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Research Article

SYNTHESIS AND BIOCHEMICAL STUDIES OF TRANSITION METAL COMPLEXES OF ISATIN N(4)-METHYL(PHENYL)THIOSEMICARBAZONE

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ABSTRACT

Complexes of Fe(III), Co(II), Ni(II), Cu(II) and Zn(II) with isatin N(4)-methyl(phenyl)thiosemicarbazone (ISTSC)) were synthesized in satisfactory yields. These complexes were characterized based on various physico-chemical methods. The antimicrobial activities of the metal complexes and isatin- N(4)-methyl(phenyl)thiosemicarbazone showed that the complexes are more active than the free thiosemicarbazone ligand. Moreover, *in vitro* cytotoxicity of all the complexes and the ligand against Dalton's Lymphona Ascites (DLA) and Ehrlich's Ascites Carcinoma (EAC) cell lines was assayed and found that they are capable of destroying the cancer cells even at low concentrations. In particular, the Cu(II) complex, [CuL]Cl.H2O exhibited higher cytotoxicity against the above cancer cell lines with an IC50 value of 38 µg/ml.

Keywords: Antimicrobial activities, *in vitro* cytotoxicity, isatin N(4)-methyl(phenyl)thiosemicarbazone, Dalton's Lymphona Ascites (DLA) cell

INTRODUCTION

The superabundant interest in the preparation of a new ligand in inorganic chemistry is ascribed to the formation of structurally varied coordination compounds, endowed with potential applications. Hence, the synthesis and characterization of nitrogen and sulfur donor ligands, especially thiosemicarbazones, have received considerable attention and they became the main research areas in coordination chemistry due to their broad range of pharmacological applications and a positive response in their antibacterial, antiviral and antitumor activities. Incorporation of metals onto these thiosemicarbazone ligands can result in an exceptionally stable and attractive metal chelates with a modified or enhanced biological activity[1,2]. In addition to enhanced biological activity, metal complexes of thiosemicarbazones and substituted thiosemicarbazones through synergic effects, also lead to reduced toxicities and have turn out to be a reliable source for discovering novel biologically active compounds[3,4].

It is prominent that the first-row transition metals are important in human life and many indole derivatives generally present endogenously in both human and other mammalian tissues, is a major structural motif found in several pharmacologically active compounds. Isatin, an indole derivative possesses potentially significant biological activity by virtue of its distinctive size and privileged electronic properties[5-7]. Thus, the first-row transition element and indole moiety together with the thiosemicarbazone give rise to a biologically active drug due to their cooperative efficacy.

The biological studies of iron, cobalt, nickel, copper and zinc complexes of isatin-β-thiosemicarbazone, carried out *in vitro* on human leukaemic cells have revealed that the free ligand and the copper complex are more active in the inhibition of cell proliferation than the other complexes, and no compound was capable of inducing apoptosis[8]. Among the thiosemicarbazones, those with electron withdrawing substituents at N(4)-position have been studied extensively due to their promising biological and cytotoxic activity[9-12]. In view of the above literature survey, which revealed the pronounced biological activities of thiosemicarbazone and related compounds of isatin, it is considered worthwhile to report the synthesis and evaluate the biocidal activities of isatin N(4)-methyl(phenyl) thiosemicarbazone as well as its metal(II) complexes.

MATERIALS AND METHODS

All the chemicals and solvents of Analytical Reagent grade were used without further purification. The metal salts used mainly include chlorides of Fe(III), Co(II), Ni(II) and Cu(II) and acetate of Zn(II). Solvents like methanol, ethanol, diethyl ether, petroleum ether, chloroform and dimethyl sulphoxide were used for the preparation, extraction and recrystallisation of the ligand and its complexes. The solvents of spectroscopic grade were used for the spectral studies. Physical constants such as melting points of all the compounds were found out using a Fisher-Johns apparatus. Elemental microanalyses of the compounds were conducted by Vario EL-III CHNS analyzer. The ligand and its complexes were also characterized by various techniques that include ^{1}H-NMR, IR and UV-Vis spectroscopy. The magnetic susceptibility measurements of the complexes were carried out by Gouy method at room temperature using a magnetic susceptibility balance and Hg[Co(NCS)$_4$] as the calibrant. The diamagnetic corrections were obtained by adding the diamagnetic contributions of various atoms and structural units using Pascal's constants[13]. The effective magnetic moments were then calculated from the corrected molar susceptibilities.

