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Synthesis, Characterization and Biological Activity of New Complex Cobalt, Nickel and Chromium of (Z)-4-(3-Carboxyacrylamido)-2-Hydroxybenzoic Acid

Khansa Abdul-Razaq Ali Al-Assadi
Chemistry Department, Collage of Science, University of Basra, Iraq

Abstract
Synthesis of(Z)-4-(3-carboxyacrylamido)-2-hydroxybenzoic acid ligand from acetic anhydride and p- amino salicylic acid was complex with Co(II),Ni(II) and Cr(III),the complexes have been characterized by spectral(FTIR,Uv-Vis)and electrochemical method using conductmetric ,the resulting nanoparticles were characterized by X-ray diffraction (XRD) and biological activity .

Introduction

Aminosalicylic acid was introduced to clinical use in 1944. It was the second antibiotic found to be effective in the treatment of tuberculosis, after streptomycin. PAS formed part of the standard treatment for tuberculosis prior to the introduction of rifampicin and pyrazinamide.[4]

Its potency is less than that of the current five first-line drugs (isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin) for treating tuberculosis and its cost is higher, but it is still useful in the treatment of multidrug-resistant tuberculosis.[1] PAS is always used in combination with other anti-TB drugs.

The dose when treating tuberculosis is 150 mg/kg/day divided into two to four daily doses; the usual adult dose is therefore approximately 2 to 4 grams four times a day. It is sold in the US as "Paser" by Jacobus Pharmaceutical, which comes in the form of 4 g packets of delayed-release granules. The drug should be taken with acid food or drink (orange, apple or tomato juice).[5] PAS was once available in a combination formula with isoniazid called Pasinah[6] or Pycamisan 33.[7]

The European Medicines Agency (EMA) has recommended granting a marketing authorization for PAS in multidrug-resistant tuberculosis in adults and children when other treatments cannot "be devised for reasons of resistance or tolerability [8,9]

Gastrointestinal side-effects (nausea, vomiting, diarrhoea) are common; the delayed-release formulation is meant to help overcome this problem.[10] It is also a cause of drug-induced hepatitis. Patients with glucose-6-phosphate dehydrogenase deficiency should avoid taking aminosalicylic acid as it causes haemolysis.[11] Thyroid goitre is also a side-effect because aminosalicylic acid inhibits the synthesis of thyroid hormones.[12]

Drug interactions include elevated phenytoin levels. When taken with rifampicin, the levels of rifampicin in the blood fall by about half.[9]

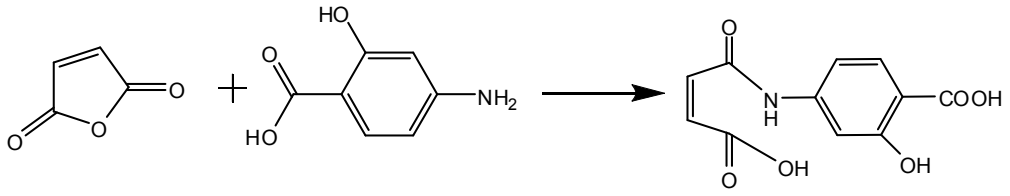
Matrial

para-aminosalicylic acid manufacture by Fluka ,dry ethyl ether and acetic anhydride manufacture by BDH,nickel chloride manufacture by Alpha,coblet chloride manufacture by Marck,cyclohexane ,chromium chloride and sodium acetate manufacture by RDH.

Method

Preparation of ligand

In a 1L two necked round bottom flask provided with a reflux condenser and dropping funnel ,30 g (0.3 mole)and 382 ml of dry ethyl ether were placed stirring was started by using a magnetic was dissolved a solution of 0.3 mole of compound in 30 ml of dry ethyl ether the resulting thick suspension was stirred at room temperature for 1hr and then cooled to 15-20^{o}C in an ice bath, the product was obtained by suction filtration in the form of fine yellow powder with reaction bellow

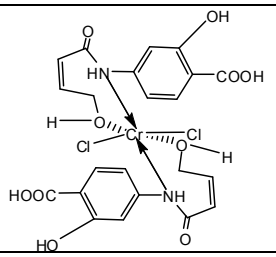
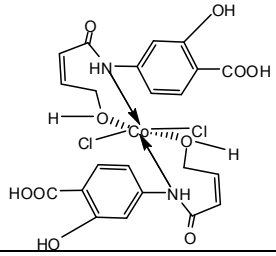
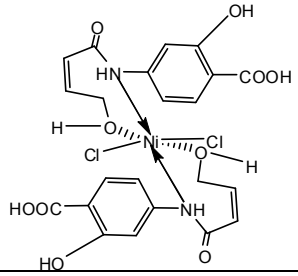


maleic anhydride — para-aminosalicylic acid — (*Z*)-4-(3-carboxyacrylamido)-2-hydroxybenzoic acid

Preparation of complexes

The aqueous solution of 0.1 mol of metal salts of(CoCl2 ,CrCl3 and NiCl2) was added with constant stirring to an ethanol solution of 0.2mol of(Z)-4-(3-carboxyacrylamido)-2-hydroxybenzoic acid. Reaction mixture was stirred at room temperature for 5 hours. The colored precipitate was obtained .The precipitate was filtered and washed with water and then with methanol and dried over calcium chloride in a desiccator .All the complexes were prepared in 1:2 ratio metal to ligand the suggestion structure of complexes show below .

