Dalton Transactions

PAPER

View Article Online
View Journal | View Issue

Cite this: *Dalton Trans.*, 2019, **48**, 936

Synthesis, characterization and biological investigation of platinum(II) complexes with asparagusic acid derivatives as ligands†

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Received 22nd June 2018,
Accepted 5th December 2018

DOI: 10.1039/c8dt02553c

rsc.li/dalton

After more than 50 years of platinum-based anticancer research only three compounds are in clinical use worldwide. The use of the well-known lead compound of this class of anticancer agents, cisplatin, is limited by its side effects and varying resistance mechanisms. Therefore, we report on platinum(II) compounds with asparagusic acid derivatives as ligands which show interesting anticancer results on cisplatin resistant cell lines.

Introduction

Cisplatin and analogues

Since its first description as a molecule with anticancer activity in the 1960s, cisplatin has acted as one of the major drugs in chemotherapeutic treatment.[1,2] The compound is mainly used in the treatment of lung, head and neck, ovarian, bladder and testicular cancer types.[2–6] The drug application is limited by several side effects *e.g.* hepato-, nephro-, neuro- and ototoxicity as well as several resistance mechanisms inside the human body.[3,7–10] Although there is a great research community working on improving platinum(II) cancer agents, only two additional molecules are approved worldwide, namely carboplatin and oxaliplatin.[3,7,10,11] Carboplatin, developed in 1989, is clinically used against advanced ovarian carcinomas, whereas oxaliplatin has been well-implemented against metastatic colorectal cancers since 2002.[10,12,13] All three complexes contain a square-planar platinum(II) core and on one side, amine-ligands.[11,13,14] The rational design of platinum(II) anticancer agents putting effective leaving groups on the other two coordination sides seems to be an important characteristic. In the case of cisplatin the molecule exhibits two chlorido ligands, whereas carboplatin and oxaliplatin have *O*,*O*-bidentate ligands. Inside the cell, these ligands can be substituted with aqua-complexes which are able to bind to the genomic DNA.[9,15–17] This interaction with the DNA results in a distortion of the dsDNA structure and erroneous DNA replication and leads to apoptosis of the proliferating cells.[9] Although this previously described mechanism is well accepted as the mechanism of action, more and more publications additionally concentrate on the understanding of the bioavailability of the drug after i.v. application. Importantly, the potential interaction with other molecules will just lead to the inactivation of cisplatin.[18–20] Many compounds are designed to follow cisplatin's mechanism of action and target the DNA, although the effectiveness of compounds is likely reduced by resistance mechanisms *i.e.* those mediated by the DNA repair enzymes removing the platinum-adducts from the DNA.[9] Additionally, more than 50 years of research did not identify a drug superior to cisplatin. Thus, new strategies for drug design should be investigated.[3,10] Therefore, other researchers developed compounds for interaction with other, so-called non-classical targets, *e.g.* proteins and enzymes.[6,7,14,21] These complexes do not follow the "basic rules" for platinum-based anticancer compounds but some of them exhibit acceptable anticancer activity.[6,7,22,23]

Asparagusic acid

Natural products are of high interest for medicinal applications. Sulfur-containing metabolites exemplify one group of such compounds with biological activities influencing human health.[24] Next to metabolites, small sulfur-containing compounds like glutathione also have important physiological roles.[25] Asparagusic acid is a sulfur-containing five membered heterocyclic ring (1,2-dithiolane-4-carboxylic acid) with a carboxylic acid function which is unique to asparagus from which it was isolated first in 1948.[26–28] The structure is close to that of α-lipoic acid which can act as a co-factor for *e.g.* pyruvate

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†CCDC 1514265 for **Pt1** and 1514266 for **Pt7** (excluding structure factors). For crystallographic data in CIF or other electronic format see DOI: 10.1039/C8DT02553C

multienzyme and is often compared regarding its activity and chemical behavior to this molecule.[27,29,30] The reactivity of the disulfide moieties is essential for mechanisms in biology, biochemistry, medicinal chemistry, organic synthesis, catalysis, coordination chemistry and materials science.[29–38] This contemplation supplemented with the wide range of observed medicinal properties for this compound leads to high interest in asparagusic acid and its analogues for medicinal chemists. The pharmacological properties of ingredients of asparagus are numerous and the research on that increased in the last few years.[24,25,27,28,39,40] Concentrating on asparagusic acid itself, several useful characteristics have been observed: anticancer, antioxidant, antifungal, antibacterial, anti-dysenteric, anti-inflammatory, anti-abortifacient, anti-oxytocic, antiulcer and anticoagulant activities, and it should reduce the risk of rheumatism and diabetes.[27,39] These observations are based on the knowledge that asparagusic acid acts as a growth-inhibitor on higher plants as well as it prevents plants from fungal-growth, which has been observed already in the 1970s.[27,41] Important for medicinal applications of asparagusic acid and its analogues or modified compounds is the cellular uptake which is well-identified as a thiol-mediated mechanism. Asparagusic acid uptake is mediated by binding to a cysteine molecule on the surface of the transferrin receptor.[42,43] These facts and the ability to synthesize metal-complexes with dithiolato and diselenolato ligands (see below) form the basis for the design of our compounds discussed in this publication.

