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Metal Complex Interactions with DNA

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Abstract

Increasing numbers of DNA structures are being revealed using biophysical, spectroscopic and genomic methods. The diversity of transition metal complexes is also growing, as the unique contributions that transition metals bring to the overall structure of metal complexes depend on the various coordination numbers, geometries, physiological relevant redox potentials, as well as kinetic and thermodynamic characteristics. The vast range of ligands that can be utilised must also be considered. Given this diversity, a variety of biological interactions is not unexpected. Specifically, interactions with negatively-charged DNA can arise due to covalent/coordinate or subtle non-coordinate interactions such as electrostatic attraction, groove binding and intercalation as well as combinations of all of these modes. The potential of metal complexes as therapeutic agents is but one aspect of their utility. Complexes, both new and old, are currently being utilised in conjunction with spectroscopic and biological techniques to probe the interactions of DNA and its many structural forms. Here we present a review of metal complex-DNA interactions in which several binding modes and DNA structural forms are explored.

Introduction

Small organic molecules have been employed as therapeutic agents since the early twentieth century when the mustard gases were found to exhibit chemotherapeutic properties.[1] Since that time, developments have progressed towards metal complexes as an additional area providing an extremely effective class of biological agents. For example, *cis*-diamminedichloridoplatinum(II) (cisplatin, **1**) was the first clinically successful platinum anticancer drug; itself and various analogues were found to be able to bind to cellular DNA, halting replication and inducing apoptosis.[2, 3] However, these compounds have several disadvantages, such as limited solubility,[4] severely dose-limiting side effects such as nausea, neurotoxicity and nephrotoxicity,[5, 6] and intrinsic or acquired resistance in some cancer types.[7, 8]

The inherent problems accompanying chemotherapy necessitate the development of new anticancer approaches. The development of compounds that can disrupt cancerous cellular machinery by non-classical interactions with nucleic acids is an example of such an approach, and has been the focus of many medicinal chemists.[9-13] Nucleic acids fascinated researchers even before Watson and Crick published the structure of DNA in 1953,[14] as they were already known to be vital to cellular function. The functions of DNA such as replication, transcription and regulation by specific protein interactions have been intensely investigated.[15-17] Small molecules that can induce or suppress cellular interactions related to DNA are of value as they manipulate the function of cells to produce a desired result, thereby allowing the diagnosis or treatment of disease.[18-21] Transition metals are ideal for these purposes, as their unique properties can allow for specific interactions between DNA and other biomolecules,[22] while their spectroscopic characteristics facilitate use as probes for biophysical studies.[23, 24] Consequently there is extraordinary interest in the development of transition metal complexes given the extensive array of readily available ligands for

coordination and the different geometries, coordination numbers, redox potentials, kinetic and thermodynamic characteristics of the metals.[25] Transition metals that have been extensively utilised in medicinal chemistry include platinum,[26] ruthenium,[27-30] titanium,[31] rhodium,[32] copper,[33, 34] palladium,[35] gold,[36] and iron.[37]

Deoxyribonucleic Acid (DNA)

DNA is a critical therapeutic target that is responsible for, and the focus of, a wide variety of intracellular interactions.[38] Each of the complementary strands of DNA are stabilised by hydrogen bonding between adenine and thymine (A-T) and guanine and cytosine (G-C) nucleic acids.[14] In B-DNA, the most common DNA form, the strands are held in the anti-parallel double helix by stacking interactions between parallel oriented bases.[39] The formation of this helix results in the presence of a major and minor groove which provide sites for the binding of small molecules.[40] The major and minor groove differ significantly in size, shape, hydration, electrostatic potential and position of hydrogen bonding sites.[40, 41]

A, B and Z-DNA are the most well-known forms of DNA, and typically random nucleic acid sequences only form A-DNA or B-DNA.[42] The conformation differences exhibited by A, B and Z-DNA are mainly as a consequence of sugar puckering that fixes the chirality of the helix; A and B-DNA are right-handed while Z-DNA is left-handed.[42] The distance between consecutive base-pairs and the degree of rotation of the helix per residue results from the changes in the sugar pucker from a C3′-*endo* to C2′-*endo*.[43] Environmental conditions including base pair sequence, relative humidity, salt concentration, and molecules that bind, by electrostatic, coordinate, intercalation or groove association either independently or in combination, all of which contribute to affect the sugar puckering and therefore overall conformation.[42] Many other conformations and structural forms have been described in the literature when certain DNA sequences are present and these can be functionally important.[44] Distinct sequences or defined symmetry elements are required to form these alternative

structures which may result in motifs such as hairpins,[45] cruciforms,[46, 47] intramolecular triplexes,[48] slipped-strand DNA,[49] parallel-stranded DNA,[50] unpaired DNA structures,[51] and G-quadruplex DNA.[52] These unique DNA conformations may provide discrete binding targets for small molecules, allowing for the modulation of DNA function.

Structural Diversity of Metal Complexes

The varied structural complexity and polymorphic nature of DNA presents a number of potential intermolecular interactions, including irreversible covalent binding, reversible groove association or intercalation[7] The degree of variability of transition metal complexes imparted by the metal, oxidation state, coordinated ligands, overall size and shape of the complex (Fig. 1) allows for a high degree of selectivity towards various biological targets.[18, 22, 53, 54]
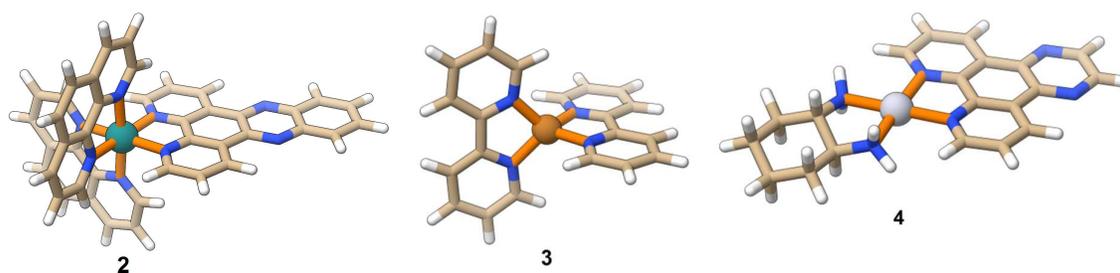
Fig. 1. Three-dimensional representations of various metal complex geometries: octahedral complex [Ru(dipyrido[3,2-*a*:2',3'-*c*]phenazine)(1,10-phenanthroline)₂]²⁺; (**2**) tetrahedral complex [Cu(2,2′-bipyridine)₂]²⁺; (**3**) and square-planar complex [Pt(dipyrido{*3,2-f:2',3'-h*}quinoxaline)(1*S*,2*S*-diaminocyclohexane)]²⁺ (**4**).

Dwyer recognised that the diversity of coordination metal complexes could be utilised to provide insight into the structure of biomolecules.[55-57] His clear vision that "the size, charge distribution, stereochemistry, redox potential and other physical properties of the metal chelates can be varied readily during chemical synthesis, these substances would seem to be ideal pharmacological tools with which to investigate many functional systems in the living cell" is still evident. [55-59] Metal complex-DNA interactions showcase the influence that

the coordination geometry of the metal and the disposition of the ligands have on the binding activity. For example, square planar complexes permit deeper insertion of an intercalator compared to octahedral or tetrahedral geometries (Fig. 1).[60] Complexes such as $[Pt(phen)(en)]^{2+}$ (where phen = 1,10-phenanthroline and en = 1,2-diaminoethane) can intercalate between the base pairs of DNA,[61, 62] and depending on the choice of the ancillary ligands, may insert beyond the platinum(II) centre, effectively offsetting the size of small intercalating ligands, such as phen.[63-65] However, when incorporated into octahedral complexes such as $[Co(phen)_3]^{2+}$ or $[Ru(phen)_3]^{2+}$, the geometric arrangement of the phen ligands can hinder full insertion.[60, 66] For complexes such as $[Ru(phen)_2Cl_2]$, the phen ligands can inhibit covalent binding due to steric crowding by the DNA phosphate backbone.[67] Additionally, a study that compared zinc (tetrahedral) and cobalt (octahedral) complexes incorporating a porphyrin ligand showed that the cobalt complex bound to DNA *via* intercalation, however the zinc complex was inhibited by the presence of an axial water ligand.[68] It is clear that different transition metal complexes can undergo vastly different binding interactions with DNA. Here we present a review of transition metal-DNA binding, including a variety of metal complexes, binding modes and structural motifs.

Platinum Compounds

Mononuclear Complexes

Covalent binding

Covalent binding is a common method of DNA interaction for anticancer drugs. Cisplatin (**1**, Fig. 2) is the most clinically successful DNA covalent binder, although it reacts with a diverse range of other biomolecules.[33, 69] For cisplatin, binding is dependent on the hydrolysis of its labile chloride ligands. In the bloodstream, high chloride ion concentration (100 mM) suppresses this process, however once inside the cell, the lower chloride ion concentration

(4–20 mM) assists hydrolysis; this give rise to the formation of the complex $[Pt(NH_3)_2Cl(OH_2)]^+$ that binds to purine bases in DNA at the N^7 position.[70] This binding results in the unwinding of the double helix and subsequent inhibition of transcription,[7] in turn, leading to recognition by DNA damage-response proteins and following failed repair attempts, cell-induced apoptosis occurs.[71] Cisplatin and its derivatives are capable of forming various DNA adducts including: monofunctional adducts in which one bond is formed with DNA and the other coordination site ligand remains aquated or protein-bound; 1,2-intrastrand adducts, the most common type (Fig. 2), in which two bonds are formed upon the same strand between consecutive base pairs; 1,3-intrastrand adducts in which the bonds are formed with base pairs that are one base apart; and interstrand adducts in which bonds are formed on opposite strands of the double-helix.[3] The *cis* geometry of cisplatin is vital to its *in vivo* activity; due to the *trans* effect, the *trans* isomer transplatin is much more rapidly degraded *in vivo*, is incapable of forming the most effective 1,2-intrastrand adducts, and its 1,3-intrastrand adducts are rapidly repaired relative to cisplatin.[72]

