



Interaction of Bivalent Transition Metal(II) Ions with Substituted Pyrimidines: Mixed Ligand Complexes of Co(II), Cu(II), Ni(II) & Zn(II) with 5-Fluorouracil and Some Amines

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In this work we explored the synthesis of twelve transition metal mixed ligand complexes (**1-12**). A new series of 5-fluorouracil (5-FU) with some amines namely ethylenediamine(en)/1,3-diaminopropane(1,3-dp)/*ortho*-phenylenediamine (opd) of general formulae [MAB(OAc)(H₂O)], where M = Co(II), Cu(II), Ni(II) & Zn(II), A = 5-FU and B = en/1,3-dp/opd are presented. Micro elemental analysis, IR and UV were used to characterize these complexes. The antioxidative activity was also tested.

Keywords: 5-Fluorouracil, Amines, Cobalt(II), Copper(II), Ni(II), Zn(II), Antioxidative.

INTRODUCTION

A break in the biological and medical fields was made with the discovery of the therapeutic functions of substituted pyrimidines¹. Not only have the pyrimidines presented in the nucleic acids (cytosine, uracil and thymine) but also a great number of other pyrimidines play an important role in many biological processes. A number of pyrimidine derivatives are antimetabolites, being of clinical interest in cancer chemotherapy. The most important class of these molecules is the 5-fluorouracils, which are analogue of uracil with a fluorine atom at the C5 position in place of hydrogen as the methyl group in thymine² (Fig. 1).

Fluorinated pyrimidines have been prepared as potential antitumour, antibacterial, antiviral and antioxidative agents³. Although 5-fluorouracil (5-FU) was first introduced by Heidelberger in 1957, it remains as a necessary part of the treatment of a wide range of tumours⁴. It is still the most broadly prescribed agent for the treatment of colorectal cancer and is used for the patients with breast and other cancers, like those of the head and neck⁵, less than one-third of patients achieve objective responses. Recent research has focused on the bimodulation of 5-fluorouracil to improve the cytotoxicity and therapeutic effectiveness of this drug in the treatment of advanced disease. Due to its structure, 5-fluorouracil interferes with nucleoside metabolism and can be incorporated into RNA

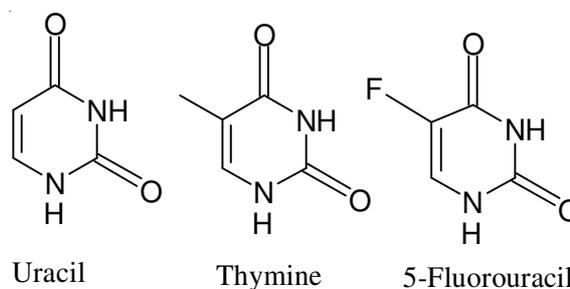


Fig. 1. Chemical structure of uracil, thymine and 5-fluorouracil

and DNA, leading to cytotoxicity and cell death⁶. Capecitabine (Fig. 2), chemically 5'-deoxy-5-fluoro-N-4-pentyloxy carbonyl cytidine is the pro-drug for 5-fluorouracil. It is a novel oral tumour-activated and tumour-elective fluoropyrimidine carbamate⁷ and an oral chemotherapeutic agent which is also used in the treatment of breast, esophageal and larynx, gastrointestinal and genitourinary tract cancer.

It is well known that mixed ligand coordination complexes of 5-fluorouracil play a vital role in many biological systems and a number of bivalent transition metal mixed ligand complexes of 5-fluorouracil have been reported⁸. They possess more significant activity than that of 5-fluorouracil. In the continuation of our work^{7,9}, we present the synthesis, elemental analysis, spectral characterization (IR and UV) and antioxidative activity of twelve transition metal mixed ligand

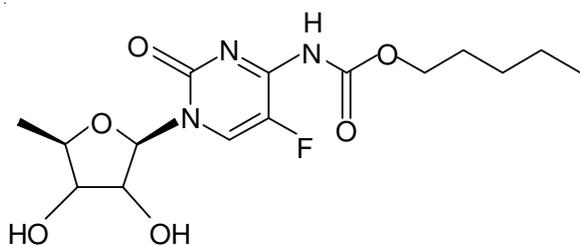


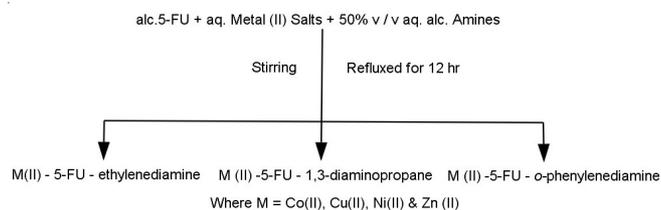
Fig. 2. Chemical structure of capecitabine

complexes of 5-FU with ethylenediamine(en)/1,3-diaminopropane(1,3-dp)/*ortho*-phenylenediamine(opd).

