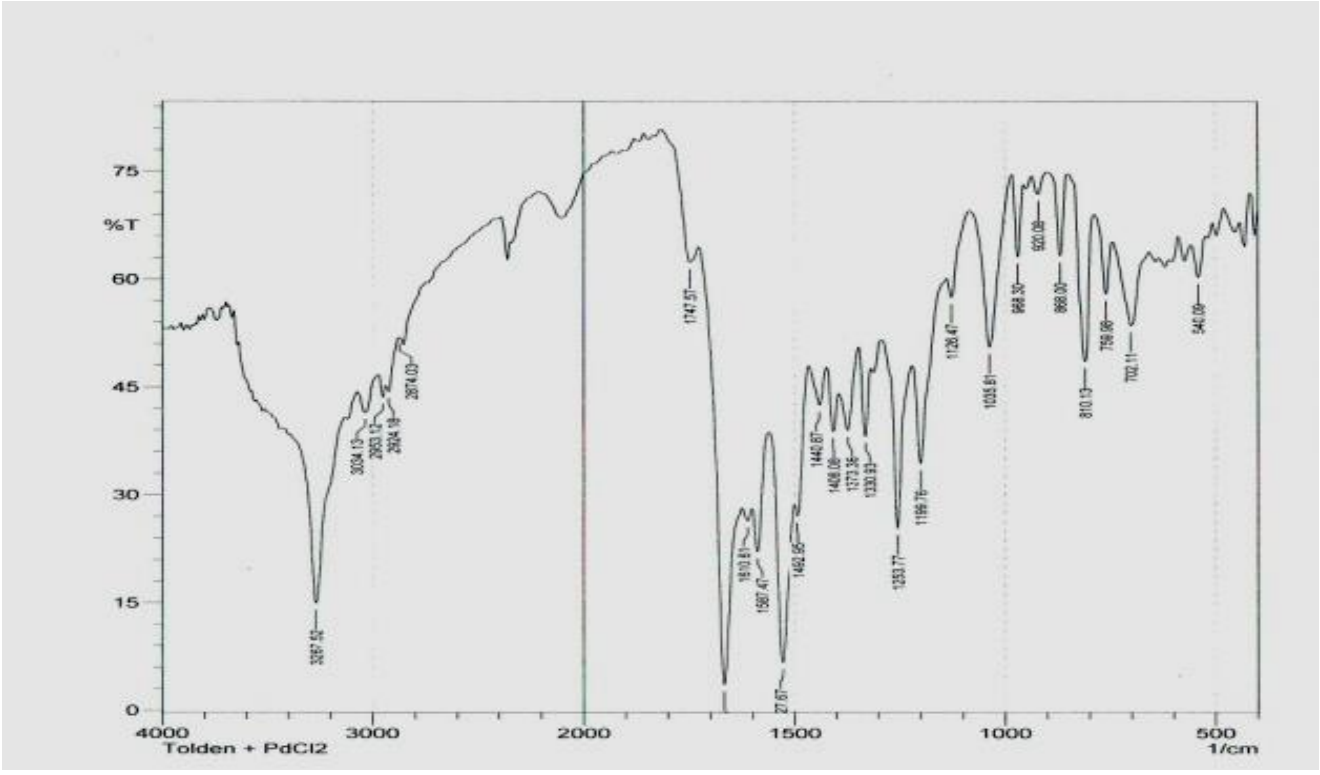

Fig. 4: FTIR spectrum of the ligand

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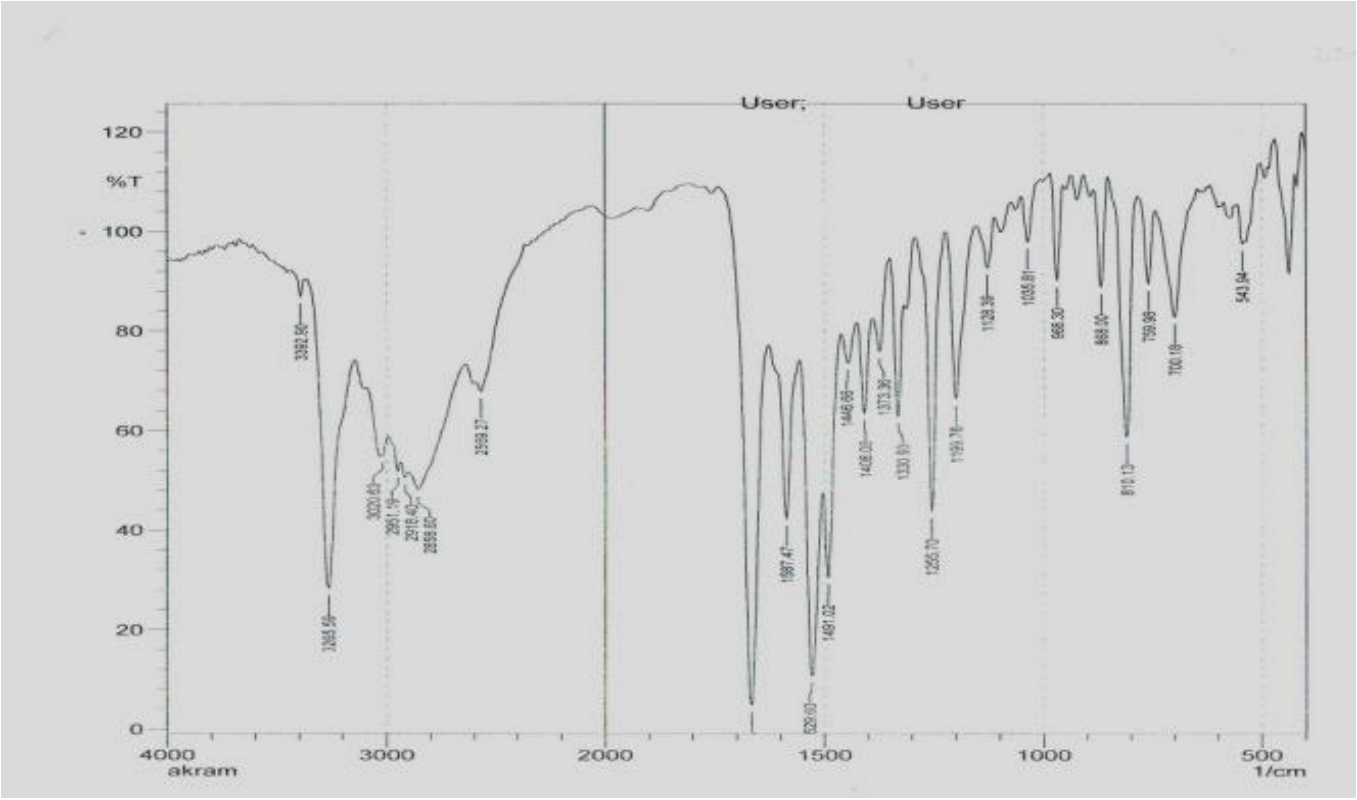

