https://doi.org/10.59761/RCR5096

Platinum(IV)-based prodrugs as an alternative to Pt(II)-based drugs: synthesis and biological action

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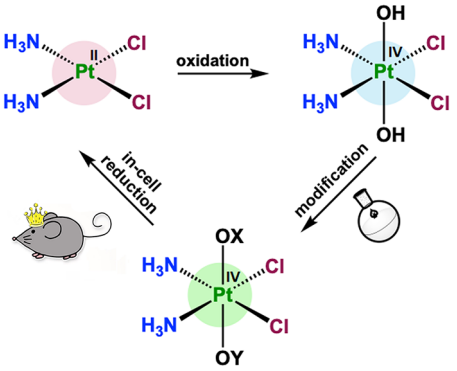
The chemotherapy with cisplatin and its analogues, widely used in medical practice, is associated with undesirable side effects caused by non-selective ligand exchange and binding of the complexes to various biomolecules in the body. An alternative to classical platinum(II)-based drugs are platinum(IV) prodrugs, that is, platinum(II) complexes additionally modified with diverse biologically active axial ligands, including known pharmaceutical products. In recent years, quite a few studies devoted to the design of effective Pt(IV) prodrugs have been published, with some of the developed agents being markedly superior to clinically used cisplatin and carboplatin in therapeutic efficacy. This review summarizes the synthetic approaches to the design of Pt(IV) prodrugs and modification of the axial ligands. The second part of the review is devoted to the biological activity of Pt(IV) prodrugs reported in the period from 2018 to 2023 and comparison of various approaches to the design of effective anticancer agents based on these compounds.

The bibliography includes 239 references.

Keywords: Pt(IV) prodrugs, cisplatin, controlled release, anticancer activity.



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Received 14 July 2023

1. Introduction

Platinum(II) coordination compounds have been used in the therapy of cancer since the discovery of the cytotoxic properties of cisplatin in the mid-20th century.[1] Currently, the U.S. Food and Drug Administration (FDA) has approved three Pt(II)-based drugs for clinical use, namely, cisplatin (CDDP), oxaliplatin (OLP) and carboplatin (Fig. 1). In addition, the drug nedaplatin is used in Japan for the therapy of lung and neck tumours, lobaplatin has been approved in China for the therapy of metastatic breast cancer, and heptaplatin is used in Korea to treat the gastric cancer.

Platinum(II)-based drugs are square planar Pt^{2+} coordination compounds containing two am(m)ine ligands and two *cis*-arranged anionic ligands in the molecule.[2] The mechanism of cytotoxic action of Pt(II) complexes has been addressed in numerous publications (see, for example, Refs 3, 4). It was proved that these drugs penetrate into cells, then the leaving ligands are exchanged for water, and the aquated Pt(II) complex binds to the N(7) atom of a purine base of DNA to give cross-links, which disrupt the cell functioning and trigger apoptosis, a process of programmed cell death. The results of studies of the last two decades also revealed alternative mechanisms of the antiproliferative action of cisplatin. In particular, binding of cisplatin to a number of proteins such as ubiquitin, G-actin and other cytoskeleton proteins causes disruption of their biological functions.[5] In some studies, it is indicated that cisplatin and oxaliplatin can cause immunogenic cell death, *i.e.*, stimulate an immune response to the appearance of malignant neoplasms.[6,7] It was also noted that cisplatin can induce apoptosis by damaging mitochondrial rather than nuclear DNA.[8]

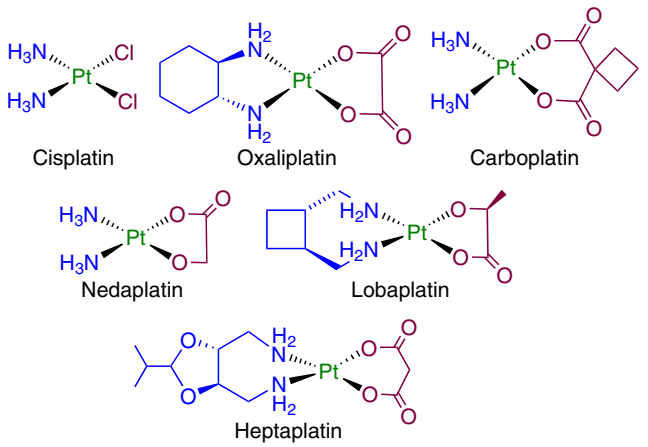

Figure 1. Structural formulae of the platinum(II)-based drugs used for the therapy of cancer.

Despite of being widely used in clinical practice, Pt(II)-based drugs suffer from a number of crucial drawbacks.[9] A large portion of cisplatin introduced into the body (up to 90%) irreversibly binds to macromolecules in the bloodstream, and only 1% reaches the therapeutic target, that is, nuclear DNA.[10] The non-specific binding is responsible for some severe side effects that accompany treatment with platinum-containing drugs such as hearing loss, nephrotoxicity and neurotoxicity.[11,12] One more important side effect is the acquired drug resistance, which decreases the efficacy of Pt(II)-based anticancer drugs due to decreasing platinum uptake by the cells or intracellular deactivation of pharmaceuticals.[13,14] Cisplatin analogues such as oxaliplatin and carboplatin have lower general toxicity; however, they are not superior to cisplatin in selectivity or antitumour actvity.[6,15]

Therefore, important challenges of medicinal chemistry are to overcome the above drawbacks of the existing medications and to develop new highly efficacious drugs based on platinum. A number of approaches have been developed for addressing this task, in particular, the synthesis of cisplatin analogues with other equatorial ligands,[16] non-traditional trans-platinum(II) compounds and Pt(IV) complexes.[17]

Platinum(IV)-based prodrugs are octahedral low-spin d^6 coordination compounds consisting of a platinum atom, four equatorial ligands identical to those of Pt(II) complexes, and two axial ligands.[18] Due to the increase in the coordination number, these compounds are less prone to ligand exchange in the bloodstream and, as a consequence, they are less likely to undergo side reactions with biological macromolecules.[19] Platinum(IV) coordination compounds are unable to bind to DNA, but they can be reduced in the intracellular medium, thus releasing the cytotoxic Pt(II) complex and free ligands (Fig. 2).[20]

Since the axial position of Pt(IV) complexes can be easily modified, varying axial ligands makes it possible not only to tune the physicochemical properties, but also to modify the biological activity of the products.[21–23] Since the introduction of vector groups into the axial position of Pt^{IV} complexes is favourable for increasing the affinity of prodrugs to tumour cells,[24–26] the introduction of a cytotoxic axial ligand may afford compounds that act on several therapeutic targets,[27–30] while the use of compounds responsive to the external physicochemical stimuli as axial ligands may give compounds with controllable action.[31–34]

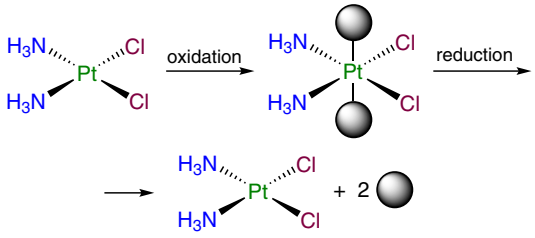

Figure 2. General synthetic scheme and principle of action of Pt(IV)-based prodrugs. The grey sphere designates the biologically active axial ligand.

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Translation: Z.P.Svitanko

Platinum(IV)-based prodrugs have been the objects of research for more than two decades. To date, there are quite a few publications devoted to variation of the axial ligands and the starting Pt(II) complexes and to elucidation of the structure–activity relationships. A number of highly ranked reviews deal with the synthesis and biological activity of Pt(IV) prodrugs. In 2016, Johnstone *et al*.[17] analyzed the most recent achievements in the development of new platinum-containing therapeutic agents and methods for their delivery to the tumours. In 2017 and 2019, reviews addressing the biological action of Pt(IV) prodrugs were published.[35,36] A review by Xu *et al*.,[31] which appeared in 2021, surveys the methods of synthesis and mechanistic studies of the intracellular reduction of Pt(IV) compounds. Professor Gibson from the Hebrew University of Jerusalem presented a series of small review papers on the biological activity of Pt(IV) prodrugs. A review[37] addresses Pt(IV) compounds with a multiple biological action, while another paper[38] gives examples of increasing prodrug selectivity to cancer cells. Survey publications by Beloglazkina and co-workers are devoted by photocontrolled activation of Pt(IV) compounds[34] and combination of these compounds with non-steroidal anti-inflammatory drugs in axial positions.[23]

The present review integrates and systematizes the available data on the synthesis of Pt(IV) prodrugs and investigations of their physicochemical and biological properties. The first part considers synthetic approaches to the design of these drugs, with the attention being paid both to oxidation reactions in chemical media where platinum(II) compounds are converted to platinum(IV) complexes and to chemical modification of axial ligands. The second part of the review considers the biological effects of Pt(IV) prodrugs using the data of publications of the period from 2018 to 2023.

In view of the high interest in the development of new effective Pt(IV) prodrugs meant for the therapy of malignant neoplasms, the large number of publications on this subject in scientific journals, and the lack of Russian-language reviews on the synthesis and biological activity of Pt(IV) complexes, we believe that this review will be of interest to a broad range of researchers specializing in organic and medicinal chemistry.

2. Synthetic approaches to the design and modification of Pt(IV) prodrugs

Coordination compounds of platinum(IV) have been investigated for more than 40 years.[39] A large body of data on the synthesis of compounds of this class has been gained to date (see, for example, reviews by Wilson and Lippard[18] and Xu *et al*.[31]). In this part of the review, we consider the key synthetic approaches used to prepare and modify Pt(IV)-based prodrugs and discuss the benefits and drawbacks of the considered methods.

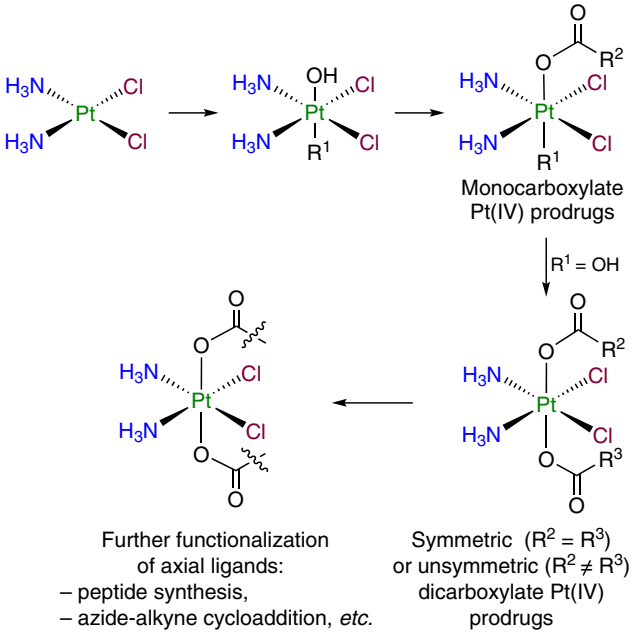
The design of Pt(IV) prodrugs implies the synthesis of kinetically inert octahedral coordination compounds based on cytotoxic Pt(II) complexes. The synthetic strategy consists of the following steps:

(1) oxidation of the Pt(II) complex,

(2) replacement of the hydroxyl group at the Pt(IV) atom by various ligands,

(3) replacement of the second nucleophile at the Pt(IV) atom or further modification of the ligand introduced in the previous stage (Fig. 3).

Each synthetic stage is considered in detail below.



R^1 = OH, OAc, Cl; R^2 = OH, Cl

Figure 3. Approaches to the synthesis and modification of Pt(IV)-based prodrugs.

2.1. Synthesis of Pt(IV) coordination compounds by oxidation of Pt(II) compounds

The major synthetic approach used for the design of Pt(IV) complexes is the oxidation of Pt(II) complexes. The oxidants used most often for the Pt(II) atom are chlorine and hydrogen peroxide.[40,41] As a result of this reaction, two additional ligands enter the coordination sphere of the Pt(IV) ion in *trans*-positions. The structure of product resulting from hydrogen peroxide oxidation depends on the solvent in which the reaction is carried out.[42] Thus in water, cisplatin is converted to the complex *cis*,*cis*,*trans*-$[Pt(NH_3)_2(Cl)_2(OH)_2]$ (oxoplatin) [Fig. 4, reaction (2)], while the reaction in acetic acid gives *cis*,*cis*,*trans*-$[Pt(NH_3)_2(Cl)_2(OH)(OAc)]$ (Ref. 44) [reaction (3)].

The synthesis of asymmetric Pt(IV) complexes containing a chlorine atom and a nucleophilic oxygen atom in the axial positions *via* mild oxidation with *N*-chlorosuccinimide (NCS) [reaction (4)] was described in more recent publications.[45,46] An unusual example of oxidation of Pt(II) complex in the presence of hydrogen peroxide, acetonitrile and methanol with introduction of acetamide into the axial position has been reported [reaction (5)].[47]

Thus, by varying the solvent and the oxidant in the oxidation of Pt(II) complexes, it is possible to obtain Pt(IV) complexes with diverse axial ligands and with different numbers of functional groups meant for the subsequent modification. The main strategies of modification of Pt(IV) complexes used to introduce various organic groups into the metal coordination environment are considered below.

2.2. Modification of O-nucleophile at the Pt(IV) centre

In the vast majority of cases, modification of Pt(IV) complexes involves the O-nucleophile at the Pt(IV) atom (see, for example, Ref. 48); therefore, these methods are considered in a separate Section.

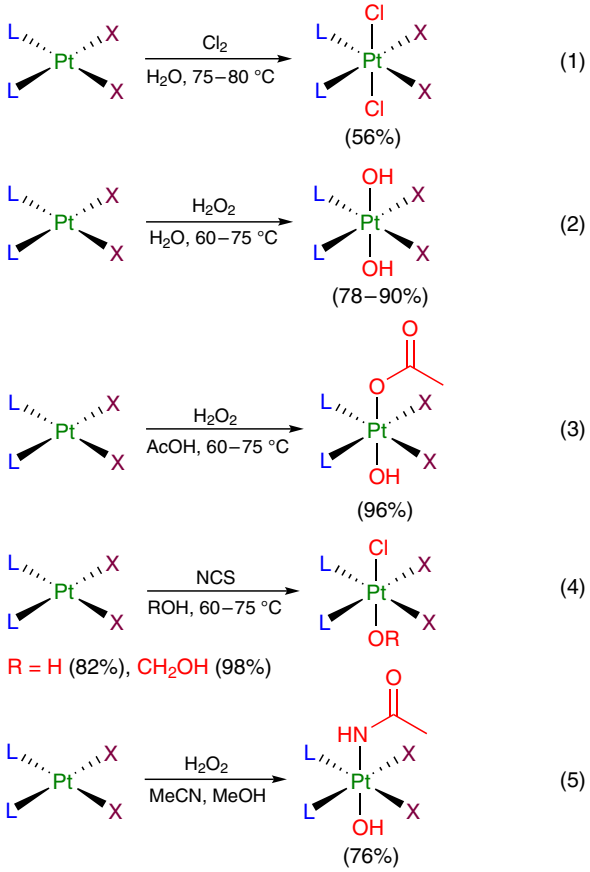


Figure 4. Methods for the oxidation of Pt(II) complexes (the yields are indicated for L = NH_3, X = Cl).

2.2.1. The introduction of the carboxyl group into the axial position of Pt(IV) complexes

A popular strategy for the introduction of organic groups into the axial position of the Pt(IV) atom is esterification, which gives rise of a carboxyl group and affords an ester containing a C(O)O–Pt moiety. A drawback of this approach is the necessary presence of a carboxyl group in the molecule of the introduced ligand, which restricts the range of substrates applicable as axial ligands.

2.2.1.1. Synthesis of Pt(IV) dicarboxylate complexes

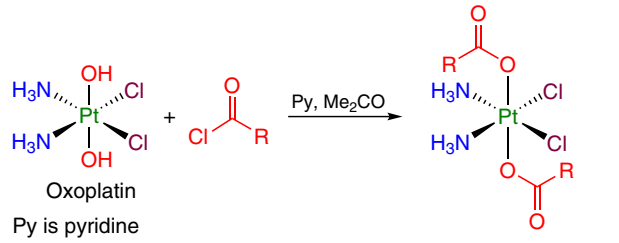
Using a highly reactive acylating reagent and/or a large excess of the acylating reagent, esterification can be carried out at both available O-nucleophiles in the axial positions of platinum(IV).[48] This gives symmetrical Pt(IV) dicarboxylate complexes with two identical organic ligands.

2.2.1.1.1. Synthesis from acyl chlorides

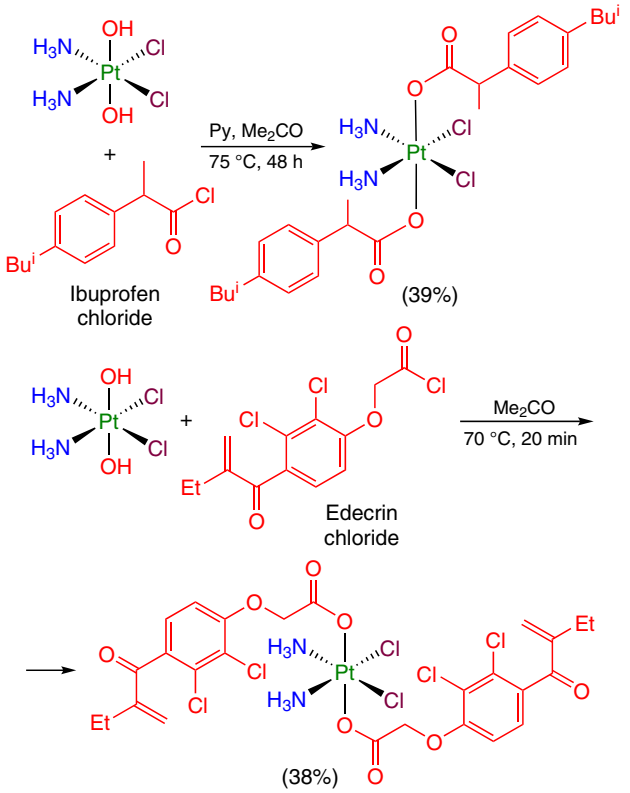
Acyl chlorides derived from the appropriate carboxylic acids can be used as the acylating reagents. Acyl chlorides react with oxoplatin to give a symmetrical Pt(IV) dicarboxylate complex (Scheme 1).

This approach was used[49–53] to convert oxoplatin to a variety of Pt(IV) prodrugs bearing non-steroidal anti-inflammatory drugs, which were formed in satisfactory yields (32–87%). In particular, cisplatin analogues containing two ibuprofen or Edecrin (ethacrynic acid) moieties are formed from oxoplatin and the corresponding acyl chlorides (Scheme 2).[54]

Scheme 1



Scheme 2

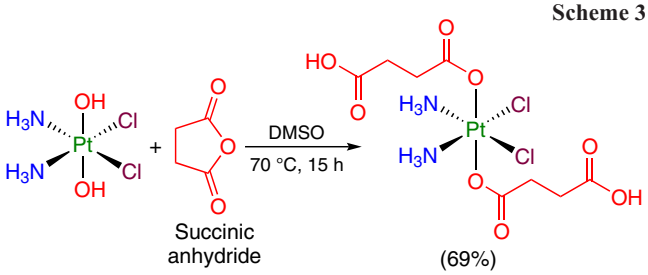


Serious drawbacks of this method are that the reactions proceed under relatively drastic conditions, which restricts the number of suitable substrates, and the lack of possibility of terminating the reaction after monocarboxylate formation.

2.2.1.1.2. Synthesis from anhydrides

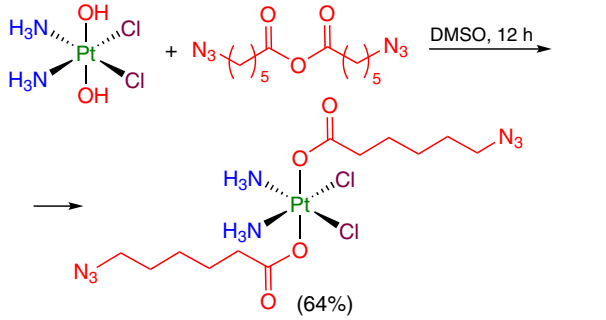
In the design of Pt(IV)-based prodrugs, an important role belongs to dicarboxylic acid dianhydrides, which are less reactive acylating agents than acyl chlorides. Commercially available succinic (Scheme 3) and glutaric anhydrides are widely used for this purpose.[44,55]

Scheme 3



6-Azidohexanoic acid anhydride was allowed to react with oxoplatin. This gave a Pt(IV) compound with two azido groups amenable to further modification *via* the azide–alkyne cycloaddition reactions (Scheme 4).[56]

Scheme 4



Despite the synthetic accessibility of carboxylic acid anhydrides, these derivatives are mainly used for modification of Pt(IV) monocarboxylate complexes to obtain unsymmetrical Pt(IV) dicarboxylate compounds. For this reason, they will be addressed in more detail in the following Sections of the review.

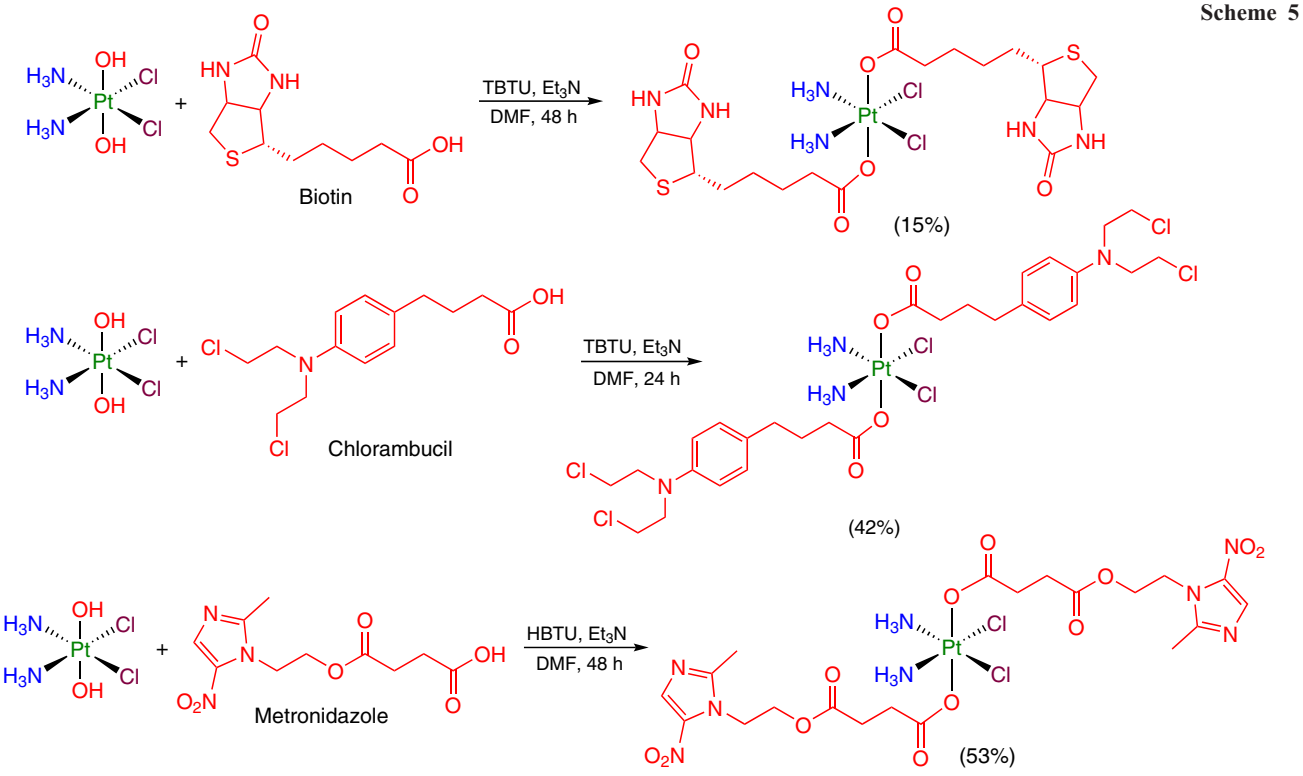
2.2.1.1.3. Synthesis from carboxylic acids

A widely used approach to the synthesis of symmetrical Pt(IV) dicarboxylate complexes implies the participation of activating reagents,[57–60] most often, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate[58,59] and hexafluorophosphate[60] (TBTU and HBTU, respectively). These reagents were used to introduce diverse ligands, including conjugate of vitamin B12 with biotin (vitamin B7), the alkylating agent chlorambucil and the antimicrobial drug metronidazole, into the axial position of oxoplatin (Scheme 5).

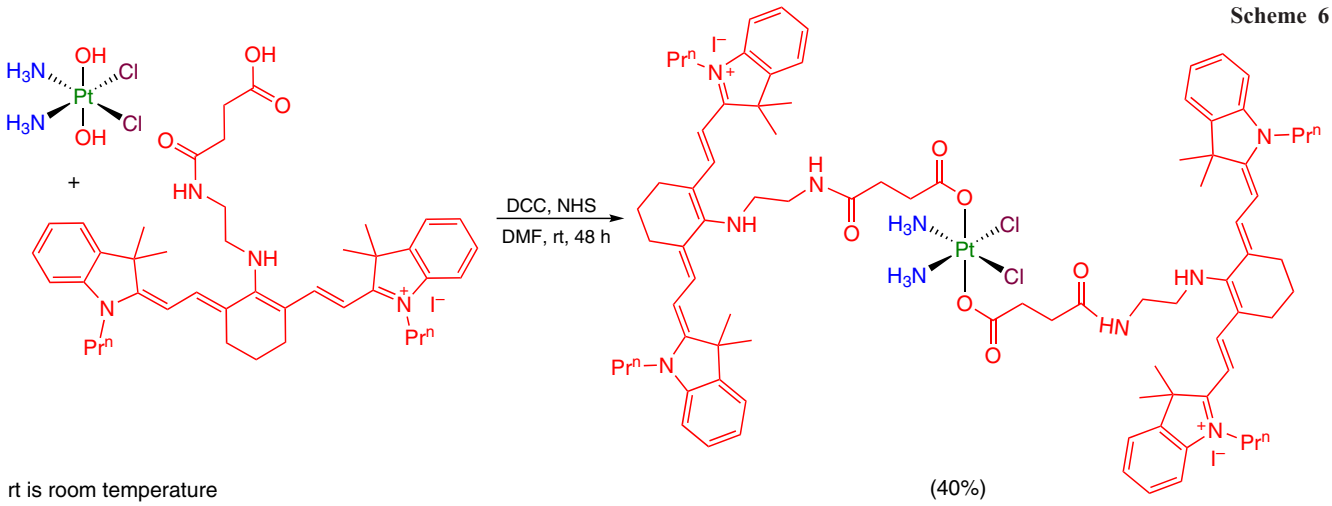
A drawback of this method is the long reaction time, which is usually 48 h, *i.e.*, it is much longer than the time of reactions using acyl chlorides (0.5–2 h) or acid anhydrides (2–12 h).

N-Hydroxysuccinimide (NHS) esters of carboxylic acids obtained *in situ* are also utilized according to this approach in the presence of 1,3-dicyclohexylcarbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC). For example, Pt(IV) prodrug containing two heptamethine cyanine

Scheme 5



Scheme 6



rt is room temperature

dye moieties in the axial positions was obtained in this way (Scheme 6).[57]

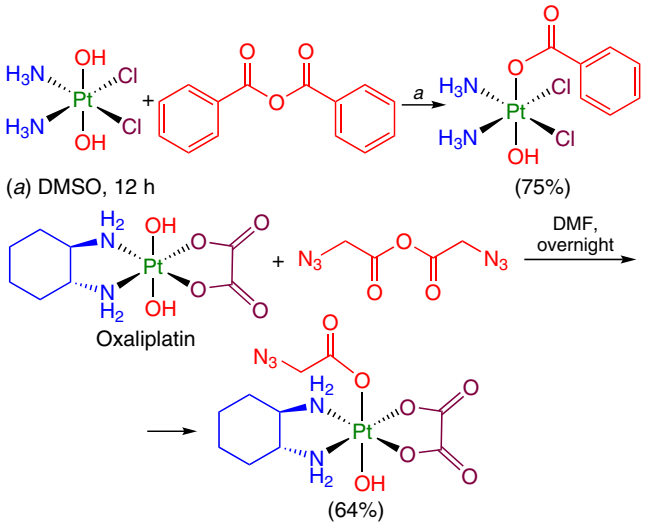
2.2.1.2. Synthesis of Pt(IV) monocarboxylate complexes

The possible control of esterification of the hydroxyl group at Pt(IV) and termination of the reaction after monocarboxylate complex has formed are of interest owing to the high biological activity of monocarboxylate derivatives.[51,61,62] In addition, the second OH group at the Pt(IV) atom can be additionally modified using a ligand with a different type of activity, which would give a multiple-action Pt(IV) prodrug.[27,63,64]

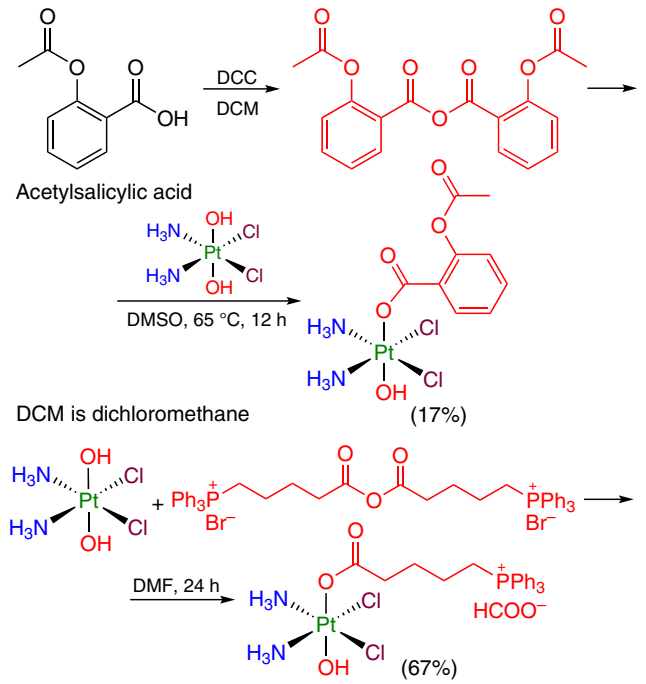
2.2.1.2.1. Synthesis from anhydrides

Selective modification of Pt(IV) complexes at an axial OH group of oxoplatin is possible in the presence of a slight excess (1.1–1.5 equiv.) of the anhydride of the corresponding carboxylic acid. The anhydride can be obtained *in situ* in the presence of DCC as a dehydrating agent. A series of Pt(IV) coordination compounds with various benzoic acids and azidoacetic acid in the axial position were synthesized in this way (Scheme 7).[61,65]

Scheme 7



Scheme 8



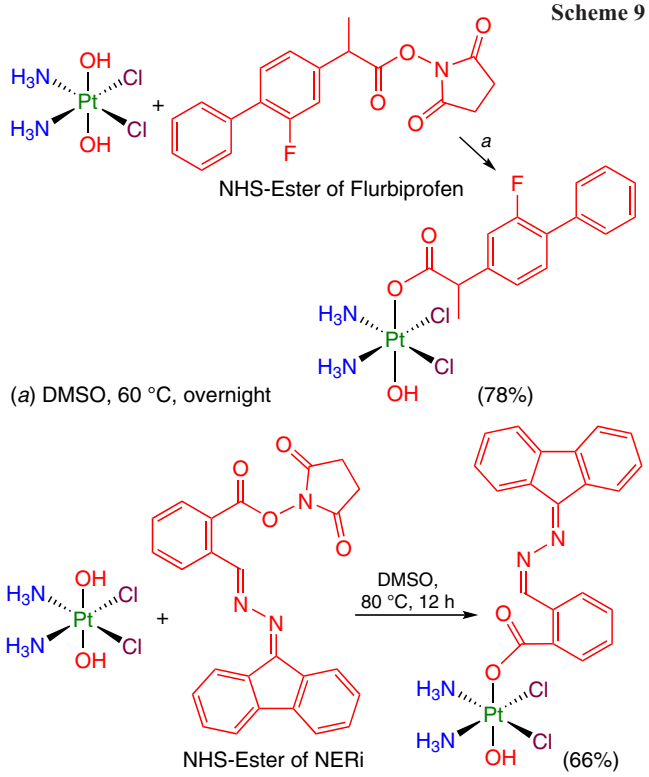
This approach was used[43,66] to obtain Pt(IV) monocarboxylate complexes containing non-steroidal anti-inflammatory drugs (*e.g.*, acetylsalicylic acid) (Scheme 8), alkylating agents [(4-carboxybutyl)thiophenylphosphonium bromide] anhydride and inhibitors of metabolic processes as axial ligands.

A drawback of this method is that 1 equiv. of the ligand present in the anhydride actually does not participate in the reaction and is released as a by-product.

2.2.1.2.2. Synthesis from N-hydroxysuccinimide esters

One more widely used method for the synthesis of Pt(IV) monocarboxylate prodrugs is *in situ* preparation of the NHS esters of carboxylic acids, which readily react with the OH group at the oxoplatin Pt(IV) atom. This method was used to obtain Pt(IV) monocarboxylate prodrugs with the ligands representing a non-steroidal anti-inflammatory drug (NSAID) (*e.g.*, flurbiprofen) or DNA repair inhibitors (NERi) (Scheme 9).[62,67]

Scheme 9

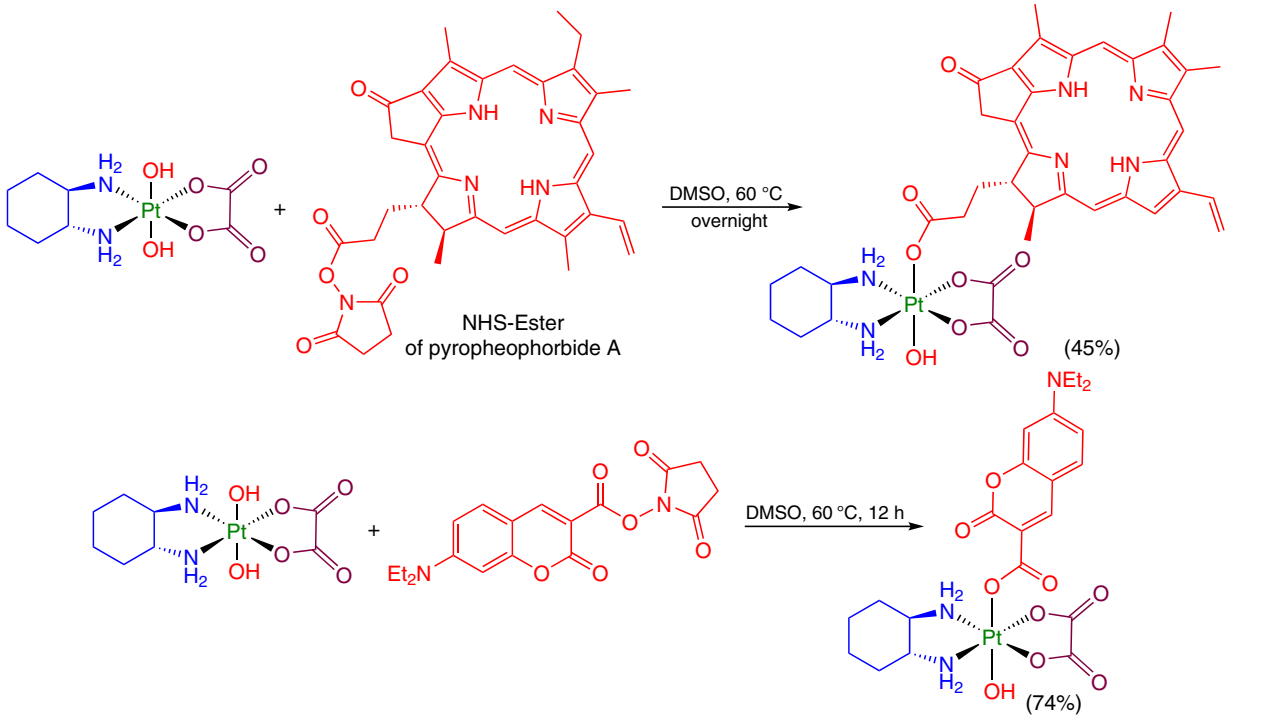


Similarly, Pt(IV) prodrugs capable of controlled activation were prepared from dihydroxy-oxaliplatin with preliminary synthesis of the NHS ester of the corresponding ligand. In this case, pyropheophorbide A and the NHS ester of 7-diethylaminocoumarincarboxylic acid served as the axial ligands (Scheme 10).[32,68]

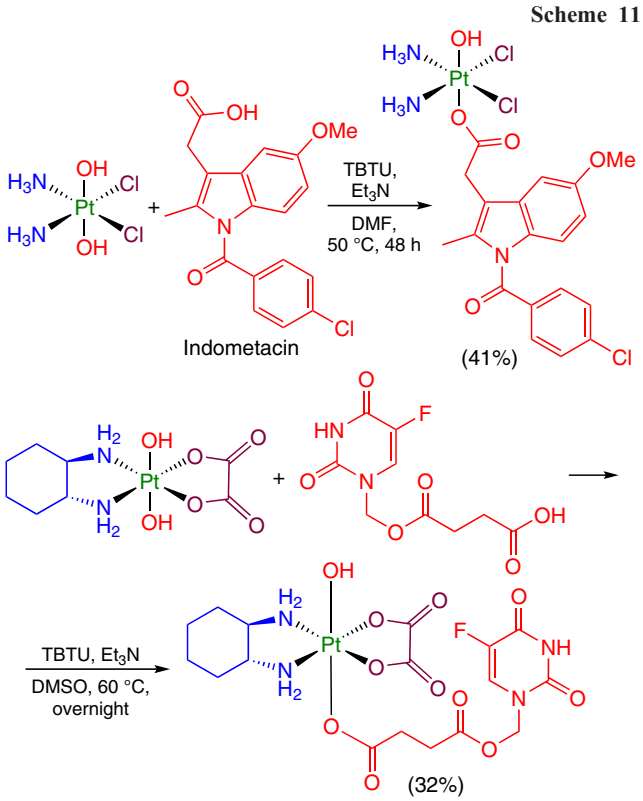
2.2.1.2.3. Synthesis from carboxylic acids

Tetramethyluronium activators of carboxyl group, such as TBTU, were proposed in a number of publications to obtain Pt(IV) monocarboxylate complexes. Platinum(IV) prodrugs containing indomethacin and 5-florouracil moieties in the axial position were prepared from oxoplatin and dihydroxy-oxaliplatin, respectively (Scheme 11).[28,46]

Scheme 10



Scheme 11



2.2.1.3. Modification of the second OH group in Pt(IV) monocarboxylate coordination compounds

The Pt(IV) monocarboxylate complexes are modified to form unsymmetrical dicarboxylate complexes according to the scheme depicted in Fig. 5.

