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Aluminium(III), chromium(III) and iron(III) complexes with 5-iodouracil and 5-iodouracil-histidine and their antitumour activity

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Abstract

Complexes of the type $[Al(HL)(OH)Cl_2]$, $[M(HL)(OH)_2Cl]$ and $[M'(HL)(L')(OH)Cl]$, where HL = 5-iodouracil; HL′ = histidine; M = Cr(III), Fe(III) and M′ = Al(III), Cr(III), Fe(III), were synthesized and characterized. The complexes are polymeric showing high decomposition points and are insoluble in water and common organic solvents. The μ_{eff} values, electronic spectral bands and ESR spectra suggest a polymeric 6-coordinate spin-free octahedral stereochemistry for the Cr(III) and Fe(III) complexes. 5-Iodouracil acts as a monodentate ligand coordinating to the metal ion through the O atom of $C_{(4)}$=O while histidine through the O atom of $-COO^-$ and the N atom of $-NH_2$ group. *In vivo* antitumour effect of 5-iodouracil and its complexes was examined on C_3H /He mice against P815 murine mastocytoma. As evident from their T/C values, Cr(III) and Fe(III) complexes display significant and higher antitumour activity compared to the 5-iodouracil ligand. The *in vitro* results of the complexes on the same cells indicate that Cr(III) and Fe(III) complexes show higher inhibition on ^{3}H-thymidine and ^{3}H-uridine incorporation in DNA and RNA replication, respectively, at a dose of 5 μg/mL.

Keywords: *5-Iodouracil, 5-iodouracil-histidine, antitumour activity, magnetic moments and electronic spectra*

Introduction

The role of several drugs in relation to their metal binding has been established. The antitumour activity of platinum(II) complexes with nucleosides and their bases have been investigated extensively [1–4]. It is accepted that the antitumour activity is due to inhibition of DNA synthesis in cancer cells [5]. Aluminium(III) has been shown to bind with the chelating ligands in a simple human blood plasma model [6]. It has been established that the liability of chromium(III) complexes with distorted octahedral geometry is the possible factor for its active role in biological systems [7]. Iron is quite essential to oxidative metabolism of all body cells as well as in enzymatic functions. Iron deficiency produces many structural and functional abnormalities [8].

It has been suggested that metal ions play a significant role in the maintenance of the configuration of the nucleic acid molecule possibly linking nucleic acid bases through covalent bonds. 5-Iodouracil is similar to nucleic acid bases and has some antitumour properties. It has lethal and mutagenic effects on bacteriophage T_4 [9]. The lethal effect of 5-iodouracil is a consequence of its incorporation into DNA. It has a lethal effect on the adult Drosophila melangaster also, by inhibiting egg-laying [10].

Metal ions in biological systems promote the interaction of proteins and nucleic acids through the formation of ternary complexes. The formation of nucleic acid-enzyme-transition metal ternary complexes during DNA replication and RNA synthesis are known [11]. The study of such ternary complexes

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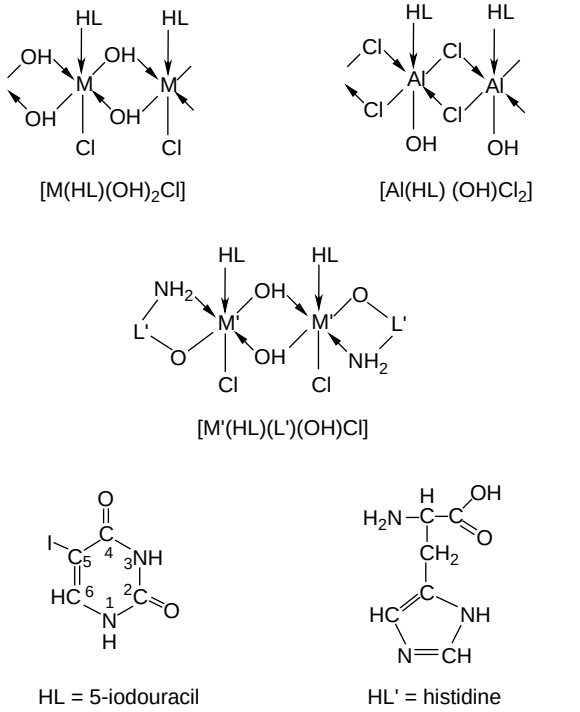

