REVIEW ARTICLE

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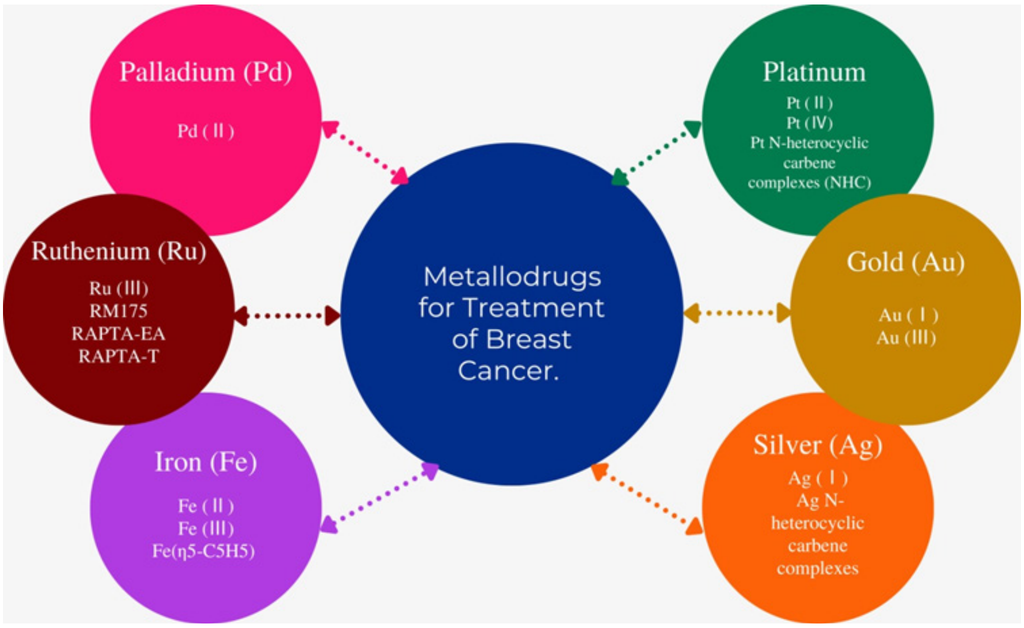

Highlights

- Breast cancer is increasingly being attributed to improper medication therapy.
- Metallodrugs have a significant function to play in a number of diseases, but primarily in cancer.
- One of the earliest metallodrugs, platinum, can be effectively treated with combination therapy.
- Ruthenium complexes, such as RAPTA, NAMi-A, and KP1019, can bind proteins, leading to mitochondrial apoptosis and ultimately cell death, thus can also inhibit the invasion of tumour cells and lessen metastasis.

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A Comprehensive Review on Metallodrugs in Breast Cancer Treatment

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Abstract: It is shocking that breast cancer (BC) now outnumbers lung cancer in terms of global cancer diagnoses. Being deadly to some extent, such a disease's treatment is crucial. Surgery, radiation therapy, chemotherapy, hormonal therapy, and targeted therapy are just a few of the treatment options available for this condition. By using ligand substitution to alter the current chemical structure or by creating an entirely new element with a higher safety and cytotoxic profile, the metallodrugs are created. Due to their tempting treatment against cancer and their capacity to produce reactive oxygen species (ROS) and reactive nitrogen species (RNS), which cause oxidative damage and cellular death, metals are extremely efficient in the fight against cancer. The whole list of recently found complexes (in vivo/vitro), their mode of action against the tumour, and the mechanical information gathered by various scientists have all been discussed in the following paragraphs. This review highlights the research that has been conducted over the past 22 years by many experts and provide comprehensive information regarding the use of metals as a medicine for the treatment of BC. Also, this review covers a variety of prospective metal therapies down the line with their success stories.

Keywords: Anticancer drugs; Breast cancer; Proliferation; Hormones; metallodrugs

INTRODUCTION

Initially, the research topic was selected based on the potential of metallodrugs as a type of medication, and breast cancer was chosen as it is one of the most prevalent types of cancer. For data collection, a comprehensive literature search was conducted using publicly available electronic databases such as PubMed, Science Direct, Bentham Science, Scopus, Wiley, and Taylor & Francis database. The search utilized keywords such as "Breast Cancer," "Platinum as a metallodrug," and similar titles with various metal names including gold, palladium, copper, ruthenium, and iron. The terms "physiology" and "anatomy" were used in their appropriate contexts. The literature search spanned from the early 1900s to November 2022, including non-English language literature that was translated into English for analysis.

Breast Cancer

BC has surpassed lung cancer as the most common malignancy diagnosed worldwide, approximately 2.3 million of new-fangled cases (11.7 percent of all malignancies worldwide) (Sung *et al*., 2021). Five to ten percent of those with BC are first identified with advanced or metastatic disease; up to one-third of those with early BC may go on to develop advanced or metastatic sickness (Harding *et al*., 2013a; Cardoso *et al*., 2017; Drury *et al*., 2022). The 5-year relative survival rate for denovo metastatic BC increased from 18% to 36% between 1992 and 2012, while people with advanced BC are surviving longer on average as a result of better treatment choices (Drury *et al*., 2022).

Three types of additional BC subtypes are identified (Harbeck *et al*., 2019):

i) Histological subtypes:

a) Preinvasive

Ductal carcinoma in situ (DCIS), Spreads through ducts and distorts ductal architecture; can progress to invasive cancer; unilateral.

b) Invasive

Ductal carcinoma no special type (NST), Develops from DCIS; fibrous response to produce a mass; metastasizes via lymphatics and blood.

ii) Intrinsic subtypes (PAM50):

a) Basal

BRCA (Breast Cancer gene) mutations; TP53 mutations; genetic instability; medullary-like histology poorly differentiated.

b) Claudin low

Largely triple negative; metaplastic.

c) HER2-enriched (human epidermal growth factor receptor 2)

HER2-enriched HER2 amplification; GRB7 (Growth factor receptor-bound protein 7) amplification; PIK3CA (Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic) mutations; TOP2 (Topoisomerase II) and/or MYC amplification; NST, micropapillary histology and pleiomorphic lobular.

d) Luminal B

ESR1 mutations (30–40%) a; Luminal B PI3KCA mutations (40%); ERBB3 and ERBB2 mutations; NST, atypical and micropapillary lobular histology.

e) Luminal A

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Activation of FOXA1 (Forkhead box protein A1), GATA3, ERS1, XBP1 (X-box binding protein 1); NST, classic lobular histology and tubular cribriform.

iii) Surrogate intrinsic subtypes:

a) Triple-negative

PR–, HER2–, ER–; high grade; high NST histology; Ki67 index; special type histology (adenoid cystic, secretory, metaplastic and medullary-like); save for a few unique varieties, dismal prognosis.

b) HER2-enriched (non-luminal)

HER2+, PR–, ER–; high grade; NST histology; high Ki67 index; intermediate prognosis; aggressive illness that is responsive to specific treatments.

c) Luminal B-like HER2+

ER+ but less pronounced ER and PR than luminal A-like; HER2+; high Ki67 index; higher grade; pleiomorphic and NST; responds to targeted therapies; intermediate prognosis.

d) Luminal B-like HER2–

ER+ nevertheless PR and ER expression inferior than in luminal A-like; HER2–;high Ki67 index; high-risk GES; higher grade; NST, lobular and micropapillary pleiomorphic histology; transitional prognosis.

e) Luminal A-like

Luminal A-like Sturdily PR+ and ER+; HER2–; low-slung proliferation rates; typically, low grade; low Ki67 index; low-risk GES; NST, classic lobular histology and tubular cribriform; upright prognosis.

All BCs originate in the terminal duct lobular units of the collecting duct, which is the functional unit of the breast. Molecular and Histological characteristics have been used to create a variety of classifications because they have substantial therapeutic implications. The most common subtypes of BC are represented by the histological subtypes shown here. Ductal carcinoma, also known as NST, and lobular carcinoma are the invasive lesions, while lobular carcinoma in situ and DCIS, also known as lobular neoplasia, are the preinvasive forms of these lesions. The essential subtypes of Sorlie and Perou (Perou *et al*., 2000) rely on the PAM50, a list of 50 genes that express themselves, as their foundation (Cheang *et al*., 2015). The main proteins that are expressed in histology and immunohistochemistry to ascertain the surrogate essential subtypes, which are frequently used in clinical settings, include the progesterone receptor (PR), oestrogen receptor (ER), the proliferation marker Ki67, and HER2. Tumors that are triple-negative lack the countenance of PR, HER2, and ER. Tumors articulating PR and/or ER are referred to as hormone receptor-positive tumours. The qualities (such proliferation and grade) in green are correlated with the relative location of the boxes. Negative -; positive +. GES stands for gene expression signature. ESR1 mutations are brought on by targeted therapy with aromatase inhibitors. The countenance of normal breast components is an artefact because of the restricted tumour cellularity (Harbeck *et al*., 2019).

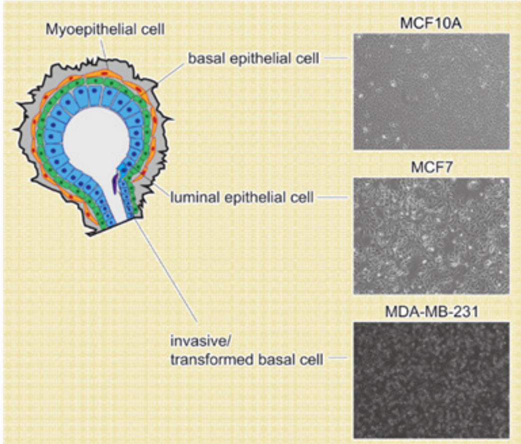


Figure 1: Different types of breast cell lines (Source: Bruce, 2019).

Physiology of the Breast

Physically, the breast is an organ with a focus on producing milk (lactation), including secretion, ejection and synthesis of milk (Grey, 2008; Ellis *et al*., 2013; Bistoni *et al*., 2015). The lactiferous ducts and tiny saccules known as alveoli make up the breasts' secretory organs. These secretory organs are managed by a complex system of growth factors and hormones that control milk production. The fluctuation of these hormones results in significant histologic changes in the breast throughout pregnancy and the menstrual cycle (Anderson, 2002; Bistoni *et al*., 2015).

There are no obvious functional or anatomical distinctions between the male and female breasts before puberty. According to histology, the prepubertal breast in both boys and females is made up of several rudimentary ducts that are circumferentially oriented and converge towards the nipple. Each primitive duct has underdeveloped but possibly secretory acini at the blind end (Ellis *et al*., 2013).

The female breast undergoes significant change throughout puberty, culminating in a discernible sexual dimorphism. These changes are the result of the breast's unique response to certain common hormonal stimuli. The breast physiology explanation that follows only relates to female breasts (Ellis *et al*., 2013).

Lactation, which refers to the creation, secretion, and evacuation of milk, is the primary function of the female breast. The female breast is another obvious secondary sexual trait. Oestrogen (oestradiol), which causes the duct system to multiply and branch out as well as the nipples to mature and become more noticeable, is crucial for the development of the female breast throughout puberty. But at the ab-areolar extremities of the ducts, oestrogen and progesterone function together and synergistically to promote the formation and proliferation of acini (alveoli). In the breast tissue, a range of paracrine factors, some of them which are stimulatory and others of which are inhibitory, regulate cell division and differentiation. These paracrine regulators include the growth factors insulin-like growth factor B (IGF), epidermal growth factors, and transforming growth factors (TGF) (Ellis *et al*., 2013).

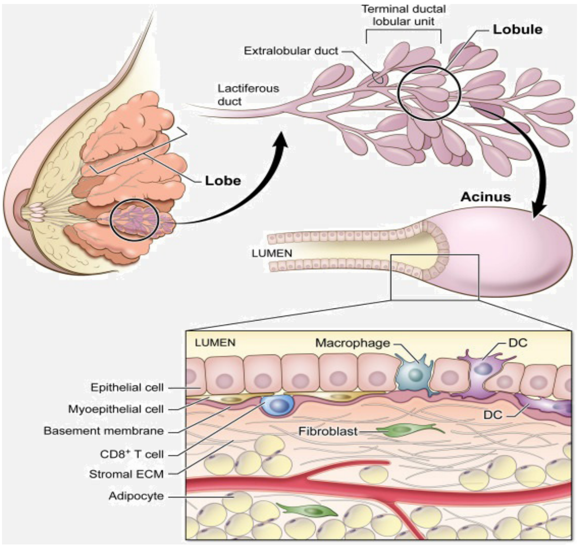


Figure 2: Breast Physiology (Messier *et al*., 2016).

Metallodrugs for treatment of BC

Due to its high rate of metastasis and invasion of the lymph nodes, lungs, bones, and even the brain at the final phase of the disease, BC is one of the major causes of mortality in women (Cheung *et al*., 2013; Marmot *et al*., 2013; Q. Wu *et al*., 2014). There are several therapies available to ease cancer-related symptoms, slow the spread of the disease, lengthen and enhance quality of life, but metastatic BC (MBC) is still a fatal disease (Eckhardt *et al*., 2012; Harding *et al*., 2013b).

With regard to BC in particular, the triple negative BCs (TNBC) are a significant molecular subtype, including the basal-like type that lacks the expression of the ER-/PR-/HER2- and the oestrogen, progesterone. TNBC, which makes up roughly 15% to 20% of all BCs, has one of the worst prognoses and patient survival rates. TNBC mortality and incidence are often greater among younger women, as well as disproportionately among those with African and Hispanic heritage (Li *et al*., 2003; Lara-Medina *et al*., 2011; Sineshaw *et al*., 2014; Kohler *et al*., 2015; Everton *et al*., 2021; Nayeem *et al*., 2021). Its "molecular heterogeneity, which is defined as "a lack of recurring oncogenic driver changes," is a significant contributor to TNBC morbidity (Lehmann *et al*., 2016). TNBCs may be classified into four molecular subtypes (BL1, BL2, M, and LAR) based on their transcriptional heterogeneity, "taking into account the input of transcripts from normal stromal and immune cells in the tumour environment" (Lehmann *et al*., 2016). In addition, individuals with (ER)-negative BC have a considerably higher chance of recurrence over the first five years after diagnosis than do those with ER-positive tumours. Human BRCA1 and BRCA2 gene mutations significantly raise the risk of breast and other cancers in women, with a BRCA1 mutation increasing the chance of TNBC.

