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An overview of the anticancer activity of some mononuclear and polynuclear platinum(II) complexes

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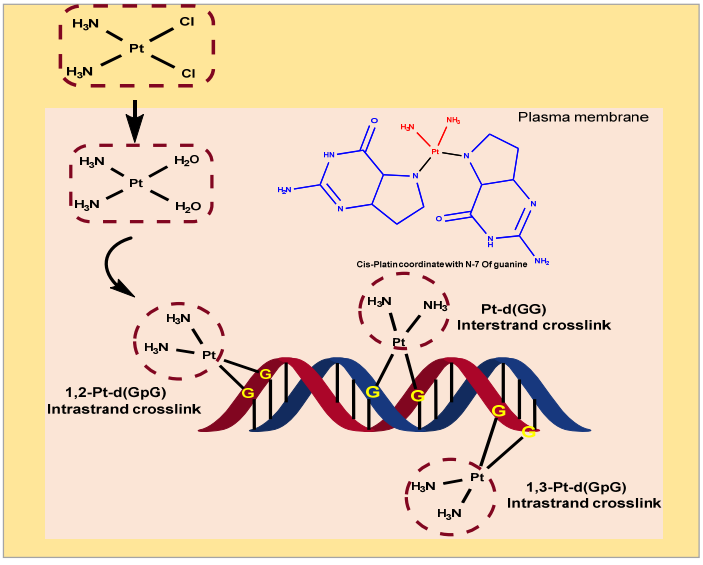
A B S T R A C T

A famous cisplatin anticancer agent is one of the most widely used chemotherapeutics for treating several human solid tumors. Toxicity of the normal cell is a life-threatening issue that restricts the therapeutic potential of cisplatin complex as an anticancer drug. Even though every year thousands of cisplatin-based analogs have been prepared, screened, and reported, only very few compounds entered the medical trials. Hence, new research work is still sensible. In the last few years, many mononuclear and polynuclear platinum complexes have been considerably investigated, *in-vitro* and *in-vivo* studies evaluated, with some compounds demonstrating significant anticancer potential. In this review, various mono-metallic and poly-metallic platinum-based complexes with various derivatives used as ligands that have anticancer potential are defined and numerous typical examples are discussed briefly. Present investigation, numerous mononuclear cisplatin derivatives exhibited greater anticancer potency than the parent cisplatin drug. However, polynuclear cisplatin derivatives showed much better anticancer activity than mononuclear cisplatin analogs against various cancer cell lines.



Graphical abstract

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1. Introduction

An uncontrolled or abnormal growth of cells in the body is called cancer. That provides the ability to occupy or spread to adjacent tissues and all over parts of the body hence no functional purposes. It can be identified in almost all organs of the body, including the breast, blood, prostate, lung, liver, colon, brain, and pancreas.[1-3] Barnett Rosenberg, Biophysicist, accidentally discovered cisplatin compound as found potentials and potencies as an effective anticancer drug.[4-6] The first metal-containing complex anticancer agent named cisplatin [$PtCl_2(NH_3)_2$] was discovered in 1964 and opened a new area of advance of metal-based anticancer drugs. The FDA approved cisplatin drugs in the middle of 1977 and 1978. The therapeutic uses of cisplatin compounds in the case of cancer have led to the treatment of many types of cancers like ovaries, bladder, head and neck malignancies, etc.[7]

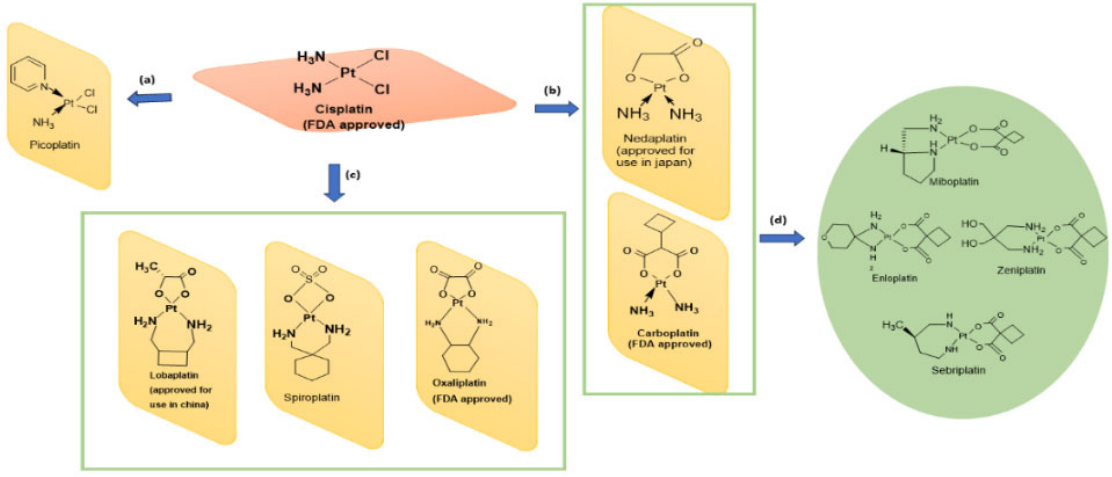


Fig. 1. Structures of the clinically used Platinum analogs anticancer Drugs. (**a**) Modification of mono ammine ligands, (**b**) Modification of Chloride ligands, (**c**) Modification of both ammine and chloride ligands, and (**d**) Modification of ammine ligands from carboplatin.

Many organic compounds are used as drugs for the treatment of various diseases including cancer.[8-10] The pharmacological activity of Cisplatin drugs is moderated by various functions such as DNA binding, interfering with transcription, DNA replication, and influencing apoptosis.[11,12] Despite its medical success various disadvantages including acquired resistance, lack of selectivity, and severe side effects such as hepatotoxicity, nephrotoxicity, ototoxicity, and neurotoxicity in combination with bone marrow suppression have led to significant attempts to synthesize various Pt(II) analogs with potential for anticancer activity but less toxicity.[13-16] Some recent studies indicate various Pt(II) complexes synthesized and reported with greater anticancer activity, high selectivity and less toxicity.[17-19] Several clinically successful Cisplatin analogs were synthesized, evaluated, and reported namely, Carboplatin, Oxaliplatin, Nedaplatin, Spiroplatin, Lobaplatin, and Picoplatin. The structure of some Cisplatin analogs is shown in **Fig. 1**.

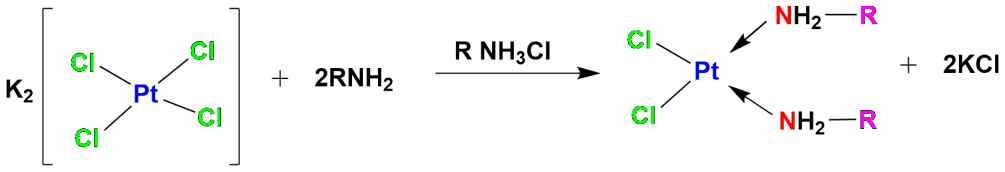
2. The Review and assessment methods

In this review, Biblio semantic and analytical methods were used. Throughout the literature review, databases of chemical compounds were used, namely *PubChem, Reaxys, Chemical Book*, and *SciFinder*. In addition, *Google Scholar* was used for the searching of literature. Various databases were used to prepare this review manuscript including Science Direct, Springer, Scopus, and Wiley. The literature survey covered all publications about modified cisplatin analogs, from the year 1979 to 2023.

3. Mono-Nuclear Platinum(II) Complexes

In this study, various mono-metallic Cisplatin analogs with different ligand derivatives were reported. In 1979, T. A. Nile and Crystal A. Smith reported that novel platinum(II) complexes of 2-fluoroaniline derivatives were synthesized from potassium tetrachloroplatinate(II) with respective amine in the presence of the amine hydrochloride (**Scheme 1**). The *in-vitro* MTT assay of the synthesized metal complexes was done against L-1210 lymphoid leukemia and P588 lymphocytic leukemia cancer cell lines. The structure of all synthesized complexes is given in **Fig. 2**. Complexes **1** and **2** showed good anti-cancer activity against P388 lymphocytic leukemia with no activity against L-1210 lymphoid leukemia cancer cells.

Complexes **3** showed no activity against both the cancer cell lines. Complexes **4** and **5** displayed no activity against L-1210 lymphoid leukemia cancer cells.[20]



Scheme 1. Synthesis of Cis-bis-2-fluroanilinedichloro platinum(II) complexes

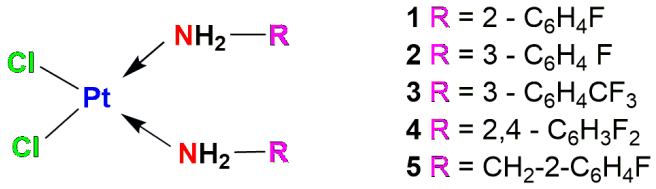
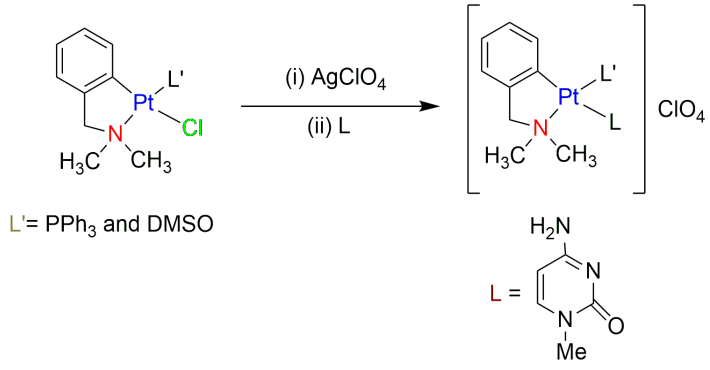


Fig. 2. Structure of Cis-bis-2-fluroanilinedichloro platinum(II) complexes

In 2005, Jose Ruiz et al. proposed the nucleobase 1-methyl cytosine platinum(II) complexes (**Fig. 3**) were synthesized by the acetone solution of [Pt(dmba)(DMSO)Cl] and [Pt(dmba)(PPh_3)Cl] was mixed with $AgClO_4$ and AgCl was removed by filtration. 1-methylcytosine (L) was added to the filtrate and stirred for 6 h at room temperature (**Scheme 2**). The *in-vitro* anti-tumor activity of prepared complexes and cisplatin (reference drug) was evaluated against the human tumor cell line HL-60. From the result, Complexes **6** and **7** were about 10-fold (at a 24h incubation time) and 2-fold (at a 72h incubation time) better active than cisplatin respectively, towards HL60 cancer cells.[21]



Scheme 2. Synthesis of 1-methyl cytosine platinum(II) complexes

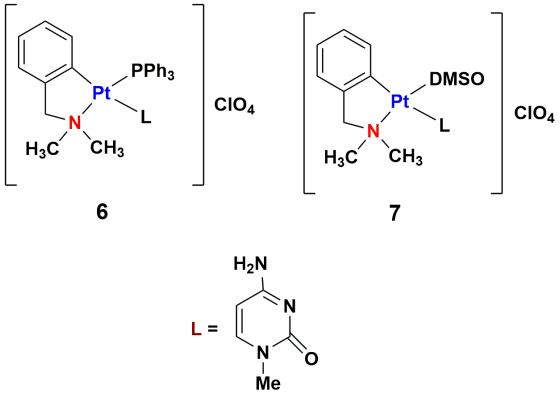


Fig. 3. Structures of nucleobase 1-methyl cytosine platinum(II) complexes

In 2021, Abeer A. Ibrahim et al. reported the platinum(II) complex was synthesized using thiocarbohydrazone as a ligand and the structure of the complex is given in **Fig. 4**. The *in-vitro* cytotoxicity of the new platinum(II) complex was determined towards two cancer cell lines (human colorectal adenocarcinoma (HT-29) and ovarian adenocarcinoma (Caov-3)) through MTT assays at various incubation times (24, 48 and 72h). Complex **8** showed higher anticancer potential against Caov-3 than the HT-29 cell with the observed IC_{50} value being 3.34, 2.41, 1.74 µg mL^{-1} and 10.32, 4.25, 2.5 µg mL^{-1} against Caov-3 and HT-29 cell respectively.[22]

