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Anti-cancer palladium complexes: a focus on PdX_2L_2, palladacycles and related complexes

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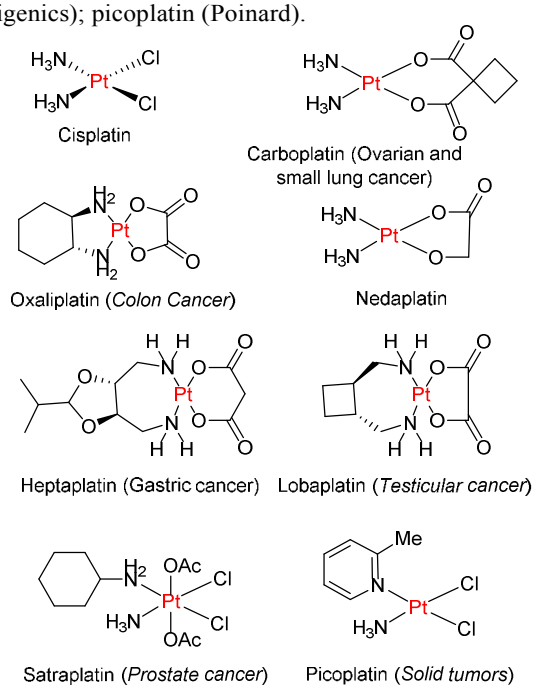
Much success has been had with platinum-based chemotherapeutic agents, i.e. through interactions with DNA. The long-term application of Pt complexes is thwart with issues, leading to scientists to examine other metals such as palladium which could exhibit complementary modes of action (given emphasis wherever known). Over the last 10 years several research groups have focused on the application of an eclectic array of palladium complexes (of the type PdX_2L_2, palladacycles and related structures) as potential anti-cancer agents. This review therefore provides readers with an upto date account of the advances that has taken place over the past several decades.

1. Introduction

Anti-cancer properties of cisplatin or *cis*-diamminedichloroplatinum(II) and its commercially successful analogues, carboplatin and oxaliplatin, have been known for sometime, leading to an unprecedented upsurge in the synthesis and application of platinum-based potential anti-cancer agents.[1-11] Other drug compounds have been approved such as nedaplatin (Japan; Shionogi & Co. Ltd), heptaplatin (South Korea; SK Pharma), lobaplatin (China). Others are in the developmental stages like satraplatin (GPC Biotech & Pharmion); miriplatin (Dainippon Sumitomo Pharma and Bristol-Myers K.K.); prolindac (Access Pharmaceuticals); BP-C1 (Meabco); cisplatin Lipid Complex (Transave); aroplatin (Antigenics); picoplatin (Poinard).



Scheme 1: Commercial platinum-based anticancer agents.

Globally, the demand for platinum-based drugs has grown steadily, although several side effects ranging from nephrotoxicity to drug resistance of the tumour cells have posed real challenges to researchers.[12-15] Side effects associated with cisplatin administration, alongwith limited applicability arising from specificity shown towards certain cancer cell lines have prompted researchers to look for alternatives.

One of the alternatives that has shown considerable promise has been the development of other transition-metal based drug candidates.[16-21]The combination of transition metals with biologically active molecules has also been exploited showing promising activity due to their unique ability to bind different biological targets.[22-24] Palladium-based complexes are closely related to their platinum analogues, due to their structural similarities and significant overlap of coordination chemistry for the two metals. One of the early studies by Graham and co-workers[25] advocated the use of palladium complexes as possible anti-cancer agents. Since this report a series of novel palladium complexes have been synthesized which exhibit promising activity against tumor cell lines (lung, prostate etc.). In several cases the palladium complexes have exhibited better anti-tumor activity than their platinum counterparts (cisplatin, carboplatin etc.).

In terms of usefulness the slow dissociation pattern of platinum complexes compared to palladium (10^5 times faster) makes them more applicable. A recent trend observed in palladium-based anticancer drugs is to focus on the development of palladium complexes with slower rates of hydrolysis brought about by the judicious choice of the ligands. In this respect cyclopalladated complexes containing a strong C-M σ-bond that could counter all of the above problems has shown a lot of promise.

This review includes a detailed account on the application of cyclopalladated complexes as potent anti-cancer agents. This will be carried out via systematic classification of palladium-based complexes and a comparison will be drawn between monomeric palladium complexes and their palladacyclic or cyclopalladated analogues towards the inhibition of various types of tumours. Throughout the review, the chemical

structures are accompanied with IC_{50} values and cell line details, where known.

2. *Trans*-Palladium Complexes as Anti-Cancer Agents

The judicious choice of ligands around the palladium centre governs the geometry exhibited by the complexes produced. Bulky monodentate ligands have rarely been employed for the synthesis of *cis*-palladium complexes as the steric effects play a major role in defining the geometry around the palladium centre which in most cases is *trans* in nature. The importance of the *trans*-geometry around the palladium centre has been attributed to the comparatively higher cytotoxicity values as those for *cis*-isomers.[26] A marked improvement has also been reported for these analogs to those of the *cis*-platin, carboplatin and other platinum based analogs.

One of the early examples suggesting the improved antitumour activity of the *trans*-palladium complex **1** was put forward by Tusek-Bozic and co-workers in 1991 (Figure 1).[27] One of the features of these complexes was the introduction of monoethylphosphonate and diethylphosphonate moiety on the quinolmethyl substructure that allowed for better solubility of the resultant complexes. A comparative study was conducted revealing that the diethylphosphonate moiety outperformed its monoethylphosphonate analog. One of the assumptions for better activity was the easier dissociation of chloride ligand from the palladium centre, however this claim has not been verified. This laid the foundation for further studies into the application of *trans*-palladium complexes as antitumour agents.

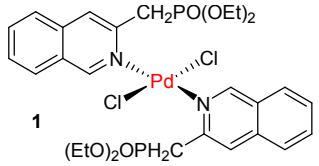
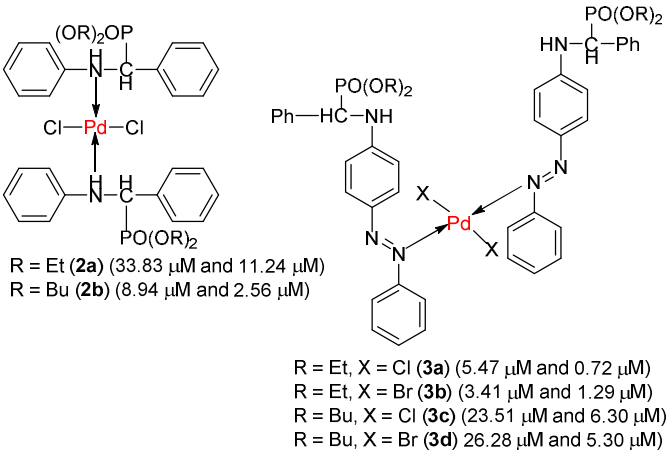


Figure 1: *trans*-Palladium bis(quinonyl-phosphonate) complex as an early example of a palladium-based potential anti-cancer agent.

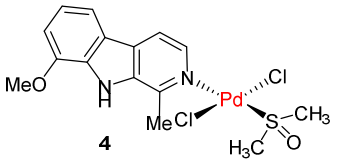
An extension of the above study was put forward by the same group where diethyl and dibutyl esters of (α-anilino-*N*-benzyl) phosphonic acid and [α-(4-benzeneazoanilino)-*N*-benzyl]phosphonic acid were synthesised.[28] The *in vitro* cytostatic activity of the complexes was evaluated against both the human epidermoid carcinoma derived KB cell line[29] and murine leukemia L1210 cell line,[30] by solvating the complexes into acetone or DMSO with the best results obtained in DMSO as the solvent. A comparable cytostatic activity to that of cisplatin was observed for complex **3a** (IC_{50} in μg/mL = 4.97 and 0.72, respectively) which bears similarity to the quinolmethylphosphonate ester (Figure 2) in terms of the chloride ligand, although exhibiting better cytotoxicity. An improvement in activity was assumed to be due to the presence of N-bonded hydrogen suitable for hydrogen bonding, i.e. assisting effective binding of metal ions to the nucleic acid fragments over those containing heterocyclic N-donor ligands[31-33].



Cancer cell lines: KB cells, L1210 cells

Figure 2: α-Anilinobenzylphosphonate based palladium complexes with cytostatic behaviour comparable to *cis*-platin.

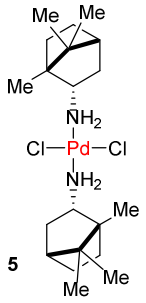
Naturally-occurring compounds[34,35] have played a significant role in the rapid development of new drug discovery brought about by the advent of spectroscopy as an important tool for their structure elucidation. These compounds have exhibited a wide spectrum of biological activities including antitumour activity such as the case with alkaloid Harmine[36]. In an attempt to explore the possible enhancement in the antitumour properties of the metal coordinated analogue of Harmine, Al-Allaf and co-workers reported the synthesis of *trans*-[Pd(harmine)(DMSO)Cl_2] complex **4** (Figure 3).[37] Cytostatic studies performed on P388, L1210 and K562 cell lines revealed the superior activity of the metal-coordinated version of harmine than cisplatin or the uncoordinated Harmine itself.



Cancer cell lines: P388, L1210 and K562

Figure 3: The alkaloid-Harmine-coordinated *trans*-palladium complex containing DMSO as a ligand

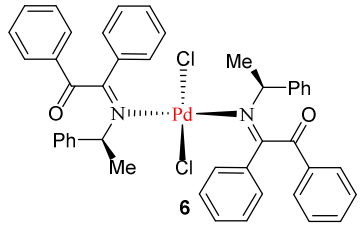
A chiral palladium complex was recently reported by Abu-Surrah and co-workers, which contains a bulky amine ligand *R*-(+)-bornylamine (endo-(*1R*)-1,7,7-trimethyl bicycle[2.2.1]-heptan-2-amine) **5** (Figure 4).[38a] The enantiomerically pure *trans*-Pd(II) complex was tested for antitumour properties against L929, K562 and HeLa cell lines using the MTT assay, the values indicating similar cytotoxic activity compared to cisplatin, carboplatin and oxaliplatin. Anticomplimentary activity (capable of reducing or destroying the tumor cells) for the inhibition of proteins also showed similar results to those of commercially-known platinum-based analogues.



Cancer cell lines: L929, K562 and HeLa

Figure 4: Enantiomerically-pure *trans*-palladium complex**5**.

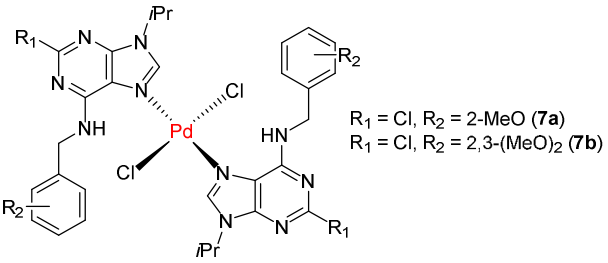
Another example of an enantiomerically-pure *trans*-Pd(II) complex, containing chiral ligand (*S*)-(-)-(1-phenylethylimino)benzyl phenyl ketone, obtained under microwave irradiation, was reported recently by Gutierrez and co-workers (Figure 5).[38b] The *in vitro* cytotoxicity study on palladium complex **6** displayed growth inhibition against different cell lines such as K-562 (Leukemia), HCT-15 (colon cancer), MCF-7 (breast cancer), U-251 Glio (central nervous system) and PC-3 (prostate cancer).



K-562 (Leukemia-26.5 μM), HCT-15 (colon cancer-100 μM),
MCF-7 (breast cancer-34.5 μM),
U-251 Glio (central nervous system 100 μM)
and PC-3 (prostate cancer-40.5 μM)

Figure 5: Chiral ketoimine of benzil based *trans*-Pd(II) complex.

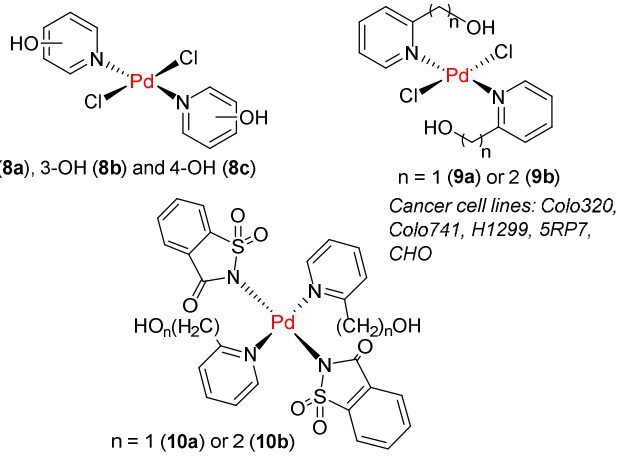
Substituted benzylaminopurine derivatives have proven to be important structural motifs in a variety of bioapplications due to their ability to inhibit cyclin-dependent kinase (CDK).[39-41] They have also exhibited good IC_{50} values for in vitro cytotoxicity against different human cancer cell lines.[42] Complexation of these with different transition metal ions have shown better cytotoxicity.[43-46]The palladium complexes bearing molecules having structural similarity to the CDKs were synthesised (Figure 6).[47,48] Although, trans-Pd complexes are represented here, cis-Pd complexes were also isolated and subjected to in vitro studies against four human cancer cell lines: MCF7, K562, G361 and HOS. The ligands were also tested as controls against the palladium complexes with platinum based analogs such as cisplatin, oxaliplatin or clinically tested anticancer agent roscovitine serving as standards. In most cases the cytotoxicity was found to be negligible, however trans-Pd(II) complex **7a** showed significant IC_{50} value for G361 cancer cell line (15 μM).



Cancer cell lines: MCF7, K562, G361, HOS.

Figure 6: Purine based square planar palladium complexes with good cytotoxicity.

