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Zinc (II) metal appended Artificial Nucleases as Anticancer Agents: A Brief Review

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Abstract

Zinc (II) complexes have recently gained attention for their unique ability to mimic natural nucleases and selectively target deoxyribonucleic acid (DNA), making them attractive candidates in the search for more effective and less toxic anticancer agents. This review explores the evolving landscape of Zn (II)-based artificial nucleases, focusing on how structural modifications—such as macrocyclic scaffolds, aromatic appendages, and bio-relevant ligands—enhance their ability to bind and cleave DNA. These complexes operate through both hydrolytic and oxidative pathways, disrupting genetic material and triggering programmed cell death in cancer cells. Their redox stability, biocompatibility, and catalytic efficiency offer distinct advantages over other metal-based systems. By bridging the fields of inorganic chemistry and oncology, these zinc complexes show great potential not only as therapeutic agents but also as molecular tools in gene editing and biomedical research. This review brings together recent findings to provide a clearer understanding of how Zn (II) based systems function and where their future applications might lie.

Keywords: Zn (II) complex, DNA, artificial nuclease, cancer

1. Introduction

Cancer remains a leading cause of global morbidity and mortality, despite major advances in disease understanding and therapeutic development [1]. A primary challenge in oncology is the emergence of drug resistance, which often leads to treatment failure and disease relapse [2]. Mechanisms such as altered drug targets, enhanced efflux, and activation of deoxyribonucleic acid (DNA) repair pathways contribute to this resistance. Consequently, DNA has emerged as a critical therapeutic target, offering a more fundamental strategy for inducing selective cytotoxicity [3]. The shift from broad-spectrum cytotoxic agents to precision-targeted treatments reflects the recognition of cancer as a genetic disease, driven by mutations that disrupt normal cell proliferation and survival [4]. These genetic changes also promote resistance via mechanisms including target mutation and epigenetic reprogramming. Targeting DNA provides a direct approach to interfere with the cellular blueprint. Structurally, DNA's double-helical architecture with accessible phosphate backbones and nitrogenous bases presents multiple interaction sites [5]. This enables small molecules and metal complexes to engage DNA through intercalation, groove binding, or covalent linkage, disrupting replication and transcription. However, the exceptional stability of the phosphodiester backbone—with hydrolysis half-lives exceeding millions of years—poses challenges for artificial manipulation [6]. Artificial nucleases have thus gained interest for their ability to catalyze site-specific cleavage of nucleic acids. Their activity is frequently enhanced by metal ions such as Zn (II), Mg (II), and Fe (II), which act as Lewis acids to activate water nucleophiles and stabilize transition states [7]. These design principles mimic natural metalloenzymes, validating the use of biomimetic strategies in drug design. Transition metal complexes, particularly those based on Zn (II), Cu (II), Ru (II), and Au (III), have been

extensively explored for anticancer applications due to their capacity to cleave DNA and influence intracellular signaling [8]. Such systems can target multiple pathways simultaneously, supporting their potential as multi-functional therapeutics. This review specifically examines zinc (II)-based artificial nucleases, emphasizing their mechanisms of DNA interaction—hydrolytic cleavage, oxidative damage, and intercalation—and their ability to induce apoptosis. Focus is placed on the rational design of Zn (II) complexes and their integration into DNA-targeted anticancer strategies as promising tools for next-generation chemotherapy.

2. Mechanism of DNA Cleavage

DNA cleavage is a crucial and ubiquitous process that is essential for the proper functioning of all living organisms. Enzymes like topoisomerases and restriction enzymes are essential for maintaining DNA integrity, resolving issues during replication and transcription, protecting cells from viruses, and degrading DNA during apoptosis. To achieve selective DNA cleavage, understanding the binding mechanisms of small drug molecules to DNA is crucial. The therapeutic effectiveness of anticancer agents is fundamentally dependent on their capacity to inflict significant DNA damage within the targeted malignant cells. Research on DNA cleavage mechanisms has employed various chemical strategies, including oxidative, hydrolytic, photoactivated, and electron transfer-mediated cleavage. DNA cleavage can occur through direct strand scission or base modification, targeting basic DNA constituents like bases or sugars via *oxidative pathways* or *phosphoester hydrolysis* [9]. Given the high stability of these bonds, artificial catalysts must accelerate the reaction rate dramatically. Metal complexes, especially those of zinc, copper, cobalt, manganese and lanthanides, have emerged as efficient artificial nucleases due to their ability to selectively cleave DNA [10]. Their coordination versatility and Lewis acidity make them valuable tools in genetic manipulation and therapeutic design. The oxidation states of the metal ions, coordination number, geometry, and the nature of the ancillary ligands play a crucial role in the DNA cleavage efficiency [11]. Efficient DNA hydrolysis requires reactive catalysts due to DNA's negative charge, which hinders nucleophilic attacks. Natural nucleases neutralize this charge, facilitating hydrolysis. Metal-containing enzymes and phosphoryl transfer reactions share catalytic pathways in nucleic acid biochemistry.

