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REVIEW



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anticancer chemotherapy

Received 15th March 2019, Accepted 26th April 2019 DOI: 10.1039/c9qi00288j rsc.li/frontiers-inorganic Diazido Pt(IV) complexes with a general formula $[Pt(N_3)_2(L)(L')(OR)(OR')]$ are a new generation of anticancer prodrugs designed for use in photoactivated chemotherapy. The potencies of these complexes are affected by the *cis/trans* geometry configuration, the non-leaving ligand L/L' and derivatisation of the axial ligand OR/OR'. Diazido Pt(IV) complexes exhibit high dark stability and promising photocytotoxicity circumventing cisplatin resistance. Upon irradiation, diazido Pt(IV) complexes release anticancer active Pt(III) species, azidyl radicals and ROS, which interact with biomolecules and therefore affect the cellular components and pathways. The conjugation of diazido Pt(IV) complexes with anticancer drugs or cancertargeting vectors is an effective strategy to optimise the design of these photoactive prodrugs. Diazido Pt(IV) complexes represent a series of promising anticancer prodrugs owing to their novel mechanism of action which differs from that of classical cisplatin and its analogues.

Diazido platinum(IV) complexes for photoactivated

1. Introduction

The treatment of cancer, a group of diseases involving uncontrolled growth and spread of cells and representing the leading cause of death globally, remains a major challenge.¹ Phototherapy, consisting of photodynamic therapy (PDT) and photoactivated chemotherapy (PACT), has attracted much

Department of Chemistry, University of Warwick, Coventry, CV4 7AL, UK. E-mail: p.j.sadler@warwick.ac.uk attention in cancer treatment due to its high spatial-temporal controllability and minimal invasiveness. The mechanism of action of clinically approved PDT is based on the combination of a photosensitiser, light and oxygen.² High oxygen dependence limits the application of PDT since the oxygen concentration in hypoxic tumours is low. PACT, in contrast to PDT, is an oxygen-independent phototherapy, which involves chemical changes of prodrugs upon irradiation and provides a new avenue in anticancer drug development.^{3,4}

The serendipitous discovery of the antiproliferative properties of cisplatin in 1968 by Rosenberg et al. stimulated a



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Cinzia Imberti

Cinzia Imberti obtained a M.Sci degree in Chemistry at the University of Padova (Italy) in 2012. She then obtained a PhD at King's College London, working on the development of new radiometal-based radiopharmaceuticals under the supervision of Professor Philip J. Blower. On completion of her PhD she was awarded a Sir Henry Wellcome Postdoctoral Fellowship and joined Peter Sadler's group at the University

of Warwick in 2018. Her research is focussed on the mechanism of action of platinum-based anticancer agents with particular emphasis on photoactivatable platinum complexes.

 Table 1
 Comparative properties of bioactive platinum complexes

Pt complexes	Mechanism of action	Advantages	Disadvantages	Ref.
Cisplatin-like Pt(II) complexes	Hydrolysis, covalent DNA binding	FDA approved, high cure rate	Poor pharmacokinetics, dose-limiting side effects, restricted anticancer spectrum, lack of selectivity, high incidence of resistance	5 and 6
Pt(II) complexes different from cisplatin	Covalent or non-covalent DNA binding	Overcome cisplatin resistance	Limited selectivity, inherent systemic toxicity	16-19
Photosensitive Pt(II) complexes	Excitation of triplet oxygen (PDT)	Good photoselectivity, overcome cisplatin resistance	Oxygen dependence, limited $\lambda_{\rm ex}$ wavelength range	20 and 21
Photoactive Pt(II) complexes	Photoactivation to form cytotoxic Pt(II) species (PACT)	Oxygen independence	High dark cytotoxicity, low photocytotoxic indices	45-53
Chemically reductive Pt(IV) complexes	Reduction by bio-reductants	Easy modification, improved selectivity and cellular accumulation	Poor stability before entering cells	30-32
Photoactive Pt(IV) complexes	Photoreduction to release cytotoxic Pt(II) species and radicals (PACT)	Oxygen independence, good dark stability, overcome cisplatin resistance, spatial and temporal selectivity, easy modification	Low photocytotoxic indices, short $\lambda_{\rm ex}$ wavelength range, limited light penetration	62, 68, 77 and 81

wide research for other platinum-based anticancer drugs.^{5,6} Platinum drugs are now used to treat over 40% of all cancer patients in chemotherapy since cisplatin was approved by FDA in 1978 to treat testicular and ovarian cancers. 7-10 Several classes of platinum anticancer agents, as summarised in Table 1, have been investigated in the past decades and extensively reviewed in recent publications. 11-21 Compared with Pt(II) complexes, 22 Pt(IV) complexes with d⁶ electronic configuration are more kinetically inert to ligand substitution, and more stable under physiological conditions. 14,23 Pt(IV) complexes can be reduced by bio-reductants (e.g. GSH, ascorbic acid, cysteine) to form active Pt(II) species through which they exert their anticancer activity.24-26 Although some Pt(IV) complexes entered clinical trials, none of them has been approved for clinical use.²⁷⁻³²



Peter J Sadler

Peter Sadler obtained his BA, MA and DPhil at the University of Oxford. Subsequently he was a MRC Research Fellow at the University of Cambridge and National Institute for Medical Research. From 1973-96 he was Lecturer, Reader and Professor at Birkbeck College, University of London, and from 1996-2007 Crum Brown Chair of Chemistry at the University of Edinburgh. Then he became Head of the Department of Chemistry at the

University of Warwick, where he is now a Professor. He is a Fellow of the Royal Society of Chemistry (FRSC), Royal Society of Edinburgh (FRSE) and the Royal Society of London (FRS), and an EPSRC RISE Fellow (Recognising Inspirational Scientists and Engineers).

Notably, photodecomposition is a prominent feature of Pt(IV) complexes, suggesting their potential as PACT prodrugs. 15,33-35 Transition metal azido complexes are usually light sensitive. 36,37 The first photoreductive Pt(IV) complex with azide ligands reported by Vogler et al. in 1978 was trans- $[Pt(N_3)_2(CN)_4]^{2-.38}$ Upon irradiation with UVA at 302 nm, the wavelength of its maximum electronic absorbance, assigned as a ligand-to-metal ($N_3 \rightarrow Pt$) charge-transfer transition, trans-[Pt $(N_3)_2(CN)_4^{2-}$ was converted to $[Pt(CN)_4]^{2-}$ via the formation of two azidyl radicals without a Pt(III) intermediate. The unstable azidyl radicals released nitrogen gas, preventing the re-oxidation of the platinum centre.36 Another azido Pt(IV) complex $[Pt(N_3)_6]^{2-}$ was found to undergo photoreduction, yielding $[Pt(N_3)_4]^{2-}$ and even metallic Pt, accompanied by the release of nitrogen gas.39,40 These early studies provided a basis for our group to develop diazido Pt(w) complexes that are stable in the dark, and exhibit promising cytotoxicity upon irradiation. 11,15,34,35,41,42

In this review, our discussion begins with a brief introduction to photoactivated chemotherapy and focuses on the development of photoactive diazido Pt(IV) complexes, including the design of new complexes, their photochemistry and photobiology, mechanism of action, derivatisation of axial ligands and conjugation to nanoparticles to improve photocytotoxicity and selectivity. We give a comprehensive description of diazido Pt(IV) complexes and consider feasible strategies for their future clinical use.