Synthesis of isatin N(4)-methyl(phenyl)thiosemicarbazone

Isatin N(4)-methyl(phenyl)thiosemicarbazone was synthesized by refluxing methanolic solutions of isatin (0.05 mol) and N(4)-methyl(phenyl)thiosemicarbazide (0.05 mol) in the presence of a catalytic amount of glacial acetic acid on a water bath for less than 2 h. An orangish-yellow solid separated at room temperature was filtered and dried under vacuum.

Synthesis of the thiosemicarbazone complexes

The complexes of isatin N(4)-methyl(phenyl)thiosemicarbazone were prepared by adding warm methanolic solution of hydrated metal chlorides (0.05 mol in 15 ml) of Fe(III), Co(II), Ni(II), Cu(II) or acetate (0.025 mol in 15 ml) of Zn(II) to an ethanolic solution of the ligand. The mixture was refluxed for 4 h on a water bath. The resulting solution was evaporated, and the complexes formed were filtered off, washed several times with methanol and dried under vacuum.

Characterization of the ligand and its complexes

The structure of the ligand was confirmed from elemental analysis, infrared, UV-Vis and ^{1}H NMR spectral studies. Physical characterization of the complexes was done and further characterized by infrared, electronic spectral studies and magnetic susceptibility measurements. Scheme 1 shows the preparation of the ligand and its Cu(II) complex. Their physico-chemical properties are presented in Table 1. The structures of the ligand and Cu(II) complex are shown in Figure 1.

Cytotoxicity studies

The drug was prepared by dissolving 50 mg of the copper complex in 1 ml dimethyl sulphoxide (DMSO). This solution was further diluted with distilled water to get the desired concentrations for *in vitro* and *in vivo* cytotoxicity studies. The cell lines of Dalton's Lymphona Ascites (DLA) and Ehrlich's Ascites Carcinoma (EAC) were entrenched into the intraperitoneal cavity of the mouse. The cell lines required for the above cytotoxic studies were obtained from Adayar Cancer Institute, Chennai.

Female mice (24-29 g) required for the study were obtained from the Small Animal Breeding Station (SABS), Mannuthy, Thrissur, Kerala. These animals were retained under the standard conditions in the animal house of Amala Cancer Research Centre. They were fed with standard mouse chow (Sai Durga Feeds and Foods, Bangalore, India) and water. These female mice were housed in ventilated cages (six each) in air-controlled rooms (25^0C). The animals got approved from the Institutional Animal Ethics Committee (IAEC), and the experiments were done strictly according to the strategy of Committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA) constituted by the Animal Welfare Division, Government of India.

The phosphate buffered saline (PBS) prepared from NaCl (8.00 g), KCl (0.20 g), $Na_2HPO_4.2H_2O$ (1.44 g) and KH_2PO_4 (0.20 g) was dissolved in distilled water and further diluted upto 1 litre, which has a pH of 7.2.

The preparation of normal saline was done by dissolving AR NaCl (0.85 g) in 100 ml distilled water.

Trypan blue exclusion method for *in vitro* cytotoxic studies

The short-term *in vitro* cytotoxicity of isatin N(4)-methyl(phenyl)thiosemicarbazone and its metal(II) complexes were studied using Dalton's lymphoma ascites (DLA) cells. The tumour cells aspirated from the peritoneal cavity of tumour bearing mice were washed three times with PBS or normal saline. Cell viability was checked by Trypan blue exclusion method. Viable cell suspension ($1x10^6$ cells in 0.1 ml) added to different concentrations of the drug were made upto 1 ml with PBS and incubated for 3 h at 37^0C. The cell suspension mixed with 0.1 ml of 1% Trypan blue, was loaded after 2-3 minutes on a haemocytometer. The blue colour will be taken up by the dead cells while the live cells will not. The percentage of dead cells was determined with a haemocytometer, by counting separately the number of stained and unstained cells.

