Palladium Metal Complexes as Platforms for Anti Tumor Therapy

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ABSTRACT:

The often severe side effects displayed by currently used platinum and ruthenium complexes have motivated researchers to design and develop Palladium metal complexes as anti-tumor agents with reduced toxicity. Distinct from organic anti-tumour drugs, Palladium metal complexes possess several properties that render them as promising scaffolds for anti-cancer drug discovery. While a vast number of metal complexes have been synthesized and reported to be promising and potent *in vitro* anticancer active compounds, fewer have shown efficacy in *in vivo* models. The demonstration of *in vivo* potency is an essential step for lead candidates for clinical trials. In this review, we highlight examples of Palladium metal complexes that have shown *in vivo* anti-tumor activities that have been described in recent years.

Keywords: Palladium metal, Anti-tumor, Cancer

I-Introduction: The identification and characterization of the powerful anti-tumor agent cisplatin and its derivates established a milestone in the history of inorganic medicinal chemistry development [1,2]. However, drug-resistance from long-term treatment and non-specific toxicity are drawbacks of current platinum anti-cancer drugs [3,4]. This has stimulated the development of alternative transition metal-based anti-tumor therapeutic agents in recent years. Two ruthenium derivates, imidazolium trans-DMSO-imidazole-tetrachlororuthenate (NAMI-A) (complex 1) and imidazolium trans-[tetra-chlorobis(1H–indazole)-ruthenate(III)] (KP-1019) (complex 2) (Fig. 1) are anti-metastatic and anti-neoplastic compounds that have been tested in clinical trials [5,6]. A sodium analogue of KP1019, NKP-1339 (complex 3), is set to enter clinical trials [7], while the anti-proliferative agent titanocene dichloride (complex 4) (Fig. 1) was tested in Phase I/II trials [8]. Other transition metal-based complexes with anti-tumor activities include redox-mediating mono(thiosemicarbazone) copper complexes [9–11], the gold(I) complex auranofin, which acts via inhibiting DNA, RNA and protein synthesis ,and osmium(II) arene complexes that target mitochondria and induce cell apoptosis [13]. Transition metal complexes possess attractive properties that make them as potential alternatives to organic compounds for anti-tumor agents. Firstly, transition metals can adopt various geometries based on the number of coordination bonds they possess, such as octahedral, square-planar, square-pyramidal and trigonal-bipyramidal, while purely organic molecules are limited to tetrahedral, planar, or linear geometries. This also has the effect of increasing the structural diversity of metal compounds, for example, an octahedral metal complex bonds with 6 different ligands can form up to 30 different stereoisomeric configurations, whereas a tetrahedral carbon atom with 4 different substituents can produce only one pair of enantiomers.[15] This can enhance flexibility in drug design allowing metal compounds to effectively interact with the binding sites of target biomolecules.[40] Secondly, auxiliary ligands can induce significantly trans effects on metal-carbon bonds that can change the reactivity of other ligands in the complex. This can allow the thermodynamic and kinetic properties of the overall complex to be finely tuned, as demonstrated by research into "halfsandwich" ruthenium complexes by the groups of Sheldrick and Sadler .[32] Thirdly, metal ions can co-ordinate ligands that themselves are biologically active, such as the cytotoxic polypyridyl ligands (pp) that act as DNA intercalators.[34] Lastly, the preparation of metal complexes is highly modular and usually can be done in fewer steps, while organic compounds synthesis can be lengthy and involve multiple protecting group manipulations .[16] Today, a tremendous amount of biological evidence is shown that Palladium complexes are used as a platform for anti tumor activities.[35]

II-Synthesis: The literature survey uncovered mainly two general procedures describing the synthesis of the classical and primary synthetic route to uracil from Formalaceticacid (made in situ from malic acid) and urea in sulphuric acid is still important[17]. Some alternative syntheses use malic acid, urea, and PPA(2) or maleic/ fumaric acid , urea, and poly phosphonic acid (PPA) (2).The reaction of formyl acetate with thiourea is convenient for the synthesis of 2-thio uracil. Another main synthesis involves the reaction of ureas with β-keto esters diketene or acid anhydride [18]. Orotic acids are synthesized from oxaloacetate and ureas in the presence of hydrogen chloride via ring transformation of hydantoin into the uracil ring system. Treatment of the easily