Modification of the second OH group is performed using methods described in the previous Sections for other classes of Pt(IV) prodrugs with addition of carboxylic acid anhydrides and tetramethyluronium activators.

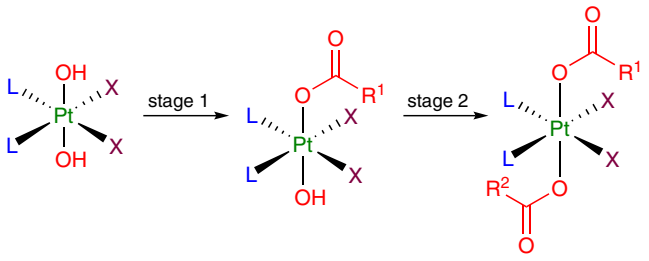


Figure 5. General scheme for the synthesis of unsymmetrical Pt(IV) dicarboxylate prodrugs.

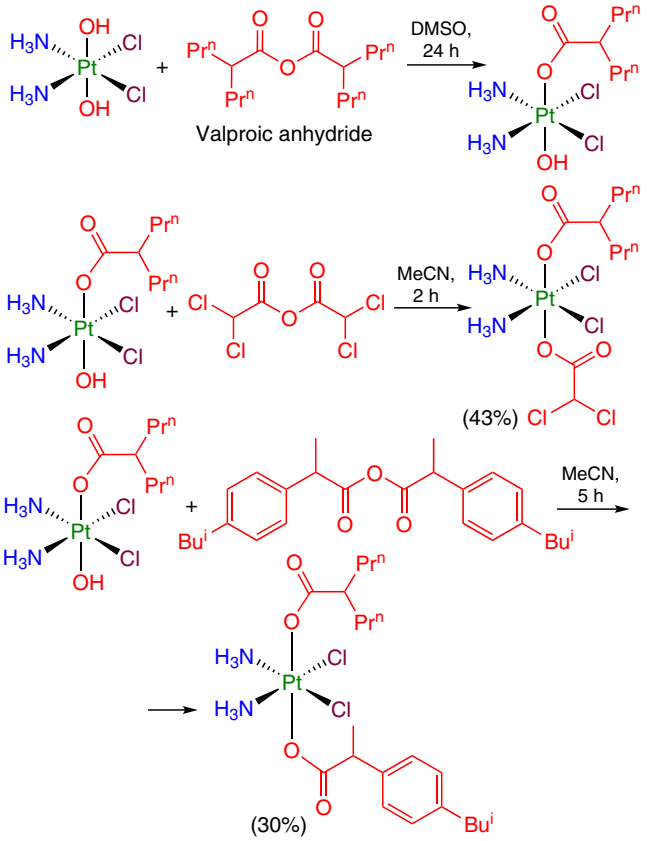
2.2.1.3.1. Synthesis from anhydrides

Carboxylic acid anhydrides are the most widely used reagents for the synthesis of unsymmetrical Pt(IV) complexes. Using this approach, oxoplatin was converted to a series of Pt(IV) prodrugs containing two axial ligands with different biological action, namely, valproic acid and dichloroacetic acid residues or ibuprofen residue. The yields of products were 30–40% over the two steps (Scheme 12).[27]

One strategy for modification of the second axial position of Pt(IV) complex is to introduce a linker moiety containing a functional group that could be further modified (see Section 2.2.3). Indeed, the above monocarboxylate complexes of oxaliplatin with pyropheophorbide A and 7-diethylamino-coumarincarboxylic acid moieties were additionally modified with succinic anhydride (Scheme 13).[68,69]

The replacement of the second OH group at the Pt(IV) atom is also meant to increase the lipophilicity of products. For example, the above-mentioned Pt(IV) monocarboxylate complexes with 5-fluorouracil and biotin were modified in the

Scheme 12



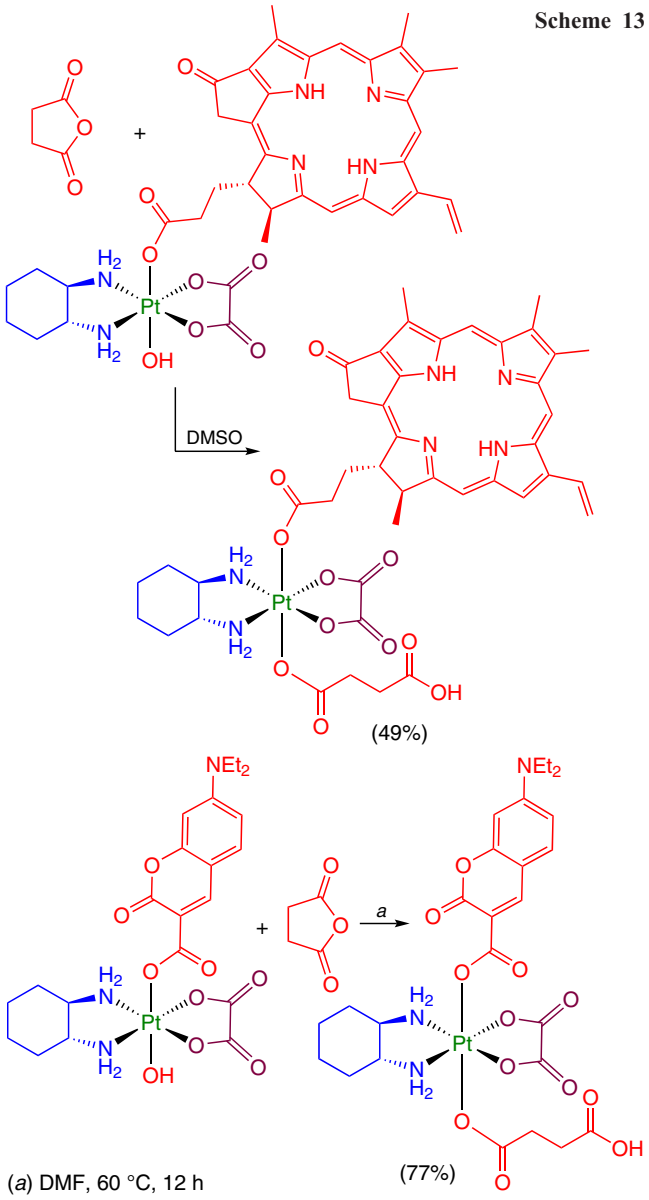
axial position with a lipophilic stearic acid moiety by treatment with the corresponding anhydride (Scheme 14).[28,70]

Thus, carboxylic acid anhydrides are versatile acylating agents for the synthesis of Pt(IV) prodrugs. Nevertheless, a drawback of this method is the release of one equivalent of the initial carboxylic acid during the reaction, which is undesirable if the ligand is sparingly accessible.

2.2.1.3.2. Synthesis from carboxylic acids

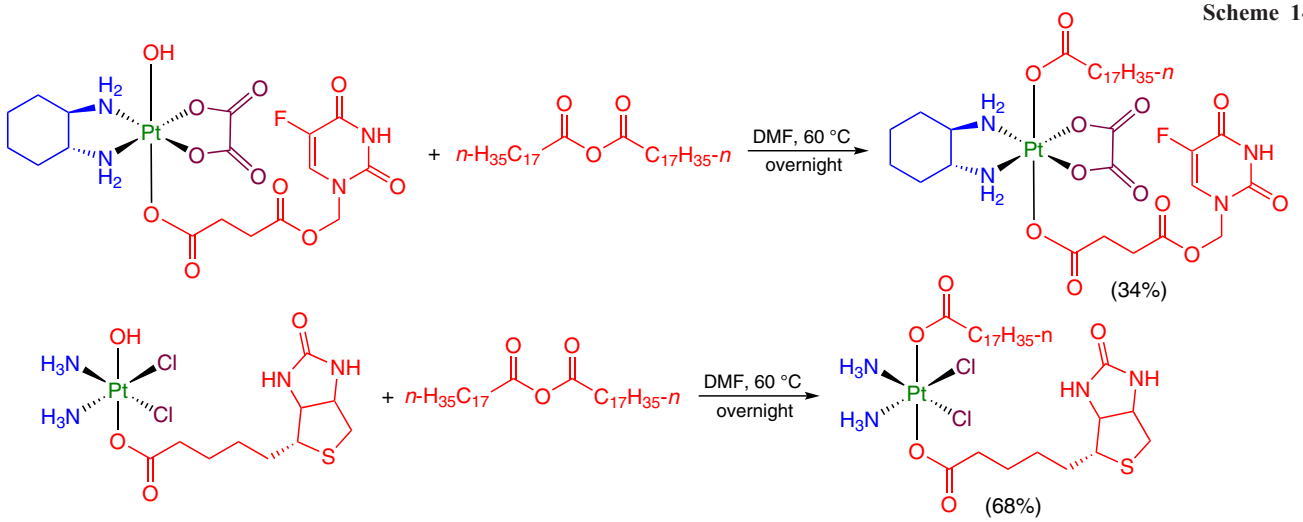
Unsymmetrical Pt(IV) dicarboxylate complexes can also be synthesized using reagents based on tetramethylurea, in particular TBTU. This enables more efficient use of the parent ligand than in the case of anhydrides of carboxylic acids.

Scheme 13

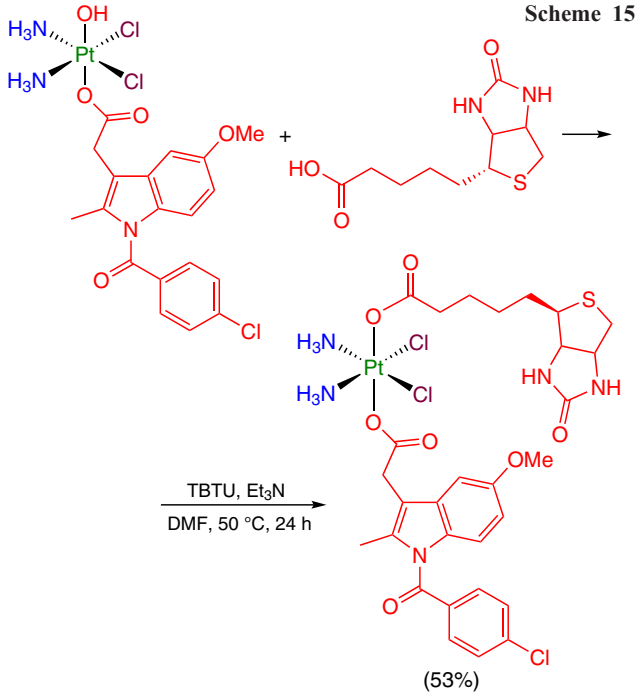


For example, the activation of biotin under the action of TBTU in the presence of triethylamine was used to modify

Scheme 14



Scheme 15

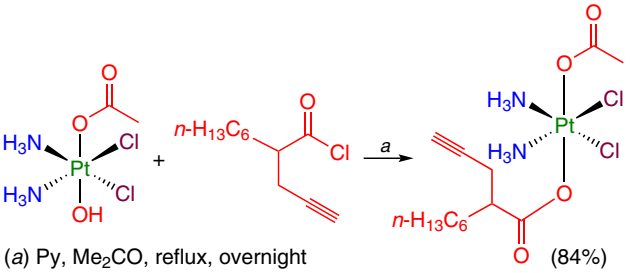


Pt(IV) monocarboxylate complex with indomethacin (Scheme 15).[46]

2.2.1.3.3. Synthesis from acid chlorides

The substitution of the OH group in the Pt(IV)-based monocarboxylate prodrugs can also be carried out on treatment with acyl chlorides. For example, 2-(prop-2-yn-1-yl)octanoyl chloride was allowed to react with the complex $[Pt(Cl)_2(NH_3)_2(OH)(OAc)]$ to give the corresponding unsymmetrical dicarboxylate (Scheme 16).[71]

Scheme 16



2.2.2. The introduction of functional groups other that carboxylate group into the axial position of Pt(IV) complexes

The Pt(IV)-based prodrugs considered above were obtained using axial ligands containing a carboxylic acid moiety. In some examples, where the biologically active ligand contained no carboxyl group, it was introduced into the axial position using a linker, most often, succinic anhydride. This approach was implemented in the synthesis of prodrugs by reactions of platinum(IV) complexes with 5-fluorouracil, metronidazole and heptamethine cyanine dye.[28,57,60]

Meanwhile, many medications used in the anticancer therapy such as gemcitabine, Taxol and estramustine contain a hydroxyl group or amino group rather than a carboxyl group. For axial ligands present in the complexes to exhibit their biological action after they have been released, they should be eliminated in an active form.[72]

In order to select an appropriate linker to be inserted between the Pt(IV) centre and the axial ligand, a number of synthetic approaches have been developed, which are considered below.

2.2.2.1. Carbonate-based linker

Gibson and co-workers[72] utilized the unsymmetrical carbonate RO–C(O)–OR′ as a bridging moiety between the ligand and the Pt(IV) ion. The authors assumed that the carbonic acid monoester formed upon hydrolysis of the Pt(IV) complex rapidly decomposes to release an alcohol and CO_2 (Fig. 6).

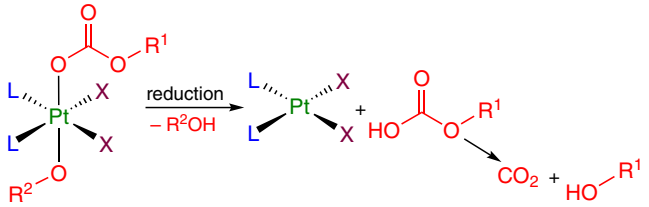
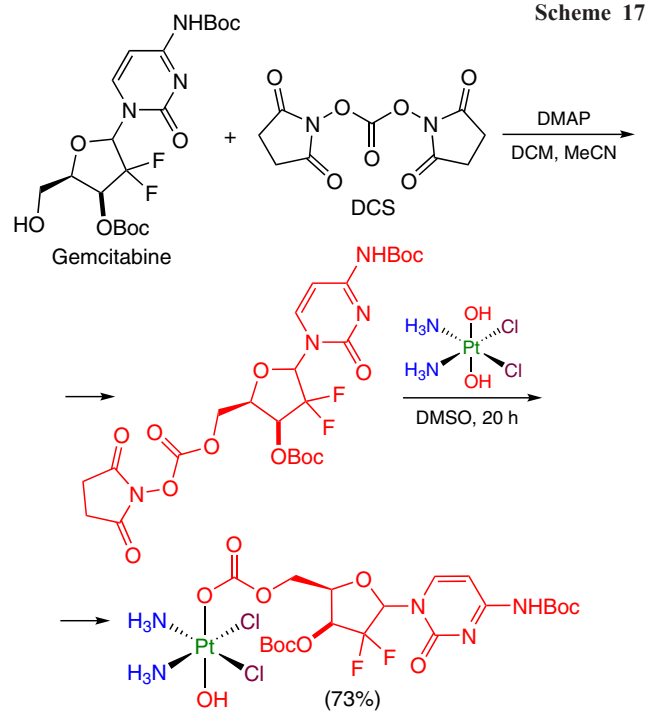


Figure 6. General scheme of the release of the axial ligand bound to the Pt(IV) centre *via* a carbonate linker.

Anticancer agents targeting a site other than cisplatin does were chosen as ligands. An example is gemcitabine, which is incorporated into DNA, thus preventing its further synthesis.[73] To be introduced into the axial position of oxoplatin, the OH group of gemcitabine group was activated with *N*,*N*′-disuccinimidyl carbonate (DSC), and then the product reacted with oxoplatin to give a carbamate linker between gemcitabine and Pt(IV) (Scheme 17).

Scheme 17

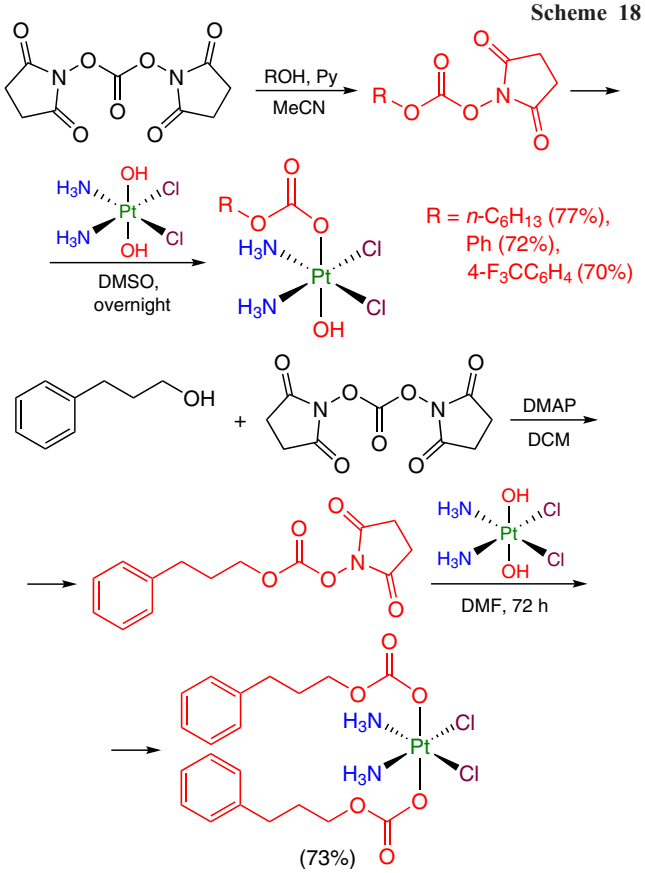


DMAP is 4-dimethylaminopyridine, Boc is *tert*-butyloxycarbonyl

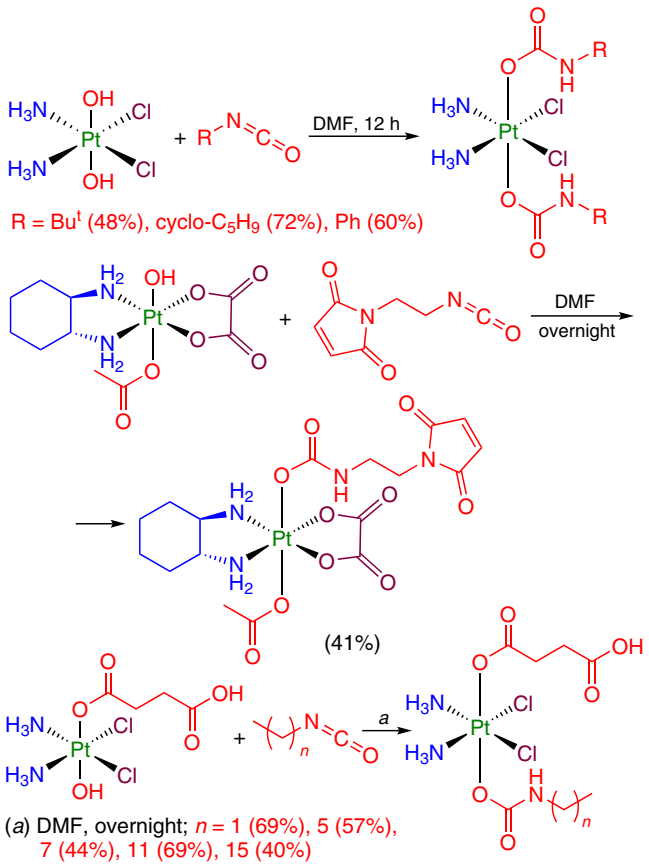
A similar approach was employed to convert oxoplatin into a series of Pt(IV) monocarbonate and dicarbonate complexes in which the metal is linked to various aromatic and aliphatic hydrocarbons *via* a carbonate group (Scheme 18).[74,75]

An important drawback of Pt(IV)-based prodrugs with a carbonate linker is low stability in water and fast reduction in the presence of sodium ascorbate [the reduction half-life ($t_{1/2}$) is 0.5–3 h][74,75]

Scheme 18



Scheme 19



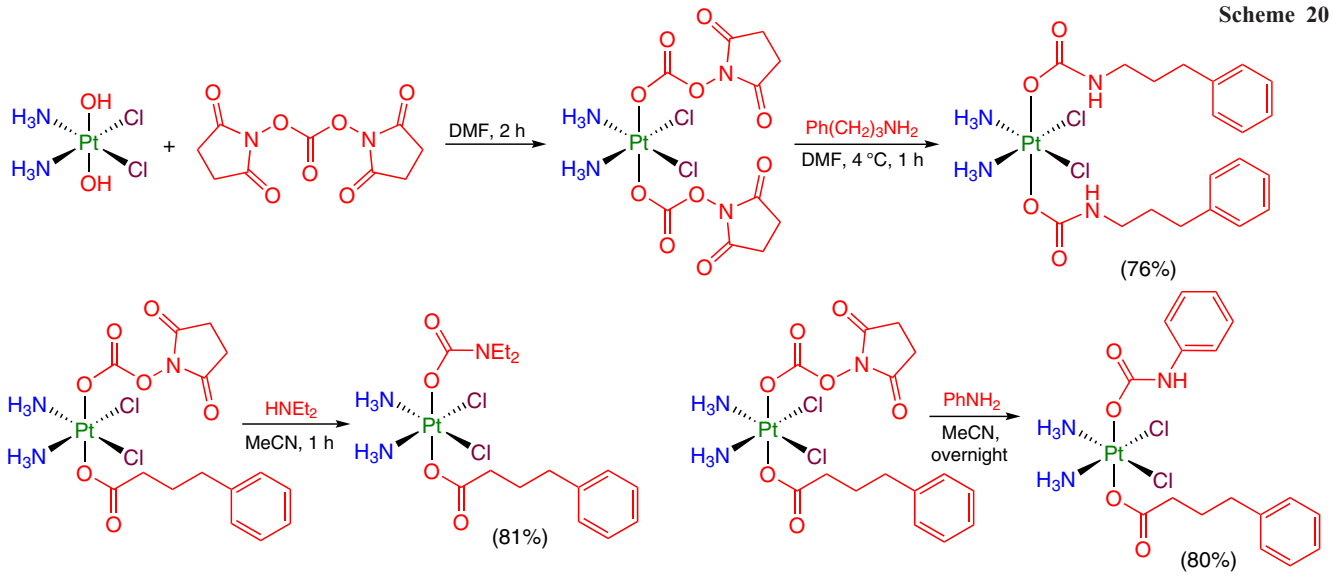
2.2.2.2. Carbamate-based linker

The carbamate moiety NH–C(O)–O is an analogue of the carbonate bridge for ligands containing an amino group in the molecule. Carbamates containing simple organic substituents (aliphatic or aromatic hydrocarbon residues) were synthesized, in some cases, using appropriate isocyanates (Scheme 19).[76–78]

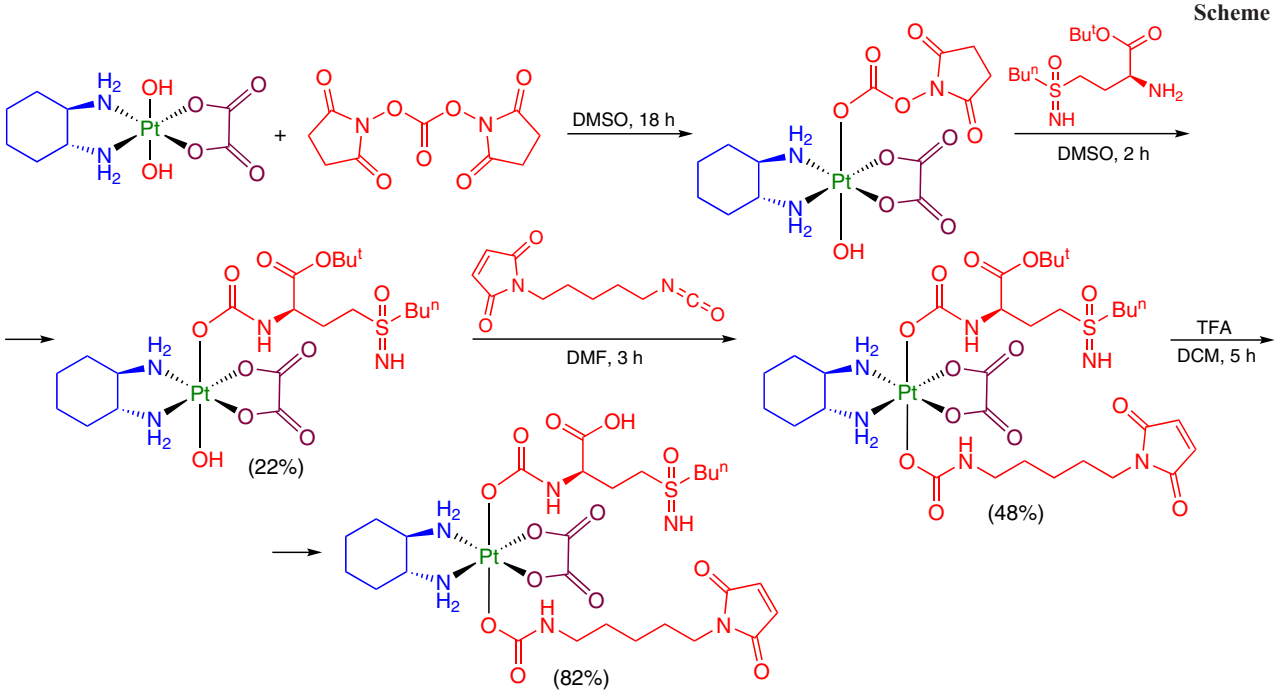
Babu *et al*.[75] developed a method for the synthesis of Pt(IV) prodrugs with a carbamate bridge. The method includes, first, complex formation of Pt(IV) with activated carbonate as an axial ligand, which is then allowed to react with amine. This method affords the target coordination compounds in high yields over a very short reaction time (1–2 h). Furthermore, both aliphatic and aromatic amines are suitable for the reaction, *e.g*., 3-aminopropylbenzene, diethylamine and aniline (Scheme 20).

The possibility of successive modification of the OH groups at the Pt(IV) atom by introduction of two axial ligands *via* carbamate bridges was demonstrated in the development of a Pt(IV) prodrug capable of overcoming the oxaliplatin resistance.[79] The Pt(IV) monocarbamate complex was obtained by the reaction of dihydroxy-oxaliplatin with *N*,*N*′-disuccinimidyl carbonate and an amino group-containing ligand, (2*S*)-*tert*-butyl 2-amino-4-(n-butylsulfonimidoyl)butyrate. The

Scheme 20



Scheme 21



intermediate compound was then allowed to react with isocyanate bearing a second axial ligand (Scheme 21).

2.2.2.3 Thiocarbonate-based linker

An example of unusual bridge between a ligand and the Pt(IV) centre was reported by Barth *et al.*,[80] who demonstrated the possibility of introduction of organic groups into the axial position of coordination compounds *via* a thiocarbonate linker. In the first step, aromatic (thiophenol) or aliphatic thiol (methyl (*R*)-2-acetamido-3-sulfanylpropanoate) was reacted with DSC to give the NHS ester of thiocarbonate, which then reacted with dihydroxy-oxaliplatin (Scheme 22).

2.3. Modification of the axial ligands of Pt(IV) complexes

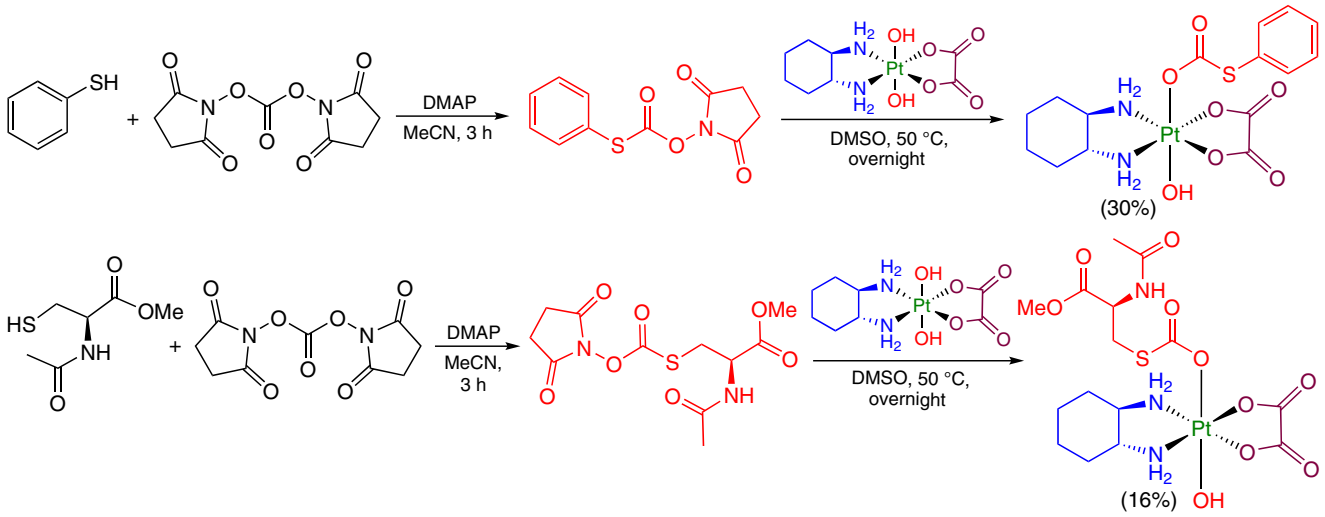
The methods considered above were limited to the direct acylation of the OH group at the Pt(IV) atom. The axial ligands introduced in this way become amenable for further modification. There are two main approaches proposed in the literature for introducing an additional organic moiety to the axial ligand at Pt(IV): peptide synthesis and azide–alkyne cycloaddition.

In the situations where the organic moiety has no carboxyl group, it can be introduced into the axial position of the complex by forming an amide or ester bond. For example, a bond of this type is formed when a succinic acid residue in the axial position of Pt(IV) reacts with an amino or hydroxyl group present in the organic moiety. The carboxyl group can be activated using cross-linking agents of carbodiimide synthesis (DCC or EDC) and NHS, diisopropylcarbodiimide (DIPC) or carbonyldiimidazole (CDI) (Scheme 23).[28,81]

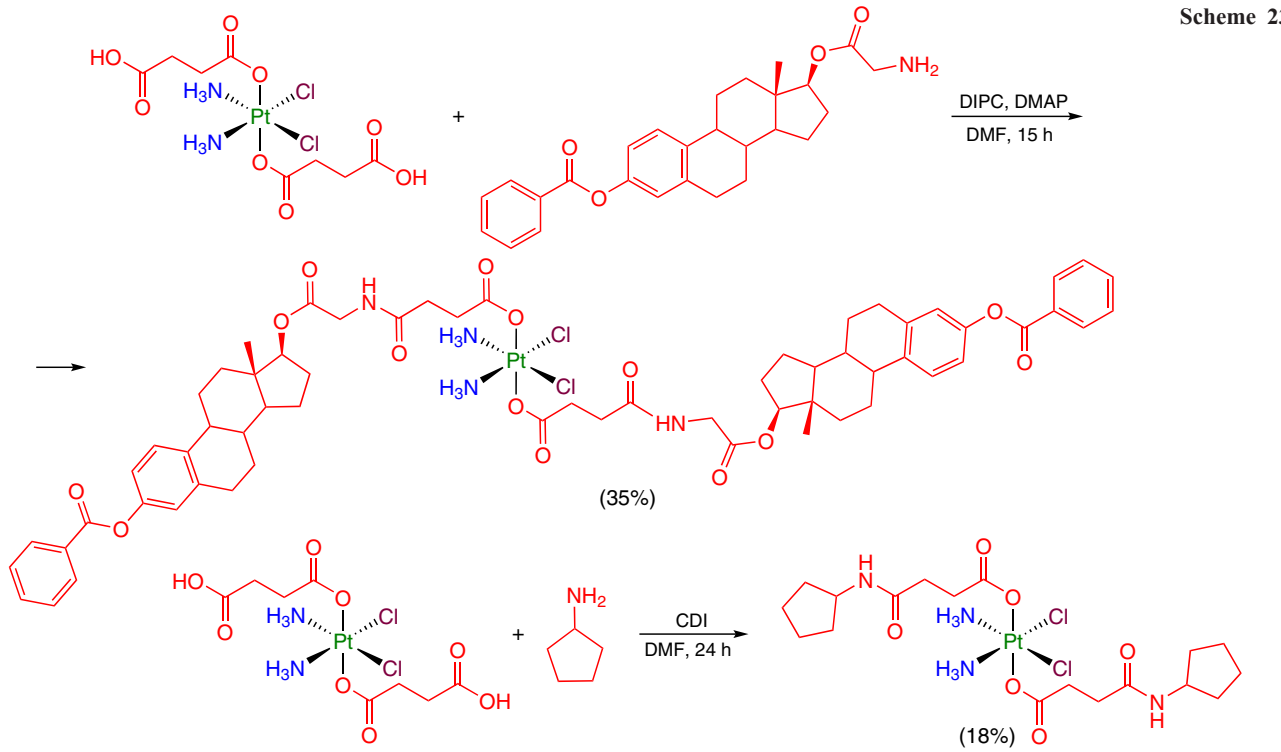
Platinum(IV) complex with 7-diethylaminocoumarin as an axial ligand was modified with a vector peptide to enhance the prodrug accumulation in the cell nuclei. The first step was the synthesis of the NHS ester of Pt(IV) complex. Then the ester was allowed to react with R8K peptide in DMSO (Scheme 24).[68]

There are a few cases in which a carboxylate ligand with a protected amino group is formed in the axial position of Pt(IV)

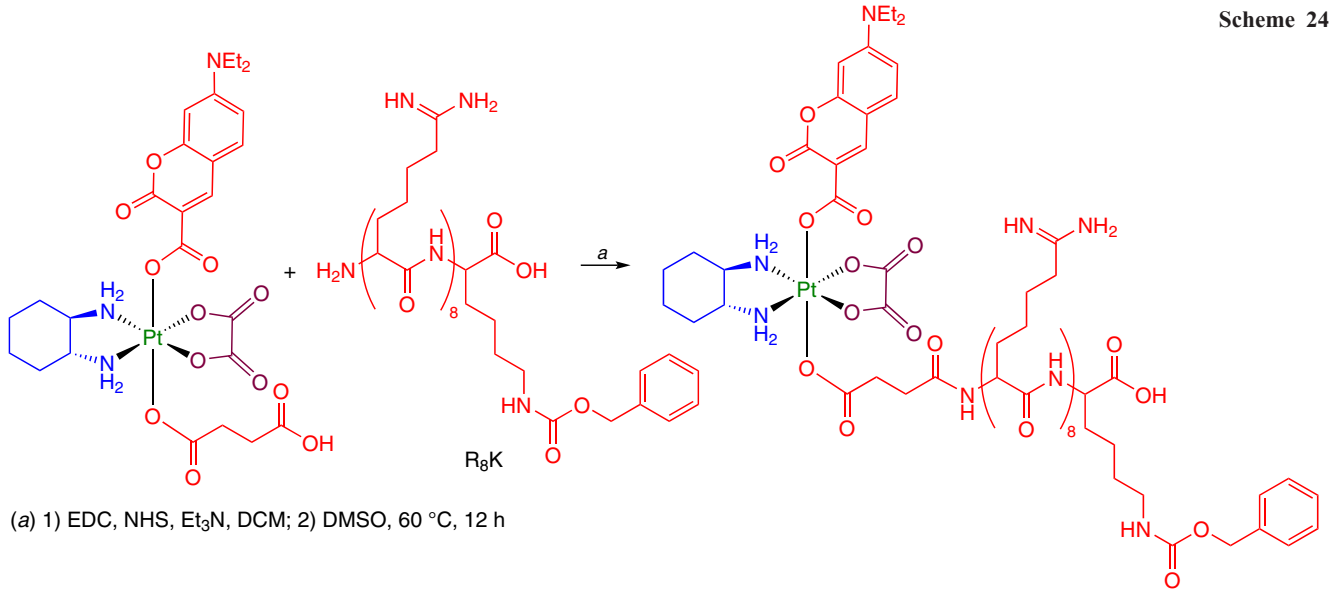
Scheme 22



Scheme 23



Scheme 24

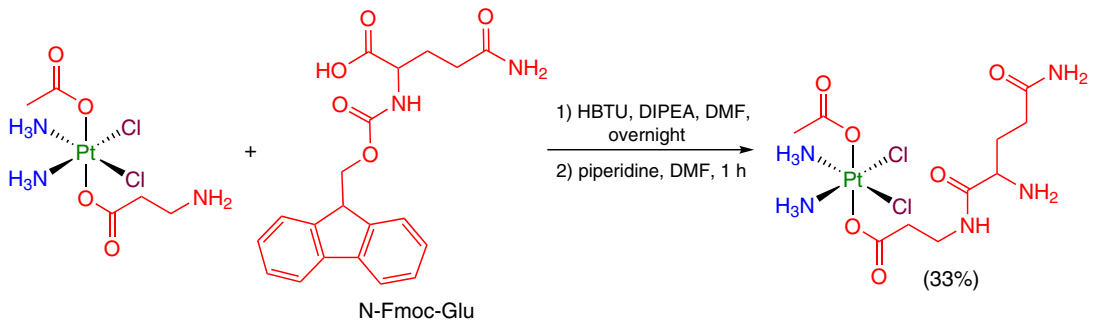


(*a*) 1) EDC, NHS, Et_3N, DCM; 2) DMSO, 60 °C, 12 h

complex, while in the next step, the amino group reacts with a carboxylic acid. As an activating reagent, HBTU is used most often (Scheme 25).[44]

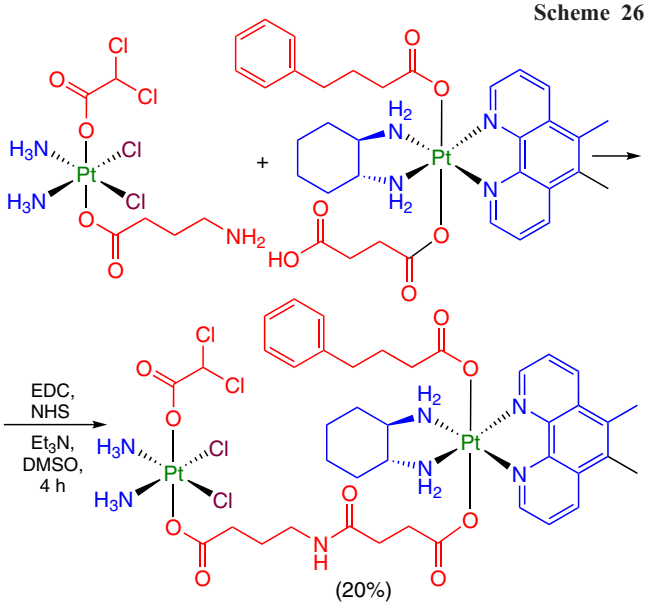
An elegant example of modification of Pt(IV) prodrugs with formation of an amide bond was reported by Petruzella *et al*.[29] They prepared an agent with a potential quadruple action

Scheme 25



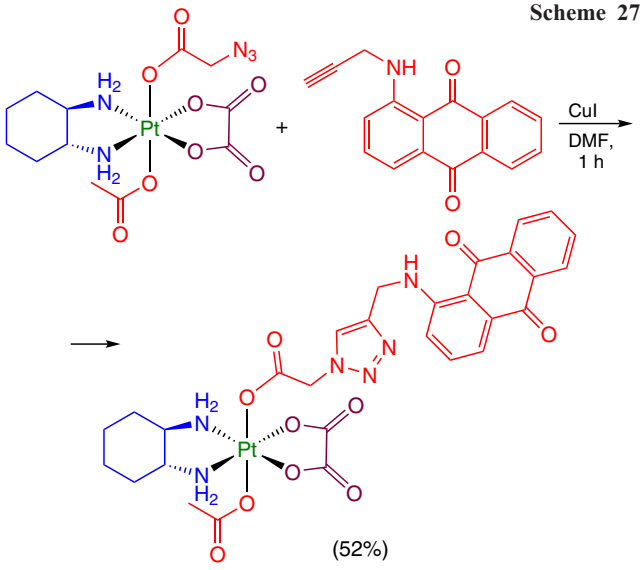
Fmoc is 9-fluorenylmethyloxycarbonyl; DIPEA is diisopropylethylamine

Scheme 26



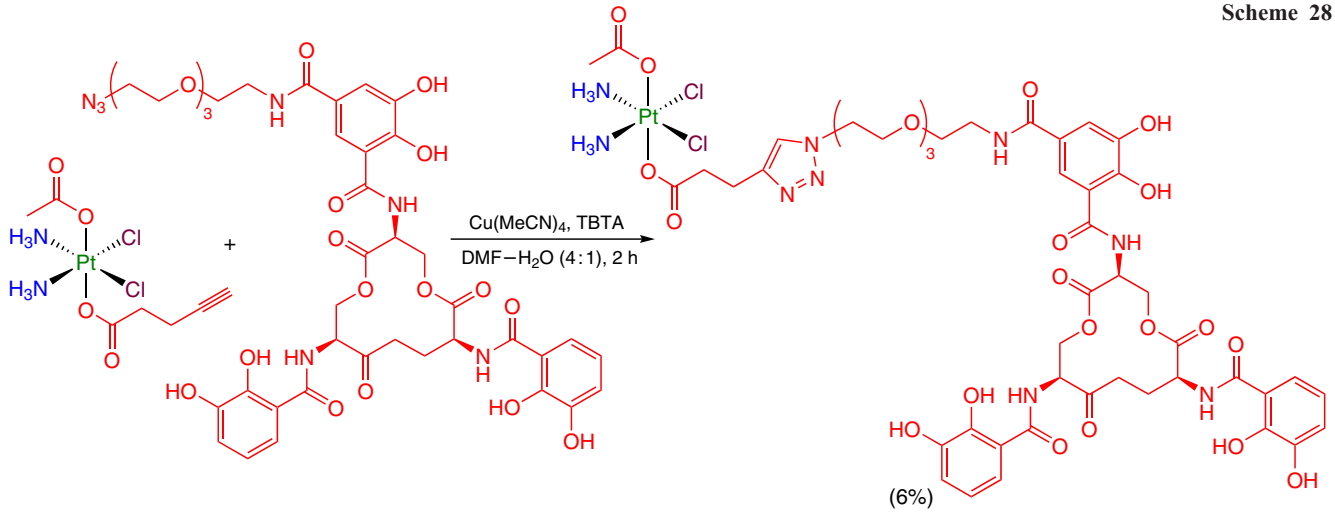
containing two Pt(IV) centres and two biologically active axial ligands, phenylbutyrate and dichloroacetate, in the molecule (Scheme 26).