Table (1) physical properties of complexes

Code	m.p °C	Color	G Ω^{-1} $X10^{-6}$	Complexes
1	210	Yellow	10	
2	200	Green	56.5	
3	150	Orange	4.5	

Results and discussion

1- Spectroscopy study (FTIR),UV visible and X-ray

1.1-FTIR analysis of the complexes

The relevant band in the (FTIR)of the complexes are listed in Table (2).In Figure (1)FTIR for ligand show two vibration -OH band for carboxyl group and for phenol group at 3496.94cm^{-1} and 3338.93cm^{-1} and for -NH group at 3317.66cm^{-1} .When the two band of carbonyl group for carboxyl group and amide group recognized at 1771cm^{-1} and at 1668.43 as for C=C we show band at 1616.53$cm^{-1.}$

In Figure (2) for Cr complex with ligand we show that starching -OH band for carboxyl group at3400.0 $cm^{-1}$and starching band for -OH for phenolic group at 3049.4cm^{-1} but –NH group at 3000cm^{-1} , and C=O of carbonyl group at 1716.65 cm^{-1} for carboxylic acid ,and at 1688.43cm^{-1} for amid group as for C=C at 1616.35cm^{-1} .For N-Cr group at 661.58cm^{-1} but for O-Cr at 779.24$cm^{-1.}$

In Figure (3) for Co complex with ligand we show that starching -OH band for carboxyl group at3469.94 $cm^{-1}$and starching band for -OH for phenolic group at 3388.93cm^{-1} but –NH group at 3000cm^{-1} , and C=O of carbonyl group at 1622.13 cm^{-1} for carboxylic acid ,and at 1553.91cm^{-1} for amid group as for C=C at 1558.48cm^{-1} .For N-Co group at 650cm^{-1} but for O-Co at 710$cm^{-1.}$

In Figure(4) for Ni complex with ligand we show that starching -OH band for carboxyl group at3388.93$cm^{-1}$and starching band for -OH for phenolic group at 3555.4cm^{-1} but –NH group at 3300cm^{-1} , and C=O of carbonyl group at 1616.35cm^{-1} for carboxylic acid ,and at 1558.34cm^{-1} for amid group as for C=C at 1508.33cm^{-1} .For N-Ni group at 600cm^{-1} but for O-Ni at 750$cm^{-1.}$