Photoactivated chemotherapy

light-mediated chemical changes, relies on transforming an inactive prodrug into an active agent upon irradiation.3,4,43,44 Platinum-based PACT anticancer drugs can be activated via different mechanisms as described below.

• Photoreduction: Pt(IV) complexes can be reduced upon irradiation to release cytotoxic Pt(II) species and ligands. 34,41

- Photosubstitution: Pt(II) complexes with photolabile ligand (e.g. curcumin) undergo ligand dissociation followed by solvent substitution. 45-49
- · Photocleavage of ligand: Photon absorption by the metal centre can result in the cleavage of organic bonds, (e.g. C-N, N-O) in photosensitive o-nitrobenzyl alcohol derivatives coordinated to platinum. 50,51
- Photoswitching: Pt(II) complexes bridged by a diarylethene ligand change the configuration of the ligand upon irradiation to alter the cytotoxic properties. 52,53

Although PACT is often compared with PDT since they both require light to activate relatively non-toxic drugs, these two classes of treatments present many differences.4 Generally, PACT agents decompose upon irradiation, while PDT agents are photostable. Notably, the oxygen-independent mechanism of action of PACT agents improves their efficiency in hypoxic tumours and represents a major advantage of PACT over PDT.

However, the development of PACT is still in its infancy, and the current performance of PACT complexes is not competitive with PDT photosensitisers. Some photosensitisers in clinical trials exhibit extremely high photocytotoxicity indices (photo-cytotoxicity/dark-cytotoxicity, e.g. TLD-1433, up to 10⁵),⁵⁴ and some can be excited by near infrared (NIR) irradiation (e.g. WST-09, 763 nm).55 In contrast, the highest reported photocytotoxicity index of PACT agents is 1880,56 and the longest excitation wavelengths reported for simple metal complex-based PACT agents are in the red region, which limits light penetration into tissue to a depth of ca. 5 mm. ^{57–59} To enter clinical trials, more effort needs to be invested into the preclinical development of new PACT complexes.

Development of photoactive Pt(IV) complexes

In general, photoactive Pt(IV) complexes contain axial, nonleaving, and leaving ligands. Axial ligands can be used to tune the physical and chemical properties of the complexes without altering the structure of the active pharmacophore that is ultimately released.60 Non-leaving ligands do not significantly alter the reduction potential of Pt(IV) complexes and can be varied to change their properties without reducing the dark stability.61 Leaving ligands play key roles in photoactive Pt(IV) complexes. Two main classes of Pt(IV) complexes, namely diiodo- and diazido-Pt(IV) complexes, have been investigated as photoactive Pt(IV) anticancer prodrugs (Scheme 1).

Diiodo-Pt(IV)-ethylenediamines bearing various ligands (Cl, OH, OCOCH3, OSO2CH3, or OCOCF3) were reported by Kratochwil et al. in 1996 as the first-generation photoactive Pt(IV) complexes with a general formula trans, cis- $[Pt(X)_2I_2(en)]$ (Fig. 1). $6^{\overline{2}-66}$ Iodide is a weak field ligand with a low optical electronegativity,67 and thus the LMCT bands of these complexes are centred at the relatively longer wavelength of ca. 400 nm with a tail extending out into the visible range. 62 As a result, all of these complexes are photolabile to light λ_{irr} > 375 nm. However, their application is limited due to their poor dark stability, which might be due to facile cellular bioreduction. For example, electron donation to Pt(IV) can occur through thiolate attack on iodide ligands. 65

The second-generation photoactive Pt(IV) complexes with azide ligands, were developed later to achieve better dark stability and photobiological properties with a general formula [Pt(N₃)₂(L)(L')(OR)(OR')] (Fig. 2, Table 2). The first diazido-Pt(iv) complexes, cis, trans- $[Pt(en)(N_3)_2(OH)_2]$ (1) and cis, trans, $cis-[Pt(N_3)_2(OH)_2(NH_3)_2]$ (2) were reported in 2003.⁶⁸ Cytotoxicity studies showed that these complexes caused very low inhibition of growth in the dark, but significantly enhanced cytotoxicity upon irradiation in both 5637 bladder

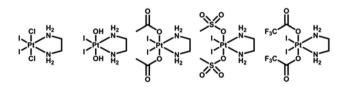
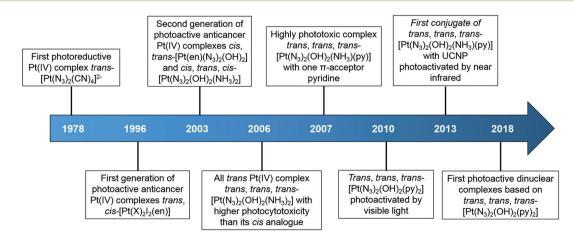


Fig. 1 First-generation photoactive diiodo-Pt(IV) complexes.



Scheme 1 Timeline illustrating the publication year for important photoactive Pt(IV) complexes.

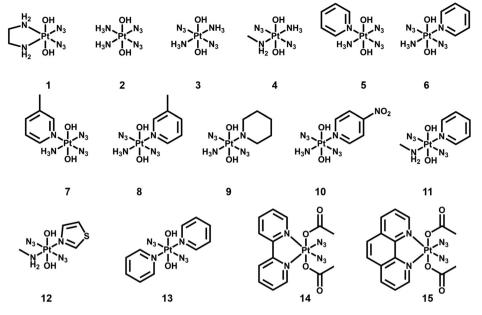


Fig. 2 Selected second-generation photoactive diazido-platinum(IV) complexes.

