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Review

Synthesis and Biological Activities of Some Metal Complexes of 2-Thiouracil and Its Derivatives: A Review

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Abstract: The thionamide antithyroid drugs were discovered largely following serendipitous observations by numerous researchers in the 1940s who found that sulfhydryl-containing compounds were goitrogenic in animals. Prof. Edwin B. Astwood was the first to use these compounds to treat hyperthyroidism. In this review, we summarize the history of the development of these drugs and the coordination possibility of 2-thiouracil and its derivatives, as well as the biological activities of some of its complexes. Some of them are used as agents for the treatment of tuberculosis, and arthritis, others have bactericidal and fungicidal activity, the third cytotoxic properties, and could be used to treat various types of cancer.

Keywords: antibacterial activities; cytotoxic properties; uracil; 6-methyl-2-thiouracil; 6-propyl-2-thiouracil; 2-thiouracil

Introduction

Uracil is a pyrimidine derivative found in nucleic acids [1]. It is a pyrimidine base that contains four different binding sites, such as N1, N3, O2, O4-atoms. It belongs to the group of the most important pyrimidines that play a crucial role in the structure and function of enzymes and drugs.

2-thiouracil has been found to inhibit thyroid hormone biosynthesis. In 1942, prof. Edwin W. Astwood started using 2-thiouracil to treat patients with Graves' disease [2]. The thyroid gland (Lat. Glandula thyr(e)oidea) is an important endocrine gland. It reproduces the hormones T3, T4 and calcitonin, which main role is to stimulate metabolism, growth and development of cells and several organs.

It should be noted that possible ways to treat patients with Graves' disease include conservative treatment, which consists in taking antithyroid drugs - thiamazole (methizol, tyrozole) and propylthiouracil (propicillin), surgical treatment or radioactive iodine therapy. Methylthiouracil has been identified as an antithyroid drug. It enhances cell growth and proliferation, accelerates wound, ulcer and burn healing, and increases resistance to infection. A characteristic feature of the drug is that it stimulates the effect of hematopoiesis (formation and strengthening of leukocytes and erythrocytes in bone marrow). It shows a similar mechanism of action and side effect as propylthiouracil. The drug acts to reduce the production of stored hormones, such as thyroglobulin in the thyroid gland.

Recently, Xiao-Ming Mao et al. have assessed the reduction effects associated with intrathyroidal injection of dexamethasone on the relapse rate of hyperthyroidism in individuals newly diagnosed with Graves' disease [3]. At present, propylthiouracil is regarded as the preferred treatment for hyperthyroidism during pregnancy [4]. The literature contains various reviews on the subject [5–8].

Oladipo and Isola have provided a comprehensive review of the coordination possibilities of uracil and the practical applications of some of its complexes [9]. Recently, Masoud et al. have presented a review of complexing properties and applications of some biological activities of the nucleic acid [10].

Figure 1 presents the structures of 2-thiouracil and some of their derivatives:

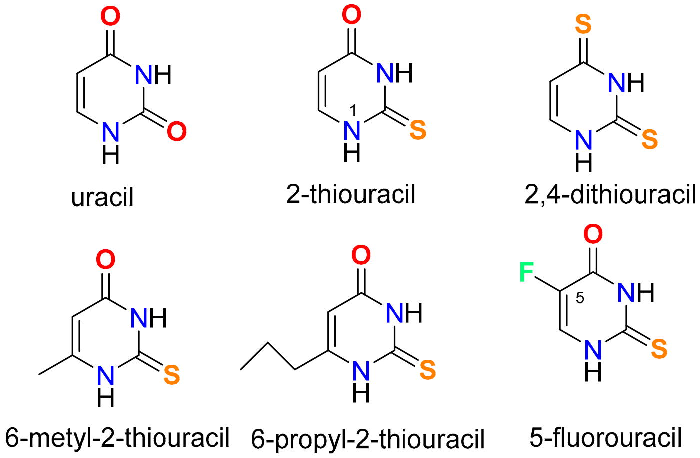

Figure 1. Structures of uracil, 2-thiouracil and some of their derivatives.

It is worth noting that uracil, 2-thiouracil, 2,4-dithiouracil, and its derivatives are of chemical interest as they have four donor atoms for coordination with a metal ion /two O- and two N- or 1-O, 1-S- and 2-N atoms or 2 S- and 2-N atoms/. It is evident they demonstrate various possible ways to coordinate 2-thiouracil with metal ions, as follows:

- Monodentate coordination with one of the four donor atoms, without any prior deprotonation (see Figure 2).

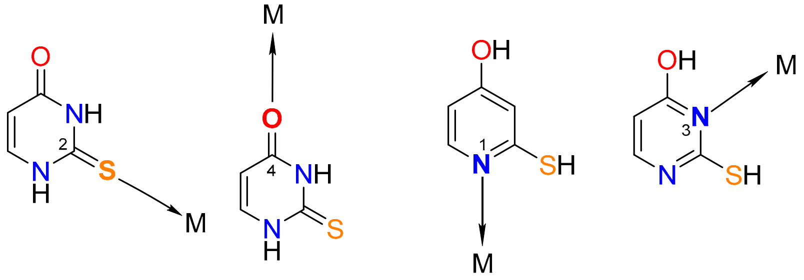

Figure 2. Monodentate coordination of 2-thiouracil with one of the four donor atoms, without any prior deprotonation (the tautomeric form participates in N1- and N3-coordination).

- Monodentate coordination with one deprotonated nitrogen atom in the first N1 or third N3 position (see Figure 3).

