



# Metal Complexes as DNA Synthesis and/or Repair Inhibitors: Anticancer and Antimicrobial Agents

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## Abstract

Medicinal inorganic chemistry involving the utilization of metal-based compounds as therapeutics has become a field showing distinct promise. DNA and RNA are ideal drug targets for therapeutic intervention in the case of various diseases, such as cancer and microbial infection. Metals play a vital role in medicine, with at least 10 metals known to be essential for human life and a further 46 nonessential metals having been involved in drug therapies and diagnosis. These metal-based complexes interact with DNA in various ways, and are often delivered as prodrugs which undergo activation *in vivo*. Metal complexes cause DNA crosslinking, leading to the inhibition of DNA synthesis and repair. In this review, the various interactions of metal complexes with DNA nucleic acids, as well as the underlying mechanism of action, were highlighted. Furthermore, we also discussed various tools used to investigate the interaction between metal complexes and the DNA. The tools included *in vitro* techniques such as spectroscopy and electrophoresis, and *in silico* studies such as protein docking and density-functional theory that are highlighted for preclinical development.

## Keywords

- ▶ metal-based complexes
- ▶ DNA inhibitors
- ▶ drug therapies
- ▶ nonessential metals

## Introduction

Since the Barnett Rosenberg's discovery of cisplatin in 1965,<sup>1</sup> the use of metal-based compounds in medicine, particularly in the treatment of cancer, has been revolutionized by further development of other platinum drugs such as carboplatin and oxaliplatin.<sup>2</sup> The study of metal-based complexes with potential biological applications has expanded over the course of the years. There are numerous records from the history of metal-based treatments, ranging from the use of mercury(II) sulfide (cinnabar) by the ancient Greeks to the use of arsenic trioxide (trisenox) by traditional Chinese medical practitioners and the use of zinc(II), gold, and copper chelating agents in ancient Egypt to treat various diseases. In nature, various metals found in metalloenzymes and biocatalysts are essential for normal cellular functions. Most of

the metals involved in biological processes belong in the transition metal group, occurring in the d-block of the periodic table (groups 3–12). These metal ions are positively charged and exhibit variable oxidation states in aqueous solution, making them very ideal for interaction with negatively charged biological molecules, such as nucleic acid or amino acids. These metal complexes are able to form various three-dimensional configurations due to the range of coordination geometries, leading to various metal–ligand interactions. One of the most common metal complexes in human biology is vitamin B<sub>12</sub> (cobalamin) (▶ Fig. 1), which is required for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis and acts as an intracellular superoxide scavenger.<sup>3</sup>

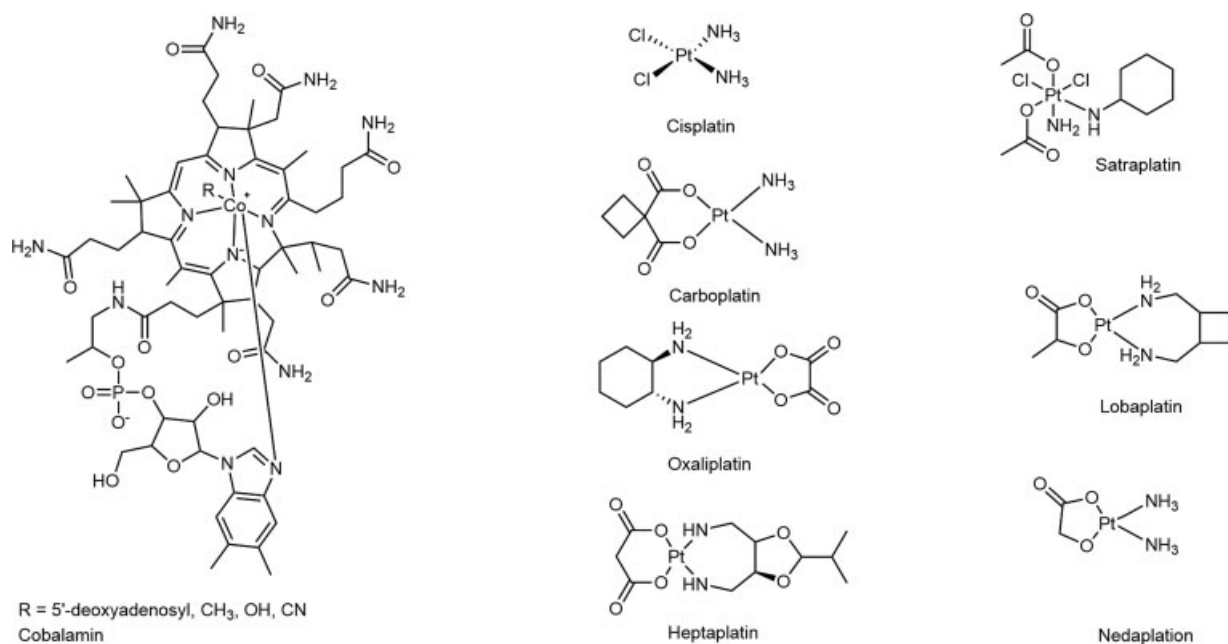
The transition metal complexes are typically distinguished by metal ions with more than one coordination

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**Fig. 1** Anticancer platinum drugs and vitamin B<sub>12</sub> (cobalamin).

number, which can lead to the formation of a large number of stereochemically and geometrically diverse and stable scaffolds.<sup>4</sup> Metal complexation leads to dramatic changes in the biological activity of ligands, such as improved potency of drug molecules (ligands) that are complexed to metal ions and/or reductions in adverse side effects.<sup>5</sup> The discovery of ferrocene by Kealy and Pauson at Duquesne University, and the subsequent incorporation of this molecule in chloroquine (CQ), suggested that the combination of organometallic compounds with known antimalarial drugs could result in potent antimalarials.<sup>6</sup> Ferroquine (FQ; SSR 97193) is a 4-aminoquinoline CQ analogue which is functionalized with the organometallic ferrocenyl moiety. The metal-modified FQ has been shown to be active against CQ-resistant and CQ-sensitive *Plasmodium falciparum* strains and against *Plasmodium vivax*.<sup>7</sup> FQ has also been shown to potently inhibit autophagy, perturb lysosomal function, and impair prostate tumor growth *in vivo*.<sup>8</sup>

N-heterocyclic carbenes (NHCs) are one of the most widely used ligands in the formation of metal–ligand complex because of their strong  $\sigma$ -donating and adaptable  $\pi$ -accepting abilities.<sup>9</sup> NHCs have a very modular structure that allows for the selective modification of their steric and electronic properties. The electronic structure of NHCs can be tuned almost at will by changing the nature of the heterocyclic ring or its substituents, while the steric requirements can be strongly tuned by the nature of the N-substituents.<sup>10</sup> In addition to NHCs, Schiff base ligands are widely used in metal complexes due to their low cost, ease of access, simplicity of synthesis, and chemical and thermal stability.<sup>11</sup>

In general, the use of metal-based drugs gives rise to toxic side effects due to the *in vivo* development of free radicals and reactive oxidant species.<sup>12</sup> The metals normally found in the body that are essential in biological processes include

iron, which is involved in redox reactions of oxygen and copper to form heme, a catalytic cofactor in enzymes that can assist in overcoming these side effects. With similar properties to calcium ions, lanthanide(III) ions (classified as rare earth metal ions) can also be used in metal complexes because they possess pharmacological properties such as anticoagulation, anti-inflammatory, antibacterial, antiallergic, and anticancer properties, and exhibit paramagnetic properties at meanwhile.<sup>13</sup> Lanthanides present in pyrroloquinoline quinone-dependent alcohol dehydrogenases in methylotrophic bacteria, where the highly selective Ln(III)-binding protein lanmodulin plays a role in intracellular transport.<sup>14</sup>

### Mechanisms of Action

Endogenous and environmental damage is constantly being inflicted on cellular DNA, resulting in cellular dysfunction and cell death. Nucleic acids remain a key player in the central dogma of molecular biology, where the genetic code in DNA can be transcribed onto messenger RNA and translated into a protein form.<sup>15</sup> DNA damage response (DDR) signaling networks have evolved in cells to ensure genomic stability and to sustain continuous cellular progression and growth.<sup>16</sup> DDR defects play a role in the development of cancer and drug resistance in microbes. One of the mechanisms of action of metal complexes is to target nucleic acid (DNA/RNA), contributing to the disruption of transcription, translation, and other processes, which may ultimately cause death of the cell. In addition to targeting the nucleic acids, the metal complexes can also interact with proteins such as key DNA repair enzymes in DDR signaling pathways. Roughly 30 to 40% of known proteins require transition metals for their normal human biological activity. These metals play a role in proteins by acting as Lewis acids, thus providing reactivity in biocatalytic processes.

These metal ions facilitate redox chemistry through their multiple oxidation states, and they are able to act as cross-linking agents by coordinating at multiple sites in proteins.<sup>17</sup> The action of metal complexes is not, however, selective, in that they do not differentiate between normal cells and tumor cells, and therefore severe side effects would occur due to normal tissue damage.<sup>18</sup> By substituting the metal, changing its oxidation state, and/or coordinating geometry and coordination number, it is possible to fine-tune the metal-complex chemical stability, ligand exchange rate, metal–ligand bond strength, redox potential, ligand conformation, and outer-sphere interactions. Therefore, through the rational design of ligands and metal complexes, it is possible to prepare a variety of metal complexes with potential biological application.<sup>19</sup> Depending on the design of the metal complex, the mechanism of action can proceed via several very different binding interactions with DNA.