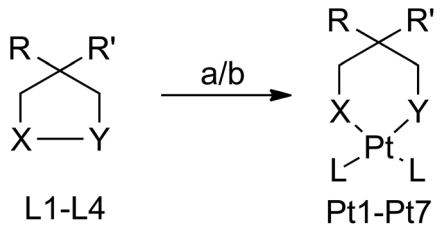
Platinum(II) complexes with S/Se and P containing ligands

In 2010 Siemeling *et al.* reported on the oxidative addition of platinum(0) complexes to asparagusic acid along the sulfur–sulfur bond.[36] We reported previously and later on this kind of reaction to build dithiolato platinum(II) compounds with phosphane ligands.[44–50] Because it is already well-known how to synthesize platinum(II) complexes with sulfur and selenium based ligands some researchers focus on the anticancer activity of these groups of metal complexes.[51–61] In general, most researchers found high IC_{50} values for sulfur-containing platinum(II) complexes in comparison to cisplatin, but results proving higher cytotoxic activity were identified for the selenium-containing species.[52,55,57,62] Fuks *et al.* reported in 2010 on a comparison study between platinum(II) complexes with sulfur or selenium containing ligands showing that the selenium compound was the most promising on HeLa cervical carcinoma cells.[55] Next to sulfur phosphor donor ligands also form strong and inert bonds with the platinum(II) ion.[59,63] Therefore, several phosphane containing platinum(II) complexes are known in the literature.[64–74] Several publications examine the cytotoxic activity of these kinds of compounds, and most of them have a higher IC_{50} value compared to cisplatin.[67,69,70,74] Nevertheless, some publications show lower IC_{50} values for their compounds compared to that of cisplatin on resistant-cell lines pointing to a different mechanism of action overcoming the resistance mechanisms.[65,66,70,75] Concentrating on the structure–activity-relationships of these compounds Ramos-Lima *et al.* found that the replacement of amine ligands by phosphanes results in lower IC_{50} values. Moreover the PPh_3 containing complexes are more active than those with PMe_2Ph-ligands because of their steric effects.[73] In 2011 the synthesis and cytotoxic activity of 14 different platinum(II) compounds with the PtP_2S_2 pharmacophore have been published.[59] Researchers observed high IC_{50} values on the cell line A2780 in comparison to cisplatin for their phosphane platinum(II) complexes. Also the simple $PtCl_2(PPh_3)_2$ which acts as a starting compound for many platinum(II) complexes exhibits very low cytotoxic activity.[59,67] Interestingly, the resistance ratio for these PtP_2S_2 complexes was much lower than that for cisplatin, caused by lower IC_{50} values on resistant cell lines compared to cisplatin itself. To point out, the IC_{50} value for cisplatin on A2780cis/r is 17.1 whereas the average resistant ratio of all eight analyzed compounds is 1.9 (range from 1.5 to 3.0).[59] This may be a consequence of circumventing the resistance mechanisms proving the relevance of this group of compounds despite the fact that their IC_{50} values are in general very high. The most promising phosphane ligand in this previous work has been PPh_3, because of the best resistance factor. Therefore, we focus in our work on the $(PPh_3)_2Pt$ group with dichalcogenolato ligands. Due to the biological relevance of asparagusic acid, this kind of structure completes our platinum-complexes to generate compounds with lower IC_{50} values than cisplatin. It can be expected that they have the same effects on the resistance factors, as previously described by Mügge *et al.* In addition, as described above, selenium containing complexes result in low IC_{50} values in comparison to sulfur containing ones. Thus, the aim of this study was to compare sulfur and selenium containing compounds as well as the mixed ones. To the best of our knowledge, this has not been discussed before. To shed light on the biological activity of the above discussed complexes we designed seven platinum(II) compounds with four different asparagusic acid derivatives and dppma, whereas dppma is bis(diphenylphosphino)methylamine or PPh_3 ligands. These compounds were tested on cisplatin sensitive and resistant cell lines.

Results and discussion

Synthesis and characterization

For **Pt2**, **Pt4** and **Pt6**, the first step is the preparation of $(dppma)PtCl_2$ starting from $(COD)PtCl_2$ which was prepared by adding COD (1,5-cyclooctadiene) to K_2PtCl_4 as described in the literature.[76,77] General synthesis of **Pt1–Pt7** is described in Scheme 1. For the dithiolate compounds **Pt1** and **Pt2** (Scheme 1a), the first step is the deprotonation of both SH groups at the dihydroasparagusic acid with K_2CO_3. In a next step the corresponding $PtCl_2L_2$ (L = PPh_3 or $\frac{1}{2}$ dppma, for more information see Scheme 1) component is added to the solution of the deprotonated diasparagusic acid in $CHCl_3$/EtOH, followed by stirring at room temperature for 16 hours. After the addition of an aqueous solution of $KHSO_4$ (c = 2 mol L^{-1}), the crude product is purified by column chromatography (see



Scheme 1 Synthesis and overview of the platinum(II) complexes **Pt1–Pt7** with their corresponding asparagusic acid derivatives as ligands L1–L7. **Pt1** was first published by Siemeling *et al.*[36] Reagents and conditions: a (for **Pt1**/**Pt2**): (i) 1 equiv. dihydroasparagusic acid, 4 equiv. K_2CO_3, 10 ml EtOH, r.t.; (ii) 1 equiv. $PtCl_2L_2$, 10 ml $CHCl_3$, r.t., 16 h; (iii) $KHSO_4$; b (for **Pt1–Pt7**): (i) 1.05 equiv. corresponding ligand, 3.15 equiv. $NaBH_4$, 10 ml EtOH, r.t., 10 min; (ii) 0.5 M HCl, r.t., 5 min; (iii) K_2CO_3, 1 equiv. $PtCl_2L_2$, 10 ml $CHCl_3$, r.t., 16 h; (iv) $KHSO_4$.

the Experimental section). Another option for the preparation of **Pt1**/**Pt2** as well as for all other Pt(II) compounds (**Pt3–Pt7**) is to start with the asparagusic acid derivatives L1–L4. The first step is reduction to a dianionic species using $NaBH_4$ followed by removal of unreacted $NaBH_4$ with an aqueous solution of HCl and addition of K_2CO_3 to adjust the pH value. Next steps are similar to those described above: addition of $PtCl_2L_2$ (L = PPh_3, dppma), stirring overnight and work up steps (see the Experimental section).