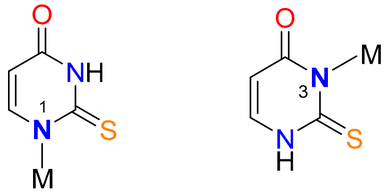

Figure 3. Monodentate coordination with deprotonated ligand who participate as a monoanionic (through a deprotonated nitrogen atom in the first position N1 or a nitrogen atom in the third position N3).

- Different variants of chelating or bridge coordination are presented in Figures 4 and 5.

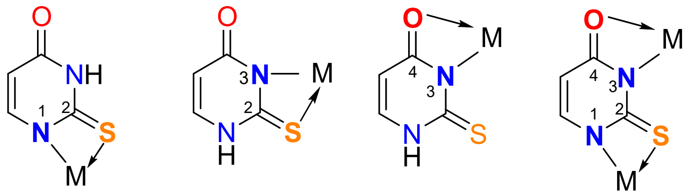

Figure 4. Bidentate coordination with formed chelate.

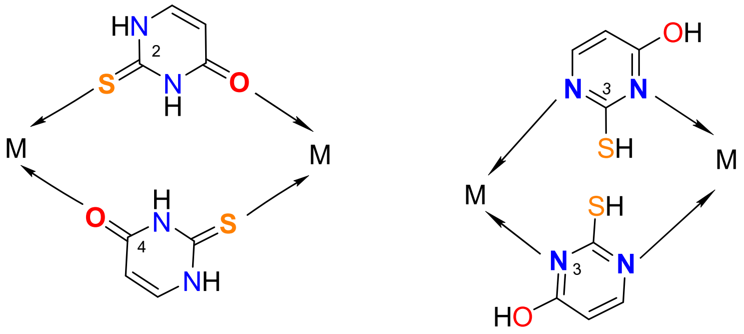

Figure 5. Possible bridge ways of 2-thiouracil coordination with metal ions.

It presents the biological activity of 2-thiouracil and metal complexes: some of them are used as agents for fighting tuberculosis and arthritis, others have bactericidal and fungicidal action, and the third is cytotoxic activity.

Synthesis of metal complexes with uracil and its derivatives

Narang et al. [11] have obtained complexes of Fe(III) and Cr(III) with uracil and with the general formula $[M(Uracil)(H_2O)_2\text{-}(OH)Cl]$, where M=Cr(III) or Fe(III). The complexes have been characterized via elemental analysis, UV-Vis, EPR and IR spectroscopic methods. Based on the obtained results, the authors suggest a polymer structure with an octahedral geometry of the metal center, with the ligand coordinated through the O(4)- and N(1)-atoms, while histidine coordinates through the O atom of $-CO_2^-$ and the N atom of the $-NH_2$ groups. Cartwright et al. [12] have obtained a bis-(1,3-dimethyluracil)-dichloridocopper(II) complex, which have been investigated via elemental analysis, IR spectroscopy and X-ray diffraction. The data from the analysis show that the uracil is coordinated to the metal center monodentately with the participation of an O-atom in the fourth position of the pyrimidine ring and two chloride ions are coordinated to Cu(II) so that the complex is neutral with a planar-square geometry. The structure of the complex is given in Figure 6.

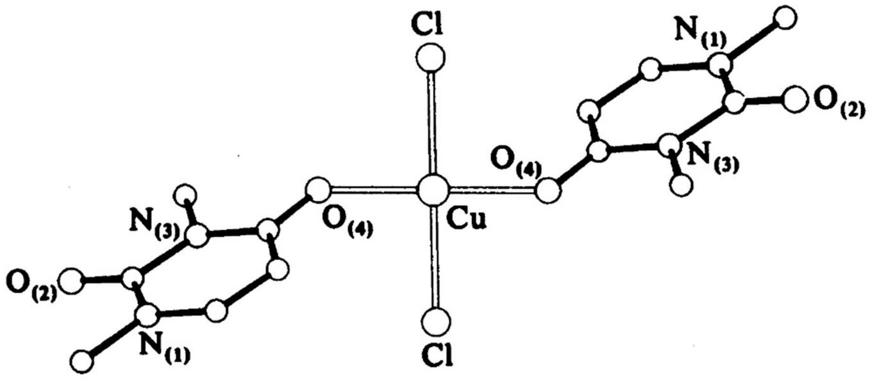

Figure 6. The structure of bis-(1,3-dimethyluracil)-dichloridocopper(II) complex [12].

A complex of Fe(III) with uracil and complexes of thiouracil and 5-(phenylazo)-thiouracil with Co(II), Ni(II) and Cu(II) have been obtained [13]. The new metal complexes have been characterized via elemental analysis, DTA, UV-Vis, IR and Mössbauer spectroscopy. In all complexes uracil and other free ligands act in a bidentate fashion with coordination occurring through the O(4)- and N(3)-atoms. The coordination bond lengths of the octahedral Co(II) and Ni(II) complexes are smaller compared to the square-planar Cu(II) complex [13].

Ghosh et al. [14] have synthesized new complexes of uracil with general formula: $[ML_2(H_2O)_2]$, where M = Mn, Fe, Co, Ni, or Cu; L = uracil. Electronic spectra indicate octahedral coordination for all complexes and data from comparative IR spectra show chelate structure via the O(2)- and N(3)-atoms of uracil.

