Catalytical and Anticancer studies of complexes of 2-[(5-Methoxy-1H-Benzimidazol-2-yl)Sulfonyl]-N-Phenylacetamide with Transition metal ions

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ABSTRACT:-

Many important Bio-chemical compounds and drugs of natural origin contain heterocyclic ring structures. Among carbohydrates, essential amino acids, vitamins, alkaloids, glycosides etc. the presence of heterocyclic structures in such diverse types of compounds strongly indicates that these compounds possess different types of the pharmacological activity. The present work has been done in the search of some potential biochemically active derivatives of 2-mercaptobenzemidezole for medicinal as well as nutritional purposes. Currently used compounds which upon substitution at either functional group or linked with heterocyclic rings or molecules with metal ions, many times, capable of performing better. Synthesis of newer molecules is usually carried out by new linkage through functional groups present in molecules. After the synthetic procedure, the newer molecules require spectroscopic characterization in order to ascertain their structure. In the present work ,2-mercapto 5- methoxy benzimidazolmolecule has been linked with N-(4-acetylphenyl)-2-chloroacetamide heterocycles and instrumental methods like C,H,N,S Analyzer , FT IR spectroscopy, MASS spectrometry, UV spectroscopy etc. have been used for structure elucidation and their important biological activities and also catalytic properties have been studied.

Key Words:- Transition metal complexes, 2-[(5-Methoxy-1H-Benzimidazol-2-yl) Sulfonyl]-N- Phenylacetamide (MBSPA), Antimicrobial Activity, Anticancer Activity, catalysis

Introduction:-

The compound2-[(5-methyl-1H-Benzemidezole–2-yl)sulfonyle]–N- phenyl Acetamide (MBSPA) is the important intermediate required for the synthesis of omeprazole. The reactions were also performed in the presence of phase-transfer catalysts.

Experimental:-

Aniline, toluene, TEA (tri ethylamine), dichloromethane, acetone (all analytical grade)and 2-mercapto-5-methoxy-1H-benzimidazole were used for the preparation of ligand. Mg(II),Ca (II), Sr(II) and Ba(II) perchlorates in DMSO were prepared. The exact strength of 0.2M perchloric acid was determined by pH metric titration against 0.2M NaOH solution (standardized with 0.2N oxalic acid). Metal perchlorates were prepared by mixing solid carbonates with perchloric acid solution. To a well stirred solution of 4-methoxy aniline (a) (0.01 mol. 1.23gm) in dichloromethane (0.11 mol. 9.34 gm) acetic anhydride (0.01 mol. 1.02gm) was added drop wise at room temperature in a period of 30 minutes. Organic layer containing N-(4-methoxyphenyl) acetamide (b) (0.01 mol) was taken in a round bottom flask and cooled to 20 -25 0C. To this solution, concentrated sulphuric acid (0.015 mol, 0.8 ml) was added followed by the addition of fuming nitric acid (0.02 mol, 0.88 ml) at 20 – 25 ^{0}c in a period of 2 hours. Organic layer was neutralized by 10% NaOH solution. Methanol (8 ml) was added to crude 4-methoxy-2-nitrophenyl) amide (0.009 mol) and the resulting yellow solution was stirred. NaOH (0.027 mol, .1.08gm) was slowly added to it and refluxed at 80 ^{0}C. Reaction mass was then stirred at room temperature for another 3 hrs. Organic layer containing 4-methoxybenzene -1,2-diamide (0.008mol) was reduced by adding Na_2S $9H_2O$ (0.016mol, .84gm) and $NaHCO_3$ (0.014mol, 1.18gm) and water (6ml). The reaction mixture was refluxed for 5 hours at 80 ^{0}C. Organic layer containing 2-mercapto-5-methoxy-1H- Benzimidazole (1.0gm, 0.0072mole) was cooled at 30 ^{0}C. To this, NaOH (1.08gm, 0.027mole) was added and stirred at room temperature. CS_2 (1.21gm, 0.016 mole) was added slowly in 1 hrs. at temperature below 30^{0}C. Reaction mass was very carefully heated to reflux for 6 hours. Solvent was evaporated under reduced pressure and reaction mass was acidified to pH=2 by adding 33% hydrochloric acid 4.0gm, 0.036mole).Yield: 72%, 254-255 ^{0}C. The organic compound was synthesized out of 11 ml aniline by drop wise addition of 300 ml of the dichloromethane and 25 gm of the potassium carbonate was added then after. Drop wise addition of 25 ml of chloracetyl chloride was followed. The precipitates obtained were filtered. This product –A (2-chloro-*N*-phenylacetamide) (25 gm) was dissolved in 300 ml acetone and the compound – B (2-mercapto-5-methoxy-1H-benzimidazole) (18.78 gm) was mixed with it and this mixture was stirred well with 25 gm K_2CO_3 in ice bath. The light white solid [compound