The amazing biological potential of silver (Ag), particularly its anticancer potential, has led to the introduction of Ag coordination complexes, nanoparticles, and organometallic compounds during the last several years (Fichtner *et al*., 2012; Haque *et al*., 2015; Kalaiarasi *et al*., 2015; Mittal *et al*., 2015; Mohamed *et al*., 2015; Nayak *et al*., 2015; Mollick *et al*., 2019). Numerous Ag(I)-NHC (Pt N-heterocyclic carbene complexes) complexes made from azolium salts with an unsubstituted benzene ring have been tested against different cancer cell lines, including ovarian cancer (OVCAR-3), cervical cancer (HeLa), BC (MB157), and renal cancer (Caki-1) (Habib *et al*., 2019). According to research, the lipophilic or hydrophobic nature of Ag(I)-NHC complexes, which in turn relies on the electronic or steric component of substituents, largely controls their anticancer potential (Haque *et al*., 2018).

Although the metallodrug cisplatin is a highly efficient anticancer therapy, there are several downsides to its use, including the fact that it only works against a few types of cancer and that prolonged use may cause serious side effects such bone marrow suppression, nausea, and kidney damage. Due to its great potency, it forces patients to stop treatment since it causes them severe pain (Habib *et al*., 2019).

The RAPTA complexes, also known as ruthenium (II)-arene 1,3,5-triaza-7-phosphaadamantane (PTA) complexes, have potential anticancer properties (Weiss *et al*., 2014; Lee *et al*., 2015; Murray *et al*., 2016). These RAPTA complexes precise mode of action is still mostly unknown. They are known to behave biochemically differently from traditional Pt anticancer medications, whose interactions with nucleic acids are assumed to be their main mechanism of action (Ratanaphan *et al*., 2010; Ang *et al*., 2011; Atipairin *et al*., 2011; Adhireksan *et al*., 2014). RAPTA complexes seem to prefer to bind to proteins (Babak *et al*., 2015). A variety of BC cells have been used in experiments to elucidate the biological basis of RAPTA action. It has been shown that RAPTA-C, [Ru(6-pcymene) Cl2(PTA)], inhibits tumour cells removed from mice via the mitochondrial apoptotic mechanism (Chatterjee *et al*., 2008). Its derivative, RAPTA-EA1 (Ruthenium(II)-arene 1,3,5-triaza-7- phosphaadamantane (pta) complex with an arene-tethered ethacrynic acid ligand), was created and shown to inhibit glutathione S-transferase (GST) activity in cisplatin-resistant cancer cells, such as the A2780cisR ovarian carcinoma cell lines (Ang *et al*., 2007). RAPTA-EA1 is a ruthenium (Ru) complex with an ethacrynic acid (EA) ligand bound to an arene. Additionally, RAPTA-EA1 possesses a variety of mechanisms for inducing apoptosis in MCF-7 cells, including an increased permeability of the mitochondrial membrane that resulted in the release of apoptosis-inducing enzymes (Chatterjee *et al*., 2011). We looked at the cellular response to its direct interaction with a familial (BRCA1-defective) BC cell line and compared the outcome to the effect on a sporadic (BRCA1-competent) BC cell line because the anticancer activity of this RAPTA-EA1-type complex on BRCA1-defective BC cells has not been investigated.

Ru complexes, particularly arene Ru(II) complexes, have recently shown great prospects for the cure of BC. A growing body of research has shown that arene Ru complexes have minimal toxicity and significant anti-invasion and anti-metastasis belongings in vivo and in vitro (Scolaro *et al*., 2005; Bergamo *et al*., 2010; Q. Wu *et al*., 2014). For instance, NAMI-A (imidazolium trans-[tetrachloro(dimethylsulfoxide)(1H-imidazole) ruthenate(III)]) has the ability to block tumour cell invasion and diminish tumour metastasis with high specificity in vitro (Wu *et al*., 2014). KP1019 (trans-[tetrachlorobis(1H-indazole)-ruthenate(III)]) may also prevent MDA-MB-231 BC cells from migrating and invading by lowering the release of MMP-2/9 from the extracellular matrix (Wu *et al*., 2014). RAPTA-B ([Ru(Z6 -C6H6)(pta)Cl2]) and RAPTA-C ([Ru(Z6 - p-C6H4Mei Pr)(pta)Cl2]), two arene Ru complexes described by Dyson, may stop tumour development and metastasis in CBA mice carrying the MCa (Mucin-like Carcinoma-associated Antigen) mammary cancer via preventing angiogenesis. Furthermore, the arene Ru complex RM175 ([(Z6 -biphenyl)Ru(ethylenediamine) Cl]+) inhibits tumour metastasis in vivo and lessens invasion and metastasis by encouraging cell-cell re-adhesion and reducing the release of metalloproteinases (MMPs) (Bergamo *et al*., 2010).

BC-related metal complexes with clinical evidence

Platinum (Pt)

Spanish scientist Antonio de Ulloa received credit for discovering Pt in 1748 (Odularu *et al*., 2019). With an atomic mass of 195.084, an atomic number of 78, and the symbol Pt, Pt is a transition metal. The term “platina,” which translates to “small Ag,” is where the name Pt first appeared. Inorganic chemistry experts often cite the chemical cis-[PtCl2(NH3)2], also known as cisplatin, as an illustration of how certain beneficial health benefits of inorganic compounds have been found accidentally throughout history. Escherichia coli stopped replicating in the presence of Pt electrodes in 1960 (Shah *et al*., 2009), and Barnett Rosenberg *et al*. mistakenly hypothesised that one of the compounds produced from the experimental materials and conditions, [(NH4)2][PtCl6], was the cause of the observed inhibition (Barnett Rosenberg *et al*., 1965; B. Rosenberg *et al*., 1967). This observation was made with the initial goal of studying the influence of electric fields on the mitosis of Escherichia coli. Cisplatin is now one of the chemotherapeutic drugs used to treat cancer in situ. It is also successfully utilised in combination treatments to treat metastatic cancer. For instance, (Franciosi *et al*., 2011) investigated the effectiveness of cisplatin/etoposide treatment in patients who had previously had radiation for brain metastases from BC, non-small-cell lung carcinoma, and melanoma. According to this study’s findings, individuals with brain metastases from BC and non-small-cell lung cancer respond well to the cisplatin/etoposide combination treatment (Franciosi *et al*., 1999).

Additionally, in a small nonclinical investigation, tocilizumab decreased the epithelial-mesenchymal transition (EMT) and boosted apoptosis, which increased the lethal effects of cisplatin in vitro and in vivo in a triple-negative BC model. These findings suggest that the tocilizumab/cisplatin combination treatment may reduce the ability of highly aggressive BC cells to proliferate (Alraouji *et al*., 2020).

Originally known as JM8, carboplatin is a second-generation anticancer medication that is mostly used to treat OVCAR but has also shown promise in treating head and neck, cervical, breast, lung, and bladder cancers (Ardizzoni *et al*., 2007). The low toxicity of carboplatin, which may be caused by the presence of a chelating 1,2-cyclobutanedicarboxylate ring (leaving group) and a

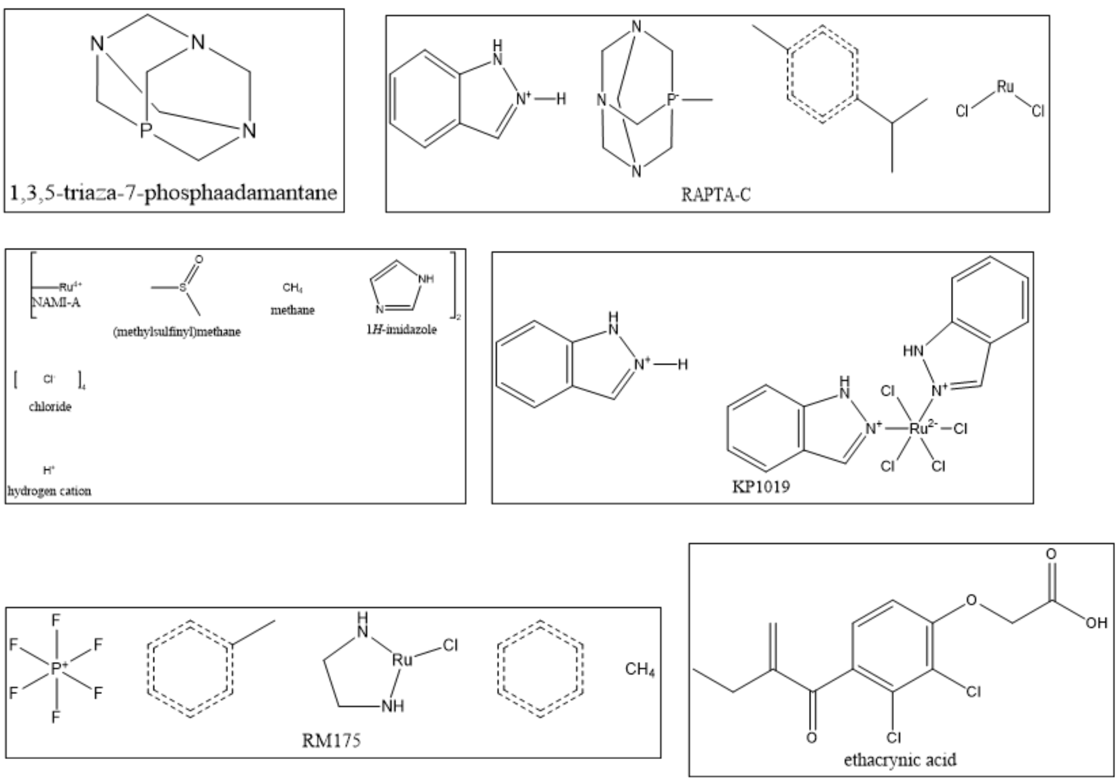


Figure 3: Actively used metals as drugs with few ligands.

particular shape of the ligand, is largely responsible for its efficacious intervention (Lazarević *et al*., 2017).

When referring to Pt (II) and Pt (IV) as a pair, any reduction and intracellular alteration of these complexes provide many chances to alter bioactive ligands as tumor-targeting molecules (Frezza *et al*., 2010). Barnes *et al*. developed a Pt(IV)-estrogen combination to sensitise ER(+)-BC cells and overcome cisplatin resistance based on the discovery that estrogen-treated ER(+) BC cells are sensitised to cisplatin (He *et al*., 2000). One equivalent of cisplatin and two equivalents of estrodiol were released as a result of the substance's intracellular decrease. The high mobility group protein (HMGB1), a protein critical for inhibiting Pt-DNA (Deoxyribonucleic acid) adduct repair, is upregulated as part of its mechanism (Barnes *et al*., 2004; Frezza *et al*., 2010). Additionally, they have several negative effects.

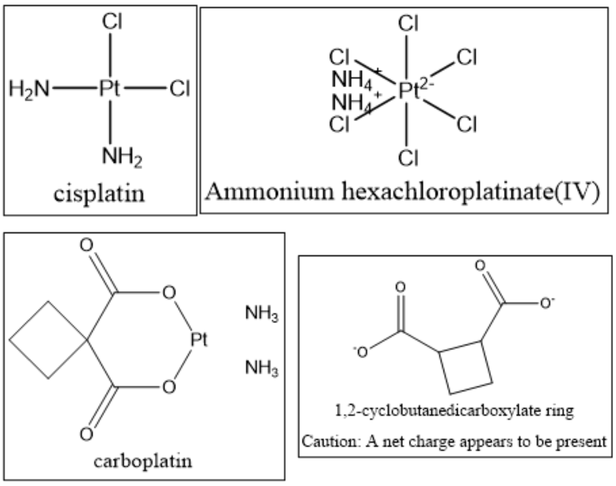


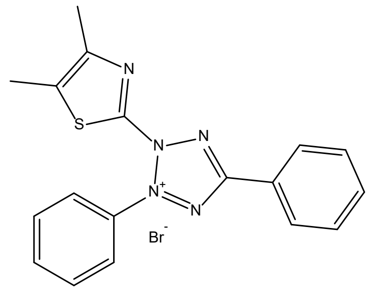
Figure 4: Pt based metallodrugs as well as its ligand.

Pt (II)

BC therapy study with Pt (II) has several evaluations and investigations, and the review will evaluate some of them.

According to Carmichael research, the vitality of MCF-7 and MDA-MB-231 BC cells was assessed using the Carmichael technique, which used 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Evaluation of a tetrazolium-based semiautomated colorimetric assay: assessment of chemosensitivity testing - PubMed, n.d.). MCF-7 and MDA-MB-231 cells were treated for 24 hours with varied doses of the chemicals Pt10 Pt2(3-ethylpyridine)4(berenil)2, Pt11 Pt2(3-butylpyridine)4(berenil)2, and cisplatin. Although cytotoxicity was concentration-dependent in both cell lines, it was more evident in MDA-MB-231 at shorter durations than in MCF-7. They discovered that the chemicals Pt10 and Pt11 reduced the number of viable cells in both ER-positive (MCF-7) and ER-negative (MDA-MB-231) BC cells more than cisplatin. According to the findings of this investigation, the examined Pt10 and Pt11 have strong impacts that reduce BC cell's capacity to survive, with IC_{50} (Inhibitory concentration) value after 24h of incubation in MCF-7 and MDA-MB231 BC cells 45 ± 2M and 30 ± 2M for Pt10 and 20 ± M and 11 ± 2M for Pt11, respectively. After 24h of incubation IC_{50} values for the cisplatin alone in MDA-MB-231 and MCF-7 cells were 93 ± 2 and 82 ± 2M, respectively (Bielawski *et al*., 2013).

The anti-growth impact of the Pt (II) complex was further studied using the RTCA system (xCELLigence) for additional investigations in another research. This technique allows for the determination of the individual dosages of the complex that cause cytotoxic, cytostatic, or anti-proliferative effects. The combination was applied 24 hours after the cells were seeded. Both cell lines were cytotoxic at significantly greater dosages of 25 and 50 M. 12.5µM was likewise cytotoxic to MDA-MB-231 cells, however it seems to be cytostatic to MCF-7 cells. The combination had an antiproliferative impact on both cell lines at 6.25µM and lower dosages. The findings showed that MDA-MB-231 cells were somewhat more sensitive than MCF-7 cells, which was consistent with the MTT and ATP viability test results (Oral *et al*., 2015). Pt (II) complexes may have anticancer properties in many cancer types (Özçelik *et al*., 2012; Proetto *et al*., 2012; Ibrahim *et al*., 2014). Indeed, they discovered that the Pt (II) complex inhibited the proliferation of MCF-7 and MDA-MB-231 human BC cell lines in a dose-dependent way (Oral *et al*., 2015).