The synthesis, spectroscopic analysis, and investigation of the biological activity of Ni(II), Cu(II), and Co(II) complexes formed by Schiff base ligands derived from 5-aminouracil, 2-hydroxy-1-naphthaldehyde, 2,4-dihydroxybenzaldehyde, and salic-ylaldehyde have been reported: [15]. In each instance, the complexes seem to exist as monomers. The ligands exhibit bidentate coordination with Ni(II) and Co(II), while with Cu(II), they coordinate in a tridentate manner, involving the carbonyl oxygen atom in the 4th position of the uracil ring.

Complexes of M^{2+}, M=Co, Ni and Zn with 6-chloromethyluracil, 5-hydroxymethyluracil, uracil, 6-methyluracil and dimethyl-6-uracilmethylphosphonate have been synthesized [16]. Based on the data obtained, it is assumed that the ligands are coordinated to the metal ion through the N(3)-atom fof Co(II) and Ni(II), as well as a hydroxo complex MLH_{-1}—with a deprotonated water of the inner coordination sphere. [16].

Mixed ligand complexes play an important role in biological systems. Some mixed ligand complexes of Co(II), Ni(II), Cu(II), Zn(II), and Cd(II) have been obtained by Tyagi et al. by using the corresponding nitrates as starting metal salts and 5-fluorouracil and histamine [17]. New complexes have been characterized by elemental analysis, UV-Vis, and IR-spectroscopy, as well as by the X-ray diffraction method. Data from X-ray structural analysis indicates that 5-fluorouracil is coordinated through the N(3)-atom.

Mixed ligand complexes of Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) with adenine and uracil have been obtained [18]. The complexes have been characterized via elemental analysis, UV-Vis and IR-spectroscopy, as well as using powder X-ray diffraction studies. The authors suggest that the complexes are polymeric in nature involving adenine, as well as –OH group as bridging ligands. During polymerization one metal atom is bound via – N(3) atom of one adenine ligand and – N(7) atom of another adenine ligand. Uracil acted in coordination via O-atom in second position of the pyrimidine ring [18]. Based on the results obtained, Abdullah suggests a polymer structure with an octahedral geometry of the metal center for all synthesized complexes.

Mixed ligand complexes of Th(II), Ce(II), and Gd(II) with uracil and omeprazone have been synthesized as per the general formula: $[M(Ome)(ura).4H_2O)]SO_4.xH_2O$ [19]. The compounds have been researched via elemental analysis, UV-Vis, IR-, Mass - and ^1H NMR spectroscopy. Based on the data obtained, it is suggested that uracil acts as a bidentate ligand, binding through the N(3)- and O(2)-atoms [19].

Mixed ligand complexes of Ni(II), Cu(II) and Zn(II) with 5-fluorouracil and amino acids have been obtained by Shobana et al. [20]. Magnetic moment values together with the electronic spectral data indicate that 5-fluorouracil coordinates with the metal ion in a bidentate fashion through the C(4)=O and N(3) atoms. They also identify that the amino acids behave as bidentate by nitrogen and carboxylate oxygen with formed 4, 5, and 6-membered chelate rings. All the Cu(II) mixed ligand complexes show distorted tetrahedral geometry, which is further supported by the ESR studies.

Cu(II), Ni(II), Co(II), and Zn(II) mixed ligand complexes, comprising alanine in conjunction with either uracil or 2-thiouracil, have been synthesized and characterized.
[21]. The findings indicate alanine consistently exhibits bidentate coordination, utilizing both $-NH_2$ and COO^- groups. Uracil acts as a bidentate ligand in the Cu(II) complex, coordinating through one carbonyl O- and N-atoms, while in other instances, it is monodentate, coordinating solely through N-atom. In the presence of thiouracil, Cu(II) and Ni(II) complexes involve coordination from carbonyl

O- and one N-atoms, whereas the Co(II) complex coordination occurs from S- and N-atoms. The Zn(II) complex displays tridentate behavior, coordinating through O-, S-, and N-atoms. The mixed complexes of Cu(II), Co(II), and Zn(II) with uracil, as well as Ni(II) and Zn(II) complexes with thiouracil, exhibit octahedral geometry. The mixed Ni(II) complex with uracil displays distorted tetrahedral geometry, while the mixed Co(II) thiouracil complex adopts a square planar structure. Notably, the mixed Cu(II) thiouracil complex features a binuclear structure with a square planar arrangement around each copper atom. [21].

Srivastava et al. have reported the synthesis and characterization of mixed ligand complexes of glycine and uracil or 2-thiouracil, thymine or adenine with histidine and uracil, thymine or 2-thiouracil with glycine, alanine, valine, and leucine with Cu(II), Ni(II), Co(II) and Zn(II) *[22–25*].

Synthesis of metal complexes with 2-thiouracil and its derivatives

Recently, we have reported on Cu((II), Pd(II) and Au(III) complexes with 2-thiouracil [26]. The structures of the new compounds have been reviewed with UV-Vis, IR, ^{1}H, ^{13}C NMR and Raman spectral data. The interpretation of complexes spectra is assisted by the data for 2-thiouracil obtained from ^{1}H-^{1}H COSY, DEPT-135, HMBC and HMQC spectra. The spectral data points out the bonding of the ligand through sulfur, oxygen and nitrogen atoms in Cu(II) and Pd(II) complexes and through S and N atoms in the complex of gold. In addition, the antimicrobial activity against both Gram-positive, Gram-negative bacteria and yeasts has also been studied.