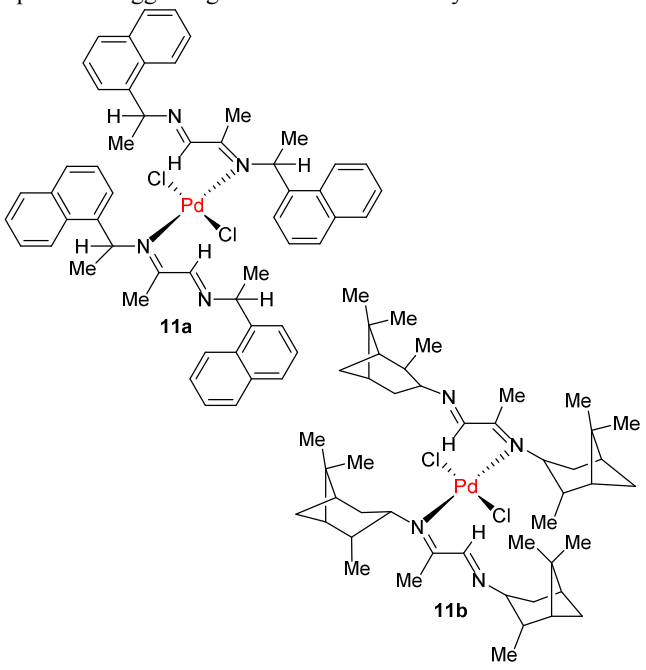
Pyridine-based ligands bind metal centres as 2-electron donors; indeed, several pyridine-ligated transition-metal complexes are known in literature[49], out of which a few have exhibited good anticancer activity.[50-54] Palladium complexes containing hydroxy and hydroxymethyl substituted pyridine ligands have recently been reported. In most cases the substituents were placed *trans* with respect to each other. Complexes **8a-c** containing hydroxyl-substituted pyridine ligand were first to be investigated for antitumour activity against ovarian cancer cell lines A2780 (cisplatin sensitive; the parent cell line), $A2780^{cisR}$ (cisplatin resistant) and $A2780^{ZD0473R}$ (picoplatin resistant) (**8a-c**, Figure 7).[55] The compounds were found to be less active than cisplatin. Changing the substituent on the pyridine ring from hydroxy to hydroxyalkyl also failed to give any appreciable improvement in cytotoxic activity for the palladium complexes **9a-b** against colon cancer (Colo320, Colo741), lung cancer (H1299), sarcoma (5RP7), and normal/unmalignant (CHO) cells (**9a-b**, Figure 7).[56] Replacement of the chloride ligand for a more labile pseudohalide,[57-68] saccharinate, showed no particular enhancement in activity when the synthesised *trans*-Pd(II) complexes **10a,b** were evaluated against lung cancer (A549 and PC3), human hepatoma Hep3B and rat C6 glioma cell lines, using MTT assay (**10a,b**, Figure 7).[69]



Cancer cell lines: A549 and PC3 for lung cancer,
C6 for glioblastoma and Hep3B for liver cancer

Figure 7: Hydroxy and hydroxyalkyl substituted pyridine-based *trans*-palladium complexes.

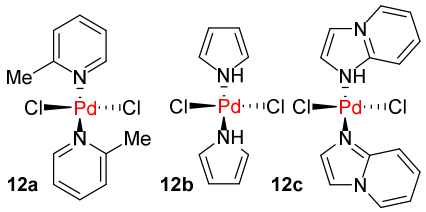
α-Diimines are another class of versatile organic compounds that have shown a varied coordination behaviour towards transition metals. Flexible skeletal-arrangement and exceptional electron-accepting and -donating properties make these ligands an attractive proposition for the synthesis of more elaborate metal complexes.[70] With this idea in mind Gutierrez and co-workers employed these ligand systems for the synthesis of chiral *trans*-Pd(II) complexes **11a,b** (Figure 8).[71] IC_{50} values for the complexes against U251 (CNS), PC-3 (prostate), K562 (leukemia), HCT-15 (colon) and MCF-7 (breast) human cancer cells with cisplatin as the reference standard were not very impressive suggesting lower inhibition ability.



Cancer cell lines: U251 (CNS), PC-3 (prostate), K562 (leukemia), HCT-15 (colon) and MCF-7 (breast)

Figure 8: Chiral diimine palladium complexes derived from glyoxal and optically-pure diamines.

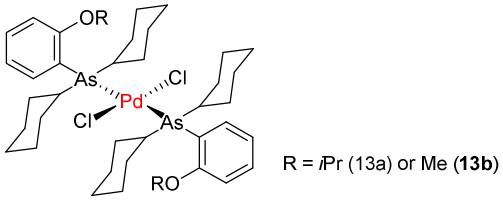
To study the effect of bulky ligands on the cytotoxic ability of the complexes Huq and co-workers performed an elegant structure-activity correlation study on palladium complexes obtained from planaramines such as 2-methylpyridine, imidazole and 1,2-α-imidazopyridine as ligands showing varied degree of steric hindrance (Figure 9).[72] The complexes were then tested against the human ovarian cancer cell lines A2780 (cisplatin sensitive; the parent cell line), $A2780^{cisR}$ (cisplatin resistant), $A2780^{ZD0473R}$ (picoplatin resistant) and SKOV-3 (Sloan–Kettering HER2 3+ ovarian cancer). It was observed that, as compared to cisplatin, the cytotoxic activity reduced in the following order, cisplatin >**12c**>**12b**>**12a**. Based on the values obtained for the complexes it was also concluded that the complex **12c** bearing a bulky 1,2-α-imidazopyridine ligand caused much greater distortion of the DNA possibly brought about by the higher level of palladium-DNA binding.



12a: *A2780 (34.7 μM), $A2780^{cisR}$ (27.2 μM), $A2780^{ZD0473R}$ (25.0 μM), SKOV-3 (19.9 μM)*
12b: *A2780 (32.1 μM), $A2780^{cisR}$ (25.1 μM), $A2780^{ZD0473R}$ (25.2 μM), SKOV-3 (18.8 μM)*
12c: *A2780 (6.78 μM), $A2780^{cisR}$ (7.95 μM), $A2780^{ZD0473R}$ (6.03 μM), SKOV-3 (4.36 μM)*

Figure 9: *trans*-Palladium complexes containing planaramines- cytotoxicity in Human Ovarian tumors.

An interesting example of the use of a bulky arsine ligand for the synthesis of *trans*-palladium complexes **13a,b** was reported by Fischer-Fodor and co-workers (Figure 10).[73] The antitumour properties of these complexes was evaluated *in vitro* on the chemo-resistant hepatic tumour stem cell line (CSC), the normal hepatic stem cells (HEPG2) and towards the hepatocellular carcinoma (non-stem) cells (LIV). Compared to oxaliplatin these complexes showed limited toxicity in normal liver cells, although against the stem cells damage to the DNA was observed. This was attributed to their capacity to form DNA interstrand cross-linkages.



Cancer cell lines: CSC, HEPG2, LIV

Figure 10: Palladium complexes containing arsenic based ligand systems.

Another class of bulky and highly electron-rich σ-donor ligand systems are the N-heterocyclic carbenes that have found application in a variety of fields ranging from coordination chemistry[74], transition-metal catalysed reactions[75], functional material applications[76] and biomedical applications[77a]. Recent studies for biomedical applications have focussed on NHC-coordinated transition-metal complexes of Au, Ru Ag, Cu Pt and Ni.[77a] Recent work by Willans and co-workers on Ag-based NHC complexes has attracted interest.[77b] Palladium-based *N*-heterocyclic carbene complexes have been introduced recently, also having some promise.

The first example of Pd-NHC complexes as possible antitumour agents was reported by Ghosh and co-workers in 2007 (**14-15**, Figure 11).[78] Due to the bulky nature of the substituents on the NHC the ligands are arranged *trans* with respect to each other. On subjecting the complexes to antitumour activity against three human tumour cells namely cervical cancer (HeLa), breast cancer (MCF-7), and colonadenocarcinoma (HCT 116), complex **15** showed strong

antiproliferative activity considerably stronger than cisplatin. A mechanistic proposal for the antitumour activity of complex **15** suggested prevention of cell cycle progression at the G-2 stage and P-53 pathway, presumed to be followed through a programmed cell death. Structurally similar NHC-palladium complex **16** containing bulky mesityl substituent was also evaluated for *in vitro* binding capacity on guanosine (**16**, Figure 11).[79] The genotoxicity of the complex was also checked on plasmid DNA although in both the cases poor activity was observed.

Another example of substituted NHC-Pd(II) complex obtained through transmetallation of corresponding Ag(I)-NHC complexes was disclosed by Haque and co-workers (**17-18**, Figure 11).[80] Evaluation of the Pd(II)-NHC complexes for anticancer activity against human colorectal cancer cell lines HCT 116 using MTT assay where **17** revealed higher levels of cytotoxicity at surprisingly low IC_{50} values a promising prospect for future exploration as potent anticancer agents.

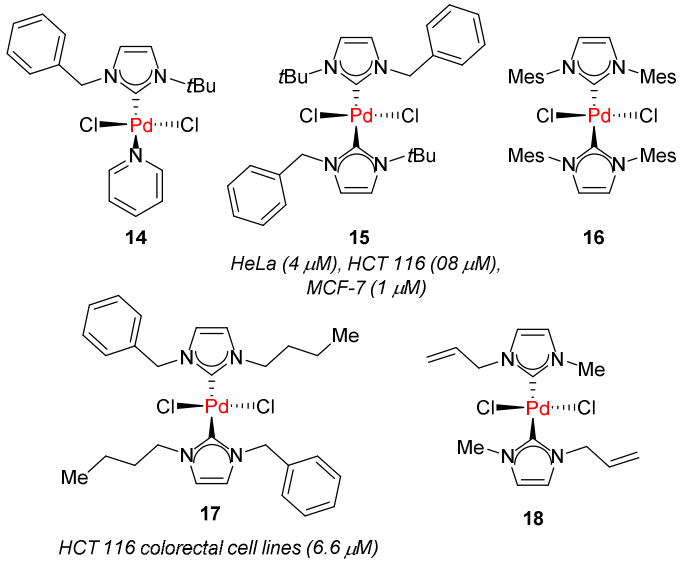


Figure 11: *N*-Heterocyclic Carbenes coordinated palladium complexes as potential anti-cancer agents.

Water solubility of organometallic complexes is an important criterion that has found far-reaching applications in synthesis and biological sciences.[81] This could be achieved using ligands that could help solubilise the metal complexes. 1,3,5-Triaza-7-phosphaadmantane (PTA)[82] is one such readily available and air-stable ligand that has proved to be a versatile and electron-rich phosphine ligand and has found varied applications.[83-85] With an idea to extend the applications of PTA, Mendia and co-workers developed water soluble *trans*-palladium complexes and their antiproliferative activity was studied (**19-24**, Figure 12).[86,87]

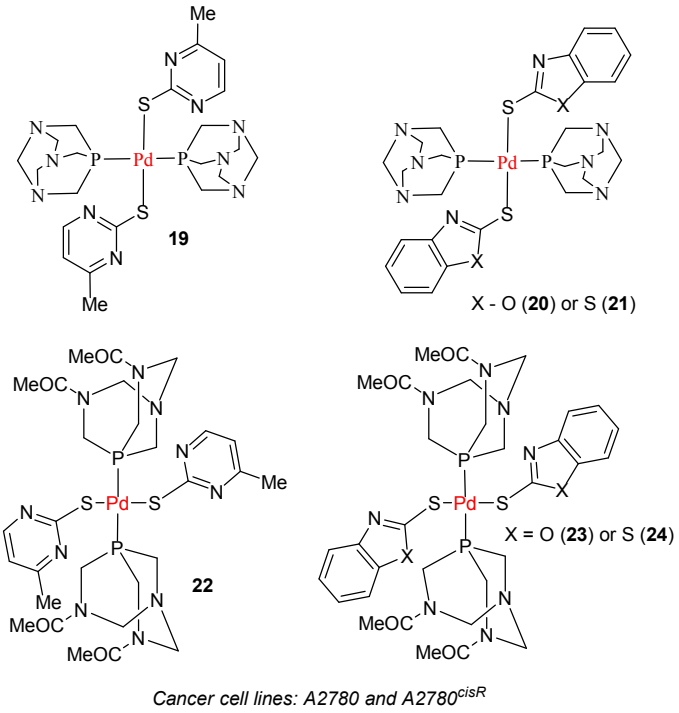


Figure 12: Imminophosphorane based palladium complexes: Potential water soluble anti-cancer agents.

In vitro cytotoxic activity for the synthesised complexes **19-24**ere performed on human ovarian cancer cell lines A2780 and $A2780^{cisR}$ (cisplatin resistant) with most of the complexes showing comparable activity in the normal A2780 cell lines to that of cisplatin. However, an incredibly high cytotoxic activity could be observed against the $A2780^{cisR}$ cancer cell lines.

All the above examples for monomeric palladium complexes with *trans*-geometrical positioning of the ligands have shown good cytotoxic activity, however in comparison to their platinum counterparts the activity is either comparable or negligible. Reports have emerged within the literature suggesting a marked improvement in cytotoxicity for cyclopalladated complexes.[88] This literature material is reviewed in detail in the next section.

Palladacyclic or Cyclopalladated complexes

Palladacycles or cyclopalladated complexes are classical examples of heterocyclic compounds containing palladium as one of the central 'heteroatoms' and are typically characterised by the presence of Pd–C bond which is stabilized by intramolecular coordination. One of the earliest examples of cyclopalladated complexes was reported by Cope and co-workers[89] with aromatic azo compounds, two years after Dubeck[90] had wrongly assigned the structure to a cyclopentadienyl nickel complex with the same azobenzene ligand. Although this led the foundation for the synthesis and application of palladacyclic or cyclopalladated complexes they continued to remain as reactive intermediates in catalytic processes such as palladium-catalysed cycloaddition[91] and

Heck[92] coupling reactions. The introduction of cyclopalladated tri-*o*-tolylphosphine complex **28** by Herrmann and co-workers[93] generated excitement and considerable expectation in the field of catalysis which slowly-triggered major developments in cross-coupling processes (**28**, Figure 13).

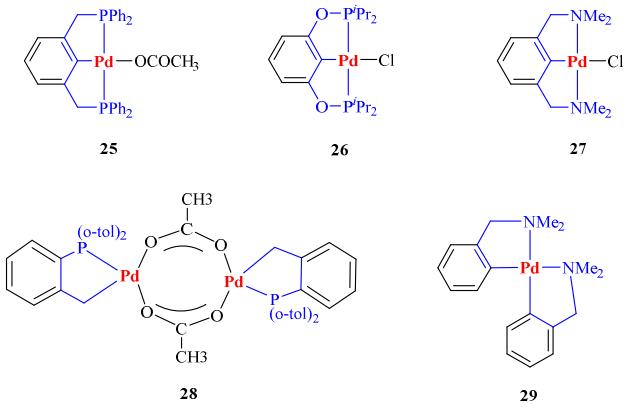


Figure 13: Few examples of important palladacyclic or cyclopalladated complexes.

Cyclopalladated or palladacyclic complexes show considerable potential as biological probes and potent anticancer agents.[94,95] A systematic classification of these complexes based on the type of ligand system employed and the kind of coordination they exhibit is highlighted below.

3. Mononuclear Cyclopalladated or Palladacyclic Complexes as Anti-Cancer Agents

Mononuclear cyclopalladated or palladacyclic complexes are simple coordination compounds that are obtained via coordination of single metal atom (in this case- palladium) with different multidentate ligands. Multidentate ligands have received considerable attention due to their ability to tailor the steric and electronic properties of a given metal center. Furthermore, the structural flexibility associated with different kapticities provides a means to influence reaction pathways. A wide variety of neutral multidentate (bi- and tridentate) ligands have been employed successfully in literature and in this section an attempt will be made to categorise the complexes obtained based on the type of coordination these ligands exhibit with the metal ion.

3.1. Nitrogen based Multidentate ligands

Nitrogen-containing donor ligands exhibit several distinct advantages over other ligand systems, such as their ease of availability and relevance as industrially-applicable intermediates This has resulted in numerous synthetic possibilities that allow tailor-made modifications for the preparation of ligands with specific physicochemical properties. Recent Advances have led to a steady shift from traditional catalytic applications to their metal-coordinated compounds being used as anticancer agents, which will be discussed below.