Fig. 5: FTIR spectrum of the Pt^{IV} complex

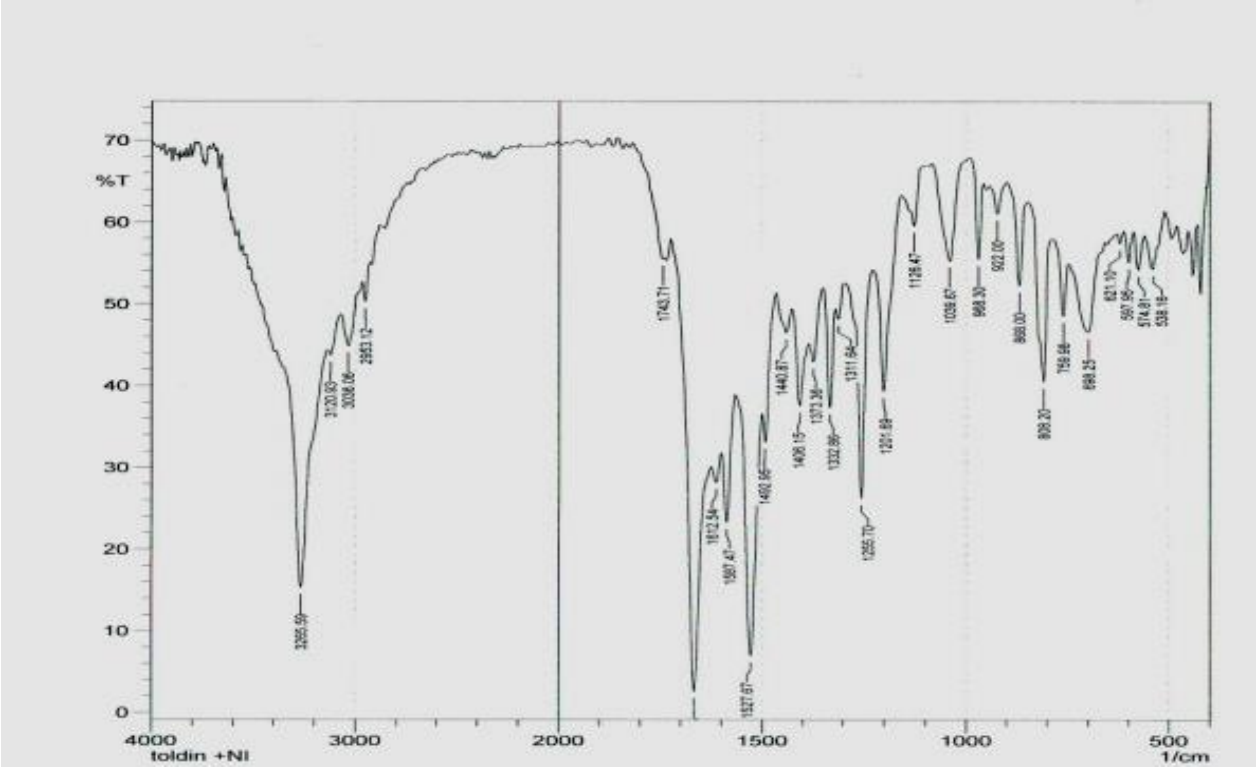

Fig. 6: FTIR spectrum of the Pd^{II} complex

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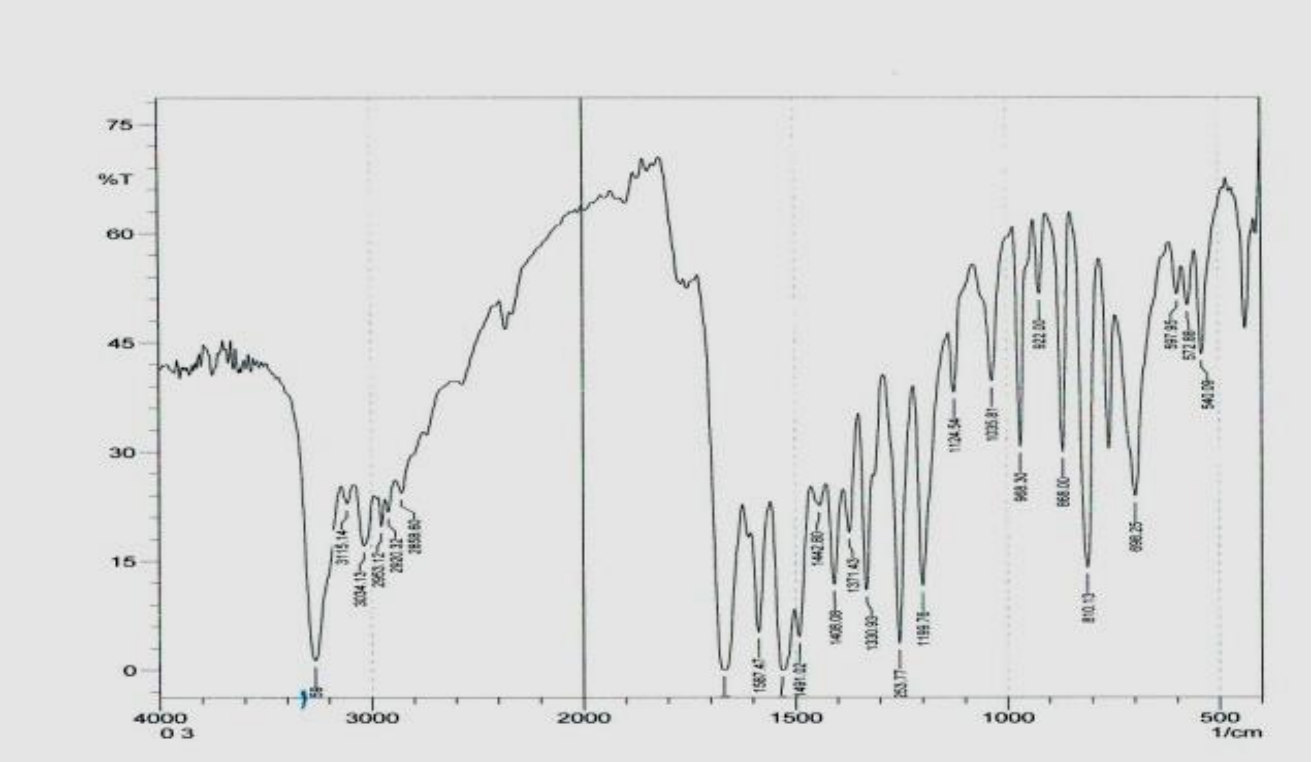