New complexes of Cu(II) and Pd(II) with 6-methyl-2-thiouracil and 6-propyl-2-thiouracil have been obtained [27]. All metal complexes have been obtained after mixing water solutions of the corresponding metal salts and the ligand dissolved in DMSO and water solutions of NaOH, in metal-to-ligand ratio 1:4:2. The structures of the new compounds are reviewed based on melting point analysis, MP-AES for Cu and Pd, UV-Vis, IR, ATR, ^{1}H NMR, ^{13}C NMR and Raman spectroscopy. The interpretation of complex spectra is assisted by the data for 6-methyl-2-thiouracil and 6-propyl-2-thiouracil obtained from ^{1}H-^{1}H COSY, DEPT-135, HMBC and HMQC spectra [27]. We have suggested, in Cu(II)L1 complex, probably the ligand could coordinate in a monodentate way through S2 and/or O4 atoms. The coordination binding site we would suggest for 6-propyl-2-thiouracil in Cu(II)L2 is a monodentate coordination mode binding through S-atom. For Pd(II)L1 and Pd(II)L2 complexes we suggested that one of the ligands participates in coordination via N1, S2-atoms and other with N3, O4-atoms. In all the complexes, the solvent DMSO acts as a ligand (one molecule coordinate in Cu(II)L1 and Pd(II)L1 and two molecules - in Cu(II)L2 and Pd(II)L2). Formation of polymeric complexes in solid state has also been suggested, whereas dissolution in DMSO lowers.

Complexes of Cu(I), Ni(II), Co(II), Zn(II), Ag(I), Cd(II) and Hg(II) with 6-amino-2-thiouracil have been synthesized, isolated and studied by thermogravimetric analysis, differential scanning calorimetry (DSC) and IR spectroscopy [28]. Based on the results obtained, the authors suggest that the ligand acts as a monoanion and coordinates via the N-atom in the complexes of Cu(I), Ni(II), Co(II), Zn(II), Ag(I) and Cd(II), and via the S-atom in Hg(II) and Ni(II). The Zn(II) and Cd(II) complexes are assumed to be polymeric, and the ligand is bridged and acts as a dianion. It is crucial to mention the water in the first six complexes is both coordination and crystallization, whereas in the last it is only crystallization.

Complexes of 6-amino-2-thiouracil with Ni(II), Co(II), Zn(II), Cd(II), Cu(I), Ag(I) and Hg(II) have been obtained by Romero et al. [29]. The complexes have been studied via elemental analysis, IR-, UV-Vis- and NMR-spectroscopy, as well as magnetochemical measurements. The structure of one of these has been established by X-ray structure analysis [Zn(6-amino-2-thiouracil)2H_2O].2H_2O, in which the ligand is coordinated bidentate chelate throught S-atom in second and N-atom in the first position.

It is important that complexes of 2-thiouracil with Cu(II), Ni(II), Co(II) and Fe(III) have been synthesized [30]. The compounds have been characterized via IR, UV-Vis spectroscopic methods, as well as magnetochemical measurements and DTA (Differential thermal analysis). Based on the results obtained, the authors suggest that 2-thiouracil has coordinated to the metal center via a deprotonated N-atom and via an S-atom from the thiocarbonyl group in the Cu(II) and Ni(II) complexes, in addition there is the presence of 2 water molecules. The authors also suggest, that in the complex of Co(II), one ligand is not deprotonated and binds via an S-atom from the thiocarbonyl group and an O-atom from the carbonyl group. For the Fe(III) complex, coordination is most likely via N- and O-atoms [30]. All of these complexes exhibit high insolubility in typical organic solvents, indicating their likely polymeric nature. As a result, the structure of the nickel(II) complex seems to be octahedral, while the structures of the other complexes remains uncertain. However, tentative structures are proposed as follows:

Fe(III) complex - octahedral;

Co(II) complex - A tetrahedral structure has been observed, where each cobalt atom within the dimer forms bonds with three nitrogen atoms and one water molecule. In the dimer, four ligands exhibit monodentate bonding, connecting through a deprotonated nitrogen. The fifth ligand has both nitrogen atoms protonated, with one nitrogen bonding to one cobalt atom and the other nitrogen atom bonding to the other cobalt atom [30];

Cu(II) complex - octahedral possibly having Cu-Cu bond [30].

Garrett et al. have reported on complexes of 2-thiouracil, 6-n-propyl-2-thiouracil, 6-methyl-2-thiouracil, 5-methyl-2-thiouracil, 5,6-dimethyl-2-thiouracil, 2-ethylmercapto-4-hydroxypyrimidine and 6-methyl-N,N'-diethyl-2-thiouracil with Cu(II), Cd(II), Pb(II), Fe(II) and Fe(III) [31].

Dozens of complexes have been prepared and isolated using chlorides, bromides, iodides, sulfates and nitrates of Co(II), Zn(II), Ni(II) with 5-morpholinomethyl-2-thiouracil [32]. The complexes have been formed by mixing a solution of the ligand in 2-propanol and the metal salt in ethanol, the molar ratio was 2:1 and the temperature of the reaction mixture was 70℃. The suggested structure of the new complexes is given in Figure 7.