C] (2-[(5-methyl-1H-Benzemidezole–2-yl) sulfonyle]–N- phenyl Acetamide) was obtained by addition of cold water and purified to give the ligand MBSPA. The formation of complexes was carried out by mixing 50 ml 0.2 M metal perchlorate solution and 50 ml 0.2 M ligand in DMSO solution. The reaction mixture was refluxed for 2.5 to 3.0 hours at 95 ^{0}C temperature. The pH of the above solution was then raised up to 6.5 using with aqueous which resulted in the precipitation of the complex.

Analyses and physical measurements:-

M.P. and TLC were taken with usual apparatus [solvent system for TLC 70% toluene + 30% methanol]. Elemental analyses were performed with a Vario-MICRO CUBE C, H, N, S analyzer. The metal content was determined by titration with a solution of standardized disodium salt of EDTA [1].Magnetic susceptibilities were measured by the Gouy's method [2], at room temperature using $Hg[Co(CNS)_4]$as calibrant. The IR spectra were recorded on a BRUKER ALPHA FT-IR 400 – 4000 cm^{-1} spectrophotometer. The UV – visible spectra were measured on a UV-1800 Shimadzu (Double beam) spectrophotometer. Thermal measurements were performed using a METTLER TOLEDO STAR^e system TGA/DSC1(1150^{0}C) thermal analyzer. The mass spectra analyses were performed with a model QDA of Waters and Alliance 2690 analyzer.

Table: –1 Analytical Data and Some Physical Properties of the Ligand and Metal Complexes.

Metal complex	Molar Conductions In DMSO Mili Mhos cm^{-1}	RfValue	Color	%of Yield	%of Metal Exp. (calc.)	M.P. ^0C	%of C Exp. (calc.)	%of H Exp. (calc.)	%of N Exp. (calc.)	%of S Exp. (calc.)
MBSPA	--	0.368	Cramy white	--	--	173	--	--	--	--
Cr-MBSPA	87.6	0.33	Bright orange	89 %	6.24 (6.88)	>300	53.78 (56.69)	4.76 (4.822)	11.76 (10.59)	8.96 (15.574)
Fe-MBSPA	44.1	0.33	Bright orange	92 %	6.70 (6.99)	189-190	54.85 (60.93)	4.85 (4.555)	10.0 (11.98)	9.14 (19.871)
Co-MBSPA	46.5	0.29	Dark green	96 %	9.42 (9.42)	123-125	53.25 (58.00)	4.71 (4.78)	11.65 (12.09)	8.87 (25.11)
Ni-MBSPA	41.7	0.35	Bright brown	93 %	7.04 (7.6)	180	54.70 (57.78	4.55 (4.455	11.96 (10.89	9.11 (25.568)

*Solvent system = toluene (70 %) : methanol (30%), % of (calc.) = calculated,

% of metal = By EDTA titration method, experimental.

Physico chemical properties:

Molar conductances of complexes indicate nonionic nature. Rf and melting point values suggest complexes formation. Elemental analyses support the molecular formula that is thought of. However, percentages of sulfur do not agree with the experimental values probablybecause of some instrumental disturbances.

IR Spectra:

Infrared spectroscopic technique [3-6] is of an immense importance to organic chemists for the identification of the presence of functional groups as well as carbon skeleton in the organic compounds.

