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"Physicochemical Characterization, Antioxidant and Antimicrobial Assessment of Some Newly Synthesized Aza Macrocyclic Complexes of Cr (III) Metal Ions"

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ABSTRACT:A fresh set of macrocyclic complexesof chromium typed $[Cr(C_{30}H_{20}N_8O_2)](C_5H_7OO^-)_3$ and $[Cr(C_{30}H_{18}Cl_2N_8O_2)](C_5H_7OO^-)_3$ were synthesized in methanolic medium viatemplate synthetic route. These complexes were preparedby [2+2] cyclocondensation reaction of diamines i.e. 4-aminobenzoic hydrazide and 2-aminobenzhydrazide with α-diketones i.e. isatin and 5-chloroisatin in presence of chromium acetylacetonate template ion. Physicochemical properties were studied by decomposition temperature, conductance measurement, elemental analyses and magnetic moment measurements. These complexes were found soluble in DMSO. Various techniques were utilizedfor spectral analysis of synthesized complexes such as SEM, IR, NMR, mass spectrometry and UV/Vis. All the produced complexes were assessed for their antibacterial potency contrary to the bacterial strains (E. coli and S. aureus)and fungal strains(Alternaria altermate and Fusarium solani) by using Agar well diffusion method. Antioxidant activities ofall these complexes were also tested by the help of DPPH method and compared with standard ascorbic acid and showed satisfactory results.

KEY WORDS: -Macrocyclic complexes, chromium(III), antibacterial, antifungal, antioxidant.

I. INTRODUCTION

Recently, researchers developed their interest on aza macrocycles in the area of coordination chemistry due to their remarkable features [1–6].Study of this metal macrocyclic chemistry is growing very quickly [7-14].Today creation of well-ordered macrocycles containing metal is the most intriguing area of chemistry and research [15-18].Due to the macrocyclic effect, macrocyclic ligands are favoured over acyclic analogues [19] as they exhibit greater value of thermodynamic stability, conformational restrictions, tiny hole for the metal ion's and preferred a well-organized ligand molecule that can be bent with little entropy and a powerful field simultaneously [20].The structure and reactivity of a large number of marvellous naturally occurring compounds that are well known to undergo selective cation complexation are comparable to those of macrocyclic compounds [21-22].These macrocyclic complexes have remarkable role in a number of biological activities namely antitumor,antidiabetic, antibacterial, anticancer, antifungaletc.[23-30].The production of macrocyclic complexes can take place via template condensation process at the core of macrocyclic chemistry [31-32].Thus, the synthesis of macrocyclic compounds has frequently employed thetemplate process[33],wherein the transition metal ions are typically utilised as templates [34-35].There are a great number and variety of transition metal complexes containing novel aza groups have been produced by varying cavity sizes, donor types,ring substituents several other factors [36-40].Due to their biocidal effects, such as antiviral, anticarcinogenic, antifertility, antibacterial, and antifungaletc., transition metal macrocyclic complexes have tremendous interest in research[41–45].On the basis of reported research work, approximately daily dietary intake of chromium as 25 µg for women and 35 µg for malesplays a crucial role for properfunctioning of the brain and heart, to regulate blood sugar, and to breakdown of sugars and lipids.Metal ions as a combing component with biological systems play crucial role in various biological processes and used to treat various diseases. Numerous naturally occurring complexes (Hb, chlorophylls, vitamin B12, etc.) having metals as a central atom have been discovered to perform important roles in a variety of biological processes [46]. In this study, we provide the findings from the synthesis, physicochemical analysis, and numerous biological

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activities of the Cr(III) complexes derived from 4-aminobenzoic hydrazide and 2-aminobenzhydrazide with α-diketones i.e. isatin and 5-chloroisatin.

II. EXPERIMENTAL

2.1 Materials and methods

In the synthesis process, all of the used chemicals and solvents were taken in pure form. Chromium (III) acetylacetonate ($C_{15}H_{21}CrO_6$) metal salt was of Merck and ligand precursors namely5-chloroisatin, 2-aminobenzhydrazide, 4-aminobenzoichydrazide and isatin were of Sigma Aldrich.Reaction was carried out in methanolic medium and methanol solvent was purified before use.