Cytotoxic studies of copper(II) complex of ISTSC

Twenty four Swiss albino female mice were grouped into four (6 animals per group). According to the dosage of drug treatment, they were grouped as, Group 1: 5 mg/kg, Group 2: 10 mg/kg, Group 3: 20 mg/kg, Group 4: 25 mg/kg. The drug administration was done once in a day (i.p) and continued upto 6 weeks, inorder to observe their mortality rate.

Effect of copper(II) complex of isatin N(4)-methyl(phenyl)thiosemicarbazone on the animals bearing ascites tumour

This study was carried out with five groups of six female mice in each group, weighing 24-29 g and of 6-8 weeks old. Viable EAC one million cells in 0.1 ml PBS were aspirated from the peritoneal cavity and injected intraperitoneally to the mice to develop the ascites tumour. There were five groups of six animals each, with the control and standard drug (cyclophosphamide) in Group 1 and 2 respectively. Groups 3, 4 and 5 were treated with a drug concentration of 5 mg, 10 mg and 20 mg per kg body weight of the animal. The prepared drug concentrations and the standard drug (cyclophosphamide) were given intraperitoneally. The fatality pattern of the animals were noted and the life span increase was calculated using the equation, % ILS = [T-C/C x 100], where, T and C are mean survival rate of treated and control mice, respectively.

Effect of copper(II) complex of isatin N(4)-methyl(phenyl)thiosemicarbazone on the expansion of solid tumour

This study was carried out on five groups of Swiss albino female mice (6-7 weeks old), with each group comprising of six animals. Tumour induction was done by injecting 0.1 ml of one million DLA cells into the right hind leg of each mouse. The control and cyclophosphamide treated groups were 1 and 2, whereas, groups 3, 4 and 5 were treated with the different concentrations of copper(II) complex of ISTSC. The tumour development in animals of each group was determined, right from the 7 th day of tumour induction. This was done by measuring the tumour growth diameter in two vertical planes by a digital vernier caliper, and it was continued for 34 days. The size of tumour growth was calculated using, $V=4/3\pi r_1^2 r_2$, where, r_1 and r_2 are the minor and major diameters obtained from the vernier caliper[14].

Antimicrobial screening

The antimicrobial activities of the ligand and its metal(II) complexes were screened against two-Gram positive bacteria;

Staphylococcus, Bacillus and two Gram negative bacteria; *Pseudomonas, Escherichia coli* and two fungal cultures; *Penicillium* and *Aspergillus species*, by Kirby Bauer or Disc diffusion method.

Antibacterial activity by Kirby Bauer or Disc Diffusion Method

Antibacterial test was done by Disc diffusion method (Collins & Lyner.,1987) [15] with some modifications. The bacterial cultures maintained in nutrient broth, was prepared from the yeast extract (1.5 g), sodium chloride (5 g), peptic digest of animal tissue (5 g) in 1000ml distilled water. Nutrient agar was prepared from the yeast extract (1.5 g), sodium chloride (5 g), peptic digest of animal tissue (5 g), agar (15 g) in 1000ml distilled water and agar plates were used for keeping the culture media. Sterile filter paper discs of 3mm diameter were placed on the surface of nutrient agar plates at a distance of 2cm using sterile forceps. The drug was dissolved in 2% DMSO and it was found to have no unfavorable effect on the bacterial cultures. Appropriate concentration of the drug was prepared from the stock solution in DMSO. A drug concentration of 200 µg/ml was added on each disc using a micropipette. Disc with DMSO, but without drug was used as control and the standard drug, Ciprofloxacin of the same concentration was used to compare the antibacterial activities of the compounds. Then the plates were incubated at 37^{o}C for 24 hrs. After incubation, the measured zone diameter was found to be greater for the compounds than the control, but comparable with the standard drug.

Antifungal activity by Kirby Bauer or Disc Diffusion Method

Antifungal activity was also studied by Disc diffusion method (Collins & Lyner., 1987)[15]. The fungal cultures were maintained in Sabouraud's dextrose broth. Each culture was distributed homogeneously on Sabouraud's dextrose agar (SDA) plates. Sterile filter paper discs of 2mm diameter were placed on the surface of SDA plates. The drug of concentration 200 µg/ml was added on each disc with a micropipette. The control was 2% DMSO and Fluconazole (200 µg/ml) was taken as the standard drug. The antifungal activities of the ligand and its metal complexes was then compared with the control and the standard drug. The plates were kept at room temperature for 2 days. After incubation, the measured zone diameters showed a comparable activity of the compounds with Fluconazole, but highly active than the control.