The compounds are characterized by NMR spectroscopy, mass spectrometry and elemental analysis (see the Experimental section). The $^{31}P\{^1H\}$NMR spectrum of **Pt1** shows one singlet at 26.3 ppm with the corresponding ^{195}Pt-satellites as well as for **Pt6** at 34.0 ppm with ^{195}Pt- as well as ^{77}Se-satellites ($^2J_{Se-P}$ = 34.6 Hz). The unsymmetrically substituted S/Se platinum(II) compounds **Pt3** and **Pt4** show a typical AB spin system in the $^{31}P\{^1H\}$ NMR spectra. Mass spectra show the molecular peak as well as the characteristic isotopic pattern for compounds **Pt1**, **Pt3**, **Pt5** and **Pt7** with the PPh_3 ligand. All of them show the fragment m/z = 720 in the Micro-ESI pos. spectrum, which can be detected as a loss of the asparagusic acid derivative. For the dppma containing compounds **Pt2** and **Pt6** their molecular peaks are observed as well as characteristic isotopic patterns. Compound **Pt4** has been characterized only by NMR spectroscopic methods.

Platinum(II) complexes **Pt1** and **Pt7** (Fig. 1) are characterized by means of single crystal X-ray structure determination. Molecular structures of the ligands L2 and L3 were discussed previously.[78] For compound **Pt7** are at least two independent molecules in the unit cell but just one is shown and discussed because bond lengths and angles are very similar. All of them are in the same range like those reported earlier.[36,44,59] In both structures platinum(II) atoms reside in a slightly distorted square-planar coordination sphere similar to those reported previously.[44,59] Because of the steric demand of the PPh_3 ligands the P1–Pt–P2 angle is, in both cases, larger than 90° (99.96°(5) for **Pt1** and 97.38°(5) for **Pt7**), contrary to angles reported for the platinum(II) compounds by Mügge *et al.*, which show P–Pt angles typically for the dppe ligand of ~85°. The S1/Se1–Pt–S2/Se2 angles are close to 90°. The two Pt–P bond lengths are slightly longer (~2.28 Å) than those which were published previously (~2.25 Å).[59] The angles P1–Pt–S1, P2–Pt–S2, P1–Pt–Se1, are P2–Pt–Se2 are between 81° and 90°. The bond lengths of the corresponding X/Y to platinum(II) are longer for **Pt7** than for **Pt1** (for example S1–Pt 2.3375(13) and Se1–Pt 2.4427(5)). The carboxylic function of **Pt1** forms intermolecular hydrogen bonds with another unit (Fig. 1) leading to a dimeric structure in the crystal.

Biological activity

The IC_{50} values of all platinum(II) complexes were determined with the MTT-assay (see the Experimental section for further conditions) on two different ovarian carcinoma cell lines SKOV3 and A2780 (par – parental) as well as on their cisplatin-resistant analogues (SKOV3cis and A2780cis; see the Experimental section for preparation details).[79] Cisplatin acts as a reference and IC_{50} values were determined under the same conditions for platinum(II) compounds. Determined IC_{50} values (Table 1) for cisplatin confirmed significantly higher

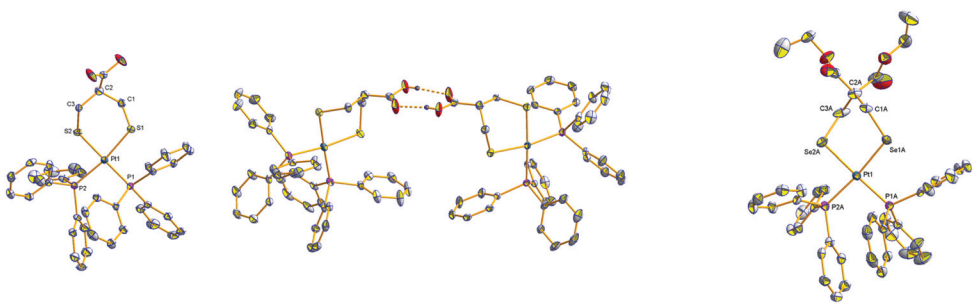


Fig. 1 Left: Molecular structures of **Pt1** in the crystal. Middle: Dimeric unit of **Pt1** in the crystal, displaying intermolecular hydrogen bonding. Ellipsoids are drawn at 50% probability level, hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angels (°): P1–Pt 2.2847(13), P2–Pt 2.2925(12), S1–Pt 2.3375(13), S2–Pt 2.3472(13), C1–S1 1.818(6), C3–S2 1.822(5), P1–Pt–P2 99.96(5), P1–Pt–S1 88.75(5), S1–Pt–S2 90.09(4), P2–Pt–S2 81.09(5), C1–S1–Pt 107.60(19), C3–S2–Pt 103.09(19). Right: Molecular structures of **Pt7** in the crystal. Only one of the two individual molecules present in the asymmetric unit is shown. Ellipsoids are drawn at 50% probability level, and hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angels (°): P1–Pt 2.2351(14), P2–Pt 2.2866(13), Se1–Pt 2.4427(5), Se2–Pt 2.4733(6), C1–Se1 1.962(5), C3–Se2 1.971(6), P1–Pt–P2 97.38(5), P1–Pt–Se1 88.32(3), Se1–Pt–Se2 90.23(2), P2–Pt–Se2 84.12(4), C1–Se1–Pt 107.02(16), C3–Se2–Pt 101.09(19).

