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Uracilato and 5-halouracilato complexes of Cu(II), Zn(II) and Ni(II). X-ray structures of $[Cu(uracilato\text{-}N^1)_2(NH_3)_2]\cdot 2(H_2O)$, $[Cu(5\text{-chlorouracilato-}N^1)_2(NH_3)_2](H_2O)_2$, $[Ni(5\text{-chlorouracilato-}N^1)_2(en)_2]\cdot 2H_2O$ and $[Zn(5\text{-chlorouracilato-}N^1)(NH_3)_3]\cdot(5\text{-chlorouracilato-}N^1)\cdot(H_2O)$ ☆

A. Terrón [a,*], A. García-Raso [a], J.J. Fiol [a], S. Amengual [a], M. Barceló-Oliver [a], R.M. Tótaro [b], M.C. Apella [b], E. Molins [c], I. Mata [c]

[a] *Departament de Química, Universitat de les Illes Balears, 07071 Palma de Mallorca, Spain*
[b] *Facultad de Ciencias Naturales, Universidad Nacional de Tucumán and CERELA-CONICET, Chacabuco 145, 4000 San Miguel de Tucumán, Argentina*
[c] *Institut de Ciència dels Materials de Barcelona (CSIC), Campus de la Universitat Autònoma, 08193 Cerdanyola, Spain*

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Abstract

Four new complexes of uracilato and 5-halouracilato with the divalent metal ions Cu(II), Zn(II) and Ni(II) were obtained and structurally characterized. $[Cu(uracilato\text{-}N^1)_2(NH_3)_2]\cdot 2(H_2O)$ (**1**) and $[Cu(5\text{-chlorouracilato-}N^1)_2(NH_3)_2](H_2O)_2$ (**2**) complexes present distorted square planar co-ordination geometry around the metal ion. Although an additional axial water molecule is present [Cu(II)–OH_2 = 2.89 Å (for **1**) and 2.52 Å (for **2**)] in both cases, only in the complex **2** would be considered in the limit of a bond distance. The Zn(II) in $[Zn(5\text{-chlorouracilato-}N^1)(NH_3)_3]\cdot(5\text{-chlorouracilato-}N^1)\cdot(H_2O)$ presents a tetrahedral co-ordination with three ammonia molecules and the N^1 of the corresponding uracilato moiety. A non-coordinated uracilato molecule is present as a counterion and a recognition between co-ordinated and free ligands, by means a tandem of H-bonds, should be mentioned. Finally, the complex $[Ni(5\text{-chlorouracilato-}N^1)_2(en)_2](H_2O)_2$ (where en is ethylenediamine) presents a typical octahedral *trans* co-ordination with additional hydrogen bonds between 5-chlorouracilato and the NH_2 groups of ethylenediamine units.

Keywords: Uracil; 5-Halouracil; 3d Metal ions; X-ray structure

1. Introduction

Combined chemotherapy with *cis*-platin and 5-fluorouracil is a standard therapy for the treatment of certain types of cancer [1–5].

The mechanism of action of the drug 5-fluoruacil (a pro-drug) in a first step is to became 2′deoxy-5-fluorouridinemonophosphate (5FdUMP) over the action on the divalent metal dependent 5-phosphoryl-ribosyl-1-pyrophosphatase (PRPP) to act as substrate of the thymidylate synthetase enzyme. The substrate 5FdUMP inhibits the enzyme and precludes the synthesis of 2′deoxy-thymidinemonophosphate (dTMP) because of the C–F bond is more inert than a normal C-H bond; thus the synthesis of DNA in a cancer cell stops due to the lacking of the necessary thymidine nucleotides. By a similar strategy 5′-chlorodeoxycytidine is used as a pro-drug to produce the ultimate radiosensitizer 2′deoxy-5-chlorouridinetriphosphate (5CldUTP) that effectively controls human tumours in nude mice [6].

In spite of the widespread use of these antineoplastic agents and its future potentialities, the knowledge of the

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* Corresponding author. Tel.: +34-971-173-249; fax: +34-971-173-426.
E-mail address: dquath0@uib.es (A. Terrón).

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coordination chemistry of 5-haloruracils is limited [1–5,7,8]. A great number of metal 1-methyluracilato [9] and uracilato complexes with Cd(II) [10], Ni(II) [11,12], Hg(II) [13], Pt(II) [12,14,15] and Zn(II) [16–18] have been described, but, to our knowledge, only an example of X-ray structure of metal complexes with 5-halouracilatos is known: the $[Cu(5\text{-fluorouracilato-}N^1)_2(NH_3)_2(H_2O)]$ complex, where the metal is bound to 5-fluorouracilato via N^1 in a limit 4 + 1 square-pyramidal coordination [7]. Recently, the interaction 5-fluorouracil with cisplatin derivatives has been studied [19]. In these complexes the metal interacts with the uracilato moiety through N^1; but other different metal ion binding patterns for uracil are known [9]. Moreover a 5-chloro-1-methyluracilato Pt(II) complex have been structurally characterised [20]. The pharmacological properties of 5-halouracils and some of its metal derivatives [1,3,5] have prompted us to study the co-ordination chemistry of these ligands. In the present paper several Cu(II), Zn(II) and Ni(II) complexes with uracil (ura) and 5-halouracils (X-ura) have been synthesized and characterized, and the X-ray structures of $[Cu(uracilato\text{-}N^1)_2(NH_3)_2]\cdot 2(H_2O)$ (**1**), $Cu(5\text{-chlorouracilato-}N^1)_2(NH_3)_2(H_2O)_2$ (**2**), $[Zn(5\text{-chlorouracilato-}N^1)(NH_3)_3]\cdot(5\text{-chlorouracilato-}N^1)\cdot H_2O$ (**3**) and $[Ni(5\text{-chlorouracilato-}N^1)_2(en)_2]\cdot 2H_2O$ (**4**) are described.

