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Transition Metal Complexes with Tridentate Schiff Bases (ONO and ONN) Derived from Salicylaldehyde: An Analysis of Their Potential Anticancer Activity

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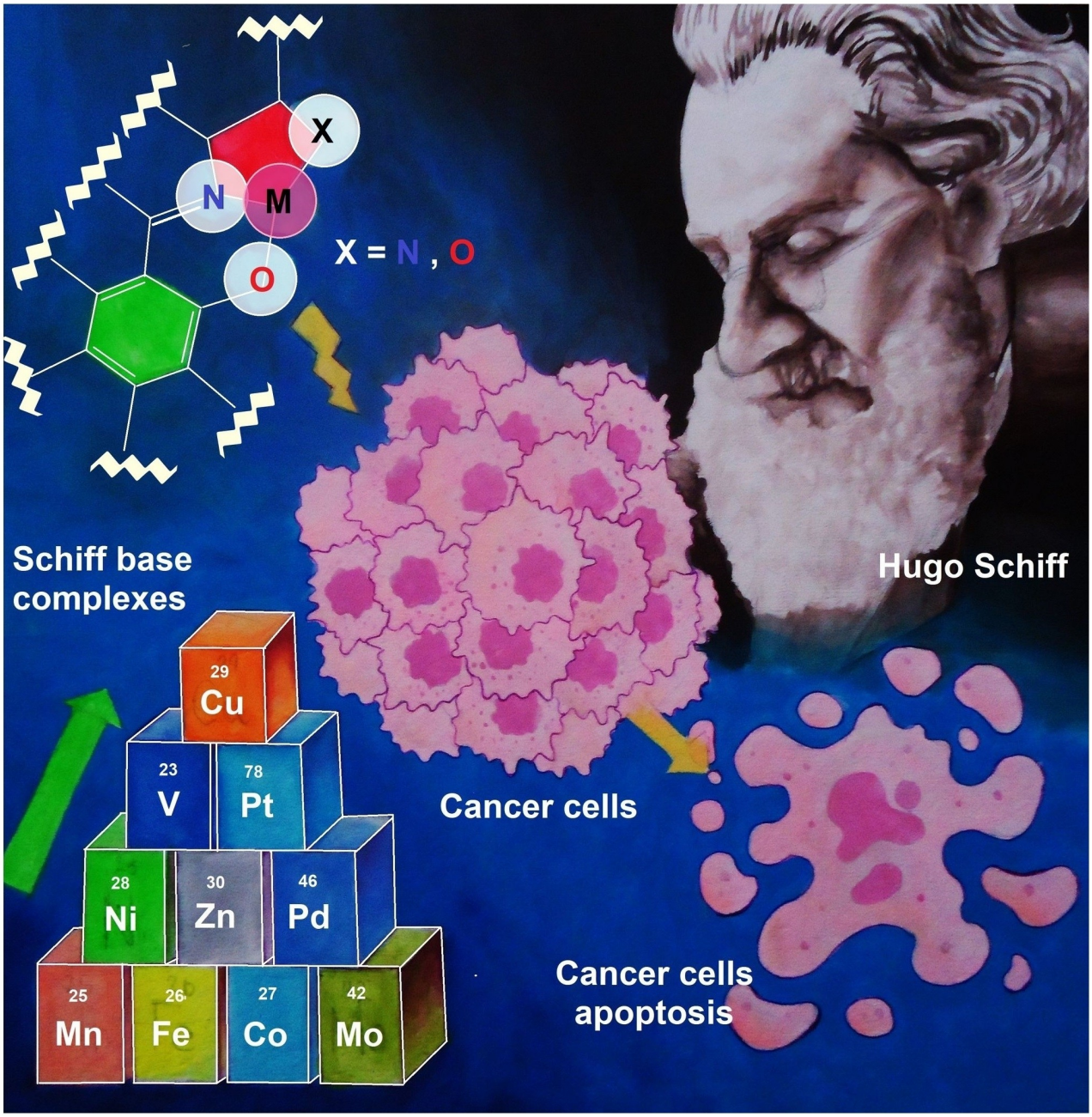

Although it is known that the first case of cancer was recorded in ancient Egypt around 1600 BC, it was not until 1917 during the First World War and the development of mustard gas that chemotherapy against cancer became relevant; however, its properties were not recognised until 1946 to later be used in patients. In this sense, the use of metallopharmaceuticals in cancer therapy was extensively explored until the 1960s with the discovery of cisplatin and its anticancer activity. From that date to the present, the search for more effective, more selective metallodrugs with fewer side effects has been an area of continuous exploration. Efforts have led to considering a wide variety of metals from the periodic table, mainly from the *d*-block, as well as a wide variety of organic ligands, preferably with proven biological activity. In this sense, various research groups have found an ideal binder in Schiff bases, since their raw materials are easily accessible, their synthesis conditions are friendly and their denticity can be manipulated. Therefore, in this review, we have explored the anticancer and antitumor activity reported in the literature for coordination complexes of *d*-block metals coordinated with tridentate Schiff bases (ONO and ONN) derived from salicylaldehyde. For this work, we have used the main scientific databases CCDC® and SciFinder®.

1. Introduction

The term Schiff base was given in honour of the German chemist Hugo Schiff, who first described the products resulting from the reactions between primary amines with carbonyl compounds.[1] Schiff bases are found in nature to play significant roles in various biological processes and have inspired many scientists to synthesize them in the laboratory, generating multiple ways to combine a variety of alkyl or aryl substituents. The main structural characteristic of Schiff bases is the presence of a double bond that unites one carbon atom with one nitrogen atom, they are also defined by the IUPAC as imines, and many others know them under the term of azomethines.[2] Schiff bases are prepared from amines and carbonyl compounds by nucleophilic addition forming a hemiaminal group, its synthesis takes place under different reaction conditions and in different solvents, followed by dehydration that normally favours the generation of imine compounds.[3] Some other preparation techniques involve solventless synthesis using microwave irradiation[4,5] or through the use of catalysts.[6,7] In the FT-IR characterization studies of the Schiff bases, a strong absorption band is shown around 1608 cm^{-1}, which corresponds to the azomethine group, while in its metal complexes the band changes to higher values. In ^{1}H and ^{13}C NMR spectroscopy, the chemical shifts of the azomethine group are at 8 ppm and 165 ppm, respectively. In UV-Vis spectra, their complexes reveal a strong intra-ligand charge transfer transition absorption at 400 nm and a broadband d-d transition at 500 nm.[8]

Schiff bases have the ability to form coordination complexes with various transition metals,[9,10] forming adducts between the metal ion and azomethine nitrogen.[11] For this reason, there is a global interest in the use of transition metal complexes with Schiff bases in the health area.[12–16] The formation of coordination complexes derived from Schiff bases occurs when the latter, in addition to the azomethine nitrogen, contains other donor atoms with free electron pairs. These donor atoms coordinate with the metal ion forming dative bonds, modifying its steric and electronic environment as well as its reactivity.[17] Therefore, Schiff bases have a variable denticity, classified according to the number of donor atoms as monodentate,[18] bidentate,[19] tridentate,[20] tetradentate,[21] pentadentate,[22] hexadentate[23] ligands, among others. Schiff bases have gained medical importance for their versatile applications in the treatment of various diseases. Its metal complexes have shown important biological activity as anti-inflammatory,[24] antiviral,[10] antimicrobial,[9,25] antituberculosis,[26] antioxidant[27] and of course anticancer.[28–31] Furthermore, there are several reports indicating that transition metal-based compounds have higher chemotherapeutic activity with respect to their free ligands.[32,33] Therefore, this growing interest in the use of metal derivatives obtained from Schiff bases in anticancer therapy is what motivated this literature review.

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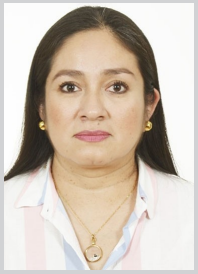

Sharon Rosete-Luna was born in Orizaba Veracruz, is a professor at the Universidad Veracruzana (UV), did her doctorate in the area of supramolecular chemistry and is currently interested in researching compounds with biological activity studying their antioxidant properties, she is also interested in studying materials that can act as drug carriers, using computational chemistry.

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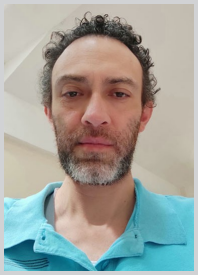

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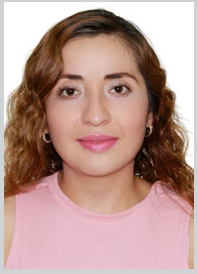

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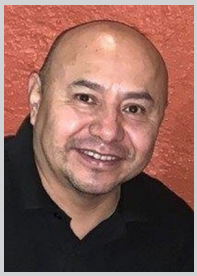

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Secondly, cancer is an assemblage of numerous diseases in which irregular cells divide uncontrollably and continuously proliferate in the blood, resulting in the formation of tumours.[34] At present time, cancer is considered one of the leading causes of death in the world and a significant barrier to increasing life expectancy.[35,36] According to the type of tissue affected, cancer can be classified into four main groups: leukaemia, lymphoma, sarcoma, and carcinoma.[37–39] Carcinoma is any type of cancer that affects the epithelium, it is found both in the skin and in other tissues related to internal organs.[40] On the other hand, sarcoma is a kind of cancer that affects mesenchymal tissue such as bone, fibrous tissue, muscle, adipose tissue, or other connective tissues.[41] In addition, leukaemia is defined as progressive cancer within the bone marrow arising from the uncontrolled proliferation of developing leukocytes, and ultimately lymphoma, which is cancer arising from the immune system.[42] In compliance with the WHO, in 2020 there were 18.1 million cancer cases around the globe. Of these cases, 2.26 million were related to breast carcinoma, 2.20 million to lung carcinoma, and 1.93 million to lung carcinoma. During the same year, 1.39 million cases were reported in Latin America. Of all these, prostate, breast and colorectal carcinoma were the most frequent, with an accumulated number of about 2 million cases each. In this respect, researchers and physicians are constantly working to develop the best treatments and decrease cancer cases in the population.[43–45]

There are different treatments to combat cancer, but the three most used are surgery, radiotherapy and chemotherapy.[46] Specifically, chemotherapy is considered the most widely used option for cancer treatment, where platinum-based metallodrugs have been applied as anticancer agents for several decades.[47] However, these compounds do not have selective cytotoxicity and induce serious side effects, such as temporal hair loss, drug resistance, and kidney and liver damage, among others.[48,49] For this reason, the reduction of the toxicity of metal ions and their reactivity is the principal obstacle to be solved during the development of metal-based drugs. A great effort has been made to try to reduce dependence on platinum-derived drugs and discover new antitumor agents.[50] Therefore, research in the field of metallodrugs has increased constantly in recent years. Specifically, the use of transition metal complexes in medical practice for the treatment of diverse illnesses is a promising application that has demonstrated impressive results.[51] In addition, it is expected that in the near future the development of novel drugs can improve pharmacological results and reduce side effects. In this regard, coordination chemistry is achieving important advances in cancer therapy with selectively cytotoxic transition metal complexes. Numerous variables such as metal ion, ligands, and metal-ligand interaction offer multiple ways to tune the selectivity and reactivity of coordination complexes, which provides a vast collection of metallodrugs that can display a higher diversity of functions compared to traditional organic compounds.[52]

Additionally, diverse transition metal complexes based on *d*-block possess a varied range of coordination geometries and oxidation states, that allow the modulation of steric or electronic properties,[53] which influence the thermodynamics and kinetics during biochemical reactions.[54] At present time, some transition metal metallodrugs have been approved for clinical and diagnosis use, whilst others are in clinical trials stages.[55,56] Due to the wide area of opportunity for metallodrugs in cancer treatment, this review summarizes recent advances in coordination complexes based on tridentate Schiff bases derived from salicylaldehyde, with antitumor and anticancer properties. Diverse complexes presented in this review are promising and some of them have impressive selectivity towards various cell lines without affecting non-cancer cells. It is important to note that the order of the elements in the text is not related to their location in the periodic table, but to the number of compounds that report their antineoplastic activity (Figure 1).

2. Complexes with tridentate Schiff bases ONO with metals of the first transition series

2.1. Copper(II) compounds

2.1.1. Compounds with coordination number four

The design of new molecules is of vital relevance for the discovery of new therapeutic chemopharmaceuticals. Under this premise, families of coordination compounds with metals other than platinum have been studied, highlighting copper compounds. Copper molecules have sizes and geometries suitable for use in chemotherapy.[57] Therefore, in this section, we will mainly describe copper compounds coordinated to ONO ligands, verifying their possible use as anticancer agents. In the first case, copper radioisotopes have been considered suitable for imaging and/or radiotherapy due to their stability. In particular, ^{61}Cu, with an excellent $T_{1/2}$ of 3.33 h, is used for application in the PET method and molecular imaging. In this line, Jalilian *et al.* reported the synthesis of **Cu-01** and **Cu-02** complexes. To evaluate radiocopper activity, **Cu-02** was administered to the tumour- and normal-bearing mice by biodistribu-

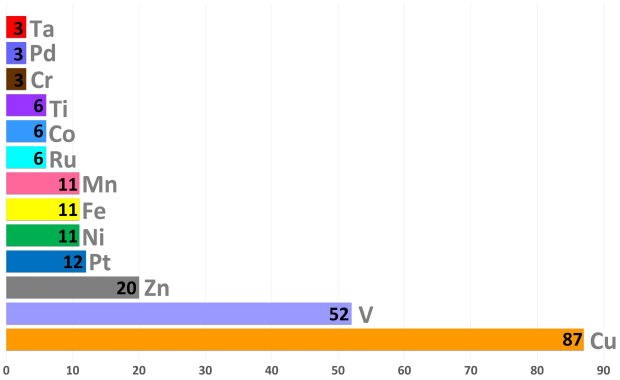

Figure 1. Number of recently published compounds evaluated for their cytotoxic or antiproliferative activity.

tion studies (up to 3 h). Due to the presence of several polar functional groups in its structure, the complex can penetrate all perfused cells because it is highly lipophilic. The best tumour accumulation result was at 2 h (tumour/blood and tumour/muscle ratios were 3.43 and 25.64, respectively). Based on the results obtained, **Cu-02** has potential application as a PET radiotracer for tumour imaging.[58]

HSA-based drug delivery systems are among the most promising due to their advantages over other drug carriers. HSA is the most plentiful protein in plasma, it has many special active residues, such as cysteine and lysine, and it also has several binding sites for a diverse group of exogenous and endogenous compounds. This feature of HSA is used to increase the targeting and efficiency of anticancer agents. **Cu-03** with square-planar geometry binds to the hydrophobic cavity in subdomain IIA of HSA to obtain **Cu-04** with the same geometry for copper(II), displacing pyridine by His-242. The two complexes were tested on cancer cells: Hep-G2, BEL-7402, BEL-7404, and normal cells: HL-7702 using the MTT assay (48 h of treatment) and cisplatin as a positive control. Remarkably, **Cu-04** (IC_{50} values, Hep-G2 5.18 ± 0.19 μM, BEL-7402 6.23 ± 0.12 μM, BEL-7404 8.92 ± 0.21 μM and HL-7702 12.18 ± 0.15 μM) had a stronger anticancer capacity relative to **Cu-03** (IC_{50} values, Hep-G2 7.27 ± 0.26 μM, BEL-7402 8.66 ± 0.22 μM, BEL-7404 11.84 ± 0.31 μM and HL-7702 12.02 ± 0.16 μM). **Cu-04** selectively accumulated in cancer cells increasing their cytotoxicity up to approximately 1.4-fold but did not affect normal cells. Both compounds improved the IC_{50} values reported in this work for cisplatin (Hep-G2 18.34 ± 1.92 μM, BEL-7402 15.84 ± 1.32 μM, BEL-7404 14.37 ± 1.42 μM and HL-7702 9.67 ± 1.23 μM). Additional results indicated that both complexes promote cancer cell apoptosis, can cause cell accumulation in the G_0/G_1 phase of the cell cycle by delaying or inhibiting their progression and can produce ROS.[59]

Paeonol has been used in European and Asian countries in herbal medicine. Moreover, the interactions of paeonol with HSA have been investigated, which makes it an excellent ligand that, transformed into a Schiff base, allows the development of new compounds with possible anticancer activity. The copper(II) complexes (**Cu-05**–**Cu-07**) were obtained from a Schiff-base ligand derived from paeonol. **Cu-05** was selected to explore its DNA-binding properties, which are highly affected by complex structure and its methanol solubility, it was also tested for its cytotoxicity on Hep-2 cells after **Cu-05** interacted with tumour cells for 24, 48 and 72 h. The nearly square planar geometry of **Cu-05** allows it to easily intercalate into DNA, exhibiting moderate binding capacity and groove DNA-binding mode. On the other hand, **Cu-05** showed more than 95% inhibition at a 1.25×10^{-4} M concentration, improving the results achieved by the free ligand, which only showed 20% inhibition, when passing from 24 to 72 h of treatment[60] (Figure 2, Table 1).

2.1.2. Compounds with coordination numbers five and six

Koley *et. al.*, synthesized **Cu-08** and **Cu-09** using *imdz* and *phen* as co-ligands, respectively. The coordination geometry of monomeric copper(II) in **Cu-09** is square pyramidal, while in **Cu-08** is square planar. In both structures, the nitrogen iminic of the Schiff base is placed *trans* to the nitrogen atom of the co-ligand. The complexes were tested on malignant (A-549 and MCF-7) and benign (L-132 and HaCaT) cell lines by MTT assay and cisplatin as a positive control after 24 h of incubation. The IC_{50} values of **Cu-08** and **Cu-09** for A-549 (0.59 and 0.67 μM, respectively) were better than the reported IC_{50} value for cisplatin (4.13 μM for A-549), while for MCF-7 the results were moderate for both complexes (8.88 and 6.30 μM, respectively) with respect to cisplatin (3.92 μM for MCF-7). Both compounds

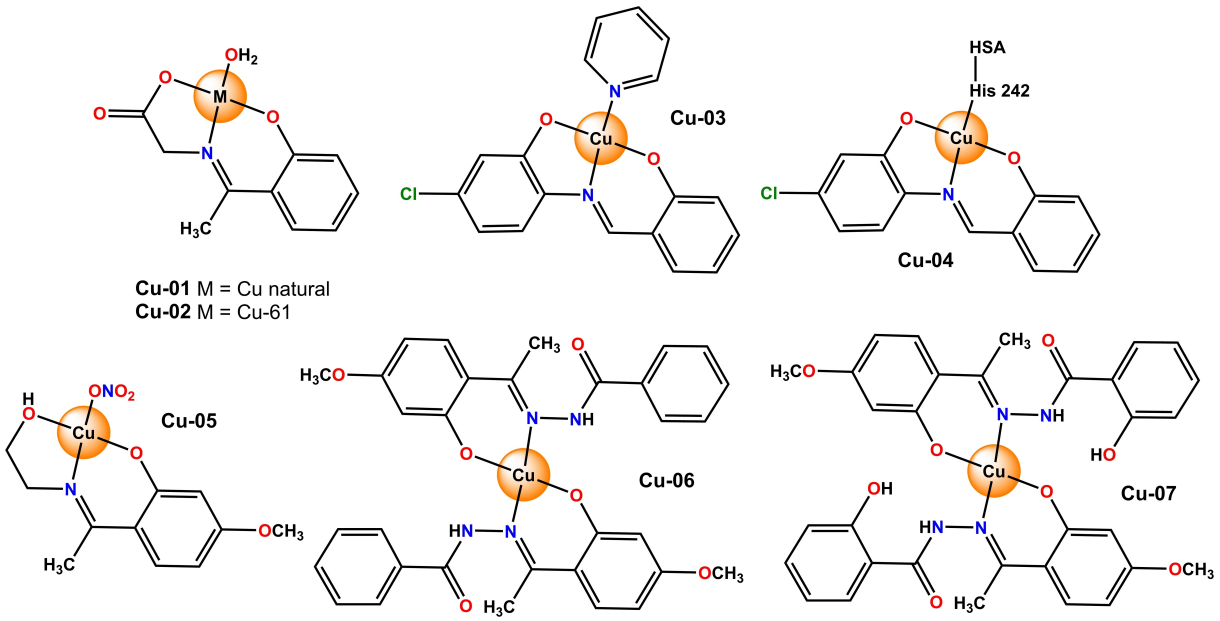

Figure 2. Copper(II) complexes (**Cu-01**–**Cu-08**) obtained from tridentate Schiff bases ONO.

Table 1. Summary of tetracoordinated copper(II) complexes with better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [μM]	Main feature	Ref.
Cu-03	Square planar	48	Hep-G2	7.27 ± 0.26	Anticancer activity depends on the binding of the complex with HSA that acts as a drug delivery system	[59]
			BEL-7402	8.66 ± 0.22		
			BEL-7404	11.84 ± 0.31		
			HL-7702	12.02 ± 0.16		
Cu-04	Square planar		Hep-G2	5.18 ± 0.19		
			BEL-7402	6.23 ± 0.12		
			BEL-7404	8.92 ± 0.21		
			HL-7702	12.18 ± 0.15		
Cu-76	Tetrahedral		HCT-116	3.26[a]	The anticancer activity depends on the positive charge of the central metal, the nature of the ligand and the hydrogen bonds	[119]
			MCF-7	7.40[a]		

[a] $\mu g\,\mu L^{-1}$.

were less toxic to L-132 normal cells (8.95 and 7.60 μM, respectively), suggesting their suitability as anticancer agents, specifically for the A-549 cell line. Furthermore, the viscosity measurements suggest an intercalated mode of binding of both complexes to DNA. **Cu-08** binds more strongly to DNA (calf thymus) due to the planar square structure coordinate to copper(II) that allows the intercalated ligand to insert into the DNA base pair. However, intriguing results were also reported for the HaCaT normal cell line (0.60 and 0.99 μM, respectively), which could contradict the proposal of the authors.[61]

Complexes derived from salicylaldehyde and amino acids that form versatile Schiff base ligands are suitable for exploring greater effectiveness and lower toxicity in drugs based mainly on transition metals. Li *et. al.*, reported the synthesis of **Cu-10**, **Cu-11** and **Cu-12**, these copper(II) complexes have square planar, square pyramidal and octahedral distorted geometries, respectively. All complexes were tested for cytotoxic activity in NCI-H460 and Hep-G2 cells using the MTT assay (48 h of incubation). The cytotoxicity of **Cu-11** was better ($IC_{50} = 13.2 \pm 4.6$ and 14.3 ± 5.3 μM, respectively) than the cytotoxicity of **Cu-12** ($IC_{50} = 47.9 \pm 7.9$ and 33.3 ± 7.6 μM, respectively) and **Cu-10** ($IC_{50} = 48.5 \pm 9.6$ and 33.1 ± 6.6 μM, respectively); however, there was no comparative study with a commercial drug. Furthermore, **Cu-11** showed more efficient DNA-binding due to the presence of an ancillary ligand (*bpy*) that led to two mutually perpendicular planes, which enlarge the binding sites, improving the intercalative interaction between DNA and complexes. Fluorescence spectral methods and viscosity experiments suggest that the complexes interacted with DNA (calf thymus) in an intercalative mode. All three derivatives exhibited efficient oxidative cleavage of supercoiled DNA in the presence of hydrogen peroxide.[62]

The coordination behaviour of *N*-(2-hydroxyacetophenone)glycinate (NHAG) has been explored to obtain new non-toxic, water-soluble copper(II) coordination compounds. Majumder *et al.* obtained **Cu-13** using NHAG as a ligand and studied its cytotoxic and antitumor properties *in vivo*. **Cu-13** was injected intraperitoneally into male Swiss albino mice and then blood was collected at different time intervals. The best dose to avoid haematological toxicity in the spleen and bone marrow was from 6 to 10 $mg\,kg^{-1}$, since no results were shown that evidenced toxicity. Additionally, in both studies, the NHAG ligand was not toxic up to doses of 100 $mg\,kg^{-1}$. Even the ligand was not toxic at a dose of 120 $mg\,kg^{-1}$, but the complex is quite toxic at a dose of 35 $mg\,kg^{-1}$. Finally, **Cu-13** and NHAG did not show antitumor properties *in vivo* as revealed by the value of treated mice compared to control.[63]

