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ICROWAVE SYNTHESIS OF TEMPLATE ENGINEERED BIOPOTENT MACROCYCLIC COMPLEXES INVOLVING NINHYDRIN AND 1, 2-DIAMINOBENZENE

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ABSTRACT

A series of the complexes prepared by the conventional method by template condensation of ninhydrin and 1,2-diaminobenzene in the methanolic medium forming the complexes of the type $[M(TML)X]X_2$; where TML is a tetradentate macrocyclic ligand; M=Cr(III) and Fe(III); $X=Cl^-$, NO_3^-, CH_3COO^- has been reported. In the present work , bioactive Cr and Fe complexes derived from ninhydrin and 1,2-diaminobenzene in the molar ratio 2:2:1 have been engineered via MWI method. The complexes have been characterized in the light of various physicochemical techniques like elemental analyses, conductance measurements, molecular weight determination, magnetic measurements, electronic, infrared , far infrared and mass spectral studies. Molar conductance values predicted them to be 1:2 electrolytes. All these studies point towards the formation of five coordinate square pyramidal geometry for these complexes. It is found that MWI method is economic and fast method as compared to the conventional method. The complexes were also evaluated for their in vitro antibacterial activity. Some of the complexes found to have notable antibacterial activity against pathogenic microbes.

Keywords: Electronic Spectra, Mass Spectra, Magnetic Measurements, Microwave Irradiation, Trivalent Metal Salts, Template Synthesis

I. INTRODUCTION

The chemistry of Schiff base macrocycles has fetched a massive significance both in macrocyclic and supramolecular chemistry in recent years[1-3]. The condensation reaction between diketones and primary diamines in presence of metal ions has played a vital role in the development of tetraaza macrocyclic complexes[4-7]. The family of complexes with aza-macrocyclic ligands has remained a focus of scientific attention for many decades[8].The chemistry of macrocyclic complexes is also important due to their catalytic and biological applications[9]. Some macrocyclic complexes have been reported to exhibit potent antibacterial, antifungal and anti-HIV activities[10-12]. The relationship of electronic properties and reactivity of these synthetic macrocyclic complexes, such as porphyrin[13,14] and corrins continue to promote great interest in their design and preparation. Macrocyclic metal complexes of lanthanides *e.g.* Gd^{3+} are used as MRI contrast agents[15]. Prompted from these applications, in the present work, macrocyclic complexes of Cr(III) and Fe(III)

derived from ninhydrin and 1,2-diaminobenzene are reported. Besides the characterization of complexes by physicochemical technique like IR, mass, elemental analyses, magnetic susceptibility and conductance measurements, the biological activities of the synthesized complexes have been examined against some bacterial strains Bacillus subtilis (MTCC 8509), Bacillus stearothermophilus (MTCC 8508), Escherichia coli (MTCC 51) and Pseudomonas putida (MTCC 121).The results obtained were compared with standard antibiotics Chloramphenicol and Streptomycin.

II. EXPERIMENTAL

2.1 Chemicals

All the chemicals used were of Anal R grade. Metal salts were purchased from E. Merck and were used as received. All the solvents used were of high purity.

2.2 Isolation Of Complexes

All the reported macrocyclic complexes were prepared by template and microwave irradiation methods.

1.2.1 Conventional method

To a hot, well-stirred methanolic solution (~50 ml) of 1,2 diaminobenzene (10 mmol), trivalent chromium or iron salts (Cl^-, NO_3^- and CH_3COO^-) (5 mmol) dissolved in ~20 ml of methanol was added. The resulting solution was refluxed for 0.5 h. After, that ninhydrin (10 mmol) dissolved in ~20 ml methanol was added in the refluxing mixture and refluxing was continued for 6-8 h. The mixture was concentrated to half of its original volume, cooled to room temperature and kept in desiccator for overnight. After overnight standing, dark coloured precipitates were separate out, which were filtered and washed with methanol, acetone, diethylether and dried *in vacuo*.