obtainable 2-thio uracil with chloro acetic acid followed by acid hydrolysis or by oxidation with dimethyl sulphoxide (DMSO) in conc. Sulphuric acid[19] are alternative pathways .1,3- dimethyl uracil is transformed with urea in ethanolic sodium ethoxide in to uracil. Some more recent uracil syntheses start with propanoic acid and urea in PPA (or conc. sulfuric acid and benzene as solvent. [20]A broad choices of hetrocondensed uracils are easily and generally accessible from heterocyclic β- enamino esters and isocynates.[25].the mixed urea intermediate is smoothly cyclized with 5% aq.NaOH; the whole procedure cab be carried out in a one step reaction, when pyridine serves as solvent and base catalyst for the ring closure.[21] The condensation of urea with protected β-keto esters gives 6- or (di)substituted uracils [26]by means of retro Diels Alder splitting, nonbornene condensed tricyclic dihydrouracils , accessible from aminononbornene carboxylic acid and 1,1 – carbonyl di imidazole , afford ,upon heating ,uracils [27] in good yield Substituted uracils are obtained from imido esters, isocyanates, and malononitrile. Similarly N-substituted N-cyanoacetyl ureas cyclize in an alkaline medium. Hetrocondensed uracils are easily accessible from acyl lactones, lactums, and thio lactones[28], and heterocyclic β-enamino esters, especially .The later gives a broad range of novel types of condensed systems . With the aid of the hexamethyldisilazane trimethylchlorosilane [24] (HMDS/TMSCl) technique or the use of NaOH and halo sugars , respectively , simple approaches have been developed to obtain unusual nucleosides[27].

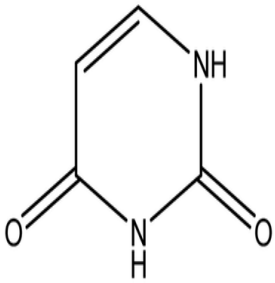
Preparation of [Pd (5 – methyl Uracil)$_2$ Cl$_2$]:

A mixture of $PdCl_2$ (500mg) and ligand 5-Methyl Uracil (1gm) in water and methanol (50ml) was refluxed at 80^0C 6-7 hours until it become a clear yellowish colour solution .This volume was reduced to 5ml and treated with methanol . The resulting gray white crystals were collected and washed well with ethanol and acetone . The analytical data is given in the table –I.

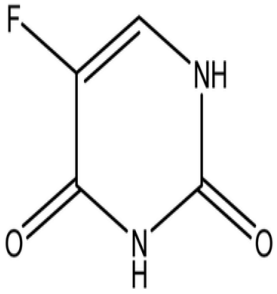
The General reaction for the preparation of coordination compound of palladium is as follows:

$$[Pd(Cl)_2] + 2L \xrightarrow[H_2O]{CH_3OH} [Pd(L_2)(Cl)_2]$$

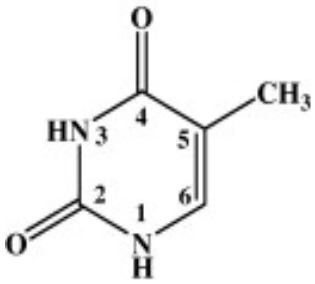
Where L = 5-Fluoro Uracil and 5-Methyl Uracil



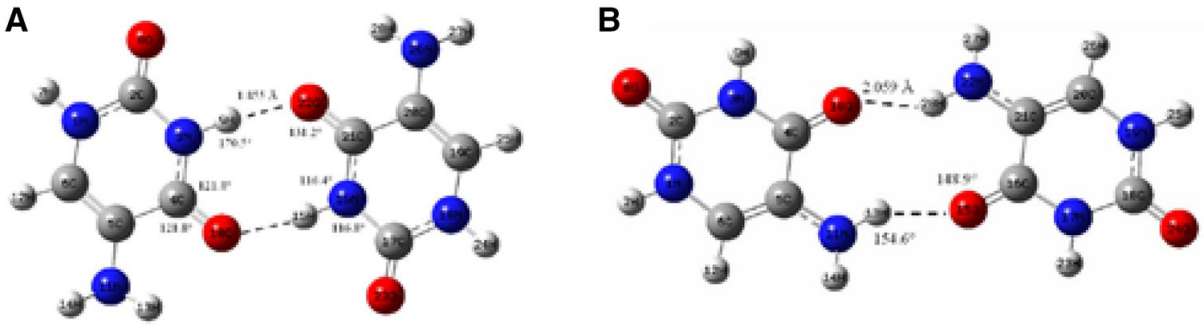
Uracil



5-Fluorouracil



5-methyluracil



Predicted dimer forms of 5-aminouracil at the theoretical level **a.** Uracil dimer. **B.**5-Methyl uracil dimer.