3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

Figure 5: Most frequently used methods for measuring cell proliferation and neural cytotoxicity.

Pt (IV)

In TNBC cell lines, Pt (IV) coordination compounds with cisplatin and bioactive ligands in axial positions—such as COX- and PD-L1 inhibitors, RAD51-targing moieties, vitamins, DNA-alkylating agents, tumour vascular disrupting agents, and other drugs—have proven to be effective. These compounds can also combine effects on various cellular compartments (Neumann *et al*., 2014; Muhammad *et al*., 2017; Shuren Zhang *et al*., 2018; Guo *et al*., 2019; Nayeem *et al*., 2021;).

NSAIDs (Non-steroidal anti-inflammatory drug) (indomethacin and ibuprofen) and other cyclooxygenase inhibitor-containing cisplatin conjugates, such as Pt-IBu, have been described by Hey-Hawkins and colleagues (Neumann *et al*., 2014), on the TNBC MDA-MB-231 cell line, were discovered to be cytotoxic (with complex displaying IC_{50} value in the nanomolar range 0.05 nM, 72 h). However, it was shown that the potency was not primarily caused by COX-2 (cyclooxygenase-2) suppression (Neumann *et al*., 2014). The biotinylated Pt(IV) conjugates disclosed by Guo, Wang, and colleagues include Pt-Bio-1 (Muhammad *et al*., 2017), exhibited more cytotoxicity than cisplatin (18 ± 2.7 µM, 48 h) on the MDA-

MB-231 cell line, but was more selective when tested on healthy MCF a breast cell lines. The authors discussed how platination of the cell and better interactions with DNA upon reduction to Pt (II) species were both enhanced by having one unsubstituted axial ligand (Muhammad *et al*., 2017). Additionally, these authors discussed cisplatin conjugates containing RAD51-targeting moieties, which mediate how sensitive cancer cells are to DNA-damaging substances through homologous recombination. Examples of these compounds include artesunate (PtArt2) (Shuren Zhang *et al*., 2018).

Recently, Guo, Wang, and colleagues reported the discovery of a Pt(IV) combination with a tumour vascular disrupting drug (DMA=5,6-dimethylxantthenone-4-acetic acid) and cisplatin (10, PDMA) (Guo *et al*., 2019). MDA-MB-231 TNBC cell lines were shown to be more cytotoxic to a substance than cisplatin (3.3 ± 0.4 µM, 72 h). Compounds with axial ligands have higher lipophilicity and cellular uptake. The substance was discovered to have antimigratory and antiangiogenic characteristics as well as to damage DNA (by increasing expression of the H2AX DNA damage marker). A Tg zebra fish model was used to illustrate the compound's antiangiogenic effects, and it also showed that it was less hazardous than cisplatin in this model (Guo *et al*., 2019).

Pt NHC

Cisplatin exerts its antitumor activity through interaction with the DNA and forming adducts that interfere with transcription and replication, thereby triggering programmed cell death (PCD) (apoptosis) (Cleare *et al*., 1973; Jamieson *et al*., 1999; Jung *et al*., 2007; Ott *et al*., 2007b). Cisplatin's interactions with DNA have been thoroughly researched, and it is now well understood that a cis-Pt-G-G intrastrand crosslink is the essential lesion that causes cisplatin toxicity (W. Liu *et al*., 2013). The phenomena of hazardous side effects and tumour resistance, however, limit the usefulness of cisplatin, as was previously noted (Wong *et al*., 1999; Ott *et al*., 2007a; W. Liu *et al*., 2013). Over the years, a large variety of Pt complexes have been studied with the intention of bypassing these restrictions by setting particular objectives (Wong *et al*., 1999; W. Liu *et al*., 2013). These include reduction in toxicity of cisplatin (such as nausea, vomiting, nephrotoxcity, neurotoxicity and ototoxicity), circumvention of the acquired drug resistance observed in certain tumors, increased spectrum of activity since cisplatin is ineffective against some of the most prevalent tumour types (e.g. in breast and colon) and oral administration for the new anticancer drugs (Wong *et al*., 1999; Siddik, 2003; W. Liu *et al*., 2013).

Pt-NHC complexes have been cited as an innovative and promising platform for creating novel cytotoxic medications in the cisplatin family (Skander *et al*., 2010; Chardon *et al*., 2011; W. Liu *et al*., 2013;). Mixed NHC–amine Pt(II) complexes were created using a simple, modular two-step process that results in organisms with trans-configured square planar structures by Marinetti *et al*. (Skander *et al*., 2010).

In order to possibly enhance selectivity and specificity towards cancer cells, Bellemin-Laponnaz *et al*. designed an oestrogen functionalized Pt(II) complex as a possible candidate to target hormone dependent diseases (e.g. BC) (Chardon *et al*., 2011). This complex was obtained by reaction of functionalized Pt complexes with the oestrogen derived azide via using ruthenium-catalyzed azide alkyne cycloaddition. Despite the ability of the complex to act as potential chemotherapeutic agent which is currently under study, they are currently extending the scope of this method to a more diverse set of azides with the aim to generate chemical libraries and later to endow cytotoxic NHC complexes of transition metals with new properties (Liu *et al*., 2013).

Palladium (Pd)

It is a transition metal, as well as a PGM (Platinum group metal), with a symbol of Pd, atomic number of 46, and atomic mass of (Sharma *et al*., n.d.). Pd has medical application in the timely treatment of tuberculosis, but other options were sought due to deleterious drawbacks. further uses for Pd in medicine are their activities as

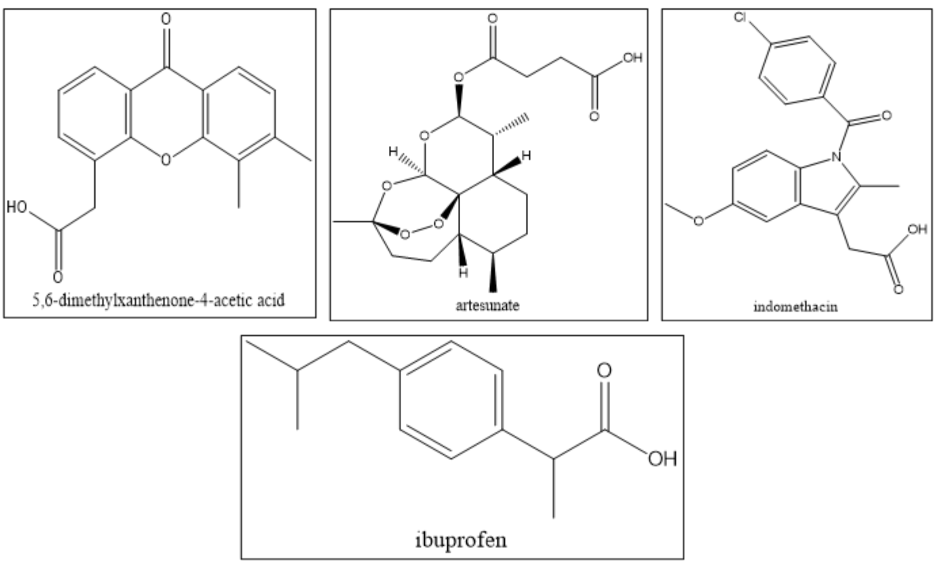
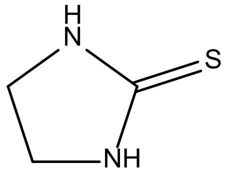


Figure 6: Pt IV drugs with the ligands and anti-tumour drugs.

antimicrobial and anticancer agents (Salim Abu-Surrah *et al*., 2008; Odularu *et al*., 2019). Ahmad *et al*. synthesized Pd(II) complex, [Pd(PPh3)2(Imt)2Cl2.3.5H2O], where Imt is imidazolidine-2- thione, and screened it against two Gram-negative bacteria (Escherichia coli and Pseudomonas aeruginosa) and two yeasts (Candida albicans and Saccharomyces cerevisiae) (Salim Abu-Surrah *et al*., 2008; Odularu *et al*., 2019). They came to the conclusion that the yeast test produced substantial activity whereas the antibacterial test only produced modest activity. In order to create four Pt(II), Pt(IV), Pd(II), and Pd(IV) coordination compounds, Bakalova *et al*. used the carrier ligand 3-amino—tetralonespiro-5′-hydantoin. In vitro tests were performed on all substances using the SKW-3 human tumour cell line. Compared to Pd(II) coordination compounds, the antitumor activity of the Pt(II) coordination compound was stronger, although it was less active than cisplatin (Odularu *et al*., 2019).



imidazolidine-2- thione

Figure No. 7: Pd attaching ligand.

In the case of anticancer research, Elhusseiny and Hassan stated that the complexes were tested against three cell lines (breast carcinoma (MCF-7), colon carcinoma (HCT 116), and liver carcinoma (HEPG2). They also observed that three of the twelve synthesised Pd(II) complexes demonstrated the best efficiency against three cancer cell lines at 10 mg/ml concentration (HCT116, HEPG2, and MCF-7) (Odularu *et al*., 2019).

Many new mononuclear, dinuclear and multinuclear Pd complexes with reduced cross-resistance to cisplatin, decreased toxicity and high specificity have been developed (Abu-Surrah *et al*., 2006; Hindi *et al*., 2009; Teyssot *et al*., 2009; van Rijt *et al*., 2009). Similar to Pt agents, DNA is also their major target in the cell. The Pd(II) ions are capable of interacting with DNA, thus enabling cross bindings and inhibiting its synthesis as well as inducing apoptosis. Pd complexes might materialize a concept of tumour targeting which would result in drugs with other spectrum of activity and lack of cross-resistance as compared with Pt drugs (W. Liu *et al*., 2013).

Two Pd(II)-NHC complexes were studied by Panda *et al*., including “A,” a bis(NHC) complex, and “B,” a mixed complex, both of which included pyridine as a characteristic ligand for the active trans Pt complexes (Ray *et al*., 2007). The Pd centre was replaced in a trans-geometric fashion in both complexes. With regard to HeLa, BC (MCF-7) and HCT 116 cell lines, “A” demonstrated more cytotoxicity (from 2- to 20-fold) than cisplatin. Additional research revealed that “A” prevented the multiplication of tumour cells by stopping the cell cycle in the G2 phase and preventing the cell from entering the mitotic phase. This findings revealed that a p53-dependent mechanism led to PCD in the treated cells. These findings together made it abundantly evident that compound “A” followed the same cellular mechanism as cisplatin (W. Liu *et al*., 2013).

Li *et al*. developed a Pd(II)–NHC complex “C” with higher cytotoxic activities than cisplatin and the corresponding Au(I)–NHC and Ag(I)–NHC complexes against BC cells (MCF-7 and MDA-MB 231) (C. H. Wang *et al*., 2011). The IC_{50} of “C” (4.50 mM) in MDA-MB 231 cells is 3-fold lower than that of Au(I)–NHC complex 21 (14.22 mM) and approximately 10-fold lower than that of Ag(I)–NHC complex 7 (46.58 mM) and cisplatin (48.43 mM). This finding demonstrated that the antitumor activities of the amino-NHC metal complexes were not solely dependent on molecular hydrophobicity and that activities could be altered by the choice of the metal ion. Interestingly, IC_{50} of the complex displayed similar trends in the estrogen receptor positive (ER+) cell line MCF-7 and estrogen receptor negative (ER-) cell line MDA-MB 231, indicating that the effects on cell viability might be caused by an ER-independent pathway (W. Liu *et al*., 2013).

Chemotherapeutic mechanisms of Pd(II) complexes against TNBC:

DNA damage: Pd complexes can act as a novel class of metal-based agents that bind covalently to the nitrogen bases of DNA, resulting in DNA fragmentation by hindering an adequate DNA synthesis and RNA transcription from the affected DNA areas. DNA damage occurs through formation of crosslinks, preventing DNA strands from being separated for synthesis or transcription, and inducing mispaired nucleotides, leading to mutations (N. Wu *et al*., 2018). A number of Pd complexes, including “L,” “H,” “E,” “M,” “N,” “J,” and “K,” have been shown to alter DNA conformation or break DNA (Vojtek *et al*., 2019).

Cell cycle arrest: It is well accepted that carcinogenesis is associated with cell cycle deregulation and/or overexpression of growth kinases (Pitts *et al*., 2014). The effects of Pd complexes (“D,” “E,” and “I”) on TNBC cells’ cell cycle arrest in G1 or G1/S phase might be either direct or indirect. It has also been noted that cells designated “D” and “E” have the sub-G1peak, which is often associated with dying cells. In fact, DNA damage may cause a cell cycle to be stopped by activating the p53 pathway, which can either start DNA repair or cause apoptosis (Vojtek *et al*., 2019).

ROS/RNS are produced during metabolic processes and can interact with biomolecules to cause DNA mutations, oxidation of amino acyl residues in proteins, and lipid peroxidation. These reactions also result in the production of more free radicals, which raises the possibility of mutation (Somasundaram *et al*., 2016). ROS production was reported for “F” and “G”. Notwithstanding ROS-induced damage, this can be restored by internal surveillance and repair systems. High ROS levels, however, overwhelm cellular detoxification mechanisms and halt cell proliferation and, after prolonged arrest, cells can die from apoptosis. The decrease in glutathione levels, indicating an increase in the intracellular redox status, was reported for “H” (Vojtek *et al*., 2019).

Table 1: Pd complexes and their activity against triple negative breast carcinoma.