Of the different modes of coordination for nitrogen containing-ligands, N,N-coordination can be achieved using bidentate ligand systems, typically involving a 2,2□-bipyridyl substructure, substituted ethylene diamine or other nitrogen-containing mixed heterocyclic compounds. A Systematic evaluation of the antitumour properties of the palladium complexes for the above mentioned ligand systems gives an insight into the possible effect of ligand backbone on the cytotoxicity against different cancer cell lines.

2,2'-Bipyridyls are privileged ligand scaffolds that have found considerable attention due to their occurrence in naturally-occurring molecules such as caerulomycins or collismycins,[96-98] for metal-coordinated complex synthesis[99-103] and supra-molecular applications.[104,105] 1,10-Phenanthroline exhibits similar coordination characteristics as the 2,2□-bipyridines but has several distinct properties like: a) rigid structure restricting the two nitrogens to be held in a juxta-position, and b) entropically-favoured chelation with different metal ions which has vastly contributed towards the application of these structural motifs in a variety of fields. Given the importance of these molecules, the bio-applications of the palladium-based complexes derived from bipyridyl or phenanthroline derivatives for cytostatic studies on cancer cell lines are of utmost improtance.

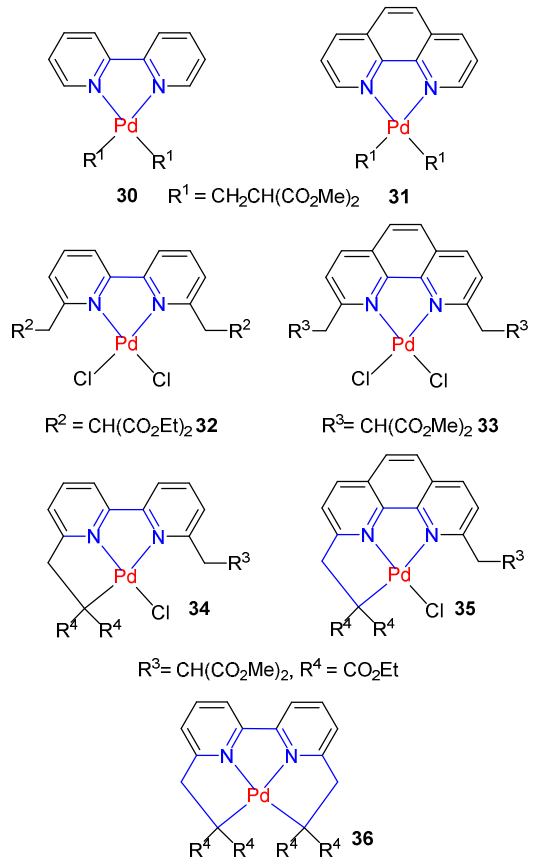
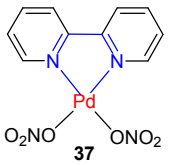


Figure 14: N-Electron deficient bipyridyl and phenanthroline based palladacyclic or cyclopalladated complexes for binding with phage PMA2 DNA.

The first example was reported as early as 1985 by Newkome and co-workers.[106] The bidentate properties of substituted-bipyridines and phenanthroline were exploited to obtain four novel palladacyclic complexes (**30-33**, Figure 14). Modification of the bipyridyl and phenanthroline substructures allowed the denticity to be changed from a bidentate coordination to tri- (**34**&**35**) and tetradentate (**36**). Preliminary studies with the synthesised cyclopalladated complexes were performed on Phage PM2 DNA to understand their interactions based on the difference in ligand backbone. A marked difference in the level of DNA binding was observed with tetradentate cyclopalladated complex **36** outperforming all others even at significantly lower concentrations. Although, the cytotoxicity studies were not conducted on the above mentioned complexes these results prompted rapid developments in this area and are outlined below.

Subsequently, palladacyclic complex containing a bipyridine ligand backbone in addition to nitrate groups, was investigated for cytotoxic activity against different human cancer cell lines like sarcoma 180 and P388 leukemia (**37**, Figure 15).[107] The anticancer activity displayed was relatively low for both the cancer cell lines. Incidentally it was found that besides having *N,N*-bidentate ligand which has been found to have least influence on the activity, certain oxygen coordinated leaving groups seemed to have a more pronounced effect as was found by Mansuri-Torshizi and co-workers.[108] The introduction of selenite group on the palladium centre brought about an invariable enhancement in the cytotoxic activity against P388 lymphocytic leukemia cancer cell lines compared to its tellurite analogue, as well as cisplatin (**38**, Figure 15). It was established that complex **38** interacted with calf thymus DNA (bound to the DNA covalently). Finally, a phenanthroline-based cyclopalladated complex was synthesised taking into the account the DNA intercalation brought about by the planarity of the structure.[109] Modified-tetradentate phenanthrolines were employed give new Pd complexes, which were tested against mouse leukemia L1210 and the mouse liver carcinoma Bel7402 cell lines (**39a-d**, Figure 15).



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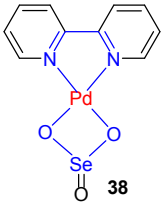
Cancer cell lines:Sarcoma 180 and P388 leukemia



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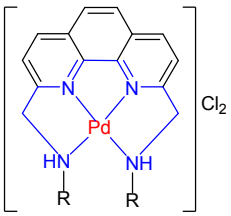


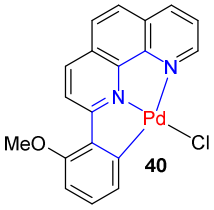
R = Me (**39a**), Et (**39b**), Pr (**39c**), Cy (**39d**)

Mouse cancer cell lines: L1210 and Bel7402

Figure 15: Early examples of palladacyclic bipyridine and phenanthroline based anticancer agents.

The cytotoxic activity for these complexes was significantly dependent on the nature of the substitutent present on the nitrogen atoms (R group). It was observed that the bulkier substituent brought about appreciable improvement in activity when compared to cisplatin (**39d**>**39c**>**39b**>**39a**).

A unique cyclopalladated complex was recently reported by Higgins III and co-workers via cyclopalladation of 2-arylphenanthroline (**40**, Figure 16).[110] Several other monomeric cyclopalladated complexes were prepared as a part of a systematic study of cytotoxicity performed on such complexes against a panel of six human cancer cell lines SW6020 (5 μM), SW1116 (7 μM), SW403 (6 μM), ZR75-1 (7 μM), HT1376 (8 μM), SK-OV-3 (7 μM). The *in vitro* cytotoxicity studies revealed good activity for the synthesised complexes, including **40**. The study was intended for extrapolation to *in vivo* antitumour activity for those complexes that have exhibited differential activity against cell lines.

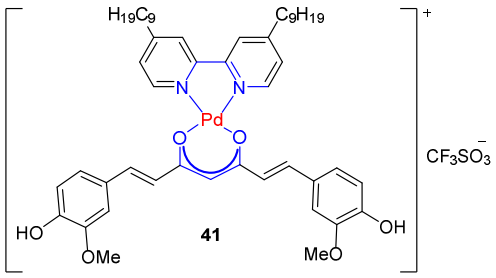


40

Cancer cell lines: SW6020 (5 μM), SW1116 (7 μM), SW403 (6 μM), ZR75-1 (7 μM), HT1376 (8 μM), SK-OV-3 (7 μM)

Figure 16: 2-Arylphenanthroline-based cyclopalladated complexs as potent anticancer agent.

Curcumin [1,7-*bis*(4-hydroxy-3-methoxyphenyl)-1,6-heptane-3,5-dione] is one of the main constituent of turmeric (Curcuma longa L.). For several centuries the beneficial effects concerning the consumption of curcumin have been well-documented.[111] One of the most well-studied bio-applications of curcumin (and its derivatives) are its anti-inflammatory and cancer chemoprotective properties.[112-116] With a view to enhancing the antitumour activity further Valentini and co-workers reported an ionic palladacyclic complex, containing a substituted bipyridine ligand and curcumin (**41**, Figure 17).[117] The complex **41** was investigated for its activity against human prostate cancer cell lines LnCaP-SF, LnCaP, PC3, andDU145 by MTT assay and compared to pure curcumin (free ligand). Based on the IC_{50} values obtained for the complex and pure curcumin, **41** showed lower toxicity towards the cancer cell lines and is more active in inhibiting cell proliferation.

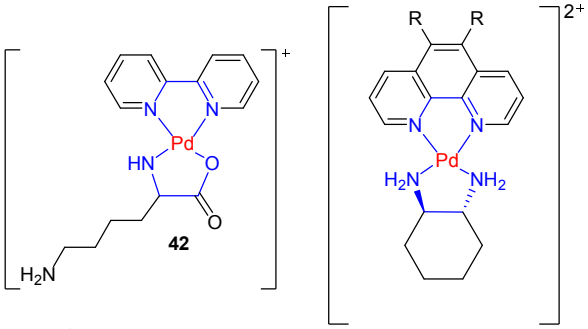


LnCaP-SF (100 μM), LnCaP (19.7 μM), PC3 (22.2 μM), and DU145 (24.2 μM)

Figure 17: Improved anticancer activity for curcumin-coordinated palladacyclic complex.

Metal-coordination to the active curcumin group affords a more potent anticancer agent, therefore proving to be an effective strategy. Further studies were performed on complex **41** to understand the mechanism of cell growth inhibition and cell death through mitochondrial bearing membrane depolarization. The authors performed a similar study on the palladium-coordinated complexes of curcuminoid fragments, showinh greater cytotoxicity than curcumin against DU145 human prostate cancer cell lines.[118]

Finally, Aldrich-Wright and co-workers have reported a simple and mild synthetic protocol for obtaining cationic palladacyclic complexes (Figure 18).[119] Cytotoxicity studies performed using complexes **42**, **43a-b** against L1210 murine leukemia cell lines were not so encouraging. This suggests that a more rigid ligand backbone could lead to faster dissociation of the complex thus leading to a lowering of palladium concentration in DNA.



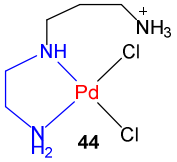
Cancer cell line: L1210

R = H (**43a**), 5-Me, 6-H (**43b**), 5,6-Me_2 (**43c**)

Figure 18: Cationic palladacyclic complexes.

Diamine ligands such as ethylenediamine and cyclohexadiamine are important organic molecules exhibiting bidentate coordination with different metal ions. Ethylenediamine has proven to be a highly useful molecule, finding applicability towards the industrial scale synthesis of ethylenediaminetetraacetic acid (EDTA), carbamates, fungicides, surfactants and dyes.[120] *trans*-1,2-Cyclohexadiamine is one more versatile ligand in this category which shows bidentate N,N-coordination. Palladium complexes of these ligand systems also known, however their employment as antitumour agent has been more recent.[119]

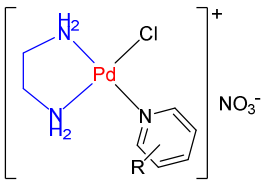
Pioneering work by Navarro-Ranninger and co-workers[121] demonstrated the easy accessibility of palladium complexes derived from modified ethylenediamine-Spermine[122] (a polyamine that is involved in cellular metabolism in eukaryotic cells, as well as putrescine (tetramethylenediamine) (**44**, Figure 19). Initial studies performed to understand the interaction of the Pd(II)-polyamine compounds revealed the induction of conformational changes in the circular forms of plasmid DNA. The Pd(II)-putresciene and Pd(II)-spermine were then tested against MDA-MB 468 and HL-60 human cancer cell lines for *in vitro* antiproliferative activity. A lower antitumour activity was observed for the spermine based palladium complexes but putrescine showed promising antitumour activity due to the lower IC_{50} obtained compared to cisplatin.



Cancer cell lines: MDA-MB 468 and HL-60

Figure 19: Spermine based Pd(II) complexes.

An extension to the work done by Navarro-Ranninger, involving the preparation of cationic palladacyclic complexes, a structure-activity correlationship study was undertaken by Lin and co-workers for a new set of cationic palladacyclic complexes **45a-c** (Figure 20).[123] The ligand set used for preparing these complexes was ethylenediamine, which acts as the bidentate ligand with substituted pyridines. *In vitro* evaluation of the synthesised complexes against human leukemia cell line HL-60 was undertaken, which revealed significant but largely comparable cytotoxicity values.



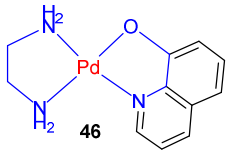
R = 4-Me (**45a**), 4-OH (**45b**), 4-NH_2 (**45c**)

Cancer cell line: HL-60

Figure 20: Ethylenediamine coordinated palladacyclic complexes containing additional substituted pyridines.

Recently, Mansouri-Torshizi and co-workers reported the simple and efficient synthesis of ethylenediamine modified 8-hydroxyqunolinato palladium(II) complex and its evaluation against calf thymus DNA binding was carried out as the first step towards assessing its potential as antitumour agent (**46**, Figure 21).[124] Preliminary results for the complex **46** suggested strong intercalation with the DNA, which could bring about a reduction in DNA replication and cell proliferation, a key

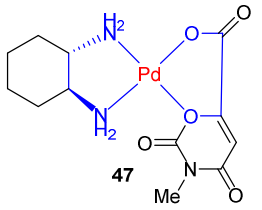
parameter for determining antiproliferative activity. Based on these results, complex **46** was tested for cytotoxicity against the leukaemia cell line, K562.[125] The activity was found to be lower than that compared to cisplatin.



Cancer cell line: K562 (0.08 μM)

Figure 21: Ethylenediamine 8-hydroxyquinolinato palladacyclic complex as potent anticancer agent.

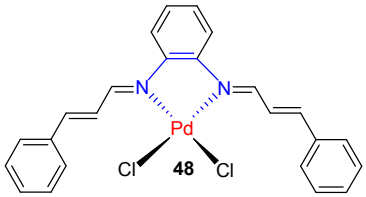
To demonstrate the potential of *trans*-1,2-cyclohexadiamine ligand backbone containing palladacyclic complexes antiproliferative compounds, Wimmer and co-workers synthesised 2-methylorotate coordinated palladacyclic complex (part of their study with palladacyclic complexes given in ref. 107).[107] Variation in ligand backbone compared to complex **37** (Figure 22) brought about a dramatic improvement in the antitumour activity for **47** against human cancer cell line Sarcoma 180, while a slightly lower activity was obtained against P388 leukemia cancer cell line. This result suggests the importance of strongly-chelating ligands and their activity enhancing effect compared to relatively smaller anionic ligands such as Cl and NO_3.



Cancer cell lines: Sarcoma 180 and P388

Figure 22: Cyclohexadiamine ligand backbone for promising antitumour activity for palladacyclic complexes.

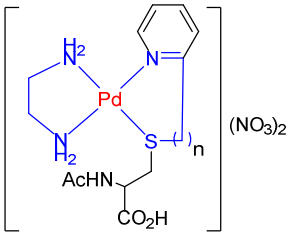
Independent studies by Gouvea and co-workers investigated an imine-based ligand backbone for complexation with palladium and the resultant complex **48** was evaluated against MDA-MB-435 human breast adenocarcinoma cell lines (**48**, Figure 23).[126] *In vitro* studies on the cell lines were performed using the sulforhodamine B (SRB) colorimetric assay[127] along with cisplatin as the reference standard suggested induced alteration in cell morphology, indicating cytoskeleton disruption.