Some amino acids are small molecules with planar aromatic moieties capable of intercalating through π–π stacking between RNA bases at specific minor groove sites. Taking this characteristic into account, amino acids have been used as scaffolds to obtain new metal complexes in order to provide new insights into the mechanisms for cancer treatment. Furthermore, the introduction of chirality through the use of amino acids could enrich the pharmacological behaviour of compounds by adopting a specific conformation and offering a selective binding affinity towards chiral biomolecules. Zehra *et al.* used L or D-valine for **Cu-14**–**Cu-15** complexes and L or D-phenylalanine for **Cu-16**–**Cu-17** complexes. All four complexes had a distorted square pyramidal geometry around the copper(II) centre. All compounds were tested in the MCF-7, HeLa and MIA-PaCa-2 cell lines by SRB assay using adriamycin as a positive control (48 h of treatment). The best result was found in the MCF-7 cell line with a GI_{50} value < 1 μM for **Cu-16**, comparable to the value found for the reference drug. This result was related to the planar aromatic group of L-phenylalanine that increased lipophilicity, which improved cell uptake and therefore greater cytotoxic activity. Additionally, the low cytotoxic activity of **Cu-14** and **Cu-15** could be attributed to their polymeric nature. Additional studies demonstrated that all four complexes (**Cu-16** > **Cu-17** > **Cu-14** > **Cu-15**) preferentially interact with RNA compared to DNA *via* intercalative mode. **Cu-16** and **Cu-14** showed a preferential oxidative cleavage mechanism towards plasmid pBR322 DNA mediated by ROS radical scavengers. SEM analyses of the **Cu-16** and **Cu-14** complexes revealed the formation of different morphologies with the DNA/RNA biomolecules. RNA cleavage mechanism caused by **Cu-16** and **Cu-14** was dependent on the time and concentration of the complexes.[64]

The use of ligands derived from bioactive compounds such as amino acids and sulphonamides allows them to be conferred with different physicochemical and pharmacological properties. In addition, N-substituted sulphonamide ligands can act as SOD

mimics, behaving as efficient scavengers of the superoxide anion, which is implicated in DNA damage, cancer, ageing, amount others. **Cu-18** and **Cu-19** were obtained from a Schiff base formed from the reaction between *o*-vanillin and L or D-phenylalanine, using 4-(2-aminoethyl)benzenesulfonamide as co-ligand. Both polymeric complexes are derived from enantiomerically pure ligands and contain a copper(II) metal centre with a distorted square pyramidal geometry. Comparative studies (DNA-binding, Topo I, SOD and cytotoxicity assays) of both enantiomers were performed to assess their enantioselective behaviour at the target site at the molecular level showing that **Cu-18** was more potent compared to **Cu-19**. Both complexes act as Topo I inhibitors and SOD-mimicking agents, so they could be used in cancer therapy. **Cu-18** cleavage efficiency was evaluated, showing efficient single-stranded cleavage of pBR322 DNA mediated through a hydrolytic cleavage pathway. **Cu-18** and **Cu-19** were tested on MCF-7, MIA-PaCa-2, A-498, HeLa, and Hep-G2 cell lines using the SRB assay and adriamycin as positive control. **Cu-18** showed moderate and selective inhibition towards the MCF-7 cell line with a GI_{50} value = 27.28 μg mL^{-1} and TGI value = 59.5 μg mL^{-1}, but in the other cell lines, the results were poor. The best result of **Cu-19** was also in the cell line MCF-7 (GI_{50} value = 45.79 μg mL^{-1} and TGI value = 87.04 μg mL^{-1}), while in the other four lines the result was very weak. Neither compound was able to exceed the activity achieved by the reference drug in all cell lines (GI_{50} < 10 μg mL^{-1} and TGI < 10 μg mL^{-1}).[65]

VB_6 is known to be necessary for the survival and proliferation of cancer cells since they require increased uptake to diffuse it through membrane carriers. On the other hand, BODIPY has a selective ability to locate mitochondria, as well as a strong emissive property and photosensitising ability that is increased by the inclusion of heavy atoms such as iodine. These characteristics were considered by Mukherjee *et al.* to synthesize copper(II) complexes (**Cu-20**–**Cu-22**) with a distorted square-pyramidal geometry around the metal centre. All complexes were tested on cancerous (HeLa, MCF-7 and Hep-G2) and non-cancerous (HPL1D) cell lines using MTT assay and cisplatin as a positive control. **Cu-21** exhibited a photoinduced antiproliferative effect with an IC_{50} value of 13.2 ± 1.7 and 12.4 ± 1.3 μM in light-treated Hep-G2 and HeLa cells; respectively. However, in light-treated MCF-7 cells a lower IC_{50} value of 6.05 ± 1.4 μM was obtained, in addition to a relatively low dark cytotoxicity in all three cell lines (> 25 μM). In addition, **Cu-22** showed low IC_{50} in all photo-exposed cancer cells (Hep-G2 = 0.64 ± 0.14 μM, HeLa = 0.60 ± 0.07 μM and MCF-7 = 0.43 ± 0.09 μM). The dark cytotoxicity of **Cu-22** was > 25 μM in all explored cells, thus showing a high phototoxic index (PI = 40–60) very useful in PDT applications. **Cu-20** did not show any cytotoxicity neither in the dark nor in visible light in all cell lines (IC_{50} > 25 μM). Regarding healthy HPL1D cells, a non-cytotoxic behaviour of all compounds was found both in the dark and in the light. The results suggest that the introduction of iodine atoms in BODIPY enhanced its photosensitizing capacity[66] (Figure 3, Table 2).

2.1.3. Compounds with ancillary ligands derived from bpy and phen

It is known that the ligand *phen* can bind to DNA by intercalated and non-intercalated interactions, either as a free ligand or as part of a metal complex, and has been proposed as an excellent agent for DNA cleavage, binding or oxidative modification. Acilan *et al.* reported the synthesis of **Cu-23**–**Cu-25** using *phen* and its derivatives as co-ligands. Cell viability was tested on cancer cell lines A-549, HCT-116, HeLa, MDA-MB-231 and SH-SY5Y, as well as non-cancer controls HASM-C1 and HASM-C2 by MTT assay after 24 and 72 h of treatment. All three complexes were cytotoxic in all cancer cell lines tested, but only **Cu-24** with square pyramidal geometry showed the best results, even having considerably less toxicity in non-cancer cells [IC_{50}(μM, 72 h) A-549 = 1.93 ± 1.56, HCT-116 = 1.79 ± 0.43, HeLa = 3.13 ± 0.51, MDA-MB-231 = 3.60 ± 0.37, SH-SY5Y = 1.08 ± 0.63, HASM-C1 > 12.50 and HASM-C2 > 12.50]. The presence of the amino group increases the affinity for DNA (calf thymus), possibly due to electrostatic interactions and hydrogen interactions between the positively charged amino group (NH_3^+) and the phosphate and pentose moieties of the DNA. All complexes induced DNA damage due to the increase in ROS, and apoptosis was the main form of cell death[67] (Figure 4).

Table 2. Summary of penta- and hexacoordinated copper(II) complexes with better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [μM]	Main feature	Ref.
Cu-08	Square planar	24	A-549	0.59	Anticancer activity depends on the metal centre and the molecular structure	[61]
			MCF-7	8.88		
			L-132	8.95		
			HaCaT	0.60		
Cu-09			A-549	0.67		
			MCF-7	6.30		
			L-132	7.60		
			HaCaT	0.99		
Cu-22	Square pyramidal	1[a]	Hep-G2	0.64 ± 0.14	Anticancer activity depends on iodine atoms in the co-ligand	[66]
			HeLa	0.60 ± 0.07		
			MCF-7	0.43 ± 0.09		
			HPL1D	> 25		

[a] Photo-exposed.

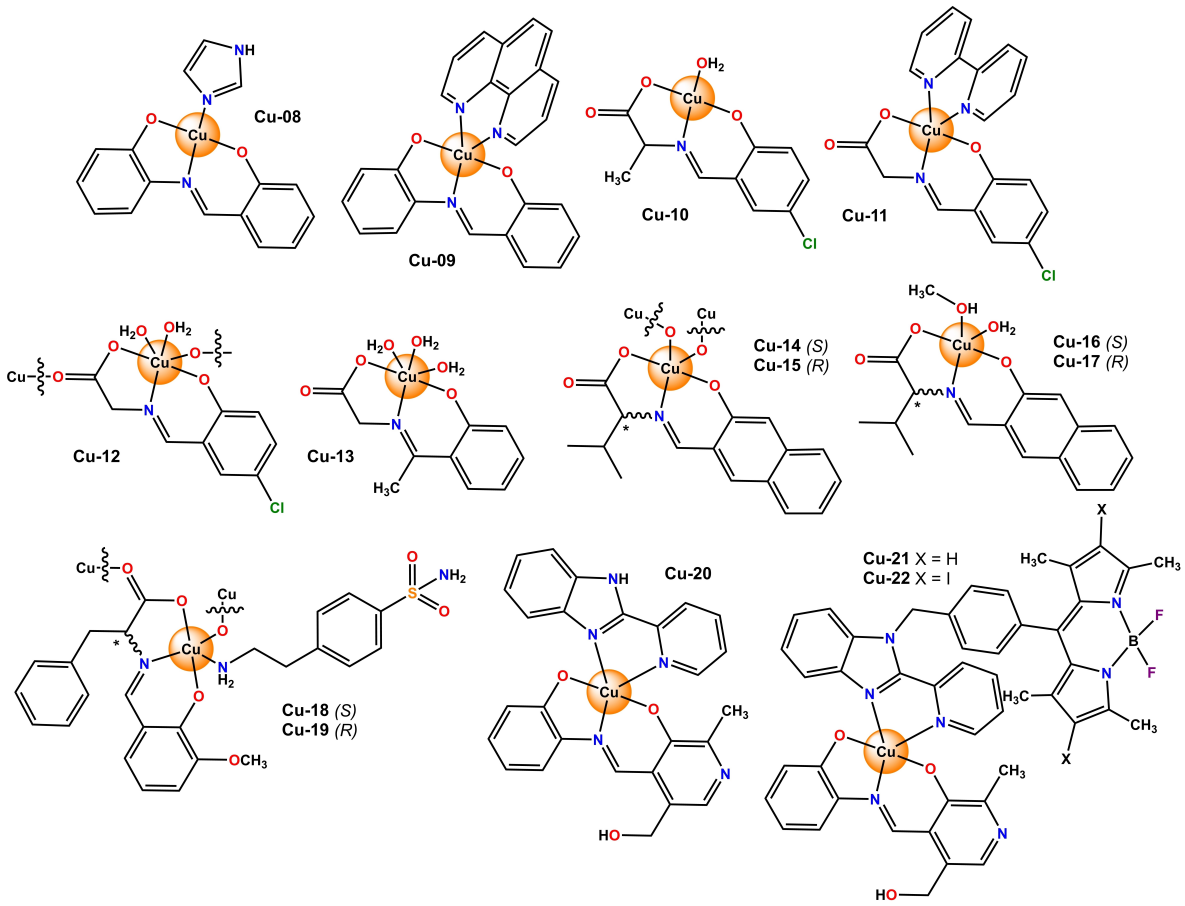

Figure 3. Copper(II) complexes (**Cu-09**–**Cu-22**) obtained from tridentate Schiff bases ONO.

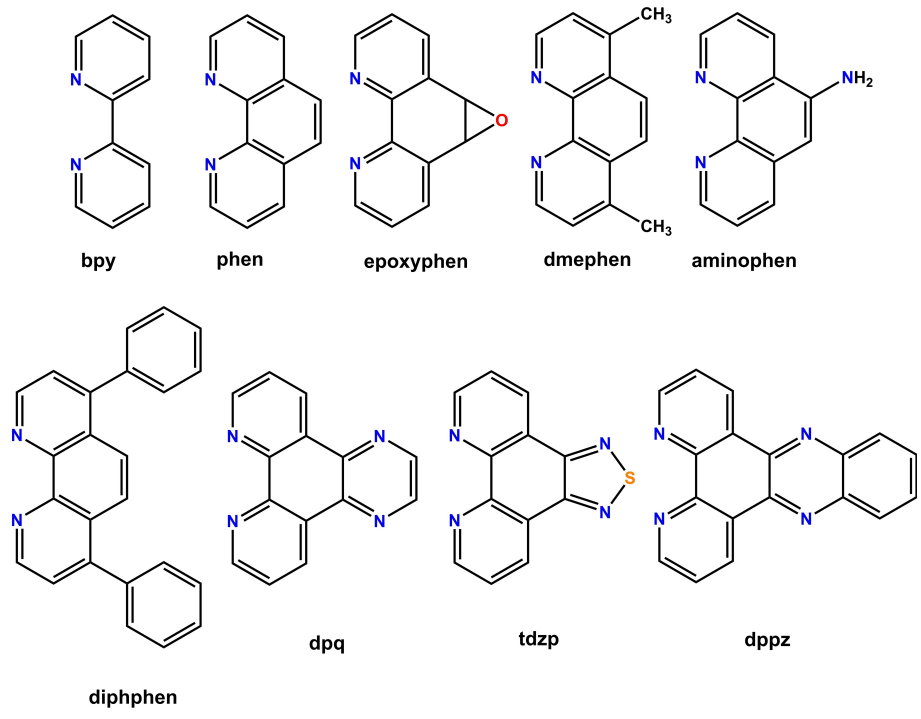

Figure 4. Derivatives of *bpy* and *phen* utilised as co-ligands in the formation of coordination complexes.

The interaction of small molecules such as amino acids with DNA eventually causes DNA damage in cancer cells, inducing cell death by blocking malignant cell division. Theetharappan *et al.* reported the synthesis of three mixed copper(II) complexes (**Cu-26**–**Cu-28**) using *o*-vanillin and L-tryptophan to form the Schiff base and different co-ligands (*bpy*, *phen* and *dmephen*, respectively). Cytotoxic activity on the cancer cell line MCF-7 was determined using the MTT assay (24 h of treatment) and cisplatin as a positive control. All three complexes with square pyramidal geometry showed potent cytotoxic activity against MCF-7 cells (IC_{50}, **Cu-26** = 36.38 ± 0.9 μM, **Cu-27** = 28.72 ± 1.1 μM and **Cu-28** = 31.70 ± 0.5 μM), but with less effect than cisplatin (IC_{50} = 26.70 ± 2.2 μM), markedly suppressing cell propagation in a dose-dependent manner. Additional studies demonstrated that the complexes interact with DNA (calf thymus) *via* intercalation and induce little change in the secondary structure of BSA. In addition, all three complexes cleaved supercoiled pUC19 DNA and showed condensed apoptotic nuclei in cancer cells, as well as mitochondrial membrane loss, inducing apoptosis in cancer cells.[68]

Continuing with the use of amino acids, Sasikumar *et al.* reported the synthesis of copper(II) complexes (**Cu-29** and **Cu-30**) using L-alanine derivatives as Schiff bases construction scaffolds, as well as *bpy* or *phen* as auxiliary ligands; respectively. **Cu-29** and **Cu-30** with square pyramidal geometry were analysed in the cancer cell lines A-549, HeLa, MCF-7; as well as the normal cell line NHDF by MTT assay using cisplatin as a positive control (48 h of treatment). From the IC_{50} values, it was observed that as the concentration increased, cell viability decreased. **Cu-30** (IC_{50}, A-549 38.01 ± 0.54 μM, HeLa 39.65 ± 0.44 μM, MCF-7 29.63 ± 0.54 μM and NHDF 74.28 μM) exhibited higher anticancer ability compared to **Cu-29** (IC_{50}, A-549 46.73 ± 0.81 μM, HeLa 54.37 ± 0.24 μM, MCF-7 45.16 ± 0.57 μM and NHDF 59.94 μM). Neither of the two compounds managed to exceed the values found for cisplatin (IC_{50}, A-549 17.91 ± 0.12 μM, HeLa 16.13 ± 0.16 μM, MCF-7 13.01 ± 0.44 μM and NHDF 94.12 μM). This result was attributed to the fact that **Cu-30** with the *phen* co-ligand has more conjugation and aromaticity compared to **Cu-29** with the *bpy* co-ligand. In addition, the strong hydrophobic interaction of **Cu-30** with DNA and proteins leads to its increased cytotoxic activity.[69]

Copper(II) complexes with polypyridyl ligands and Schiff bases are capable of binding to HSA at physiological pH, undergoing good cellular absorption, generating intracellular ROS level imbalance, inducing the G-rich sequence of VEGF DNA, unbalancing proapoptotic protein BAX, activating Erk1/2 and Akt as important signalling pathways and thus exhibiting significant anticancer and antiangiogenic potential. In this way, **Cu-31** and **Cu-32** with a slightly distorted tetragonal pyramid geometry were obtained using *bpy* and *phen* as co-ligands, as well as a Schiff base derived from L-phenylalanine and 5-bromo-3-methoxy-salicylaldehyde. Cytotoxicity was evaluated using the MTT assay after 48 h of incubation against two cancer cell types (C33A and HeLa), one non-cancer cell type (HUVEC) and cisplatin as a positive control. Both complexes exhibited dose-dependent cytotoxicity and presented a preference for cancer cells over non-cancer cells. **Cu-32** showed better growth inhibition in all cell lines (HUVEC = 3.60 ± 0.05, C33 A 2.22 ± 0.17 and HeLa = 1.02 ± 0.03 μM), even surpassing the results found for the reference drug cisplatin HUVEC = 48.07 ± 0.72, C33A 16.01 ± 0.32 and HeLa = 10.77 ± 0.38 μM). Additionally, both complexes induce apoptosis, inhibit proliferation and angiogenesis, and suppress migration and metastasis. The authors argued that the significant differences in anticancer activity could be attributed to the presence of the co-ligand *phen*.[70]

In the search for novel coordination complexes with biological activity, the characteristics and properties of amino acids and polypyridyl ligands have been studied. Zuo *et al.* reported the copper(II) complexes, where the central atom adopted a distorted square pyramidal geometry. **Cu-33** and **Cu-34** contain in their structure a Schiff base derived from *o*-vanillin and L-methionine, while **Cu-35** and **Cu-36** contain a Schiff base derived from *o*-vanillin and L-valine. On the other hand, *bpy* was used as auxiliary ligand for **Cu-33** and **Cu-35**, while *phen* was used for **Cu-34** and **Cu-36**. The authors found that **Cu-34** and **Cu-36**, which contain *phen* as a co-ligand, inhibit cell proliferation by inducing apoptosis in MDA-MB-231, MCF-7 and PC-3 cancer cells, and they do so through inhibition of the ubiquitin-proteasome pathway. Only **Cu-34** and **Cu-36** suppressed the proliferation of human cancer cells in a concentration-dependent manner, inhibiting the proliferation of MDA-MB-231 cells by 99% and 98%, respectively, at a concentration of 20 μM after 24 h of treatment (MTT assay). In contrast, **Cu-33** and **Cu-35** exhibited very little proteasome inhibitory and cell death-inducing activity in MDA-MB-231 cells. In addition, **Cu-34** and **Cu-36**, but not **Cu-33** and **Cu-35**, were reported to have similar effects on the other two cancer cell lines (MCF-7 and PC-3). The results in **Cu-34** and **Cu-36** were related to the hydrophobic character due to the presence of ancillary ligand *phen*, which is a flat and rigid molecule with a higher degree of conjugation compared to *bpy*.[71]

Aromatic nitrogen heterocycles such as *bpy* and *phen* are important due to their high SOD activity, propensity to bind DNA, and high cleavage efficiency. In addition, *phen* promotes the entry of copper(II) complexes into tumour cells, inducing apoptosis by inhibiting proteasome activity. In this way, Ma *et al.* synthesized **Cu-37** using a Schiff base as the primary ligand and *phen* as the secondary ligand. This complex exhibited a pentacoordinate structure with a distorted square pyramidal coordination environment obtained by XRD. The cleavage and binding properties of **Cu-37** in biomacromolecules such as BSA and DNA were evaluated by experimental methods. In addition, the cytotoxic activity of **Cu-37** on HeLa, MCF-7 and Hep-G2 cell lines was tested using the MTT assay after 48 h of treatment using cisplatin as the positive control. In DNA cleavage experiments in the presence of hydrogen peroxide, **Cu-37** was proposed to cause oxidative cleavage of DNA, causing double-strand breaks at certain concentrations. The results of DNA-binding studies (calf thymus) confirm that **Cu-37** interacts through an intercalative mode. Additionally, the strong interaction with HSA suggested that **Cu-37** could be transported by proteins. **Cu-37** exhibited a more significant cytotoxicity on cell lines tested (IC_{50}, HeLa = 0.46 ± 0.01 μM, MCF-7 = 0.94 ± 0.06 μM, Hep-G2 = 0.47 ± 0.06 μM) compared to

cisplatin (IC_{50}, HeLa = 10.61 ± 0.86 μM, MCF-7 = 13.58 ± 1.42 μM, Hep-G2 = 8.17 ± 0.66 μM). The authors suggested that **Cu-37** induced apoptosis with cell cycle arrest and ROS production in a dose-dependent manner, inducing severe fragmentation through an oxidative DNA damage pathway.[72]

Kiran *et al.* reported the synthesis of eight pentacoordinate complexes using polypyridyl co-ligands to improve the planarity, intercalation behaviour, binding potential and nucleolytic efficiency of compounds towards DNA. **Cu-38**–**Cu-41** were obtained using N-(2-hydroxy-1-naphthalidene)-2-aminophenol as main ligand, while **Cu-42**–**Cu-45** were obtained using N-(2-hydroxy-1-naphthalidene)-2-mercaptoaniline as main ligand, in both cases *bpy*, *phen*, *dpq* and *dppz* were used as co-ligands. DNA-binding and cleavage properties of all eight complexes were analysed, but only the cytotoxic activity of **Cu-41** and **Cu-45** on Hep-G2 cells was evaluated by MTT assay (24 h of incubation). All complexes showed the ability to bind to DNA *via* an intercalation binding mode with the order **Cu-41**, **Cu-45** > **Cu-40**, **Cu-44** > **Cu-39**, **Cu-43** > **Cu-38**, **Cu-42**. Furthermore, all eight complexes showed potent cleavage of pBR322 DNA, with **Cu-41** and **Cu-45** exhibiting high cleavage efficiency compared to other derivatives. Due to these results, **Cu-41** and **Cu-45** exhibited significant cytotoxicity in Hep-G2 cells with IC_{50} values of 40.82 and 29.74 μg mL^{-1}, respectively. However, the authors do not discuss the relevance of IC_{50} value *versus* a control drug[73] (Figure 5, Table 3).

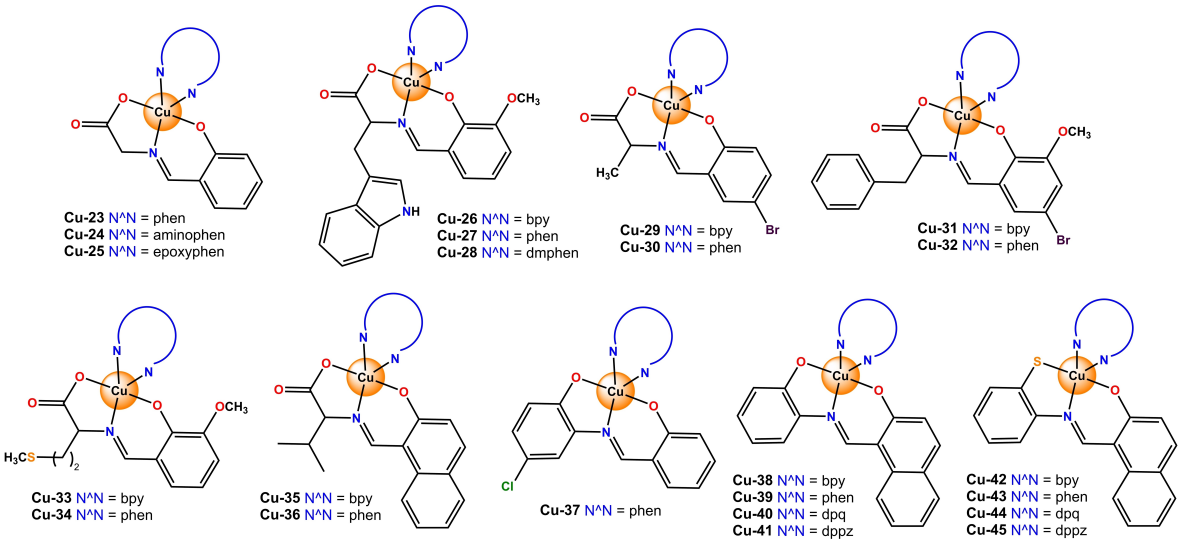

Figure 5. Copper(II) complexes (**Cu-23**–**Cu-45**) obtained from tridentate Schiff bases ONO and ONS.