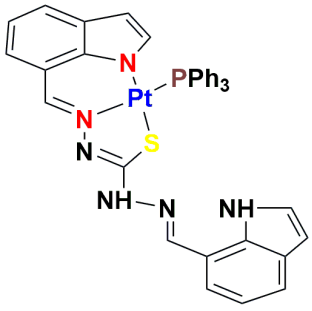


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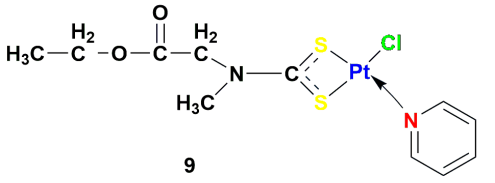
Fig. 4. Structure of platinum(II) thiocarbohydrazone complex



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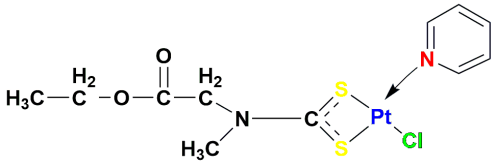

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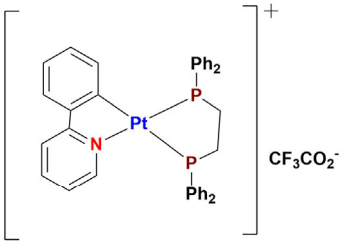
Fig. 5. Two isomeric structures of mixed dithiocarbonate-amino platinum(II) complexes

In 2002, C. Marzano et al. described two new Pt(II) complexes (**Fig. 5**) that have been synthesized with mixed dithiocarbamate–amino ligands. *In-vitro* anticancer activity of two new complexes was evaluated against human leukemia HL60 and human adenocarcinoma HeLa cells. The cytotoxicity of newly synthesized complexes (**9** and **10**) showed remarkable activity against both cancer cells. The observed IC_{50} value of new complexes was very similar to or less than the cis-platin standard drug.[23]

In 2014, Mehrnaz Jamshidi et al. reported some new novel cationic platinum(II) Complexes were prepared from various ligands containing 1,1 -bis(diphenylphosphino)ferrocene (dppe), deprotonated benzo[h]quinoline (dhq), 1,1 -bis(diphenylphosphino)ferrocene (dppf) and deprotonated 2- phenyl pyridine (ppy), and the structures was shown in **Fig. 6**. Anticancer activity of all the newly prepared metal complexes was inhibited opposed to Jurkat (human breast adenocarcinoma cell line) and MCF-7 (human T cell lymphoblast cell line) cancer cell lines by 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) assay. The prepared Pt(II) complexes (**11–13**) showed high anticancer activities compared to the cisplatin standard drug. The Pt(II) complexes **11** and **13** demonstrated remarkable anticancer potency against MCF-7 and Jurkat cancer cell lines.[24]



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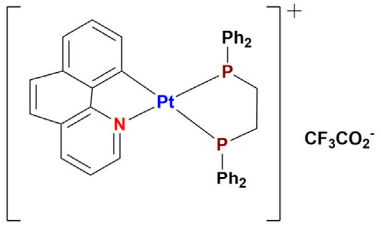

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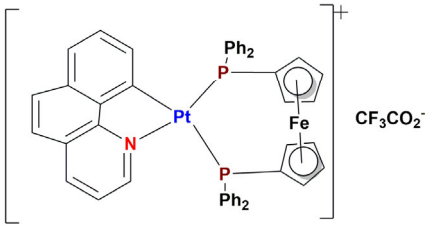

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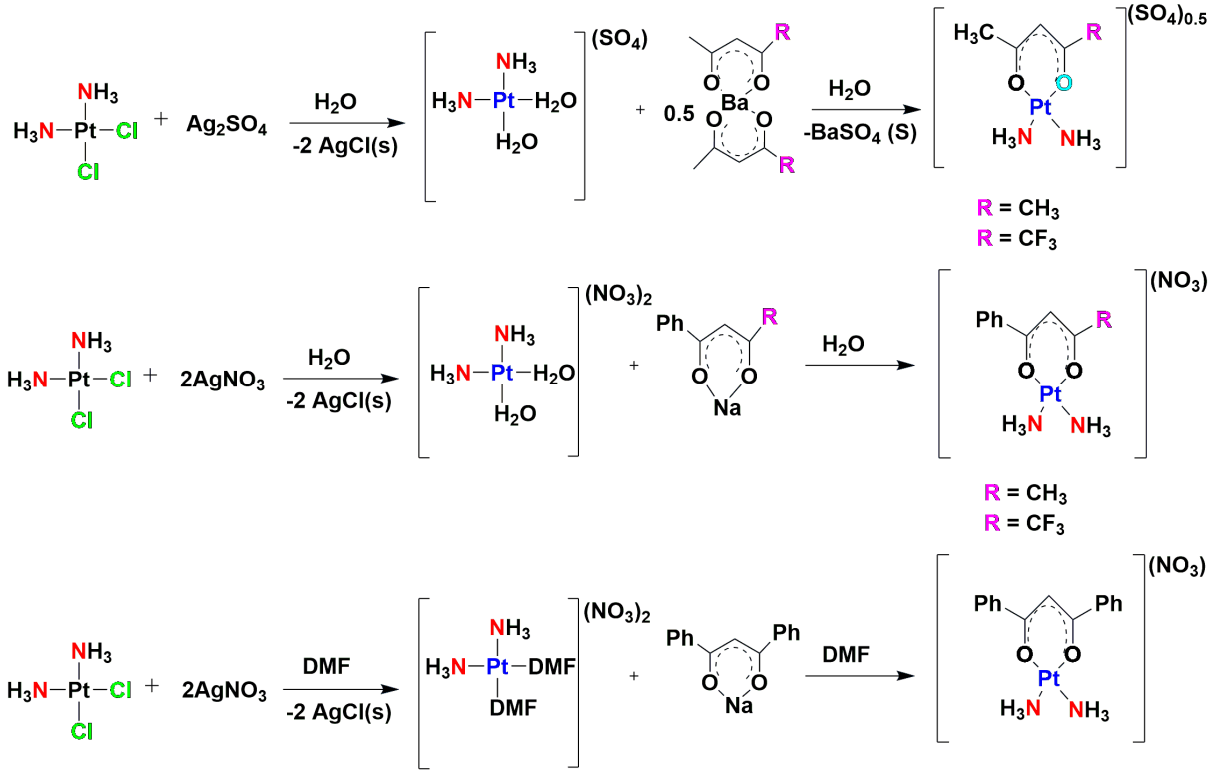
Fig. 6. Structures of new synthetic Platinum(II) complexes

In 2012, J.J. Wilson and S.J. Lippard devised five cationic platinum(II) complexes (**Fig. 7**) were prepared by the solution of Cis-platine with β-diketonate ligand such as acetylacetonate (acac), 1,1,1,-trifluoroacetylacetonate (tfac), benzoylacetonate (bzac), 4,4,4-trifluorobenzoylacetonate (tfbz), and dibenzoylmethide (dbm) was stirred at room temperature for 12h in the dark condition (**Scheme 3**). The anticancer activities of complexes **14**–**18** and standard drug cisplatin were inhibited through the MTT method against HeLa (cervical), A549 (lung), U2OS (osteosarcoma), and MCF-7 (breast) human cancer cell lines. The cytotoxicity studies showed that complexes **15**, **17,** and **18** have similar activity compared to cisplatin drug while **14** and **16** are fewer active complexes.[25]



Scheme 3. Synthesis of β-diketonate platinum(II) complexes

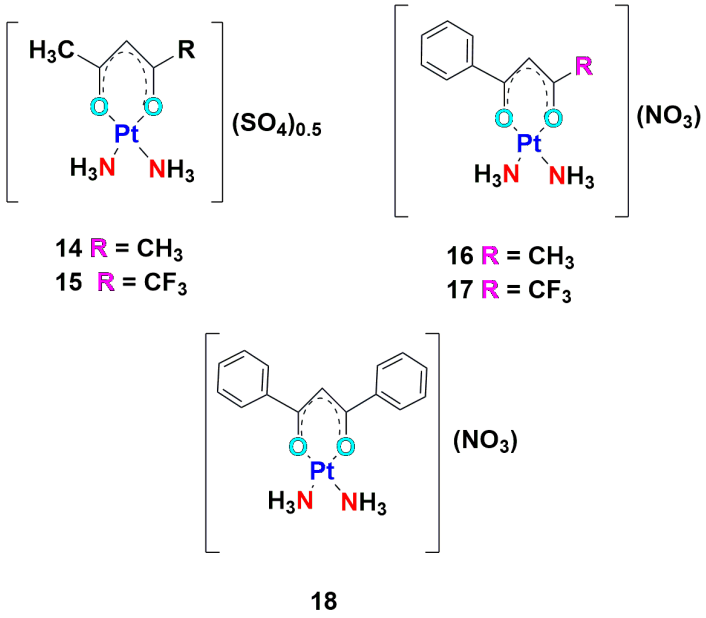


Fig. 7. Structures of β-diketonate platinum(II) complexes

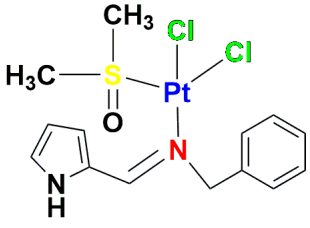


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Fig. 8. Structure of pyrrole-based platinum(II) complex

In 2020, Simon N. Mbugua et al. reported new platinum(II) complexes (**Fig. 8**) were prepared with R-(phenyl) methanamine Schiff base ligand, and characterized by several spectral techniques. The *In-vitro* anticancer activity and mechanism of the synthesized complexes were studied toward MCF-7, Caco-2, HeLa, HepG2, and PC-3 (human cancerous) and MCF-12A (noncancerous) cell lines. Complex **19** showed highly selective, cytotoxicity and no cytotoxicity against 5 cancerous cell lines and noncancerous breast cell lines respectively. The Pt(II) complex **19** also of cis-conformation, displayed strong DNA intercalation activity. The above fact suggests that complex **19** needs further in vivo tests for proof of a good drug for cancer treatment.[26] Further, in 2021, Luyao Niu et al. described three novel luminescent Pt(II) complexes (**Fig. 9**) that were synthesized with 2-Phenyl pyridine derivatives such as 2-phenyl-5-nitropyridyl, 2-(2,4-difluorophenyl)pyridine and 2-(3,5-difluorophenyl)pyridine and reported. *In-vitro* anticancer activities of prepared complexes were tested against four human cancer cell lines such as BGC823, MGC803 (gastric), HepG2 (hepatocellular carcinoma), A549 (non-small-cell lung), and HL-7702 (human normal liver cell line) by MTT assay. The observed IC_{50} values of complex **22** against BGC823 and MGC803 are 13.03 μM and 26.59 μM respectively, revealing that good drug candidates for the treatment of gastric cancer.[27]