Scheme 27

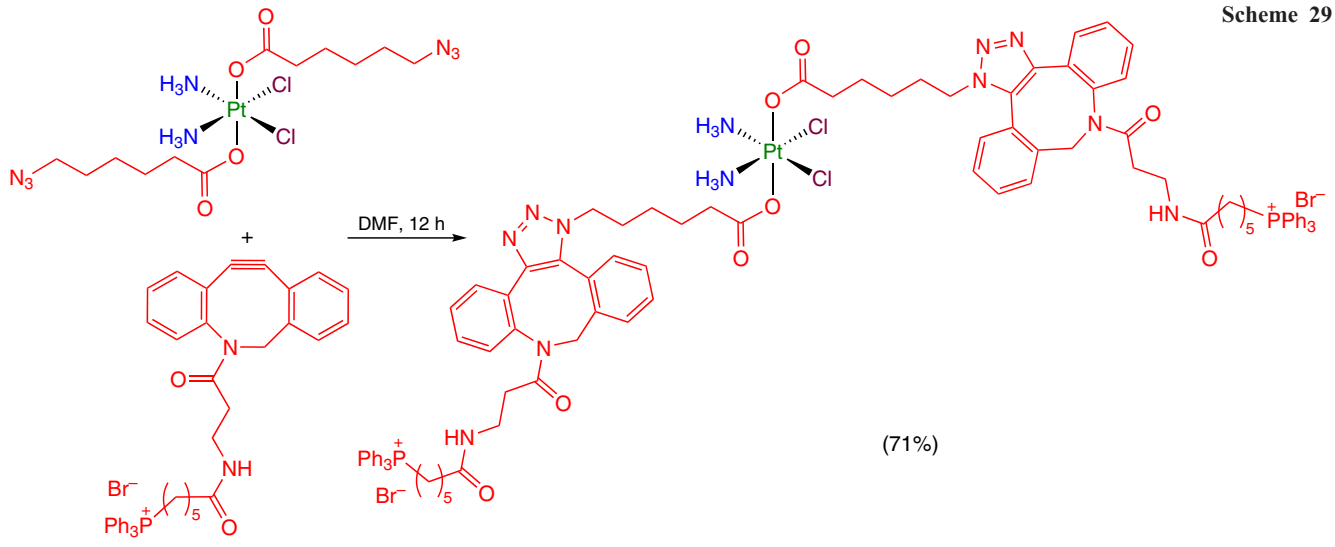


In some publications, azide–alkyne cycloaddition was used to modify an axial ligand. For instance, Hambley and co-workers[61] carried out a click-reaction between a Pt(IV) complex with an azidoacetic acid moiety and propargylated anthraquinone

Scheme 28



Scheme 29



derivatives in the presence of a copper(I) iodide as a catalyst (Scheme 27).

A Pt(IV)-based prodrug containing an enterobactin derivative, a vector facilitating the accumulation of Pt(IV) in *Escherichia coli* bacteria, was synthesized using a homogeneous catalyst based on the copper(I) hexafluorophosphate acetonitrile complex in the presence of a copper-chelating ligand–tris(benzyltriazolyl)amine (TBTA).[82] TBTA acted as a stabilizing ligand preventing copper(I) disproportionation and oxidation with oxygen (Scheme 28).[83]

A Pt(IV) coordination compound containing two 6-azidohexanoic acid moieties was used as the substrate in the sterically promoted azide–alkyne cycloaddition reaction that did not require catalysis by copper salts.[84] As a result, the axial ligand was modified with a triphenylphosphonylphosphonioalkyl moiety (Scheme 29).

Thus, the introduction of ligands with functional groups, *e.g.*, carboxyl, amino or azide groups, into the axial position of Pt(IV) complexes enables further modification of these compounds. This opens the way to finer tuning of the physicochemical and biological properties of Pt(IV) prodrugs.

2.4. Analysis of synthetic approaches to the preparation and modification of Pt(IV) prodrugs

Comparison of methods for the synthesis of Pt(IV) prodrugs given in this Section indicates that carboxylic acids chlorides are the optimal reagents for the preparation of symmetrical dicarboxylate complexes.[49–54] A milder synthetic approach includes the reaction of Pt(II) compounds with carboxyl-containing organic ligands in the presence of tetramethyluronium activators.[57–60] For the synthesis of Pt(IV) monocarboxylate derivatives and selective modification of one axial hydroxyl group in a Pt(IV) complex, it is advisable to use carboxylic acid anhydrides[43,61,65,66] or NHS esters[32,62,67,68] in a slight excess (1.1–1.3 equiv.) with respect to the initial coordination compound. The subsequent modification of the second OH group in the axial position of Pt(IV) monocarboxylate prodrugs is accomplished almost exclusively by treatment with carboxylic acid ahydrides.[27,28,68–70]

Apart from carboxylic acids, organic ligands containing hydroxyl or amino functional groups can be introduced into the axial position of Pt(IV) complexes using disuccinimidyl carbonate; this pathway involves the intermediate formation of carbonates or carbamates, respectively.[74,75,79] According to an alternative approach to the synthesis of Pt(IV) prodrugs, the initial complex is allowed to react with the isocyanate of the specified ligand, which also results in the formation of the carbamate bond.[76–78]

The axial organic ligands in Pt(IV) prodrugs are mainly subjected to further functionalization by peptide synthesis methods if they contain a carboxyl or amino group.[44,55,68,81] One more way of modification of axial ligands is the azide–alkyne cycloaddition reaction using copper(I) catalysts or strained cyclooctynes.[61,83,84]

3. Biological activity of Pt(IV)-based prodrugs

A major benefit of the Pt(IV) prodrug design strategy is the possibility of easy variation of axial ligands. This Section of the review addresses a number of Pt(IV) complexes synthesized over the last 5 years and demonstrates the effect of axial ligands on the biological activity of the compound.

3.1. Platinum(IV) complexes with ligands possessing cytotoxic action

An efficient strategy for enhancing the antiproliferative properties of Pt(IV) prodrugs is the use of molecules possessing their own cytotoxicity as axial ligands. These agents may possess a synergistic effect, *i.e.*, they may act more effectively than a physical mixture of the starting compounds.[36,85]

3.1.1. Tubulin polymerization inhibitors

The formation of microtubules upon polymerization of α- and β-tubulin heterodimers has a crucial importance for a large number of fundamental cell functions.[86] Microtubules, which play a significant role in mitosis, have been recognized as an effective target for the development of novel anticancer agents.[87] Microtubule inhibitors can be classified into two types: microtubule destabilizers such as combretastatin A4 (CA4), colchicine and vinblastine and microtubule stabilizers such as taxanes.[88]

3.1.1.1. Combretastatin

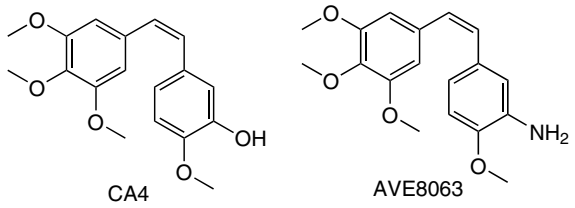
The natural compound CA4 is a promising anticancer agent, which acts *via* inhibition of tubulin polymerization, thus preventing the formation of new blood vessels and destroying the vessels that are already present in the tumour.[89,90]

In 2018, Li *et al.*[91] synthesized prodrugs based on platinum(II) complexes (cisplatin and oxaliplatin) and combretastatin or its analogue AVE8063 containing an amino group instead of the hydroxyl group.

Prodrugs **1**–**4** proved to be less cytotoxic against any of the studied cell lines than the ligands CA4 and AVE8063. The activity of compounds **1** and **3** was 8–22 times higher than the activity of the initial cisplatin. In addition, they showed selectivity, being less toxic to normal cells.

A study of the cellular uptake of prodrug **1** demonstrated cellular uptake 2.2 times as high as that for cisplatin. Complex **1** also showed activity to mitochondria and destroyed the microtubule network, which attests to the activity of CA4 moiety located in the axial position.

Structures CA4 and AVE8063

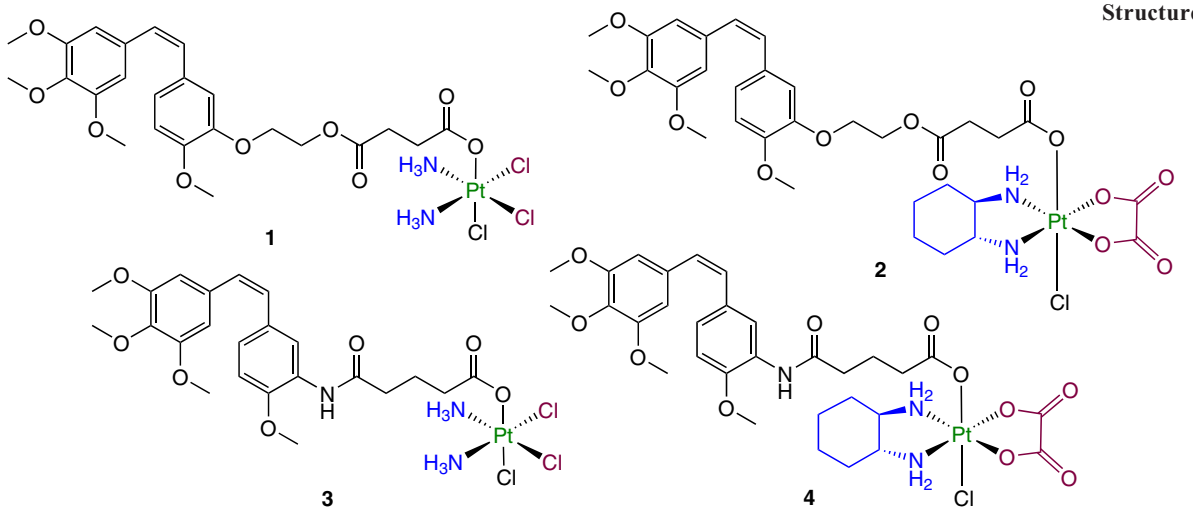


A study of the anticancer efficiency of prodrug **1** against SKOV-3 human ovarian adenocarcinoma xenograft model in BALB/c mice demonstrated a more pronounced tumour growth inhibition (TGI) than the parent ligand CA4, but less pronounced TGI than cisplatin. It is noteworthy that the weight loss in the group of mice administered with compound **1** was lower than that for mice treated with cisplatin.

Platinum(IV) prodrugs **5**–**7** with combretastatin in the axial position were reported in 2019 by Huang *et al.*[92] Complex **5** demonstrated the ability to arrest the cell cycle in the G2/M phase and to inhibit the microtubule formation.

In 2021, Schmidt *et al.*[93] described Pt(IV) prodrugs **8**–**15**. These are triple-action medications containing axial combretastatin, histone acetylase (HDAC) inhibitors (phenylbutyrate and valproate), pyruvate dehydrogenase kinase

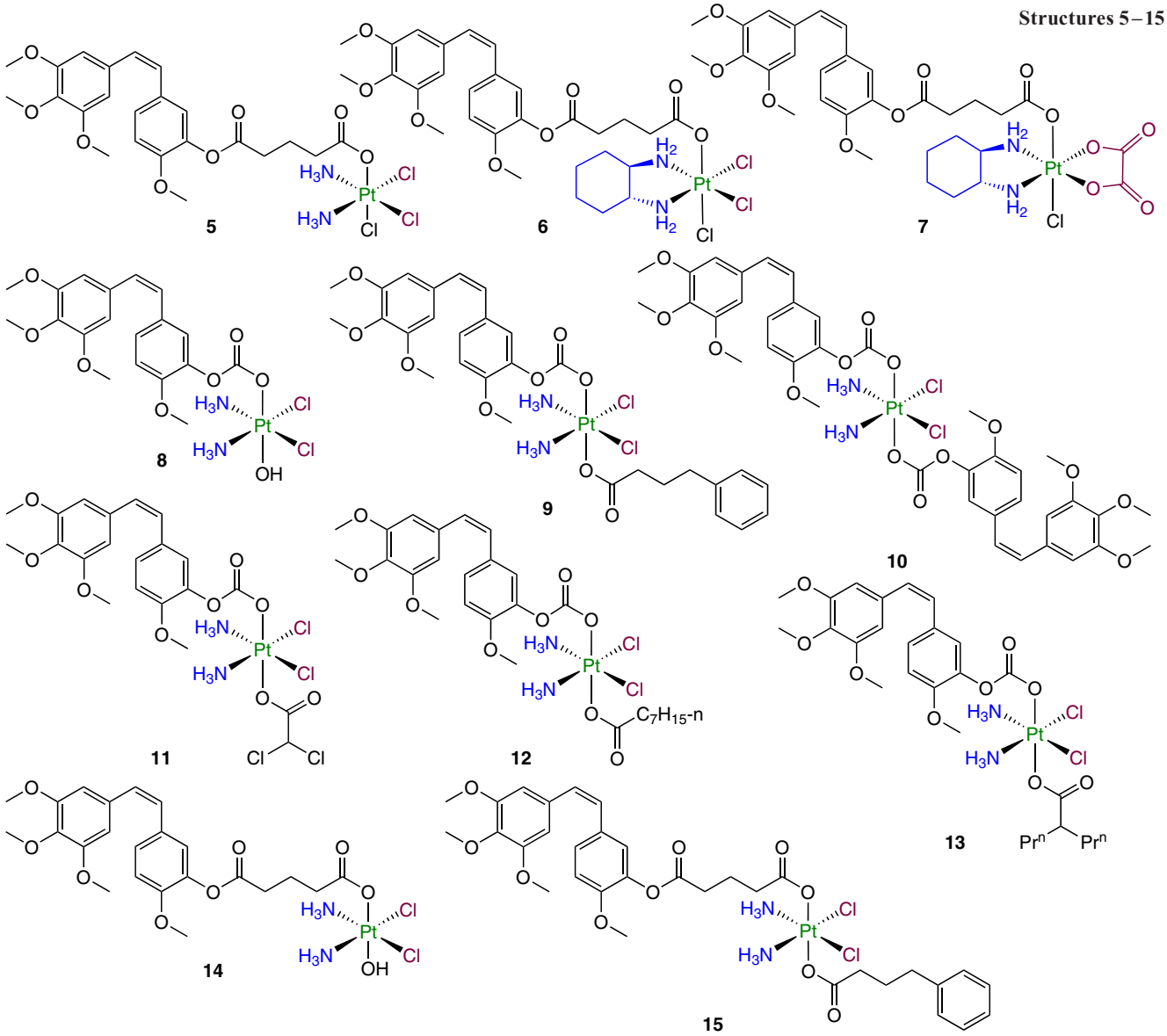
Structures 1–4

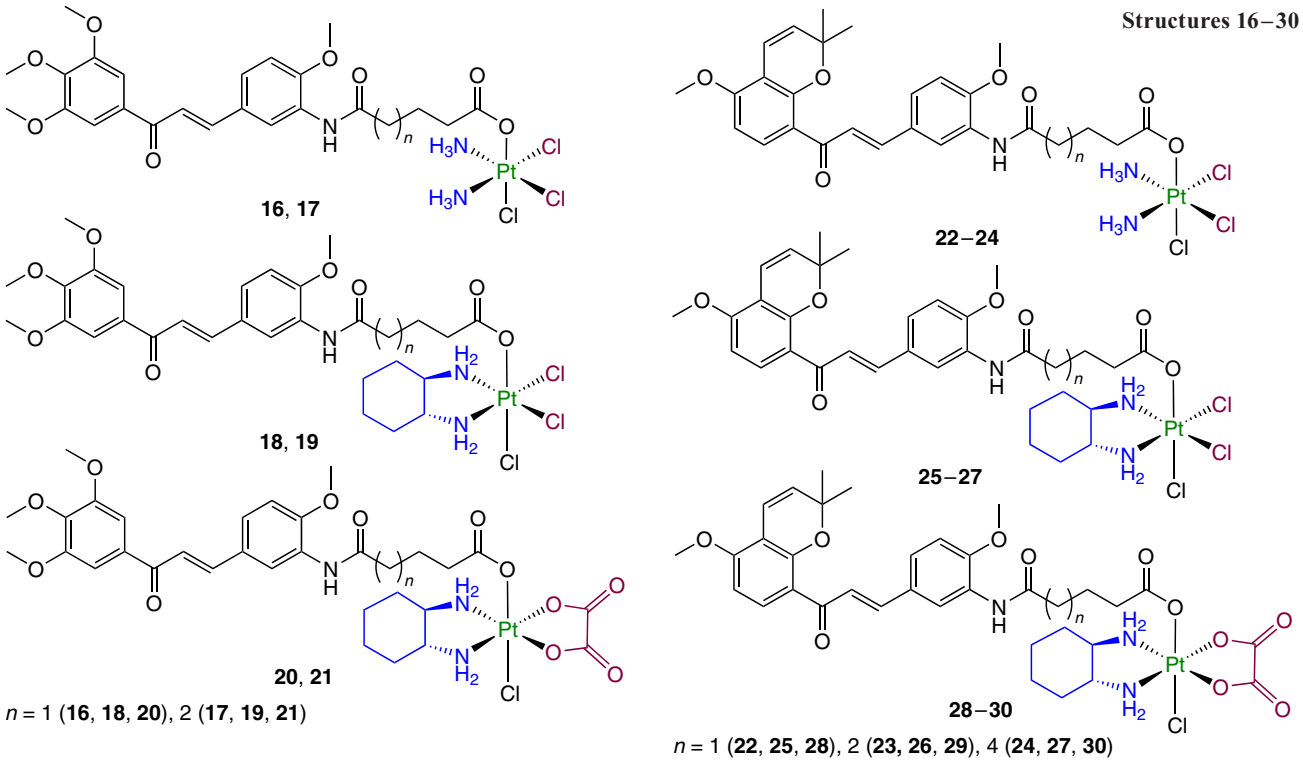


(PDK) inhibitor (dichloroacetate) or octanoate, which enhanced DNA methylation.

These prodrugs showed a cytotoxicity comparable with or exceeding that of combretastatin in the nanomolar concentration range (<10 nM) and greater cellular uptake compared to cisplatin. In addition, they were found to inhibit microtubule formation. A study of the therapeutic efficacy of these compounds *in vivo* against the Lewis lung carcinoma model

Structures 5–15





showed that CA4, which is the most potent cytostatic *in vitro*, exhibited the least pronounced anticancer effect *in vivo*. The reduction of the tumour volume induced by complex **8** was comparable to that for cisplatin (84% inhibition), while the administration of compounds **15** and **9** caused TGI of 91.5 and 92.6%, respectively.

The greatest efficacy of derivative **9** with phenylbutyrate and combretatstatin residues in the axial positions was attributed to the higher stability of triple-action prodrugs in comparison with double-action agents.

3.1.1.2. Chalcones

Chalcones, α,β-unsaturated carbonyl compounds with two aromatic cores, are classic Michael acceptors able to alkylate protein residues including thioredoxin reductases TrxRs and nuclear factors NF-κB and Nrf2.[94] Chalcones and their derivatives can act as antioxidants, antibacterial and anti-inflammatory agents; they show noticeable antitumour activity, in particular through inhibition of tubulin polymerization by binding to the colchicine site.[95–97] In view of the multiple biological activities, development of Pt(IV) prodrugs with a chalcone moiety in the axial position is of obvious interest.

In 2018, Huang *et al.*[98] synthesized Pt(IV) complexes **16**–**21**, containing chalcone in the axial position. Prodrugs **16**–**21** exhibited cytotoxicity exceeding the cytotoxicity of the parent Pt(II) complexes against a number of cell lines, including cisplatin-resistant ones. The half-maximal inhibitory concentration (IC_{50}) against HepG2 human hepatocellular carcinoma cells was 0.97 to 2.23 μM. Furthermore, these compounds showed an increased cellular uptake. Compounds **16** and **17** noticeably inhibited the motility of human umbilical vein endothelial cells (HUVEC), arrested the cell cycle in the G2/M phase and caused mitochondria-mediated apoptosis by regulating the expression of Bcl-2 proteins. As expected, prodrugs **16** and **17** were able to inhibit tubulin polymerization.

Millepachine is a chalcone first isolated from the *Millettia pachycarpa* shrub in 2013; it shows anticancer activity *in vitro* and *in vivo* and also has a potent inhibitory effect on tubulin polymerization *via* binding to the colchicine site.[97] In 2018, Huang *et al.*[99] developed Pt(IV) prodrugs **22**–**30** with millepachine and its homologues in the axial position.

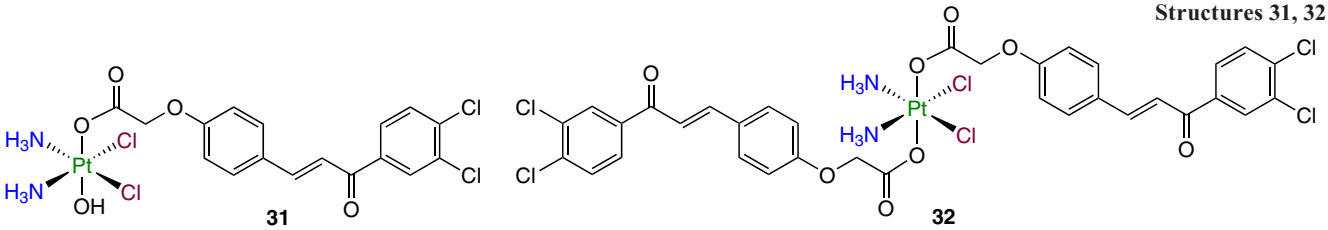
Prodrug **22** had a higher cytotoxicity than cisplatin. The selectivity characteristics of these prodrugs were also higher than those of the parent Pt(II) agents, and the cytotoxicity decreased with increasing carbon chain length. Compound **22** showed a higher (by a factor of up to two) uptake in tumour cells than cisplatin and the ability to inhibit tubulin polymerization.

A study of the mechanism of cytotoxic action showed that prodrug **22** can induce the cell cycle arrest in the G2/M phase, change the expression of cell cycle-associated proteins and induce apoptosis *via* the ROS-mediated (ROS are reactive oxygen species) mitochondrial pathway. Experiments *in vivo* on SKOV-3 tumour xenografts exhibited efficient TGI without a clear-cut weight loss by the animals.

The inhibition of the interaction of the p53 transcription factor, regulating the cell cycle, with the MDM2 protein is an attractive therapeutic target for the development of anticancer drugs. It is known that the MDM2 protein is overexpressed in various tumours, its interaction with the p53 protein promotes uncontrolled cell proliferation, while inhibition of the p53–MDM2 interaction triggers apoptosis of tumour cells.[100] In 2018, Ma *et al.*[101] used dichloro-substituted chalcone as an inhibitor of the p53–MDM2 interaction and obtained complexes **31** and **32**.

The IC_{50} values for monocarboxylate complex **31** were in the nanomolar concentration range, being 422 times lower than those for cisplatin (0.023 and 9.7 μM against HCT-116 colorectal carcinoma cells, respectively). Prodrug **31** also showed activity in the nanomolar range against cisplatin-resistant cell lines [0.07 and 0.14 μM against the cisplatin-resistant A2780cisR ovarian cancer cell line (A2780/CDDP) and cisplatin-resistant A549cisR lung carcinoma cell line (A549/CDDP), respectively]. Unlike cisplatin, this compound induced apoptosis and promoted a considerable growth of expression of

Structures 31, 32

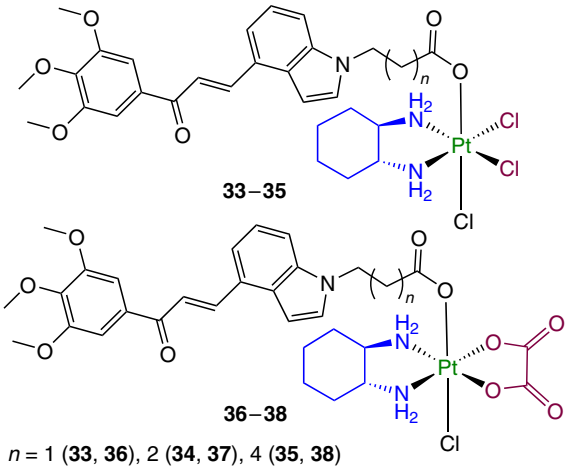


DNA damage marker (γH2A.X). In addition, prodrug **31** was more efficiently taken up by cells (36 and 111 times higher cellular uptake than that of cisplatin in A2780 and A2780cisR cells, respectively).

The antitumour activity of complex **31** was studied *in vivo* against the HCT-116 tumour xenograft model in BALB/c mice. After 27 days of therapy with this agent, TGI was 80%, while for the groups of mice that were administered with cisplatin, this value was 68%.

In 2023, Cao *et al.*[102] reported Pt(IV) prodrugs **33**–**38** with an indole analogue of chalcone in the axial position.[99] These compounds showed a pronounced cytotoxicity, with complex **36** containing two methylene units in the axial ligand being the most active. Prodrug **36** showed a moderate selectivity toward normal cells (L02 human fetal hepatocytes and HUVEC) and inhibited migration of HCT-116 cells. A study of the mechanism of cytotoxic action demonstrated that prodrug **36** can destroy the Bcl-2/Bax proteins, promote the release of cytochrome C (Cyt C) and activates the cascade of caspases, thus causing mitochondria-mediated apoptosis. Using immunofluorescence assay of intracellular microtubules and molecular docking, it was ascertained that this compound can interact with the colchicine-binding site and inhibit tubulin polymerization.

Structures 33–38

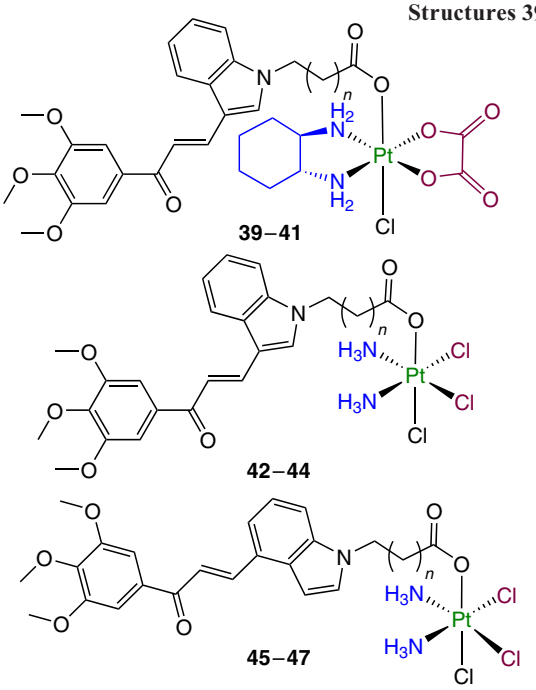


n = 1 (**33**, **36**), 2 (**34**, **37**), 4 (**35**, **38**)

In 2023, Liu *et al.*[103] studied analogous Pt(IV) complexes **39**–**47** containing an indolochalcone moiety in the axial position.

Prodrugs **39**–**47** exhibited cytotoxicity against several cell lines; their cytotoxic activity decreased with increasing number of methylene units in the chain: complexes **42**–**47** based on cisplatin proved to be more active than oxaliplatin derivatives **39**–**41**. The highest cytotoxic activity was found for complex **45** (IC_{50} = 0.11–1.53 μM), in particular against cisplatin-resistant cell lines. In a study of the mechanism of cytotoxic action, it was found that this compound is efficiently taken up by the cells and triggers mitochondria-mediated apoptosis by inhibiting the activity of the Bcl-2 protein, enhancing the activity of the Bax and Cyt C proteins and activating the caspase cascade. In addition, prodrug **45** showed the ability to induce the endoplastic reticulum (ER) stress in A549/CDDP cells through the PERK/ATF4/CHOP signalling pathway.

Structures 39–47



n = 1 (**39**, **42**, **45**), 2 (**40**, **43**, **46**), 4 (**41**, **44**, **47**)

A study of the therapeutic efficacy *in vivo* for A549/CDDP xenograft model in mice showed that complex **45** inhibits the tumour growth more efficiently than cisplatin (TGI of 65.9 and 25.7%, respectively) and also has a lower general toxicity.

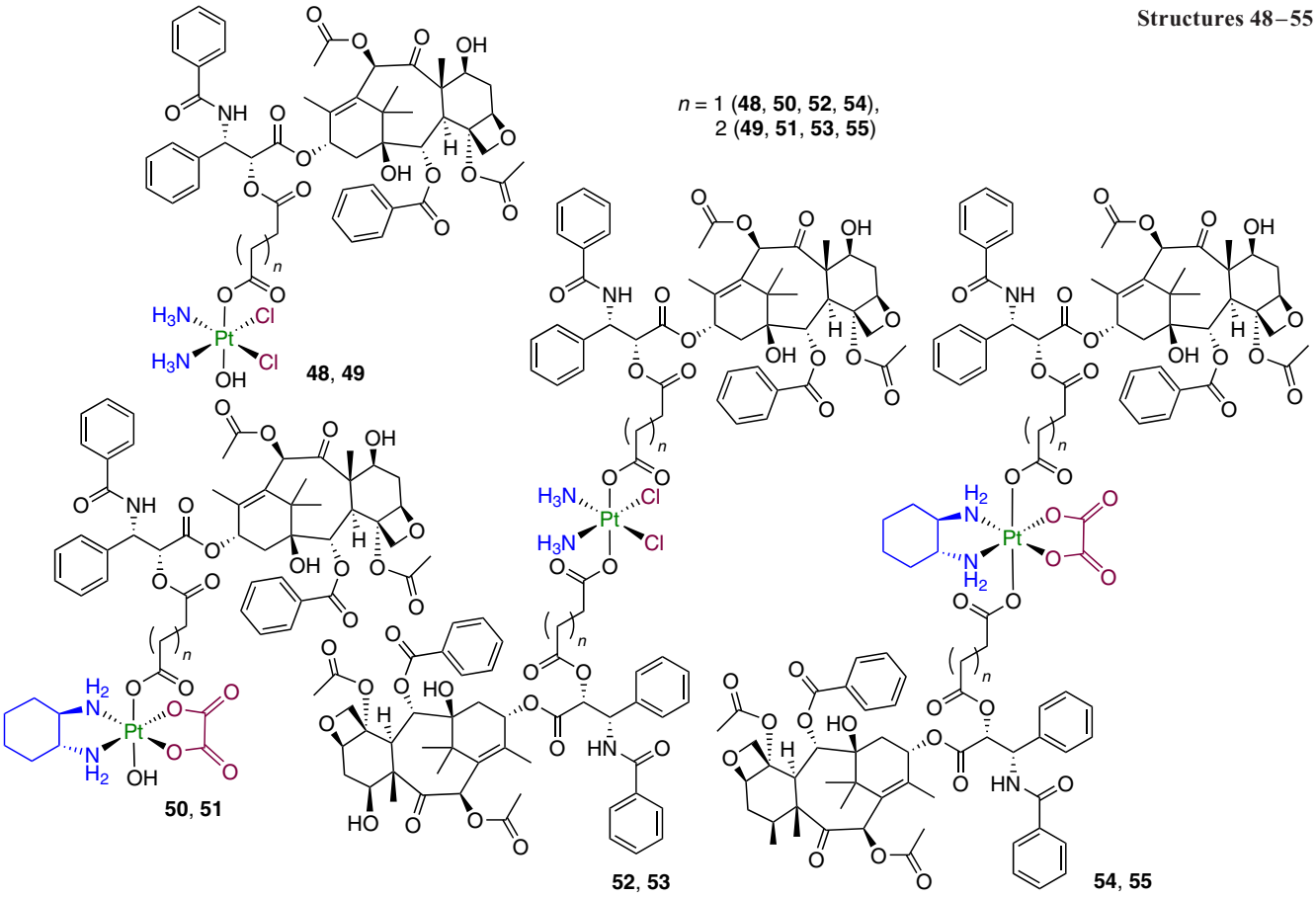
3.1.1.3. Paclitaxel

Paclitaxel (PTX), a microtubule depolymerization inhibitor, is one of the most successful antimitotic drugs for the therapy of a broad range of solid malignant tumours.[104] In addition, Pt(II) agents in combination with PTX are often clinically used for the treatment of various types of breast cancer, non-small cell lung cancer and gastric cancer.[105,106]

In 2022, Zhang *et al.*[107] described Pt(IV) prodrugs **48**–**55** containing PTX in one or two axial positions. A study of the antiproliferative activity of these complexes revealed high activity against all cancer cell lines in comparison with cisplatin; the IC_{50} values varied in the range of 0.13–5.98 μM.

Prodrug **48** showed selectivity towards MCF-7 breast carcinoma cells: it was 344 times higher than that of cisplatin. This compound efficiently inhibited the migration of HCC1937 and MCF-7 breast carcinoma cells and was taken up by cancer cells 30 times more efficiently than the parent cisplatin. Furthermore, prodrug **48** showed the ability to induce DNA damage, arrest the cell cycle in the G2 phase and inhibit tumour metastasis. It induced mitochondria-mediated apoptosis of MCF-7 cells and increased the intracellular ROS levels. It also

Structures 48–55



induced the endoplasmic reticulum stress and promoted the release of Ca^{2+} ions.

