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Progress in Synthesis and Antitumor Activities of Estradiol-linked Platinum Complex

Ping Zhang, Ye-wei Yang and Zheng-rong Shen*

Institute of Materia Medica, Zhejiang Academy of Medical Sciences, Hangzhou, China

Abstract: Platinum complexes such as cisplatin and caboplatin are widely used in cancer chemotherapy. However, their clinical applications are substantially limited by unexpected toxic side effects. In this review, we discuss the current progress on the design and synthesis of estradiol-linked platinum complexes as the targeted antitumor drugs. Many of them display a high antitumor activity against the growth of breast cancer cell lines *in vitro*. The estradiol-linked platinum complexes could be used as target therapeutics for breast cancer.

Keywords: Estradiol-linked platinum complex, Cisplatin, Target therapy, Antitumor activity, Cytotoxicity, Breast cancer.

INTRODUCTION

Cisplatin (*cis*-diamminedichloroplatinum(II)) has a major impact on cancer therapy since it was first found by Rosenberg *et al.* in 1960s [1, 2]. In 1978, cisplatin was approved in clinical usage for testicular and ovarian cancers by the U.S. Food and Drug Administration. Since then, a variety of platinum anticancer drugs have been designed and synthesized, such as carboplatin, oxaliplatin, and nedaplatin [3] (Fig. (**1**)). Of note, cisplatin and its second-generation analogues, carboplatin, are still widely used as anticancer agents in clinics for the treatment of solid tumours, including small cell lung, ovarian, testicular, head and neck tumors [4-7]. It has been clearly demonstrated that nuclear DNA is believed to be the primary target of platinum drugs [8, 9], which undergo covalent coordination [10, 11] or intercalative binding [12-15] with the DNA bases. It is generally accepted that platinum drugs binds to the N7 position of the guanine bases of DNA molecules, commonly in the form of 1,2-intrastrand d(GpG) and d(ApG) crosslinks, as well as 1,3-intrastrand and interstrand crosslinks [16-18], thus blocking the replication and/or transcription of DNA, and ultimately inducing cell apoptosis [19]. Despite of their high activities, clinical use of platinum antitumor drugs has been limited by two main disadvantages: chemoresistance to the drugs [16, 19] and non-specificity toward cancer cells which lead to unexpected toxic side effects, particularly nephrotoxicity and neurotoxicity [20-22]. Therefore, many research teams have made significant efforts to design novel platinum-based drugs with low toxicity and high specificity targeting tumor cells of particular organs [5, 9, 23]. One of the approaches is to use a biological carrier to directly deliver the cytotoxic drug into the tumor cells, as long as they have some biochemical differences as compared to normal tissues [24].

*Address correspondence to this author at the Institute of Materia Medica, Zhejiang Academy of Medical Sciences, Hangzhou, China;
Tel:/Fax: +86(571)88215506; E-mail: shenzr601@163.com

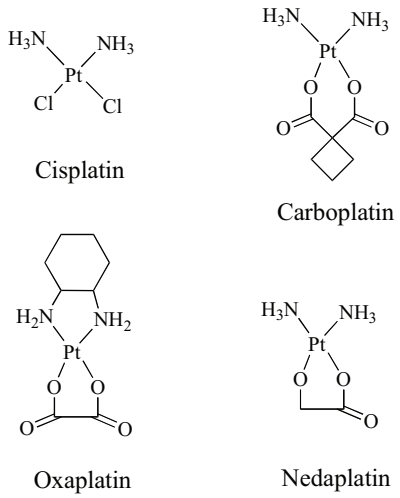

Fig. (1). Structure of the known platinum(II) complexes.

It is well known that estrogenic steroids are transported through the blood (bound to steroid transport proteins). After crossing the cellular membrane, they are transported into the cell nucleus by binding to the estrogen receptor (ER) in the cytoplasm [25, 26]. ER is a biological target that has attracted considerable attention over the years. It is highly expressed in several different cancers, such as breast (60-70%), uterus (70-73%) and ovarian (61%), which represent overall 40% of all human cancers diagnosed in women and is responsible for a 25% mortality rate [27-29]. Therefore, the intercellular interaction between 17β-estradiol and its cognate receptor could be used to direct a cytotoxic agent to the target cells. By conjugating the platinum drugs to estrogen, the estrogenic portion of the molecule would be used to direct the cytotoxic Pt moiety toward the target cells, thus increasing specificity and reducing systemic toxicity. Here, we summarize the recent progress of estradiol-linked platinum complexes with particular highlights of some significant advances and trends.