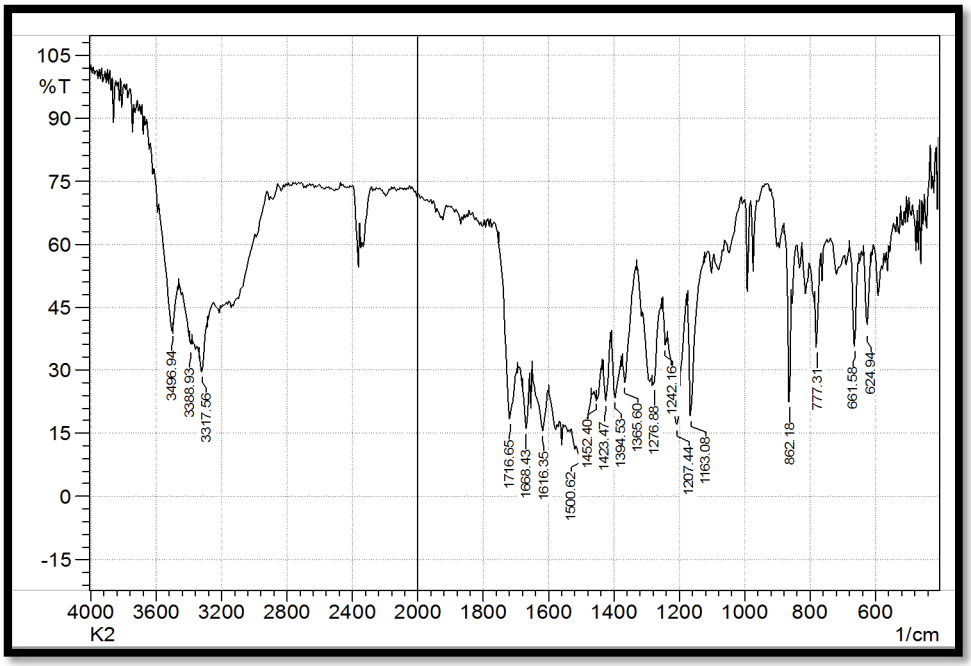


Figure (1) FTIR for ligand

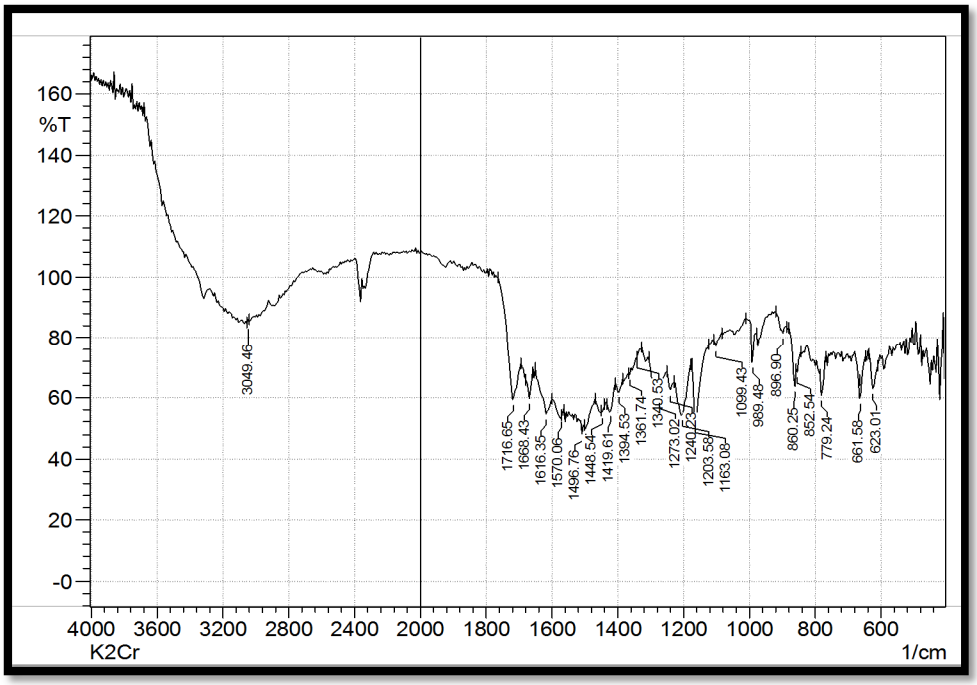


Figure (2) FTIR for Cr complex with ligand

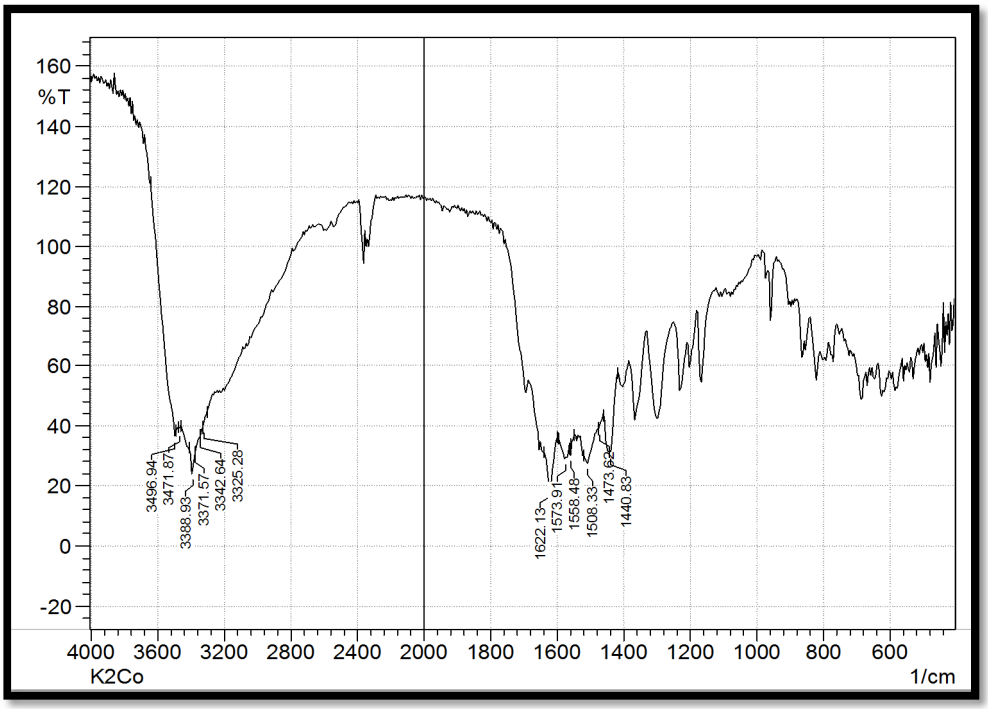


Figure (3) FTIR for Co complex with ligand

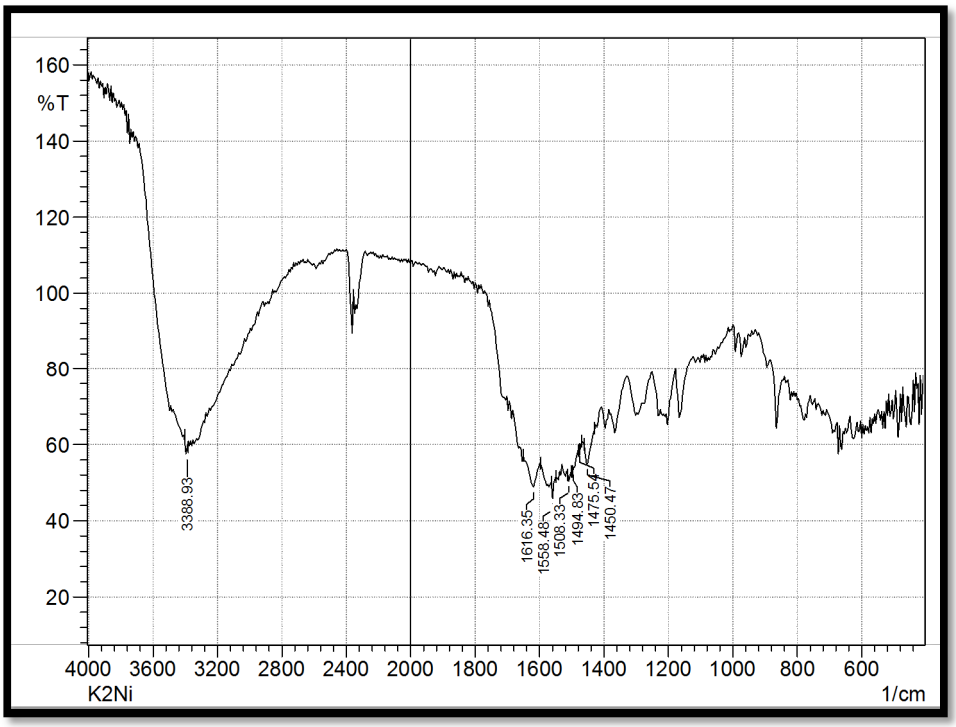


Figure (4) FTIR for Ni complex with ligand

1.2-UV-Visible spectroscopy

The solution electronic spectra of the ligand and the complexes were recorded in UV-Visible region . Figure(5) shows single band in 308cm^{-1} of ligand but shifted of the band to 330cm^{-1} in Ni-ligand complex to $\pi \longrightarrow \pi^*$ tension that in figure (6). Figure (7) shows four band in(218,252,280,286)cm^{-1} for $\pi \longrightarrow \pi^*$ and $n \longrightarrow \pi^*$ transion of Cr-ligand complex ,when in Co-ligand complex we shows tow band in 330and 590 cm^{-1} for $\pi \longrightarrow \pi^*$ and $n \longrightarrow \pi^*$ shows in figure (8).

The powder X-ray diffraction data showed identical features with very poor crystallinty . The patterns of the complex had been indexed by standard method s dispersive in intensity for Ni, Cr and Co metal complexes.