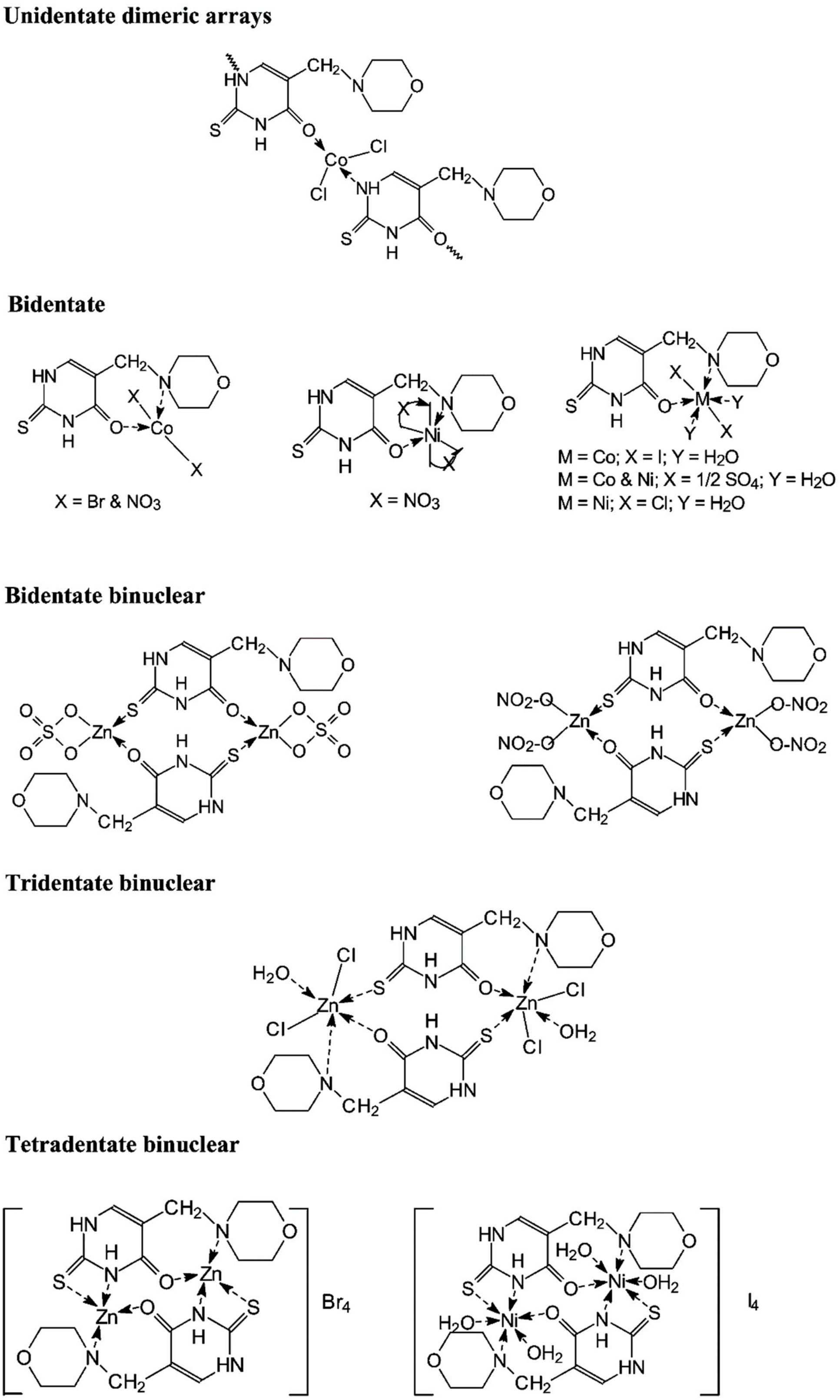

Figure 7. The structure of the metal complexes reported by Kamalakannan et al. [32].

Complexes of 2-thiouracil and 6-methyl-2-thiouracil and their derivatives with $W(CO)_5$ have been obtained [33]. The structure of one of the complexes has been established via X-ray structural analysis. The authors prove the ligand coordinated to the metal ion through the S-atom of the 2-thiouracil. The pentacarbonyl complexes of 2-thiouracilate and 6-methyl-2-thiouracilate have been demonstrated to undergo cis CO dissociation with stereoselectivity, leading to the concurrent formation of tetracarbonyl derivatives chelated by the exocyclic sulfur and the endocyclic N(1) [33].

A mononuclear complex with the general formula $[CuL(NH_3)_4]Cl_2.0.5H_2O$ and three heterometallic complexes $[Cu_2Ni(L)_2(NH_3)_2Cl_2.6H_2O].2H_2O$, $[Cu_3Co(L)_4.8H_2O]Cl.4,5H_2O$ and $[Cu_4Co_2Ni(L)_3(OH)_4(NH_3)Cl_4.3H_2O].4H_2O$, where the ligand is 2-thiouracil has been obtained [34]. The complexes have been characterized via elemental analysis, magnetochemical studies, and IR, UV-Vis, EPR, TG, DTG, and DTA. The results show that the ligand acts bidentate or tetradentate, with the geometry of the metal center on an octahedron, except for $[Cu_4Co_2Ni(L)_3(OH)_4(NH_3)Cl_4.3H_2O].4H_2O$, in which a planar-square structure of Co(II), Ni(II) and Cu(II) is suggested.

Papazoglou et al. have prepared a dinuclear complex of Cu(I) (CuX, where (X = Cl, Br, I)) involving 5-carbethoxy-2-thiouracil (eitotH$_2$) as a ligand with the general formula $[CuX(eitotH_2)_2]_2$ [35]. The molecular crystal structure of the complex is presented in Figure 8. Mixed-ligand mononuclear complexes of Cu(I), with the general formula [CuX(PPh3)2(eitotH2)], the crystal structure of which is presented in Figure 9.