The successes and limitations of cisplatin have inspired researchers to explore new designs for covalently binding platinum drugs. Initially, square-planar platinum(II) complexes with the general formula *cis*-$[PtX_2(NH_2R)_2]$, where NH_2R is an inert amine and X is an anionic leaving group, were developed where the weak *trans* effect facilitated DNA binding and provided an overall neutral charge when administered.[73-75] Despite the large amount of research hours dedicated to creating complexes of this type, only five (Fig. 3) have gained approval for clinical use, and only some in all countries;[76] this is due to the problems of dose-limiting toxicity and intrinsic and acquired resistance that these agents experience.[77, 78] Each of these compounds are capable of binding to DNA *via* similar hydrolysis-mediated mechanisms as cisplatin.[79, 80]
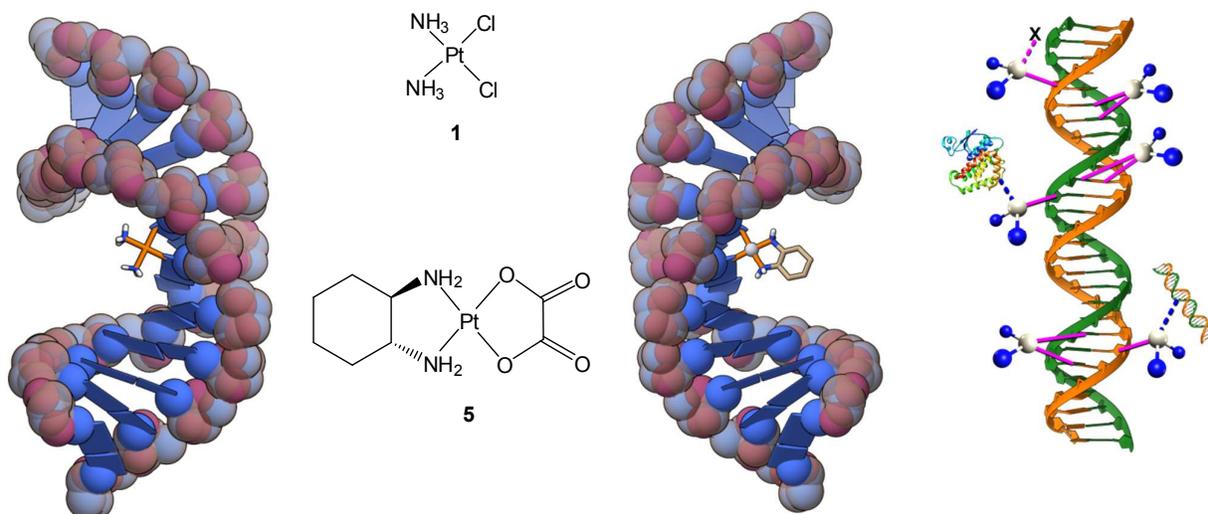
Fig. 2. Examples of 1,2-intrastrand adducts formed between DNA and cisplatin (**1**, left) and oxaliplatin (**5**, right), and an illustration of the numerous types of possible adduct formations (right).[3] Structures sourced from PDB files 2NPW,[81] 1PG9[79] and 1BNA,[82] respectively.
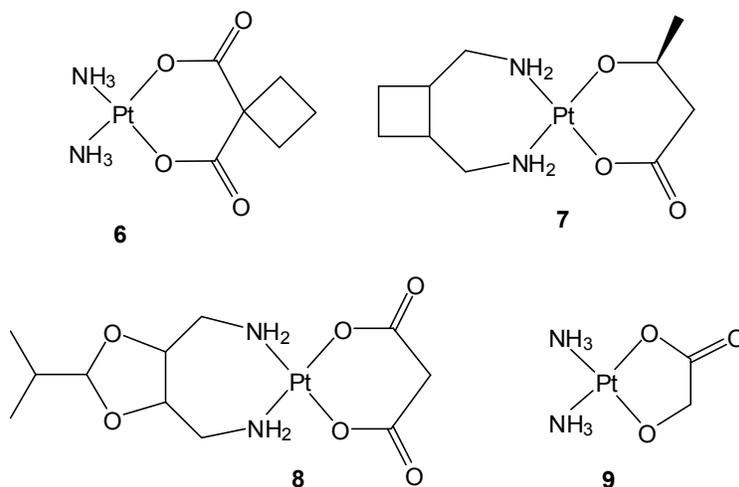
Fig. 3. Some clinically relevant platinum(II) chemotherapeutics: carboplatin (**6**), lobaplatin (**7**), heptaplatin (**8**), and nedaplatin (**9**).

The limitations of the above complexes have prompted medicinal chemists to study platinum complexes with structures that are far different from the typical cisplatin paradigm.[70, 83] The use of metals with different coordination geometries to platinum(II) and a greater variety of ligands has resulted in a new library of complexes that exhibit different cellular behaviour and higher *in vitro* efficacy than current clinical compounds.[70, 84] For

example, platinum(IV) agents are currently being investigated as prodrugs that can preserve the active platinum(II) species until its release *via* intracellular reduction once the target cells are reached.[85-87] Oxidation can afford platinum(IV) complexes two additional ligands, which can be exploited for attaching tumour-targeting species,[88] fluorescent ligands to allow tracking of the complex,[89] hydrophobic groups to increase lipophilicity,[90] enzyme inhibitors to further increase survivability,[91] and more.[88-91] An alternative approach to covalent binding metal complexes is that of intercalation.

Intercalation

The insertion of a positively charged planar polycyclic aromatic molecule between two adjacent base pairs of DNA is known as intercalation.[92] This insertion is stabilised by π–π stacking between the base pairs and aromatic ring system which results in the lengthening, stiffening and unwinding of the DNA helix.[93, 94] This effect however is dependent upon the "depth of insertion".[95-97] Intercalation is reversible, and is stabilised by a combination of electrostatic, hydrogen bonding, entropic, van der Waals and hydrophobic interactions.[98-100] Common organic intercalators include phenanthrolines,[101] phenanthridines,[102] acridines,[102] anthraquinones,[103] anthracenes,[104] and ellipticines.[105]

Platinum complexes that intercalate with DNA typically exhibit anticancer activity. A prominent series of active complexes are of the type $[Pt(I_L)(A_L)]^{2+}$, where I_L is an intercalating ligand and A_L is a non-intercalating ancillary ligand. Complexes such as the aforementioned $[Pt(phen)(en)]^{2+}$ (**10**) intercalate into the minor groove of DNA predominantly between the base pairs C_3–G_4 and T_2–A_5, and as a result the helix is lengthened and rigidified (Fig. 4).[63, 106-108]
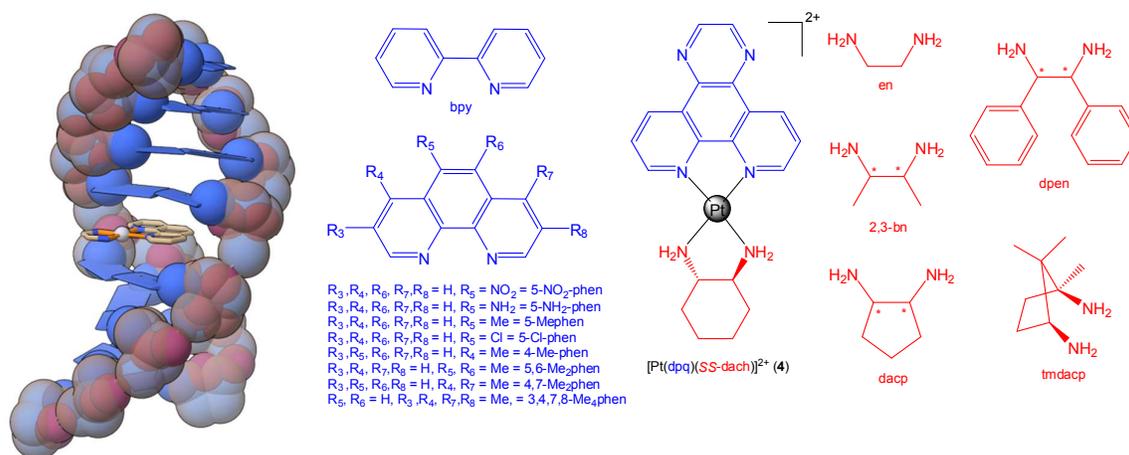
Fig. 4. Left: molecular docking simulation of the complex $[Pt(phen)(en)]^{2+}$ (**10**) intercalated with DNA sequence d(GTTGCAAC)$_2$ (original model using Chimera).[109] Right: the chemical structures of the intercalating ligands (blue) and the achiral and chiral ancillary ligands (red) of some platinum intercalators.[101, 108, 110-112] * indicates a chiral centre (either *S* or *R*).

The positive charge of these complexes allows for improved solubility, selective cellular uptake *via* active transport and high DNA affinity.[113, 114] Additionally, it has been reported that independent changes to I_L and A_L can modify both biological activity and DNA affinity, and that functional group type and position have an effect.[112, 115-117] For example, methyl substituents in the 5/6 position of phen is known to be particularly effective, with some complexes achieving cytotoxicity at nanomolar concentrations.[111, 118] Complexes where the I_L is 5,6-dimethyl-1,10-phenanthroline have also demonstrated higher DNA affinity than complexes incorporating phen with no substituents, and even higher than complexes with larger I_Ls such as dipyrido(*3,2-f:2',3'-h*)quinoxaline (dpq) and 2,3-dimethyl-dpq.[112] The A_Ls of these complexes greatly influence their activity,[101, 110] which suggests that their cytotoxicity is not just a consequence of DNA binding, but of additional intracellular interactions also. Indeed, these complexes have been found to interact with many proteins such as glutathione, serum albumin, and proteins associated with the mitochondria and cell cycle.[24, 119, 120]

Another example of platinum intercalators with high anticancer activity are tetraplatinated porphyrins; rather than act as a tetradentate ligand as with most transition metals, the porphyrin in this study coordinated to four platinum centres using terminal pyridine groups.[121] Upon irradiation with light at 420 nm, these complexes demonstrated nanomolar IC_{50} values against several cell lines, and their nuclear uptake within HeLa cells was found to be 30 times more than that of cisplatin. DNA binding was hypothesised to contribute to the activity of these complexes; a combination of several spectroscopic studies revealed that the DNA binding mode of these complexes was intercalation, with binding constants at approximately 10^6 M^{-1}.[121] Some evidence of covalent platination was also observed, however this interaction occurred over a much longer timescale.
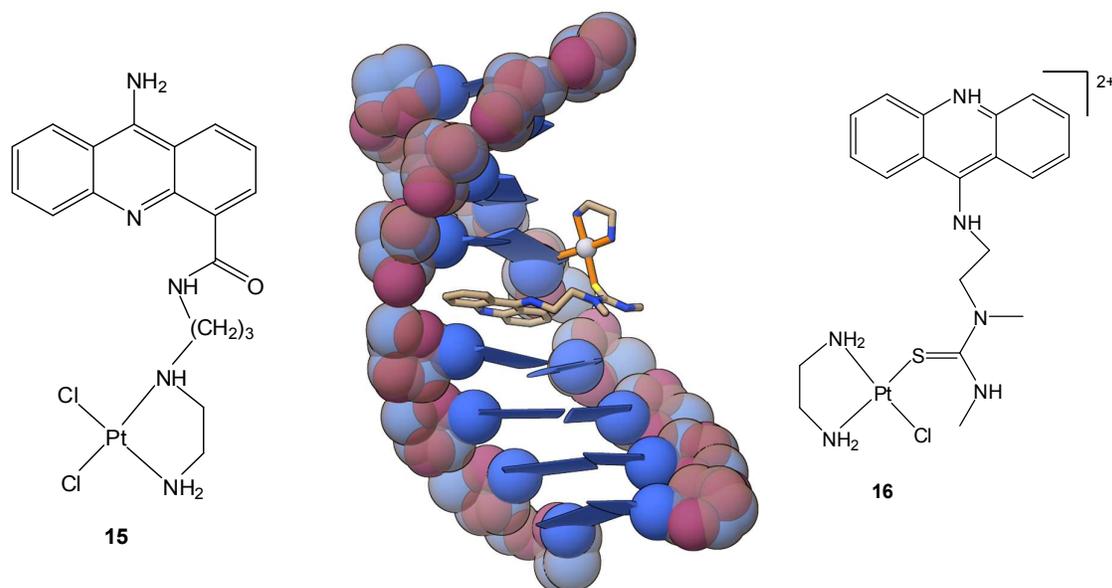
Bimodal – covalent binding and intercalation

There is potential for many coordination metal complexes to interact with DNA in more than one way. The simplest example of this is the complex [chlorido(2,2′:6′,2″-terpyridine)platinum(II)], $[Pt(terpy)Cl]^+$ (**11**, Fig. 5). Binding studies have revealed that this complex will initially intercalate with DNA, and subsequently form covalent bonds to base pairs after the loss of the labile chloride ligand.[122-126] Substitution of the chloride ligand results in different rates of hydrolysis; coordination of a sulphur-containing atom to the platinum centre inhibits hydrolysis and results in the complex interacting with DNA *via* intercalation alone.[63a,69a] Many different complexes of this type have been synthesised (Fig. X), and some have exhibited higher cytotoxicity than carboplatin in human ovarian cancer cell lines.[127]
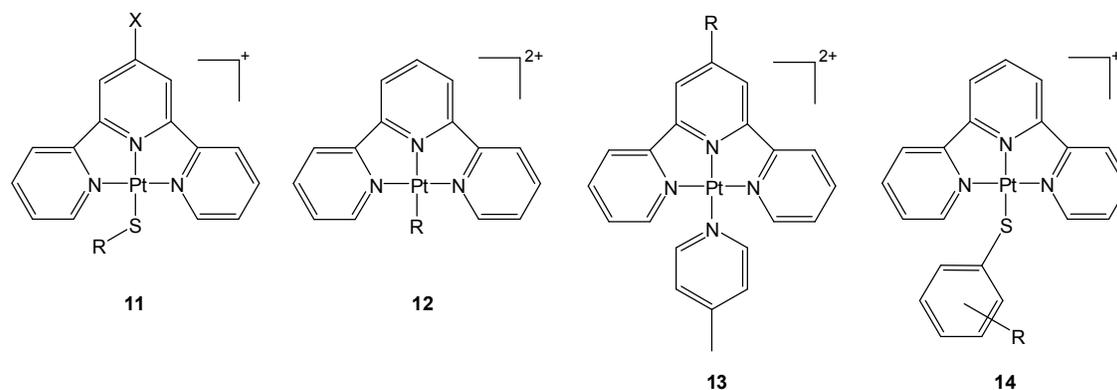
Fig. 5. The chemical structures of some of platinum(II) terpyridine intercalators.