Cancer cell line: MDA-MB 435 (1 μM)

Figure 23: Imine ligand backbone containing palladacyclic complexes as antineoplastic agent.

van Eldik and co-workers elegantly demonstrated the use of *L*-cysteine amino acid derived ligands alongside the bidentate ethylenediamine to obtain cationic Pd(II) complexes (**49a,b**, Figure 24).[128] Although these complexes were never tested for cytotoxicity the approach employed for their synthesis presents researchers with an opportunity to obtain more potent water soluble palladium-based anticancer agents.



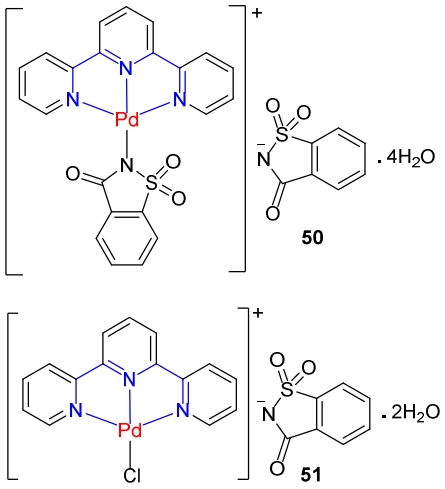
n = 1 (**49a**) or 2 (**49b**)

Figure 24: Amino acid derived cyclopalladated complexes.

2,2□:6□,2□□-Terpyridine structural motif is another class of chelating ligand systems exhibiting N,N,N-tridentate coordination with different metal ions. Their importance expands from catalytic applications and optoelectronics to their use in life science applications. The area has been systematically reviewed recently by Newkome.[129] Although the bioorganic and medicinal chemistry aspects of the Pd and Pt complexes[130] with 2,2□:6□,2□□-terpyridine are known, their cytotoxic activity has been recently evaluated for two novel palladacyclic complexes.

First, complex **50** that was synthesised by Ulukaya and co-workers was tested for *in vitro* evaluation against human breast cancer cell lines MCF-7 and MDA-MB-231 (**50**, Figure 25).[131] Excellent antiproliferative activity observed for complex **50** was further confirmed in an *in vivo* Ehrlich ascites model on Balb/c mice by the inoculation of tumours and comparison of the tumour sizes with cisplatin and paclitaxel. Results obtained from this comparative study suggested significant reduction in the size of the tumours for complex **50** and paclitaxel with only a single mice death from 10 (mices) at relatively low concentrations to that of cisplatin (2 deaths out of 10). Induced apoptosis was proposed to be taking place through cell death genes of DR4 and DR5.

To identify potent anticancer agents, extensive studies were undertaken on a structurally-similar complex **51** (substitution of saccharinate ligand in **50** with chloro on the palladium centre) by Ulukaya and co-workers (**51**, Figure 25).[132]

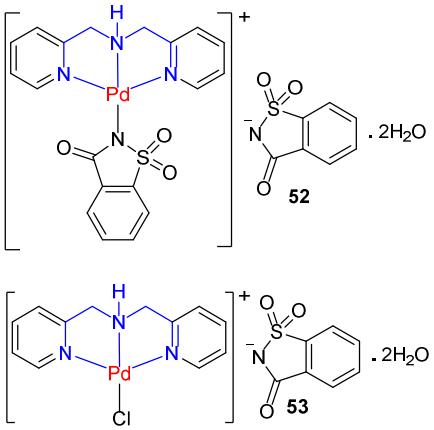


Cancer cell lines: PTNT1A, PNT2-C2, BPH-1, P4E6, PC-3 and LNCaP

Figure 25: Terpyridine-based palladacyclic complexes as highly potent anticancer agents.

In vitro cytotoxicity screening were performed against a series of six prostate cancer cell lines, namely PTNT1A, PNT2-C2, BPH-1, P4E6, PC-3 and LNCaP with the complex **51** inhibiting the growth at lower IC_{50} values in most cases other than PNT2-C2 (lower antiproliferative activity observed for **50**). The study was further extended towards understanding the cytotoxic effect of complex **51** on primary cultures obtained from seven Gleason 6/7 prostate cancers, three Gleason 8-9 prostate cancers, four benign prostate hyperplasia patient samples and few cancer stem cells.

Past studies on cytotoxicity analysis have revealed the beneficial effects of improved solubility of palladium complexes than their platinum analogues.[133] A more attractive alternative is in the employment of lypophilic palladium-based complexes for antitumour activity and with the view of achieving better cytotoxicity Ulukaya and co-workers developed both palladium and platinum complexes possessing a bis(2-pyridylmethyl)amine (bpma) ligand backbone which assists in imparting N,N,N-tridentate coordination (**52** and **53**, Figure 26).[134] The palladium complexes **52** and **53**, along with their platinum counterpart's, were tested against human breast cancer cell lines MCF-7 and MDA-MB-231 using MTT assay and further confirmed by ATP assay. An appreciable reduction in tumour cell growth was observed for complexes **52** and **53**, represented by lower IC_{50} values than the platinum counterpart's. This result points towards the potential of these complexes to bring about apoptosis more efficiently and warrants further investigations which were undertaken on complex **52** (more active than other complexes).



52: *MCF-7 (18.7 μM), MDA-MB 231 (9.3 μM)*
53: *MCF-7 (3.9 μM), MDA-MB 231 (4.2 μM)*

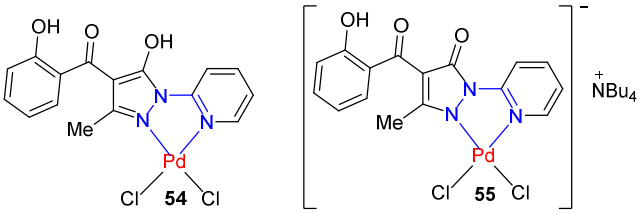
Figure 26:Bis(2-pyridylmethyl)amine coordinated palladium complexes.

One of the most malignant forms of tumours with a relatively high fatality rate are the fibrosarcomas.[135,136] In recent years a number of chemotherapeutic agents have been developed that have proven to be effective against the sarcomas.[137-139] Metal-based chemotherapeutic agents and especially platinum complexes are more effective.[140] With the quest for developing more potent metal-based anticancer drugs for the treatment of these malignant sarcomas, Ulukaya and co-workers subjected the most active complex **52** in their *in vitro* studies,[134] against mouse embryonic fibroblast NIH/3T3(normal cell line) and rat embryonic fibroblast 5RP7 (H-ras transformed cell line) using both an MTT assay and ATP assay.[141,142] The results suggested a marked improvement in the cytotoxicity of complex **52**. To determine the mode of cell death (apoptosis or necrosis) the team initially performed flow cytometry analysis, that revealed apoptosis as the possible pathway for cell death. This was later confirmed by triple-staining the cells with 'Hoechst 33342/Pl/Calcein AM triple' resulting in the formation of a pyknotic nucleus.

In the earlier sections we have gathered examples of palladium complexes derived from a privileged class of coordinating-nitrogen ligands. With the possibility of achieving improved cytotoxic activity researchers have explored alternatives (*i.e.* ligands),[143] coming-up with several possibilities which will be the part of the discussion of this section.

In one such study Budzisz and co-workers disclosed the synthesis of a series of palladacyclic (M = Pt and Pd) complexes **54-56** using a modified pyrazole ligand (acylpyrazolone),[144] derived from substituted coumarin and 2-hydrazinopyridine (Figure 27).[145] A cisoidal arrangement of the pyrazole ligand was confirmed in the palladacyclic complexes by X-ray crystallographic analysis. The antiproliferative activity for complex **54** (and its platinum analogue) were performed on human acute leukaemia HL-60 and NALM-6 cancer cell lines with the commercial anticancer drugs cisplatin

and carboplatin serving as reference standards. Although the cytotoxicity for both complexes was observed to be similar to carboplatin, a slightly higher potency was exhibited by cisplatin.



54: *HL-60 (7.0 μM) and NALM-6 (8.3 μM)*

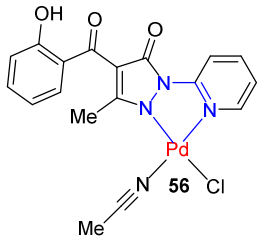
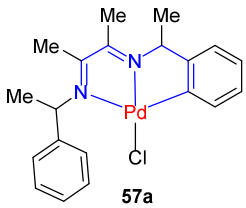


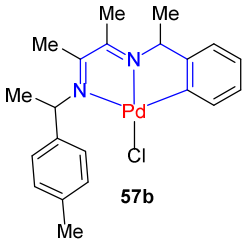
Figure 27: Acylpyrazolone ligand based palladacyclic complexes.

Further analysis of the complex **54**, its platinum analogue and the free ligand was carried out by testing the alkylating properties[146] using the Preussmann test[147] (test involves the quantification of levels of alkylation of 4-(4-nitrobenzyl)pyridine (NBP) by spectrometric analysis at 560 nm). Depending on the absorbance's obtained for each of the complexes a moderate response was observed in each case (appreciable differences in activity were not observed).

Chiral diimines have also been employed as chelating ligands with differing coordination possibilities. One of the examples for their application as a multidentate ligand was explored recently by Gutierrez and co-workers towards the synthesis of two air-stable cyclopalladated complexes (**57a,b**, Figure 28).[148] The complexes were tested *in vitro* against a series of human cancer cell lines U251 (CNS), PC-3 (Prostate), K562 (Leukaemia), HCT-15 (colon) and MCF-7 (breast). Relative to cisplatin, the palladium complexes were less effective although in certain cases appreciable cytotoxicity was observed (mainly against U251 and K562 cancer cell lines). Complex **57b** outperformed **57a** in terms of IC_{50} value obtained against most cell lines (only MCF-7 was an exception with complex **57a** showing better activity).

Modified-pyrazole derivatives demonstrating bi and tridentate coordination were recently synthesised with the purpose of preparing novel palladacyclic and cyclopalladated complexes (M = Pt or Pd) (**58a-c** and **59**, Figure 29).[149] Initially, the ligands along with the complexes were tested for *in vitro*antimalarial activity (*Plasmodium falciparum strains* 3D7 and W2). Cytotoxicity studies were next performed on the complexes against lung (A549) and breast (MDA MB231 and MCF7) cancer cell lines with the platinum analogue of complex **59** found be the most active amongst the tested complexes.

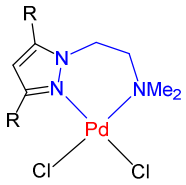




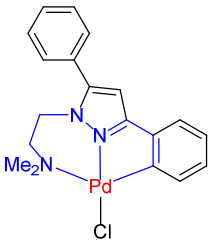
57a: *U251 (CNS) 23.6 μM, PC-3 (Prostate) 100 μM, K562 (Leukaemia) 25.4 μM, HCT-15 (colon) 100 μM and MCF-7 (breast) 88.5 μM*
57b: *U251 (CNS) 19.8 μM, PC-3 (Prostate) 51.5 μM, K562 (Leukaemia) 22.5 μM, HCT-15 (colon) 54.3 μM and MCF-7 (breast) 93.3 μM*

Figure 28: Chiral diimine based cyclopalladated complexes.

Palladacyclic complexes **58a-c** were comparatively lower in their cytotoxic response against the cell lines but a better response was achieved in comparison to the free ligands.



R = H (**58a**): *A549 (100 μM), MDA-MB231 (100 μM) and MCF7 (100 μM)*
Me (**58b**): *A549 (73.5 μM), MDA-MB231 (100 μM) and MCF7 (100 μM)*
Ph (**58c**)

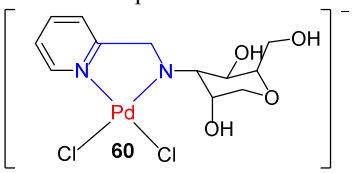


59: *A549 (38.5 μM), MDA-MB231 (16.2 μM) and MCF7 (38.4 μM)*

Figure 29: Cytotoxicity studies of N,N and C,N,N-ligand coordinated palladacyclic (**58a-c**) and cyclopalladated (**59**) complexes.

Cancer cells during their growth process are known to take high levels of glucose in comparison to the normal cells (an effect described as the *Warburg effect*).[150] Synthesis of several non-metallic glycoconjugated drugs with good cytotoxicity, improved solubility and tumour selelctivity was achieved recently.[151,152] To improve the cytotoxicity further, a novel synthetic route was designed for the preparation of glycoconjugated palladacyclic complexes of platinum and palladium (Figure 30).[153] To investigate the cytotoxic activity of the prepared complexes, CCDP (cisplatin)-resistant human gastric cancer cell lines (MKN28 and MKN45) were first obtained by continuous exposure to cisplatin. *In vitro* studies were performed on four different cell lines MKN28 (0-normal gastric cancer cell lines), MKN28 (CCDP), MKN45 (0) and MKN45 (CCDP). The palladacyclic complex **60** was found to induce apoptosis and the cytotoxicity levels were found to be

lower than CCDP but higher than CABDA. However, in the case of DNA double strand breaks induction for CCDP-resistant gastric cancer cell lines, complex **60** outperforms most of the other complexes. Finally, *in vivo* studies on a xenograft tumour model, established by subcutaneous implantation of the gastric cancer cell lines into mice and treatment with the different complexes, showed that complex **60** suppressed tumour growth in both CCDP-resistant gastric tumour cells significantly than others. The strategy of conjugating glucose with metals such as palladium therefore seems to be a useful and effective strategy for bringing about a significant enhancement in cytotoxic activity compared to the non-conjugated gluco-based compounds.



MKN28 (78.9 μM), MKN28 (CDDP) (80.8 μM), MKN45 (61.2 μM), MKN45 (CDDP) (69.7 μM)

Figure 30: Glucoconjugated palladacyclic complexes as potential anticancer drugs.

3.2. Carbon-based Multidentate ligands:

In the earlier section we have seen the activity enhancing effect of cyclopalladated complexes containing nitrogen-coordinated bi and tridentate ligands. A comparative account of the carbon-based ligands is made below for anticancer activity against a variety of cancer cell lines.

Newkome and co-workers suggested the importance of bipyridyl and phehanthroline ligand backbone and their activity enhancing effect on the antitumour properties (Figure 14), which was elaborated with respect to the presence of N,C-type ligand coordination.[107] In this case too, studies were focused toward understanding their interactions on Phage PM2 DNA (Figure 31).