EXPERIMENTAL

All the solvents and reagents used were of AnalaR grade. The metal acetates [Ni(CH₃(COO)₂·4H₂O, Co(CH₃(COO)₂·6H₂O, Cu(CH₃(COO)₂·H₂O and Zn(CH₃(COO)₂·2H₂O)], 5-fluorouracil, ethylenediamine, 1,3-diaminopropane and *o*-phenylenediamine employed were of E. Merck grade and purchased from Aldrich. Solvents for the physical measurements were purified according to literature methods¹⁰.

Synthesis of mixed ligand complexes: A calculated amount of 5-fluorouracil was dissolved in boiling ethanol and to this aqueous solution; calculated amount of the corresponding metal acetates was added and well stirred. To this resulting solution, 50 % v/v water-ethanol mixture of amines (**Scheme**) was added so that the overall ratio of metal: 5-fluorouracil: amines was 1:1:1. The resulting solution was refluxed for 12 h. On cooling, the complexes were obtained and collected by vacuum filtration, washed several times with diethyl ether and then dried *in vacuo* over anhydrous CaCl₂ (Yield: 61-82 %).



Scheme: Synthetic route of M(II)-5FU-amine mixed ligand complexes (1-12)

Micro elemental analyses were performed on an elemental vario EL III analyzer. Molecular weight was determined by rasi method. Melting points of all these mixed ligand complexes were determined on a Gallenkamp apparatus in open glass capillaries and are uncorrected. Molar conductance of free ligands and their mixed ligand complexes were determined in DMSO solvent (1×10^{-3} M) at room temperature using an Elico CM 180 conductivity meter. Magnetic susceptibility measurements on powder samples were carried out by the Gouy method using Hg[Co(SCN)₄] as calibrant and the diamagnetic corrections were applied in compliance with Pascal's constant¹¹. Electronic absorption spectra were recorded in DMSO solution with a Hitachi U-2000 double beam spectrophotometer (cell length, 1 cm) in the 200-1100 nm range. Vibrational spectra were recorded using KBr pellets on a FT-IR spectrophotometer, Shimadzu 8400S, in the 400-4000 cm⁻¹

range. For antioxidative activity, the reduced NBT were determined by the absorbances on a 751 spectrophotometer at $\lambda = 560$ nm.

Antioxidative activity tests: The superoxide radicals O₂^{•-} were produced by a system of NADH/PMS/NBT and measured by the amount of NBT reduced by O₂^{•-} free radical²⁰. The final concentration of the reagents were c(NADH) = 73 $\mu\text{mol dm}^{-3}$, c(NBT) = 50 $\mu\text{mol dm}^{-3}$ c(*tris*-HCl buffer, pH=8) = 0.016 mol dm⁻³ and c(tested compound) = 30 $\mu\text{mol dm}^{-3}$. The reaction was kept for 5 min at room temperature. The amount of reduced NBT was detected by the absorbance at 560 nm as the reduced product formed absorbs at this wavelength. The suppression ratio for O₂^{•-} was calculated by the formula,

$$\text{Suppression ratio} = 100(A_0 - A/A_0)$$

where A = Absorbance in the presence of the ligand or the complex; A₀ = Absorbance in the absence of the ligand or the complex.

RESULTS AND DISCUSSION

The synthesized mixed ligand complexes are air stable and non-hygroscopic in nature. The complexes are found to be partly soluble in water, methanol, ethanol and insoluble in common organic solvents like benzene, acetone, petroleum ether *etc.*, but soluble in DMSO, DMF and dioxan. The obtained result of micro elemental analysis (C, H, N) with their molecular formulae and some of their physical properties of the prepared complexes were summarized in Table-1. Micro elemental analytical data are in good agreement with the calculated values which shows 1:1:1 ratio (metal: 5-fluorouracil: amines) in MAB complexes. Also, the observed low molar conductance value of the metal chelates in DMSO solution (10^{-3} M) reveals that non-electrolytic nature of all the complexes due to the absence of any counter ions in the proposed structures¹². These complexes melt between 214-282 °C and decompose above 300 °C.