2.2 Synthesis of the complexes

All the complexes were producedvia [2+2] cyclocondensation reaction of 4-aminobenzoic hydrazide or 2-aminobenzhydrazide with isatin or 5-chloroisatin in methanol solvent in the existence of chromium acetylacetonate metal salt as template. For the synthesis of complex **(1)**,in a round bottom flask 0.2 g. of 2-aminobenzhydrazidein 15-20 mL metholic solution was taken and started to reflux on a magnetic stirrer. This solution was added drop by drop to the previous solution with continuous stirring. On the other hand (0.206 g) of isatin wasalso dissolved in the methanol (15-20 mL). To this mixture, methanolic solution of chromium acetylacetonate (0.0433 g. in 15-20 mL methanol) was added drop by drop with continuous stirring and then after whole mixture was refluxed for 6-7 hours [47]. After refluxing, the mixture was kept to cool for overnight then it settled down andcoloured precipitation was produced.Same process was opted for the synthesis of complexes **(2)**, **(3)** and **(4)** with the change of their respective molar masses. Both ligands and salt of the metal were taken in [2:2:1] molarratios respectively as shown in scheme **(1)**&**(2)**.

2.3 Isolation of the complexes

The coloured precipitate of the complexes was filtered by the help of suction pump, washed many times with methanol and dried in vacuo. The complexes had a yield in between 70 and 80%.

2.4 Characterization andphysicochemical properties of the complexes

Solubility of the synthesized complexes was found in DMF and DMSO. The produced complexeswere yellow, orange and light orange coloured solid. Decomposition temperature of these complexes was found in the range240 to 259 °C. Magnetic moments of these complexes were obtainedin the range of 3.87 to 4.30 B.M. at room temperature, which indicated the presence of three unpaired electrons in chromium metal ion.In the complex, presence of metal was determined by the help of previously reported articles [48]. The SEM images of the synthesized complexes**(1)**&**(3)** respectively, as shown in (**Fig.١**), demonstrated needle shaped structure of complexes with unordered distribution.

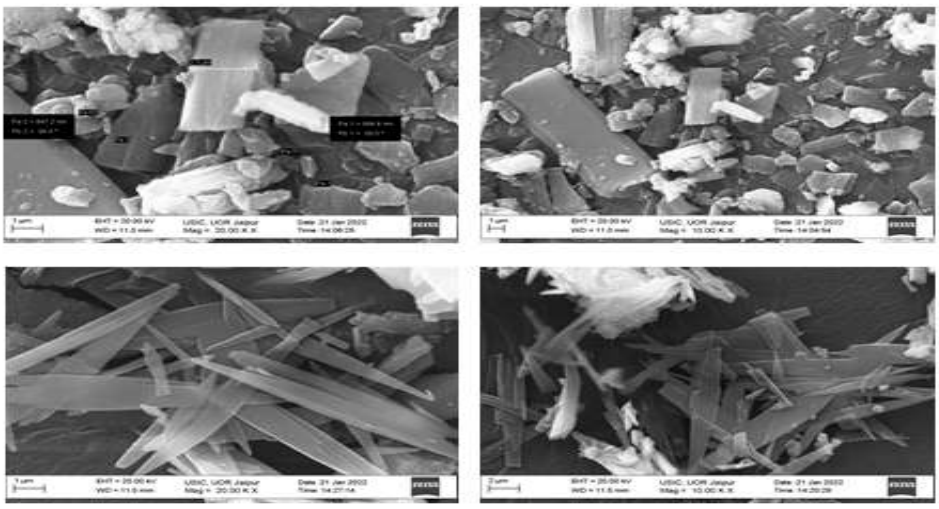

Fig.١ SEM images of the complexes **(1)**&**(3)**

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Scheme١ Synthesis of complexes **1**&**2** derived by the reaction of 2-aminobenzhydrazide with isatin or 5-chloroisatin respectively