The syntheses of the complexes may be shown by Fig. (1)

1.2.2 Microwave irradiation method:

A mixture of 1,2 diaminobenzene (10 mmol) dissolved in 5 cm^3 methanol and trivalent chromium or iron salts (5 mmol) dissolved in 5 cm^3 methanol was subjected to microwave irradiation at an output of 300 Watt for a specified time of 0.5-1 min. After that, ninhydrin (10 mmol) dissolved in 10 cm^3 methanol was added to the reaction mixture. Irradiation to the reaction mixture was continued under the specific conditions for the next 1-2 min. The contents were cooled and kept in dessicator. The complexes thus obtained were washed with methanol, acetone, diethylether and dried *in vacuo*.

The syntheses of the complexes by microwave irradiation method may be shown by Fig. (2)

2.3 Analytical and Physical Measurements

The microanalyses of C, H and N were carried out at Sophisticated Analytical Instrument Facility, CDRI, Lucknow. Melting points were determined using capillaries in electrical melting point apparatus. The metal contents were estimated by standard EDTA methods. The magnetic susceptibility measurements were carried at SAIF, IIT Roorkee on vibrating sample magnetometer. Electronic spectra (DMF) were recorded on Cary 14 spectrophotometer. The IR spectra were recorded on Infrared spectrophotometer in the range 4000-200 cm^{-1} using Nujol Mull/KBr pellets. The conductivity was measured on digital conductivity meter (HPG System, G-3001).

2.4 Biological Assay

The synthesized complexes were tested for the antibacterial activity

2.4.1Test microorganisms

Four test pathogenic bacterial strains *viz.* Bacillus subtilis (MTCC 8509), Bacillus stearothermophilus (MTCC 8508), Escherichia coli (MTCC 51) and Pseudomonas putida (MTCC 121) were considered for determination of MIC (Minimum Inhibitory Concentration) of selected complexes.

2.4.2 In-vitro Antibacterial Activity

Primary Screening: The antibacterial activity of synthesized macrocyclic complexes has been evaluated by the agar well diffusion method. All the cultures were adjusted to 0.5 McFarland standards, which is visually comparable to a microbial suspension of approximately 1.5×10^8 cfu/ml. A 20 ml of Muller Hinton agar medium was poured into each Petri plate and the agar plates were swabbed with 100 µl inocula of each test bacterium and kept for 15 min for adsorption. Using sterile cork borer of 8 mm diameter, wells were bored into the seeded agar plates and these were loaded with a 100 µl volume with concentration of 4.0 µg/ml of each metal complex in DMSO. All the plates were incubated at 37°C for 24 h. Antibacterial activity of each synthesized complex was evaluated by measuring the zone of growth inhibition against the test microorganisms with zone reader (Hi Antibiotic zone scale). DMSO was used as a negative control whereas standard antibiotics Chloramphenicol and Streptomycin were used as a positive control. This procedure was performed in three replicate plates for each microorganism.

2.4.3 Determination of minimum inhibitory concentration (MIC) of synthesized complexes

Minimum Inhibitory concentration**(**MIC) of the various complexes against various bacterial strains were tested through a macrodilution tube method. In this method, various test concentrations of the synthesized metal complexes were made from 128 to 0.25 µg/ml in sterile tubes No. 1-10. A 100 µl sterile Muller Hinton Broth (MHB) medium was poured in each sterile tube followed by addition of 200 µl test complex in tube 1. Two fold serial dilutions were carried out from the tube 1-10 and excess broth (100 µl) was discarded from the last tube No-10. To each tube, 100 µl of standard inoculum (1.5×10^8 cfu/ml) was added. Standard antibiotics Chloramphenicol and Streptomycin were used as control. Turbidity was observed after incubating the inoculated tubes at 37°C for 24 h.

III. RESULTS AND DISCUSSION

3.1 Chemistry

The analytical data of metal complexes has been given in TABLE 1, which show that the formula of macrocyclic complexes may be represented as: $[M(C_{30}H_{16}O_2N_4)X]\ X_2$; where M = Cr(III) and Fe(III) and X = Cl^-, NO_3^-, CH_3COO^-. The complexes were soluble in dimethylformammide and dimethylsulphoxide, but were insoluble in water. They were thermally stable up to ~245°C and after that decomposed. The tests for anions were positive both before and after decomposing the complexes, indicating their presence both inside as well as outside the coordination sphere. Conductivity measurement in DMSO indicated them to be 1:2 electrolytes (135-170 S cm^2 mol^{-1}) [16]. Various attempts such as crystallization using mixtures of solvents and low temperature crystallization were unsuccessful in obtaining a single crystal suitable for X-ray crystallography. However, the analytical, spectroscopic and magnetic data enable us to predict the possible structure of the

synthesized macrocyclic complexes. The comparative data of metal complexes of conventional method and microwave irradiation method is given in TABLE 2.