Table 3. Summary of pentacoordinated copper(II) complexes with ancillary ligands and better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [μM]	Main feature	Ref.
Cu-24		72	A-549	1.93 ± 1.56	The anticancer activity depends on the presence of the amino group in the *phen* co-ligand	[67]
			HCT-116	1.79 ± 0.43		
			HeLa	3.13 ± 0.51		
			MDA-MB-231	3.60 ± 0.37		
			SH-SY5Y	1.08 ± 0.63		
			HASM-C1	> 12.50		
			HASM-C2	> 12.50		
Cu-32			HUVEC	3.60 ± 0.05, 2.22 ± 0.17	Anticancer activity depends on the *phen* co-ligand and its aromaticity	[70]
			C33A	1.02 ± 0.03		
			HeLa			
Cu-37	Square pyramidal	48	HeLa	0.46 ± 0.01	Anticancer activity depends on the presence of the *phen* ancillary ligand	[72]
			MCF-7	0.94 ± 0.06		
			Hep-G2	0.47 ± 0.06		
Cu-66			A-2780	0.75 ± 0.2		
			MCF-7	2.5 ± 0.6		
Cu-67			A-2780	0.54 ± 0.2		
			MCF-7	2.7 ± 0.8		
Cu-68		72	A-2780	0.29 ± 0.01	Anticancer activity depends on the presence of the *phen* ancillary ligand	[88]
			MCF-7	3.5 ± 1.2		
			HL-60	1.51 ± 0.37		
			HeLa	4.2 ± 0.6		

2.1.4. Dinuclear and trinuclear compounds

As we have seen so far, essential and non-essential amino acids are excellent candidates for synthesizing Schiff base ligands. Such is the case of L-glutamine and L-asparagine capable of forming Schiff bases when reacting with *o*-vanillin, improving the solubility of copper(II) complexes due to the presence of the hydroxyl group. Xia *et. al.*, considered these features to synthetized the **Cu-46** and **Cu-47** complexes. **Cu-47** is a trinuclear complex with a tetrahedral geometry for its two terminal copper(II) atoms and square pyramidal geometry for its central copper(II) atom, while **Cu-46** is a mononuclear complex with octahedral geometry for its central copper(II) atom. The antiproliferative activity of both complexes was evaluated in MDA-MB-231 cells using the MTT assay (24 h of treatment). **Cu-46** inhibited approximately 40%, while **Cu-47** inhibited approximately 80% of the cell growth of MDA-MB-231 cells at a concentration of 50 μM. In the words of the authors, **Cu-47** is capable of penetrating the cell membrane and transporting more copper(II) ions, binding to cellular targets and inhibiting the growth of MDA-MB-231 cells due to its enhanced hydrophobicity.[74]

GSH is an important intracellular antioxidant, responsible for drug detoxification, maintenance of redox state and cellular protection from damage caused by peroxides, free radicals and toxins. The properties of this tripeptide jointly with the previously described properties of *phen* co-ligand were used to obtain the **Cu-48** and **Cu-49** complexes. The complexes were tested by MTT cell proliferation assay (24 h of incubation) and proteasome activity on the MDA-MB-231 cell line. The impact on biological activity of tetra- and penta-coordinated copper(II) geometry was not discussed in this article. **Cu-48** inhibited cell proliferation by 11, 22 and 20% at a concentration of 15, 30 and 60 μM, respectively; while **Cu-49** inhibited cell proliferation by 92% at a concentration of 15 and 30; as well as 99% at a concentration of 60 μM. Furthermore, **Cu-49** with as *phen* co-ligand induced apoptosis in MDA-MB-231 cells through inhibition of the ubiquitin-proteasome pathway with cellular morphology changes such as rounding and shrinkage, even at low concentrations (10 μM). This result allows the authors to propose that **Cu-49** could be a potential anticancer drug.[75]

Salman *et al.* reported the synthesis of dinuclear copper(II) complexes derived from galactochloralose (**Cu-50** and **Cu-51**) and α-chloralose (**Cu-52** and **Cu-53**), considering that these monosaccharides can form Schiff bases, which contain donor atoms (oxygen and nitrogen) and that have shown interesting biological activities, being of special interest the variety of ways in which they can bind to metal ions. In the crystallographic study of **Cu-51** it was shown that it adopts a slightly distorted square planar geometry in the two copper(II) centres. This geometry applies to the other three isostructural compounds as shown by the spectroscopic data. All complexes were tested on the HeLa cell line using the MTT assay after 24 and 48 h of treatment. **Cu-50** and **Cu-52** exhibited the best results after 48 h (IC_{50} = 7.1 and 68.9 μg mL^{-1}, respectively) due to their lipophilic nature conferred by the *tert*-butyl groups in the Schiff bases, which allows them to be more efficiently absorbed by the cell. However, only **Cu-50** managed to overcome the activity shown by cisplatin under the same experimental conditions (IC_{50} = 7.8 μg mL^{-1})[76] (Figure 6, Table 4).

2.2. Copper(II) clusters

The chemistry of copper gives an exciting approach to the coordination complexes synthesized with this metal, which are useful in cancer therapy, since, as we have seen in this document, they present a cytotoxicity similar to that of platinum-based drugs.[77] Nevertheless, copper offers several advantages compared to platinum; for example, cancer cells require high amounts of copper to carry out their biological processes, which can produce highly selective drugs, reducing the adverse side effects of chemotherapy.[78,79] Additionally, copper is a more available element than platinum, reducing the

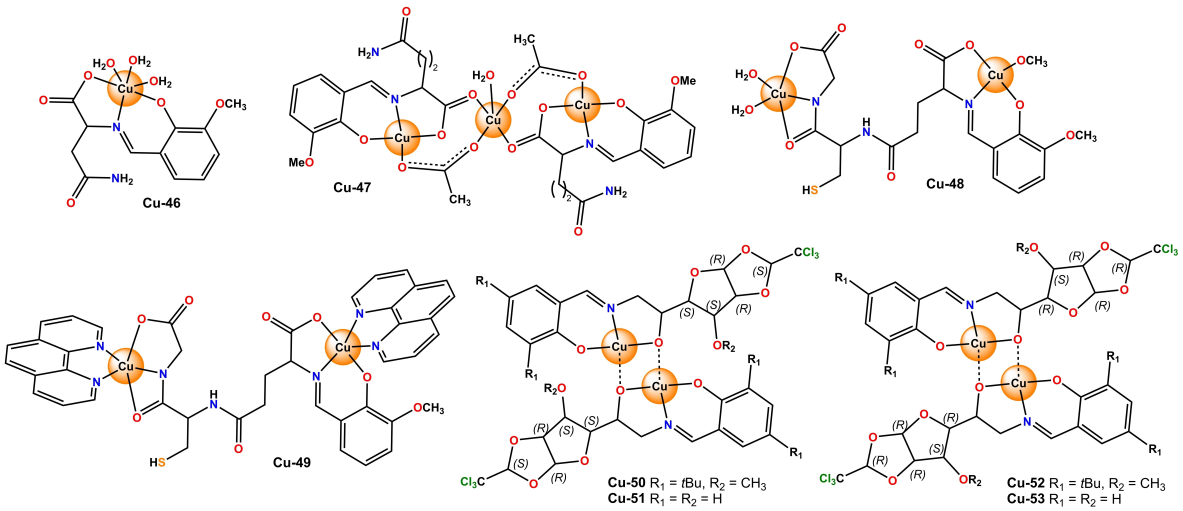

Figure 6. Copper(II) complexes (**Cu-46**–**Cu-53**) obtained from tridentate Schiff bases ONO.

Table 4. Summary of dinuclear and trinuclear copper(II) complexes with better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [$\mu g\,mL^{-1}$]	Main feature	Ref.
Cu-50	Square planar	24 48	HeLa	16.9 7.1	Anticancer activity depends on the lipophilic character conferred by the *tert*-butyl groups, being absorbed more efficiently in the cell	[76]

cost of anticancer drugs based on this element. The effectivity of cupper anticancer drugs depends on the chemical structure of ligands, the metal oxidation state, and the synergy ligand-metal.[80]

In cancer therapy, the pharmacological activity of coordination complexes is highly influenced by drug-DNA interaction. Chiral ligands can enhance this interaction, producing selective binding to target DNA. For example, in 2015, Yan *et al.* proposed the tetranuclear coordination complex **Cu-54** as an anticancer drug. The four copper(II) atoms in the Cu_4O_4 core presented two different geometries and coordination numbers. Two copper(II) atoms were five-coordinate and adopt a distorted square pyramidal geometry. The other two additional copper(II) atoms were six-coordinate and showed an octahedral geometry. The Schiff base ligand exhibited an absolute configuration *(R)* at the chiral carbon. **Cu-54** was studied against HeLa, HL-60, Caco-2 and A-549 cancer cell lines using the MTT method after 48 h of treatment. The IC_{50} values determined for each cancer cell line were 13.50 ± 1.21, 13.85 ± 1.39, 13.88 ± 1.22, and 20.01 ± 1.09 μM, representing a high cytotoxicity; nonetheless, these studies were not carried out in the presence of any reference drug. The coordination complex showed higher anticancer activity than the free ONO Schiff base ($IC_{50} >$ 100 μM), which was attributed to the low polarization of the cluster, which promotes its insertion across the cell membrane. Spectroscopy methods showed an interaction *via* the intercalative mode and a high K_b, which indicates a strong **Cu-54**/DNA (calf thymus) interaction. Therefore, the high cytotoxicity of **Cu-54** is associated with the strong interaction with DNA, promoted by chirality.[81]

Polynuclear coordination complexes have shown excellent redox properties, making them suitable options to induce cell death through ROS. The anticancer activity of polynuclear coordination complexes is influenced by the topology of the metal centre, being the cubane structure of special interest. For instance, in 2017 Tabassum *et al.* synthesized the tetranuclear coordination complex of copper(II) labelled as **Cu-55**. This compound presents an open cubane structure with copper(II) atoms disposed in an extended "butterfly-like" arrangement. The tetranuclear Cu_4O_4 core showed four copper(II) atoms with non-equivalent symmetry. One pair is five-coordinated and exhibited a square pyramidal geometry, whereas the second pair is six-coordinated and showed an octahedral geometry. **Cu-55** was evaluated against PC-3 and K-562 cancer cell lines after 48 h of treatment by semi-automated SRB assay to check cell proliferation after treatment. Additionally, **Cu-55** presented an activity close to the anticancer drug adriamycin (**Cu-55**, $GI_{50} =$ 35.3 and 32.2 $\mu g\,mL^{-1}$ for PC-3 and K-562, respectively; adriamycin, $GI_{50} < 10\ \mu g\,mL^{-1}$ in both cell lines). Spectroscopic results indicated that **Cu-55** binds to DNA (calf thymus) through the electrostatic mode. **Cu-55** also interacts with HSA and is associated with the microenvironment of the Trp-214 residue. **Cu-55** showed significant nuclease activity causing single-strand breaks, confirming the contribution of ROS. The interaction of **Cu-55** with HSA and DNA was confirmed by molecular docking studies.[82]

A year later, Usman *et al.* synthesized the tetranuclear copper(II) coordination complexes **Cu-56** and **Cu-57**. The first compound showed a classic closed Cu_4O_4 cubane structure, while the second compound showed a less common open Cu_4O_4 cubane structure. The geometries determined around the copper(II) atoms in **Cu-56** and **Cu-57** were distorted octahedral and distorted octahedral/square pyramidal, respectively. **Cu-56** and **Cu-57** were evaluated against Hep-G2 and MCF-7 cancer cell lines after 24 h of treatment using MTT method. Both compounds showed high cytotoxicity towards MCF-7 ($IC_{50} = 17$ and 20 μM, respectively) and moderate activity against Hep-G2 ($IC_{50} = 30$ and 35 μM, respectively). The higher anticancer activity of **Cu-56** could be associated with a higher production of ROS, which would be related to its closed cubane structure, its higher DNA-binding affinity and its lower LUMO energy compared to **Cu-57**. Additional results revealed oxidative cleavage of DNA *via* ROS. In addition, ROS and TBARS levels were amplified in cancer lines while GSH levels decreased, showing the role of ROS in the apoptosis induced by **Cu-56** and **Cu-57**, validating their possible use as efficient anticancer agents.[83]

In 2015, Niu *et. al.* proposed the tetranuclear copper(II) coordination complex **Cu-58** as an anticancer drug. **Cu-58** presented two copper(II) metal centres with distorted octahedral geometry and two more with square pyramidal geometry. After 48 h of treatment (MTT assay), **Cu-58** was evaluated against cancer cell lines A-549, HCT-116, HL-60 and K-562, showing higher cytotoxicity than cisplatin (**Cu-58**, $IC_{50} = 16.05$, 30.02, 13.17 and 27.28 μM, respectively; cisplatin $IC_{50} > 50$ μM in all four cell lines). These results were attributed to a moderate interaction between **Cu-58** and DNA (calf thymus), through an intercalative mode, which was mainly related to the Cu_4O_4 (boat-shaped) tetranuclear coordination sphere and the electron-donor OCH_3 group of the ligand. By way of comparison, a non-substituted mononuclear analogue exhibited a lower intrinsic K_b and thus higher IC_{50} values in all four cell lines. On the other hand, the intrinsic K_b calculated for the **Cu-58**/BSA interaction showed a moderate interaction associated with polynuclearity and ligand substitution. This result is important because it is useful to understand the **Cu-58** transport and

delivery. Other relevant results reported in this article are discussed in section 2.5.[84] In this same line of work, in 2019, Chang *et al.* synthesized the chiral coordination complex of copper(II) labelled as **Cu-59**. The central copper(II) atoms in this compound showed a distorted square pyramidal geometry. This is the second report where an enantiomerically pure Schiff base with an absolute configuration *(R)* was used. Using the MTT method, the cytotoxicity of **Cu-59** against three cancer cell lines (HeLa, MDA-MB-231 and A-549) was evaluated, 48 h after administration at different concentrations of **Cu-59**, showing a higher activity than cisplatin (**Cu-59**, $IC_{50} = 17.94 \pm 1.25$, 6.20 ± 0.79 and 29.68 ± 1.47 μM, respectively; cisplatin, $IC_{50} > 60$ μM). The chirality of the ligand and the nuclearity of the cluster probably promote a strong interaction of **Cu-59** with DNA (calf thymus) through electrostatic and groove binding, which is crucial to causing cell death. In addition, **Cu-59** showed a high affinity for BSA proteins, which would suggest an efficient drug delivery Other relevant results reported in this article are discussed in section 2.6.[85]

It has been reported that the stereoisomers usually present different biological activities. While one isomer may exhibit beneficial pharmacological properties, the other may be inactive and even produce undesirable effects. In this way, the study of the biological activity of stereoisomers is crucial to developing highly efficient and safe anticancer drugs. In 2016, again Niu *et al.* synthesized the **Cu-60** and **Cu-61** stereoisomers, which were obtained from a pair of Schiff bases with *(R)* and *(S)* configurations at the chiral carbon, respectively. These copper(II) coordination complexes contain a closed cubane-like tetranuclear cluster (Cu_4O_4) with distorted octahedral geometry in most of the metal centres. **Cu-60** *(R)* and **Cu-61** *(S)* were evaluated against four types of human cancer cell lines (A-549, HeLa, HL-60 and Caco-2) after 48 h of treatment (MTT assay), showing a higher anticancer activity than cisplatin. For **Cu-60**, $IC_{50} = 18.12 \pm 1.13$, 12.67 ± 1.29, 11.83 ± 1.43 and 15.61 ± 1.15 μM respectively; for **Cu-61**, IC_{50} (μM) $= 16.21 \pm 1.41$, 11.91 ± 1.17, 10.97 ± 1.22, and 16.24 ± 1.41, respectively; for cisplatin, $IC_{50} > 100$ μM in all cases. The authors also reported the IC_{50} values of the Schiff bases used and in both cases, the result was greater than 100 μM. In general, the highest cytotoxicity of **Cu-61** was associated with the *(S)* configuration of the coordinated ligand that enhanced its non-intercalative interaction with DNA (calf thymus), as evidenced by spectroscopy, viscosity and thermal denaturation studies. Additional studies showed that **Cu-61** also presented a stronger interaction than **Cu-60** with BSA proteins, indicating better drug transport and delivery.[86]

Adding amino acids and amino alcohols to the ligand structure is an exciting way to induce chirality in their coordination complexes. The use of methionine derivatives in ONO ligands is an interesting strategy in the design of chiral Schiff bases, since this amino acid or amino alcohol could confer different pharmacological properties to them. For example, methionine presents a protective effect on the myocardium, it is an antidepressant, decreases blood pressure and prevents the harmful effects of toxic metals and non-metals in the human body. In 2020, Zhang *et al.* utilised a modified ligand with ONO-(L)methioninol structure to synthesize the tetranuclear copper(II) coordination complexes **Cu-62** and **Cu-63**. The clusters showed an open-Cu_4O_4 core for **Cu-62** and closed-Cu_4O_4 core for **Cu-63**. The metal centres for **Cu-63** presented a distorted octahedral geometry and for **Cu-62** a mixture of distorted geometries (two square pyramidal and two octahedral structures). **Cu-62** and **Cu-63** were evaluated against MDA-MB-231 and HUVEC cells using the MTT method and 48 h of exposure. Both compounds showed comparable IC_{50} values with cisplatin (**Cu-62**, 10.02 ± 0.10 and 10.94 ± 0.21 μM; **Cu-63**, 12.65 ± 0.21 and 14.62 ± 0.09 μM; cisplatin 10.02 ± 0.27 and 7.13 ± 0.10 μM; for MDA-MB-231 and HUVEC cells, respectively), which represents a high anticancer activity. According to the authors, the higher cytotoxicity of **Cu-62** was related to the halogen substituents (Br and Cl), which probably enhance the drug interaction with DNA. Moreover, the authors reported that both metal complexes can, in addition to inhibiting cell proliferation, induce apoptosis, inhibit angiogenesis and cancer growth, as well as suppress metastasis and migration. These antiangiogenic and anticancer functions are achieved by activating major proteins or their phosphorylated molecules through the VEGF/VEGFR2 signalling pathway, destroying the mitochondrial membrane and damaging the ROS level [87] (Figure 7, Table 5).

2.3. Vanadium(IV/V) compounds

2.3.1. Compounds with vanadium(IV) and ancillary ligands derived from bpy and phen

Many examples of *d*-block metals that coordinate with Schiff bases have been widely described in the literature; especially, the chiral compounds that are at the forefront of pharmaceutical research. Furthermore, it is known that chiral amino acids can be utilised to prepare better-targeted drugs and bioactive materials. Therefore, adding an amino acid moiety offers great potential to increase the solubility of the molecule and minimize its toxicity. In the same vein, heterocyclic compounds such as Schiff bases are important biological building blocks that are present in many existing pharmaceuticals. Correia *et al.* reported vanadium(IV) and copper(II) complexes coordinated with Schiff base-type ligands, and co-ligands such as *bpy* and *phen*. The amino acids employed (glycine, L or D-alanine and L-phenylalanine) were dissolved in water and an equimolar amount of salicylaldehyde in ethanol was added to obtain the ligands, followed by the addition of vanadium(IV) and copper(II) salts. The copper(II) compounds (**Cu-64**-**Cu-68**) were pentacoordinate, while the vanadium(IV) compounds (**V-01**-**V-04**) were hexacoordinated. **V-05** was the only compound that did not contain co-ligands in its structure, so it was pentacoordinate is important to note that the geometry of the compounds was not determined by the authors by any spectroscopic or diffractometric technique. All compounds exhibited cytotoxic activity against A-2780 and MCF-7 human cells (MTT assay and 72 h of treatment). Cell growth inhibition of complexes **Cu-64**, **Cu-65** and **Cu-68** in HL-60 and HeLa human cells were also explored (MTT assay, 24 and 72 h of treatment). Copper(II)

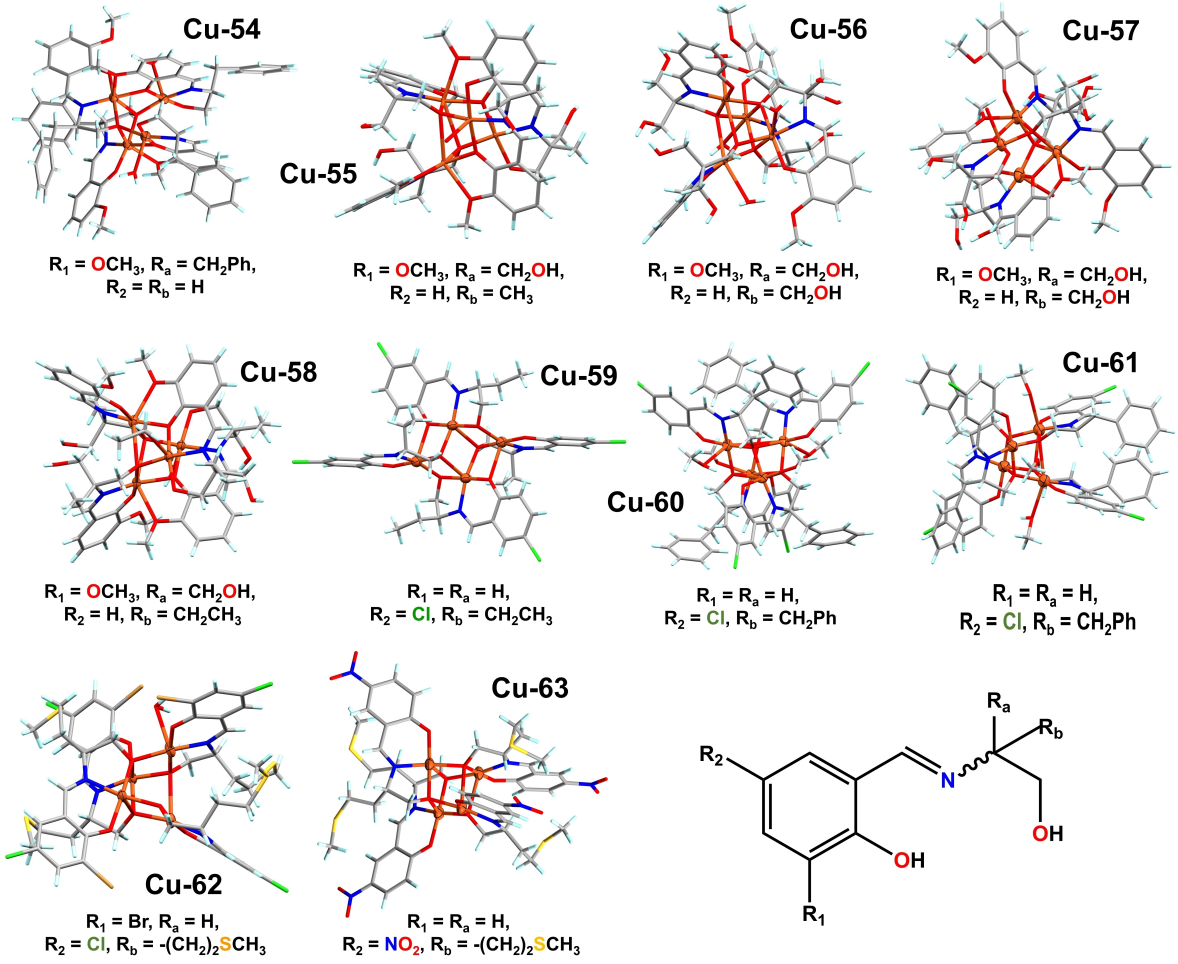

Figure 7. Copper(II) clusters (**Cu-54**–**Cu-63**) obtained from tridentate Schiff bases ONO.

complexes exhibited higher cytotoxic activity than vanadium(IV) complexes, even than cisplatin (except **Cu-64** and **Cu-65**). The *phen* compounds (**Cu-66**, **Cu-67** and **Cu-68**) are ten times more cytotoxic than cisplatin and obviously more cytotoxic than their *bpy* analogues (**Cu-64** and **Cu-65**). IC_{50} (μM) values at 72 h were **Cu-66** (A-2780 = 0.75 ± 0.2, MCF-7 = 2.5 ± 0.6), **Cu-67** (A-2780 = 0.54 ± 0.2, MCF-7 = 2.7 ± 0.8), **Cu-68** (A-2780 = 0.29 ± 0.01, MCF-7 = 3.5 ± 1.2, HL-60 = 1.51 ± 0.37 and HeLa = 4.2 ± 0.6) and cisplatin (A-2780 = 2.5 ± 0.1, MCF-7 = 28 ± 6, HL-60 = 2.2 ± 0.1 and HeLa = 4). The complexes interacted with DNA (calf-thymus) and efficiently cleaved plasmid DNA. The cleavage capacity was concentration, ligand and metal dependent. The *phen*-containing complexes presented a greater capacity for interaction with DNA than the *bpy*-containing analogues and all complexes were able to induce conformational changes in DNA, some by groove binding, others by forming adducts and by intercalating *phen* molecules between the DNA base pairs.[88]

An alternative to circumvent the problems of chemotherapeutic agents is the design of anticancer drugs that are activated in cancer cells selectively by light and remain inactive in the dark. This concept applies to photoactivated compounds that are used as anticancer agents in PDT, providing a non-invasive treatment, in which the photosensitizing drug is photoactivated, generating ROS, killing cancer cells. Sasmal *et al.* published a study of vanadium(IV) cationic complexes coordinated to Schiff bases derived from L-arginine (**V-06**–**V-08**) and L-lysine (**V-09**–**V-11**) using some *phen* derivatives as co-ligands (*phen*, *dpq* and *dppz*, respectively). The imino group of the tridentate Schiff bases was present in the structures forming rings of five and six members with respect to the metal centre, obtaining compounds with a hexacoordinated structure. The structure obtained for **V-06** by XRD studies showed a hexacoordinated vanadium(IV) atom in a distorted octahedral arrangement. Cell photo cytotoxicity of all complexes was studied in HeLa human cancer cells using the MTT assay, 2 h of incubation in dark and 45 min of photo exposure in visible light. The complexes derived from *dppz* were active in visible light giving IC_{50} values of 15.4 and 17.5 μM for **V-08** and **V-11**, respectively, exhibiting no toxicity in the dark ($IC_{50} > 100$ μM). However, these results were higher than those achieved with the reference drug photofrin®-efficient PDT agent but with undesirable toxic effects- under the same experimental conditions ($IC_{50} = 2.57$ μM in light and > 25 μM in dark). Additionally, the complexes were found to bind to DNA (calf thymus) *via*