Table 2 LMCT bands and IC_{50} values for selected photoactive diazido-Pt(IV) complexes

	Non-leaving ligands			1.160m b		IC ₅₀ values ^a /μM				
Complex	L_1	L_2	cis/trans	LMCT band $\lambda_{\text{max}} \text{ nm}^{-1}$ (N ₃ \rightarrow Pt)	λ_{irr}/nm	Cell line	Light	Dark	PI	Ref.
$[Pt(N_3)_2(CN)_4]^{2-}$	CN	CN	t	302	302	_	_	_	_	38
$[Pt(N_3)_6]^{2-}$	_		_	308	314	_	_	_	_	39 and 40
1	en		С	315	365 365	5637 5637-CDDP	63.0 ± 20.2 79.8 ± 16.6	440 ± 143 >200	7.0 >2.5	68 and 69
2	NH_3	NH_3	С	256	365 365	5637 HaCaT	49.3 ± 28.1 169.3	357 ± 81 > 287.9	7.2 >1.7	68 and 69 74
3	NH_3	NH_3	t	285	365	НаСаТ	121.2	>287.9	>2.4	70 and 74
4	NH_3	MA	t	286	365	НаСаТ	65.6	>276.8	>4.2	74 and 76
5	NH_3	Py	c	258	365	НаСаТ	100.9	>244.4	>2.4	74
6	NH_3	Py	t	289	365	НаСаТ	6.8	>244.4	>35.9	74 and 77
7	NH_3		С	259	365	НаСаТ	>236.2	>236.2	_	74
8	NH_3		t	289	365	НаСаТ	22.0	144.1	6.6	74 and 76
9	NH_3		t	288	366	5637	29.17 ± 2.23	>80	>2.7	79
10	NH_3		t	287	365	_	_	_	_	75
11	Ру	ÑO₂ MA	t	289	365 420	HaCaT HaCaT	2.6 14.7	>236.3 >236.3	>90.8 >16.0	80
12	Tz	MA	t	289	365 420	HaCaT HaCaT	3.5 11.2	>232.9	>66.5 >20.7	80
13	Ру	Ру	t	294	365 420 365 365	HaCaT HaCaT A2780 A2780cis	1.4 9.5 1.4 14.5	>212.3 >212.3 >212.3 >212.3	>151.6 >22.3 >151.6 >14.6	81
14	Вру		С	304/315	365	_	_		_	83
15	Phen		c	300	365	_	_	_	_	83

 $[^]a$ Note that IC $_{50}$ values were obtained via different methods/conditions. PI = Photocytotoxicity index.

cells and cisplatin-resistant 5637 bladder cells, even though to a less extent than cisplatin.⁶⁹

Intriguingly, the all trans photoactive Pt(IV) prodrug, trans, trans, trans-[Pt(N₃)₂(OH)₂(NH₃)₂] (3), exhibited higher aqueous solubility and a more intense and red-shifted LMCT band compared with its cis isomer 2.70 Higher photocytotoxicity induced by 3 upon irradiation (as toxic as cisplatin) was determined in cancer cells, which was in contrast to the early structureactivity relationship for classical anticancer platinum complexes that the cis geometry was more favourable. 71-73 Comparisons between other diazido Pt(IV) complexes incorporating a wide range of aliphatic and aromatic amines confirmed the higher potency of the *trans* configuration. ^{74,75}

The introduction of a methyl substituent into an ammonia ligand improved the photocytotoxicity of the Pt(IV) complexes trans, trans, trans- $[Pt(N_3)_2(OH)_2(NH_3)(MA)]$ (4, MA = methylamine).74,76 Furthermore, replacement of an ammine ligand in 3 by a π -acceptor pyridine (Py) ligand resulted in the highly phototoxic complex trans, trans, trans-[Pt(N₃)₂(OH)₂(NH₃)(Pv)] (6) that showed 13-80× higher photocytotoxicity compared with cisplatin, and 15× higher towards cisplatin-resistant human ovarian A2780cis cells.⁷⁷ Notably, 6 is the only simple diazido-Pt(IV) prodrug that has been tested in vivo. Two of seven nude mice bearing OE19 oesophageal cancer xenografts treated with 6 at low dose with short irradiation times (420 nm, 100 J cm⁻², 2×30 min) survived at 35 days, while none of the control mice without drug or irradiation survived, and the complex was well tolerated.⁷⁸ Encouraged by the success of 6, a series of ligands was introduced to replace one or both of the ammine ligands. The replacement of pyridine by 3-methylpyridine (8), 74,76 piperidine (9), 79 or 4-nitro-pyridine (10)75 did not result in significant differences. Higher cytotoxicity of complexes with methylamine trans, trans, trans, trans- $[Pt(N_3)_2(OH)_2(MA)(Py)]$ (11) and trans, trans, trans. $[Pt(N_3)_2(OH)_2(MA)(Tz)]$ (12, Tz = thiazole) was attributed to the high stability of Pt-MA bonds. 80 In addition, the Tz-containing analogue 12 was more effective towards the cisplatin resistant cell lines.

The key role of pyridine ligands in the high phototoxicity and the mechanism of action different from cisplatin promoted the development of a novel diazido-Pt(IV) complex with two pyridine ligands, trans, trans, trans-[Pt(N₃)₂(OH)₂(Py)₂] (13).81 Upon irradiation with UVA or visible blue light, 13 exhibited significant toxicity toward a number of human cell lines with high phototoxicity indices. Dinuclear complexes based on 13 also displayed photodecomposition with blue light irradiation.82

Diazido-Pt(IV) complexes incorporating π -conjugated bidentate diimine ligands trans, cis-[Pt(2,2'-Bpy)(OAc)₂(N₃)₂] (14, 2,2'-Bpy = 2,2'-bipyridine) and trans, cis-[Pt(Phen)(OAc)₂(N₃)₂] (15, Phen = phenanthroline) exhibited greater absorption at longer wavelengths compared with previously reported diazido-Pt(IV) complexes.⁸³ Their photodecompositions were observed upon irradiation with both UVA and visible green light.

Other than iodide and azide, chloride is also a potential candidate as leaving ligand for photoactive Pt(IV) complexes.

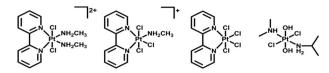


Fig. 3 Photoactive Pt(IV) complexes with chlorides as leaving ligands.

Upon irradiation, photoreduction to Pt(II) species was observed for trans-[PtCl₂(2,2'-Bpy)(MA)₂]Cl₂, mer-[PtCl₃(2,2'-Bpy)(MA)]Cl, [PtCl₄(2,2'-Bpy)], and trans, trans, trans-[PtCl₂(OH)₂(DMA)(IPA)] (Fig. 3, DMA = dimethylamine, IPA = isopropylamine). 84-86 Some Pt(IV) complexes with chloride ligands, such as oxoplatin, even though not photoactive on their own, exhibit photorelease of Pt(II) species when conjugated to specific nanoparticles.87,88