3.2 Infrared Spectra

A pair of strong bands at ~ 3200 and 3250 cm^{-1} corresponding to $\nu(NH_2)$ which is present in the spectrum of 1,2-diaminobenzene but absent in the spectra of all the complexes[17]. A strong peak at ~ 1715 cm^{-1} in the spectrum of all the complexes is attributed to the CO gp. formed by the dehydration of geminal hydroxyl gps. due to heating[18,19]. A new strong absorption band in the region ~ 1590-1645 cm^{-1} was observed which may be attributed to ν(C=N) stretching vibration[20,21]. This confirms the condensation of carbonyl gp. of pyridine and amino gp. of 1,2-diaminobenzene[22,23]. These results provide strong evidence for the formation of macrocyclic frame[24]. The lower value of ν(C=N) indicates coordination of azomethine nitrogen to metal[25]. The bands present at ~1345-980 cm^{-1} may be assigned due to ν(C-N) vibration. The bands appeared at 1460 and ~1515 cm^{-1} may be due to >C=C< skeleton of benzenoid rings. A band at 771 cm^{-1} indicate the C-H deformation of ortho substitution.

The Far infrared spectra show bands in the region ~420-470cm^{-1} corresponding to ν(M-N) vibrations in all the complexes[26,27]. The presence of bands in all complexes in 410-435 cm^{-1} region originate from ν(M-N) azomethine vibrational modes and give an idea about coordination of azomethine nitrogens[28]. The bands present at 295-310 cm^{-1} correspond to ν(M-Cl) vibrations[29,30]. The bands present at 215-255 cm^{-1} in all nitrato complexes are assignable to ν(M-O)[29].

3.3 Mass Spectra

The mass spectra of trivalent chromium(III) and iron(II) macrocyclic complexes derived from ninhydrin and 1,2-diaminobenzene have been recorded using NBA matrix. All the spectra exhibit parent peaks due to molecular ions $[M]^+$ and $[M+2]^+$. The proposed molecular formula of these complexes was confirmed by comparing their molecular formula weights with m/z values. The molecular ion peaks and other fragments arising from the thermal cleavage of the complexes have been given in TABLE 3.

3.4 Magnetic Moments and Electronic Spectra

3.4.1Chromium complexes:

The magnetic moment of chromium complexes was found in the range 3.94-4.15 B.M. The electronic spectra of chromium(III) complexes show bands at ~9155-9240cm^{-1} (ν_1), ~13115-13420 cm^{-1}(ν_2) , ~17442-18314cm^{-1}(ν_3) and ~27218-27652 cm^{-1}(ν_4) respectively. These spectral bands can not be interpreted in terms of four or six coordinated environment around the metal atom . The spectra are comparable with that of five coordinated Cr(III) complexes[31]. Thus, keeping in view the analytical data and electrolytic nature of these complexes, five coordinated square pyramidal geometry can be assigned for these complexes. Thus, assuming the symmetry C_{4V} for these complexes[32], various spectral bands can be assigned as : $^4B_1 \rightarrow {}^4E^a$, ($\nu_1$), $^4B_1 \rightarrow {}^4B_2$, ($\nu_2$), $^4B_1 \rightarrow {}^4A_2$,($\nu_3$) and $^4B_1 \rightarrow {}^4E^b$($\nu_4$), respectively .

3.4.2 Iron complexes*:*

The magnetic moments of iron complexes lay in the range 5.80-5.92B.M. The electronic spectra of trivalent iron complexes show various bands at ~ 9820-9946 cm^{-1}, 15,418-15,825cm^{-1} and 27,535-27,760 cm^{-1}. These

bands do not suggest the octahedral or tetrahedral geometry of the complexes around the metal atom. The spectral bands are consistent with the range of spectral bands reported for five coordinated square pyramidal iron (III) complexes[33]. Assuming C_{4V} symmetry for these complexes, various bands can be assigned as: $d_{xy} \rightarrow d_{xz}$, $d_{xy} \rightarrow d_{yz}$ & $d_{xy} \rightarrow d_{z2}$. Any attempt to make accurate assignment is difficult due to interactions of the metal-ligand-π bond systems lifting the degeneracy of d_{xz} and d_{yz} pair.