Table 5. Summary of copper(II) clusters coordinated to ONO ligands with better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [μM]	Main feature	Ref.
Cu-54	Square pyramidal and octahedral	48	HeLa	13.50 ± 1.21	Anticancer activity depends on chirality and interactions with DNA	[81]
			HL-60	13.85 ± 1.39		
			Caco-2	13.88 ± 1.22		
			A-549	20.01 ± 1.09		
Cu-58			A-549	16.05	Anticancer activity depends on the nuclearity and nature of the metal centre	[84]
			HCT-116	30.02		
			HL-60	13.17		
			K-562	27.28		
Cu-59	Square pyramidal		HeLa	17.94 ± 1.25	Anticancer activity depends on chirality and nuclearity	[85]
			MDA-MB-231	6.20 ± 0.79		
			A-549	29.68 ± 1.47		
Cu-60	Octahedral			12.67 ± 1.29	Anticancer activity depends on chirality. Both configurations *(R)* and *(S)* were active.	[86]
				11.83 ± 1.43		
Cu-61			HeLa	15.61 ± 1.15		
			HL-60	18.12 ± 1.13		
			Caco-2	11.91 ± 1.17		
			A-549	10.97 ± 1.22		
				16.24 ± 1.41		
				16.21 ± 1.41		
Cu-62	Square pyramidal and octahedral			10.02 ± 0.10	Anticancer activity depends on chirality and halogen substituents on the ligand.	[87]
				10.94 ± 0.21		
			MDA-MB-231			
Cu-63	Octahedral		HUVEC	12.65 ± 0.21		
				14.62 ± 0.09		

DNA groove. The *dpq* and *dppz* derivatives are excellent photo cleavers of plasmid DNA *via* the singlet oxygen pathway ($^1O_2$).[89]

Vanadium compounds are studied by medical researchers as anticancer agents due to their numerous clinical, analytical, and pharmacological applications. For instance, Cao *et al.* prepared two vanadium(IV) complexes utilising chiral Schiff bases as ligands and 1,10-bathophenanthroline (*diphphen*) as co-ligand. The Schiff bases utilised are formed by the reaction of 3-(1-naphthyl)-L-alanine and 2-hydroxy-1-naphthaldehyde in the case of **V-12**, and of L-methionine and *o*-vanillin in the case of **V-13**. XRD results showed that the vanadium(IV) atoms in both compounds were hexacoordinated with octahedral distorted geometry in their final structure. The authors again introduced chirality in the amino acid fragment employed (L-alanine and L-methionine) to obtain the tridentate Schiff bases; in addition, a second chelating agent derived from *phen* was used due to its known anticancer activity. The anticancer activity of compounds **V-12** and **V-13** was evaluated against human cancer cell lines A-549 and Hep-G2 (MTT assay). The results revealed that both compounds were weakly cytotoxic with IC_{50} values of 8.22 ± 1.0 (A-549) and 26.8 ± 0.6 (Hep-G2) μmol L^{-1} for **V-13**, 60.53 ± 2.3 (A-549) and 94.89 ± 3.2 (Hep-G2) μmol L^{-1} for **V-12**, and 3.1 ± 0.5 (A-549) and 1.7 ± 0.8 (Hep-G2) μmol L^{-1} for cisplatin.[90]

The development of transition metal-based drugs has proven to be a promising approach to finding a pharmacological answer for the treatment of different diseases, such as cancer. The antitumor and chemopreventive effects of vanadium compounds have been extensively studied in experimental animal models and in various tumour cell lines; however, the mechanisms of action are still unknown. In this sense, Scalese *et al.* reported vanadium (IV) complexes (**V-14**–**V-27**) derived from Schiff bases obtained from glycine as well as polypyridyl co-ligands. The MTT assay (24 h of treatment) was used to evaluate the cytotoxic activity of **V-14**–**V-18** against three cancer cell lines (PC3, A-2780 and MDA-MB-231). With the evidence reported by the authors, it is suggested that the complexes exhibit a distorted octahedral geometry. In addition, it has been demonstrated that the nature of the polypyridyl co-ligands (*bpy*, *phen*, *aminophen*, *epoxyphen*, *dppz* and *tdzp*) determines the extent of activity of the complexes, with those that include *bpy* as a co-ligand being much less active than all the others. **V-14**–**V-19** showed moderate cytotoxicity towards ovarian and prostate cells, being the derivatives **V-18** with *dppz* co-ligand (IC_{50} values, A-2780 2.6 ± 0.25 μM, PC3 9.5 ± 1.8 μM, MDA-MB-231 16.8 ± 3.2 μM) and **V-16** with *aminophen* co-ligand (IC_{50} values, A-2780 7.6 ± 1.8 μM, PC3 4.6 ± 1.3 μM, MDA-MB-231 30.9 ± 9.0 μM) the most active complexes, while **V-14** with *bpy* co-ligand being the least active of the series, indicating that the naphthalene moiety significantly improved the cytotoxic effect. Interestingly, **V-18** was the most cytotoxic on all cancer cell lines and was also the most active against *T. cruzi*.[91]

On the other hand, this same working group used the MTT assay (24 and 72 h of treatment) to evaluate the cytotoxic activity of **V-20**–**V-27** against five cancer cell lines (PC3, A-2780, A-2780cisR, MCF-7 and HEK-293). According to the authors, the cytotoxic activity is dependent on the incubation time, since at 72 h all the compounds showed high cytotoxic activity in all cell lines. HEK-293 and A-2780cisR cells were also included to assess selectivity and resistance to cisplatin, respectively. With exception of complexes with the same co-ligand, such as **V-24**/**V-26** and **V-25**/**V-27**, the bromo-substituted derivatives were

generally more active than the unsubstituted derivatives. Interestingly, **V-20**–**V-27** were generally more cytotoxic than cisplatin for cancer cell lines (A-2780, MCF-7 and PC3) at both 24 h and 72 h exposure. After 24 h of treatment, the IC_{50} value of cisplatin in the cell line A-2780cisR is much higher than the value found for the complexes. Among all the complexes, **V-20** and **V-21** showed higher selectivity with respect to non-tumour cell line HEK-293. Some important IC_{50} (μM) values to highlight at 24 h of treatment were **V-20** (A-2780 = 10.2 ± 5.05, HEK-293 = 82.8 ± 47.5), **V-21** (A-2780 = 10.3 ± 3.35, HEK-293 = 28.8 ± 7.2), **V-23** (HEK-293 = 38.1 ± 15.8), **V-26** (A-2780cisR = 13.5 ± 4.2, MCF-7 = 10.4 ± 1.70) and **V-27** (A-2780 = 5.90 ± 1.45). Some important IC_{50} (μM) values to highlight at 72 h of treatment were **V-20** (HEK-293 = 30.2 ± 16.6), **V-21** (PC3 = 0.82 ± 0.29), **V-22** (PC3 = 0.94 ± 0.35), **V-24** (MCF-7 = 2.84 ± 1.27), **V-26** (A-2780 = 0.73 ± 0.13, MCF-7 = 2.79 ± 1.32) and **V-27** (A-2780 = 1.35 ± 0.34).[92]

As we have seen so far, vanadium compounds can be an alternative to platinum-based drugs. In this way, Kazemi *et al.* studied the photocytotoxicity and DNA cleavage of some vanadium(IV) complexes with Schiff base-type ligands and *phen*-type co-ligands. The complexes (**V-28**–**V-30**) had a discrete monomeric octahedral structure in which the VO^{2+} ion bonded to a tridentate dianionic Schiff base and an N N bidentate co-ligand. The cellular photocytotoxicity of **V-30** was studied in HeLa human cancer cells by the MTT assay. **V-30** was incubated for 2 h in the dark and subsequently photo exposed to light for 45 min, dose-dependently decreasing cell viability (IC_{50} = 13 μM). Non-photo exposed cells showed an IC_{50} value of 97 μM. Therefore, sevenfold higher cytotoxicity is observed upon photoexcitation with visible light. Comparatively, photofrin® has an IC_{50} value of 2.57 μM, which is lower than that found for **V-30**; however, the drug has undesirable toxic effects. Further studies showed that the complexes are good DNA binders (calf thymus) with poor chemical nuclease activity due to redox inactivity, while **V-29** and **V-30** also showed UV-light-induced DNA cleavage activity and near-IR light-induced DNA cleavage activity.[93]

Oxovanadium salts are generally less expensive than platinum or ruthenium salts, making them attractive for new drug development. Although oxovanadium salts have poor biological activity and high toxicity, oxovanadium complexes with organic ligands enhance their benefits and minimize their adverse effects. Therefore, it is important to obtain new vanadium complexes and delve into their biomedical applications. Continuing studies on the anticancer activity of vanadium(IV) complexes with chiral Schiff bases and *phen*-derived co-ligands, Cao *et al.* reported the use of different modified aldehydes to synthesize Schiff bases. In the search to increase the solubility of the vanadium(IV) complexes, aldehydes 4-(diethylamino)salicylaldehyde (**V-31**), 3-methoxysalicylaldehyde (**V-32**), 3,5-di-*tert*-butylsalicylaldehyde (**V-33**) and 2-hydroxy-1-naphthaldehyde (**V-34**) were utilised. The chirality of the complexes was conferred thanks to the use of D or L-methionine (**V-31** and **V-32**) and 3-(1-naphthyl)-L-alanine (**V-33** and **V-34**). The compounds presented similar structures based on the general formula [VO(O N O)(*phen*)]and all complexes were mononuclear with distorted octahedral geometry. The anticancer activity of the four derivatives and cisplatin against A-549 and Hep-G2 cells was tested by the MTT assay during 24 h of treatment. Only **V-33** and **V-34** were found to have weak anticancer activity towards A-549 and Hep-G2 cells with IC_{50} values of 28.4 to 45.2 μmol L^{-1}. Furthermore, the activity of these complexes was shown to be lower than the cisplatin and $VO(acac)_2$ controls[94] (Figure 8, Table 6).

Table 6. Summary of vanadium(IV) complexes with ancillary ligands and better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [μM]	Main feature	Ref.
V-16	Octahedral	24	A-2780	7.6 ± 1.8	Anticancer activity depends on the presence of the polypyridyl-derived ancillary ligand, in this case *aminophen* and *dppz*.	[91]
			PC-3	4.6 ± 1.3		
			MDA-MB-231	30.9 ± 9.0		
V-18			A-2780	2.6 ± 0.25		
			PC-3	9.5 ± 1.8		
			MDA-MB-231	16.8 ± 3.2		
V-20			A-2780	10.2 ± 5.05		
			HEK-293	82.8 ± 47.5		
V-21			A-2780	10.3 ± 3.35		
			HEK-293	28.8 ± 7.2		
V-26			A-2780cisR	13.5 ± 4.2		
			MCF-7	10.4 ± 1.70		
V-27			A-2780	5.90 ± 1.45	Anticancer activity is substituent dependent, brominated derivatives were generally more active than unsubstituted derivatives.	[92]
V-21		72	PC-3	0.82 ± 0.2		
V-22			PC-3	0.94 ± 0.35		
V-24			MCF-7	2.84 ± 1.27		
V-26			A-2780	0.73 ± 0.13		
			MCF-7	2.79 ± 1.32		
V-27			A-2780	1.35 ± 0.34		

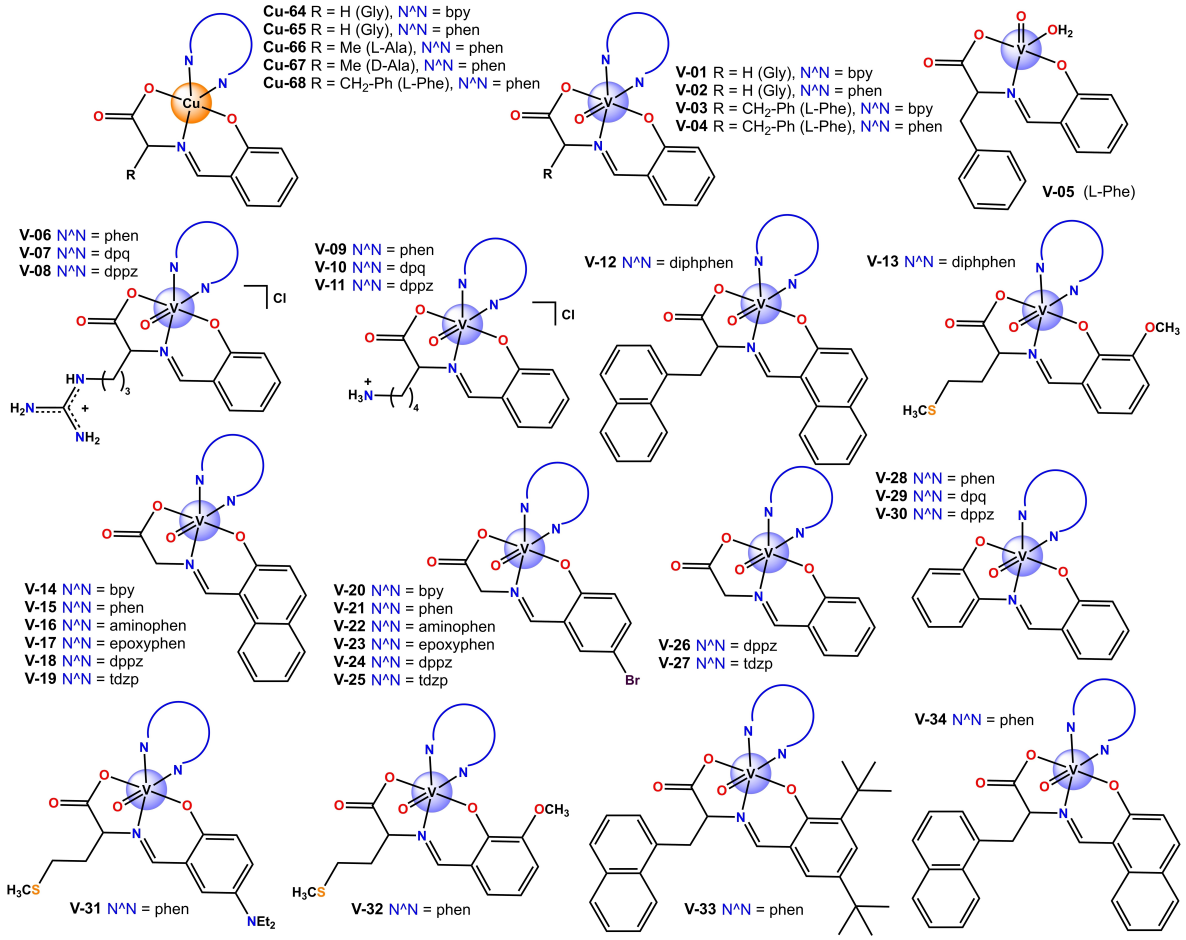

Figure 8. Vanadium(IV) and copper(II) complexes (**V-01**–**V-34** and **Cu-64**–**Cu-68**) obtained from tridentate Schiff bases ONO.

2.3.2. Compounds with vanadium(IV) and other ancillary ligands

Currently, there are very few systematic studies on the use of vanadium complexes as potential anticancer agents, so this review allows several examples of success with this metal to be reported. In a study reported by Lewis *et al.* the Schiff base named *N*-salicylidene-L-tryptophanate was used as a support for the three synthesized complexes. In each of them the structure was modified through an auxiliary ligand derived from thiosemicarbazone: 9-anthraldehyde-*N*(4)-methylthiosemicarbazone (**V-35**), (*E*)-*N*-ethyl-2-(4-hydroxy-3-methoxybenzylidene)-hydrazinecarbothioamide (**V-36**) and (*E*)-*N*-ethyl-2-[1-(thiazol-2-yl)ethylidene]hydrazinecarbothioamide (**V-37**). The anticancer properties of the three complexes were examined by MTT assay (24, 48 and 72 h of exposure) in three colon cancer cell lines (Caco-2, HT-29 and HTC-116) and one noncancerous colon cell line (CCD18-Co). The results indicated that the three compounds had a very weak anticancer activity that could not match the results found for the two positive controls (etoposide and cisplatin). The best IC_{50} values (μM) were found for **V-37** at 72 h of treatment (Caco-2 = 85.4 ± 14, HT-29 = 47.8 ± 5.5, HTC-116 = 89.5 ± 14.5 and CCD18-Co = 152.2 ± 12.0).[95]

On the other hand, Holder *et al.* reported two new binuclear complexes of mixed metals (ruthenium(II) and vanadium(IV)) bridged with polypyridyl-type ligands, proposing them as potential photodynamic drugs for the inhibition of melanoma cell growth. In both molecules, the ruthenium(II) metal centre exhibited an octahedral geometry coordinated to two 2-(2′-pyridyl)benzothiazole molecules and operated as a photosensitizer, while the vanadium(IV) metal centre also presented an octahedral geometry and was coordinated to a Schiff base named *N*-salicylidene-L-tryptophanate (sal-L-trip) adding chirality to the system. The difference between the two molecules is conferred by the porypyridyl-derived bridging ligand: tetrapyrido[3,2-a:2′,3′-c:3″,2″-h:2‴,3‴-j]phenazine (**V-38**) and 1,4-bis(1,10-phenanthrolin-5-yl-sulfanyl)butane-2,3-diol (**V-39**). Cellular toxicity studies were performed for both compounds through the MTT colorimetric assay under light and dark conditions using a cancer cell line (A-431) and a non-cancer (HFF) cell line. The results of cell viability in the A-431 line after 24 h of incubation in dark conditions for **V-38** (IC_{50} = 41.3 ± 7.6 μM) and **V-39** (IC_{50} = 48.6 ± 13.1 μM), as well as those of its precursor VO(sal-L-trip)(*phen*) (IC_{50} = 41.6 ± 5.8 μM), were com-

parable to those found for the reference drug cisplatin (IC_{50} = 40.1 ± 11.5 μM). They even showed a higher selectivity when analysing the IC_{50} values in the healthy cell line HFF (**V-38** = 100.7 ± 17.7 μM, **V-39** = 204.4 ± 45.1 μM, VO(sal-L-trip)(*phen*) = 63.1 ± 28.3 μM and cisplatin = 82.0 ± 8.9 μM). When compared to the cytotoxicity results in light conditions, **V-38** and **V39** exhibited light-enhanced cytopathic effects (20 μM) on A-431 cancerous cells in contrast to no effect on noncancerous HFF cells. On the other hand, light and dark cytotoxicity studies on amelanotic malignant melanoma cells revealed less apoptosis when irradiated in the presence of **V-38** at a concentration of 5 μM, while complete apoptosis was observed when irradiated at a concentration of 20 μM[96] (Figure 9, Table 7).

2.3.3. Compounds with vanadium(V) and other ancillary ligands

Vanadium salts are known to have high toxicity and low biological activity, so coordination of vanadium with organic ligands such as Schiff bases increases benefits and minimizes adverse effects. Currently, most research focuses on IV-oxidation state, with very few studies on V-oxidation state. For example, Ebrahimipour *et al.* reported di- and monoxo-vanadium(V) complexes (**V-40**–**V-42**) coordinated to a tridentate Schiff base ligand. ONO ligand was synthesized from 2-hydroxynaphthaldehyde and 2-amino-4-chlorophenol. The crystal structures of all complexes showed a pentacoordinate vanadium(V) atom with a distorted square pyramidal geometry. The anticancer activity of the three complexes was investigated using MCF-7 cells and compared to the starting salt $VO(acac)_2$ utilising the MTT assay after 24 h treatment. According to the results, the three complexes exhibited greater anticancer activity than $VO(acac)_2$; however, it is difficult to establish the magnitude of the finding, since the authors did not report IC_{50} values and there is no comparative analysis with reference drugs.[97]

Another example of the use of vanadium(V) coordination complexes was reported by Correia and coworkers. They used the L-isomer of the Schiff base named: 1-(((1-hydroxy-3-phenylpropan-2-yl)imino)methyl)naphthalen-2-ol for both monomeric (**V-44**, **V-45** and **V-46**) and dimeric (**V-43**) derivatives. **V-44** and **V-46** employed quinolin-8-ol as a secondary ligand while **V-45** used the 5-chloroquinolin-8-ol ligand. The characterization of the complexes by spectroscopic techniques and XRD in **V-45** showed a distorted octahedral geometry for the four derivatives. The cytotoxic activity of **V-44**–**V-46** against A-2780 and A-2780cisR cancer cells (sensitive and resistant to cisplatin), and non-tumour HEK cells were analysed (MTT assay y 24, 48 and 72 h of exposure). Time-dependent cytotoxicity tests showed that after 48 h of continuous treatment, the IC_{50} best values (μM) were in the range from 5.7 to 10.9 μM. In A-2780 cells, the complexes were more active than cisplatin (22 μM), even in A-2780cisR (cisplatin-resistant) cells (2.4 to 8.0 μM), they also outperformed the activity. In HEK cells, low selectivity was observed for both the complexes and cisplatin.[98]

Khan *et al.* have studied the influence of chirality on vanadium(V) complexes derived from Schiff bases on DNA and BSA. Salicylaldehyde and $VO(acac)_2$ were used as starting

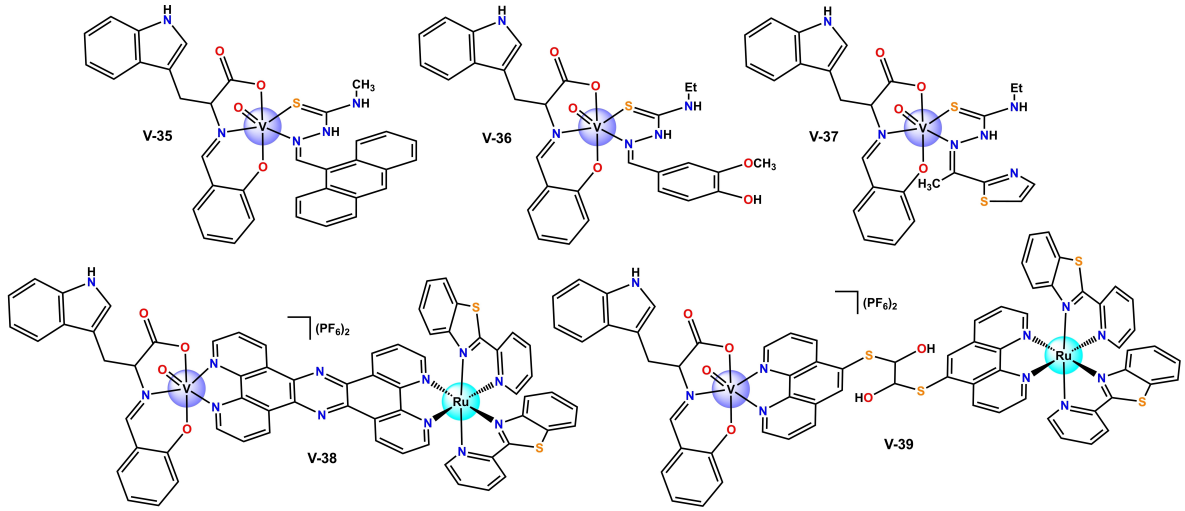

Figure 9. Vanadium(IV) complexes (**V-35**–**V-39**) obtained from tridentate Schiff bases ONO.

Table 7. Summary of vanadium(IV) complexes coordinated to ONO ligands with better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [μM]	Main feature	Ref.
V-38	Octahedral	24	A-431	41.3 ± 7.6	Anticancer activity depends on nuclearity with mixed metals and the presence of polypyridyl-type ligands	[96]
			HFF	100.7 ± 17.7		
V-39			A-431	48.6 ± 13.1		
			HFF	204.4 ± 45.1		

materials, in addition to *1R,2S*-(−)-2-amino-1,2-diphenylethanol in the case of **V-47** and *1S,2R*-(+)-2-amino-1,2-diphenylethanol in the case of **V-48**. Both complexes exhibited a distorted square pyramidal geometry with the vanadium(V) atom located slightly outside the square plane. According to the authors, chirality should enhance the pharmacological behaviour of vanadium(V) complexes, by adopting a specific conformation and a selective binding affinity with DNA and BSA. The antitumor activity of **V-47** and **V-48** in Hep-2 cells was evaluated by exposing them to different concentrations for 72 h using the MTT assay. **V-48** exhibited greater cytotoxicity than **V-47** with IC_{50} values of 1.77 ± 0.04 μM and 2.45 ± 0.07 μM, respectively. Also, **V-48** exhibited a strong DNA-binding affinity compared to **V-47**. Both enantiomeric complexes displayed binding to the DNA surface or groove. In addition, **V-48** efficiently cleaves DNA in the presence of white fluorescent light through a mechanism that forms singlet oxygen. Furthermore, chiral vanadium(V) complexes, in particular, **V-48**, showed strong BSA-binding, cleavage activity, and cytotoxic activity.[99]

To close this section, Kansemi *et al.* studied the anticancer activity and self-recognition of a racemic Schiff base in the formation of a homochiral dinuclear vanadium(V) complex (**V-49**). The Schiff base used in this work was synthesized from 2-hydroxy-1-naphtaldehyde and (*R/S*)-1-aminopropan-2-ol in the presence of triethylamine and $VO(acac)_2$. In this reaction, the metal centre was oxidized utilising molecular oxygen from the air, changing the oxidation state of the vanadium atom from IV to V. The vanadium(V) atom in **V-49** is covalently bonded in a VO_4N environment displaying a pentacoordinate structure with square pyramidal geometry. Cytotoxicity test (MTT assay and 48 h of exposure) revealed moderate anticancer activity of **V-49** on two cancer cell lines MCF-7 (IC_{50} = 14 μM) and HeLa (IC_{50} = 36 μM), with low cytotoxicity on healthy human fibroblast cells. A maximum cell mortality of 12.3% was obtained after 48 h of incubation in normal human fibroblast cells at a concentration of 100 μM for **V-49**. These results clearly exhibit a cell line and dose-dependent anticancer activity; however, no studies were reported using a reference drug such as cisplatin, nor the IC_{50} value with normal human fibroblast cells. In addition, the DNA- and HSA-binding constants were found to be 1.9×10^5 and 8.0×10^4 M^{-1}, respectively[100] (Figure 10, Table 8).