Photochemistry and photobiology of diazido Pt(IV) complexes

4.1. Photodecomposition pathways

Photodecomposition of diazido Pt(IV) complexes mainly relies on the reduction of Pt(IV) and the release of azide ligands triggered by light (Fig. 4a).38 The strong absorbance, assigned to a dissociative LMCT band (N3 -> Pt), is a key transition in photodecomposition. 70,74,75 Upon irradiation, a rapid decrease in intensity of the LMCT band can be observed for diazido Pt(IV) complexes due to the release of azide ligands (Fig. 4b and c).38,41 The wavelength of the LMCT band is affected significantly by the overall configuration of Pt(IV). 70,74,75,89 In general, complexes with cis-{PtIV(N3)2} motifs exhibit LMCT bands at shorter wavelength (ca. 260 nm), while those of trans isomers are red-shifted by 30 nm (ca. 290 nm) (Table 2).74 However, complexes with bidentate chelating non-leaving ligands display LMCT bands at longer wavelength (ca. 300 nm) than diazido Pt(IV) complexes with only monodentate ligands, despite of their cis configuration. 68,83,89 Electronic transitions

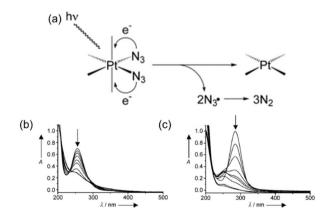


Fig. 4 (a) A possible mechanism for the photoreduction of diazido-Pt(IV) complexes; 91 UV-vis spectral changes for (b) 2 and (c) 3 in aqueous solution upon UVA irradiation.⁷⁰ Adapted from ref. 91 and 70.

for cis isomers tend to arise from transitions from orbitals of the azide ligands to metal d orbitals, whereas those for alltrans isomers are more likely to arise from both axial and azide ligands to the metal d orbitals, and thus lead to different photoproducts.⁷⁵ The electron-donating and steric properties of non-leaving ligands are also important factors which affect the LMCT band. The replacement of NH₃ by a π -acceptor pyridine ligand results in a red-shift of the intense LMCT band (ca. 5 nm for each substitution). 70,77,81 The substituents on pyridine ligands affect the maximum absorption slightly.⁷⁵

The low-intensity transitions (the "tail") that have mixed dissociative ¹LMCT/¹IL (IL = interligand) character might account for the photoactivity induced by longer wavelength activation, 75,81 which is a major challenge in the development of new diazido Pt(IV) complexes. The low-intensity transitions have significant contributions from the LUMO orbital that is strongly σ-antibonding towards the two Pt-N₃ bonds.⁸¹ Light excitation to populate this orbital induces elongation of the Pt-N₃ bond, and eventually leads to azide release. 81 The weak absorption of 13 in the blue region (414 nm) might be responsible for its photodecomposition with visible light.⁸¹

Much effort has been devoted to the investigation of the photodecomposition pathways of the most promising diazido Pt(iv) complexes. The early studies suggested that the photodecomposition involved the release of two azide ligands as N₃* radicals, which can combine to form N2 molecules.38 However, during further investigation of diazido Pt(IV) complexes, different pathways have been proposed depending on the configuration of Pt(IV), non-leaving ligands, and the solution environment.

1D ¹⁴N{¹H} NMR spectra of ¹⁵N-labelled 2 with two ¹⁵NH₃ in acidic aqueous solution (pH = 5.1) upon irradiation with UVA (365 nm) suggested the formation of N2 and unlabelled free NH3, with a pH increased to 10.7 and O2 liberation detected.90 In addition, the major Pt(II) species detected was assigned to trans-[Pt(NH₃)₂(H₂O)₂]²⁺, indicating photoisomerisation with photoreduction. Nitrene intermediates generated during the photodecomposition were trapped by dimethyl sulphide (DMS), which suggested a possible new mechanism. 90 However, the photodecomposition of 2 in PBS involved the photosubstitution of at least one azide ligand by H₂O/OH and the release of azide ions (Fig. 5). 91 Ammonia ligands were also released from Pt(IV) as confirmed by NMR with an increase in pH. After replacement of both azides (or even ammonia ligands) by H₂O/OH, photoreduction may occur by one-electron transfers from each of two hydroxide groups coordinated to the Pt(IV) leading to some species containing trans-{Pt(OH)₂} motifs and hydroxyl radicals. DFT and TD-DFT calculations demonstrated the theoretical possibility of the replacement of both NH₃ and N₃ groups trans to each other by H₂O/OH.⁹²

The photodecomposition pathways for 3 in PBS and acidic solution are similar to that of its cis isomer 2, in which the azide ion was detected in PBS, while N2 was found in acidic solution.93 Trans Pt(II) species, O2 and free ammonia were detected as photoproducts of 3 with a subsequent increase in pH in both basic and acidic solution. However, the trans isomer 3 gave fewer types of Pt species in acidic solution, but more minor side-products and less hydroxo-/oxo-bridged species compared to its cis isomer 2.93 In addition, no photoisomerisation was observed in the photodecomposition of 3.

Even though azidyl radicals are regarded as important cytotoxic photoproducts of diazido Pt(IV) complexes, they were not considered further in the early work. 90-93 A recent study on the first stage of photodecomposition using ultrafast kinetic spectroscopy and nanosecond laser flash photolysis suggested that the photodecomposition of both cis 2 and trans 3 is a chain process beginning with the replacement of one azide ligand by a water molecule and the release of azidyl radicals.94 Two successive Pt(III) intermediates participated in chain initiation and $[Pt^{III}(NH_3)_2(OH)_2]^+$ was a chain carrier.

Possible pathways for photodecomposition and photoreactions of complex 2 with 1-methylimidazole in PBS. Adapted from ref. 91.

Trans- $[Pt(OH)_4(^{15}NH_3)(Py)]$ and trans- $[Pt(N_3)(OH)_3(^{15}NH_3)]$ (Py)] were detected as photoproducts of 6 using ¹⁵NH₃ and 1D ¹H and 2D [¹H, ¹⁵N] HSQC NMR spectroscopy, indicating the release of azides.⁷⁷ In contrast, no evidence of pyridine release was found. Furthermore, very little reduction to Pt(II) species was detected by NMR. Consistently, [Pt(OH)2NH3(Py)] and [Pt(OH)(N₃)(NH₃)(Py)] at low concentration were detected by LC-MS. 95 In addition, [Pt(N₃)₃(OH)(NH₃)(Pv)] was observed by LC-MS as a photosubstitution product of 6 as well as azide ions, indicating the release of azide ligands. 95 No platinum species without pyridine were detected by LC-MS, in accordance with NMR data. However, no detailed photodecomposition pathway has been proposed for 6 so far. For its piperidine analogue 9, only [Pt(OH)₂(piperidine)NH₃] was detected as a product by LC-MS, suggesting an effect of the heterocyclic ring on the photodecomposition pathways. 96 The MA analogue of 6, 11 produced N₂, N₃, N₃ radicals and ¹O₂ upon irradiation, with Pt-nitrene intermediates involved in the pathway (Fig. 6).97

