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Synthesis and crystal structures of pyridine-2-carboxaldehyde thiosemicarbazone, its mononuclear and cytotoxic Cu(II)- and polynuclear Pb(II) complexes: Effect of size of metal ion on nucleation of the complexes

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Synthesis and X-ray structural characterization of pyridine-2-carboxaldehyde thiosemicarbazone (**L**), and its metal complexes, $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$ and $[Pb(\mathbf{L})(ONO_2)_2]_n$ are reported. X-ray diffraction reveals that the metal centres in the two complexes are distorted square planar and square pyramid geometries, respectively. Among the three compounds $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$ is found to be active against human keratinocyte cell line.

Keywords: Coordination chemistry, Thiosemicarbazones, Copper, Lead, Anticancer activity, X-ray structure

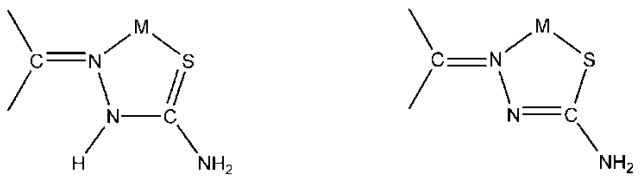
Pharmacological properties of transition metal-thiosemicarbazone complexes attracted considerable attention of chemists during a long period[1,2]. Thiosemicarbazone can bind to metal ions either in its neutral thione form (**1**, Scheme 1) or it can tautomerize to its thiolate form (**2**, Scheme 1) as bidentate N,S-donor ligand forming a five membered chelate ring at metal centre[2b-2d]. Introduction of additional donor site through the carbonylic carbon can increase the donor centres in the ligand backbone. Some unusual mode of coordination of thiosemicarbazone is also reported in literature[3]. Biological activities of transition metal-thiosemicarbazone complexes, as we mentioned, have also made the compounds promising. These can act as antineoplastic, antimalarial, antibacterial, antiviral and antifungal[2b,4]compounds. In 1956, for the first time, the anticancer activities of pyridine-2-carboxaldehyde thiosemicarbazone was reported by Skipper *et al*[2a]. In subsequent years, bis(thiosemicarbazone) complexes of Cu(I/II) were found to be potential anticancer agents[5]. The ligand thiosemicarbazone has some analytical applications as those have strong affinity for metal ion binding[6]. Further, recent research on *s*-, *d*- and even *f*-block metal ions are highly focused whereas less attention has been paid to the studies of *p*-block metal ions[7]. As a heavy *p*-block element, Pb(II) with its large radius, flexible coordination numbers, varied stereochemical activities is important for designing different functional materials[7c,7d]. Considering all these aspects, we have synthesized and X-ray crystallographically characterized pyridine-2-carboxaldehyde thiosemicarbazone (**L**) which was previously reported to be as antileukemic agents[2a], its new metal complexes $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$ and $[Pb(\mathbf{L})(ONO_2)_2]_n$. Compound $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$ is found to be cytotoxic against keratinocyte cell lines, while **L** and $[Pb(\mathbf{L})(ONO_2)_2]_n$ have no specificity on those cell lines.

Experimental

Pyridine-2-carboxaldehyde, copper(II) perchlorate hexahydrate, lead(II) nitrate were purchased from Sigma Aldrich and used as received. Thiosemicarbazide was purchased from E. Merck India. Solvents were of reagent grade and used without further purification.

Elemental analyses (carbon, hydrogen and nitrogen) were performed on a Perkin-Elmer 2400 CHNS/O elemental analyzer. UV-vis and IR spectra (KBr discs, 4000-300 cm^{-1}) were recorded on Shimadzu UV-vis 2450 spectrophotometer and Perkin-Elmer FT-IR (model RX1) spectrometer, respectively.