IR spectra: The characteristic IR spectral data (KBr pellet, cm⁻¹) with the principal IR frequencies of 5-fluorouracil and its mixed ligand complexes are given in Table-2. The presence of $\nu(\text{M-O})_{\text{aqua}}$ in the lower region (449-410 cm⁻¹) of 5-fluorouracil mixed ligand complexes confirm the bonding of water molecules inside the sphere in these complexes¹³. No characteristic band due to coordinated water is observed in the far IR spectra of these complexes which confirm the water molecule are crystal water. This is consistent with the results of micro elemental analysis¹⁴.

The $\nu(\text{C}_{(4)} = \text{O})$ band occurring at 1695 cm⁻¹ in 5-fluorouracil is shifted considerably towards a lower frequency (about 35-50 cm⁻¹) in all the mixed ligand complexes suggesting the coordination of the (C₍₄₎ = O) group with the metal¹³. The $\nu(\text{C}_{(2)} = \text{O})$, $\nu(\text{C}-\text{F})$ and $\delta(\text{N}_{(1)}-\text{H})$ bands appear at 1710, 1470 and 1512 cm⁻¹, respectively in free 5-fluorouracil. These bands either do not shift or show slight shifts in the mixed ligand complexes indicating that these groups are not taking part in coordination. (The $\delta(\text{N}_{(3)}-\text{H})$ band of 5-fluorouracil at 1430 cm⁻¹ disappears in all the mixed ligand complexes suggesting the deprotonation of N₍₃₎ H proton and bonding of N₍₃₎ nitrogen with the metal. The $\nu(\text{M-O})$ stretching vibrations appear in the region 245-225 cm⁻¹ for six coordination¹⁵. The presence

TABLE-1
ELEMENTAL ANALYSIS, MOLAR CONDUCTIVITY AND MELTING POINT OF MIXED LIGAND COMPLEXES (1-12)

Comp.	Colour	Empirical formula	Molecular weight	Yield (%)	m.p. (°C)	Elemental analysis: Found (Calc.) (%)				$\Lambda_m(\Omega^{-1} \text{ cm}^{-1} \text{ mol}^{-1})$
						C	H	N	M	
1	Deep blue	C ₈ H ₁₅ N ₄ O ₇ FCu	330.0	81	231	29.10 (29.09)	4.51 (4.55)	16.91(16.97)	19.23(19.26)	18.10
2	Blue	C ₉ H ₁₇ N ₄ O ₇ FCu	344.0	77	247	31.39 (31.40)	4.89 (4.90)	16.18 (16.20)	18.43 (18.47)	16.16
3	Light blue	C ₁₂ H ₁₅ N ₄ O ₇ FCu	378.0	72	229	37.98 (38.10)	4.41(3.97)	14.77 (14.81)	16.79 (16.81)	13.21
4	Deep green	C ₈ H ₁₅ N ₄ O ₇ FNi	325.1	71	267	29.51 (29.53)	4.58 (4.61)	17.19 (17.23)	17.99 (18.05)	13.96
5	Greenish blue	C ₉ H ₁₇ N ₄ O ₇ FNi	339.1	69	254	31.91 (31.85)	5.07 (5.01)	16.49 (16.51)	17.10 (17.06)	17.01
6	Greenish blue	C ₁₂ H ₁₅ N ₄ O ₇ FNi	373.1	64	233	38.71 (38.60)	4.05 (4.02)	15.03 (15.01)	15.77 (15.73)	11.88
7	Deep violet	C ₈ H ₁₅ N ₄ O ₇ FCo	325.3	61	244	29.49 (29.51)	4.58 (4.61)	17.27 (17.21)	18.09 (18.12)	17.04
8	Pale violet	C ₉ H ₁₇ N ₄ O ₇ FCo	339.4	67	227	31.88 (31.82)	5.54 (5.00)	16.55 (16.50)	17.27 (17.29)	16.71
9	Light violet	C ₁₂ H ₁₅ N ₄ O ₇ FCo	373.3	61	242	38.61 (38.57)	4.01 (4.02)	14.91 (15.00)	15.74 (15.79)	14.31
10	White	C ₈ H ₁₅ N ₄ O ₇ FZn	331.8	62	228	38.94 (38.91)	4.49 (4.52)	16.86 (16.88)	19.68 (19.70)	14.31
11	White	C ₉ H ₁₇ N ₄ O ₇ FZn	345.9	61	254	56.10 (31.22)	4.89 (4.92)	16.21 (16.19)	18.88 (18.90)	15.33
12	White	C ₁₂ H ₁₅ N ₄ O ₇ FZn	379.8	61	244	37.95 (37.91)	3.97 (3.95)	14.71 (14.74)	17.24 (17.21)	14.33