Comprehensive spectroscopic studies of the photodecomposition of the most promising diazido Pt(IV) complex 13 have been performed by Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) and NMR. 81,98 ATR-FTIR revealed the binding of water to platinum in the final product, which was assigned as trans-[PtII(Py)2(H2O/OH)2] fitted by Multi-Curve Resolution Alternating Least Squares (MCR-ALS). Trans-[Pt^{II}(N₂)(Py)₂(H₂O/OH)] was detected as an intermediate, implying release of at least one hydroxyl radical and one azidyl radical or two hydroxyl radicals during the photoreduction. 98 No pyridine release was detected by 1H NMR, in contrast to NH3 complexes, and might contribute to its higher potency.81

4.2. Photoreactions with important biomolecules

The cytotoxicity of diazido Pt(IV) complexes is mediated by the photoreduction products, including Pt(II) species, azidyl radicals and ROS, and their interactions with biomolecules, including nucleotides, DNA, amino acids, peptides and proteins.35,41

The RNA monomer nucleotide guanosine monophosphate (5'-GMP) is often used as a model for nucleobase guanine, considered to be the major target of Pt anticancer drugs on DNA. 99,100 Unlike Pt(II) complexes, diazido Pt(IV) complexes do not interact with 5'-GMP in the dark, but only upon irradiation, forming mono- and/or bis-GMP adducts. A bis-GMP adduct [Pt(en)(GMP-N7)₂]²⁺ was detected by NMR when 1 reacted with two mol. equiv. of 5'-GMP upon irradiation with visible light (457.9 nm), while $[Pt(en)\{d(GpG)-N7^1,N7^2\}]^{2+}$ was the only major photoproduct of 1 in the presence of one mol. equiv. of d(GpG).⁶⁸ Similar results were found for 2 and 3.^{68,70} Interestingly, trans 3 was able to form a bis(5'-GMP) adduct under UVA irradiation at a faster rate than transplatin. 70 In addition, the photodecomposition of 3 was accelerated in the presence of 5'-GMP, and a few Pt-GMP adducts were even detected upon red light irradiation. 70 For 6, the Pt(II) mono-GMP adduct [Pt(N₃)(NH₃)(5'-GMP)(Py)]⁺ was detected as the initial main photoproduct from reaction with 5'-GMP, while the bis-5'-GMP adduct trans- $[Pt(NH_3)(Py)(5'-GMP)_2]^{2+}$ became predominant at longer irradiation times.⁷⁷ Unexpectedly, guanine photooxidation by 11 was observed via a mechanism involving ${}^{1}O_{2}$, while the NH₃ ligand in the adducts probably arose from the formation of a Pt-nitrene intermediate (Fig. 6).97 Both mono- and bis-GMP adducts (trans-[Pt(N₃) $(Py)_2(5'-GMP)_1^+$ and trans- $[Pt(Py)_2(5'-GMP)_2]^{2+}$) were detected as photoproducts of 13 and 5'-GMP by NMR, LC-MS and ATR-FTIR spectra. 81,98

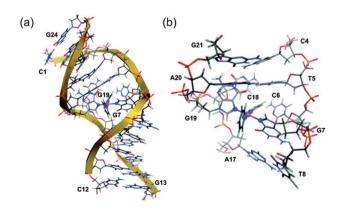
DNA platination photoinduced by 1 with $r_b = 0.01$ ($r_b = Pt$ coordinated per nucleotide residue) gave a preference for GG sequences, forming bifunctional GG adducts, which is similar to cisplatin. 101 Intriguingly, photoactivated 1 and 2 formed GG adducts more rapidly than cisplatin.⁶⁹ Transcription mapping revealed similar major stop sites in a DNA fragment treated with 6 and irradiation or with transplatin, while the level of DNA adducts formed by irradiated 6 was significantly higher than that by cisplatin and transplatin.⁷⁷ DNA interstrand cross-links and DNA-protein cross-links were also induced by 6 with light. Remarkably, a plasmid treated with 6 and UVA exhibited considerably lower levels of damage-induced DNA

Fig. 6 Possible pathways for photodecomposition and photoreactions of 11 with 5'-GMP upon irradiation with UVA. Adapted from ref. 97.

repair synthesis than those with cisplatin. Significantly larger unwinding angles and a higher percentage of interstrand cross-links were observed when DNA was treated with **11** or **12** compared to cisplatin. The nature of DNA lesions induced by **13** upon irradiation was expected to be different from those induced by cisplatin. Treversible DNA coordination was observed for **13** with light, including *ca.* 12% interstrand (intramolecular) cross-links, *ca.* 37% monofunctional adducts, and *ca.* 51% intrastrand cross-links. The interstrand cross-links formed by **13** and light were characterised, and the structure of a *trans*-{Pt(Py)₂}²⁺-DNA showing a bend toward the minor groove, a global bend of *ca.* 67° and an unwinding of *ca.* 20° was simulated by computational studies (Fig. 7).

Other than nucleotides and DNA, amino acid, peptides and proteins are also targets for Pt(II) species released from diazido Pt(IV) complexes. The photoactivated platinum centre of 2 can also react with dimethyl sulphide, a thioether related to that in the side chain of the amino acid methionine (Met), in acidic solution. The nitrene intermediate formed dimethylsulfilimine adducts that can undergo a Stevens-like rearrangement in which the Pt-N=SMe₂ group becomes Pt-N(H)-CH₂-SMe, giving a N-(methylthiomethylene)amido derivative. The derivative can release two hydroxyl radicals upon irradiation. The photoreaction between 2 and 1-methylimidazole, a histidine (His) side chain analogue, in PBS (Fig. 5) gave 6 different Pt-coordinated 1-methylimidazole species, suggesting it can bind to proteins.

Azidyl radicals are potentially key species, which might kill cancer cells by oxidative attack. Azidyl radicals generated by **13** can be trapped by 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) and detected using EPR (Fig. 8a). However, in the presence of Trp, the azidyl radicals were quenched, which reduced the photocytotoxicity of **13**. He resulting tryptophan (Trp) radicals have been trapped by 2-methyl-2-nitrosopropane (MNP)



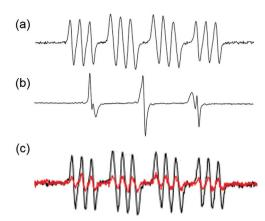


Fig. 8 EPR spectra of 13 in PBS upon irradiation in the presence of spintraps (a) DMPO for N_3 radicals; (b) Trp + MNP for Trp radicals (and background DTBN radicals); (c) pentagastrin + DMPO for N_3 radicals (red: with pentagastrin; black: without pentagastrin). Adapted from ref. 105.

and such radicals might be involved in the cytotoxicity towards cancer cells (Fig. 8b). ¹⁰⁵ Background signals from di-*tert*-butyl nitroxide (DTBN) radicals arose from MNP upon irradiation. The Trp containing peptide pentagastrin also quenched azidyl radicals (Fig. 8c), although not as efficiently as Trp. ¹⁰⁵ The antioxidant melatonin (MLT) quenched azidyl radicals and formed MLT radicals in a similar way to Trp. ¹⁰⁵ In contrast, other amino acids, including Tyr (tyrosine) and His, were unable to quench azidyl radicals despite of their important roles in electron transfer. ^{104,105}