The ligand, pyridine-2-carboxaldehyde thio semicarbazone (**L**) was prepared as follows: Ethanolic solutions of pyridine-2-carboxaldehyde (8 mmol, 0.88 g) and thiosemicarbazide (8 mmol, 0.97 g) were



1 2

Scheme 1

mixed and refluxed for six hours to yield the thiosemicarbazone, **L**. After cooling, the solution turned green and brown crystals of **L** appeared on keeping the solution in open air overnight. Yield: 0.844 g (87% based on thiosemicarbazide). Anal. (%): Calc. for $C_7H_8N_4S$: C, 46.67; H, 4.47; N, 31.11 Found: C, 46.20; H, 4.39; N, 31.21. IR cm^{-1} (KBr): 1612, 1524, 1460, 1433, 1353. UV-vis (MeOH, nm): λ_{max} (ε) at 326 (5710).

Synthesis of $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$ was as follows: Aqueous ethanolic solution of copper(II) perchlorate hexahydrate (1 mmol, 0.30 g) was added dropwise to the ligand **L** (1 mmol, 0.20 g) in ethanol with stirring. The greenish brown coloured ligand solution changed to deep green. Keeping the solution in open air for about 60 days yielded green coloured block shaped diffraction-quality single crystals of complex $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$. Yield 0.225 g (75% based on metal salt). Anal. (%): Calc. for $C_7H_{14}N_4O_{11}SCl_2Cu$: C, 16.91; H, 2.84; N, 11.27 Found: C, 16.02; H, 2.79; N, 11.20. IR cm^{-1} (KBr): 3252, 1627, 1392, 1048. UV-vis (MeOH, nm): λ_{max} (ε) at 293 (60160), 323 (45680), 402 (24760).

Synthesis of $[Pb(\mathbf{L})(ONO_2)_2]_n$ was as follows: The gradual mixing of ethanolic solution of lead(II) nitrate tetrahydrate (1 mmol, 0.30 g) and **L** (1 mmol, 0.2 g) in ethanol with gentle heating and stirring resulted in a yellow solution mixture. The mixture was then kept in open air for slow evaporation. Yellow coloured block shaped crystals of $[Pb(\mathbf{L})(ONO_2)_2]_n$ appeared after about 60-65 days. Yield: 0.216 g (72% based on metal salt). Anal. (%): Calc. for $C_7H_8N_6O_6SPb$: C, 16.43; H, 1.57; N, 16.43 Found: C, 16.52; H, 1.50; N, 15.99. IR cm^{-1} (KBr): 1575, 1382, 1030. UV-vis (MeOH, nm): λ_{max} (ε) at 327 (13800).

Single crystal X-ray diffraction data were collected using a Rigaku XtaLABmini diffractometer equipped with mercury CCD detector. The data were collected with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å) at 100 K using ω scans. The data were reduced using Crystal Clear suite 2.0[8] and the space group determination was done using Olex2[9]. The structure was resolved by direct method and refined by full-matrix least-squares procedures using the SHELXL[10] package using OLEX2 suite. The crystal data and refinement details are listed in Table 1. All the figures have been generated using ORTEP-32[11].

Results and discussion

Ligand (**L**) was prepared by refluxing pyridine-2-carboxaldehyde and thiosemicarbazide in ethanol. Complexes $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$ and $[Pb(\mathbf{L})(ONO_2)_2]_n$ were prepared by mixing copper(II) perchlorate hexahydrate and lead(II) nitrate, respectively with the ligand. **L** and its two complexes are soluble in CH_3CN and DMSO. IR spectrum of **L** (Supplementary data, Fig. S1) exhibits a band at 2923 cm^{-1} indicating ν(-NH-) stretching frequency. A strong band at 1353 cm^{-1} in **L** is assigned to ν(C-N). This band is shifted to some higher frequencies in its metal complexes (Supplementary data, Figs S2 and S3). This shifting of ν(C-N) frequencies to higher value is attributed to the deprotonation of the α-nitrogen atom in the ligand framework making some elongation the C-N bond. Band at ~1030-1060 cm^{-1} in the ligand and metal complexes arises because of the ν(C=S) frequencies. Band at ~1600 cm^{-1} is because of imine bond in the structures[12]. The ligand and each of the complexes were X-ray crystallographically characterized (Tables 1, 2, 3, 4).