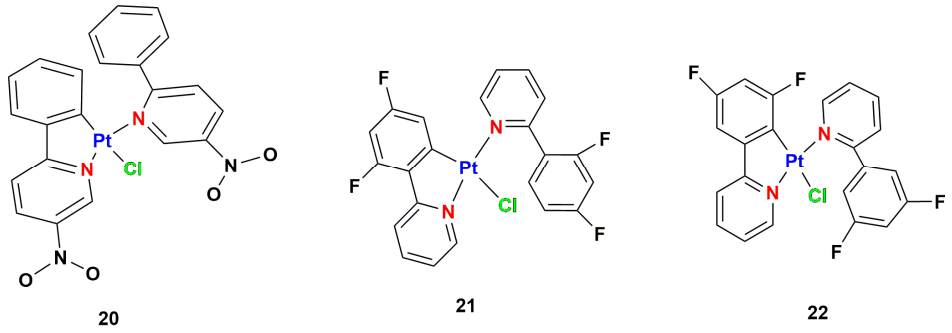
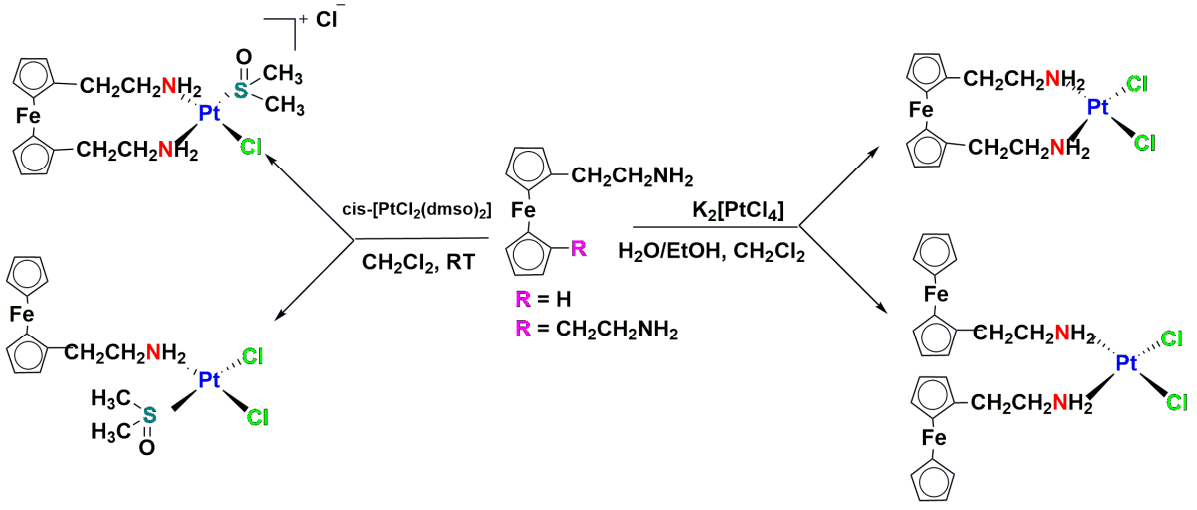


Fig. 9. Structures of platinum(II) complexes with 2-phenyl pyridine derivatives

In 2012, Daniel Nieto et al. reported that heterometallic platinum(II) complexes were synthesized by chloroform solution of ferrocenyl derivatives such as 1-β-aminoethyl ferrocenes and 1,1-bis(β-aminoethyl)ferrocene was stirred with $K_2[PtCl_4]$ and cis-$[PtCl_2(dmso)_2]$ respectively at room temperature (**Scheme 4**). The structure of complexes is shown in **Fig. 10** (**23-26**). The *in-vitro* MTT assay anticancer activity of all the complexes was done against different cell lines such as HBL-100 (human breast cancer), HeLa (human cervix cancer), SW1573 (human non-small cell lung cancer), and WiDr (human colon cancer). The observed result of the anticancer activity studies showed that complex **26** has remarkable activity toward all cancer cell lines. Particularly, complex **26** showed excellent activity against the human colon cancer cell line (WiDr) compared to the cisplatin anticancer standard drug. Hence, complex **26** was chosen as a lead for further anticancer treatment.[28]



Scheme 4. Synthesis of heterometallic platinum(II) complexes

Later, in 2018, M. D. Zivkovic et al. Proposed ferrocenyl derivative platinum(II) complexes **Fig. 10** (**27-29**) were synthesized using various ligands such as ferrocenyl-terpyridine (Fc-tpy), N-propargyl carbazole (NPC), and ferrocenylmethyl-bis-(2-pyridylmethyl)amine (Fc-bpa)**.** The *in-vitro* cytotoxic activity of the prepared complexes was determined against HaCaT (immortalized human skin keratinocytes) cell lines by MTT assay. The IC_{50} value of all the complexes was observed by light and dark conditions. The Complexes **27** and **28** displayed excellent photocytotoxicity

towards HaCaT cell lines. The observed IC_{50} values (9.8) for both complexes in light and in the dark condition are ~10 μM and > 60 μM respectively.[29]

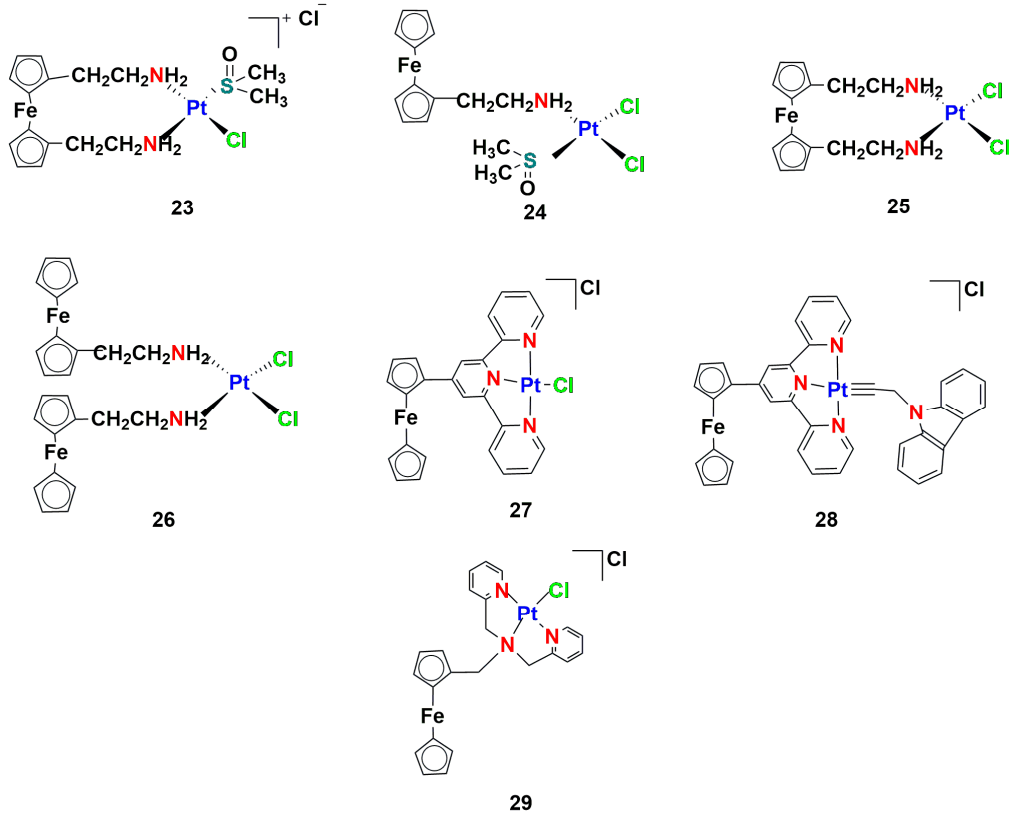
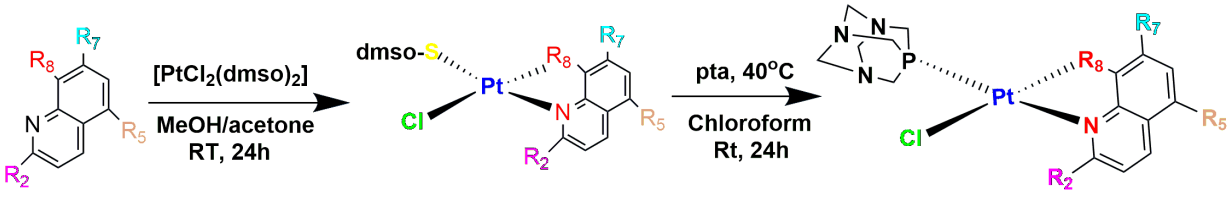
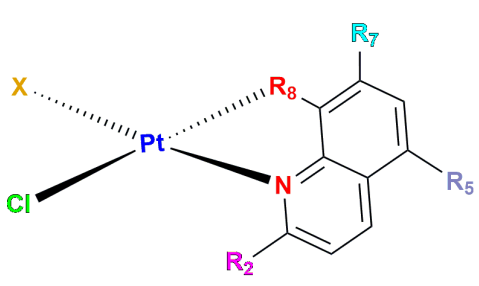


Fig. 10. Structures of ferrocenyl derivatives of platinum(II) complexes

In 2008, Yao Yu et al. reported a new novel sixteen platinum(II) complexes (**Fig. 11**) were prepared with various ligands such as DMSO, 1,3,5-triaza-7-phosphaadamantane (Pta), and 5-chloro-7-iodo-8-quinoline (hq) derivatives in the mixer of methanol-acetone (1:2) solvent system for 24h at the room temperature (**Scheme 5**). All the prepared complexes were evaluated by in vitro cytotoxicity assay against human fibroblasts (MRC5) and two carcinoma cell lines (A375 and A549). All complexes showed good cytotoxic activity against MRC5 cell lines except **35** while complexes **33, 34, 38,** and **39** displayed selective toxicity against carcinoma cell lines (A375 and A549).[30]



Scheme 5. Synthesis of platinum(II) complex with phosphine ligand



X=S-dmso	X=Pta	R2	R5	R7	R8
30	38	H	Cl	I	O
31	39	H	NO_2	H	O
32	40	H	Cl	Cl	O
33	41	H	I	I	O
34	42	H	Br	Br	O
35	43	Me	Cl	Cl	O
36	44	H	H	H	O
37	45	H	H	H	S

Fig. 11. Structures of platinum(II) complex with phosphine ligand

In 2014, Koushambi Mitra et al. described three new novel lipophilic platinum(II) complexes were synthesized with leaving group ligand 3,5-diisopropylsalicylate (DIPS) (**Fig. 12**) and the *in-vitro* cytotoxic activity of all the complexes was evaluated against different human cancer cell lines such as 3AO (ovarian carcinoma), A549 and NCI-H460 (non-small-cell lung), and SGC-7901 (gastric adenocarcinoma). Complexes **46-48** showed notable cytotoxicity against all the human cancer cell lines with the observed lower IC_{50} values compared to the standard drug (oxaliplatin, eptaplatin, and carboplatin). *In-vivo* anticancer activity study showed out of all the complexes, **47** were more highly active than oxaliplatin and carboplatin against NCI-H460 non-small-cell lung tumor-bearing mice. From the result of *in-vitro* and *in-vivo* studies, complex **47** attributed better anticancer activity, less toxicity, and good lipophilic ability. So, complex **47** is a hopeful candidate for stable and active liposomal platinum-based drug for cancer treatment.[31]