Aside from terpyridine complexes, there are a variety of other platinum complexes that can both intercalate and covalently bind. The most prominent are those that incorporate labile leaving groups at the platinum centre, yet also possess a tether that ends with an intercalating moiety (Fig. 6).[9, 128, 129] An early example of this is a series of complexes of the type $[Pt\{AO(CH_2)_n(en)\}Cl_2]Cl$, where AO is acridine orange an I_L, which is connected by a polymethylene chain where $n = 3$ or 6 to the en.[128] These complexes both intercalate and covalently bind with DNA at binding sites 1–2 base pairs apart. They are capable of achieving cytotoxicity in a variety of cell-lines at micromolar concentrations and complexes with shorter tethers are more active.[9] A recent series of platinum acridinylthiourea complexes have shown nanomolar cytotoxicity against non-small-cell lung cancer.[129] These complexes have been reported to both intercalate and form adducts with DNA (Fig. 6),[130] resulting in the lengthening and aggregation of DNA strands.[131]

Fig. 6. The chemical structures of an acridine orange platinum complex (**15**) and Pt(ACRAMTU-S)](en)Cl](NO₃)₂ (**16**) (where ACRAMTU is 1-[2-(acridin-9-ylamino)ethyl]-1,3-dimethylthiourea). Centre: the bimodal (intercalation and covalent) binding of **16** with DNA octamer 5′-CCTCGTCC-3′/3′-GGAGCAGG-5′. Derived from NMR and molecular modelling experiments (PDB:1XRW).[130]

Multinuclear Complexes

Covalent binding

Platinum anticancer complexes consisting of two or more centres that are tethered together have been in development since the late 1980s.[71, 132-134] These complexes have attracted considerable interest as their multinuclear nature allows for a greater number of possible DNA binding adducts than cisplatin,[132, 135, 136] making it more difficult for cells to repair DNA damage and subsequently develop drug resistance.[71, 137] In addition, many multinuclear compounds are charged and therefore water soluble, allowing for ease of administration, faster DNA binding and higher cellular uptake than cisplatin due to electrostatic attractions.[132, 138, 139] The leading complexes of this type were initially based upon cisplatin motifs with aliphatic amine substituents.[134] This triggered the development of multinuclear

complexes with a large variety of tethers and active ligands.[140-147] In many cases, the resulting cytotoxicity was equal to or greater than that of cisplatin, cellular uptake was significantly higher, and interstrand cross-linking was confirmed (Fig. 7).[142, 143, 146-149] Part of the utility of multinuclear platinum compounds is the sheer variety of complexes that can be synthesised, as one can vary the external and tethering ligands in order to modulate the chemical properties of the complex. The external ligands present dictate the primary DNA binding mode,[150] while the tethering ligands influence many properties of the complex; longer chains will result in DNA interstrand links that are further apart and can further distort the helix,[151] and rigid chains will form a higher proportion of interstrand adducts due to low flexibility,[142, 152] The functional groups present and the shape of the linker can govern the interactions between the metal complex and biomolecules.[139, 153, 154] Chain length has also been found to affect the cytotoxicity of multinuclear complexes, although trends vary depending on the rigidity of the linker.[151, 155, 156] Currently, the most well-known multinuclear Pt complex is $[(\{trans\text{-}PtCl(NH_3)_2\}_2\mu\text{-}(trans\text{-}Pt(NH_3)_2(H_2N(CH_2)_6NH_2)_2)]^{4+}$ (BBR3464, **18**, Fig. 7); this trinuclear complex entered Phase II trials in 2001.[157, 158] BBR3464 is more active than cisplatin in a wide variety of cell lines, including those that are cisplatin-resistant.[76] This high cytotoxicity is attributed to a variety of factors, including the formation of interstrand crosslinks up to six bases apart,[139] high DNA binding affinity due to a 4+ charge,[159] increased cellular uptake relative to cisplatin,[160] lower DNA repair protein expression[161] and lower reactivity with intracellular thiols.[162, 163] Phase I clinical trials of BBR3464 revealed high systematic toxicity in participants.[164] This was mediated through alternate treatment plans and the complex proceeded to Phase II trials,[158, 165] however it has not progressed further due to a low rate of activity in patients.[76]

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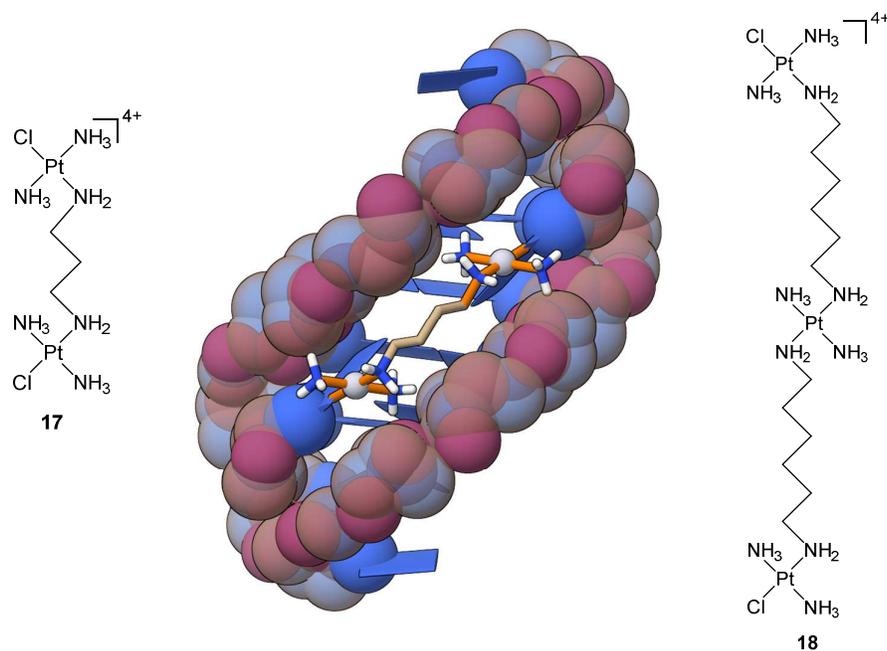
Fig. 7. Chemical structures of the complexes [{*trans*-PtCl(NH$_3$)$_2$}$_2$(NH$_2$(CH$_2$)$_4$NH$_2$)]$^{2+}$ (**17**) and BBR3464 (**18**), and the NMR solution structure of **17** forming an interstrand cross-link to DNA oligomer CATGCATG. Sourced from PDB file 1AU6.[149]

Bisintercalation

Bisintercalators have been of interest since the biological activity of echinomycin was first reported.[166] They form reversible DNA interstrand links and intrastrand 'staples' via the intercalation of each I$_L$ between base pairs (Fig. 8).[167] The tether often resides in the minor groove during these interactions.[166] DNA binding affinities of most transition-metal based bisintercalators are higher than their mononuclear counterparts due to increased charge and aromatic surface area; this affinity can often lead to higher cytotoxicity.[156, 168, 169] Modulation of the I$_L$s and types of tethers used can also lead to enhanced selectivity toward DNA sequences.[170, 171] Bisintercalating platinum complexes are usually mononuclear with two tethers leading to I$_L$s or multinuclear with an I$_L$ at each end (Fig. 8).[150, 172, 173] The properties of these complexes can be tuned *via* modification of the I$_L$ or modulation of the size and rigidity of the tethers present.[155, 172, 174] Many studies of these types of complexes have

involved the use of terpy and its derivatives as the I_L. Dinuclear complexes incorporating terpy have demonstrated high double-stranded DNA binding affinity,[168, 174] potent cytotoxicity in a range of cancerous cell lines[155, 156, 173] and the ability to inhibit enzymes that are important to the function of cancerous cells.[175] Acridines are another prominent I_L used in bisintercalators that have achieved micromolar-level cytotoxicity in the HL-60 cell line.[172] Upon binding to B-DNA, these complexes have demonstrated the ability to induce Hoogsteen base-pair formation,[172] unwind the helix by 44° and increase thermal stability by over 30 K.[176]
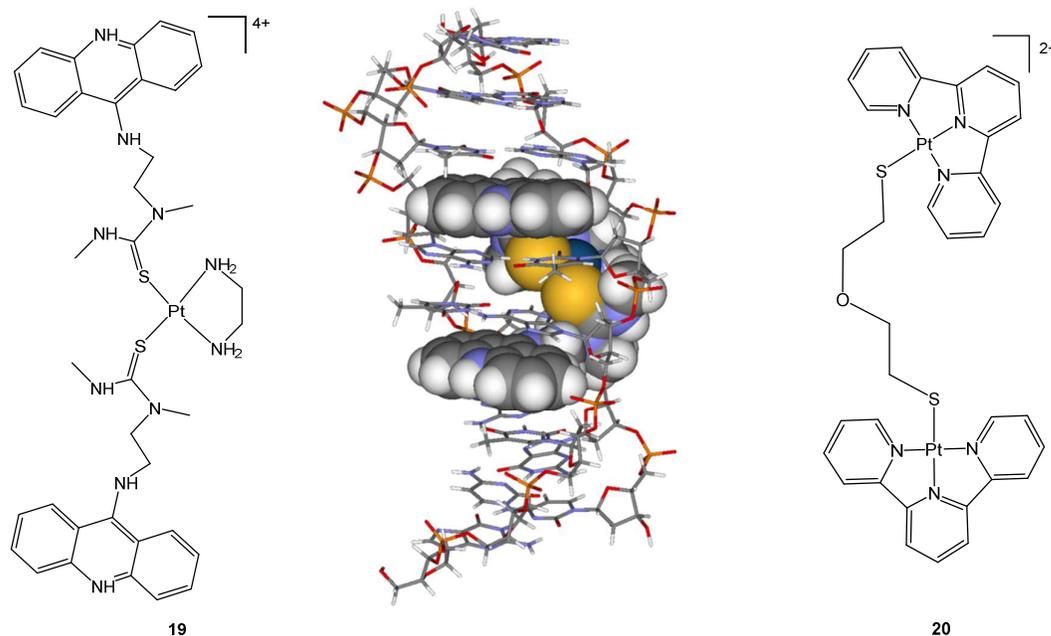

Fig. 8. The chemical structures of bisintercalators [Pt(ACRAMTU)$_2$(en)]$^{4+}$ (**19**) and [{Pt(terpy)}$_2$(SOS)]$^{2+}$ (where SOS is [2-(2-mercapto-ethoxy)-ethanediol], **20**), and an NMR-based simulation of the bisintercalation of **19** with the DNA sequence d(GCTATAGC)$_2$.[176] This simulated structure was kindly provided by Prof U. Bierbach.