Group	Complex no.	Complex designation	Cell line	IC_{50}	Target/mode of action	Selectivity toward TNBC	Reference
Derivatives of ethyl diamine	D	3a dichlorido[O,O'-diethyl-(S,S)-ethylenediamine-N,N'-di-2-(4-methyl) pentaneate]palladium(II)	MDA-MB-453	72 h: 3a >200 µM	DNA fragmentation, induction of apoptosis and sub-G1 cell cycle arrest	NA	Vujic *et al*., 2014
Derivatives of biogenic polyamines	L	Pd_2SpmCl_4	MDA-MB-231	72 h: 2.8 µM Ref. drug: cisplatin 3.2 µM	Induction of doublestranded Breaks in DNA (stronger effect than for cisplatin). Interfering with microtubules. Synergism with cisplatin	Tested vs normal human fibroblasts (BJ)	Fiuza *et al*., 2011
	H	Pd_2BENSpm	L56Br-C1	72 h: 0.4 µM	DNA damage. Reduction of GSH and polyamine levels	Tested vs normal breast epithelial cells (MCF-10A)	Silva *et al*., 2014
Derivatives of benzyl amine/imine	E	$[\{ClPd(C_6H_4)CH{=}N(2,6\text{-di-iPr-}C_6H_3)\}_2(mPh_2P(CH_2)_2PPh_2)]$	MDA-MB-231	48 h: 0.193 µM	DNA damage. Intrinsic induction of apoptosis via release of cytochrome c, upregulation of PUMA, Bax and downregulation of Bcl-2. Extrinsic induction of apoptosis via activation of caspase 8. Induction of autophagy and G1 cell cycle arrest. Putative anti-cancer stem cell activity	NA	Albert *et al*., 2014
Derivatives of pyridine/ pyrazole/imidazole/ pyrrol/triazole and their combinations	M	Pd_2Hmtpo	BT-20	Exposure of 2.81 µM for 48 h reduced	DNA fragmentation	NA	Akdi *et al*., 2002
	N	([PdCl(terpy)](sac).2H_2O)	Ehrlich ascites carcinoma MDA-MB-231 (in vivo)	48 h: 46.50 µM In vivo: complex 70% reduction, cisplatin 47% reduction, paclitaxel 59% reduction	Increase of cleaved PARP, caspase 3 activity and pyknotic nuclei	NA	Ari *et al*., 2014

	F	[Pd(sac)(terpy)](sac).4H_2O	Ehrlich ascites carcinoma MDA-MB-231 (in vivo)	72 h: 0.09 μM In vivo: complex 68% reduction, cisplatin 33% reduction, paclitaxel 69% reduction	Disruption of tubules. Apoptosis via DR4 and DR5	NA	Engin Ulukaya *et al*., 2011
	K	19a ([Pd(bpma)(sac)](sac).2H_2O) 19b ([Pd(bpma)Cl](sac).2H_2O)	MDA-MB-231	72 h: 19a 9.3 μM 19b 4.2 μM	Induction of apoptosis via Fas death receptor. Increase of cleaved PARP and caspase 3 activity	NA	Ari *et al*., 2013a
	I	27a [{Pd(2,2'-bipy)Cl}$_2$(μ-pz)] (ClO]$_4$)$_2$	MDA-MB-231	48 h: 27a 17 μM	Induction of apoptosis and necrosis. G1/S cell cycle arrest	Tested vs normal human fibroblast (MRC-5)	Hung *et al*., 2017

Pd (II)

A group of cationic Pd (II) compounds with saccharinate and triamine ligands, such as bis(pyridinylmethyl)amine (bmpa) or 2,2':6',2'-terpyridine (terpy), were reported by Ulukaya and colleagues. These compounds were effective against TNBC cell lines and, in some cases, mice models (selected compounds "P"–"K") (Ari *et al*., 2013b; Adiguzel *et al*., 2014; Nayeem *et al*., 2021). The compounds are apoptotic (Ari *et al*., 2013b). DNA damage (induction of double strand breaks, DNA fragmentation, and change of secondary structure) as well as an increase in cleaved PARP, induction of caspase activity, and pyknotic nuclei are present for compound "O" (Nayeem *et al*., 2021). An in-depth biochemical and proteomic analysis of compound "K" revealed that its mechanism of action involves inducing ROS, DNA damage (primarily by formation of Double Strand Break), and NHEJ was suggested as a potential mechanism of repair. For compound "K," apoptosis was shown to proceed via the DR4 and DR5 genes (Adiguzel *et al*., 2014; Nayeem *et al*., 2021).

According to another study by the same researcher, they examined the potential apoptosis-inducing action of the complex at precisely this level, taking into mind that the dose of roughly 3.12 mM is nearly an equal dose to the IC_{50} value. MDA-MB-231 cells were treated for 48 and 72 hours, however there was no change in the levels of the apoptotic marker M30-antigen. It was greatly enhanced in MCF-7 cells with the same treatment, in contrast, demonstrating the complex's ability to cause apoptosis in MCF-7 cells but not MB-MDA-231 cells. The Using agarose gel electrophoresis to find DNA fragmentation and observation of the ladder pattern both supported the conclusion that apoptosis had occurred in the MCF-7 cells (Ulukaya *et al*., 2011).

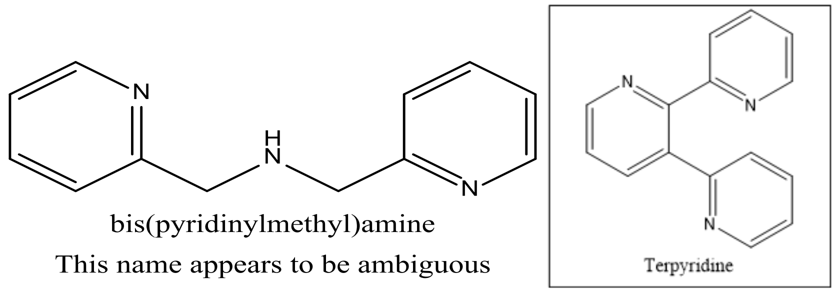


Figure 8: Pd II attaching ligands.

Gold (Au)

In the last few decades, researchers have focused on the study of coated Au nanoparticles. These nanoparticles are intriguing prospects for various biological applications, including the treatment of cancer, due to their optical characteristics, chemical stability, biocompatibility, and size (Ding *et al*., 2020). Consequently, recently developed Au-based compounds with anti-cancer potential have been created. Some interesting Au (I) phosphane antitumor compounds have been reported, such as [Au(d2pypp)2]Cl, [Au(PPh3)]Cl, [Au2(dppe)]Cl2, and [Au3(dpmp)]Cl; in addition, a heterometallic compound [(gC5H5)2TiMe(l-mba)Au(PR3)] has been reported, with its mode of action identified as mitochondrial dysfunction or autophagy (Humphreys *et al*., 2007; Rackham *et al*., 2007; Tian *et al*., 2011; Fernández-Gallardo *et al*., 2015).

Bis-[4,5-dichloro-(N-methyl-N'(2-hydroxy-2-phenyl) ethyl-imidazole-2-ylidene)gold(I)][dichloro-gold] (AuL7) is a Au-based compound with potential antimetastatic activity in the BC metastatic cell line MDAMB-231. This substance inhibits topoisomerase II and tubulin polymerization; Apoptosis is brought on by cellular arrest at the G2-M checkpoint, which is also exacerbated by it, as well as by an increase in oxidative stress and caspases (Iacopetta *et al*., 2020).

Au (I)

Au(I) complexes' exact mode of action is still unknown, but several studies have suggested that they may cause apoptosis by inhibiting selenium and sulfur-containing enzymes like glutathione reductases, glutathione peroxidases, glutathione-S-transferases, cysteine proteases, thioredoxin reductase (TrxR), and poly (ADPribose) polymerase 1 (PARP-1) (Tolbatov *et al*., 2021). In fact, the metal ion Au(I) is a soft metal centre with a significant attraction for soft ligands like thiols of cysteines and thioethers of methionines. It also exhibits a stronger affinity for selenols of selenocysteine residues (Urig *et al*., 2006; Bhabak *et al*., 2011). However, multiple X-ray crystallographic investigations shown that Au(I) ions may bind solvent-exposed material even when free thiols are present. Moreover, even in the absence of cysteines, methionines, and histidines, Au(I) complexes may bind the Arg and Lys side chains as well as the N-terminal of Ala. For example, the model protein thaumatin binds to Au(NHC)Cl (where NHC = 1-butyl-3-methyl-imidazole-2-ylidene) at the lysine side chains and at the N-terminal tail; the metal binds the protein after releasing the Cl ligand but keeping the NHC fragment (Ferraro *et al*., 2016; Tolbatov *et al*., 2021). Due to their great selectivity for thiols, linear Au(I) complexes are potent inhibitors of the Se-free enzyme glutathione reductase (GR) (Tolbatov *et al*., 2021).

Those with phosphine, thiosugar, NHC, alkynyl, and other sulfur-based ligands, such as thiosemicarbazone, are among the most popular Au(I) compounds produced and studied as possible anticancer medicines (Tavares *et al*., 2017; Tolbatov *et al*., 2021).

One study found that, when compared to cisplatin, the two provided chemicals (a, b) exhibit better anti-tumor action on basal-like BC (BLBC):

Cancer cell viability was estimated by MTT assay at 24h treatment using the human MDA-MB-231 cells and the murine A17 cells as models of BLBC (Marchini *et al*., 2010). Among the tested drugs, only compounds "a" and "b" exhibited a remarkable in vitro anticancer efficacy against both murine and human cell lines, being able to decrease in a dose-dependent manner, cell viability with IC_{50} values at low µM concentrations. compounds "a" and "b" displayed a stronger antineoplastic activity respect to cisplatin. In particular, the response of MDA-MB231 cells to compounds "a" and "b" compared to cisplatin, but was stronger and more rapid in its effects. In fact, compounds "a" and "b" showed IC_{50} values of 19.28 µM and 14.83 µM, respectively, after 24h treatment, whereas cisplatin displayed an IC_{50} value of 50.49 µM only after a 48h treatment. In addition, in vitro screening was completed evaluating the cytotoxicity of the separate moieties of compounds "a" and "b", corresponding to free azoles (ImH(Cl)2 and ImH(CN)2 for compounds "a" and "b", respectively), and triphenylphosphane moieties (Ph_3PAuCl and the bare Ph3P). Of note, only Ph3PAuCl Both MDA-MB-231 and A17cells' viability might be reduced by moiety at 24h, with an IC_{50} value of 22.27 µM and 18.29 µM, respectively (Gambini *et al*., 2018). The anticancer efficacy of compounds "a" and "b" was also confirmed on two other in vitro models of BC: the human BLBC MDA-MB-468 cells and human mammary epithelial HMLE cells overexpressing FoxQ1, characterized by stemness traits and chemoresistance (Gambini *et al*., 2018; Lehmann *et al*., 2011). HMLE/FoxQ1 line revealed to be the most responsive cells to both compound 1 and 2, displaying IC_{50} values of 7.41 µM and 9.27 µM at 24h, respectively. Of note, cisplatin was less effective than compounds "a" and "b" also in HMLE/FoxQ1 and MDA-MB-468 cells, inducing a significant decrease in cellular viability only after 48h treatment with an IC_{50} value of 34.12 µM in HMLE/FoxQ1, and after 24h treatment with an IC_{50} value of 32.50 µM in MDA-MB468 cells (Gambini *et al*., 2018).

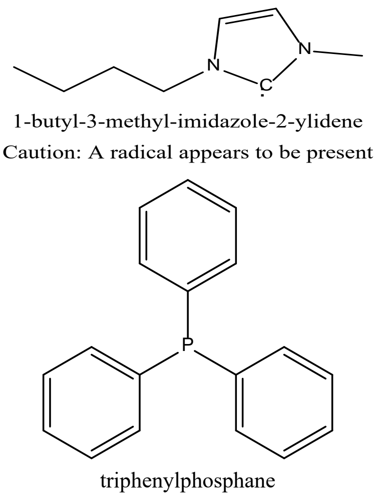


Figure 9: Moieties.

Auranofin and Auranofin Analogs: Auranofin (2,3,4,6-tetra-O-acetyl-Lthio—D-glyco-pyranosato-S-(triethyl-phosphine)-gold(I)) is the most popular Au-based metallodrug (AF) (Onodera *et al*., 2019). It was first shown to have antibacterial, antiviral, antifungal, and antiparasitic therapeutic properties after being initially identified as an anti-arthritic drug (Tolbatov *et al*., 2021). Additionally, this substance's antitumoral properties enable it to effectively induce apoptosis in a variety of human cancer cell types, including ovarian, prostate, blood, bone, lung, breast and cancer cells (H. Li *et al*., 2016; Yue *et al*., 2020). Its method of action differs significantly from the Pt-based complexes, which are based on DNA binding, since it specifically targets proteins that contain sulphur and selenium. For instance, AF swiftly and extensively binds the TrxR, proteasome system, albumin, and NF-B protein complex, all of which are involved in defining the anticancer action (Tolbatov *et al*., 2021).

Au(I) Complexes with NHC Ligands: Due to their strong catalytic capabilities, metal complexes containing NHC

Table 2: IC50 Values of Compounds 1−2, cisplatin on MDA-MB-231 and HMLE/FOXQ1.

Compound	Cell Line	Time	IC_{50} Mean ± SD[a] [μM]	Reference
Compound "a"	MDA-MB-231	24h	19.28 ± 1.06	(Gambini *et al*., 2018)
	HMLE/ FoxQ1	24h		
Compound "b"	MDA-MB-231	24h		
	HMLE/ FoxQ1		24h	
Cisplatin	MDA-MB-231		48h	
		HMLE/ FoxQ1	48h	

[a]SD: standard deviation.

ligands are often used in chemistry (Diaz Velazquez *et al*., 2012). It was discovered that Au complexes containing NHC ligands are a family of potent anticancer metallodrugs with strong in vitro and in vivo activity. However, their exact method of action was not entirely understood (Tolbatov *et al*., 2021). Direct DNA damage, mitochondrial damage caused by the inhibition of TrxR and consequent mitochondrial dysfunction, changes to certain kinases, and proteasome suppression are all potential processes that might cause a cell to undergo apoptosis (Mora *et al*., 2019).

[Au(IPr)(Seu)}, another Au(I)-carbene complex was shown to be less effective than cisplatin (cis-diamminedichloroPt) at inhibiting cellular proliferation in the lung carcinoma A549, colon cancer HCT15, and BC MCF7 lines. Seu = selenourea, and IPr = 1,3-Bis(2,6-diisopropylphenyl) imidazol-2-ylidene (Tolbatov *et al*., 2021).