### Structure–Activity Relationship

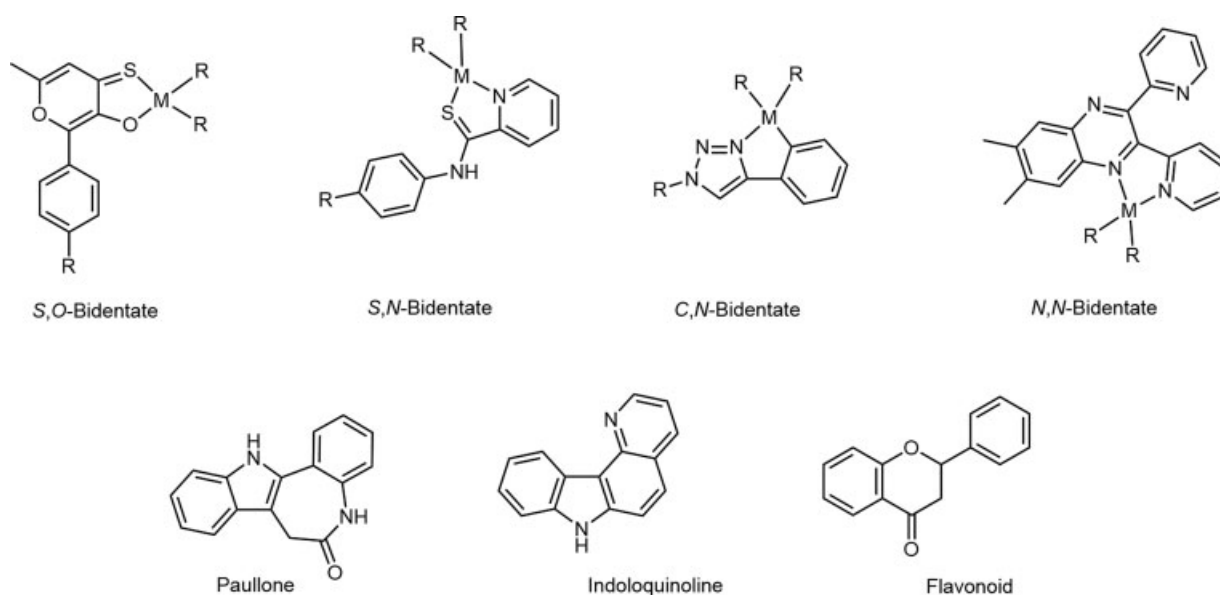
The structure–activity relationship (SAR) describes the correlation between the chemical structure of a drug molecule and its biological activity. The SAR can be a powerful tool to permit the selection and optimization of potential drug candidates in drug discovery research. SAR studies favor the discovery of structural elements, such as metal components, coordination mode variations, labile water molecules, chelated ligands, etc., that may have an important cooperative effect on biological activity.<sup>20</sup> The SAR can be influenced through the choice of ligand type (e.g., arene), metal, coordination mode, rate of hydrolysis, charge, and  $pK_a$ . The choice of the ligand (lipophilicity) can influence the cytotoxic activity and coordination mode (where *S,O*-<sup>21</sup>; *S,N*-<sup>22</sup>; *C,N*-<sup>23</sup>; and *N,N*-bidentate donor systems [excluding bipyridines and bipyrimidines] generally are reported to yield high biological activity with more potency toward metallodrugs tethered to bioactive ligands such as indoloquinolines, paullones, and flavonoids) (–Fig. 2).<sup>24</sup> Thus, both ligand structure

and organometallic fragment are beneficial in bioactivity, where the latter entity modulates the solubility of the bioactive ligands.

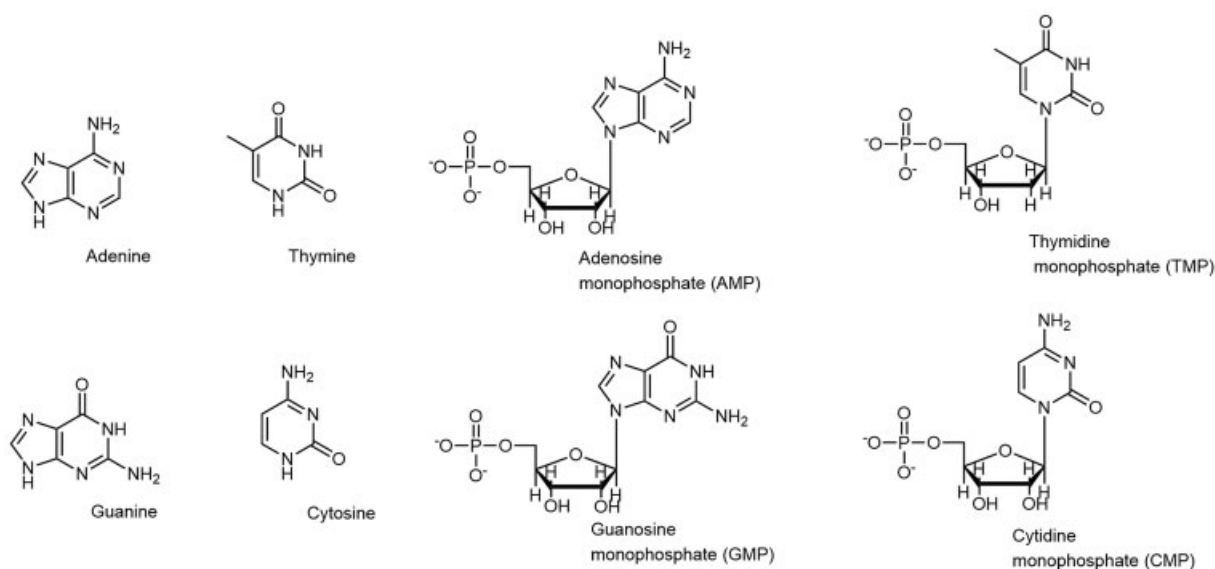
A key feature of metal complexes acting as a prodrug is the labile ligand which dissociates from the metal to give the active species. The presence of the leaving group can exert subtle effects, where chlorido and iodido complexes are more potent than the bromido analogues. The rate of hydrolysis is critical, because if the complexes hydrolyze too quickly, they may not reach the target site, thus, the rate of hydrolysis is a key factor for metal complexes.<sup>25</sup> A study on a series of charged (promoting interaction with oppositely charged biomolecules) ruthenium polypyridyl complexes revealed good antibacterial activity, owing to the target of this class of compounds being the highly negatively charged bacterial surface, resulting in damaged and deformed cell walls.<sup>26</sup> Many properties of molecules, such as solubility, lipophilicity, permeability, and protein-binding ability, are influenced by  $pK_a$  values, which have an impact on pharmacokinetic processes such as absorption, distribution, metabolism, and excretion.<sup>27</sup> According to a study on Ru(II) coordination complexes as antiproliferative agents, the  $pK_a$  values of the aquated species control the reactivity of the active complex and allow the drug to be active in specific cells.<sup>28</sup>

### Binding to Nucleic Acids

DNA is a key therapeutic target for transition metal complexes and has a wide range of intracellular interactions. Nucleobases follow Chargaff's rules whereby a 1:1 (purine: pyrimidine) relationship exists between guanine (G) and cytosine (C), and adenine (A) and thymine (T) (–Fig. 3). The B-form of duplex DNA, which is the most common in biology, is a right-handed double helix with two antiparallel sugar–phosphate chains.<sup>29</sup> The minor (4.8 Å) and major (10.5 Å) grooves in the helical structure are the result of the angle between the glycosidic bonds and



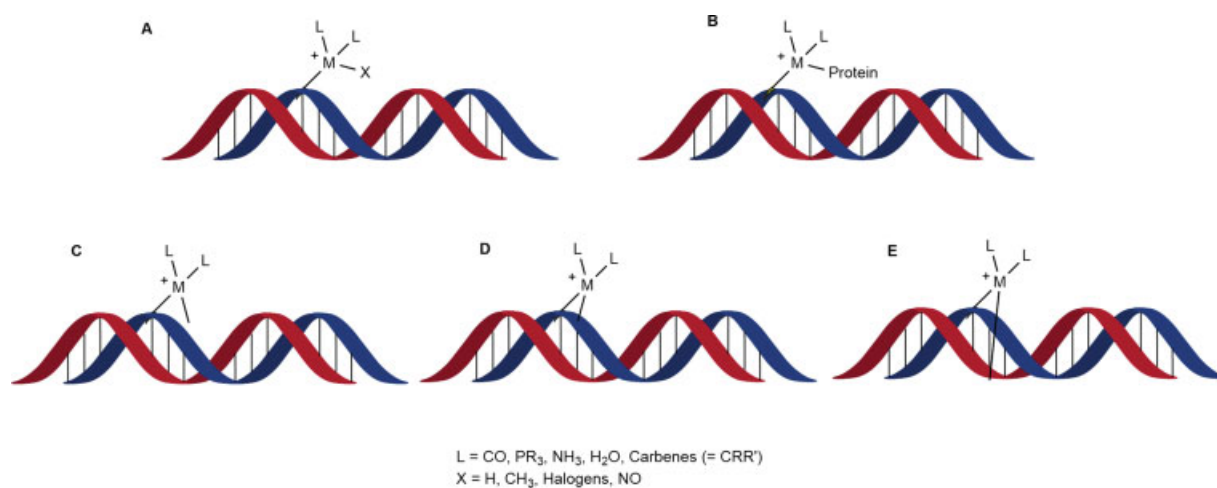
**Fig. 2** Active ligand scaffolds with improved bioactivity.