III.Spectroscopic analysis:

Carbon , hydrogen, nitrogen and oxygen present in the investigated complex were estimated micro analytically. For the estimation of Palladium as Palladium 1, 2, 3 benzotriazole, the synthesized compound solution were mixed with 10ml of 2M. acetic acid- sodium acetate buffer and 5ml of 4% EDTA solution.[29]Then 2.5 % acetic acid, was added with shaking . Digest the solution between 60^0C-90^0C, are 20 minutes. The resulting precipitate was filtered (G 3), washed several times with very dilute HCl (1:100), finally with distilled water and dried to a constant weight at 110^0C.[31]Molecular weight determination of the synthesized complex was made by Rast's method.Magnetic susceptibility measurement were made at room temperature by Gouy method. [38]A magnetic field strength of 8500 gauss was employed. The apparatus was calibrated using cobalt mercury thiocyanate Hg [$Co(NCS)_4$]. The diamagnetic corrections were computed using Pascal's constant. For calculation of effective magnetic moments, following equation has been used[30].

Effective magnetic moments (μeff) = $2.84 (x_m^{corr} .T)^{1/2}$

Where T = temperature in absolute scale , and x_m^{corr} = corrected molar susceptibility Conductance's was measured in analytical grade Methanol using dip type cell with the help of a Philips Conductivity Bridge.

Infrared spectra (4000-600cm^{-1}) of the uncoordinated ligands and the synthesized complex was recorded in nujol mulls supported between sodium chloride platex(rock salt region) on Perkin Elmer Spectrum(RXI) spectrometer .

^{1}**H** NMR spectra of the synthesized compound will be recorded on AC 300F spectrometer (300MHz) using TMS as an internal standard.

Electron spin resonance spectra of the complex was recorded at room temperature on a VariumE-3 spectrometer using powdered sample at the microware frequency 9.53GHz. The 'g' values were calculated using the given equation.

$$G = \frac{714.44 \text{ X } \sqrt{(GHz)}}{H(G)}$$

Where √(GHz) = microwave frequency in GHz at which sample operated , and H(G) = field in Gauss for the sample.

The analytical and physical data of the ligand and its metal complex are given in table I .The complexes are non hygroscopic and stable at room temperature. The solubility of complex are given .They are soluble in DMF and DMSO, slightly soluble in acetonitrile and insoluble in other organic solvent.

Conclusion:

We herein describe the chemistry of 5-aminouracil derivatives including either their synthetic methodologies or their potent biological activity. It is worth mentioning that this class of heterocycles has received considerable interest.

The magnetic values of the synthesized complex measured at room temperature. The magnetic moment values of all the complex are zero. Hence, they are diamagnetic. The square planar geometry of the complex is evident from their diamagnetic nature.

The Analytical and physical data of the ligand and its metal complex are given in table I .

Table -I

Analytical Data of the Complexes

Compound	% Pd Found (Calc.)	% C Found (Calc.)	% H Found (Calc.)	% N Found (Calc.)	% Cl Found (Calc.)	% F Found (Calc.)
[Pd(5-fluoroUracil)$_2$Cl$_2$]	24.79 (24.63)	27.93 (27.80)	2.79 (2.64)	13.03 (13.13)	16.53 (16.56)	-
[Pd(5-Methyl Uracil)$_2$Cl$_2$]	24.34 (24.56)	21.94 (21.46)	1.37 (1.36)	12.80 (12.81)	16.23 (16.26)	8.68 (8.60)

The value of molar conductance are in the range 0.052-0.058 Ω^{-1} cm^{-1} mol^{-1} suggesting non electrolyte nature of the synthesized complex.

Spectroscopic analysis:

The details of infrared spectral bands of the synthesized complex containing coordinated 5-methyl uracil possesses 3 possible donor sites , (i) Two cyclic nitrogen and (ii) oxygen of the ketonic group in ring respectively. Out of these two the cyclic nitrogen of ring system is supposed to be involved in coordination through the Nitrogen atom . In the IR spectra of the synthesized complex of 5-methyl uracil studied here , the

IR frequency of cyclic nitrogen of ring has been changed , thereby ,suggesting that the cyclic nitrogen has been participate in the coordination.[38]

In the IR spectra of both the complexes with 5- methyl uracil the bands at 640cm^{-1} suffered a lower shift of 640cm$^{-1,}$ indicating that metel nitrogen coordination present in the synthesized compound. Hambright et al. confirmed metal nitrogen co-ordination in the large series of the complex of Zn(II), Cu(II), Ni(II),Co(II) and Pd(II). Recently, Pennell and co-workers have experimentally confirmed the metal – nitrogen co-ordination in the complexes.

The electronic spectral bands of the complexes (table II) were assigned according to the literature.