2.4. Zinc(II) compounds

Since zinc is essential in human growth and development and plays a determining role in several biological processes, its deficiency is associated with an increased risk of cancer. Therefore, zinc supplementation modulates oxidative stress, improving immune function and preventing cancer. Currently, transition metal complexes, such as zinc, coordinated to Schiff bases, have been explored to determine their anticancer and antitumor activity. In this vein, Ghost *et al.* obtained a tetrahedral neutral zinc(II) complex (**Zn-01**) and evaluated its

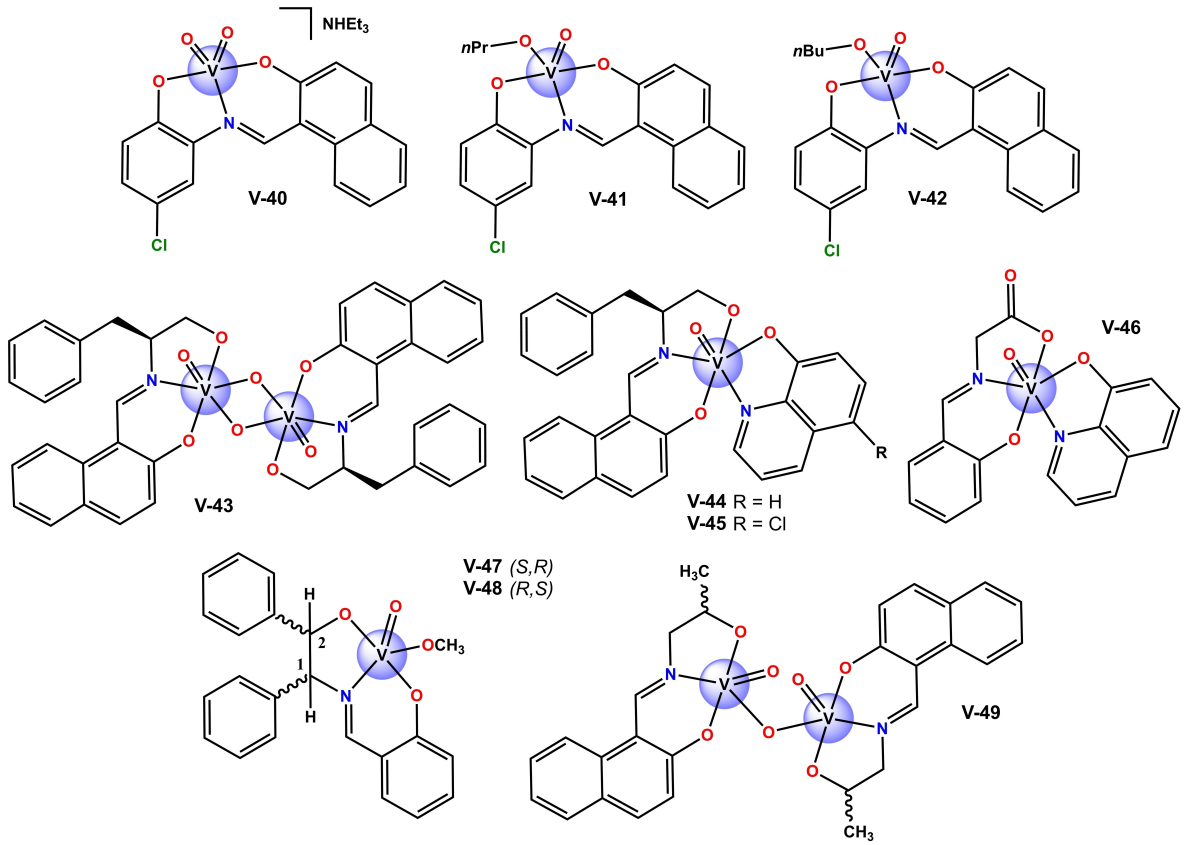

Figure 10. Vanadium(V) complexes (**V-40**–**V-49**) obtained from tridentate Schiff bases ONO.

Table 8. Summary of vanadium(V) complexes coordinated to ONO ligands with better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [μM]	Main feature	Ref.
V-45	Octahedral	48	A-2780	5.7 ± 1.6	Anticancer activity depends on chirality and the presence of the 8-hydroxyquinoline-derived co-ligand	[98]
V-47 V-48	square pyramidal	72	Hep-2	2.45 ± 0.07 1.77 ± 0.04	Anticancer activity depends on chirality	[99]

antitumor activity *in vitro* against CCRF/CEM (drug-sensitive) and CEM/ADR5000 (drug-resistant) cells and *in vivo* against EAC cells implanted in female Swiss albino mice. The *in vivo* antiproliferative effect of **Zn-01** was analysed using the MTT assay (24, 48 and 72 h of exposure) in both malignant cell lines and the results were compared with the effect caused in non-malignant cells (NIH 3T3). The IC_{50} values in NIH 3T3, CCRF/CEM and CEM/ADR 5000 and cells at 72 h were 5.96 ± 10^{-4} M, 5.40 ± 10^{-4} M and 5.36 ± 10^{-4} M, respectively. These data suggest that both malignant cell lines were equally sensitive to **Zn-01** and that under the same experimental conditions; they showed a similar cytotoxic effect on the non-malignant cell line. The *in vivo* toxicity study after intraperitoneal administration of **Zn-01** in mice bearing EAC tumours (after 72 h) at doses of 15 and 20 mg Kg^{-1} body weight, showed no pathological/symptomatic changes, no differences in body/organs weight or in biochemical/haematological parameters, no apparent kidney/liver damage and no changes in spleen/bone marrow cell counts. The most interesting contribution of this article was the combination of **Zn-01** with vinblastine which was able to induce apoptosis and reverse drug resistance in the CEM/ADR 5000 cell line. **Zn-01** caused EAC tumour reduction in doxorubicin-sensitive (EAC/S) and doxorubicin-resistant (EAC/DOX) Swiss albino mice, both in the absence and presence of doxorubicin[101]

Zinc is, after iron, the second most abundant trace element in the human body. Due to the diversity of physiological functions in which zinc participates, zinc(II) complexes have been used in medicinal chemistry. Lately, zinc(II) complexes have also attracted attention as possible anticancer or antitumor drugs with lower toxicity and different modes of action compared to platinum-based drugs. Based on these facts, Matos *et al.* explored the cytotoxic activity of zinc(II) complexes coordinated to *N*-salicylideneglycinate, using *phen* (**Zn-02**), *aminophen* (**Zn-03**), *epoxyphen* (**Zn-04**), *chlorophen* (**Zn-05**) and *diphphen* (**Zn-06**) as secondary polypyridyls ligands. The cytotoxicity of all octahedral and neutral compounds was evaluated against A-2780, MCF-7 and HeLa human cancer cells, as well as V-79 non-tumour cells (MTT assay, 24 and 48 h of treatment). In general, all five compounds are more cytotoxic toward A-2780 cells, showing the following trend: HeLa < MCF-7 < A-2780. In fact, the polypyridyl ligands by themselves showed better cytotoxic activity, with IC_{50} values even lower than their zinc(II) complexes. **Zn-06** showed the best IC_{50} values, surpassing the reference drug cisplatin and competing with the results found for the auxiliary ligand. The IC_{50} (μM, 48 h of incubation) values were **Zn-06** (HeLa = 4.58 ± 1.0, MCF-7 = 3.04 ± 1.2, A-2780 = 1.73 ± 0.4, V-79 = 4.06 ± 0.55), *diphphen* (HeLa = 2.00 ± 0.5, MCF-7 = 3.20 ± 0.9, A-2780 = 0.50 ± 0.5, V-79 = 1.20 ± 0.7) and cisplatin (HeLa = 3.59 ± 2.2, MCF-7 = 20.7 ± 6.4, A-2780 = 22.5 ± 0.5, V-79 = 23.5 ± 5.0). In general, all five complexes showed higher selectivity for A-2780 cells than for V-79 cells, even outperforming cisplatin. Interestingly, almost all complexes induced caspase-dependent apoptosis in A-2780 cells, except **Zn-06**, the most cytotoxic of all compounds. Furthermore, this compound was highly toxic to both cancerous and healthy cells, showing low selectivity.[102]

An interesting investigation was proposed by Tabassum *et al.*, who reported the design of chiral monometallic complexes of copper(II) and zinc(II) (**Cu-69** and **Zn-07**, respectively), and heterobimetallic complexes of copper(II)-tin(IV) and zinc(II)-tin(IV) (**Cu-70** and **Zn-08**, respectively). Chirality was introduced by the Schiff base which was obtained from the amino acid L-valine and the aldehyde *o*-vanillin. The coordination numbers of the metal atoms of copper(II) and zinc(II) were pentacoordinate, while the tin(IV) atom was hexacoordinate, which was proposed on the basis of spectroscopic and analytical studies. The antiproliferative effect at different times 0, 24 and 48 h of **Cu-70** was examined in HUH-7 cells, reducing cell doubling time and showing limited cytotoxicity at a concentration of 25 μM. Furthermore, **Cu-70** showed a high inhibitory effect on Topo I, at a lower concentration compared to some standard drugs. This work focused more on the design of DNA groove-specific binders and Topo I inhibitors, and since these facts are related to the antiproliferative effect, they show **Cu-70** as a possible drug candidate.[103]

It is clear that zinc(II) offers interesting chemical and biological properties for the development of novel anticancer drugs. The combination of zinc(II) with bioactive organic ligands is a strategy that allows for obtaining new effective and selective metallopharmaceuticals. Liu *et al.* compared the anticancer properties of two derivatives, one copper(II) and the other zinc(II), coordinated to a Schiff base derived from glycine and *o*-valine. **Cu-71** was a neutral, mononuclear and pentacoordinate derivative with square pyramidal geometry that used *bpy* as a secondary ligand, while **Zn-09** was a neutral, dinuclear and hexacoordinate derivative with octahedral geometry for each of its metal centres and used *phen* as auxiliary ligand. MTT assay was used to measure the effectiveness of both complexes and their ONO ligand on cell proliferation in the cancer lines HeLa, HT-29, MDA-MB-231 and PC-3 after 48 h of incubation. Cell viability of **Cu-71** and **Zn-09** was tested in the range from 10 to 60 μM, and the IC_{50} values in these four cancer cell lines were from 19.05 to 32.66 and from 34.68 to 50. 66 μM, respectively. **Cu-71** exhibited a high anticancer activity with better values than those found for **Zn-09**; however, there is no

comparative analysis with analogous species or with reference drugs.[104]

The anticancer activities of zinc(II) complexes and their ability to interact with DNA are currently one of the most studied research topics. Recently, Zhao *et al.* reported three new multinuclear derivatives of zinc(II) obtained from the Schiff bases named 2-ethyl-2-((2-hydroxybenzylidene)amino)propane-1,3-diol (**Zn-10** and **Zn-11**) and 2-((5-chloro-2-hydroxybenzylidene)amino)-2-ethylpropane-1,3-diol (**Zn-12**). **Zn-10** is a dinuclear and neutral compound with two metal centres with pseudo-octahedral geometry, while **Zn11** and **Zn-12** are trinuclear and neutral compounds with three metal centres, the external ones with the geometry between trigonal bipyramidal and square pyramidal and the central one with geometry octahedral. The cytotoxicity of the three complexes against the cancer cell lines HeLa and K-562 was analysed and compared to cisplatin using the MTT assay. The IC_{50} values of **Zn-10** were HeLa = 14.28 μM and K-562 = 25.07 μM, slightly lower than cisplatin (IC_{50} > 50 μM). **Zn-11** and **Zn-12** did not show a clear toxic effect against both tumour cell lines under identical experimental conditions (IC_{50} > 50 μM). According to the authors, cytotoxicity depends on the nuclearity and geometry of the complexes, emphasizing that the dinuclear complex is more active than the trinuclear complexes. In Addition, **Zn-10** exhibited a higher DNA-binding affinity than **Zn-11** and **Zn-12** *via* the intercalative mode.[105]

The zinc(II) ion forms complexes with a variable coordination environment due to its d^{10} electronic configuration, so its geometries can vary from tetrahedral to octahedral. In addition, the interactions of dinuclear and trinuclear zinc(II) complexes with DNA have attracted attention due to their potential applications as anticancer agents. In this sense, Dey *et al.* reported a new trinuclear zinc(II) complex (**Zn-13**) containing a Schiff base ONO named 2-[(2-hydroxyphenylimino)methyl]-6-methoxyphenol. According to XRD findings, **Zn-13** contained three zinc(II) centres with distorted octahedral geometry for one of them. Since **Zn-13** had the ability to strongly bind and cleave DNA, and DNA cleavage is important for a compound to act as an anticancer drug, the cytotoxicity of **Zn-13** against a cancer cell line (Hep-G2) was investigated by MTT assay (24 h or 48 h of treatment). The IC_{50} value at 48 h (60 ± 0.2 μM) is lower than that at 24 h (70 ± 0.1 μM) of treatment, showing that **Zn-13** exhibited dose- and time-dependent cytotoxicity. Therefore, the cytotoxicity of **Zn-13** was consistent with its DNA cleavage efficiency and strong DNA-binding, however, no comparative studies with reference drugs were done[106] (Figure 11, Table 9).

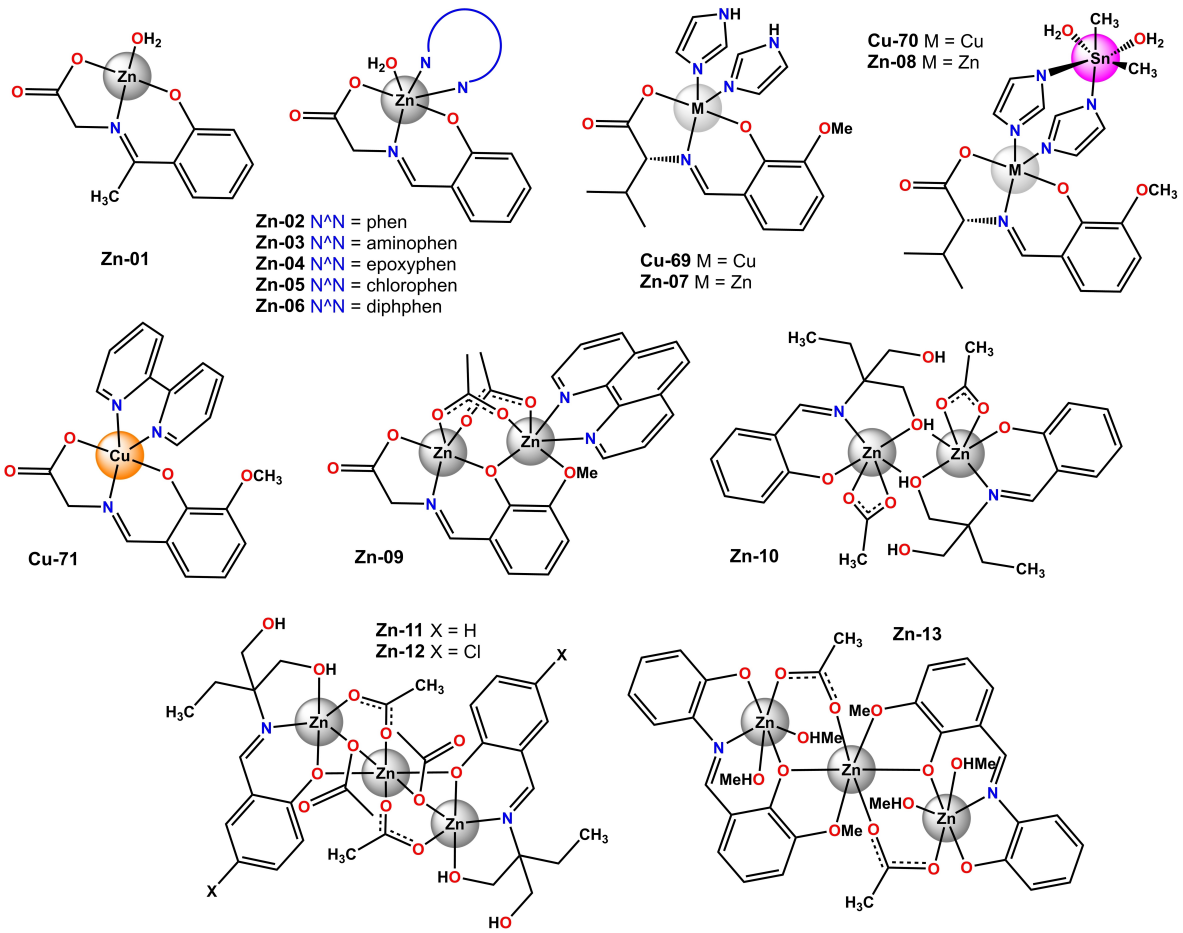

Figure 11. Zinc(II) and copper(II) complexes (**Zn-01**–**Zn-13** and **Cu-69**–**Cu-71**) obtained from tridentate Schiff bases ONO.

Table 9. Summary of zinc(II) complexes coordinated to ONO ligands with better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [μM]	Main feature	Ref.
Zn-06	Octahedral	48	HeLa	4.58 ± 1.0	Anticancer activity depends on the presence of the co-ligand, in this case *diphphen*	[102]
			MCF-7	3.04 ± 1.2		
			A-2780	1.73 ± 0.4		
			V-79	4.06 ± 0.55		
Zn-10		NR	HeLa	14.28	Anticancer activity depends on the nuclearity and geometry of the complexes	[105]
			K-562	25.07		

2.5. Nickel(II) compounds

Imine ligands can coordinate many different metals, and can stabilize them in various oxidation states. Outstandingly, these ligands have been used against certain types of tumours. In this context, Abdel-Rahman *et al.* described three novel imine complexes with nickel(II), chromium(III) and vanadium(IV) derived from the condensation of 2-aminophenol with 2-hydroxynaphthaldehyde (**Ni-01**, **Cr-01**, and **V-50**). The results suggest that the parent ligand behaves as a dibasic tridentate ONO ligand when coordinated to nickel(II) in tetrahedral geometry and to chromium(III) in an octahedral geometry. In the case of vanadium(IV), it coordinated in distorted square pyramidal geometry. Moreover, the cytotoxic activity of the parent ligand and its complexes on HCT-116, Hep-G2 and MCF-7 cell lines within the concentration range 0–10 μM (SRB assay and 48 h incubation) were examined. The IC_{50} values of most of the complexes showed greater cytotoxic potency than that of the free ligand (IC_{50} > 100 μg/μL). In general, all complexes tested exhibited moderate cytotoxicity against HCT-116 (IC_{50} = 25.4–98.4 μg/μL), Hep-G2 (IC_{50} = 19.3–68.6 μg/μL) and MCF-7 (IC_{50} = 14.0–55.3 μg/μL) cancer cells. However, none of the three synthesized complexes managed to overcome the activity shown by vinblastine (IC_{50} = 4.12–13.3 μg/μL) in the three cancer cell lines. The general trend in cytotoxic activity reported in this paper for the three cell lines studied was vinblastine > **V-50** > **Cr-01** > **Ni-01** > ligand. In the words of the authors, the positive charge of the metal intensifies the acidity of the coordinated ligand that gives up protons, generating stronger hydrogen bonds that increase the cytotoxic potency. Other relevant results of this publication demonstrated that the binding affinity with DNA (calf thymus) follows the order **Cr-01** > **V-50** > **Ni-01**.[107]

Nickel(II) complexes coordinated to a Schiff base ligand containing mixed donors are intensively investigated since they have shown wide applications in catalysis and exceptional biological activities. Moreover, Nickel is an essential element for life, and it has been considered one of the most promising alternatives to traditional cisplatin as an anticancer drug. In 2014, Niu *et al.* reported a nickel(II) complex derived from salicylidene Schiff base ligand with the formula [NiL_2] labelled as **Ni-02**. The ligand used was L = 2-ethyl-2-(2-hydroxybenzylideneamino)propane-1,3-diol. Regarding XRD studies, it was revealed that **Ni-02** contains a six-coordinate nickel(II) atom at the centre of a slightly distorted octahedron. The inhibition effects of **Ni-02** against four cancer cell lines A-549, HCT-116, HL-60 and Caco-2 at a concentration of 20.0 μg mL^{-1} (MTT assay and 24 h of treatment), displayed outstanding cytotoxicity, which is consistent with the high ability to bind to DNA. For instance, the reported IC_{50} values (μM) for **Ni-02** were 31.98 ± 1.6 (A-549), 59.84 ± 3.3 (HCT-116), > 100 (HL-60 and Caco-2), which were higher than those found for cisplatin (IC_{50} > 100 μM in all cell lines tested), further experiments revealed that **Ni-02** could interact with DNA (calf thymus) by intercalation and that **Ni-02** interacts with BSA.[108]

In 2016, Saha *et al.* studied the coordination complexes derived from Schiff base ligands coordinated to the first-row transition metals, such as nickel(II), copper(II) and zinc(II), which are bio-essential metal ions and can form compounds with square planar geometry. They prepared the Schiff-base ligand from *o*-vanillin and 2-aminophenol to obtain three mononuclear complexes **Ni-03**, **Cu-72**, and **Ni-04**. Single-crystal XRD analysis showed that both nickel(II) and copper(II) form a distorted square planar geometry in all three compounds. DNA study displayed that **Ni-03** had the highest affinity for DNA (calf thymus), while **Cu-72** and **Ni-04** showed moderate binding capacity. A-549 cells were used to study cytotoxicity (MTT assay and 24 h of incubation), only **Cu-72** was cytotoxic at a concentration of 50 μM or higher. Neither **Ni-03** nor **Ni-04** showed cytotoxic activity up to a concentration higher than 150 μM.[109]

So far we have seen how copper(II) and nickel(II) complexes have shown great anticancer activity, so it is proposed that they could substitute cisplatin in the near future. As shown by Li *et al.* with the cytotoxicities of the **Ni-05**–**Ni-08**, **Cu-73** and **Cu-74** complexes, which were studied using the A-549, HeLa, and MCF-7 cell lines (MTT assay and 48 h of treatment). The structure of the **Ni-05**–**Ni-08** complexes contains binuclear nickel(II) units surrounded by two chiral ligands with an octahedral arrangement for each metal centre. Meanwhile, **Cu-73** and **Cu-74** contain two copper(II) centres coordinated with two chiral Schiff bases around each metal centre with square pyramidal geometry. Both chiral copper(II) complexes displayed a relevant effect on the DNA and BSA binding ability, greater than the activity shown by the nickel(II) complexes. The IC_{50} values (μM) of **Cu-73**, which is derived from the (*R*) Schiff base ligand, showed both stronger and higher antiproliferative activity (HeLa, 5.77 ± 0.76; MCF-7, 19.99 ± 1.30; A-549, 17.17 ± 1.23) with respect to the rest of the complexes. The authors suggest a synergistic effect due to chiral Schiff base ligands chelating copper(II) metal ions, and they also remarked that substituents on the Schiff base ligand could potentiate

cytotoxicity activity; however, they did not show comparative studies with a reference drug. Furthermore, it was observed that the IC_{50} values for the complexes with the ethyl group as substituent are lower than the values for the complexes with the benzyl group. They conclude that chirality plays an important role in anticancer activity and interactions with BSA/DNA.[110]

Since the discovery of the antiproliferative properties of cisplatin by Rosenberg *et al.*, some transition metal complexes, preferably with copper(II), zinc(II), and nickel(II), have been reported. For instance, Niu *et al.* described in 2015 four coordination complexes based on two Schiff base ligands derived from amino alcohols. The compounds are mononuclear (**Cu-75**), dinuclear (**Ni-09**), and tetranuclear (**Cu-58** and **Ni-10**). In fact, **Cu-58** was discussed widely in section 2.2. The ligand used for **Cu-75** and **Ni-09** was 2-ethyl-2-((2-hydroxybenzylidene)amino)propane-1,3-diol, while for **Cu-58** and **Ni-10** it was 2-ethyl-2-((2-hydroxy-3-methoxybenzylidene)amino)propane-1,3-diol. In **Cu-75**, the copper(II) centre is tetra-coordinate, affording it a square planar coordination geometry, while in **Ni-09**, the nickel(II) centre provided a distorted octahedral geometry. In addition, in **Ni-10** each ligand coordinates tetradentately, obtaining a trigonal bipyramidal geometry for each nickel(II) centre. The cytotoxic effect of these complexes on cancer cell lines, A-549, HCT-116, HL-60 and K-562, at a concentration of 20.0 $\mu g\,mL^{-1}$, exhibited moderate cytotoxic activity (MTT assay and 48 h of incubation). The IC_{50} values (μM) for the **Cu-58** tetranuclear cluster suggest both greater cytotoxicity and stronger binding ability in this series of compounds. **Cu-58** showed the following IC_{50} values (μM) for A-549 (16.05), HCT-116 (30.02), HL-60 (13.17), K-562 (27.28). Furthermore, the interactions with DNA (calf thymus) and BSA showed the following trend between these complexes: **Cu-58** > **Ni-10** > **Ni-09** > **Cu-75**. The results suggest that nuclearity and metal centres play an important role in the anticancer properties of the complexes[84] (Figure 12, Table 10).