In a 2013 study by Nolan and his colleagues, two different series (neutral and cationic) of Au complexes were prepared and screened against prostate carcinoma (LNCaP) and MDA-MB 231 cell lines. The study focused on the synthesis of novel Au(I)-NHC complexes and the associated synthetic routes made possible by a flexible Au(I)-NHC synthon (Weaver *et al*., 2011). The fact that the cationic complexes could induce cell death via an apoptotic pathway in cancer cell lines may have contributed to their superior efficacy over the neutral complexes, suggesting a role for the mitochondrial apoptotic pathway in the action of the potent chemicals (Berners-Price *et al*., 2011).

The unique Au-NHC complexes had impacts on tumour cell lines that inhibited their ability to proliferate. There are at least six Au- NHC complexes among the thirteen complexes that were as effective as auranofin and more effective than cisplatin and Et3PAuCl against the colon (HT-29) and breast (MCF-7 and MDAMB 231) cancer cell lines. Particularly, the most potent compound had noticeably greater antiproliferative efficacy than cisplatin (W. Liu *et al*., 2013).

The Au-bis(NHC) complexes had a markedly improved growth inhibitory impact on colon (HT-29) and breast (MCF-7 and MDA-MB 231) cancer cells. The oxidation state of the metal and the anionic counter ion have no bearing on this action, which is more than ten times stronger than that of cisplatin. Additionally, the significant cytotoxic activity of cationic Au-bis(NHC) complexes appears to be caused by the Au core; as a result, the growth inhibitory effects were reduced by replacing the Au centre with a methylene group (W. Liu *et al*., 2013).

Complex with Sulphur Donar Ligands: Lessa *et al*. described the cytotoxicity and TrxR activity of 2-acetylpyridine thiosemicarbazone, its N(4)-methyl and N(4)-phenyl derivatives, and N(4)-phenyl2-benzoylpyridine thiosemicarbazone in Au(I) complexes. The Jurkat (immortalised line of T lymphocyte), MCF-7 (human breast adenocarcinoma), HL-60 (acute myeloid leukaemia), and HCT-116 (colorectal carcinoma) cancer cell lines were all susceptible to the activity of the complexes. Interesting results showed that Jurkat and HL-60 cells were more affected than MCF-7 and HCT-116 cells (Lone1 *et al*., 2020).

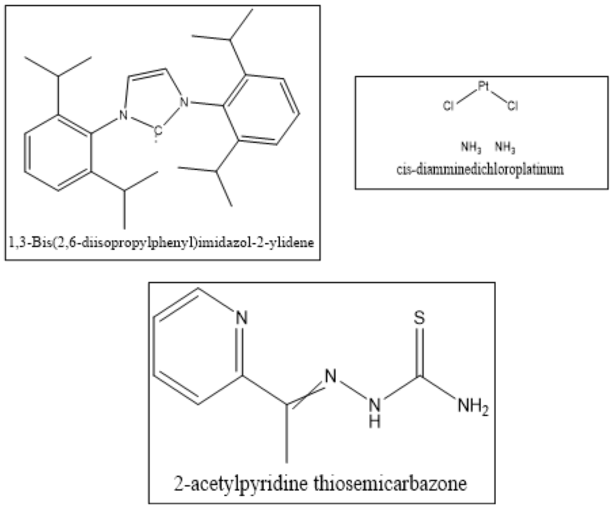


Figure 10: Au ligands showing anticancer properties.

Complex with phosphorus Donar Ligands: Humphreys and co-workers reported the anticancer activities of Au(I) chloride adducts of 1,3-bis- (di-2-pyridylphosphino) propane. A complex was selectively toxic to breast (MDA-MB-468) cancer cells. This work was further extended by Rackham *et al*. who reported that complex induced apoptosis via the mitochondrial pathway involving mitochondrial membrane potential depolarization, glutathione pool depletion and caspase-3 and caspase-9 activation. Besides, complex inhibited both thioredoxin and TrxR and this effect was more profound in BC cells and this was accounted for the selective cell death seen in the BC cells. The mechanism of action of this complex were provided by Wedlock and co-workers (Wedlock *et al*., 2011). They reported the subcellular distribution of this complex in situ in human BC cells using nano-scale secondary ion mass spectrometry. It was observed that the subcellular distribution of Au was associated with sulphur-rich regions in the nucleus and cytoplasm, indicating the mechanism of action of Au(I) complexes involves the inhibition of thiol-containing protein families, such as the thioredoxin system (Mohammad *et al*., 2020).

Au (III)

UBIQUITIN-PROTEASOME PATHWAY (2010 study)

The ubiquitin-proteasome pathway plays a crucial role in maintaining cellular homeostatic function by selectively degrading proteins involved in critical cellular functions. These include selective degradation of oxidatively damaged, mutated, or misfolded proteins, as well as those involved in cell proliferation, cell cycle progression, and apoptosis (Nalepa *et al*., 2006). Proteins destined for degradation are first tagged with a chain of ubiquitin molecules by a multi-enzymatic system consisting of Ub-activating (E1), Ubconjugating (E2), and Ub-ligating (E3) enzymes (Newton *et al*., 2007). The ubiquitin-tagged protein is then translocated to the 26S proteasome where it undergoes protein degradation, and the ubiquitin molecules are subsequently recycled. The 20S proteasome constitutes the proteolytic core of the 26S proteasome complex and mediates at least three distinct enzymatic activities, which function as a catalytic machine. These activities include the chymotrypsin-like, trypsin-like, and peptidylglutamyl peptide hydrolyzing-like (PGPH) activities (Frezza *et al*., 2010).

The anticancer activity of Au coordination compounds has been studied in order to produce a stronger cytotoxicity profile with a wider spectrum of activity than that of Pt-based compounds (Ronconi *et al*., 2006; Frezza *et al*., 2010). The inquiry into Au-protein interactions was prompted by studies that revealed interactions of Au(III) complexes with DNA, the preferred target of Pt, did not present a suitable binding mechanism (Frezza *et al*., 2010). The exploration of Au compounds as possible anticancer drugs resulted from the discovery that Au(III) is isoelectronic to Pt(II) and that tetracoordinate Au(III) complexes are in square-planar geometries similar to cisplatin (Ronconi *et al*., 2006). Additional research on the mechanisms underlying two new Au dithiocarbamate derivatives, (AUL12) with a trivalent oxidation state and (AUL15) with a monovalent oxidation state, which differ in the metal's oxidation state. The chymotrypsin-like activity of isolated 20S and 26S proteasome was shown to be inhibited by both types of Au dithiocarbamate, although at dramatically different amounts. This led to an accumulation of ubiquitinated proteins, proteasome target proteins, and the triggering of cell death (Frezza *et al*., 2010).

Two Au(III) complexes, square-planar $[Au(DPP)Cl_2]^+$ - Complex 1 and distorted square-pyramidal $[Au(DMP)Cl_3]$ Complex 2, have been recently (2022) studied. Apoptosis was triggered from the mitochondria in MDA-MB-231 cells using Complex 2 (where DPP=4,7-diphenyl-1,10-phenanthroline and DMP=2,9-dimethyl-1,10-phenanthroline). This was because there was an imbalance in the expression of pro- and anti-apoptotic Bcl-2 family members, and caspase 9 was activated. Comparing Complex 1 with Complex 2, Complex 1 has more activity, which is consistent with its structural properties (Milutinović *et al*., 2022).

Ag

For many years, Ag complexes were utilised as antibacterial agents, and they are presently used as antiseptics (Liu *et al*., 2013). Some of them also showed in vivo and in vitro anticancer activity. Some forms of cancer have been shown to be resistant to the anticancer effects of Ag complexes made from coumarin, and Ag carboxylate dimers have similar properties (Zhu *et al*., 2003). Additionally, a new hydrogen-bonded bimetallic supramolecular coordination polymer $[SnMe_3(bpe)]$ and several Ag complexes with phosphine

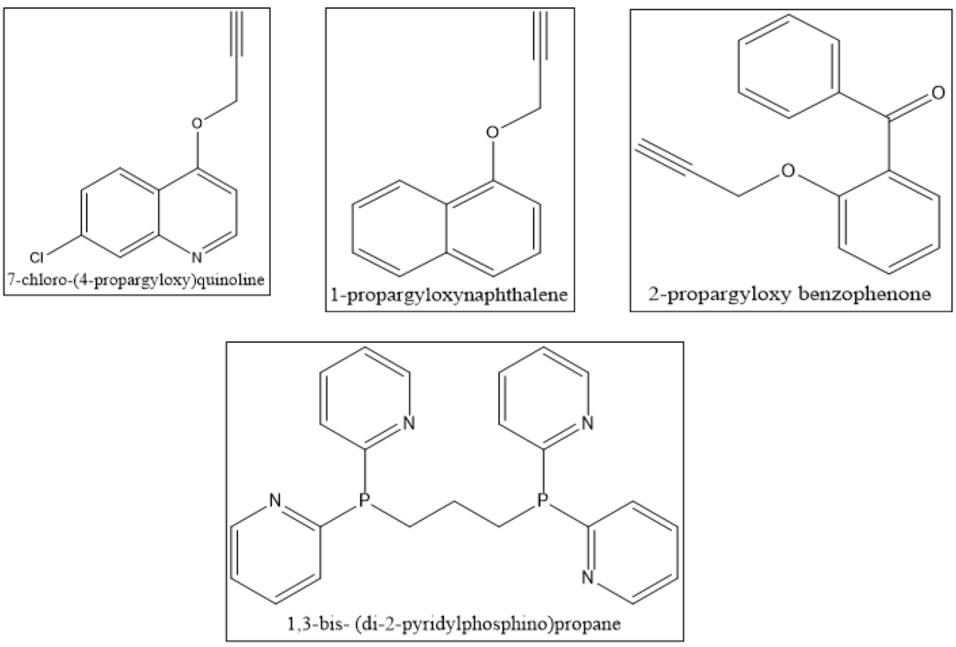


Figure 11: Anticancer possessing ligands.

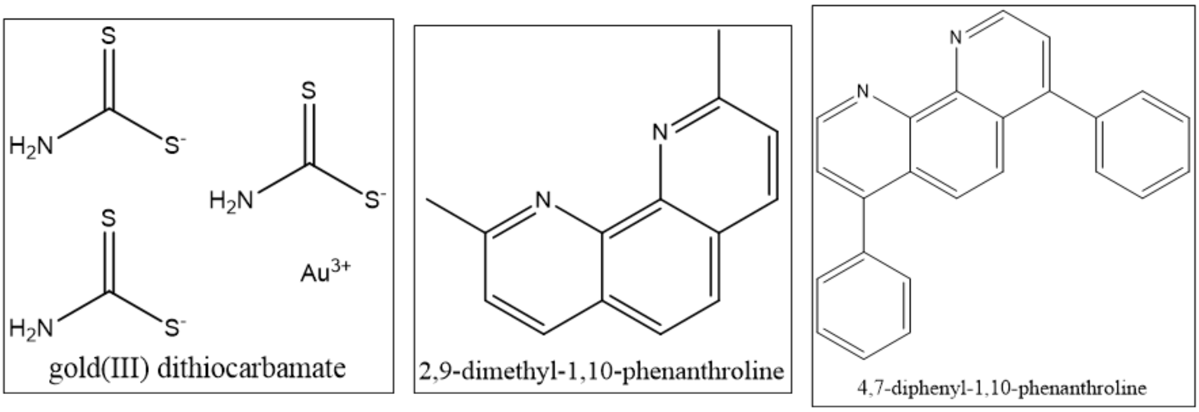


Figure 12: Complexes and derivatives.

ligands were able to inhibit cisplatin-resistant cell lines. [Ag(CN)2] Specific in vivo and in vitro anticancer effects of 2H2O were observed (Liu *et al*., 2008). The release of Ag+ ions into the environment, which then infiltrate cell membranes and interfere with their function, appears to be the common mechanism of action for all Ag complexes. The major drawback of current Ag medications, such as Ag sulfadiazine, is that they rapidly lose their effectiveness as a result of the Ag+ ions' fast release. In order to limit the rapid release of Ag ions, it is crucial for Ag complexes to have ligands that tightly coordinate with the Ag. Ag-NHC complexes were used as part of a really clever technique to get around these challenges (Liu *et al*., 2013).

Ag (I)

On the TNBC cells MDA-MB-157 and MDA-MB-231, considerable cytotoxicity has been reported for Ag (I) compounds with N-heterocyclic carbene ligands generated from 4,5-dichloro-1H-imidazole or 4,5-diarylimidazole, respectively (Liu *et al*., 2013).

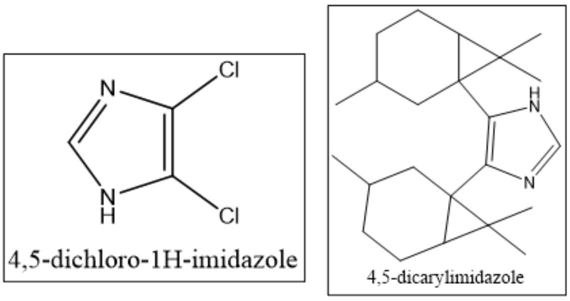


Figure 13: Ligands of Ag.

Ag N-heterocyclic carbene complexes

Youngs *et al*. 2008 described a series of Ag–NHC complexes derived from 4,5-dichloro-1H-imidazole (Youngs *et al*., 2008). All complexes exhibited cytotoxic activity against ovarian (OVCAR-3) and breast (MB157) cancer cells in vitro (W. Liu & Gust, 2013).

Willans *et al*. 2012 created a range of monodentate, bidentate, and macrocyclic cationic Ag-bis(NHC) complexes with cytotoxicity on par with cisplatin. In MCF-7 and DLD-1 cell lines, complexes containing bidentate ligands were more active than those with monodentate and macrocyclic ligands. The pace at which Ag salt is released appears to have a significant impact in the stability of the complex. Since the maximum concentration at which these compounds were tested, 100 mM for AgBr, AgPF6, and imidazolium salts utilised for comparison, the synergistic impact of both the Ag centre and the NHC ligand definitely plays a role in the cytotoxicity of Ag NHCs (Monteiro *et al*., 2012).