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REPLACEMENT OF THE OH GROUP IN POSITION 3 OR 17β IN THE STEROID SKELETON OF ESTRODIAL BY PT-PHARMACOPHORES

In an early report, Gandolfi *et al.* [30] presented a platinum complex with a 17β-estradiol ligand modified in position 3 of the steroid backbone (**1**, Fig. (**2**)). The biological effect proved to be of the same order of magnitude as cisplatin on a human breast tumor cell line MCF-7.

Altman *et al.* [31] prepared a platinum complex of 17β-estradiol with an aminoethoxy group also in position 3 (**2**, Fig. (**2**)) and investigated the antiproliferative effects on hormone dependent MCF-7 breast cancer cells. It exhibited antiproliferative effects at a concentration of 5 μM that was comparable with the effect of tamoxifen (10 μM). However, the authors reported that the compound **2** was also active against leukemia of the mouse, which made a contribution of hormonal activity to the antiproliferative effects unlikely.

Schobert *et al.* [32] reported the active conjugates of dichloro(6-aminomethylnicotinate)platinum(II) with 17β-estrodial linked in 3-O-(**3**, Fig. (**2**)) and 17-O-position (**4**, Fig. (**2**)) by ester bonds, respectively. The most potential complex **3** strongly interacted with sex hormone binding globulin (SHBG), which acted as a specific carrier and the storage of sex steroids. The complex **4** with a 17-O-linked estradiol, however, did not bind to SHBG at all. The complex **3** bound strongly and agonistically to ERα while isomer **4** bound less effectively to ERα. It is of interest to note that complex **3** exhibited a distinct inhibitory effect on the growth of MCF-7 (ER^+) breast cancer cells, but had little, if any, effect on MDA-MB-231 and MCF-7 (ER^-) cells. The complex **4** showed less effective on both ER^+ and ER^- breast cancer cells. Cisplatin had an unwinding effect on DNA. However, only compound **4** but not **3** interacted with DNA demonstrated by gel electrophoresis, suggesting a model of action different from that of cisplatin.

The synthesis of platinum(II) complex **5** (Fig. (**2**)) coordinated *via* L-methionine with 17β-estradiol was described by Kvasnica *et al.* [33]. The *in vitro* cytotoxicity was tested in several tumor cell lines. Complex **5** failed to demonstrate any significant activity against breast carcinoma MCF-7. In contrast to cisplatin (IC_{50} = 5 μM) complex **5** was not cytotoxic to human fibroblast BJ, a normal cell line.

Early studies on estradiol-linked platinum complexes primarily focused on cisplatin derivatives linked to estradiol through one of the two steroid hydroxy groups. The results described above showed that a free 3-OH is more important than a free 17-OH group in the context of binding of the Pt(II) complexes to ERα. Because the two hydroxy groups of 17β-estradiol have a high contribution to the receptor recognition and binding affinity [34, 35], this type of Pt(II) complexes exhibit poor binding activity to ER. This is unfavorable for targeting platinum drugs to specific tissues.

ATTACHMENT OF PT-PHARMACOPHORE TO THE STEROID SKELETON OF ETHYNYLESTRADIOL WHILE RETENTION OF THE OH FUNCTIONS IN THE 3- AND 17β-POSITIONS

Complexes with ethynylestradiol ligands modified at the 17α position have been shown this position is more suitable for the modification. 17α-Ethynylestradiol represents a good starting molecule by virtue of its reactive acetylene hydrogen atom, which can easily be linked to arms ending with either a diamine or a dicarboxylate group.

Jackson *et al.* [36] prepared the monochloroplatinum(II) complexes **6** and **7** (Fig. (**3**)), in which 17α-ethynylestradiol was attached to the tridendate ligands pyridine-2,6-dicarboxylate and 2,6-bis[(methylthio)methyl]pyridine, and examined their binding to the ER both as isolated receptor and in whole cell assays (ER^+ MCF-7 cells). The complex **7** showed a strong binding to the ER while much lower binding affinity was observed for the neutral compound **6**. This attributed to the more hydrophilic nature of the metallo-unit introduced by the dicarboxylate binding site. The result confirms that the estrogenic steroids are effective delivery vectors that can be used to mediate the transport of metal ions into cells.