2.6. Manganese(II/III/IV) compounds

Manganese is a fairly abundant trace element and a valuable nutrient that have an important role in human health. Manganese(II) complexes have been reported as anti-proliferative agents on several cancer cell lines. Interestingly, Ghosh *et al.* described the synthesis of the manganese(II) complex using the NHAG as a ligand (**Mn-01**). The authors reviewed the antiproliferative effect of **Mn-01** against CEM/ADR 5000 and CCRF/CEM (MTT assay), and also reported the antitumor activity of **Mn-01** against Swiss albino mice bearing EAC/DOX and EAC/S. The IC_{50} values at 72 h of **Mn-01** treatment in CEM/ADR 5000 and CCRF/CEM leukemic cells were 1.08×10^{-4} M and 4.3×10^{-4} M, respectively. To obtain information on the cytotoxicity of normal cells, **Mn-01** was also tested in PBMC. The results suggest that **Mn-01** is non-toxic to normal PBMC cells and is more active in CEM/ADR 5000 cells than in CCRF/CEM cells. It was concluded that the complex disclosed a relevant antitumor

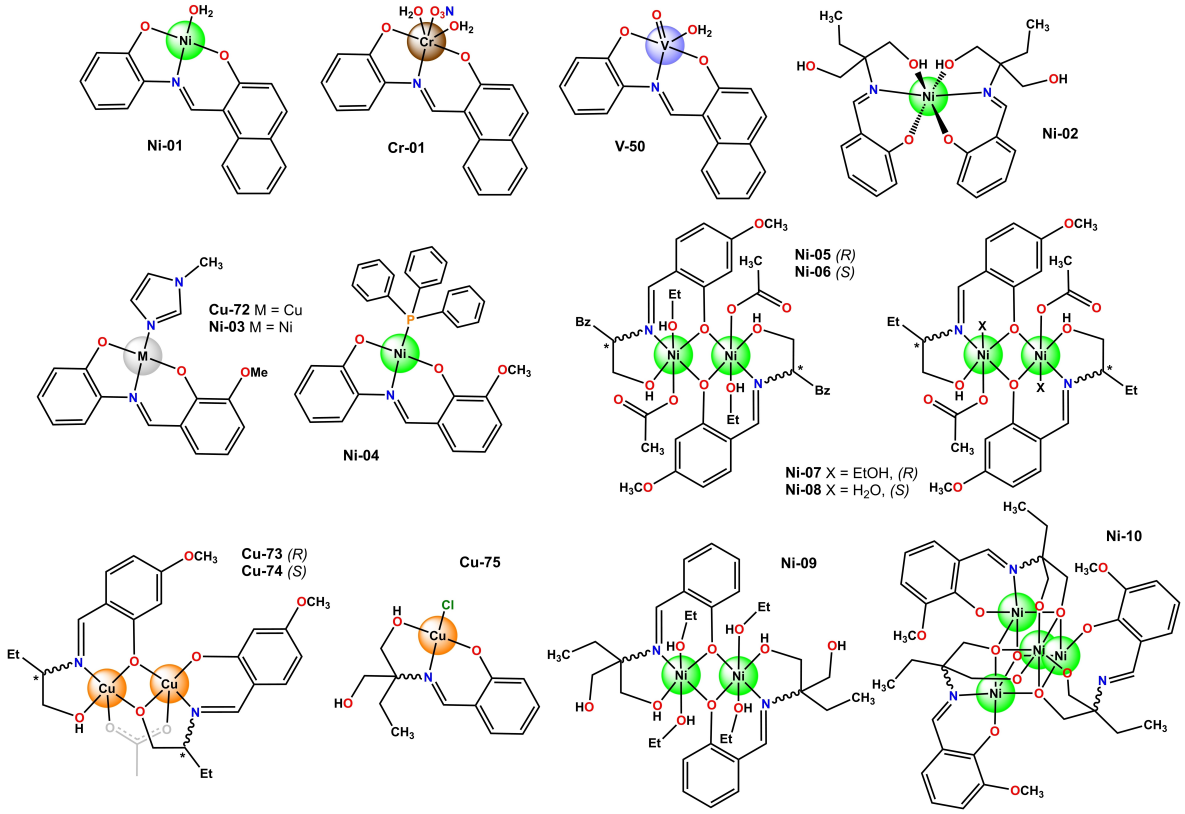

Figure 12. Nickel(II) and other transition metal complexes (**Ni-01**–**Ni-10**) obtained from tridentate Schiff bases ONO.

Table 10. Summary of nickel(II) complexes coordinated to ONO ligands with better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [μM]	Main feature	Ref.
Ni-02	Octahedral	24	A-549	31.98 ± 1.6	Anticancer activity depends on its high ability to bind to DNA and interact with BSA	[108]
			HCT-116	59.84 ± 3.3		
			HL-60	> 100		
			Caco-2	> 100		
Ni-11		48	HCT-116	11.33[a]	The anticancer activity depends on the positive charge of the central metal, the nature of the ligand and the hydrogen bonds	[119]
			MCF-7	3.42[a]		

[a] μg μL^{-1}.

effect in sensitive and resistant tumour-bearing mice. Besides, it was shown that **Mn-01** effectively induces apoptosis by killing CEM/ADR5000 cells probably through the generation of ROS.[111]

Manganese(II/IV) complexes have recently been reported to show anticancer activity, thus they have become the subject of extensive research. Besides, manganese complexes are of considerable interest due to their important applications in biological systems and also because manganese is less environmentally damaging than other transition metals. In this regard, Li *et al.* reported four isomers of chiral manganese(IV) complexes with Schiff-base ligands, **Mn-02**–**Mn-05**. In **Mn-02** and **Mn-03** the coordination geometry of the manganese(IV) centre is octahedral, since the **Mn-02** and **Mn-03** complexes are a pair of enantiomers that have similar crystal structures. In the **Mn-04** and **Mn-05** complexes, the manganese(IV) atom is hexacoordinated with octahedral geometry, due again to the fact that **Mn-04** and **Mn-05** are enantiomers. The results showed that **Mn-03** and **Mn-05** complexes (*S* configuration) exhibited more efficient DNA (calf thymus) interactions with respect to the **Mn-02** and **Mn-04** complexes (*R* configuration). Therefore, it follows that the interactions of chiral complexes with DNA/BSA are stronger than those of non-chiral complexes. All complexes showed cytotoxicity against A-549, HeLa, HL-60 and Caco-2 cell lines (MTT assay after 48 h of incubation). However, IC_{50} (μM) values displayed that **Mn-02** is superior to the others in three cell lines (A-549 = 22.07 ± 1.34, HeLa = 12.04 ± 1.21 and HL-60 = 11.16 ± 1.06), which is consistent with the ability of this complex to bind to DNA and cause a conformational change on it. Only **Mn-01** showed a better IC_{50} value for the Caco-2 cell line, outperforming the other three compounds (IC_{50} = 17.60 ± 1.24 μM). Each complex displayed an unlike inhibition effect against the four cell lines tested despite being isomers. In the words of the authors, the absolute configuration could work in different ways addressing different cellular responses.[112]

Manganese(II), copper(II), and zinc(II) complexes have been extensively studied due to their potential use in drug synthesis, bioinorganic chemistry and industrial catalysis. The most relevant of these compounds is that they have been reported as inhibitors of the proliferation of some cancer cells. In this context, Chang *et al.* reported three new complexes of manganese(II) or copper(II), **Mn-06** $[Mn(L^1)_2]$ L^1 = (*S*)-2-phenyl-2-(2-hydroxy-5-chlorobenzylideneamino)ethane-1-ol, **Mn-07** $[Mn_3(L^2)_2(OAc)_4(H_2O)_2]$ L^2 = (*S*)-2-phenyl-2-(2-hydroxy-3-methoxybenzylideneamino)ethane-1-ol and **Cu-59** $[Cu(L^3)]_4$ L^3 = (*R*)-2-(2-hydroxy-5-chlorobenzylideneamino)butane-1-ol. The activity of the **Cu-59** cluster was extensively discussed in section 2.2. The structure of the neutral mononuclear complex **Mn-06** showed a hexacoordinated octahedral geometry around the manganese(II) ion, while the structure of the neutral trinuclear complex **Mn-07** displayed the three manganese(II) ions hexacoordinated with octahedral geometry conferred by the two ligands, the four acetate ions and the two water molecules. All three complexes had efficient cytotoxicity against HeLa, MDA-MB-231 and A-549 cells compared to cisplatin (MTT assay and 48 h of treatment). Outstandingly, **Cu-59** was more potent against MDA-MB-231 cells than the other two manganese complexes **Mn-06** and **Mn-07** with an IC_{50} value of 6.20 ± 0.79 μM. Of the three compounds, **Mn-06** showed the weakest anticancer effect in the three cell lines tested; while **Mn-07** had the best inhibitory effect against HeLa with an IC_{50} value of 10.54 ± 1.02 μM. It is important to mention that all the complexes presented greater cytotoxicity than cisplatin (IC_{50} > 60 μM). DNA (calf thymus) revealed that **Mn-06** binds to DNA through intercalation, while **Cu-59** and **Mn-07** interact with DNA probably through electrostatic and groove binding mode. The authors concluded that metal ion types, chirality, and nuclearity play an essential role in biological activity.[85]

Even though cisplatin and its analogues are deemed as one of the most important drugs in anticancer therapy, their significant side effects and growing drug resistance have restricted their clinical applications. Therefore, the anticancer activity of some metal complexes mainly relied on their ability to bind to, and subsequently disrupt DNA replication, blocking cancer cell division. In this context, in 2019 Li *et al.* synthesized four new mixed-valence manganese complexes: $[Mn^{II}Mn^{III}_2(S\text{-}L^1)_2(H_2O)_2(OAc)_4]\cdot$(**Mn-08**), $[Mn^{II}Mn^{III}_2(R\text{-}L^1)_2(H_2O)_2(OAc)_4]\cdot$(**Mn-09**), $[Mn^{II}Mn^{III}_2(S\text{-}L^2)_2(H_2O)_2(OAc)_4]$ (**Mn-10**), $[Mn^{II}Mn^{III}_2(R\text{-}L^2)_2(H_2O)_2(OAc)_4]$ (**Mn-11**). The ligands used in this work were L^1 = *(S)/(R)*-4-chloro-2-(((1-hydroxybutan-2-yl)imino)methyl)phenol and L^2 = *(S)/(R)*-2-(((1-hydroxy-3-phenylpropan-2-yl)imino)methyl)-5-methoxyphenol. The authors showed that all complexes are hexacoordinated mixed-valence trinuclear manganese compounds, ideally with distorted tetragonal bipyramidal geometry in each of them. The linear Mn^{III}-Mn^{II}-Mn^{III} cores are triply bridged by acetate, phenolate, and alkoxy groups. Since **Mn-08** and **Mn-09** as well as **Mn-10** and **Mn-11** are enantiomers, the coordination modes are exactly similar to each other. The asymmetric unit consists of three manganese atoms, two deprotonated chiral Schiff base ligands, four acetate ions, and two water molecules. Concerning the antiproliferative

test, all complexes disclosed moderate cytotoxicity activity against Hep-G2, MDA-MB-231 and A-549 (MTT assay and 48 h of exposure). The most outstanding IC_{50} values (μM) were **Mn-08** (A-549, 11.59 ± 1.06; MDA-MB-231, 10.78 ± 1.03), **Mn-09** (A-549, 7.24 ± 0.86; MDA-MB-231, 15.66 ± 1.20), **Mn-10** (A-549, 10.69 ± 1.03; MDA-MB-231, 6.14 ± 0.79; Hep-G2, 21.85 ± 1.34), **Mn-11** (MDA-MB-231, 18.44 ± 1.279; Hep-G2, 25.90 ± 1.41) and cisplatin (A-549, > 100; MDA-MB-231, 24.08 ± 1.40; Hep-G2, 26.84 ± 1.28). As expected, the free ligands did not show any significant antiproliferative activity. In general, complexes derived from *(S)*-ligands were more potent in inhibiting the growth of cancer cell lines than those derived from *(R)*-ligands. The authors think that the *(S)*-ligands probably contribute to improving cellular uptake, thereby enhancing the anticancer activity. Furthermore, **Mn-10** exhibited better inhibition capacity on MDA-MB-231 cells than the other derivatives, while **Mn-09** showed weaker effects against Hep-G2 cells. All four complexes bound to DNA (calf thymus) via an intercalative mode, and *(S)*-Schiff base derivatives exhibited a stronger interaction with DNA than *(R)*-Schiff base derivatives. According to the authors, the chirality and structure of the ligands had a great influence on the BSA-/DNA-binding capacity and the cytotoxicity of manganese (II/III) complexes[113] (Figure 13, Table 11).

2.7. Iron(III) compounds

Recently, an innovative technology is being extensively researched to develop frontier science in photo-chemotherapeutic agents. This technology aims to direct it to other organelles instead of the cell nucleus to avoid the disadvantages associated with nuclear DNA targeting anticancer drugs. Using the mitochondria as a target provides a novel pathway for apoptotic cell death. Another equally useful strategy could be to target the endoplasmic reticulum to induce protein folding stress. Thus, the use of tumour-specific delivery agents could improve the efficacy of anticancer agents by distinguishing normal cells from tumour cells. As depicted by Basu *et al.*, five iron(III) complexes (**Fe-01**–**Fe-05**) derived from *N*-substituted dipicolylamines with pyridoxal (VB_6) and salicylaldehyde Schiff-bases were prepared, and their phototoxicity and uptake in cancer cells were studied. Here, the pyridoxal moiety was expected to facilitate the diffusion of the complexes within cells

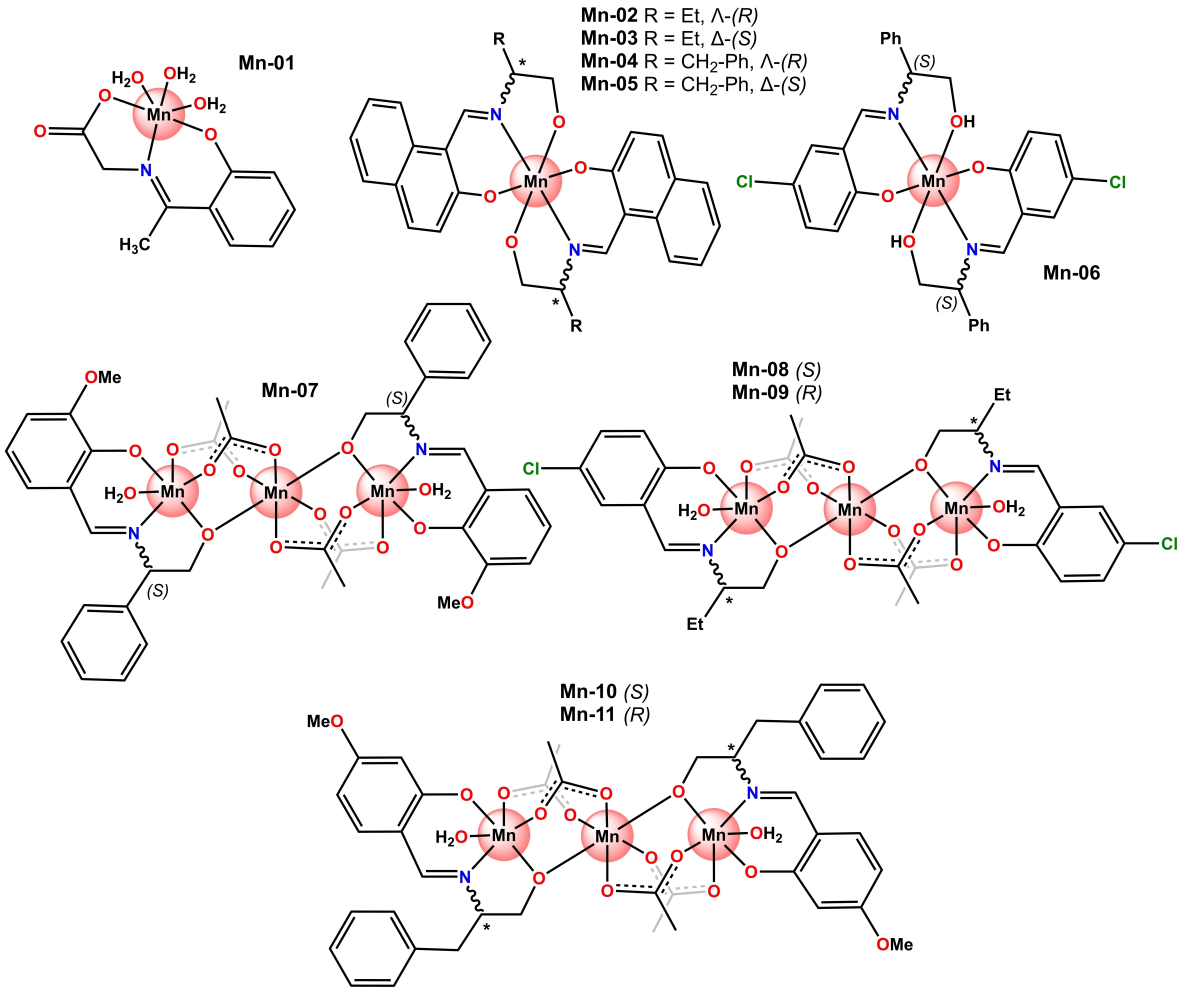

Figure 13. Manganese(II/III/IV) complexes (**Mn-01**–**Mn-11**) obtained from tridentate Schiff bases ONO.

Table 11. Summary of manganese(II/III) complexes coordinated to ONO ligands with better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [μM]	Main feature	Ref.
Mn-07	Octahedral	48	HeLa	10.54 ± 1.02	Anticancer activity depends on metal ion types, chirality and nuclearity	[85]
Mn-08				11.59 ± 1.06		
			A-549	10.78 ± 1.03		
Mn-09			MDA-MB-231	7.24 ± 0.86		
				15.66 ± 1.20		
Mn-10			A-549	10.69 ± 1.03	Anticancer activity depends on the chirality and structure of the ligands	[113]
			MDA-MB-231	6.14 ± 0.79		
			Hep-G2	21.85 ± 1.34		
Mn-11			MDA-MB-231	18.44 ± 1.279		
			Hep-G2	25.90 ± 1.41		

ensuring faster cellular uptake and thus better cytotoxicity. All complexes were monocationic and have a distorted hexacoordinate octahedral FeN_4O_2 core, where the metal has a 3+ oxidation state with five unpaired electrons. MTT assays showed that **Fe-01** did not present significant photocytotoxicity (IC_{50} > 40 μM) when irradiated with visible light (400–700 nm). Nonetheless, **Fe-02** and **Fe-03** exhibited moderate phototoxicity in visible light for HeLa, MCF-7, HaCaT and A-549 cell lines with IC_{50} values ranging between 0.4 and 6.6 μM with ten times lower dark toxicity. The non-vitamin compounds (**Fe-04** and **Fe-05**) displayed three times lower phototoxicity (IC_{50} = 7.2–20.0 μM) compared to their VB_6 analogues, possibly due to preferential and faster uptake of the VB_6 complexes in the cancer cells. Interestingly, none of the complexes showed pronounced dark toxicity with IC_{50} values > 50 μM. The authors also observed a selective photocytotoxicity of complexes containing a pyridoxal derivative towards cancer cells over normal cells (HPLD1, IC_{50} = 26.3–88.6 μM), suggesting better uptake properties of the VB_6 group. Regarding the uptake in the endoplasmic reticulum, **Fe-02** and **Fe-03** showed significant results, while **Fe-04** and **Fe-05** are distributed throughout the cells without any specific localization pattern.[114]

PDT research using metal complexes has recently focused on developing compounds that act selectively on cancer cells rather than normal cells and on selective drug localization in a particular cell organelle rather than other organelles. In this context, iron(III) is an element found in the human body as part of various enzymatic processes, and VB_6 plays an important role in several cellular processes by acting as a cofactor. Both could be combined to furnish metal complexes that could enhance cellular uptake. As described by Sahoo *et al.*, four iron(III) complexes (**Fe-06**–**Fe-09**), which are derived from functionalised *N*-BODIPY dipicolylamines with pyridoxal (VB_6) or salicylaldehyde Schiff-bases were prepared and studied in PDT. Here, VB_6 was expected to facilitate the uptake of the coordination complex selectively into cancer cells over healthy cells. The donor dipicolylamine ligand NNN attached to BODIPY in the structure of **Fe-07** and **Fe-08** was expected to produce $^1O_2$ generating light-induced cell death through a type-II pathway that is identified in the photofrin® mechanism. **Fe-07**–**Fe-09** contain BODIPY, which is highly emissive and could be utilised for cell imaging to identify the target organelle of these compounds. **Fe-09** contains a salicylaldehyde Schiff-base instead of VB_6. **Fe-06** lacks photosensitizing groups and was employed as a control to determine the photosensitizing capacity of the other compounds. The four complexes were studied using three cancer cell lines HeLa, MCF-7, Hep-G2 and a non-cancer cell line HPL1D MTT assay). In general, all complexes showed significant phototoxicity on cancer cell lines and were relatively non-toxic under dark conditions. The IC_{50} values of the **Fe-06** control complex under light conditions (400-700 nm) were greater than 100 μM in all cell lines tested. In the case of **Fe-07**, the IC_{50} values under light conditions were significantly low (HeLa, 5.5 ± 1.2 μM; MCF-7, 3.25 ± 0.08 μM and Hep-G2, 3.9 ± 0.6 μM) due to the presence of the photosensitizing BODIPY unit. Outstandingly, **Fe-08** showed noteworthy values (HeLa, 0.11 ± 0.08 μM; MCF-7, 0.20 ± 0.04 μM and Hep-G2, 0.22 ± 0.01 μM) even outperforming photofrin® (HeLa, 4.3 ± 0.2 μM), and was 200 times less cytotoxic in the dark (IC_{50} > 100 μM). The authors suggest that the complex with I_2-BODIPY (**Fe-08**) exhibited supercoiled pUC19 cleavage activity and a high quantum yield of $^1O_2$ as a ROS. Another advantage was that all complexes remained essentially non-toxic in HPL1D cells under both light (IC_{50} > 50 μM) and dark (IC_{50} > 100 μM) conditions[115] (Figure 14, Table 12).

Table 12. Summary of iron(III) complexes coordinated to ONO ligands with better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [μM]	Main feature	Ref.
Fe-08	Octahedral	1[a]	HeLa	0.11 ± 0.08	Anticancer activity depends on BODIPY, pyridoxal (VB_6) and iodine in the structure	[115]
			MCF-7	0.20 ± 0.04		
			Hep-G2	0.22 ± 0.01		
			HPLD1	> 50		

[a] Photo-exposed.