A combined attack on peptides by photoactivated 13, involving sequence-dependent platination and radical mechanisms, was observed using UHR-FT-ICR MS and EPR. 106 Two model peptides with amidated C-termini, Substance P (SubP) and [Lys]³-Bombesin (K³-Bom), were treated with 13 and irradiation. SubP gave rise to only monoplatinated adducts with different amino acids, while K³-Bom showed both mono- and di-platinated adducts with a preference for His. In contrast, oxidation of SubP occurred only at Met, whereas oxidation of both Met and Trp was observed for K3-Bom. Thioredoxin (Trx) is an important enzyme in the redox signalling pathway and is usually overexpressed in tumour cells.107 Platination of His, Glu (glutamic acid), and Gln (glutamine) residues of Trx and oxidation of Met, Trp, and the Cys catalytic sites induced by 13 upon irradiation can inhibit the activity of Trx enzyme and Trx system, and further increase the cellular ROS level. 108

4.3. Effects on cancer cellular components and pathways

Photoreactions between photoactivated diazido Pt(IV) complexes and important biomolecules can result in the dysfunction of cellular components, changes to cellular morphology and disruption of cellular pathways, and eventually cell death.

The ability to damage DNA in intact cells has been investigated for both *cis* 2 and *trans* 3 using comet assays. ⁷⁰ Both complexes produced DNA cross-links in living cells upon

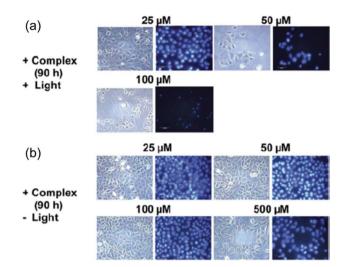


Fig. 9 Fluorescence microscopy images of 5637 cells treated by 2 with and without irradiation. Adapted from ref. 69.

irradiation and the effects were similar to those produced by cisplatin. When 5637 bladder cells were treated with 2 in the presence of light, dramatic changes in the morphology of the cells occurred, including cellular shrinkage, loss of adhesion with neighbouring cells, a large amount of nuclear packing, and nuclei disintegration, suggesting a different mechanism of cell death compared to cisplatin (Fig. 9).69 None of these effects was observed without irradiation. Intriguingly, typical hallmarks of apoptosis, budding and cellular fragmentation, were not observed.

Single-cell electrophoresis experiments indicated that different DNA damage in HaCaT keratinocyte cells was caused by 6 and light with limited inhibition of DNA migration compared to cisplatin.⁷⁷ Also, p53 protein did not accumulate in cells, and caspase 3 activity was not detected when treated with 6 and irradiation, which was different from cells treated with cisplatin.⁷⁷ An autophagic mechanism was envisaged for 6 based on a significant increase in LC3B-II level and a decreased p62 level in treated cells.⁷⁸ Cell swelling and very little blebbing was seen for HL60 cells treated with irradiated 6.78 Notably, light activation was found to enhance the cellular accumulation of 6.79

Excellent nuclear DNA binding properties were observed for photoactivated 13 that was shown to be a potent inhibitor to stall RNA pol II for RNA synthesis. 102 In contrast to cisplatin, photoactivated 13 did not produce fragmented or condensed nuclei, indicating a different mechanism.81

Derivatisation of photoactive diazido Pt(IV) complexes

The axial ligands (with arbitrary choice of OH as axial ligands) of photoactive Pt(IV) complexes can not only be released, similar to azide ligands, upon photoreduction to Pt(II), but also greatly affect the reduction potential of Pt(IV). 66,75 Generally, Pt(IV) complexes with a lower reduction potential (depending on the axial ligand: I -> Cl -> OAc -> OH -) exhibit higher stability to reductants. 60,66 Thus, the hydroxide ligands can enhance aqueous solubility and also stabilise the Pt(IV) oxidation state. 109 Modification of axial ligands is a feasible method to improve the selectivity and cytotoxicity of diazido-Pt(IV) complexes.

5.1. Multi-action diazido-Pt(IV) complexes

By combining photoactive Pt(IV) complexes with other anticancer active agents, such as stable radicals, enzyme inhibitors, and photosensitisers, multi-action prodrugs are obtained. Upon irradiation, these prodrugs release not only the reactive Pt(II) species and azidyl radicals, but also additional cytotoxic agents, enhancing the anticancer efficacy of the drugs. Owing to their different cellular targets and mechanism of action, combination of these cytotoxic species often results in a synergistic effect, producing greater cytotoxicity than that expected by simple addition of the two agents. Examples of diazido-Pt(IV) multi-action agents are summarised below.

Dinuclear complexes such as 16, in which two molecules of 13 are bridged in an axial position by bisamide dicarboxylato linkers (Fig. 10) display similar photocytotoxicity towards cisplatin-resistant ovarian A2780cis and A2780 cells, and interestingly are relatively non-toxic toward normal cells (MRC-5 lung fibroblasts).82

The TEMPO radical has been conjugated to 13 since nitroxide radicals themselves can possess potent anticancer activity (17, Fig. 10). The presence of the TEMPO radical in the complex was confirmed by EPR spectroscopy. Upon irradiation with blue light (420 nm), azidyl and TEMPO radicals were released, accompanied by the formation of toxic Pt(II) species.

Suberoyl-bis-hydroxamic acid (SubH) is a histone deacetylase (HDAC) inhibitor, which exhibits a profound dose-dependent inhibition of cancer cell proliferation. 111 Two SubH ligands have been attached to the axial positions of cis, trans- $[Pt(N_3)_2(OH)_2(tBu_2bpy)]$ to generate a diazido-Pt(v) complex, cis, $trans-[Pt(N_3)_2(Sub)_2(tBu_2bpy)]$ (18, Fig. 10), that was stable

Fig. 10 Multi-action diazido-Pt(IV) complexes 16-18

in the dark. 112 Complex 18 released SubH and cytotoxic Pt(II) species, which targeted similar DNA regions as cisplatin efficiently upon UVA irradiation. Photoactivated 18 exhibited significant cytotoxicity in cancer cells with a low resistance factor compared with cisplatin and its Pt(IV) analogues containing inactive axial ligands. This suggested a different mechanism of action involving inhibition of HDAC that allowed platinum species to access chromatin DNA, introduced effective steric blockage of RNA polymerase II and formed DNA adducts (e.g. interstrand cross-links).