The thermal ellipsoid probability plots of **L**, $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$ and $[Pb(\mathbf{L})(ONO_2)_2]_n$ are given in Figs 1-3. **L** is found to be in its normal thione form (C-S, 1.65 Å (**1**) (Table 2), Scheme 1) with four molecules in the asymmetric unit and crystallized in monoclinic non-centrosymmetric *Pc* space group. From the bond angle-bond distance data (Table 3) the Cu(II) centre in $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$ is found to be in a distorted square planar geometry. Upon coordination with Cu(II), **L** is in its thione form (C-S, 1.71 Å (**1**), Scheme 1) with minor elongation in the C-S bond. Among the four corners of the square plane, three come from the ligand framework (one pyridine nitrogen, N1; one imine nitrogen, N2; and one thione, S1) and the fourth coordination site is occupied by a water molecule. The bond distances are also very close. The deviation between maximum and minimum bond distances is 0.343 Å. Coordination geometry of Pb(II) of $[Pb(\mathbf{L})(ONO_2)_2]_n$ is best described as distorted square pyramid as exemplified by its τ value (= 0.21)[13]. Considering bond angle-bond distance data (Table 4), pyridine and imine nitrogen from the **L** and two oxygen atoms from two different nitrates form the basal plane. The thione sulphur resides in its axial position. Here the equatorial bond distances range from 2.54-2.88 Å (Δ = 0.34 Å). The Pb(1)-S(1) bond distance is 2.90 Å. This compound is assumed to be a neutral polymer as firstly, there is no charge balancing

Table 1 — Crystal data and structure refinement parameters of **L**, $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$ and $[Pb(\mathbf{L})(ONO_2)_2]_n$

Parameters	**L**	$[Cu(\mathbf{L})(OH_2)](ClO_4)_2$	$[Pb(\mathbf{L})(ONO_2)_2]_n$
Emperical formula	$C_7H_8N_4S$	$C_7H_{14}N_4O_{11}SCl_2Cu$	$C_7H_8N_6O_6SPb$
Formula weight	180.24	496.74	779.51
T (K)	293	293	100
Wavelength (Å)	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	*P1c1*	*P121/c 1*	*P2ybc*
Unit cell dimensions			
a (Å)	17.410(6)	12.9545(11)	21.7273(14)
b (Å)	4.7899(19)	9.7618(6)	6.9192(4)
c (Å)	20.691(7)	14.9853(12)	19.0657(13)
α (˚)	90	90	90
β (˚)	90.170(16)	111.582(3)	115.385(2)
γ (˚)	90	90	90
V (Å^3)	1725.5(11)	1762.2(2)	2589.5(3)
Z	8	4	4
D_{calc} (mg m^{-3})	1.388	1.872	2.624
Absorption coeff. (mm^{-1})	0.323	1.724	13.232
F(000)	752	1004	1904
Crystal size (mm^3)	0.25 × 0.14 × 0.1	0.3 × 0.3 × 0.2	0.21 × 0.18 × 0.12
Theta range for data collection (°)	3.054 - 27.540	2.548 - 27.492	2.137 - 27.483
Index ranges	$-22 \le h \le 22$, $-6 \le k \le 6$, $-26 \le l \le 25$	$-16 \le h \le 16$, $-12 \le k \le 12$, $-19 \le l \le 19$	$-28 \le h \le 28$, $-8 \le k \le 8$, $-24 \le l \le 24$
Reflections collected	13425	13519	26693
Independent reflections	7519 [Rint = 0.1194]	4004 [Rint = 0.0438]	5908 [Rint = 0.1365]
Completeness of theta	99.7% [θ = 25.242]	98.7% [θ = 25.242]	99.5% [θ = 25.242]
Absorption correction	Multi-scan	Multi-scan	Multi-scan
T_{max} and T_{min}	1.000 and 0.707	1.000 and 0.847	1.000 and 0.802
Refinement method	Full matrix	Full matrix	Full matrix
Data/restrains/parameters	7519/2/ 436	4004/0/ 255	5908/0/ 379
Goodness-of fit (GOF) F^2	0.987	1.024	1.115
Final R index [$l > 2\sigma(l)$]	R_1 = 0.1031 and wR_2 = 0.2498	R_1 = 0.0421 and wR_2 = 0.1149	R_1 = 0.0527 and wR_2 = 0.1395
R index (all data)	R_1 = 0.1949 and wR_2 = 0.3430	R_1 = 0.0529 and wR_2 = 0.1259	R_1 = 0.0573 and wR_2 = 0.1423
Largest difference between peak and hole (e Å^{-3})	0.877, -0.366	0.789, -0.533	3.210, -3.669