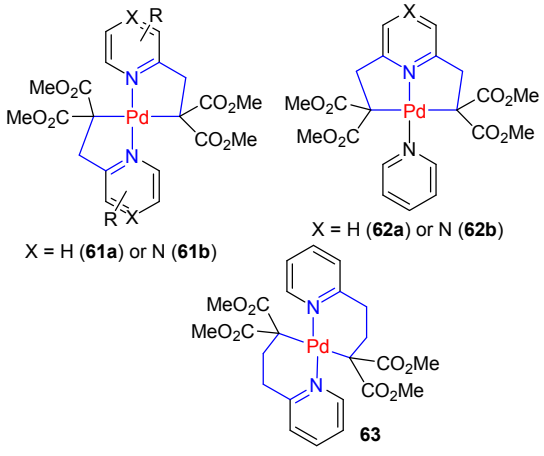
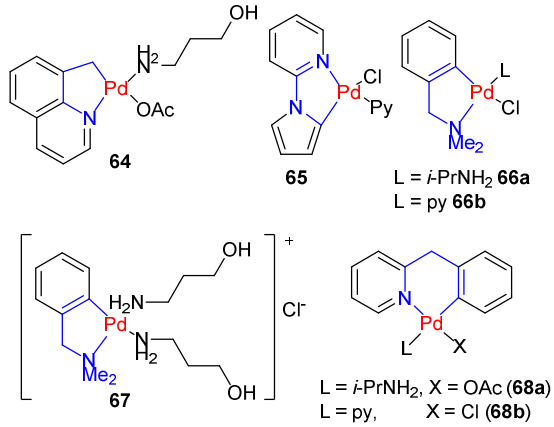


Figure 31: Pyridine-based C,N-coordinated cyclopalladated complexes.

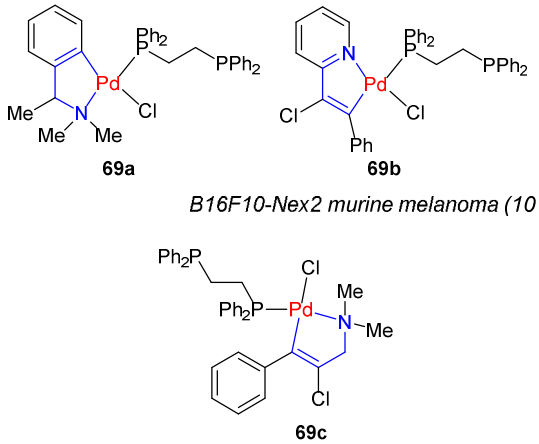
Another example for the employment of N,C-type coordinating bidentate ligand (Figure 32) was reported by Higgins III and co-workers as a part of their work directed toward developing antitumour active cyclopalladated complexes.[110] An extensive cytotoxicity study against a series of seven cancer cell lines was carried out *in vitro*on complexes **64-68** with complexes **66a** and **66b** showing differential activity and therefore portraying as a promising lead for further *in vivo* studies.



Cancer Cell lines: SW6020, SW1116, SW403, ZR75-1, HT29/219, HT1376, SK-OV-3

Figure 32: C,N-coordinated cyclopalladated complexes.

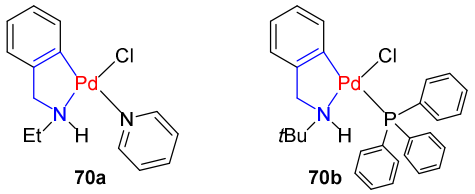
Biphosphines are important ligand backbones exhibiting differential bite angle on metal coordination. Diphenylphosphinoethane (dppe) is one such example that provides both mono and bidentate coordination modes. These ligands were recently employed in the development of antitumour cyclopalladated complexes **69a-c** (Figure 33).[154] Whilst dppe generally exhibits bidentate metal coordination, monodentate coordination with palladium was observed in this study. The synthesised complex **69b** was the only one tested *in vitro* and *in vivo* against syngeneic B16F10-Nex2 murine melanoma cancer cell line that were implanted subcutaneously in mice.



B16F10-Nex2 murine melanoma (10 μM)

Figure 33: Biphosphine-based cyclopalladated complexes

Karimi and co-workers, have disclosed the synthesis of mononuclear benzylamine-based cyclopalladated complexes **70a** and **70b** from initially prepared dimeric Pd complexes (Figure 34).[155] These complexes, along with cisplatin as the reference standard, were tested *in vitro* against a series of cancer cell lines such as HeLa (human cervix carcinoma), HT-29 (colon cancer cell), K562 (leukemia cancer cell line) and MDA-MB-468 (human breast carcinoma). Better cytotoxicity values were observed for the synthesised complexes than the commercially available cisplatin.

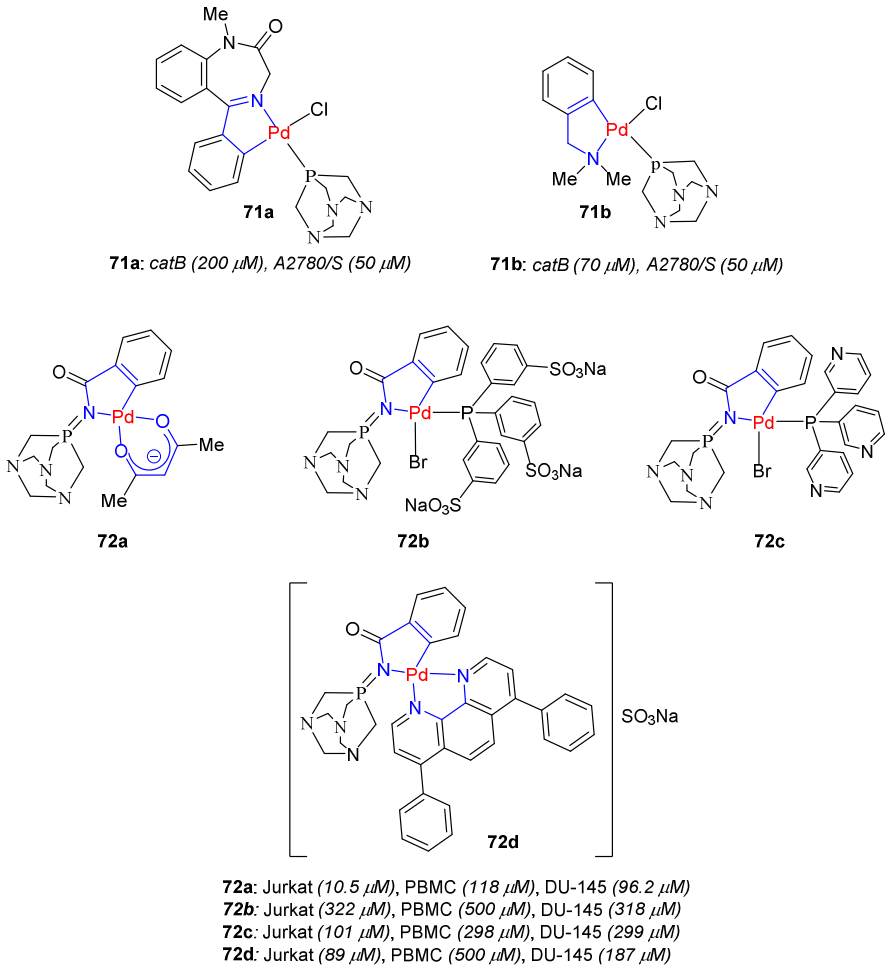


Cancer cell lines: HeLa, HT-29, K562 and MDA-MB-468

Figure 34: Benzylamine as ligand scaffold for cyclopalladated anticancer agents.

The water solubility of the cyclopalladated complexes is a desired property. Spencer and co-workers utilised the beneficial water solubilising properties of the PTA ligand (PTA = 1,3,5-triaza-7-phosphaadamantane) towards the synthesis of monomeric cyclopalladated complexes containing substituted diazepin-2(*3H*)-one and *N,N*-dimethylbenzylamine(dmba) as bidentate ligands (**71a,b**, Figure 35).[156] Several other complexes were also prepared and tested *in vitro* against A2780/S cancer cell line with **71a** exhibiting good activity while lower cytotoxicity was observed for complex **71b**.

In keeping with the above data, Contel and co-workers developed more elaborate water-soluble cyclopalladated complexes which were tested *in vitro* against human Jurkat-T acute lymphoblastic leukemia cells, normal T-lymphocytes (PMBC) and DU-145 human prostate cancer cells. Of all the complexes, **72a** exhibited excellent cytotoxicity against the given cancer cell lines (**72a-d**, Figure 35).[157] In addition, complex **72a** was found to be toxic towards cisplatin resistant Jurkat shBak. These results suggest that the cytotoxicity enhancing effect on different cancer cell lines could be brought about by improvement to the water-soluble nature.



72a: Jurkat *(10.5 μM)*, PBMC *(118 μM)*, DU-145 *(96.2 μM)*
72b: Jurkat *(322 μM)*, PBMC *(500 μM)*, DU-145 *(318 μM)*
72c: Jurkat *(101 μM)*, PBMC *(298 μM)*, DU-145 *(299 μM)*
72d: Jurkat *(89 μM)*, PBMC *(500 μM)*, DU-145 *(187 μM)*

Figure 35: C,N=coordinated cyclopalladated complexes as potential anticancer agensts.

3.3. Sulphur based bidentate ligands

Sulphur-containing ligands have found importance due to the unique coordination mode presented towards metal corrdination. In recent years some of the most commonly employed sulphur-containing ligands like thiocarbonyls and thiols for the development of metal-based (platinum) chemotherapeutic agents.[158,159]

Thiosemicarbazones are important synthetic scaffolds that are obtained by a condensation reaction between an aldehyde and thiosemicarbazide.[160] These molecules have consistently exhibited promising pharmacological activity against a wide range of parasites, bacterias and cancer cell lines.[161-165] Their coordination chemistry with different transition metals is also well-established; several reviews highlight this aspect.[166-168] In this section, mononuclear palladacyclic or cyclopalladated complexes containing bidentate thiosemicarbazones are discussed.

The chelating strength of thiosemicarbazones has widely been utilised; the palladium-coordinated thiosemicarbazone complexes represent the latest addition to a long list of other transition metal complexes. In this respect Navarro-Ranninger and co-workers[169-171] exploited the strong chelating properties of thiosemicarbazones to synthesise cyclopalladated complexes (**73**, Figure 36). Although, the complex was not tested for any cytotoxic activity, it laid the foundation for the application of thiosemicarbazones coordinated complexes as possible anticancer agents.

The considerable antineoplastic potential of thiosemicarbazone-coordinated palladacyclic complexes was first investigated by Quiroga and co-workers.[172] The thiosemicarbazone was synthesised using phenyl acetaldehyde as the starting material which was then complexed with palladium to afford palladacyclic complex **74** (Figure 36). The complex was then tested *in vitro* against several human and murine cancer cell lines that are sensitive or resistant to cisplatin. The results obtained in terms of the IC_{50} values point strongly towards the potential of complex **74** as an anticancer agent. The cytotoxicity was also found to be better than cisplatin as well as two other commercial drugs namely, etoposide and adriamycin.

The success obtained by the complexation of thiosemicarbazones to palladium towards better cytotoxicity against cancer cell lines was further exploited by Souza and co-workers.[173] A series of substituted-thiosemicarbazones were synthesised and complexed with palladium to give palladacyclic complexes. One of the represented complexes **75** consists of a thiosemicarbazone ligand that exhibits tetracoordinate chelation due to the presence of four donor atoms (**75**, Figure 36). This complex was tested for *in vitro*cytotoxic activity against several human, monkey and murine cancer cell lines, HeLa, Vero and Pam 212. Similar cytotoxicity, to that shown by cisplatin, was obtained in the case of complex **75**.

Natarajan and co-workers utilized the coordination propensities of a diethylaminosalicylaldehyde-substituted thiosemicarbazones towards coordination to palladium leading to the formation of palladacyclic complexes **76a-d** (Figure 36).[174] Initial studies on the complexes were centered on exploring their binding ability towards calf-thymus DNA which suggested an intercalating binding mode. MTT assays for cytotoxic activity performed on complex **77c** exhibited higher cytotoxicity against human lung cancer cell line (A549) and liver cancer cell lines (HepG2). These complexes were subjected to antibacterial studies against pathogenic bacterias.

Natarajan and co-workers further synthesised several methoxysalicylaldehyde substituted thiosemicarbazone derived palladacyclic complexes **77a,b** and **78a,b** (Figure 36).[175] A similar series of studies to that of the above mentioned complexes were performed. Anticancer activity was performed by MTT assay against lung cancer cell line A549. Improved cytotoxic activity was obtained in comparison to cisplatin and doxorubicin at lower incubation period as compared to most other reports, involving longer incubation periods.

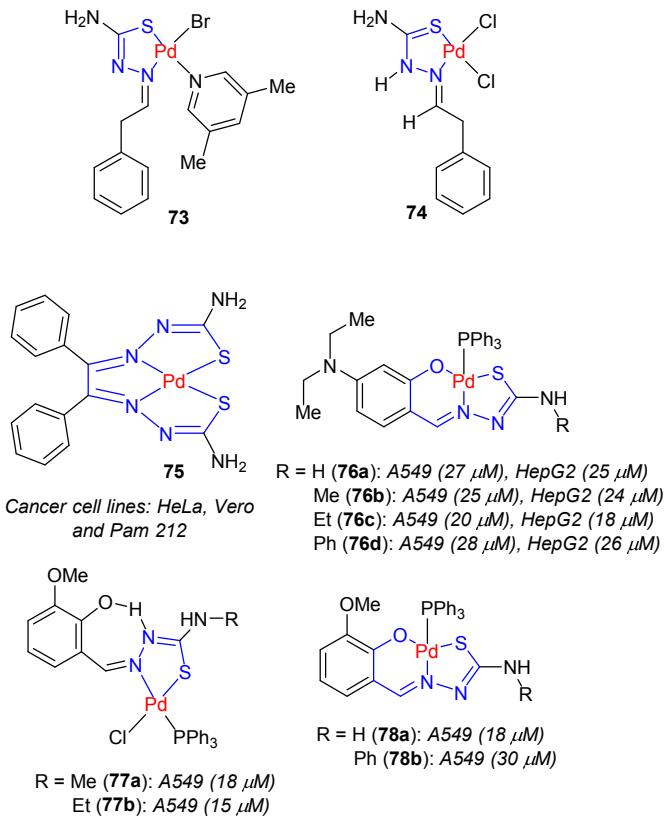
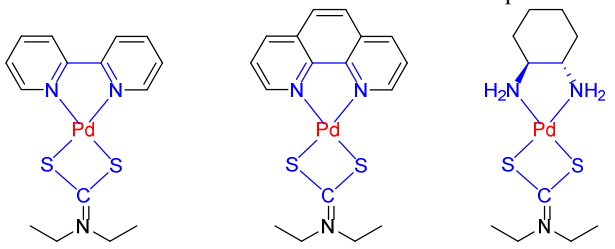


Figure 36: Thiosemicarbazone-based palladacyclic complexes as anticancer agents.

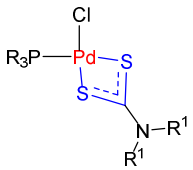
One of the most commonly applicable ligand systems for obtaining an S,S-type coordination possibility to different metal ions are the dithiocarbamates, due to their capacity to bind strongly to the transition metals.[176] This property of the

dithiocarbamates has provided researchers with a useful handle to synthesise a variety of transition metal complexes which on evaluation for antiproliferative activity, have shown considerable promise.[177-179]

For investigating the cytotoxic activity enhancement for metal-coordinated dithiocarbamates complexes, Srivastava and co-workers synthesised three palladacyclic complexes possessing 2,2□-bipyridine, 1,10-phenanthroline and 1,2-diaminocyclohexane ligands (**79a-c**, Figure 37).[180] Their potential as anticancer agents was tested *in vitro* against P388 lymphocytic leukemia cancer cell lines, with IC_{50} values that were found to be lower than those observed for cisplatin.