2.1 Hydrolytic cleavage

The hydrolysis of nucleic acids is a fundamental biochemical process wherein phosphodiester bonds are cleaved in the presence of water, leading to the formation of nucleic acid fragments. This reaction is essential across all living systems and is typically catalyzed with remarkable efficiency by natural nucleases. As illustrated in Figure 1, the widely accepted mechanism of DNA hydrolysis involves the nucleophilic attack of a hydroxide ion—originating from water—on the phosphorus atom of the phosphate moiety. This leads to the formation of a transient five-coordinate transition state. Subsequent protonation of the leaving group facilitates cleavage of either the 3′-O–P bond (commonly observed in enzymatic systems) or, less frequently, the 5′-O–P bond, resulting in strand scission [12]. A metal cofactor is essential for binding with oxygen atoms, polarizing bonds (Lewis acidity), and facilitating rapid ligand exchange. Metal ions accelerate phosphate ester hydrolysis through three inner sphere activation modes: Lewis acid activation (lowering pKa of metal-bound water nucleophile), nucleophile activation (coordination of nucleophile like hydroxide to metals), and leaving group activation (coordination of leaving group oxygen to metals) [12].

DNA hydrolysis requires nucleophile and double Lewis acid activation, while ribonucleic acid (RNA) hydrolysis only needs double Lewis acid activation. Additionally, three outer sphere activation modes mediated by metal ions are involved in DNA hydrolysis. Figure 1 depicts the proposed reaction mechanism for the hydrolysis of DNA by metal complex. Metal complexes facilitate DNA cleavage through the activation of water or hydroxide, which then act as nucleophiles to attack and cleave the phosphodiester backbone of the DNA molecule. Figure 2 demonstrate, zinc (II)-tetrapeptide complex that facilitates DNA hydrolysis through a non-oxidative, metal-assisted catalytic mechanism [13]. The presence of a coordinated water molecule in the Zn(II) complex plays a crucial role in initiating the cleavage process. Upon coordination to the zinc center, the water molecule becomes more nucleophilic due to polarization by the Lewis acidic metal ion. This activated water molecule attacks the phosphorus center of the DNA’s phosphodiester linkage, leading to the formation of a transient pentacoordinated phosphate intermediate. The subsequent rearrangement of this intermediate results in the cleavage of the DNA backbone, generating fragments with 3′-OH and 5′-phosphate termini.