Scheme: ٢ Synthesis of complexes **3**&**4** derived by the reaction of 4-aminobenzoichydrazide with isatin or 5-chloroisatin respectively

III. RESULT AND DISCUSSION

Fresh series of complexes of chromium having type $[Cr(C_{30}H_{20}N_8O_2)](C_5H_7OO^-)_3$ and $[Cr(C_{30}H_{18}Cl_2N_8O_2)](C_5H_7OO^-)_3$ was synthesized as shown in **scheme**١&٢for complexes**(1 to 4)**. Each compound was found soluble and stable in DMSO and DMF and all were air stable. Based on the results of SEM, NMR, UV/Vis, IR, and mass spectrometry, it was assumed that the complexes formed.

NMR spectra

The ^1H NMR and ^{13}C NMR spectra of complexes, which were taken at room temperature in DMSO-d6 solution, showed no signals of the primary amine protons. The ^{13}C NMR signals gave characteristic of carbon of the macrocyclic skeleton and ^1H NMR gave types of the protons. Appropriate positions of the carbon and hydrogen corresponding to the proposed structure were selected after analysing the spectral peaks.The ^1H NMR and ^{13}C NMR spectrum of the $[Cr(C_{30}H_{20}N_8O_2)](C_5H_7OO^-)_3$ complex shownin **Fig.**٢and **Fig**.٣respectively are justifying skeleton of the compound as proposed in **Complex-3**. Two Singlet signal appeared at 5.94 ppm due to (aromatic ring connected -NH-) protons. Multiple signals at the range from 7.30-7.95 ppm are characteristic of(aromatic =CH) protons. The signals in the ^{13}C NMR range from 113.35 to 152.15 ppm are classified as aromatic =C-, whereas the aliphatic C=N and C=O signals showed at 150.21 and 163.82 ppm, respectively. The ^1H NMR and ^{13}C NMR spectrashown in **Fig**.٤ and **Fig.**٥respectively were obtained for complex for **Complex- 1**. Two singlet signals appeared at 6.20 ppm due to (aromatic ring connected –NH-) protons. Multiple signals at the range from 7.19-7.95 ppm are characteristics of (aromatic =CH) protons. Multiple singlet signals appearedin between113.35-151.86 ppm range are assigned to =C- aromatic carbon. Two doublet signals appeared at 125.38 and 127.79 ppm also assigned to aromatic =C- carbon. Two singlet signals at 143.59 ppm and 143.23 ppm appeared for –C=N carbonand C=O carbon at 167.97 ppm. Signal appeared at 151.80 ppm due to –N= connected aromatic carbon [49].

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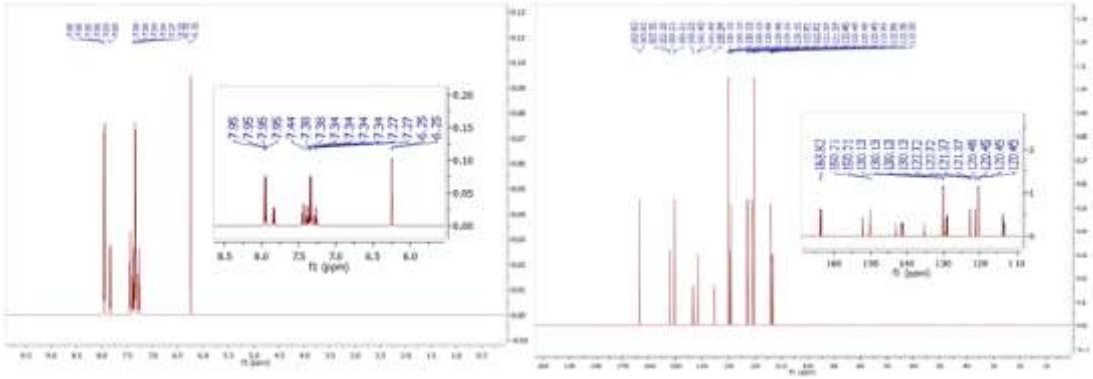