Bimodal - covalent and groove binding

Groove binding is a reversible intermolecular association that is characterised by complexes with topologies that are crescent shaped,[177] complementing either the DNA major or minor

groove. These grooves are vastly different in size, shape and properties, and so association with one or the other can occur under different circumstances.[40, 41] For example, binding to the major groove of DNA is an enthalpy-driven process, while minor groove interactions are dominated by entropic effects.[44, 178] Groove binding is based upon intermolecular interactions such as electrostatic and van der Waals attractions; however, it does not involve explicit stacking between base pairs, and relatively minor changes to the structure of the double helix occur as a result of this binding.[41] Platinum complexes have been developed that closely associate with the grooves of DNA *via* non-covalent interactions before forming DNA adducts. The advantages of this two-mode association approach are an increased affinity for DNA and in some cases base sequence specificity, for example, binding to $d(T_4A_4)_2$ sequences in the minor groove followed by subsequent coordinative binding (Fig. 9). [159, 179-183]
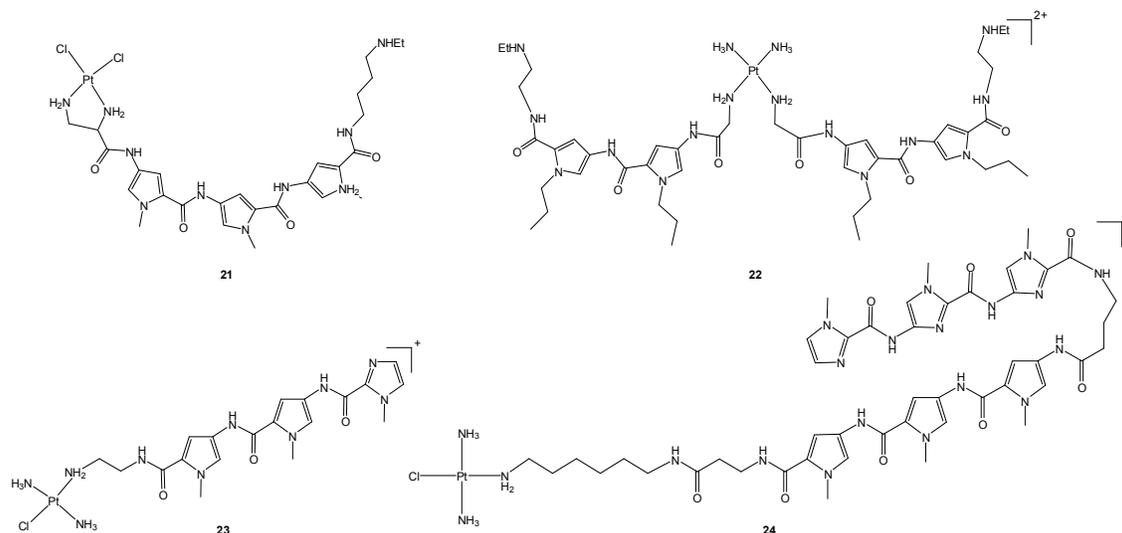

Fig. 9. Some platinum(II) complexes designed to both associate within the grooves of DNA and form nucleotide adducts: cisplatin-distamycin (**21**),[98a] *bis*-linked cisplatin-netropsin (**22**),[179, 181] DJ1953-2 (**23**),[182] and HSP-6 (**24**).[183]

Phosphate backbone association

An unusual example of intermolecular force-driven binding that does not occur between base pairs or along the grooves of DNA is association along the phosphate backbone. An example of this type of interaction was produced in a study of an analogue of the multinuclear complex BBR3464, [{*trans*-Pt(NH$_3$)$_2$(NH$_2$(CH$_2$)$_6$(NH$_3^+$))}$_2$-μ-{*trans*-Pt(NH$_3$)$_2$(NH$_2$(CH$_2$)$_6$NH$_2$)$_2$}]$^{8+}$ (TriplatinNC, **25**).[184] This complex was reported to associate within the minor groove, yet also along the phosphate backbone; the amine protons in this complex formed hydrogen bonds with the oxygen atoms along the DNA chain (Fig. 10).
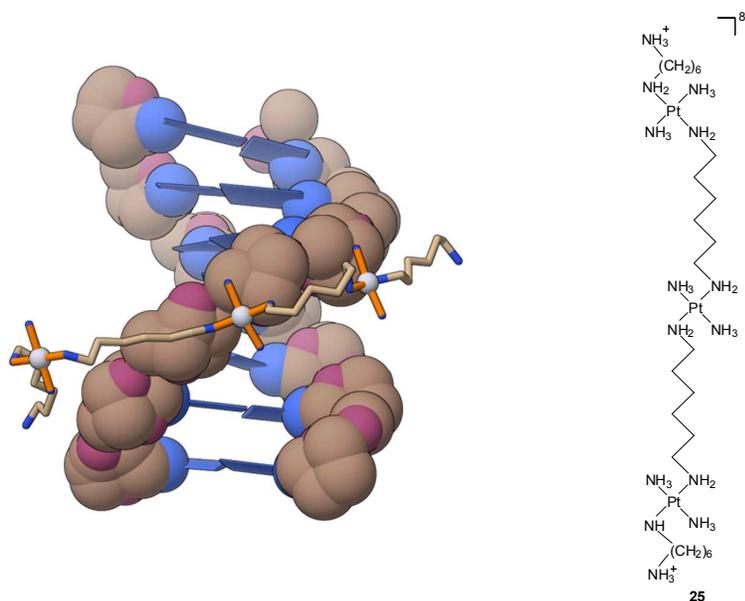
Fig. 10. Crystal structure of the dodecomer [d(CGCGAATTCGCG)]$_2$ associated with TriplatinNC (**25**), obtained from PDB file 2DYW.[184]

Ruthenium Compounds

Covalent Binding

The biological effects of ruthenium(II) and (III) complexes are increasingly being recognised, due in part to the stable, well characterised and predictable structures that can be produced through judicious choice of ligands.[185] After the discovery of the antitumor potential of ruthenium red,[186] research revealed that ruthenium(III) complexes such as *fac*-[RuCl$_3$(NH$_3$)$_3$]

and *cis*-[RuCl$_2$(NH$_3$)$_4$]Cl (**26**, Fig. 11) also demonstrated anticancer activity.[187] Further development produced the first and only ruthenium(III) complexes to reach clinical trials: NAMI-A (imidazolium *trans*-[tetrachlorido(imidazole)(dimethylsulfoxide) ruthenate(III) (**27**), and KP1019 (indazolium *trans*-[tetrachloridobis(1H-indazole)ruthenate(III)] (**28**, Fig. 11)), each of which were reported to prevent metastasis formation and inhibit already advanced tumours with relatively low toxicity.[188-190] These ruthenium(III) complexes are theorised to be inert until activation by reduction within hyperoxic cancerous cells.[185] Each complex is capable of covalent binding to DNA;[189, 191] however, their overall mechanisms differ in that NAMI-A interferes with the regulation of the cell cycle and the extracellular matrix, preventing further tumour metathesis,[192] while KP1019 causes direct cell apoptosis *via* the intrinsic mitochondrial pathway and the formation of reactive oxygen species.[189] NAMI-A and KP1019 have each completed a phase I clinical trial in 2004 and 2008, respectively, while further trials are being planned for KP1019.[30, 192]
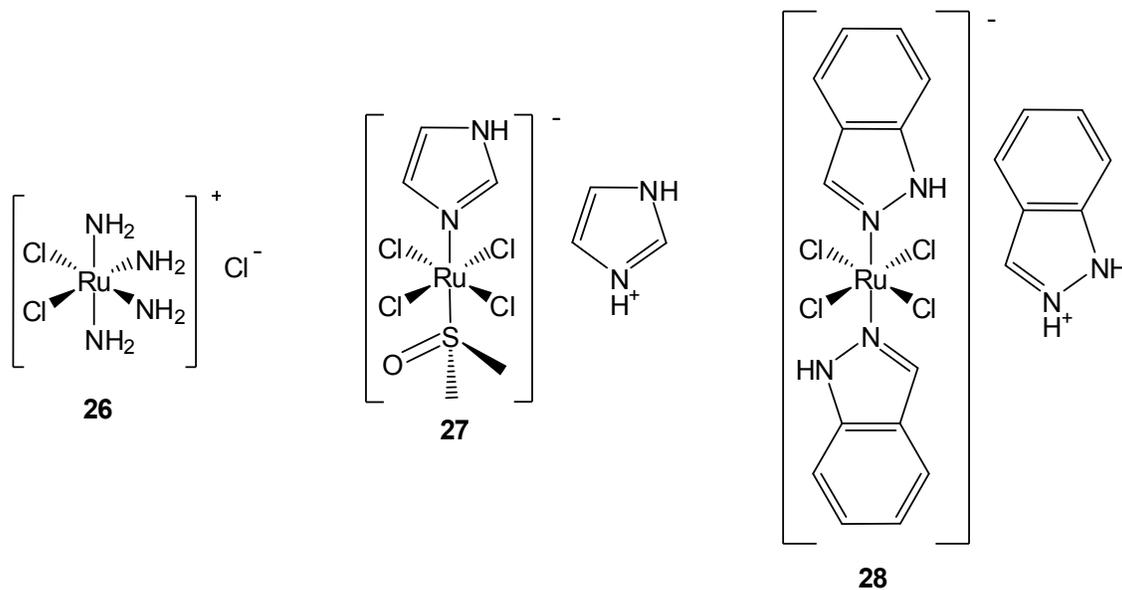
Fig. 11. Chemical structures of some ruthenium(III) covalent binders: *cis*-[RuCl$_2$(NH$_3$)$_4$]Cl (**26**), NAMI-A (**27**), and KP1019 (**28**).

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Ruthenium complexes such as $[Ru(\eta^6\text{-arene})(A_L)X]^+$, where A_L is a bidentate ligand and X is a halide, have also been developed that are generally water soluble, relatively inert toward degradation under physiological conditions,[193] and have shown potent cytotoxicity in a range of cancerous cell lines.[194, 195] Similarly to platinum intercalators, a range of properties can be achieved through modulation of the η^6-arene and A_L.[196] For example, complexes of the type $[Ru(\eta^6\text{-arene})(en)(Cl)]^+$ form monofunctional adducts with the guanine bases of DNA[197, 198] and anticancer activity increases with the size of the arene (benzene < *p*-cymene < biphenyl < dihydroantracene < tetrahydroanthracene).[193, 199] NMR studies have shown that these complexes can covalently bind to DNA, although the arene can also intercalate from the minor groove of DNA (Fig 12).[195, 197, 200, 201]
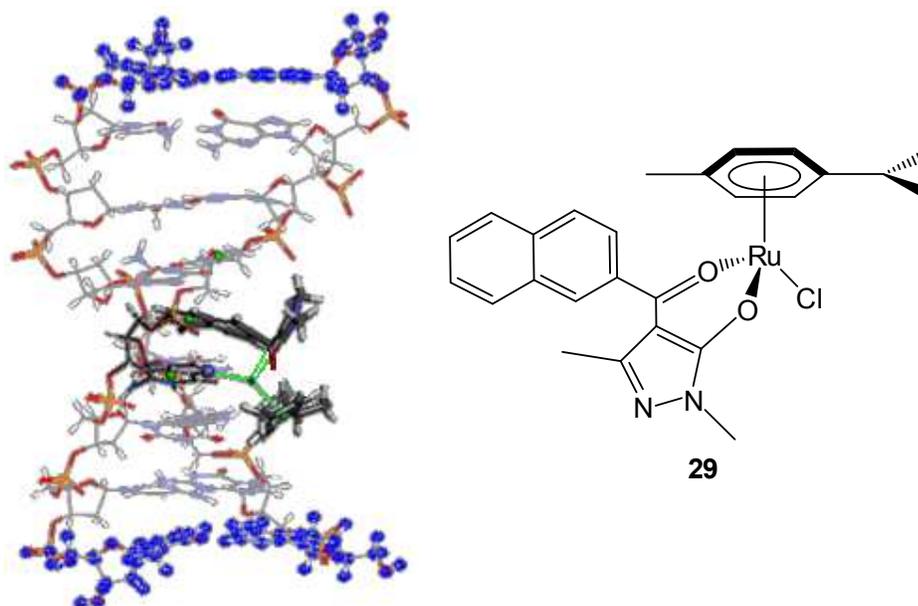
Fig. 12. Molecular docking simulation of the complex $[Ru(\eta^6$-*p*-cymene)(1,3-dimethyl-4-(1-naphthoyl)-pyrazolon-5-ato)Cl] (**29**) bound to a DNA octamer, showing both covalent ruthenium binding and intercalation of the *p*-cymene ligand.[195] This binding model was kindly provided by Dr F. Marchetti.
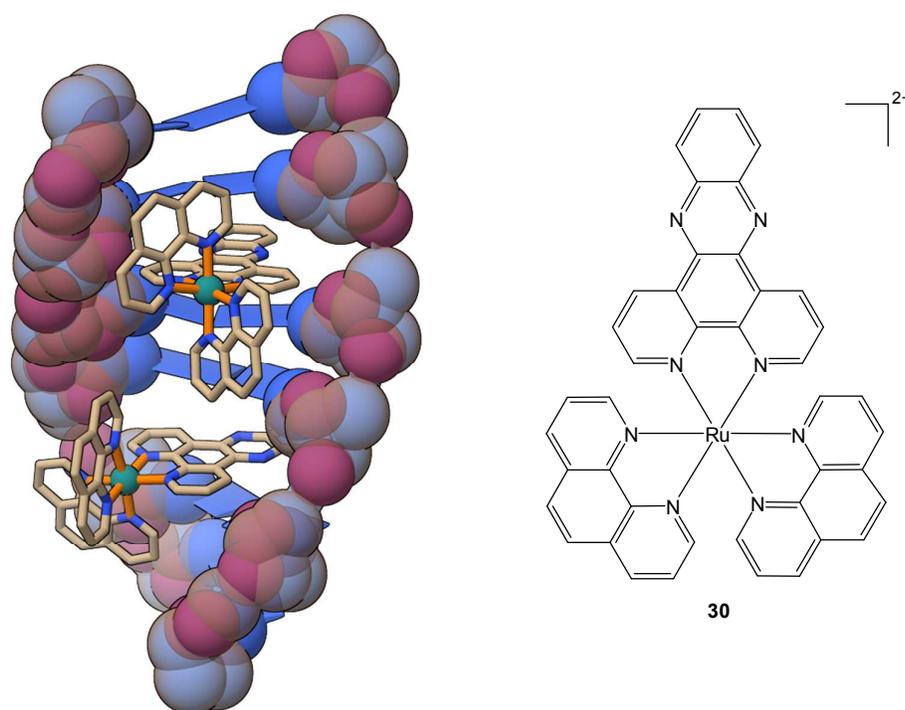
Intercalation