Schobert *et al*. 2012 coupled Ag fragment with N-methyl-4,5-diarylimidazolium salts, which were modelled after the naturally occurring anticancer medication combretastatin A-4 and shown potential antitumor effects (Kaps *et al*., 2012). These Ag complexes were less cytotoxic than the comparable Au(I)-NHC complexes but nevertheless had notable antiproliferative effects in the chosen cell types. Additionally, the p-ethoxy group (complex a) replaced the p-methoxy group (complex b), which resulted in unpredictable changes to the activity of the Ag complexes. Results of cytotoxicity tests on BC (MCF-7 and MDA-MB 231) and colon (HT-29) carcinoma cells showed that the activity of the Ag complexes was regulated by the substituents at the 4,5-standing phenyl rings. In comparison to the fluoro- and methoxy-substituted complexes, the 4-OH substituted complex was less active. The most active compound, bromo[1,3-diethyl-4,5-bis(4-fluorophenyl) imidazol-2-ylidene] Ag(I), had activity levels that were equivalent to cisplatin against HT-29 cells but somewhat lower against MCF-7 cells and higher against MDA-MB 231 cells. These targets may be ruled out as being implicated in the mode of action because they were only sporadic active at the ER, COX enzymes, and DNA (Liu & Gust, 2013).

Cu

Being a necessary micronutrient and a crucial cofactor for several metalloenzymes involved in mitochondrial metabolism (cytochrome c oxidase), or cellular radical detoxification against ROS, Cu plays vital roles in several cellular processes (superoxide dismutase) (Hordyjewska *et al*., 2014). For endothelial cells to proliferate and migrate and for angiogenesis to occur, Cu is necessary (Molinaro *et al*., 2020). The development, invasion, and metastasis of tumour cells depend on the complicated process known as angiogenesis (Dykhuizen *et al*., 2013). It has been established that the growth of new blood vessels is necessary for tumours to grow larger than 1-2 mm^3. Studies conducted in vitro have demonstrated that Cu stimulates

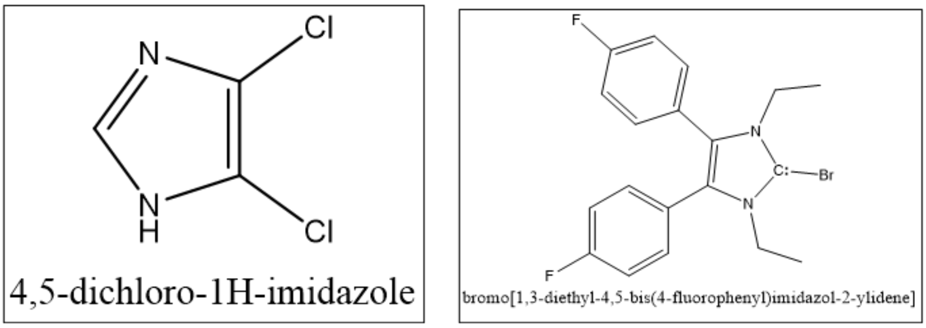


Figure 14: Ag complexes.

endothelial cell growth and migration, acting as a key angiogenic effector (Hjaltelin *et al*., 2019). The idea of employing Cu chelators in antiangiogenic therapy as a kind of cancer treatment has attracted a lot of interest because of research showing how important angiogenesis and Cu are in the growth of tumours (Molinaro *et al*., 2020). Increased Cu promotes metastasis and tumour development. It is found in a number of lung, breast, prostate, colon, and brain cancers and acts as a prognostic marker for the illness. The development of Cu complexes (CuC) as anticancer medicines was sparked by the divergent reactions of normal and malignant cells to Cu. Many discovered CuC exhibit great cytotoxicity and effective anticancer activity and contain various sets of S, O, or N ligands (Santini *et al*., 2014). The anticancer properties of Cu medicines are mediated by many mechanisms. They have chelating properties, interact with endogenous Cu, and sequester it, lowering the amount of Cu that is available for tumour development and angiogenesis (Baldari *et al*., 2020). Ionophores, on the other hand, cause cytotoxicity, intracellular Cu buildup, and the activation of the apoptosis inhibitor factor (XIAP) (Molinaro *et al*., 2020). Other CuC are proteasome inhibitors (Molinaro *et al*., 2020). Clinical trials are currently being conducted for a number of CuC, including a number of Cu/disulfiram-based drug combinations for therapy and as diagnostic tools (metastatic BC and germ cell tumour), a number of casiopenas compounds and elesclomol (leukaemia), and thiosemicarbazone-based Cu complexes labelled with a radioactive isotope for positron emission tomography imaging of hypoxia (in head and neck cancers) (Krasnovskaya *et al*., 2020).

Cu (II)

Cu (II) metallodrugs have emerged as an attractive chemotype against cancer due to their ability to generate ROS and RNS, resulting in oxidative damage and cellular death. TOP are inhibited by several of these Cu complexes or can bind to DNA. Additionally, these complexes have the ability to influence death effector proteins and cell cycle checkpoints (Molinaro *et al*., 2020). Phenanthroline or bipyridine, which belong to the CAS family of Cu(II)-containing compounds, is the first charged ligand and is of the diamine (N-N) type bidentate; the second charged ligand is of the O-O donor (salicylaldehyde or acetylacetonate) or N-O type (a-aminoacidate). Methanol, Water, and intravenous dextrose solution are all soluble in caciopenas. Different in vivo and in vitro cancer models have been used to describe the anticancer efficacy of these drugs. (González-Ballesteros *et al*., 2022). Regarding the mode of action, Casiopenos increases endonuclease G, DNA fragmentation, and caspase 3 activation to cause apoptosis (González-Ballesteros *et al*., 2022). Additionally, they increase the production of cytochrome C and mitochondrial ROS (Kachadourian *et al*., 2010).

On MDA-MB-231, dinuclear Cu (II) compounds with isoxazole-derived aroylhydrazones showed cytotoxicity (sub-micromolar range), and it was shown that these compounds interacted with calf-thymus DNA. Dou and colleagues reported the development of more effective Cu (II) compounds with dithiocarbamate ligands (Nayeem *et al*., 2021). Disulfiram (DSF), a medication used to treat alcoholism that also has antitumor and chemosensitizing properties, is combined with Cu to create a complex known as DSF-Cu, which is highly selective when compared to MCF10a breast cells and is cytotoxic to MDA-MB-231 cells. It also inhibits the proteasomal activity of these cells before inducing apoptosis (Chen *et al*., 2006).

CuC Top1 Inhibitors

Oxindolimine-Cu(II) Planar Cu compounds known as Top1 inhibitors prevent the formation of enzyme-DNA complexes. Additionally, they release ROS (Castelli *et al*., 2018). DNA and the Top enzyme can be bound by hydrazone-Cu(II) derivative complexes of the hydrazone ligand with triphenylphosphonium moiety. Plumbagin-Cu(II) 3 intercalates into DNA with preference. The latter substance and the phenanthroline-Cu(II) complexes [Cu(phen)(aa)(H2O)] that are controlled by amino acids

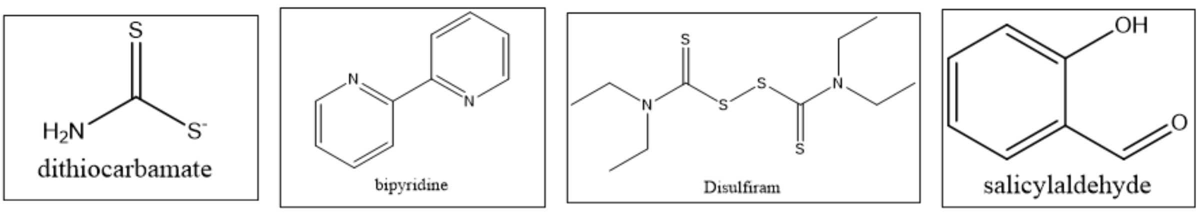


Figure 15: Cu II ligands.

through mitochondrial signalling, NO. 3 can cause cancer cells to apoptose. Based on the redox chemistry of Cu, the Cu pyrophosphate-bridged binuclear complex 5[Cu(phen)(H2O)]2(-P2O7) interacts with DNA and significantly increases oxidative stress in cancer cell types (Molinaro *et al*., 2020). The planar phenanthroline heterocyclic ring in the heterobimetallic Cu(II)-Sn2(IV) (Cu/tin) complex approaches the Top-DNA complex Cu(II)-Sn2(IV) near the DNA cleavage site and forms a stable complex with Top1. There are other Cu(II)-Sn2(IV) analogues that cause apoptosis (Afzal *et al*., 2019).

Cu (II) complexes of semi carbazones

Semicarbazone derivatives have received less attention than thiosemicarbazones as potential drugs, but interest in semicarbazones have gained in the past decade as they are structurally analogous to thiosemicarbazones and have lower side effects (Dimmock *et al*., 2000). Patole *et al*. 2012 reported two Cu(II) salicylaldehyde semicarbazone complexes that show anti-tumor activity against the human BC cell line MCF7. The activity of these complexes was attributed to their ability to generate considerable intracellular oxidative stress via the Cu2+/Cu+ redox couple (Valko *et al*., 2006). Another series of Cu(II) salicylaldehyde semicarbazone complexes was synthesized and tested for cytotoxicity towards MCF-7, MOLT4, A-549 and SK-II cells. These complexes showed strong cytotoxic activity on all the tested cancer cell lines (IC_{50} values of 2–15 μM) (Tan *et al*., 2010).

Osmium (Os)

Given that Os was the dark residue left behind after Pt broke down in aqua regia, the discovery of Os and the discovery of Pt were related. According to Arbiaster, it is the element with the highest density at all pressures and temperatures. The metal is a robust, glossy blue-white colour, solid at room temperature, and has a solid surface. Both in free form and in alloys containing Cu and nickel can be found naturally (Odularu *et al*., 2019).

Os (II)

A half-sandwich Os (II) molecule with bathophenanthroline attached to the metabolic regulator dichloroacetate (dca) was developed by Brabec and coworkers (Osdca) (Pracharova *et al*., 2018). The compound was demonstrated to have deadly effects on MDA-MB-231 cells (IC_{50}= 0.50.02 M, 72 h) and to significantly lower lactate generation, suggesting glycolytic inhibition as a method of action. The protein expression of aquaporin, a water channel linked to the development of cancer, was also markedly decreased in MDA MB-231 cells treated with Os-dca. The improved hydrolytic activity of the metal (Os) makes it simpler to release the dca ligand in water-containing solvents and improves the pharmacological profile (Pracharova et al., 2018; Nayeem & Contel, 2021).

Ru

Ruthenium, symbol Ru, is a d-block transition metal, PGM, with the atomic number 44 and mass number 101.0

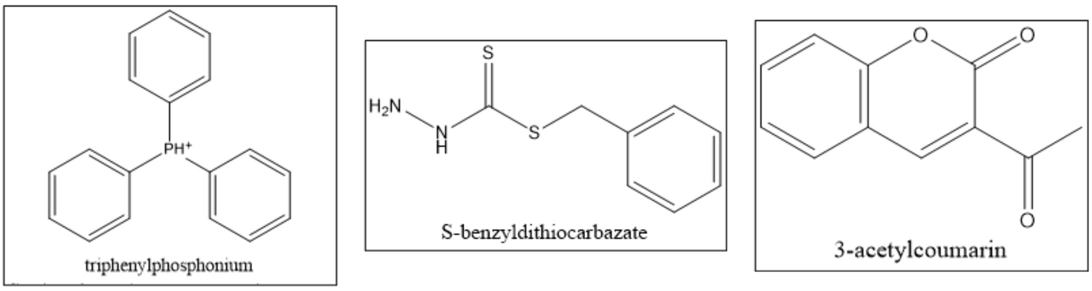


Figure 16: CuC TOP ligands.

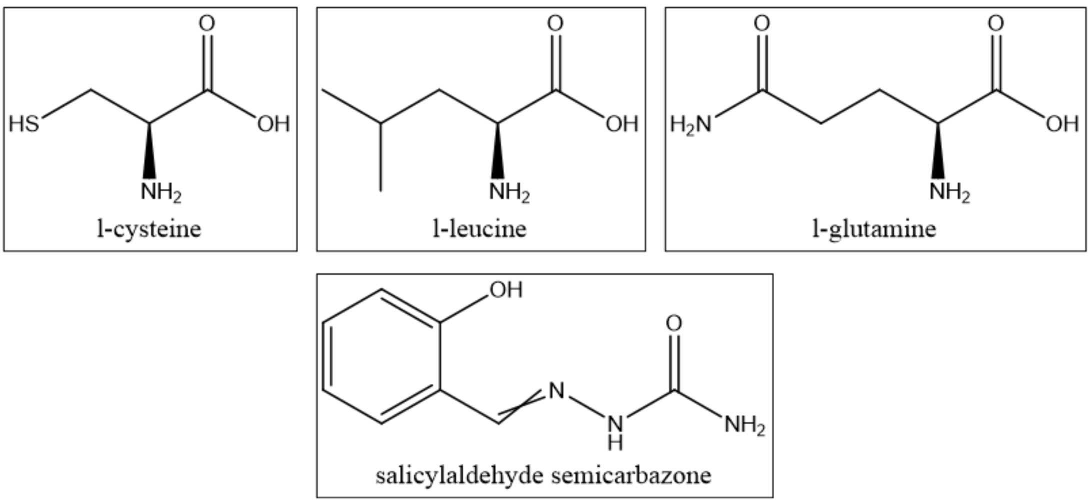
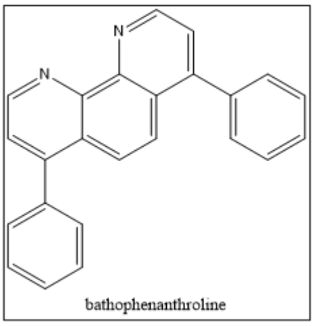


Figure 17: Amino acids and Cu II complexes.



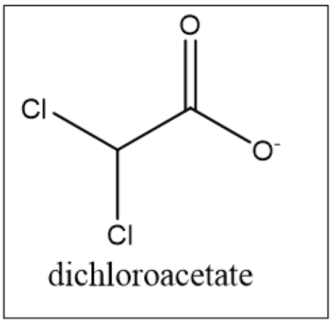
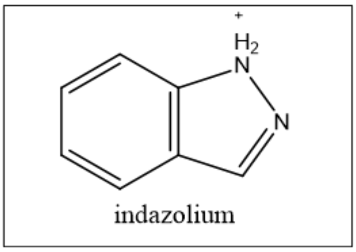


Figure 18: Buffer and compound.