Metal complexes with curcumin ligands exhibit photoinduced anticancer activity. 113 Light activation of curcuminloaded Dex-2 nanoparticles 19 led to instant production of ROS by curcumin and released Pt(II) species from 2 (Fig. 11), and gave rise to photocytotoxicity and in vivo antitumour efficacy with low systemic toxicity to KM mice bearing subcutaneous H22 murine hepatocarcinoma tumour. 114

The amphiphilic oligomer Ce6-PEG-Pt(IV) (CPP, 20, Fig. 12) can self-assemble into micelles, and upconversion nanoparticles (UCNP) NaYbF4: Tm@CaF2 have been co-assembled to convert NIR into shorter wavelength irradiation that can induce decomposition of diazido-Pt(IV) complexes. 115 Micelles as self-assembled nanoparticles with a hydrophilic corona and hydrophobic core have been widely used in anticancer drug delivery. 116 Attachment of the photosensitiser Chlorin e6 to

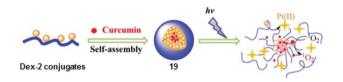


Fig. 11 Preparation and photodecomposition of curcumin-loaded Dex-2 nanoparticles 19. Adapted from ref. 114.

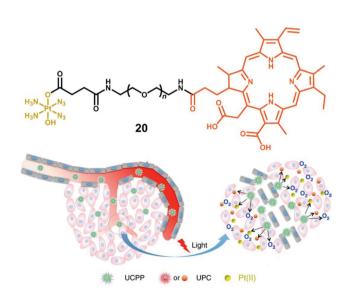


Fig. 12 The amphiphilic oligomer 20 and the photodecomposition of UCPP in a tumour microenvironment. Adapted from ref. 115.

complex 2 resulted in an O2-self generating PACT-PDT agent, where the photosensitiser relied on the oxygen produced by photoactivation of the diazido-Pt(IV) fragment to supply the oxygen required for PDT in hypoxic tissues. Dramatically enhanced photocytotoxicity was observed for this PACT-PDT system in hypoxic tumour models.

The nanoparticle-based agent 21 has complex 13 loaded onto silica-coated UCNP to allow photoactivation with NIR, together with a fluorescent probe that can be selectively switched-on in apoptotic conditions (Fig. 13a). 117 The probe included a fluorescence resonance energy transfer (FRET) pair, consisting of a far-red fluorescence donor Cv5 and a NIR quencher Qsy21, linked by a peptide sequence that can be recognised and cleaved by caspase-3, a key enzyme in apoptosis. Accordingly, when 21 was photoactivated by NIR irradiation, a chain reaction in A2780 ovarian cancer cells started on triggering apoptosis, thus activating caspase-3, which in turn cleaved the peptide-linker, switching on emission of the Cv5 dve and enabling imaging of apoptosis in living cells. Notably, when both peptide probe and Pt(IV) complex 13 were conjugated to human serum albumin protein (HSA, 22, Fig. 13b), instead of UCNP, improved photocytotoxicity and real-time imaging was also achieved upon UVA irradiation.118

The nano-system 23, combining Yb/Tm-codoped UCNP and 6, exhibited better tumour inhibition under NIR irradiation than that under UV irradiation (Fig. 14). 119 Notably, this nanosystem functioned as a theragnostic agent, whose therapeutic action could be informed and guided by different imaging modalities, such as upconversion luminescence (UCL), magnetic resonance (MR) and computer tomography (CT).

Targeted delivery of diazido-Pt(IV) complexes

One of the major advantages of phototherapy over traditional chemotherapy is the ability to provide spatial and temporal control of the activation of prodrugs and their resulting cytotoxic activity. However, inefficient accumulation of photoactive prodrugs at the tumour site is still an issue and results in the

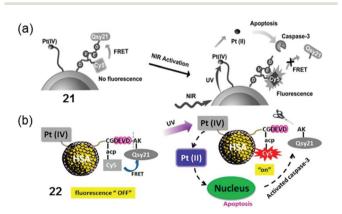


Fig. 13 Photoactivation of conjugates 21 and 22 based on (a) UNCP¹¹⁷ and (b) HSA, 118 respectively. Adapted from ref. 117 and 118.

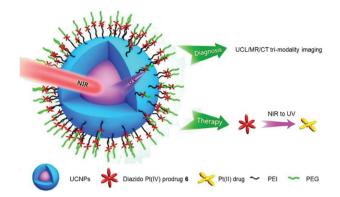


Fig. 14 Schematic illustration of the photodecomposition of conjugate 23. Adapted from ref. 119.

need for higher concentrations to achieve therapeutic efficacy, increasing the risk of side effects. The conjugation of diazido Pt(iv) complexes with cancer-targeting vectors can improve their selectivity, increase their accumulation in cancer cells, and enable the prodrugs to be activated specifically within cancer cells.

Overexpression of particular receptors on the surface of cancer cells provides an excellent strategy for the targeted delivery of diazido-Pt(iv) complexes by tethering them to ligands that can bind selectively to those receptors. The RGD sequence (-Arg-Gly-Asp-) can be selectively recognised by $\alpha_{\rm v}\beta_3$ and $\alpha_v \beta_5$ integrins that are overexpressed on the surface of several tumour cells and related to tumour angiogenesis. 120,121 The conjugate of photoactive Pt(IV) prodrug 13 and a cyclic RGD-containing peptide c(RGDfK) (24, Fig. 15) showed remarkably enhanced selectivity and increased cellular accumulation for cells overexpressing $\alpha_v \beta_3$ and $\alpha_v \beta_5$ integrins, although the IC50 values for irradiated cells were higher than those of its parent succinylated complex. 122 Another example of targeting for complex 13 is its conjugate with guanidinoneomycin, which is a RNA-binding ligand and allows the complex to be taken up by cancer cells in a selective proteoglycandependent manner (25, Fig. 15). 123 The photoproducts of Pt-guanidinoneomycin conjugate 25 with 5'-GMP or 5'-dCATGGCT were similar to that of the parent complexes under the same conditions. Similar to the Pt-c(RGDfK) conjugate, the Pt-guanidinoneomycin conjugate exhibited an enhanced cellular uptake with a preference for the SK-MEL-28 malignant melanoma cell line due to the expression of negatively charged cell-surface proteoglycans.

Nanoparticle-based drug delivery systems have attracted particular attention due to their enhanced accumulation in tumour tissue through the enhanced permeation and retention (EPR) effect caused by the leaky nature of angiogenic blood vessels in solid tumours. 88,124,125 The Pt^{IV}-N₃-FA@CDs nanoplatform 26 (Fig. 15) consisted of carbon dots decorated with the photoactive diazido Pt(IV) prodrug cis, trans, cis-[Pt(N₃)₂(OH)₂(NH₃)(3-NH₂-Py)] and folic acid (FA) molecules, and exhibited a preference for folate receptor FR-positive

Fig. 15 Diazido-Pt(IV) complexes 24-26 with cancer cell-targeting vectors. CDs = carbon dots.