Figure 1. Representative structures of the complexes and ligands.

involving 5-iodouracil and amino acid like L-histidine may provide models for the more complicated metal-protein-nucleic acid interaction. A few bivalent transition metal complexes with uracil derivatives and its mixed ligand complexes have been reported [12–14]. In continuation of our earlier work on metal(III) complexes of uracil derivatives [15] and our interest in the biological applications of such complexes, we have synthesized and characterized a number of aluminium(III), chromium(III) and iron(III) complexes with 5-iodouracil and 5-iodouracil–histidine ligands (Figure 1) and investigated their antitumour properties. The results are discussed in this paper.

Experimental

Materials

All chemicals used were of AnalaR or equivalent grade. The metal chlorides employed were of E. Merck grade. 5-Iodouracil was purchased from Ega Chemie Co., Germany and L-histidine from Sisco Research Laboratory (SRL), India. ^{3}H-thymidine and ^{3}H-uridine used for antitumour activity was obtained from the Bhabha Atomic Research Centre, Mumbai. The mice used for the antitumour activity studies were obtained from Tata Institute of Fundamental Research, Mumbai. The P815 (murine mastocytoma) tumor cells was obtained from Tata Memorial Cancer Research Institute, Mumbai and was maintained in Prof. Ajit Sodhi's Research Laboratory, School of Biotechnology, Banaras Hindu University, Varanasi.

Preparation of the complexes

5-Iodouracil complexes. A quantity of 1 mmol of 5-iodouracil (0.2380 g) was dissolved in a mixture of 35 mL ethanol and 15 mL triethyl orthoformate. The solvent triethyl orthoformate was used to increase the solubility of 5-iodouracil ligand. To this solution was added 1mmol of $AlCl_3.6H_2O$ (0.2415 g) in 10 mL hot ethanol and refluxed for 2-3 h at the boiling point. A clear solution was thus obtained. From this solution, the metal complex was precipitated by raising the pH to between 5 and 6 by adding drop wise 0.2 N NaOH. The precipitate was digested, filtered, washed with ethanol and ether successively and dried in an oven at 50°C. Fe(III) and Cr(III) complexes were prepared by taking 1 mmol of $FeCl_3.6H_2O$ (0.2705 g) and $CrCl_3.6H_2O$ (0.2665 g), respectively, in 10 mL hot ethanol under similar experimental conditions.

5-Iodouracil-histidine complexes. Using the same quantities of 5-iodouracil and metal salts and conditions of precipitation maintained as above, 1 mmol (0.1550 g) L-histidine, dissolved in 10 mL of hot distilled water, was added in each case after the precipitation of the complex. On reacting with L-histidine the precipitate was again dissolved. The resultant solution was concentrated over a water bath to 50% of its volume. The mixed-ligand complexes were precipitated by adjusting the pH up to 6 by adding few drops of 0.2 N NaOH. The precipitates were filtered and washed with ethanol and finally with ether and dried in an oven at 50°C.

Analysis and instrumentation

The metal contents of the complexes were determined after dissolving the complexes in very dilute HNO_3 and titrating the excess 0.01 M EDTA at pH 5 by following the standard procedures [16]. Analyses of C, H and N were carried out micro analytically on a Perkin-Elmer 240C model micro analyzer.

Room temperature magnetic susceptibilities of the complexes were determined with a Faraday type balance (Cahn magnetic susceptibility apparatus) using $[CoHg(SCN)_4]$ as calibrant and correcting the experimental values for diamagnetism [17]. Electronic spectra of the complexes were recorded in Nujol mull on a Shimadzu 160A UV-visible recording spectrophotometer. Infrared spectra of the ligands and their complexes were recorded in Nujol mull on a Perkin Elmer 783 infrared spectrophotometer. X-band ESR spectra of the Iron(III)-5-iodouracil-histidine complex were recorded on a JESME-3X type spectrometer of powdered sample at room temperature and liquid nitrogen temperature using diphenyl picryl hydrazyl (DPPH) as g marker (g = 2.00238).