2. Experimental

2.1. Analysis and physical measurements

Elemental microanalyses were carried out using a Carlo Erba model 1106 microanalyser. IR spectra in the solid state (KBr pellets) were recorded on a PE 683 with a PE 1600 IR data station. ^{1}H NMR spectra were recorded on a Brucker AMX 300 spectrophotometer at room temperature. Proton chemical shifts in deuterated dimethylsulfoxide (DMSO-d_6) were referenced to DMSO-d_6 [δ (DMSO): 2.60 ppm]. Reagents were used as received from Sigma, Merck (5-chlorouracil) or Aldrich (metallic salts).

2.2. Crystallographic studies

X-ray data for single crystals of **1**–**4** were collected with an Enraf-Nonius CAD4 diffractometer using monochromatic Mo-Kα radiation ($\lambda = 0.71069$ Å). The cell parameters were determined from a least-squares refinement against a set of reflections randomly searched. Data were collected at room temperature using ω-2θ *scans*. Lorentz-polarisation and ψ-scan empirical absorption corrections [20] were applied using the WinGX program [21]. The structures were solved by direct methods and refined by a full-matrix, least squares method using the SHELX97 programs [22]. H-atoms were positioned in calculated positions, except those in water molecules, which were localised in Fourier difference maps, and their isotropic thermal vibrations were fixed to 1.2–1.5 times the U_{iso} of the bonded atom. Crystal parameters, data collection details and results of the refinements are summarized in Tables 1 and 2. Selected bond lengths and angles for **1**–**4** are given in Tables 3 and 4.

2.3. General procedure for the synthesis of complexes

5-X-Uracil (X = H, F, Cl, Br and I) was dissolved in aqueous concentrated ammonia (X = H and F, 10 ml;

Table 1
Selected crystallographic data for $[Cu(ura)_2(NH_3)_2]\cdot 2H_2O$ (**1**) and $Cu(5\text{-Cl-ura})_2(NH_3)_2(H_2O)_2$ (**2**)

Crystal data	**1**	**2**
Empirical formula	$C_8H_{16}CuN_6O_6$	$C_8H_{14}Cl_2CuN_6O_6$
Crystal size (mm)	$0.62 \times 0.36 \times 0.10$	$0.58 \times 0.15 \times 0.13$
Crystal system	Orthorhombic	Monoclinic
Space group	*Pnma*	$P2_1/n$
Unit cell dimensions (parameters in Å and angles in degrees)	$a = 14.702(2)$, $b = 16.234(5)$, $c = 5.721(3)$	$a = 7.31(2)$, $b = 12.89(3)$, $\beta = 92.149(15)$, $c = 16.339(18)$
Volume (Å^3)	1365.4	1537 (6)
Z	4	4
Formula weight	355.81	424.69
Density (calc.)/(mg m^{-3})	1.731	1.835
Absorption coefficient (mm^{-1})	1.639	1.808
$F(0\,0\,0)$	732	860
Data collection and refinement		
θ range	2.51–30.40	2.01–24.98
Index ranges	$0 \leqslant h \leqslant 20$; $0 \leqslant k \leqslant 23$; $0 \leqslant l \leqslant 8$	$-8 \leqslant h \leqslant 8$; $0 \leqslant k \leqslant 15$; $0 \leqslant l \leqslant 19$
Reflections collected	2133	2800
Independent reflections	2133	2703 ($R_{int} = 0.0109$)
Data/restraints/parameters	2133/14/120	2703/4/223
Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0401$; $wR_2 = 0.1118$	$R_1 = 0.0474$; $wR_2 = 0.1220$
R indices (all data)	$R_1 = 0.0628$; $wR_2 = 0.1182$	$R_1 = 0.064$; $wR_2 = 0.1304$
Largest difference peak and hole (e Å^{-3})	0.781 and −1.090	0.566 and −0.563

Table 2
Selected crystallographic data for $[Zn(Cl\text{-}ura)(NH_3)_3]\cdot(Cl\text{-}ura)\cdot(H_2O)$ (**3**) and $[Ni(Cl\text{-}ura)_2(en)_2]\cdot 2H_2O$ (**4**)

Crystal data	**3**	**4**
Empirical formula	$C_8H_{15}Cl_2N_7O_5\ Zn$	$C_6H_{12}N_4O_3ClNi_{0.5}$
Crystal size (mm)	$0.70\times0.29\times0.09$	$0.45\times0.38\times0.06$
Crystal system	Monoclinic	Triclinic
Space group	$P2_1$	$P\bar{1}$
Unit cell dimensions (parameters in Å and angles in degrees)	$a = 6.213(2),\ b = 17.514(3),$ $\beta = 99.33(3),\ c = 7.173(3)$	$a = 7.764(2),\ \alpha = 108.38(2),\ b = 8.099(3),$ $\beta = 103.57(3),\ c = 8.554(2),\ \gamma = 93.22(3)$
Volume (Å^3)	770.3	491.2
Z	2	2
Formula weight	425.54	253.00
Density (calc.)/(Mg m^{-3})	1.835	1.711
Absorption coefficient (mm^{-1})	1.978	1.309
$F(0\,0\,0)$	432	262
Data collection and refinement		
θ range	2.88–30.41	2.60–29.96
Index ranges	$-8\leqslant h\leqslant 8;\ 0\leqslant k\leqslant 24;\ -10\leqslant l\leqslant 0$	$-10\leqslant h\leqslant 10;\ -11\leqslant k\leqslant 10;\ 0\leqslant l\leqslant 12$
Reflections collected	2563	3022
Independent reflections	2402 ($R_{int} = 0.0373$)	2844 ($R_{int} = 0.0168$)
Data/restraints/parameters	2402/4/217	2844/0/141
Final R indices ($I > 2\sigma(I)$)	$R_1 = 0.0427;\ wR_2 = 0.0810$	$R_1 = 0.0340;\ wR_2 = 0.0916$
R indices (all data)	$R_1 = 0.1156;\ wR_2 = 0.0908$	$R_1 = 0.0386;\ wR_2 = 0.0948$
Largest difference peak and hole (e Å^{-3})	0.0716 and −0.995	0.669 and −1.096