Fig. 7: FTIR spectrum of the Ni^{II} complex

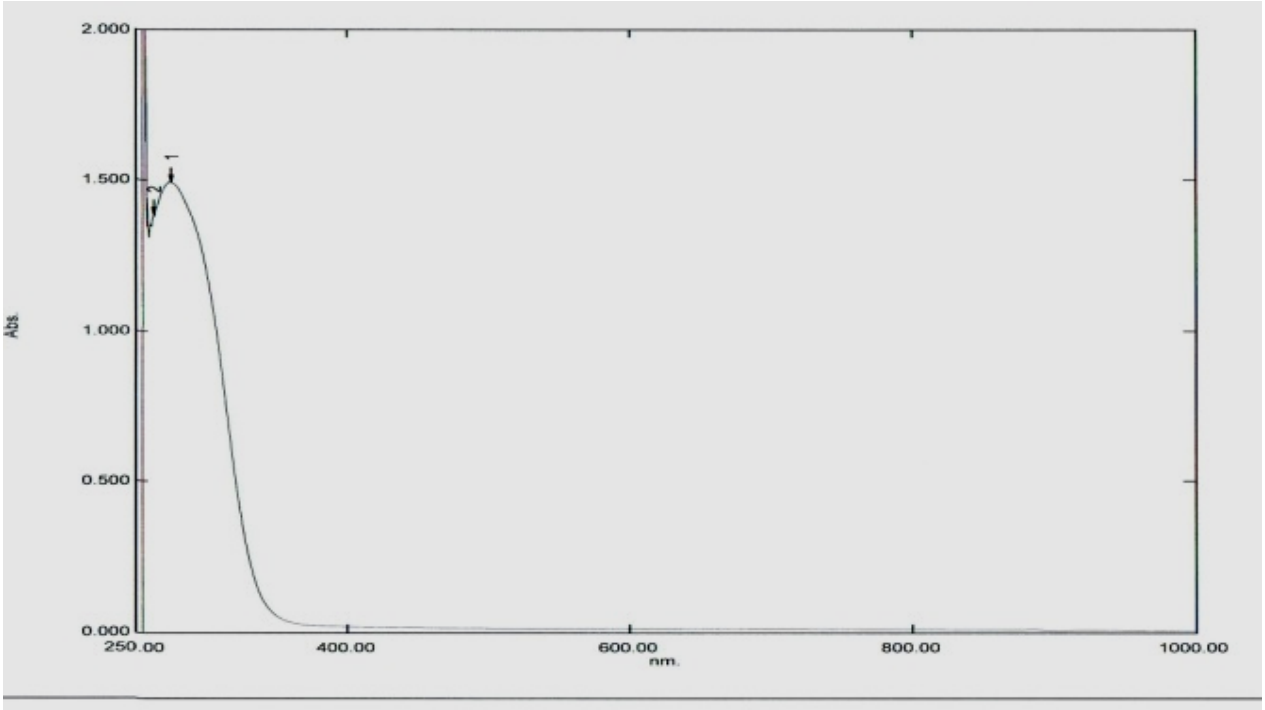

Fig.8: UV-Vis spectrum of the ligand

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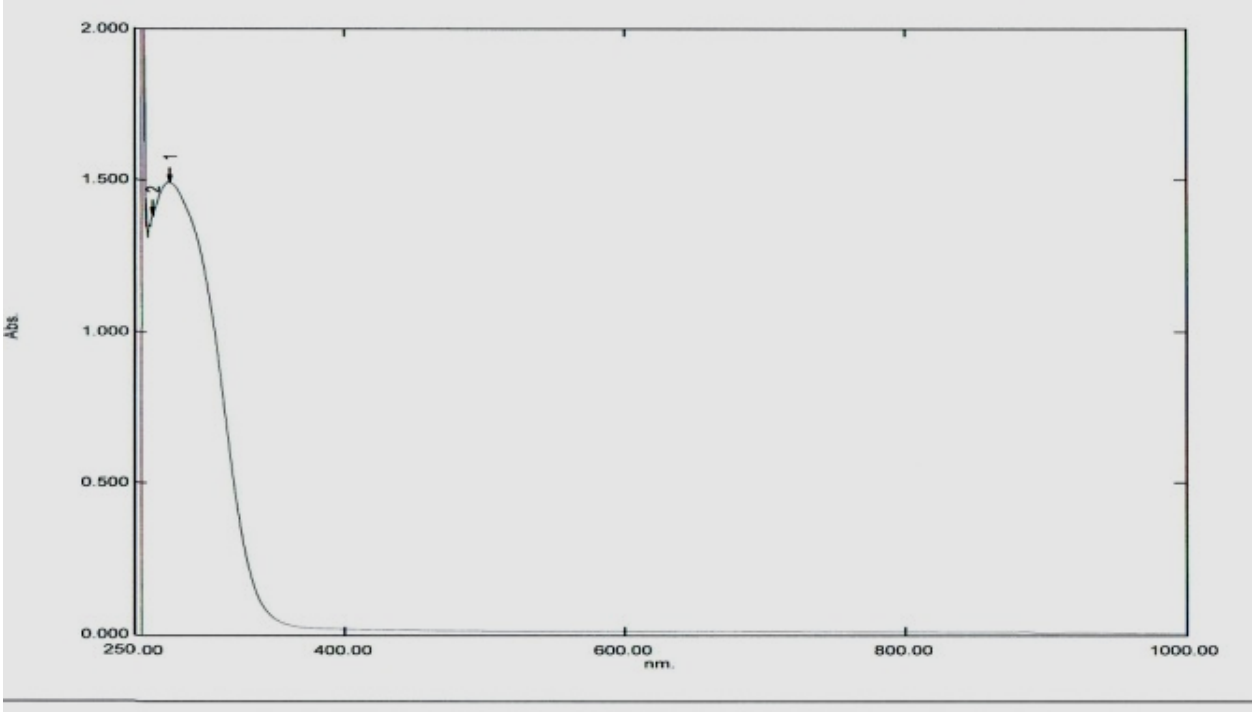