3.5 Biological Results and Discussion

In this study, all the synthesized macrocyclic complexes were tested for their *in vitro* antibacterial activity against Gram-positive and Gram-negative bacteria. The antibacterial activity of synthesized macrocyclic complexes has been evaluated by the agar well diffusion method. Minimum Inhibitory concentration (MIC) of the various complexes against various bacterial strains was tested through a macrodilution tube method. Standard antibiotics namely Chloramphenicol and Streptomycin were used for comparison with antibacterial activities shown by these complexes. *Chloremphenicol* showed MIC of 2, 2, 2 and 4 µg/ml against Bacillus subtilis (MTCC 8509), Bacillus stearothermophilus (MTCC 8508), Escherichia coli (MTCC 51) and Pseudomonas putida (MTCC 121), respectively, while Streptomycin showed MIC of 2, 2, 4, 4 µg/ml against Bacillus subtilis (MTCC 8509), Bacillus stearothermophilus (MTCC 8508) Escherichia coli (MTCC 51) and Pseudomonas putida (MTCC 121) respectively. Some complexes of the tested series possessed good antibacterial activity against both Gram-positive and Gram-negative bacteria (TABLE 4, TABLE 5).

Complexes (2) and (3) exhibited good antibacterial activity against the bacterial strain E.coli and B. stearothermophilus with zone of inhibition of 26.2 and 28.1 mm, respectively. Complexes (2) and (3) showed the activity against both Gram (+)ve and Gram (-)ve bacteria with zone of inhibition ranging from 20.4 to 23.6 mm. The values are comparable with the zone of inhibition shown by standard antibiotics Chloramphenicol and Streptomycin. Complex (1) did not show any activity against the bacterial strain P. ptudia.

Complexes (2) and (3) showed remarkable MIC of 4 µg/ml and 2 µg/ml against E.coli and B. stearothermophilus. It is equal to the MIC showed by standard antibiotics Chloremphenicol and Streptomycin for the same bacterial strains. Complex (2) showed MIC of 16 µg/ml against B. subtilus and B. stearothermophilus. Whereas complexes (3) and (4) showed MIC of 16 µg/ml against P. ptudia and E. coli, respectively. Among all the series under testing for the determination of MIC, complex (2) was found to be the most potent complex. Complexes (1), (5) and (6) showed poor antibacterial activity against all bacterial strains among the whole series.

IV. CONCLUSIONS

4.1 Chemistry

Based on various studies like elemental analyses, conductance measurements, magnetic susceptibilities, infrared, mass and electronic spectral studies, a five coordinated square pyramidal geometry as shown in Fig.(3) may be proposed for all of these complexes.

It is found that microwave irradiation method is economic and very fast method as compared to the conventional method and the % yield of the products obtained is much more as compared with the conventional method.

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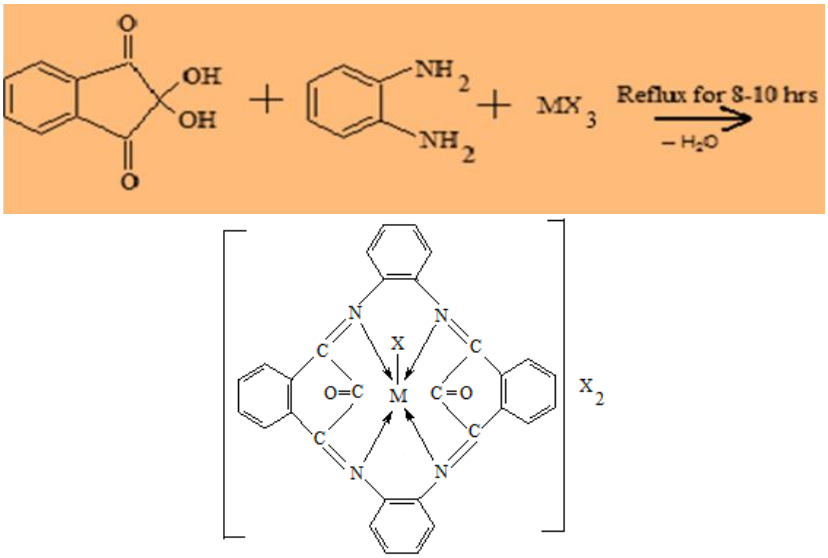
4.2 Biological Activity