Table 3
Selected bond lengths (Å) and angles (°) for complexes **1** and **2**

1		**2**	
Cu–N(8)	1.985(3)	Cu–N(7)	1.995(7)
Cu–N(7)	1.999(3)	Cu–N(7′)	1.990(7)
Cu–N(1)	2.0132(19)	Cu–N(1′)	2.021(5)
Cu–N(1)[a]	2.0132(19)	Cu–N(1)	2.031(5)
Cu–O(10)	2.89	Cu–O(8)	2.51
N(8)–Cu–N(7)	168.11(13)	N(7′)–Cu–N(7)	168.4(2)
N(8)–Cu–N(1)	91.27(5)	N(7′)–Cu–N(1′)	90.12(18)
N(7)–Cu–N(1)	90.09(5)	N(7)–Cu–N(1′)	90.79(19)
N(8)–Cu–N(1)[a]	91.27(5)	N(7′)–Cu–N(1)	91.73(18)
N(7)–Cu–N(1)[a]	90.09(5)	N(7)–Cu–N(1)	93.16(18)
N(1)–Cu–N(1)[a]	166.78(11)	N(1′)–Cu–N(1)	150.4(2)
O(10)–Cu–N(1)	96.54(4)		

[a] Symmetry transformations used to generate equivalent atoms: $x, -y+1/2, z$.

Table 4
Selected bond lengths (Å) and angles (°) for complexes **3** and **4**

3		**4**	
Zn–N(8)	1.991(5)	Ni–N(7)[a]	2.1016(15)
Zn–N(9)	1.997(4)	Ni–N(7)	2.1016(15)
Zn–N(7)	2.002(5)	Ni–N(10)[a]	2.1027(15)
Zn–N(1)	2.044(5)	Ni–N(10)	2.1027(15)
		Ni–N(1)[a]	2.1956(16)
		Ni–N(1)	2.1956(16)
N(8)–Zn–N(9)	112.5(2)	N(7)[a]–Ni–N(7)	180.00(6)
N(8)–Zn–N(7)	110.5(2)	N(7)[a]–Ni–N(10)[a]	82.57(6)
N(9)–Zn–N(7)	108.9(2)	N(7)–Ni–N(10)[a]	97.43(6)
N(8)–Zn–N(1)	10.9.6(2)	N(7)[a]–Ni–N(10)	97.43(6)
N(9)–Zn–N(1)	110.02(19)	N(7)–Ni–N(10)	82.57(6)
N(7)–Zn–N(1)	105.10(18)	N(10)[a]–Ni–N(10)	180.00(8)
		N(7)[a]–Ni–N(1)	91.18(6)
		N(7)–Ni–N(1)	88.82(6)
		N(10)[a]–Ni–N(1)	88.03(6)
		N(10)–Ni–N(1)	91.97(6)
		N(7)–Ni–N(1)[a]	88.82(6)
		N(7)–Ni–N(1)[a]	91.18(6)
		N(10)[a]–Ni–N(1)[a]	91.97(6)
		N(10)–Ni–N(1)[a]	88.03(6)
		N(1)–Ni–N(1)[a]	180.00(6)

[a] Symmetry transformations used to generate equivalent atoms: $x+1, -y, z$.

X = Cl and Br, 40 ml; X = I, 50 ml) at room temperature. When the ligand was completely dissolved, an equimolar amount of the metal was added dropwise in the form of a solution of the corresponding salt solution of the corresponding salt of metal ($CuSO_4\cdot 5H_2O$ or $NiCl_2\cdot 6H_2O$ or $Zn(NO_3)_2\cdot 6H_2O$) in several ml of water. The mixture was heated to reflux with stirring during 30 min and then left to evaporate slowly. After several days, crystals of the corresponding product appeared. The product was filtered off and dried over silica gel. Generally, the complexes crystallized very slowly and the yields were about 30% in all cases. The Zn(II)-complexes are highly hygroscopic materials and we only have been able to unequivocally characterize the 5-chlorouracil derivative.

- $[Cu(uracilato\text{-}N^1)_2(NH_3)_2]\cdot 2H_2O$ (**1**)

Blue crystals. Found: C, 26.90; H, 4.35; N, 23.20. Calc. for $C_8H_{16}N_6O_6Cu$: C, 27.00; H, 4.50; N, 23.62. Several crystals were suitable for X-ray diffraction studies. IR (cm^{-1}): 1637vs, 1475s, 1408s, 1385m, 1294s, 1263w, 1201w, 1294s, 1029m, 1008m, 898m, 812m, 787m, 629m, 451w, 433w.