Antitumour activity evaluation

Animal experimentation was in accord with protocols laid down by the Department of Shalya and Centre of Experimental Medicine and Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India.

In vivo *testing*. C_3H/He mice of either sex, about 6 - 8 weeks old and average body weight of 20 g, were used for *in vivo* antitumour activity tests against P815 (murine mastocytoma). Six animals were used for each set of experiment. An intraperitoneal injection of 2×10^5 tumour cells in phosphate buffered saline solution was given to each mouse at weekly intervals. Fine suspension of the test compounds, prepared in 0.89% saline solution (NaCl), were injected once a week after two days after the tumour transplantation at doses of 12.5 and 25 mg/kg body weight of mouse. The same volume of sterile saline solution was injected in the control set.

The therapeutic effectiveness of each compound against tumour bearing mice was assessed from the ratios of the mean survival time (in days) of the treated animals and control, and the T/C percentage was calculated as

$$\%T/C = \frac{\text{Mean life span of treated mice}^{\star}}{\text{Mean life span of untreated mice}} \times 100$$

⋆Excluding tumour free survivor

In vitro *testing*. A P815 murine mastocytoma tumour cell suspension (1×10^6 cells/mL) was prepared in a medium containing the tissue culture of RMPI 1640 supplemented with antibiotics, penicillin, streptomycin and 10% heat inactivated fetal calf serum. For the determination of the effects of various compounds on DNA replication, duplicate culture plates (NUNC, Denmark) containing 96 wells in each plate were taken and 2×10^6 tumour cells were added to each cell well. The test compounds at different doses (1, 5 and 10 μg/mL) were added in one set of culture plates while the other set was without test compound. After 24 h of incubation in a CO_2 incubator at 37°C, the cells were washed thrice with a RMPI 1640 culture medium by centrifugation for 10 minutes. The cell pellets were resuspended in 0.2 mL of a medium of RMPI 1640 + antibiotics +10% heat inactivated fetal calf serum containing 0.5 μCi/mL ^{3}H-thymidine for 18 h of reincubation. Again, cell pellets were centrifuged and the supernatant liquid was discarded, washed thrice with a balanced salt solution (phosphate buffered normal saline solution). The cell pellets were digested with 0.5% sodium dodecyl sulphate (SDS) and the effluent was counted for radioactivity in a LKB β-liquid scintillation counter. Since the test compounds inhibit the incorporation of ^{3}H-thymidine in DNA of the tumour cells, the percentage inhibition was calculated as

$$\%\text{ inhibition} = 1 - \frac{\text{CPM in treated tumour cells}}{\text{CPM in untreated tumour cells}} \times 100$$

where CPM = counts per minute of radioactivity of ^{3}H-thymidine.

For the determination of the effect of the compounds on RNA synthesis, ^{3}H-uridine (0.5 μ Ci/mL) was used in place of ^{3}H-thymidine and the other procedures were the same as discussed above.

Results and discussion

It appears from the analytical data of the complexes (Table I) that the 5-iodouracil complexes display 1:1 (M:L) stoichiometry and the mixed ligand complexes exhibit 1:1:1 (M:L:L′) stoichiometry. The course of reactions is shown below:

$$MCl_3.6H_2O + HL \rightarrow M(HL)Cl_3.6H_2O$$

$$M(HL)Cl_3.6H_2O \xrightarrow[pH\,5-6]{NaOH} M(HL)(OH)Cl_2 + NaCl + 6H_2O$$

or

$$M(HL)(OH)_2Cl + 2NaCl + 6H_2O$$

$$M(HL)(OH)CL_2 + HL \xrightarrow[pH\,6]{NaOH} [M(HL)(L')(OH)Cl] + NaCl + H_2O$$

The Al(III) complexes are colourless while the Fe(III) and Cr(III) complexes are coloured. They are insoluble in water and other common organic solvents like ethanol, benzene, chloroform, carbon tetrachloride, acetone, acetonitrile, pyridine, ether, DMF and DMSO. The Al(III) complexes melt between 276–280°C while Fe(III) and Cr(III) complexes decompose without melting above 300°C.