Fig.٢ Fig.**٣**

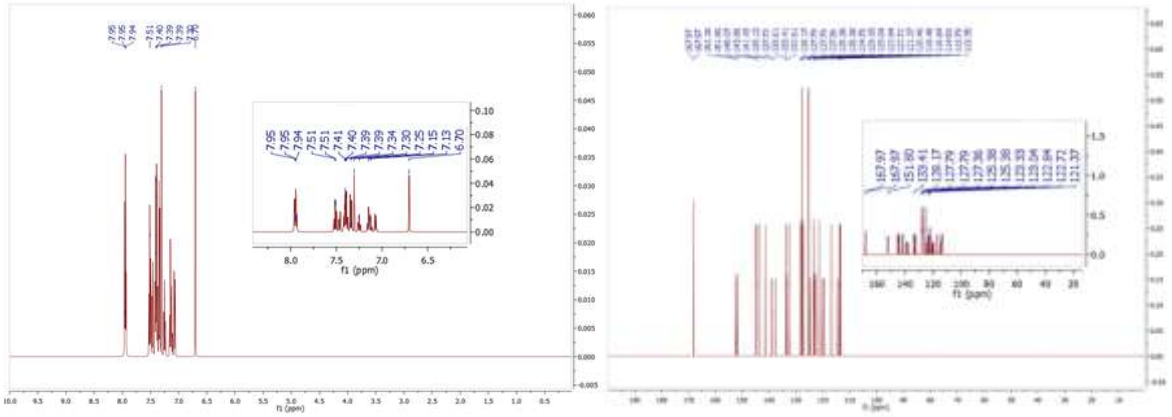

Fig.٤Fig.٥

IR spectra

Two bands that were present in the spectrum of 4-aminobenzoichydrazide (at 3350 cm^{-1} and 3390 cm^{-1}) and in the spectrum of 2-aminobenzhydrazide (at 3350 cm^{-1} and 3385 cm^{-1})were discovered to be missing from all of the complexes spectra, corresponded to the $\upsilon(NH_2)$ group. At 1650 cm^{-1}, a prominent absorption band was seen associated with the υ(C=O) downfield signal due to neighbouring electron donor group [50]. In all complexes, absence of individual (>C=O) and (NH_2) bands at the reported range and presence of new band at ≈ 1590 to 1690 cm^{-1} attributed to (>C=N) group, representing the condensation reaction of diketone with diamine.The benzene ring's υ(C=C) aromatic stretching vibrations were responsible for the many forms of absorption bands in between the range 1400-1588 cm^{-1}[51-52]. The bands which were in the range of 740-785 cm^{-1} may correspond to the υ(C-H) out of the plane bending to the aromatic ring [53]. The IR spectra of all the complexes showed absorption bands at 1408–1440 cm^{-1}, 1290–1320 cm^{-1}, and 1010–1030 cm^{-1} that indicated that N atoms are unidentifiably coupled to the core metal ion [54]. It can be shown that the coordination of the acetylacetonate group with the central metal ion was unidendate because 390-370 cm^{-1} is the difference between (υ_{as}- υ_{s})that is greater than144 cm^{-1}[55]. IR spectra of the synthesized compounds (**Complex-3**and**Complex-4**) are represented in **Fig.٦**.