Fig. 9: UV-Vis spectrum of Pt^{IV} complex

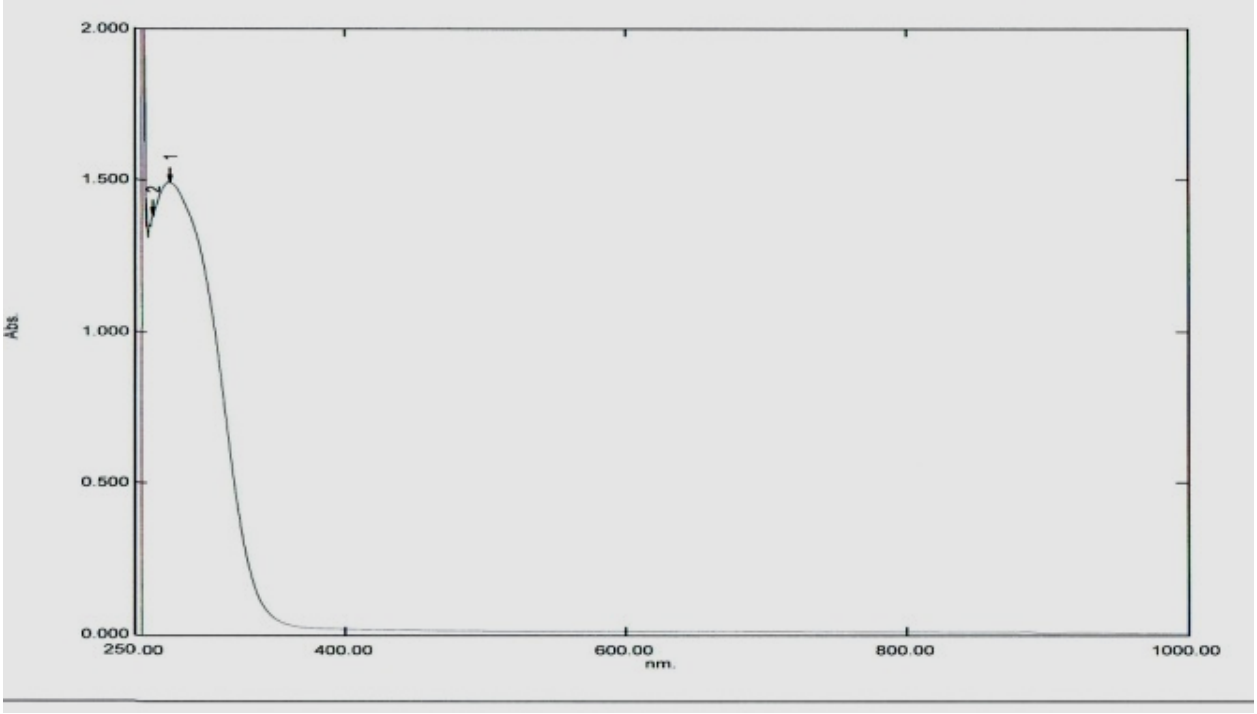

Fig. 10: UV-Vis spectrum of Pd^{II} complex

