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**SYNTHESIS AND CHARACTERIZATION OF BENZIL THIOSEMICARBAZONE Au (III) COMPLEXES
AS POTENTIAL ANTICANCER DRUGS**

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Introduction

The investigation of metal complexes with sulfur containing Schiff bases is a subject of current interest and it has been shown that many of them present anticancer activity [1,2]. A particular important group of such ligands include those containing thiosemicarbazone moieties, because complexes formed with many of the first row transition metals have shown a wide range of biological properties [3–5]. Thiosemicarbazones are sulfur donor ligands and modified thiosemicarbazones as ligands is of interest not only for their pharmacological properties as antibacterial, antiviral and anticancer agents but also as powerful metal-binding (chelating) agents. These biological activities are often attributed to their chelating ability with metal. Marked antitumor activity has been shown by thiosemicarbazones as well as a substantial number of N⁴ substituted thiosemicarbazones [6]. Several benzils and their derivatives exhibited excellent antiproliferative activity by inhibiting the cell growth and antimetabolic activity by arresting the cell cycle and have received significant attention because of their simple chemical structures, excellent antitumor efficacy and novel mechanism of action [7]. Medical and therapeutic value of gold has been recognized thousands of years ago and since Au (III) is iso-electronic with Pt (II) and tetra coordinate Au (III) complexes have the same square-planar geometries as Cis-platin, the activity of Au(III) compounds has been investigated [8]. Studies were reported on transition metal (Cu, Co, Ni, Cd, Zn, Pd, Pt, Ru, Rh & Ir) complexes with Benzil monothiosemicarbazone as ligand [9]. In view of the biological importance of the ligand and the metal

Gold , we have synthesized a series of Au complexes and characterized them as a first step followed by screening of their potential biological activities especially their anti cancer activities .

Experimental

Materials All the chemicals used were of Anala R grade and from HIMEDIA Chemicals .

Synthesis of Metal complex

The complex has been synthesized in three stages.

Stage I – Substitution of Thiosemicarbazide

Stage II – Synthesis of ligand

Stage III – Synthesis of metal complex .

Stage I - Substitution of Thiosemicarbazide

For all the aliphatic and aromatic substituents on thiosemicarbazide , the preparation methods are from established procedures using amines as starting materials [10]

Stage II – Synthesis of ligand

Benzil monothiosemicarbazones and Benzil 4-substituted monothiosemicarbazones were synthesized by condensing equimolar solutions (0.01M) of Benzil and Thiosemicarbazides / 4- substituted thiosemicarbazides in methanol in the presence of few drops of acetic acid. This mixture was refluxed water bath for 2hrs.It was filtered and the filtrate was concentrated to half the volume. On cooling the solution, cream colored crystals were obtained. The crystals were separated and recrystallised from Ethanol.

Stage III - Synthesis of metal complex

a) Equimolar solutions of $\text{HAuCl}_3 \cdot 3\text{H}_2\text{O}$ and ligand in methanol were mixed in 1:1 ratio and a few drops of acetic acid were added. The solution was refluxed on water bath for 3 hrs. On cooling the contents, colored complexes were separated out in each case. The complex was then filtered and washed with 50% Ethanol and dried.

Analysis

C, H and N were analyzed on Flash EA 1112 Series CHN Analyser

IR were recorded on Jasco 420 Spectrophotometer (using KBr disks $4000 - 400 \text{ cm}^{-1}$),

^1H NMR and ^{13}C NMR were recorded on ((Bruker ,)

UV-VIS was carried out on JASCO V 670 Spectrophotometer

Result and Discussions The complexes obtained are variously colored microcrystalline powders; air stable, , insoluble in common organic solvents, but soluble in dimethylformamide (DMF). The results of elemental analysis (C, H, and N), along with molecular formulae and melting points of the complexes are presented in Table 1. Molar electric conductivities show that all the complexes are 1:1 electrolytes, with $\lambda M = 140\text{--}170 \Omega^{-1} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$ in 10–3DMF solutions at room temperature. The analytical data confirms the ligand to metal ratio as well as the presence of three water molecules . The general molecular formula of the complex is $[\text{Au}(\text{L})\text{Cl}_3]3\text{H}_2\text{O}$. where L is Benzil monothiosemicarbazone, $[\text{C}_{15}\text{H}_{13}\text{N}_3\text{OS}]$.

Table -1: Physical properties and analytical data for complex.

COMPOUND	M.P	CONDUCTIVITY	C-found(cal)	H found(cal)	N found(cal)
B Tsc-Au	240 °c	140 $\Omega^{-1} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$	28.13(27.13)	2.03(2.13)	6.56(6.25)
BmT-Au	231 °c	150 $\Omega^{-1} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$	29.37(29.15)	2.29(3.11)	6.42(6.40)
BeT-Au	233 °c	170 $\Omega^{-1} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$	30.58(31.02)	2.84(2.60)	6.29(6.01)
Bipr-Au	212 °c	150 $\Omega^{-1} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$	31.71(31.41)	3.08(3.02)	6.16(6.02)

Table-2: IR spectra data of ligand and complex.