Table 2 — Bond lengths (Å) and bond angles (°) of **L**

Bond lengths			
C(1)-C(2)	1.42(2)	C(1)-C(6)	1.41(2)
C(2)-C(3)	1.37(2)	C(6)-N(2)	1.275(18)
C(3)-C(4)	1.39(2)	N(2)-N(3)	1.378(17)
C(4)- C(5)	1.41(2)	N(3)-C(7)	1.347(18)
C(5)-N(1)	1.30(2)	C(7)-N(4)	1.343(18)
C(1)-N(1)	1.308(18)	C(7)-S(1)	1.640(15)
Bond angles			
N(1)-C(1)-C(6)	116.5(14)	N(3)-C(7)-N(4)	114.6(13)
C(1)-C(6)-N(2)	123.8(14)	N(4)-C(7)-S(1)	123.9(12)
C(6)-N(2)-N(3)	117.3(12)	N(3)-C(7)-S(1)	121.4(12)
N(2)-N(3)-C(7)	122.8(12)		

Table 3 — Bond lengths (Å) and bond angles (°) of $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$

Bond lengths			
Cu(1)-N(1)	2.013(2)	Cu(1)-S(1)	2.2787(8)
Cu(1)-N(2)	1.940(2)	Cu(1)-O(9)	1.935(2)
Bond angles			
N(1)-Cu(1)-N(2)	80.45(9)	N(1)-Cu(1)-O(9)	96.15(10)
N(2)-Cu(1)-S(1)	85.17(7)	N(1)-Cu(1)-S(1)	165.62(7)
O(9)-Cu(1)-S(1)	98.21(7)	N(2)-Cu(1)-O(9)	175.98(10)

counter anion in its X-ray structure and secondly, the ligand is in its neutral form **1** (Scheme 1) with thione group (C-S bond distance in **L**, 1.64 Å (Table 2) and in $[Pb(\mathbf{L})(ONO_2)_2]_n$, 1.68 Å (Table 4)). As the ligand is neutral, the +2 formal charge on Pb in each unit of the polymer is neutralized by the two coordinated nitrate groups. As Pb(II) is larger than Cu(II) in terms of atomic size, it prefers higher coordination number. As a result the counter anion nitrate which was present with the starting Pb(II) salt is found coordinated with the Pb(II)L moiety. The appended oxygen atoms of the metal bound nitrates bind with different Pb(II)L moieties to make it a polymeric chain.

All the three compounds **L**, $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$ and $[Pb(\mathbf{L})(ONO_2)_2]_n$ were investigated for cytotoxic activity. **L** and $[Pb(\mathbf{L})(ONO_2)_2]_n$ did not