Subsequently, Hannon *et al.* [37] reported the synthesis of 17α-[4'-ethynyl-2,2':6',2''-terpyridine]-17β-estradiol platinum(II) chloride (PtEEtpy, **8**, Fig. (**3**)), in which a terpyridyl group linked the steroid to the metal. The X-ray

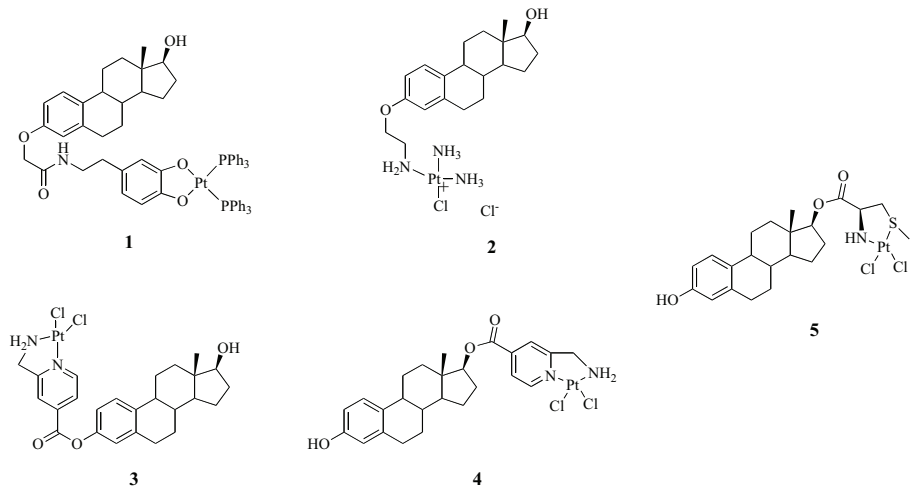


Fig. (2). Replacement of the OH group in position 3 or 17β in the steroid skeleton of estrodial by Pt-pharmacophores.

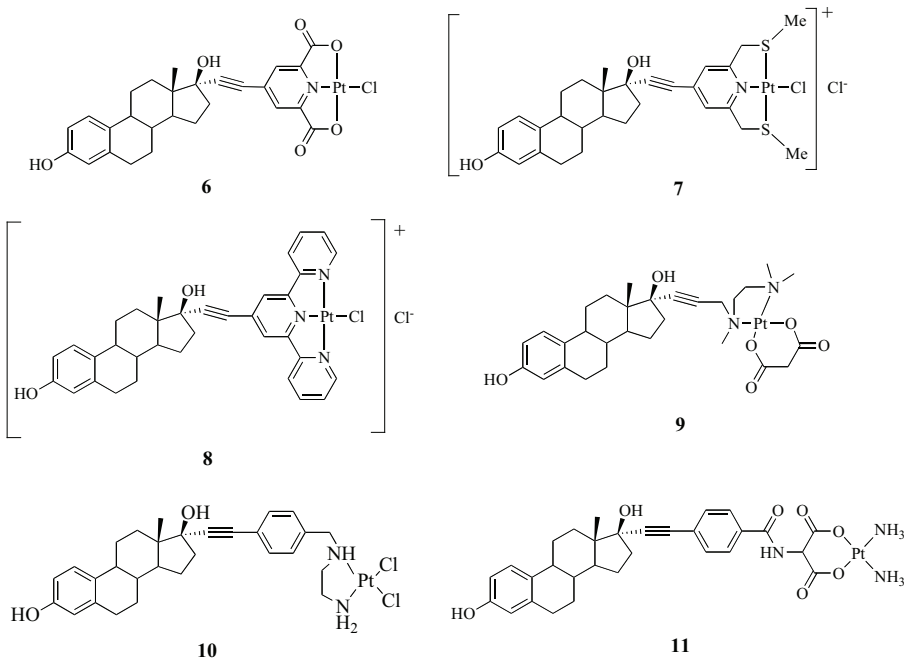


Fig. (3). Platinum(II) complexes with ethynylestradiol ligands.