**Fig. 3** Nucleobases with respective monophosphate nucleotides.

hydrogen bonds. The dehydrated form of B-DNA, termed A-DNA, has a similar but more stable and compact structure, with 11 base pairs per helical turn and a 2.55 Å axial rise between base pairs.<sup>30</sup> Z-DNA (linked to cancer, autoimmune and neurological diseases) is produced *in vivo* during the transcription process as a result of torsional strains generated by RNA polymerase moving along the sequence of the DNA double helix.<sup>31,32</sup> This provides a range of possible intermolecular interactions, including irreversible covalent binding, reversible groove interactions, or intercalation between metal complexes and DNA, due to the structural complexity and polymorphism of DNA. Studies on the effect of DNA metal complexes have shown that metal coordination geometry and the ligand configuration can influence binding behavior: square planar metal complexes were observed to have a greater capacity for deeper insertion as an intercalator than complexes with octahedral or tetrahedral geometry.<sup>33</sup>

In contrast to intercalation, different DNA adducts can form as a result of covalent bonding, which is the most common type of interaction for metal-based anticancer drugs (►Fig. 4). These adducts range from monoadducts (one bond is formed with DNA and the other coordination site of the ligand remains equated or protein-bound), to intrastrand crosslinks (1,2-intrastrand or 1,3-intrastrand where two bonds are formed on the same strand between consecutive base pairs, or bonds are formed with base pairs that are one base apart, respectively) and interstrand crosslinks (bonds are formed on opposite strands of the double helix) between the metal complexes and DNA bases.<sup>34</sup> These interactions can lead to various changes to the DNA structure such as bending of the DNA double helix and unwinding of the DNA, leading to cell death. Under certain conditions, binding with DNA can inhibit winding or ensure that no bending occurs, thus affecting replication and transcription. Studies have also shown that different metal ions can



**Fig. 4** DNA adduct formation with metal complex: (A) monoadduct, (B) protein–DNA, (C) 1,3-intrastrand, (D) 1,2-intrastrand and (E) interstrand crosslinks.

interact with the DNA in different ways. The alkali and alkaline earth metals mainly interact with the DNA phosphate groups, whereas the metal ions, such as  $\text{Cd}^{2+}$ ,  $\text{Pb}^{2+}$ , and trivalent lanthanides can interact with both phosphates and bases.<sup>35</sup>

### Metal-Ion-Mediated Base Pairs

Studies on the binding of metals to nucleosides have extended to metal-ion-mediated base pair formation. The incorporation of metal complexes into DNA via metal-mediated base pairing has been established as having the potential to expand the genetic alphabet (incorporating nonstandard bases into DNA) and to afford new DNA structures (noncanonical), and functionalities in which the metal properties can be shared with the DNA structure.<sup>36</sup> The use of metal-ion base pairs can lead to the design of noncomplementary base pairs of natural pyrimidine bases such as thymine–thymine (T–T) and cytosine–cytosine (C–C) pairs. The most common are metal-ion-bridged T– $\text{Hg}^{2+}$ –T and C– $\text{Ag}^+$ –C. The applications of metal-mediated base pairing range from metal-ion sensors (detection of  $\text{Hg}^{2+}$ , which is capable of forming T– $\text{Hg}^{2+}$ –T base pairs), to redox sensors and biomolecule sensors for detecting single-nucleotide polymorphisms.<sup>37</sup> It has been proposed that metal-ion base pairs could either activate or inhibit the activity of enzymes such as DNA polymerases, endonucleases, ligases, and exonucleases. This could lead to the development of a DNA aptamer capable of inhibiting DNA polymerase.<sup>38</sup> The metal ions can also be incorporated in the design of DNA molecular switches as observed on divalent metal ions such as  $\text{Mg}^{2+}$ ,  $\text{Ca}^{2+}$ , and  $\text{Mn}^{2+}$ , which are able to stabilize DNA duplexes and form stable complexes (hairpin, triplex, G-quadruplex, and i-motif) with ethylenediaminetetraacetate (EDTA) adducts useful for bioimaging.<sup>39</sup>

### Drug Resistance

It is well known that drug resistance (extrinsic and intrinsic) to anticancer and antimicrobial medications is high. Although metal complexes, such as platinum drugs, may be initially effective against cancer, cancer cells develop resistance over time due to factors such as more efficient DNA damage repair, inactivation of drug with glutathione and metallothionein, and drug efflux with various transport systems located in the cell membrane.<sup>40</sup> Elevated levels of copper transporters ATP7A and ATP7B have been linked to a decreased accumulation of cisplatin in cells and, as a result, to lower cytotoxicity.<sup>41</sup> There are proteins which consist of an abundance of cysteine, such as glutathione and metallothionein, which inactivate cisplatin and other similar drugs within the cell by coordinating to thiol groups. The World Health Organization reports that with regard to microbes, we are now on the verge of a postantibiotic era, and that antibiotic treatment failures will be common over the next few decades.<sup>42</sup> Cationic silver ( $\text{Ag}^+$ ) resistance has been recognized for several years, and it has been observed that exposing bacteria to toxic heavy metals such as silver can induce the emergence of antibiotic resistance via the process of co-selection.<sup>43</sup> As a result, novel strategies and formulations for anticancer and anti-

microbial metal complexes with nonclassical modes of action are being investigated.

## Metal-Catalyzed Cleavage of Nucleic Acids

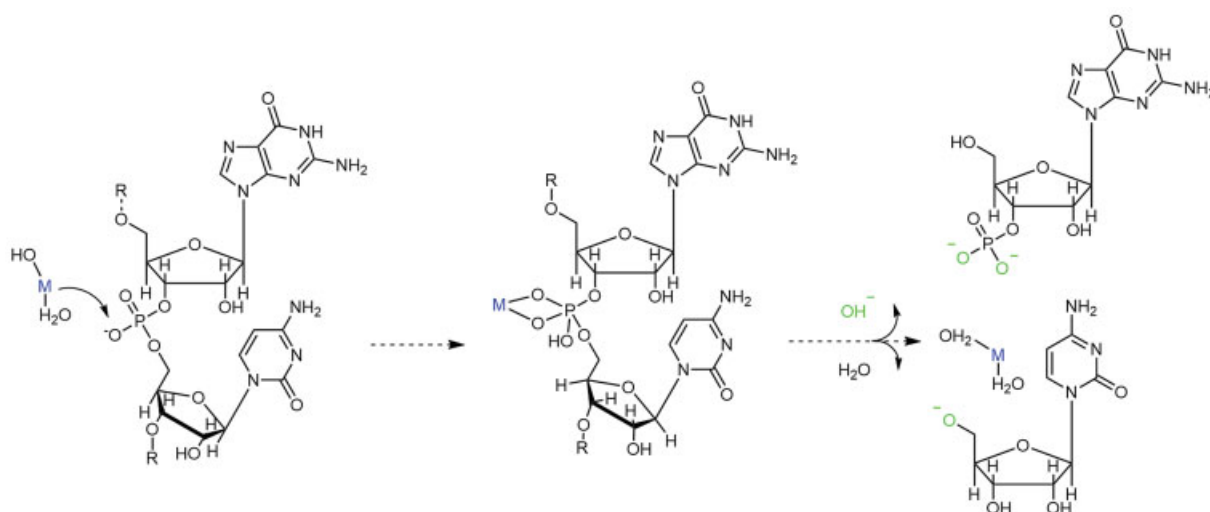
### Hydrolysis

Nucleic acids can undergo hydrolytic (enzymatically reversible), oxidative, and photocatalytic cleavage as a result of interactions with metal complexes. The Lewis acidity of the metal has been shown to determine the hydrolysis rate of the metal-bound phosphoester after the formation of the metal-phosphate intermediate, as demonstrated by the biological activity of natural metallonucleases.<sup>15</sup> Since the neighboring 2'-OH group can be deprotonated by metal complexes in the RNA backbone, in comparison to DNA, RNAs are more hydrolysis-prone by nucleophilic attack. The phosphoester bond (mono-, di-, or tri-ester) can be found in proteins, nucleic acids, and lipids. This bond forms the backbone of DNA and RNA by connecting the adjacent nucleotides. In nature, the hydrolysis of this bond is required during DNA repair, posttranslational modification of proteins, and energy metabolism.<sup>44</sup> Metal complexes, unlike enzymatic activity, can be used as cost-effective therapeutics with tunable functionality. The catalysis of the phosphoester bond (P–O) has highlighted the fact that metal ions can act as Lewis acids by activating the phosphoryl group for nucleophilic attack (**► Fig. 5**). The  $\text{pK}_a$  of the leaving group through the coordination of the alcoholic oxygen of the phosphodiester can also be reduced and metal-coordinated water molecules can be deprotonated.<sup>45</sup> Using the metal complex based on copper and cobalt, the rate of DNA cleavage in comparison with the non-metal-catalyzed reaction was demonstrated to increase by a factor of 10 to 100 million.<sup>46</sup> Several artificial nucleases that promote hydrolysis of the nucleic acid phosphate backbone have been synthesized, including Cu(II), Cr(III), Zn(II), Ce(IV), Zr(IV), La(III), Fe(III), and Co(III) complexes.<sup>15</sup>

### Oxidation

Another mechanism for nucleic acid degradation is irreversible oxidative cleavage, which requires redox-active metals. In this process, reactive oxygen species (ROSS) are required for the hydrogen abstraction of the deoxyribose/ribose ring, which is followed by spontaneous cleavage of C–C and C–O bonds.<sup>47</sup> The discovery of  $[\text{Cu}(\text{phen})_2]^{2+}$  (phen = 1,10-phenanthroline) provided the first synthetic chemical nuclease for the development of new artificial metallonucleases.<sup>48</sup> Colibactin, a human intestinal bacterial genotoxin (colorectal cancer) metabolite, has been shown to cause DNA damage (double strand breakage) and genomic instability following the formation of a copper complex that releases ROS such as superoxide and singlet oxygen species.<sup>49</sup> Similarly, Cu(II) complexes with either phenanthroline or hydrazone ligands have been identified as self-activating metallonucleases where DNA can be damaged or cleaved by ROS generation in the absence of a reducing agent.<sup>50</sup>

Copper derivatives generally interact noncovalently with DNA through intercalation, electrostatic interaction, and/or major or minor groove-binding; and in this they differ from