3.1.2. Miscellaneous cytotoxic agents

3.1.2.1. 5-Fluorouracil

5-Fluorouracil is a clinically used thymidylate synthase (TS) inhibitor. 5-Fluorouracil metabolites bind to DNA, which induces DNA damage, while TS inhibition blocks the synthesis of DNA and disrupts the repair mechanisms.[108,109]

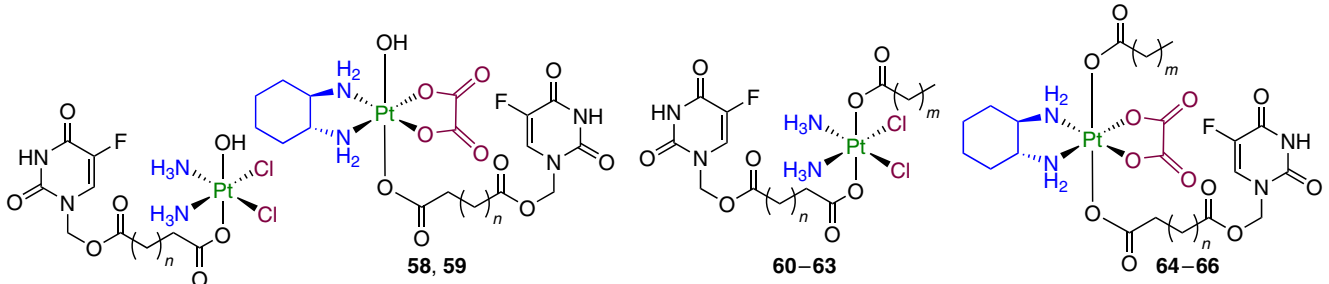
Platinum(IV) complexes **56**–**67** based on cisplatin (or oxaliplatin) and fluorouracil were synthesized and studied by Zhang *et al.*[28]

Monocarboxylate prodrug **58** proved to be less active than an equimolar mixture of oxaliplatin and fluorouracil against any of the tested cell lines. For this reason, to enhance the cytotoxic activity, the second axial position was modified with palmitate or stearate, which increased the lipophilicity of compounds. Prodrugs **60**–**67** obtained in this way proved to be 64 times more active than the corresponding Pt(II) complexes: IC_{50} values for HCT-116 cells were 0.13 and 8.34 μM for compound **64** and oxaliplatin, respectively. Meanwhile, when tested against normal MRC-5 lung fibroblasts, prodrug **64** was more than 2.5 times less toxic than oxaliplatin.

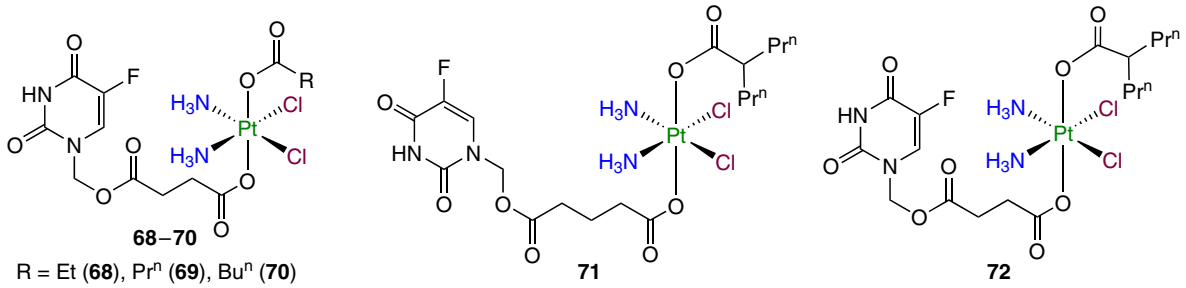
A study of the cellular uptake of the prodrugs in HCT-116 cells showed a high uptake for complex **64**, which was 62 times as high as that of oxaliplatin. This prodrug efficiently damaged DNA and induced an increase in the expression of TS and p53 protein, markers of 5-fluorouracil activity, in HCT-116 cells. The high anticancer activity of compound **64** was also confirmed in an *in vivo* experiment in which the prodrug inhibited the growth of the HCT-116 tumour xenograft in NOX/SCID mice by 84.8% after 21 days of therapy. Note that for oxaliplatin and the oxaliplatin + fluorouracil combination, inhibition was 57.8 and 75.8%, respectively.

More recently, Pt(IV) prodrugs **68**–**72** bearing 5-fluorouracil and aliphatic carboxylic acids, including valproic acid as an HDAC inhibitor, as axial ligands were investigated by Ding *et al.*[110]

Structures 56–67



Structures 68–72



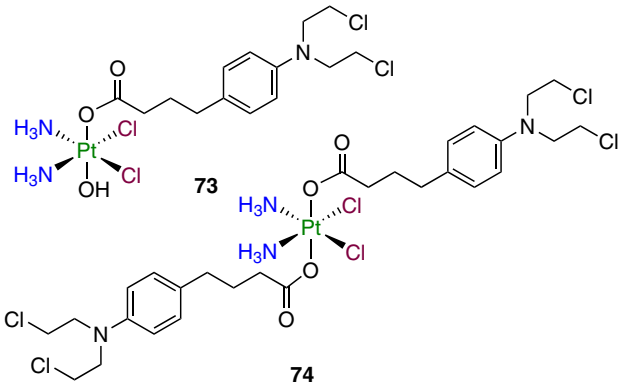
An increase in the length of the linker in the axial position entailed an increase in the cytotoxic activity of the prodrugs. The highest activity against MCF-7 cells and MDA-MB-231 triple negative breast cancer cells was inherent in complex **71**, while the highest selectivity over HUVEC normal cells was identified for compound **72**. The cellular uptake of **72** in HeLa cervical cancer cells proved to be three times as high as that of cisplatin, which correlates with the difference between the cytotoxic activities of these agents. In addition, prodrug **72** inhibited the HDAC expression and promoted the TS expression.

3.1.2.2. Chlorambucil

Chlorambucil is an FDA-approved anticancer drug capable of binding to the guanine or adenine N(7) atom in DNA.[111,112]

In 2018, Ma *et al.*[59] reported dual-action mono- and dicarboxylate complexes **73** and **74** based on cisplatin and chlorambucil.

Structures 73, 74



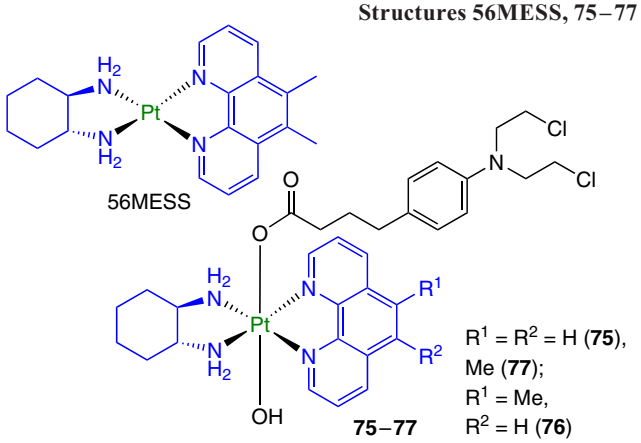
Prodrugs **73** and **74** showed activity against A549 and HeLa cells similar to that of cisplatin, with a 1.5- to 3.3-fold increase in the toxicity. The most pronounced increase in the cytotoxicity (5.5–6-fold) was found for MCF-7 cells. The highest efficiency relative to cisplatin was found for these compounds tested against MDA-MB-231 cell line where complex **74** was 20 times more active than cisplatin (the IC_{50} values were 2.5 and 51.7 μM, respectively).

The increase in the cytotoxicity of prodrug **74** was correlated with the increase in the cellular uptake. This compound induced much more pronounced DNA damage and apoptosis than cisplatin. When studied for the *in vivo* antitumour efficacy in BALB/c mice bearing MDA-MB-231 tumour xenograft, prodrug **74** was not superior to cisplatin; however, the therapy with this agent did not induce weight loss of the animals.

Chlorambucil was also used as an axial ligand for another class of Pt(II)-based anticancer agents, complexes **75**–**77** with equatorial ligands based on phenanthroline, which were studied by Aputen *et al.*[113]

Some representatives of this class, in particular the compound designated as 56MESS, showed high antiproliferative activity against a number of cell lines, presumably due to an alternative cytotoxicity mechanism that targets the tumour by affecting mitochondria.[114,115] Prodrugs **75**–**77** showed high cytotoxicity in sub-micromolar and nanomolar concentration ranges against several cell lines. Compound **77** proved to be the most active antitumour agent: the GI_{50} values (concentration providing 50% cell growth inhibition) reached 2.7 nM for prostate cancer cell line (Du145) and 10 nM for cisplatin-resistant ovarian cancer cell line (A2780cisR). Despite the fact that this agent was 2800 times more toxic than cisplatin, when tested on A2780cisR cell line, it showed cytotoxicity comparable to that of the precursor Pt(II) complex 56MESS (GI_{50} for these cells were 10 and 13 nm, respectively). The incubation of colorectal adenocarcinoma cells (HT-29) with prodrug **77** resulted in up to three times more efficient formation of ROS than incubation with 56MESS. It is known that the high level of ROS in cells induces a significant DNA damage and activates the apoptotic cell death.[116,117]

Structures 56MESS, 75–77



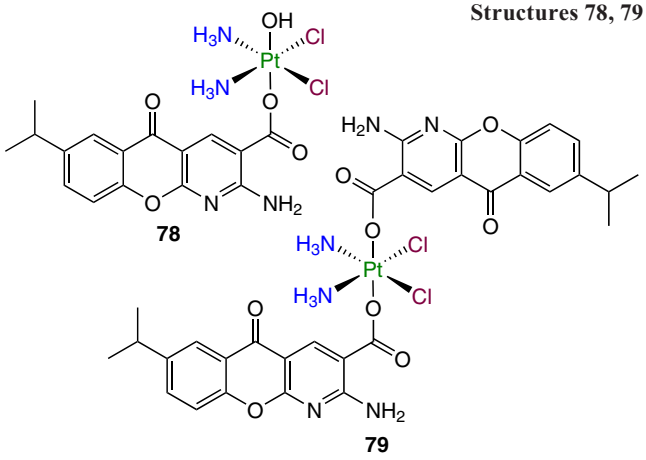
3.1.2.3. Amlexanox

Platinum(IV) mono- and dicarboxylate complexes **78** and **79** with axial position(s) occupied by the anti-asthmatic drug amlexanox possessing a pro-apoptotic effect[118] were synthesized by Guo *et al.*[119]

A cytotoxic activity assay demonstrated that dicarboxylate complex **79** has almost no antiproliferative properties, while monocarboxylate **78** has IC_{50} values in the micromolar concentration range, in particular against cisplatin-resistant Caov-3 (primary ovarian cancer) and A549/CDDP cell lines.

Detailed study of the mechanism of cytotoxic action demonstrated that prodrug **78** triggers apoptosis by a mechanism resembling that for cisplatin. In addition, this agent induces significant mitochondrial depolarization and mitochondria-

Structures 78, 79



mediated apoptosis of Caov-3 cells, which is due to the presence of the amlexanox moiety in the axial position. Compound **78** also induces the autophagy in Caov-3 cells.

3.1.2.4. Clioquinol

Clioquinol is an antimicrobial and antiprotozoal agent. This compound was also studied as an antitumour drug possessing anti-metastatic properties, which may markedly enhance the autophagy by inhibiting the mammalian target of rapamycin (mTOR).[120]

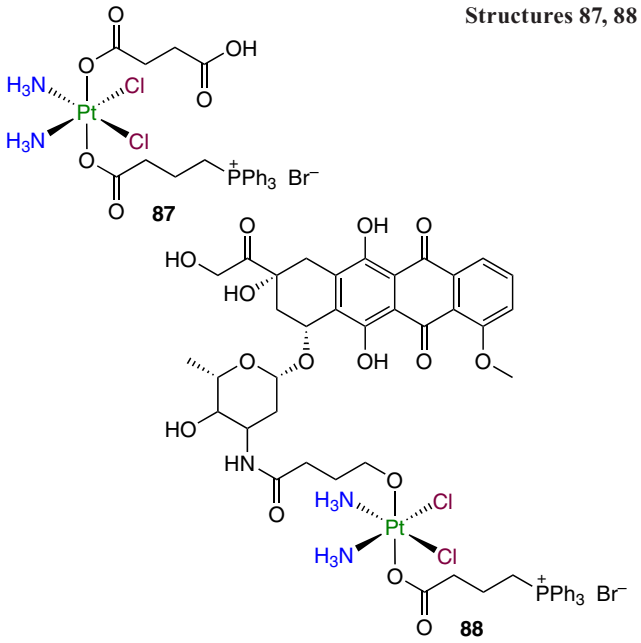
In 2023, Zhang *et al.*[121] developed Pt(IV) prodrugs **80**–**86** with clioquinol in the axial position.

Antiproliferative activity assays demonstrated that complexes based on cisplatin have a higher activity than the prodrugs derived from oxaliplatin and carboplatin. The highest antiproliferative activity (in particular, against cisplatin-resistant cell lines) was found for complex **84** containing a valeric acid residue in the axial position ($IC_{50} \leqslant 0.70$ μM). According to *in vivo* experiments on BALB/c mice bearing 4T1 mouse breast cancer, prodrug **84** was found to be less toxic than cisplatin and oxaliplatin and than monosubstituted complex **85**. Higher toxicity of the last-mentioned compound is attributable to the lower stability of the agent in the bloodstream: TGI attained after the therapy with prodrug **84** was comparable with that for cisplatin. Compound **84** also showed an antimetastatic activity in *in vitro* and *in vivo* experiments. Study of the mechanism of antitumour activity for prodrug **84** identified its ability to damage DNA, increase the expression of γH2AX and p53 proteins, trigger the mitochondria-mediated apoptosis *via* the Bcl-2/Bax/caspase3 cascade and induce autophagy by inhibiting the PI3K/AKT/mTOR signalling pathway and activating the HIF-1α/Beclin1 pathway. Furthermore, this agent suppressed the secretion of the programmed cell death ligand (PD-L1) in tumour cells and stimulated the formation of CD4+ and CD8+ T-lymphocytes (helper and killer cells, respectively.).

3.1.2.5. Doxorubicin

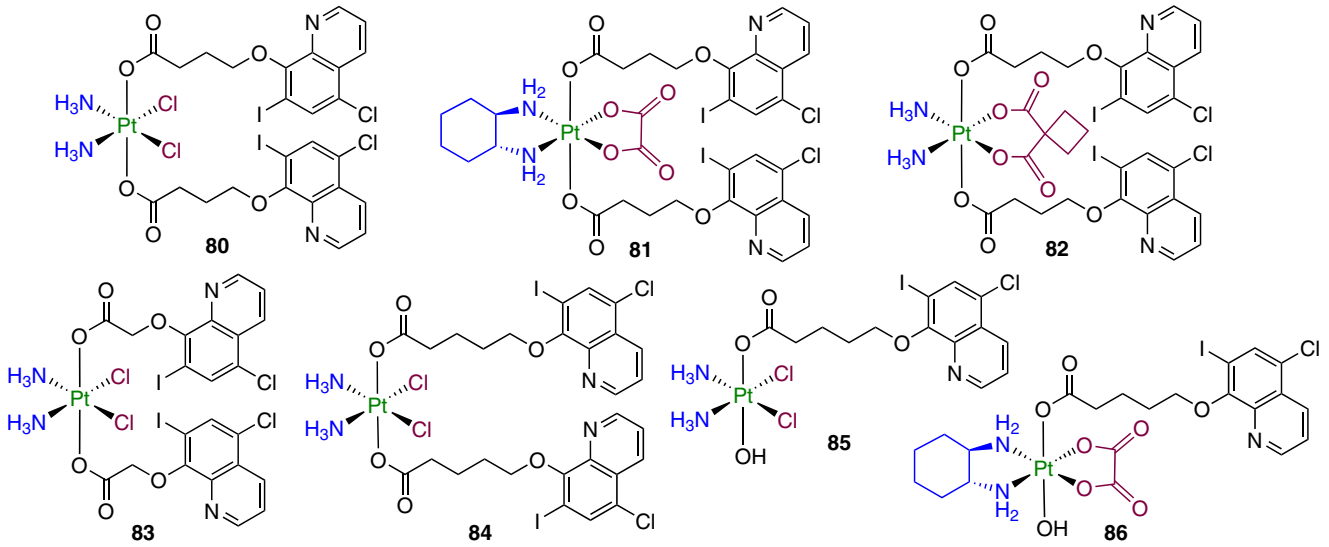
In 2021, Muhammad *et al.*[122] converted cisplatin complex **87** to prodrug **88**, which contained doxorubicin and mitochondria-targeting triphenylphosphine ligand in the axial positions.

Structures 87, 88



Compound **88** exhibited cytotoxicity comparable with that of doxorubicin and exceeding the toxicity of cisplatin. Prodrug **88** had a higher cellular uptake and the ability to be localized in mitochondria, arrest the cell cycle in the G2 phase and induce cell necrosis. This compound can cause mitochondrial depolarization and can form ROS inside the cells.

Structures 80–86



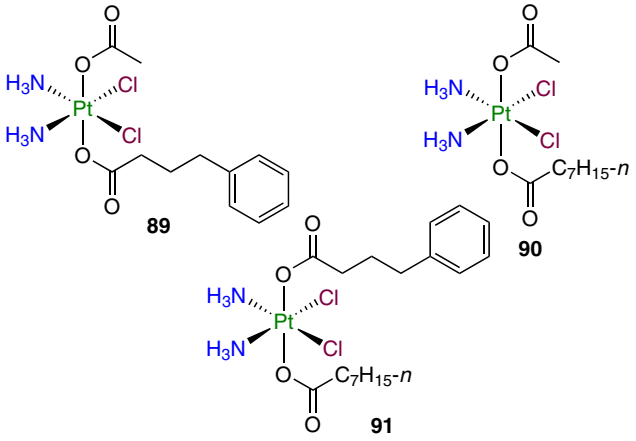
3.1.3. Conjugates with biologically active molecules

3.1.3.1. Phenylbutyrate and aliphatic and (aromatic) hydrocarbons

The effect of combination of various bioactive ligands on the antiproliferative activity of Pt(IV) prodrugs was studied Kostrhunova *et al*.[123] A triple-action prodrug, platinum complex with phenylbutyrate and octanoate in the axial positions (**91**), was studied in comparison with cisplatin and related dual-action prodrugs **89** and **90**.

Complexes **89** and **90**, in which phenylbutyric or caprylic acid residue was present along with the acetate group, were 2–15 times more active than cisplatin, whereas prodrug **91** with three biologically active moieties had IC_{50} values 100–900 times higher than that for cisplatin. The cellular uptake level of compound **91** in MDA-MB-231 cells after a six-hour incubation was 30 and 10 times higher than those for prodrugs **89** and **90**, respectively, and ~60 times higher than that for cisplatin, which is correlated with the lipophilicity ratio of these four compounds (log*P* varies in the following order: **91** ≫ **90** > **89** ≫ CDDP). Complex **91** exhibited the ability to inhibit HDAC and promoted the transmethylation of DNA, which is due to the action of axial ligands.

Structures 89–91



The physicochemical properties and bioactivity of prodrugs **92**–**102** containing carbamate moieties based on aromatic and aliphatic amines as axial ligands were investigated by Babu *et al*.[75]

It was shown that in the presence of sodium ascorbate, the carbamate ligand of prodrugs **92**–**98** is eliminated as the carbamate anion $RNHC(O)O^-$, which undergoes fast decarboxylation to give free amine. Succinic acid monoamide is formed as the major reduction product of complex **92**. Prodrugs with a carbamate linker (**92**, **94**, **101**) showed the highest stability [half-life ($t_{1/2}$)>300 h] in the culture medium. Compound **96** with an aromatic carbamate ligand and dicarbonate complex **100** were the least stable in the aqueous medium.

The highest activity and the ability to overcome the cisplatin resistance of A2780cisR ovarian cancer cells was found for triple-action prodrug **96** containing phenylbutyrate and 3-aminobenzoate, whereas the activity of compounds **97** and **98** was similar to that of cisplatin.

3.1.3.2. 4-Halophenylacetic acids

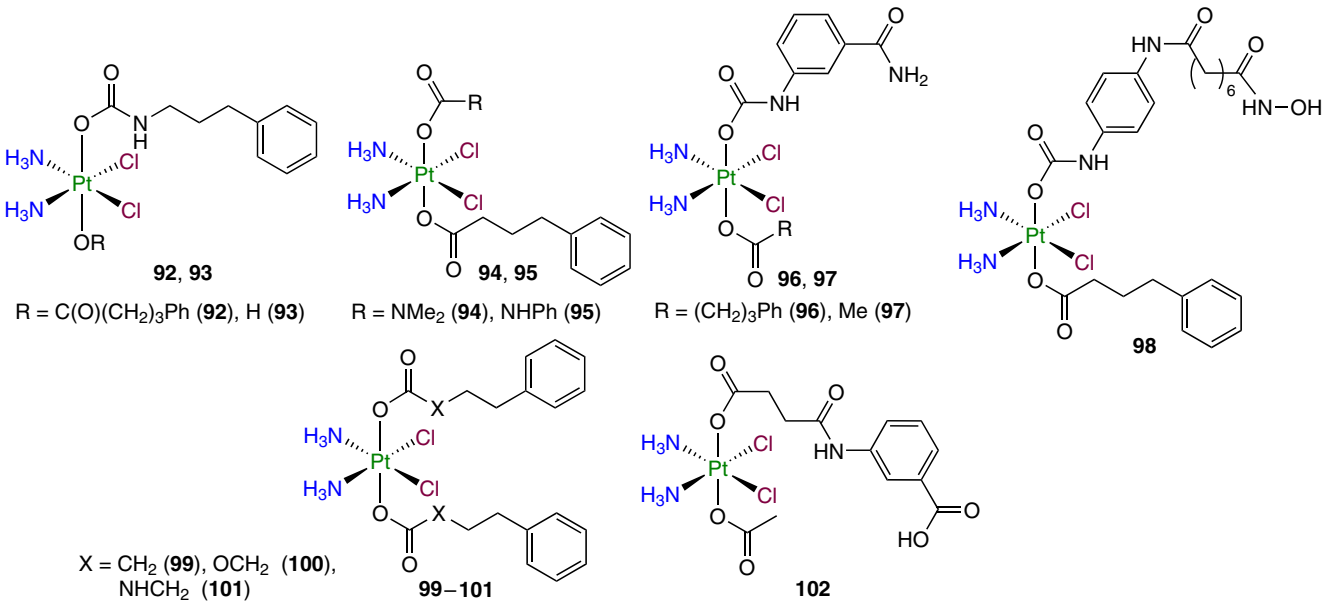
Non-classical Pt(II) complexes with the commercial codes PHENSS and 56MESS were used by Aputen *et al*.[124] to create Pt(IV) prodrugs **103**–**110** with 4-halophenylacetic acids.

Complexes **107**–**110** showed a substantially higher cytotoxicity than the series of compounds **103**–**106**, which correlates with a higher (by more than 10 times) cytotoxicity of 56MESS in comparison with PHENSS. For the most active prodrugs **107** and **109**, the GI_{50} values indicated 1.5- to 7-fold increase in the toxicity in comparison with that of the parent Pt(II) complex and reached a value of 0.7 nM for compound **107** against Du145 cell line. Complexes **108** and **110** proved to be significantly less active than the parent complex. Prodrugs **107** and **109** were also characterized by the highest ROS level in the cells, which was three times as high as that for the parent Pt(II) complex and twice as high as that for cisplatin.

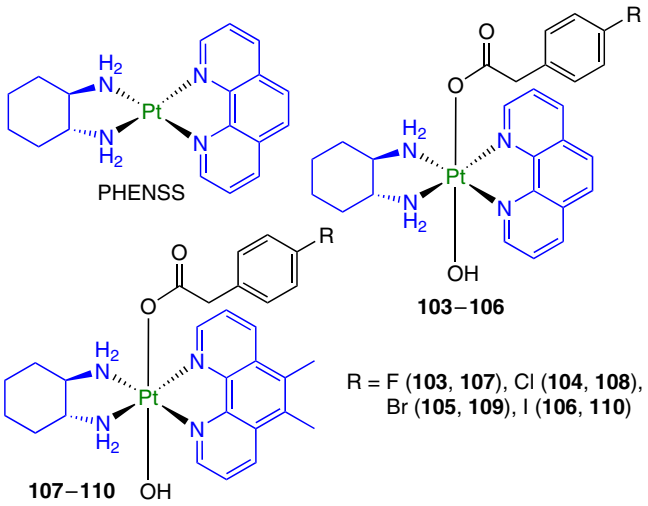
3.1.3.3. Lipoic acid

Lipoic [(*R*)-5-(1,2-dithiolan-3-yl)pentanoic] acid (LA) attracts attention as a compound capable of suppressing the anaerobic glycolysis of tumour cells.[125] This acid is synthesized in the

Structures 92–102



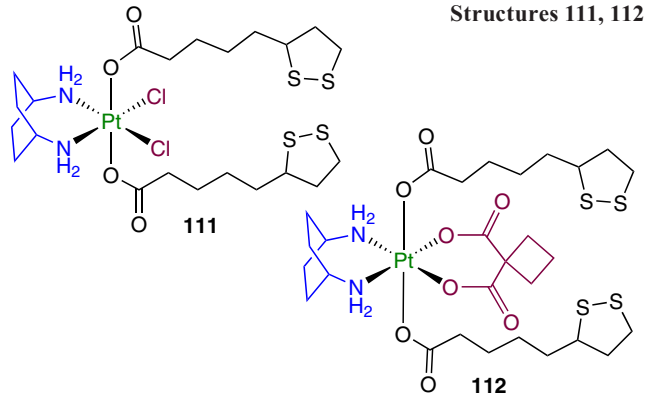
Structures PHENSS, 103–110



cellular mitochondria and has a low redox potential (E_0 = –0.29 V); therefore, it inhibits the formation of ROS.[126,127] In addition, LC induces apoptosis of head and neck squamous cell cancer (FaDu) cells.[128]

The biological activity of kiteplatin [$PtCl_2$(*cis*-1,4-diaminocyclohexane)] and its derivatives containing LA residues (**111**, **112**) was studied by Savino *et al.*[129]

Structures 111, 112



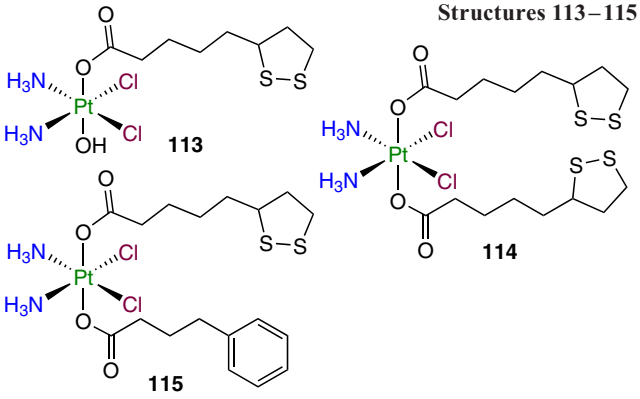
Complex **111** was active in the sub-micromolar concentration range down to IC_{50} = 0.1 μM against the cervical carcinoma cell line (A431). This value is 40 times lower than that for kiteplatin. In 3D spheroids of A431 cells, this prodrug was also the most active among the tested compounds (>3 times more active than kiteplatin).

Prodrugs based on cisplatin and LA (**113**–**115**) were reported by Liu *et al.*[130]

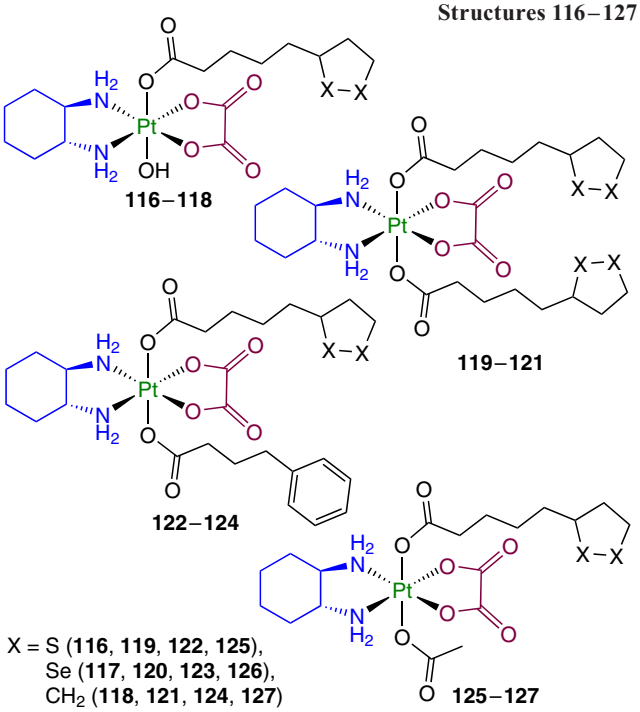
Coordination compounds **113** and **115** exhibited higher cytotoxic activity than cisplatin or an equimolar mixture of cisplatin and LA against a number of cell lines. It is worth noting that monocarboxylate complex **113** and unsymmetrical dicarboxylate **115** proved to be equally active against SW480 colorectal carcinoma cell line (IC_{50} = 0.74 and 0.70 μM, respectively). However, the former was 1.3 times more active against A549 cells, despite the presence of phenylbutyrate, a HDAC inhibitor, in the molecule of prodrug **115**. The ability to inhibit the formation of ROS in the cell was also demonstrated for both compounds.

A series of oxaliplatin derivatives **116**–**127** containing LA and its selenium and cyclopentane analogues was studied in a more recent work by Liu *et al.*[131]

Structures 113–115



Structures 116–127



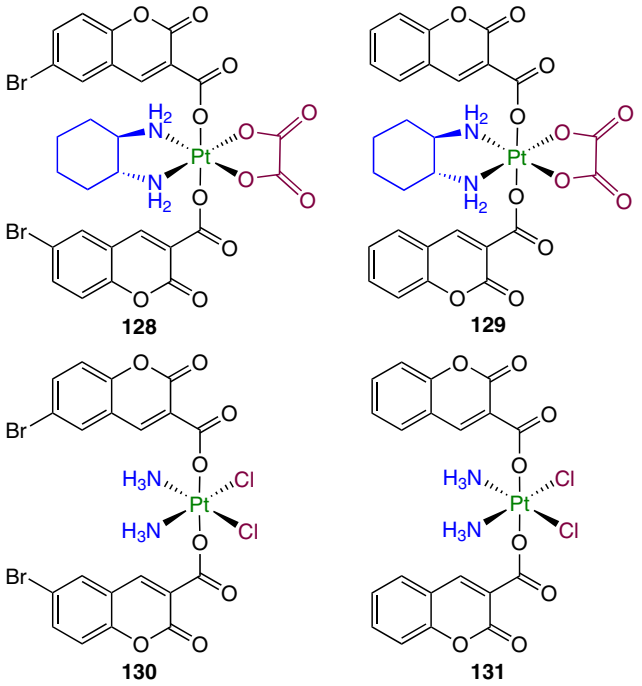
Similarly to cisplatin-based prodrugs, complex **121** proved to be stable in the presence of ascorbic acid for 72 h, unlike monocarboxylate complexes **116**–**118**. The highest cytotoxic activity was inherent in prodrugs with the lipoic acid cyclopetane analogue in the axial position. The lowest IC_{50} values were found for prodrug **124** with phenylbutyrate: down to 18 nM against CH1/PA-1 ovarian carcinoma cells and 190 nM against SW480 colorectal carcinoma cells. The cellular uptake was examined for a series of symmetrical complexes **119**–**121**; the highest platinum content was observed for compound **120**, although it had the lowest lipophilicity among the three prodrugs. A possible explanation to this fact is the involvement of the active transport in the cellular uptake of the compound. The ability of complexes **116**, **119**–**122** to inhibit the formation of ROS was assessed for SW480 cell line; a considerable increase in the ROS level was observed only when the concentration of the prodrugs was 50 times higher than IC_{50}.

3.1.3.4. Coumarin

Promising anticancer agents inhibiting tubulin polymerization and possessing activity against drug-resistant cancer cell lines were found among coumarin derivatives.[132] Ma *et al.*[133] investigated prodrugs **128**–**131** containing the residue of coumarin-3-carboxylic acid or its 6-bromo derivative.

In *in vitro* experiments, bromine-containing complexes **128** and **130** showed the highest antiproliferative activity, and oxaliplatin derivatives **128** and **129** proved to be more active than complexes **130** and **131** based on cisplatin. Oxaliplatin-based prodrug **128** provided the possibility of overcoming cisplatin resistance for A549cisR cell line; the resistance factor (RF) was 0.81.

Structures 128–131



Cellular uptake assays for complex **128** and A549 and A549cisR cancer cell lines revealed higher uptake in A549cisR cells compared to A549 cells, while in the case of Pt(II)-based agents, the A549cisR cell line was characterized by a lower uptake than cisplatin-sensitive A549.

Evaluation of the therapeutic efficacy of complex **128** *in vivo* indicates that the maximum therapeutic dose (MTD) and half-lethal dose (LD_{50}) are much higher for prodrug **128** than for cisplatin and oxaliplatin. In addition, the calculated therapeutic index (TI) (LD_{50}/IC_{50} ratio) of **128** was 1.6 times higher than TI of cisplatin or oxaliplatin, indicating a reduced toxicity of complex **128** in comparison with traditional Pt(II) drugs.

3.2. Platinum(IV) prodrugs with ligands overcoming cisplatin resistance

3.2.1. Fatty acids

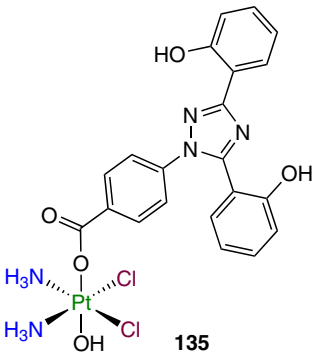
Resistance of tumour tissues to platinum-based drugs is a major problem of chemotherapy with cisplatin or its analogues; therefore, the search for approaches to overcome this drawback is an attractive strategy towards a better efficacy of platinum-based prodrugs.[134] Complexes **132**–**134** containing a long aliphatic chain mimicking a fatty acid residue were synthesized by Jayawardhana *et al.*[135] These agents tend to penetrate cancer cells by means of the CD36 receptor, which is overexpressed in cisplatin-resistant cell lines such as A2780cisR.

Prodrug **132** demonstrated the ability to overcome cisplatin resistance in A2780cisR cell line; RFs for the prodrug and cisplatin were 0.9 and 5.4, respectively. Compound **133** and **134** proved to be even more cytotoxic against A2780cisR cell line (IC_{50} = 0.24 and 0.31 μM); they were efficiently accumulated in mitochondria and decreased the mitochondrial membrane potential (MMP) of the A2780cisR cells.

3.2.2 Iron chelators

Cancer cells are more dependent on the content of iron ions than normal cells and also show increased iron uptake, accompanied by a decrease in its release.[136,137] In 2022, Pan *et al.*[138] developed Pt(IV)-based prodrug **135** containing a clinically used chelator of iron, deferasirox (DFX), possessing a high *in vitro* and *in vivo* activity against triple-negative breast cancer.

Structure 135

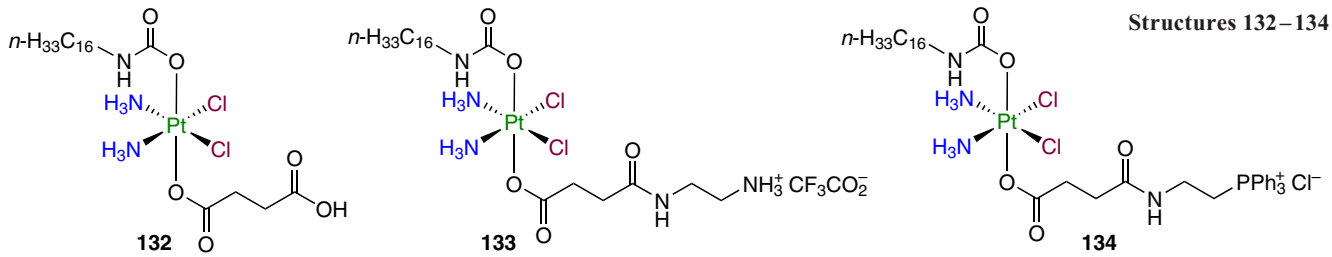


Antiproliferative activity assays showed a noticeable selectivity of compound **135** to the MDA-MB-231 cells over MCF-7 cell line or normal MCF-10A breast epithelial cells and a cytotoxic activity 43 times exceeding that of cisplatin. Studies of the cellular uptake and the ability to platinate DNA also confirmed the high activity of this complex compared to cisplatin. Despite the fact that, according to inductively coupled plasma mass spectrometry (ICP-MS) data, agent **135** did not cause a significant change in the iron content in the cell, its ability to reduce the level of the pool of chelatable iron in the cell was proved using the Phen Green dye.

The repair of DNA damages is an important mechanism for the cisplatin resistance of cancer cells. Prodrug **135** can reduce the efficiency of DNA repair in MDB-MA-231 cells and regulate the homeostasis of intracellular iron.

An *in vivo* study of xenograft mouse models of MDA-MB-231 tumours showed that the therapeutic efficacy of prodrug **135** was higher than that of cisplatin. At the end of the therapy, TGI was 77% for compound **135** and 41% for cisplatin; the general toxicity of the former was lower than that of cisplatin.

Structures 132–134

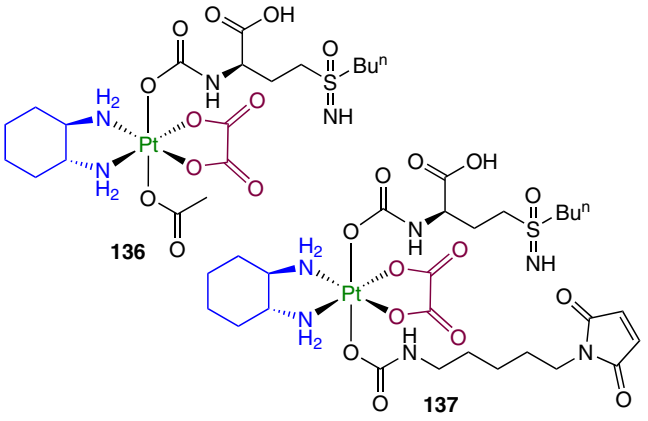


3.2.3. Glutathione S-transferase inhibitors

The inactivation of Pt(II) compounds with biologically active thiols such as glutathione and cysteine is considered to be one of the mechanisms of cancer cell resistance to platinum-based drugs.[139] The inactivation can occur both *via* the passive binding of platinum complexes to glutathione and *via* the chemical reaction catalyzed by enzymes, in particular glutathione S-transferase (GST).[140] GST inhibitors are promising axial ligands for Pt(IV) prodrugs, since agents of this type can overcome the cisplatin resistance of cancer cells.[54]

Oxaliplatin-based prodrugs **136** and **137**, containing L-buthionine-(*S*,*R*)-sulfoximine (BSO), an irreversible GST inhibitor, in the axial position and acetate or *N*-(maleimido-pentylcarbamate) in the second axial position, were synthesized and studied by Fronik *et al.*[79] The maleimide moiety in the blood binds to albumin; this increases the stability of the therapeutic agent in the bloodstream and the tumour uptake of the agent.[78,141]

Structures 136, 137



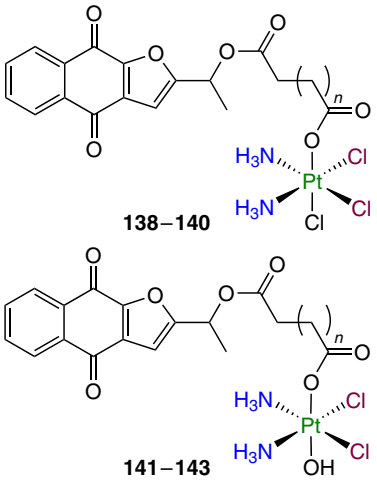
The cytotoxicity of complex **136** was assessed against HCT-116 and oxaliplatin-resistant HCT-116/oxR cell lines using oxaliplatin as the reference drug and against A2780 and A2780/cis cells in comparison with cisplatin. The cytotoxicity of prodrug **136** was found to be 10–50 times lower than the cytotoxicities of both Pt(II)-based drugs. However, RFs for this compound were 2.9 (HCT-116 cells) and 1.4 (A2780 cells) *vs.* 17.2 and 4.1 for oxaliplatin and cisplatin, respectively, for the same cell lines. Study of the cellular uptake of the agent by HCT-116 cells demonstrated that Pt(IV) prodrug **136** is accumulated in the cells five times less efficiently than oxaliplatin. It is noteworthy that the oxaliplatin uptake was two times lower in the drug-resistant HCT-116/OxR cells than in HCT-116 cells, whereas in the case of complex **136**, the platinum level was identical in both cell lines.