Many ruthenium(II) polypyridyl complexes are well-established DNA intercalators with useful spectroscopic properties and relatively low toxicity[202] which makes them ideal diagnostic agents.[203] Octahedral ruthenium(II) complexes can exist as optical isomers (Λ/Δ) that do not degrade significantly over time and their chirality can influence biological activity.[204] Dwyer established that Λ- and Δ- $[Ru(phen)_3]^{2+}$ exhibited biological activity long before their interactions with DNA were identified,[205-209] and demonstrated that the activity of each isomer was different.[58] The Λ- and Δ- enantiomers of $[Ru(phen)_3]^{2+}$ and various derivatives such as $[Ru(phen)_2(dppz)]^{2+}$ (**30**),[121] $[Ru(bpy)_2(dppz)]^{2+}$,[202, 210, 211] and $[Ru(phen)_2(dpq)]^{2+}$ (where dppz = dipyrido[3,2-*a*:2',3'-*c*]phenazine and bpy = 2,2′-bipyridine) have been investigated for their DNA binding strength, binding orientations, base sequence dependency and binding modes by a variety of spectroscopic techniques.[65] In particular, the complex $[Ru(phen)_2(dppz)]^{2+}$, which is not fluorescent in solution, exhibits fluorescent properties when bound to DNA; this was the first example of a ruthenium complex with application as a light-switching DNA probe.[212] Modulation of the intercalating ligand can lead to dramatic changes in the fluorescent properties of these complexes.[203]

There was initially some controversy over the mode of DNA binding of ruthenium(II) polypyridyl complexes. Barton *et al.* initially proposed that $[Ru(phen)_2(dppz)]^{2+}$ interacted with DNA through either surface binding or intercalation *via* the major groove of DNA; this was later modified to suggest that the Λ- isomer preferred to bind in the major groove while the Δ-isomer preferred the minor groove.[213, 214] However, using biophysical and NMR experiments, Nordén and co-workers concluded that $[Ru(phen)_2(dppz)]^{2+}$ associated within the minor groove.[215] Conclusive evidence of minor groove binding using 2D NMR experiments and derivatised complexes such as $[Ru(2,9-dimethyl-phen)_2(dppz)]^{2+}$ was

demonstrated by Aldrich-Wright and Collins, *et al,*[40c,130] and has been recently confirmed using X-ray crystal structures by Cardin *et al.*[216]

The choice of intercalator can influence the binding preferences of octahedral metal complexes, and the non-intercalating ligands can also interact with DNA, influencing specificity.[217-219] For example, complexes of the type *cis*-α-[Ru(*N,N'*-dimethyl-1,2-di(2′-picolyl)-*S,S*-diaminocyclohexane)(I$_L$)]Cl$_2$ reportedly intercalate with DNA, and the binding affinity increases with intercalator size in the order bpy < phen < dpq < dppz. [220-223]

Fig. 13. X-ray crystal structure of the complex *rac*-[Ru(phen)$_2$(dppz)]$^{2+}$ (**30**) intercalated with the DNA sequence d(ATGCAT)$_2$. Sourced from PDB file 4JD8.[216]

Bisintercalation

The joining of two ruthenium centres with intercalating ligands can result in complexes with high DNA affinity and biological activity. For example, the complex [{Ru(dpq)$_2$}$_2$μ-(phen-5-SOS-5-phen)]$^{4+}$ (where SOS = 2-mercaptoethyl ether, **31**, Fig. 14) has displayed DNA binding affinity 1000 times greater than the mononuclear complex [Ru(dpq)$_2$(phen)]$^{2+}$.[222] The

bisintercalating complex $[\{Ru(phen)_2\}_2\mu\text{-}(I_L)_2]^{4+}$ (where I_L = 11,11′-bis(dipyrido[3,2-*a*:2′,3′-*c*]phenazinyl), **32**, Fig. 14) has been shown to act as a DNA 'molecular staple' with very slow kinetics;[167, 224] complexes of this type initially associate with the grooves of DNA, then the I_L threads through the DNA, stapling it together.[111,147d] Interestingly, the ΔΔ-isomer of **32** exhibited higher DNA affinity than the ΛΛ-isomer.[225] The latter isomer was found to dissociate from the strand an order of magnitude faster than the former, which could account for this difference in binding affinity.
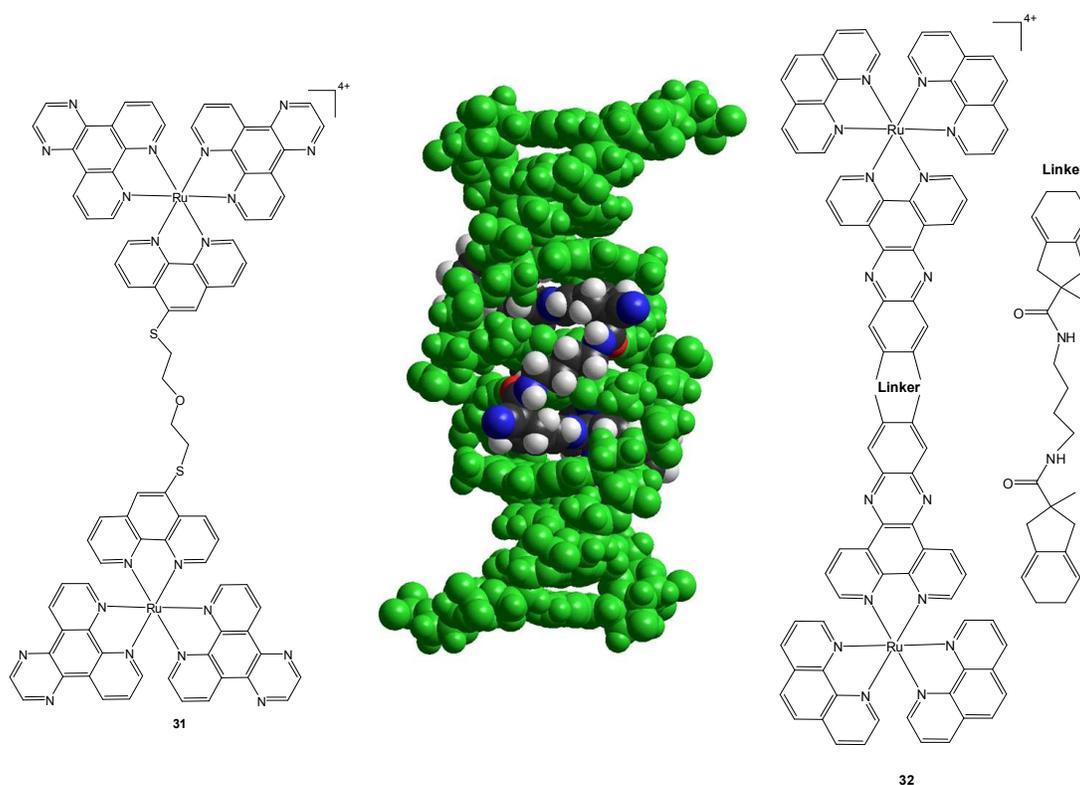
Fig. 14. Chemical structures of the ruthenium bisintercalators $[\{Ru(dpq)_2\}_2\mu\text{-}(phen\text{-}5\text{-}SOS\text{-}5\text{-}phen)]^{4+}$ (**31**) and $[\{Ru(phen)_2\}_2\mu\text{-}\{11,11'\text{-}bis(dipyrido[3,2\text{-}a:2',3'\text{-}c]phenazinyl)\}_2]^{4+}$ (**32**), and a molecular docking simulation of a staple of **32** within DNA.[225] This image was kindly provided by Prof P. Lincoln.

The binding of ruthenium(II) *bis*-terpyridine complexes with functionalised aryl tail groups (by 9-anthracenyl, 4,4'-biphenyl, β-naphthyl, 9-phenanthrenyl, or 1-pyrenyl) in the 4′ position of the terpyridine ligands is dominated at low metal complex concentration by

intercalation of the aryl groups between the DNA bases. The biphenyl tail exhibits groove

binding with no significant intercalation, whereas extended aromatic tails such as the

naphthyl derivative bind both by intercalation and groove binding even at low metal complex

concentrations.[226]

Groove Binding

Ruthenium complexes such as $[Ru(bpy)_3]^{2+}$ (**33**, Fig. 15) and $[Ru(Me_4phen)_3]^{2+}$ (where

Me_4phen = 3,4,7,8-tetramethyl-phen, **34**, Fig. 15) associate electrostatically within the

grooves of DNA without disrupting the double helix, despite the presence of ligands that

usually intercalate. These complexes are capable of DNA cleavage upon irradiation.[227, 228]

Dinuclear groove binders with flexible bridging ligands such as $[\{Ru(I_L)_2\}_2$-μ-(4,4′-Me_2bpy)-

$(CH_2)_n$-$(Me_2bpy)\}]^{4+}$ (where Me_2bpy = 4,4′-dimethyl-bpy and I_L is bpy or phen), bind

similarly to their mononuclear counterparts, yet with higher affinity.[224, 229, 230]
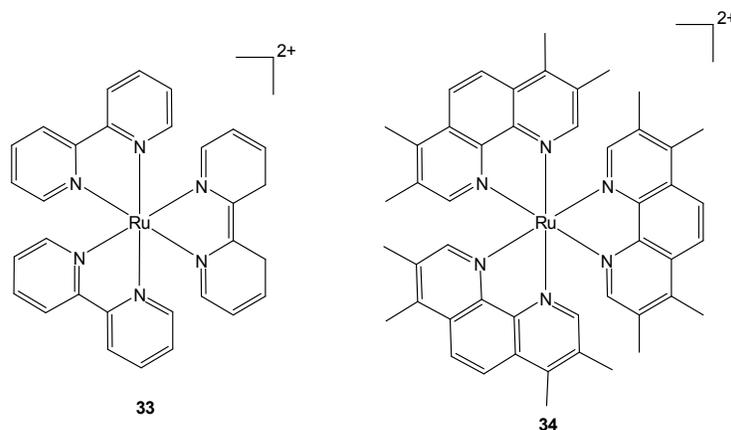
Fig. 15. Structures of the groove binders $[Ru(bpy)_3]^{2+}$ (**33**) and $[Ru(Me_4phen)_3]^{2+}$ (**34**).