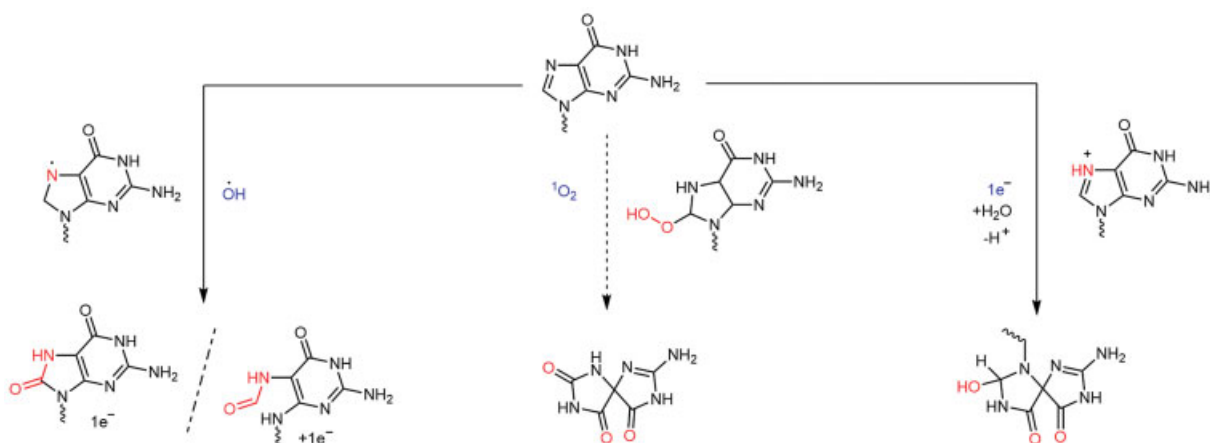


**Fig. 5** Hydrolytic cleavage pathways for nucleic acids promoted by metal complexes.

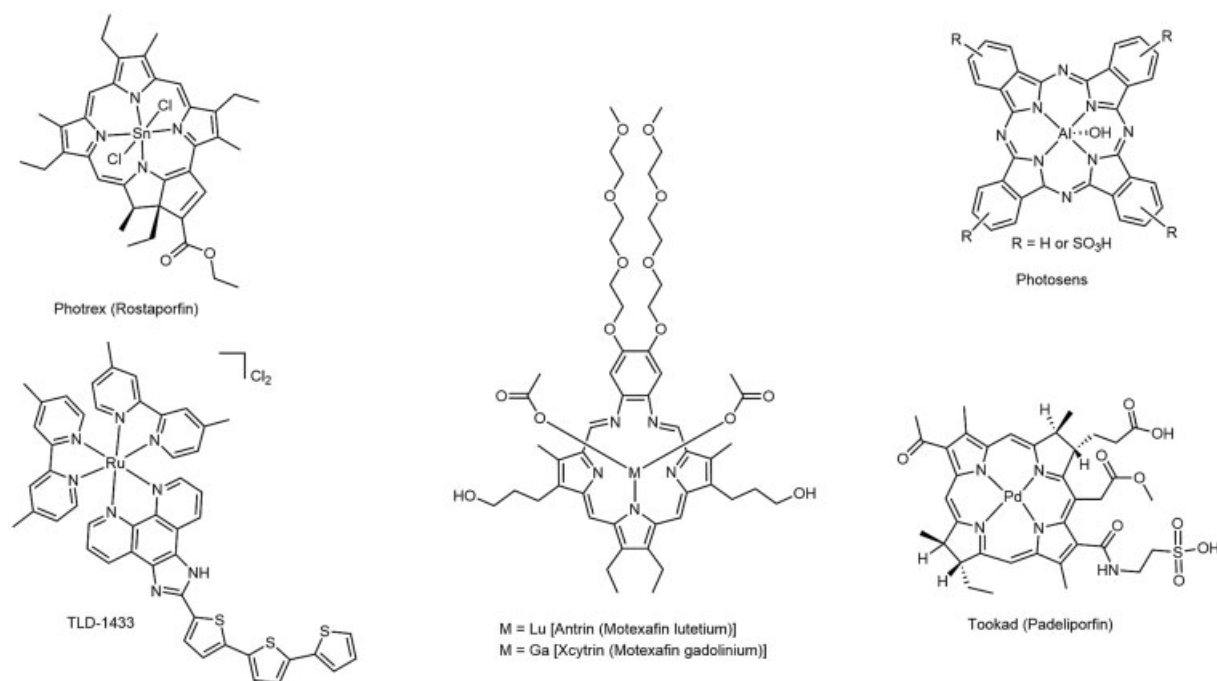
platinum drugs, such as cisplatin, which interact covalently with DNA nucleobases.<sup>51</sup> Several naturally occurring antimicrobial peptides (AMPs) require metal ions such as  $Zn^{2+}$ ,  $Na^+$ , and  $Mn^{2+}$  for antimicrobial activity. Upon formation of the AMP–metal complex, through redox chemistry they are able to inhibit DNA and RNA replication, retard protein synthesis, permeabilize the cell membrane, as well as disrupt proton and ion transmembrane gradients, and suppress cell-wall biosynthesis.<sup>52</sup> The nucleobase guanine has been observed to be the most sensitive toward oxidation due to hydroxyl radicals (Fenton reaction), singlet dioxygen (Diels–Alder cycloaddition), or electron transfer as depicted in ► **Fig. 6**. The hydroxyl radicals attack the carbon atom C8 of guanine (and also the ribose sugar at  $C5' > C4' > C3' > C2' > C1'$ ), while the singlet dioxygen undergoes a Diels–Alder cycloaddition with guanine across the imidazole ring; during electron-transfer pathways this leads to abstraction of one electron from guanine to produce the guanine radical cation.<sup>53</sup>

Metal complexes with redox properties are also capable of oxidizing the sugar unit via the production of radical species. The shape of the DNA duplex and the C–H bond-energy

differences between the distinct carbon atoms play a key role in influencing the accessibility of the Csp<sup>3</sup>–H bonds of the deoxyribose within the major and minor grooves. The C1' position is buried within the minor groove of B-DNA, thus making it inaccessible to some free radicals. The 2'-position of deoxyribose, in comparison, has high C–H bond strength and low accessibility of the corresponding hydrogen atoms, which means that the position can be changed only by  $\gamma$ -irradiation of DNA. Modification of the C3' position, which is located in the major groove of DNA, makes a minor contribution to DNA strand break in B-DNA. The C4' is situated on the outer edge of the minor groove of the DNA. The C4'–H4' bond is relatively weak, which makes the 4'-position of deoxyribose a major target for hydroxyl radicals and other minor groove-binding oxidants, accessible to metal complexes such as iron bleomycin,  $[Cu(phen)_2]^{2+}$  and Fe(II)-EDTA. Both hydrogen atoms at the 5'-position of deoxyribose are highly accessible in the minor groove of B-DNA. Computational studies have indicated that H4' abstraction can disrupt the deoxyribose moiety, while H5' abstraction can lead to DNA cleavage at the 5'-position.<sup>54</sup>



**Fig. 6** Degradation of guanine induced by hydroxyl radicals, singlet dioxygen, and electron transfer.



**Fig. 7** Approved metallo-drugs.

### Photocatalysis

In photocatalysis, the inorganic or organic chromophores, once irradiated, induce an energy or electron transfer to the substrate. Both respond to ultraviolet light, leading to photocatalysis, photocaging, and photoswitching.<sup>55</sup> Photocatalysis using metal complexes has been well studied in the context of modification of amino acids, peptides, and proteins.<sup>56</sup> In terms of nucleic acid cleavage, visible light-based photosensitizers (PSs), relying on metal complexes such as ruthenium(II) and iridium(III) with riboflavin as a ligand, have resulted in the design of more efficient and site-selective DNA photocleavage induced by the generation of ROS.<sup>57</sup> In photodynamic therapy, the drug **TOOKAD Soluble**, which utilizes a palladium-based PS, has been approved for use in treating low-risk prostate cancer, while the ruthenium-based PS **TLD-1433** is currently undergoing clinical trials.<sup>58</sup> There are different mechanisms of photocatalytic action of metal complexes which can lead to cell death. During irradiation, which can lead to the formation of toxic singlet oxygen species, local heat production and dissociation (oxidation state remains unchanged) are responsible for radicals binding to biomolecules. Reduction of the metal leads to biomolecule interaction and bidentate ligand cleavage, resulting in ligand dissociation and subsequent binding to a biomolecule.<sup>59</sup> Approved drugs (→**Fig. 7**) include Xcytrin (Gd(III)), Antrin (Lu(III)), Tookad (Pd(II)), Photrex (Sn(IV)), and Photosens (Al(III)).<sup>60</sup>

### Anticancer Activity

Cancer is defined as a malignant disease caused by unusual cell growth due to carcinomas (epithelial cell-derived), sarcomas (connective tissue), germ cell seminoma and dysgerminoma (testes and ovary), blastomas (embryonic tissue)

and lymphoma, and leukemia (hematopoietic [blood-forming] cells).<sup>61</sup> Global statistics indicate that lung cancer had the highest mortality rate (18.4%), followed by breast cancer (6.6%), colon cancer (5.8%), stomach cancer (8.2%), esophagus (5.3%), pancreas (4.5%), liver cancer (8.2%), and prostate cancer (3.8%).<sup>62</sup> DNA remains the main target for metal-based anticancer drugs. Over the years, DNA metallointercalation has been extensively explored because this process can be used in potential anticancer drugs. Several metal complexes, ranging from ruthenium, osmium, iron, and titanium to copper, have been found to exhibit both anticancer and antibacterial properties.<sup>61</sup>

However, to date only platinum-based drugs have been used extensively to treat cancer. Cisplatin is the first-generation platinum-based drug, which subsequently led to the development of carboplatin and oxaliplatin, both of which have been approved worldwide. Later generations of platinum drugs such as lobaplatin, nedaplatin, and heptaplatin are used in China, Japan, and South Korea, respectively.<sup>63</sup> The mechanism of action of these drugs is based on binding to DNA in cancer cells through the formation of adducts with the cellular DNA, which lead to distortions that cannot be recognized by DNA repair mechanisms. The cisplatin analogues of titanium, vanadium, and iron have been shown to react with DNA specifically in tumor cells.<sup>64</sup> Platinum-based anticancer agents, which are clinically used to treat 50% of malignant cancers, have several disadvantages, such as low bioavailability, severe side effects, poor stability, and inherent or acquired resistance. Pt(IV) complexes can be designed as prodrugs with kinetic inertness and a low spin  $d^6$  octahedral geometry, making them more stable for oral administration, while axial ligand modification can improve pharmacological properties and reduce side effects and drug resistance.<sup>65</sup>

Inactive platinum(IV) prodrug complexes, such as Satraplatin, need to undergo reductive elimination by endogenous reductants to release the active square-planar platinum(II) core pharmacophore with concomitant dissociation of the axial ligands (to improve lipophilicity and solubility).<sup>66</sup> Under (pseudo)physiological conditions, anticancer transition metal complexes containing biologically active ligands can behave in a variety of ways, including no release of a bioactive ligand, release of a bioactive ligand and cytotoxic metal-containing species from the initial multi-targeted complex (prodrug), and release of a bioactive ligand from an inactive metal-containing species in which the initial complex represents a drug carrier.<sup>67</sup> To overcome the intrinsic resistance as well as prevent the development of acquired resistance, combining the mechanisms of action appears to be beneficial for cancer therapy. Complexes with dual anticancer and antibacterial properties can also be beneficial for cancer therapy because cancer patients have a weakened ability to fight infections. The siderophore deferoxamine B was successfully derivatized to form mono- and bi-dentate complexes with ruthenium, thus generating the dual anticancer and antibacterial agents.<sup>68</sup> Siderophores are essential in order for bacteria to scavenge iron(III) from their environment. The release of biologically active ligand from the complex has been shown to be essential for potent activity to occur, in which cleavable linkers triggered by phosphatase, esterase, or reductase enzymes can be used.