The antitumour efficacy of prodrugs **136** and **137** was studied *in vivo* against CT-26 tumour in BALB/c mice. Both oxaliplatin and the test compounds showed comparable antitumour efficacy and provided a considerable (twofold) decrease in the tumour size compared to the control group by the 40th day of the therapy.

3.2.4. Inhibitors of signal transducer and activator of transcription 3

Signal transducer and activator of transcription 3 (STAT3), which regulates multiple oncogenic processes and is an important regulator of normal and cancer stem cells (CSCs), is activated in various types of cancer. This protein often serves as a therapeutic target for the development of anticancer drugs.[142,143] The cancer stem cells, which initiate the tumour formation and metastasing, are also considered to be one of the major causes for drug resistance of tumour tissues.[144] Napabucasin (BBI608), acting as STAT3 inhibitor and inducing CSC death in various types of malignant growth, was approved for phase III clinical trials.[145] In 2022, Wang *et al.*[146] used a napabucasin derivative with the commercial code BBI608-OH as an axial ligand to prepare a series of prodrugs **138**–**143** based on cisplatin.

Structures 138–143



The cytotoxicity of these complexes was evaluated using a number of cell lines, including both cisplatin-sensitive and cisplatin-resistant ones (A549 and A549/CDDP). The cytotoxicity of prodrugs **138**–**140** and **141**–**143** increased with increasing length of the linker, with the highest activity being inherent in monocarboxylate complex **143** with an adipic acid linker ($n = 3$). Compounds **138**–**143** efficiently overcame cisplatin resistance in the A549/CDDP cells, with RF being in the 0.56–0.97 range.

Prodrugs **138**–**143** inhibited aldehyde dehydrogenase, the main marker of CSC; complex **143** was the most active, providing 36.31% inhibition. This compound also efficiently inhibited the CSC biomarkers, CD44 and CD133, and actively prevented the formation of A549/CDDP cell spheroids, which implies inhibition of CSC proliferation.

Complex **143** was more active in wound healing than cisplatin or napabucasin: the delay of healing was 50% relative to the control group of cells. In *in vivo* determination of the antitumour efficacy against A549/CDDP cells in BALB/c mice, the dose of 11.5 mg kg^{-1} (equivalent to 5 mg kg^{-1} of cisplatin in terms of Pt) induced 64.76% inhibition of the tumour growth, which was much higher than the percentage of inhibition in the group administered with cisplatin (12.77%). This indicates a high anticancer activity of complex **143** even against cisplatin-resistant tumours.

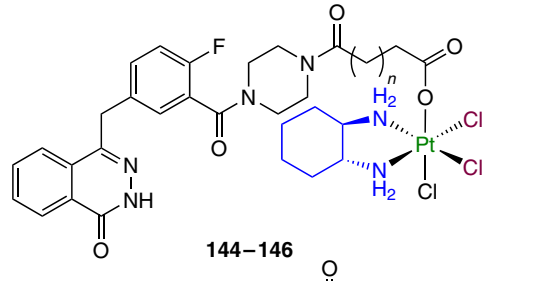
3.2.5. Poly(ADP-ribose) polymerase inhibitors

Olaparib is an anticancer drug that acts by inhibiting poly(ADP-ribose) polymerases (PARP-1, PARP-2 and PARP-3), that is, enzymes promoting the repair of DNA single-strand breaks. In the cancer therapy, olaparib is used in combination with cisplatin.[147]

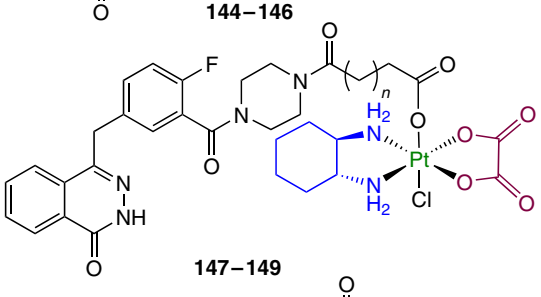
In 2023, Li *et al.*[148] developed Pt(IV) prodrugs **144**–**152** containing an olaparib moiety in the axial position. Antiproliferative activity assays revealed good inhibitory properties of complex **151** against PARP-1 and a cytotoxic activity against MDA-MB-231 cells (IC_{50} = 1.13 μM) exceeding that of cisplatin, in particular against the cisplatin-resistant MDA-MB-231/CDDP cell line (IC_{50} = 1.72 μM). Furthermore,

this compound showed high cellular uptake, the ability to inhibit DNA repair mechanisms and activate the mitochondria-mediated apoptosis. Determination of the therapeutic efficacy *in vivo* in MDA-MB-231/CDDP tumour xenografts in mice showed higher efficacy of prodrugs **151** compared to that of cisplatin (TGIs of 64.1 and 26.5%, respectively), along with lower general toxicity of the conjugate.

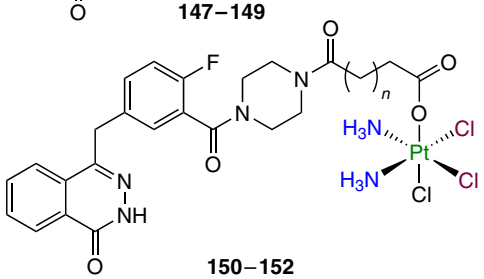
Structures 144–152



144–146



147–149



150–152

n = 1 (**144**, **147**, **150**), 3 (**145**, **148**, **151**), 5 (**146**, **149**, **152**)

3.2.6. P-Glycoprotein inhibitors

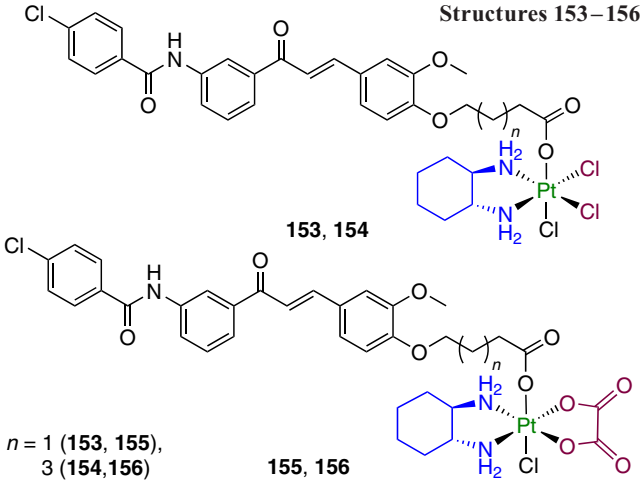
The membrane P-glycoprotein (Pgp) plays an important role in the drug pharmacokinetics. One of the mechanisms giving rise to chemotherapy resistance is the activation of Pgp, the action of which decreases the intracellular content of the drugs and, hence, reduces the therapeutic effect.[149] In 2021, Cao *et al.*[150] reported Pt(IV) prodrugs **153**–**156** with Pgp inhibitors as the axial ligands.

According to the results of antiproliferative activity assays, compound **156** was efficient against a cisplatin-resistant gastric cancer cell line (SGC-7901/CDDP; IC_{50} = 3.37 μM) and showed selectivity over HL-7702 normal liver cell line (the selectivity index was 6.9). Study of the mechanism of cytotoxic action demonstrated that this agent efficiently inhibits the expression of Pgp, induces the mitochondria-mediated apoptosis and arrests the cell cycle in the G2/M phase. Experiments *in vivo* showed efficacy of prodrug **156** for the therapy of cisplatin-resistant SGC-7901/CDDP tumour xenografts in mice, exceeding the efficacy of cisplatin or oxaliplatin (TGIs were 75.6, 25.9 and 43%, respectively).

3.3. Platinum(IV) prodrugs with non-steroidal anti-inflammatory drugs

Chronic inflammation is one of the markers of tumour tissues and a key factor in the development of the inflammatory

Structures 153–156



153, **154**

n = 1 (**153**, **155**), 3 (**154**,**156**)

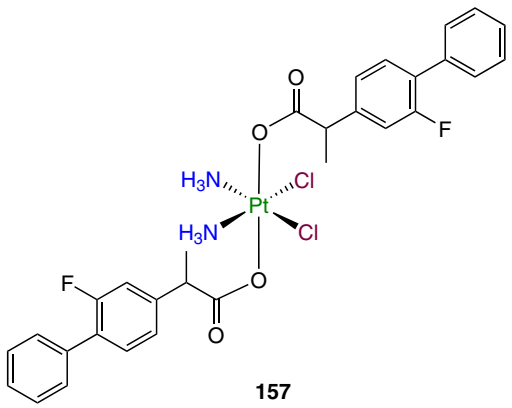
155, **156**

response. A key enzyme of prostaglandin synthesis required for the development of the inflammatory response, cyclooxygenase-2 (COX-2), is overexpressed in many tumours.[151,152] Prostaglandins promote tumour cell proliferation and evasion of detection by the immune system, while downregulation of COX-2 expression has an antiproliferative effect on cancer cells.[153] Therefore, NSAIDs attract attention of researchers who develop approaches to cancer therapy, in particular for the design of new platinum-based drugs.[43] Combinations of cisplatin with COX inhibitors enhance the drug activity and mitigate side effects.[62]

3.3.1. Flurbiprofen

Platinum(IV) complex **157** with two flurbiprofen moieties was obtained by Tan *et al.*[51] Prodrug **157** was found to be superior to cisplatin in cytotoxicity and to overcome the cisplatin resistance when tested on A549/CDDP cells. The RFs for A549 cell line were 0.92 and 2.7 for compound **157** and cisplatin, respectively. A study of the cellular uptake demonstrated that prodrug **157** is accumulated in the cells 20–50 times better than cisplatin, and the DNA platination level is 5–11 times higher for the prodrug than for cisplatin.

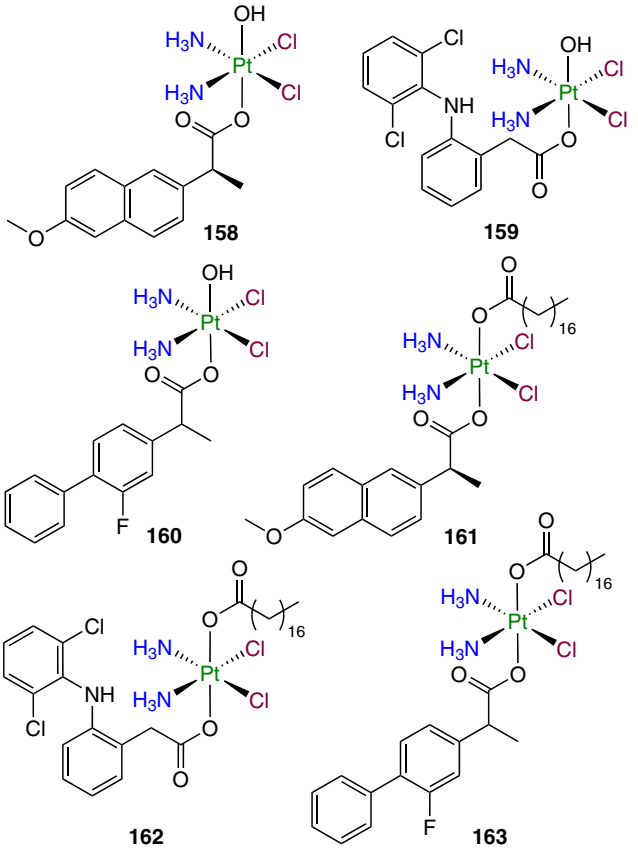
Structure 157



157

A series of Pt(IV) prodrugs **158**–**163** containing NSAIDs, naproxen, diclofenac and flurbiprofen, were prepared and investigated by Krasnovskaya and co-workers.[62] The authors showed that the cytotoxicity of compounds **158**–**163** depends on the lipophilicity: indeed, monocarboxylates **158**–**160** with retention factors ($\log k'$) of 2 to 4 were toxic in the nanomolar and submicromolar ranges of IC_{50}.

Structures 158–163



The highest activity, up to 153 times that of cisplatin, against MCF-7 cell line, was revealed for complex **160** with a flurbiprofen moiety. This compound also showed high activity against 3D cell cultures of MCF-7 cells (>30 times that of cisplatin). It was also established that prodrug **160** is an efficient agent for cisplatin delivery to the depth of MCF-7 cell spheroids. In addition, this compound efficiently delivered cisplatin deep into the EMT-6 mammary carcinoma tumour in BALB/c mice upon intravenous and intratumour injections.

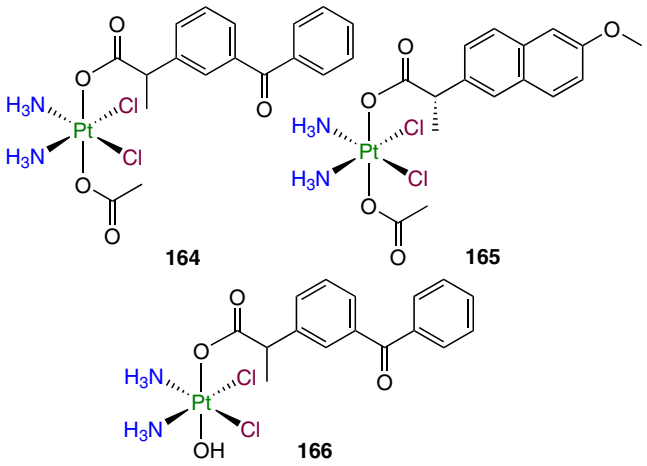
3.3.2. Ketoprofen

Cisplatin dicarboxylate derivatives **164** and **165** with COX inhibitors, ketoprofen and naproxen, as axials ligands were reported by Ravera *et al.*[53]

The lipophilicity of these prodrugs was investigated by high-performance liquid chromatography (HPLC) with determination of the retention factors, which directly correlated with the octanol–water partition coefficients.[154] The cytotoxicity was assessed against A549, HT-29 and HCT-116 cell lines expressing COX and against MSTO-211H (mesothelioma), SW480 and A2780 cells, which do not express COX. The IC_{50} values for prodrugs **164** and **165** exceeded IC_{50} for cisplatin by a factor of 20, and no unambiguous correlation between COX expression and cytotoxicity was established. Meanwhile, the cytotoxicity was found to be directly correlated with the lipophilicity of compounds: the most active compound **165** was the most lipophilic among the series of derivatives. Study of the cellular uptake of platinum complexes in A2780 cancer cells revealed the greatest uptake for the most lipophilic prodrugs **164** and **165**.

Ketoplatin **166**, a monocarboxylate ketoprofen and cisplatin derivative, was investigated by Ma *et al.*[155] Ketoplatin exhibited a cytotoxic activity 3–50 times exceeding that of cisplatin in a

Structures 164–166



low micromolar range. Unlike cisplatin or ketoprofen, ketoplatin (**166**) induced a pronounced DNA damage in MDA-MB-231 cells and inhibited the cell repair and motility.

In evaluation of the antitumour efficacy *in vivo*, compound **166** showed retardation of the MDA-MB-231 tumour growth in BALB/c mice similar to that of cisplatin; however, unlike cisplatin, in caused no weight loss of the animals.

A series of prodrugs **167**–**175** based on cisplatin, oxaliplatin and carboplatin, containing ketoprofen and loxoprofen, were synthesized and evaluated by Li *et al.*[156] Cisplatin-based prodrugs proved to be more cytotoxic than ketoprofen-containing compounds **167** and **166** or the loxoprofen-containing complexes **170** and **174**. In addition, dicarboxylates **167** and **170** were more active than monocarboxylate analogues **166** and **174**. Cisplatin derivatives **166, 167** and **170** were also able to overcome the cisplatin resistance of A549cisR cell line.

In determination of the antitumour efficacy *in vivo* against CT-26 colon cancer, the greatest TGI (57%) among cisplatin-based prodrugs (**166**, **167**, **170** and **174**) was found for complex **166**; furthermore, this complex was less toxic than cisplatin. In addition, this compound also showed a similar TGI (54.6%) in an *in vivo* experiment using 4T1 tumour.

Prodrug **166** exhibited antimetastatic effect and ability to damage DNA, which was accompanied by overexpression of γ-H2AX and p53 protein (DNA damage markers) and resulted in inhibition of PD-L1 (programmed cell death ligand).

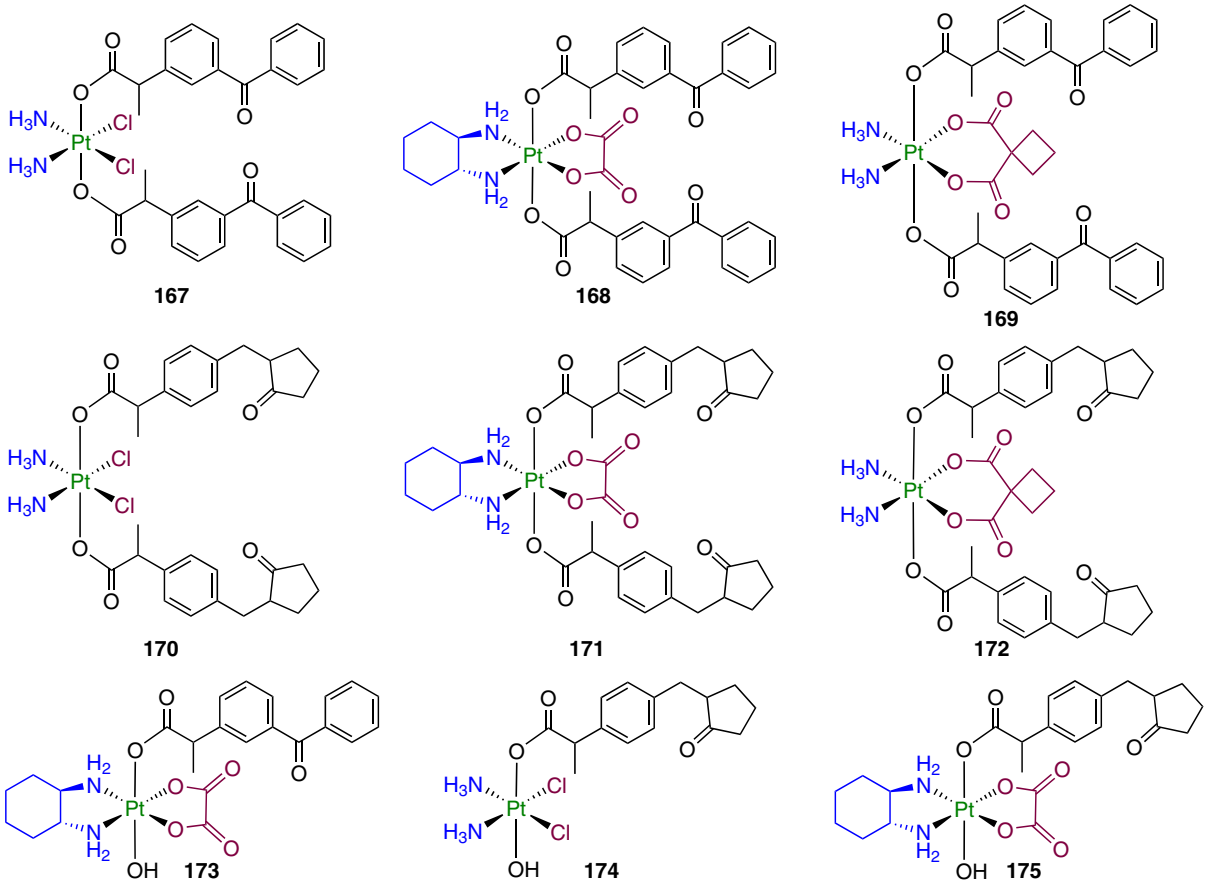
3.3.3. Naproxen

On the basis of cisplatin, oxaliplatin and carboplatin, Tolan *et al.*[157] synthesized and studied complexes **158** (for the structure, see above) and **176**–**180** containing naproxen as an axial ligand.

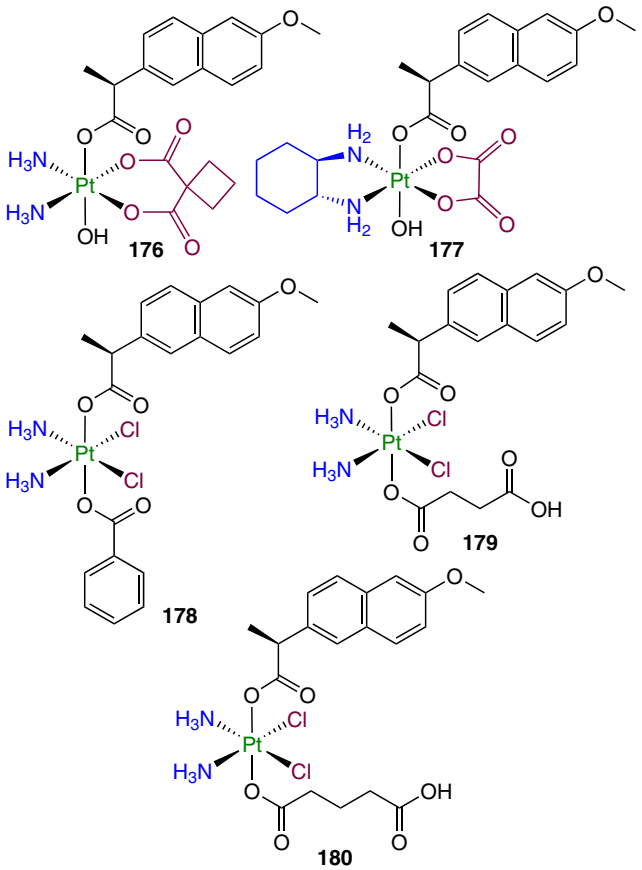
When tested against MCF-7 cells, Pt(IV) prodrugs **158** and **176**–**180** showed cytotoxicity 1.5–2 times as high as that of cisplatin, while in the case of MDA-MB-231 cells, they were 11–30 times more active than cisplatin. It is worth noting that the most lipophilic complex **178** showed the greatest cytotoxicity, as well as the ability to induce partial necrosis of MCF-7 tumour cells.

One more series of prodrugs based on cisplatin, oxaliplatin and carboplatin with naproxen **181**–**185** was reported by Chen *et al.*[158] The cytotoxic activity of these prodrugs was evaluated against a number of cell lines including cisplatin-sensitive and cisplatin-resistant cells (A549 and A549cisR, respectively). The highest antiproliferative activity was found for monocarboxylates

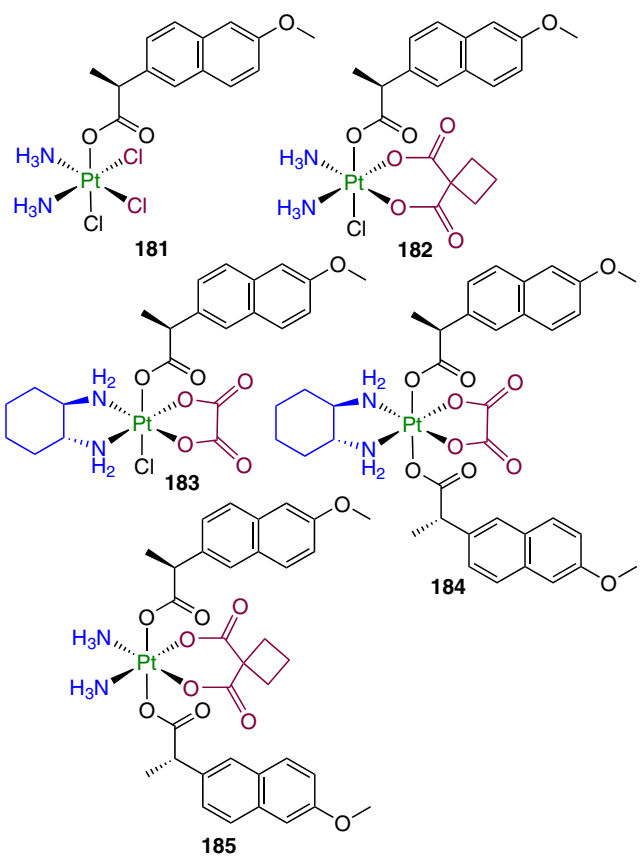
Structures 167–175



Structures 176–180



Structures 181–185



181 and **183** based on cisplatin and oxaliplatin, whereas oxaliplatin dicarboxylate **184** had the greatest selectivity to tumour cells over the normal L02 cells.

Matrix metallopeptidase 9 (MMP-9) is overexpressed in tumours, which is associated with tumour progression, metastasis and inflammation.[159] Complex **183** inhibited MMP-9 expression in CT-26 tumour of BALB/c mice; its inhibitory activity exceeded that of oxaliplatin (6.8 and 8.1%, respectively). According to the study of the antitumour efficacy *in vivo*, this complex suppressed the growth of the CT-26 tumour to an extent comparable with those of cisplatin and oxaliplatin: the tumour volumes were 317±119 mm^3, 390±162 mm^3 and 477±223 mm^3, respectively.

Platinum(IV) dicarboxylate prodrugs with biotin, naproxen and stearic acid as axial ligands (**158**, **186**–**189**) were reported by Krasnovskaya and co-workers.[70]

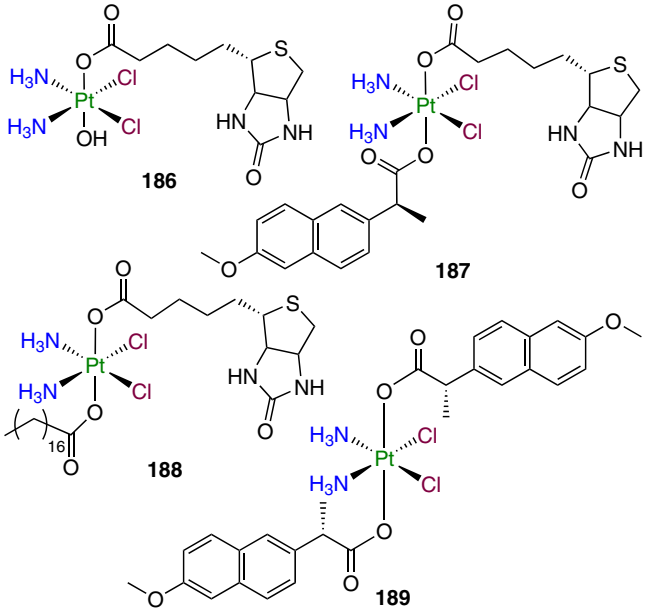
In the evaluation of the cytotoxic activity by MTT assay, naproxen-containing compound **187** showed antiproliferative activity comparable to that of cisplatin, while more lipophilic complex **188** containing stearic acid was active in the sub-micromolar and low micromolar concentration ranges (for A549 cells, IC_{50} was 0.87 μM). According to XANES investigation of the reduction of dicarboxylate **187** in an intracellular medium, this prodrug gradually releases the Pt(II) complex.

Cyclooxygenase-2 is not only a key enzyme in prostaglandin synthesis, but also a regulator of PD-L1 expression, which helps tumour cells to avoid detection by the immune system.[125] In order to combine the cytotoxicity and the ability to activate immune response of tumour tissues in the same antitumour agent, Jin *et al*.[58] synthesized prodrug **189**, along with complex **158**. When tested against MCF-7 and MDA-MB-231 cell lines and MDA-MB-435 melanoma cells, both compounds showed exceptionally high antiproliferative activity, exceeding the cisplatin activity by up to 187 times. After 24 h of incubation of MCF-7 cells with these agents, the platinum content in the cells treated with prodrugs **158** and **189** exceeded this value for cisplatin by factors of 65 and 11, respectively.

Compound **189** proved to inhibit the COX-2 and PD-L1 expression in MCF-7 tumour cells and interleukins IL-1β and IL-6 critical for the development of the inflammatory response. A study of the antitumour efficacy of prodrugs **189** *in vivo* in BALB/c mice bearing MDA-MB-231 tumour resulted in a substantial TGI (66 mm^3 *vs*. 926 mm^3 in the control) by the 15th day of the therapy with prodrug **189**, while for cisplatin the volume of the tumour was 660 mm^3.

In a XANES spectroscopy study of the intracellular reduction of prodrug **158** and **189**, monocarboxylate **158** proved to have low stability, while dicarboxylate **189** was more stable, which accounts for the marked *in vivo* efficacy of prodrug **189**.[160] Evaluation of the ability of complex **189** to deliver cisplatin to tumour cells with a platinized nanoelectrode also indicated higher efficacy of this agent in comparison with cisplatin.[161]

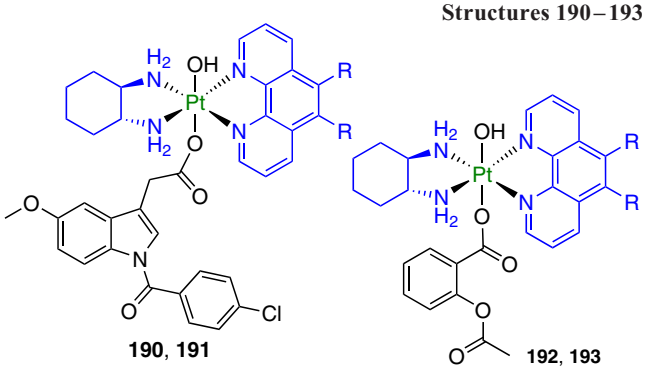
Structures 186–189



3.3.4. Indomethacin and aspirin

Indomethacin and aspirin derivatives **190**–**193** based on non-traditional Pt(II) complexes with commercial codes PHENSS and 56MESS were investigated by Khoury *et al*.[162]

Structures 190–193

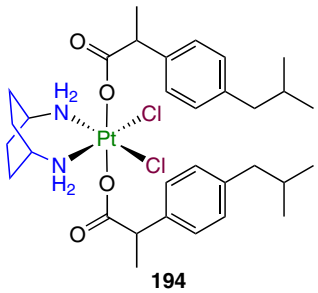


Prodrugs **191** and **193** derived from 56MESS showed the highest antiproliferative activity: the GI_{50} values were, on average, 20 times lower for these compounds than for their analogues **191** and **193** based on PHENSS. Complexes **192** and **193** did not show a significant inhibitory activity against COX-2, whereas the activity of indomethacin derivatives **190** and **191** was comparable with that of free indomethacin.

3.3.5. Ibuprofen

Curci *et al*.[50] prepared and investigated prodrug **194** based on kiteplatin containing an ibuprofen moiety in the axial position.

Structure 194



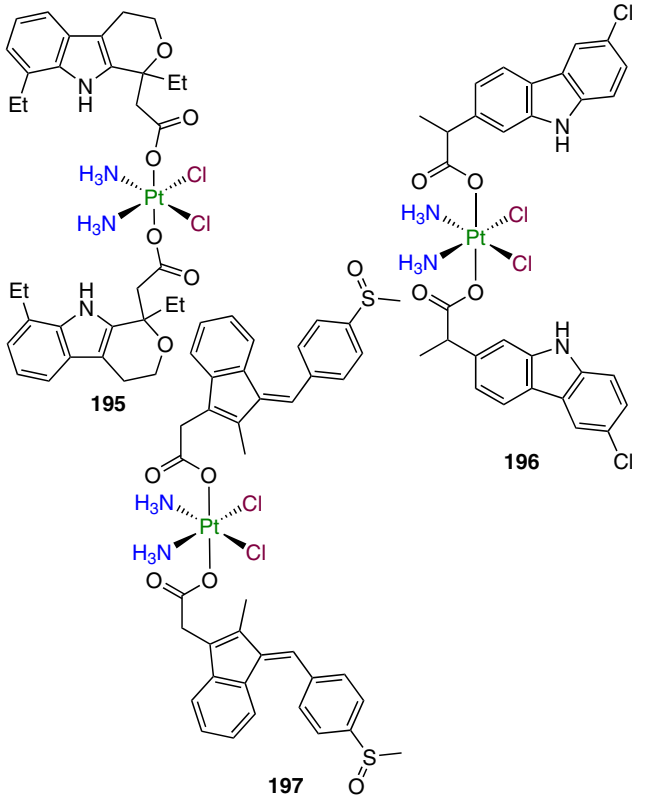
A study of the antiproliferative activity of complex **194** against HCT-115 and HCT-116 colorectal carcinoma cells resulted in sub-micromolar IC_{50} values, up to 42 times lower than the values for cisplatin and kiteplatin.

3.3.6. Etodolac, sulindac and carprofen

Three cisplatin complexes with NSAIDs containing etodolac, sulindac and carprofen (compounds **195**–**197**, respectively) were investigated by Song *et al*.[163]

The cytotoxicity of prodrugs **195**–**197** against MCF-7, A549 and HeLa cancer cell lines was higher than that of cisplatin; meanwhile, the activity of these complexes against normal MRC-5 cell line was lower than that for cisplatin. The highest cytotoxic activity against the cancer cells was inherent in complex **195**, which had an optimal lipophilicity (log $P = 0-3$).[164]

Structures 195–197



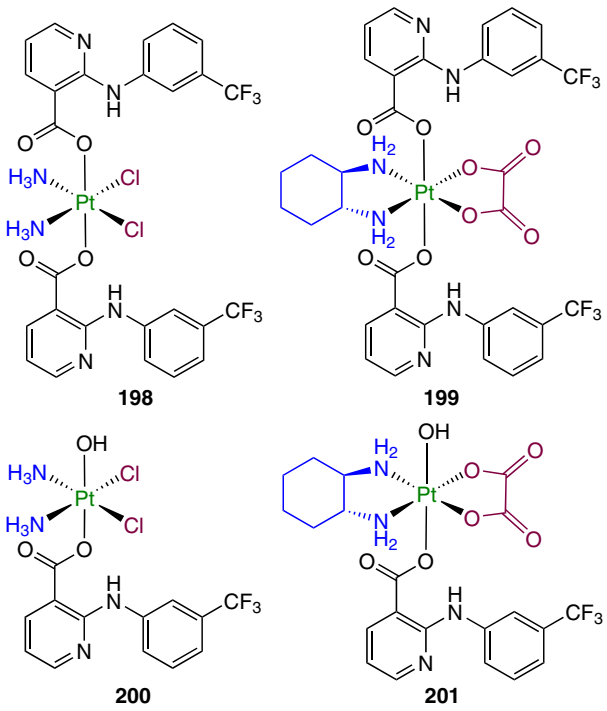
Lead compound **195** efficiently inhibited COX-2 and MDM-2 in MCF-7 cells; it also promoted upregulated the expression of pro-apoptotic Bax and p53 genes. In addition, this complex inhibited migration of MCF-7 cells. In experiments on determination of the antitumour efficacy *in vivo*, the suppression of growth of the MCF-7 tumour in BALB/c mice by complex **195** was comparable with that for cisplatin (tumour volumes were 457 and 570 mm^3, respectively). However, no decrease in the animal weight was observed in the group treated with agent **195**, unlike that for mice administered with cisplatin.

3.3.7. Niflumic acid

In 2023, Li *et al.*[165] developed Pt(IV) prodrugs **198**–**201** containing niflumic acid as an axial ligand. Niflumic acid can suppress tumour metastasing by inhibiting ERK 1/2 kinases and matrix metalloproteinases.[166]

Complexes **198** and **200** had a higher cytotoxic activity than cisplatin, oxaliplatin, carboplatin or satraplatin ([$PtCl_2(OAc)_2NH_3(NH_2C_6H_{11}$-*cyclo*)], code JM216) against SKOV-3, CT26 (mouse colon cancer) and 4T1 cell lines. Prodrug **198** accumulated in the cells 4.5 times more efficiently than cisplatin. Evaluation of the *in vivo* therapeutic efficacy in BALB/c mice bearing 4T1 breast cancer showed similar efficacy for compound **198** and cisplatin, along with less pronounced weight loss in the former case. Prodrug **198** was found to inhibit the COX-2 and MMP-9 enzymes and also ERK 1/2 and HIF-1α. Immunohistochemical analysis showed an increase in the

Structures 198–201



number of CD3+, CD4+ and CD8+ lymphocytes in tumour tissues after therapy with this agent.