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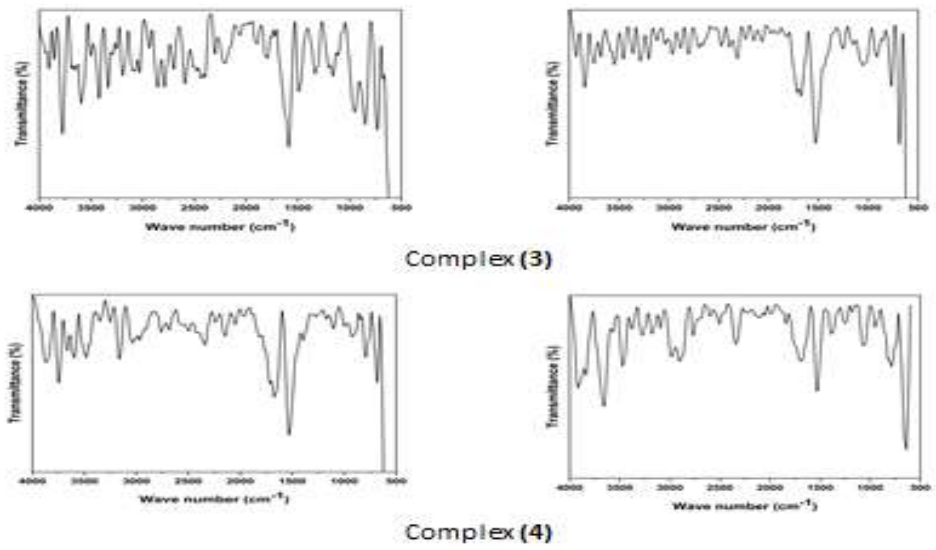

Fig.٦ IR spectra of the $[Cr(C_{30}H_{20}N_8O_2)](C_5H_7OO^-)_3$ and $[Cr(C_{30}H_{18}Cl_2N_8O_2)](C_5H_7OO^-)_3$ complexes

Mass spectrometry

The mass spectra of $[Cr(C_{30}H_{20}N_8O_2)](C_5H_7OO^-)_3$ and $[Cr(C_{30}H_{18}Cl_2N_8O_2)](C_5H_7OO^-)_3$complexes have been recorded and shown in **Fig.٧** and **Fig.٨** respectively. The compound $[Cr(C_{30}H_{20}N_8O_2)](C_5H_7OO^-)_3$ exhibited the molecular ion peak (M^+) at m/z = 524.17. The development of the macrocyclic structure $[Cr(C_{30}H_{20}N_8O_2)]$ was confirmed by this peak. Additional peaks at m/z = 521, 522.90, 523, 525.17 etc. may be correspondedto several fragments. The complex $[Cr(C_{30}H_{18}Cl_2N_8O_2)](C_5H_7OO^-)_3$displayedthe molecular ion peak (M^+), at m/z was 592.09. The macrocyclic structure with the chemical formula $[Cr(C_{30}H_{18}Cl_2N_8O_2)](C_5H_7OO^-)_3$was confirmed by this peak. Additional peaks at m/z = 425.31, 445, 500, 593.10, 595.09 etc. may be corresponded to several fragments. Intensity of the peaks explains the stability of various fragments[56].