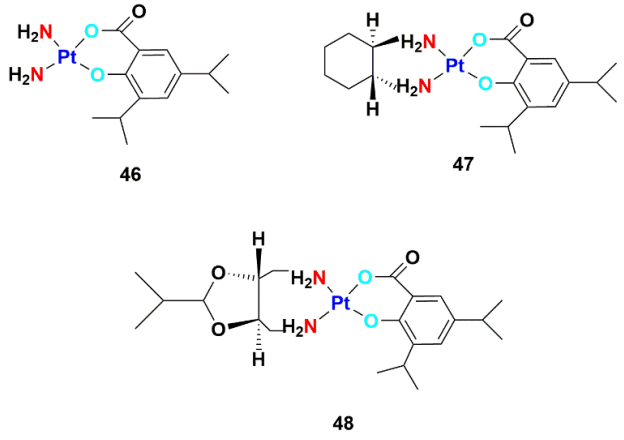
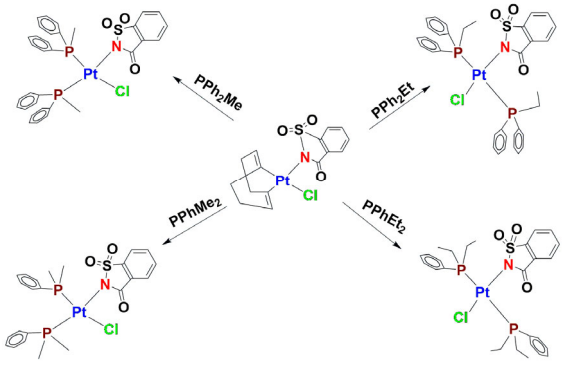


Fig. 12. Structures of platinum(II) complexes of 3,5-diisopropylsalicylate



Scheme 6. Synthesis of platinum(II) saccharinate complexes with phosphine derivatives

In 2019, Ceyda Icsel et al. devised a new class of chlorido platinum(II) saccharinate complexes (**Fig. 13**) were prepared by the phosphine ligand (PPh_2R and $PPhR_2$; where, R = Me or Et) was added to the starting material [PtCl(sac) (COD)] (COD = 1,5-cyclooctadiene) in the presence of MeOH and MeCN (1:1) and the mixture of solution was refluxed for 24h (**Scheme 6**). The anticancer activity of the complexes was evaluated towards various human cancer cells such as A549 (lung), MCF-7 (breast), HCT116 (colon), and BEAS-2B (bronchial epithelial). The cis-isomer complexes **49** and **50** showed more anticancer activity on MCF-7 and HCT116 cancer cells, almost like cisplatin (reference) drug, but the trans isomeric complexes **51** and **52** showed no activity against all the cancer cell line.[32]

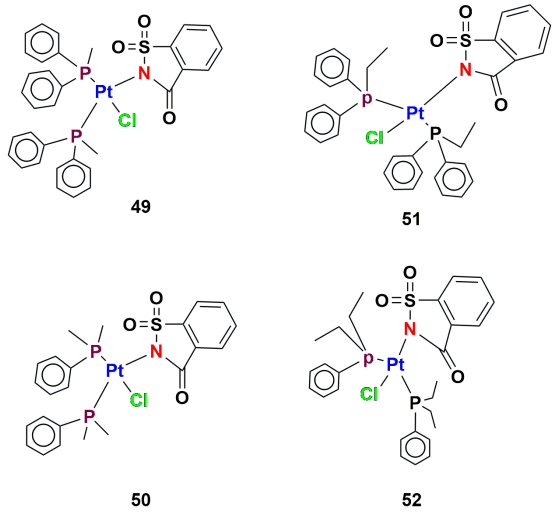


Fig. 13. Structures of platinum(II) saccharinate complexes with phosphine derivatives

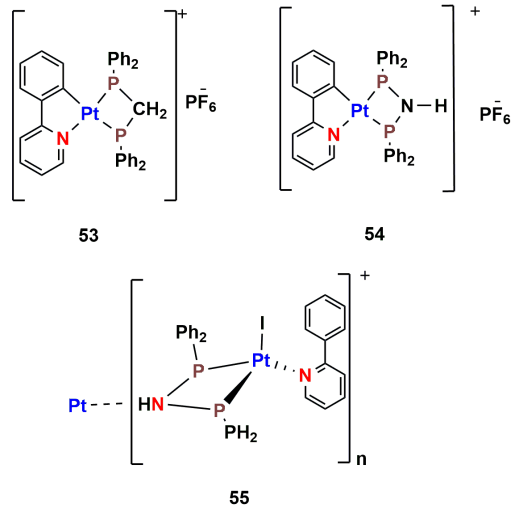


Fig. 14. The geometry of four coordinated (**53** and **54**) and five coordinated (**55**) platinum(II) complexes

In 2012, Reza Yousefi et al. proposed a new series of novel platinum(II) complexes (**Fig. 14**) that were synthesized with some ligands including dppa (bis(diphenyl phospino)amine), and dppm (bis(diphenylphosphine) methane). The anticancer potency of the Pt complexes was inhibited against K56 (chronic myelogenous), and MCF-7 (Breast cancer) cell lines using

3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. The structure-activity relationship studies indicate that the four coordinated complexes **53** and **54** showed remarkable anticancer activity compared to the five coordinated platinum(II) complexes (**55**).[33]

In 2015, Jing-Jing Zhang et al. reported four novel terpyridine Platinum(II) complexes (**Fig. 15**) of caffeine-derived ligands containing N-heterocyclic carbene (**56** and **57**) and N-coordinated theobromine-derived ligands (**58** and **59**) were synthesized and structurally characterized. The cytotoxic activity was evaluated against two breast cancer cell lines (MCF-7 and MDA-MB-231) and colon adenocarcinoma cancer cell (HT-29) with a cisplatin reference drug. Particularly, caffeine-derived organometallic complexes **56** and **57** exhibited better cytotoxicity (IC_{50} = 0.24 - 0.83 µM) compared to the theobromine-derived N-coordinated complexes **58** and **59** (IC_{50} = > 100 µM) which were biologically inactive.[34]

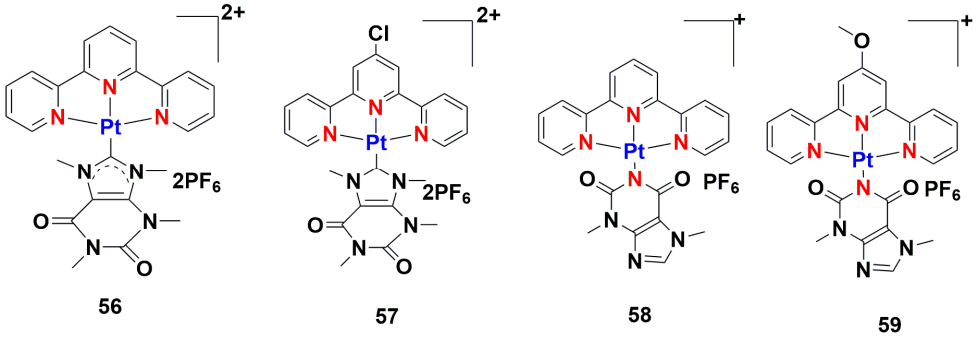
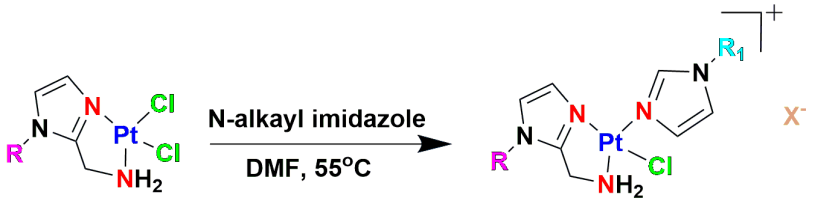


Fig. 15. Structures of terpyridine platinum(II) complexes with caffeine and theobromine derivatives

In 2017, Isabella Rimoldi et al. described some new cationic platinum(II) complexes were prepared by the dry DMF solution of dichloro platinum(II) complex was slowly added to the respective substituted N-alkyl imidazole and the resulting mixture was heated at 55°C under nitrogen condition for overnight (**Scheme 7**). The structure of complexes was shown in **Fig. 16**. The cytotoxic potency was studied toward breast cancer MDA-MB-231, MCF-7 cell line, colorectal cancer DLD-1 cell lines and non-cancer human primary smooth muscle cells with anticancer standard drug cisplatin through MTT assay. Complex **63** showed the most cytotoxic activity against the MDA-MB-231 cell line with the observed IC_{50} value is 61.9 µM and better active than standard drug (cisplatin) against DLD-1 and MCF-7 cell lines with the IC_{50} value of 57.4 µM and 79.9 µM respectively. Hence, complex **63** leads to promising drugs for cancer treatment.[35]



Scheme 7. Synthesis of cationic platinum(II) complexes with imidazole moiety

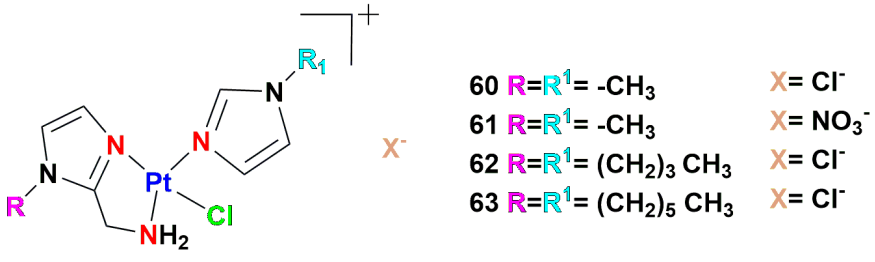
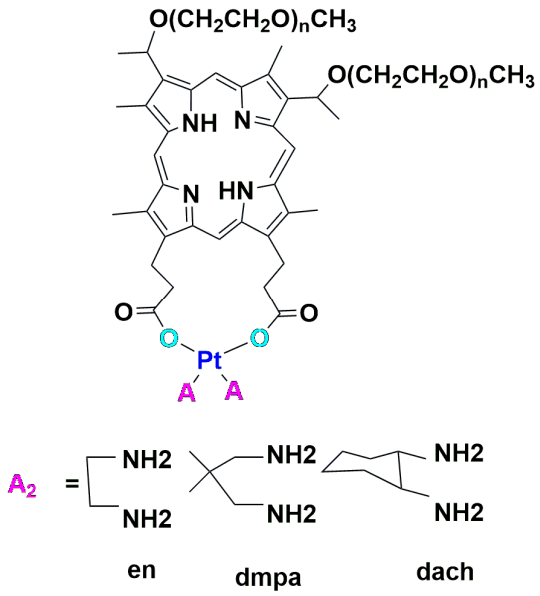


Fig. 16. Chemical structures of cationic platinum(II) complexes with imidazole moiety

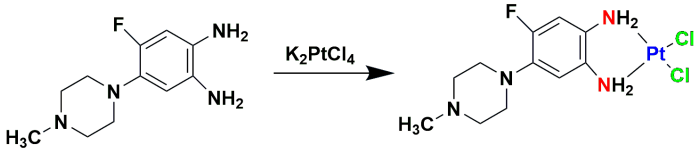
In 2003, Yeong-Sang Kim et al. reported a new class of novel platinum(II) complexes (**Fig. 17**) were synthesized from pegylated hematoporphyrin derivatives. The antitumor activity (*in-vitro* and *in-vivo*) of the prepared complexes were evaluated against A-549 (human lung cancer), SK-OV-3 (human ovarian cancer), SK-MEL-2 (human Melanoma cancer), XF-498 (human brain cancer), HCT-15 (human colon cancer) and normal leukemia L1210 cell line with cisplatin and carboplatin as a standard drug through SRB assay. The newly prepared complexes showed better water solubility and high lipophilicity as well as remarkable antitumor activity towards all cancer cell lines. Especially complex **73** (T/C% = 258) exhibited better *in-vivo* anti-tumor activity than standard drug cisplatin (T/C% = 184) and carboplatin (T/C% = 165). Interestingly, complex **77** showed remarkable cytotoxicity towards all cancer cell lines.[36]