• [Cu(5-fluorouracilato-N^1)$_2$(NH_3)$_2$(H_2O)] · (H_2O)

Blue crystals. Found: C, 24.35; H, 3.43; N, 21.15. Calc. for $C_8H_{14}N_6O_6F_2Cu$: C, 24.52; H, 3.61; N, 21.45. An "extra" water molecule compared to the previously described [Cu(F-uracilato-N^1)$_2$(NH_3)$_2$ · (H_2O)] [7] is present. IR (cm^{-1}): 1657br,vs, 1487s, 1407s, 1338w, 1264s, 1226w, 1020m, 943m, 880m, 828m, 774m, 759m, 738m 640m, 600m, 542m, 450w 372w, 321w.

• Ni(5-fluorouracilato-N^1)$_2$(NH_3)$_2$(H_2O)$_{2.5}$

Turquoise-blue microcrystals. Found: C, 24.51; H, 3.58; N, 21.49. Calc. for $C_8H_{13.5}N_6O_{5.5}F_2Ni$: Ni(F-ura)$_2$($NH_3$)$_2$($H_2O$)$_2$: C, 24.83; H, 3.65; N, 21.72. IR (cm^{-1}): 1660-1597vs, 1397m, 1271s, 1225m, 1015m, 950w, 872w, 822s, 814m, 775w, 758w, 665m, 626w, 587m, 526w, 493w, 427w, 363vw.

• Cu(5-chlorouracilato-N^1)$_2$(NH_3)$_2$(H_2O)$_2$ (**2**)

A mixture of two different types of crystals were obtained which present the same elemental analysis: blue crystals, suitable for X-ray studies (main product) and lilac macles. Compound blue: Found: C, 22.54; H, 3.26; N, 19.61. Calc. for $C_8H_{14}N_6O_6Cl_2Cu$: C, 22.62; H, 3.33; N, 19.79. IR (cm^{-1}): 1640vs, 1590s, 1474m, 1424m, 1400m, 1322m, 1284m, 1229m, 1186m, 1098m, 1022m, 969m, 868m, 799w, 787w, 778w, 756w, 697m, 605vw, 446w, 378w. Compound lilac: Found: C, 22.77; H, 3.21; N, 19.61. IR (cm^{-1}) 1640vs, 1575s, 1467m, 1411m, 1401sh, 1338m, 1277m, 1257 m, 1184m, 1105m, 1018m, 980w, 960w, 800m, 775m, 756w, 697m, 599vw, 441w, 376w.

• Ni(5-chlorouracilato-N^1)$_2$(NH_3)$_3$(H_2O)

Pale-blue crystals (macles). Found: C, 22.86; H, 3.58; N, 23.61. Calc. for $C_8H_{15}N_7O_5Cl_2Ni$: C, 22.93; H, 3.58; N, 23.41. IR (cm^{-1}): 3371vs, 1665br,vs, 1644-35vs, 1596vs, 1567s, 1456m, 1409m, 1362w, 1329m, 1273m, 1189m, 1088m, 1010vw, 992w, 980vw, 882w, 798m, 784m, 757w, 679-667m, 630 w, 447w, 419sh, 369w.

• [Zn(5-chlorouracilato-N^1)(NH_3)$_3$] · (5-chlorouracilato-N^1) · (H_2O) (**3**)

White crystals. Found: C, 22.12; H, 3.39; N, 22.51. Calc. for $C_8H_{15}N_7O_5Cl_2Zn$: C, 22.57; H, 3.52; N, 23.04. A few crystals were suitable for X-ray diffraction study. IR (cm^{-1}): 1669–1600vs, 1465m, 1416m, 1387m, 1339w, 1318m, 1284s, 1213m, 1177w, 1177m, 1098m, 1029m, 1002m, 957w, 864m, 797m, 775m, 753w, 692m, 682m, 600w, 575w, 449w, 433w, 377w, 313vw.

• Cu(5-bromouracilato-N^1)$_2$(NH_3)$_{11/3}$

Blue-lilac crystals. Found: C, 18.95; H, 2.90; N, 21.27. Calc. for $C_8H_{45/3}N_{23/3}O_4Br_2Cu$: C, 18.99; H, 2.99; N, 21.22. IR (cm^{-1}): 1646s, 1587vs, 1538s, 1465m, 1402m, 1339vw, 1317m, 1273m, 1172w, 1067w, 997m, 954w, 900m, 796m, 735m, 719w, 647m, 570m, 452w, 439w, 422w, 295w.

• Ni(5-bromouracilato-N^1)$_2$(NH_3)$_{11/3}$

Blue-violet crystals (macles). Found: C, 19.14; H, 3.04; N, 21.61. Calc. for $C_8H_{45/3}N_{23/3}O_4Br_2Ni$: C, 19.18; H, 3.02; N, 21.43. IR (cm^{-1}): 1661-1597vs, 1556s, 1446m, 1406m, 1314m, 1275m, 1239w, 1185m, 1136m, 1064w, 993m, 946w, 869m, 781m, 752m, 715w, 654m, 448w, 374w.

• Cu(5-iodouracilato-N^1)$_2$(NH_3)$_2$(H_2O)$_2$

Blue crystals (macles). Found: C, 15.70; H, 2.10; N, 13.57. Calc. for $C_8H_{14}N_6O_6I_2Cu$: C, 15.81; H, 2.31; N, 13.83. IR (cm^{-1}): 1640-1540vs, 1458m, 1405m, 1325m, 1283m, 1272m, 1229m, 1174m, 1058w, 1076m, 966w, 951vw, 869m, 775m, 753w, 728w, 642m, 598w, 528w, 453w, 430w.

