Biological activities of s-triazine based metal complexes

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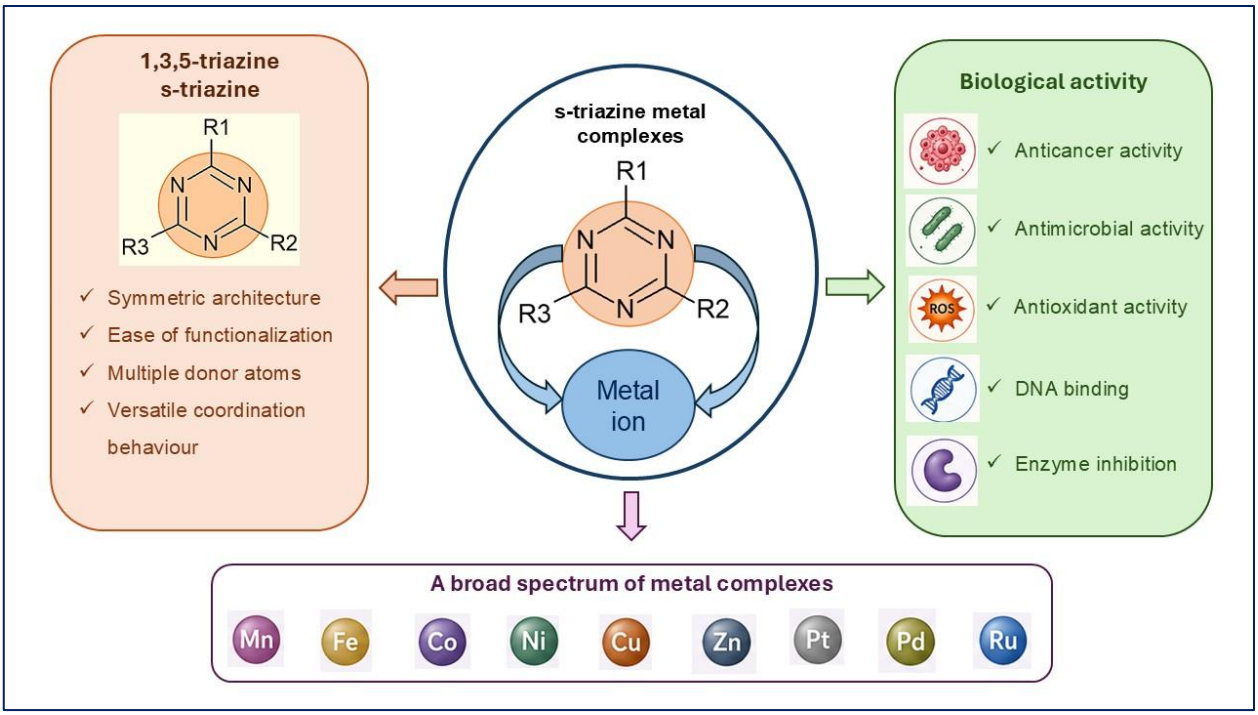

Abstract

1,3,5-triazines (s-triazines) are a class of heterocyclic compounds bearing three N atoms in a symmetric molecular architecture. They have gained attention in synthetic chemistry and coordination chemistry due to the ease of derivatization of this scaffold into compounds with desired properties, especially favourable biological activities. Recent research work lays a solid background that these s-triazines can be synthesized via straightforward synthetic routes utilizing cyanuric chloride and related synthetic precursors. These synthetic strategies enable the successful synthesis of ligand systems with N, S, and O donors with the structurally interesting s-triazine moiety paving the pathway for them to coordinate with metal centres forming biologically relevant stable metal complexes. This review focuses on the growing importance of s-triazine based metal complexes for biological applications. Upon complexation with metal cores the solubility, electronic and geometric effects of these s-triazines can be modulated to offer better platforms to interact with biomolecules. As evident by recent literature, s-triazine derived metal complexes possess promising anticancer, antibacterial, and antiviral activities, leading to their recognition as important hybrid compounds at the interface of medicinal and inorganic chemistry with the potential to be developed as novel drug leads.

Keywords: *1,3,5-triazine, s-triazine, anticancer, antioxidant, antimicrobial activity*

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1.0 Introduction

The development of multifunctional metallo-pharmaceuticals is a major frontier in modern bioinorganic and medicinal chemistry, stimulated by the urgent need for novel therapeutic agents to combat global problems such as widespread antimicrobial resistance and aggressive oncological diseases (*2024 Global Tuberculosis Report*, 2024; Ferlay *et al*., 2021). The symmetric 1,3,5-triazine (s-triazine) core is one of the most versatile and privileged pharmacophoric scaffolds in various heterocyclic platforms (Rathod *et al*., 2024; Straube *et al*., 2020). The nitrogen-rich planar aromatic framework of s-triazine has highly tunable substitution sites which can be strategically engineered to target structural, physical and electronic properties. Sophisticated pincer-like, tripodal or macrocyclic multidentate ligands can be constructed by anchoring various chelating components such as pyrazolyl, pyridyl, thiazole, hydrazone, amino acid or extended Schiff base motifs to the core nucleus. These rigid architectures provide ideal spatial arrangements of donor atoms, which are capable to provide stable coordination microenvironments well suited for hosting a wide range of Lewis acids.

Cyanuric chloride is a versatile precursor for the construction of sophisticated s-triazine based ligands (Figure 1). The anchoring points can be carefully substituted by different alkyl, aryl or chelating arms, allowing to tune precisely the steric bulk and electronic landscape of the desired ligands (H. A. Ali *et al*., 2025; Mahmoodi and Mohammadi, 2016). Thus, this general derivatization route offers an extremely adaptable and facile approach for the synthesis of a wide array of 1,3,5-triazine ligands with high chelating potential, enabling the targeted synthesis of a variety of highly specialized coordination complexes (Al-khodir *et al*., 2019).