(Markowska *et al*., 2015). Ruis the sole element in Group 8 with two electrons in the outermost shell. It has eight oxidation states, the most frequent of which are +2, +3, and +4. In 1808, Polish scientist Jedrzej Sniadecki found Ru in South America and dubbed it "vestium" after the planet Vesta (Markowska *et al*., 2015). Due to the failure to validate Jedrzej Sniadecki's finding, Gottfried W. Osann, a Russian scientist, found Ru in 1928. Karl Karlovich Klaus (Carl Ernst Claus), another Russian scientist, discovered Ru a second time in 1944, also owing to the inability to confirm Gottfried W. Osann's discovery, which could be validated. As a result, authorities referred to him as the discoverer. The name is derived from the Greek word "Ruthenia," which means "Russia" (Odularu *et al*., 2019).

Ruthenium-based treatments are prospective candidates with acceptable biological characteristics for chemotherapy, and they have emerged as a viable adjuvant to Pt-derived medicines (Alessio, 2017). Ru therapies have been utilised effectively in clinical research for several decades, and their mechanisms of antitumor activity have been documented. In 2016, many reviews of anticancer Ru compounds were published. Ruthenium-based anticancer metallotherapeutics are interesting options due to their distinct mechanisms of action, and they have been shown to offer advantages over Pt-based therapies (Thota *et al*., 2018). Ru compounds have desirable characteristics, making these Ru scaffolds appealing options for therapeutic applications. They are efficacious against some cisplatin resistant cell lines, have less side effects due to their increased selectivity for cancer cells compared to normal cells, and may be connected to preferential absorption by the tumour compared to healthy tissue. Ru can attach to some biological molecules in the same way as iron (Fe) does (Ruthenium in Medicine: Current Clinical Uses and Future Prospects - technology.matthey.com, n.d.). Alessio has revealed numerous fallacies in the realm of Ru anticancer therapies, including the low toxicity of Ru treatments because Ru mimics iron. He proposed that Ru therapies have minimal toxicity by nature, but that ruthenium's capacity to imitate Fe is frequently misinterpreted with toxicity. Ru is in the same periodic table group as iron, as evidenced by its strong affinity for transferrin and reductive activation in cells (Clarke *et al*., 1999; Ruthenium in Medicine: Current Clinical Uses and Future Prospects - technology.matthey.com, n.d.).

Arene Ru compounds contain strong metal-organic molecules, which are necessary for the development of organometallic chemistry. Ru compounds are appropriate for medicinal applications due to three primary properties: their ability to mimic Fe in binding to particular biological components, their sluggish rate of ligand exchange, and their varied oxidation states (Odularu *et al*., 2019). Because of its capacity to selectively target metastasized solid tumours and cisplatin-resistant malignancies, Ru compounds have gained interest as anticancer treatments. Because of interactions with blood transporter proteins, Ru metal allows access to different oxidation states and enhanced selectivity to tumour site (Pongratz *et al*., 2004). Ru complexes have advanced the most, with clinical studies including two ruthenium(III)-based drugs, indazolium trans-[tetrachlorobis(1H-indazole) ruthenate(III)] (KP1019) and imidazolium trans-[tetrachloro(dimethylsulfoxide)(1H-imidazole)ruthenate(III)] (NAMI-A). Ruthenium(III) complexes, on the other hand, are vulnerable to ligand exchange events in physiological buffer /aqueous media, which, to some extent, makes it difficult to logically design new compounds with pertinent therapeutic properties (Lee *et al*., 2017).



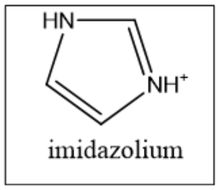


Figure No. 19: Ligands for Ru.

Arene Ru(II) complexes with N,N-chelating ligands

Aliphatic diamine, aromatic diamine, and pyridine derivatives are examples of common N,N-chelating ligands. Sadler has thoroughly investigated arene ruthenium compounds including ethylenediamine (en) chelating ligands (Morris *et al*., 2001). Variation in the leaving group, the N,N-chelating ligand, and the arene ring, according to Sadler's group, can have a considerable influence on chemical and biological activity (Morris *et al*., 2001). Montani *et al*. investigated 4e's in vivo anticancer efficacy and discovered that it significantly reduced the development of A17 triple negative breast cells implanted into mice (Montani *et al*., 2016). Because of its high hydrosolubility, 4e was swiftly removed from the liver, kidney, and circulation, and it had remarkable therapeutic effectiveness with little side effects. 4e induced a considerable decrease in the number of tumor-infiltrating regulatory T cells, according to immunohistological tests.

Chow *et al*. used high-throughput screening to create a more effective arene Ru(II) molecule, when compared to cisplatin. Compound had IC_{50} values in the micromolar range against A2780, A2780cisR, MCF7, HCT116, and SW480 cells. The water-soluble and stable half-sandwich arene Ru(II) Schiff-base (RAS) complexes were also found to induce non-apoptotic PCD via the ER stress pathway. Despite minor structural differences, the mechanisms of action of the two complexes were considerably different. A compound caused ROS-mediated ER stress, but other compound had no effect on ROS. When compared to therapeutic medications like oxaliplatin, these two complexes were more effective against apoptosis-resistant cells. This study lays the groundwork for targeting ER stress regulation with Ru(II) complexes to circumvent apoptosis resistance (Zeng *et al*., 2017).

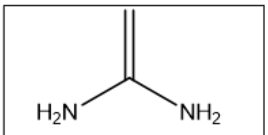


Figure 20: Ligand for Ru II.

Ru (III)

Although this oxidation state has the potential to produce prodrugs, it is rarely researched due to the relatively inert nature of Ru (III) complexes. While Ru (III) compounds NAMI-A and KP1019/KP1339 have passed phase clinical studies in other cancer types, it is still unclear if they are effective against TNBC. When compared to the control line HBL-100, whole transcriptome analysis of NAMI-A in MDA-MB-231 cells demonstrated choosing the TNBC cell line with preference, with early response genes associated with direct or indirect roles in metastasis, cellular invasion, cytoskeleton remodelling, and cell cycle regulation being involved. In the aforementioned research by Amici and coworkers, NAMI-A demonstrated tumour decrease in vivo (approximately 28% compared to control), although showing essentially minimal cytotoxicity in the same TNBC cell line (IC_{50}= 840.21±0.03 M, 72 h). Although its salt counterpart KP1339 did not exhibit this activity, KP1019 showed significantly stronger cytotoxicity in MDA-MB-231 cells (IC_{50}= 0.847±0.22 M, 24 h), resistance to detachment after treatment, inhibition of MMP2/MMP9 activity, and antimigratory and anti-invasion capabilities. (Bergamo *et al*., 2009; Schreiber-Brynzak *et al*., 2015).

Following encapsulation, there was an increase in cytotoxicity (IC_{50}

= >250 M Azi-Ru, IC_{50} = 12.1±3 HoThyRu/DOTAP, 48 h), and autophagic cell death was seen after treatment with rapamycin and verified by increased expression of autophagosome-related proteins LC3I and LC3-II. Additionally, the in vivo effectiveness of this nanosystem was examined in MCF-7 xenografted athymic nude mice dosed with 15 mg/kg once weekly throughout a 28-day trial, which revealed a substantial reduction in tumour weight and volume with HoThyRu/DOTAP therapy and no evidence of toxicity. (Nayeem *et al*., 2021).

Arene Ru (II) complexes with N,O-, O,O- and C,N-ligands

Tetrahydroisoquinoline, a few amino acid ligands, and the O,O-ligands are typical b-diketonate and pyrone ligands. These ligands all act as N,O-chelating ligands. In the human cancer cell lines MCF-7, A549, and MDAMB-231, Chelopo *et al*. evaluated the anticancer effectiveness of several arene Ru(II) complexes containing 1,2,3,4-tetrahydroisoquinoline amino alcohol ligands. Only MCF-7 cells were somewhat responsive to these complexes, with the lowest IC_{50} value for a complex being 34 mM.

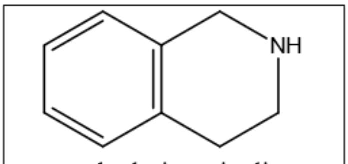


Figure 21: Amino acid ligand.

Ru (II)–silica composites

Silica has long been employed as a nanocarrier for medication delivery in medicinal applications (Tarn *et al*., 2013; Zeng *et al*., 2017). Silica nanoparticles are non-toxic to cells and endocytose easily in acidic liposomes. These nanoparticles are a suitable nanocarrier for Ru(II) complexes and other medications due to their release in certain pH conditions, photon activation, redox activation, and tumour targeting. Frasconi and colleagues created ruthenium-silica nanoparticles with improved cellular uptake and photoactivation. By coordinating the monodentate ligand (3-isocyanato-propylethoxysilane with 4-(aminomethyl)-benzonitrile), the Ru(II) complex was covalently bonded to the mesoporous silica nanoparticles (MSNPs) to create MSNPs2. The MSNPs2 cellular absorption was quick, and the Ru complexes were promptly released and converted into a cytotoxic aqua complex that formed monoadducts with DNA following light irradiation. Furthermore, the MSNPs2 had an 82% absorption efficiency and a 35% release efficiency when loading paclitaxel. Cytotoxicity tests revealed that empty MSNPs2 exhibited no cytotoxicity against MDAMB-231 cells. Light activation, on the other hand, greatly increased the cytotoxicity of docetaxel-loaded MSNPs2 in MDAMB-468 and MDAMB-231 BC cell lines but had no effect on the cytotoxicity of free paclitaxel (Zeng *et al*., 2017).

RM175

RM175 and its homologue HC11, [RuCl(en)(Z6 -tetrahydroanthracene)]PF6, were studied in a panel of 13 cell lines in 2006 (Guichard *et al*., 2006). The two metallodrugs were especially active in BC and non-small cell lung cancer cell lines, with HC11 showing the most activity in vitro. Both drugs significantly delayed tumour development in the A549 in vivo xenograft model following i.p. single-dose treatment (Guichard *et al*., 2006).

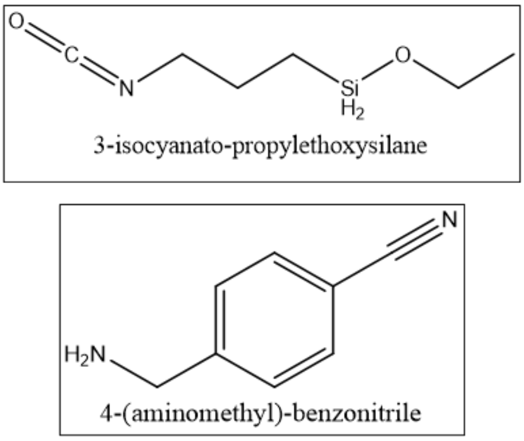


Figure 22: Monodentate ligand.

RM175 has also been studied in vivo for its antimetastatic activity in MCa mammary cancer xenograft models. RM175 was found to inhibit the development of both primary and secondary tumours at a daily dosage of 10 mg kg-1 for 5 days. Furthermore, MDA-MB-231 cells were prevented from detaching from the main tumour. Matrix metalloproteinase 2 inhibition (MMP-2). The reduction of MMP-2 production highlighted RM175's potential antimetastatic efficacy (Meier-Menches *et al*., 2018).

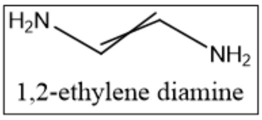


Figure 23: Moiety.

FITExP analysis of RAPTA-T

The effects of RAPTA-T were evaluated in a series of experiments that simulate the main steps of metastatic progression in vitro, i.e., detachment from the primary tumor; degradation of the extracellular matrix; and migration, invasion, and adherence to a new organ. The behavior of highly invasive BC MDA-MB-231 cells was compared to that of MCF-7 cells (which are tumorigenic but not invasive) and nontumorigenic mammary epithelial HBL-100 cells (Modulation of the metastatic progression of breast cancer with an organometallic ruthenium compound - PubMed, n.d.). According to the findings, RAPTA-T is able to suppress each of these processes, and its effects are more obvious when trials are carried out on the highly invasive MDA-MB231 cells as opposed to the non-invasive MCF-7 cells or the non-tumorigenic HBL-100 cells. Interestingly, the results of tests to determine the interaction between tumor cells and extracellular matrix components might suggest that this Ru compound exerts its activity by interacting with cell surface molecules. Notably, in this context there was a report on the in vitro inhibitory effects of a series of RAPTA compounds on cathepsin B, a lysosomal cysteine protease of the papain family, which is involved in metabolic processes and has been implicated in tumor progression and metastasis (Komeda *et al*., 2012).

FITExP analysis of RAPTA-EA

RAPTA-EA is made up of the same ruthenium(II) arene fragment as RAPTA-T, but with an EA moiety attached to the arene ring. EA is a GST inhibitor, which is important in the elimination of foreign chemicals such as cancer chemotherapeutic agents, and the drug was developed to overcome GST-based resistance. Notably, GSTP1 is often overexpressed in solid tumours after anti-cancer medication exposure. RAPTA-EA inhibits GST more effectively in vitro than EA alone and produces substantially greater differential cytotoxicity in BC cell lines than basic RAPTA-type complexes (Lee *et al*., 2017; Ratanaphan *et al*., 2017).

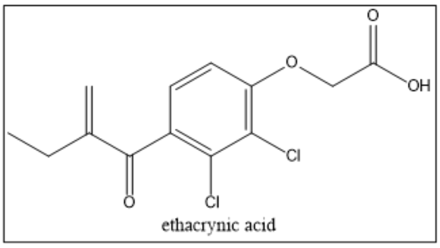


Figure 24: Moiety.

Ru and Os N-heterocyclic carbene complexes

Ru and Os have lately sparked significant interest in metal-based anti-cancer medication research. Clinical studies have been conducted on Ru complexes such as NAMI-A and KP1019. They are far less toxic than Pt-based medications and can overcome the resistance established by Pt treatments in cancer cells. The advancements in the field of ruthenium-based anti-cancer medicines sparked interest in Os complexes. Os compounds are regarded promising anti-cancer drugs due to their relative inertness and their stability under physiological conditions (W. Liu *et al*., 2016).