In biological studies, none of the synthesized macrocyclic complexes were found to as potent as that of the standard antibiotic; however some of the complexes possess good antibacterial activities. Chelation, solubility, dipole moment, conductivity influenced by metal ion, may be the possible reasons for antibacterial activities of these complexes[33,34]. It also has been observed that some moieties such as azomethine linkage or heteroaromatic nucleus introduced into such compounds exhibit extensive biological activities that may be responsible for the increase in hydrophobic character and liposolubility of the molecules in crossing the cell membrane of the microorganism and enhance biological utilization ratio and activity of complexes[35,36].

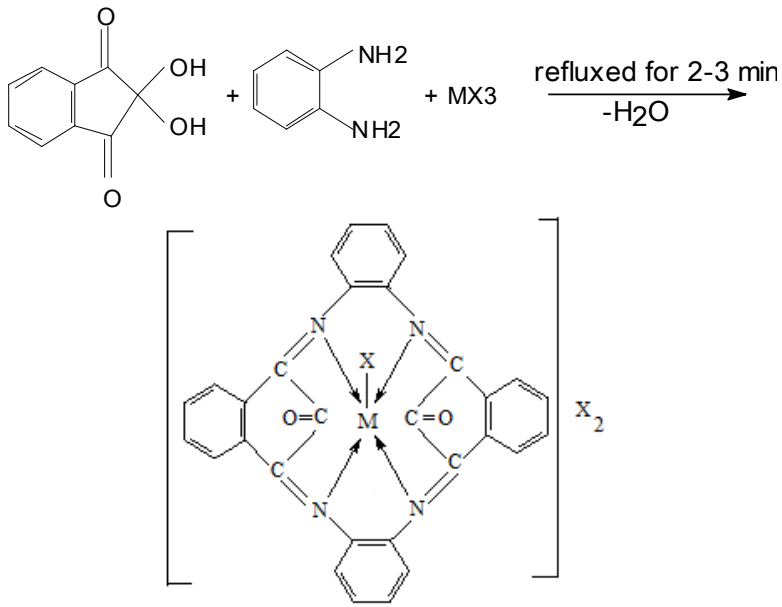
Fig.(1) Schematic representation of synthesis of trivalent complexes by conventional method:



Where M = Cr(III), Fe(III); X = Cl^-, NO_3^-, CH_3COO^-

Figure (1)

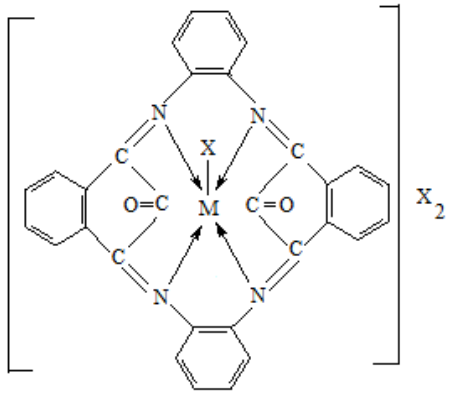
Fig.(2) Schematic representation of synthesis of trivalent complexes by microwave irradiation method:



Where M = Cr(III), Fe(III); X = Cl^-, NO_3^-, CH_3COO^-

Figure (2)

Fig.(3) Proposed structure of the synthesized trivalent complexes:



Where M = Cr(III), Fe(III); X = Cl^-, NO_3^-, CH_3COO^-

Figure (3)

Table 1: Analytical data of trivalent complexes derived from ninhydrin and 1,2-diaminobenzene.