Table 1 IC_{50} values for **Pt1–Pt7** on ovarian carcinoma cell lines SKOV3, A2780 and their cisplatin-resistant analogues SKOV3cis and A2780Cis. Resistant factors (RF) were calculated for each substance[78]

Substance	SKOV3par [μM]	SKOV3cis [μM]	A2780par [μM]	A2780cis [μM]
Pt1	5.5 (±1.3)	23.5 (±1.8)	9.8 (±1.6)	11.8 (±0.9)
RF(**Pt1**)	4.3		1.2	
Pt2	22.0 (±0.2)	12.2 (±2.3)	11.7 (±1.6)	16.1 (±1.7)
RF(**Pt2**)	0.6		1.4	
Pt3	17.8 (±5.2)	18.7 (±3.7)	9.7 (±2.7)	16.0 (±1.9)
RF(**Pt3**)	1.1		1.6	
Pt4	n.m.	n.m.	n.m.	n.m.
RF(**Pt4**)	—		—	
Pt5	13.7 (±6.6)	15.9 (±2.1)	5.4 (±2.4)	17.0 (±4.5)
RF(**Pt5**)	1.2		3.1	
Pt6	9.8 (±1.8)	12.2 (±6.4)	5.0 (±3.5)	5.4 (±1.9)
RF(**Pt6**)	1.2		1.1	
Pt7	6.3 (±0.9)	4.3 (±1.4)	7.8 (±0.9)	5.9 (±1.6)
RF(**Pt7**)	0.7		0.8	
CDDP	**3.8 (±2.8)**	**13.5 (±4.4)**	**1.3 (±0.2)**	**6.1 (±2.1)**
RF (CDDP)	**3.6**		**4.7**	

values for the cisplatin-resistant analogues of both cell lines. Parental SKOV3 and A2780 show higher cytotoxic activity of cisplatin in comparison to **Pt1–Pt7**. Interestingly, whereas IC_{50} values for cisplatin increase in SKOV3cis and A2780cis cells, IC_{50} is not increasing for most of the platinum(II) complexes with asparagusic acid derivatives. Contrarily, in some cases IC_{50} values decrease in a significant way. Similar results have been shown under the same conditions for our latest published platinum(II) complexes with sulfur- and oxygen-containing ligands.[80] Compound **Pt2** shows for SKOV3 an IC_{50} value of 22.0 (±0.2) μM but SKOV3cis exhibits a significantly lower IC_{50} value of 12.2 (±2.3) μM. Also compound **Pt7** has an increased influence on SKOV3cis and A2780cis in comparison to SKOV3 and A2780 (see Table 1). This results in improved resistant factors (RF). Cisplatin shows RF 3.6 (SKOV3) and 4.7 (A2780) whereas the investigated compounds resulted in a RF near to 1, Table 1. Previously reported results of sulfur containing platinum(II) compounds showed for A2780 and its resistant-analogue that these molecules exhibit a higher IC_{50} value on the resistant cell line than on the sensitive one.[59] This is also observable for **Pt1** and **Pt2** (Table 1). IC_{50} values for most of our compounds are in the same range than those already reported.[59] Nevertheless, herein we used different incubation times (48 h to 72 h) pointing to a higher cytotoxic activity of our complexes. The best results are detected for selenium-containing compounds **Pt6** and **Pt7**, both of them show lower IC_{50} values on resistant cell lines than cisplatin and **Pt7** shows lower IC_{50} values for the resistant cell lines than for the sensitive ones. This means that complex **Pt7** exhibits an increased cytotoxic activity for resistant tumour cells in comparison to the parental, sensitive carcinoma cells. To conclude, we can confirm from the previously published results that these kinds of compounds show good RF, that Se/Se-containing platinum(II) complexes show a higher activity than sulfur containing ones and we can add the fact that especially **Pt7** is a promising candidate to target resistant cell lines.[55,59]

An overview of all IC_{50} values, the mean IC_{50} for the compounds and their properties are given in Fig. 2. This overview depicts some SARs of the compounds. As mentioned before **Pt7**, with a Se–Se ligand, is the most active compound and has a mean IC_{50} value of 6.09 μM which is comparable to that of cisplatin (mean IC_{50} value 6.18 μM). Interestingly, also the second most active compound **Pt6** contains a Se/Se ligand. Moreover, the hydrophobicity of the residue R may play an important role. **Pt7** is more active than **Pt5** despite the identical structure except the residues (–COO–Et *vs.* –H and –COOH).

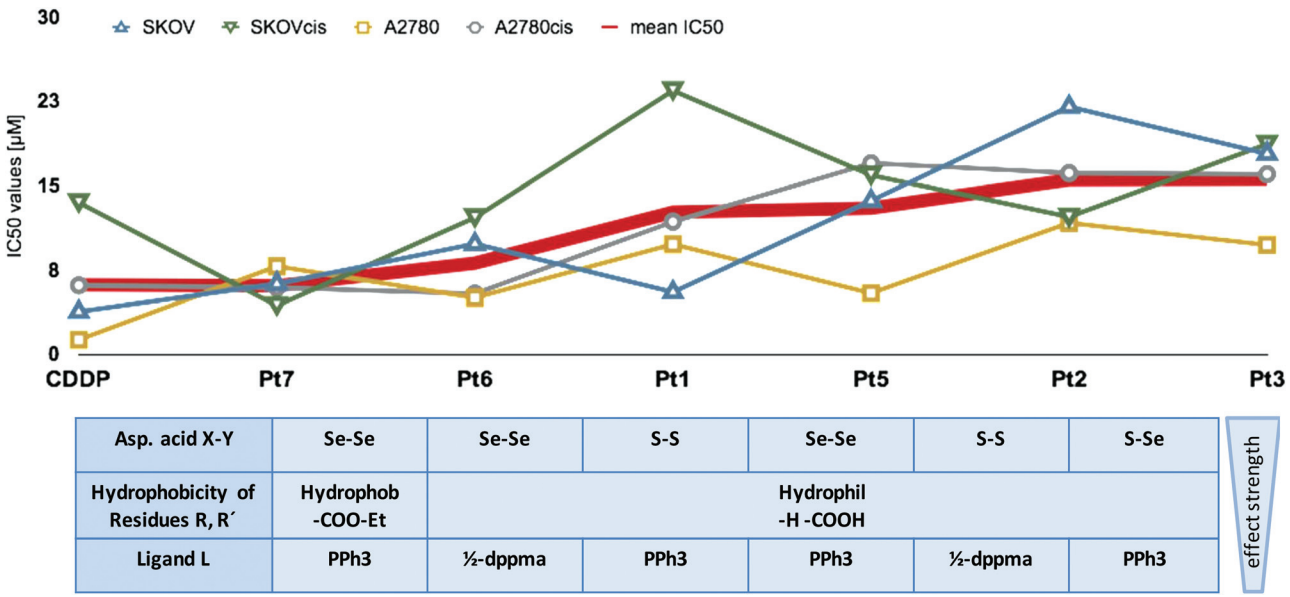


Fig. 2 IC_{50} values for the platinum(II) complexes ordered by rising mean IC_{50} (calculated with all four IC_{50} values per substance) and the characteristics of the compounds. The strength of the SARs for the different characteristics is depicted on the right.