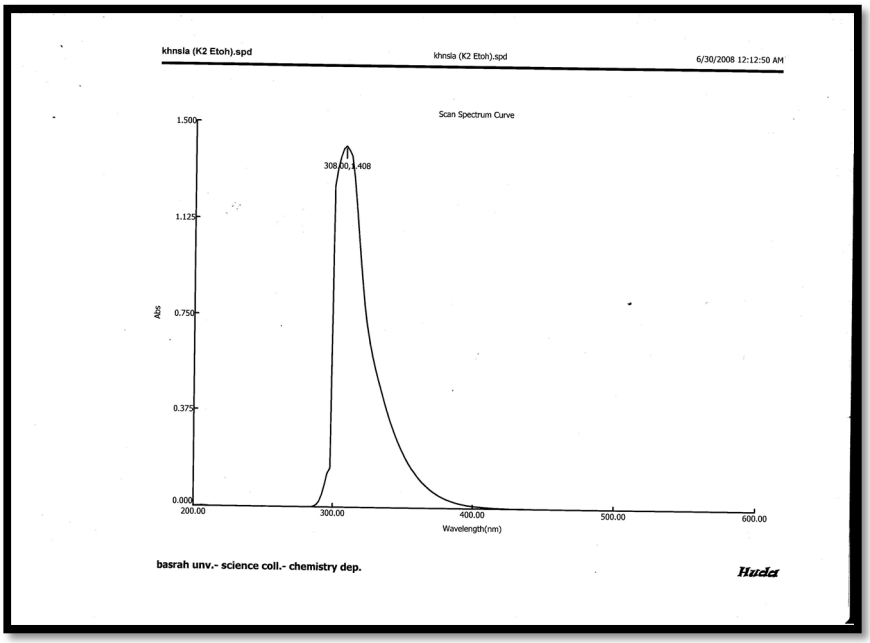


Figure (5) UV-Visible of ligand

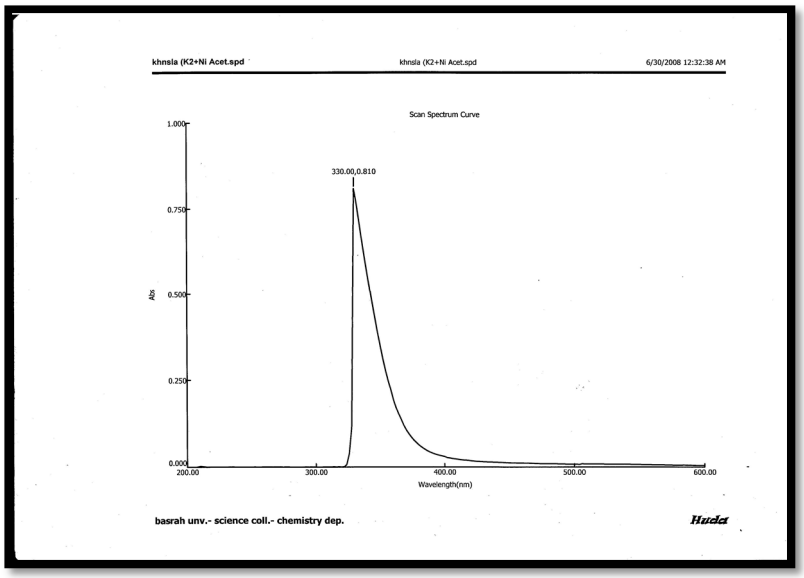


Figure (6) UV-Visible of Ni-ligand complex

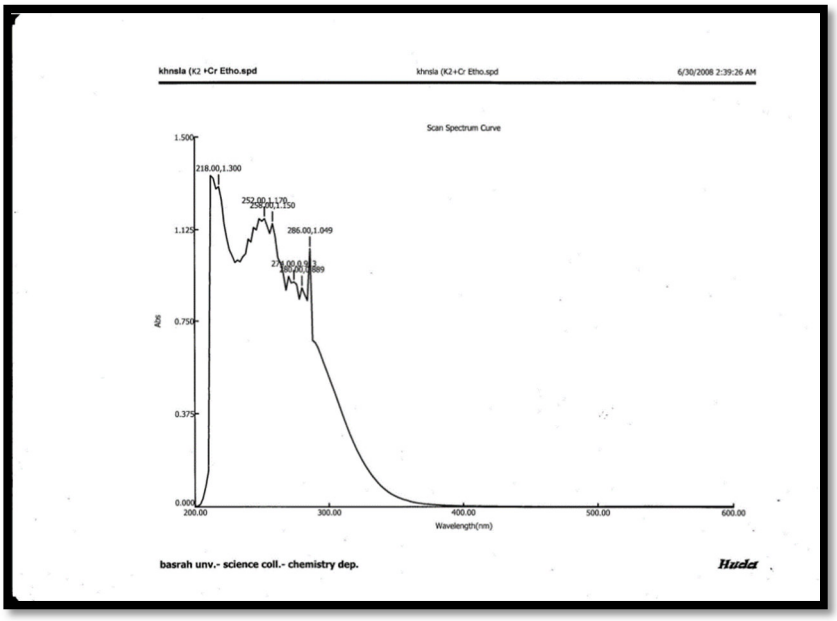


Figure (7) UV-Visible of Cr-ligand complex

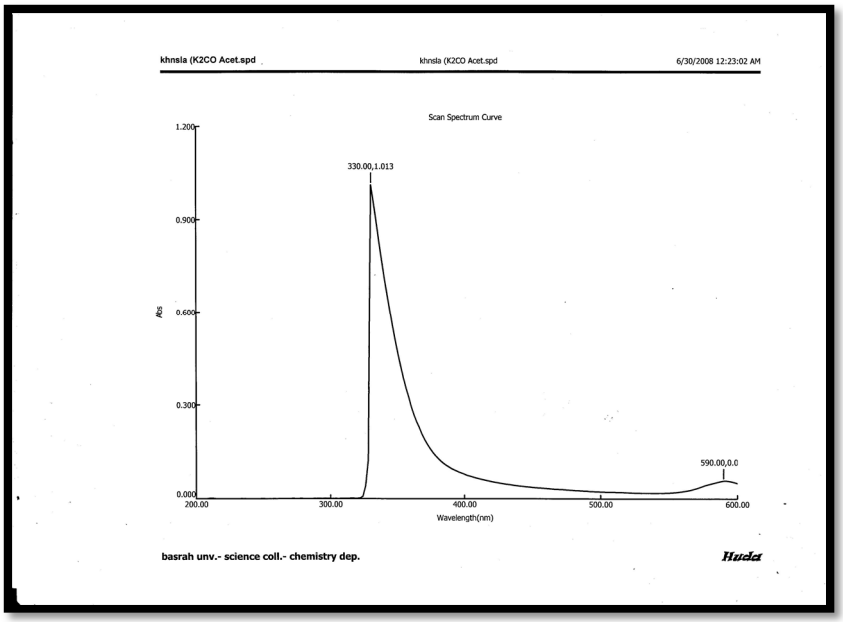


Figure (8) UV-Visible of Co-ligand complex

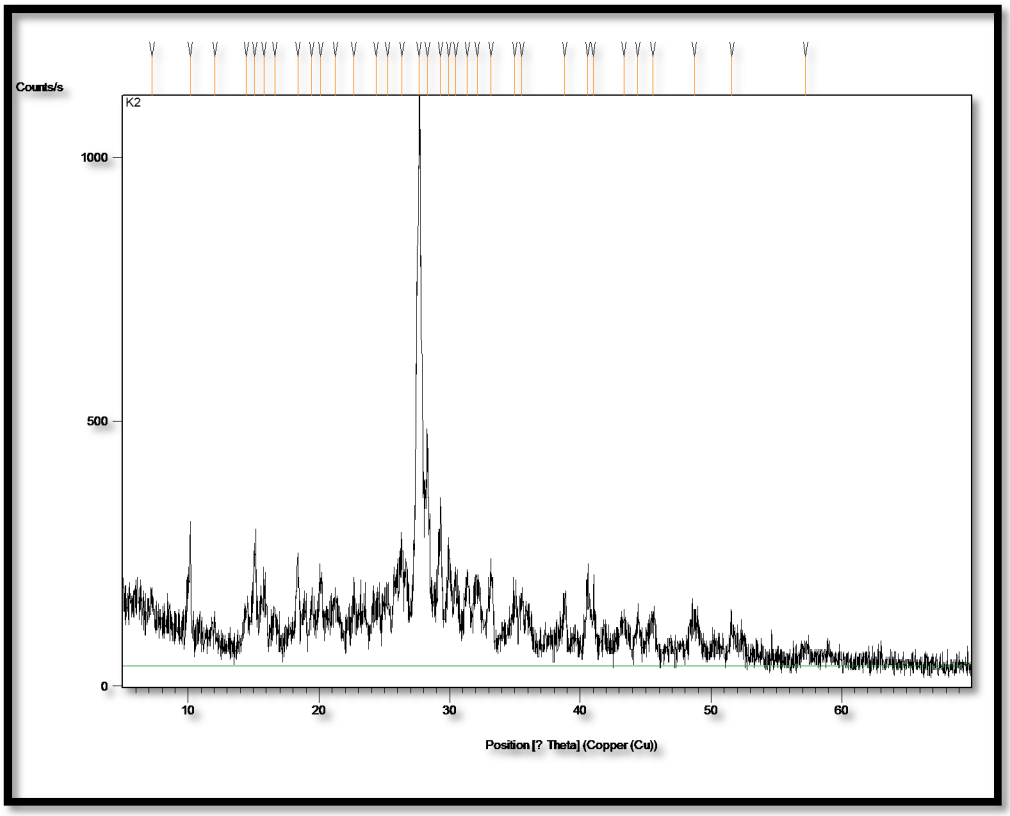


Figure (9) XRD of ligand

Table (2) powder X-ray diffraction data of the ligand

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
7.2039	26.81	0.2362	12.27122	13.04
10.1502	54.94	0.0787	8.71497	26.73
12.0202	18.56	0.1378	7.36301	9.03
14.4343	21.02	0.3149	6.13657	10.23
15.1014	42.80	0.1574	5.86695	20.83
15.8203	27.10	0.2362	5.60192	13.19
16.6062	19.75	0.3149	5.33855	9.61
18.3695	36.39	0.1968	4.82987	17.71
19.4617	24.77	0.2362	4.56121	12.05
20.1320	32.64	0.1968	4.41083	15.88