TABLE-2
IR SPECTRAL DATA OF 5-FLUOROURACIL (5-FU) AND MIXED LIGAND COMPLEXES (1-12) (cm⁻¹)

S. No	Comp.	$\nu(\text{NH}_2)$ amine	$\nu(\text{C}_{(2)}=\text{O})$	$\nu(\text{C}_{(4)}=\text{O})$	$\delta(\text{N}_{(1)}-\text{H})$	$\delta(\text{N}_{(3)}-\text{H})$	$\nu(\text{M}-\text{O})$ aqua	$\nu(\text{M}-\text{N})$	$\nu(\text{M}-\text{O})$	$\nu(\text{COO}^-)_{\text{asym}}$	$\nu(\text{COO}^-)_{\text{sym}}$
1	5-FU	—	1710	1695	1512	1430	—	—	—	—	—
2	(1)	3361,1584	—	1665	—	1435	430	276	240	1603	1457
3	(2)	3310,1571	—	1660	—	1432	437	280	240	1578	1438
4	(3)	3362,1629	—	1664	—	1435	432	278	242	1568	1430
5	(4)	3356,1574	—	1662	—	1433	449	279	248	1569	1431
6	(5)	3003,1584	—	1667	—	1428	431	272	240	1570	1437
7	(6)	3357,1632	—	1660	—	1432	444	280	248	1567	1428
8	(7)	3357,1578	—	1675	—	1432	435	282	240	1565	1433
9	(8)	3306,1577	—	1667	—	1429	440	281	242	1568	1429
10	(9)	3365,1622	—	1664	—	1435	430	276	240	1575	1442
11	(10)	3359,1574	—	1660	—	1430	432	273	248	1563	1430
12	(11)	3301,1581	—	1662	—	1432	444	272	242	1563	1437
13	(12)	3359,1626	—	1669	—	1430	435	277	242	1572	1434

of characteristic bands in the region 248-240 cm⁻¹ strongly supports for 6-coordination number of all the mixed ligand complexes. The $\nu(\text{M}-\text{N})$ bands are tentatively assigned in the region 282-272 cm⁻¹ indicating the complexation of the ligands with transition metal ions.

In addition, some new vibrations due to coordination of amines are observed in these complexes. The two weak bands at 3377 and 3326 cm⁻¹ are due to the asymmetric and symmetric NH stretching frequencies of aromatic amines which confirmed from the $\delta(\text{NH})$ inplane bending vibration at 1620-1600 cm⁻¹. This indicates the formation of mixed ligand complexes with the amino group *o*-phenylenediamine. Further, the two weak bands at 3357 and 3279 cm⁻¹ and are due to the asymmetric and symmetric NH stretching frequencies of aliphatic amines which confirmed from the NH bending (scissoring) vibration at 1599-1571 cm⁻¹. This indicates the formation of mixed ligand complexes with the amino group of ethylenediamine and 1,3-diaminopropane. Also CH₂ rocking vibration mode of ethylenediamine was also appeared at about 850-950 cm⁻¹ for 5-fluorouracil-ethylenediamine mixed ligand complexes (1, 4, 7 & 10). Subsequently, these mixed ligand complexes displayed both asymmetric and symmetric vibrations of COO⁻ at 1605-1565 and 1459-1429 cm⁻¹, respectively. The difference between asymmetric and symmetric vibrations (magnitude of $\Delta\nu$ of COO⁻) falls in the range 146-136 cm⁻¹ which indicates that the unidentate mode of coordination for COO⁻. The coordination of amino group is further

confirmed by negative shifting of C-N stretching band in these complexes. Thus, IR data confirm that 5-fluorouracil indicates bidentate coordination through C₍₄₎ = O and N₍₃₎ also identify that here the amines are also of bidentate mode of coordination through both the amino nitrogens and form N₃O type environment with the metal ion and hence confirm the above proposed structure.