The most active compounds harbour either PPh_3 (**Pt7**) or dppma (**Pt6**) as ligands pointing to a slightly higher activity of PPh_3. Nevertheless, the ligand seems not to be able to break the superior role of the asparagusic acid structure (Se *vs.* S) as **Pt1** (PPh3, S–S) is less active compared to **Pt6** (1/2 dppma, Se–Se).

Conclusions

The investigated platinum(II) complexes containing dichalcogenolato ligands were all characterized using NMR spectroscopy, MS spectrometry and elemental analysis. **Pt1** and **Pt7** were characterized in addition to X-ray diffraction analysis showing a slightly distorted square-planar coordination sphere for the platinum(II) atom. All of these compounds were tested with MTT-assays for their cytotoxic behaviour. Albeit the compounds do not show a higher activity as Cisplatin against the tested sensitive ovarian cancer cell lines, the data suggest that some compounds are able to specifically target resistant cell lines under the tested conditions. For the cell line SKOV3cis the compounds **Pt2**, **Pt6** and **Pt7** have a lower IC_{50} value than cisplatin; for A2780cis this is observable for the compounds **Pt6** and **Pt7**. To point out **Pt7** shows a high cytotoxic activity on all four cancer cell lines and lower IC_{50} values for the two cisplatin-resistant cell lines. In SKOV3cis for example the IC_{50} is significantly lower than that for cisplatin (4.3 ± 1.4 μM in comparison to 13.5 ± 4.4 μM, respectively). Therefore, this compound should be validated as a substitute for cisplatin in the treatment of resistant tumours. High resistance factors (RF IC_{50} resistant/IC_{50} sensitive) for CDDP (3.6 and 4.7 for A2780 and SKOV3) reflect the resistance status for cisplatin, whereas the RF values for substances **Pt1–Pt7** are lower. For **Pt7** and **Pt2** it is, as described above, lower than 1. This indicates that the platinum(II) compounds with asparagusic acid derivatives as ligands are not detoxified by the same resistance mechanisms as cisplatin in the resistant cell lines. Moreover, some platinum(II) compounds (*i.e.* **Pt7**) may specifically target cells with cisplatin resistance associated aberrations because of lower IC_{50} values on resistant cell lines than on sensitive ones.

Experimental section

General

If not otherwise mentioned, all reactions were carried out under a dry nitrogen or argon atmosphere using standard Schlenk techniques. The reagents were purchased from Acros, Fisher Scientific, Merck, Umicore or Aldrich and were used without further purification. Solvents were dried according to common procedures prior to use. ^{1}H, ^{13}C{^{1}H} and ^{31}P{^{1}H} NMR spectra were recorded on either a Bruker Avance 200, Bruker Avance 400 or Bruker Avance 600 NMR spectrometer. ^{1}H^{77}Se HMBC NMR measurements were performed on a Bruker Avance 400 NMR spectrometer. The NMR spectra were calibrated with respect to the signal of the residual protons (^{1}H) or the signal of the deuterated solvent (^{13}C). For ^{31}P{^{1}H} and ^{1}H ^{77}Se HMBC NMR spectra 85% H_3PO_4 and Me_2Se was used as an external standard, respectively. Mass spectra were recorded with a Finnigan MAT SSQ 710 instrument. Elemental analysis was performed with a Leco CHNS-932 apparatus. Silica gel 60 (0.015–0.040 mm) was used for column chromatography and TLC was performed using Merck TLC aluminium sheets (Silica Gel 60 F_{254}).

Preparation of the platinum(II) complexes

Method A. One equivalent of dihydroasparagusic acid was dissolved in ethanol (10 ml for 0.1 mmol) and a fourfold excess of an aqueous solution of K_2CO_3 was added. After stirring for 5 minutes one equivalent of a [PtP_2Cl_2] suspension in chloroform was added and stirred overnight. The resulting yellow solution was acidified with an aqueous $KHSO_4$ solution and extracted with $CHCl_3$ three times. Before removal of the solvent, the combined organic phases were washed with water and dried with Na_2SO_4. Purification of the crude product by column chromatography using dichloromethane/acetone (5 : 1) gave the complexes after precipitation from chloroform/hexane as slight yellow solids.

Method B. The cyclic 1,2-dichalcogenolane derivatives (1.05 equivalents) were suspended in ethanol (10 ml for 0.1 mmol). After addition of 3.15 equivalents $NaBH_4$ and stirring for 10 minutes the resulting clear solution was acidified with diluted hydrochloric acid and then treated with aqueous K_2CO_3 to deprotonate the intermediately occurring dichalcogenolate. To this solution a suspension of [$PtCl_2L_2$] (one equivalent) in chloroform was added and stirred overnight. After treatment with aqueous $KHSO_4$ the mixture was extracted with chloroform three times and the combined organic phases were washed with water and dried with Na_2SO_4, followed by removal of the solvent under reduced pressure. Subsequent column chromatography with dichloromethane/acetone (5 : 1) as the mobile phase and precipitation from chloroform/*n*-hexane gave the complexes as yellow powders.