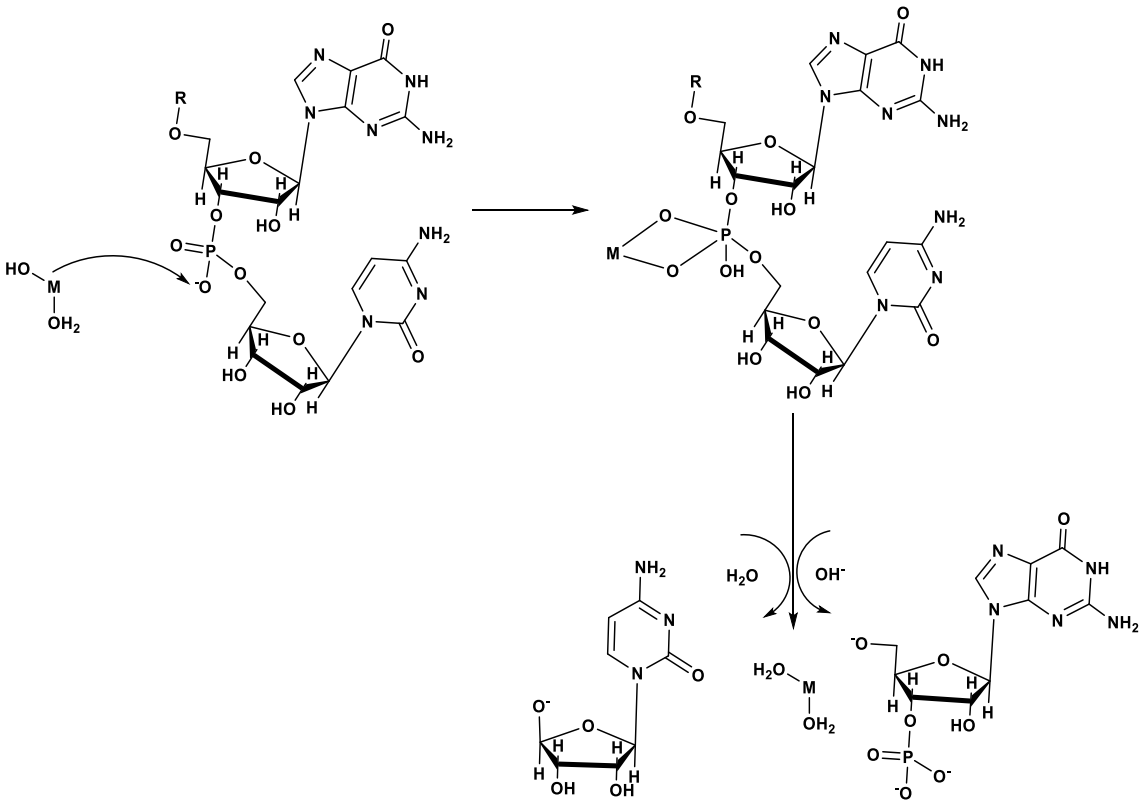

Figure 1 A mechanistic pathway for the Hydrolytic cleavage of nucleic acids promoted by metal complexes.

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2.2 Oxidative cleavage

Oxidative cleavage entails the oxidation of the deoxyribose sugar or nucleobases in DNA, often mediated by hydroxyl radicals [14]. Transition metal complexes, in the presence of reductants like ascorbate, generate these radicals through Fenton-type reactions, inducing oxidative DNA damage. This process involves electron transfer from DNA to the metal complex and sugar hydrogen abstraction, leading to phosphodiester bond cleavage. The activation of artificial nucleases through photoinduction generates reactive oxygen species (ROS), including singlet oxygen and superoxide, which then induce oxidative damage to the DNA structure. Photosensitizers like methylene blue and acridine orange absorb light and transfer energy to molecular oxygen, generating singlet oxygen [15]. This mechanism, valuable in antitumor therapy, includes photochemically generated radicals, hydrogen atom abstraction, singlet oxygen production, and direct electron transfer from guanine to the photoexcited cleaver. Understanding these mechanisms is vital for advancing the study of DNA structure and its interactions, with significant implications for cancer therapy and other biomedical applications.

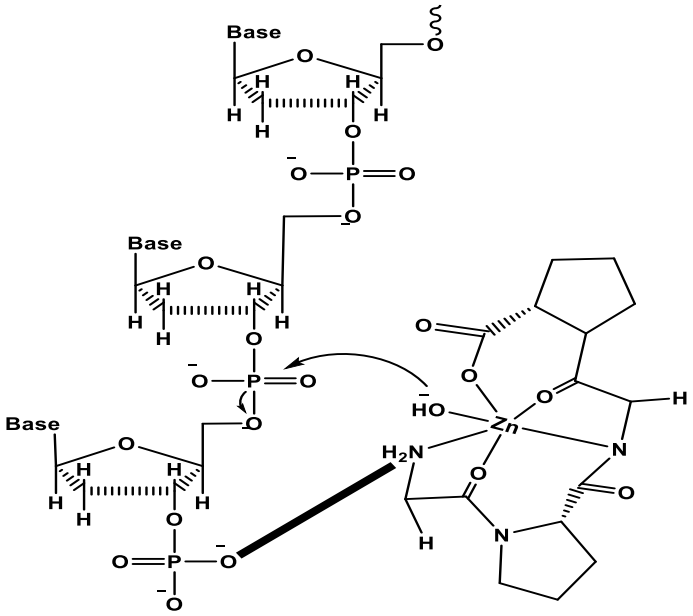

Figure 2 Hypothetical intermediate step in the Zn-mediated hydrolysis of DNA cleavage facilitated by a Pro-Gly Zn^{2+} complex.

2.3 Zinc (II) Complex of Macrocyclic polyamine as DNA Hydrolytic agent

Zinc (Zn), the second most abundant transition metal in biological systems after iron, plays a critical role in numerous cellular processes due to its redox-inert +2 oxidation state. This property enables Zn (II) to serve as a catalytic and structural cofactor in over 300 enzymes, notably hydrolases involved in nucleic acid metabolism. In these enzymes, Zn (II) typically adopts a tetrahedral geometry coordinated by histidine and cysteine residues, which facilitates the activation of bound water molecules for nucleophilic attack on phosphodiester bonds in DNA and RNA [16]. Its strong Lewis acidity stabilizes negative charges during the transition state and promotes ligand exchange, enhancing hydrolytic efficiency. Tight cellular regulation of zinc homeostasis prevents cytotoxicity even at elevated intracellular levels. Beyond catalysis, Zn (II) regulates diverse biological functions including gene expression, protein folding, and apoptosis [17]. In cancer contexts, zinc stabilizes tumor suppressor p53, inhibits NF-κB signaling, and activates AP-1, thereby suppressing proliferation and inducing apoptosis.