Cancer cell lines: P388 lymphocytic leukemia cancer



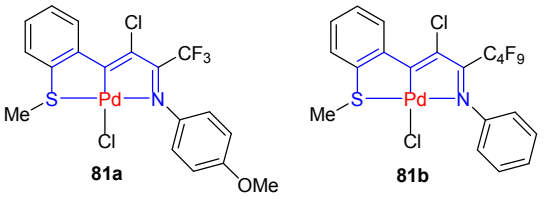
PR_3 = PPh_2(benzyl) (**80a**) (3.67 μM), PPh_2(o-tolyl) (**80b**) (9.52 μM), PPh_2(*t*Bu) (**80c**) (4.57 μM), PPh_2Cl (**80d**) (21.7 μM), PPh_3 (**80e**) (2.12 μM)
R^1 = ethyl, butyl, propyl, 2-methoxy ethyl

Cancer cell line: DU145 prostate carcinoma (HTB-81)

Figure 37: Dithiocarbamates-based palladacyclic complexes.

As a part of their efforts to synthesise palladacyclic complexes containing dithiocarbamate ligand backbone,[181] Badshah and co-workers developed an efficient route for obtaining such complexes via ligand displacement reaction with the commercially available palladium(II) precursor $PdCl_2(PPh_3)_2$ (Figure 37).[182] The phosphine based complexes were evaluated against DU145 human prostate carcinoma (HTB-81) cancer cells for anticancer activity. An interesting correlationship between the size of the phosphine ligand on the palladium centre and the activity exhibited by each complex was observed. Complex **80e** was found to be the most active followed by other complexes **80a-d** (the bulkier the phosphine ligand the lower the activity recorded).

LakshmiKantama and co-workers recently reported the synthesis of two novel SCN pincer cyclopalladated complexes by the employment of substituted thioanisole ligand (**81a,b**, Figure 38).[183] The complexes initially were employed as catalysts for performing synthetically challenging cross-coupling processes and was later tested against three human leukemia cell lines, HL60 (Human promyelocytic leukemia cells), K562 (Chronic myelogenous leukemia) and CCRF-CEM (Human acute lymphocytic leukemia). Complex **81a** was found to exhibit highest inhibition against all the three cancer cell lines, thus portraying excellent antitumour activity.



81a: *HL60 (4.8 μM), K562 (5.1 μM), CCRF (4.9 μM)*
81b: *HL60 (19.9 μM), K562 (9.9 μM), CCRF (19.9 μM)*

Figure 38: Thioanisole-based cyclopalladated antitumour agents.

3.4. Phosphorus based ligands

Phosphorus-containing compounds have proven to be the most important scaffolds in terms of their applicability in biomedical field[184]. The application of phosphine-coordinated metal complexes for tumour treatment has been more nascent with only few examples reported in literature which will be discussed in this section.

Continuing on the use of biphosphine ligand dppe (bidentate coordination), Travassos and co-workers employed these ligand substrates towards the development of antitumour cyclopalladated complexes **82a-c** (Figure 39).[154] In comparison to the monodentate-coordinated dppe complexes (Figure 33) these complexes when tested *in vitro* and *in vivo* against B16F10-Nex2 murine melanoma cancer cell lines, that were implanted subcutaneously in mice, showed lower cytotoxicty. Complexes **82b** and **82c** were found to be most active.

Another interesting example of bidentate phosphine (diphenylphosphino propane, dppp)-coordinated palladacyclic complex containing dimethylbenzylamine (dmba), isothiocyanate ligands as possible anticancer agents was recently revealed by Carlos and co-workers (**83**, Figure 39).[185] An MTT assay established that complex **83**,when tested against Ehrlich ascites tumour[186-188] (EAT) in mice, revealed a lower IC_{50} value than that of cisplatin. *In vivo* studies were performed on mice; the mice population were divided into five groups, and on inoculation with complex **83** and cisplatin, they were evaluated for different parameters such as tumour cell percentage in the peritoneal exudate, levels of seric nitric oxide (NO) and tumour necrosis factor-alpha (TNF-α) and increase in life span. It was deduced that complex **83** shares similar activity with cisplatin.

Structurally-related palladacyclic complex **84**[189] to the one discussed above (replacement of isothiocyanate by chloro ligand) was evaluated for antitumorigenic potential against MDA-MB-435 human breast adenocarcinoma cancer cell line (cell lines not expressing estrogen receptor α (-ER) (**84**, Figure 39).[126] *In vitro* studies on the cell lines revealed growth inhibition effect represented by lower IC_{50} value. The cytotoxic

studies thus revealed decreasing cell growth and induced apoptosis.

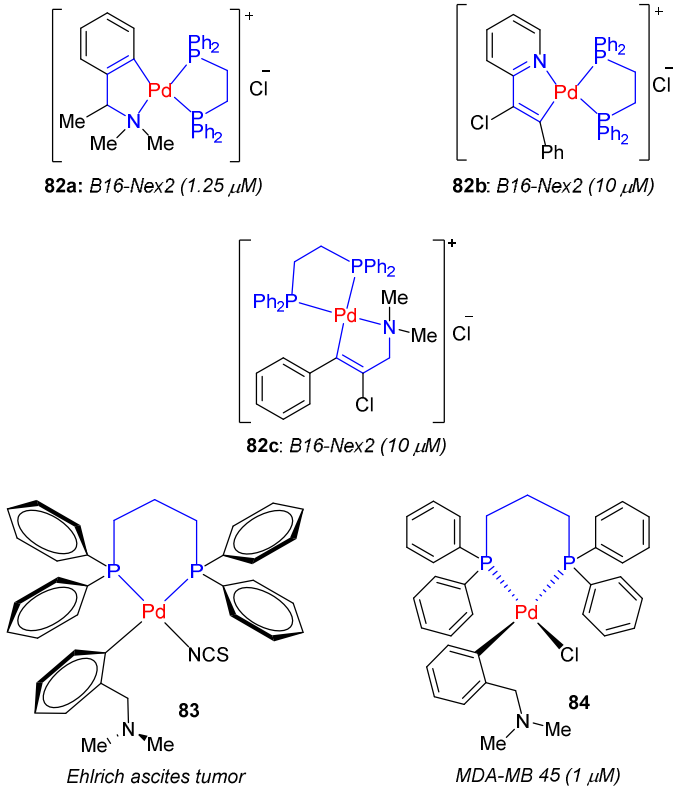


Figure 39: Dppe or dppp-based cyclopalladated and palladacyclic complexes.

In the earlier section we discussed the utility of monomeric palladacyclic and cyclopalladated complexes as antitumourogenic agents, including their potential to inhibit cancer cell growth as a comparison with either cisplatin or commercial anticancer drugs. Palladium as the central metal atom has played a key role for the better activity of these complexes due to its binding capacity to DNA (better than platinum). In view of this ability of palladium, it was envisaged by several researchers that by increasing the palladium content would allow better cytotoxicity to be achieved towards different cancer cell lines. The verification of this proposal for the possible enhancement in activity will therefore be the focus of this section.

4. Dimeric Cyclopalladated or Palladacyclic Complexes

One of the earliest examples of dimeric cyclopalladated complexes **85** and **86** obtained as adducts from the reaction of $PdCl_2$ with Diazepam and Prazepam was reported in 1988 by Manassero and co-workers (**85** and **86**, Figure 40).[190] Diazepam and Prazepam belong to the benzodiapine class of drugs that have found applications as muscle relaxants and are commonly used for the treatment of insomnia.[191,192] These molecules are capable of exhibiting monodentate coordination, however in this case a bidentate coordination mode with palladium resulted in the formation of the dimeric complexes **85** and **86**. No antitumour activity was reported for these complexes. However, the idea of coordinating commercial drugs with transition metals like palladium could present researchers with an important handle for developing highly-efficient metal-based combination therapeutic drugs.

Pioneering work by Navarro-Ranninger, which involved the synthesis of isostructural dimeric cyclopalladated complexes **87** and **88** derived from *N*-(4-methoxyphenyl)-α-benzoylbenzylidenamine as potential antitumourogenic complexes, laid the foundation for the rapid development of this area (*e.g.* **87** and **88**, Figure 40).[193] The antiproliferative activity of these complexes was tested *in vitro* against MDA-MB-468 (breast carcinoma) and HL-60 (leukemia) human cancer cell lines. IC_{50} values for the complexes (IC_{50} for **87** = 8.95 and 8.37 μM; **88** = 6.75 and 6.35 μM respectively) suggested inhibition in the growth of the cancer cells at relatively lower concentrations, however they are less effective than cisplatin.

In continuation of their study towards the use of putrescine or spermine, Navarro-Ranninger and co-workers[121] synthesised dimeric palladacyclic complexes **89** and **90** (Figure 40) with the aim of comparing their cytotoxicity to the monomeric complexes (Figure 19). The dimeric palladacyclic complexes **89** and **90** were then tested against MDA-MB 468 and HL-60 human cancer cell lines for *in vitro* antiproliferative activity. The antitumour activity was observed to be better than the monomeric complexes and comparable to that observed for cisplatin. These results again reiterate the potential of dimeric palladium complexes towards enhancing the cytotoxic activity.

Carlos and co-workers employed *N,N*-dimethylbenzylamine (dmba) ligand exhibiting bidentate ligand coordination towards the synthesis of a novel cyclopalladated complex **91** which was later used as a precursor for obtaining a phosphine bound cyclopalladated complex **91** (Figure 39) and was subsequently tested for *in vitro* and *in vivo* cytotoxic activity against Ehlrich ascites tumours in mice (Figure 40).[185] The activity however was found to be considerably lower than those for cisplatin (used as reference standard) suggesting a possible activity enhancing effect of the bidentate phosphine employed in complex **91**.

Imidazoline-based halide and pseudo-halide bridged dimeric cyclopalladated complexes were recently disclosed by Navarro-Ranninger and co-workers (**92a-c**, Figure 40).[194] Initial studies performed on the complexes were focussed towards determining the possible alterations in the melting temperatures of DNA brought about by the drug-DNA interactions, indicating a change in DNA conformation (B type). This was determined by the change in the circular dichroism spectra, which was pronounced in the case of complexes **92b** and **92c**, while the complex **92a** showed little change compared to others. *In vitro* antiluekaemic cytotoxicity studies were also performed on complex **93c** against HL-60 human leukaemic cancer cell lines with comparable activity observed to cisplatin.

Another example of halide-bridged dimeric cyclopalladated complexes was put forth by Tusek-Bozic and co-workers as a part of their study to understand the effect of phosphonates on

the cytotoxic activity (**93a** and **93b**, Figure 40).[195] The complexes **93a** and **93b** were evaluated against human epidermoid KB cell line and were found to be comparable to the monomeric cyclopalladated complexes reported by the same group (Figures 1 and 2).

Similarly, Guiterrez and co-workers during their study towards the synthesis of enantiomerically pure palladium complexes using containing chiral ligand (*S*)-(-)-(1-phenylethylimino)benzyl phenyl ketone, alongwith the monomeric palladium complex **6** (see Figure 5) also obtained a dimeric cyclopalladated complex **94** which was evaluated against a series of cancer cell lines such as U251 (CNS), PC-3 (prostate), K562 (leukaemia), HCT-15 (Colon) and MCF-7 (Breast) with cisplatin being used as a reference standard (**94**, Figure 40).[38b] A direct comparison of the IC_{50} values showed that the dimeric complex **94** outperforms the monomeric *trans*-palladium complex **6** (**6**, Figure 5), although relatively lower activity to that of cisplatin was observed.

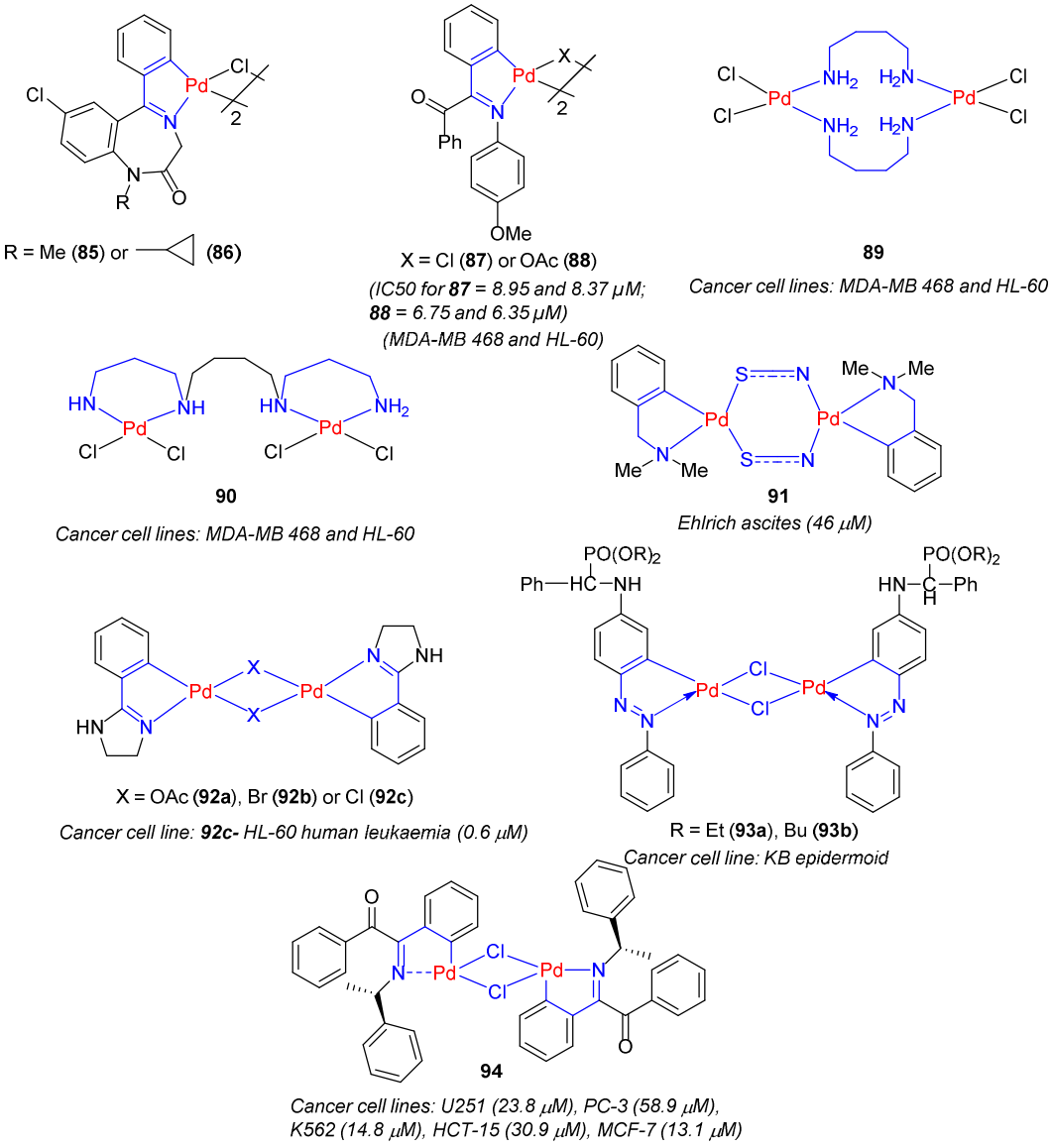


Figure 40: Potential of dimeric palladacyclic or cyclopalladated complexes as anticancer drugs.