[Pt(dppma)Cl_2][81]

In a Schlenk flask 0.498 g (1.331 mmol) of [Pt(cod)Cl_2] was dissolved in 70 mL of $CHCl_3$ and 532 mg (1.331 mmol) dppma was added. The mixture was stirred overnight at room temperature and reduced to 5 mL, resulting in the formation of a white precipitate. This was filtered off, washed with a small amount (1 mL) of $CHCl_3$ and dried *in vacuo*. Yield: 0.610 g (69%) white powder.

[Pt(1,2-dithio-4-carboxylic acid)(PPh_3)$_2$] (Pt1)

This compound was prepared according to method A using 30 mg (0.20 mmol) dihydroasparagusic acid and 111 mg (0.80 mmol) [Pt(PPh_3)Cl_2]. Yield: 50 mg (0.057 mmol, 29%) ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.02–3.44 (m, 5 H, HOOC–C*H* and S–CH_2), 7.14 (m, 12 H, *o*-C*H*), 7.28 (m, 6 H, *p*-C*H*), 7.40 (m, 12 H; *m*-C*H*) ppm; ^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$): δ = 25.79 (s, S–CH_2), 46.38 (s, HOOC–*C*H), 127.69 (m, *m*-*C*H), 130.41 (s, *p*-*C*H), 134.69 (m, *o*-*C*H), 177.52 (s, *C*OOH) ppm, i-*C*H not detected; ^{31}P{^{1}H}-NMR (81 MHz, $CDCl_3$): δ = 26.26 (s with

^{195}Pt-satellites, $^{1}J_{Pt-P}$ = 2887 Hz) ppm; MS (ESI): 892 $[M + Na]^+$ 870 $[M + H]^+$ 720 $[M - Asp]^+$; $C_{40}H_{36}O_2P_2PtS_2$ (869.868 g mol^{-1}): calcd C 55.23, H 4.17, S 7.37; found C 54.36, H 4.39, S 7.34.

[Pt(1,2-dithio-4-carboxylic acid)(dppma)] (Pt2)

This compound was prepared according to method A using 30 mg (0.20 mmol) dihydroasparagusic acid and 122 mg (0.20 mmol) [Pt(dppma)Cl_2]. Yield: 28 mg (0.038 mmol, 19%) ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.42 (t, $^{3}J_{P-H}$ = 10.2 Hz; 3 H; N–C*H*$_3$), 2.91–3.37 (m, 5 H, HOOC–C*H* and S–C*H*$_2$), 7.42–7.53 (m, 12 H, *o*-C*H* and *p*-C*H*), 7.66 (m, 8 H, *m*-C*H*) ppm; ^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$): δ = 24.19 (s, S–*C*H$_2$), 33.10 (s, N–*C*H$_3$), 49.56 (s, HOOC–*C*H), 129.11 (m, *m*-*C*H), 132.31 (s, *p*-*C*H), 132.44 (s, *p*-*C*′H), 132.77 (m, *o*-*C*H), 133.10 (m, *o*-*C*′H), 177.54 (s, *C*OOH) ppm, i-*C*H not detected; ^{31}P{^{1}H}-NMR (81 MHz, $CDCl_3$): δ = 37.19 (s with ^{195}Pt-satellites, $^{1}J_{Pt-P}$ = 2478 Hz) ppm; MS (ESI): 767 $[M + Na]^+$ 745 $[M + H]^+$; $C_{29}H_{29}NO_2P_2PtS_2$ (744.702 g mol^{-1}): calcd C 46.77, H 3.93, N 1.88; S 8.61; found C 46.87, H 3.95, N 1.88; S 8.73.

[Pt(1,2-Thiaselenolane-4-carboxylic acid)(PPh_3)$_2$] (Pt3)

This compound was prepared according to method B using 41 mg (0.21 mmol) monoselenoasparagusic acid, 24 mg (0.63 mmol) $NaBH_4$ and 158 mg (0.20 mmol) [Pt(PPh_3)Cl_2]. Yield: 56 mg (0.061 mmol, 31%) ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.12–3.46 (m, 5 H, HOOC–C*H*, S–C*H*$_2$ and Se–C*H*$_2$), 7.15 (m, 12 H, *o*-C*H*), 7.29 (m, 6 H, *p*-C*H*), 7.43 (m, 12 H, *m*-C*H*) ppm; ^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$): δ = 17.10 (s, Se–*C*H$_2$), 29.29 (s, S–*C*H$_2$), 45.59 (s, HOOC–*C*H), 127.51 (m, *m*-*C*H), 127.72 (m; *m*-*C*H), 130.38 (s, *p*-*C*H), 134.4–134.9 (m, *o*-*C*H), 177.21 (s, *C*OOH) ppm, i-*C*H not detected; ^{31}P{^{1}H}-NMR (81 MHz, $CDCl_3$): δ = 22.53 (d with ^{195}Pt-satellites, $^{2}J_{P-P}$ = 19.4 Hz, $^{1}J_{Pt-P}$ = 2896 Hz), 24.89 (d with ^{195}Pt-satellites, $^{2}J_{P-P}$ = 19.5 Hz, $^{1}J_{Pt-P}$ = 2907 Hz) ppm; ^{1}H–^{77}Se-HMBC (400/76.3 MHz, $CDCl_3$): 67 (m; 1 Se; Pt–*Se*); MS (ESI): 917 $[M]^+$ 720 $[M - Asp]^+$; $C_{40}H_{36}O_2P_2PtSeS$ (916.763 g mol^{-1}) calcd C 52.40, H 3.96, S 3.50; found C 51.33, H 4.38, S 4.04.