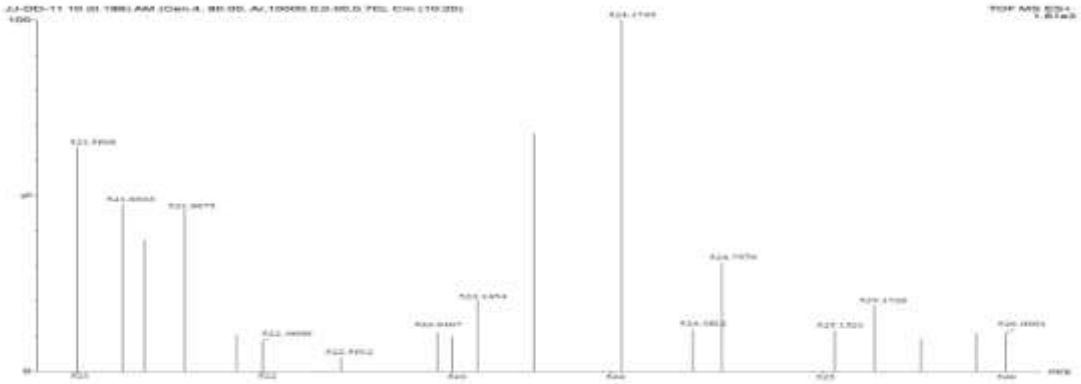

Fig.٧ Mass spectrum of the complex $[Cr(C_{30}H_{20}N_8O_2)](C_5H_7OO^-)_3$

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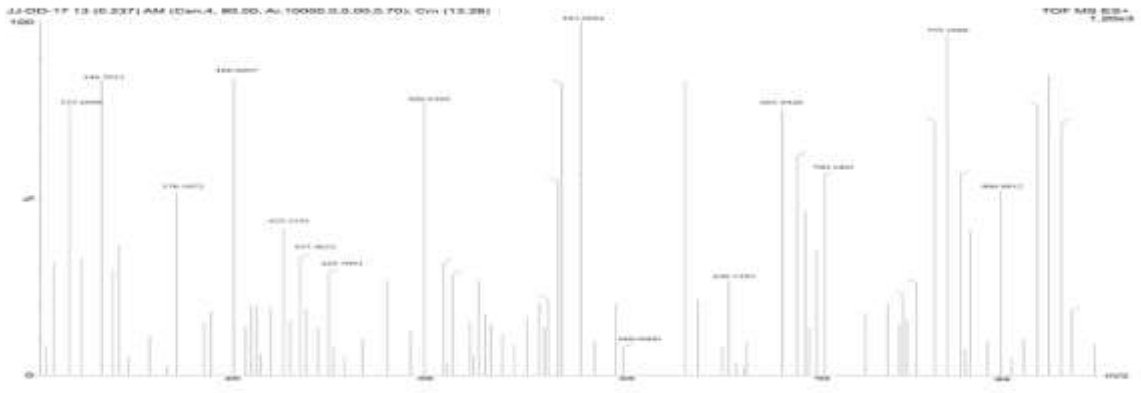

Fig.٨ Mass spectrum of the complex $[Cr(C_{30}H_{18}Cl_2N_8O_2)](C_5H_7OO^-)_3$

UV Spectra

UV-Vis spectra of respective complexes indicatedstrong and weak peaks around 255-257 nm and 350- 400 nm respectively revealed the π to π*and n to π* transitions. π to π* transitions are associated longer wavelength (255-257nm) than normal range of transitions (180-200nm) because of extended conjugation and polar solvent. When conjugation increases than energy gap in between HOMO and LUMO decreases so less energy is required for transition, resultsbathochromic shift. Effect of polar solvents on orbitals follow the order of n>π*>π, so in the presence of polar solvent wave length of π to π* transitions increases while n to π* decreases, so earlier transitions show bathochromic while later shows hypsochromic shift**Fig.٩**.