Magnetic moment and electronic spectra: Electronic spectra of the mixed ligand complexes (1-12) were recorded in DMSO (1 × 10⁻³ M) solution at room temperature. The corrected magnetic moment and electronic spectra are summarized in Table-3 and indicate distorted octahedral geometry. All the Cu(II) mixed ligand complexes (1-3) exhibit only one strong broad bands, situated in the region 15500-14000 cm⁻¹ centered at 15,360, 15,130 and 15,290 cm⁻¹, respectively which may be assigned to the transition ²E_g → ²T_{2g} and indicate the hexacoordination of the metal ions¹⁹. For all the Ni(II) mixed ligand complexes (4-6) show three bands at 10010, 14 660 and 29240 cm⁻¹ for complex (4), 10100, 14,680 and 24,810 cm⁻¹ for complex (5) and 9990, 14510 and 25000 cm⁻¹ for complex (6) and the transition were assignable to ³A_{2g}(F) → ³T_{2g}(F), ³A_{2g}(F) → ³T_{1g}(F), ³A_{2g}(F) → ³T_{1g}(P) and L → M charge transfer, respectively with an distorted octahedral geometry¹⁶. Also, the observed magnetic moment value (3.15 BM) support octahedral environment for the complexes (4-6) with D_{4h} symmetry¹⁷. Mixed ligand complexes (7-9) show three spin allowed transitions in 11142, 16156 and 21767 cm⁻¹ for (7),

TABLE-3
ABSORPTION SPECTRAL DATA (DMSO) AND MAGNETIC SUSCEPTIBILITY
OF 5-FLUOROURACIL (5-FU) MIXED LIGAND COMPLEXES (1-12) AT 37 °C

Comp.	λ_{\max} (cm ⁻¹)	Band assignments	Geometry	μ_{eff} (BM)	Ligand field parameter					
					Dq(cm ⁻¹)	B (cm ⁻¹)	β	β (%)	LFSE (kJ mol ⁻¹)	v_2/v_1
1	15,360	² E _g → ² T _{2g}	Distorted octahedral	1.88	—	—	—	—	—	—
2	15,130	² E _g → ² T _{2g}	Distorted octahedral	1.87	—	—	—	—	—	—
3	15,290	² E _g → ² T _{2g}	Distorted octahedral	1.87	—	—	—	—	—	—
4	10,010	³ A _{2g} (F) → ³ T _{2g} (F)	Distorted octahedral	3.26	1001	629.33 (1041 for free ion)	0.61	39.88	143.51	1.46
	14,660	³ A _{2g} (F) → ³ T _{1g} (F)								
	24,810	³ A _{2g} (F) → ³ T _{1g} (P)								
5	10,100	³ A _{2g} (F) → ³ T _{2g} (F)	Distorted octahedral	3.22	1010	612.70	0.59	40.87	144.80	1.45
	14,680	³ A _{2g} (F) → ³ T _{1g} (F)								
	24,810	³ A _{2g} (F) → ³ T _{1g} (P)								
6	9,990	³ A _{2g} (F) → ³ T _{2g} (F)	Distorted octahedral	3.24	999	636	0.61	38.97	143.2	1.45
	14,510	³ A _{2g} (F) → ³ T _{1g} (F)								
	25,000	³ A _{2g} (F) → ³ T _{1g} (P)								
7	11,142	⁴ T _{1g} (F) → ⁴ T _{2g} (F)	Distorted octahedral	4.12	1114	617.6 (971 for free ion)	0.63	36.98	159.7	1.45
	16,156	⁴ T _{1g} (F) → ⁴ A _{2g} (F)								
	21,767	⁴ T _{1g} (F) → ⁴ T _{2g} (P)								
	26,534	LMCT (n → π^*)								
8	11,213	⁴ T _{1g} (F) → ⁴ T _{2g} (F)	Distorted octahedral	4.86	1121	628	0.65	34.99	160.72	1.45
	16,327	⁴ T _{1g} (F) → ⁴ A _{2g} (F)								
	19,646	⁴ T _{1g} (F) → ⁴ T _{2g} (P)								
	26,734	LMCT (n → π^*)								
9	11,119	⁴ T _{1g} (F) → ⁴ T _{2g} (F)	Distorted octahedral	4.62	1158	600	0.62	37.89	166	1.45
	16,123	⁴ T _{1g} (F) → ⁴ A _{2g} (F)								
	21,510	⁴ T _{1g} (F) → ⁴ T _{2g} (P)								
	26,240	LMCT (n → π^*)								
10	26622 (b)	LMCT (M ← N)	Distorted octahedral	Dia.	—	—	—	—	—	—
11	26593 (b)	LMCT (M ← N)	Distorted octahedral	Dia.	—	—	—	—	—	—
12	26590 (b)	LMCT (M ← N)	Distorted octahedral	Dia.	—	—	—	—	—	—