3.3.8. Dichloroacetate in combination with cyclooxygenase inhibitors

A series of triple-action prodrugs **202**–**209** were investigated by Petruzella *et al.*[27]

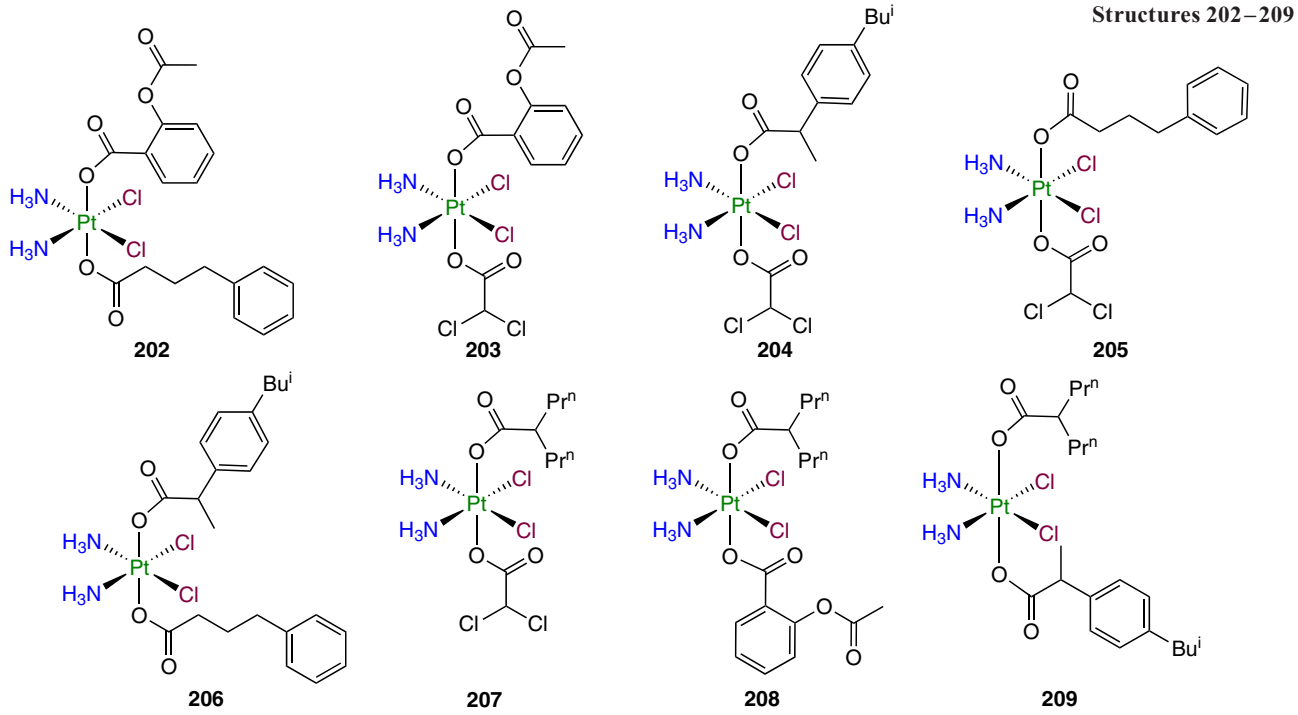
Aspirin and ibuprofen were chosen as COX inhibitors. Dichloroacetate is an efficient PDK inhibitor and also induces cell death by damaging mitochondria.[167,168] The PDK enzyme inhibits the pyruvate dehydrogenase complex, which is significant for chain respiration.[169] This complex does not function in tumour cells; therefore, the intrinsic cellular metabolism changes, and glycolysis takes place instead of glycose oxidation (Warburg effect).[170] The inhibition of PDK stops this process, which results in the death of tumour cells. Phenylbutyrate and valproic acid were chosen as HDAC inhibitors.[168,171] The inhibition of HDAC causes chromatin decondensation, which makes DNA more sensitive towards platination.[172]

Eight prodrugs were found to be much more active than cisplatin. The average IC_{50} values for prodrugs **202**–**209** tested on thyroid cancer (BCPAP) and pancreatic cancer (PSN-1) cells were 51 and 71 times lower than those for cisplatin. The cytotoxicity of the compounds was also assessed against the 3D spheroids of PSN-1 pancreatic cancer cells. Complexes **205**, **208** and **209** were 50 times more active than cisplatin. Study of the mechanism of cytotoxic action revealed no correlation between the inhibitory activity of axial ligands and the cytotoxicity, or between the ability of these complexes to alkylate DNA of PSN-1 cells and the cytotoxicity, which may indicate a possible synergistic effect between the ligand and the Pt(II) atom.

3.3.9. Combination of estramustine with histone acetylase and cyclooxygenase

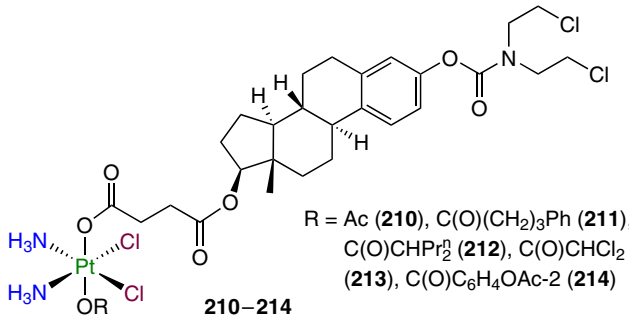
Karmakar *et al.*[63] developed prodrugs **210**–**214**, the molecules of which contained, in addition to platinum(IV), a residue of

Structures 202–209



estramustine (a steroidal anticancer drug) and various carboxylate ligands such as acetate and HDAC, PDK and COX-2 inhibitors: phenylbutyrate, dichloroacetate, valproate and *o*-acetylsalicylate.

Structures 210–214



According to cytotoxicity assays, prodrugs **211**, **212** and **214** were 50–145 times more active than cisplatin, with the IC_{50} values against a prostate carcinoma cell line (LNCaP) being 31, 49 and 90 nM, respectively. Furthermore, all prodrugs were 13–50 times less active against normal MRC-5 cells. Compound **212**, which was most cytotoxic against LNCaP cells, had the highest selectivity index (50) over the normal MRC-5 cell line, which was due to the effect of estramustine.

The cellular uptake of the prodrugs in LNCaP cells correlated with the cytotoxicity: compound **212** penetrated tumour cells 64 times better than cisplatin; however, the platinum level in DNA after incubation with this prodrug proved to be only 12 times higher than that for cisplatin, which indicates that other factors also make a contribution to the cytotoxicity. For the most cytotoxic prodrugs **211** and **212**, no biological effect of estramustine was observed; however, an effect caused by the inhibitory activity of valproate and phenylbutyrate against HDAC was manifested.

3.4. Platinum(IV) prodrugs with immunomodulating axial ligands

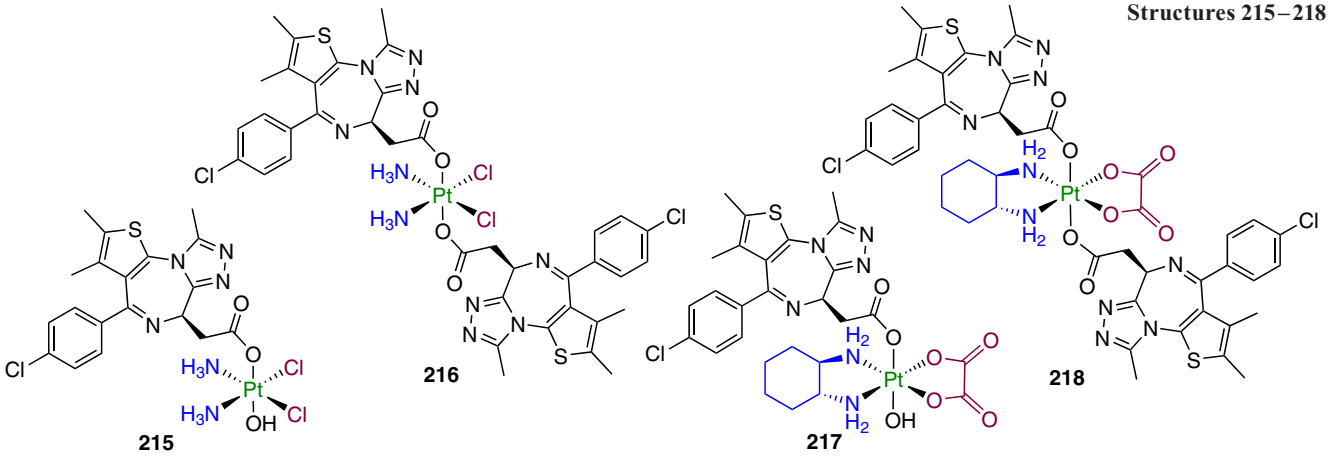
Combination of immunotherapy with chemotherapy is a widely used clinical protocol for the treatment of cancer. For example, first-line therapy for patients with non-small cell lung cancer includes the combination of cisplatin and pembrolizumab.[173,174] In view of the synergism of cisplatin with immune response checkpoint inhibitors, the development of Pt(IV) prodrugs with ligands that stimulate the immune response should be of obvious interest of researchers.[175]

3.4.1. Inhibitors of bromodomain-containing protein 4

The programmed cell death ligand PD-L1 is a transmembrane protein interacting with the PD-1 receptor. Upon the specific binding to the PD-1 receptor on cytotoxic lymphocytes, this ligand blocks their cytotoxic activity, thus enabling the tumour to evade the immune response. The heteroannulated benzodiazepine with the code JQ1 is an inhibitor of bromodomain-containing protein 4 (BRD4), which stimulates transcription of the CD274 gene encoding the PD-L1 protein.[176] Overexpression of the PD-L1 ligand may also lead to development of cisplatin resistance or radiation therapy resistance of the cell.[177,178]

In 2023, Fan *et al.*[179] synthesized Pt(IV) complexes **215**–**218** with a JQ1 moiety in the axial position. While studying the cytotoxicity, the authors demonstrated high efficacy of prodrugs **216**: IC_{50} = 0.89 μM against a melanoma cell line (B16F10), which is 40.66 times better than that of cisplatin. This compound was found to induce cell apoptosis, decrease MMP and cause DNA damage. In addition, the parent JQ1 ligand and complex **216** considerably inhibited the expression of the BRD4 and PD-L1 proteins in cells. Experiments *in vivo* using mouse model of B16F10 melanoma revealed a significant therapeutic effect of prodrug **216**, which exceeded the action of cisplatin or the JQ1 + cisplatin equimolar mixture and caused a less pronounced weight loss of the animals. A synergistic effect of the therapy with agent **216** and the immunotherapy with anti-PD-1 monoclonal antibodies was also detected. Immunohistochemical

Structures 215–218



analysis of the tumour after treatment with compound **216** showed an increased infiltration of the tumour with the CD8+ T-cells; this provides evidence for the action of this prodrug through activation of the immune response.

3.4.2. Melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine) is an indoleamine hormone synthesized from serotonin by the pinealocytes of the pineal gland. This hormone has an antitumour activity against breast cancer and can also affect the estrogen synthesis.[180,181] In addition, melatonin has immunomodulating properties and affects the expression of CD4+ and CD25+ lymphocytes in the tumour microenvironment.[182]

In 2020, Song *et al.*[183] proposed cisplatin-based prodrugs **219**–**222** in which platinum(IV) atom is connected to one or two melatonin residues through various linkers in the axial positions.

Compound **219** surpassed cisplatin in efficacy by a factor of 100 (IC_{50} = 0.06 μM) when tested against ER(+) MCF-7 cells; the toxicity against ER(–) MDA-MB-231 cells was only 0.36 μM. Prodrugs **219** and **220** also showed a high cellular uptake, which exceeded the uptake of cisplatin by 76 and 27 times, respectively. In addition, complex **219** stimulated the expression of the γH2AX and p53 proteins, arrested the cell cycle in the S-phase and triggered apoptosis.

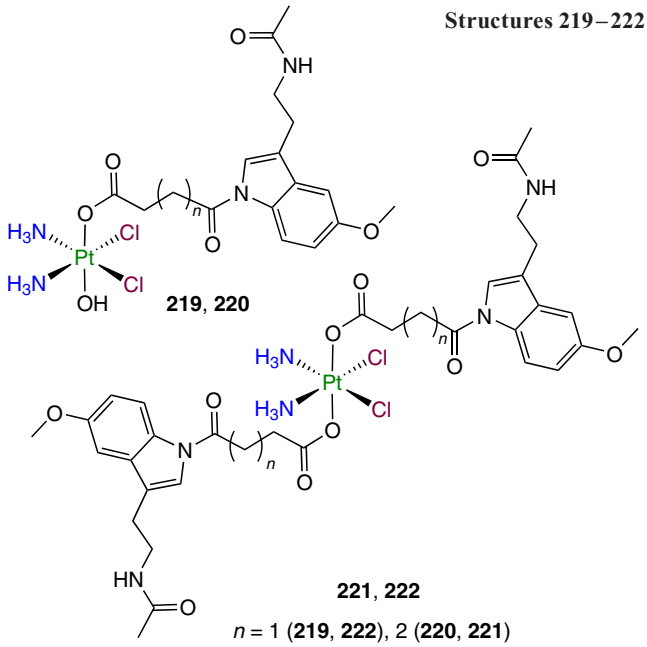
Study of the therapeutic efficacy *in vivo* against MCF-7 tumour xenografts in BALB/c mice showed similar efficacy of prodrug **219** and cisplatin, with lower weight loss of animals in the former case. A higher platinum accumulation in spleen was found for mice treated with cisplatin. Lymphocyte proliferation in spleen was found for the groups of mice administered with melatonin and compound **219**. Thus, prodrug **219** acts through immunomodulation and improves the overall survival rate of individuals with ER(+) breast cancer.

3.4.3. 1-Methyl-D-tryptophan

One of the mechanisms by which malignant cells can evade the immune response is the expression of indoleamine-2,3-dioxygenase (IDO1), which catabolizes the conversion of tryptophan to kynurenine suppressing the T-cell immunity. 1-Methyltryptophan is an indoleamine-2,3-dioxygenase inhibitor, with a higher immunogenic anticancer activity *in vivo* being inherent in the D-isomer.[184,185]

In 2021, Fronik *et al.*[186] investigated triple-action Pt(IV) prodrugs **223**–**226**, which contained 1-methyl-D-tryptophan and succinimide in the axial positions. These compounds were

Structures 219–222



compared with oxaliplatin dicarboxylates **227**–**229**. The same publication describes complexes **230**–**233**, which are analogues of compounds **223**–**226** containing a maleimide moiety to enhance binding of the agent to albumin.

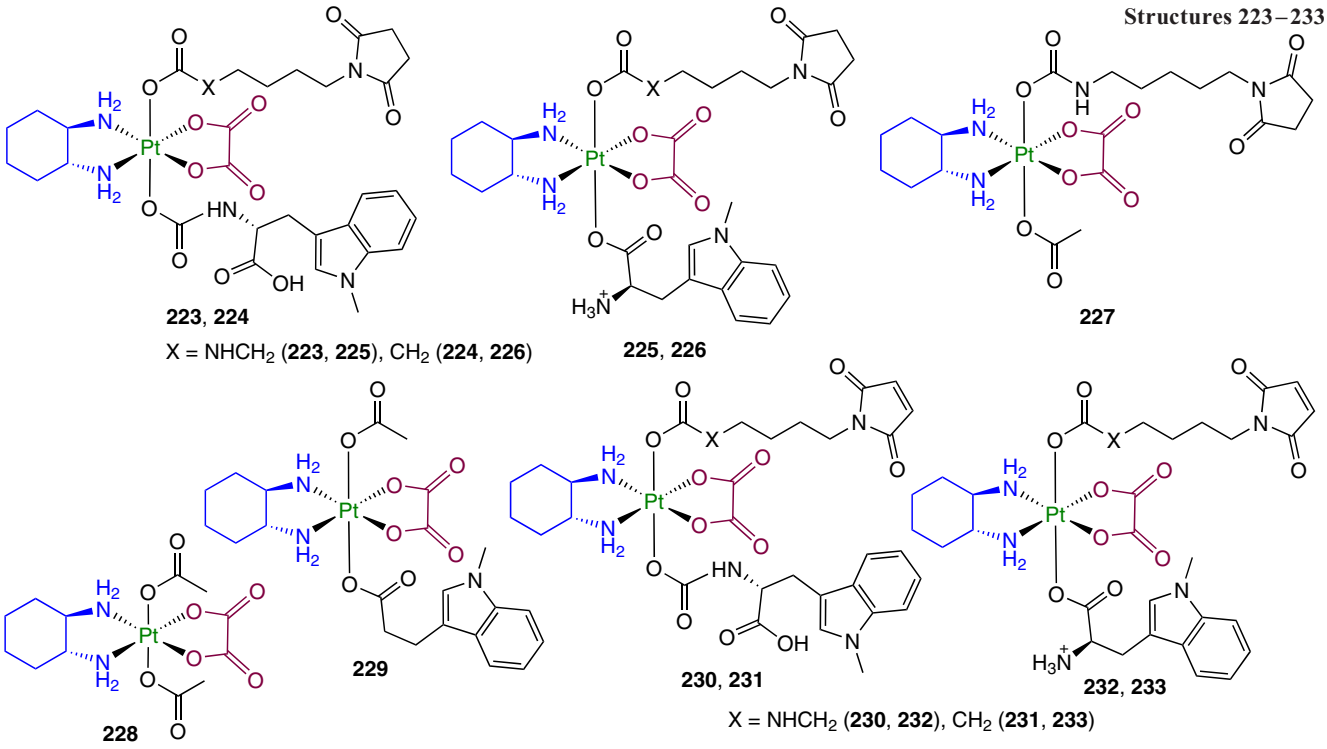
The ability of prodrugs **223**–**229** to inhibit IDO1 was proved by analyzing cell lysates after incubation with the test compounds. Compounds **225** and **226**, which are rapidly reduced, provide a more pronounced inhibition of this enzyme than complexes **223** and **224**, which are reduced slowly.

Study of the therapeutic efficacy against CT26 colon cancer allografts in mice demonstrated that prodrug **230** surpassed the oxaliplatin in both the inhibition of the tumour growth and the survival rate of mice. Flow cytometry data for the immune cells isolated from the tumour tissue and from tumour-draining lymph nodes after administration of compound **231** demonstrated a significant shift in the ratio of CD4+ (immunosuppressive) and CD8+ (immunostimulatory) T cells.

3.5. Platinum(IV) prodrugs with ligands promoting increase in the selectivity

A crucial drawback of the therapy with Pt(II)-based anticancer agents is that the lack of selectivity of cisplatin or its analogues over normal tissues, which accounts for severed side effects.[187]

Structures 223–233

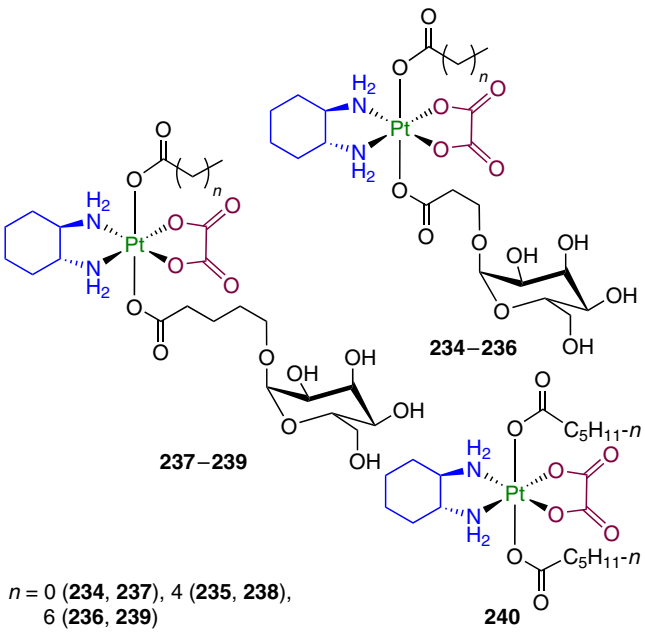


Below we consider Pt(IV) prodrugs in which axial ligands promote higher uptake of the agents mainly in the tumours cells.

3.5.1. Carbohydrates

It was shown previously that Pt(II) conjugates with carbohydrates possess good selectivity to cells that overexpress glucose transporters (GLUT), which makes carbohydrates promising axial ligands for Pt(IV) prodrugs.[188,189] GLUT receptors are overexpressed in many tumours, including lung, breast and liver carcinomas; therefore, this group of transporter proteins are considered to be an optimal target for a Pt(IV) prodrug vector moiety.[190]

Structures 234–240



Wang *et al.*[25] investigated a series of oxaliplatin-based prodrugs **234**–**239** with glucose derivatives in the axial position.

The antiproliferative activity of these compounds against HeLa, HepG2, MCF-7 and A549 cancer cell lines and cisplatin-resistant A549cisR cell line exceeded the oxaliplatin activity by 1.5–3 times. All prodrugs were able to overcome the cisplatin resistance of the A549cisR cell line.

The selectivity of the agents was evaluated for HepG2 cancer cells over the normal liver cells (L02). The oxaliplatin toxicity against L02 cells was somewhat higher than that against HepG2 (IC_{50} was 8.34 and 10.90 μM). Prodrugs **234**–**239** had a lower cytotoxicity against L02 cells, with the highest selectivity factor (24.10) being observed for complex **238**.

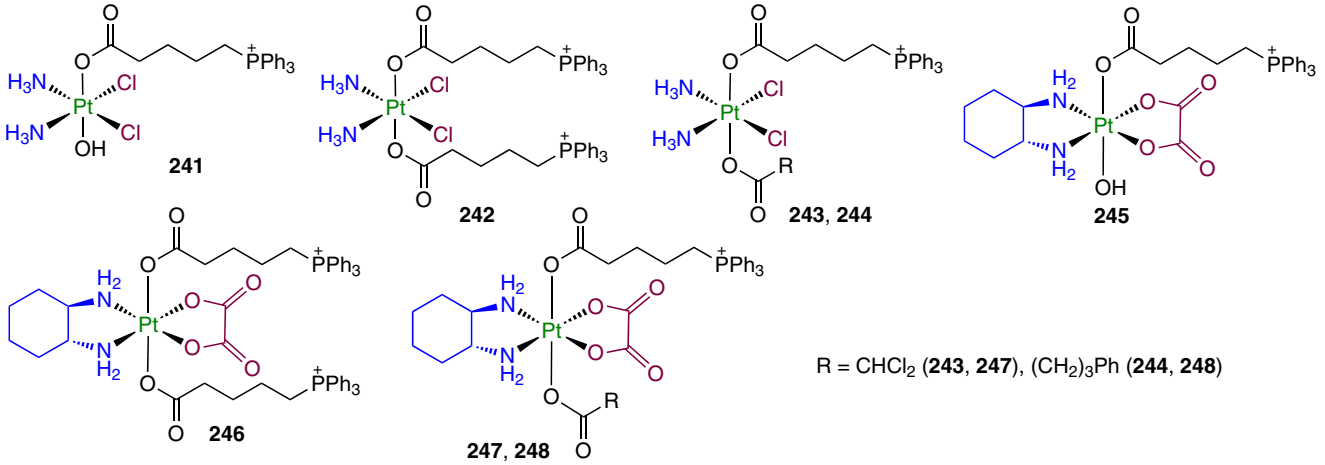
Prodrugs containing axial ligands based on carbohydrates entered MCF-7 cells 1.7–3 times more efficiently than model complex **240** and 10 times more efficiently than cisplatin. The cellular uptake of the prodrugs varied in the order **237** > **238** > **239**, *i.e.*, it increased with increasing carboxylic acid chain length in the axial position. The level of DNA platination with prodrugs **234**–**239**, oxaliplatin and cisplatin correlated with the cellular uptake level.

3.5.2. Triphenylphosphine

Mitochondria are critical organelles of cells, as they produce most of the energy; therefore, the search for compounds affecting mitochondria is a promising task.[191] Triphenylphosphonium, being a delocalized lipophilic cation, efficiently penetrates the lipid membranes and can be accumulated in mitochondrial cells with excess negative charge.[192] A series of cisplatin-based prodrugs (**241**–**244**) and oxaliplatin-based prodrugs (**245**–**248**) containing an alkyltriphenylphosphonium moiety in the axial position were synthesized by Babak *et al.*[66] In all compounds, the formate anion ($HCOO^-$) served as the counter-ion.

As the second axial ligand, the authors used a hydroxyl group, one more alkyltriphenylphosphonium moiety, and

Structures 241 – 248



dichloroacetate or phenylbutyrate. The cytotoxicity of compounds **241** – **248** was assessed against A2780 cell line and MOR lung adenocarcinoma cell line and against their cisplatin-resistant analogues (A2780cisR and MORcisR). The activity of prodrugs **241**, **242**, **245** and **246** turned out to be lower compared to the parent Pt(II) complexes. The highest activity was inherent in complexes **244** and **248** containing phenylbutyrate as the second axial ligand; the same compounds were the least effective in overcoming the cisplatin resistance. The cellular uptake of the prodrugs correlated with the antiproliferative activity. Most of platinum in A2780 cells was accumulated in mitochondria, while the most clear-cut targeting effect was observed for compounds **243**, **244** and **247**, **248**. Further investigation of the ability of complexes to induce mitochondrial depolarization showed the highest efficiency for prodrugs **243**, **244**, **247** and **248**, which also markedly inhibited the mitochondrial respiratory function.

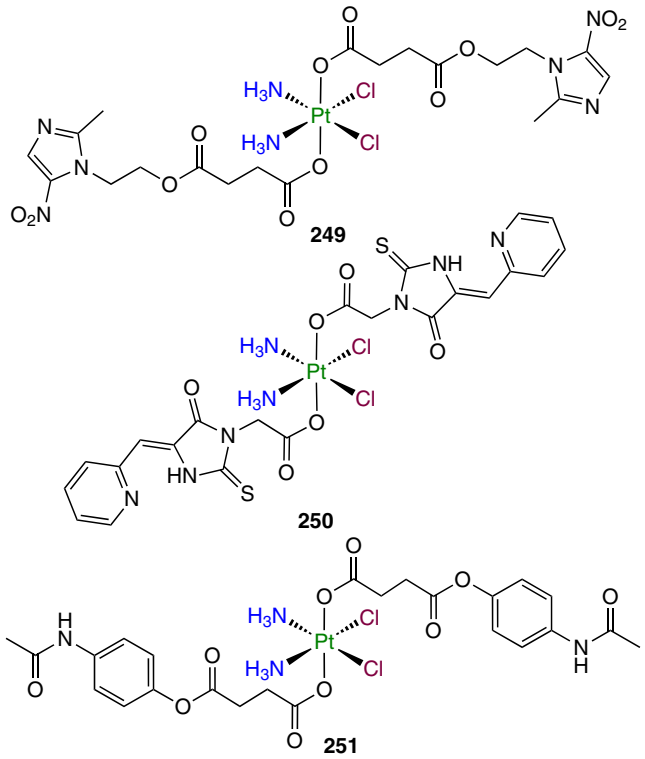
The *in vivo* experiments performed in BALB/c mice with CT-26 adenocarcinoma tumour model identified a high therapeutic efficacy of agent **243**. Indeed, by the 32nm day of the therapy, the tumour size in the group administered with prodrug **243** was five times smaller than that in the group treated with cisplatin and eight times smaller than that in the control group. To increase the bioavailability, the liposomal form of agent **243** was obtained. After 32 days of the therapy at a dose of 1.95 mg kg^{-1} of platinum, complete remission of the disease was observed in the group of animals treated with the liposomal form of **243**.

3.5.3. Metronidazole

Hypoxia is one of the markers of solid tumours, being important for tumour growth, angiogenesis and metastasis.[193] Metronidazole is a drug widely used for the treatment of anaerobic infections; it is also able to inhibit aldehyde dehydrogenase, one of the markers of hypoxia.[194] Platinum(IV) prodrug **249** containing metronidazole in the axial position was described by Krasnovskaya *et al.*[60]

For comparison, platinum(IV) complexes with 2-thioimidazol-4-one (**250**) and paracetamol (**251**) were prepared. Complex **249** was similar to cisplatin when tested for the antiproliferative activity against a monolayer of cancer cells; however, in the case of spheroids of MCF-7 cancer cells, it showed an antiproliferative activity exceeding that of cisplatin by more than 31 times.

Structures 249 – 251



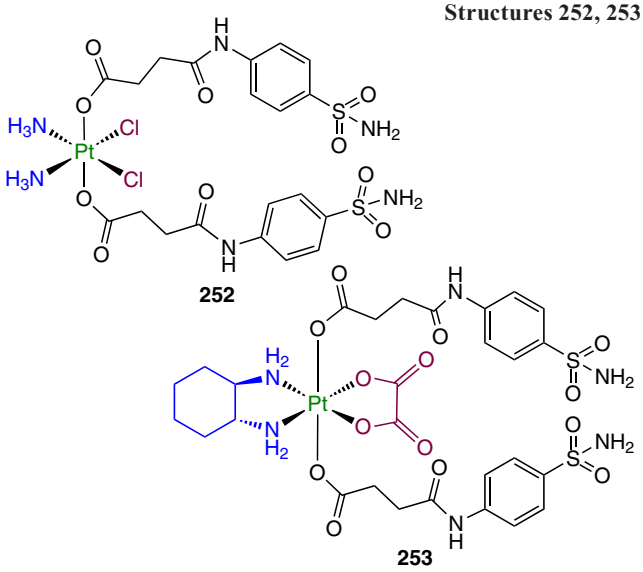
Determination of the intracellular reduction rate by XANES spectroscopy demonstrated that prodrug **249** gradually released the Pt(II) complex. After 26 h of incubation of A549 cells in the presence of complex **249**, less than 60% of the starting compound was reduced. Study of the cisplatin distribution profile in MCF-7 spheroids preincubated with compound **249** using a nanoelectrode demonstrated that this complex can deliver cisplatin to the hypoxic area inside the tumour spheroid.

3.5.4. Hypoxia-sensitive agents

Carbonic anhydrases (CAIX) are transmembrane proteins that catalyze the conversion of CO_2 to bicarbonate and a proton.[195] These enzymes are overexpressed in many tumour tissues and acidify them.[196,197]

Cao *et al.*[195] used CAIX inhibitors in both axial positions to obtain prodrugs based on cisplatin and oxaliplatin (**252** and **253**).

Structures 252, 253



252

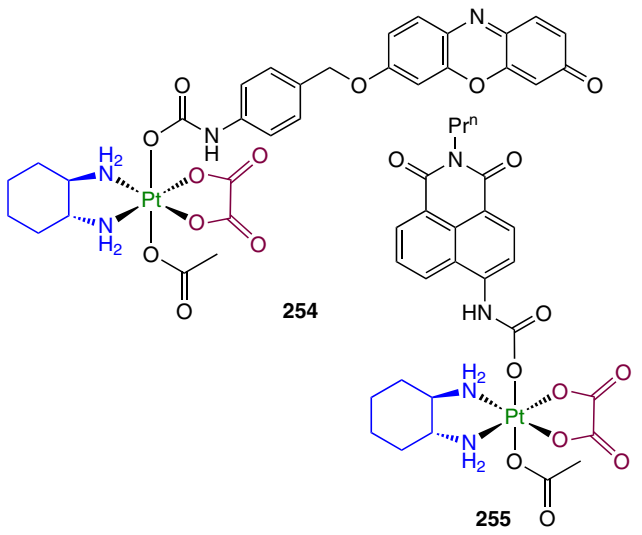
253

Under normoxic conditions, complexes **252** and **253** exhibited enhanced cytotoxicity against MDA-MB-231, HeLa and HepG2 malignant cells compared to normal cells–L02, HLF (human lung fibroblasts) and MCF-10A. The selectivity indices for MDA-MB-231 cells over MCF-1A cells under normoxia were 8.5 and >7.3 for compounds **252** and **253**, respectively. Under hypoxic conditions, the cytotoxicity of both prodrugs against cancer cells increased 3–9-fold and, hence, the selectivity index increased up to 80 and 34.5, respectively. The observed selectivity is attributable to a 10 times lower platinum accumulation in normal MCF-10A cells than in MDA-MB-231 hypoxic cancer cells.

When MDA-MB-231 cells were incubated with a CAIX inhibitor (compound encoded SLC-0111), the cellular uptake of the agents decreased; this is evidence for the contribution of active transport to the transfer of prodrugs **252** and **253** into the cells. In addition, it was shown that the oxygen content and pH of the MDA-MB-231 hypoxic cells increased after the cells had been incubated with these compounds.

The *in vivo* antitumour efficacy of the compounds was studied for the MDA-MB-231 tumour in BALB/c mice. After 24 days of the therapy with cisplatin, oxaliplatin and compounds **252** and **253** in 5 mg kg^{-1} dose, the tumour growth inhibition was 57 and 65% for prodrugs **252** and **253**, respectively, and only 32–43% for cisplatin and oxaliplatin.

Structures 254, 255



254

255

An alternative approach to the development of hypoxia-sensitive prodrugs was described by Boulet *et al.*[198] As the axial ligands in the platinum(IV) complexes **254** and **255** obtained in this study, the authors used known fluorophores.

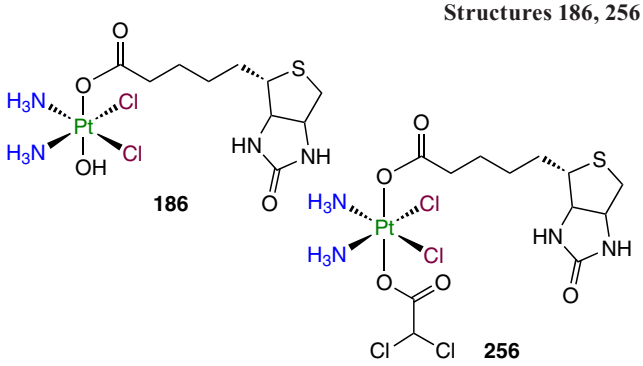
The reduction of prodrugs **254** and **255** accompanied by the release of axial ligands was monitored by dose-dependent increase in the fluorescence in the presence of sodium ascorbate. Oxygen-dependent reduction of the prodrugs and an increase in their cytotoxicity under hypoxic conditions were found. Thus, agents **254** and **255** are hypoxia markers possessing increased cytotoxicity in tumour tissues.

3.5.5. Combination of biotin with dichloroacetate

Jin *et al.*[64] used a biotin moiety and its combination with dichloroacetate as axial ligands for cisplatin and thus obtained prodrugs **186** and **256**.

The cytotoxicity of prodrugs **186** and **256** was assessed against HeLa and HepG2 cell lines expressing biotin receptors and against HCT-116 cells in which there is no expression of biotin receptors. Compound **256** was selective to biotin-(+) cell lines (IC_{50} < 2 μM) but proved to be less toxic against the cells without expression of biotin receptors (IC_{50} > 18 μM). This complex also inhibited PDK, altered MMP of HeLa cells and induced mitochondria-mediated apoptosis, as evidenced by increased expression of cytochrome C, a marker of apoptosis in mitochondria.

Structures 186, 256



186

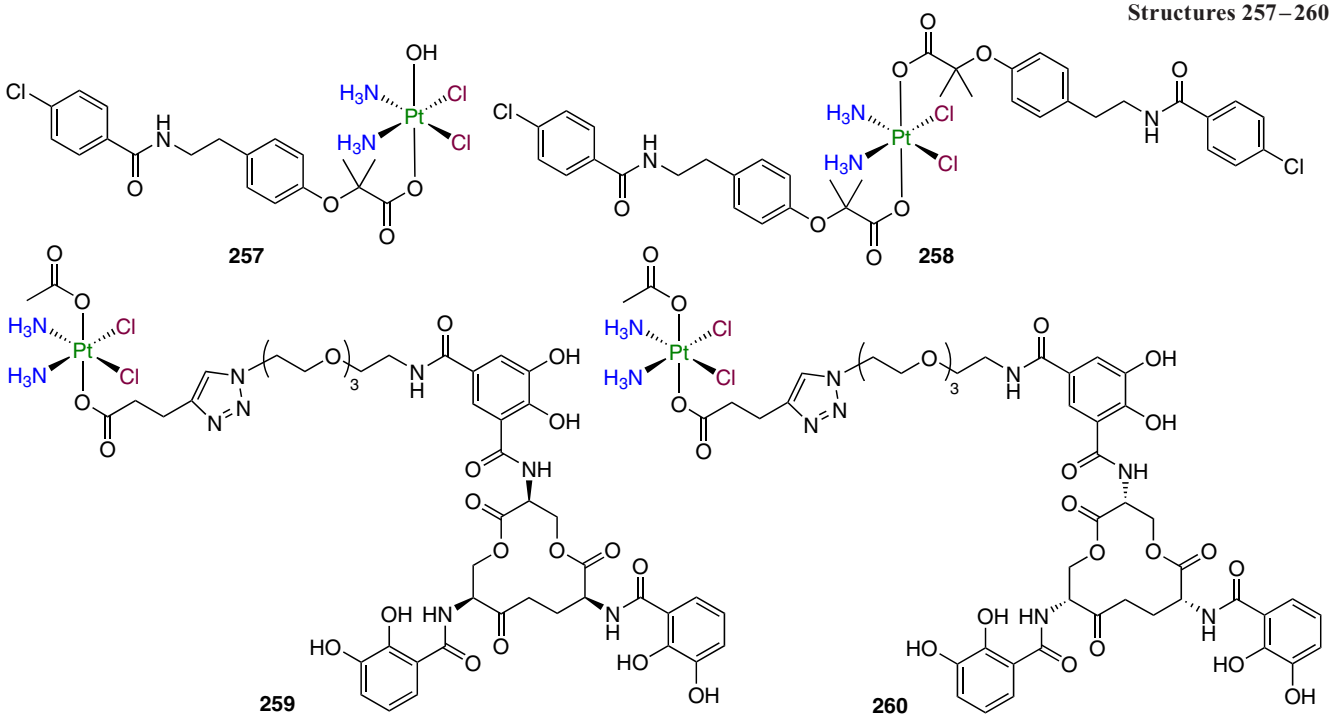
256

3.6. Platinum(IV) prodrugs with lipid regulating agents

The change in the lipid metabolism is a distinctive feature of tumour diseases.[199] Drug combinations of hypolipidemic statins and cytotoxins, such as cisplatin, have antiproliferative and proapoptotic effects.[200] In 2021, Qiao *et al.*[201] developed Pt(IV) prodrugs **257** and **258** containing bezafibrate, an FDA-approved hypolipidemic drug, in one or both axial positions.

Cytotoxicity assays demonstrated that both complexes had IC_{50} in the nanomolar concentration range, but monosubstituted prodrug **257** was more cytotoxic: the IC_{50} values for compound **258** against A549 and HeLa cells were 0.15 and 0.35 μM, respectively, while those for prodrug **257** were 0.04 and 0.06 μM, respectively. It is of interest that a mixture of cisplatin and bezafibrate in a molar ratio of 1 : 1 showed a 9-fold increase in the activity against A549 cells in the absence of cytotoxicity of bezafibrate. Thus, bezafibrate promoted increase in the cytotoxicity of cisplatin even in a mixture. Complex **257** also had a 13.6 times greater cellular uptake than cisplatin, whereas in the case of compound **258**, only 1.3-fold increase compared to cisplatin was observed. Study of the mechanism of cytotoxic action revealed the ability of prodrugs **257** and **258** to damage

Structures 257–260



DNA, increase the intracellular ROS levels, change MMP, arrest the cell cycle in the S-phase and trigger apoptosis in A549 cells. In addition, these agents could activate 5′AMP-activated protein kinase (AMPK; 5′AMP is adenosine monophosphate), a cellular metabolic sensor.