RESULTS

Short-term *in vitro* cytotoxic studies

The short-term *in vitro* cytotoxic action of the ligand and its complexes on DLA cells showed a marked activity (Table 2). The copper(II) complex showed an outstandingly high cytotoxicity with an IC_{50} value of 38 µg/ml (Figure 2), while the free ligand exhibited 70% cytotoxic activity.

Toxicity studies

The toxicity studies of copper(II) complex performed on four groups of twenty four Swiss albino mice, at four different concentrations of 5, 10, 20 and 25 mg/kg, showed that the last concentration of 25 mg/kg was toxic to animals. Hence, the *in vivo* studies were done using 5, 10 and 20 mg/kg concentrations.

Effect of copper(II) complex of isatin N(4)-methyl(phenyl)thiosemicarbazone on animals bearing ascites tumour

The animals of the control group bearing ascites tumour survived for 15 days. While the cyclophosphamide drug-treated animals survived until a stage of 24.7 days (Figure 3). Dosage of copper(II) complex at 5, 10 and 20 mg/kg increased the continued existence of animals by 19.6, 21.2 and 18.3 days, respectively. Hence, the copper(II) complex of ISTSC was found to be capable of increasing the duration of life of the animals by 30.7, 41.3, and 22%, respectively, at 5, 10 and 20 mg/kg (Table 3).

Effect of copper(II) complex of isatin N(4)-methyl(phenyl)thiosemicarbazone on the development of solid tumour

The copper(II) complex treated animals showed a considerable reduction in the tumour volume, whereas, the tumour volume got enlarged to 2.8432 cm^3 on the 34th day in the control group animals. The tumour volume reduced to 0.2529 cm^3 in the cyclophosphamide (standard drug) treated group. The tumour volumes at concentrations of 5 and 20 mg/kg were 1.4425 and 1.3373 cm^3, while the tumour volume was 1.0734 cm^3 at 10 mg/kg, respectively (Table 4).

Antibacterial activity of isatin N(4)-methyl(phenyl)thiosemicarbazone and its metal(II) complexes

The antibacterial effects of the samples were tested against a set of clinically important species of two-Gram positive and two-Gram negative bacteria by Disc diffusion method. After incubation, the inhibition zone diameter was measured in millimeter. A comparative study of the ligand and its complexes against the tested bacterial strains indicate that the metal complexes exhibit a higher activity than the ligand (Figure 4).

Antifungal activity of isatin N(4)-methyl(phenyl)thiosemicarbazone and its metal(II) complexes

The antifungal activities of the thiosemicarbazone ligand and its metal(II) complexes were tested against two species, *Penicillium* and *Aspergillus* by Disc diffusion method. After incubation, the ligand and its complexes yielded clear zone of inhibition around the disc (Figure 5).

DISCUSSION

The common feature of compounds with the carcinostatic potency is the presence of NNS or ONO donor atoms. Thus, the anticancer studies carried out on isatin N(4)-methyl(phenyl)thiosemicarbazone and its transition metal complexes have proven their cytotoxic potentiality against EAC and DLA cell lines. The copper(II) complex was found to be proficient against DLA and EAC induced tumours and showed the maximum cytotoxicity with an IC_{50} value of 38 µg/ml. In both the cell lines, a body weight of 10 mg/kg showed marked effect than the two other concentrations of 20 and 5 mg/kg b.wt. Thus the present study has proved the copper (II) complex of isatin N(4)-methyl(phenyl)thiosemicarbazone as a potential anticancer agent at a medium concentration.