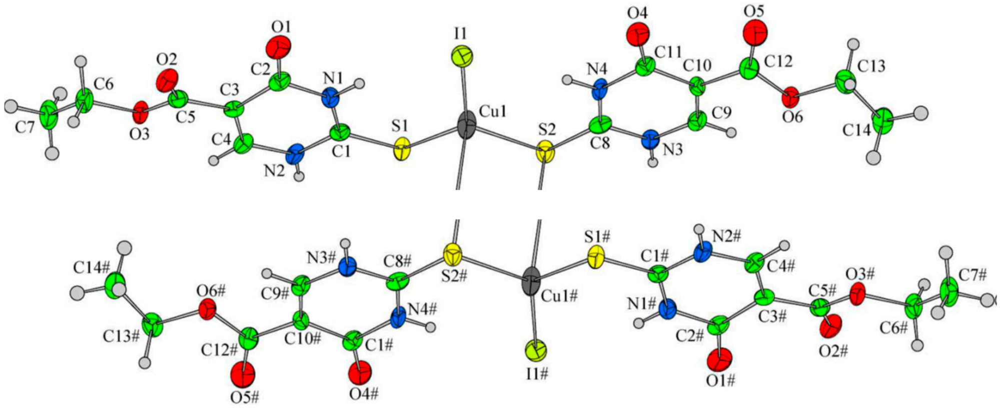

Figure 8. Molecular crystal structure of Cu(I) dinuclear complex reported by Papazoglou et al. [35].

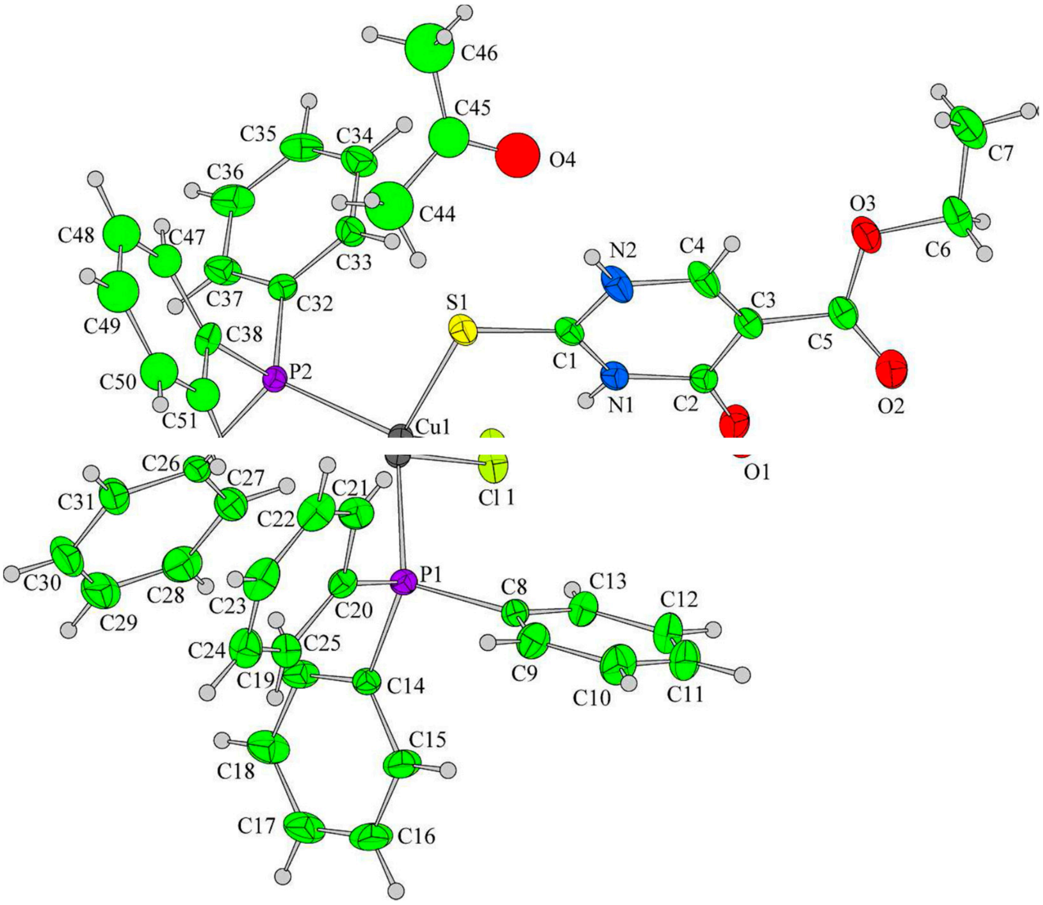

Figure 9. Molecular crystal structure of mononuclear Cu(I) complex with general formula [CuX(PPh$_3$)$_2$(eitotH$_2$)] reported by Papazoglou et al. [35].

Recently, new dinuclear copper(I) complexes with 5-carbethoxy-2-thiouracil have been synthesized [36].

It is known that heavy metal compounds such as platinum, gold, rhodium, palladium, ruthenium, and others can be used as biologically active agents in chemotherapy and for the treatment of various types of human tumors. We should take into consideration the coordination compounds of Pd with amino acids, catecholamines and some heterocyclic nitrogen-containing compounds have found application as immunomodulators, facilitating the recovery of cells after radiation damage [37]. The treatment with gold preparations, called chrysotherapy, was known as early as 2500 BC in China. In the form of official pharmaceuticals, Au compounds were used in the 1920s [37].

New complexes of rhenium(I) involving certain 5-nitrosopyrimidines, characterized with the general formula [ReCl(CO)$_3$L], have been synthesized and identified through elemental analysis, conductivity measurements, and spectroscopic methods including IR, ^{1}H, ^{13}C, and ^{15}N NMR. [38]. The complexes seem to exist as monomers, and the pyrimidine ligands function in a neutral form. The structure of [ReCl(CO)$_3$(DANU)].CH$_3$CN has been elucidated through X-ray diffraction. The coordination environment around Re(I) is best described as a distorted octahedron, with the ligand adopting a bidentate configuration through N5 and O4 atoms, forming a five-membered chelate ring.