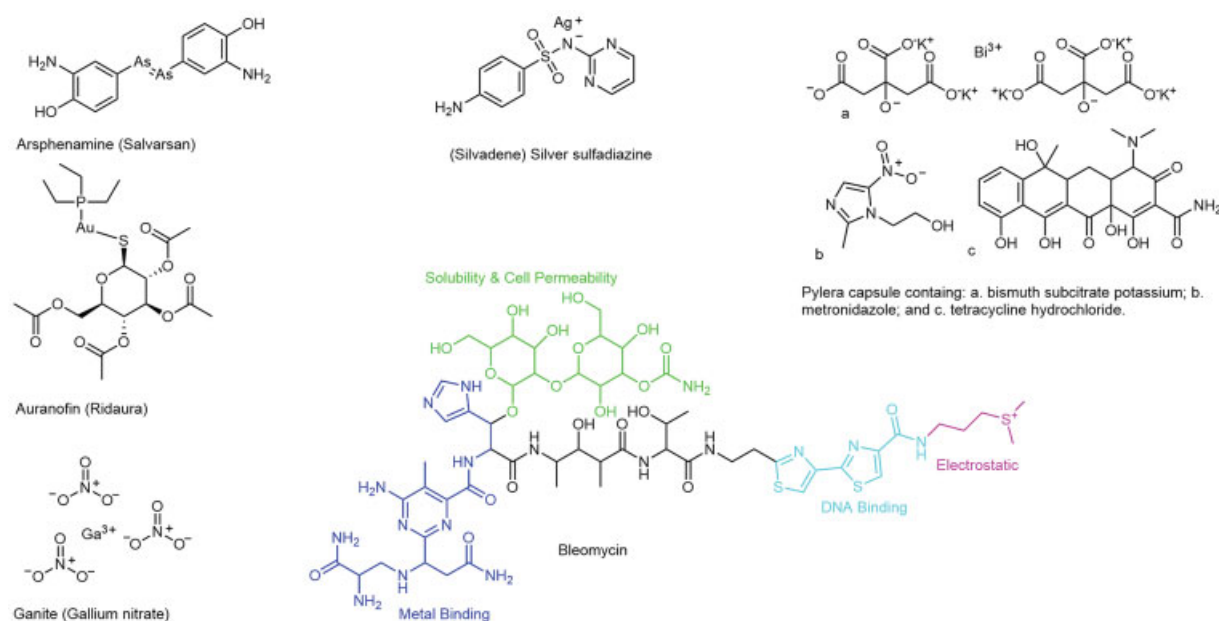
## Antimicrobial Activity

It was estimated that in 2018, approximately 2.4 million people in Europe, North America, and Australia would die from drug-resistant microbes over the following 30 years, at a cost of up to 3.5 billion U.S. dollars annually, due to global increase in microbial resistance.<sup>69</sup> Over the years, the study

of metal complexes as potential antimicrobial agents has attracted significant interest. Complexes of antibiotics with metal ions can affect the geometry of the antibiotic, leading to improved biological activity due to the presence of the metal ion within the organic compound structure.<sup>70</sup> The drug Arsphenamine (Salvarsan), which contains an arsenic ion, was developed in 1909 and observed to be an effective treatment for syphilis and African trypanosomiasis.<sup>71</sup> Other Food and Drug Administration (FDA)-approved metal-based complexes, termed metalloantibiotics, for antimicrobial applications include silvadene (silver), auranofin (gold), ganite (gallium), and pylera (bismuth) (► Fig. 8).<sup>72</sup> DNA interaction via an intercalative binding mode for photo and oxidative cleavage of bacterial DNA through an ROS and OH radical mechanism was well demonstrated in Cu(II), Ni(II), and Co(III) complexes of 2-furlylmethylamine Schiff base ligands.<sup>73</sup> Peptide antibiotics have also been studied, and when complexed to metal ions, they will gain a higher positive charge, allowing them to interact more strongly with polyanionic DNA and RNA molecules. Bleomycin, for example, is able to form stable complexes with redox metal ions, and generate free radicals to cleave the nucleic acid chain.<sup>74</sup>

## Antibacterial Activity

Resistance arises from the misuse and overuse of antibiotics. Currently, there has been an alarming increase in bacterial resistance to several the antibiotics available. Historically, clay was used to prevent wound infection. The study of the clay from the Amazon region (kaolin and smectite) or volcanogenic hydrothermal clay (illite-smectite) has been shown to inhibit even drug-resistant bacteria.<sup>75</sup> The clay consists of aqueous Fe(II) in synergy with Al(III) to generate ROS, which is able to inhibit bacteria through disruption of the cell membrane and DNA. Currently bismuth (bismuth



**Fig. 8** Approved metal-based complexes, termed metalloantibiotics.



tribromophenate) and silver-based (silver sulphadiazine) antimicrobials are two metal-based therapeutics in clinical use. Over 906 metal-containing compounds have been submitted to the Community for Open Antimicrobial Drug Discovery for evaluation, of which 246 compounds have been observed to have antibacterial and antifungal activity.<sup>76</sup> From investigations of antibacterial activity of metal complexes, several factors have been defined as significant, including (1) the chelate effect of ligands; (2) the structure of the *N*-donor ligands; (3) the total charge of the complexes; (4) the presence and nature of the complex counter ions; and (5) the nuclearity of the metal complex.<sup>77</sup>

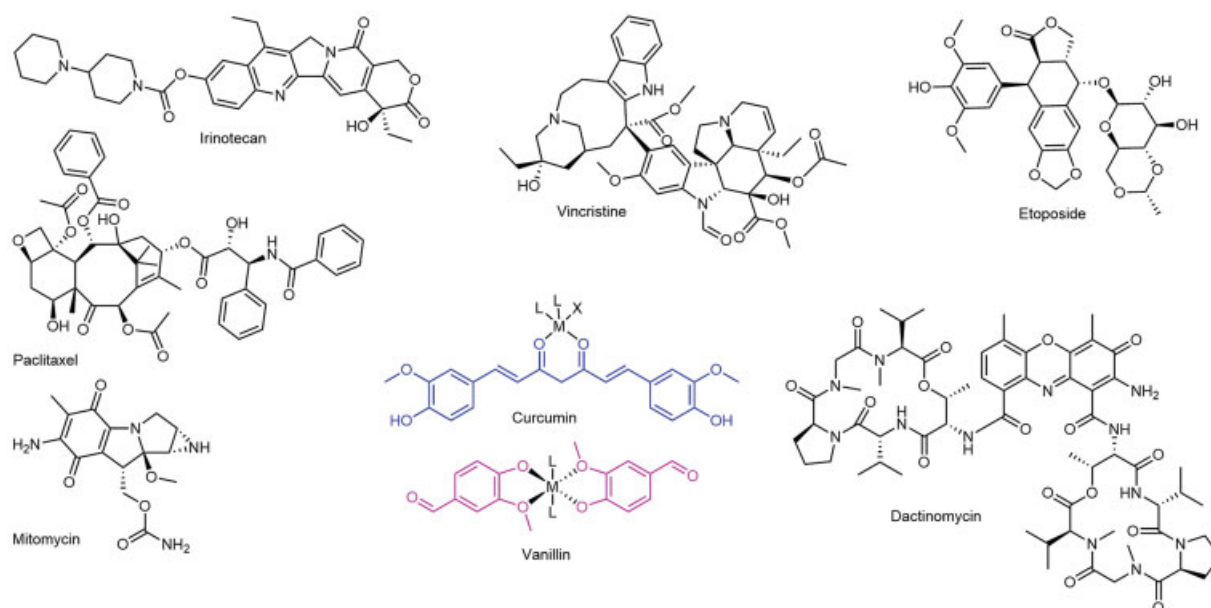
### Antiviral Activity

The use of metal-based therapeutics, including gold, bismuth, arsenic, antimony, and mercury-based compounds to combat diseases such as tuberculosis and syphilis, caused cytotoxic problems, and lead to discontinued use.<sup>78</sup> Over the years, the world has witnessed the (re)emergence of infectious diseases of viral origin, such as those caused by the dengue virus, Zika virus, chikungunya viruses (CHIKV)1–3, human immunodeficiency virus (HIV), yellow fever, measles, influenza A, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle-East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV2/Covid-19, as well as Ebola. Various metal complexes have been observed to have activity against: (1) HIV (nickel, copper, magnesium, lanthanum, ruthenium, and vanadium); (2) herpes simplex virus (cobalt, silver, iridium, gold, palladium, and platinum); (3) influenza (magnesium and copper); (4) hepatitis C (copper); (5) Sindbis virus (cobalt); (6) SARS-CoV (zinc); (7) SARS-CoV-2 (gold and bismuth); (8) cytomegalovirus (platinum); (9) chikungunya virus (gold); (10) poliovirus (platinum); (11) Zika virus (gold), and (12) West Nile virus (lanthanum, cerium, neodymium, and praseodymium).<sup>79</sup> Zinc ions exhibit antiviral properties against influenza and herpes in that they suppress

the viral life cycle; they also play a major role in innate and adaptive immune signaling pathways.<sup>80</sup> Like the antimicrobial properties of metallothioneins (small, cysteine-rich proteins) which bind to either zinc or copper to induce antiviral activity, synthetic metal-based complexes could also be a tool against viral infections. Phototherapy can induce antiviral activity from metal complexes in addition to antiviral activity caused by oxidative stress.<sup>81</sup> Chelating the metal ion(s) within the active site is another method of antiviral inhibition.<sup>82</sup>

### Natural Products

Natural-based compounds such as curcumin have been shown to exhibit various therapeutic properties such as anti-inflammatory, antimicrobial (antivirus, antibacterial, and antifungal), antioxidant, and anticancer properties.<sup>5</sup> These compounds are also capable of forming metallocomplexes once they chelate various metal ions. Quinone and polyphenol metabolites are produced by microorganisms, plants, and some animals. These metabolites have been widely used in medicine to combat bacterial infections. These natural products have been shown to exhibit metal-binding activity which would be useful in the formation of metal complexes for therapeutic use.<sup>83</sup> Several widely used anticancer therapeutics are originated from natural sources, examples being irinotecan, vincristine, etoposide, and paclitaxel from plants (► Fig. 9); as well as actinomycin D and mitomycin C from bacteria and marine-derived bleomycin.<sup>84</sup> Camptothecin and taxol are undoubtedly the two most successful examples. *o*-Vanillin, the main phytochemical present in vanilla, has anti-inflammatory, analgesic, and antiviral activity. Mn(II), Co(III), Ni(II), Fe(II), Cu(II), and Zn(II) complexes were synthesized using *o*-vanillin as a ligand; and complex of Fe(II) and Cu(II) showed significant DNA cleavage activity.<sup>85</sup> This activity was attributed to increased



**Fig. 9** Widely used anticancer natural products.

lipophilicity due to electron shift from donor atoms of the ligand to the positively charged metal ion.