[Pt(1,2-Thiaselenolane-4-carboxylic acid)(dppma)] (Pt4)

This compound was prepared according to method B using 41 mg (0.21 mmol) monoselenoasparagusic acid, 24 mg (0.63 mmol) $NaBH_4$ and 133 mg (0.20 mmol) [Pt(dppma)Cl_2]. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.46 (t, $^{3}J_{P-H}$ = 10.2 Hz, 3 H, N–C*H*$_3$), 3.07–3.38 (m, 5 H, HOOC–C*H*, S–C*H*$_2$ and Se–C*H*$_2$), 7.45–7.58 (m, 12 H, *o*-C*H* and *p*-C*H*), 7.70 (m, 8 H, *m*-C*H*) ppm; ^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$): δ = 13.21 (s, Se–*C*H$_2$), 26.50 (s, S–*C*H$_2$), 48.41 (s, HOOC–*C*H), 129.0 (m, *m*-*C*H), 130.38 (s, *p*-*C*H), 132.2–133.2 (m, *o*-*C*H), 177.29 (s, *C*OOH) ppm, i-*C*H not detected; ^{31}P{^{1}H}-NMR (81 MHz, $CDCl_3$): δ = 33.87 (d with ^{195}Pt-satellites, $^{2}J_{P-P}$ = 50.3 Hz, $^{1}J_{Pt-P}$ = 2503 Hz), 37.21 (d with ^{195}Pt-satellites, $^{2}J_{P-P}$ = 50.3 Hz, $^{1}J_{Pt-P}$ = 2439 Hz) ppm; ^{1}H–^{77}Se-HMBC (400/76.3 MHz, $CDCl_3$): 573.5 (m; 1 Se; Pt–*Se*).

[Pt(1,2-Diselenolane-4-carboxylic acid)(PPh_3)$_2$] (Pt5)

This compound was prepared according to method B using 51 mg (0.21 mmol) diselenoasparagusic acid, 24 mg (0.63 mmol) $NaBH_4$ and 158 mg (0.20 mmol) [Pt(PPh_3)Cl_2]. Yield: 63 mg (0.065 mmol, 33%); ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.10–3.45 (m, 5 H, HOOC–C*H* and Se–C*H*$_2$), 7.15 (m, 12 H, *o*-C*H*), 7.29 (m, 6 H, *p*-C*H*), 7.45 (m, 12 H, *m*-C*H*) ppm; ^{13}C{^{1}H}-NMR (50.3 MHz, $CDCl_3$): δ = 25.79 (s, Se–*C*H$_2$), 44.54 (s, HOOC–*C*H), 127.52 (m, *m*-*C*H), 130.31 (s, *p*-*C*H), 134.73 (m, *o*-*C*H); 177.28 (s, *C*OOH) ppm, *iC*H not detected, Se*C*H$_2$: n.z.; ^{1}P{^{1}H}-NMR (81 MHz, $CDCl_3$): δ = 21.51 (s with ^{195}Pt-satellites and ^{77}Se-satellites; $^{1}J_{Pt-P}$ = 2923 Hz, $^{2}J_{Se-P}$ = 49.3 Hz) ppm; MS (DEI): 961 $[M]^+$ 719 $[M - Asp]^+$; $C_{40}H_{36}O_2P_2PtSe_2 \cdot \frac{1}{4}$ $CHCl_3$ (993 503 g mol^{-1}) calcd C 48.66, H 3.68; found C 48.58, H 3.51.

[Pt(1,2-Diselenolane-4-carboxylic acid)(dppma)] (Pt6)

This compound was prepared according to method B using 51 mg (0.21 mmol) diselenoasparagusic acid, 24 mg (0.63 mmol) $NaBH_4$ and 133 mg (0.20 mmol) [Pt(dppma)Cl_2]. Yield: 85 mg (0.101 mmol, 51%); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.44 (t, $^{3}J_{P-H}$ = 10.4 Hz, 3 H, N–C*H*$_3$), 3.10–3.35 (m, 5 H, HOOC–C*H* and Se–C*H*$_2$), 7.49 (m, 8 H, *o*-C*H*), 7.55 (m, 4 H, *p*-C*H*), 7.71 (m, 8 H, *m*-C*H*) ppm; ^{13}C{^{1}H}-NMR (100.6 MHz, $CDCl_3$): δ = 16.31 (s, Se–*C*H$_2$), 33.28 (s, N–*C*H$_3$), 47.57 (s, HOOC–*C*H), 129.07 (m, *m*-*C*H), 132.28 (s, *p*-*C*H), 132.34 (s, *p*-*C*′H), 132.81 (m, *o*-*C*H), 132.98 (m, *o*-*C*′H), 177.54 (s, *C*OOH) ppm, i-*C*H not detected; ^{31}P{^{1}H}-NMR (81 MHz, $CDCl_3$): δ = 33.98 (s with ^{195}Pt-satellites and ^{77}Se-satellites, $^{1}J_{Pt-P}$ = 2465 Hz, $^{2}J_{Se-P}$ = 34.6 Hz) ppm; MS (ESI): 839 $[M]^+$; $C_{29}H_{29}NO_2P_2PtSe_2 \cdot \frac{1}{4}$ $CHCl_3$ (868.336 g mol^{-1}) calcd C 40.46, H 3.40, N 1.61; found C 40.85, H 3.28, N 1.19.