Other Transition Metals

Covalent Binding

The first non-platinum(II) covalently binding metal complex to undergo clinical trials for

cancer treatment was the titanium complex budotitane ($[Ti(bzac)_2(OEt)_2]$, where bzac = 1-

phenylbutane-1,3-dionate, **35**, Fig. 16).[231] Metallocence dihalides, such as the metal

dichloride ($M(CP)_2(Cl)_2$) (where M = Ti or V, CP = cyclopentadienyl anions, **36**, Fig. 16) were also reported to have effective anticancer activity and offered a different spectrum of activity.[232, 233] Specifically, titanocene dichloride has also been tested in some phase I and II clinical trials,[234] and has been found to localise within the nucleus of xenografted cells.[31] The DNA binding of these titanium complexes is attributed to the hydrolysis of the ethoxy or halide ligands; however, this occurs extracellularly unlike cisplatin,[235, 236] and can result in the formation of multinuclear complexes that are also active.[237] Aside from the proven covalent DNA interactions,[235] and studies that suggest that transferrin may play a role in the tumour penetration of these compounds,[238] not much else is known regarding the cytotoxic mechanisms of titanium complexes.

35   **36**

37   **38**
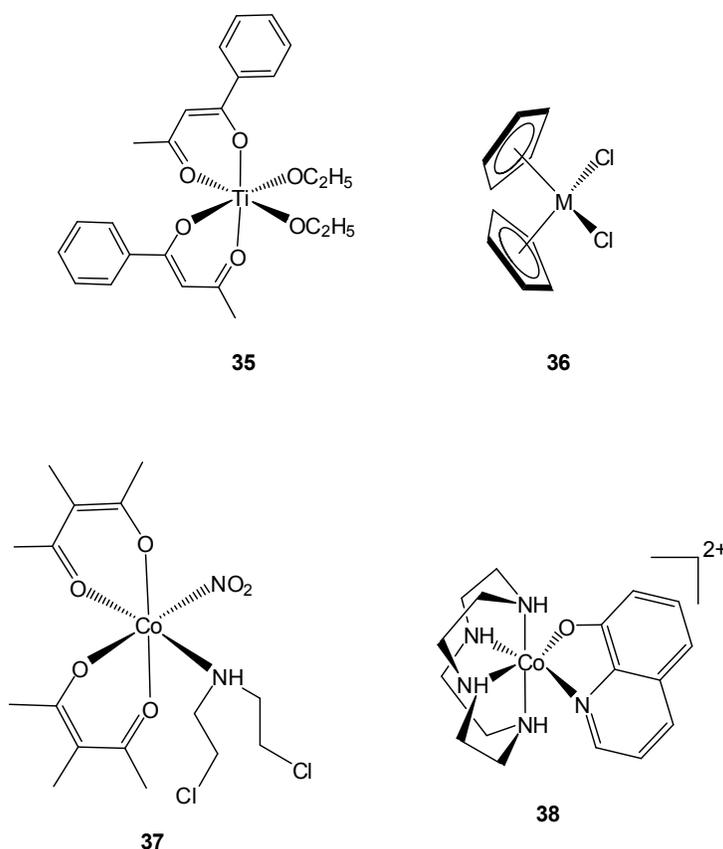
Fig. 16. Transition metal DNA covalent binders: budotitane (**35**), a metallocence dichloride where M = Ti or V (**36**), and cobalt carrier complexes with nitrogen mustard ligands (**37**) and 8-hydroxyquinoline (**38**).

Cobalt has been used to deliver coordinative DNA binders to cancerous cells such as nitrogen mustard ligands (**37**) or 8-hydroxyquinoline (**38**, Fig. 16).[239, 240] Similarly to the prodrug approach for platinum(IV) complexes, the release of the active species is mediated *via* reduction from Co(III) to Co(II); this can be artificially induced with ionising radiation,[240] or it can occur without stimuli within the hypoxic regions of cancerous cells.[241]

Intercalation

Rhodium complexes have been extensively studied due to their selectivity toward DNA sequences and their nuclease-cleaving ability.[32, 242] For example, the N_4-tetradentate complex [Rh(N_4-tetradentate)(I$_L$)]$^{3+}$ (where N_4-tetradentate = 2*R*,9*R*-diamino-4,7-diazadecane and I$_L$= phenanthrene-9,10-diimine, **39**) was specifically designed to intercalate, from the major groove, into the 5′-TGCA-3′ sequences of DNA (Fig 17).[243] It was found that both π-stacking forces and water-mediated hydrogen bonds each contributed to the interaction.
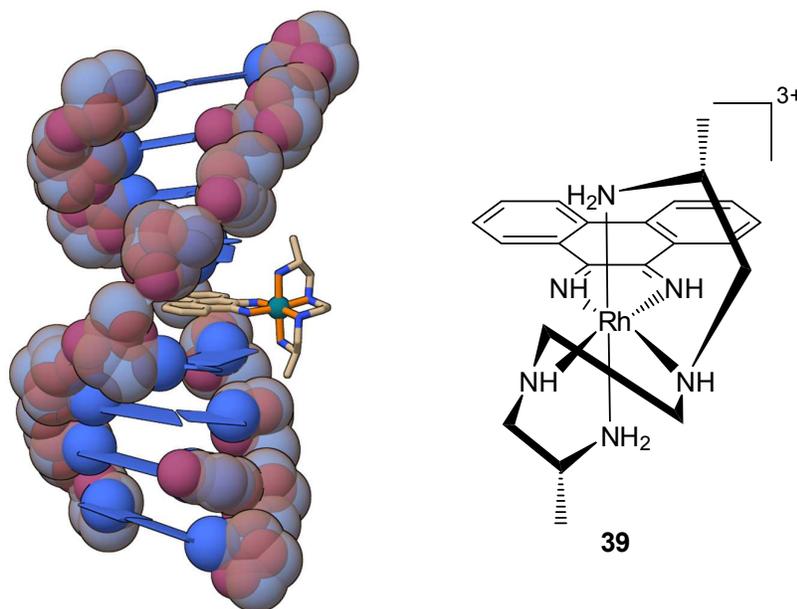
Fig. 17. Image generated from X-ray data of the sequence-selective intercalation of [Rh(Me₂trien)(phi)]³⁺ (**39**) into the DNA sequence 5'-TGCA-3'.[243] Sourced from PDB file 454D.

Other intercalating metal complexes that incorporate a N_4-tetradentate ligand such as [M(*N,N'-bis*-5-(triethylammoniummethyl)-salicylidene-2,3-naphthalendiiminato)]$^{n+}$ (where *M* = copper, nickel or zinc, **40**, Fig. 18) have been synthesised and their DNA binding affinities determined by spectroscopic and computational methods.[244] It was reported that each complex bound to DNA *via* intercalation, although large differences in binding affinity between each metal were observed. It was hypothesised that the Ni complex bound with the highest affinity due to its square planar coordination geometry which would allow it to insert deeply between the DNA base pairs, relative to the octahedral geometry of the Cu and Zn complexes.[244]
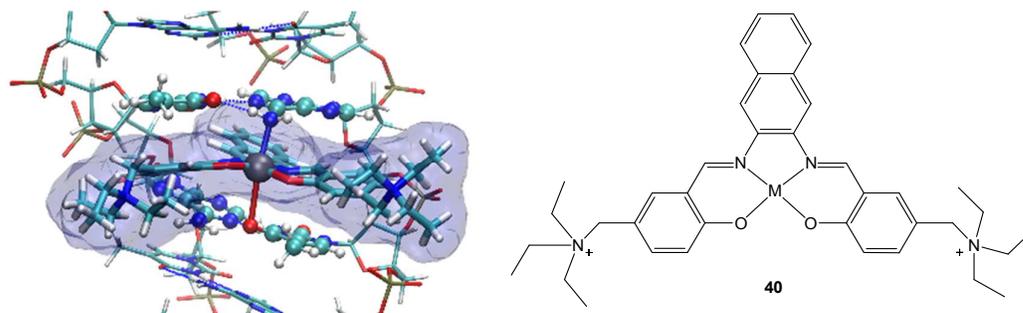
Fig. 18. The general structure of *N,N'-bis*-5-(triethyl ammoniummethyl)-salicylidene-2,3-naphthalendiiminato complexes of copper, nickel and zinc (**40**) and the molecular docking model of the nickel complex with the DNA sequence [dodeca-(dA-dT)]$_2$.[244] The image was kindly provided by Dr G. Barone.

The initial work of Sigman with copper nucleases generated substantial interest in copper complexes of phen and its derivatives as anticancer and antibacterial agents.[245, 246] *Bis*-(1,10-phenanthroline)copper(II) complexes (**41**, Fig. 19) are well known for their ability to cleave DNA, particularly in the presence of hydrogen peroxide.[247] While mechanism of action of these compounds is still under examination, it is believed the complex associates by intercalation with DNA at the minor groove.[248, 249] The DNA-copper complex is then oxidised in the presence of an activating compound, leading to an oxidative attack that results in DNA cleavage.[250] For example, the copper(II) complex, [Cu(N9-ABS)(phen)$_2$] (where N9-

ABS = *N*-(9H-purin-6-yl)benzenesulfonamine), was reported to intercalate with DNA, effectively cleave DNA in the presence of ascorbate, and was more active than $[Cu(phen)_2]^{2+}$ in Caco-2 cells and Jurkat T lymphocytes.[251] Copper complexes where two phenanthroline ligands are linked by a serinol bridge *via* position 3 or 2 (**42**, **43**, Fig. 19) show increased DNA affinity and nuclease activity.[252]
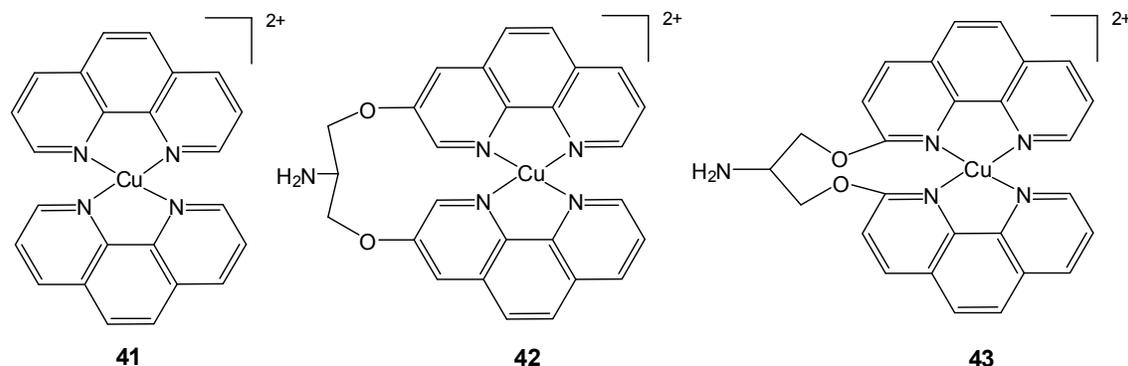
Fig. 19. Some copper(II) intercalating complexes with nuclease activity: $[Cu(phen)_2]^{2+}$ (**41**), $[Cu(3\text{-clip-phen})]^{2+}$ (**42**), and $[Cu(2\text{-clip-phen})]^{2+}$ (**43**) (where 'clip' is a serinol bridge).[247, 252]