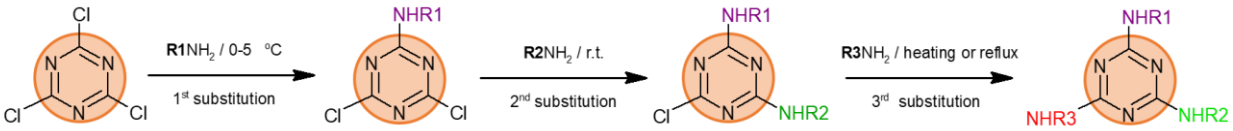

Figure 1. Synthesis of s-triazine ligands utilizing cyanuric chloride

Profound biophysical transformations are observed upon coordination of these functionalized organic shells to transition metals, closed-shell d^{10} nodes, heavy main-group elements or macrocyclic lanthanide(III) centers (Pavelek *et al*., 2016). Metal coordination effectively delocalizes the positive charge of the central ion over the organic framework, thus decreasing the overall polarity of the system. The polarity of the coordination complex is systematically reduced, resulting in a dramatic increase in its lipophilicity. This enhanced lipophilic profile allows for efficient penetration through the hydrophobic lipid bilayers of microbial cell walls and cancer cell membranes, leading to enhanced cellular uptake and intracellular accumulation. As a consequence, such metallo-chemotherapeutics often exhibit an exceptional increase in biological activity compared to the potency of their respective free, monomeric organic moieties and the conventional clinical standards such as cisplatin or 5-fluorouracil (Bellagamba *et al*., 2016; Mylonakis *et al*., 2010). In addition to improving the main permeability limits, the different metal centers generate diverse coordination geometries, including distorted square planar, trigonal bipyramidal to complex octahedral, square pyramidal and high coordination number such as nine-coordinated spherical capped square antiprismatic geometries. Such highly specific spatial arrangements dictate how the complex interacts with and binds to intracellular macro-biomolecules, leading to different mechanisms of action such as covalent nucleobase coordination, external groove binding, or strong intercalative DNA interactions (Chupakhin, 2020).

To comprehensively assess recent progress in this field and to establish clear structure-activity relationships (SARs), this review systematically organizes the scientific literature into five interconnected thematic areas based on biological application. The discussion starts with an evaluation of anticancer activity, including the antiproliferative profiles and IC_{50} thresholds of transition and main-group metal architectures against various human cancer lines, considering single-crystal

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configurations and mechanisms of cell cycle arrest or induced apoptosis. It also covers the evaluation of the wide-range antibacterial and antifungal potencies against severe pathogenic microorganisms such as *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*, justifying membrane clearance zones via chelation-oriented parameters. Next, the review explores antioxidant and enzyme inhibitory activities from the viewpoint of free radical trapping abilities using DPPH and FRAP assays and describes the regiochemical and electronic mechanisms which control the alteration of baseline hydrogen atom transfer pathways. The next section deals with DNA binding and mechanistic studies, which explore the exact biophysical mechanisms of interaction with nucleic acids, such as groove binding, partial intercalation, and oxidative cleavage via chemical nuclease. These studies are supported by multi-spectroscopic titrations and molecular docking simulations. Finally, the review emphasizes the synergistic effect of the metal complexes, providing insights into multi-targeted versatile coordination systems and hybrid nanocomposites exhibiting dual or triple biological activities, successfully bridging the gap between novel *in vivo* therapies, antimalarial applications and analytical chemosensing pathways.

2.0 Anticancer activity

2.1 Platinum group metal complexes: Pd(II), Pt(IV) and Ru(IV)

The design of targeted chemotherapeutic agents based on s-triazine coordination complexes has grown significantly in popularity due to the structural tuneability of the 1,3,5-triazine core and its ability to synergize with bioactive metal centres. Researchers have been able to modify the triazine skeleton with different chelating arms such as pyrazoles, hydrazones, pyridines and amino acids to modify lipophilicity, DNA binding affinity and cellular uptake. This section reviews the recent progress in the design, structural topography and mechanism of action of s-triazine based metallo-chemotherapeutics against different human cancer cell lines.

The model for metallodrug design has been traditionally platinum-group metal complexes, but the present approach is directed towards circumventing the classical cisplatin-resistance pathways through structural diversification. Chelation often modifies the biophysical properties of the parent organic scaffold. For example, the evaluation of antitumor activity against human breast adenocarcinoma (MCF-7) and human hepatocellular carcinoma (HepG2) cell lines showed much lower IC_{50} values for Pd(II) and Pt(IV) complexes of s-triazine derivatives in comparison to the free s-triazine derivatives (Al-khodir *et al*., 2019). The systematic enhancement of the cytotoxic potency with respect to the reference drug cisplatin is mainly ascribed to the higher lipophilicity and better cellular uptake through the chelation process.

Generally, the design of these systems is driven by metal mediated transformations either in solution or upon crystallization. Lasri *et al*. have reported the synthesis of a square planar Pd(II) complex, $[Pd(PT)Cl(H_2O)]\cdot H_2O$ (HPT: 6-(3,5-dimethyl-1H-pyrazol-1-yl)-1,3,5-triazine-2,4(1H,3H)-dione) with the pincer ligand 2-methoxy-4,6-bis(3,5-dimethyl-1H-pyrazol-1-yl)-1,3,5-triazine (MBPT). The *in vitro* biomedical assays have shown a very uniform antiproliferative profile against both cell lines MCF-7 and MDA-MB-231, leading to the same IC_{50} values (Lasri *et al*., 2021).

Ruthenium based organometallic architectures have also shown promising potential as multi-targeted alternatives. A new bifunctional Ru(II) arene aqua-complex with the bidentate ligand 2,4-diamino-6-(2-pyridyl)-1,3,5-triazine is reported (Lozano *et al*., 2013). Solution studies demonstrated that in chloride rich media, this complex is rapidly converted to aqua for monochloro exchange and therefore, a high level of the active aqua species can be maintained under conditions similar to physiological environments. A multimodal binding mode was established by mechanistic interactions with calf thymus DNA (CT-DNA). The complex simultaneously participates in external groove binding, minor intercalation of the rigid ligand and covalent coordination to the nucleobases. Thus, it showed cytotoxic profiles, superior to cisplatin against human ovarian carcinoma and cisplatin resistant lines, a property directly driven by the active aqua leaving site working in concert with the extensive hydrogen-bonding network of the s-triazine amino groups (Lozano *et al*., 2013).