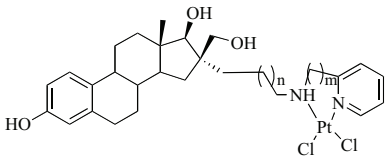
diffraction (XRD) crystal structure of PtEEtpy (**8**) confirmed that linkage of the terpyridyl unit through the 17α-position ensured an orientation below the hydrophobic scaffold of 17β-estradiol away from the two hydroxy groups and the upper face of the steroid, which are important for receptor recognition and binding. The rings of the terpyridyl unit were approximately coplanar (torsion angles in the range 10–16°) and oriented approximately parallel to the long axis of the steroid ligand. This orientation presumably allowed the most efficient packing of the molecule. The whole cell ER assay in ER^+ MCF-7 breast cancer cells showed that PtEEtpy (**8**) was transported into the tumor cells and bound to the ER. Although PtEEtpy (**8**) has a lower relative binding affinity (RBA) compared to diethylstilbestrol (DES) (IC_{50} values: PtEEtpy = 500 nM, DES (control) = 0.6 nM), its receptor binding and cellular delivery were retained upon conjugation of the steroid to the quite large terpyridine unit, indicating cationic charge (due to the Pt^{2+}) was not significantly detrimental to either delivery or binding. Circular dichroism (CD) indicated that a termolecular entity involving PtEEtpy, human serum albumin (HSA) and DNA was formed. The Fourier transform ion cyclotron resonance (FTICR) mass spectra also demonstrated that PtEEtpy (**8**) bound monofunctionally to the DNA, presumably to the N7 of guanine in the major groove and a linkage through coordination to Pt with displacement of the chloride ligand.

Cassino *et al.* [38] reported the tethering of malonatoplatinum(II) moiety to 17α-ethynylestradiol using chelating ethylenediamine arms (**9**, Fig. (**3**)). Unfortunately, the RBA value for complex **9** was less than 1%. The reduction in the RBA value might be due to the partial protonation of the amino groups at physiological pH, thus making the carrier quite hydrophilic. This was confirmed by the lipophilicity (log $P_{o/w}$), which was a rough measure of the drug lipophilicity, related to its ability to cross cell membranes. The log $P_{o/w}$ value of complex **9** was lower than that of estradiol (log $P_{o/w}$ value: **9** = 2.90, 17β-estradiol = 3.14). The hydrophilic group underwent an electrostatic repulsion, likely due to a methionine group, in the active site of the ER. Therefore, the complex **9** was incapable of entering the hydrophobic pocket of ERs.

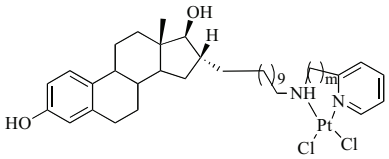
The same group further synthesized two new Pt(II)-derivatives of 17α-ethynylestradiol, in which the steroid was linked via its ethynyl residue to the Pt-pharmacophores [N-benzylethylenediamine]dichloroplatinum(II) (**10**, Fig. (**3**)) or diammine[benzoylaminomalonato] platinum(II) (**11**, Fig. (**3**)) [39]. The binding affinity of complexes **10** and **11** to ERα was improved to 2%, likely owing to the presence of an aromatic spacer in the arm between estradiol and ethylenediamine moieties. The two complexes proved to be inactive or even stimulated the proliferation of the ER^- cell line at a concentration of 1μM on ER^+ MCF-7 and ER^- MDA-MB-231.

LINKAGE OF PT-PHARMACOPHORE TO THE STEROID SKELETON OF 17β-ESTRADIOL IN THE POSITION 16

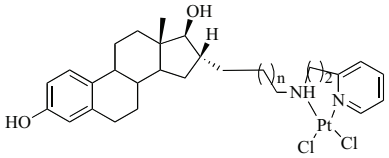
Bérubé *et al.* [40, 41] reported the synthesis of a series of 17β-estradiol-linked Pt(II) complexes (**12,** Fig. (**4**)). These compounds had a 16β-hydroxymethyl side chain and a platinum(II) complex locked in position 16α of the steroid nucleus. They presented a higher affinity than that of 17β-estradiol for ERα. Particularly, the hybrid with *m = 1* and *n = 2* (**12a**) was the most potent affinity for ERα due to the presence of the 16β-hydroxymethyl group, which allows additional hydrogen bonding to the ER. The Pt(II) complex with *m = 2* and *n = 8* (**12h**) was the most promising derivative of the series. It exhibited a three- to four-times higher cytotoxicity than parental cisplatin on all types of breast cancer cells (ER^+ and ER^-), presumably due to a large organic portion enhanced the cellular penetration of the



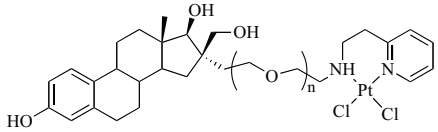
12a: m = 1, n = 2; **12b**: m = 1, n = 4;
12c: m = 1, n = 6; **12d**: m = 1, n = 8;
12e: m = 2, n = 2; **12f**: m = 2, n = 4;
12g: m = 2, n = 6; **12h**: m = 2, n = 8;