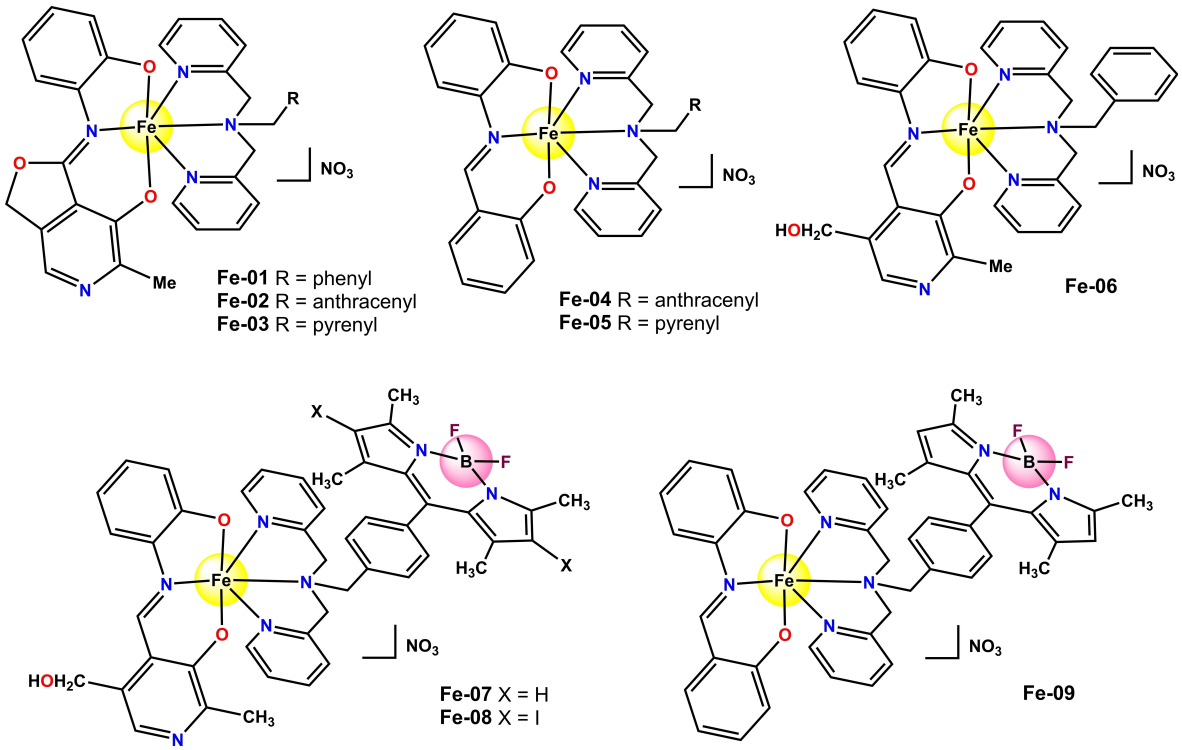

Figure 14. Iron(III) complexes (**Fe-01**–**Fe-09**) obtained from tridentate Schiff bases ONO.

2.8. Cobalt(II/III) compounds

In recent years, ONO donor tridentate Schiff ligands have attracted attention due to their important biological applications. Recently, Ghosh *et al.* reported this type of ligand and its cobalt(III) complex as antiproliferative agents against some cancer cells. Here, the $[CoL_2]Et_3N$ (L = 2-(2-hydroxybenzylideneamino)phenol) named **Co-01** was obtained as a slightly distorted octahedral complex, where the cobalt(III) ion coordinates with two ONO donors tridentate Schiff bases ONO donors and the overall charge of the complex is counterbalanced by Et_3NH^+. The antiproliferative activity of **Co-01** was compared to cisplatin using HeLa cells at a concentration of 0.05–0.5 μM (MTT assay after 48 h and 72 h of exposure). It was observed that the higher the concentration of the complex, the higher the antiproliferative activity; however, IC_{50} values are not reported. **Co-01**, at a concentration of 0.5 μM, presented the maximum activity. In addition, the analysis showed the best inhibitory action of cisplatin at 0.5 μM, while **Co-01** exhibited comparatively less inhibitory action for HeLa cells at the same concentration. The authors support their results by proposing that chelation generally reduces the polarity of metal ions by sharing their positive charge with donor groups, due to π-electrons delocalization throughout the chelate ring. Chelation could enhance the lipophilic character of the central metal atom, which may help it penetrate through the lipid layer of the target cell membrane. The lipophilicity of the metal complex is perhaps responsible for better anticancer activity, together with the interaction of hydrogen bonds between the donor groups of the cobalt(III) complex (C=N) with the existing bio-receptors in the cell.[116]

Since cancer represents an important threat to mankind, the scientific community has studied platinum-based metallodrugs as a potential treatment for this disease. Nonetheless, due to toxic side effects and drug resistance phenomena, the research of new technologies is an active endeavour among chemists. Various transition metals have been studied, and cobalt complexes are among the most encouraging and promising candidates for generating anti-cancer drugs. Besides, cobalt is so important that it can be found as a metal centre in VB_{12} and is involved in several biological processes. On the other hand, phenolic ligands derived from Schiff bases have been used in the field of medicinal chemistry, since they can form stable complexes that allow the design of new chemotherapeutic agents. Mondal *et al.* prepared new cobalt(III) complex and tested it against the MCF-7 and A-549 cell lines based on these observations (MTT assay). Some other complexes of copper(II) and cobalt(II) with bidentate Schiff bases were also published in this article, curiously **Co-02** was the only compound coordinated to two tridentate Schiff bases in a distorted octahedral arrangement around the metal centre of cobalt(III). In addition, **Co-02** showed an outstanding antiproliferative activity, surpassing the rest of the complexes. The IC_{50} values after 48 h of treatment were 2.46 and 2.77 μM for the A-549 and MCF-7 cell lines, respectively, and were lower than the cisplatin values (IC_{50} = 25 and 15 μM, respectively). The authors hypothesized that the higher DNA-binding affinity and higher K_b value are possible reasons for the increased cytotoxic activity of **Co-02**.

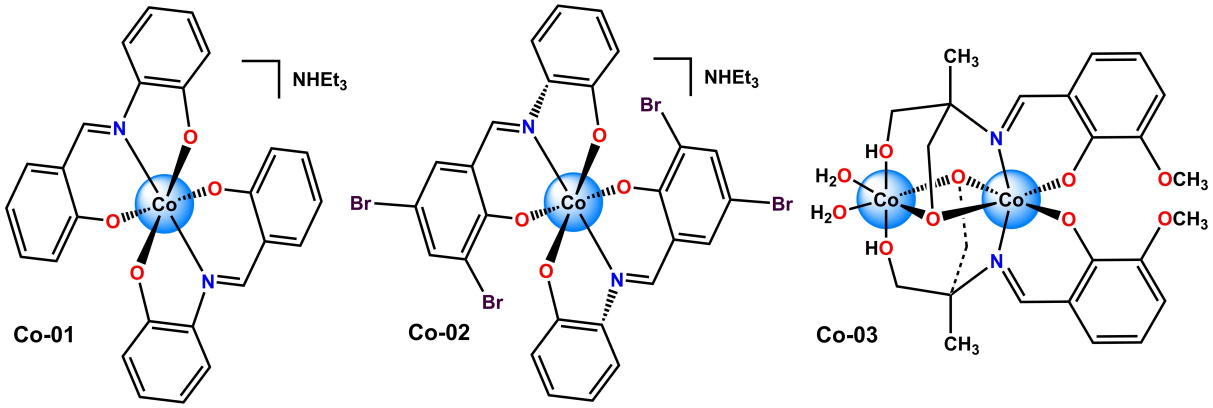

Figure 15. Cobalt(II/III) complexes (**Co-01**–**Co-03**) obtained from tridentate Schiff bases ONO.

Additional experiments confirm that **Co-02** binds to DNA (calf thymus) in a non-intercalated manner, that it is an excellent inhibitor of BSA fluorescence intensity via the static pathway, and that it induces cell death by apoptosis by generating ROS through cellular oxidative stress.[117]

As a part of the research program by Ahamad *et al.* in finding antiproliferative agents, described in 2019 the coordination chemistry and biological evaluation of the novel dinuclear complex **Co-03** with the formula $[Co_2(HL)_2(H_2O)_2]$. XRD analysis showed that the complex is dinuclear with a distorted octahedral environment around both cobalt(II) metal centres. In this case, the Schiff base named 2-((2-hydroxy-3-methoxybenzylidene)amino)-2-methylpropane-1,3-diol coordinates tetradentally and loses only two of the three possible protons in its hydroxyl groups. **Co-03** showed moderate anticancer activity (MTT assay) towards HeLa and A-549 cancer cell lines with IC_{50} values of 30.20 and 30.88 μM, respectively, after 24 h of treatment; as well as 7.34 and 20.29 μM, respectively, after 48 h of treatment. Therefore, **Co-03** presented better anticancer activity than cisplatin (IC_{50}, 24 h, HeLa = 10.5 μM and A-549 = 21.3 μM; 48 h, HeLa = 16 μM and A-549 = 40 μM). Additionally, **Co-03** exhibited apoptosis in HeLa cells by showing blebs with conspicuous morphology[118] (Figure 15, Table 13).

2.9. Titanium(IV) compounds and other metals

Lately, cancer treatment with chemotherapeutic agents has focused on DNA. In this endeavour, nanotechnology has proven to be a useful tool, with which the goal is to manufacture nanostructures with special properties to obtain novelty particles. As depicted by Abdel-Rahman *et al.* it is possible to synthesize three novel nano-sized complexes (**Cu-76**, **Co-04**, and **Ni-11**) from 2-amino-3-hydroxypyridine and 3-methoxysalicylaldehyde. The results reported by this research group showed that **Co-04** and **Ni-11** had an octahedral geometry, while **Cu-76** had a tetrahedral geometry. Cytotoxicity was studied using HCT-116 and MCF-7 cancer cell lines (SRB assay and 48 h of incubation), and the complexes showed significant cytotoxic activities. In the case of MCF-7, the anticancer activity follows the order **Co-04** (IC_{50} = 3.30 μg/μL) > **Ni-11** (IC_{50} = 3.42 μg/μL) > **Cu-76** (IC_{50} = 7.40 μg/μL), whereas using HCT-116 the biological activity showed a reverse trend **Cu-76** (IC_{50} = 3.26 μg/μL) > **Co-04** (IC_{50} = 4.88 μg/μL) > **Ni-11** (IC_{50} = 11.33 μg/μL). These tendencies were within the 0–10 μM concentration range and all complexes showed potent cytotoxic activity against all the cancer cell lines compared to the vinblastine standard. In the words of the authors, the improvement of cytotoxicity could be explained in terms of the positive charge of the metal that increased the acidity of the proton-carrying coordinated ligand, causing stronger hydrogen bonds. Additionally, the results showed that the investigated complexes could bind to DNA through an intercalative mode. The authors

Table 13. Summary of cobalt(II/III) complexes coordinated to ONO ligands with better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [μM]	Main feature	Ref.
Co-02	Octahedral	48	A-549	2.46	Anticancer activity depends on higher DNA binding affinity and higher K_b value	[117]
			MCF-7	2.77		
Co-03			HeLa	7.34	Anticancer activity depends on structural changes in complexes	[118]
			A-549	20.29		
Co-04			HCT-116	4.88[a]	The anticancer activity depends on the positive charge of the central metal, the nature of the ligand and the hydrogen bonds	[119]
			MCF-7	3.30[a]		

[a] μg $μL^{-1}$.

suggest that changing the coordination sites in the complexes and the nature of the metal ion has an impact on antiproliferative activity by modifying the binding ability of DNA.[119]

Chromium(III) and iron(III) are important transition metals in several biological processes. For instance, iron(III) complexes are part of heme iron enzymes. While chromium (III) is an important nutrient for glucose tolerance factors to maintain normal carbohydrate and lipid metabolism. Derived from these observations, Abdel-Rahman *et al.* reported complexes derived from chromium(III), iron(III) and ruthenium(III) with an imine ligand synthesized from *o*-vanillin and 2-amino-3-hydroxypyridine. The isostructural derivative of ruthenium(III) reported by the same authors is discussed in section 3.2. Thus, the **Cr-02** and **Fe-10** complexes were studied using the HCT-116, MCF-7 and Hep-G2 cancer cell lines within the concentration range from 0 to 10 μM (SRB assay after 24 h of exposure). The results showed that the different coordination positions and the metal affect the biological potency. Both metal-imine complexes showed strong antiproliferative activity against HCT-116, with IC_{50} values of 4.86 and 5.90 μM, respectively. In the case of the MCF-7 cancer cell line, the result showed potent activity with IC_{50} values of 3.54 and 5.77 μM, respectively. Additionally, the Hep-G2 cancer cell line, also revealed potent antiproliferative activity with IC_{50} values of 1.97 and 3.97 μM, respectively. However, although these values are very relevant, they do not exceed the results found with the reference drug vinblastine (IC_{50}, HCT-116 = 4.79 μM, MCF-7 = 0.55 μM and Hep-G2 = 1.24 μM). The antiproliferative activity *versus* cancer cell lines increases in the order **Cr-02** > **Ru-02** > **Fe-10** and this coincides with the K_b values that have the same order. The authors think that the antiproliferative potency of these complexes could be attributed to the metal that has the positive charge, as a result, the acidity of the proton-carrying imine is raised, which led to the existence of hydrogen bonds that are stronger and improve biological activity. Furthermore, **Cr-02**, **Ru-02** and **Fe-10** strongly interact with DNA through intercalative binding mode.[120]

Chromium(III), zinc(II), and copper(II) have a great affinity for coordination due to their small size and high nuclear charge. Therefore, these transition metals can be used to develop metallodrugs that could serve as chemotherapeutic agents. In this context, Abu-Dief *et al.* prepared novel azomethine chelates of chromium(III), zinc(II), and copper(II) with the tridentate ligand 2-[(2-hydroxyphenylimino)methyl]-6-methoxyphenol. Therefore, the synthesized **Cr-03**, **Zn-15** and **Cu-77** complexes showed distorted octahedral, square planar and tetrahedral geometries, respectively. A fourth compound (**Pd-01**) with the same ligand but with a third transition series metal, palladium, is discussed in section 3.3. The antiproliferative activity was investigated against the HCT-116, Hep-G2 and MCF-7 cell lines by MTT assay after 48 h of exposure. The results displayed that cell proliferation is inhibited for all complexes in a dose-dependent manner exhibiting the following **Cu-77** > **Zn-15** > **Cr-03** trend. The IC_{50} values (μg/μL) reported for the best compound of this triad, **Cu-77** (HCT-116, 30.4 ± 0.08; MCF-7, 15.7 ± 0.31 and Hep-G2, 20.9 ± 0.16), do not exceed those reported for the standard drug vinblastine (HCT-116, 13.5 ± 0.07; MCF-7, 4.15 ± 0.13 and Hep-G2, 8.00 ± 0.05). The higher cytotoxicity exhibited by **Cu-77** can be attributed to the stronger binding ability of this complex with DNA. The authors mention that the cytotoxicity of metal chelates depends on their ability to bind DNA and thus damage its structure, which is followed by inhibition of replication and transcription processes and, eventually, cell death.[121]

Titanium(IV) is a widely useful transition metal for several applications due to its low toxicity and relative abundance on the earth. However, titanium(IV) complexes used as antiproliferative agents have failed phase II trials due to rapid hydrolysis and low efficacy. Trying to sidestep these difficulties, Shpilt *et al.* have reported six homoleptic titanium(IV) complexes coordinated with dianionic tridentate Schiff base ligands ONO with different substitution patterns. The complexes were prepared from chiral amino acids, 2-hydroxybenzaldehyde and titanium(IV) isopropoxide, to generate **Ti-01**–**Ti-06**. The electronic and steric properties of the ONO donor groups and their spatial separation in the ligand were adjusted by selecting several amino acids with chiral groups. The amino acids used in this work were L-alanine (**Ti-01**), L-valine (**Ti-02**), L-isoleucine (**Ti-03**), L-leucine (**Ti-04**), L or D-phenylalanine (**Ti-05**) and L-tryptophan (**Ti-06**). The antiproliferative study displayed modest cytotoxicity using A-2780 and HT-29 cancer cells (MTT assay and 72 h of treatment), with IC_{50} values ranging from 23 to 48 μM for A-2780, and 36 to 103 μM for HT-29. Nonetheless, the values were higher than those found for cisplatin (IC_{50} = 1.6 ± 0.3 for A-2780 and 12.2 ± 2.3 for HT-29). The authors also conclude that the six titanium(IV) complexes studied had poor hydrolytic stability. Among these complexes, **Ti-03** displayed both more activity and more stability (IC_{50} = 23.0 ± 2.0 for A-2780, 36.2 ± 2.4 for HT-29, $T_{1/2}$ = 15 ± 2 h), which could be attributed to the higher steric bulk, which prevents interactions with water molecules,[122] Figure 16.

3. Complexes with tridentate Schiff bases ONO with metals of the second or third transition series

3.1. Platinum(II) compounds

Currently, there are very few studies on the anticancer or antitumor properties of coordination compounds of elements of the second or third transition series coordinated to trivalent Schiff bases of the ONO type. in this way, the most explored metals are platinum, ruthenium, palladium, molybdenum and tantalum, which are described in the next section. Li *et al.* reported a study of eleven monochlorinated cationic platinum(II) compounds coordinated to Schiff bases derived from amino acids. The platinum(II) complexes **Pt-01**-**Pt-11** presented certain selectivity towards the HeLa cells *versus* A-549 cells and exerted a certain cytotoxic effect on it, showing IC_{50} values comparable to those of cisplatin (CCK-8 assay and 24 h treatment). **Pt-05** (IC_{50} = 25.65 μM) displayed a moderate cytotoxic effect against HeLa cells; however, **Pt-06** (IC_{50} =

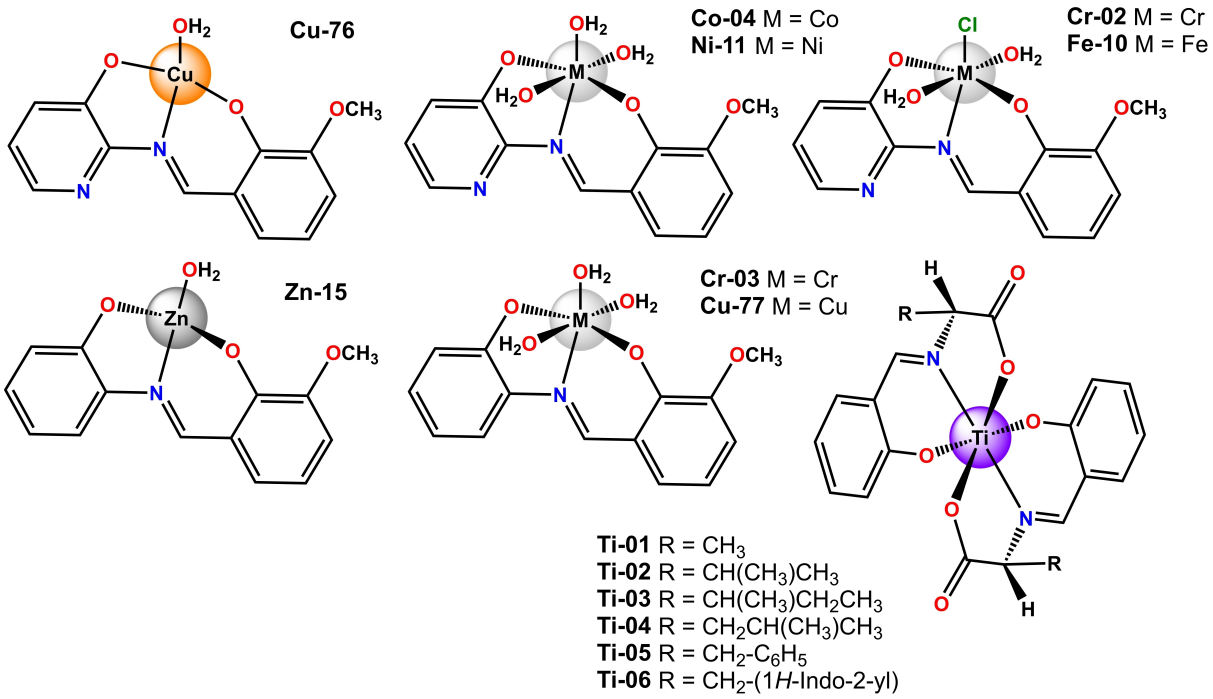

Figure 16. Titanium(IV) and other transition metal complexes (**Ti-01**–**Ti-06**) obtained from tridentate Schiff bases ONO.

21.93 μM), **Pt-10** (IC_{50} = 21.05 μM) and **Pt-11** (IC_{50} = 19.14 μM) exhibited better cytotoxic activities against HeLa cell line compared to cisplatin (IC_{50} = 25.23 μM). The most notable IC_{50} values in the A-549 cell line were for the **Pt-09** (IC_{50} = 40.79 μM) and **Pt-10** (IC_{50} = 48.16 μM) compounds; however, they are twice as large as that reported for cisplatin (IC_{50} = 23.02 μM). The SAR suggests that the presence of a bromine substituent at the C5 position of the Schiff bases enhanced the cytotoxic activity (**Pt-09**–**Pt-11**). This substitution made the phenolic hydroxyl group more acidic and the Pt–O bond less stable, facilitating its hydroxylation and coordination with DNA guanine residues. Therefore, compounds with electron donor groups in the same position (C5) have decreased antitumor activity (**Pt-06**–**Pt-08**), since the phenolic hydroxyl group is more alkaline in the Schiff base and the Pt–O bond is more stable, which makes it difficult to coordinate to DNA guanine residues[123] (Figure 17, Table 14).

3.2. Ruthenium(III) compounds

Novel ruthenium-based drugs are known to have shown outstanding antitumor activity with several advantages over classical platinum-based drugs.[124] Therefore, Alsalme *et al.* synthesized and characterized the complexes of platinum(II) and ruthenium(III) from the tridentate Schiff base named 2-((2,3-dihydroxybenzylidene)amino)-3-methylbutanoic acid. In addition, they evaluated the cytotoxicity of the compounds in the mitochondrial metabolism of the Hep-G2 cell line, exposed for 24 h using the MTT assay. The observed results indicated a decrease in the viability of the Hep-G2 cell line when treated with both complexes. **Ru-01** with octahedral geometry induced more cell death compared to **Pt-12** with square planar geometry. The inhibition of cell metabolism was statistically significant at higher concentrations of **Pt-12** (30 μM), while at lower concentrations of **Ru-01** (20 μM), almost the same degree of inhibition (50%) of viable cells was obtained. Therefore, the IC_{50} value of **Pt-12** (30 ± 0.7 μM) and **Ru-01** (20 ± 0.2 μM) were better than that of the commercial drug cisplatin (26.8 μM) and that of the free ligand (> 100 μM). Other studies showed that

Table 14. Summary of platinum(II) complexes coordinated to ONO ligands with better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [μM]	Main feature	Ref.
Pt-06 Pt-10 Pt-11	Square planar	24[a]	HeLa	21.93 21.05 19.14	Anticancer activity depends on the inductive effect and the position of the substituents in the ligand (*trans* effect).	[123]

[a] CCK-8 assay.

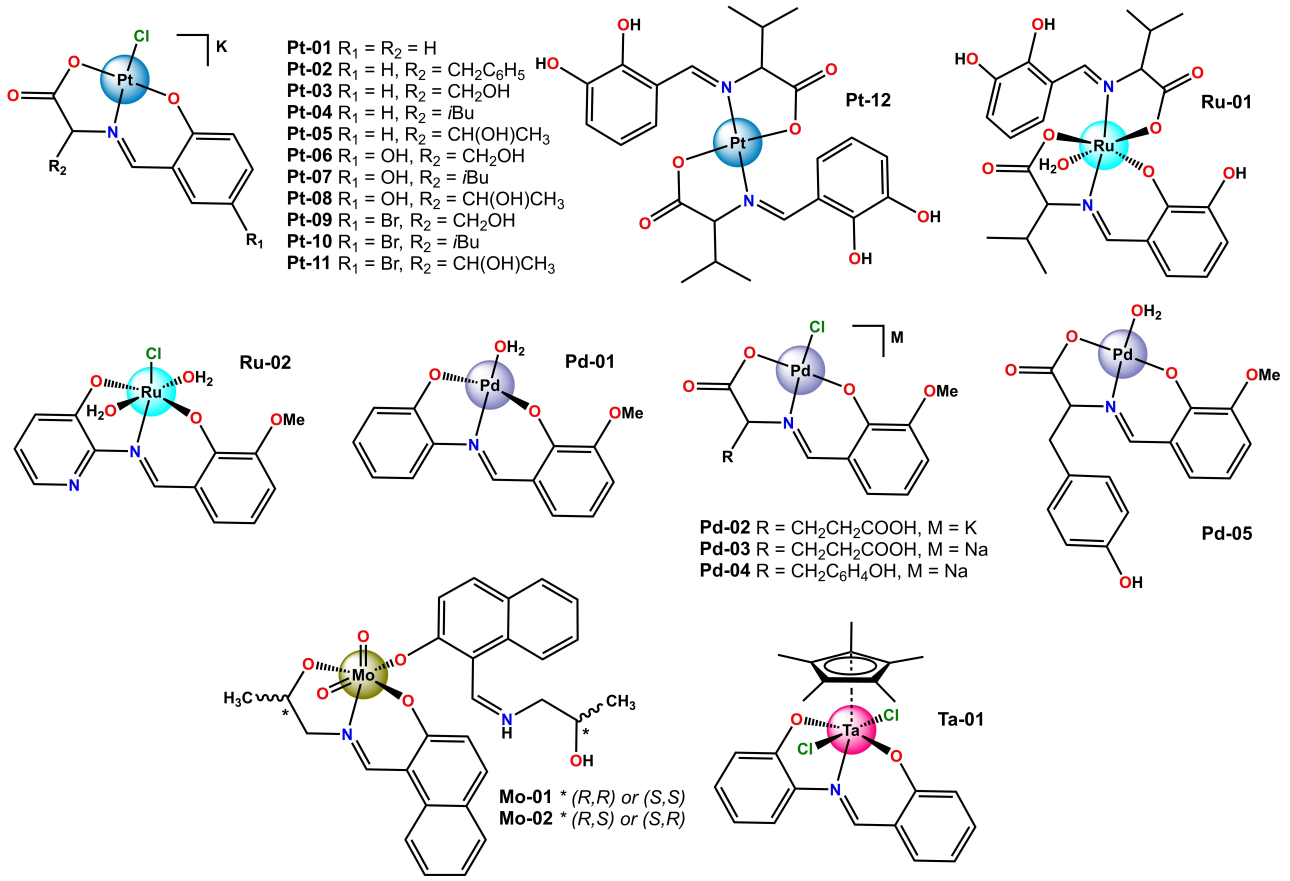

Figure 17. Complexes of the second or third transition series (**Ta-01**–**Ta-06**) obtained from tridentate Schiff bases ONO.

the cytotoxic activity of **Pt-12** and **Ru-01** affected the function of lysosomes in Hep-G2. **Ru-01** caused a greater decrease in lysosomal activity at 20 μM concentration, while **Pt-12** showed significant cellular toxicity at 30 μM concentration. **Ru-01** displayed a greater affinity for the HSA protein, more generation of ROS and greater cytotoxicity against Hep-G2 cells, showing the important role of protein binding in cytotoxicity.[125]

In this same line, the study of three new complexes of chromium(III), iron(III) and ruthenium(III) coordinated to the tridentate ligand ONO named 2-((2-hydroxy-3-methoxybenzylidene)amino)pyridin-3-ol was reported. **Cr-02** and **Fe-10** were already discussed in section 2.9; so in this section, we will focus on the octahedral complex **Ru-02**. The cytotoxic potency of **Ru-02** was determined in three human tumour cell lines HCT-116, MCF-7 and Hep-G2 after exposure for 24 h by SRB colourimetric assay. The results demonstrated a strong cytotoxic activity against the three cancer cell lines HCT-116 (IC_{50} = 5.11 μM), MCF-7 (IC_{50} = 3.97 μM) and Hep-G2 (IC_{50} = 2.66 μM). However, although these values are very relevant, they do not exceed the results found with the reference drug vinblastine (IC_{50}, HCT-116 = 4.79 μM, MCF-7 = 0.55 μM and Hep-G2 = 1.24 μM). The strong anticancer activity of the complexes with respect to the free ligand (IC_{50}, HCT-116 = 9.56 μM, MCF-7 = 6.63 μM and Hep-G2 = 8.88 μM) could be attributed to the presence of the metal positively charged, which increased the acidity of the protons in the ligand, leading to stronger hydrogen bonds, improving the cytotoxic potency. The general trend observed in anticancer activity in this paper increased in the order: vinblastine > **Cr-02** > **Ru-02** > **Fe-10** > free ligand. This is in agreement with the values of the binding constants (intercalative mode) of these complexes with DNA (calf thymus) since they followed the same trend[120] (Figure 17, Table 15).