• Ni(5-iodouracilato-N^1)$_2$(NH_3)$_4$

Blue crystals (macles). Found: C, 15.87; H, 2.64; N, 18.44. Calc. for $C_8H_{16}N_8O_4I_2Ni$: C, 15.99; H, 2.66; N, 18.65. IR (cm^{-1}): 1650vs, 1594s, 1546m, 1456m, 1402m, 1316m, 1273m, 1206m, 1186m, 1048w, 1004vw, 989w, 949w, 865w, 782m, 752w, 711w, 640m, 629m, 450w, 440w.

2.4. Preparation of [Ni(5-chlorouracilato-N^1)$_2$(en)$_2$] · 2H_2O

5-Chlorouracil (1 mmol) was dissolved in aqueous sodium hydroxide 0.06 M (16 ml) at room temperature. When the ligand was completely dissolved, an aqueous solution (8 mL) of the dichlorobis(ethylenediamine) complex Ni(en)$_2$Cl$_2$ · 0.5H_2O (0.5 mmol) was added drop by drop. The mixture was filtered and the solution was heated during 2 h with stirring. After a week, blue-violet needles of [Ni(5-chlorouracilato-N^1)$_2$(en)$_2$] · 2H_2O were collected and dried over silica gel which were suitable for diffraction studies. An equivalent procedure based in the dissolution of the 5-chlorouracilato in ammonium hydroxide and subsequent addition of Ni(en)$_2$Cl$_2$ · 0.5H_2O yields the same product, but in this case the solid is amorphous and crystals are not formed. Found: C, 28.37; H. 4.78; N, 22.00. Calc. for $C_{12}H_{24}N_8O_6Cl_2Ni$: C, 28.49; H, 4.74; N, 22.16. IR (cm^{-1}): 1643vs, 1635vs, 1592vs, 1568m, 1467vs, 1406s, 1320m, 1279s, 1174m, 1093m, 1012-1005vs, 683vs, 540m, 518m, 454w, 429 w, 379w, 350w, 319vw.

3. Results and discussion

*3.1. Crystal structures of copper complexes: [Cu(uracilato-N^1)$_2$(NH_3)$_2$] · 2(H_2O) (**1**), Cu(5-chlorouracilato-N^1)$_2$(NH_3)$_2$(H_2O)$_2$ (**2**)*

The crystal structures of complexes **1** and **2** are shown in Figs. 1 and 2. Selected bond distances and angles are given in Table 3. In these two complexes, the Cu(II) presents a distorted square planar co-ordination geometry for copper(II) defined by two N^1-(5-X-uracilato) moieties [Cu–N^1 distances: Cu–N(1) and Cu–N(7), 2.0132(19) Å for X = H; Cu–N(1) and Cu–N(1′), 2.021(5) and 2.031(5) Å for X = Cl] and two ammonia

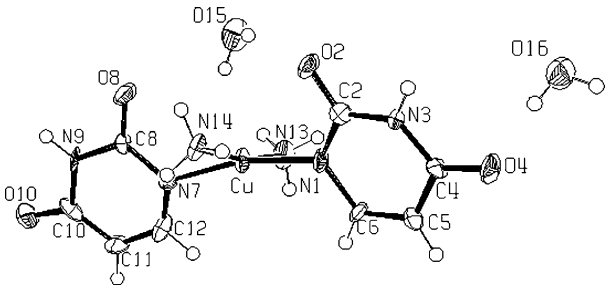

Fig. 1. ORTEP of $[Cu(ura)_2(NH_3)_2]\cdot 2H_2O$.

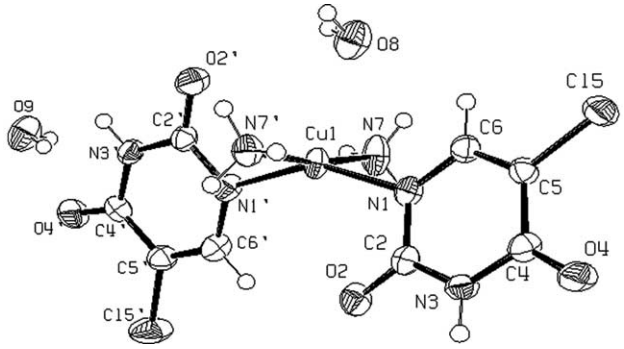

Fig. 2. ORTEP of $Cu(5\text{-cl-ura})_2(NH_3)_2(H_2O)_2$.

molecules [Cu–NH_3 distances: Cu–N(13) and Cu–N(14), 1.985(3) and 1.999(2) Å for X = H; Cu–N(7) and Cu–N(7′), 1.990(7) and 1.995(7) for X = Cl]. An additional distal water is present [Cu–OW distance: Cu–O(15), 2.89 Å for X = H; Cu–O(8), 2.51 Å for X = Cl] which could be considered within (X = Cl) or outside (X = H) the limits of a co-ordination bond. These values are similar to the previously described $[Cu(F\text{-ura})_2(NH_3)_2(H_2O)]$ [Cu–N^1(F-ura) = 2.046 Å and Cu–NH_3 = 1.995 Å; Cu-distal OW = 2.51 Å] [7]. Contrarily to the F-ura and Cl-ura complexes where no H bonds are present in the complex unit, two hydrogen bonds between the distal water [O(15)] and the O^2 atoms of the two coordinated uracils are observed in $[Cu(uracilato\text{-}N^1)_2(NH_3)_2]\cdot 2H_2O$ (**1**) [O(2)···O(8) = 2.90 Å, O(2)–O(15)–O(8) = 124°]. On the other hand, $[Cu(uracilato\text{-}N^1)_2(NH_3)_2]\cdot 2H_2O$ (***1***) present a *totally eclipsed-syn conformation* between the two uracilato moieties [dihedral angle C(2)–N(1)···N(7)–C(8) = −0.05°] while a *totally eclipsed-anti conformation* is observed for $[Cu(F\text{-uracilato-}N^1)_2(NH_3)_2\cdot(H_2O)]$ [equivalent dihedral angle = −0.02°]. Finally in the $Cu(5\text{-chlorouracilato-}N^1)_2(NH_3)_2(H_2O)_2$ (**2**) complex a *gauche* conformation is present [dihedral angle C(2)–N(1)···N(1′)–C(2′) = −22.84°]. The two 5-X-uracilato moieties are not symmetrically distributed in the complex unit for ura and F-ura [the distances of each O^2 to the two ammonia groups are 2.98 and 4.15 Å for X = H; 2.91 and 4.21 Å for X = F] while the values are very similar for Cl-ura [the distances of each O^2 to the two ammonia groups are 3.02 and 3.12 Å] as a consequence of the *gauche* conformation previously mentioned.