IR (KBr):3282(N-H Stre.),1600 (>C=O stre.), 1444 (-C=N stre.), 1075,1114 (Ar-C-H aromatic), 1330-1444 (-CH_2- stre.), 751,750,759,756 (C-S stre., M= Cr^{3+}), 417(M-S stre., M= Fe^{2+} ,Co^{2+}. Ni^{2+}), 478,462,472 (M-O stre.),673,691,692(M-N stre.), and 673 (o-di substituted benzene stre.). 1454-(CH_2)Scissoring,1395- wagging and twisting,1114 (-C-O-C stre.)-Asymmetric stretching, 1648 (-N-H) in plane bending. All the figures in cm^{-1}.

Mass spectrometry:

Probably the most common uses of mass spectrometry by the chemist is for the accurate determination of molecular weight as well as structure elucidation.

Cr-MBSPA :-Mass m/z : Base peak = 314.1 amu, (B. P. +1) is around 13 % of B.P. (314.1) therefore 12 carbon atoms present in the fragment corresponding to base peak and Base peak +2 presence of = confirms presence of sulphur, Thus base peak is due to ligand molecule MBSPA, Base peak+ metal = 337.67 amu, Base peak – Aniline = 221.1 amu, Base peak + Metal = 365.36amu

Fe-MBSPA:- Mass m/z : Base peak = 314.2 amu ,(B. P. +1) is around 15 % of B.P. (314.1) therefore 14 carbon atoms present in the fragment corresponding to base peak and Base peak +2 = confirms presence of sulphur ,Base peak is due to ligand molecule MBSPA Base peak – Aniline = 221.1 amu , Base peak + Metal = 336.2 amu ,Metal + base peak = 369.21 amu

Co-MBSPA:- Mass m/z : Base peak = 314.2 amu,(B. P. +1) is around 13 % of B.P. (314.1) therefore 12 carbon atoms present in the fragment corresponding to base peak and Base peak +2 = confirms presence of sulphur ,Thus base peak is due to ligand molecule MBSPA ,Base peak – Aniline = 221.1 amu, Base peak + Metal = 336.2 amu, Metal + base peak = 372.3 amu

Ni-MBSPA:- Mass m/z : Base peak = 314.2 amu ,(B. P. +1) is around 13 % of B.P. (314.1) therefore 12 carbon atoms present in the fragment corresponding to base peak and presence of = Base

peak +2 confirms presence of Sulphur.Thus base peak is due to ligand molecule MBSPA . Base peak – Aniline = 221.1 amu , Base peak + Metal = 336.2 amu ,Metal + Base peak = 372.06 amu

Magnetic moments:-

The magnetic moments of the chelates were meausured by the Gouy's method. The room temperature magnetic moment of the solid Cr-MBSPA was found to be 3.98 BM. This indicates three unpaired electrons per Cr(III) ion in octahedral environment. The room temperature magnetic moment of the solid Fe-MBSPA was found to be 5.67 BM. This indicates four unpaired electrons perFe(II) ion in octahedral environment. The room temperature magnetic moment of the solid Co-MBSPA was found to be 5.23 BM. This indicates three unpaired electrons per Co(II) ion in octahedral environment. The room temperature magnetic moment of the solid Ni-MBSPA was found to be 3.13 BM. This indicates two unpaired electrons per Ni(II) ion in octahedral environment.

Table -2 Electronic spectra and Transitions:-

Ion	Cm^{-1}	Assignment
Cr3+	17400 H.S 24600 H.S 37800 H.S	$4A_2g \rightarrow 4T_2g$ $4A_2g \rightarrow 4T_1g$ (F) $4A_2g \rightarrow 4T_1g$ (P)
Fe2+	10000 H.S	$5T_2g \rightarrow 5Eg$
Co2+	16000 H.S 19400 H.S	$4T_1g$ (F) $\rightarrow 4A_2g$ $4T_1g$ (F)$\rightarrow 4T_1g$ (P)
Ni2+	10800 12960 26300	$3A_2g \rightarrow 3T_2g$ $3A_2g \rightarrow 3T_1g$ (F) $3A_2g \rightarrow 3T_1g$ (P)

Table:-3 Magnetic and Electronic Assignment of transition metal complexes.