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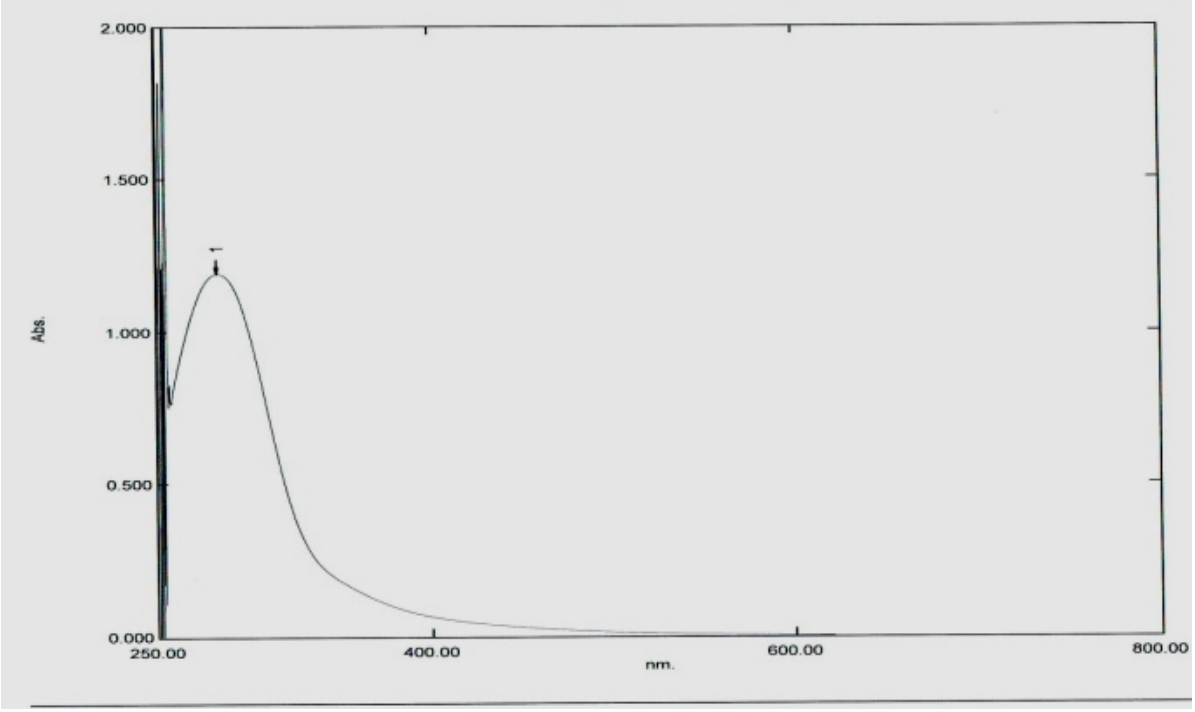
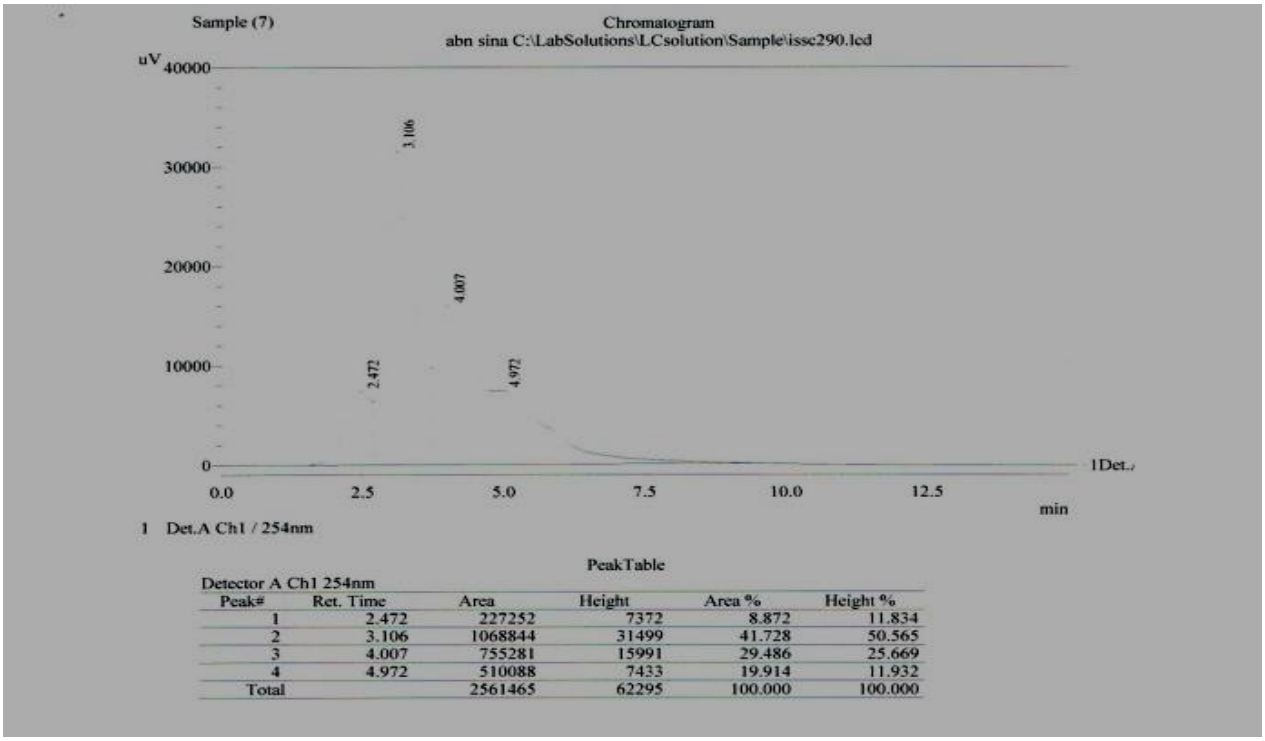