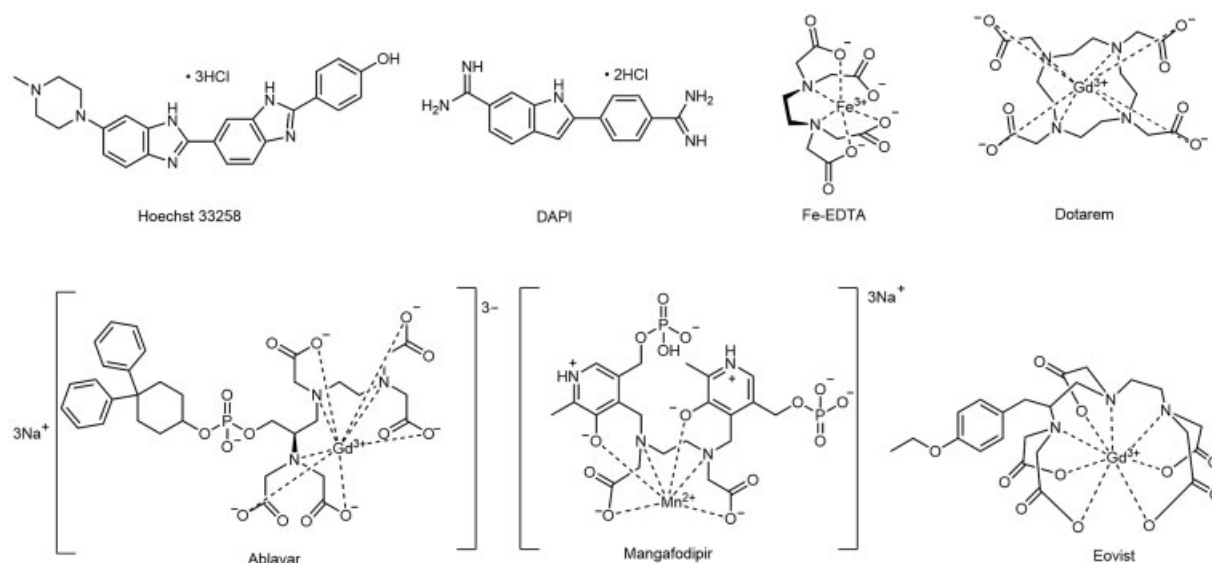
## Sensing and Imaging

Over the years, several fluorophores (e.g., hoechst and 4'-6-diamidino-2-phenylindole, known as DAPI) that target DNA have been used for sensing and imaging applications for genetic diseases, biological process, and tumorigenesis (theragnostic application). The metal complex Fe-EDTA ( $C_{10}H_{12}FeN_2O_8$ ) is one of the widely used molecular probes which provides information on biological activities associated with nucleic acids, including protein-DNA/RNA interactions, structure of DNA/RNA, and foot printing of nucleic acids.<sup>15</sup> The use of luminescent transition and lanthanide metal complexes has been shown to be an alternative, as these complexes are able to achieve long wavelengths of luminescence and longer emission lifetimes, which are ideal for real-life application due to deep tissue penetration in the tissue optical window. It has been reported that the complexes are able to bind to DNA via  $\pi$ - $\pi$  interactions between polyaromatic systems on the metal complex and nucleobases, resulting in intercalation and insertion between base pairs of duplex DNA.<sup>86</sup>

Binding into the grooves of DNA or direct coordination has also been observed. Phosphorescent transition metal complexes generally display large absorption-emission Stokes shifts, which can also be advantageous for potential biological applications. Through the use of strong  $\sigma$ -donor groups and multidentate ligands, the observed cleavage of the metal-ligand bonds can be avoided, leading to the reduction of the phosphorescence metal complex fluorophores. A variety of luminescent metal complexes, based on rhenium, ruthenium, osmium, iridium, rhodium, platinum, europium, and terbium, have been designed for DNA sensing and imaging application.<sup>87</sup> These compounds can be used in photodynamic therapy due to their light-responsive proper-

ties. In addition, the photoluminescence properties of metal-organic frameworks have also been applied in drug delivery and bioimaging. The presence of the conjugated  $\pi$ -electron system allows for binding single-stranded DNA molecules.<sup>88</sup> The approved magnetic resonance imaging (MRI) contrast agents include Gd(III)-based complexes such as Eovist, Ablavar, and Dotarem (**Fig. 10**); for Mn(II) they include Lumenhance and Mangafodipir, and for Fe(III) they include Ferumoxsil and Feridex I.V.(iron oxide nanoparticles).<sup>60</sup>

Radiometals are becoming more widely available and are routinely used in the development of radiotracers for diagnostic and therapeutic purposes. With more than half of the cancer patients requiring radiotherapy to target localized solid tumors, the combination of multiple variants of immunotherapy with different forms of radiotherapy has given rise to radioimmunotherapy. Unlike the conventional radiotherapy treatment technique, radioimmunotherapy helps to overcome organs exposure to direct or scattered irradiation. Nuclear properties of radiometals, ranging from  $\gamma$ -ray and  $\beta^+$  particle emission (imaging) to Auger electron and  $\alpha$ -particle emission (treatment) in combination with long half-lives, are excellently suited with the comparatively long biological half-life of monoclonal antibodies *in vivo*.<sup>89</sup> In radiotherapeutics, cancer cells are tracked and eliminated using monoclonal antibodies/peptide that have been radiolabeled with a  $\beta$ -emitting radionuclide. The FDA has approved only one radioimmunoconjugate (RIC)-[90Y]-Ibritumomab tiuxetan (Zevalin) for the treatment of indolent CD20-positive B cell lymphoma.<sup>90</sup> While the Novartis' peptide-based Lutetium-177 (<sup>177</sup>Lu) prostate-specific membrane antigen (<sup>177</sup>Lu-PSMA) was granted a breakthrough therapy designation for patients with metastatic castration-resistant prostate cancer (CRPC).<sup>91</sup> The  $\alpha$ -particle emitter <sup>223</sup>RaCl<sub>2</sub> (Xofigo) was also successfully launched by Bayer for the treatment of osseous metastases in CRPC.<sup>92</sup> A recent review of therapeutic radiopharmaceutical concepts and concerns was published elsewhere.<sup>93</sup>



**Fig. 10** Approved photodynamic therapy agents and widely used molecular probes.

## Molecular Techniques for DNA Interaction Characterization

The electron-rich phosphate backbone, donor heteroatoms in the nucleobases, and intricate secondary and tertiary structures create potential binding environments for both “free” metal ions and discrete complexes. Metal complexes bind to DNA through various modes, for example (1) non-covalent intercalation (insertion of a planar, usually aromatic, ligand [or part thereof] between the stacked base pairs of DNAs); (2) insertion (incorporation of a ligand into the base pair stack); (3) groove binding; and (4) coordination by discrete phosphate, such as the phosphate clamp, with shape and charge of the complex determining the mode of interaction.<sup>94</sup> The transition metal complexes are able to bind to DNA via these two interactions, which can be elucidated by using electronic absorption spectroscopy (fixed concentration of metal complexes with incremental addition of calf thymus DNA), fluorescence quenching (ethidium bromide [EB] competitive binding), cyclic voltammetry, X-ray crystallography, circular dichroism, or viscosity measurements (►Table 1). Gel electrophoresis experiments can be conducted to characterize DNA cleavage by means of the interaction between plasmid DNA and the complex.

The melphalan protection assay (DNA/RNA ladders crucial for accurate sizing), which also requires an agarose gel, can aid in DNA alkylation (monoalkylated covalent DNA adduct) inhibition studies where preferred drug–DNA binding into the minor groove is established. When using crystallography to study drug interactions with DNA or oligonucleotides, the main difficulty lies in growing a high-quality crystal of reasonable size. This requires a significant quantity of homogeneous and pure materials. To conduct DNA–metal complex interaction via X-ray crystallography, 3G synchrotron facilities/microsource X-ray diffractometer techniques are required. This method allows definitive visualization of metallodrug–DNA binding interactions. In the past, X-ray crystallography has been an effective choice for atomic-level visualization of metalloproteins, despite some drawbacks such as the fact that X-ray-induced structural and electronic changes often occur at the site of greatest interest.