Intercalating palladium and gold complexes have been explored as alternative anticancer agents due to their coordination properties, cytotoxicity and DNA binding potential.[253, 254] Some palladium complexes (Fig. 20) have: exhibited higher cytotoxicity than their platinum analogues;[255] shown the ability to promote cell death in cancerous cells while leaving peripheral mononuclear blood cells healthy;[256] and demonstrated intercalation with DNA with binding constants as high as $10^6 \ M^{-1}$.[257] Some gold complexes have shown high biological activity, however the primary target of most of these compounds appears to be mitochondrial DNA.[258-260] Gold complexes (e.g. $[Au(terpy)Cl]Cl_2$ and $[Au(phen)Cl_2]Cl$, Fig. 20) have demonstrated spectroscopic evidence of intercalation,[261-263] and cytotoxicity equal to or greater than cisplatin analogues.
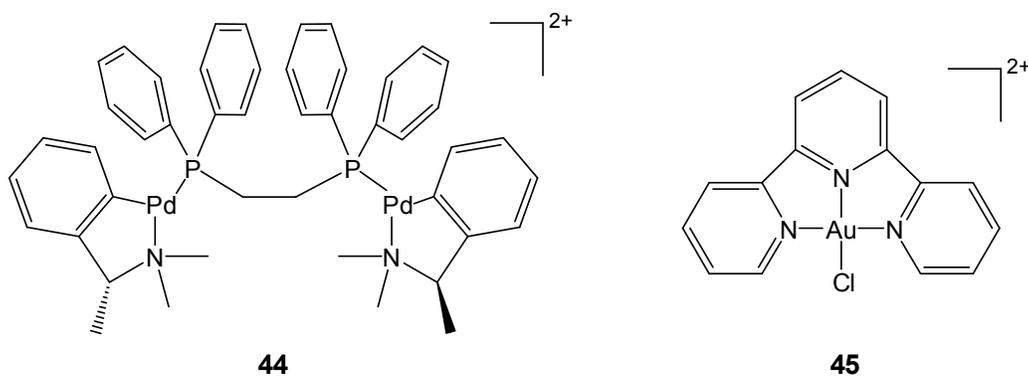
Fig. 20. Chemical structures of a palladium (**44**) and gold (**45**) intercalator.[256, 261-263]
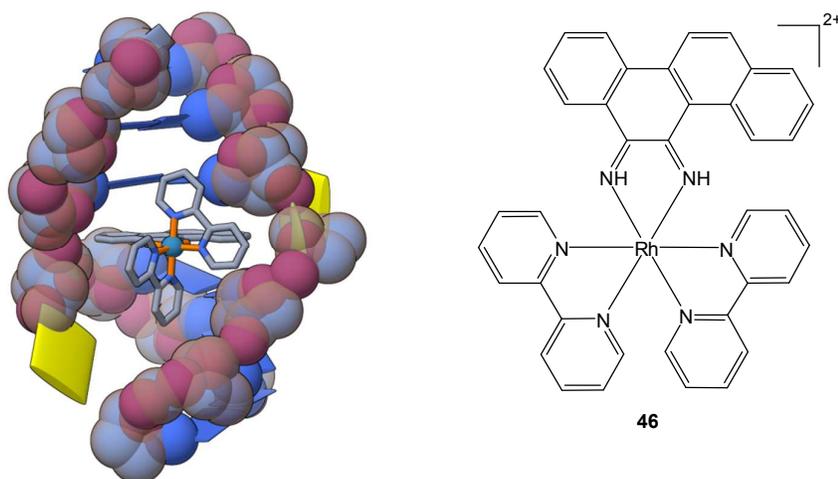
Fig. 21. Crystal structure of Δ-[Rh(bpy)$_2$(chrysi)]$^{3+}$ (**46**) inserted within the oligonucleotide 5′-CGG*A*AATT*A*CCG-3′, resulting in the ejection of the A-A mismatch (yellow) from the DNA strand.[264] The structure was sourced from PDB file 3GSK.

The shape of the intercalating ligand can influence the binding interactions as is the case with the rhodium complex Δ-[Rh(bpy)$_2$(chrysi)]$^{3+}$ (where chrysi = chrysene-5,6-diimine, **46**). Δ-[Rh(bpy)$_2$(chrysi)]$^{3+}$ was shown to bind specifically *via* π-stacking interactions at the mismatched base-pair in the oligonucleotide, 5′-CGG*A*AATT*A*CCG-3′ (where bold-italics indicate the site of an A-A mismatch) (Fig. 21). This interaction did not lengthen the oligonucleotide, and so was referred to as 'insertion', rather than intercalation. Correlations between binding affinity and the cytotoxicity of a series of these complexes have been

determined, suggesting that the displacement of these base-pair mismatches plays a significant role in the antiproliferative action of these compounds.[242]

Groove Binding

Cobalt(III) complexes such as $[Co(en)_3]^{3+}$, $[Co(en)_2(bpy)]^{3+}$, and $[Co(en)_2(phen)]^{3+}$ have been reported to bind in the grooves of DNA and cleave the strand upon irradiation.[265-268] Zinc and copper dinuclear complexes, linked by a *cis* or *trans* azobenzene bridge, were found to associate within the minor groove of DNA, and were capable of hydrolytically cleaving the strand, although only when in *cis* form.[269, 270] Spectroscopic and viscometric studies of metal porphyrin complexes (**47**, Fig. 22) found that while nickel, copper and non-metal-containing variants intercalated with DNA, the zinc and cobalt variations were found to self-associate within the grooves of the strand instead due to the presence of axial ligands.[271, 272] Finally, a study of the P and M isomers of the supramolecular iron complex $[Fe_2(L_2)_3]^{4+}$ (where L_2 = [μ-[4,4′-methylenebis[N-[(2-pyridinyl-κ*N*)methylene]benzenamine-κ*N*]]], **48**, Fig. 22) found that the M enantiomer bound in the major groove and induced dramatic intramolecular coiling, while the P enantiomer did not induce coiling and possibly resided along the minor groove spanning the two phosphate backbones instead.[37]
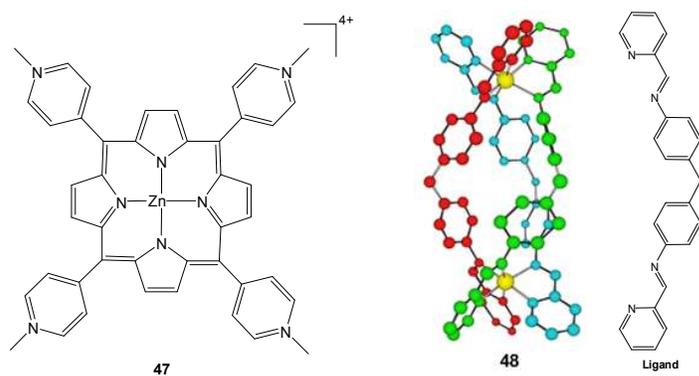
Fig. 22. Chemical structure of the groove binder [Zn{*meso*-tetrakis(*N*-methyl-4-pyridyl)porphine}]$^{4+}$ (**47**, left) and molecular representation of [Fe$_2${μ-[4,4′-methylenebis[N-[(2-pyridinyl-κ*N*)methylene]benzenamine-κ*N*]]}$_3$]$^{4+}$ (**48**) and its ligand [μ-[4,4′-

methylenebis[N-[(2-pyridinyl-κ*N*)methylene]benzenamine-κ*N*]]] (right).[37] The molecular representation was kindly provided by Prof M. Hannon.

Binding to Unique DNA Structural Motifs

DNA can also adopt other conformations such as hairpins, cruciform structures, Y-junctions or G-quadruplexes that are now being attributed to critical biological functions. In order to form these structures, DNA strands are folded in a different manner from B-DNA, involving unusual pairs of hydrogen bonds among nucleic bases compared with the classical Watson-Crick base pairing. These non-canonical DNA structures represent a new direction for genetically targeted chemotherapeutics. Not only are these conformations sequence specific, some are also explicitly associated with a cellular process or intermediary structures. This specificity allows for the possibility of a more specialised approach to chemotherapeutics and ultimately better treatment. For example, coordinatively saturated metal complexes lacking hydrogen bonding groups, such as $[Ru(Me_4phen)_3]^{2+}$, have been reported to preferentially bind in the grooves of A-like DNA conformations, whereas Λ-[Co(4,7-diphenyl-phen)$_3$]$^{3+}$ and Λ-[Ru(4,7-diphenyl-phen)$_3$]$^{3+}$ are reported to recognize Z-DNA.[210, 273, 274] Additionally, the binding of a variety of transition metal complexes to B-DNA can cause a transformation to Z-DNA; Z-DNA is a gene regulating element, and so this induced transformation has potential applications in the control of gene expression.[275-278]

Y-Junctions

A three way or Y junction is formed either when three mutually complementary nucleic acid strands converge,[223, 279] or when a double-strand of DNA binds a third strand in the major groove under acidic conditions.[280] The bases of the third strand bind to the existing base pairs via Hoogsteen base pairing, where T binds to A in a novel fashion and protonated C binds to G, forming the triplets T•AT and C•GC complementary sequence.[281] Triple helices are not as stable as duplex DNA and these structures have been associated with stalled or blocked replication forks and a higher potential for double strand breaks.[280] The presence of Y-junctions has been found to be detectable by DNA damage response proteins;[282, 283] therefore,

this motif can potentially be selectively bound by metal complexes. The aforementioned iron complex [Fe$_2${μ-[4,4'-methylenebis[N-[(2-pyridinyl-κN)methylene]benzenamine-κN]]}$_3$]$^{4+}$ (**48**) has been proven to fit perfectly within the central hydrophobic cavity of a three-way junction (Fig. 23).[284, 285] This mode of DNA recognition is without precedent and demonstrates that this important structural feature is a potential target for metal complexes.
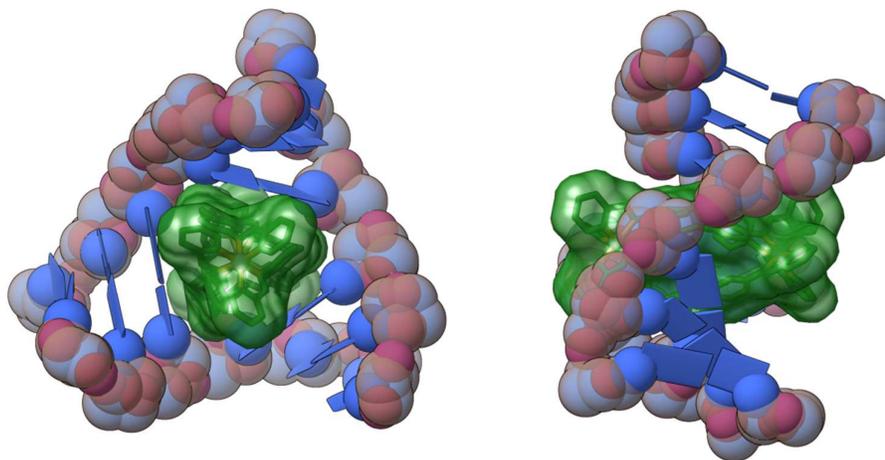
Fig. 23. X-ray crystal structure of a Y-junction bound with the space-filling model of the complex [Fe$_2${μ-[4,4'-methylenebis[N-[(2-pyridinyl-κN)methylene]benzenamine-κN]]}$_3$]$^{4+}$ (**48**), and the orthogonal view (right). Structure sourced from the PDB file 3I1D.[285]

Cruciforms and Hairpins

Cruciform DNA structures arise from sections of DNA that consist of inverted repeating sequences. Self-complementary sections of single strand DNA can form hairpins, where a single strand binds and folds over on itself; cruciform structures form where two hairpins occur on opposing strands (Fig. 24).[286] Hairpin and cruciform structures have been identified in genomic DNA and have implicated roles in replication, transcriptional regulation and recombination.[287, 288] The formation of hairpin and cruciform structures has the potential to block DNA promoter regions, thus influencing the production of particular proteins.[45, 289] The stabilisation of these structures through metal complex binding is therefore a viable strategy to target a particular gene product of cancerous cells. For example, a degree of specificity

was reported for targeting a cruciform structure with the rhodium complex, [Rh(4,7-diphenyl-phen)$_3$]$^{3+}$. Once bound, photoactivation results in cleavage at a specific AT-rich site neighbouring the stem of the minor cruciform on PBR322, indicating that the asymmetry in the cruciform structure was recognized by the complex.[290] A study of each isomer of the complex [{(Ru(Me$_2$bpy)$_2$)}$_2$μ-(bpym)]$^{4+}$ (where bpym = 2,2'-bpyrimidine, **49**, Fig. 24) found that the ΔΔ-isomer preferentially bound to bulge regions of DNA, whereas the ΛΛ-isomer did not.[291] Similar complexes to these have also shown bulge-binding specificity, which includes hairpin and cruciform structures; this preference may have applications for targeted gene expression modulation.[291-296]
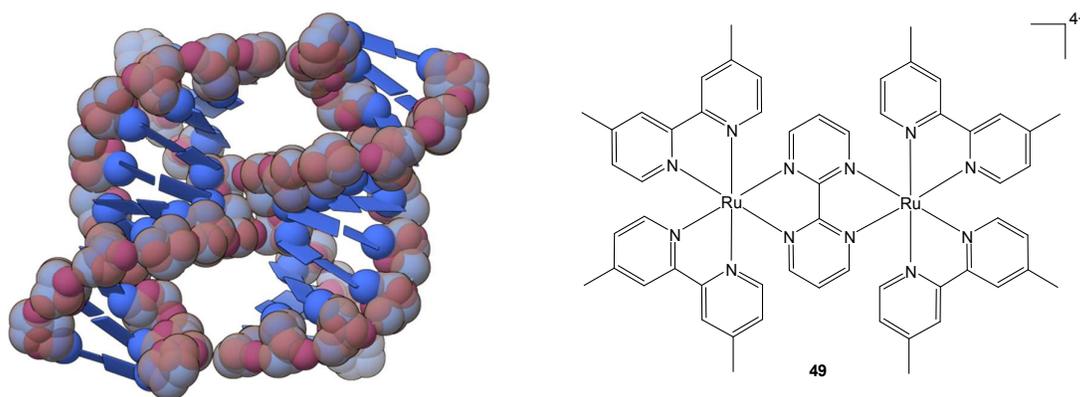
Fig. 24. Structure of a DNA cruciform sequence d(TCGGTACCGA) (left) and the chemical structure of the hairpin-specific complex [{(Ru(Me$_2$bpy)$_2$)}$_2$μ-(bpym)]$^{4+}$ (**49,** right). Structure sourced from PDB file 1M6G.[297]