Fig. 11: UV-Vis spectrum of Ni^{II} complex



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	2.472	227252	7372	8.872	11.834
2	3.106	1068844	31499	41.728	50.565
3	4.007	755281	15991	29.486	25.669
4	4.972	510088	7433	19.914	11.932
Total		2561465	62295	100.000	100.000

Fig. 12: HPLC chromatograph of the standard compound

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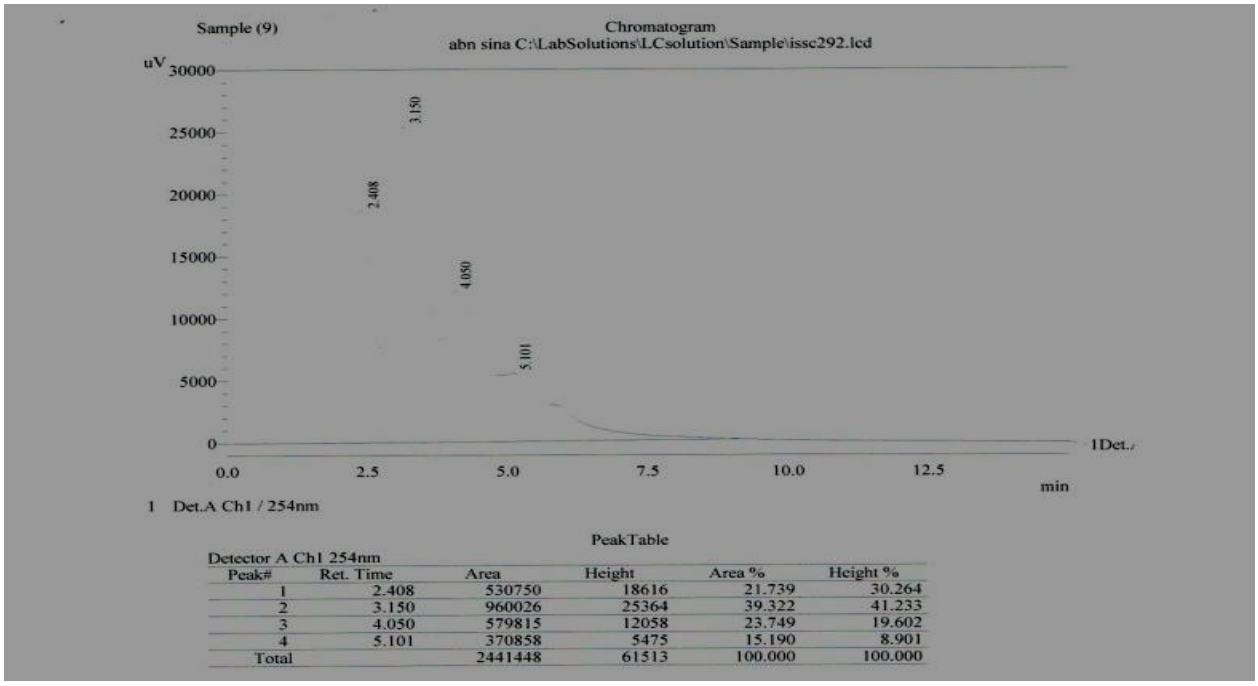
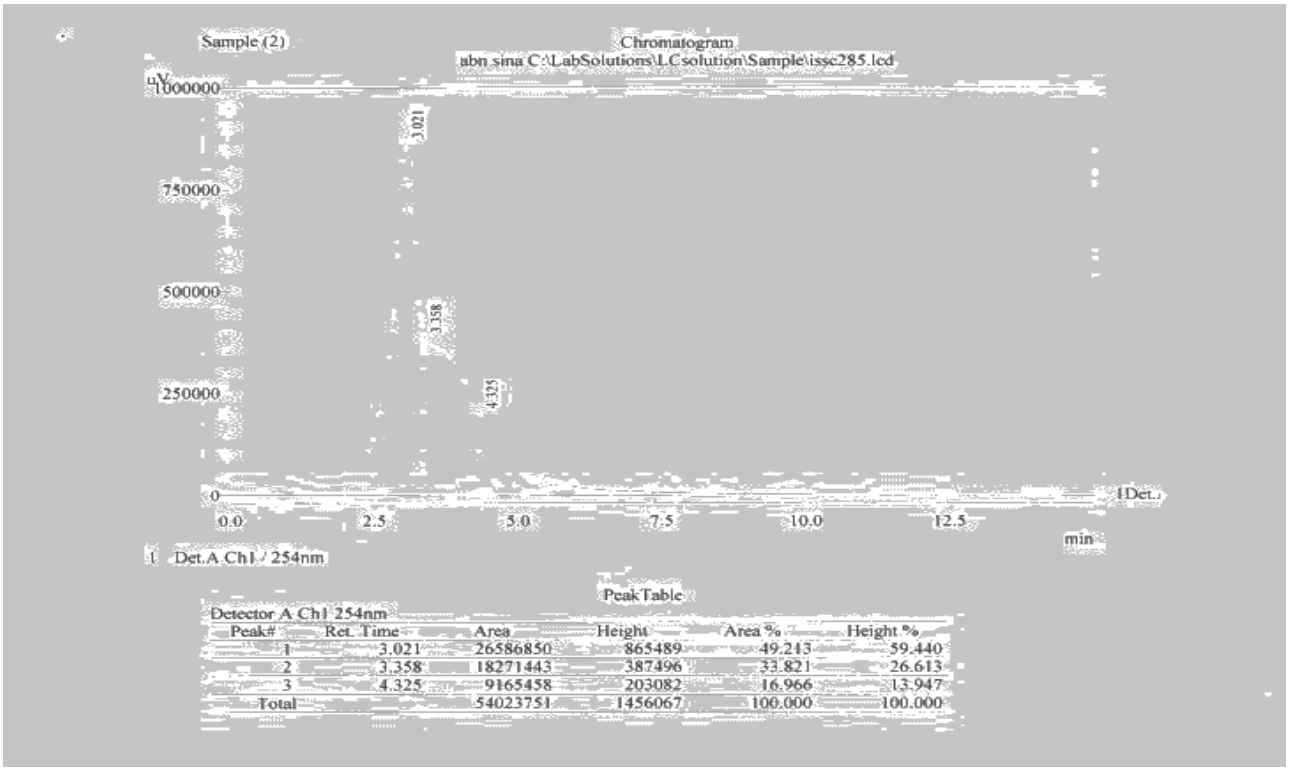