To avoid radiation damage, techniques including serial synchrotron crystallography and/or X-ray free-electron lasers (XFELs) can be used.<sup>95</sup> Serial synchrotron and XFEL crystallography have been used in studying metalloproteins through the collection of metal redox and ligation state data at room temperature.<sup>96</sup> Mass spectrometry data are able to give information on covalent metallodrug–DNA binding interactions/binding stoichiometry/noncovalent binding

**Table 1** Characterization methods for metallodrug–DNA interactions (adapted from Kellett et al<sup>94</sup>)

Technique	Advantage	Limitations
X-ray crystallography	Detailed structural data	Solid-state interactions only
NMR	Modification of electronic properties of complex	Active nuclei and diamagnetic compounds
Mass spectrometry	Very small quantities	Gas-phase results may not always translate to solution
Viscosity	<ul style="list-style-type: none"> <li>Ease of use</li> <li>Low cost</li> <li>Suitable for bulk analysis</li> </ul>	Metal ions themselves can compact DNA (charge neutralization)
Circular dichroism	<ul style="list-style-type: none"> <li>Excellent sensitivity and reproducibility</li> <li>Provides structural information related to specific binding interactions</li> <li>Small sample size</li> </ul>	<ul style="list-style-type: none"> <li>Caution must be taken with chiral metallodrugs</li> <li>Experimental conditions must carefully maintain DNA structure</li> <li>Limited solvent choice (UV activity)</li> </ul>
UV thermal melting	<ul style="list-style-type: none"> <li>Simple experimental setup</li> <li>High sensitivity and reproducibility</li> <li>Suitable for comparing/ranking binding affinity (SAR)</li> <li>Small sample size</li> </ul>	<ul style="list-style-type: none"> <li>Metallodrugs stability/optical transparency at elevated temperatures</li> <li>Nonphysiological temperatures (&gt;37°C)</li> </ul>
Fluorescence	High-throughput analysis possible when combined with 96-well plates	Reliance on signal from a fluorogenic reporter
Agarose gel electrophoresis	<ul style="list-style-type: none"> <li>Simple experimental setup</li> <li>Cost effective</li> <li>Small sample size</li> <li>Fast analysis time</li> </ul>	Quantitation of DNA damage/modification
On-chip microfluidics	Quantitative method with high sizing resolution	Expense, and scaling between DNA sizes requires change of microfluidic chip, and results in analytically challenging.
UV-Vis	Direct binding analysis	Solvent choice

Abbreviations: NMR, nuclear magnetic resonance; UV, ultraviolet; Vis, visible.

(gas phase). Thermodynamics binding studies of ligands targeting G-quadruplex nucleic acid structures were shown to be successful using a temperature-controlled nano-electrospray source on mass spectrometry.<sup>97</sup> Ion mobility–mass spectrometry can be used for protein–drug interactions.<sup>98</sup> And inductively coupled plasma mass spectrometry and other techniques used in metallodrugs have also been recently reviewed.<sup>99</sup> Nuclear magnetic resonance (NMR) spectroscopy generates information on the conformation of metallodrug–DNA solution interactions, as well as viscosity hydrodynamic (solution) phase modification to nucleic acids. NMR spectroscopy has been demonstrated to be a versatile tool for tracking the fate of metallodrugs (e.g., Gd(III), Ru(III), Au(I), and Pt(IV) complexes) in cells and biofluids, where the metal compounds and/or biological targets are isotopically labeled, and their interactions are monitored at the atomic level.<sup>100</sup> EB is used in terms of fluorescence quenching, as it contains planar heteroaromatic structures, often with extended  $\pi$ -backbones, to facilitate penetration into the DNA backbone, and subsequently affect van der Waals contacts between Watson–Crick pairs.<sup>101</sup>

### Ligands with Biological Properties

Schiff bases are compounds that are formed through the reaction of a primary amine with aldehydes or ketones. They have a wide range of medicinal properties, ranging from antifungal to antibacterial, antimalarial, anti-inflammatory, antiviral, and antipyretic properties due to intramolecular H-bonding and proton transfer equilibrium.<sup>102</sup> Different Schiff bases yield different ligands, for example (1) the salen-type ligands, which are synthesized from salicylaldehyde, ethylenediamine, and their derivatives, and behave as [O,O',N,N'] tetradentate ligands; (2) the salen-type ligands, which are synthesized from salicylaldehyde, *o*-phenylenediamine, and their derivatives, and also have four donor atoms; (3) the hydrazone-type ligands, which are synthesized from carbonyl compounds with hydrazine/hydrazide and their derivatives, and possess a single donating atom (imino nitrogen, N); as well as (4) the semicarbazone/thiosemicarbazone-type ligands, which are synthesized through condensation of carbonyl compound (aldehyde or ketone) with thiosemicarbazide or semicarbazone with ligands having two donating sites (N, O/S).<sup>103</sup> Ligands such as phosphines (PR<sub>3</sub>) and NHCs are also widely used in metallodrugs, as they display significant antitumor, antimicrobial, and antiparasitic effects. The ligand group NHCs are recognized as versatile precatalysts for the development of different types of organic catalytic transformations.<sup>104</sup> In recent years, with the addition of novel functional groups (such as carbohydrates to the NHC ring), the application of NHC ligands in medicinal chemistry has been expanding.<sup>105</sup> Carbohydrates have the potential to form metal complex due to their selective uptake into tumor cells, multihydroxy functionality and well-defined stereochemistry suitable for metal coordination.<sup>106</sup> They also have properties of biocompatibility, chirality, water solubility, and low toxicity.

### Heteronuclear Bimetallic Complexes

Heteronuclear bimetallic complexes are designed for their enhanced bioactivity when compared with that of monometallic species expected in combining two distinct metal centers within the same molecule.<sup>107</sup> With the limitations of single metal complexes such as auranofin and cisplatin, various other metal ions can be added to the coordination sphere to give a bimetallic complex with introduced properties. The combination of the classical transition metals such as Pt, Ru, and Au with other metal moieties may produce complexes with improved pharmacokinetic and pharmacodynamic properties.<sup>108</sup> The multiple metal ions can influence the overall redox properties of the complexes, hydrolysis behavior, as well as interactions with biomolecules. In cancer or microbes that have developed a resistance mechanism that renders one of the metals redundant, the second or third metal may show some activity. Evidence suggested that a heterometallic titanocene–gold chemotherapeutic compound was successfully synthesized and characterized and found to be effective against renal cancer by inhibiting migration, invasion, and angiogenesis.<sup>109</sup> Mechanistic studies of the gold–titanocene complex revealed that the anticancer activity of the complex is partly attributable to the interaction of gold ions with ubiquitin, suggesting that the titanocene moieties are cleaved off under biological conditions. The complex was observed to have no interaction with DNA.<sup>108</sup>

### Computational Studies

#### Quantum Mechanical Modeling

Various computational tools are available for the characterization of metal complexes and investigation of electronic properties and reactivity. Computational methods can be used to determine molecular structures, including bond length, bond angle parameters, molecular orbital analysis, quantum chemical electronegativity ( $\chi$ ), absolute hardness ( $\eta$ ), chemical potentials ( $\mu$ ), absolute softness ( $\omega$ ), global softness ( $\sigma$ ), global electrophilicity ( $S$ ), and electronic charge ( $\Delta N_{\max}$ ).<sup>110</sup> These calculated molecular and electronic properties provide key insights into the rationalization of the observed reactivity. Density functional theory (DFT) is a useful tool in computational chemistry. Various software programs, such as Gaussian, Vienna Ab initio Simulation Package, Amsterdam Density Functional, and ORCA, have implemented this theory and are highly cited. The merit and accuracy of the metal complex data generated by DFT depends on the level of theory employed in the study. Main group metals usually require hybrid functionals and functionals such as the Becke 3 series (e.g., B3LYP and B3PW91), whereas for transition metals, a higher level of theory is required for alterable spin multiplicity and various coordination patterns of metal.<sup>111</sup> To ensure accuracy of the DFT studies, it is recommended to verify the calculated results with experimental data. The usefulness of computational studies has been cited to highlight the SAR of the platinum complexes based on the DFT reactivity parameters.

Increased DNA repair is the main mechanism of cisplatin resistance in A2780 ovarian cancer cell lines. According to DFT studies using relativistic reactivity descriptors, DNA repair is increased because *cis*-planaramineplatinum(II) complexes (e.g., cisplatin) primarily form bifunctional intra-strand Pt(GG) adducts.<sup>112</sup>

### Molecular Docking

Various DNA structures such as A-, B-, and Z-DNA from PDB files 1VJ4, 1BNA, and 2DCG can be used in docking studies. Several docking techniques have been found to be effective for investigating molecular docking of metal complexes. To conduct docking studies, the target DNA structure is first imported into the software, and then hydrogen atoms are added followed by energy optimization. For the metal-complex ligand, it is ensured that hydrogen atoms have been added to the compound, and a conformational search is conducted in the case of all the compounds to identify the best conformers; then the MMFF94 force field was used to minimize energy minimization. In some docking softwares, the DNA remains rigid, while the torsional bonds of the metal complexes are free to rotate. Studies on Co(II), Cu(II), Ni(II), and Zn(II) complexes of naphthoquinone have shown strong binding interaction between these compounds (Cu(II) > Zn(II) > Ni(II) > Co(II)) and DNA through an intercalative mode of binding stabilized by intermolecular hydrogen bonding.<sup>113</sup>

More than 60 different docking tools and programs have been developed for both academic and commercial use (►Table 2). Examples of the applications of DNA binding using these programs include: (1) AutoDock for copper (II), cobalt (II), Ni(II), Ru(II), and Zn(II) complexes<sup>114–117</sup>; (2) AutoDock Vina for Zn(II) metal complex<sup>118</sup>; (3) Molecular Operating Environment (MOE) software for Cu(II), Co(II), Ni(II), Fe(II), VO(II), Cr(III), Mn(II), Zn(II) complexes, Pd(II), and Ag(I)<sup>119–121</sup>; and (4) GOLD for Cu(II), Co(II), Zn(II), and Cr(II).<sup>122</sup> Docking can take two forms: flexible (flexible side chain) and rigid (rigid receptor). Rigid docking is an ideal

choice when standard computational systems were used to screen databases (large numbers of ligands), while flexible docking is an ideal choice when high-end computational power is available, and pocket shape changes are required during docking.<sup>123</sup> Based on their treatment of ligand flexibility, search algorithms range from systematic conformational searches, which allow ligands (metal complexes) of interest to rotate in all directions, which allows more docking interactions but is time consuming (e.g., Dock and FlexX), to stochastic algorithms, which randomly change the structure or the position of the allowed ligands (metal complex) of interest (e.g., GOLD and AutoDock) and simulation algorithms, which require high computational cost to make the potential protein–ligand complex structure ideal for molecular dynamics (MD) and energy minimization (e.g., CHARMM, Amber, and GROMACS).<sup>124</sup>