3.7. Platinum(IV) prodrugs with antibacterial action

In 2022, Guo and Nolan[82] proposed an unusual application of Pt(IV) prodrugs **259** and **260** based on cisplatin, that is, the application as antibacterial agents. These complexes were obtained by conjugation of cisplatin with enterobactin (Ent).

Conjugate **259** showed antibacterial activity against *E. coli* K12 and uropathogenic isolate *E. coli* CFT073. Prodrug **259** also acted similarly to cisplatin, causing a filamentous morphology in *E. coli*. It was shown that Ent mediated the delivery of compound **259** into the bacteria. The uptake of prodrugs **259** and **260** was ⩾10 times that of cisplatin (in terms of Pt). Furthermore, complex **260** had an enhanced antibacterial activity compared to L-isomer **259**, probably, because the former cannot be hydrolyzed by esterases and, hence, cannot release iron. Meanwhile, human embryonic kidney cells (HEK293T) had a low uptake of this prodrug, indicating its low toxicity.

3.8. Controlled-release platinum(IV) prodrugs

3.8.1. Ligands for controlled photoactivation

One approach to the design of Pt(IV)-based prodrugs involves the use of photoactive compounds as axial ligands. Prodrugs of this type do not exhibit cytotoxic effects in the absence of radiation and are able to release a cytotoxic Pt(II) complex in a controlled manner. The use of a photodynamic therapy (PDT) agent as a photoactive ligand may produce dual-action medications, which form ROS on exposure to radiation.[202,203]

Data on the photoactive Pt(IV) prodrugs obtained to date are summarized in Table 1. The Table presents the types of photoactive ligands located in the axial positions of platinum(IV), data on the increase in the cytotoxicity of complexes under irradiation and specifies the irradiation conditions used in experiments (for the chemical structures of compounds, see the relevant Sections).

3.8.1.1. Pyropheophorbide A

One of the first Pt(IV) prodrugs that contained a photoactive axial ligand, pyropheophorbide A (PPA), (compound **261**) was reported by Wang *et al.*[32] Pyropheophorbide A absorbs light with a maximum wavelength of ~650 nm and efficiently generates singlet oxygen.[212]

The established mechanism of photoactivation of prodrug **261** implies the formation of PPA radical anion in the axial position of the complex upon the reaction of triplet PPA with sodium ascorbate, which is followed by a fast single-electron transfer from the ligand radical anion to the Pt(IV) centre to give oxaliplatin and free axial ligands.

Complex **261** does not possess activity in the dark; however, under exposure to red light, it is cytotoxic in the sub-micromolar concentration range. The most pronounced (1786-fold) increase in the toxicity induced by radiation was observed for MCF-7 cells. In experiments *in vivo* in BALB/c mice bearing 4T1 tumour, the volume of the tumour decreased by 67% on the 12th day of therapy combined with irradiation ($\lambda = 660$ nm, $p = 10$ mW, $t = 10$ min) for the mice that were treated with complex **261** compared to that for mice treated with oxaliplatin.

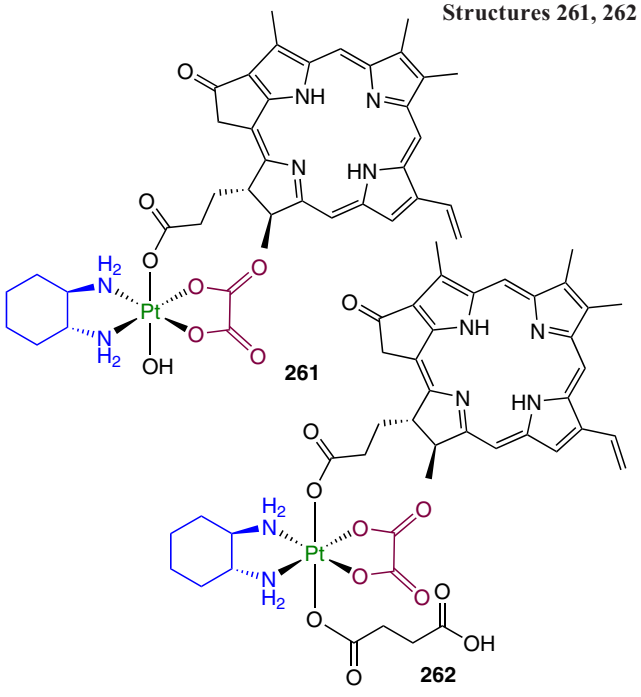
In a following study,[69] the dicarboxylate analogue of **261**–complex **262** with a succinic acid moiety in the axial position–was linked by covalent bond to NaYbF4 : Er@NaYF4 : Yb/Nd@NaYF4 : Ca nanoparticles to give nanocrystals **263** (Fig. 7 *a*). In this Figure, the large grey sphere shows the nanocrystal core, complex **262** is designated by green spheres, ERY peptide is shown as orange spheres and blue zigzag lines are poly(ethylene glycol) (PEG) moieties.

On exposure to near-infrared (NIR) light, nanocrystals **263** had IC_{50} values in the low micromolar range, while in the absence of light, the cytotoxicity was insignificant. For increasing the

Table 1. Platinum(IV)-based photoactive prodrugs.

Prodrug	Type of axial ligand	CER [a]	Irradiation [a]				Ref.
			λ, nm	D, J cm^{-2}	p, mW cm^{-2}	t, min	
261	Porphyrin	974 (A2780cisR)	650	6.3	7	15	32
262	Porphyrin	–	–	–	–	–	69
263	Nanocrystals modified with **262**	~16 (A2780cisR)	808	150	500	5	69
264 [b]	Nanocrystals modified with **262** and EPY peptide	–	808	900	500	30	69
265	Coumarin	>2 (A2780cisR)	450	28.8	8	60	68
266	Coumarin	26 (A2780)	450	28.8	8	60	68
267	Coumarin	18 (A2780cisR)	880	–	400	80	204
268	Coumarin	12 (A2780cisR)	880	–	400	80	204
269, **270**	Rhodamine B	9.8 (A2780cisR)	400–760	7.2	4	30	205
271	BODIPY [c]	7.2 (A2780)	~490	23.4	13	30	206
272–280	BODIPY	≫2 (A2780)	400–760	3.6	2	30	207
281	BODIPY	33 (HeLa)	400–700	10	13	30	208
282	BODIPY	117 (HeLa)	600–720	30	25	20	209
283	Heptamethine cyanine	>4 (A2780cisR)	650	18	10	30	57
284	Tetraacetyl riboflavin	>6.2 (MCF-7)	450	0.4	13.3	0.5	210
285	Poly(phenylene ethynylene)	–	460	8.4	7	20	211

Note. A dash means that no data are available. [a] CER is the cytotoxicity enhancement ratio against a number of cell lines (ratio of IC_{50} under irradiation to IC_{50} of the same compound without irradiation), the cell line used in the cytotoxicity assays is given in parentheses; λ is wavelength, D is dose, p is power, t is time. [b] Evaluated *in vivo*. [c] BODIPY are boron dipyrromethenes.



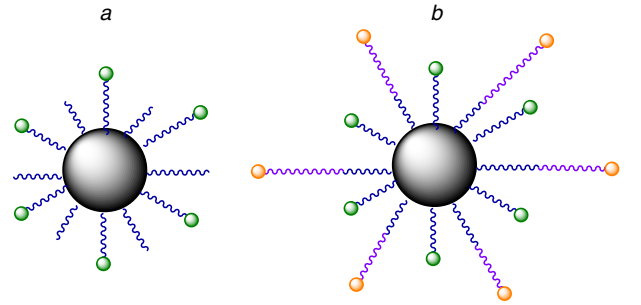


Figure 7. Schematic image of Pt(IV) prodrugs **263** (*a*) and **264** (*b*).

selectivity to tumours, this prodrug was modified with ERY peptide specific to mouse red blood cells, which was linked to the nanocrystal by a PEG-based linker. Nanocrystals **264** obtained in this way had an exceptionally long blood circulation time ($t_{1/2}$ = 907 h). In *in vivo* experiments, after one dose of **264** (2.5 μM of Pt per kg) and seven irradiation sessions (λ = 808 nm, p = 500 mW cm^{-2}, t = 30 min), the average tumour volume was 109 times smaller than that in the control group, and complete remission of the disease was observed for two out of five mice.

3.8.1.2. Coumarin

7-Diethylaminocoumarin with an absorption maximum in the blue spectral range (450 nm) was chosen as an axial ligand for Pt(IV) prodrug **265**.[68]

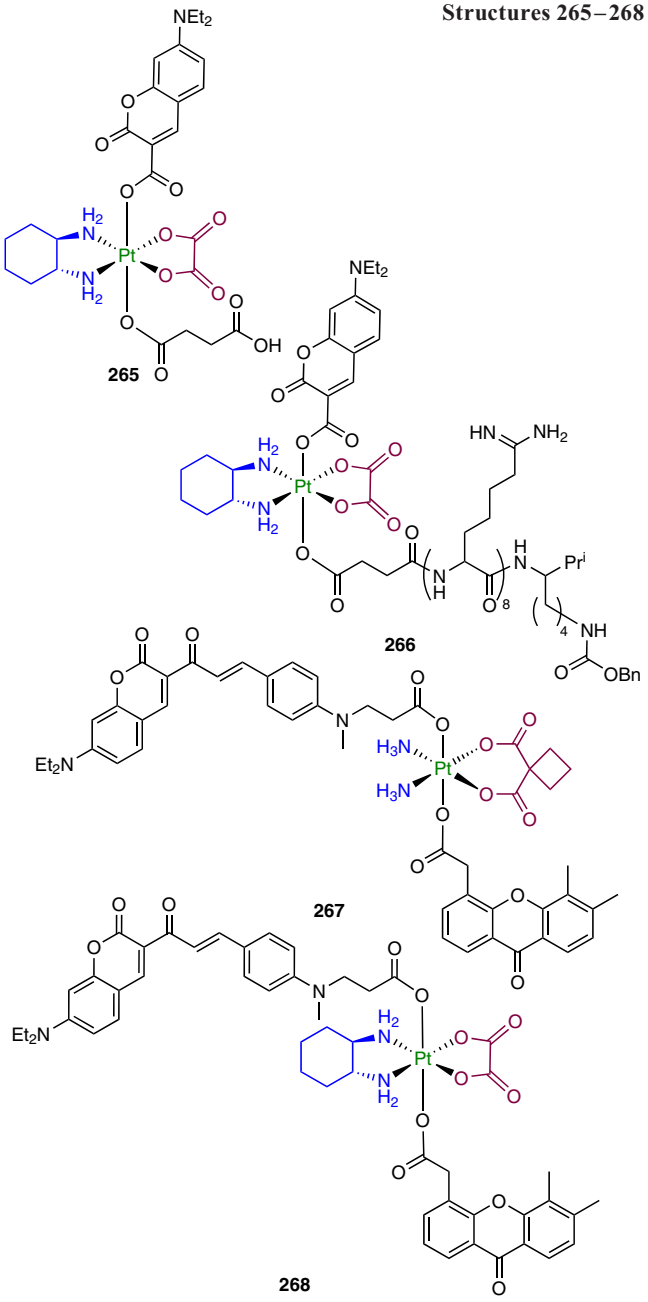
It was established that photoreduction of complex **265** is accompanied by oxidation of water and gives oxygen. In order to increase the ability of the complex to be accumulated in tumour cells, the second axial position of the platinum(IV) complex was modified by the R8K peptide vector, which gave prodrug **266**. This product was efficiently accumulated in the nuclei of A549cisR cells; the platinum content exceeded 68%.

The phototoxicity of compound **266** was evaluated using a few cell lines, including cisplatin-resistant A2780cisR cells. The dark toxicity was similar to that observed for oxaliplatin, but under blue light irradiation, the toxicity increased 7–62-fold.

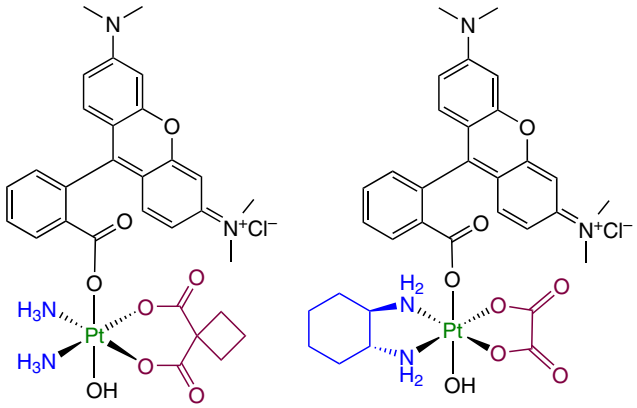
Deng *et al.*[204] described carboplatin and oxaliplatin derivatives **267** and **268**, which contain a coumarin-based axial ligand capable of being excited upon two-photon absorption. A xanthenone derivative was introduced into the second axial position to increase the cellular uptake of the compound. Both Pt(IV) prodrugs **267** and **268** were mainly accumulated in the endoplasmic reticulum; therefore, these compounds induced cell death by oxidation of biomolecules and formation of ROS rather than by DNA damage.

In *in vitro* experiments, these prodrugs were not toxic in the dark. Under laser irradiation at 880 nm (p = 0.4 W cm^{-2}, t = 80 min), the toxicity against a number of cisplatin-sensitive

Structures 265–268



Structures 269, 270



and cisplatin-resistant cell lines was low: the IC_{50} values were in the micromolar range (2–5 μM). Under hypoxic conditions, the antiproliferative activity of these compounds did not decrease, indicating an oxygen-independent mechanism of phototoxicity.

Complex **267** showed a high activity *in vivo* against 4T1 tumour in BALB/c mice; on the 16th day of therapy, the volume of the tumour decreased by 89% compared to that in the control group. In addition, this complex suppressed metastasis of 4T1 tumour and also stimulated the immune response in the tumour microenvironment.

3.8.1.3. Rhodamine B

Rhodamine B is a widely used fluorescent dye with the absorption peak at ~570 nm. Deng *et al.*[205] used rhodamine B as an axial ligand for Pt(IV) prodrugs **269** and **270** based on carboplatin and oxaliplatin, respectively.

The mechanism of photoreduction under irradiation of a solution of complex **270** was studied in the presence of sodium ascorbate by detecting the ascorbate radicals by EPR; this confirmed the involvement of this reducing agent in the release of platinum(II) complex from the prodrugs. The IC_{50} values for a number of cell lines, including cisplatin-resistant A2780cisR and A549cisR cells, proved to be 3–7 times lower upon irradiation with white light (λ = 400–760 nm, p = 4 mW cm^{-2}, t = 30 min) than in the absence of irradiation. Moreover, prodrugs **269** and **270** were 10 times more toxic upon irradiation than the corresponding Pt(II) compounds.

3.8.1.4. Boron dipyrromethenes

Boron dipyrromethenes (BODIPY) represent a class of organoboron fluorophores characterized by high fluorescence quantum yields, chemical stability and photostability.[213] Using BODIPY, platinum(IV) complexes **271**–**282** were synthesized.

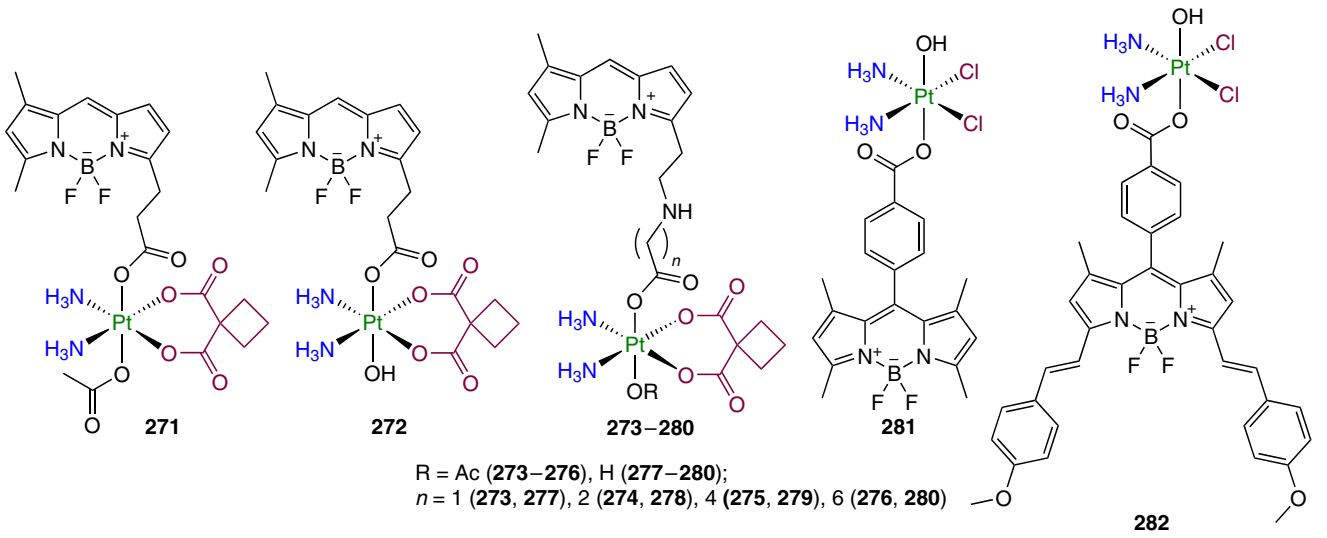
Carboplatin derivative **271** containing BODIPY in an axial position was described by Yao *et al.*[206] Complex **267** was subjected to photoreduction by irradiation with green light either in the presence or in the absence of a reducing agent. The antiproliferative activity of prodrugs **271** were studied against several cell lines, including MDA-MB-231 and A2780. Under green light irradiation, compound **271** proved to be 2–11 times more cytotoxic than in the dark and 6.5–43 times more cytotoxic than carboplatin.

In a subsequent study, Yao *et al.*[207] evaluated the effect of the length of the linker between the Pt(IV) centre and the photoactive ligand on the prodrug photoreduction rate. It was shown that dicarboxylates **271** and **273**–**276** are reduced on exposure to light up to 24 times faster than monocarboxylates **272** and **277**–**280**. Three methylene units, as in prodrugs **273** and **277**, proved to be the optimal length of the linker for the photoreduction.

Bera *et al.*[208] used an alternative BODIPY derivative synthesized from dimethylpyrrole and *p*-formylbenzoic acid as an axial ligand to obtain prodrug **281**. Complex **281** showed low toxicity against MCF-7, HeLa, A549 cells and lung epithelial cells (HPL1D) in the absence of radiation. However, upon irradiation with white light, the toxicity of this compound increased 10–25-fold and exceeded the toxicity of cisplatin by more than 10 times.

More recently, the same authors[209] obtained prodrug **282** containing a similar BODIPY derivative, which absorbed in the red spectral region. Complex **282** did not show cytotoxicity in the dark; however, red light irradiation resulted in sub-micromolar IC_{50} values. Prodrug **282** was also capable of inducing the formation of ROS on exposure to light and

Structures 271–282

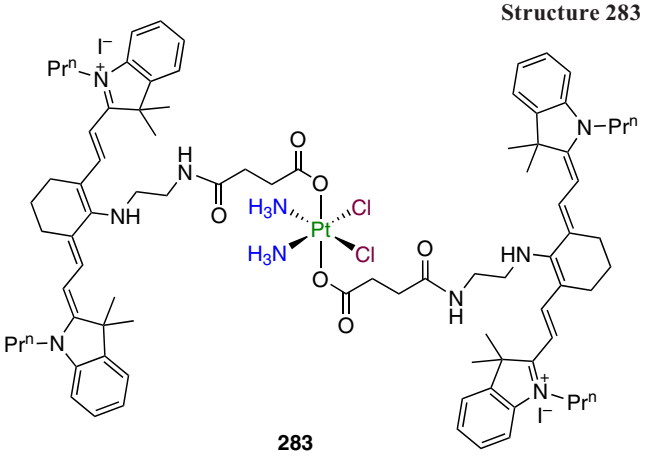


decreasing MMP upon irradiation of HeLa cells (λ = 600–720 nm, D = 30 J cm^{-2}).

3.8.1.5. Cyanine dye

Cyanine dyes are widely used as PDT agents that absorb in the NIR range. Li *et al.*[57] obtained prodrug **283** with two cyanine dye molecules in the axial positions able to absorb NIR light.

Structure 283



The toxicity of the complex in the dark was comparable with that of cisplatin, while red light irradiation induced a 3–5-fold increase in the toxicity. Prodrug **283** was equally toxic against cisplatin-sensitive and cisplatin-resistant cell lines.

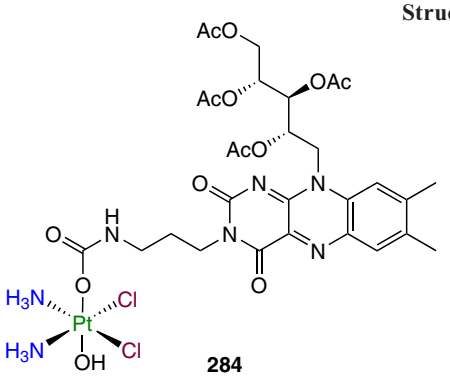
3.8.1.6. Riboflavin

Riboflavin is a group B vitamin, which plays a key role in the energy metabolism and cellular respiration. Krasnovskaya *et al.*[210] obtained cisplatin-based prodrug **284** (riboplatin) with tetraacetylriboflavin (TARF) in the axial position.

Study of physicochemical properties, the photochemical and biological activity and the photoreduction mechanism of riboplatin showed that it is a true prodrug with low toxicity in the dark releasing cisplatin upon photoexcitation with blue light.

In the absence of radiation, complex **284** turned out to be at least 3 times less toxic than cisplatin, while the efficiency attained upon blue light irradiation was more than four times higher than that of cisplatin. Moreover, riboplatin had a unique photosensitivity and was active even when the irradiation dose

Structure 284



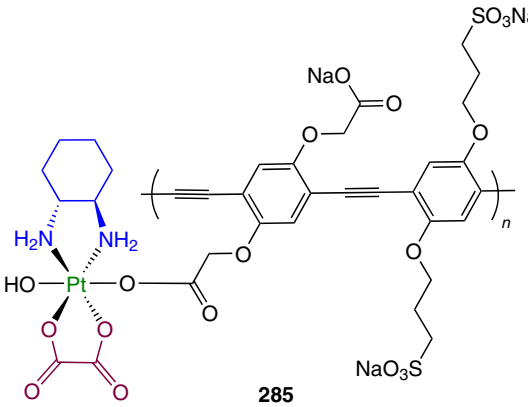
was 0.04 J cm^{-2}. Compound **284** was accumulated in the cells more efficiently than cisplatin, while under the action of blue light, the cellular uptake of the agent increased 14-fold compared to that of cisplatin. A detailed study of the riboplatin photoactivity demonstrated that at an irradiation dose below 0.2 J cm^{-2}, the cytotoxic effect is due to the release of cisplatin, whereas at irradiation doses above J cm^{-2}, a synergistic effect of chemotherapy and photodynamic therapy was observed for this agent.

3.8.1.7. Poly(phenylene ethynylene)

As indicated above, Pt(IV) prodrugs are usually octahedral coordination compounds with a low-molecular-weight (in some cases, photoactive) ligand in the axial position. An alternative approach was demonstrated by Sun *et al.*,[211] who used poly(phenylene ethynylene) (PPE) as the photoactive ligand. This macromolecule contains carboxyl groups in the side chain and can react with dihydroxy-oxaliplatin to give polymer **285**, which has a Pt(IV) complex at the periphery.

Owing to the presence of the sulfonate anion in the PPE side chain, polymeric prodrug **285** demonstrated a good solubility in water. The irradiation of complex **285** with light (λ = 400 nm, p = 5 mW cm^{-2}, t = 120 min) resulted in the release of oxaliplatin, which was manifested in the absorption spectrum, irrespective of the presence of sodium ascorbate. The release of oxaliplatin from the prodrug under the action of blue light (λ = 400 nm, p = 5 mW cm^{-2}, t = 30 min) was also confirmed by HPLC/MS. Prodrug **285** was reduced not only on exposure to blue light (λ = 400 nm, p = 5 mW cm^{-2}, t = 120 min), but also due to two-

Structure 285



285

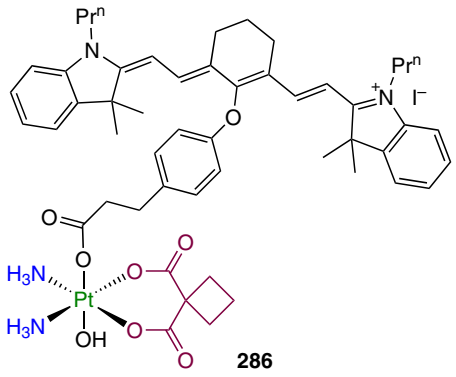
photon absorption induced using 100 fs pulsed light (λ = 725 nm, p = 800 mW cm^{-2}, t = 1 h, 50% degradation). A mechanism of photoreduction was proposed, the key step of which is the electron transfer from the polymer ligand to the Pt(IV) centre to give the PPE radical cation.

The cytotoxicity of agent **285** after irradiation with light at λ = 460 nm (p = 7 mW, t = 20 min) was comparable with the cytotoxicity of oxaliplatin; in the dark, this prodrug showed an insignificant cytotoxicity.

3.8.2. Ultrasound-induced release

Ultrasound waves represent a non-invasive and highly penetrating treatment that is widely used in neurosurgery, drug delivery and anticancer therapy.[214–216] Liu *et al.*[217] employed focused ultrasound (FUS) for the controlled activation of Pt(IV) prodrug **286**.

Structure 286



286

The heptamethine dye IR780 sensitive to ultrasonic treatment was used as the axial ligand.[218] Platinum(IV) prodrug **286** was selectively reduced on treatment with ultrasound in the presence of sodium ascorbate, which indicates that reduction occurs *via* the extramolecular electron transfer. The ability to form singlet oxygen under the action of FUS (type II sonosensitization) was shown for complex **286** and the free ligand.

Evaluation of the antiproliferative activity showed that prodrug **286** was inactive without sonication, while FUS increased its cytotoxicity more than 10-fold to reach IC_{50} of 2–4 μM. Complex **286** was equally active against cisplatin-sensitive and cisplatin-resistant cell lines (A2780 and A2780cisR; or A549 and A549cisR). In 4T1 cells incubated with this compound and sonicated, markers of immunogenic cell death, including calreticulin exposure, ATP secretion and extra-nuclear HMGB1 expression, were detected. This attests to the potential ability of prodrug **286** to stimulate the anticancer immune response.

The anticancer efficacy *in vivo* was investigated against the 4T1 tumour in BALB/c mice. After the therapy with prodrug **286** and sonication, the tumour volume on the 18th day was 24.3% of the initial volume, and complete remission was observed for two out of five mice. In addition, markers of the antitumour immune response, CD3+ and CD4+, were detected in the tumours of mice after treatment with **286** and sonication.

Thus, the use of ultrasound is a new, fairly promising approach to the controlled activation of Pt(IV) prodrugs, which combines high penetration capacity and safety for normal organs and tissues. Prodrug **286**, capable of controlled sonoactivation, showed a high antitumour efficacy *in vivo*, owing to the antiproliferative action caused by the release of the chemotherapeutic agent carboplatin, formation of singlet oxygen and stimulation of the antitumour immune response.

3.9. Efficacy of Pt(IV) prodrugs *in vivo*

A highly important characteristic of efficacy of Pt(IV) prodrugs is the tumour growth inhibition *in vivo*. Table 2 summarizes the results of studies of the therapeutic efficacy of Pt(IV) prodrugs described in this review.

Considering these data, worthy of note is the correlation between the rate of reduction of the coordination compounds in the presence of reducing agents and their ability to inhibit the tumour growth *in vivo*. It can be seen that Pt(IV) monocarboxylate complexes are less stable than the dicarboxylates. The half-lives of Pt(IV) monocarboxylate prodrugs in the presence of reducing agents vary from several minutes[93] to 4–6 h.[101,158] Abnormally high stability ($t_{1/2}$ > 24 h) is inherent in monocarboxylate oxaliplatin and carboplatin derivatives with photoactive ligands (**261**, **269**, **270**).[32,206] In *in vivo* assays, the unstable Pt(IV) monocarboxylates differ little in efficacy from cisplatin and show enhanced activity only against cisplatin-resistant tumours. As an exception, note the high efficacy of prodrug **31** against HCT-116 cell line.[101]

Meanwhile, Pt(IV) dicarboxylate prodrugs usually have half-lives of several hours[93] to >24 h,[58,79,163] but there are also examples of unstable dicarboxylates, which are reduced within one hour.[186,195] For Pt(IV) prodrugs **8**, **15**, **84** and **230**, which have a relatively short (up to 12 h) half-lives in the presence of reducing agents, the efficacy in *in vivo* experiments was comparable to that for cisplatin. However, the stability of the agents did not directly affect their efficacy in animals. Indeed, highly stable prodrugs **189**, **216** and **253** are more active *in vivo* than Pt(II) compounds; the ability of prodrugs **137** and **195** to inhibit the tumour growth is at the cisplatin level, despite their stability in the presence of reducing agents. This indicates that stability of Pt(IV) prodrugs in the presence of reducing agents is a necessary, but not sufficient condition for high anticancer efficacy.

The highest activity in *in vivo* experiments among all Pt(IV) prodrugs considered in this review was inherent in complexes **243** and **262**, for which delivery vehicles ensuring longer blood circulation time have been developed.[66,69] After 32 days of the therapy of BALB/c mice bearing CT26 tumour with the liposomal form of prodrug **243** with alkyltriphenylphosphonium and dichloroacetate in the axial positions, complete remission of the disease was attained. A very high anticancer efficacy was also demonstrated for nanocrystals **264** containing a photoactive Pt(IV) prodrug **262** with pyropheophorbide A: after administration of only one dose of agent **264** and seven irradiation sessions at 808 nm (D = 900 J cm^{-2}), remission was observed in two out of five mice on the 14th day of therapy.

Table 2. Therapeutic efficacy of Pt(IV) prodrugs developed between 2018 and 2023.

Compound	Pt(II) drug	Axial ligand (linker)[a]		Experimental conditions					Comparison of *in vivo* activity		Ref.
		first	second	mouse breed	tumour	dose,[b] mg kg^{-1}	duration, days	administration frequency	Pt(II) agent[c]	test indicators	
Pt(IV) prodrugs with cytotoxic ligands											
1. *Tubulin polymerization inhibitors*											
1	CDDP	Combretastatin (ethylene glycol succinate)	Chloride	BALB/c	SKOV-3	5 (I.V.)	21	once in 7 days	5.0 mg/kg (I.V.), TGI = **65.8%**	TGI = **53%** Lower weight loss of animals No damage to vital organs	91
8	CDDP	Combretastatin (carbonate)	Hydroxyl	C57BL	LLC	20 (P.O.)	7	daily	3.0 mg/kg (I.P.), TGI = **84%**	TGI = **84%** Weight loss of animals <10%	93
9	CDDP	Combretastatin (carbonate)	Phenylbutyrate	C57BL	LLC	20 (P.O.)	7	daily	3.0 mg/kg (I.P.), TGI = **84%**	TGI = **92.6%** Weight loss of animals <10%	93
15	CDDP	Combretastatin (glutarate)	Phenylbutyrate	C57BL	LLC	20 (P.O.)	7	daily	3.0 mg/kg (I.P.), TGI = **84%**	TGI = **91.5%** Weight loss of animals <10%	93
22	CDDP	Millepachine (glutaric acid monoamide)	Chloride	BALB/c	SKOV-3	5 or 13.5 (I.V.)	21	once in 7 days	5.0 mg/kg (I.V.), TGI = **65.1%**	TGI = **60.3** or **70.2%** No significant changes in the animal weight or significant damage to vital organs	99
31	CDDP	Chalcone (hydroxyacetate)	Hydroxyl	BALB/c	HCT-116	0.72 (I.V.)[d]	28	once in 2 days, 8 days	0.95 mg Pt/kg (I.V.), tumour size ~65% relative to the control	Tumour size of 20% relative to the control and 32% relative to cisplatin Animal weight loss <20%	101
45	CDDP	Indolochalcone (propionate)	Chloride	BALB/c	A549/ CDDP	12.40 (I.V.)	28	once in 8 days	5.0 mg/kg (I.V.), TGI = **25.7%**	TGI = **65.9%** No significant changes in the animal weight High biocompatibility	103
2. *Other cytotoxic agents*											
64	OLP	5-Fluorouracil (succinate)	Palmitate	NOX/ SCID	HCT-116	2.5 (I.V.)	21	once in 3 days, 18 days	2.5 mg/kg (I.V.), TGI = **57.8%**	TGI = **84.8%** No significant changes in the animal weight Low accumulation in kidneys; high accumulation in the tumour	28
74	CDDP	Chlorambucil	Chlorambucil	BALB/c	MDA-MB-231	2.0 (I.V.)[d]	12	once in 3 days	2.0 mg Pt/kg (I.V.)	Tumour size of 59% of the control (similarly to cisplatin) No significant changes in the animal weight or significant damage to vital organs	59
84	CDDP	Clioquinol (valerate)	Clioquinol (valerate)	BALB/c	4T1	2.0 (I.V.)[d]	15	by 4, 7 and 10 days	2.0 mg Pt/kg (I.V.), <u>for CDDP:</u> TGI = **64.6%**, <u>for OLP:</u> TGI = **41.9%**	TGI = **61.6%** No significant changes in the animal weight Pt content in DNA is 8.4 and 21.1 times higher than that for CDDP and OLP	124

Table 2 (continued).

Compound	Pt(II) drug	Axial ligand (linker)[a]		Experimental conditions					Comparison of *in vivo* activity		Ref.
		first	second	mouse breed	tumour	dose,[b] mg kg^{-1}	duration, days	administration frequency	Pt(II) agent[c]	test indicators	
Pt(IV) prodrugs with cytotoxic ligands											
3. *Conjugates with biologically active molecules*											
128	OLP	6-Bromocoumarin-3-carboxylic acid	6-Bromo-coumarin-3-carboxylic acid	BALB/c	–	–	–	–	For CDDP: MTD/ LD_{50} = 9/16 mg/kg, TI (see[e]) = 10.13; for OLP: MTD/ LD_{50} = 15/30 mg/kg TI = 9.99	MTD = 25 mg/kg, LD_{50} = 50 mg/kg, TI = 16.37	133
Pt(IV) prodrugs with ligands overcoming cisplatin resistance											
1. *Iron chelators*											
135	CDDP	DFX	Hydroxyl	BALB/c	MDA-MB-231	5.0 **(I.V.)**	14	on 4th and 8th day	5.0 mg/kg (I.V.), TGI = **41%**	TGI = **77%** No significant changes in the animal weight or significant damage to vital organs Decrease in FTO and XRCC4 expression	138
2. *GST inhibitors*											
137	OLP	L-Buthionine-(*S*,*R*)-sulfoximine	Maleimide (pentylamine carbamate)	BALB/c	CT-26	23.5 **(I.V.)**	14	once in 7 days	9 mg/kg (I.V.), TGI = **51.3%**	TGI = **61.2%** High accumulation in the tumour Decrease in the GSH level No significant changes in the mouse weight or significant damage to healthy kidney and lung cells	79
3. *STAT3 inhibitors*											
143	CDDP	Napabucasin (BBI608-OH) (adipate)	Hydroxyl	BALB/c	A549/ CDDP	11.5 **(I.V.)**	28	once in 7 days	5 mg/kg (I.V.), TGI = 12.77%	TGI = **64.76%** No significant changes in the animal weight Inhibition of the ALDH1A1 and OCT4 expression	146
4. *PARP-1 inhibitors*											
151	CDDP	Olaparib (adipate)	Chloride	BALB/c	MDA-MB-231/ CDDP	13.8 **(I.V.)**	28	once in 7 days	5 mg/kg (I.V.), TGI = 26.5 %	TGI = **64.1%** No significant changes in the animal weight or significant damage to vital organs Inhibition of the Ki67 expression	148

Table 2 (continued).

Compound	Pt(II) drug	Axial ligand (linker)[a]		Experimental conditions					Comparison of *in vivo* activity		Ref.
		first	second	mouse breed	tumour	dose,[b] mg kg^{-1}	duration, days	administration frequency	Pt(II) agent[c]	test indicators	
Pt(IV) prodrugs with ligands overcoming cisplatin resistance											
5. *P-glycopritein inhibitors*											
156	OLP	P-glycopritein inhibitor (capronate)	Chloride	–	SGC-7901/ CDDP	16.2 (I.V.)	28	once in 7 days	For CDDP: 5 mg/kg (I.V.), TGI = 25.9%; for OLP: 6.7 mg/kg (I.V.), TGI = **43%**	TGI = **75.6%** No significant changes in the animal weight or significant damage to vital organs Increased Pt(II) amount in the tumour Increased accumulation in the tumour	156
Pt(IV) prodrugs with non-steroidal anti-inflammatory drugs											
166	CDDP	Ketoprofen	Hydroxyl	BALB/c	MDA-MB-231	2.0 (I.V.)[d]	22	once in 3 days	2.0 mg Pt/kg (I.V.)	Tumour volume of 41% relative to the control (comparable with cisplatin) No significant changes in the animal weight	155
				BALB/c	CT-26	4.0 (I.P.)[d]	14	once in 3 days	4.0 mg Pt/kg (I.P.), for OLP:[f] TGI = **57.8%**	TGI = **57.1%** No significant changes in the animal weight or significant damage to vital organs PD-L1 inhibition DNA damage	156
				BALB/c	4T1	4.0 (I.P.)[d]	14	once in 3 days	For CDDP: 2.0 mg Pt/kg (I.P.), TGI = **57.1%**; for OLP: 4.0 mg Pt/kg (I.P.), TGI = **62.5%**	TGI = **54.6%** Antimetastatic effect PD-L1 inhibition DNA damage	156
183	OLP	Naproxen	Chloride	BALB/c	CT-26	4.0 (I.V.)[d]	15	on day 6, 9, 12 and 14	For CDDP: 2.0 mg Pt/kg (I.V.)), TGI = **86.5%**; for OLP: 4.0 mg Pt/kg (I.V.), TGI = **82.5%**	TGI = **82.5%** Lower weight loss by the animals Triggering apoptosis and necrosis No significant damage to vital organs Inhibition of matrix metalloproteinase expression	158
189	CDDP	Naproxen	Naproxen	BALB/c	MDA-MB-231	1.5 (I.V.)[d]	15	once in 3 days	1.5 mg Pt/kg (I.V.), tumour volume of 71% relative to the control	Tumour volume of 7% relative to the control No significant changes in the animal weight	58
195	CDDP	Etodolac	Etodolac	BALB/c	MCF-7	3.0 (I.V.)[d]	14	once in 3 days	3.0 mg Pt/kg (I.V.), TGI = **50%**	TGI = **60%** No significant changes in the animal weight Low Pt accumulation in healthy organs	163

Table 2 (continued).