TABLE 1: ANALYTICAL AND APHYSICAL DATA OF THE THIOSEMICARBAZONE LIGAND AND ITS COMPLEXES
* Isatin N(4)-methyl(phenyl)thiosemicarbazone, ******BohrMagneton,

Compound (formula)	Mol. Wt	Color	M.p (°C)	Found (calculated) %				μ_{eff} (B.M)**
				%C	%H	%N	%S	
ISTSC (HL)* $C_{16}H_{14}N_4OS$	310.13	Orange-Yellow	183	61.81 (61.91)	4.58 (4.51)	18.17 (18.07)	10.43 (10.31)	-
$[FeL_2]Cl.H_2O$ $C_{32}H_{28}ClFeN_8O_3S_2$	728.61	Brown	225	52.74 (52.70)	3.79 (3.84)	15.40 (15.37)	8.67 (8.78)	5.63
$[Co(LH)_2Cl_2]C_{32}H_{28}Cl_2CoN_8O_2S_2$	748.34	Maroon	234	47.68 (47.92)	3.26 (3.24)	17.42 (17.47)	7.89 (7.99)	5.28
$[NiL_2].2H_2O$ $C_{32}H_{30}NiN_8O_4S_2$	713.10	Light Maroon	249	53.89 (53.85)	4.17 (4.21)	15.76 (15.71)	8.86 (8.97)	3.13
$[CuL]Cl.H_2O$ $C_{16}H_{15}ClCuN4O_2S$	425.48	Dark Brown	255	53.62 (53.54)	4.10 (4.18)	15.43 (15.61)	8.84 (8.92)	2.12
$[ZnL_2].2H_2O$ $C_{32}H_{30}ZnN_8O_4S_2$	720.26	Light Red	218	55.86 (55.79)	4.58 (4.65)	16.21 (16.27)	9.21 (9.30)	Diam.

TABLE 2*: IN VITRO* CYTOTOXICITY OF LIGAND AND ITS METAL(II) COMPLEXES
*Isatin N(4)-methyl(phenyl)thiosemicarbazone

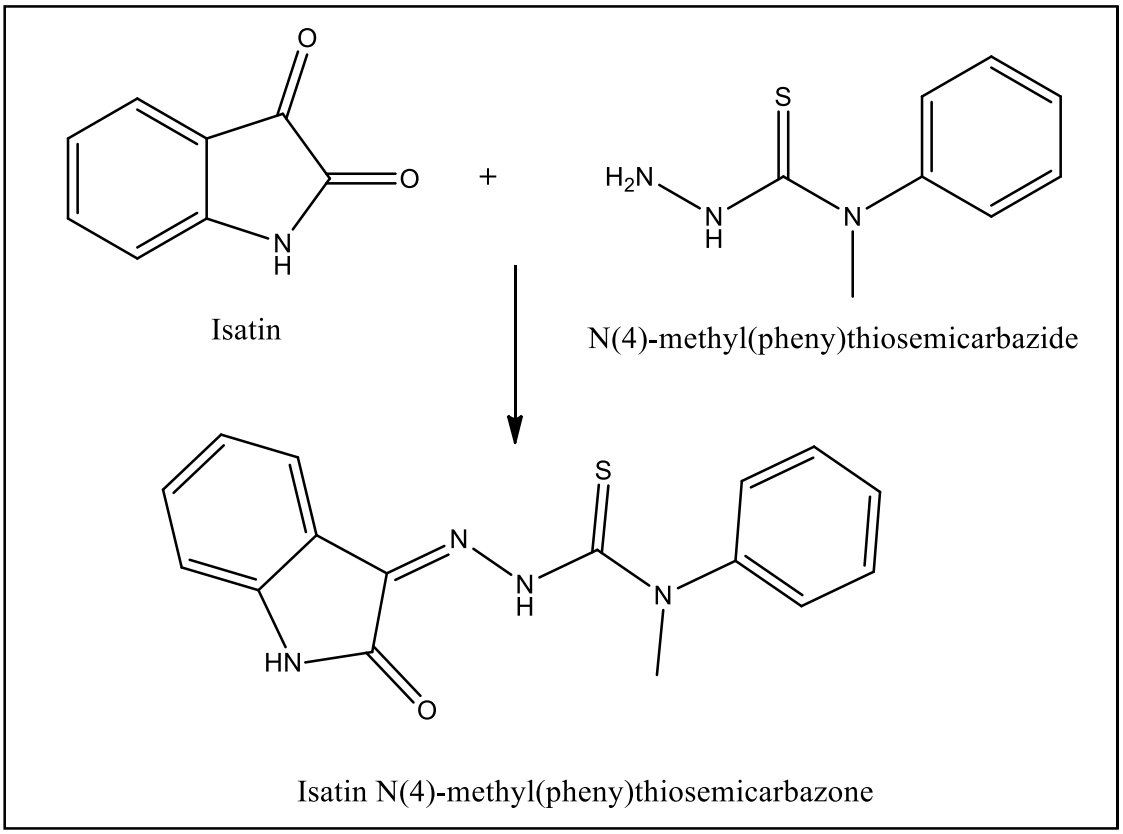
Drug Concentration (µg/ml)	Percentage of Cytotoxicity of complexes and ligand					
	Fe(III)	Co(II)	Ni(II)	Cu(II)	Zn(II)	ISTSC*
10	4	7	4	35	6	4
20	8	14	11	42	12	18
50	16	26	28	60	30	32
100	32	32	41	83	58	56
200	48	40	60	95	72	70