21.2322	23.97	0.4723	4.18470	11.66
22.6749	30.83	0.1574	3.92160	15.00
24.3608	22.13	0.3149	3.65389	10.77
25.2211	24.24	0.2362	3.53118	11.79
26.3353	42.76	0.1968	3.38426	20.81
27.6761	205.52	0.3936	3.22328	100.00
28.2982	80.43	0.1968	3.15381	39.14
29.2732	47.97	0.1574	3.05095	23.34
29.9558	40.01	0.1968	2.98296	19.47
30.4804	32.83	0.2362	2.93281	15.97
31.3681	35.18	0.1968	2.85182	17.12
32.1058	30.47	0.3936	2.78795	14.83
33.1924	34.49	0.1968	2.69913	16.78
34.9825	24.57	0.2362	2.56500	11.96
35.4970	25.00	0.1574	2.52900	12.16
38.8009	23.88	0.1968	2.32092	11.62
40.5429	27.56	0.1574	2.22513	13.41
40.9729	22.74	0.2362	2.20277	11.07
43.3252	15.44	0.6298	2.08847	7.51
44.3979	17.53	0.3149	2.04047	8.53
45.5481	17.28	0.3149	1.99158	8.41
48.7149	17.14	0.7872	1.86926	8.34
51.5987	16.38	0.3149	1.77137	7.97
57.2369	6.60	0.5760	1.60823	3.21