Table II
Important IR spectral bands and their assignments
(Reported Compounds)

Sl.No.	Compound	ν_{M-C}(cm^{-1})	$\delta_{Me(sym)}$ (cm^{-1})
1	$[(PEt_3)_2Pd(CH_3)X]$		
	X=Br	510	1162
	SCN	526	1180
	CN	502	1161
2	$[(PEt_3)_2Pd(CH_3)_2]$	491, 457	1164
3	$[(AsEt_3)_2Pd(CH_3)_2]$	498, 479	1152,1124
4	$[(PPh_3)_2Pd(CH_3)_2]$	529, 482	1129
5	$[(bipyr)Pd(CH_3)_2]$	534, 522	
6	$[MeS(CH_2)_2(SMe)Pd(CH_3)_2]$	525 ,512	1168

The molecular orbital approach was used to explain the structure of square –planar complexes of the d^8 elements. The metal orbital's involved in σ bonding in square planer complexes are the ndz^2, ndx^2-y^2, (n+1)P$_x$ and (n+1)P$_y$. Nevertheless, judging from the values of the overlap integrals, nd$_{x2-y2}$ (n+1)s, (n+1)P$_x$ and (n+1)P$_y$ account for most of the σ – bonds , and ndz^2 makes only a minor contribution of π- orbital's of the ligands.

The correlation of the bands observed in the electronic spectra for the studied complexes with those of [M (CN)$_4$]$^{2-}$ [M= Pd^{II}] prompted us to assume the following assignments (Table II) $^1A_{1g} \longrightarrow {}^1A_{2g}\,[b_{2g}(\pi^*) b_{1g}(\sigma^*)]$, (d-d): $^1A_{1g} \longrightarrow {}^1B_{1g}\,[b_{2g}(\pi^*) \longrightarrow a_{1g}(\sigma^*)]$, $\longrightarrow$(d-d); $^1A_{1g} \longrightarrow {}^1E_g\,[e_g(\pi^*) \longrightarrow b_{1g}(\sigma^*)]$, $\longrightarrow$(d-d); $^1A_{1g} \longrightarrow {}^1B_{1u}\,[b_{2g}(\pi^*) \longrightarrow a_{2u}(\pi^*)]$,(C.T) ; $^1A_{1g} \longrightarrow {}^1E_u\,[e_g(\pi^*) a_{2u}(\pi^*)]$, (C.T).

The relation between the bands in the present complex and the described for the typical complexes [M (CN)$_4$]$^{2-}$ leads to the conclusion that all the new complex has the same square planer geometry.

The analytical data and all the evidences presented above suggest the formulation of these complex as. The mixed ligand complex [PdL$_2$Cl$_2$] where (L = 5-methyl uracil), have been prepared by the interaction of parent compound [PdCl$_2$] with ligand. The complexare characterized by elemental analysis, magnetic measurement, electron spin resonance and infrared spectral studies containing Pd (II) d^8 configuration.[39]

IV.Scope of Palladium complexes in the treatment of tumours

Therapeutic potential of metal complexes in cancer therapy has attracted a lot of interest mainly because metals exhibit unique characteristics, such as redox activity, variable coordination modes and reactivity toward the organic substrate.[11] These properties become an attractive probe in the design of metal complexes that selectively bind to the biomolecular target with a resultant alteration in the cellular mechanism of proliferation. Table 1 provides a summary of in vitro cytotoxic effect of various metal-based compounds within the period of 6 years with particular reference to their proposed mechanism of action and target.

Several metal-based compounds have been synthesized with promising anticancer properties, some of which are already in use in clinical practice for diagnosis and treatment while some are undergoing clinical trials. Metal-based compounds synthesized recently are products of drug design targeted at achieving specific objectives that the original compound could not achieve and such compounds exhibit a different spectrum of cytotoxicity. Compounds in this group include the following.

V.Conclusion

Palladium compounds, are the heartbeat of the metal-based compounds in cancer therapy. Clinical use of palladium complexes as an adjuvant in cancer therapy is based on the desire to achieve tumor cell death and the spectrum of activity of the candidate drug. Such complexes are mostly indicated for the treatment of cervical, ovarian, testicular, head and neck, breast, bladder, stomach, prostate and lung cancers. Their anticancer activities are also extended to Hodgkin's and non-Hodgkin's lymphoma, neuroblastoma, sarcoma, melanoma and multiple myeloma. Although resistance emerged, it was the fundamental basis that triggered the search for alternative metallic compounds with improved anticancer and pharmacokinetic properties. On this basis, alternative

Palladium compounds were derived. These are all products of extensive research of Palladium complexes .All the complex is diamagnetic suggesting square planner geometry. It is observed that the synthesized compound are light yellow in colour, non hygroscopic, soluble in DMF, DMSO, slightly soluble in acetonitrile and sparingly soluble in other solvents, thermally stable and do not decomposed up to 260^0C,The compound have d^8 configuration. The complex has anti tumor activity.

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