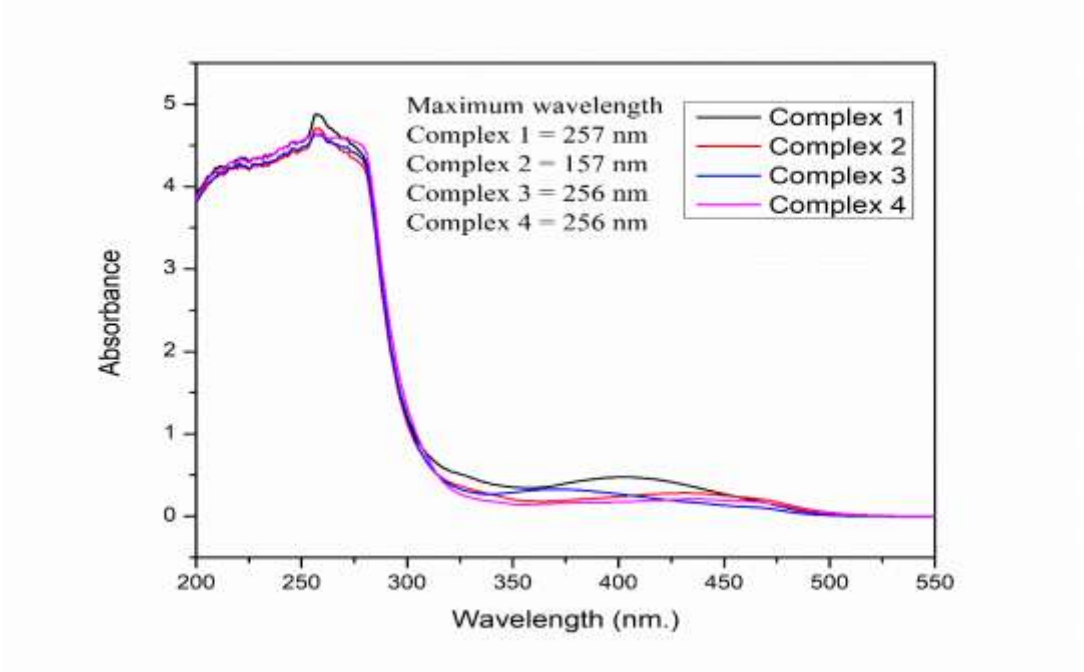

Fig.٩UV-Vis spectra of the synthesized macrocyclic complexes

IV. BIOLOGICAL ACTIVITIES

Antibacterial and Antifungal assay by well diffusion method: -

In-vitro antibacterial assays were conducted by agar well diffusion method [57]. 10% Dimethyl sulphoxide (DMSO) was used to dilute the various samples, and three different concentrations of each drug (50 mg/mL, 100 mg/mL, and 200 mg/mL) were taken. To inoculate the test microorganisms, nutrient agar medium (for antibacterial) and potato dextrose agar (PDA) medium (for antifungal) was placed in clean petri

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dishes. The spreader was used to evenly distribute the inoculum, and the dish was let to stand for 30 minutes. The seeded agar plates were constructed with 6 mm-diameter wells. The control well was additionally set up at the same distance. The prearranged wells of the seeded plates were filled with various concentrations of each sample and the standard medication (30 µl).These plates were incubated at 37°C for 24 hours. Inhibition zone (IZ) measurements surrounding each prepared well were used to determine the antifungal and antibacterialspectrum of the test material. Comparisons were made between the test sample's diameter of the inhibitory zone and commercially available control antibiotic Cipro (1 mg/mL) for antibacterial whereas Ketoconazole (1 mg/mL) for antifungal. Results of antibacterial (against S. aureus and E. coli) and antifungal (against Alternaria alternative and Fusarium solani) assay are given in **Table ١**, and **Fig.١٠.**

Table ١ Antibacterial and Antifungal activity of complexes

Sample's Name	**Anti-Bacterial Action**						**Anti-Fungal Action**					
	E. coli			**S. aureus**			**Alternaria alternative**			**Fusarium solani**		
	Concentration						**Concentration**					
	50	**100**	**200**	**50**	**100**	**200**	**50**	**100**	**200**	**50**	**100**	**200**
	IZ	**IZ**	**IZ**	**IZ**	**IZ**	**IZ**	**IZ**	**IZ**	**IZ**	**IZ**	**IZ**	**IZ**
Standard	25	27	32	27	31	36	32	36	41	28	30	34
Complex 1	NA	1	3	3	4	6	8	13	17	5	8	10
Complex 2	5	8	11	2	4	5	7	10	14	5	8	10
Complex 3	NA	NA	3	3	6	9	NA	3	5	2	4	7
Complex 4	2	3	4	4	5	8	6	9	13	5	9	13

Note: NA= Non active, IZ= Inhibition zone

(a) (b) (c) (d)

Fig.١٠(a,b, c and d) Figure a & b (complex-2)show antibacterial activity against E.coli, S. aureus respectively, and **figure c & d (complex-1)**show antifungal activity against Alternaria alternate, Fusarium solani respectively

Antioxidant activity: -

The DPPH free radical scavenging activity to assess the extract's antioxidant propertieswas done by using 1, 1-diphenyl 2-picryl-hydrazil (DPPH) as proposed by Alothman et al. [58]. The mixing of 100 µL aliquot from compounds in different concentrations (20-100 mg/L) was done in 3.9 mL taken from 0.1 mM DPPH (methanolic) solution. Then blend was subjected to vortex and left for incubation in the dark for half an hour. Its

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OD was calculated at 515 nm while methanol was used as blank.