Abou-Melha has synthesized new complexes of VO(II), Ni(II), Pd(II), Pt(IV) and UO$_2$(II) with N-(4-((Z)-(6-oxo-2-thioxo-1,2,3,4-tetrahydro-6l5-pyrimidin-5-yl)diazenyl)phenyl)- 4-((E)-(6-oxo-2-thioxo-1,2,5,6-tetrahydropyrimidin-5-yl)diazenyl)benzamide [39]. The structure of the complexes has been studied by IR, UV-Vis, ^{1}H NMR, EPR, ^{13}C NMR, TGA, TEM, XRD methods.

The interest to complexes of platinum and palladium is due to their high cytostatic activity. Recently, cis-dihalogeno complexes of platinum(II) and palladium(II) with 6-tert-butyl-2-thiouracil have been synthesized [40].

To date, numerous metal complexes of uracil and thiouracil derivatives have been synthesized and their composition and structure with various metals like copper, iron, cobalt, nickel, zinc, manganese, cadmium, vanadium *[13,21,41–43*] as well as palladium, platinum, and gold have been studied [44].

New thiolate gold(I) complexes with $P(NMe_2)_3$ (HMPT) as a phosphane group have been synthesized [Au(SR)(HMPT)] (R= Spy, Spyrim, SMe2pyrim, Sbenzothiazole, Sthiazoline, Sbenzimidazole and 2-thiouracil). Two of thiolate gold(I) complexes were good and effective candidates to be used in chemotherapy [45].

The chemistry of Au^{III} is much less developed than that of the isoelectronic and often isostructural PtII atom. The first crystallographically characterized AuIII complex with a pyrimidine derivative is the N(3)-bonded compound with 1-methylcytosine [46]. In the same manner, a gold complex was isolated [47] by reacting $HAuCl_4$ with 6-amino-1,3-dimethyl-5-(2-chlorophenylazo)uracil (DZCH) to give $[Au(DZC)Cl_2]$ complex. X-ray diffraction showed that the crystal of $[Au(DZC)Cl_2]$ contains individuals complex molecules in which the metal has a slightly distorted square-planar coordination. Two cis corners are occupied by Cl ligands. The uracil derivative formed a six-membered chelate ring via the deprotonated amino group and the phenylsubstituted nitrogen atom of the azo group [47].

Biological Activities

Antibacterial Activity

The antimicrobial activity of the numerous metal complexes of thiouracil derivatives was screened in vitro against a Gram-positive, Gram-negative bacteria, filamentous fungi, and yeast.

The in vitro testing of the biological activities of both Schiff bases and metal complexes was conducted against several bacteria and a fungus. [15]. Nickel(II) complexes, formed from the Schiff base ligand derived from salicylaldehyde, exhibited effective antimicrobial activity. Meanwhile, a cobalt(II) complex derived from the same ligand demonstrated notable anticandidal activity.

The in vitro antimicrobial evaluations showed more potent activities for both Ni(II) and Cu(II) mixed ligand complexes [20]. It was determined that the free ligands and their mixed ligand complexes display significant activity against pathogenic Gram-positive bacterial strains such as Bacillus subtilis, as well as against Escherichia coli and fungal strains like Aspergillus niger and Enterobacter species.

The highest activity against Gram-negative bacteria representatives was noted with the Cu(II) complex when tested against S. enterica. [26]. The free ligand 2-thiouracil did not hinder the growth and proliferation of P. vulgaris, but its Cu(II) and Au(III) complexes displayed mild to moderate activity. The introduction of metal ions to 2-thiouracil generally maintained or enhanced antimicrobial activity against Gram-positive bacteria, with two exceptions. Among these bacteria, S. aureus exhibited the greatest susceptibility, particularly in response to the influence of the Cu(II) complex. [26]. Both yeast strains were impacted by the unbound ligand and its complexes. C. albicans exhibited higher sensitivity to the complexes, with the addition of Cu(II), Pd(II), and Au(III) to 2-thiouracil showing a more pronounced antimicrobial effect. S. cerevisiae was generally more susceptible among the yeast strains, except in the case of the Pd(II) complex. The most potent antifungal activity was observed with the Cu(II) complex against S. cerevisiae. [26].

The highest antimicrobial activity was exhibited by the Cu(II) complex with 6-methyl-2-thiouracil [27]. It was active against all of the test microorganisms. The Pd(II)L1 complex did not hinder the growth of S. aureus, E. faecalis and S. cerevisiae. 6-methyl-2-thiouracil exhibited the narrowest antimicrobial spectrum, being inactive against S. aureus, E. coli, S. enterica, and S. cerevisiae. The introduction of Cu(II) enhanced the antimicrobial activity of 6-methyl-2-thiouracil against all test microorganisms, except B. cereus. However, isolated cell colonies were observed in the inhibition zones (IZ) against E. coli, P. vulgaris, and K. pneumoniae, indicating varying resistance within the microbial population. Conversely, the addition of Pd(II) resulted in a loss of activity against E. faecalis and reduced activity against L. monocytogenes and C. albicans. [27].