Table I. Analytical and electronic spectral data of the complexes.

Complex/ Empirical Formula	Colour (Formula Wt.)	Decomp. Temp °C	Found (Calcd) (%) M	Cl	C	H	N	μ_{eff} (B.M.)	λmax (nm)	Yield (%)
$[Al(HL)(OH)Cl_2]$	White	290	7.70	19.90	13.46	1.15	8.07	–	–	65
$C_4H_4N_2O_3ICl_2Al$	(353)		(7.65)	(20.11)	(13.60)	(1.13)	(7.93)			
$[Cr(HL)(OH)_2Cl]$	Dark green	>300	14.37	9.80	13.28	1.42	7.88	3.66	530, 345	75
$C_4H_5N_2O_4IClCr$	(359.5)		(14.46)	(9.87)	(13.35)	(1.39)	(7.79)			
$[Fe(HL)(OH)_2Cl]$	Light brown	>300	15.20	9.70	13.06	1.40	7.57	5.36	512, 393, 347	70
$C_4H_5N_2O_4IClFe$	(363.5)		(15.40)	(9.76)	(13.20)	(1.37)	(7.70)			
$[Al(HL)(L')(OH)Cl]$	White	295	5.80	7.42	25.30	2.60	14.69	–	–	70
$C_{10}H_{12}N_5O_5IClAl$	(471.5)		(5.72)	(7.53)	(25.45)	(2.54)	(14.84)			
$[Cr(HL)(L')(OH)Cl]$	Dark green	>300	10.55	7.05	24.02	2.43	13.96	3.75	535, 351	75
$C_{10}H_{12}N_5O_5IClCr$	(496.5)		(10.47)	(7.15)	(24.17)	(2.41)	(14.10)			
$[Fe(HL)(L')(OH)Cl]$	Dark brown	>300	11.10	7.02	23.79	2.44	14.07	5.26	490,389, 350	70
$C_{10}H_{12}N_5O_5IClFe$	(500.5)		(11.19)	(7.09)	(23.97)	(2.40)	(13.98)			

HL = 5-Iodouracil, HL′ = Histidine.

Magnetic moments and electronic spectra

Both Cr(III) complexes show μ_{eff} values of 3.66 and 3.75 B.M., respectively, corresponding to three unpaired electrons, suggesting a high–spin octahedral stereochemistry [18]. The Fe(III)-5–iodouracil and Fe(III)-5-iodouracil-histidine complexes exhibit μ_{eff} values of 5.36 and 5.26 B.M., respectively. Both of these values are slightly less than the corresponding value for 5 unpaired electrons ($\mu_{eff} = 5.94$ B.M.) indicating magnetic exchange interaction due to polymerization.

The octahedral Cr(III) complexes are expected to show three spin allowed d-d transitions viz. $^4A_{2g}(F) \rightarrow {}^4T_{2g}$ (v_1), $\rightarrow {}^4T_{1g}(v_2)$ and $\rightarrow {}^4T_{1g}(P)$ (v_3). In both Cr(III) complexes in this study only two bands are observed at 530, 535 nm (v_1) and 345, 351 nm (v_2), respectively. The v_3 band, expected below 300 nm overlaps with the ligand bands or L → M charge transfer bands and is, m therefore, not assigned [19]. A slight splitting in the above bands of the Cr(III) complexes is also observed which may partly be due to low–symmetry, hexa-coordinated configurations and partly due to the presence of different chromophores in the polymeric complexes.

The first two bands appearing in the Fe(III)-5-iodouracil and Fe(III)-5-iodouracil-histidine complexes at 512, 490 nm and 393, 389 nm, respectively, may be assigned to $^6A_{1g}$ $^4T_{1g}$ and $^4T_{2g}$ transition. The third band at 347 and 350 nm for the two complexes, respectively, may be due to the L → M charge transfer which obscures the low intensity d-d absorption bands.