The % Radical scavenging activity = [(Ao − Ac) / Ao] x 100

Where A_0 = absorbance of the control & A_c = sample's absorbance at C concentration

Linear plot of concentration versus % inhibition was plotted and by this IC_{50} values were determined. The antioxidant potential of each extract was showed in form of IC_{50} (stated as the quantity of concentration necessary to prevent DPPH radical development by 50%), find out with the help of inhibition curve. Results towards antioxidant action of complexes are shown in **Table 2** and **Fig.**١١.

Table ٢Antioxidant activity

Name of Compound	**Concentration(mg/L)**					**Regression Equation**	**IC50**
	20	**40**	**60**	**80**	**100**		
Complex 1	26.02	28.94	30.99	34.5	36.69	Y=0.1345x+23.358	198.08
Complex 2	29.54	31.66	32.47	34.61	36.67	Y=0.0861x+27.827	257.52
Complex 3	17.54	21.05	22.95	24.56	26.6	Y=0.1082x+16.051	313.76
Complex 4	22.22	22.95	26.6	29.38	32.45	Y=0.1345x+18.653	233.06
Ascorbic acid	48.09	61.11	70.46	72.8	74.85	Y=0.3261x+45.899	12.57

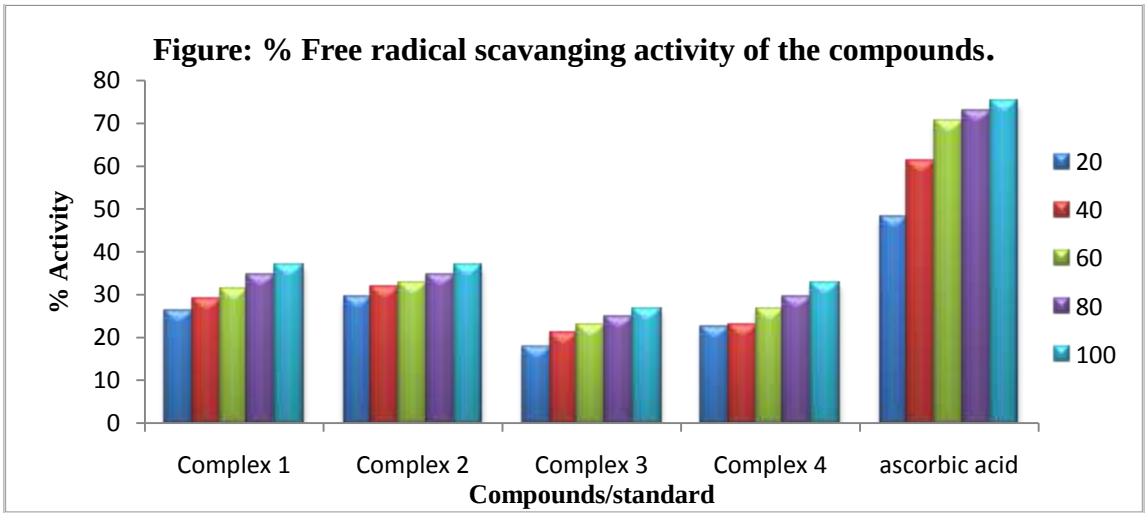

Fig.١١Comparison of the percentage free radical scavenging activity of the complexes with standard ascorbic acid

V. CONCLUSION

Several techniques, including SEM, NMR, mass spectrometry, IR, and UV/Vis, were utilised to construct and characterise Cr(III) complexes with hexadentate macrocyclic ligands. The polarity of the metal ion was reduced by the coordination/ chelation with N-donor ligand within the whole chelate ring, because metal ion shared its partial positive charge with donor group. Against E. coli, **complex-2**exhibited strong antibacterial activity.All complexes showed activity against S. aureus but **complex-3** &**4** showed satisfactory activity. **Complex-1&2**showed good antifungal activity against Alternaria alternate were

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as**complex-2**&**4**showed good antifungal activity against Fusarium solani. **Complex-1**&**Complex-2** showed good antioxidant activity but less than ascorbic acid. Solubility, magnetic moments, decomposition temperature etc. properties also have been discussed.

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