13a: m = 1
13b: m = 2



14a: n = 4; **14b**: n = 6
14c: n = 9; **14d**: n = 12



15a-e, n = 1-5

Fig. (4). Platinum(II) complexes with 17β-estradiol ligands linked in the position 16.

membranes to the nucleus. Meanwhile, the complex **12h** was a little more cytotoxic to ER^+ MCF-7 than ER^- MDA-MB-231 breast cancer cells (IC_{50} values: MCF-7 = 4.0 ± 0.6 μM, MDA-MB-231 = 4.7 ± 2.6 μM). In order to understand the differences in cytotoxicity and affinity, **12a** and **12h** were docked into the active site of the ER (PDB 1ERE). Molecular modeling showed that **12a** formed seven hydrogen bonds while **12h** presented four hydrogen bonds. Due to the additional hydrogen bonds, the binding energy is much greater for **12a** than for **12h** which explained its stronger ER binding affinity. This also made the steric hindrance (bumping atoms) different between ER and those molecules. In **12a**, the platinum and the chlorine atoms were fully buried in the ER site, which made it unavailable for binding to DNA. In **12h**, in contrast, the chlorine atoms were much less crowded within the protein and readily available to be hydrolyzed. Therefore, the platinum atom of **12h** bound more easily to DNA and exerted its higher cytotoxic activity.

N'soukpoé-Kossi *et al.* [42] examined the binding of estradiol-platinum(II) hybrid **12** with *m = 2* and *n = 4* (**12f**) and cisplatin drugs to transfer RNA (tRNA) *in vitro* and compared the results to those of the corresponding Pt-DNA complexes. Interestingly, **12f** showed the superior cytocidal activities than those of cisplatin in most of the cases for breast and uterine cancers, indicating that **12f** was a stronger drug than cisplatin. Using Fourier transform infrared (FTIR), ultraviolet-visible (UV-vis), and CD spectroscopic methods, the drug binding mode, the binding constant and RNA structural variations were determined for Pt-tRNA complexes in aqueous solution. Structural analysis showed the direct binding of cisplatin drug to guanine and adenine N7 sites, while both direct and indirect interactions of **12f** with tRNA bases and the backbone phosphate group were observed. The higher stability of **12f**-RNA complexes over cisplatin-RNA adducts is due to a major interaction (H-bonding) of estradiol moiety with tRNA in addition to the Pt-base and Pt-phosphate bindings. Major aggregation of tRNA occurred at high **12f** concentrations, while RNA remained in the A-family structure.

Perron *et al.* [43] introduced the synthesis of two complexes **13a** and **13b** (Fig. (**4**)) in which 17β-estradiol was linked at position 16 via an alkyl chain to two different platinum chelates. The complex **13b** was equally cytotoxic against ER^+ MCF-7 and ER^- MDA-MB-231 breast cancer cells, while **13a** was less cytotoxic to MCF-7 than MDA-MB-231 cells. The most promising estrogen-Pt(II) complex **13b** presented a greater activity than tamoxifen with 22 times more cytotoxic on MCF-7 cells and 37 times more cytotoxic on MDA-MB-231 cells. It was significantly more cytotoxic than cisplatin. These data showed that the Pt(II) complex bearing the 2-(2'-aminoethyl)pyridine ligand presented a higher activity than those bearing the 2-aminomethylpyridine ligand. In a binding assay, the most cytotoxic derivative **13b** showed high affinity for ERα (IC_{50} values: **13b** = 0.35 nM, 17β-estradiol = 4.79 nM). Taking into account the great cytotoxic activity and its high binding affinity for ERα, the complex **13b** was likely to transport the cytotoxic Pt(II) moiety to the ERα-expressing target cells.

DescÔteaux *et al.* [44] reported a further study of the influence of the linking chain length on the biological activity of this type of hybrids. Several analogs **14** (Fig. (**4**)) with the same estrogenic scaffold but various chain lengths separating the estradiol from the Pt-pharmacophore were synthesized. The cytotoxicity assay *in vitro* revealed that the hybrids **14** showed potent cytocidal activity on ER^+ (MCF-7) and ER^- (MDA-MB-231) breast cancer cell lines with four to nine times more cytotoxic than cisplatin itself. However, for the MDA-MB-468 (ER^-) and MDA-MB-436 (ER^-) breast cancer cell lines the hybrid molecules **14** were less cytotoxic than cisplatin itself. The complexes **14a-d** were more cytotoxic to the ER^- (MDA-MB-231, MDA-MB-468, MDA-MB-436) than the ER^+ (MCF-7) cells, except that the cytotoxicities of **14b** were comparable in MCF-7 and MDA-MB-231 cells (IC_{50} values: MCF-7 = 2.18 ± 0.11 μM, MDA-MB-231 = 2.16 ± 0.16 μM). As shown by the ER binding affinity assay, these hybrids **14** had similar binding affinity for the ERα and ERβ, close to that of 17β-estradiol. In general, the length of the alkyl chain between the estradiol and the cytotoxic part did not significantly interfere the