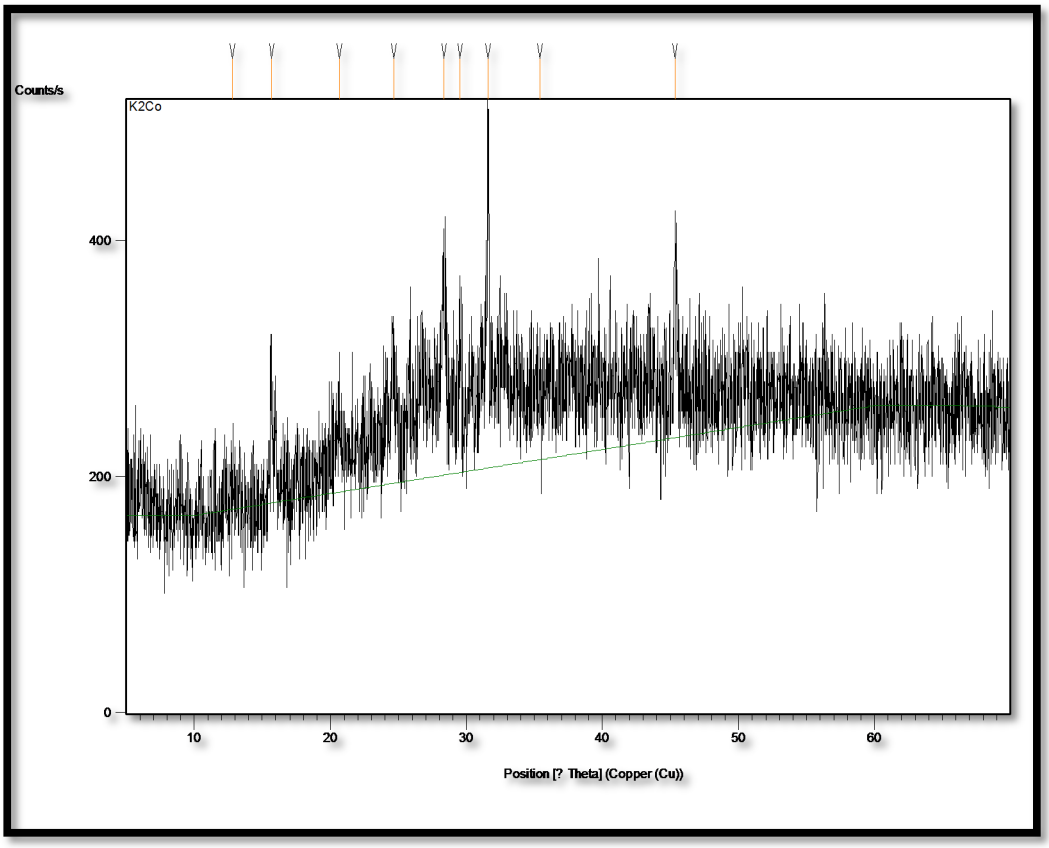


Figure (10) Co-ligand complex

Table (3) powder X-ray diffraction data of the ligand-Co complex

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
12.7927	1.38	1.5744	6.92008	2.50
15.6500	22.07	0.1181	5.66249	40.01
20.6492	10.32	0.9446	4.30151	18.70
24.6300	18.37	0.6298	3.61457	33.31
28.3326	33.80	0.2362	3.15006	61.27
29.5194	23.58	0.2362	3.02606	42.74
31.5942	55.16	0.1181	2.83192	100.00
35.4138	16.12	0.1378	2.53475	29.22
45.3382	34.37	0.1920	1.99866	62.30

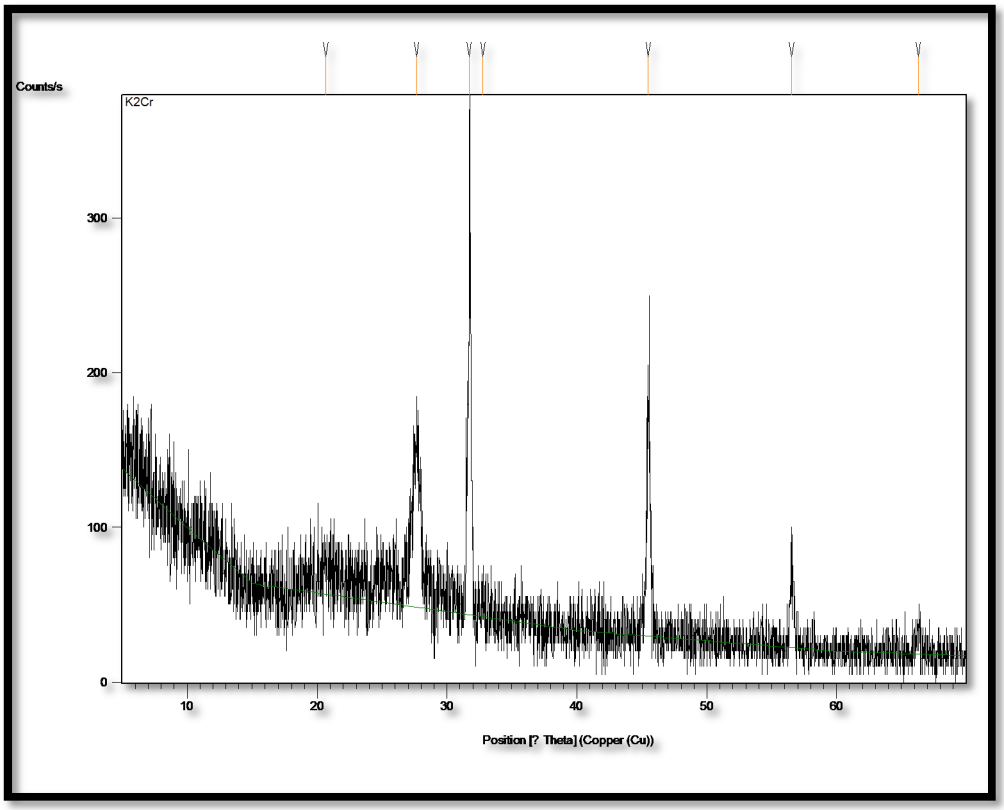
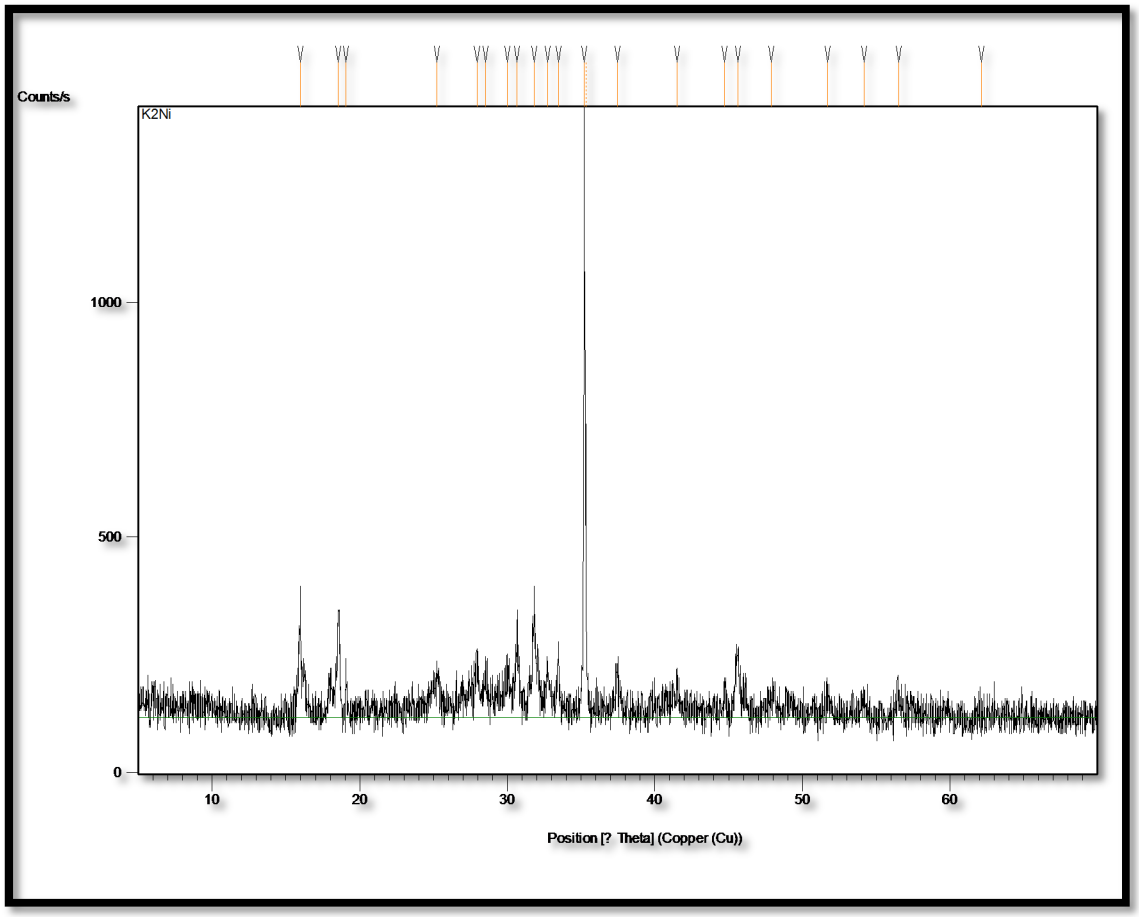