*3.2. Crystal structure of $[Zn(5\text{-Chlorouracilato-}N^1)(NH_3)_3]\cdot(5\text{-chlorouracilato-}N^1)\cdot(H_2O)$ (**3**)*

$[Zn(Cl\text{-ura})(NH_3)_3]\cdot(Cl\text{-ura})\cdot(H_2O)$ (***3***), as shown in Fig. 3, presents a tetrahedral co-ordination of Zn(II) bound to three ammine ligands [1.991(5), 1.997(4) and 2.002(5) Å] and to the N^1 of one 5-chlorouracilato anion [2.044(5) Å]. A tandem of two hydrogen bonds [O(2)···N(12) = 2.87 Å, N(12)–H···O(2) = 161.19° and N(3)···O(13) = 2.81 Å, N(3)–H···O(13) = 157.67°] is observed which could be considered as a molecular recognition between the cationic Zn(II) complex and the free 5-chlorouracilato anion. Both species located in two different parallel planes. In general, the distances in co-ordinated Cl-ura and free Cl-ura are similar, although C=O and N^1=C distances are shorter in Zn-(Cl-ura) [C(2)=O(2) = 1.247 and N(1)–C(6) = 1.357 Å] than in free Cl-ura [1.260 and 1.386 Å].

*3.3. Crystal structure of $[Ni(5\text{-chlorouracilato-}N^1)_2(en)_2]\cdot 2H_2O$ (**4**)*

In this complex, the Ni(II) is located on an inversion centre with approximately regular octahedral co-ordination to two 5-chlorouracilato [Ni–N(1) = 2.1956(16) Å] and two ethylenenediammine [Ni–N(7) = 2.1016(15) and Ni–N(10) = 2.1027(15) Å] ligands (Fig. 4). Moreover an intramolecular H-bond between 5-chlorouracilato and ethylenediammine moieties is present [distance ethylenediammine–N(7)···O(2)–uracilato = 2.96 Å, angle N(7)–H···O(2) = 134.7°]. The retained molecules interact via H-bonds with O(4) of 5-chlorouracilato [O(4)···OW = 2.83 Å, angle O(4)···H–OW = 163.9°]. On the other hand, both uracilato molecules are slightly twisted from the normal plane [dihedral angle Ni–N(1)–C(2)–O(2) ≈15°].

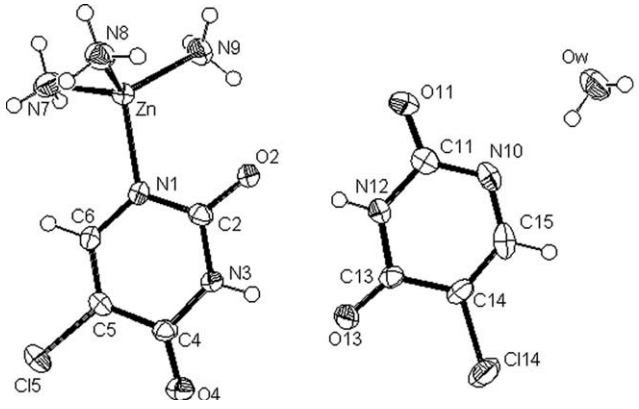

Fig. 3. ORTEP of $[Zn(Cl\text{-ura})(NH_3)_3]\cdot(Cl\text{-ura})\cdot(H_2O)$.

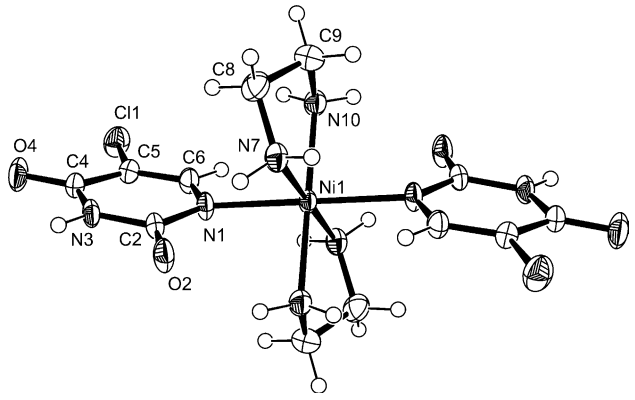

Fig. 4. ORTEP of $[Ni(Cl\text{-}ura)_2(en)_2]\cdot 2H_2O$.

3.4. NMR studies

A similar $\delta_{H(6)}$ value of $[Zn(Cl\text{-}ura)(NH_3)_3]\cdot(Cl\text{-}ura)\cdot(H_2O)$ (**3**) (7.72 ppm) and free 5-chlorouracil (7.77 ppm) [23] show that the Zn(II) complex is not stable in DMSO and only the signal assigned to 5-chlorouracil is observed [24]. In other typical NMR solvents (D_2O and $CDCl_3$) this complex is not soluble.