biological activity *in vitro*. Consequently, this type of 17β-estradiol-linked Pt(II) hybrids had the potential to target ER *in vivo* and showed the selective anticancer activity as well as reduced systemic toxicities.

Recently, Provebcher-Mandeville *et al.* [45] reported a new family of 17β-estradiol-platinum(II) hybrid molecules **15** (Fig. (**4**)) which replaced the carbon spacer by a polyethylene glycol (PEG) chain. The hybrids **15** were linked with a PEG chain at position 16α of the steroid nucleus and bore a 16β-hydroxymethyl side chain. The cytotoxicity assay *in vitro* revealed that the hybrids **15** were less cytotoxic to ER^+ MCF-7 than ER^- MDA-MB-231 breast cancer cell lines. The biological activities of these derivatives in ER^+ MCF-7 and ER^- MDA-MB-231 cell lines were lower than that of the hybrids with carbon spacer. The most promising compound **15e** with the longest PEG chain (*n* = *5*) was equipotent to cisplatin itself. Molecular modeling revealed that the orientation of the reactive site, $PtCl_2$ portion, was an important factor for its biological activity. For compound **15e**, the $PtCl_2$ moiety was oriented toward ERα and might unavailable for further interaction with its targets. For **12h**, the $PtCl_2$ was oriented outside the ERα pocket and the reactive site is likely accessible for its targets. The orientation of the reactive site could account for its cytocidal activity. Despite a relatively low cytocidal activity, the PEG hybrids could have *in vivo* biological potential due to their enhanced solubility. Further chemical and pharmacological studies are necessary to evaluate the therapeutical value of these interesting drugs.

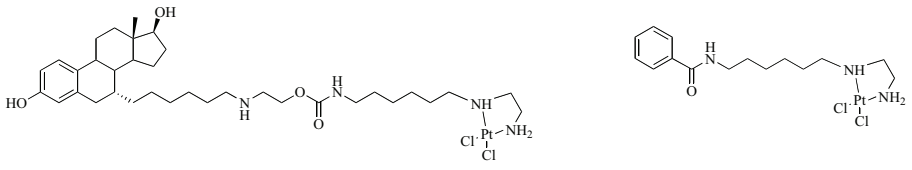
Froehlich *et al.* [46] proceeded a further study on the interaction of 1**5e** with calfthymus DNA using FTIR, UV-vis and CD spectroscopic methods. The drug binding mode, binding constant and structural variations of DNA in aqueous solution were carried out. Spectroscopic evidence showed that the various Pt-based drugs bound indirectly to the major and minor grooves of DNA duplex with some degree of drug-phosphate interaction. They were indirectly bound to DNA bases and the backbone phosphate group (H-bonding). DNA aggregation occurred at high drug concentration, while DNA remained in the B-family structure.

LINKAGE OF PT-PHARMACOPHORE TO THE STEROID SKELETON OF 17β-ESTRADIOL AT OTHER POSITIONS WHILE RETENTION OF THE OH FUNCTIONS IN 3- AND 17β-POSITIONS

Recently, the neutral Pt-complex [6-(2-amino-ethylamino)-hexyl]-carbamic acid 2-[6-(7α-estra-1,3,5,(10)-triene)-hexylamino]-ethyl ester platinum(II) dichloride ((Est-en)$PtCl_2$) **16** (Fig. (**5**)) was described by Kim *et al.*, which the Pt-pharmacophore was linked at the 7α position of 17β-estradiol [47]. The control compound, N-[6-(2-amino-ethylamino)-hexyl]-benzamide ((Bz-en)$PtCl_2$) **17** was also synthesized to explore the feasibility of using a estradiol ligand to enhance the cytotoxicity of platinating agents in cells. The control compound **17** easily formed DNA adducts but did not interact with ER due to the absence of functional ligand. Using a competitive binding assay, (Est-en)$PtCl_2$ (**16**) had a RBA of 28% for ER as compared to 17β-estradiol. After covalent binding to a synthetic DNA duplex 16-mer, the compound **16** retained its affinity for ER. The (Est-en)$PtCl_2$ (**16**) compound was much more potently cytotoxic than (Bz-en)$PtCl_2$ (**17**) against the ER positive ovarian cancer cell line CAOV3. At concentrations < 20 μM, (Est-en)$PtCl_2$ (**16**) was also more cytotoxic to the ER^+ MCF-7 than the ER^- MDA-MB231 breast cancer cell lines. These results indicated that both the estradiol moiety in (Est-en)$PtCl_2$ and expression of ER in target cells contributed to the enhanced cytotoxicity.