TABLE 3: EFFECT OF COPPER (II) COMPLEX OF ISTSC ON THE LIFE SPAN OF MICE BEARING ASCITES TUMOUR
*Cyclophosphamide drug (10 mg/kg)

Drug Treatment (mg/kg)	Increase in life span (%)
Control	-
20	22.0
10	41.3
5	30.7
Standard*	64.5

TABLE 4: EFFECT OF COPPER COMPLEX OF ISTSC ON THE DECREASE OF TUMOUR VOLUME (cm^3)
*Tumour volume in cm^3, **Cyclophosphamide drug (10 mg/kg)

Drug Treatment (mg/kg)	Number of days of observation (V* in cm^3)							
	Initial	10	14	18	22	26	30	34
Control	0.082	0.584	0.725	1.972	2.124	2.423	2.724	2.843
5	0.07	0.703	1.024	1.446	1.685	1.539	1.631	1.442
10	0.069	0.432	0.563	0.872	0.925	1.134	1.237	1.073
20	0.072	0.512	0.641	1.312	1.523	1.775	1.146	1.337
Standard **	0.074	0.225	0.251	0.384	0.421	0.485	1.063	0.253



$$MCl_2.xH_2O + 2LH \rightarrow [ML]Cl.H_2O \text{ where, } M=Cu(II)$$

Scheme 1 Synthesis of the thiosemicarbazone ligand and its Cu(II) complex.

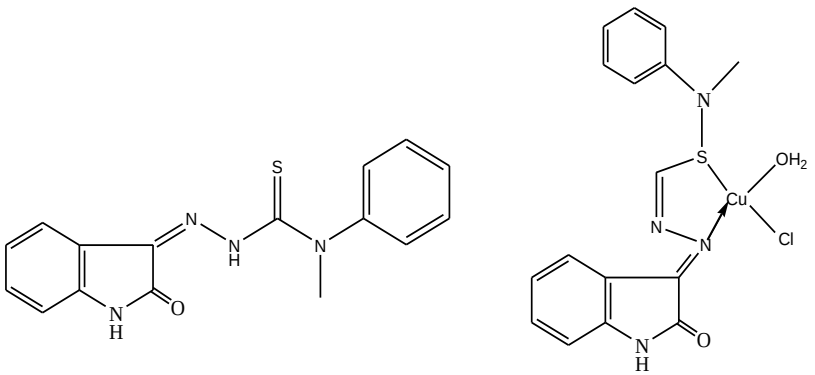


Figure 1 Structures of isatin N(4)-methyl(phenyl)thiosemicarbazone and its Cu(II) complex

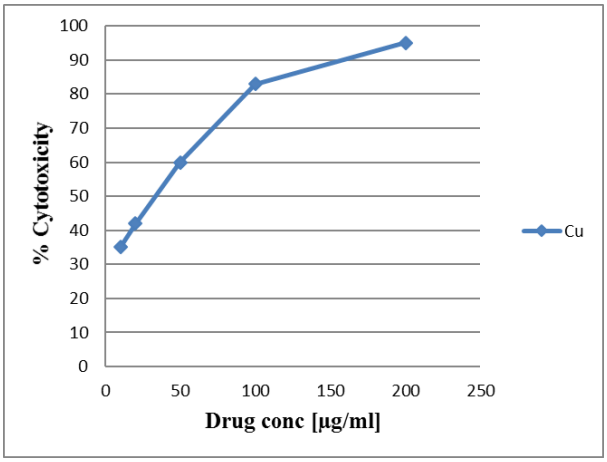


Figure 2 Cytotoxic action of the copper(II) complex of isatin N(4)-methyl(phenyl)thiosemicarbazone