[Pt(1,2-Diselenolane-diethylester)(PPh_3)$_2$] (Pt7)

This compound was prepared according to method B using 110 mg of the ligand mixture, 18 mg (0.47 mmol) $NaBH_4$ and 119 mg (0.15 mmol) [Pt(PPh_3)Cl_2]. Yield: 86 mg (0.081 mmol, 54%); ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.11 (t, $^{3}J_{H-H}$ = 7.2 Hz, 6 H, CH_2–C*H*$_3$), 3.59 (d with ^{195}Pt-satellites, $^{3}J_{Pt-H}$ = 46 Hz, 4 H, Se–C*H*$_2$), 7.09 (m, 12 H, *o*-C*H*), 7.23 (m, 6 H, *p*-C*H*), 7.41 (m, 12 H, *m*-C*H*) ppm; ^{13}C-NMR (100.6 MHz, $CDCl_3$): 13.95 (s, *C*H$_3$), 23.55 (s, Se*C*H$_2$), 58.97 (s, SeCH$_2$–*C*), 60.89 (s, CH$_3$–*C*H$_2$), 127.30 (m, *m*-*C*H), 129.94 (s, *p*-*C*H), 130.80 (m, i-*C*), 134.66 (m; *o*-*C*H) ppm; ^{31}P{^{1}H}-NMR (81 MHz, $CDCl_3$): δ = 22.09 (s with ^{195}Pt-satellites and ^{77}Se-satellites, $^{1}J_{Pt-P}$ = 2902 Hz, $^{2}J_{Se-P}$ = 47.5 Hz) ppm; ^{1}H–^{77}Se-HMBC (400/76.3 MHz, $CDCl_3$): δ = 85.5 (m, *Se*–CH$_2$) ppm; MS (ESI): 1063 $[M]^+$, 719 $[M - Asp]^+$; $C_{45}H_{44}O_4P_2PtSe_2$ (1063.75 g mol^{-1}) calcd C 50.81, H 4.17; found C 50.78, H 4.24.

Crystal structure determination

The intensity data were collected on a Nonius KappaCCD diffractometer, using graphite-monochromated Mo-K$_\alpha$ radiation. Data were corrected for Lorentz and polarization effects; absorption was taken into account on a semi-empirical basis using multiple-scans.[82–84]

The structure was solved by direct methods (SHELXS[83]) and refined by full-matrix least squares techniques against F_o^2 (SHELXL-97[83]).

The hydrogen atoms bonded to the sulfur ligand of **Pt1** were located by difference Fourier synthesis and refined isotropically. All other hydrogen atoms were included at calculated positions with fixed thermal parameters. All non-hydrogen atoms were refined anisotropically.[85]

Crystal data for Pt1. $C_{40}H_{36}O2P_2PtS_2$, $CHCl_3$, M_r = 989.21 g mol^{-1}, colourless prism, size 0.122 × 0.112 × 0.108 mm^3, monoclinic, space group $C2/c$, a = 27.8130(5), b = 19.4794(3), c = 19.1878(3) Å, β = 130.220(1)°, V = 7937.8(2) Å^3, T = −140 °C, Z = 8, ρ_{calcd} = 1.655 g cm^{-3}, μ (Mo-K$_\alpha$) = 39.59 cm^{-1}, multi-scan, transmin: 0.5671, transmax: 0.7456, F(000) = 3920, 23 970 reflections in h(−36/28), k(−25/25), l(−24/24), measured in the range 2.09° ≤ Θ ≤ 27.48°, completeness Θ_{max} = 99.7%, 9075 independent reflections, R_{int} = 0.0526, 7484 reflections with $F_o > 4\sigma(F_o)$, 484 parameters, 0 restraints, R_{1obs} = 0.0425, wR_{2obs} = 0.0799, R_{1all} = 0.0591, wR_{2all} = 0.0864, GOOF = 1.085, largest difference peak and hole: 1.136/−1.364 e Å^{-3}.

Crystal data for Pt7. $C_{45}H_{44}O_4P_2PtSe_2$, $0.5{\cdot}C_7H_8$, M_r = 1109.82 g mol^{-1}, yellow prism, size 0.05 × 0.05 × 0.05 mm^3, monoclinic, space group $P2_1/n$, a = 21.7853(3), b = 15.5909(3), c = 26.9714(4) Å, β = 105.2560(10)°, V = 8838.1(2) Å^3, T = −90 °C, Z = 8, ρ_{calcd} = 1.668 g cm^{-3}, μ (Mo-K$_\alpha$) = 49.38 cm^{-1}, multi-scan, transmin: 0.6571, transmax: 0.7456, F(000) = 4376, 63 123 reflections in h(−28/28), k(−20/16), l(−34/35), measured in the range 2.04° ≤ Θ ≤ 27.48°, completeness Θ_{max} = 99.8%, 20 228 independent reflections, R_{int} = 0.0864, 11 743 reflections with $F_o > 4\sigma(F_o)$, 1041 parameters, 0 restraints, R_{1obs} = 0.0434, wR_{2obs} = 0.0764, R_{1all} = 0.1080, wR_{2all} = 0.0928, GOOF = 0.935, largest difference peak and hole: 1.212/−1.288 e Å^{-3}.

MTT assays

Ovarian cancer cell lines were cultured under standard conditions (5% CO_2, 37 °C, 90% humidity) in RPMI medium supplemented with 10% FCS, 100 U ml^{-1} penicillin and 100 μg ml^{-1} streptomycin (Life Technologies, Germany). Cisplatin (Sigma, Germany) was freshly dissolved at 1 mg ml^{-1} in 0.9% NaCl solution and diluted appropriately. New platinum(II) complexes and ligands were dissolved in dmso. Platinum-resistant A2780 and SKOV3 cells were established by repeated rounds of 3 day incubations with increasing amounts of cisplatin starting with 0.1 μM. The concentration was doubled after 3 incubations interrupted by recovery phases with normal medium. The cells that survived the third round of 12.8 μM cisplatin were defined as resistant cultures. Determinations of IC_{50} values were carried out using the CellTiter96 non-radioactive proliferation assay (MTT assay, Promega). After seeding 5000 cells per well in a 96-well plate the cells were allowed to attach for 24 h and were incubated for 48 h with different concentrations of the substances ranging from 0 to 1000 μM for platinum and 0 to 1000 μM for ligand tests. Each measurement was done in triplicate and repeated 3-times. The proportion of live cells was quantified by the MTT assay and after background subtraction relative values compared to the mean of medium controls were calculated. Non-linear regression analyses applying Hill-slope were run in GraphPad 5.0 software.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Umicore AG & Co. KG is acknowledged for a generous gift of K_2PtCl_4.

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