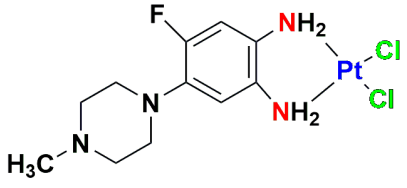
64 n= 0, $(MeO)_2HP(COO)_2Pt(dach)$
65 n= 0, $(MeO)_2HP(COO)_2Pt(dmpda)$
66 n= 1, $(MEG)_2HP(COO)_2Pt(dach)$
67 n= 1, $(MEG)_2HP(COO)_2Pt(dmpda)$
68 n= 2, $(MDEG)_2HPiCOO)_2)Pt(dach)$
69 n= 2, $(MDEG)_2HP(COO)_2Pt(dmpda)$
70 n= 2 , $(MDEG)_2HP(COO)_2Pt(en)$
71 n= 3, $(MTEG)_2HP(COO)_2Pt(dach)$
72 n= 3, $(MTEG)_2HP(COO)_2Pt(dmpda$
73 n= 7, $(MpEG350)_2HP(COO)_2Pt(dach)$
74 n= 7, $(MPEG350)_2HP(COO)_2Pt(dmpda)$
75 n= 7, $(MPEG350)_2HP(COO)_2Pt(en)$
76 n= 12, $(MPEG550)_2HP(COO)_2Pt(dach)$
77 n= 12, $(MPEG550)_2HP(COO)_2Pt(dmpda)$

Fig. 17. Chemical structures of platinum(II) complexes of hematoporphyrin derivatives

In 2016, K.A.A. Safieh et al. produced a new cis-dichloro-platinum(II) complex (**Fig. 18**) of 1,2-diamino-4-fluoro-5-(4-methyl-1-piperazinyl) benzene (DFMPB) has been synthesized by water solution of $K_2[PtCl_4]$ was added slowly the ligand (DFMPB) in methanol solution. The mixture of solution was stirred for 24h at room temperature in the dark condition (**Scheme 8**) and well characterized by several analytical and spectral techniques. The anticancer activity study was done against (MDA-231 and MCF-7) two human breast cancer cell lines and the K562 human leukemia cell line. Particularly, complex **78** (IC_{50} = 90.79 µM) exhibited higher cytotoxic activity than the parent ligand DFMPE (IC_{50} = 129.61 µM) and the standard drug cisplatin (IC_{50} = 133.65 µM) against the MCF-7 cell line.[37]



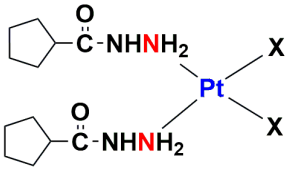
Scheme 8. Synthesis of Pt(II) complex of fluoropiperazinyl derivatives



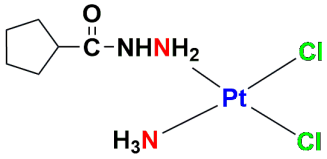
78

Fig. 18. Chemical structure of Pt(II) complex of Fluoropiperazinyl derivatives

In 1999, Daniel Kushev et al. devised new novel platinum(II) complexes that were prepared with cyclopentane carboxylic acid hydrazide (cpcah) and the structure of the complex is shown in **Fig. 19**. The *in-vitro* and *in-vivo* cytotoxicity were studied against ovarian tumor (A2780), friend leukemia cells and Lewis lung carcinoma, murine L1210 leukemia cells respectively. An antitumor activity of the Pt(II) complex **79** displayed similar to that of cisplatin reference drug against L1210 leukemia in mice.[38]



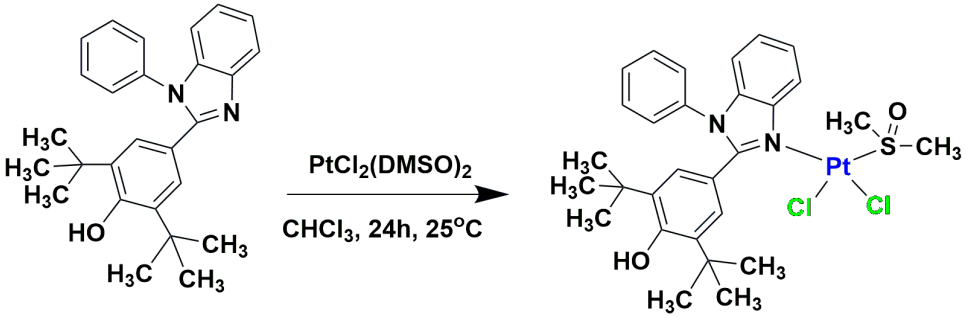
79 X=Cl
81 X=Br
82 X=I



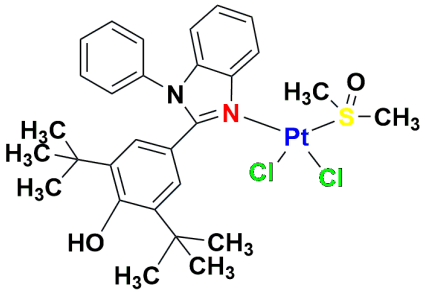
80

Fig. 19. Structures of cyclopentane carboxylic acid hydrazide contain Pt(II) complexes

Recently, in 2021, Umut Dogan et al. proposed a new series of three Platinum complexes of general formula [$PtCl_2$(dmso)(L1)], [$PtCl_2$(dmso)(L2)] and [$PtCl_2$(dmso)(L3)] with 2,6-di-tert-butyl-4-(1-phenyl-1H-benzimidazol-2-yl) phenol (L1), N, N-dimethyl-4-(1-phenyl-1H-benzimidazol-2-yl) aniline (L2) and 4-(1Hbenzimidazol-2-yl)-N, N-dimethylaniline (L3) were prepared from appropriate ligand and cis-$PtCl_2(DMSO)_2$ were mixed in chloroform at room temperature for 24h (**Scheme 9**). The cytotoxic activities of all the complexes were evaluated towards U-87 and SHSY-5Y cancer cell lines with standard drug cisplatin. Among the complexes particularly, complex **83** (**Fig. 20**) showed much better activity against SHSY-5Y and U-87 cancer cell lines than cisplatin (Reference drug). More cytotoxicity of complex **83** than the other complexes can be described by the fact that it contains a bulky and pi-coordinated heterocyclic ligand.[39]



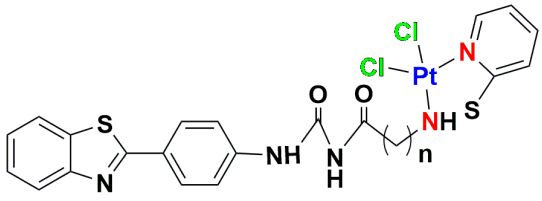
Scheme 9. Synthesis of cis-dichloro Pt(II) complex with benzimidazole derivatives



83

Fig. 20. Structure of cis-dichloro Pt(II) complex with benzimidazole derivatives

In 2016, Barbara Mavroidi et al. reported a novel Pt(II) complexes of 2-(4'-aminophenyl) benzothiazole-based ligands (**Fig. 21**) were prepared, and characterized by several tools. The *in-vitro* cytotoxicity of newly synthesized complexes was inhibited against MCF-7 and MDA-MB-23 (human breast carcinoma) also normal human skin fibroblasts (DSF) with cisplatin drug were used as positive control. Cytotoxicity studies showed that the complex **85** exhibited greater anticancer potency against MDA-MB-231 cell lines related to the parent ligand but less activity than cisplatin (reference drug).[40]

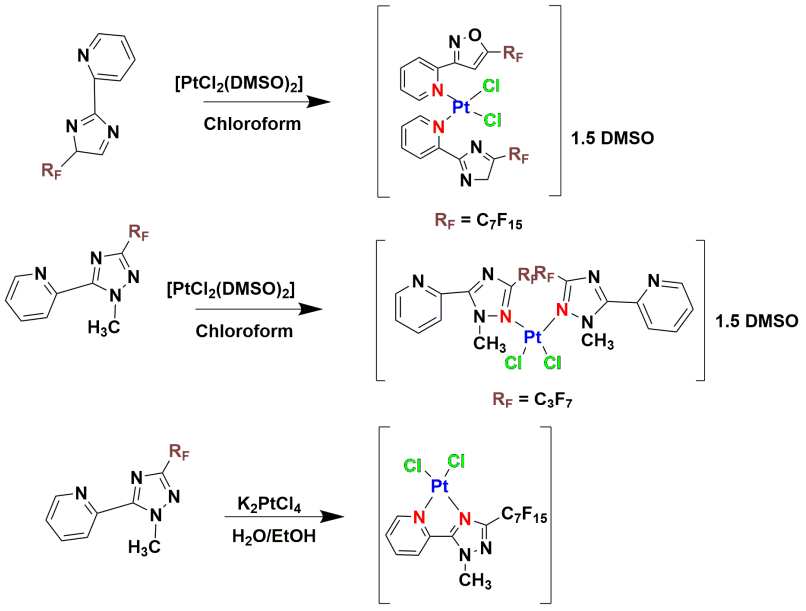


84 n= 1
85 n= 4

Fig. 21. Chemical structures of Pt(II) complexes of 2-(4'-aminophenyl) benzothiazole derivatives

In 2016, Simona Rubino et al. described new class of mononuclear Pt(II) complexes (**Fig. 22**) with 5-perfluoroalkyl-1,2,4-oxadiazolyl-pyridine and 3-perfluoroalkyl1,2,4-triazolyl-pyridine ligands containing pfhop [2-(5-perfluoroheptyl-1,2,4-oxadiazole-3yl)-pyridine], pfpop [2-(5-perfluoropropyl)-1,2,4-oxadiazole-3yl)-pyridine], pfhtp [2-(3-perfluoroheptyl-1-methyl-1,2,4- triazole-5yl)-pyridine], and pfptp [2-(3-perfluoropropyl-1-methyl-1,2,4-triazole-5yl)-pyridine] were prepared by Cis-[$PtCl_2(DMSO)_2$] and the respective ligands was dissolved in chloroform. The solution mixture was stirred continuously for 24h at 40 °C (**Scheme 10**). *In-vitro* antitumor activity of the new complexes was tested

through MTT assay against three human tumor cell lines: MCF-7 (breast), HepG2 (hepatocellular carcinoma), and HCT116 (colorectal carcinoma). Complexes **86** and **90** displayed very high activity against HepG2, MCF-7, and HCT 116 tumor cell lines.[41]