N 0	Brief name of comple x	Formula	Molecula r weight Gm/mol	Magnetic Suseptibilit y CGS	Magneti c moment (B.M.)	Un pairedele .	Hig h spin/ Low spin	Spin orbit coupin g
1.	Cr-MBSPA	**$[Cr(C_{16}H_{15}O_2N_3S)_2(H_2O)]H_2O$**	**714**	**0.9306x10-5**	**3.9822**	**3**	**--**	**No**
2.	Fe-MBSPA	**$[Fe(C_{16}H_{15}O_2N_3S)_2(H_2O)]$**	**700**	**1.9296x10-5**	**5.6777**	**4**	**Hig h spin**	**Yes**
3.	Co-MBSPA	**$[Co(C_{16}H_{15}O_2N_3S)_2(H_2O)_2]$**	**721**	**1.5931x10-5**	**5.2358**	**3**	**Hig h spin**	**Yes**
4.	Ni-MBSPA	**$[Ni(C_{16}H_{15}O_2N_3S)_2(H_2O)]$**	**702.69**	**0.5853x10-5**	**3.1316**	**2**	**--**	**No**

Thermo gravimetric analysis:-

Thermo gravimetric analysis (TGA) can provid about physical phenomena, such as second-order phase transitions, including vaporization, absorption, sublimation, adsorption and desorption. chemical (especially dehydration), decomposition and solid gas reactions (e.g., oxidation or reduction)[7] TGA is commonly used to determine selected characteristics of materials that exhibit either mass loss or gain due to decomposition, oxidation or loss of volatiles (such as moisture).

Table:-4 Thermo gravimetric analysis

Compound	RT - 150^{0}C			150^0C–250^0C		
	% weight loss	% Loss of weight(gm) for1mole complex	water molecules	% weight loss	% Loss of weight(gm) for1mole complex	water molecule
Cr-MBSPA	3.81	11.01	1	3.65	13.33	1
Fe-MBSPA	1.85	6.82	0	4.72	17.43	1
Co-MBSPA	1.63	6.06	0	9.71	36.94	2
Ni-MBSPA	1.45	5.37	0	4.30	15.95	1

RT = room temperature

BASED UPON THE RESULTS OF PHYSICOCHEMICAL ANALYSES THEIR PROBABLE STRUCTURES ARE AS SHOWN IN FIGURES BELOW.