Additionally, zinc oxide nanoparticles induce apoptosis in HepG2 and astrocyte models via ROS generation and JNK pathway activation [18]. These findings highlight zinc's multifaceted therapeutic potential. Unlike redox-active metals such as copper or iron that promote DNA cleavage via oxidative stress, Zn (II) mediates phosphodiester hydrolysis through redox-inert mechanisms, reducing off-target oxidative damage. Macrocyclic ligands like cyclen (1,4,7,10-tetraazacyclododecane) offer a robust scaffold for Zn (II) coordination, closely emulating natural metalloenzyme active sites. The rigidity and geometry of cyclen enable fine control of zinc reactivity, making Zn (II)-cyclen complexes valuable candidates for artificial nucleases capable of selective DNA cleavage under physiological conditions [16, 17]. The catalytic efficiency of Zn (II) complexes in DNA hydrolysis is highly dependent on the coordinating ligand's size, denticity, and geometry. Comparative studies of macrocyclic ligands—such as tridentate [12] aneN3, tetradentate [12] aneN4 and [14] aneN4, and tripodal ligands like TREN—demonstrate how structural differences influence metal ion activation. Although Zn (II)-TREN and Zn (II)- [14] aneN4 exhibit similar pKa values (~9.8) for coordinated water, the latter shows higher hydrolytic activity, attributed to more favorable coordination geometry. Smaller macrocycles, like Zn (II)- [12] aneN4 (pKa 8.0), enhance the acidity and nucleophilicity of Zn-bound water, accelerating cleavage. Tridentate ligands such as [12] aneN3 further increase activity by providing unsaturated coordination environments, although this may compromise complex stability and limit their suitability for biological applications [19]. Tetradentate macrocycles like cyclen strike a balance between reactivity and stability, with Zn (II)-cyclen complexes showing high formation constants (log Kf = 16.2), comparable to clinically used agents like Gd (III)-DTPA [20]. Their catalytic performance can be tuned by ligand modification. For instance, hydrophobic N-tosyl substituents enhance hydrolytic activity toward phosphate esters like HPNP by improving substrate alignment and transition-state stabilization [21], while N-mesyl or unsubstituted variants show reduced activity. Polar substituents such as pseudourea groups introduced via N-propylcarboxamide linkers improve DNA binding but do not significantly enhance catalytic efficiency, highlighting that affinity alone does not ensure turnover [22]. Further modifications with lipophilic and aromatic substituents, such as triazine or pyridine rings, improve π–π interactions with

phosphate substrates and promote favorable orientations for nucleophilic attack [23]. Pendant alkoxide groups—mimicking natural enzymatic nucleophiles—directly participate in catalysis, with optimal pKa values (~7.3) for physiological activation [24]. Cyclen ligands functionalized with carbamoyl-diamine groups also show enhanced hydrolysis at pH > 8.0, attributed to mono-hydroxo Zn (II) species [25]. These tailored modifications refine the metal center's coordination sphere and substrate recognition, enabling versatile artificial nucleases. Figure 3 depicts chemical structure of Zn (II) appended cyclen derivatives that has been explored for artificial nuclease activity.