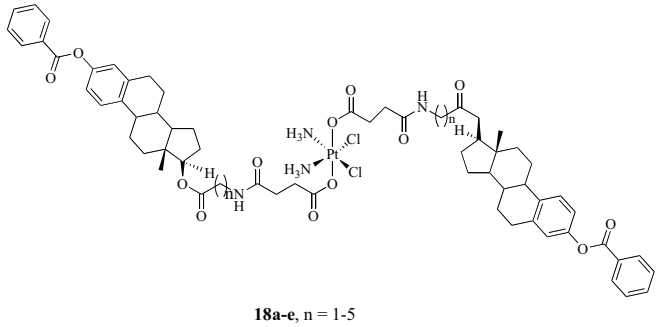
ATTACHMENT OF PT-PHARMACOPHORE WITH TWO ESTRADIOL LIGANDS

Several estrogen-tethered Pt(IV)-complexes (**18**, Fig. (**6**)) were prepared by Lippard *et al.* [48], which estradiol was tethered to the terminal carboxylate groups of *cis*, *cis*, *trans*-diamminedichlorodisuccinatoplatinum(IV) through polymethylene chains with various lengths. Their ability to up-regulate the



16, (Est-en)$PtCl_2$ **17**, (Bz-en)$PtCl_2$

Fig. (5). (Est-en)$PtCl_2$ and the control compound (Bz-en)$PtCl_2$.



18a-e, n = 1-5

Fig. (6). Platinum(IV) complexes with two estradiol ligands.

high-mobility group box (HMGB1) was evaluated, and their cytotoxicity against breast cancer cell lines was also screened. The Pt(IV)-complexes **18** were reduced to platinum(II) in the reducing environment of tumor cell, and allowing the release of cisplatin and two equivalents of the linker-modified estrogen. The complexes induced the overexpression of HMGB1 in ER^+ MCF-7 cells, which was further validated by comparative testing on ER^+ MCF-7 and ER^- HCC-1937 breast cancer cell lines. The cytotoxicities of **18a** and **18b** were quite comparable in MCF-7 and HCC-1937 cells, whereas **18e** was more cytotoxic to the HCC-1937 cells. MCF-7 cells were 1.3-fold more sensitive toward **18d** treatment. It is significant that **18c** is nearly 2-fold more cytotoxic in MCF-7 than in HCC-1937 cells (IC_{50} values: MCF-7 = 2.1 ± 0.4 μM, HCC-1937 = 3.7 ± 0.9 μM). It was possible that **18c** could up-regulate HMGB1 in some degree, that is kinetically competent to shield platinum-DNA adducts from repair. This example provided a novel strategy, namely using mechanistic insights to aid the rational design of new complexes, in the development of platinum-containing anticancer agents.