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	2.408	530750	18616	21.739	30.264
2	3.150	960026	25364	39.322	41.233
3	4.050	579815	12058	23.749	19.602
4	5.101	370858	5475	15.190	8.901
Total		2441448	61513	100.000	100.000

Fig. 13: HPLC chromatograph of the ligand



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.021	26586850	865489	49.213	59.440
2	3.358	18271443	387496	33.821	26.613
3	4.325	9165458	203082	16.966	13.947
Total		54023751	1456067	100.000	100.000

Fig. 14: HPLC chromatograph of Pt^{IV} complex

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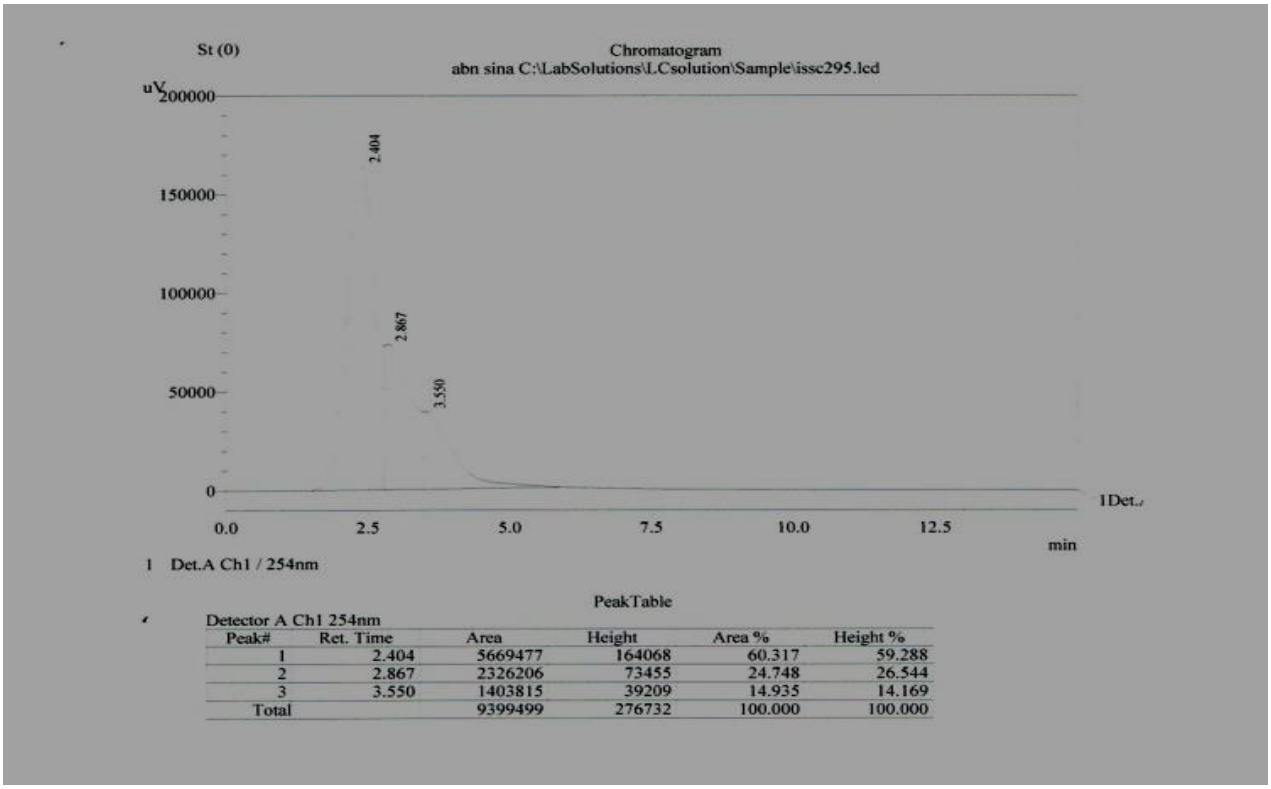