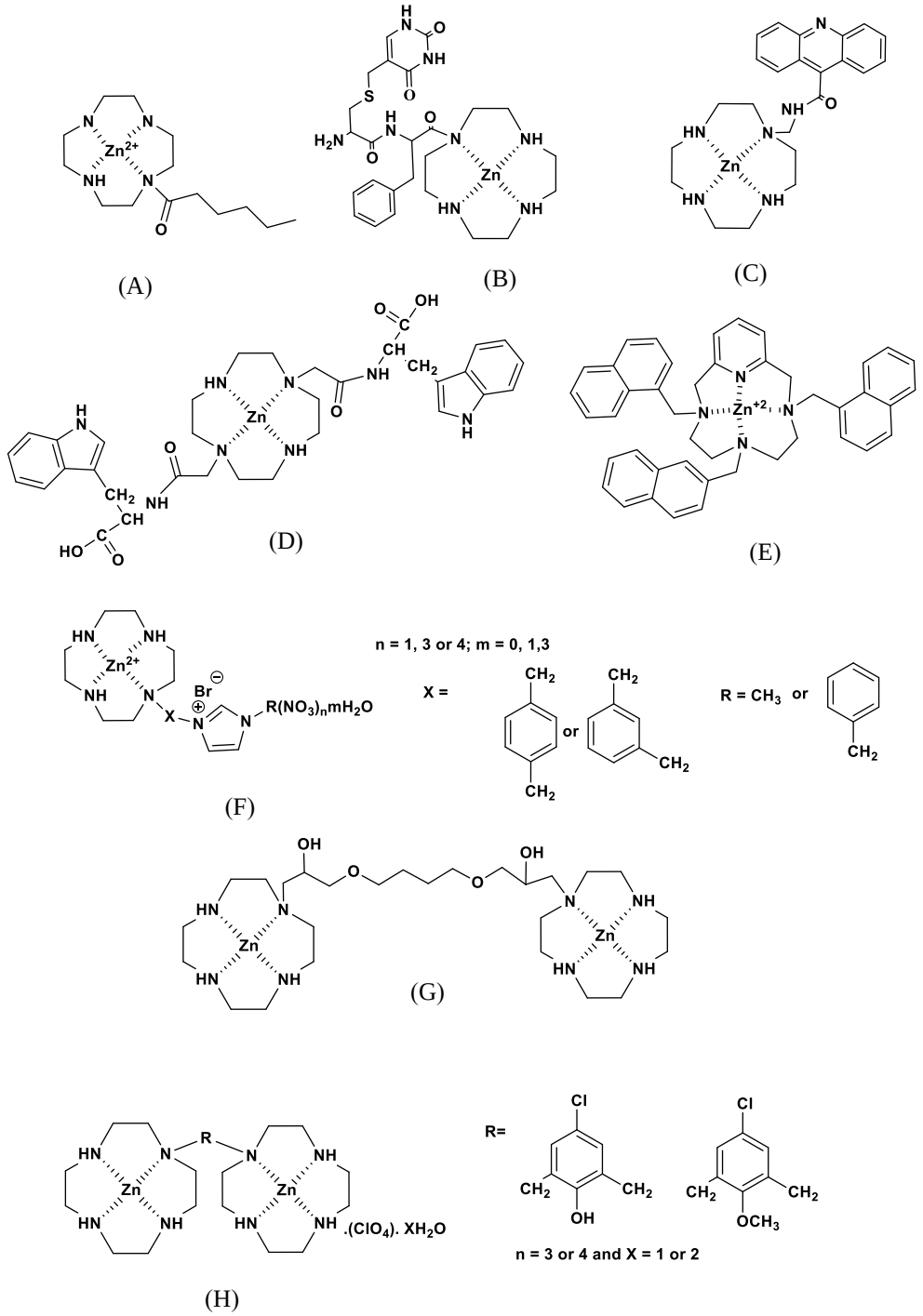

Figure 3 Chemical structures A-E Derivatives of Mononuclear Zn (II) complex of cyclen, G-H Derivatives of Dinuclear Zn (II) complex of cyclen.

Mononuclear Zn (II)-cyclen complexes typically adopt five-coordinate geometries, where four nitrogen donors from the macrocycle and one labile water or hydroxide ligand enable selective catalysis [26]. Peripheral modifications significantly influence reactivity: non-nucleophilic carbamoylmethyl groups can displace the reactive aqua ligand, impeding catalysis, while rigid aromatic arms like pyridine can distort coordination geometry. In contrast, nucleophilic groups such as 2-hydroxyethyl chains stabilize transition states and enhance activity. However, excessive nucleophilicity may result in phosphorylated intermediates that slow catalytic turnover [16, 27–32]. Dinuclear Zn (II)-cyclen complexes emulate natural phosphoesterases by offering cooperative dual-metal activation. One Zn (II) center stabilizes the transition state while the other activates a bridging hydroxide nucleophile. Bridging ligands like phenolic or oxyimine-linked bis-triazacyclononane scaffolds create bimetallic clefts that exhibit enzymatic behavior, including high k_cat values and Michaelis–Menten kinetics, and efficiently cleave DNA in redox-independent pathways [33]. These systems have also demonstrated cytotoxicity against HepG2 cells and induce apoptosis, validated by DNA fragmentation and cell viability assays. While mononuclear complexes provide mechanistic insights, they often show lower catalytic activity. Polyamine derivatives can exhibit inherent nucleophilicity, but efficient cleavage typically requires optimized metal-ligand geometry. Functional groups like hydroxyethyl and guanidinoethyl enhance acid–base catalysis and improve reaction rates [34].