Tacke *et al*. 2013 created six Ru(II)-NHC complexes in addition to their Au(I)-NHC complexes made from 4,5-diarylimidazoles, and they tested their antiproliferative properties on the cancer cell lines MCF-7 and Caki-1 (Hackenberg *et al*., 2013). In comparison to cisplatin, these complexes were less effective (IC_{50} > 13 M) against the Caki-1 cancer cell line. Complexes, however, had stronger activity than cisplatin (IC_{50}: 14 M) on the MCF-7 BC cell line. The most effective compound, complex 84e, was 16 times more effective against MCF-7 cells than against Caki-1 cells (IC_{50}: 2.4 M) and roughly 6 times more effective than cisplatin. These findings suggested that the imidazole substitution pattern had a significant impact on the activity of these complexes (W. Liu & Gust, 2016).

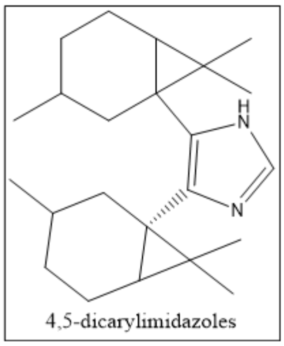


Figure 25: Ligand.

Fe

Fe is necessary for several metabolic processes, including the transfer of oxygen, the creation of DNA, and the movement of electrons. Many synthetic Fe compounds have demonstrated anticancer effects, which are typically attributed to the redox couple Fe(II)/Fe(III) in physiological settings (Yousuf *et al*., 2021). Iron-bleomycin is a noteworthy therapeutic candidate that has been utilised to treat testicular tumours with a high percentage of cure among the documented anticancer compounds of iron. Bleomycin has been discovered to have anticancer action by oxidative DNA damage in the presence of certain ROS, namely O2 and H2O2, after complexing with the Fe(II) metal ion. Ferrocifen, an analogue of tamoxifen (used in the therapeutic treatment of hormone dependent breast tumours), was created as a group of iron(II) based organometallic compounds that showed a particular manner of antiproliferative action (Yu *et al*., 2012). The ferrocifen derivatives (Fc-OH-Tam and Fc-diOH) have the ability to selectively inhibit cancer cell proliferation in both hormone-dependent (MCF-7) and hormone-independent (MDA-MB-231) cancer cell lines (Yousuf *et al*., 2021).

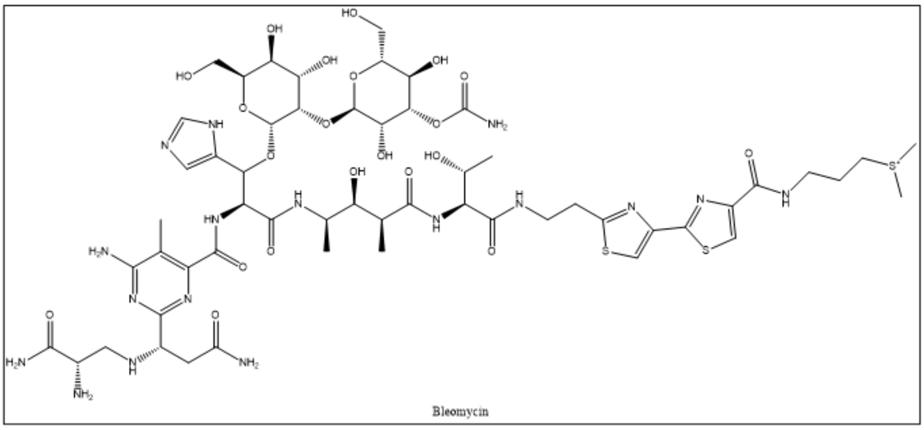
Fe (II)

TNBC cell lines have been used to test compounds containing ferrocene, a substance having a sandwich-like structure made up of two cyclopentadienyl rings attached to an Fe (II) core. In addition to having appealing reversible redox characteristics, ferrocene and its derivatives (such as ferroquine and ferrocifen) have demonstrated anticancer, antibacterial, antifungal, and antiparasitic efficacy (Nayeem *et al*., 2021). Zhang and colleagues have examined the anticancer traits shown by hybrids containing ferrocene (R. Wang *et al*., 2020). This review gathered the effects on various cancer types of distinct hybrids that have been described during the last ten years, including but not limited to: pyrazole, imidazole, chalcone, coumarin, indole, phenol, pyrimidine, and sugar hybrids (Nayeem *et al*., 2021).

Histone deacetylase inhibitors (HDACi) found in ferrocene are very efficient. These compounds prevent double-stranded break repair because their mode of action directly engages DNA (Librizzi *et al*., 2012; Luparello *et al*., 2019). These HDACi linked to other cellular inhibitors may have promising synergistic effects. The molecular effectiveness of Jay Amin hydroxamic acid (JAHA), a counterpart of HDACi suberoylanilide hydroxamic acid that contains ferrocene, was demonstrated by Luparello and colleagues (SAHA). The drug SAHA, also known as Vorinostat, is used to treat cutaneous T-cell lymphoma. A compound in Scheme 8 was produced by incorporating the ferrocene motif, and preliminary studies showed that it was effective in producing the JAHA analogue. Compound displayed cytotoxicity in the MDA-MB-231 cell line (IC_{50}= 8.45 M, 72 h), cell cycle dysfunction at G2/M phase, increased ROS production with mitochondrial membrane dissipation, and non-apoptotic cell death (Librizzi *et al*., 2012). In MDA-MB-231 cells, the molecular signature of the two acids was assessed using differential-display PCR and proteomic analysis. This revealed that while SAHA and JAHA had similar expression levels for the genes that inhibit differentiation and growth, gelsolin, IDI1, and VIDUP1, JAHA specifically upregulated the genes for oxidative stress, neurotrophic tyrosine kinase receptor type 2 (NTRK-2) and DNA repair protein RAD50 (Librizzi *et al*., 2017).

Fe (III)

Six coordination cationic Fe (III) complexes were examined in MDA-MB-231 cells by Acilan and colleagues and found to exhibit varying levels of cytotoxicity (IC_{50} values ranged from 6.5 to >50 M, 24 h). Three of these substances boosted



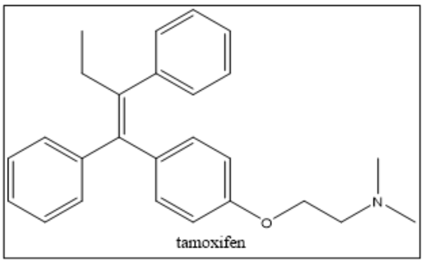


Figure 26: Anticancer metallodrugs.

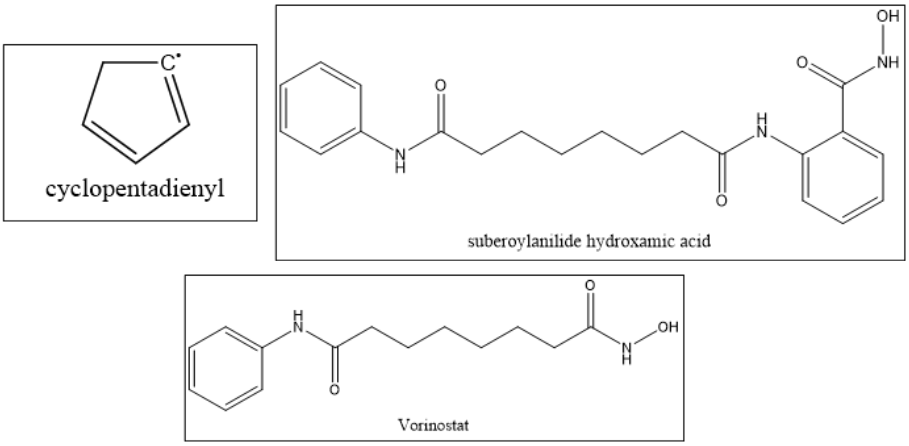


Figure 27: Combination drugs.

the production of intracellular ROS and triggered apoptosis in a caspase-dependent manner. DNA contacts were also shown by COMET and DNA cleavage assays, as well as by the phosphorylation of H2AX, a Double Strand Break marker (Nayeem *et al*., 2021).

Fe(η5-C5H5) complexes as antiproliferative agents

Two families of compounds with the generic formula [Fe(5 -C5 H5)(L) (P-P)]+ have emerged as a result of study, where L is either a nitrile ligand or an N-heteroaromatic ligand based on the imidazole molecule, and P-P is the dppe ligand (Morais *et al*., 2016; Valente *et al*., 2014). These ligands were chosen in accordance with prior research with ‘RuCp’ derived compounds that had demonstrated exceptional cytotoxicity (Morais *et al*., 2016). For all of the cell lines investigated, the tested “FeCp” derivatives all display high cytotoxicity with IC_{50} values under 10 M (Morais *et al*., 2016; Valente *et al*., 2014). Three cell lines, A2780, MCF7, and HeLa, were investigated in order to see how well the N-imidazole bonded set of “FeCp” compounds worked. The impact of the substituent depends on the tested cell line, and the most significant result is observed for the MCF7 cells where all of the compounds of the set considerably outperform cisplatin in activity (IC_{50}= 28 M), while their activity for the other cell lines is equivalent to that of cisplatin (slightly lower in most cases) (Morais *et al*., 2016).

Iridium

The iridium-phenylazopyidine compound in particular showed improved anti-proliferative effects in TNBC cell lines MDA-MB-468 and OCUB-M in a pilot investigation employing two organo-iridium (I) complexes made by Sadler and colleagues in a National Cancer Institute (NCI) 60 cell line screen (Nayeem *et al*., 2021).

CONCLUSION

The complete eradication of cancer is a pressing imperative due to its devastating and lethal nature, which significantly impacts the social and economic well-being of affected individuals. In recent years, extensive research has been conducted worldwide in the field of inorganic medicinal chemistry, focusing on the development of metal complexes for cancer treatment. Numerous scientists have been working towards the synthesis of medications using metallodrugs, as well as exploring drug combinations, to address this urgent need. We discussed the numerous Pt, Pd, Ag, iridium, Os, iron, rhenium, zinc, Cu, Ru and - Au based metal medicines’ mechanisms of action in this review study. Apoptosis and cell viability impacts, cell cycle arrest, cytoskeleton changes, angiogenesis suppression, and DNA damage are a scarce of these pathways. In the 1970s, cisplatin took the lead as an anticancer metallodrug. The development of several substitutes in the form of metallodrugs was necessary since cisplatin’s numerous adverse effects would cause the treatment to be discontinued. Since then, several well-known medications have demonstrated their own unique mechanisms of action, such as Pt, which demonstrated the value of combining many medications for successful therapy. Multiple components of the Ru complexes, including RAPTA, NAMi-A, and KP1019, have the ability to bind proteins, causing Mitochondrial apoptosis and ultimately cell death. These components also block tumour cell invasion and reduce tumour metastasis by decreasing the release of MMP-2/9 from the extracellular matrix, which, in turn, prevents MDA-MB-231 BC cells from migrating and invading respectively.

Ruthenium-based metallodrugs exhibit promising potential due to their demonstrated efficacy against cisplatin-resistant cell lines, ability to target metastasized solid tumors, and increased selectivity for tumor sites. KP1019 and NAMI-A, two specific ruthenium metallodrugs, are currently undergoing early-phase clinical trials, showing effectiveness against breast cancer. Although they have been authorized for other types of cancer, their potential for treating breast cancer is still being explored. These findings suggest a positive outlook for the future of metallodrugs in the treatment of breast cancer. This review would particularly help out the scholars who aspire or are in working in search of a potent metallodrug for the cancer treatment, not only breast cancer but also give a sight at different cancer’s.

DECLARATION OF CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 3: Abbreviation.

Abbreviations	Meaning
DCIS	Ductal carcinoma in situ
NST	No special type
ER	Oestrogen receptor
PR	Progesterone receptor
HER2	Human epidermal growth factor receptor 2
BRCA	Breast Cancer gene
GRB7	Growth factor receptor-bound protein 7
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic
TOP2	Topoisomerase II
FOXA1	Forkhead box protein A1
XBP1	X-box binding protein 1
MBC	Metastatic breast cancer
TNBC	Triple negative breast cancers
LAR	luminal androgen receptor
OVCAR	ovarian cancer
HeLa	cervical cancer
MB157, MCF-7, MDA-MB 231	breast cancer
Caki	renal cancer
HEPG2	liver carcinoma
HCT 116	Colon Cancer
A549	Lung Cancer
PTA	1,3,5-triaza-7-phosphaadamantane
RAPTA-EA1	Ruthenium(II)-arene 1,3,5-triaza-7- phosphaadamantane (pta) complex with an arene-tethered ethacrynic acid ligand
MMPs	Metalloproteinases
Pt	Platinum
Pd	Palladium
Au	Gold
Ag	Silver
Cu	Copper
Os	Osmium
Ru	Ruthenium
Fe	Iron
EMT	Epithelial-mesenchymal transition
HMGB1	high mobility group protein
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NSAID	Non-steroidal anti-inflammatory drug
COX-2	cyclooxygenase-2
NHC	N-heterocyclic carbene complexes
PGM	Platinum group metal
DNA	Deoxyribonucleic acid
ROS	Reactive oxygen species
RNS	Reactive nitrogen species
CSCs	Cancer stem cells
TrxR	Thioredoxin reductase

BLBC	Basal Like Breast Cancer
IC_{50}	Inhibitory concentration
SD	Standard deviation
LNCaP	Prostate Cancer
HL-60	Leukaemia
PGPH	Peptidylglutamyl peptide hydrolyzing
CuC	Copper complexes
XIAP	X-linked inhibitor of apoptosis protein
PCD	Programmed cell death
RAS	Renin-angiotensin system
MSNPs	Mesoporous silica nanoparticles
Mca	Mucin-like Carcinoma-associated Antigen
MMP	Matrix metalloproteinase
PLA	Phospholipase D
EA	ethacrynic acid
GST	glutathione transferase
HDACi	Histone deacetylase inhibitors
JAHA	Jay Amin hydroxamic acid
DSB	Double Strand Break
TGF	Transforming growth factor
IGF	Insulin-like growth factor
Top	topoisomerases
BC	Breast Cancer

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