HEX software is widely used for *in silico* docking studies of metal complexes (Cu(II), Co(II), Ni(II), Zn(II), and Os(IV)), as it maintains the structural conformation during docking.<sup>77,125</sup> Docking of metallodrugs has posed difficulties when dealing with the formation of coordination bonds between the metal and a donor of an amino acid side chain. Many docking programs (e.g., GOLD and AutoDock) have limitations, as the covalent docking approach is used. By including coordination scoring parameters in GOLD, Sciortino and colleagues were able to predict metal complex–protein interactions with good agreement with the experimental structures (root mean square deviation is <1.0 Å).<sup>126</sup> Studies of Pt(II)–phenanthroline complex interacting with double-stranded and G-quadruplex DNA revealed that computational studies can correlate with *in vitro* studies, in which evidence of planar aromatic cationic metal complexes and double-stranded DNA was observed by intercalation.<sup>127</sup>

### Molecular Dynamics

Current docking approaches cannot fully account for ligand reorganizations and exchange reactions in the metal-centered coordination sphere, particularly in the case of bulky

**Table 2** List of available docking software (adapted from Ferreira et al<sup>128</sup> and Prieto-Martínez et al<sup>129</sup>)

Software	Search algorithm	License
AutoDock 4.2	Lamarckian genetic algorithm	Academic
AutoDock Vina	Local optimization	Academic
DOCK	Shape matching	Academic
BIOVIA Discovery Studio	Shape matching	Commercial/academic
FlexX	Shape matching	Commercial
Glide-Schrodinger	Hybrid	Commercial
GOLD	Genetic algorithm	Commercial/academic
ICM	Hybrid	Commercial
LIGANDFIT	Shape matching	Commercial
MOE	Hybrid	Commercial
Surflex-Dock	Shape matching	Commercial
SWISSDOCK	Evolutionary optimization	Academic

Abbreviations: ICM, internal coordinate mechanics software; MOE, molecular operating environment.

metallo-drugs.<sup>128,129</sup> MD-based docking has been proposed as an alternative method, which considers the plasticity of metal-centered complexes during recognition and binding, while ligand reorganizations and exchange reactions will require the assessment of ad hoc methodological developments.<sup>130</sup> MD simulations can predict how each atom in a system moves over time based on a general model of the physics governing interatomic interactions, and highlighting important dynamic molecular processes such as conformational transition, ligand binding, and protein folding.<sup>131</sup> However, experimental techniques, such as X-ray crystallography, cryo-EM, NMR spectroscopy, and mass spectrometry, can only provide static snapshots of metal complex binding and interactions. The hydration shells of biomolecules may have an enormous impact on their structure and function.<sup>132</sup>

Mixed quantum mechanics/molecular mechanics (-QM/MM) is the most commonly adopted approach to studying metal-containing biomolecules. Since QM computations are computationally expensive, a timescale of 100s picoseconds to 1 nanosecond is commonly used, which is insufficient for chemical reactions, conformational transitions, and drug binding/dissociation study.<sup>133</sup> In 2019, Van Rixel et al used the QM/MM technique to describe aromatic Pt-compound intercalation-binding mode to a noncanonical site created by two DNA tetrads, as well as the drug-induced deformation.<sup>134</sup> The studies on Au(I)-compounds binding to telomeric DNA G-quadruplex were experimentally confirmed using ESI-MS and X-ray diffraction, while QM/MM simulations confirmed its binding mode within a G-quadruplex.<sup>135</sup> Apart from biomolecule interactions, QM/MM was also successfully used to investigate the emission spectrum of platinum(II) bipyridine complex, which was due to the excited state of metal-metal to ligand charge transfer triplet (<sup>3</sup>MMLCT).<sup>136</sup> Numerous molecular simulation packages, such as CHARMM, AMBER, NAMD, OpenMM, Gaussian, Q-Chem, Turbomole, Psi4, ORCA, and Gromacs, have QM/MM functionalities with built-in QM modules or interfaces.<sup>137</sup>

### Drug-Like Properties

In addition to carrying out docking studies, it is also possible to evaluate the drug-like properties of metal complexes such as absorption, distribution, metabolism, elimination, and toxicity (ADMET). These properties are crucial, since when a drug is administered via oral ingestion, it must cross membranes (influenced by lipophilicity [hydrophobicity]) of numerous cells to reach its site of action (absorption); it is distributed to its site of action through the circulatory systems (distribution); it is metabolized by a variety of enzymes into other products called metabolites (metabolism); it is excreted via the bowel in the feces, and kidneys through the urine or in the biliary excretion, and can lead to risk of toxicity if accumulated in the body (excretion).<sup>138</sup> According to Lipinski's rule, the molecule with  $\text{Log } p < 5$  should have drug-like characteristics, and thus have a higher tendency to penetrate the biological membrane.<sup>139</sup> The total polar surface area parameter helps us predict the way of drug transport (less than or equal to 140 Å) inside the various parts of the body, including gastrointestinal tract, blood-

brain barrier, and cell membrane, as well as oral bioavailability. Active compounds are also expected to have a molecular weight of less than 500 g/mol, no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptor sites, and less than 10 rotatable bonds for flexibility.<sup>140</sup> However, compounds such as antibiotics have been shown to violate some of the rules, but still have good pharmacokinetic and pharmacodynamic properties. Jeyaraman et al. have used SWISS ADME to determine the ADMET properties of Cu(II), Ni(II), Co(II), and Zn(II) complexes.<sup>141</sup>

### Nanotechnology

The use of nanomaterials as enzyme mimics capable of degradation of nucleic acids has received increasing attention. The "nanozymes" mimic the redox activity of enzymes, and are capable of cleaving both RNA and DNA. Similar to endonuclease, cadmium telluride quantum dots, cerium oxide nanoparticles, and single-layered graphene oxide have been shown to be able to cleave DNA through hydrolytic, oxidative, or photocatalytic mechanisms.<sup>142</sup> Through the use of metal-amphiphilic molecules, they have become a source of metal ions and serve as protective agents (surfactant) for the synthesis of stable metallic/metallic oxide nanostructure fabrication, thus providing an advantage over the conventional nanoparticle synthesis procedures.<sup>143</sup> Over the years, specific interactions between nanoparticles and DNA or protein as well as other biomolecules have been observed. Silver clusters templated by DNA (Ag-DNA) highlight the development of a new field, known as DNA nanotechnology, generating emerging fluorophores emitting wavelengths ranging from the visible to near-infrared.<sup>144</sup>

DNA duplex is used as a nanoscale rigid molecular arm in DNA nanotechnology to spatially locate addressable transition metals, which are normally coordinated by organic molecular pockets and form vertices.<sup>145</sup> Metallic nanostructures with electrical, magnetic, and optical properties can be synthesized in a well-controlled, flexible, and highly addressable motif for diagnostics and drug delivery systems.<sup>146</sup> Because of the chemical properties of DNA, it has been possible to regulate the nucleation and growth of nanocolloids in which metals or metal ions bind to specific sites on the DNA backbone, resulting in the development of silver, platinum, and gold nanowires and nanoparticles.<sup>147</sup> Biofunctionalization of metal nanoparticles using aptamer-appended DNA tetrahedron nanostructures has also been shown to be useful in medicine, as it allows selective targeting of the cancer cells and acts as a MRI contrast agent.<sup>148</sup> The interaction of thymine and mercury makes it possible to develop ultrasensitive detection methods to detect mercury at subnanomolar concentrations, due to the formation of metallo-DNA duplexes (dT-Hg-dT)<sub>n</sub>.<sup>149</sup> The use of nanoparticles is very suitable for mediating endocytosis to promote intracellular accumulation of drugs in cells, resulting in targeted delivery to reduce side effects and improve bioavailability of poorly soluble drugs. By adding Chlorin e6 (PS) to the surface of mesoporous silica nanoparticles and encapsulating cisplatin, nanotechnology was observed to provide

simultaneous chemotherapy and phototherapy in cancer eradication that can overcome cisplatin resistance.<sup>150</sup>

## Toxicity

Clinical use of the platinum (Pt) metal-based cisplatin drug has been observed to cause numerous side effects (nephrotoxicity, ototoxicity, neurotoxicity, and inborn or acquired drug resistance), which remains a challenge to overcome in the preparation of efficient anticancer drugs.<sup>151</sup> Due to the lack of tumor selectivity of cisplatin, intravenous administration of the drug leads to interaction with human serum albumin in the presence of cysteine residue. Therefore, severe nausea, vomiting, loss of hearing, and kidney damage often occur when cisplatin is used for chemotherapy. Long-term effects may be different, requiring dialysis, kidney transplant, or medication cocktails to support other systems in the body.<sup>152</sup> This means that a lower dose should be administered to avoid side effects; however, this leads to cancers rapidly developing resistance due to suboptimum therapeutic levels in comparison with cisplatin and the related drugs carboplatin, in which bidentate dicarboxylate ligands replace the more labile chlorides of cisplatin, and oxaliplatin, in which the stable 1,2-diaminocyclohexane ligand leads to more tolerable compounds.<sup>153</sup> This highlights the evidence that ligand design can help ensure the biocompatible metal complex for medicinal application. Novel strategies for rational metallodrug design have been proposed to help overcome these issues. According to the analogy principle, the essential metal ion can be used as a reference for the biological behavior of a nonessential metal ion in relation to similarity in charge, ionic radius, coordination number, coordination stability, redox potential, and so on.<sup>154</sup> As a result, if a nonessential metal ion mimics or promotes intrinsic metal signaling, it will almost certainly be tolerated. This can help in selection of metals that will have minor or no metal toxicity.

## Conclusion

It is clear that the unique properties of metal ions for the design of new drugs can be beneficial in medical inorganic chemistry. The role of transition metal complexes as therapeutic compounds has grown in importance in the field of inorganic chemistry, particularly in DNA interaction. In this review, metal-based therapeutics have made advances in the treatment of cancer and infectious diseases. In the case of metallodrugs, the metal ions are identified as enhancing the biological activity of known drugs and improving their mechanism of action by acting as metal-binding sites. With an expanding number of computer programs being used in computational chemistry and computer-aided drug discovery, these tools can now be used for *in silico* metallodrug studies. Although metallodrugs are difficult to develop, their unique properties provide valuable opportunity for discovering novel drugs with special mechanisms of action. This would assist in overcoming complex medical obstacles encountered in the world.

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## Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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