The choice of metal ion also impacts cleavage pathways; for example, uracil-linked Zn (II) complexes act via hydrolysis, whereas analogous Cu (II) complexes prefer oxidative cleavage, which may increase cytotoxic risk due to ROS generation [46]. Linker design in dinuclear systems is equally critical. Rigid linkers such as 2,6-dimethyl-4-nitrophenol provide optimal Zn···Zn spacing and minimize charge repulsion, enhancing catalytic performance even at low concentrations [35]. Macrocycles like [9] aneN3 facilitate nucleophile activation, while linkers such as 2,6-dimethylpyridine and 2,9-dimethyl-1,10-phenanthroline offer insufficient electronic bridging for cooperative reactivity [36]. In contrast, 2-hydroxypropyl linkers simultaneously stabilize the bimetallic framework and contribute directly to catalysis through their alkoxide function, resulting in superior catalytic outcomes [37]. Overall, Zn (II)-based artificial nucleases—especially dinuclear systems—offer redox-inert, site-specific hydrolytic DNA cleavage with reduced off-target effects. Their capacity to induce apoptosis and their structural tunability make them promising anticancer agents. Future research should prioritize ligand designs that optimize metal spacing, electronic cooperativity, and nucleophile activation, along with improved delivery strategies for tumor-specific applications.

2.4 Clinical Importance of Zn (II) Complex

Zinc (II) complexes have garnered increasing attention as anticancer agents, offering a mechanistically distinct and potentially safer alternative to platinum-based chemotherapeutics such as cisplatin. Unlike redox-active transition metals, Zn (II) is redox-inert under physiological conditions, enhancing its biocompatibility. Advances in ligand design have significantly improved the DNA-binding specificity and catalytic efficiency of zinc complexes, positioning them as promising candidates for targeted cancer therapy with reduced systemic toxicity [38]. The anticancer efficacy of Zn (II) complexes is primarily attributed to their ability to interact with and cleave DNA via hydrolytic and oxidative mechanisms. These interactions compromise the structural and functional integrity of DNA, leading to apoptosis in malignant cells. One class of such agents includes Zn (II)-cyclen derivatives functionalized with amino acids. A notable example bearing two pendant L-tryptophan groups demonstrated minor groove binding ($K_b = 2.12 \times 10^5\ M^{-1}$) and concentration-dependent cleavage of supercoiled pUC19 DNA, achieving yields up to 86%. This complex selectively induced apoptosis in U-87MG glioma cells while sparing normal HEK 293 cells, likely due to uptake via L-type amino acid transporters (LAT1), overexpressed in tumor cells. In vivo imaging with a ^{99m}Tc-labeled analog confirmed tumor-selective accumulation and rapid clearance from non-target tissues [39]. Peptide-functionalized Zn (II) complexes have also emerged as highly selective therapeutic agents. The use of L-amino acids promotes tumor-specific delivery through amino acid transporter pathways. Zn (II) complexes with flexible ligands such as Pro-Gly and Pro-Leu have shown efficient DNA cleavage and minor groove binding. The Pro-Gly complex exhibited a higher binding affinity ($K_b = 4.3 \times 10^4\ M^{-1}$), attributed to lower steric hindrance, and cleaved supercoiled pBR322 DNA via a hydrolytic mechanism independent of reactive oxygen species.

This conclusion was supported by radical scavenger assays and the religation of cleaved DNA using T4 DNA ligase, underscoring its potential as a biomimetic artificial nuclease [40]. Cationic Zn (II) complexes containing pyridyl or triazacyclononyl ligands exhibit enhanced DNA binding through electrostatic interactions. A dinuclear Zn (II) complex with 2,6-bis(1-methyl-1,4,7-triazacyclonon-1-yl) pyridine effectively interacted with calf thymus DNA and facilitated cleavage under physiological conditions [41]. Similarly, dipicolylamine (dpa)-based mononuclear Zn (II) complexes induced oxidative DNA cleavage in the presence of H_2O_2. These complexes demonstrated IC_{50} values comparable to cisplatin against HeLa, MCF-7, and RL952 cells and induced apoptosis and cell cycle arrest at G1 and G2/M phases, as shown by Hoechst 33342 staining and annexin V assays [42]. Zn (II) complexes mimicking hydrolytic metalloenzymes have also shown promising nucleolytic activity. Two highly

cationic Zn (II) complexes incorporating disubstituted 2,2′-bipyridine ligands efficiently cleaved supercoiled pBR322 DNA to nicked and linear forms, achieving a catalytic rate of 3.85×10^{-5} s^{-1} under physiological pH. The presence of quaternary ammonium groups enhanced DNA binding and facilitated the formation of catalytically active $[Zn(L)_2(OH)]^{5+}$ intermediates, with structural alignment to DNA's phosphate backbone (~6 Å) supporting their high activity [43]. Schiff base Zn (II) complexes, due to their structural tunability and biological compatibility, have shown strong anticancer properties. A Zn (II) complex with a Schiff base from 2-hydroxybenzohydrazide and (E)-1-(2-(p-tolyl) hydrazono) propan-2-one displayed superior cytotoxicity (IC_{50} = 1.40 μg/mL) against MCF-7 cells compared to cisplatin [44]. Another Schiff base Zn (II) complex derived from a naphthalenol backbone adopted a distorted tetrahedral geometry and exhibited intercalative DNA binding, as confirmed by bathochromic shifts in UV-Vis spectra and circular dichroism analysis [45]. Other ligands, such as cyanoazo-coumarin, yielded Zn (II) complexes that showed red-shifted absorption upon DNA interaction, indicative of minor groove or electrostatic binding. These complexes displayed potent antiproliferative effects in MCF-7 cells, correlated with reduced HOMO–LUMO energy gaps, suggesting enhanced chemical reactivity [46].