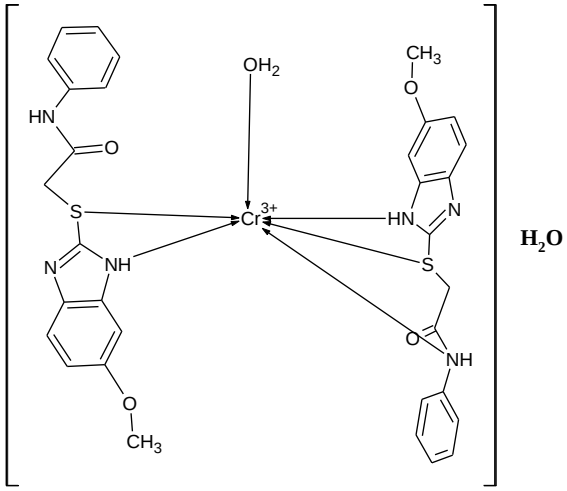

Figure:-1 Cr-MBSPA Structure

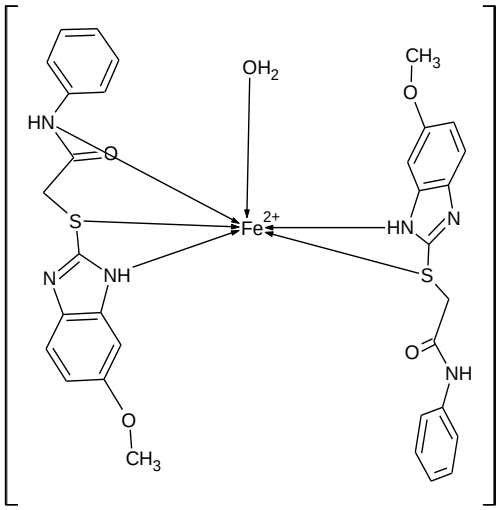

Figure:-2 Fe-MBSPA Structure

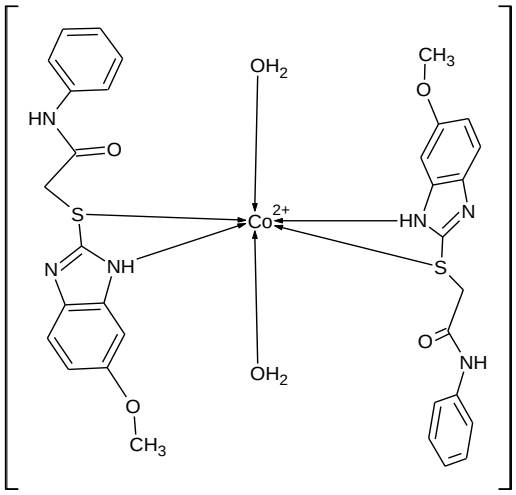

Figure:-3 Co-MBSPA Structure

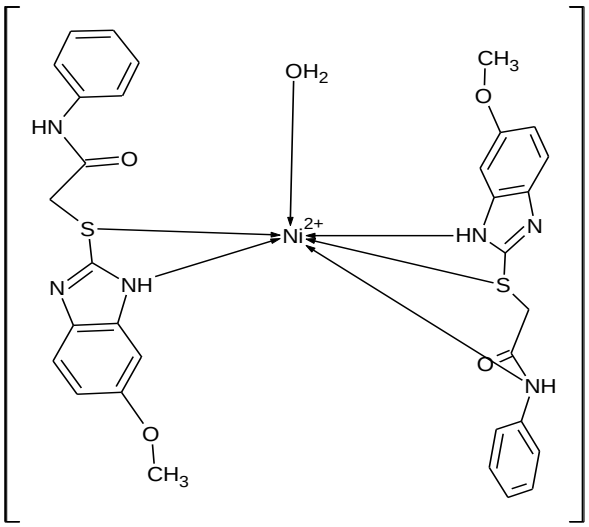

Figure:-4 Ni-MBSPA Structure

Chemical kinetics:-

Three reactions (i)$K_2S_2O_8$ + KI (ii) $KBrO_3$ + KI and (iii) H_2O_2 + KI were selected. These reactions are usually carried out in neutral or acidic medium. The reactions are such that they proceed with moderate velocity K= 10^{-2} to 10^{-5} per minute. The product of all these three reactions is iodine which is titrated with standard aqueous sodium thiosulphate. The rates of all these reactions can easily be measured by simple kinetic methods therefore one of the important applications of coordination compounds, as catalysts, is being investigated [8].

Reactions:-

(i) Reaction-1

$$K_2S_2O_8 + 2KI \longrightarrow 2K_2SO_4 + I_2$$

(ii) Reaction-2

$$KBrO_3 + HCl \longrightarrow KCl + HBrO_3$$

(iii) Reaction-3

$$H_2O_2 + 2HI \longrightarrow 2H_2O + I_2$$

Titration of librated iodine for all:

$$2S_2O_3^{2-} + I_2 \longrightarrow 2I^- + S_4O_6^{2-}$$

Table– 5 Overall results of catalytic activity for complexes of Transition metal ions.

Reactions	k without complex	k with (1%) Cr-MBSPA	k with (1%) Fe-MBSPA	k with (1%) Co-MBSPA	k with (1%) Ni-MBSPA	% Increase in reaction rate at T = 300 K for Cr-MBSPA	% Increase in reaction rate at T = 300 K for Fe-MBSPA	% Increase in reaction rate at T = 300 K for Co-MBSPA	% Increase in reaction rate at T = 300 K for Ni-MBSPA
$K_2S_2O_8$ +KI	2.085 x10-5	1.18 X 10-5	1.10 X 10-5	14.73 X 10-5	1.04 X 10-5	-43.40*	-47.24*	606.47	-50.51*
$KBrO_3$ + HI	1.44 x10-3	1.64 X 10-3	1.83 X 10-4	1.767 X 10-3	1.77 X 10-3	13.88	27.08	22.70	22.91
H_2O_2 + HI	6.78 x10-5	3.29 X 10-4	3.49 X 10-4	3.37 X 10-4	3.51 X 10-4	385.25	414.74	397.05	417.69

*Decrease in the reaction rate

Catalysis of Organic Reaction:-

Azoxybenzene is an azo compound, it gives a substitution reaction. Azoxybenzene also gives intra molecular rearrangement in presence of concentrated H_2SO_4. It reduces to give azobenzene. It can be prepared by boiling with methanol in alkaline medium. Methanol is oxidized to formic acid while nitrobenzene is converted to Azoxybenzene.