Figure (11) Cr-ligand complex

Table (4) powder X-ray diffraction data of the ligand-Cr complex

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
20.6487	2.96	2.5190	4.30161	4.63
27.6484	20.82	0.5510	3.22644	32.48
31.7227	64.09	0.0590	2.82073	100.00
32.7543	1.71	0.2755	2.73422	2.66
45.5188	33.62	0.1968	1.99279	52.46
56.5386	13.14	0.1574	1.62777	20.50
66.2979	3.44	0.2880	1.40870	5.37



Figure(12) Ni - ligand complex

Table (5) powder X-ray diffraction data of the ligand-Ni complex

Pos. [°2Th.]	Height [cts]	FWHM [°2Th.]	d-spacing [Å]	Rel. Int. [%]
15.9592	48.45	0.0984	5.55349	18.63
18.5531	43.97	0.1378	4.78248	16.90
19.1038	18.85	0.1181	4.64584	7.25
25.2492	17.33	0.2362	3.52731	6.66
27.9612	17.93	0.2755	3.19105	6.89
28.5556	16.68	0.2362	3.12597	6.41
29.9836	18.33	0.2362	2.98027	7.05
30.6741	35.23	0.1574	2.91473	13.54
31.8150	41.94	0.1574	2.81277	16.12
32.7473	19.30	0.2362	2.73479	7.42
33.4570	26.53	0.1574	2.67838	10.20
35.2282	260.13	0.0360	2.54556	100.00
35.3178	126.40	0.0480	2.54562	48.59
37.4407	19.46	0.1920	2.40006	7.48
41.5186	15.18	0.2880	2.17327	5.84
44.7559	10.67	0.2880	2.02330	4.10
45.6010	25.88	0.3360	1.98775	9.95
47.9142	7.71	0.9600	1.89704	2.96
51.6968	5.97	1.1520	1.76678	2.30
54.1679	7.15	0.5760	1.69187	2.75
56.5535	7.08	0.5760	1.62603	2.72
62.1080	2.22	0.6720	1.49328	0.85

2-Biological activity

Number (ex. three) extracts, from chemical resources were tested, chemical products used were selected by previous antimicrobial activity screening using diffusion method against at least one of the two bacterial strains used during the testing. For the diffusion method well-variant, the solvent used was dimethylsulfoxide (DMSO) and for the remaining methodologies, suitable solvents were used for the dissolution of the chemical products.

Test-bacteria

The antibacterial activity of natural products was assessed against two bacteria species: *Staphylococcus aurous* and *Escherichia coli* . Overnight cultures were used. After 24 h of incubation, bacterial suspension (inoculum) was diluted with sterile physiological solution, for the diffusion test, to 10^8 CFU/ml (turbidity = McFarland barium sulfate standard 0.5)[13].

Agar diffusion well-variant

The bacterial inoculums was uniformly spread using sterile cotton swab on a sterile Petri dish MH agar. 50 µl from 1mg/ml concentration of chemical products were added to each well (7 mm diameter holes cut in the agar gel, 20 mm apart from one another). The plates were incubated for 24 h at 36ºC ± 1ºC, under aerobic conditions. After incubation, confluent bacterial growth was observed. Inhibition of the bacterial growth was measured in mm[13].

Antimicrobial activity

Name of compound	Concentration	Inhibition diameters mm	
		Staphylococcus aurous	*Escherichia coli*
Ligand	100 ppm	18	20
Ni-ligand complex	100 ppm	Zero	11
Co-ligand complex	100 ppm	Zero	Zero
Cr-ligand complex	100 ppm	15	Zero

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