Similarly, Zn (II) thiosemicarbazone complexes derived from thiophene aldehydes demonstrated intercalative DNA binding and cytotoxicity comparable to cisplatin against HepG2 cells, with the added benefit of reduced toxicity [47]. Azo-Schiff base Zn (II) complexes have shown strong DNA-binding through groove intercalation and induced apoptosis in Hut-78 cells, supporting a DNA-targeted mechanism of action [48]. A Zn (II) complex incorporating thiosalicylic acid ligands (coordinating through O and S) showed both high DNA affinity and selective tumor cytotoxicity with reduced toxicity compared to platinum drugs. Multimetallic coordination further enhances therapeutic potential. A dinuclear Zn (II) complex with bipyridine ligands and carboxylate bridges catalyzed DNA phosphodiester bond hydrolysis and exhibited moderate cytotoxicity across various cancer lines, validating the rationale for multimetallic design [38].

Zn (II) complexes built on benzimidazole and pyrimidinyl-hydrazine frameworks demonstrated DNA groove binding, supported by docking and spectroscopic studies. The pyrimidinyl-hydrazine complex showed partial intercalation and cytotoxicity against BGC-823 gastric cancer cells [38]. Likewise, a pyrazolyl-nicotinic acid-based Zn (II) complex showed strong DNA-binding comparable to cisplatin while maintaining superior biocompatibility, even when prepared via hydrothermal synthesis, reinforcing its suitability for in vivo translation [38]. In summary, zinc (II) complexes represent a versatile platform for anticancer drug development. Their ability to cleave DNA through hydrolytic or oxidative mechanisms, along with selective tumor uptake and lower toxicity, positions them as valuable alternatives or complements to current metal-based therapies. The integration of rational ligand design, peptide targeting motifs, and multimetallic coordination provides a robust framework for next-generation DNA-targeted chemotherapeutics.

3. Conclusions

Zinc (II)-based artificial nucleases hold strong promise as redox-inert agents for targeted DNA hydrolysis in cancer therapy. Structural advancements have enhanced their catalytic activity, DNA affinity, and cellular uptake. However, challenges such as selective tumor targeting, genomic specificity, and in vivo stability limit clinical translation. Future research should prioritize targeted delivery systems, detailed mechanistic studies, and evaluation of pharmacokinetics and immunogenicity. Integration with imaging agents or responsive carriers may enable precision-guided applications. With interdisciplinary development, Zn (II) complexes could emerge as safe, selective, and multifunctional tools for next-generation anticancer therapeutics.

4. Conflicts of Interests

The authors declare no conflicts in their mutual interests, in any manner, whatsoever.

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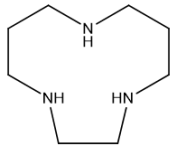
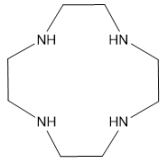
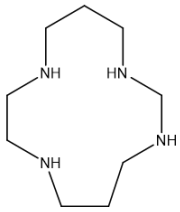
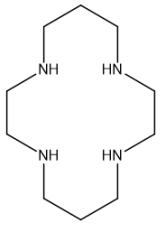
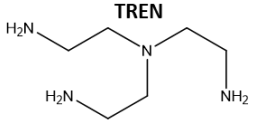
Supplementary information

Table 1 Zn (II) Complexes vs Other Metals in Anticancer Applications.