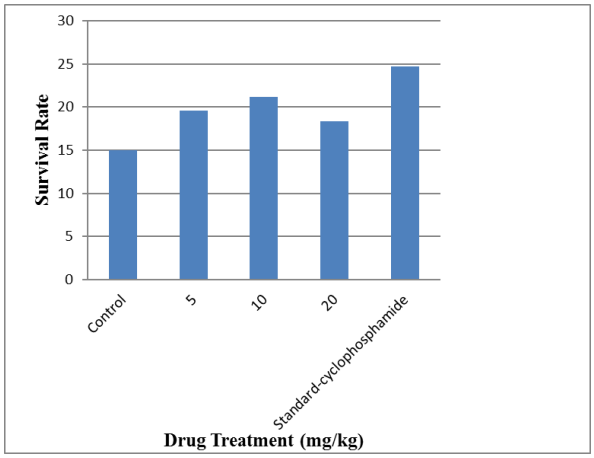


Figure 3 Effect of copper(II) complex of isatin N(4)-methyl(phenyl)thiosemicarbazone on the survival rate of ascites tumour bearing mice

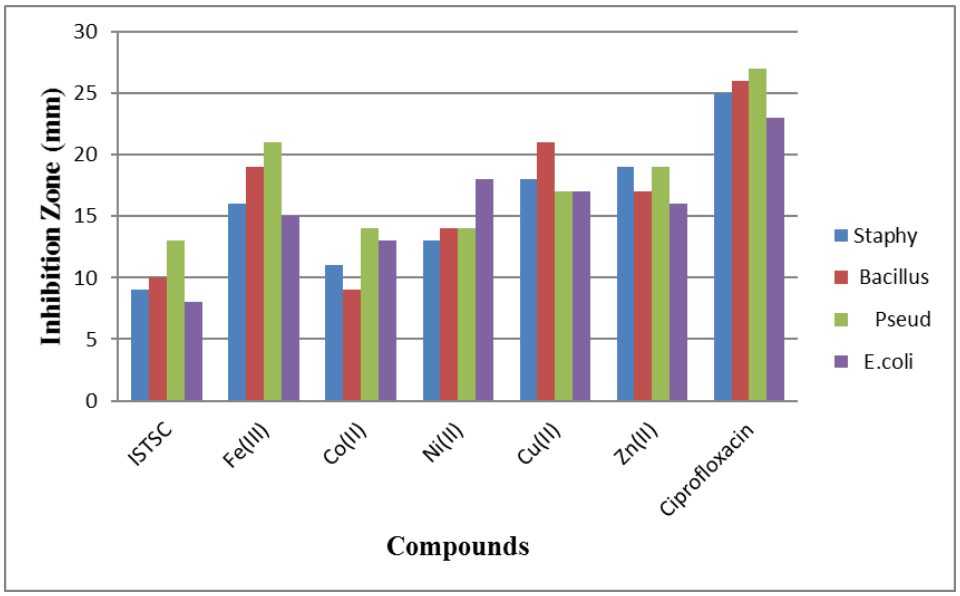


Figure 4 Antibacterial activity of isatin N(4)-methyl(phenyl)thiosemicarbazone and its complexes