COMPOUND	$\nu(\text{C}=\text{O})$	$\nu(\text{C}=\text{N})$	NH+CN	$\nu(\text{C}=\text{S})+(\text{C}=\text{N})$	$\nu(\text{C}=\text{S})$	$\nu(\text{N}-\text{N})$	$\nu(\text{M}-\text{O})$	$\nu(\text{M}-\text{N})$	$\nu(\text{M}-\text{S})$
B TSC(L)	1680	1535	1490	1365	1190	1050	-	-	-
B Tsc-Au	1661	1485	1447	1327	1173	1072	581	531	467
B mTsc -Au	1661	1593	1449	1323	1173	1080	682	642	450
B eTsc -Au	1662	1586	1445	1320	1169	1092	688	638	464
B iprTsc -Au	1664	1582	1458	1307	1200	1067	577	521	467

IR SPECTRAL bands proposed are based on previous studies , the band at 1680cm^{-1} in free ligand has been assigned to the C=O stretching [11,12]. This band shifted to a lower frequency of 1664cm^{-1} in the complex, indicating the involvement of carbonyl group in complexation . Another strong band at 1535cm^{-1} attributed to C=N [13] is shifted to higher /lower frequency by 60cm^{-1} in all the complexes [$1528\text{--}1582\text{cm}^{-1}$] suggesting co-ordination of the azomethine nitrogen atom . The (C=N) may be coupled with (C=S) mode as $[\text{C}=\text{N}+\text{C}=\text{S}]$ to give the

medium intensity bands observed at 1365cm^{-1} in the ligand [14]. The negative shift of this band in the complex at 1307cm^{-1} supports the coordination of the C=N to the metal ion.

The band at 1050cm^{-1} in free ligand has undergone a positive shift to 1067cm^{-1} to 1090cm^{-1} in all the complexes and the result has also been attributed to the coordination of the azomethine nitrogen to the metal ion [15]. The strong band at 1190cm^{-1} assigned to C=S of free ligand is shifted to higher/lower frequency [1200 to 1173cm^{-1}] in complexes with reduced intensity suggesting coordination of sulphur in the thiolate form.

Table-3: ^1H NMR data for ligand and complexes.

COMPOUND	^2NH	$^4\text{NH}_2$	m, 2H,Ar	m,2H,Ar	m,4H,Ar	m,2H,Ar
Ligand	11.85	9.49	8.00	7.80	7.50	7.25
BTsc-Au	11.36	9.68	8.18	7.70	7.55	6.99
BmT-Au	11.39	8.19	8.17	7.78	7.58	6.99
BeT-Au	11.58	9.41	7.99	7.63	7.58	7.25
Bipr-Au	12.36	8.28	8.08	7.68	7.56	6.99

^1H NMR

^1H NMR signals are well defined and the spectrum of free ligand [9] exhibits two resonances for the $^4\text{NH}_2$ protons at 9.5 ppm, a result explained in terms of hindered rotation about the C(S)- $^4\text{NH}_2$ bond due to its partial double bond character [16,17]. The metal complexes show only one resonance due to $^4\text{NH}_2$ protons, upfield for some complexes (at 9.41, 8.28, 8.19) and down field (at 9.68) for some complexes. The signal at 11.85 ppm in the spectrum of ligand due to ^2NH is present in most of the complexes with down field shifts (11.36, 11.39, 11.58) and with an upfield shift for one complex (12.36) probably indicating a change in the nature of NH resonance due to hydrogen bonding between the carbonyl oxygen and NH proton.

Table-4: ^{13}C NMR for ligand and complexes.

COMPOUND	C 1	C 2,3	C 4,5	C 6	C 7*	C8*	C9*	C10	C11,12	C13,14	C15
Ligand	134.9	128.0	129.6	133.7	179.2	146.4	160.2	131.2	128.7	129.7	129.4
BTsc-Au	134.89	128.2	129.7	133.00	194.5	-	167.7	131.1	128.8	129.7	129.4
BmT-Au	134.89	129.0	129.7	133.01	194.5	-	167.7	130.56	129.03	129.7	129.2
BeT-Au	134.89	128.1	129.9	133.01	194.5	-	-	131.7	128.7	128.9	129.03
Bipr-Au	134.90	128.2	129.9	133.02	194.0	143,18	191	131.5	129.04	129.3	129.4

¹³C-NMR

¹³C-NMR spectral data indicate in all the complexes downfield or upfield chemical shifts are obtained for the carbon resonances adjacent to the assumed coordination sites while the others remain essentially unchanged. The affected carbon resonances C7,C8,C9 in the ligands are shifted or absent, supports coordination of Carbonyl oxygen(C7),azomethine nitrogen(C8),thio keto sulphur (C9)to metal.

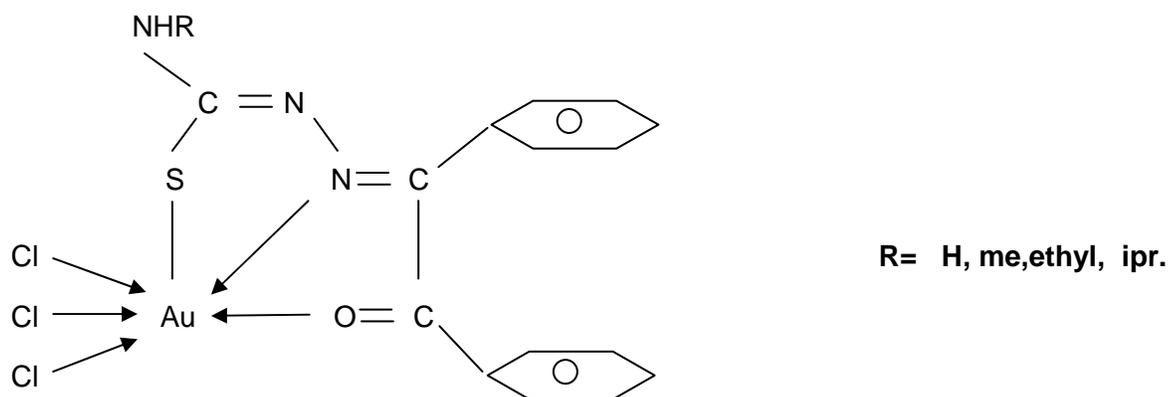
Structure

Fig. Proposed structures for the complex

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