S.No	Metal Complex	Ligand Framework	DNA Cleavage Mechanism	Anticancer Activity	Comparison with Other Metals
1	Zn (II)-cyclen with L-tryptophan [39]	Cyclen macrocycle with L-tryptophan side arms	Hydrolytic, minor groove binding ($K_b = 2.12 \times 10^5\ M^{-1}$)	Selective to U-87MG vs HEK 293, LAT1 mediated uptake	Lower toxicity and higher selectivity than Cu (II) or Ru (II) systems; ideal for LAT1-targeted delivery.
2	Zn (II)-Pro-Gly [40]	Dipeptide (Pro-Gly)	Hydrolytic, ROS-independent, minor groove	ROS-independent cleavage, biomimetic nuclease	Safer alternative to ROS-dependent Cu (II) analogs with comparable DNA cleavage efficiency
3	Zn (II)-Pro-Leu [40]	Dipeptide (Pro-Leu)	Hydrolytic, confirmed via T4 DNA ligase assay	Moderate cleavage, lower binding than Pro-Gly	Less potent than Cu (II)-Pro-Gly complex; lower cytotoxicity but better hydrolytic profile
4	Dinuclear Zn (II)-2,6-bis-TACN [41]	2,6-bis(1-methyl-1,4,7-triazacyclononyl) pyridine	Hydrolytic under physiological pH	Cleaves DNA, induces apoptosis in HepG2	Comparable to Cu (II) analogs; hydrolytic, not ROS-dependent—potentially safer
5	Zn (II)-DPA (Br/Cl) [42]	Dipicolylamine with halides	Oxidative in presence of H_2O_2	IC_{50} ~12 µM, induces apoptosis and cell cycle arrest	Shows similar IC_{50} to Cu (II) and better selectivity than Fe (II)-based agents
6	Zn (II)-2,2'-bipyridyl (quaternary ammonium) [43]	Disubstituted bipyridine with tetraalkylammonium	Hydrolytic, $k = 3.85 \times 10^{-5}\ s^{-1}$	Active under physiological pH, sequence-independent	Higher aqueous stability and activity at physiological pH vs Cu (II) bipyridine systems
7	Zn (II)-Schiff base from benzohydrazide [44]	Schiff base of 2-hydroxybenzohydrazide	Intercalative, cytotoxic	Superior IC_{50} = 1.40 µg/mL vs MCF-7 (vs cisplatin)	Outperforms cisplatin in MCF-7; Zn (II) complex is less toxic and more selective
8	Zn (II)-Schiff base (naphthalenol-based) [45]	Schiff base derived from naphthalenol	Intercalative, minor groove via CD/UV shifts	High DNA affinity, CD-confirmed structural impact	Comparable to Ru (II) systems but with simpler redox profile and fewer off-target effects

9	Zn (II)-cyanoazo-coumarin [46]	Cyanoazo-functionalized coumarin	Minor groove/electrostatic binding	Antiproliferative, reduced HOMO-LUMO gap	Performs similarly to Au (III) complexes in DNA binding with better biocompatibility
10	Zn (II)-thiosemicarbazone (thiophene-based) [47]	Thiosemicarbazone from thiophene aldehydes	Intercalative DNA binding	Comparable to cisplatin vs HepG2, lower toxicity	Lower oxidative stress compared to Cu (II) thiosemicarbazones, yet effective cleavage
11	Zn (II)-azo-Schiff base [48]	Azo-linked Schiff base	Minor groove intercalation	Induces apoptosis in Hut-78 cells	Matches ROS generation of Cu (II) analogs but shows less redox-related toxicity
12	Zn (II)-thiosalicylic acid [38]	Thiosalicylic acid (O, S donors)	Electrostatic & groove binding	Selective tumor cytotoxicity, platinum alternative	Safer profile compared to Pt (II) analogs; strong DNA affinity with minimal systemic effects
13	Dinuclear Zn (II)-bipyridine-carboxylate [38]	Bipyridine with carboxylate bridges	Hydrolytic via coordinated bridging	Moderate cytotoxicity, hydrolytic damage	Less potent than Ru (II) but shows balanced hydrolytic activity with DNA targeting
14	Zn (II)-benzimidazole [38]	Benzimidazole core	Groove binding (supported by docking)	Potential groove binder with DNA targeting	Better solubility and lower side effects than Pt (II)/Ru (II)-benzimidazole complexes
15	Zn (II)-pyrimidinyl-hydrazine [38]	Pyrimidinyl-hydrazine	Partial intercalation (spectroscopy)	Effective against gastric cancer (BGC-823)	Comparable to Cu (II)-pyrimidinyl complex; reduced ROS involvement favors Zn (II)
16	Zn (II)-pyrazolyl-nicotinic acid [38]	Pyrazolyl-nicotinic acid	Hydrolytic DNA cleavage	Strong DNA binding, biocompatible	Similar DNA binding as cisplatin; higher biocompatibility and lower systemic toxicity

Table 2 Summary of the acid dissociation constants (pKa) of metal-coordinated water and the corresponding apparent second-order rate constants (kBNPP) for BNPP hydrolysis catalyzed by each complex.

Ligand	Ring size	pKa	k_{BNP} (10^{-4} $M^{-1}s^{-1}$)
[12]ane N_3 	12	7.3	0.61 (pH 7.4)
[12]aneN_4 	12	8.0	0.031 (pH 7.4)
[13]aneN_4 	13	8.3	-
[14]aneN_4 	14	9.8	0.11 (pH 11)
TREN 	-	9.8	0.39 (pH 10)