Table 4 — Bond lengths (Å) and bond angles (°) of $[Pb(\mathbf{L})(ONO_2)_2]_n$

Bond lengths			
Pb(1)-O(1)	2.547(10)	Pb(2)-O(5)	2.702(10)
Pb(1)-N(1)	2.690(11)	Pb(2)-N(5)	2.677(9)
Pb(1)-N(2)	2.631(10)	Pb(2)-N(6)	2.640(8)
Pb(1)-S(1)	2.901(3)	Pb(2)-S(2)	2.890(3)
Pb(2)-O(4)	2.582(10)		
Bond angles			
O(1)-Pb(1)-N(1)	69.2(3)	O(4)-Pb(2)-N(6)	79.3(4)
O(1)-Pb(1)-N(2)	76.6(3)	O(4)-Pb(2)-S(2)	99.5(3)
O(1)-Pb(1)-S(1)	98.9(3)	O(5)-Pb(2)-N(5)	76.8(3)
N(1)-Pb(1)-N(2)	62.2(3)	O(5)-Pb(2)-N(6)	70.5(3)
N(1)-Pb(1)-S(1)	127.8(2)	O(5)-Pb(2)-S(2)	91.3(3)
N(2)-Pb(1)-S(1)	65.6(2)	N(5)-Pb(2)-N(6)	62.1(3)
O(4)-Pb(2)-O(5)	140.3(3)	N(5)-Pb(2)-S(2)	127.7(2)
O(4)-Pb(2)-N(5)	66.4(3)	N(6)-Pb(2)-S(2)	66.0(2)

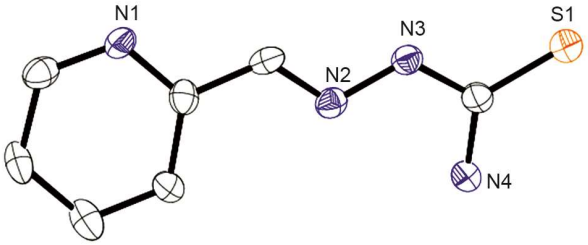


Fig. 1 — ORTEP of **L** with 20% ellipsoid probability.

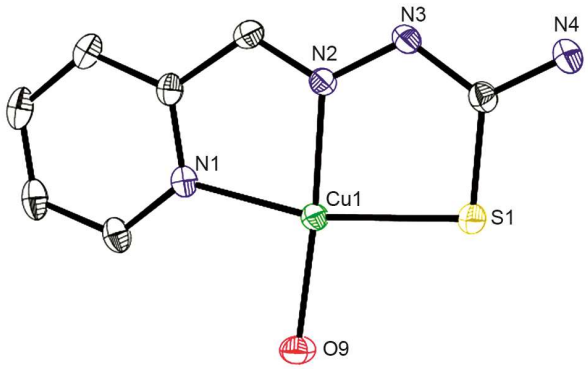


Fig. 2 — ORTEP of $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$ with 20% ellipsoid probability.

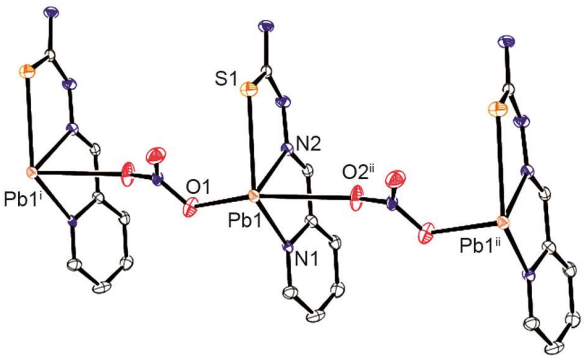


Fig. 3 — ORTEP of $[Pb(\mathbf{L})(ONO_2)_2]_n$ with 20% ellipsoid probability.