11213, 16327 and 19646 cm⁻¹ for (8) and 11119, 16123 and 21510 cm⁻¹ for (9) assigned to ⁴T_{1g}(F) → ⁴T_{2g}(F), ⁴T_{1g}(F) → ⁴A_{2g}(F) and ⁴T_{1g}(F) → ⁴T_{2g}(P), respectively and one weak broad band with less intensity in the UV region centered at 26534 (7), 26734 (8) and 26,240 (9) cm⁻¹ due to L → M charge transfer transition, suggesting a high spin octahedral environment. Also, the ratio of v_2/v_1 value lies in 1.45 as expected for octahedral environment and the magnetic measurement value (4.879 BM) for the solid Co(II) complex are also indicative of four unpaired electrons per Co(II) ion suggesting distorted octahedral environment. Complexes (10-12) show broad bands in the UV region at 26500-28400 cm⁻¹ due to L → M charge transfer in a distorted octahedral environment^{18,19} due to sp^3d^2 hybridization, centered at 26622 (10), 26593 (11) and 26,590 (12) cm⁻¹. Also, the observed ligand field parameters such as, Racah parameter (B), β and β^0 values support the covalent character of the distorted octahedral geometry around Ni(II) and Co(II) complexes. Mixing of ground state (³A_{2g}) with the excited state (³T_{2g}) in octahedral Ni(II) complexes give the

Lunde's factor, i.e., $g = 2 - \frac{8\lambda'}{10Dq}$ (where λ' = spin-orbit

coupling constant, -368 cm⁻¹). In general, the hexaquo Ni(II) complex show the g value is 2.25, for the mixed ligand complexes (4, 5 and 6) the g values are 2.294, 2.292 and 2.295, respectively.

TABLE-4
DATA OF SCAVENGING EFFECTS ON O₂^{•-} RADICAL OF
5-FLUOROURACIL (5-FU) MIXED LIGAND COMPLEXES (1-12)

S. No	Compound	Average suppression ratio for O ₂ ^{•-} (%)
1	5-FU	12.01
2	(1)	77.21
3	(2)	81.09
4	(3)	87.63
5	(4)	63.47
6	(5)	61.01
7	(6)	66.90
8	(7)	63.27
9	(8)	61.08
10	(9)	64.23
11	(10)	53.97
12	(11)	52.08
13	(12)	57.49

Antioxidative activity tests: The antioxidative activities of the mixed ligand complexes (1-12) have been studied. The concentration of the tested mixed ligand complexes is (tested compound) = 30 $\mu\text{mol dm}^{-3}$. The suppression ratios of 5-fluorouracil and the mixed ligand complexes (1-12) are summarized in Table-4. It can be seen that the ligands and the mixed ligand complexes can scavenge O₂^{•-} radical. The suppression ratios of the mixed ligand complexes for the O₂^{•-} radical are mostly higher than those of the ligands. The scavenging effect^{2,20} of the mixed ligand complex (3) on O₂^{•-} radical is stronger than those of the other complexes.

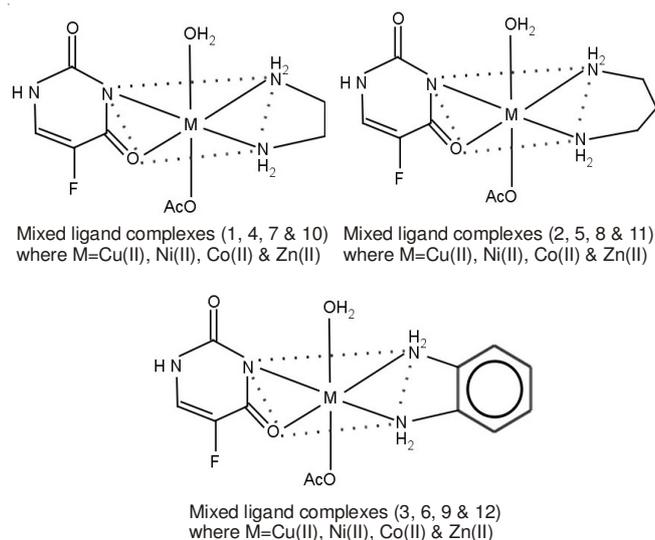


Fig. 3. Suggested structures of the mixed ligand complexes (1-12)

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