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Using this organometallic approach, Beckford and coworkers designed a family of symmetric trinuclear Ru(II) complexes bearing three [RuCl(arene)] fragments (arene = benzene, p-cymene or hexamethylbenzene) tethered onto a central 2,4,6-tris(di-2-pyridylamino)-1,3,5-triazine scaffold (Beckford *et al*., 2018). Binding interactions of the synthesized compounds with CT-DNA were studied by multi-spectroscopic titration methods and molecular docking simulations. The binding constants were found to be in the order of 10^4 M^{-1} which indicates a strong CT-DNA binding. Biological screens against human colorectal carcinoma (HCT-116) lines showed low antiproliferative potencies (Beckford *et al*., 2018).

In a comparable way, Al-Khodir *et al*. prepared a series of Ru(III) and Se(IV) complexes with substituted 1,3,5-triazine-2,4,6-triamines and diamines with pyrimidine, thiazole or triazole groups (Al-khodir *et al*., 2018). *In vitro* screening results confirmed that the combination of heavy transition and main-group elements with highly functionalized triazine platforms is a great approach for targeted drug design, as evidenced by the significant dose-dependent cytotoxicity in human lung and colon cancer cell lines (Al-khodir *et al*., 2018).

2.2 First row transition metal complexes: Cu(II), Ni(II), Co(II), Mn(II) and Fe(III)

Zhang *et al*. have reported two water-soluble Cu(II) complexes of 1,3,5-triazine derivative with amino acid (Ala, Gly) co-ligands (Zhang *et al*., 2018). The obtained structurally robust complexes showed strong preference for groove binding to CT-DNA and high affinity to human serum albumin (HSA) indicating feasible blood transport capabilities. They exhibited moderate dose-dependent cytotoxicity against A549, HeLa and PC-3 cell lines where the second derivative was found to be more potent due to subtle structural modifications (Zhang *et al*., 2018).

Similarly, Shen and co-workers built amino acid appended Cu(II) complexes; $[Cu(PyTA)(L\text{-}Thr)(ClO_4)]_2 \cdot 1.5H_2O$ and $[Cu(PyTA)(L\text{-}Arg)(ClO_4)(H_2O)] \cdot ClO_4$ (PyTA = 2,4-diamino-6-(2-pyridyl)-1,3,5-triazine) (Shen *et al*., 2017), and both complexes were found to bind tightly in the grooves of CT-DNA and to act as oxidative chemical nucleases, cleaving plasmid pBR322 DNA by the *in situ* generation of superoxide free radicals. Docking models revealed high-affinity binding within Site I of HSA. Notably, the incorporation of these amino acid recognition blocks into the coordination frame greatly enhanced the cell viability scores against human hepatocellular carcinoma (Bel-740), resulting in low IC_{50} thresholds (Shen *et al*., 2017).

Abdi *et al*. reports the synthesis of $[Cu(tptz)_2]^{2+}$ complex with water soluble properties. *In vitro* MTT cell assays against MCF-7 cell lines exhibited outstanding chemotherapeutic potential with an astonishing IC_{50} value of only 1.98 μM, far exceeding clinical-grade cisplatin by the same criteria (Abdi *et al*., 2012).

Other first-row transition metals have shown similar versatility in promoting metal-mediated structural transformations. Dahlous and co-workers have reacted the MPT pincer ligand (MPT: 4-(3,5-dimethyl-1H-pyrazol-1-yl)-6-methoxy-1,3,5-triazin-2-ol) and thiocyanate colinkers with nickel(II) to give a nickel(II) coordination polymer (Dahlous *et al*., 2023). This complex exhibited an enhanced antiproliferative potency against MCF-7 and HepG2 cell lines compared to the free ligand, which was directly attributed to the structural changes induced by the metal-templated hydrolysis (Dahlous *et al*., 2023).

Alternative architectures have been successfully combined with nickel and zinc nodes in Schiff base chemistry. El-Hakeem *et al*. synthesized a new triazine Schiff base ligand by solvent-free green chemistry approach through condensation of 2,4-diamino-6-phenyl-1,3,5-triazine with 2-hydroxy-1-naphthaldehyde (El-hakeem *et al*., 2026). The resulting octahedral Ni(II) and Zn(II) frameworks showed excellent non-covalent macromolecular recognition, partially intercalated into CT-DNA with elevated binding constants. The biological profiles showed that the complexation enhanced the therapeutic response in a systematic way over the ligand alone, demonstrating high anti-proliferative behavior against the HCT-116 and MCF-7 lines (El-hakeem *et al*., 2026).

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The structural geometry in cobalt and iron configurations also governs cellular responses. Cao *et al*. synthesized two mononuclear cobalt(II) complexes from 1,3,5-triazine derivatives functionalized with a chelating 2-(aminomethyl)pyridine motif (Cao *et al*., 2026). Some of these metal complexes showed high potency against human gastric cancer cells SGC-7901, with a IC_{50} of 12.29 M, exhibiting better activity than the free ligand (25.13 M) and the standard drug 5-fluorouracil (18.59 M), and *in silico* SwissADME models indicated good drug-likeness (Cao *et al*., 2026).

In a similar way, Yousri *et al*., designed a highly conjugated s-triazine derivative with a quinoline arm, L = N-(4,6-bis(3,5-dimethyl-1H-pyrazol-1-yl)-1,3,5-triazin-2-yl)quinolin-8-amine, to construct a mononuclear Mn(II) complex [$MnLCl_2$] and an Fe(III) complex [$FeLCl_3$] (Yousri et al., 2026). The cytotoxicity testing by MTT assays revealed the better antiproliferative profile of the Fe(III) complex with remarkably low IC_{50} values against MCF-7 and HepG2 cell lines (Yousri *et al*., 2026).

2.3 Heavy main group and d^{10} coordination complexes: Cd(II)

Dahlous and coworkers have synthesized a new cadmium(II) complex, [$Cd(BPMT)Br_2$], with the tridentate MBPT pincer ligand (Dahlous *et al*., 2022). The *in vitro* MTT assays demonstrated the remarkable anticancer potential against MCF-7 breast cancer lines and also demonstrated significantly lowers IC_{50} value than the free triazine derivative (Dahlous *et al*., 2022)

As a related work, Emad *et al*. synthesized two mononuclear cadmium(II) complexes, namely [$Cd(DPPT)Cl_2$] and [$Cd(DMPT)(NO_3)_2(H_2O)]\cdot H_2O$ based on neutral tridentate NNN-donor s-triazine ligands functionalized with 2,4-di(piperdin-1-yl)-6-(2-(1-(pyridin-2-yl) ethylidene)hydrazinyl)-1,3,5-triazine (DPPT) and 2,4-bis(morpholin-4-yl)- 6- [2-[1-(pyridine-2- yl)ethylidene]hydrazin-1-yl]-1,3,5-triazine (DMPT) framework (Emad *et al*., 2025). Metalation of the triazine core systematically improved the pharmacological efficacy of both systems compared to the isolated organic units, showing excellent antiproliferative properties against human colon carcinoma (HCT-116) and lung adenocarcinoma (A-549) lines (Emad *et al*., 2025).