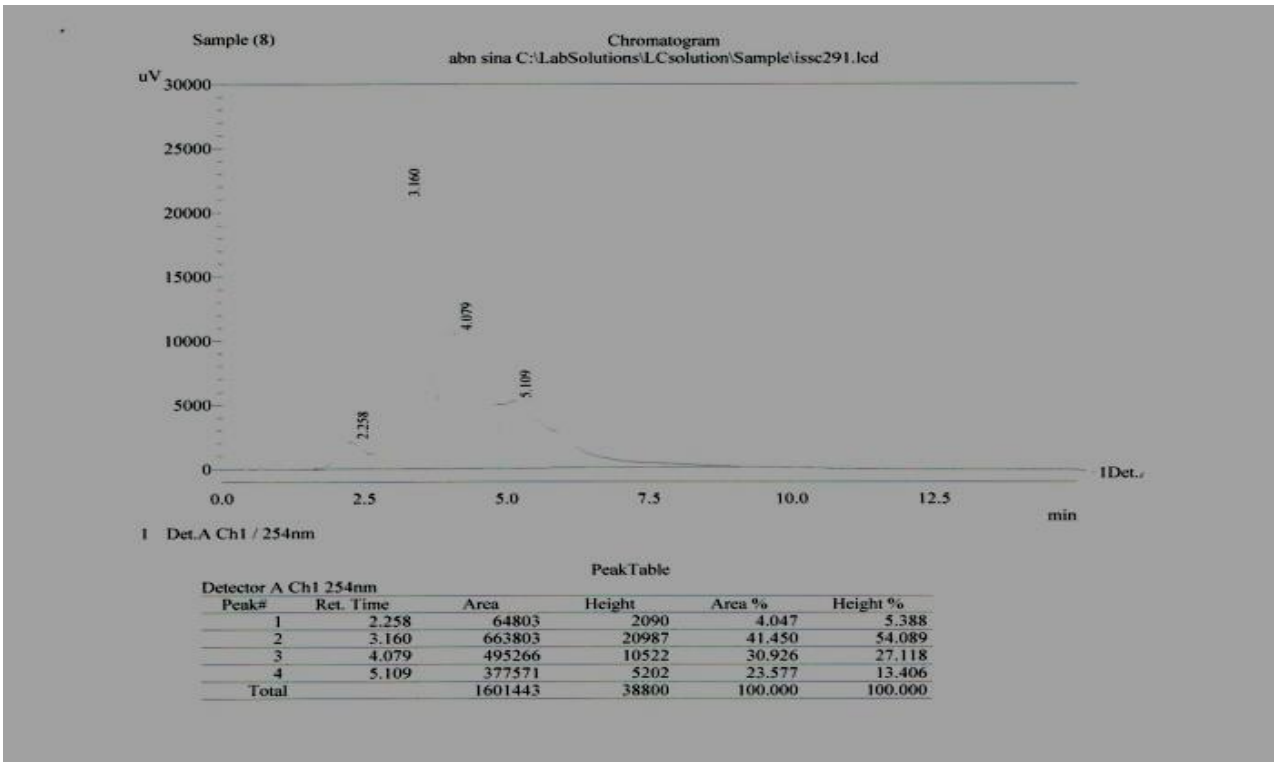


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	2.404	5669477	164068	60.317	59.288
2	2.867	2326206	73455	24.748	26.544
3	3.550	1403815	39209	14.935	14.169
Total		9399499	276732	100.000	100.000

Fig. 15: HPLC chromatograph of Pd^{II} complex



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	2.258	64803	2090	4.047	5.388
2	3.160	663803	20987	41.450	54.089
3	4.079	495266	10522	30.926	27.118
4	5.109	377571	5202	23.577	13.406
Total		1601443	38800	100.000	100.000

Fig. 16: HPLC chromatograph of Ni^{II} complex