[FR(+)] human cervical HeLa cells over FR-negative [FR(-)] MCF-7 human breast tumour cells. 126

Photo-responsive block copolymer (BCP) micelles have been widely investigated for their drug delivery applications in cancer therapy. 127 The triblock copolymer methoxy-poly (ethylene glycol)-block-poly(ε-caprolactone)-block-poly-L-lysine, $mPEG_{114}$ -b-PCL₂₀-b-PLL₁₀ that included mPEG (n = 114), polycaprolactone (p = 20) and poly-L-lysine (q = 10) self-assembles in aqueous solution, with polycaprolactone and poly-L-lysine the core with Pt(IV) complex cis, forming $[Pt(1R,2R-DACH)(N_3)_2(OH)_2]$ (DACH = 1,2-cyclohexanediamine) covalently encapsulated inside the hydrophobic core via an amide linkage (27, Fig. 16). 128 The micelles exhibit greatly enhanced cellular accumulation and photocytotoxicity to

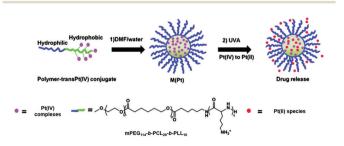


Fig. 16 The preparation and photodecomposition of micelles 27, 128 $\mathbf{28}^{129}$ $\mathbf{29}^{130}$ assembled by mPEG₁₁₄-b-PCL₂₀-b-PLL₁₀ polymer with diazido Pt(IV) complexes. Adapted from ref. 129.

SKOV-3 ovarian cancer cells compared with polymer-free prodrugs. Importantly, in vivo studies revealed that conjugation to micelles enhanced the blood circulation half-life of the Pt(IV) complex by 10-fold and displayed improved inhibition efficacy against H22 murine hepatocarcinoma with decreased systemic toxicity. Complex 3 was also attached to the biodegradable polymer mPEG₁₁₄-b-PCL₂₀-b-PLL₁₀ that can selfassemble into micelles with the hydrophobic chain and Pt species as the core to protect Pt(IV) prodrugs from potential deactivation in blood circulation. 129 The micelles 28 (Fig. 16) displayed comparable IC50 values to cisplatin upon irradiation and a resistance factor (IC₅₀ ratio: A2780CDDP/A2780) 5× lower than cisplatin. When the same micelles incorporated sterically hindered 6, they were proved to be >100 times more effective than cisplatin upon UVA irradiation (29, Fig. 16). 130

The photocleavable tri-block copolymers PEG-PUPt(N₃)-PEG (PUPt(N₃) is polyurethane with repeating 13 bricks) produced a photosensitive micelle **30** (Fig. 17). ¹³¹ The *in vivo* experiments revealed that the irradiated micelle (430 nm) was 3-4× more effective to BALB/c nude mice bearing A549 xenografts than the prodrug and cisplatin with lowest body weight loss on day 27, suggesting lower systemic toxicity.

Complex 2-loaded amphiphiles with one lactose motif selfassembled into micelles 31, while the amphiphiles with two lactose motifs formed vesicles 32 instead (Fig. 18). These nanoparticles displayed photocytotoxicity with liver cancer-targeting ability in vivo. The platinum distribution in mice was determined by fluorescence, CT and ICP-MS. 132

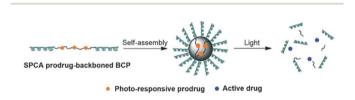
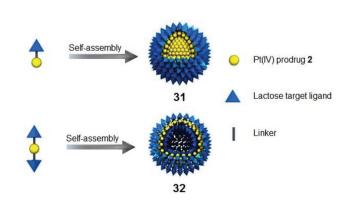


Fig. 17 The preparation and photodecomposition of micelles 30 assembled by a tri-block copolymer with complex 13. Adapted from ref.



Cancer-targeting micelles 31 and vesicles 32. Adapted from ref. Fig. 18 132

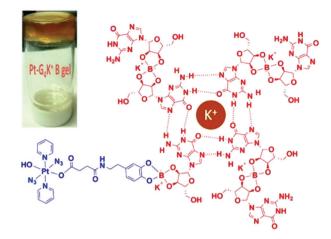


Fig. 19 Schematic illustration of self-assembled Pt-G₄K⁺B anticancer hydrogel 33. Adapted from ref. 136.

For surface tumours, such as non-melanoma skin cancer, topical medication is an ideal way for precise localisation. G₄K⁺ hydrogels are biocompatible polymers with flexibility and high water content that allow them to mimic natural tissues. 133-135 Pt(IV)-based Pt-G₄K⁺ B hydrogel 33 (Fig. 19) exhibited potent photocytotoxicity towards cisplatin-resistant A2780cis ovarian cancer cells while it displayed negligible cytotoxicity to MRC-5 normal fibroblast cells. 136

Conclusions and prospects for clinical platinum photochemotherapy

Photoactive diazido-Pt(IV) complexes represent a new generation of platinum anticancer prodrugs that allow spatial and temporal control over their cytotoxic activity. They exhibit high dark stability, promising oxygen-independent photocytotoxicity, and novel mechanisms of action that allow them to circumvent cisplatin resistance. Modification of the prototype complexes (1-15), especially the axial ligands, improves their targeting ability and pharmacological properties. In this review, we have described the development of photoactive diazido-Pt(w) complexes, including their cancer-targeting derivatives, and discussed their photodecomposition pathways, photoreaction with biomolecules, and their effect on cellular components and pathways.

Three main features of an ideal diazido-Pt(IV) complex for PACT appear to be crucial and need to be considered in any further development of these agents. (1) In contrast to cisplatin, trans geometry is more favourable than cis for diazido-Pt(IV) complexes, owing to the more intense and red-shifted LMCT bands, faster photodecomposition rate and improved photocytotoxicity. (2) The replacement of NH_3 by a π -acceptor pyridine ligand can not only red-shift the LMCT bands, but also enhance the cytotoxicity and introduce new mechanisms of action. Also, replacement of NH₃ by an aliphatic amine (e.g. CH₃NH₂) improves photocytotoxicity. (3) Axial derivatisation of hydroxide/carboxylate ligands with cancer-targeting vectors or cytotoxic motifs provides an avenue for the design of new diazido-Pt(IV) complexes with improved selectivity, cellular accumulation and photocytotoxicity, longer activation wavelength, and convenient formulation.

In spite of the notable progress with research development of photoactive diazido-Pt(IV) complexes achieved so far, none of them has yet entered clinical trials. The achievement of longer wavelength activation for deeper tissue penetration, higher photocytoxicity indices, and tumour specific drug delivery remain major challenges to be further addressed. However, there are good prospects for use of such complexes for surface cancers such as bladder and oesophageal cancer. Hence there are encouraging signs that diazido-Pt(IV) complexes can provide novel PACT anticancer drugs with new mechanisms of action which can be effective against resistant cancers, so warranting further investigation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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