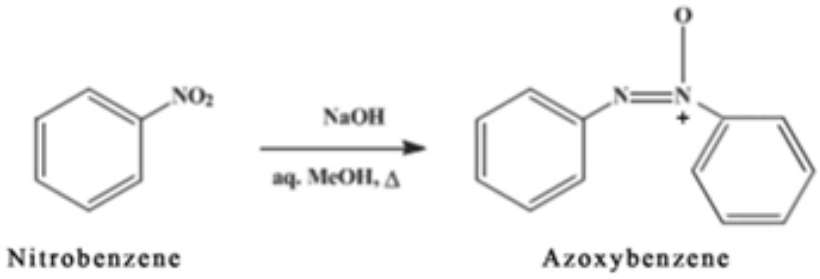

Figure: - 5 Reaction of Azoxybenzene

As per the literature, for this reaction, 23gm of sodium hydroxide is added to a solution of 15 ml of nitrobenzene in 120 ml of methanol. After 3 hours refluxing orangecoloured solution is observed. Then after methanol is distilled as much as possible. After that the reaction mixture is poured in cold water and mixture is made acidic with HCl. The crude azoxybenzene is separated by the separating funnel. The bottom organic layer is collected which solidifies at around 1°C to 2°C.[9]

Table :-6 Percentage yield with catalyst transition metal complex

(% yield for 0.05 % catalyst addition)

	Product Weight without metal complex (3 hours)	Product Weight without metal complex 2 hours	Product weight using Cr-MBSPA as catalyst 2 hours	Product weight using Fe-MBSPA as catalyst 2 hours	Product weight using Co -MBSPA as catalyst 2 hours	Product weight using Ni -MBSPA as catalyst 2 hours
Weight in gram	7.93	4.95	6.14	6.31	6.23	6.28
%yield	86.19%	60.36%	74.87%	76.95%	75.97%	76.58%

Result and Discussion:

The Azoxybenzene formation result is having industrial importance. This is typically carried out for a time period of three hours to yield product. When this reaction is carried out for two, 60.36% yield was obtained on application of 0.05% of transition metal ion complex with MBSPA ligand, the rate of reaction improved as the outcome, percentage yield also increased. The catalytic effectiveness experimental is, Fe-MBSPA > Ni-MBSPA > Co-MBSPA > Cr-MBSPA.

Antibacterial activity

This part deals with the in-vitro screening of newly prepared compounds for antibacterial activity. The species *S.aureus, E.coli, S.Pyogenes*and *P.Aeruginosa*have been taken for the antibacterial activities. Agar-cup method was employed for the in-vitro screening for antibacterial activity.[10]

Table:-6 Standard drugs

Culture	***Well No.***
Bacillus sp.	++
Staphylococcus aureus	+++
E. coli	+++
Salmonella typhi	+++

Table:- 7 Antibacterial activity of MBSPA and transition metal complexes

		Compounds Name			
		Cr-MBSPA	**Fe-MBSPA**	**Co-MBSPA**	**Ni-MBSPA**
Culture	**Well No.**				
Bacillus sp.	**4 (100 µg/ml)**	-	+	-	+
	3 (200 µg/ml)	+	+	-	+
	2 (300 µg/ml)	+	+	+	+
	1 (400 µg/ml)	++	++	+	++
Staphylococcus aureus	**4 (100 µg/ml)**	+	+	-	+
	3 (200 µg/ml)	+	+	+	+
	2 (300 µg/ml)	+	+	+	+
	1 (400 µg/ml)	++	++	+	++
E. coli	**4 (100 µg/ml)**	-	-	-	-
	3 (200 µg/ml)	-	-	-	-
	2 (300 µg/ml)	-	-	+	+
	1 (400 µg/ml)	-	-	+	++
Salmonella typhi	**4 (100 µg/ml)**	-	-	-	-
	3 (200 µg/ml)	+	-	+	+
	2 (300 µg/ml)	+	-	+	+
	1 (400 µg/ml)	+	-	++	+

Zone Size:	**Antibiotic disc/antifungal disc used in practical**
+++ 2.6 to 3.0 cm	**Streptomycin (25 µg/disc) for** *E. coli*, **S. typhi&***S. aureus*
++ 2.0 to 2.5 cm	**Ampicilin (25 µg/ml) for** *Bacillus sp.*
+ 1.0 to 1.9 cm	**Ketoconazole (10 µg/ml) for** Yeast **and** *Aspergillus*
- No zone	**Well Size is 0.8 cm**

Comparison of antimicrobial activity of synthesized compounds with that of standard antimicrobial drugs reveals that the complexes show moderate to good activity against all four bacterial strains, however by and large lower than the standard.