Scheme 10. Synthesis of Pt(II) complex with fluoroalkyl derivatives

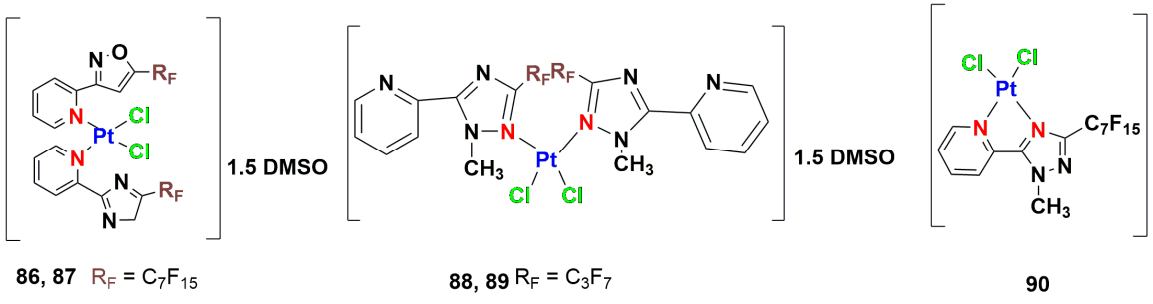


Fig. 22. Structures of Pt(II) complex with fluoroalkyl derivatives

In 2017, Cheyenna M.A. Muller et al. reported a new series of novel Pt(II) pyridinium amidate (PYA) complexes (**Fig. 23**) were synthesized with N-(1-benzylpyridin-4(1H)-ylidene)picolinamide. The cytotoxicity of parent ligand (PYA) and its metal complexes evaluated towards HCT116 (colorectal), NCI-H460 (non-small cell lung), and SiHa (cervical) human cancer cell lines with standard cisplatin drug. Anticancer activity of complex **91** (IC_{50} = 19 µM) exhibited moderate activity against HCT 116 cell lines as compared to cisplatin (IC_{50} = 2.5 µM) reference drug.[42]

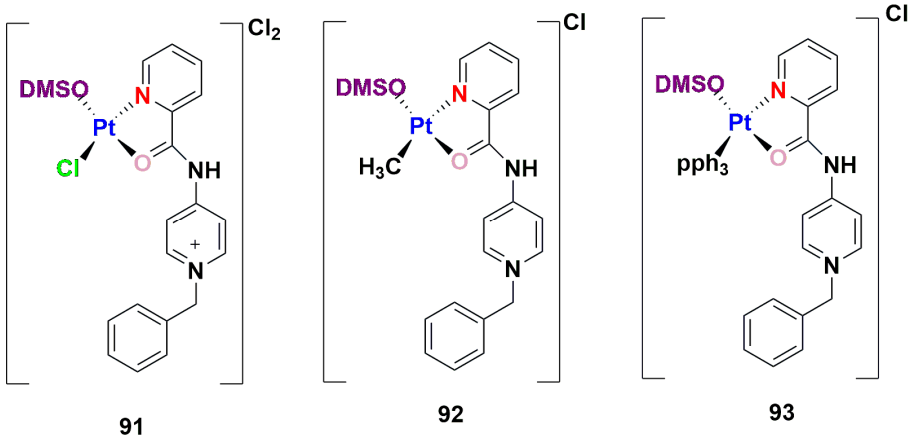


Fig. 23. Structure of platinum(II) pyridinium amidate complexes

In 2014, Aleksandar Savic et al. proposed some new Pt(II) iodido complexes of isobutyl (**94**), n-pentyl (**95**), and isopentyl (**96**) esters of (S,S)-1,3-propanediamine-N,N'-di-2-(3-cyclohexyl)propanoic acid has been prepared, well characterized by various analytical and spectral tools and the chemical structure of the complexes given in **Fig. 24**. The anticancer activity of parent ligands and respective complexes (**94-96**) were studied against various human cancer cell lines, such as HeLa (cervical adenocarcinoma), A549 (alveolar basal adenocarcinoma), MRC-5 (fetal lung fibroblast), MDA-MB-231 (breast carcinoma), LS-174 (colorectal adenocarcinoma), and EA.hy92 (lung cells-A549) using MTT assay. All the metal complexes showed two-to-four-fold high anticancer activity compared to the respective parent ligands. Complexes (**94-96**) displayed similar activity compared to cisplatin references drug and exhibited better activity against HeLa, LS-174, and EA.hy.926 cells than the other cell lines.[43]

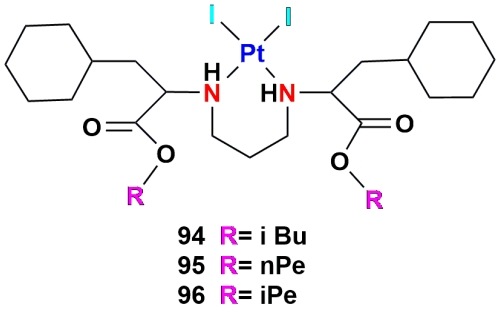


Fig. 24. Chemical structure of platinum(II) iodido complexes (**94-96**)

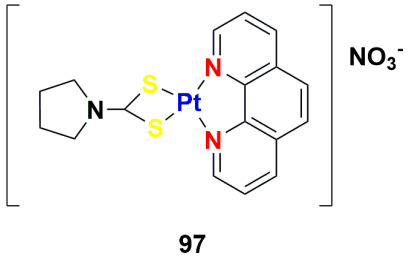
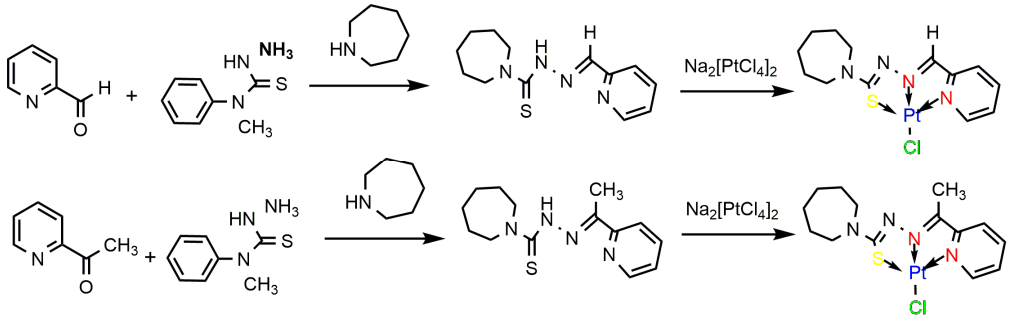


Fig. 25. Structure of Pt(II) complex of 1,10-phenanthroline and pyrrolidine thiocarbamate mixed ligands

In 2015, S. Shahraki et al. devised a novel water-soluble platinum(II) complex (**Fig. 25**) was prepared with mixed ligands of 1,10-phenanthroline and pyrrolidine dithiocarbamate, and characterized. The cytotoxic potency of the synthesized complex was studied against chronic myelocytic leukemia K562 cell lines with cisplatin standard drug. The complex (**97**) showed higher antitumor activity than the parent ligand and cisplatin drug against K562 cell lines.[44] In 2009, Dimitra Kovala-Demertzi et al. reported two new platinum(II) complexes (**Fig. 26**) with thiosemicarbazone derivatives were synthesized by solution of $Na_2[PtCl_4]$ was added to methanol solution of respective ligand. The mixture of solution was continuously stirred for 72h at 24 °C and then stored for 24h at 3–4 °C (**Scheme 11**). *In-vitro* and *in-vivo* antiproliferative activity of the synthesized ligand and corresponding platinum(II) complexes were screened against various human cancer cell lines such as breast cancer (MCF-7), bladder cancer (T24), non-small cell lung carcinoma (A-549) and a mouse L-929 (a fibroblast-like cell line cloned from strain L), leukemia P388 respectively, using MTT and SRB assay with standard drug cisplatin. The *in-vitro* antitumor study indicates that the two Pt(II) complexes (**98** and **99**) showed less activity than the respective ligand and the reference drug (cisplatin). The *in-vivo* results of complexes **98** and **99** reveal that they are less toxic than the parent ligand while their anti-leukemic activity was remarkably increased.[45]



Scheme 11. Synthesis of Pt(II) complexes with thiosemicarbazones derivatives

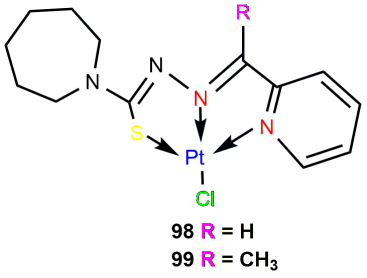


Fig. 26. Structure of Pt(II) complexes with thiosemicarbazones derivatives

In 2008, Weiping Liu et al. described five new novel platinum(II) complexes with 2-hydroxy-1,3-propanediamine (HO-pda) were synthesized, and structurally characterized and the structure of complexes (**100**-**104**) are given in **Fig. 27**. The *in-vitro* cytotoxicity of the newly prepared complexes was inhibited towards various human cancer cell lines such as A549 and A549/ATCC (lungs), SGC-7901 (gastric), and LN cap (Prostrate) using MTT assay with two reference drugs (carboplatin and cisplatin). All the complexes exhibited remarkable anticancer activity against SGC7901, LNcap, and A549 human cancer cell lines than carboplatin but less potency than cisplatin drug. Particularly, complexes **103** showed much better activity against the A549/ATCC human cancer cell line. Based on the *in-vitro* study, complex **103** was decided on *in-vivo* experiment towards sarcoma 180 in mice. It indicates complex **103** showed much better potency than carboplatin. Hence it is worthy of further growth as a potential drug for antitumor treatment.[46]

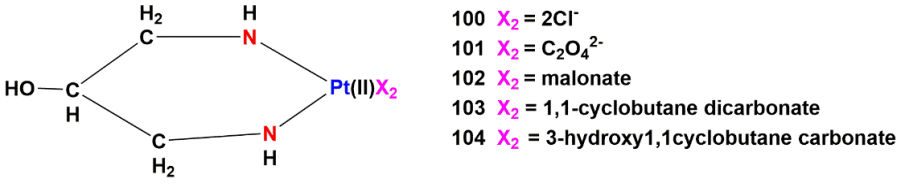
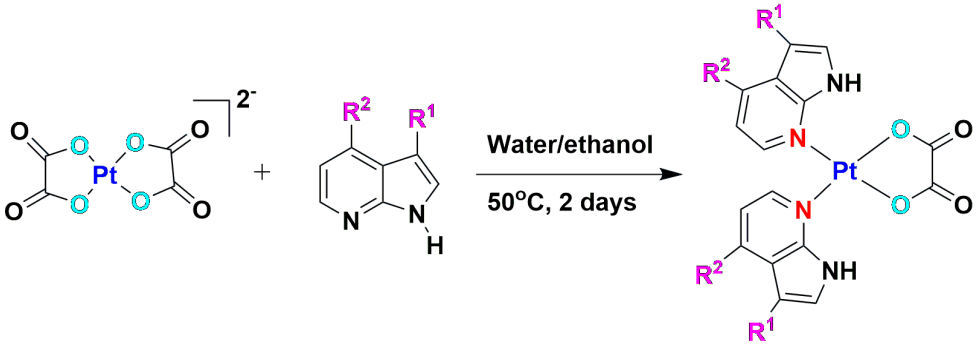