ESR spectra

ESR spectra of the powdered sample of the Fe(III)–5-iodouracil–histidine complex at room temperature (300 K) and liquid nitrogen temperature (77 K) were obtained, but in each case there was simply a strong broad band with no evidence of fine structure. These results merely indicate strong dipolar coupling between the paramagnetic ions, as expected for a polymeric structure. However the fact that $g_{iso} = 2.031$ at RT and 2.035 at LNT suggests an octahedral environment around Fe(III) [15].

IR spectra

5-Iodouracil complexes. Some important IR frequencies of 5-iodouracil and its complexes are given in Table II. There are several absorption bands in the region 3500–3000 cm^{-1} which may be attributed to —NH and —OH stretching modes. The v(O-H) band appearing at 3400, 3370 and 3406 cm^{-1} in the Al(III), Cr(III) and Fe(III) complexes, respectively, indicates the presence of water molecule or O-H

Table II. Important IR spectral data of the 5-iodouracil complexes.

Compound	v(OH)	$v(C_{(2)}=O)$	$v(C_{(4)}=O)$	$\delta(N_{(1)}-H)$	$\delta(N_{(3)}-H)$	v(M-O)	v(M-Cl)
5-Iodouracil	–	1710s	1657s	1512m	1430m	–	–
$[Al(HL)(OH)Cl_2]$	3400b	1715s	1634s	1510m	1430m	250w	315m
$[Cr(HL)(OH)_2Cl]$	3370b	1717s	1640s	1510m	1432s	252w	360w
$[Fe(HL)(OH)_2Cl]$	3406b	1717s	1635s	1512w	1435m	245m	360w

Table III. Important IR spectral data of the 5-iodouracil-histidine complexes.

Compound	v(OH)	$v(NH_3^+)$	$v(C_{(2)}{=}O)$	$v(C_{(4)}{=}O)$	$v(COO^-)$	v(C-N)	v(C = N)	$\delta(N_{(3)}-H)$	$\delta(N_{(1)}-H)$	v(M-Cl)
Histidine	–	3071m	–	–	1573 s	1510 m	1470 s	–	–	–
[Al(HL)(L′)(OH)Cl]	3410b	–	1707 s	1630 s	1554 m	1510 m	1468 m	1432 m	1508 m	355 w
[Cr(HL)(L′)(OH)Cl]	3398b	–	1707 s	1635 s	1556 m	1508 w	1465 m	1435 m	1510 m	365 w
[Fe(HL)(L′)(OH)Cl]	3490b	–	1705 s	1640 s	1556 m	1508 w	1465 m	1428 w	1510 w	365 w

group [20]. The absence of v(M-O) (aqua) bands in the lower region of the spectra of the complexes confirms the bonding of the O-H group. The medium-broad band at *ca.* 950 cm^{-1} in the Cr(III) and Fe(III) complexes may be assigned as OH bridging, suggesting an OH bridged polymeric structure for the complexes.

The $v(C_{(4)}{=}O)$ band occurring at 1657 cm^{-1} in 5-iodouracil is shifted considerably towards lower frequency (*ca.* 20-40 cm^{-1}) in all the complexes, suggesting the coordination of the $C_{(4)}{=}O$ group to the metal. The $v(C_{(2)}{=}O)$, $\delta(N_{(1)}$-H), v(C-I) and $\delta(N_{(3)}$-H) bands appear at 1710, 1512, 1466 and 1430 cm^{-1} in free 5-iodouracil. These bands either do not shift or show a slight shift in the metal complexes indicating that these groups are not taking part in coordination. The metal-oxygen stretching vibrations appear in the region 225–245 cm^{-1} for six and at 276 cm^{-1} for four-coordination [15], the presence of characteristic bands in the region 245–250 cm^{-1} strongly favours the coordination number six for all complexes. In the Al(III)-5-iodouracil complex, particularly, v(M-Cl) occurs at significantly lower wave numbers relative to the other complexes. This may be due to the presence of a bridging chloro ligand in the complex [21].