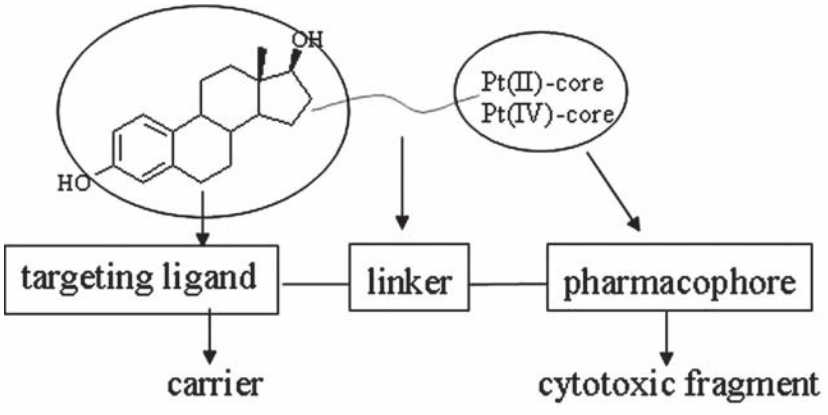
STRUCTURAL FEATURES AND MECHANISM OF ESTRADIOL-TETHERED PLATINUM COMPLEXES

The estradiol-tethered platinum complexes include three components: targeting estrogen ligand, linker and Pt-pharmacophore (Scheme **1**). The targeting estrogen ligand, as a carrier, delivers platinum complex across the cellular membrane and into specific cells. The Pt-pharmacophore is the active center for inhibiting tumor. It will accumulate in the tumor cells entailing an enhanced impairment of DNA function via formation of intrastrand crosslinking. The linker is used to connect the estrogen ligand and Pt-pharmacophore, which provide space of freedom for the complex to work cooperatively in the tumor-inhibiting process. Therefore, it is essential that the biological properties of both the estrogenic and the cytotoxic component are retained after the chemical linkage. For this purpose, the Pt-pharmacophore should be attached to the steroid at a position that has the minimal interfere with the binding of the complex to the receptor.

The binding affinity of a carrier ligand to the estrogen receptor will determine the accumulation level of the substances in the tumor cells followed by antitumor effects rendered by DNA binding via the platinum moiety. The antitumor activity and the bioavailability of platinum complexes are strongly influenced by their capability to react with bionucleophiles. It is widely accepted that the formation of DNA intrastrand cross links, especially of [Pt{d(GpG)}] and [Pt{d(ApG)}], is responsible for the inhibition of tumor growth. The cytotoxicity and antiproliferative effects on the cultured breast cancer cells are the most important parameters to evaluate the efficacy of platinum complexes. According to the reported cytotoxic effects of estradiol-linked platinum complexes, it is not clear enough concerning the relationship between molecule structure of platinum complexes and cytotoxic effects on ER-positive and ER-negative breast cancer cell lines.

CONCLUSION

Significant efforts are being taken towards the design of innovative estradiol-tethered platinum anticancer drugs. The clinical success of cisplatin remains a stimulus for the development of new complexes that address the downsides associated with cisplatin, especially the systemic toxicity and resistance. Drug targeting holds the promise of more selective and effective drug administration. It shows that ER-binding estradiol-linked platinum complexes are active on estrogen-sensitive tumors, such as breast and prostate cancer, by a complicated model of action in which ER-agonistic and ER-antagonistic properties are involved. It will expand the clinical application of platinum drugs due to the clinically approved platinum(II) complexes did not find their way into the regular therapy of breast cancer [49]. The platinum drugs presented here show the promising properties and encouraging biological results. They are currently investigated in preclinical studies for the treatment of breast cancer. Many of them conjugate a DNA binding moiety with a carrier ligand to selectively target mammary carcinoma cells. Therefore, the important issue for designing tumor-inhibiting platinum complexes is to remain and improve the bioactivity of both estrogen ligand and Pt-pharmacophore. The estradiol-linked platinum complexes may be considered as selective estrogen receptor modulators (SERMs) that could regulate the estrogen activities by binding to ERs in cells. SERMs take effect as estrogen agonists in some tissues (bone, brain and the cardiovascular system), while as antagonists in others (uterus and breast) [50, 51]. A key issue is that the targeting estrogen ligand could not display estrogen-like effect on breast cancer cells while the steroidal Pt-complex shows



Scheme 1. Schematic view of the estradiol-tethered platinum complexes.

potent cytotoxicity. A widely accepted form to describe cytotoxic and estrogenic effects is the IC_{50}-value. The IC_{50}-values for the established platinum complexes (cisplatin, carboplatin, oxaliplatin) using human breast cancer cell lines have been determined in the nanomolar to low micromolar range. The IC_{50}-values for SERMs usually is in the range of nanomolar.

Thus, the promising strategy is to design the steroidal Pt-complexes with antagonistic effect on ER. In recent years, a lot of SERMs having good binding affinity and agtagonist/ antagonist potency have been synthesized [52, 53]. It is believed that the recognization of ER subtypes and selectively delivery to specific tumor cells would be greatly enhanced by attachment of Pt-pharmacophore to the skeleton of the SERMs. Many more exciting developments can therefore be expected.

Based on the results described above, the use of estradiol-tethered platinum complexes against breast cancer seems to be a reasonable therapeutic strategy. The estrogen sensitive and breast cancer tissue selective estradiol-linked platinum complexes investigated in preclinical studies may bring bright prospect future use in clinical therapy. More intensive research on these compounds is definitely needed.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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