S. No.	Complexes	Color	Found /calcd., %				Mol. Wt. Found/ calcd.	Molar conductance ohm^{-1} cm^2mol^{-1}	$\mu_{eff.}$
			M	C	H	N			
(1)	$[Cr(C_{30}H_{16}O_2N_4)Cl]\ Cl_2$	Dirty green	8.1/ 8.3	57.5/ 57.8	2.3/2.5	8.7/ 8.9	621.6/622.5	132	4.12

(2)	$[Cr(C_{30}H_{16}O_2N_4)(NO_3)](NO_3)_2$	Dark green	7.41 /7.4	51.3/ 51.7	2.9/3.1	13.9 /14.	-/702	138	4.49
(3)	$[Cr(C_{30}H_{16}O_2N_4)(CH_3COO)] (CH_3COO)_2$	Greenish brown	7.50 /7.5	62.3/ 62.6	3.6/3.9	8.1/ 8.4	-/693	166	5.70
(4)	$[Fe (C_{30}H_{16}O_2N_4) Cl] Cl_2$	Shiny green	8.8/ 8.9	57.2/ 57.4	2.4/2.5	8.6/ 8.9	-/626.5	168	5.81
(5)	$[Fe(C_{30}H_{16}O_2N_4)(NO_3)](NO_3)_2$	Dark grey	7.93 /7.9	50.9/ 51.2	2.3/2.6	13.8 /14.	704/706	152	5.70
(6)	$[Fe(C_{30}H_{16}O_2N_4)(CH_3COO)] (CH_3COO)_2$	Black powder	8.03 /8.0	61.9/ 62.2	3.6/3.8	8.0/ 8.4	-/697	154	5.61

Table 2 : Comparative data of trivalent complexes for conventional and microwave method.

		Conventional Method			**Microwave Irradiation Method**		
Sr. no.	**Complex**	**Yield(%)**	**Period(mi n.)**	**Volm. Of solvent(cm^3)**	**Yield(%)**	**Period(mi n.)**	**Volm. Of solvent(cm^3)**
1	$[Cr(C_{30}H_{16}O_2N_4)Cl] Cl_2$	45	415	90	61	3.10	20
2	$[Cr(C_{30}H_{16}O_2N_4)(NO_3)](NO_3)_2$	43	420	90	58	3.18	20
3	$[Cr(C_{30}H_{16}O_2N_4)(CH_3COO)] (CH_3COO)_2$	42	426	90	55	3.24	20
4	$[Fe (C_{30}H_{16}O_2N_4) Cl] Cl_2$	43	418	90	57	3.15	20
5	$[Fe(C_{30}H_{16}O_2N_4)(NO_3)](NO_3)_2$	47	432	90	62	3.28	20
6	$[Fe(C_{30}H_{16}O_2N_4)(CH_3COO)] (CH_3COO)_2$	48	422	90	56	3.22	20

Table 3: FAB mass spectral data of trivalent complexes

S. No.	**Complexes**	**Molecular ion Peak $[M]^+$ & $[M+2]^+$ at m/z**	**Important Peaks due to Complex Fragmentation**
(1)	$[Cr(C_{30}H_{16}O_2N_4)Cl] Cl_2$	$[M]^+$= 622.5(^{35}Cl), $[M+2]^+$ = 624.5(^{37}Cl)	$[Cr(C_{30}H_{16}O_2N_4)Cl]^{+2}$ =551.5, $[Cr(C_{30}H_{16}O_2N_4)]^{+2}$ =516, $[C_{30}H_{16}O_2N_4]^+$ =464
(2)	$[Cr(C_{30}H_{16}O_2N_4)(NO_3)](NO_3)_2$	$[M]^+$ = 702	$[Cr(C_{30}H_{16}O_2N_4) NO_3]^{+2}$ =578.0, $[Cr(C_{30}H_{16}O_2N_4)]^{+2}$ =516, $[C_{30}H_{16}O_2N_4]^+$ =464
(3)	$[Cr(C_{30}H_{16}O_2N_4)(CH_3COO)] (CH_3COO)_2$	$[M]^+$= 693	$[Cr(C_{30}H_{16}O_2N_4)(CH_3COO)]^{+2}$ =575.0, $[Cr(C_{30}H_{16}O_2N_4)]^{+2}$ =516, $[C_{30}H_{16}O_2N_4]^+$ =464