3.0 Antimicrobial activity

The exponential increase of global antimicrobial resistance (AMR) constitutes a healthcare emergency, emphasizing the need for structural frameworks with novel mechanisms of action. s-triazine based coordination architectures among the emerging platforms have received considerable attention. The resulting complexes usually show broad-spectrum antibacterial and antifungal activities in combination with biologically active transition, main group or heavy metal nodes. In this review, we have discussed in detail the structural landscape, single crystal arrangements and structure-activity relationships (SAR) of s-triazine coordination frameworks against various pathogenic microorganisms.

3.1 First-row metal complexes: Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II)

The physiological tolerance and architectural versatility of the first-row transition metals are ideal for fine tuning the spatial arrangements of ligands for optimizing cell wall penetration. Systematic studies of antimicrobial properties of Mn(II) (Soliman *et al.,* 2020), Fe(III) (Soliman *et al*., 2020), Co(II) (Soliman *et al*., 2020[a]) and Ni(II) (Soliman *et al*., 2019) centers coordinated to mono- and bis-pyrazolyl-s-triazine (PT and BPT) pincer scaffolds functionalized by morpholine or piperidine blocks were conducted by Soliman and co-workers (Figure 2). The penta-coordinated divalent cobalt complexes with morpholinyl and piperidinyl BPT geometries have a distorted square pyramidal geometry with two terminal chloride ligands capping the geometry. *In vitro* studies showed that these cobalt(II) systems are active against a broad spectrum of bacteria and fungi, such as *Staphylococcus aureus*, *Bacillus subtilis*, *Proteus vulgaris*, *Escherichia coli* and *Candida albicans*, with comparable or better activity than amoxicillin, tetracycline and ampicillin in clinical practice (Soliman *et al.*, 2020[a]).

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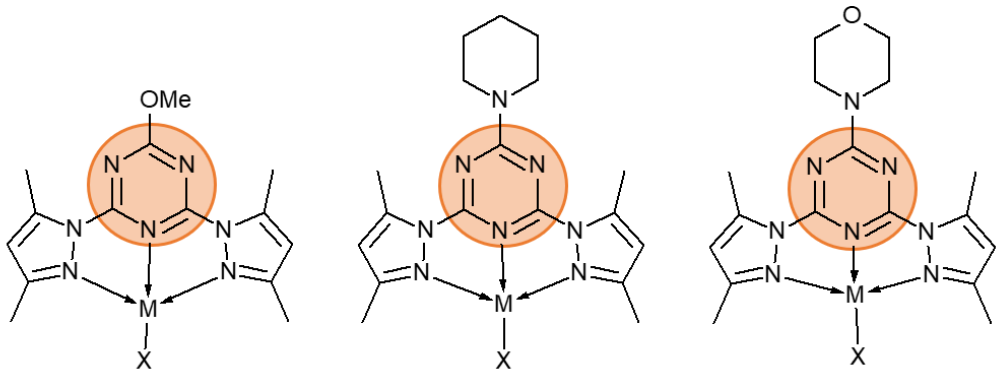

Figure 2. General chemical structure of the metal complexes derived from mono- and bis-pyrazolyl-s-triazine ligands

Similar therapeutic enhancement was seen for analogous Fe(III) complexes such as the [Fe(PiPBPT)Cl_3] (where PiPBPT = 2,4-bis(3,5-dimethyl-1H-pyrazol-1-yl)-6-(piperidin-1-yl)-1,3,5-triazine). The free PT and BPT ligands are found to be less toxic, but complexation with Fe(III) results in substantial minimum inhibitory concentration (MIC) values against a broad spectrum of bacterial and fungal targets. Similar trends in structural refinement are observed for Mn(II) pincer systems. Al-Rasheed, Soliman and El-Faham reported two mononuclear complexes of distorted octahedral geometries with nitrate inner coordination sphere. Biological screenings showed good concentration dependent activities against *S. aureus*, *E. coli* and *C. albicans* for all the variants substituted with morpholine with slightly better antifungal response due to different outer sphere interactions (Soliman *et al.*, 2020).

The antimicrobial activity of Ni(II) frameworks is highly dependent on the choice of counter anion and the coordination mode. In the heteroleptic complexes, the nitrate counter-anions are in the outer sphere. This configuration showed a very selective and strong antibacterial effect against the Gram-positive pathogens (*S. aureus* and *S. pyogenes*), providing inhibition zones similar to the control drug gentamycin with MIC values of 30–60 µg/mL (Soliman *et al*., 2019). The antimicrobial profile of these methoxy-BPT platforms, as their divalent zinc complexes, is also altered. Free BPT ligands are completely inactive against the eukaryotic yeast *C. albicans*, however zinc(II) metallation activates the framework resulting in high, selective antifungal properties (Soliman *et al*., 2020[b]).

In the search for alternative geometrical limits, Maghami and co-workers have isolated a mononuclear cobalt(II) complex, [Co(tptz)(CH_3OH)Cl_2]·CH_3OH·0.5H_2O, based on the rigid, symmetrical building block 2,4,6-tris(2-pyridyl)-1,3,5-triazine (tptz) (Maghami *et al*., 2015). Single-crystal X-ray mapping revealed a distorted six-coordinate octahedral geometry where tptz acts as a neutral tridentate ligand along with two terminal chlorides and one methanol molecule. In comparison with their Ni(II), Cu(II) and Mn(II) analogues, the complex showed excellent dose-dependent growth inhibition against Gram-negative (*E. coli*, *Pseudomonas aeruginosa*) and Gram-positive (*S. aureus*, *B. subtilis*) strains (Maghami *et al.*, 2015).