Antifungal activity:

This part deals with the in-vitro screening of newly prepared complexes for antibacterial activity. The species *C. albicans,A. niger*, *A. clavatus* have been taken for the antifungal activities. Here too, the Agar-cup method was used for the in-vitro screening for antifungal activity. [11,12]

Table:-8 Standard drugs

Yeast	+
Aspergillus	+

Table:-9Anti fungal activity of Transition metal complexes

		Compounds Name			
		Cr-MBSPA	**Fe-MBSPA**	**Co-MBSPA**	**Ni-MBSPA**
Culture	**Well No.**				
Yeast	**4 (100 µg/ml)**	-	-	+	-
	3 (200 µg/ml)	-	+	+	-
	2 (300 µg/ml)	-	+	++	-
	1 (400 µg/ml)	-	++	++	+
Aspergillus	**4 (100 µg/ml)**	-	-	-	-
	3 (200 µg/ml)	-	-	+	-
	2 (300 µg/ml)	-	-	+	-
	1(400 µg/ml)	+	+	+	-

+ 1.0 to 1.9 cm **Ketoconazole (10 µg/ml) for** Yeast **and** *Aspergillus*

- No zone **Well Size is 0.8 cm**

Comparison of antimicrobial activity of complexes with that of standard antimicrobial drugs reveals that the synthesized complexes show moderate to good activity against all three fungal strains.

ANTICANCER ACTIVITY:

To study cytotoxic activity of a compound, cytotoxic assays are carried out. It is now well-documented that apoptosis or programmed cell death is the key mechanism by which Chemotherapeutic agents exert their cytotoxicity.

Result and Discussion:

In the present investigation, all the compounds were evaluated against various cell lines named MDA-MB-468, VERO (Normal Cell) and HCT-15 for each tested compound as well as Std. anticancer drug Methotrexate, Dose Response Curve (DRC) against all cell lines was plotted with 10 analysis point i.e. with 10 different drug concentrations. The concentration causing 50% cell growth inhibition (IC50) was determined from DRC using GraphPad Prism software (Ver. 5.04) (GraphPad Software, Inc., USA) and Micorsoft Excel 2007 (Microsoft Corporation, USA) application.

Amongst all the tested compounds, for MDA-MB-468 cell line compound Cr-MBSPA (IC 50 value 42.75 µg/ml)was giving potent inhibitory effect under studied cell line. While, Fe-MBSPA ,Ni-MBSPA and Co-MBSPAhave lowest activity on above said cell line particularly named MDA-MB-468. Similarly for HCT-15 cell line, Co-MBSPA were found to be potent against Human colon cancer cell line. Normal cell study was under taken by using VERO cell and study was indicated that Co-MBSPA and Cr-MBSPA were found to be toxic to normal cell. So, one cannot used for further mechanism based study. While rest of compounds can go for further mechanism based study by selecting their potential IC_{50} values for inhibition. Then after, one can go for further *in vivo* study of the non-toxic compounds series for detail mechanistic study using Tunnel assay, Flow cytometry, DNA fragmentation assay Or CASPACASE assay.

Conclusion:

From above all the results, it can be concluded that compounds Cr-MBSPA give good cytotoxic activity on MDA-MB-468 cell lines (i.e. Human Breast cancer Cell line). While Co-MBSPA compound show potent activity on HCT-15 cell lines (Human Colon Cancer). When normal cell comparison study was carried out, it was proven by study that compounds Co-MBSPA and Cr-MBSPA were toxic to normal cell. All results were compared with standard anticancer drug Methotrexate using IC 50 values for all three cell lines.The concept of testing complex

compounds as anticancer agents is comparatively new. However, certain complex compounds are already used in medicinal application and the present investigation has given several promising results.

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