Travassos and co-workers recently reported on an efficient route to synthesise phosphine-based dimeric cyclopalladated complexes (dppe as bidentate phosphine ligand) as a part of their an extensive study into the effect of cyclopalladated complexes as anticancer agents.[154] These dimeric complexes **95a-c** (Figure 41) were directly compared with their monomeric counterparts for *in vitro* and *in vivo* cytotoxic activity against B16F10-Nex2 murine melanoma cancer cell lines,which were implanted subcutaneously in mice showing lower cytotoxicty. The dimeric complexes were found to be highly active as compared to the other monomeric analogues. Complex **95c** was found to be the most active in the *in vivo* studies, prolonging animal survival by delaying tumour growth. These results are important indicators for the improvement in cytotoxicity brought about by the introduction of one more palladium atom in the complex structure. Recently, Rodrigues and co-workers

performed *in vitro* and *in vivo* studies against K562 human leukaemia cell lines using the dimeric cyclopalladated complex **95a** which was found to be highly-effective to promote cell death (**95a**, Figure 41).[196]

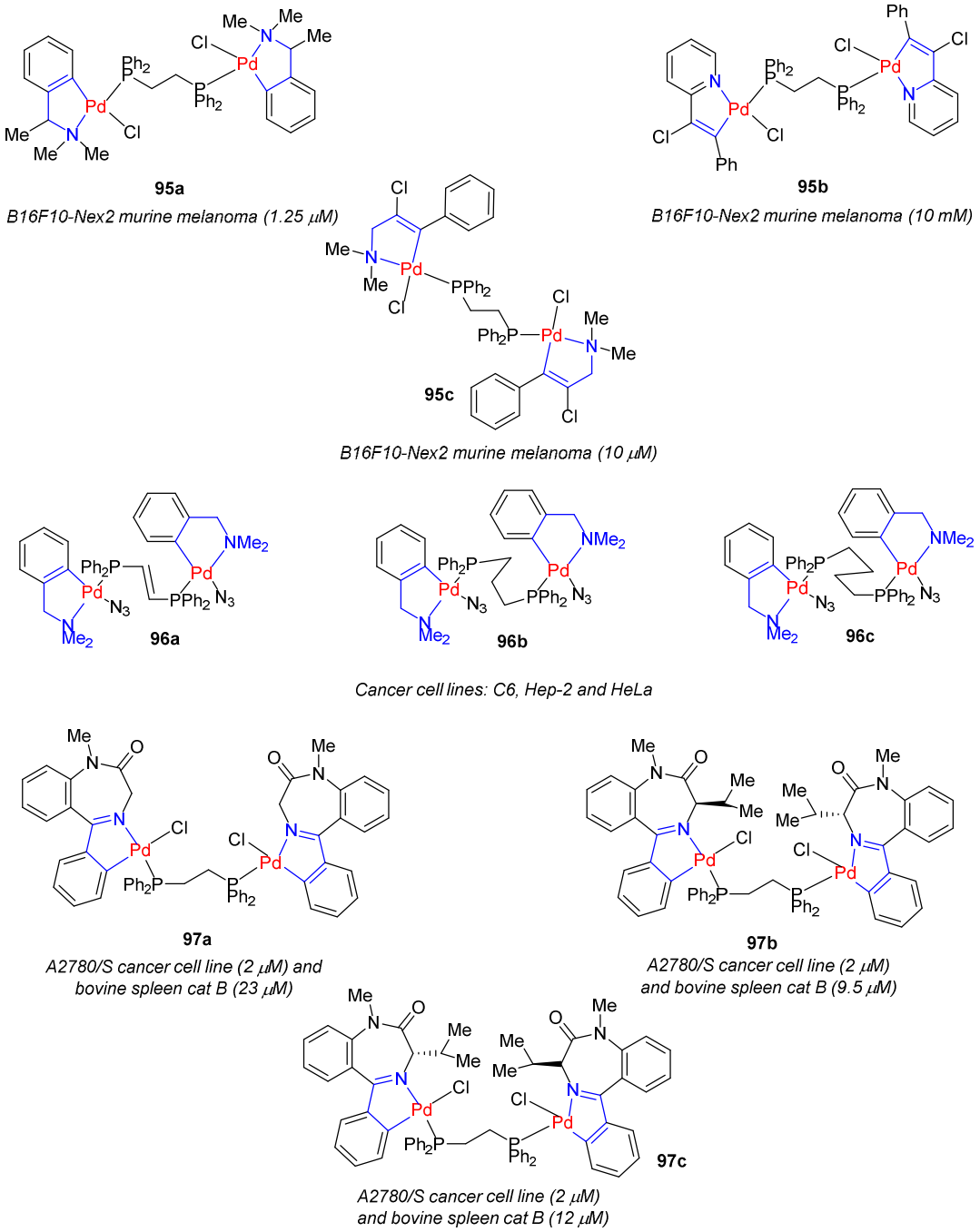


Figure 41: Phosphinated dimeric cyclopalladated complexes.

Caires and co-workers employed structurally similar dimeric cyclopalladated complexes containing coordinated azide and bidentate phosphines (*trans*-diphenylphosphinoethene, diphenylphosphinopropane and diphenylphosphinobutane) (**96a-c**, Figure 41) as potent anticancer agents against a panel of three human tumour cell lines such as C6, Hep-2 and HeLa.[189] The cytotoxic activity was found to be comparable in all the complexes irrespective of the ligand backbone employed.

As a continuation of the cytotoxicity studies performed by Spencer and co-workers against A2780/S cancer cell line and bovine spleen cat B, three novel dimeric phosphine-coordinated cyclopalladated complexes were synthesised (**97a-c**, Figure 41).[156,197] The complexes on evaluation against both cancer cell

lines showed exceptionally high cytotoxicity in comparison to their monomeric cyclopalladated analogues.

4.1. Palladacyclopropanes-Pd_2dba_3 as anticancer compounds.

$Pd^0_2(dba)_3$ (dba = E,E-dibenzylidene acetone) **98** is a convenient palladium source (Figure 42). In 2013, Fairlamb and co-workers recently reported[198] the solution and solid-state structure of $Pd^0_2(dba)_3$, which necessitated the use of isotopic labelling (^2H and ^{13}C) and high field NMR spectroscopic analysis at 700 MHz to complete the structural elucidation. Crucially, $Pd^0_2(dba)_3$ **98** exists as two freely-exchanging major and minor isomers. The dba ligands bind through the alkenes in the complex, forming an intricate network of metallocyclopropanes, which we refer to here as palladocyclopropanes.

Calculations by DFT have validated the experimentally-determined isomeric structures (Figure 42). The major isomer of $Pd^0_2(dba)_3$ possesses bridging dba ligands found in a s-*cis*,s-*trans* conformation, where the s-*trans* alkene binds more strongly to Pd^0 than the s-*cis* alkene.

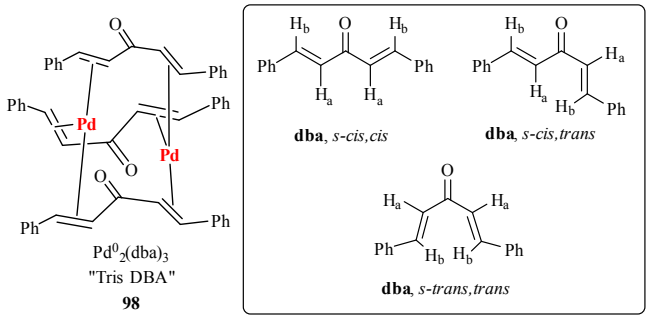


Figure 42: Structure of $Pd^0_2(dba)_3$ and conformations that can be adopted by the dibenzylidene acetone (dba) ligand – Note that s-*cis*,s-*cis* is the dominant conformer in the free ligand, whereas s-*cis*,s-*trans* is the dominant conformer in the complex.

Back-bonding to the s-*trans* alkene is therefore extensive and can be truly considered as a palladocycloproane moiety. Remarkably, one of the dba ligands in the minor isomer occupies a s-*trans*,s-*trans* 1,4-dien-3-one conformation. The single crystal X-ray diffraction analysis of several solvated $Pd^0_2(dba)_3$·solvent (solvent = $CHCl_3$, CH_2Cl_2 or benzene) indicates that each dba ligand is found over two positions.

With the structure of $Pd^0_2(dba)_3$ resolved it is interesting to consider its anticancer properties. In 2008, Arbiser and co-workers[199] reported the effects of this complex, referred to as Tris DBA in the report, against melanoma cell lines. Melanoma is a solid tumour that is often resistant to chemotherapeutic treatment. Unfortunately, its incidence is on the increase. The efficacy of Tris DBA toward proliferation of human (A375) and murine (B16) melanoma cells was examined both *in vitro* and *in vivo*; Tris DBA activity was recorded against both types of cells. The *in vitro* cell line data of Tris DBA shows it to be effective at a concentration of 10 mg/mL against B16, with a 99% decrease in cell count observed (the control vehicle was DMSO). Against A375 cells, a 96% decrease in cell count was recorded at the same concentration.

Subsequent experiments by Arbiser focussed on which receptors and pathways are affected by Tris DBA. It was found that Tris DBA inhibits the activation of certain protein kinases, *e.g.* MAPK (involved in directing cellular responses and regulating proliferation, gene expression, differentiation, mitosis, cell survival and apoptosis) and Akt (involved in glucose metabolism, apoptosis, cell proliferation, transcription and cell migration) in B16 cell lines. It is believed that this is achieved through inhibition of phosphorylated forms of these kinases, downstream. In A375 cell lines it was found that Tris DBA inhibits phosphorylated forms of S6-kinase (a phospho-S6 kinase), also down-regulating phosphor-Stat-3 (a transcription factor) during the early stages of incubation. Subsequent gene array experiments on A375 melanoma cells treated with Tris DBA revealed that the NMT1 gene was down-regulated (which was confirmed by reverse transcription-polymerase chain reaction), which encodes for N-myristoyltransferase 1. Purified human NMT when incubated with Tris DBA led to a concentration-dependent inhibition (max. inhibition at 2.5 +/- µmol/L), confirming that Tris DBA is a novel and potent inhibitor of NMT-1 activity. A significant advantage in using Tris DBA is that it inhibits several pathways required for melanoma tumourigenesis.

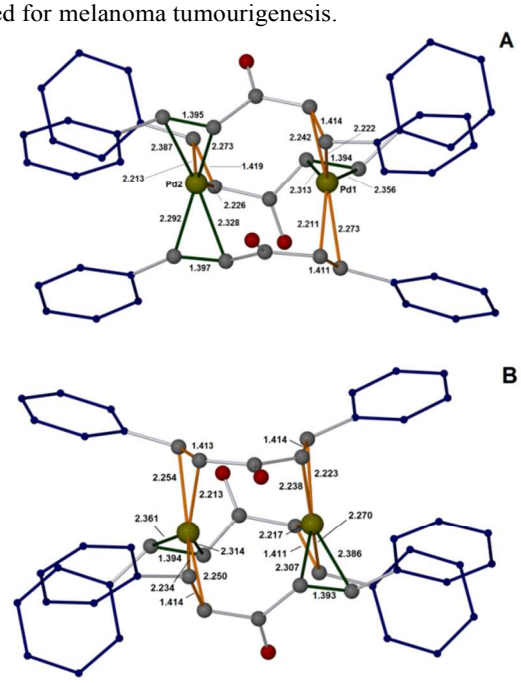


Figure 43: DFT calculated structures of the major isomer of $Pd^0_2(dba)_3$ (**A**) and the minor isomer of $Pd^0_2(dba)_3$ (**B**) (that is the most likely isomers in solution). The bonds shown in green highlight the s-*cis*alkenes and those shown in orange the s-*trans*alkenes. Reprinted (adapted) with permission from (A. R. Kapdi, A. C. Whitwood, D. C. Williamson, J. M. Lynam, M. J. Burns, T. J. Williams, A. J. Reay, J. Holmes, and I. J. S. Fairlamb, *J. Am. Chem. Soc.*, 2013, **135**, 8388–8399). Copyright (2014) American Chemical Society.

Finally, it was found that Tris DBA is well-tolerated *in vivo* (in mice) and has a novel inhibitory profile when compared against other clinical therapeutic compounds. It is perhaps of interest to

test other known[200] and related complexes of $Pd^0_2(dba)_3$ to explore their therapeutic effects further.

In the context of the anticancer activity of $Pd^0_2(dba)_3$ it is interesting to consider that the dba ligand itself exhibits anticancer properties, in that it inhibits cell growth and induces apoptosis in human oral cancer cell lines (*e.g.* HSC-2 and HSC-4 cells).[201] The mode of action of dba appears to derive from a down-regulation of specificity protein 1 (Sp 1), which is a protein involved in cell differentiation, cell growth, apoptosis, immune responses, *inter alia*; Sp1 contains a zinc finger transcription factor that binds to GC-rich motifs of many promoters. One question for Tris DBA – is the complex the active component in its own right, or simply a delivery vehicle (*i.e.* pro-drug) for free dba ligand? The solubility and efficacy of Tris DBA versus dba are different. Moreover, according to the studies which have been reported to date, it would appear that Tris DBA (complex) and dba (ligand) possess distinct modes of action.

5. Tetrameric Cyclopalladated Complexes

A significant improvement in cytotoxic activity was observed for dimeric cyclopalladated complexes compared to their monomeric counterparts. In continuation with this ideology the tetrameric cyclopalladated or palladacyclic complexes was envisaged as a more effective alternative towards identifying potential anticancer agents.

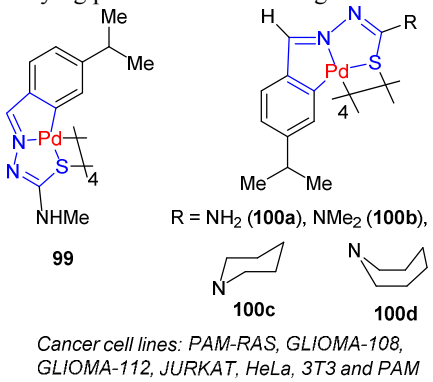


Figure 44: Tetrameric cyclopalladated complexes.

As a part of such a study Navarro-Ranninger and co-workers recently disclosed the synthesis of a novel tetrameric cyclopalladated complex (CH_3COOH coordinated complex **99** was also isolated-Figure 44).[202] The tetranuclearity[172] of the cyclopalladated complexes was made possible through the employment of *p*-isopropylbenzaldehyde substituted thiosemicarbazone.