Güven *et al*. reports a structurally similar mononuclear zinc(II) analogue [Zn(tptz)Cl_2] exhibits a five-coordinate distorted trigonal bipyramidal geometry with the tptz core anchoring in a 1:1 metal-to-ligand ratio (Güven *et al.*, 2021). The wide applicability of this zinc(II) platform is demonstrated by the significant MIC values obtained against *E. coli*, *P. aeruginosa* , *S. aureus, Bacillus cereus*, and *C. albicans*. The uniform enhancement of the biological potency on transition metal centers can be rationalized by Overtone's concept and Tweedy's chelation theory (Güven *et al.*, 2021).

3.2 Precious, heavy, and main-group complexes: Ru(II), Ag(I), Cd(II), Sb(III), Bi(III), Nd(III)

Albaqami *et al*. studied the homoleptic pincer like complexes [Ru(µ-tptz)$_2$$Cl_2$] and [Fe(µ-tptz)$_2$$Cl_2$] (Albaqami *et al.*, 2023). Electronic absorption, fluorescence and circular dichroism (CD) assays confirmed an intercalative binding pathway with Fish Salmon DNA (FS-DNA) and the Ru(II)

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variant was found to have a significantly higher binding affinity than the Fe(II) analogue. The *in vitro* antibacterial monitoring against *S. aureus* and *E. coli* showed that the two complexes easily outperformed the free tptz ligand owing to the better cell membrane permeability, supported by the frontier molecular orbital (FMO) calculations (Albaqami *et al.*, 2023).

Silver(I) systems also show important antimycobacterial profiles. Ag(I) complexes derived from pyrazolyl-s-triazine ligands show high zones of inhibition against *S. aureus*, *E. coli and C. albicans* are reported by Soliman *et al*. (Soliman *et al.*, 2020). To explore the structural implications of closed-shell d^{10} configurations, Khattab *et al*. have used a rigid tridentate s-triazine pincer ligand (BPAT) with the corresponding divalent cadmium, zinc and monovalent silver perchlorate salts (khattab *et al.,* 2025). Interestingly, the 1:2 bis ligated sandwich Cd(II) complex has displayed very strong antibacterial activity against *S. aureus* and *P. vulgaris* (MIC = 4.8 µg/mL). Meanwhile, the aqua-bound cadmium monomer showed better antifungal activity against *C. albicans* (MIC = 9.7 µg/mL) than the clinical standard ketoconazole (El-Faham, 2025). In the same way, Dahlous and coworkers reported that the penta coordinate square pyramidal cadmium complex [Cd(BPMT)Br_2] presented higher antibacterial activity against *S. aureus* and *E. coli* than the free ligand, but it was less effective than the positive control gentamycin (Dahlous *et al.*, 2022).

On the other hand, main group heavy metals are highly dependent on the identity of the core metal and peripheral halogen modifications (unlike transition metal systems). Martins and co-workers synthesized a series of star-shaped triazine Sb(III) and Bi(III) complexes, by coupling trivalent metal chlorides with multi-dentate 1,3,5-triazine hydrazones with nitro, chloro or fluoro benzylidene substituents (Martins *et al.*, 2019). The free ligand shells showed no baseline antimicrobial activity, however their corresponding Sb(III) and Bi(III) complexes showed significant dose dependent activity on clinical strains of *S. aureus*, *P. aeruginosa* and *C. albicans* (Martins *et al.*, 2019).

Lanthanide systems have also been employed to develop triazine systems, but the trends in activity are sometimes different from transition metals. In the synthesis of a tripodal symmetric trinuclear Nd(III) salen capped system, Oruma *et al*. employed a central 2,4,6-tris(4-carboxybenzimino)-1,3,5-triazine hexadentate bridging core (Oruma *et al.*, 2021). In this assembly, each Nd(III) ion is eight-coordinate with the core carboxylate oxygens, a tetradentate salen frame, and two hydroxyl groups. *In vitro* diffusion assays showed broad spectrum growth inhibition against a panel of pathogens including *S. aureus*, *B. cereus*, *E. coli*, *P. aeruginosa*, *C. albicans* and *Aspergillus niger*. Notably, bioassays have validated that the metal complexes with a single carboxylic ligand has greater antimicrobial potency than the corresponding trinuclear Nd(III) complex, suggesting that large lanthanide clusters may sometimes may be sterically hindered, thus limiting access to microbial membranes (Oruma *et al.*, 2021).

3.3 Highly extended multidentate Schiff base and hydrazone platforms

Extended highly conjugated Schiff base linkages increase the coordination area of the triazine core and develop structurally rigid networks to improve baseline bioactivity. Fathalla *et al*. reported two new hexa-coordinated Ni(II) complexes, [Ni(DMPT)$(H_2O)_3$]$(NO_3)_2.3H_2O$ and [Ni(DMPT)$(H_2O)_3$]$(NO_3)_2.H_2O$, where DMPT = (*E*)-4,4'-(6-(2-(1-(pyridin-2-yl)ethylidene)hydrazinyl)-1,3,5-triazine-2,4-diyl)dimorpholine. Both complexes showed significant concentration dependent antimicrobial and antifungal activities against *S. aureus*, *E. coli* and *C. albicans* (Fathalla *et al.*, 2023[b]).

As in the previous work, the same group has synthesized the homoleptic complexes [Ni(DPPT)$_2$]$(NO_3)_2.1.5H_2O$ and [Ni(DPPT)(NO_3)Cl].EtOH, from a related hydrazinyl derivative, (E)-2,4-di(piperidin-1-yl)-6-(2-(1-(pyridin-2-yl)ethylidene)hydrazinyl)-1,3,5-triazine (DPPT). The geometry of these systems is octahedral, dictated by coordination via the hydrazinyl and the central triazine ring nitrogens. Chelation resulted in a marked increase in the antimicrobial clearance zones compared to the free ligand, confirming that metalation is still a very reliable way to improve the bioactive potential of hydrazone matrices (Fathalla *et al.*, 2023[a]).