3.5. IR studies

Selected IR bands for uracil, 5-halouracils and the complexes are shown in Table 5(a) and (b). These bands have been tentatively assigned for the haloderivatives by comparison with the calculated and assigned bands for uracil [24,25]. Comparing the spectra of 5-halouracil ligands and free uracil it is possible to assign tentatively these bands because of the form of spectra is very similar, with the presence of new bands due to C–X stretching (at 642 cm^{-1} for F-ura, in the 400–500 cm^{-1} zone for Cl-ura and Br-ura and near 300 cm^{-1} for I-ura) [26]. Comparison of the IR spectra of the complexes and of the free uracil bases shows that the bands at ca. 1710 cm^{-1} ($\nu C_2{=}O + \nu N_1C_2$) [24,25] and ca. 1670 cm^{-1} ($\nu C_4{=}O + \nu C_4{=}C_5$) are replaced by a strong broad band with a maximum at ca. 1640 cm^{-1} (see Table 5(a) and (b)), in agreement with the presence of 5-X-uracilato-^{1}N (X = H, F, Cl, Br, I) anions. Moreover, the bands related to N(3) at ca. 1380 cm^{-1}($\nu N_3C_3 + \nu C_5C_6$) remain, in general, practically unaltered in the complexes. On the other hand, the shifts in the bands at ca. 1230 cm^{-1} in free uracils ($\nu N_1C_6 + \nu C_5C_6$) are sensitive to the nature of the complex, and the influence of the co-ordination on the conjugated part of the ligands. The large number of 5-halouracilato bands makes it difficult to assign other bands in the spectra, including the normal modes νNi–N of the ammine ligands; it seems likely however that the bands close to 430 cm^{-1} in the Cu(II) complexes could be assigned to νCu–N (in $[Cu(NH_3)_4]^{2+}$, νCu–N is located at 426 cm^{-1} [17]). A

Table 5
Selected IR bands of uracil and 5-halouracil complexes

(a) Uracil	$[Cu(uracilato\text{-}N^1)_2(NH_3)_2]\cdot 2H_2O$ (**1**)	5-Fluorouracil	$Cu(5\text{-fluorouracilato})_2(NH_3)_2(H_2O)_2$	$Ni(5\text{-fluoro-uracilato})_2(NH_3)_2(H_2O)_{2.5}$	5-Chlorouracil	$[Cu(5\text{-chloro-uracilato-}N^1)_2(NH_3)_2]\cdot(H_2O)_2$ (**2**)	$Ni(5\text{-chloro-uracilato-}N^1)_2(NH_3)_3(H_2O)$	Assignment in free uracil [24,25]
1715br,vs	1637vs	1724vs	1657br,vs	1660–1597vs	1730–1660br,s	1640vs	1665br,vs	($\nu C_2{=}O + \nu N_1C_2$)
1675br,vs		1666–47vs			1730–1660br,s			($\nu C_4{=}O + \nu C_4{=}C_5$)
1385s	1385m	1350m	1338w	1397m	1343m	1334w	1329m	($\nu N_3C_3 + \nu C_5C_6$)
1225m	1263w, 1201w	1225m	1226w	1225m	1266w	1284m	1273m	($\nu N_1C_6 + \nu C_5C_6$)
(b) 5-Bromouracil	$Cu(5\text{-bromouracilato})_2(NH_3)_{11/3}$	$Ni(5\text{-bromouracilato})_2(NH_3)_{11/3}$	5-Iodouracil	$Cu(5\text{-iodouracilato})_2(NH_3)_2(H_2O)_2$	$Ni(5\text{-iodouracil-atoN}^1)_2(NH_3)_4$	Assignment in free uracil [24,25]		
1702s	1646s	1661–1597vs	1785–1650vs	1640–1540vs	1650vs	($\nu C_2{=}O + \nu N_1C_2$)		
1667–1653vs						($\nu C_4{=}O + \nu C_4{=}C_5$)		
1343m	1339vw	1314m	1320m	1325m	1316m	($\nu N_3C_3 + \nu C_5C_6$)		
1231m	1273 m	1275m	1210m	1229m	1206m	($\nu N_1C_6 + \nu C_5C_6$)		

similar spectrum is obtained for the Zn(II)-5-chlorouracilato complex where the ($\nu C_2{=}O + \nu N_1C_2$) and ($\nu C_4{=}O + \nu C_4{=}C_5$) bands in free 5-chlorouracil shift to lower frequencies in the complex (1669–1600 cm^{-1}).

[Ni(5-chlorouracilato-N^1)$_2$(en)$_2$]$\cdot 2H_2O$ show strong bands at 1643 and 1635 cm^{-1} which are assigned to ($\nu C_2{=}O + \nu N_1C_2$) and ($\nu C_4{=}O + \nu C_4{=}C_5$) respectively. The band νNi–N, at 356 cm^{-1} in the Ni(en)$_2$Cl$_2$, splits to a doublet centred at 379 and 350 cm^{-1}. Moreover, the strong band at 1038 cm^{-1}, assigned to νC–C/νC–N in ethylenediamine, shifts to 1012 cm^{-1}. The results are in agreement with other *trans* N-bonded purine complexes, as [Ni(en)$_2$(purine)$_2$] [26–28].