5-Iodouracil-histidine complexes. In all the 5-iodouracil-histidine mixed ligand complexes, 5- iodouracil shows similar trends of bonding and shifting in the affected group frequencies as described earlier for the 5-iodouracil complexes. In addition, some new vibrations due to histidine coordination are observed in these complexes. The bands due to the C-N and C = N groups of the imidazole moiety of histidine do not shift in the spectra of the metal complexes (Table III), suggesting non-involvement of imidazole moiety in the coordination. The $v(COO^-)$ bands of histidine show a shift towards lower wave number in the complexes providing evidence that histidine is bonded to the metal ion through the carboxylic group [22]. Histidine shows a band at 3360 cm^{-1} due to v(N-H) of imidazole moiety remains unaffected in the metal complexes, suggesting that the N-H group of imidazole is not involved in bonding. Histidine also shows $v(NH_3^+)$ at 3071 cm^{-1}, which disappears on coordination, suggesting coordination of histidine through the nitrogen of the amino group. This is further supported by the disappearance of δ(N-H) of $-NH_3^+$ at 1503 cm^{-1} in histidine on complex formation.

Based on the above discussions, the general structures in Figure 1 for the metal complexes are proposed.

Antitumour properties

In vivo *effect*. The *in vivo* effect of the ligand, 5-iodouracil, and its Al(III), Fe(III) and Cr(III) complexes in this study on P815 murine mastocytoma were evaluated on the basis of their percent T/C value. A T/C value of 115 indicates significant activity whereas, >125 indicates that the compound is very useful for testing on other tumour systems [23]. At the dose of 25 mg/kg body weight, the compounds were cytotoxic and, therefore the results obtained at the dose of 12.5 mg/kg body weight were recorded. The experimental data (Table IV) indicate that the 5-iodouracil itself shows significant antitumour activity (%T/C = 117) and the Cr(III) and Fe(III) complexes show greater antitumour activity than 5-iodouracil ligand. The Cr(III)-5-iodouracil complex in particular, shows the highest activity, with %T/C = 150, among all other complexes in the present study at the above dose. The Al(III) complexes show very low antitumour activity.

Table IV. *In vivo* antitumour activity.

Compound	Dosage mg/kg body weight	Mean life span of nonsurvivors T/C	%T/C
5-Iodouracil	12.50	35/30	117
$[Al(HL)(OH)Cl_2]$	12.50	16/30	53
$[Cr(HL)(OH)_2Cl]$	12.50	45/30	150
$[Fe(HL)(OH)_2Cl]$	12.50	38/30	127
[Al(HL)(L′)(OH)Cl]	12.50	09/35	26
[Cr(HL)(L′)(OH)Cl]	12.50	52/35	148
[Fe(HL)(L′)(OH)Cl]	12.50	42/35	120

Table V. *In vitro* antitumour activity.

Compound	% Inhibition of ^{3}H-thymidine		% Inhibition of ^{3}H-uridine	
	1 μg/mL	5 μg/mL	1 μg/mL	5 μg/mL
5-Iodouracil	13.10	15.45	09.72	24.26
$[Al(HL)(OH)Cl_2]$	15.65	17.95	40.85	54.32
$[Cr(HL)(OH)_2Cl]$	49.20	82.56	63.17	73.22
$[Fe(HL)(OH)_2Cl]$	41.40	69.60	54.70	61.74
[Al(HL)(L′)(OH)Cl]	21.92	23.42	39.56	55.72
[Cr(HL)(L′)(OH)Cl]	48.82	72.45	46.12	65.29
[Fe(HL)(L′)(OH)Cl]	35.16	55.84	39.83	61.37

In vitro *effect*. The data obtained for the inhibitory effect of DNA and RNA replication *in vitro* (Table V) of the compounds indicates that the activity increases at higher doses, but all the compounds were cytotoxic at the dose of 10 μg/mL. All complexes show maximum inhibition of DNA and RNA replication at a dose of 5 μg/mL. The Cr(III)-5-iodouracil complex, which showed the highest activity by the *in vivo* studies, again shows the maximum inhibition of DNA and RNA replication *in vitro*. The Fe(III) complexes also show significant *in vitro* antitumour activity while both Al(III) complexes were found to have poor inhibitory effect on DNA as well as RNA replication.

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