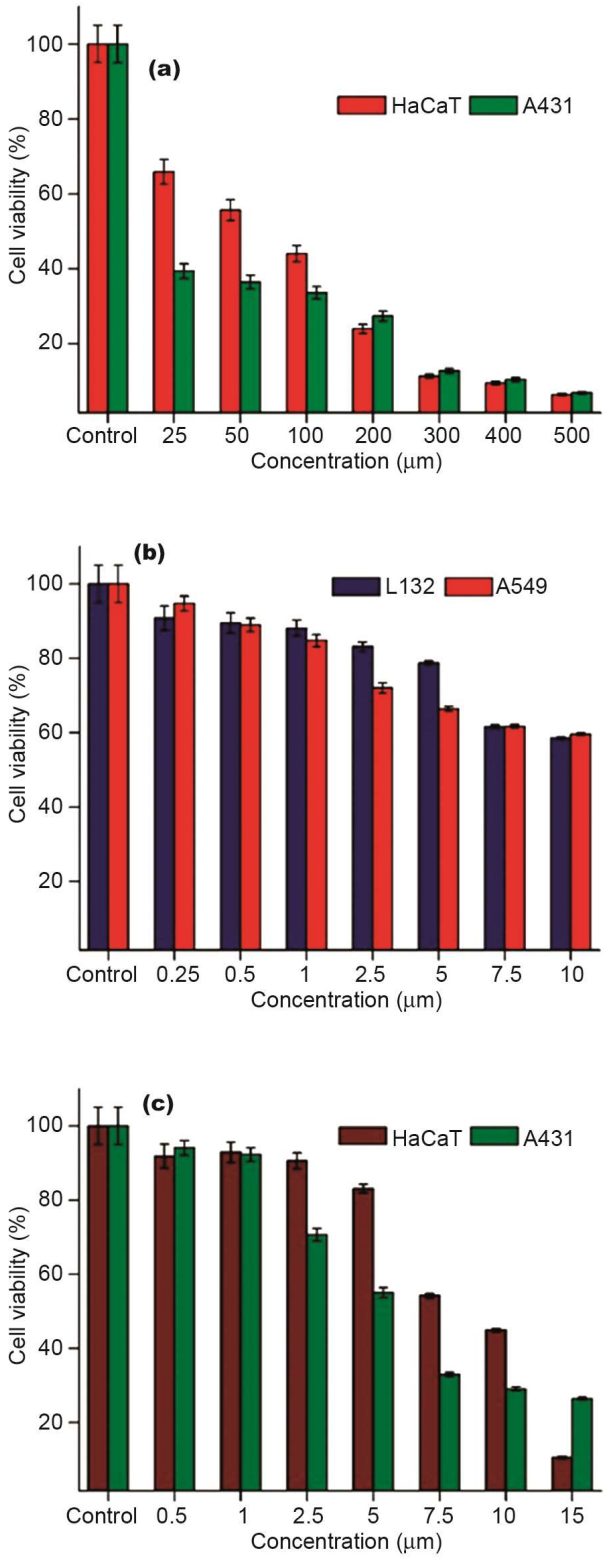


Fig. 4 — Cytotoxic activity of synthesized pyridine-2-carboxaldehyde thiosemicarbazone and its Pb and Cu complexes. [(a) **L**, (b) $[Pb(\mathbf{L})(ONO_2)_2]$ and (c) $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$].

show any specificity, but $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$ showed selectivity against cancer cells compared to normal keratinocytes (Fig. 4). The IC_{50} value of the complex against normal cell was 7.5 μ*M* and IC_{50} for cancer cell was 5.0 μ*M*.

Herein, we have reported the synthesis and X-ray crystallographic characterization of pyridine-2-carboxaldehyde thiosemicarbazone (**L**), $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$ and $[Pb(\mathbf{L})(ONO_2)_2]_n$. Polymeric nature of the Pb complex is due to larger size of the metal as well as its preference for higher coordination number. Cu(II) complex of **L** $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$ was active against keratinocyte cell lines. However, no specificity was observed for **L** and $[Pb(\mathbf{L})(ONO_2)_2]_n$. The IC_{50} value of $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$ against normal and cancer cells was 7.5 μ*M* and 5.0 μ*M*, respectively, which indicates that the complex has the potential to be explored further for anti-cancer activity.

Supplementary data

CCDC 1519838, 1519844 and 1524581 contain the supplementary crystallographic data for **L**, $[Cu(\mathbf{L})(OH_2)](ClO_4)_2$ and $[Pb(\mathbf{L})(ONO_2)_2]_n$, respectively. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk. Other supplementary data associated with this article i.e., Figs S1-S3 and cif files, are available in the electronic form at http://www.niscair.res.in/jinfo/ijca/IJCA_56A(06)616-620_SupplData.pdf.

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