Compound	Pt(II) drugw	Axial ligand (linker)[a]		Experimental conditions					Comparison of *in vivo* activity		Ref.
		first	second	mouse breed	tumour	dose,[b] mg kg^{-1}	duration, days	administration frequency	Pt(II) agent[c]	test indicators	
198	CDDP	Niflumic acid	Niflumic acid	BALB/c	4T1	2.0 (I.V.)[d]	15	once in 2 days since the 2nd day	2.0 mg Pt/kg (I.V.), for CDDP: TGI = 9.8%; for OLP: TGI = 19.2%	TGI = **50.8%** Lower weight loss by the animals No significant damage to vital organs Inhibition of COX-2 and MMP-9, ERK1/2 and HIF-1α Increase in the CD3+, CD4+ and CD8+ lymphocyte levels in tumour tissues	165
Pt(IV) prodrugs with ligands affecting the immune response											
216[g]	CDDP	BRD4 inhibitor JQ-1	JQ-1	C57BL/6	B16F10	10.0 (I.V.)	16	once in 2 days since the 7nd day	10.0 mg/kg (I.V.), tumour size of ~75% relative to the control	Tumour size: ~13% relative to the control and ~17% relative to cisplatin No significant changes in animal weight or significant damage to vital organs Enhanced tumour infiltration with CD8+ T-cells Inhibition of Ki67 expression	179
219	CDDP	Melatonin (succinic acid monoamide)	Hydroxyl	BALB/c	MCF-7	2.0 (I.V.)[d]	22	once in 2 days	2.0 mg Pt/kg (I.V.), TGI = **42.6%**	TGI = **47.4%** No significant changes in animal weight High Pt accumulation in the tumour Lymphocyte proliferation in the spleen	183
230	OLP	1-Methyl-D-tryptophan (carbamate)	Maleimide (pentylamine carbamate)	BALB/c	CT26	20.6 (I.V.)	14	twice in 7 days	9 mg/kg (I.V.), tumour size: ~60% relative to the control	Tumour size: ~50% relative to the control and ~75% relative to OLP Higher survival rate relative to OLP More efficient tumour growth inhibition compared to OLP Considerable change in the ratio of CD4+ and CD8+ T-cells	186
Pt(IV) prodrugs with ligands enhancing the selectivity											
243	CDDP	Triphenylphosphine (adipate)	Dichloroacetate	BALB/c	CT26	1.95 (I.P.)[d]	32	on day 10, 17 and 24	1.95 mg Pt/kg (I.P.)	Tumour size 5 times lower than for cisplatin and 8 times lower than for the control Decrease in the NOX4 and TNF-α levels	66
				BALB/c	CT26	1.95 (I.P.; liposomes)[d]	32	on 10, 17 and 24 day	1.95 mg Pt/kg (I.P.)	Complete remission	66
252	CDDP	CAIX inhibitor	CAIX inhibitor	BALB/c	MDA-MB-231	5 (I.V.)	24	once in 2 days	5 mg/kg (I.V.), for CDDP: TGI = **43.4%**; for OLP: TGI = **32.0%**	TGI = **57.9%** Inhibition of CAIX and CD31 expression No significant changes in animal weight or significant damage to vital organs	195

Table 2 (continued).

Compound	Pt(II) drug	Axial ligand (linker)[a]		Experimental conditions					Comparison of *in vivo* activity		Ref.
		first	second	mouse breed	tumour	dose,[b] mg kg^{-1}	duration, days	administration frequency	Pt(II) agent[c]	test indicators	
253	OLP	CAIX inhibitor	CAIX inhibitor	BALB/c	MDA-MB-231	5 (I.V.)	24	once in 3 days	5 mg/kg (I.V.), for CDDP: TGI = **43.4 %**; for OLP: TGI = **32.0 %**	TGI = **65.3 %** Inhibition of CAIX and CD31 expression No significant changes in animal weight or significant damage to vital organs	195
Pt(IV) prodrugs with controlled release											
1. *Pt(IV) with controlled photoactivation*											
261[h]	OLP	Porphyrin (propionate)	Hydroxyl	BALB/c	4T1	2.5 (I.V.)[i]	12	once on the first day	3.5[i]	Decrease in the tumour volume to 67% of the control	69
264[h]	Nanocrystal modified with complex **261** and ERY peptide			BALB/c	4T1	2.5 (I.V.)[i]	12	once in the first day	–	Average tumour volume 109 times lower than in the control Complete remission in two out of five mice Increase in the number of CD4+ and CD8+ lymphocytes No significant changes in animal weight or significant damage to vital organs	69
267[j]	Carboplatin	7-Diethylamino-aminocoumarin modified at position 3 (propionate)	5,6-Dimethyl-xanthenone-4-acetate	BALB/c	4T1	1.5 (I.V.)[d]	16	once in 3 days	1.5 mg Pt/kg (I.V.), decrease in the tumour volume by 11 ± 9% relative to the control	Decrease in the tumour volume by 89 ± 8% relative to the control Activation of the immune response No metastasing No significant changes in animal weight or significant damage to vital organs	204
2. *Prodrugs Pt (IV) capable of ultrasonic release*											
286[k]	Carboplatin	Heptamethine IR780 dye	Hydroxyl	BALB/c	4T1	3.0 (I.V.)[d]	18	on day 0 (before the experiment)	For carboplatin + IR780 : 3.0 mg Pt/kg (I.V.), no irradiation, average tumour volume ~85% relative to the control	Complete remission in two out of five mice Average tumour volume of ~5% relative to the control Decrease in the Ki67 proliferation level in the tumour Activation of the immune response No significant changes in animal weight or significant damage to vital organs	217

Notes. The most meaningful TGI values are typed in bold. [a] The name of the parent agent or the anion (in the case of simple substituents) is given. [b] The administration route, intravenous (I.V.), intraperitoneal (I.P.) or oral (P.O.), is given in parenthesis. [c] The dose and the administration route (parenthesis), TGI and, in some cases, other data are given. [d] The amount of the agent is expressed in terms of Pt content. [e] TI for HCT-116 cells. [f] CDDP was withdrawn due to high toxicity. [g] The *anti*-PD-1 antibody was additionally introduced in a dose of 40 μg per mouse (I.P.) for 16 days (once in 3 days since the 7th day). [h] Seven irradiation sessions were performed (λ = 808 nm, p = 500 mW cm^{-2}, t = 30 min). [i] Expressed in μmol Pt/kg. [j] Irradiation was performed 4 h after the injection (λ = 880 nm, p = 400 mW cm^{-2}, t = 80 min). [k] Ultrasonic sessions on day 0, 2, 4 and 6 (p = 3.5 W, 2 min of irradiation with a 1 min break, 10 times).

Thus, the efficacy of the anticancer action of Pt(IV) prodrugs is enhanced if their stability against too fast reduction and their longer blood circulation times have been attained.

3.10. Analysis of the efficacy of Pt(IV) prodrugs

Platinum(IV) complexes containing combretastatin in an axial position possess cytotoxic activity in the nanomolar concentration range.[91–93] Prodrugs **8** and **9**, in which the axial ligand is linked to the Pt(IV) centre by a cleavable carbonate linker proved to be the most active,[93] while prodrugs **1**–**7** with linkers based on dicarboxylic acids had $IC_{50} > 150$ nM.[91,92] Despite the fact that prodrugs **1**–**15** were up to 6000 times more active than cisplatin in *in vitro* experiments, studies of the *in vivo* anticancer efficacy showed that the ability of **1**, **8**, **9** and **15** to inhibit the tumour growth is comparable to that of cisplatin.

Monocarboxylates **16**–**30** and **33**–**47** with chalcone derivatives, CA-4 analogues, in the axial positions have an antiproliferative effect in low micromolar and nanomolar ranges down to $IC_{50} = 0.13$ μM, observed for prodrug **36** against HCT-116 cells.[98,99,102,103] In this case, the optimal length of the linker between the ligand and the Pt(IV) centre is a short chain containing two free methylene units based on succinic anhydride. Monocarboxylate complex **31** with a p53/MDM2-inhibiting chalcone demonstrated an exceptionally high antiproliferative activity in the nanomolar concentration range: IC_{50} (against A2780 cells) = 10 nM.[101] In *in vivo* experiments, the efficacy of prodrug **31** also considerably exceeded that of cisplatin. Complex **45** with indolochalcone in the axial position was active against cisplatin-resistant cells *in vitro* and also inhibited the growth of the A549/CDDP cisplatin-resistant tumour much better than cisplatin.

Among Pt(IV) prodrugs with known anticancer agents (paclitaxel, fluorouracil, chlorambucil and doxorubicin), clear-cut synergistic effect for the combination of two therapeutic agents *in vitro* and *in vivo* was attained only for series of compounds **60**–**67** based on oxaliplatin and fluorouracil and only after thorough tuning of the lipophilicity of the coordination compounds.[28] The most active conjugate **64** exhibited a high degree of tumour growth inhibition *in vivo*, which much exceeded that for oxaliplatin.

Platinum(IV) prodrugs **132**–**156** were synthesized to overcome the cisplatin and oxaliplatin resistance of tumour cells. Among agents of this type, the ability to fully overcome the resistance (RF < 1) *in vitro* was exhibited by prodrugs **132**–**134** containing fatty acids and by complexes **138**–**143** with napabucasin in the axial position.[135,146] Nevertheless, Pt(IV) prodrugs **135**, **143**, **151** and **156** with the DFX iron chelator and STAT3, PARP-1 and P-glycoprotein inhibitors, respectively, meant to overcome the drug resistance showed high activity *in vivo* against cisplatin-resistant tumours (A549/CDDP, MDA-MB-231/CDDP and SGC-7901/CDDP).[138,146,148,150] This is a clear-cut evidence for efficiency of the strategy of preparing Pt(IV) prodrugs with axial ligands that inhibit the mechanism of cisplatin resistance of tumour cells.

The introduction of non-steroidal anti-inflammatory drugs into the axial positions of Pt(IV) complexes (compounds **157**–**214**) markedly increases the toxicity *in vitro* (to reach nanomolar IC_{50} values). Nevertheless, in these experiments, the cytotoxicity is affected most appreciably by the lipophilicity of Pt(IV) prodrugs.[53,62] Despite the high activity of prodrugs of this group *in vitro*, the ability of complexes **1166**, **183, 195** and **198** to inhibit the tumour growth *in vivo* was comparable to that of cisplatin.[155,158,163,165] However, these agents showed lower toxicity against normal organs and induced a lower loss of animal weight than cisplatin. A number of Pt(IV) prodrugs **166**, **189** and **198** with NSAIDs (ketoprofen, naproxen and niflumic acid, respectively) proved to stimulate the immune response by inhibiting PD-L1 and increasing the level of CD3+, CD4+ and CD8+ lymphocytes.[58,155,165] Compound **189** also efficiently inhibited the growth of the MDA-MB-231 tumour.[58]

For a group of Pt(IV) prodrugs **215**–**233** with immuno-modulating ligands in the axial position, *in vivo* experiments showed the ability to increase the amount of the immunostimulating CB8+ T-cells and, hence, to trigger the immune response to the malignant growth.[179,183,186] In addition, the therapy with agents **216**, **219** and **230** containing BRD4 inhibitor, melatonin and 1-methyl-D-tryphophan as axial ligands, respectively, was accompanied by a smaller decrease in the weight of animals and less pronounced damage to healthy organs than the therapy with Pt(II)-based drugs. Whereas the ability of prodrugs **219** and **230** to inhibit the tumour growth was comparable to that of cisplatin or oxaliplatin, compound **216** showed a high anticancer activity *in vivo* markedly exceeding the effect of cisplatin or a combination of cisplatin and the axial ligand JQ-1.[179]

Among the strategies towards increasing the selectivity of Pt(IV) prodrugs to tumour cells, high characteristics were found for the approach involving the introduction of glucose into the axial position: the selectivity index of complex **238** to HepG2 cells over L02 normal cells was 24.[25] Prodrugs **252** and **253** with hypoxia-sensitive axial ligands, CAIX inhibitors, were also characterized by a high selectivity index for MDA-MB-231 hypoxic cells over the normoxic MCF-10A cells (80 and 34.5, respectively).[195] In *in vivo* experiments, the activity of prodrug **253** significantly exceeded the activity of oxaliplatin.

Combination of organic fluorophores and Pt(IV) coordination compounds afforded a series of Pt(IV) prodrugs **261**–**285**, which are stable and non-toxic in the absence of radiation, but in the presence of visible light, they can release cytotoxic Pt(II) coordination compounds and induce the formation of reactive oxygen species.[32,57,68,69,205–211]

The use of oxaliplatin or carboplatin as the parent Pt(II) complex led to the increase in the dark stability of the agents. The conjugation of complex **261** with the nanocrystals afforded prodrug **264**, characterized by long blood circulation time; the therapy with this nanocrystal resulted in remission of the disease in two out of five mice.[69]

The most important results presented in this review is the successful use of two-photon absorption and sonication for the controlled release of cytotoxic agents from Pt(IV) prodrug.[204,217] The efficacy of the therapy of malignant tumours *in vivo* demonstrated in relation to Pt(IV) complexes **267** and **286** undoubtedly indicates the high promise of using both Pt(IV) prodrugs capable of controlled release and non-classic approaches to external stimulation.

3.11. Miscellaneous metal-containing agents in clinical practice

Along with platinum complexes, a number of coordination compounds based on other metals have been actively investigated in recent years as antitumour agents. Some compounds are already in clinical trials.

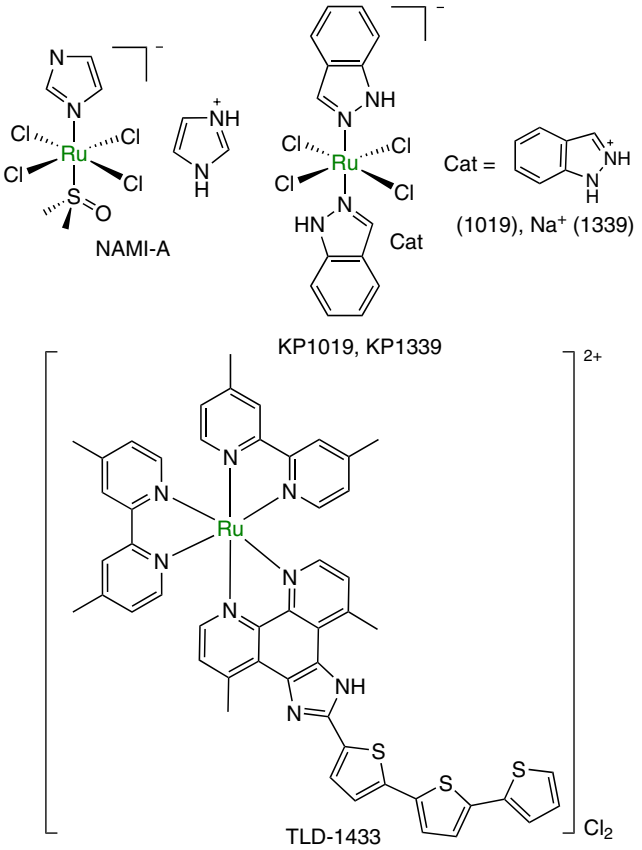
Ruthenium complexes with the codes NAMI-A and KP1019 were chosen for clinical trials for the therapy of colon cancer.[219]

Complex NAMI-A did not show a sufficient efficacy to continue phase II clinical trials, and compound KP1019 had a moderate efficacy in phase I trials.[220,221] Presumably, NAMI-A

functions *via* fast ligand exchange by binding to proteins on the surface of tumour cells and preventing metastasis, while KP1019 (or its sodium salt KP1339) penetrates into the cell and binds to proteins, causing ROS formation and DNA damage. Currently, the agent BOLD100, which is a full analogue of complex KP1339, is in phase I clinical trials as a drug for the treatment of solid tumours (code NCT04421820).

Ruthenium complex TLD1433 has passed phase Ib clinical trials as a photosensitizer, a photodynamic therapy agent against the non-invasive bladder cancer (code NCT03945162).[222]

Structures of Ru complexes

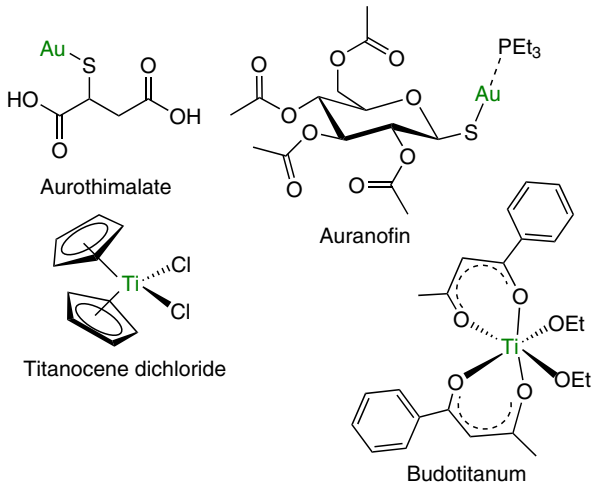


Two gold compounds, aurothimalate and auranofin, completed the clinical trials as protein kinase C (PKC) inhibitors, a kinase involved in cell proliferation, migration and apoptosis.

Phase I clinical trials of aurothimalate were carried out for the therapy of PKC-expressing types of cancer, in particular non-small cell lung cancer, ovarian cancer and pancreatic cancer (NCT00575393 code).[223] Auranofin was subjected to phase I/II clinical trials for the treatment of chronic lymphoid leukemia, small lymphocytic and prolymphocytic lymphoma; now it is in phase II clinical trials for the therapy of ovarian cancer (9NCT03456700 code).

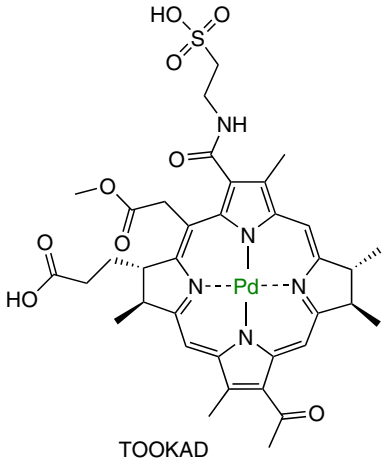
Titanium complexes, titanocene dichloride ($CpTiCl_2$) and budotitanum, were the first metal coordination compounds to be subjected to clinical trials after platinum-based compounds.[224,225] In phase I trials, the maximum tolerated doses of $CpTiCl_2$ and budotitanum were successfully determined; however, in phase II clinical trials, no noticeable beneficial effect was observed for the former compound, and difficulties in composing the formulation prevented further study of budotitanum.[226] The mechanism of antiproliferative action of titanium complexes is not entirely clear; presumably, it includes the reduction of Ti^{IV} to Ti^{II} and binding to DNA.[227,228]

Structures of Au and Ti complexes



Palladium complex with bacteriopheophorbide (TOOKAD™) was approved in Mexico for the treatment of prostate cancer and is in phase II and III clinical trials in the US (NCT04620239 code).[229] This is an agent for the vascular-targeted photodynamic therapy activated by light with a wavelength of 753 nm (NIR region).[230]

Structure of TOOKAD

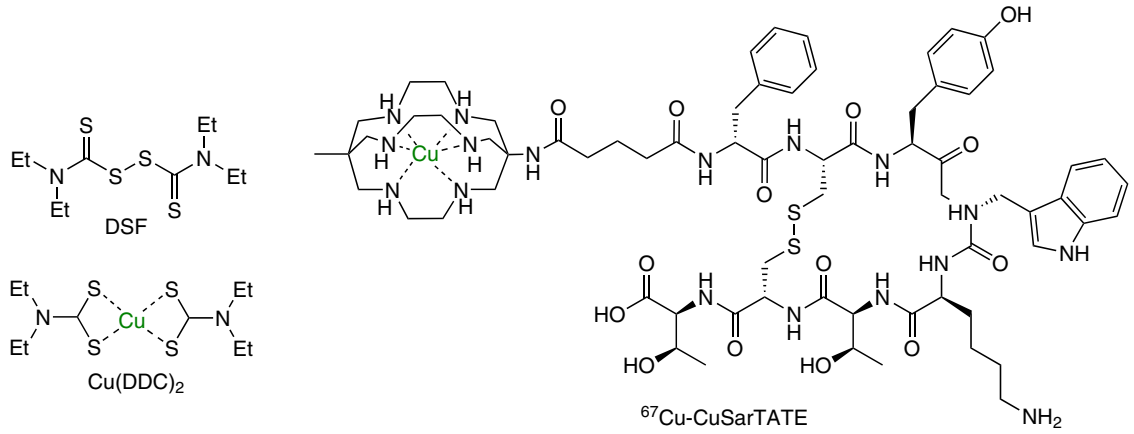


Copper coordination compounds are also promising metal-containing agents for the therapy and diagnosis of malignant neoplasms. A combination of disulfiram with copper salts (DSF/Cu) is a Cu(II) complex of disulfiram metabolite, diethyldithiocarbamate (DDC).[231]

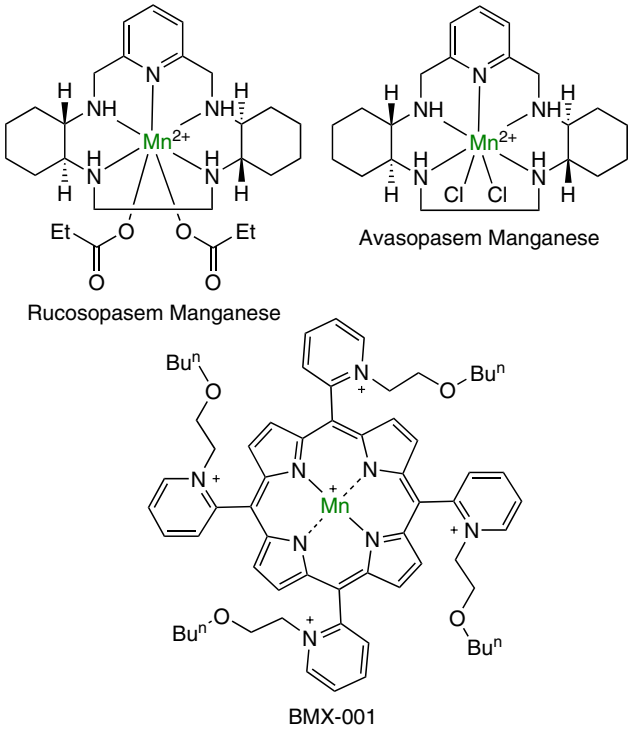
The DSF/Cu combination is in clinical trials as an anticancer agent designed to treat metastatic breast cancer (NCT03323346 code), castration resistant prostate cancer (NCT02963051), myeloma (NCT04521335), glioblastoma (NCT03363659) and sarcoma (NCT05210374). Presumably, the anticancer activity of this combination of disulfiram with copper salts is due to the ability of the coordination compound formed *in situ* to generate ROS owing to the high redox potential of copper and the ability to displace other ions from the enzyme binding sites and high affinity to DNA.[232] In addition, a copper-containing agent for radionuclide theranostics possessing affinity to the ^{67}Cu–CuSarTATE somatostatin receptor is currently in phase I clinical trials for the treatment of neuroblastoma (NCT04023331 code).[233]

Manganese, like copper, has a high redox potential, which makes manganese-based compounds promising agents for the

Structure of Cu complexes



Structure of Mn complexes



therapy of cancer.[234] Several organic manganese-containing complexes are in various plases of clinical trials.

Thus, Rucosopasem Manganese, meant for the use in stereotactic body radiotherapy (SBRT), is in phase II clinical trials for the therapy of pancreatic cancer and lung cancer (NCT04698915 code).[235] This drug is a selective mimetic of superoxide dismutase, which initiates the transformation of superoxide into hydrogen peroxide and increases the efficiency and selectivity of radiation therapy.[236] Avasopasem, an analogue of this agent, is also a superoxide dismutase mimetic; when tested in phase I/II clinical trials for the treatment of head and neck cancer, it increased the survival rate of SBRT patients.[237]

Manganese(III) porphyrins are one more promising class of anticancer agents based on manganese. The MnTnBuOE-2-PyP^{5+} (BMX-001 code) is also a dismutase mimetic and is in clinical trials as a radioprotector (NCT05254327 and NCT03386500).[238] In addition, *in vitro* and *in vivo* assays demonstrated that Mn(III) porphyrin complexes can change the activity of the cell signalling proteins and thus influence cell proliferation and apoptosis, which makes them not only promising radioprotectors, but also potential agents for the therapy of cancer.[239]

Among metal-containing therapeutic agents that are currently in clinical trials, mention should be made of BOLD-100, titanocene dichloride and budotitanum. The mechanism of action of these agents is similar to that of cisplatin and includes ligand exchange, binding to proteins and DNA damage. Complexes based on manganese and copper act *via* redox processes accompanied by the formation of ROS.

Despite the good prospects of studies of many metal-containing anticancer agents and successful completion of early phase clinical trials, the full introduction of these drugs into clinical practice is hampered by a number of factors such as side effects and too low efficacy. This is often due to the lack of understanding of the mechanism of anticancer action and the metabolism of these compounds. Conversely, Pt(IV) prodrugs represent a unique platform for the development of highly active anticancer drugs. Their main feature is the release of Pt(II) complexes approved for use under biological conditions, the mechanism of which has been thoroughly studied over the past decades.[3–6,17] This is a benefit of these prodrugs over coordination compounds of other metals that undergo clinical trials.

4. Conclusion

Platinum(IV) prodrugs represent one of the most promising alternatives to Pt(II)-based anticancer agents. These coordination compounds are less prone to untargeted ligand exchange and premature binding to proteins; the axial ligand is easily modified, which allows fine tuning of the physicochemical properties and biological activity of these agents.

This review gives a systematic account of the approaches to the synthesis of Pt(IV) prodrugs from the conventional platinum(II)-based drugs and considers studies of Pt(IV) complexes with anticancer and antibacterial activity published in 2018–2023. There is a wide range of methods available for the synthesis of Pt(IV) prodrugs, which give coordination compounds with various axial ligands and various types of bonding between the Pt(IV) atom and the ligand and enable direct modification of axial ligands. This opens up the way to the design of Pt(IV) prodrugs optimized to overcome the specific drawbacks of the therapy with platinum(II) drugs.

Over the past 5 years, significant progress has been made in the synthesis of highly efficacious Pt(IV) prodrugs (Fig. 8). As

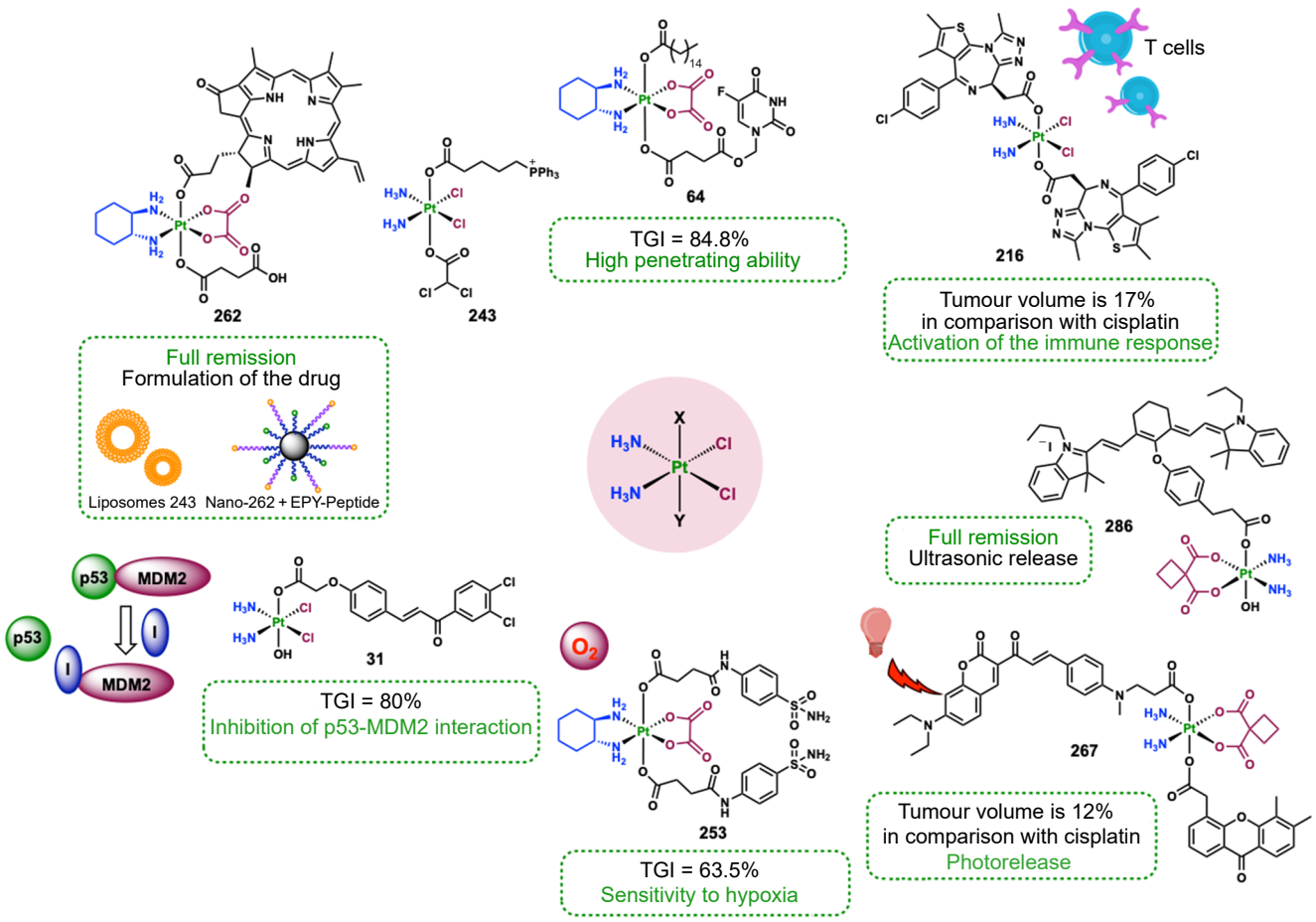


Figure 8. Most effective Pt(IV)-based prodrugs and principles of their action.

expected, higher *in vitro* activity compared to that of cisplatin is inherent in the prodrugs that contain other anticancer agents such as combretastatin A4, 5-fluorouracil, estramustine and other as axial ligands. Nanomolar IC_{50} values were also found for prodrugs that had no cytotoxic moieties in the axial position. In particular, a considerable increase in the cytotoxicity was observed for derivatives of NSAIDs (naproxen, flurbiprofen, melatonin) and carbonic anhydrase inhibitors. In addition, high antiproliferative activity can be achieved by optimizing the lipophilicity of the agent.

The controlled activation of Pt(IV) prodrugs may solve many key problems of platinum-based therapy such as low selectivity to tumours and cisplatin resistance. Over the past five years, researchers have described prodrugs with high *in vitro* activity capable of controlled release under irradiation and inactive in the absence of light. Moreover, the pyropheophorbide-containing prodrug, which absorbs in the NIR region, and coumarin-containing prodrug capable of photoactivation owing to two-photon absorption exhibited a considerable antitumour efficacy *in vivo*.

Despite the fact that most studies published between 2018 and 2023 [2] report prodrugs superior to the parent Pt(II) agents in the activity *in vitro*, the activity of many of these compounds in *in vivo* experiments was comparable to that of cisplatin. Correlation of the stability of Pt(IV) prodrugs in the presence of sodium ascorbate or glutathione with their anticancer efficacy *in vivo* suggests that the complexes that can be rapidly reduced under the action of electron donors decompose in the bloodstream to the parent Pt(II) complex and axial ligands and do not hit the tumour as prodrugs. Conversely, the compounds that showed a low reduction rate in the presence of sodium ascorbate were the best in inhibiting the tumour growth.

The highest *in vivo* activity was inherent in the Pt(IV) prodrugs used in combination with delivery vehicles that ensured longer blood circulation time, that is, liposomes or nanocrystals. A comparable efficiency was demonstrated by the approach involving controlled activation of Pt(IV) prodrugs by ultrasound. In this regard, further progress in the design of effective Pt(IV)-based antitumour agents may be related to the search and creation of optimal delivery vehicles for Pt(IV) prodrugs, which would prevent premature decomposition of the prodrugs and undesirable interactions with normal organs and tissues.

In view of the diversity of axial ligands used in Pt(IV) prodrugs investigated in recent years, it is reasonable to expect that the interest of specialists in the search for new biologically active compounds that can increase the antiproliferative activity of Pt(IV) prodrugs will continue to increase. Meanwhile, new approaches to the design of Pt(IV) prodrugs are being developed, such as controlled activation by ultrasound, and one should expect that new ways for the control of the biological action of platinum coordination compounds will appear. Although no Pt(IV) prodrugs are currently in clinical trials, we may hope that active research in this area would result in the development of highly effective anticancer agents free from the severe drawbacks of traditional platinum(II) drugs.

This review was written with the financial support of the Russian Science Foundation (Project no. 22-15-00182).

5. List of abbreviations and symbols

The following abbreviations and symbols are used in the review:

λ — wavelength,
D — radiation dose,
p — radiation power,
$\log k'$ — retention factor,
$\log P$ — lipophilicity,
$t_{1/2}$ — half-life,
AMP — adenosine monophosphate,
Boc — *tert*-butyloxycarbonyl,
BODIPY — boron dipyrromethenes,
BRD4 — bromodomain-containing protein 4,
BSO — L-buthionine-(*S*,*R*)-sulfoximine,
CA4 — combretastatin A4,
CAIX — carbonic anhydrases,
CDDP — cisplatin,
CDI — carbonyldiimidazole,
COX-2 — cyclooxygenase-2,
CSC — cancer stem cells,
Cyt C — cytochtome C,
DCC — 1,3-dicyclohexylcarbodiimide,
DCM — dichloromethane,
DIPEA — diisopropylethylamine,
DIPC — diisopropylcarbodiimide,
DMAP — 4-dimethylaminopyridine,
DSC — *N*,*N*′-disuccinimidyl carbonate,
EDC — 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide,
Ent — enterobactin,
ER — endoplastic reticulum,
FDA — US Food and Drug Administration;
Fmoc — 9-fluorenylmethyloxycarbonyl,
FUS — focused ultrasound;
GI_{50} — concentration providing 50% cell growth inhibition,
GLUT — glucose transporters,
GST — glutathione-S-transferase,
HBTU — 2-(1*H*-Benzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium hexafluorophosphate,
HDAC — histone acetylase,
HPLC — high-performance liquid chromatography,
IC_{50} — half-maximal inhibition concentration,
ICP-MS — inductively coupled plasma mass spectrometry,
IDO1 — indolamine-2,3-dioxygenase,
LA — lipoic acid,
LD_{50} — half-lethal dose,
MMP — mitochondrial membrane potential,
MMP-9 — matrix metallopeptidases-9,
MTD — maximum therapeutic dose,
mTOR — mammalian target of rapamycin,
NCS — *N*-chlorosuccinimide,
NHS — *N*-hydroxysuccinimide,
NIR — near infrared (range),
NSAID — non-steroidal anti-inflammatory drug,
OLP — oxaliplatin,
PARP — poly(ADP-ribose)polymerases,
PDK — pyruvate dehydrogenase kinase,
PD-L1 — programmed cell death ligand,
PEG — polyethylene glycol,
Pgp — P-glycoprotein,
PPA — pyropheophorbide A,
PPE — poly(phenylene ethynylene),
PTD — photodynamic therapy,
PTX — paclitaxel,
Py — pyridine,
ROS — reactive oxygen species,
RF — resistance factor,
rt — room temperature,
STAT3 — signal transducer and activator of transcription 3,
TARF — tetraacetylriboflavin,
TBTU — 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium tetrafluoroborate,
TBTA — tris(benzyltriazolyl)amine.
TI — therapeutic index,
TGI — tumour growth inhibition,
TS — thymidylate synthase,

Designations of cell lines:
A549 — lung carcinoma,
A549cisR (A549/CDDP) — cisplatin-resistant lung carcinoma,
A431 — cervical carcinoma,
A2780 — ovarian cancer,
A2780cisR (A2780/CDDP) — cisplatin-resistant ovarian cancer,
BCPAP — thyroid cancer,
B16F10 — melanoma,
Caov-3 — primary ovarian cancer,
CH1/PA-1 — ovarian carcinoma,
CT26 — colon cancer,
Du145 — prostate cancer,
EMT-6 — mouse mammary carcinoma,
FaDu — head and neck squamous cell cancer,
HCC1937 — breast carcinoma,
HCT-115, HCT-116 — colorectal carcinoma,
HCT-116/oxR — oxaliplatin-resistant colorectal carcinoma,
HEK293T — human embryonic kidney cells,
HeLa — cervical cancer cells,
HepG2 — human hepatocellular carcinoma,
HL-7702 — normal liver cells,
HPL1D — lung epithelial cells,
HLF — human lung fibroblasts,
HT-29 — colorectal adenocarcinoma,
HUVEC — human umbilical vein endothelial cells,
LNCaP — prostate carcinoma,
L02 — human fetal hepatocytes,
MCF-7 — breast adenocarcinoma,
MCF-10A — breast epithelial cells,
MDA-MB-231 — triple negative breast cancer,
MDA-MB-231/CDDP — cisplatin-resistant triple negative breast cancer,
MDA-MB-435 — melanoma,
MOR — lung adenocarcinoma,
MORcisR — cisplatin-resistant lung adenocarcinoma,
MRC-5 — lung fibroblasts,
MSTO-211H — mesothelioma cells,
PSN-1 — pancreatic cancer,
4T1 — mouse breast cancer,
SGC-7901 — gastric cancer,
SGC-7901/CDDP — cisplatin-resistant gastric cancer,
SKOV-3 — human ovarian adenocarcinoma,
SW480 — colorectal adenocarconoma.

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