Fig. 27. Structure of Pt(II) complexes with 2-hydroxy-1,3-propanediamine

In 2014, Pavel Starha et al. devised a new novel series of three oxalato platinum(II) complexes (**Fig. 28**) that were synthesized by the hot distilled water solution of $K_2[Pt(ox)_2]\cdot 2H_2O$ was dropwise added to the ethanol solution of various ligands containing 4-chloro-7-azaindole (4Claza), 3-bromo-7-azaindole (3Braza) or 4-bromo-7-azaindole (4Braza) and the resulting solution was stirred for 48h at 50 °C (**Scheme 12**). The *in-vitro* antitumor activity of prepared compounds was inhibited against MCF-7 (breast adenocarcinoma) and HOS (osteosarcoma) human cancer cell lines with standard drug cisplatin and oxaliplatin using MTT assay. Complex **106** exhibited better antitumor potency against HOS and MCF-7 cancer cell lines with the IC_{50} value 27.5 µM and 18.3 µM respectively. The Complex **106** was further screened against another six human cancer cell lines, such as G361 (the malignant melanoma), HeLa (cervix carcinoma), A2780 (ovarian carcinoma), A2780R (cisplatin-resistant ovarian carcinoma), A549 (lung carcinoma) and LNCaP (prostate adenocarcinoma). Complex **106** showed remarkable and slightly better antitumor activity against A2780, HeLa cell lines and G361, A2780, HeLa respectively, compared to reference drug cisplatin and oxaliplatin.[47]



Scheme 12. Synthesis of oxalato Pt(II) complexes containing 7-Azaindole derivatives

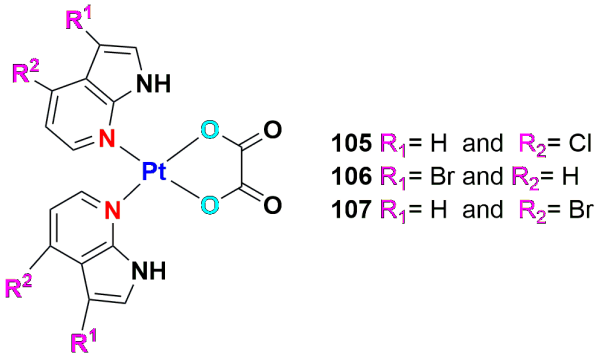


Fig. 28. Structure of oxalato Pt(II) complexes containing 7-Azaindole derivatives

In 2010, L. Fuks et al. reported three new Platinum(II) complexes (**Fig. 29**) with thiourea derivatives such as 1-(2-oxolanylmethyl)-2-thiourea, 1-(2-thiolanylmethyl)-2-thiourea and 1- (2-selenolanylmethyl)-2-thiourea were synthesized and the *in-vitro* cytotoxicity of the prepared complexes were evaluated by MTT assay against five human cell lines, such as WS1, ME18, ME18/R, HeLa, and KB-V1. Complex **110** found better cytotoxic activity than the other two complexes (**108** and **109**) against ME18/R, HeLa, and KB-V1 with the IC_{50} value are 0.099, 0.116, and 0.107 Mm respectively. The result of *in-vitro* cytotoxicity reveals that the Pt complex (**110**) with selenium-containing ligands is a good drug for cancer treatment and worthy of further research.[48]

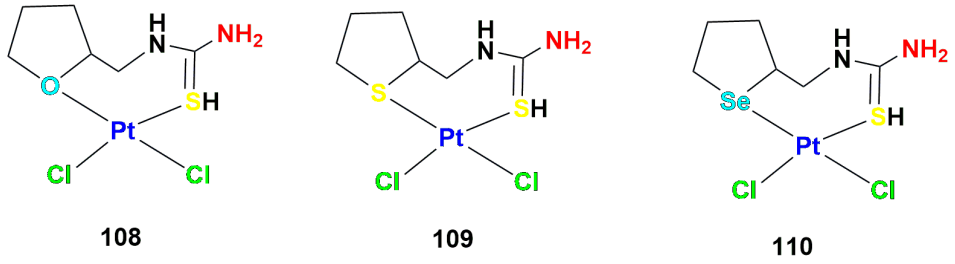


Fig. 29. Structures of Dichloro Pt(II) complexes with thiourea derivatives

In 2003, Daniel Kushev et al. proposed a series of four new platinum(II) complexes (**Fig. 30**) of 3-aminocyclopentanespiro-5-hydantoin and 3-aminocycloheptanespiro-5-hydantoin were synthesized, well characterized using various techniques. *In-vitro* cytotoxicity of the prepared complexes was evaluated using cell growth and macromolecular synthesis assay against murine erythroleukemia (MEL) cells, clone F4N. Complex **114** exhibited higher cytotoxicity than the other complexes tested but similar activity compared to standard drug cisplatin.[49]

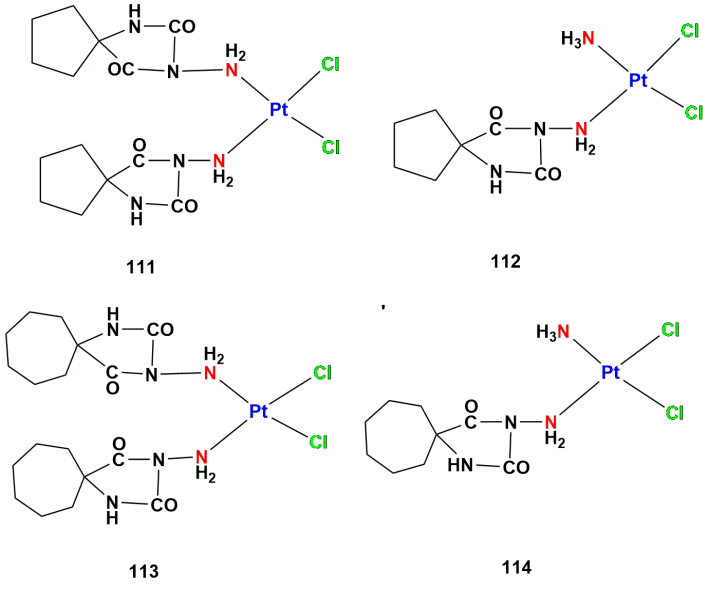


Fig. 30. Structures of Pt(II) complexes with 3-aminocyclopentanespiro-5-hydantoin and 3-aminocycloheptanespiro-5-hydantoin

In 1997, Fuan Zou et al. described a new series of novel platinum(II) complexes (**Fig. 31**) were prepared with various ligands involving selenato, the anion of squaric acid, and demethylcantharic acid and well characterized. *In-vitro* antitumor activity was screened using MTT assay towards six human neoplastic cell lines containing HCT (colon), KB (nasopharyngeal), BGC (gastric), HL60 (immature granulocyte leukemia), k-562 (erythro-leukemia), and Bel-7402 (hepatocellular) with cisplatin as a positive control. The complexes (**117**, **118**, **119**, and **120**) showed equal to or higher antitumor activity than cisplatin drug again in all the tested cancer cell lines. The observed LD_{50} value of the newly synthesized compounds indicates the toxicity relation with the reactivity of the leaving groups. Compared to cisplatin drugs, newly prepared complexes were found less acute toxicity but it does not affect the anticancer activity.[50]

In 2019, Qi-Pin Qin et al. reported a new Pt(II) complex (**Fig. 32**) with 3-(1H-benzoimidazol-2-yl)-8-fluoro-chromen-2-ylideneamine (BFCY) was synthesized by adding cis-$Pt(DMSO)_2Cl_2$ to a suspension containing BFCY ligand in DMSO and ethanol mixed solvent, followed by incubation for 24h at 80 °C (**Scheme 13**). The *in-vitro* cytotoxicity was carried out against various human tumor cell lines such as T-24, A549, HeP-G2, SK-OV-3, SK-OV-3/DDP, HeLa and one normal cell line HL-7702 by MTT assay method. The new Pt(II) complex **121** (IC_{50} = 2.08 μM) exhibited better antitumor activity

against cisplatin-resistant SK-OV-3/DDP cell line than the free BFCY ligand (IC_{50} = 95.23 µM)) and cisplatin drug (IC_{50} = 75.36 µM).[51]

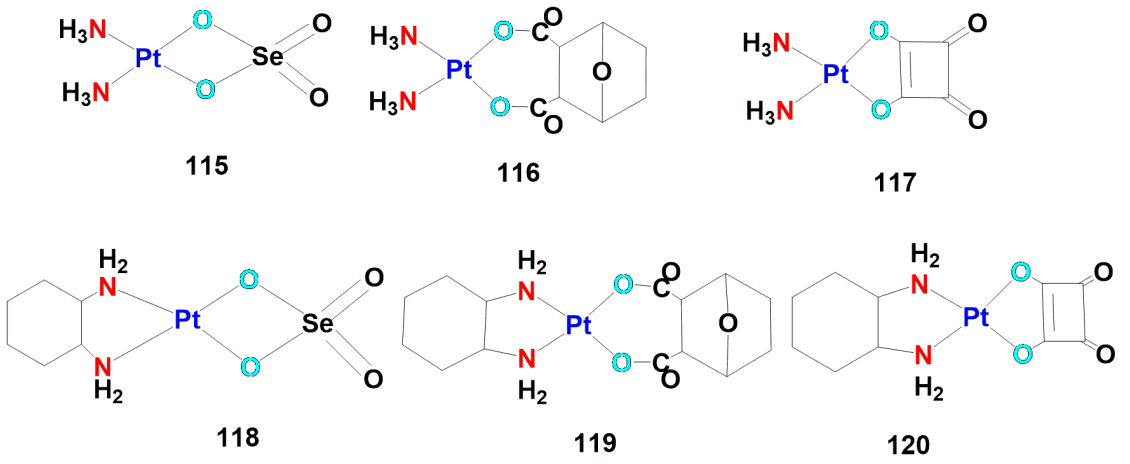
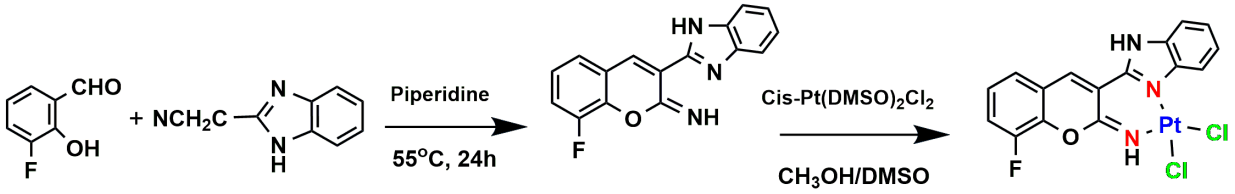


Fig. 31. Structures of diamine/diamino cyclohexane Pt(II) Complexes



Scheme 13. Synthesis of Pt(II) complex with BFCY (3-(1H-benzoimidazole-2-yl)-chromen-2-yldene amine) ligand

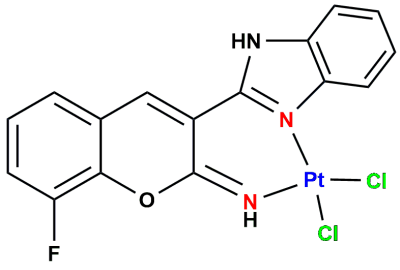
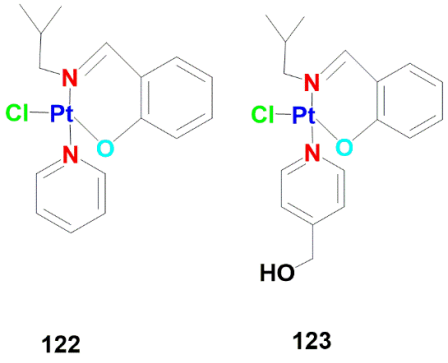


Fig. 32. Chemical structure of Pt(II) complex with 3-(1H-benzoimidazole-2-yl)-chromen-2-yldene amine (BFCY)