Among the compounds tested, the cobalt(II) bromo complex was found to be the most active against S. aureus and E. coli [32]. It should be noted that the most active are the complexes of Co(II). The order of activity of the complexes synthesized from the corresponding salts is: $Co^{II}Br_2 > Co^{II}Cl_2 > Zn^{II}SO_4 > Zn^{II}Cl_2 > Ni^{II}I_2 >$ standard > ligand. Tetrahedral complexes appeared to be more active compared to octahedral *[32]*.

Studies on the antimicrobial activity of the complexes obtained by Masoud et al. have been performed against various microorganisms [34]. Among the representatives of prokaryotes, Gram(+) and Gram(-) bacteria such as Staphylococcus aureus, Escherichia coli, etc. were used. Yeasts (Candida albicans and Aspergillus flavus) have been used as representatives of eukaryotes. The results of the antimicrobial studies carried out show that the complexes possessed remarkable activity against Escherichia coli, Staphylococcus aureus, and Candida albicans yeasts but were not active against Aspergillus flavus. The complex with the general formula $[Cu_4Co_2Ni(L)_3(OH)_4(NH_3)Cl_4.3H_2O].4H_2O$ appears to be having the most significant activity against the tested microorganisms.

The antibacterial activity under in vitro conditions of complexes of VO(II), Ni(II), Pd(II), Pt(IV) and UO2(II) with N-(4-((Z)-(6-oxo-2-thioxo-1,2, 3,4-tetrahydro-6l5-pyrimidin- 5-yl)diazenyl)phenyl)-4-((E)-(6-oxo-2-thioxo-1,2,5,6-tetrahydropyrimidin-5-yl)diazenyl)benzamide against Gram(-) E. Coli, Klebsiella sp. and Gram(+) Bacillus subtilis bacteria was reported [39]. The agar diffusion method was used to determine susceptibility to the above substances. It was found that Pt(IV) and Pd(II) complexes showed bacteriostatic effect against Proteus, while Klebsiella strain was resistant to all tested compounds.

Antifungi Activity

The complex of uracil and omeprazole with Th(II) showed a smaller inhibitory zone compared to that of the complexes of Gd(II) and Ce(II) against A. niger culture [19]. The results of the investigation show that the complexes are more active compared to the activity of the free ligands.

Mixed ligand complexes of 5-fluorouracil, alanine and phenylalanine with Ni(II), Cu(II) and Zn(II) were found to show antifungal activity against Aspergillusniger, Enterobacterssp. and Candida albicans [20].

The results of antifungi activity studies show that complexes of $Co^{II}NO_3$ with 5-morpholinomethyl-2-thiouracil are more active compared to the free ligand [32].

Antitumor and Cytotoxic activities

The in vivo and in vitro antitumor activity results show that Cr(III) and Fe(III) complexes have significant activity against P815 murine mastocytoma but Al(III) complexes show poor activity [11].

It has been observed that the ligand 5FU has significant antitumour activity against Dalton’s lymphoma tumour system [17]. The complexes with general formula Co(II)-SFU-Hm and Zn(II)-SFU-Hm exhibit significant antitumor activity [17].

Complexes of 5-morpholinomethyl-2-thiouracil with Co(II), Ni(II), and Zn(II) have been found to exhibit antitumor activity against Dalton's lymphoma and a murine leukemia cell line of P-338 [32]. The results of the studies show that the complexes are more active compared to the activity exhibited by the free ligand. Of all the complexes, the complex synthesized from $Zn^{II}SO_4$ starting salt showed the highest cytotoxic activity.

The new copper(I) complexes have been evaluated for in vitro antitumor properties against two tumor cell lines, A549 (human pulmonary carcinoma cell line) and HeLa (human epithelial carcinoma cell line) and one normal immortalized cell line MRC5 (human fetal lung fibroblast) [35]. The mixed-ligand complexes possessing triphenylphosphine appear to be highly cytotoxic in contrast to the phosphine-free ones which inhibited cell proliferation only in relatively high concentrations.

The copper(I) complexes have been studied against two tumor cell lines, A549 (human pulmonary carcinoma cell line) and HeLa (human epithelial carcinoma cell line) and one regular immortalized cell line, MRC5 (human fetal lung fibroblast). The cytotoxicity of all the above complexes is in contrast to that of each of the free ligands, higher in all the cell lines that had been tested [36].

The assessment of the antiproliferative effects on five human tumor cell lines (MCF-7 and EVSA-T for breast cancer, NB69 for neuroblastoma, H4 for glioma, and ECV for bladder carcinoma) indicate a modulating influence on cell growth at low concentrations, attributed to their estrogenic-like characteristics. [38].

The metal complexes of Cu(II), Ni(II), Co(II), Zn(II), Cd(II), Mn(II) with 5-carboxy-2-thiouracil have been screened against Sarcoma-180 tumor cells [48]. The results show that some complexes have antitumour activity both in vivo and in vitro against S-180 tumour cells.

Conclusions

We have summarized in this review the coordination sites, and applications of some synthesized metal complexes of 2-thiouracil and its derivatives. Structural reviews of metal complexes of 2-tiouracil and its derivatives as single ligand and mixed ligand have provided a significant information on the nature of metal interactions with 2-thiouracil and its derivatives. Spectrophotometric and X-ray analysis of the metal complexes of uracil, 2- thiouracil and its derivatives reveal the tendency of uracil and its derivatives to act as bidentate and monodentate agents in both binary and ternary complexes coordinating to a metal via any of O, N, S-atoms of the ring. Some of these complexes of 2-thiouracil and its derivatives have shown a variety of biological applications and should therefore be investigated. We have also researched the cytotoxic effect against a different tumor cell line of the various metal complexes of thiouracil derivatives.

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