(4)	[Fe ($C_{30}H_{16}O_2N_4$) Cl] Cl_2	$[M]^+$= 626.5(^{35}Cl), $[M+2]^+$ = 628.5(^{37}Cl)	$[Fe(C_{30}H_{16}O_2N_4)Cl]^{+2}$ =555.5, $[Fe(C_{30}H_{16}O_2N_4)]^{+2}$ =520, $[C_{30}H_{16}O_2N_4]^+$ =464
(5)	$[Fe(C_{30}H_{16}O_2N_4)(NO_3)](NO_3)_2$	$[M]^+$ =706	$[Fe(C_{30}H_{16}O_2N_4)\ NO_3]^{+2}$ =582.0, $[Fe(C_{30}H_{16}O_2N_4)]^{+2}$ =520, $[C_{30}H_{16}O_2N_4]^+$ =464
(6)	[Fe($C_{30}H_{16}O_2N_4$)(CH_3COO)] $(CH_3COO)_2$	$[M]^+$= 697	$[Fe(C_{30}H_{16}O_2N_4)\ (CH_3COO)]^{+2}$ =579.0, $[Fe(C_{30}H_{16}O_2N_4)]^{+2}$ =520, $[C_{30}H_{16}O_2N_4]^+$ =464

Table 4: *In vitro* antibacterial activities of synthesized trivalent complexes against test bacteria using agar well diffusion method.

S.No.	Complexes	Diameter of growth of inhibition zone (mm)[x]			
		a	**b**	**c**	**d**
(1)	$[Cr(C_{30}H_{16}O_2N_4)Cl]\ Cl_2$	20.2	18.3	15.4	16.1
(2)	$[Cr(C_{30}H_{16}O_2N_4)(NO_3)](NO_3)_2$	23.6	23.4	20.3	26.2
(3)	$[Cr(C_{30}H_{16}O_2N_4)(CH_3COO)]\ (CH_3COO)_2$	18.4	28.1	23.6	18.8
(4)	$[Fe(C_{30}H_{16}O_2N_4)Cl]\ Cl_2$	18.8	16.3	20.2	23.2
(5)	$[Fe(C_{30}H_{16}O_2N_4)(NO_3)]\ (NO_3)_2$	20.4	16.4	18.2	20.4
(6)	$[Fe(C_{30}H_{16}O_2N_4)(CH_3COO)](CH_3COO)_2$	16.5	18.2	17.2	20.1
(7)	***Chloremphenicol***	**28.8**	**28.4**	**26.2**	**28.7**
(8)	***Streptomycin***	**28.0**	**28.3**	**27.1**	**25.6**

[x] Values, including diameter of the well (8 mm), are means of three replicates

a- Bacillus subtilis (MTCC 8509),

b- Bacillus stearothermophilus (MTCC 8508),

c- Escherichia coli (MTCC 51),

d- Pseudomonas putida (MTCC 121)

***Chloremphenicol, Streptomycin* – Standard antibiotics**

Table 5: Minimum Inhibitory Concentration (MIC) shown by trivalent complexes against test bacteria using macrodilution tube method.

S.No.	Complexes	MIC (µg/ml)*			
		a	b	c	d
(1)	$[Cr(C_{30}H_{16}O_2N_4)Cl]\ Cl_2$	32	64	>128	128
(2)	$[Cr(C_{30}H_{16}O_2N_4)(NO_3)](NO_3)_2$	16	16	32	4
(3)	$[Cr(C_{30}H_{16}O_2N_4)(CH_3COO)]\ (CH_3COO)_2$	64	2	16	64
(4)	$[Fe(C_{30}H_{16}O_2N_4)Cl]\ Cl_2$	64	128	32	16
(5)	$[Fe(C_{30}H_{16}O_2N_4)(NO_3)]\ (NO_3)_2$	32	128	64	32
(6)	$[Fe(C_{30}H_{16}O_2N_4)(CH_3COO)](CH_3COO)_2$	128	64	128	32
(7)	***Chloremphenicol***	**2**	**2**	**4**	**2**
(8)	***Streptomycin***	**2**	**2**	**4**	**4**

* mean of three replicates

a- Bacillus subtilis (MTCC 8509),

b- Bacillus stearothermophilus (MTCC 8508),

c- Escherichia coli (MTCC 51),

d- Pseudomonas putida (MTCC 121)

***Chloremphenicol, Streptomycin* – Standard antibiotics**

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