In 2015, Faiz-Ur Rahman et al. devised two mono-metallic (**Fig. 33, 122** and **123**) and one di-metallic (**Fig. 35**, **127**) trans-Pt(II) complexes were synthesized with salicylaldimine and pyridine/pyridine-4-carbinol ligands, structurally well characterized and biologically study of *in-vitro* anticancer activity was studied against MCF-7 and HepG2 human cancer cell lines using MTT assay with cisplatin as a positive control. The newly prepared complexes found remarkable cytotoxic activity towards both cancer cell lines than the cisplatin reference drug. Particularly, mono-metallic **123** (IC_{50} = 6.3 µM) and di-metallic **127** (IC_{50} = 6.3 µM) complexes showed high anticancer potency against HepG2 and MCF-7 cancer cell lines respectively, compared to the other cell lines but less activity compared to cisplatin drug (IC_{50} = 4.1 µM for HePG2 and 4.3 µM for MCF-7).[52]

In 2016, Muhammad Kasif et al. reported a new class of heteroleptic platinum(II) dithiocarbamates (**Fig. 34**) were prepared using -(4-methoxyphenyl)piperazine-1-carbodithioate, 4-(furan-2-carbonyl)piperazine1-carbodithioate, tri(4-flourophenylphosphine) and tri(4-chlorophenylphosphine) ligand, and characterized. The *in-vitro* cytotoxicity of the new complexes was screened against five different cancer cell lines such as LU (lung), MCF-7 (breast), Hepa-IcIc7 (liver), PC-3 (prostate), MDA-MB-231 (breast) by MTT assay with cisplatin reference drug. All newly synthesized complexes were

found more active than cisplatin drugs in all tested cancer cell lines. In particular, complexes **124** showed better anticancer activity than complexes **125** and **126**. The greater potency of the complexes **124** can be ascribed to the fluoro group because of either its ability to effectively penetrate the cell membrane or to stabilize Pt complex-DNA adducts through hydrogen bonding.[53]



122 123

Fig. 33. Chemical structure of trans-Pt (II)Complexes with Salicylaldimine and pyridine/pyridine-4-carbinol

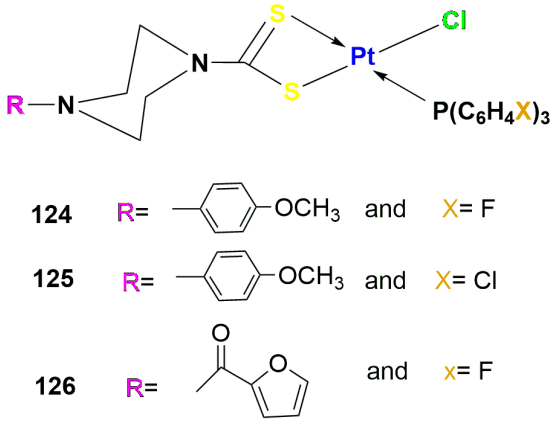
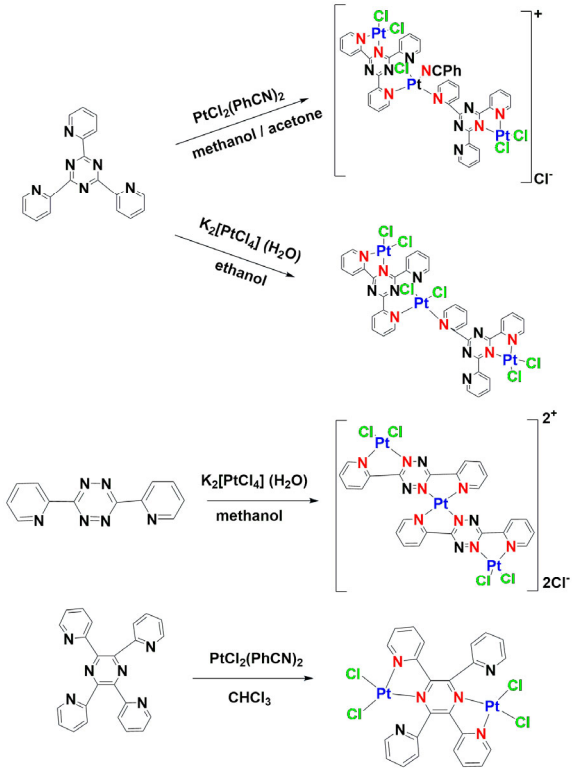


Fig. 34. Structure of heteroleptic Pt(II) dithiocarbamates

4. Polynuclear Platinum(II) Complexes

Several poly-metallic Cisplatin analogs with various ligand derivatives were reported in this study. In 2009, S. Rubino et al. proposed non-classical polymetallic platinum(II) complexes **128-131** (**Fig. 35**) with multidentate nitrogen ligands involving 2,4,6-tris(2-pyridyl)-1,3,5-triazine (tptz), 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (bptz) and 2,3,5,6-tetra(2-pyridyl)pyrazine (tppz) were synthesized using the respective Platinum complex such as $PtCl_2(PhCN)_2$, K_2PtCl_4. The reaction mixture was refluxed in the dark condition for 24h (**Scheme 14**). The cytotoxicity of newly prepared complexes was evaluated using 3-(4,5-dimethyl-2-thiazole)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay against HT29, HepG2, MG63 and MDA-MB-231 cancer cell lines with cisplatin (positive control). All newly prepared complexes exhibited remarkable anticancer activity against all the tested cell lines other than the cisplatin drug. Particularly, complexes **128** (IC_{50} = 9 µM) and **130** (IC_{50} = 8 µM) showed excellent cytotoxicity towards HT29 and MG63 cell lines respectively.[54]



Scheme 14. Synthesis of polynuclear platinum(II) complexes with heterocyclic ligands

Zhang Jinchao et al. described a new iodo-bridged di-metallic platinum(II) complex **132** (**Fig. 35**) that has been synthesized, and characterized by various spectral techniques. The cytotoxicity activity of newly prepared complexes was inhibited against HL-60, HCT-8, MCF-7, BGC-823, and EJ cancer cell lines using MTT and SRB assay. Complex **132** displayed better anticancer activity against all the tested cancer cell lines than the standard drug cisplatin. Particularly, complexes **132** showed highly remarkable cytotoxicity against the HL-60 (IC_{50} = 0.98 μM) cancer cell line than the cisplatin (IC_{50} = 4.45 μM).[55] In 2000, Seiji Komeda et al. reported a new series of azole-bridged bi-metallic platinum(II) complexes **133-136** (**Fig. 35**) was synthesized, and characterized. *In-vitro* cytotoxicity of the new Pt(II) complexes evaluated against various human tumor cell lines containing MCF-7, EBSA-T, WIDR, IGROV, M19, A498, and H226. Complexes **133** and **134** exhibited much higher potency than the standard drug (cisplatin). Complexes **135** and **136** showed moderately and marginally active than the cisplatin respectively.[56] This work confirms the high importance of bioactive compounds in different fields as shown in a lot of papers published before.[57-59]

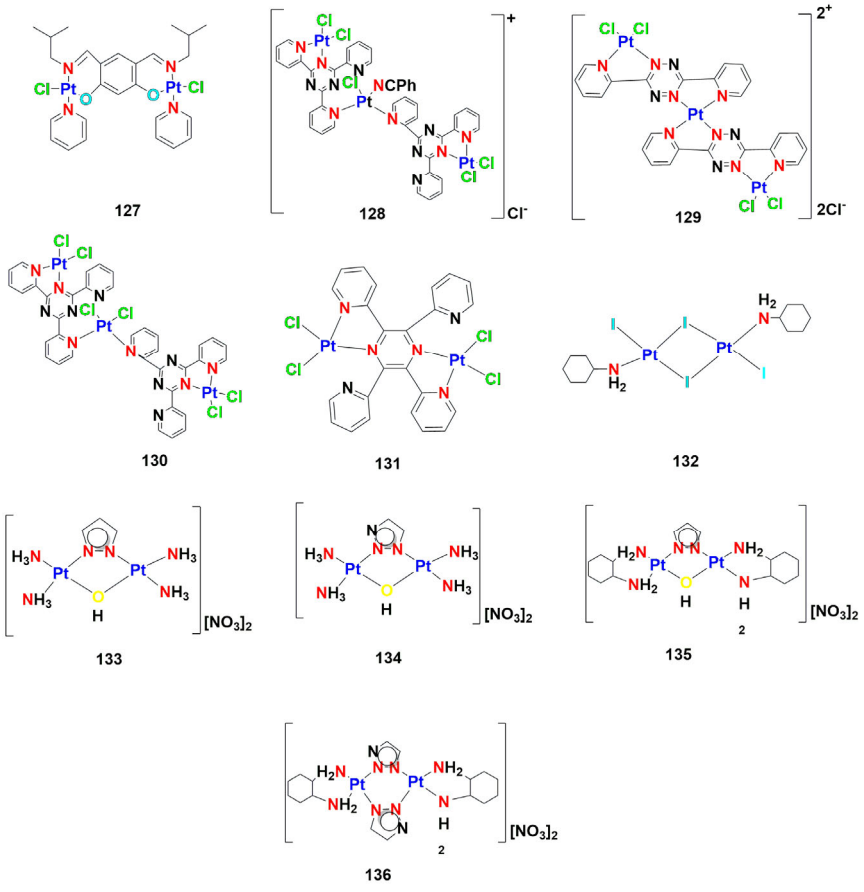


Fig. 35. Polymetallic Pt(II) complexes with various ligands

5. Conclusions

It is increasing attention on the manipulative various kinds of cisplatin analogs which have significant anticancer potency to successfully remove the defects of prevailing medical drugs. Different types of new cisplatin-modified complexes are expected to substitute the classical platinum drug cisplatin increasing the therapeutic effect and decreasing the side effects. In the present study, various mono-metallic cisplatin analogs showed similar or better anticancer activity than the parent cisplatin drug but less toxicity against normal cell lines. Particularly, mononuclear cisplatin analogs of various derivatives such as ferrocene, caffeine, thiourea, hematoporphyrin, and fluoropiperazinyl exhibited remarkable cytotoxicity against tested cancer cell lines compared to cisplatin reference drugs. Polynuclear Pt(II) complexes containing heterocyclic ligands showed better anti-cancer potency than the standard cisplatin drug. Especially, triazine heterocyclic Pt(II) complexes **129** and **130** exhibited much better anti-cancer activity than the other complex. The triazine Pt(II) complexes contain three different Pt(II) moieties, probably behaving in a bifunctional coordination mode with DNA molecules. The *in-vitro* and *in-vivo* studies of the Iodo-bridged binuclear Pt(II) complex **132** indicate greater cytotoxicity than the standard drug (cisplatin and carboplatin) with all tested cell lines. Complex **132** showed similar cytotoxicity to that of the reference drug at the dose of 4 mg/kg but remarkable activity at the dose of 12 mg/kg. Acute toxicity studies showed that the toxicity of complex **132** (LD_{50} = 815 mg/kg) is appreciably lesser than that of carboplatin (LD_{50} = 150 mg/kg) and cisplatin (LD_{50} = 14 mg/kg) standard drugs. It indicates that it may enhance the medicinal effect by using higher doses.

Overall, polynuclear (di- and tri-metallic) cisplatin analogs have greater anticancer activity towards various cancer cell lines than mononuclear cisplatin analogs. Future perspectives will pay attention to Pt(II) complexes, demonstrating enhanced tumor selectivity and activity in resistant tumor cells to increase the therapeutic potency, and combinations of these methods can afford more remarkable developments. With the advance of research, novel platinum drugs that have potent curative effects and reduced toxicity are expected.

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