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Similarly, Shanmugakala and co-workers reported the synthesis of a series of tridentate complexes Cu(II), Ni(II), and Co(II), of the triazine based ligand 4,6-bis(5-mercapto-1,3,4-thiadiazol-amine)2-phenylamino-1,3,5-triazine (BMTDT). The binding mode imposes a distorted square-planar geometry for the Cu(II) and Co(II) systems and a tetrahedral arrangement for the Ni(II) complex. All three derivatives of the metal were good antibacterial and antifungal activity against *S. aureus*, *E. coli* and *C. albicans* with better activity than the free ligand, BMTDT (Shanmugakala *et al*., 2012). To further extend the aromatic network, Shanmugakala *et al*. has synthesized a highly conjugated ligand system, 2,4-bis(indolin-3-one-2-ylimino)-6-phenyl-1,3,5-triazine) (BIPTZ), to produce octahedral coordination complexes containing divalent copper, nickel, cobalt and zinc centres. Diffusion assays confirmed that metal complexation resulted in systematic improvements of the wide spectrum antimicrobial activities over the free ligand template (Shanmugakala, *et al.*, 2013).

Josephine *et al*. studied two new s-triazine ligands (PTAPTP and PTAMTP) and the corresponding square planar, low-spin d^8 Ni(II) complexes in a different context. Ni-PTAMTP complex showed the highest overall antioxidant potential (IC_{50} = 87.04 µg/mL) and the most potent antibacterial activity against S. aureus by biological tracking. Antifungal testing revealed that Ni-PTAMTP produced the largest zone of inhibition against *C. albicans* and Ni-PTAPTP was the most effective agent against *A. niger*, indicating how small structural modifications on the ligand framework can be exploited for the tuning of pathogen selectivity (Josephine *et al.*, 2026).

Furthermore, Ali *et al*. have synthesized Ni(II), Cu(II) and Zn(II) complexes of a Schiff based ligand derived from 4-phenyl-1,3,5-triazine-2,6-diamine. These systems are based on an extended s-triazine bis-Schiff base ligand with two isatin arms. Biological evaluations confirmed the uniform improvement of the antimicrobial activity against *S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa*, *C. albicans* and *A. fumigatus* by coordination in these ternary networks (Abdulaziz Ali, 2014).

3.4 Main group and alkali coordination networks: Na(I)

Although alkali metal complexes are generally regarded as having very labile coordination spheres, the stabilization of these ions can be achieved using rigid pincer networks leading to different biological profiles. Yousri *et al*. synthesized a new polymeric Na(I) coordination complex by using the rigid MBPT pincer ligand (Yousri *et al.*, 2023). Biological evaluations revealed that the complex has unique and highly selective antimicrobial activities against *S. aureus*, *E. coli* and *C. albicans*. Interestingly, while complexation significantly improved the antibacterial activity against E. coli relative to the free ligand, it slightly decreased the antifungal activity against *C. albicans*, thus demonstrating that alkali metal triazine complexes can promote highly divergent cellular selectivity between prokaryotic and eukaryotic targets (Yousri *et al.*, 2023).

4.0 Antioxidant and enzyme inhibitory activities

Multi targeted therapeutics are of great value as oxidative stress and dysregulated enzymatic pathways are core drivers in many physiological disorders. Coordination of s-triazine ligands to transition metal nodes can significantly alter their redox properties and biological behavior and can be a direct way of tuning free radical scavenging efficiency and enzyme inhibition. In this section, the SAR of tailored s-triazine molecular networks are reviewed and the structural configurations that determine whether the metalation enhances or quenches their radical clearance capabilities are detailed.

Ali, Abdullah and coworkers have synthesized a tetradentate Schiff base ligand by condensation of 4-phenyl-1,3,5-triazine-2,6-diamine with 3,5-di-tert-butylsalicylaldehyde (Figure 03 a) to isolate 1:1 nickel(II), copper(II) and zinc(II) (A. Ali *et al.,2013*). Similarly, Abdulaziz Ali *et al*. synthesized two similar tetradentate ligands based on 3-hydroxysalicylaldehyde and 4-hydroxysalicylaldehyde (Figure 03 a and b) to form octahedral Ni(II) and Zn(II) metal complexes (Abdulaziz *et al.,* 2012). The 2,2-diphenyl-1-picrylhydrazyl (DPPH) assays in both studies consistently showed that metal coordination reduced the baseline antioxidant bioactivity. The free s-triazine ligands

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were found to be much more efficient radical scavengers than their metal derivatives, because chelation immobilizes the deprotonated phenolate oxygen and azomethine nitrogen donor sites, thus preventing the free hydrogen atom transfer (HAT) pathway needed to stabilize reactive species (Abdulaziz *et al.,* 2012).

The spatial disposition of the auxiliary hydroxyl groups on the periphery of the ligand also controls the final thermal and radical trapping properties. Mononuclear square pyramidal Cu(II) complexes coordinated with a Schiff based ligand based on 4-phenyl-1,3,5-triazine-2,6-diamine have been synthesized by Ali (Figure 3 a and b) (A. Ali, 2016). Upon chelation to the copper(II) center always decreased the overall antioxidant capacity for both isomers ad evidenced by DPPH and Ferric Reducing Antioxidant Power (FRAP) antioxidant assays (A. Ali, 2016).

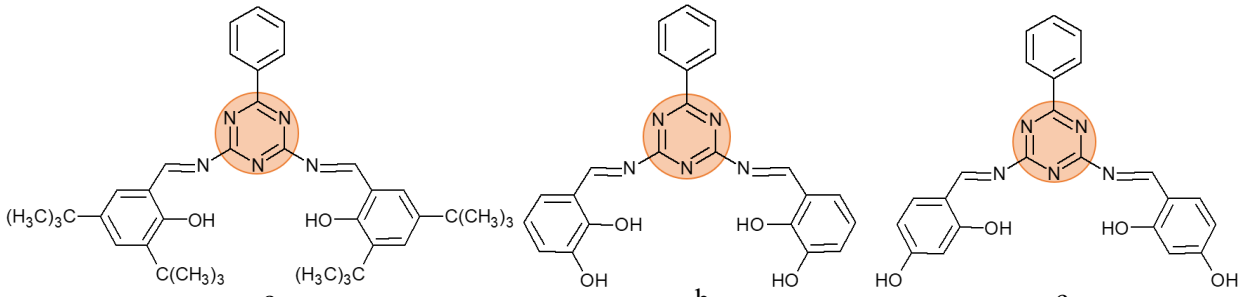

Figure 3. Line diagrams of Schiff base ligands utilized to synthesize metal complexes with antioxidant properties

5.0 Combined biological effects of s-triazine based metal complexes

The design of multifunctional inorganic medicinal compounds is important, exploiting the synergistic relationship between the 1,3,5-triazine core and coordinated metal centers. By merging intrinsic pharmacological properties of the organic scaffold with electronic properties of transition, main group or lanthanide nodes, researchers have developed versatile agents that are able to target several disease pathways at once. In this section, we present representative s-triazine coordination complexes with dual or multi-targeted biological profiles and demonstrate how metalation systematically enhances the baseline therapeutic efficacy (Table 1).