These complexes were tested for antitumour properties against several tumour and normal cell lines like PAM-RAS, GLIOMA-108, GLIOMA-112, JURKAT, HeLa, 3T3 and PAM with cisplatin, etoposide and adriamycin as reference standards. The IC_{50} values exhibited by the complexes suggest that they have potential anticancer activities as the one shown by cisplatin. However, in certain cases the values exceeded those of cisplatin too and brought about DNA interhelical cross-links on their interaction with DNA.

As an extension of the above study, Navarro-Ranninger and co-workers synthesised tetrameric cyclopalladated complexes **100a-d** containing N-protected thiosemicarbazone ligand (tetradentate coordination mode) and tested them against a series of human and murine tumour cell lines such as HL-60, JURKAT, HeLa, 3T3, PAM 212 and PAM 212-ras (**100a-d**, Figure 44).[172] The complexes were effective against most cancer cell lines with complex **100c** out-performing cisplatin towards inhibiting the cell growth in the cancer cell lines tested.

6. Heterometallic Palladium-Containing Complexes as Anti-Cancer Agents

Another aspect in terms of the application of palladium-based complexes as anticancer agents is related to the introduction of additional transition metal leading to the possible enhancement in the cytotoxic activity. Heterometallic complexes can lead to difference in interactions with multiple biological targets and therefore could have potential as possible anticancer agents.[203-207] Iron and platinum are the most commonly used transition metals in combination with palladium, which will be discussed in detail in this section.

6.1. Palladium-Iron Complexes

Ferrocene is an important class of organometallic reagents known as sandwich compounds and has found large number of applications due to low toxicity, high lypophilicity and unique electrochemical behaviour.[208-211]

One of the earliest examples for the employment of complexes possessing a ferrocenyl moiety in combination with a palladacyclic backbone was reported by Lopez and co-workers, with the intention of studying their electrochemical properties. Complexes, **101a-d** (**101b** is cyclopalladated) were tested for interaction with *Calf Thymus* DNA (**101a-d**, Figure 45).[212] Most complexes showed significant Pd^{II} accumulation in DNA (G type) which could bring about retardation in the mobility of the circular covalently-closed form of DNA. Although, cytotoxicity studies were not performed, but it could be predicted on the basis of DNA study that these complexes could also prove to be effective anticancer agents, therefore presenting researchers with the opportunity to explore such an avenue.

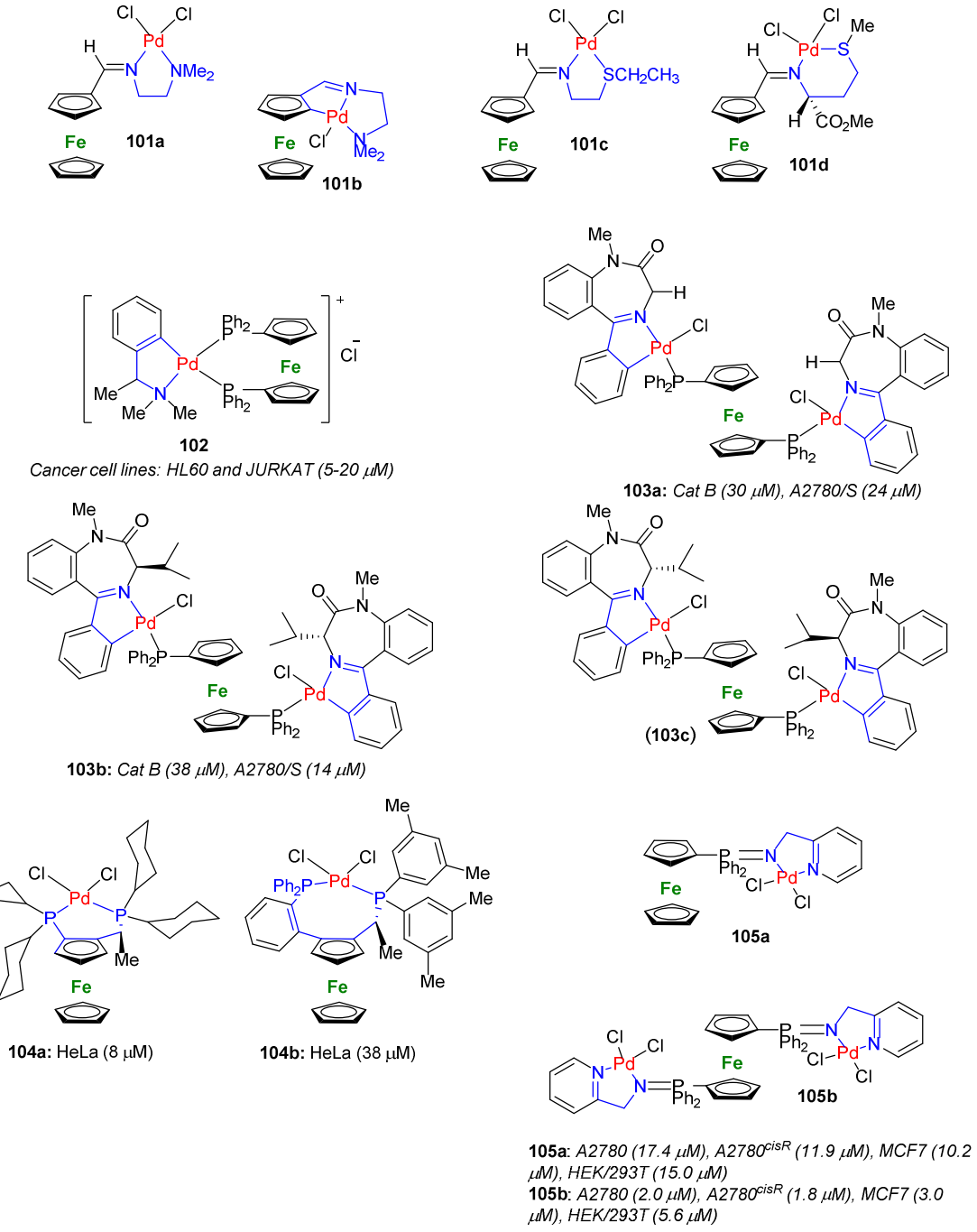


Figure 45: Ferrocenyl-based heterometallic palladacyclic or cyclopalladated complexes as anticancer agents.

Recently, a new organometallic class of antitumour drugs known as biphosphinic palladacycle complexes (BPC) with bridging bis(diphenylphosphine)ferrocene ligand and possessing promising biological properties was introduced by Bincoletto and co-workers.[213,214] In continuation of these studies, complex **102** was subjected to cytotoxic studies against leukaemia cell lines such as HL60 and JURKAT in the presence of untransformed cells consisting of peripheral blood mononuclear cells and lymphocytes carried out using MTT assay and trypan blue exclusion assays (**102**, Figure 45).[215] It was observed that complex **102** induced apoptosis in HL-60 and JURKAT and had minimal effect on normal cells. No visible toxic effects were observed in the concentration range of 5-20μM.

Dimeric cyclopalladated complexes with bridging bis(diphenylphosphine)ferrocene ligand synthesised by Spencer and co-workers portrayed relatively lower cytotoxic activity against bovine spleen cat B and human cancer cell line sensitive

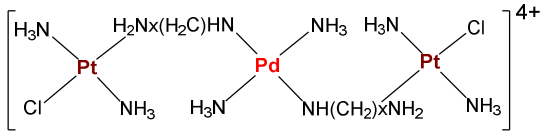
to cisplatin, A2780/S, compared to the dppp or dppb bridged dimeric cyclopalladated complexes **103a** and **103b** (Figure 45).[197]

Sterically-challenging and chiral ferrocenyl containing Josiphos and Walphos ligand systems when used allowed the synthesis of two novel and enantiomerically pure palladacyclic complexes (**104a** and **104b**, Figure 45).[216] The cytotoxicity studies for these complexes were investigated against HeLa cancer cell lines with low to moderate activity observed in both the cases, although the more bulky Josiphos-based complex performing better than the Walphos analogue.

Mono and dimeric ferrocenyl containing palladacyclic complexes **105a** and **105b** reported by Contel and co-workers were tested for antiproliferative activity against a series of human cancer cell lines such as human ovarian cancer cell line A2780 and its cisplatin resistant variant A2780^{cisR}, human breast cancer cell line MCF7 and finally noncancerous cell line HEK-293T in comparison to cisplatin (Figure 45).[217] The trimetallic complex **105b** exhibited important cytotoxic effects at lower micromolar levels and in certain cases exceeding the cytotoxic activity than cisplatin mainly for the A2780^{cisR} and MCF7 cell lines.

6.2. Palladium-Platinum complexes

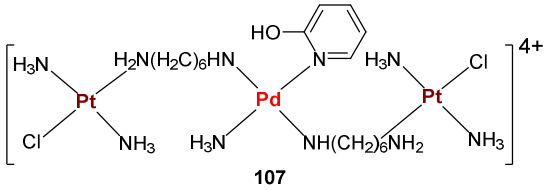
Another class of antitumour agents that has originated due to the less satisfactory activity of platinum-based complexes as well as the dramatic side effects exhibited by them, are the polynuclear platinum complexes that are found to contain two or more platinum units linked by diaminoalkane moiety of varied chain length.[218-222] These complexes exhibit promising activity compared to their commercially available platinum-based analogues such as cisplatin or carboplatin, however were found to suffer from severe side effects due to the covalent binding of peripheral platinum atoms to DNA (interstrand), while the central platinum atom was found to bind non-covalently in nature. A novel way to overcome this problem was suggested by Huq and co-workers which involved the replacement of the central platinum atom with palladium.[223] Structure-activity relationship study was performed on the synthesised multinuclear complexes based on the variation of the chain length for the diaminoalkane linker (**106a-d**, Figure 46). The complexes were then tested against human ovarian cancer cell lines: A2780, A2780cisR, A2780ZD0473R; melanoma cell line: Me-10538 and finally lung cancer cell line: NCI-H460 using MTT reduction assay with cisplatin employed as the reference standard. It was observed that the optimum chain length for obtaining higher cytotoxicity compared to cisplatin was six (**106c**), anything less or more than this chain length resulted in poor activity against the above mentioned cancer cell lines.



X = 4 (**106a**): *A2780 (3.24 μM), A2780^{cisR} (3.66 μM), A2780^{ZD0473R} (5.31 μM), Me-10538 (5.88 μM), NCI-H460 (12.62 μM)*
5 (**106b**): *A2780 (3.42 μM), A2780^{cisR} (3.99 μM), A2780^{ZD0473R} (4.49 μM), Me-10538 (5.37 μM), NCI-H460 (9.17 μM)*
6 (**106c**): *A2780 (0.048 μM), A2780^{cisR} (0.25 μM), A2780^{ZD0473R} (0.23 μM), Me-10538 (0.87 μM), NCI-H460 (1.0 μM)*
7 (**106d**): *A2780 (1.03 μM), A2780^{cisR} (2.91 μM), A2780^{ZD0473R} (4.91 μM), Me-10538 (2.52 μM), NCI-H460 (4.30 μM)*

Figure 46: Polynuclear palladium-platinum complexes

Subsequently, Huq and co-workers reported a modification of the most active complex of the above study (complex **106c** with chain length = 6), by substituting one of the ammonia group on the central palladium atom by a 2-hydroxypyridine ligand (**107**, Figure 47).[224] Such a modification was aimed at improving the cytotoxic activity and therefore the complex **107** was tested against human ovarian cancer cell lines A2780, A2780cisR, A2780ZD0473R and compared with cisplatin as standard. A significant improvement in activity of was observed for complex **107** (about 45 times in A2780, 78 times in A2780cisR and 7 times in A2780ZD0473R than cisplatin). Interestingly, comparison with the above complex **106c**, complex **107** exhibited enhanced activity possibly due to the noncovalent interactions involving 2-hydroxypyridine ligand.

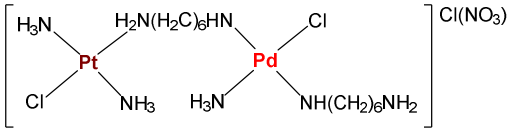


107

A2780 = 0.0103 μM; A2780cisR = 0.064 μM; A2780ZD0473R = 0.76 μM

Figure 47: 2-Hydroxypyridine-based heterometallic complex.

Building on their initial success with the multinuclear complexes, Huq and co-workers developed another novel heteronuclear complex containing a *trans*-platiniumcentre linked with a *trans*-palladium centre using a diaminoalkane linker, having chain length of six carbon atoms (**108**, Figure 48).[225] The complex **108** was then tested against human ovarian cancer cell lines: A2780, A2780cisR, A2780ZD0473R; melanoma cell line: Me-10538 and finally lung cancer cell line: NCI-H460 using MTT reduction assay with cisplatin employed as the reference standard. In most cases complex **108** performed better than cisplatin with greater cytotoxic activity was observed (indicated by lower IC_{50} values than cisplatin), however in the case of the lung cancer cell line NCI-H460 cisplatin showed better activity.



108

Cancer cell lines: A2780, A2780^{cisR}, A2780^{ZD0473R}, Me-10538, NCI-H460

Figure 48: Dimeric heteronuclear complexes as anticancer agents.

4. Conclusion

A significant amount of work has been carried out in understanding the applicability of platinum complexes as anti-cancer agents. However, dramatic side effects arising from the covalent interaction of platinum with DNA has prompted the development of other alternative metal-based anticancer drugs. Palladium complexes (palladium complexes ranging from monomeric, cyclopalladated, palladacyclic, dimeric, tetrameric as well as heterobimetallic complexes have been described), particularly palladacycles or cyclopalladated have shown promising activity. The area is still nascent and requires further studies to be carried out, particular on the mode of action of the multitude of complexes that have now been tested against simple cancer cell lines (as very few studies are reported). It could be noted that the solubility of palladium complexes is better compared to platinum-based complexes as is also evident from the water-soluble nature of some of the Pd complexes. This could also prove to be an important and attractive possibility for the treatment of cancer. Although there is a better correlationship between cytotoxicity and solubility of palladium complexes in comparison to cisplatin, more studies either in vitro or in vivo needs to be done. Fine tuning the cytotoxic activity coupled with good cellular permeability and transport properties (for more general and easier administration) represent some of the challenges that also need to be addressed.

A mechanistic understanding of the actual cellular targets for these palladium complexes is an area which will aid the development of more efficient palladium-based drugs and needs to be encouraged, particularly the difference between palladium and platinium needs to be dissected. Interesting, heterobimetallic palladacyclic complexes have shown improvement in cytotoxic activity compared to the homobimetallic complexes (mainly platinum-palladium containing complexes) an area that has the potential to generate a more potent line of defence against a variety of cancer cell lines. Moreover, higher order Pd species such as nanoparticles impart their own unique effects against cancer cell lines.[226] Knowing that many homogeneous Pd^{II} precursors can in principle be reduced under physiological conditions, then the potential involvement of Pd nanoparticles ought to be considered in future studies.

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6. Notes and references

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