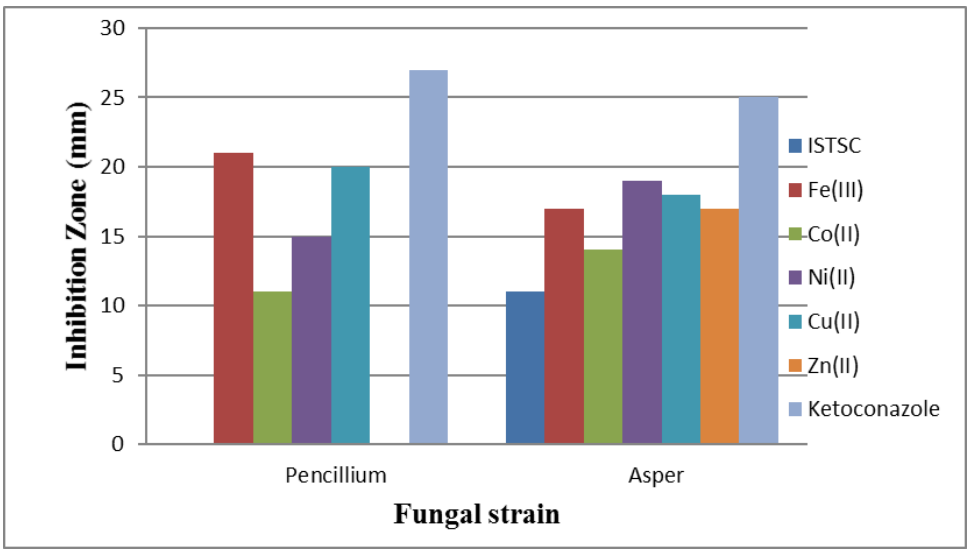


Figure 5 Antifungal activity of isatin N(4)-methyl(phenyl)thiosemicarbazone and its complexes

Though copper is essential for normal physiology, increased copper levels in tissues leads to cancer development. Hence, copper chelators have been developed as anti-cancer agents The cytotoxic potential of the thiosemicarbazone chelated copper complex in comparison with the ligand ISTSC may be due to the lipophilicity of the drug, which arises due to the metal coordination. This may lead these molecules to cross the cell wall barriers and form hydrogen bonds with the nitrogen base pairs of DNA, thereby, reducing the normal cell metabolism and block the base replication to inhibit the tumour growth[16]. Nevertheless, the real pathway by which the copper(II) complex exhibits antitumour activity is not acknowledged, but it is implicit that this will be taking place on the structure activity relationship like in the case of *cis*-platin[17].

A comparison of the antibacterial activities of the ligand and its complexes was done against the four bacterial cultures. The complexes of Co(II), Cu(II), Ni(II), Fe(III) and Zn(II) showed higher antibacterial effects than the ligand. The studies revealed that almost all the compounds show significant antibacterial activity against all the tested organisms in different manners.

Moreover, the thiosemicarbazone ligand and its metal complexes were screened to assess their antifungal activities against two fungal species- *Penicillium* and *Aspergillus*. The results showed that the complexes of Co(II), Ni(II), Fe(III) and Cu(II) are more effective towards the fungal cultures than the ligand and the Zn(II) complex.

Thus, the results obtained from antimicrobial activity of the synthesized derivatives show that the complexes are more active towards various organisms than the ligand. Such a mode of higher biological activities of the complexes may be due to the effect of metal ion in the chelated form that disturbs the normal cell process. This in turn, prevents the protein synthesis thereby, inhibiting the further growth of the organisms. The exact biochemical means by which the complexes exhibit increased activity is not truly apparent, but possibly be explained on the origin of Tweedy's chelation theory and Overtone's concept[18,19]. According to Overtone's concept of cell permeability, only liposoluble materials will pass through the lipid cell membrane. Therefore, liposolubility is an important factor that enhances the antifungal and antibacterial activities. In the complexes, the polarity of metal ion will be reduced on chelation. This is in accordance with the Tweedy's chelation theory, which predicts the overlap of ligand orbitals with the metal orbitals and thereby, a partial sharing of positive charge of the metal ion with the ligand donor atoms. This in turn, increases the π electron delocalization over the whole chelate ring, thereby making the complexes more lipophilic. This enhanced lipophilicity facilitates the penetration of the metal complexes through the lipid membranes and thereby, blocking the metal binding sites in the microbial enzymes[20,21]. Furthermore, the mode of inhibitive action of the complex compounds can be explained based on their structure. The presence of a hetero aromatic moiety and an azomethine group in the synthesized complexes form hydrogen bonds with the active centres of various cell constituents, which is responsible for their extensive biological activities[22,23].

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