5.1 Antimicrobial and antineoplastic dual systems

A single molecular architecture that combines broad-spectrum antimicrobial and targeted antiproliferative activity is an effective strategy for the development of versatile chemotherapeutic agents. Al-Khodir *et al*. demonstrated this capability with a series of Pd(II) and Pt(IV) complexes with a trisubstituted s-triazine core (Al-khodir *et al.*, 2019). The networks exhibited different dose-dependent growth inhibition activity against *Staphylococcus aureus*, *Escherichia coli*, *Aspergillus flavus* and *Candida albicans* whereas Pt(IV) derivatives showed significant *in vitro* cytotoxicity against human colon and lung cancer cell lines (Al-khodir *et al.*, 2019).

Transition metal pincer complexes often show similar dual action behavior controlled solely by their geometry and coordination spheres. Altowyan and coworkers synthesized a series of divalent transition metal complexes using a hydrazone-s-triazine ligand with a peripheral pyridyl arm (Altowyan *et al.*, 2024). The Mn(II), Co(II), Ni(II) and Zn(II) metal complexes were homoleptic octahedral while the heteroleptic Cu(II) complex, coordinated by a single pincer strand, an aqua molecule, and two nitrate anions, is identified as the most potent therapeutic candidate. This Cu(II) complex has demonstrated promising antimicrobial zones of clearing against *S. aureus*, *E. coli* and *C. albicans*, as well as caused strong and dose dependent apoptosis in human breast cancer (MCF-7) cell lines (Altowyan *et al.*, 2024). Similarly, a mononuclear Mn(II) complex, with the tridentate ligand 2,4-di(1H-pyrazol-1-yl)-6-(morpholin-4-yl)-1,3,5-triazine (DPMPT), has been synthesized by Khattab and co-workers. This complex with a distorted penta-coordinate square pyramidal geometry showed better

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in vitro tracking than its free ligand with enhanced antibacterial activity against *S. aureus* and *E. coli* and a significant decrease in the growth-inhibitory threshold on MCF-7 cell line (Khattab *et al.,*, 2024).

Further evidence for this dual action synergy is seen in a structurally diverse set of copper and cobalt networks. Fathalla *et al*. assessed a tridentate s-triazine hydrazone ligand functionalized with morpholinyl rings, employed to construct distorted trigonal bipyramidal Mn(II) and Cu(II) monomers and a hexa-coordinated octahedral Cu(II) system (Fathalla *et al.*, 2023). The nitrato-copper complex demonstrated a strong antineoplastic potential, showing excellent cytotoxic activity against human colon carcinoma (HCT-116, IC_{50} = 7.78 μg/mL) and lung adenocarcinoma (A-549, IC_{50} = 12.40 μg/mL) cell lines, but with a sharp selective growth inhibitory effect on Gram-positive pathogens over Gram-negative strains (Fathalla *et al.*, 2023). In a parallel study Khattab *et al*. compared octahedral Ni(II) and Mn(II) bis-pincer complexes with a 1:1 square pyramidal Co(II) thiocyanate system based on an amino-pyrazolo-s-triazine (ABPT) scaffold. The penta coordinated Co(II) architecture exhibited the highest biophysical performance, displaying significant antibacterial and antifungal activities, and potent half-maximal inhibitory concentrations against MCF-7 and A-549 cancerous cell lines (Khattab *et al.*, 2025).

Moreover, Cu(II) networks based on hybrid 2-iminocoumarin strands with 2,4-diamino-1,3,5-triazine core were also reported by Makowska *et al*. The systems demonstrated low-micromolar to nanomolar inhibitory potencies against a panel of 5 human tumor models including pancreatic (DAN-G) and lung (A-427) cell lines, with the diethylamino modified derivatives consistently outperforming the benchmark standard cisplatin (Makowska *et al*., 2022).

5.2 Targeted biomimetic, macromolecular and sensing platforms

Celik and Kose showed that heterometallic triazine frameworks mimic catecholase enzymes, establishing classical Michaelis Menten kinetics where a synergistic lanthanide-promoted effect accelerates the aerobic oxidation of catechols compared to homometallic analogs (Celik and Kose, 2018).

The DNA binding properties of the triazine derivatives were studied, and they exhibited a good binding ability for cellular components. Binding studies of multiple modalities show that transition metal complexes containing planar or pincer-like s-triazine cores bind to DNA via external groove binding, covalent coordination, or highly efficient intercalative pathways with large hypochromism. The structural modifications, increased lipophilicity and better membrane permeability often make the complexes more active than cisplatin against MCF-7, MDA-MB-231 and HepG2 lines after cellular internalization (Celik and Kose, 2018).

Just recently we reported two novel Pt(II) complexes with different anions coordinated with symmetric 2,4,6-tris(2-pyridyl)-s-triazine (tppz) core giving rise to distorted square planar geometries, which allow for optimal distribution in blood serum by stable binding to Bovine Serum Albumin. These metal complexes show potent cell selective cytotoxicity, inhibiting the growth of MCF-7 cells, but with no toxicity to healthy human peripheral blood mononuclear cells (PBMNCs), and highly selective, counter-anion dependent antimycobacterial activity against *Mycobacterium tuberculosis* (Edirisinghe *et al.*, 2026). A good instance of this dual analytical and therapeutic efficiency is given by a series of mononuclear Ni(II) complexes built on pyrazanyl (PzTA) or pyridyl (PyTA) triazine scaffolds and an 8-hydroxyquinoline (HQ) co ligand. These mixed ligand arrangements intercalate into calf-thymus DNA and show a sharp dose-dependent fluorescence “turn-on” response upon binding. The interaction gives a very low limit of detection and the complexes are highly sensitive targeted fluorescence probes and powerful radical scavengers in hydroxyl and superoxide anion assays (Duan *et al.*, 2015).