G-quadruplexes

Q-quadruplex DNA (QDNA) is a structure consisting of four guanine bases bound together in a Hoogsteen fashion and stabilised by monovalent metal ions. The four bases can join from multiple strands or from the same strand, depending on the conformation (Fig. 25).[298] While G-quadruplexes are a more unusual form of DNA, ~400 000 sequences have been identified within the human genome that have the potential to form QDNA, particularly in promoter regions, untranslated sequence and human telomeric DNA.[299-301] Over 85% of cancerous cells

rely on the regular extension of their telomeric DNA *via* telomerase.[302] However, the formation of a quadruplex within this DNA region would inhibit the action of this enzyme, and so for successful cancer cell proliferation, the QDNA must be disassembled.[303] The stabilisation of QDNA to prevent disassembly is a potential avenue for chemotherapy, and it has been successful *in vitro*.[303]
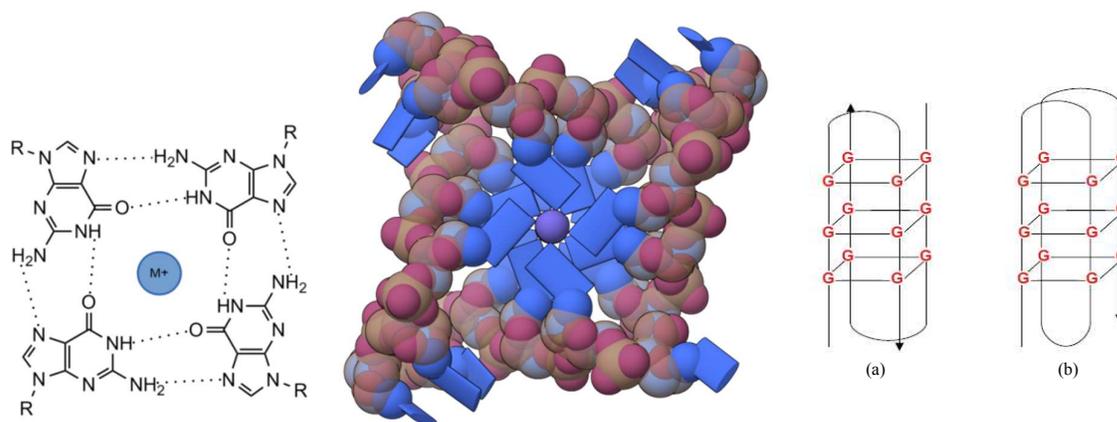
Fig. 25. Illustration of four Hoogsteen -bound guanine bases stabilised by a central cation (left), X-ray structure of human telomeric QDNA (middle), and examples of a two-strand and one-strand quadruplex structure (right). X-ray image sourced from PDB file 1KF1.[304]

Due to the stacked arrangement of the base-pairs in QDNA, insertion between base pairs is unlikely; instead, planar aromatic molecules are able to stack at either end of the QDNA structure.[72] The first metal complex-QDNA crystal structure arose from the end-stacking of nickel and copper salphen complexes to human telomeric quadruplexes (Fig. 27).[305] Each complex was not only cytotoxic against a range of cell lines and capable of inhibiting telomerase activity; the nickel complex (**50**) also to QDNA with a higher affinity than the copper complex.
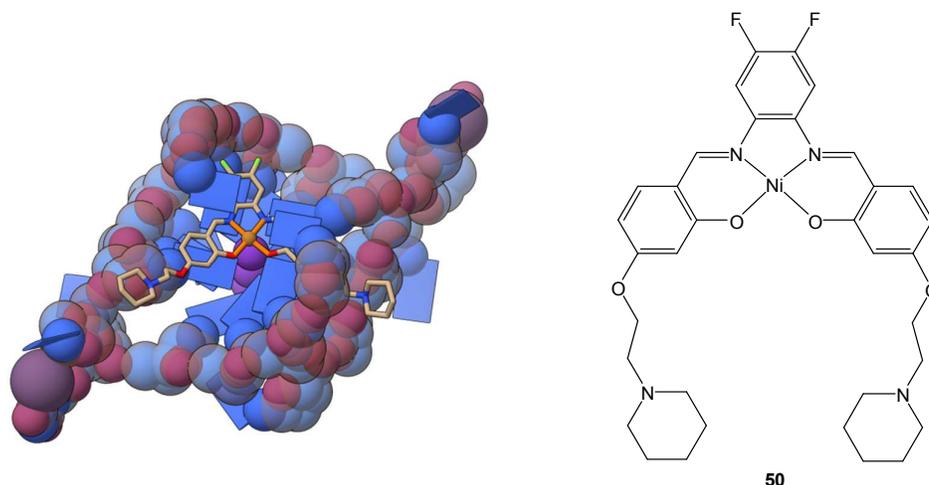
Fig. 26. X-ray structure showing the stacking between the nickel salphen complex and QDNA sequence (**50**, left) and the structure of complex **50** (right). Image produced from PDB file 3QSC.[305]

Ruthenium complexes have also emerged as potent QDNA binders. In particular, ruthenium dinuclear complexes such as ΔΔ- and ΛΛ-[{Ru(phen)$_2$}$_2$(tpphz)]$^{4+}$ have demonstrated the ability to stack within the ends of QDNA with especially high affinity.[306] The ΛΛ- isomer is reported to bind with ~40 times more affinity than the ΔΔ- isomer, and displayed strong luminescence. NMR studies confirm that the complex is able to bind at either end of QDNA, and NMR-based modelling has shown that the ΛΛ- isomer fits more effectively into the diagonal loop than the lateral (Fig. 27).[306]
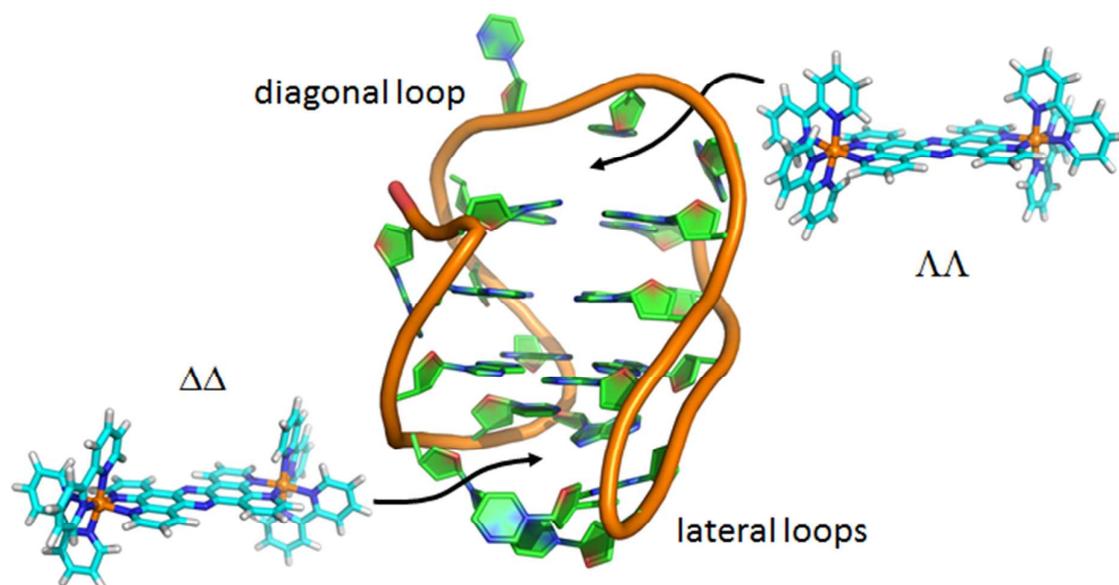
Fig. 27. Molecular representation of the sites at which the ΔΔ-, and ΛΛ-isomers of [{Ru(phen)₂}₂(tpphz)]⁴⁺ stack with the human telomere sequence d[AG3(TTAG3)3].[306] This image was kindly provided by Prof J. Thomas.

Conclusions

Metal complexes have proven themselves to be powerful tools when it comes to the diagnosis and treatment of disease. Metal complex-DNA interactions have been extensively researched in particular, and in this paper we have reviewed some examples of transition metal complexes that interact with DNA in its various structural forms, using a variety of different binding modes. It is clear that combinations of these modes of interaction can be utilized to improve the binding affinity and selectivity of metal complexes, although this is not an exhaustive review and there are many more examples. What is evident is that the design flexibility afforded by transition metals due to their inherent physiochemical variety and almost limitless range of ligands for coordination, makes metal complexes potent therapeutic and diagnostic agents that can be used to explore the structural diversity of DNA.

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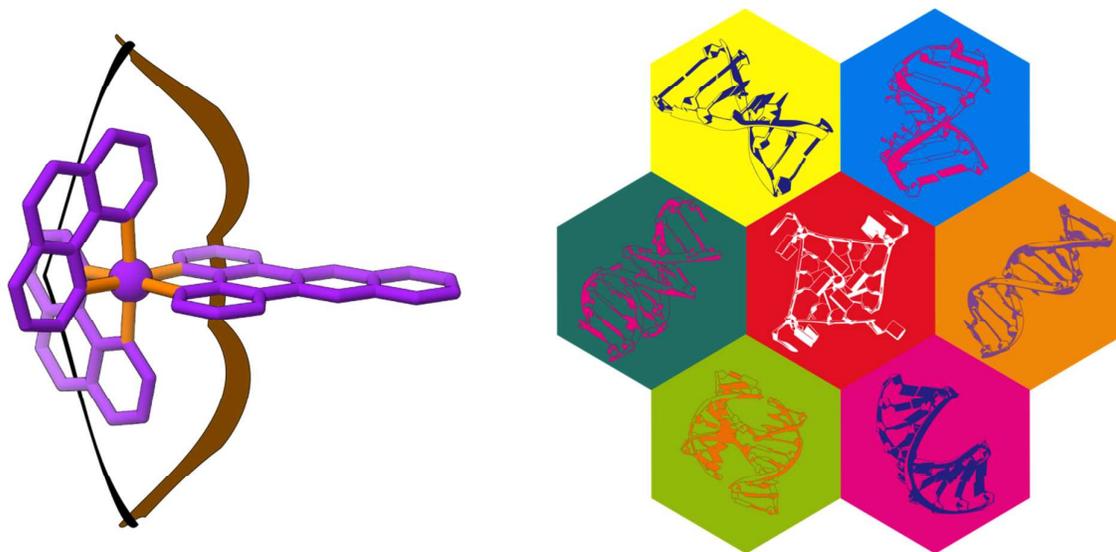
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Metal Complex Interactions with DNA

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