4. Conclusions

The coordination abilities of haloruracils, pyrimidine derivatives of biological interest, have been elucidated. The new X-ray structures of [Cu(uracilato-N^1)$_2$(NH$_3$)$_2$]$\cdot 2(H_2O)$, [Cu(5-chlorouracilato-N^1)$_2$(NH$_3$)$_2$](H$_2$O)$_2$, [Ni(5-chlorouracilato-N^1)$_2$(en)$_2$]$\cdot 2H_2O$ and [Zn(5-chlorouracilato-N^1)(NH$_3$)$_3$]$\cdot$(5-chlorouracilato-N^1)$\cdot$(H$_2$O) compounds covers a lack in the literature. In these compounds the coordination is always with N^1 in a similar pattern of the related ligand 5-fluorotic acid [29] that has been recently established where Ni(II) and Cu(II) prefer to bound N^1.

Also the capability of recognition by hydrogen bonds have been stated in the Zn(II) and Ni(II) derivatives. These recognition patterns are very important for the pro drug 5-fluorouracil. to produce the inhibitor of thymidylate synthetase 5FdUMP and also for the 5-chlorouracil derivative 5CldUTP that is the ultimate radiosensitizer [6]. In the two processes the presence of divalent metal ions, specially Zn(II), can be relevant.

5. Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. C 223734–223737 for **1**–**4**. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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References

[1] K.K. Narang, V.P. Singh, D. Bhattacharya, Polyhedron 14 (1997) 2491–2497, and references included therein.
[2] U.P. Sing, Cryst. Res.Technol. 24 (1989) K145–K147.
[3] V. Etelaniemi, R. Serimaa, T. Laitalainen, T. Paakari, J. Chem. Soc., Dalton Trans. (1998) 3001–3005, and references cited therein.
[4] J.R. Allan, V.B. McCoy, Thermochim. Acta 208 (1992) 133–137.
[5] U.P. Sing, R. Ghose, A.K. Ghose, A. Sodhi, S.M. Soingh, R.K. Singh, J. Inorg. Biochem. 37 (1989) 325–339.
[6] S. Greer, M. Alvarez, M. Mas, C. Wozniack, D. Arnold, A. Knapinska, C. Norris, R. Burk, A. Aller, M. Dauphine, Int. J. Radiat. Oncol. Biol. Phys. 51 (2001) 791–806.
[7] N.V. Nazimova, G.N. Tischenko, I.V. Nikitina, A. Ershov, E.M. Kazmina, Kristallografiya 32 (1987) 1404–1409.
[8] H.C. Nelson, J.F. Villa, J. Inorg. Nucl. Chem. 42 (1980) 1089–1092.
[9] See, for example B. Lippert, Coord. Chem. Rev. 200–202 (2000) 487–516.
[10] I. Mutikainen, P. Lumme, Acta Crystallogr. Sect. B 36 (1980) 2237–2240.
[11] I. Mutikainen, P. Lumme, Acta Crystallogr. Sect. B 36 (1980) 2251–2254.
[12] H. Rauter, I. Mutikainen, M. Blomberg, C.J.L. Lock, P. Amo-Ochoa, E. Freisinger, L. Randaccio, E. Zangrando, E. Chiarparin, B. Lippert, Angew. Chem., Int. Ed. Engl. 36 (1997) 1296–1301.
[13] J.A. Carrabine, M. Sundaralingam, Biochemistry 10 (1971) 292–299.
[14] H. Rauter, E.C. Hillgeris, A. Erxleben, B. Lippert, J. Am. Chem. Soc. 116 (1994) 616–624.
[15] R. Faggiani, B. Lippert, C.J.L. Lock, Inorg. Chem. 19 (1980) 295–300.
[16] C. Bazzicalupi, A. Bencini, E. Berni, A. Bianchi, S. Ciattini, C. Giorgi, P. Paoletti, B. Valtancoli, Eur. J. Inorg. Chem. (2001) 629–632.
[17] C. Bazzicalupi, A. Bencini, E. Berni, S. Ciattini, A. Bianchi, C. Giorgi, P. Paoletti, B. Valtancoli, Inorg. Chim. Acta 317 (2001) 259–267.
[18] M. Ruf, K. Weis, H. Vahrenkamp, Inorg. Chem. 36 (1997) 2130–2137.
[19] X. Wang, J. Lin, X. Zhang, Q. Liu, Q. Xu, R. Tan, Z. Guo, J. Inorg. Biochem. 94 (2003) 186–192.
[20] A.C.T. North, D.C. Phillips, F.S. Mathews, Acta Crystallogr. Sect. A 24 (1968) 351–359.
[21] L.J. Farrugia, J. Appl. Cryst. 32 (1999) 837–838.
[22] G.M. Sheldrick, SHELX97, Programs for Crystal Structure Analysis (Release 97-2). University of Göttingen, 1997.
[23] R. Shepherd, S. Zhang, F.T. Lin, R.A. Kortes, Inorg. Chem. 32 (1992) 1457–1462.
[24] M. Goodgame, Coord. Chem. Rev. 79 (1987) 97–134.
[25] J. Duchesnes, Physicochemical Properties of Nucleic Acids, vol. 2, Academic Press, New York, 1973.
[26] K. Nakamoto, Infrared and Raman Spectra of Inorganic and Coordination Compounds, third ed., Wiley, New York, 1978, pp. 202–208.
[27] G. Cervantes, J.J. Fiol, A. Terrón, V. Moreno, J.R. Alabart, M. Aguiló, M. Gómez, X. Solans, Inorg. Chem. 29 (1990) 5168–5173.
[28] M.B. Baldwin, J. Chem. Soc. (1960) 4369–4376.
[29] A.G. Schneider, H.W. Schmalle, F. Arod, E. Dubler, J. Inorg. Biochem. 89 (2002) 227–236.