A similar dual functional profile was synthesized by Steffy *et al*. using a nitrogen-rich bisimine ligand, 4,6-di(1H-1,2,4-triazol-4-yl)-N-phenyl-1,3,5-triazin-2-amine (BITPAT), which was designed to serve as a metallo-pharmaceutical scaffold and a colorimetric chemosensor (Steffy *et al.*, 2025). The framework acts as a colorimetric sensor in aqueous media and shows high selectivity for toxic

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copper(II) ions with color change from light green to brown with LOD of 0.04 μM. From a biological point of view the platform showed high antioxidant capacity, strong anti-inflammatory lysosomal membrane stabilization and intercalative DNA binding which inhibited the migration of human gastric cancer cells (HepG-2), being totally non-toxic for healthy Vero cells (Steffy *et al.*, 2025).

5.3 In vivo and anti-inflammatory activity with a wide spectrum

The expansion of the therapeutic profile of s-triazine architectures to complex *in vivo* disease models highlights their potential as multi-functional systemic candidates. Lanthanide(III) triazine architectures are an important class of such multi targeting systems. A series of mononuclear La(III) complexes were studied with a large, almost planar pentadentate Schiff base ligand, 2,4-bis(2-hydroxybenzylidenehydrazino)-6-methoxy-s-triazine. These nine-coordinated spherical capped square antiprismatic systems make use of the triazine core to yield multi-targeting antibacterial, antifungal and antineoplastic effects (Pavelek *et al.*, 2016).

In a broader *in vivo* context, the symmetric trinuclear lanthanide(III) complexes (Dy(III), Er(III), Gd(III)) derived from a tripodal Schiff base core obtained from 2,4,6-triamino-1,3,5-triazine displayed a strong growth inhibition against a panel of six bacterial and fungal strains. Furthermore, *in vivo* suppression assays confirmed that these polymetallic frameworks exhibit potent antimalarial efficacy against parasitic infections of *Plasmodium berghei* with good safety profiles in acute toxicity assays (Khalil *et al.*, 2021).

Table 01. Summary of synergistic biological activities of s-triazine based metal complexes

No.	Metal complex core	Biological activities	Reference
01.	Cu-BITPAT complexes	Anticancer + antineoplastic + anti-inflammatory	Steffy *et al.*, 2025
02.	Cu-MPTP complexes	Antioxidant + Antibacterial	Shanmugakala *et al.*, 2013
03.	Cu-morpholinyl complexes	Antibacterial + Antineoplastic	Fathalla *et al.*, 2023
04.	Cu-Thiazole-Triamine	Antimicrobial + Anti-inflammatory + Anticonvulsant	Vathanaruba *et al.*, 2022
05.	Divalent M(II)-Indolin Series (M= Cu, Ni)	Anti-Inflammatory + Neuroprotective	Shanmugakala *et al.,* 2013
06.	La(III)-Schiff base systems	Antimicrobial + Antimalarial	Pavelek *et al*., 2016
07.	$Pt(tptz)^{2+}$ systems	Anticancer + Antimycobacterial	Edirisinghe *et al.*, 2026
08.	Mn-DPMPT systems	Anticancer + Antibacterial	Khattab *et al.,*, 2024
09.	Pt(IV)-s-triazine systems	Anticancer + Antimicrobial	Al-khodir *et al*., 2019
10.	Cu-hydrazone systems	Anticancer + Antimicrobial	Fathalla *et al.*, 2023

Similarly, transition metal complexes can be designed for neuroprotective and systemic anti-inflammatory pathways. Shanmugakala *et al*., reported the synthesis of a series of octahedral Cu(II), Co(II), Ni(II) and Zn(II) complexes using a new 2,4-bis(indolin-3-one-2-ylimino)-6-phenyl-1,3,5-triazine Schiff base ligand (Shanmugakala *et al.,* 2013). Metal chelation consistently increased systemic responses compared to free ligand *in vivo* screenings, showing potent anti-inflammatory activity in carrageenan-induced hind paw edema models and significant anticonvulsant action against maximal electroshock-induced seizures. Most notably, these transition metal frameworks presented robust neuroprotective abilities on 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's disease mice models with a pronounced reversal of the motor coordination deficits and normalization of the neurochemical anomalies (Shanmugakala *et al.*, 2013).

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Vathanaruba *et al*. extended this systemic profile by synthesizing square-planar copper(II) coordination complexes with a trisubstituted triamine ligand, N^2-phenyl-N^4,N^6-di(thiazol-2-yl)-1,3,5-triazine-2,4,6-triamine (Vathanaruba *et al.*, 2022). The triazine-thiazole platform gave a solid multi-target response, resulting in broad-spectrum antimicrobial clearance and potent *in vivo* anti-inflammatory activity in paw edema assays and high anticonvulsant potency. Molecular docking simulations confirmed the results by showing very stable non-covalent binding energies in the active pockets of cyclooxygenase-2 (COX-2) receptors and voltage gated sodium channels (Vathanaruba *et al.*, 2022). Additionally, Karthikeyan *et al*. synthesized nano-sized flower like chalcone-triazine hybrid complexes of Cu(II), Ni(II), Fe(II) and Zn(II) metal cores. These structures have a double therapeutic relevance, showing good antioxidant radical trapping and excellent antibacterial activity with massive zones of inhibition for the copper-chalcone derivative against *E. coli* and *S. aureus* (Karthikeyan *et al.*, 2023).

6.0 Conclusions

Systematic investigations of the coordination chemistry of 1,3,5-triazines reveal that the combination of active metal centres and tailor-made s-triazine ligands lead to potent, multifunctional metallo-pharmaceuticals. The s-triazine core provides structural flexibility that allows for tuning of electronic and geometric properties upon chelation. This evolution is propelled by broad antimicrobial activity, robust antineoplastic activity against aggressive human cancer lines and efficient radical scavenging capabilities consistently outperforming standalone organic scaffolds and clinical profiles such as cisplatin. Furthermore, spatial geometries result in very specific interactions with intracellular biomolecules, favouring deep DNA binding, intercalation and oxidative cleavage mediated by chemical nucleases. To successfully translate these platforms from benchtop to clinical applications, future research must progress from basic *in vitro* screening to comprehensive *in vivo* pharmacokinetic modeling to develop accurate systemic toxicity profiles. In addition, the utilization of advanced mapping to accurate molecular receptors and designing stimuli-responsive targeted and localized drug delivery will be critical in positioning s-triazine coordination networks at the forefront of next generation clinical therapeutics.

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