Table 15. Summary of ruthenium(III) complexes coordinated to ONO ligands with better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [μM]	Main feature	Ref.
Ru-01	Octahedral	24	Hep-G2	20 ± 0.2	The anticancer activity depends on the metal centre. In this case, ruthenium outperformed platinum.	[125]

3.3. Palladium(II) compounds

In the search for therapeutic metals, palladium has become the favourite metal in addition to platinum, due to its structural stability, the versatility of its complexes and the non-mutagenic nature of its derivatives.[126] A novel tridentate dianionic chelate derived from azomethine formed coordination complexes with copper(II), zinc(II), and chromium(III) discussed in section 2.9; but also with palladium(II). The proposed structure for the **Pd-01** compound was square planar and was determined by DFT. The cytotoxic potency of **Pd-01** was determined in three human tumour cell lines (HCT-116, MCF-7 and Hep-G2), after exposure for 48 h by MTT assay. **Pd-01** exhibited greater *in vitro* cytotoxicity against all selected cell lines compared to the ligand; however, it did not exceed the activity of the standard drug, vinblastine. These results were attributed to the higher binding capacity of **Pd-01** with DNA (calf thymus), mainly through intercalation. **Pd-01** showed greater activity against the MCF-7 ($IC_{50} = 10.7 \pm 0.25$ μg/μL) and Hep-G2 ($IC_{50} = 16.9 \pm 0.32$ μg/μL) cancer cell lines, and to a lesser extent against the HCT-116 ($IC_{50} = 22.4 \pm 0.17$ μg/μL) cancer cell line. It should be noted that the IC_{50} values for vinblastine, the standard drug, in the HCT-116, MCF-7 and Hep-G2 lines, were 13.5 ± 0.07, 4.15 ± 0.13 and 8.00 ± 0.05 μg/μL, respectively. The general trend observed in anticancer activity in this paper increased in the order: vinblastine > **Pd-01** > **Cu-77** > **Zn-15** > **Cr-03** > free ligand.[121]

Muche *et al.* reported a series of novel palladium(II) complexes coordinated to a Schiff base derived from *o*-vanillin with L-glutamic acid (**Pd-02** and **Pd-03**) or L-tyrosine (**Pd-04** and **Pd-05**) that showed moderate to good antimicrobial activity, but unfortunately no cytotoxic properties. Cytotoxicity studies were carried out on the L-929 cell line by means of MTT assay after 24, 48 and 72 h of treatment at different concentrations of palladium(II) complexes with square planar geometry. The four compounds did not display cytotoxic properties up to concentrations higher than 200 μM in the L-929 cell line. The viability of L-929 cells was in the range of 75% to 90%. The reason for this result may be related to the stability of the tested palladium(II) complexes, since it was found that **Pd-02**, **Pd-03** and **Pd-05** were stable when dissolved in DMSO even after 72 h[127] (Figure 17).

3.4. Molybdenum(VI) compounds

It is well known that molybdenum is the only element of the second row in the *d*-block that is essential for life, since in molybdoenzymes the cofactor "pterin" contains a molybdenum atom coordinated to a branched dithiolated system with amino acids. Nonetheless, the cytotoxic activity of molybdenum derivatives has been little studied.[128] In this context, the use of a Schiff base in its racemic form named *R/S*-1-(((2-hydroxypropyl)imino)methyl)naphthalen-2-ol was reported to synthesize molybdenum(VI) complexes. Two isomers were obtained, **Mo-01** which is a homochiral compound *(R,R/S,S)* and **Mo-02** which is a heterochiral compound *(R,S/S,R)*. The antiproliferative activity of both octahedral complexes was investigated in MCF-7 and HeLa cancer cell lines, as well as normal human fibroblast cells after exposure for 48 h using the MTT assay. The two diastereomers showed relatively different effects in cancer cells, as IC_{50} values were 18 and 58 μM (**Mo-01**), as well as 37 and 17 μM (**Mo-02**), for MCF-7 and HeLa, respectively. The anticancer activity of **Mo-01** in MCF-7 cells was higher than in HeLa cells; in contrast, **Mo-02** exhibited greater cytotoxicity in HeLa cells than in MCF-7 cells, indicating cell-specific activity related to chirality. In addition, **Mo-02** showed a high selectivity, three to thirteen times higher, in distinguishing between cancer cells over normal cells. In this work, the authors reported the studies of the binding of HSA and DNA with molybdenum(VI) complexes. However, there were no comparative studies with commercial anticancer drugs[129] (Figure 17).

3.5. Tantalum(V) compounds

Surprisingly, so far, only one article was found that studied the cytotoxicity of tantalum complexes derived from Schiff bases. However, tantalum and its derivatives are not new in the health area, since it is used as a material in medical implants,[130] its nanoparticles are flexible and biocompatible materials in regenerative medicine.[131,132] They have even been reported as probable agents in chemothermal synergistic therapy.[133] In the previously mentioned work, Štarha *et al.* used the Schiff base named 2-((2-hydroxybenzylidene)amino)phenol for the preparation of a novel semi-sandwich tantalum(V) complex. **Ta-01** cytotoxicity results in three different cell lines (A-2780, A-2780R and HOS) were determined by MTT assay after 24, 48 and 72 h of incubation. **Ta-01** was highly cytotoxic against the three cell lines studied (IC_{50} 24 h, **Ta-01** 8.6 ± 0.9 μM for A-2780, 16.0 ± 0.3 μM for A-2780R and 16.8 ± 2.0 μM for HOS), the IC_{50} value was twice that of cisplatin after 24 h of incubation and also exceeded oxaliplatin (IC_{50} 24 h, cisplatin 20.1 ± 0.3 μM for A-2780, 34.0 ± 1.4 μM for A-2780R and 32.6 ± 2.0 μM for HOS; oxaliplatin > 25 μM in all three cell lines). Contrary to cisplatin, the exposure time of 48 or 72 h did not significantly decrease the IC_{50} values of **Ta-01** (IC_{50} 48 h, 8.4 ± 1.9 μM A-2780, IC_{50} 72 h, 6.4 ± 0.3 μM A-2780). This compound showed greater cytotoxicity on the two cisplatin-resistant cell lines (HOS and A-2780R) than the cisplatin-sensitive cell line (A-2780). Additionally, the **Ta-01** cytotoxicity against primary human hepatocyte culture ($IC_{50} > 100$ μM) and noncancerous cell line MRC-5 ($IC_{50} > 50$ μM) was markedly lower, implying high pharmacological selectivity. In addition, **Ta-01** exhibited less cytotoxicity on MRC-5 cells, relative to cisplatin and oxaliplatin. Additional studies indicated that the accumulation of **Ta-01** in A-2780 cells after 24 h of incubation is lower compared to cisplatin. **Ta-01** did not induce cell cycle modifications and its mechanism of action is different from that of cisplatin. **Ta-01** induced apoptosis in A-2780 cells causing a loss of symmetry of the plasma membrane, which is related to the alterations in the intracellular redox state caused by the elevated formation of ROS and RNS[134] (Figure 17, Table 16).

Table 16. Summary of tantalum(V) complexes coordinated to ONO ligands with better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [μM]	Main feature	Ref.
Ta-01	Polyhedral	24	A-2780 A-2780R HOS MRC-5	8.6 ± 0.9 16.0 ± 0.3 16.8 ± 2.0 > 50	The anticancer activity depends on the metal, in this case, tantalum	[134]

4. Complexes with tridentate Schiff bases ONN with transition metals

4.1 Copper(II) compounds

Although the most widely used anticancer drugs are often coordination compounds containing noble metals such as platinum, such compounds present significant disadvantages associated with high toxic side effects and inherited or acquired drug resistance.[135] In this way, the development of platinum-free coordination compounds with anticancer activity is an essential research topic, making transition metals attractive and different to platinum. Many authors consider that copper an ideal option to replace platinum base drugs because copper is involved in different biological processes, playing an essential role in the normal function of cells.[136,137] The copper anticancer activity is associated with its interaction with N7 guanine residue, producing DNA breakages and subsequent cell death.[138,139] Since cancer cells present a higher copper affinity than normal cells, the synthesis of copper-based coordination compounds is an interesting way to produce highly selectively anticancer drugs.[140,141] The effectivity of copper-based coordination compounds as anticancer drugs depends on the copper oxidation state, the ligand structure, and the ligand–metal synergy.[142] An exciting way to produce highly active anticancer drugs is the addition of anionic oxygen-donor co-ligands, which present an increased capacity to produce oxygen peroxide. These highly reactive species induce DNA damage, mitochondrial dysfunction, and finally apoptosis.[143]

In 2016, Lian *et al.* used this approach to synthesize the series of Schiff base complexes with copper(II) (**Cu-78** to **Cu-81**), whose main difference is the co-ligands (acetic acid, benzoic acid, salicylic acid and oxalic acid, respectively), which bind to copper(II) metal centre. **Cu-78**, **Cu-79**, and **Cu-80** present an octahedral geometry, whereas **Cu-81** shows a square pyramidal geometry. Such compounds were evaluated against HeLa and Hep-G2 cells through colorimetric cell proliferation (MTT assay and 48 h of treatment). All four coordination complexes presented a considerable anticancer activity related to compound-DNA (calf thymus) interaction that was studied by viscosity measurements, as well as UV-Vis and fluorescence spectrometry. The compounds showed a K_b magnitude equal to 1×10^5, indicating a moderated intercalative interaction with DNA. Electrophoresis experiments showed that coordination compounds induce pUC19 plasmid DNA cleavage (double-strand breaks) through an oxidative pathway that involves hydrogen peroxide produced by oxygen-donor co-ligands. All compounds presented IC_{50} values (μM) close to cisplatin, which convert them into potential anticancer drugs. **Cu-80** presents the highest anticancer activity ($IC_{50} = 3.70 \pm 0.94$ and 2.29 ± 1.25 μM for HeLa and Hep-G2, respectively) associated with the synergistic effect between copper(II) and salicylic acid, a non-steroidal anti-inflammatory co-ligand. The IC_{50} values for cisplatin in this publication were 10 ± 2.2 and 25 ± 31 μM for HeLa and Hep-G2, respectively.[143]

Different functional groups biding to the same Schiff base can affect the anticancer activity of copper(II) complexes. Usually, functional groups with a high capacity to produce ROS present an efficient anticancer activity. In 2020, Rigamonti *et al.* concluded that the electron-acceptor functional group ($-NO_2$) presents a higher capacity to produce ROS than the electron-donor functional group ($-OCH_3$) and the no functionalized ligand (-H). The coordination structures with square-base pyramid geometry **Cu-82**, **Cu-83** (dimeric assembly), and **Cu-84** (polymeric assembly) were evaluated against MDA-MB-231, U-87, and PC-3 cells by MTT assay. These compounds present different functional groups in aromatic rings (–H, $-OCH_3$, and $-NO_2$, respectively). The copper complexes analysed showed a high anticancer activity derived from the strong interaction between the coordinated terminal amino group and DNA chains *via* hydrogen bonds. After 72 h, **Cu-84** presented the highest anticancer activity ($IC_{50} = 8.1$, 20.7 and 10.7 μM, for MDA-MB-231, U-87 and PC-3, respectively) associated with the strong hydrogen bond interactions and the high capacity of NO_2 group to produce intracellular ROS and DNA intercalation. In addition, the copper(II) atom in each structure provides high selectivity towards the malignant cells, since the studied compounds presented lower cytotoxicity in the evaluation against healthy endothelial cell line HUVEC ($IC_{50} = 28.6$ μM).[144] It is important to note that the cell viability tests were performed at 24, 48 and 72 h and the three compounds were time-dependent. however, a reference drug was not included during the analyses (Figure 18, Table 17).

4.2. Cobalt(II), nickel(II) and zinc(II) compounds

Schiff base complexes with cobalt are another approach to producing anti-cancer drugs. The use of cobalt to synthesize anticancer drugs is interesting because it is an essential trace element present in humans, necessary to carry out several biological functions. In addition, natural compounds such as VB_{12} (cobalamin) have demonstrated an important role in anticancer therapy. For example, VB_{12} is substituted by folic acid in chemotherapy regimens, reducing the undesirable side

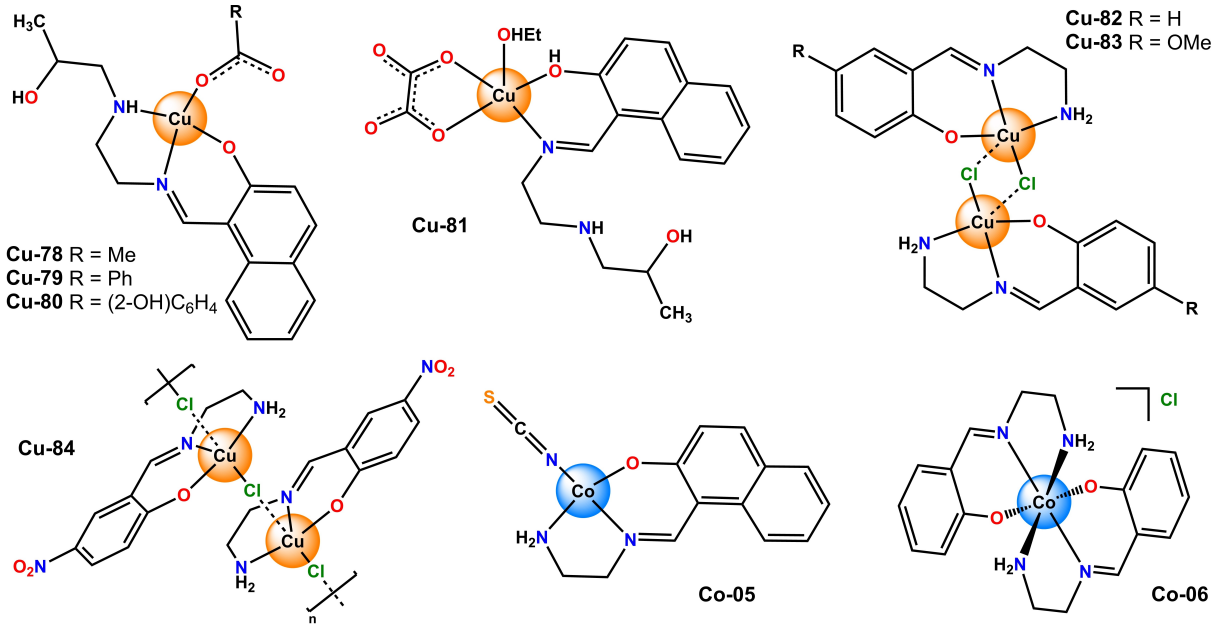

Figure 18. Copper(II) and cobalt(II) complexes (**Cu-78**–**Cu-84** and **Co-05**–**Co-06**) obtained from tridentate Schiff bases ONN.

Table 17. Summary of copper(II) complexes coordinated to ONN ligands with better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [μM]	Main feature	Ref.
Cu-79	Tetrahedral	48	HeLa	7.45 ± 1.36	Anticancer activity depends on metal-ligand synergy (anti-inflammatory co-ligand)	[143]
			HepG-2	1.24 ± 0.36		
Cu-80			HeLa	3.70 ± 0.94		
			HepG-2	2.29 ± 1.25		
Cu-84	Octahedral	72	MDA-MB-231	8.1	Anticancer activity depends on the functional group NO_2 in the Schiff base, facilitating the ROS production and the DNA intercalation	[144]
			U-87	20.7		
			PC-3	10.7		
			HUVEC	28.6		

effects of treatment. On the other hand, cancer cells usually require a high amount of VB_{12}, so anticancer drugs can be produced with high selectivity.[145] In this way, many cobalt-based coordination complexes have recently been proposed as anticancer drugs. In 2017, Kadhiravan *et al.* synthesized a new cobalt(II) tetrahedral complex named **Co-05** and evaluated it against MCF-7 cells. UV-Vis measurements showed a red shift up to 2 nm for **Co-05** in the presence of DNA (calf thymus), indicating an interaction *via* intercalative binding mode.[146] This interaction suggests the formation of a new complex with DNA double-helical and a simultaneous stabilization with DNA duplex.[147] Additional fluorescence-quenching experiments were carried out to study the interaction between **Co-05** and blood plasma proteins, such as BSA, which are fundamental in transporting drugs through the bloodstream. BSA proteins contain two tryptophan rings (Trp-134 and Trp-212), which in solution exhibit a strong emission band at 343 nm when they are excited at 295 nm.[148] The emission band presented a quenching effect that increased proportionally with the **Co-05** concentration, indicating a strong interaction between **Co-05** and BSA. The high affinity of **Co-05** towards BSA produces an IC_{50} value >100 μM, which represents weak cytotoxicity (MTT assay and 48 h incubation).[146]

On the other hand, Kirubavathy *et al.* synthesized in 2015 the cobalt(III) octahedral complex labelled as **Co-06** that contains two Schiff bases and presented it as a candidate drug in the treatment of MCF-7 cell line. The studied compound showed a low IC_{50} value (**Co-06** <100 μM), which was determined by the MTT assay after 48 h of treatment, which represents a poor anticancer activity, such results were attributed to the negative effect of cobalt(III) on normal cell processes and the presence of the azomethine group with a high potential to form hydrogen bonds with DNA (149). The cobalt-based coordination complexes in this section present a poor activity compared to analogues that exhibit another transition metal in their structure. For example, in 2019, Al-Humaidi compared the anticancer activity of the coordination complexes **Cu-85**, **Co-07**, **Ni-12** and **Zn-16**; such compounds were synthesized from the tridentate ligand 1-(((2-aminophenyl)imino)methyl)-naphthalen-2-ol and the corresponding salt. All compounds present a metal centre with an oxidation state of 2+. **Cu-85**, **Co-07** and **Ni-12** presented an

octahedral geometry around the metal centre, whereas **Zn-16** exhibited a tetrahedral geometry. Coordination complexes were evaluated against the HCT-116 cell line. The coordination complexes presented a superior activity to the free ligand, indicating that anticancer activity is directly related to the nature of the metal.[150] In contrast, ligands contribute to reducing the polarity of metal ions, promoting drug insertion across the non-polar lipid layer of cell membranes.[151] **Co-07** presented the highest IC_{50} value (>50 μg) and therefore the lowest anticancer activity, while **Zn-16** exhibited the highest cytotoxicity ($IC_{50}=6.13$ μg); however, a comparative study with any positive control was not established.[150] The general trend observed in this study was ligand-free $<$ **Co-07** $<$ **Ni-12** $<$ **Cu-85** $<$ **Zn-16** $<$ vinblastine (standard drug). In this way, zinc is an attractive alternative to copper or cobalt in the synthesis of anticancer drugs. Zinc is the second most abundant metal in biological systems and plays an important role in several processes, such as gene expression, cell growth, apoptosis and metabolism.[152]

Usually, zinc-derived coordination complexes have shown very good biological activity, which has been used as a motivation to synthesize zinc-based anticancer drugs. For example, in 2011, Li synthesized an acetate-bridged polymeric zinc(II) complex (**Zn-17**) from the ligand 2-(((2-(methylamino)ethyl)imino)methyl)-4-nitrophenol. **Zn-17** showed a square-based pyramidal geometry and was evaluated as an anticancer drug against four human carcinoma cell lines: HeLa, Hep-G2, BGC, and CNE (MTT assay after 48 h of treatment). IC_{50} values for each cell line were 73.2, 53.7, 81.2 and >100 μM, respectively; representing slightly cytotoxic activity. **Zn-17** was also evaluated against healthy cell lines L-02 and NIH-3T3, showing IC_{50} values of 86.1 and >100 μM, respectively; indicating a low selectivity.[153] On the other hand, the synthesis of coordination complexes with a high potential to inhibit the formation of free radicals is interesting, since such species can even damage the DNA of healthy cells. For example, in 2018, Das *et al.* synthesized two new zinc(II) complexes (**Zn-18** and **Zn-19**) derived from Schiff bases bonded to β-cyclodextrin (β-CD). This substituent was added to increase solubility, a crucial property that influences drug efficiency. The only difference between these compounds is a substituent; **Zn-18** presents a −Cl group, whereas **Zn-19** presents a $-NO_2$ group. The activity of **Zn-18** and **Zn-19** against oxidative stress were analysed through a detailed antioxidant profile directly related to carcinogenesis. In each experiment, **Zn-18** and **Zn-19** showed moderate inhibitory activity, obtaining the best result for **Zn-19** due to the presence of the $-NO_2$ group. These results once again demonstrate the role of ROS in diseases related to oxidative stress. However, when performing an MTT assay to determine the cytotoxicity of **Zn-18** and **Zn-19** on mouse splenocytes, a negligible effect was observed. Therefore, these derivatives have the ability to modulate immune functions and could help in disorders related to oxidative stress, but not against cancer.[154]

Functional groups with a high capacity to destroy radical species such as ketones have been reported to be able to inactivate anticancer drugs. Additionally, keto-compounds as acridone derivatives have been used in the labelling and detection of biomolecules mainly due to their resistance to photo-bleaching. This is the case of the ligand used in the synthesis of **Zn-20**, a compound reported by Adhikari *et al.* in 2015. This ligand named 4-((2-hydroxybenzylidene)amino)acridin-9(10*H*)-one showed good transport across the cell membrane; nevertheless, it did not exhibit cytotoxicity (MTT assay, 12 h of treatment, MCF-7 and HeLa cells).[155] This result could be predictable according to the already known antioxidant properties of acridone derivatives.[156] The results suggest that the ligand could penetrate the cell membrane and form the **Zn-20** complex for imaging zinc(II) ions in living cells. It should be noted that the purpose of this publication was to show that the acridone-derived ligands could be used as an effective zinc(II) sensor for the early detection of diseases such as prostate and breast cancer[155] (Figure 19, Table 18).

4.3. Compounds with different metals

Bimetallic coordination complexes with Schiff bases have also been studied as free radical inhibitory drugs in cancer therapy. For instance, Shebl in 2016, synthesized a series of compounds based on 1-(5-(1-((2-aminophenyl)imino)ethyl)-2,4-dihydroxyphenyl)ethan-1-one with different metals in diverse oxidation states: copper(II), nickel(II), cobalt(II), iron(III), zinc(II), vanadium (IV) and uranium (VI). The synthesized structures exhibited coordination numbers between four and seven. The monometallic compounds of cobalt(II) and copper(II) adopted square planar (**Cu-86**) and tetrahedral (**Co-08**) geometries, respectively. In addition, monometallic compounds of copper(II) (**Cu-87**), iron(III) (**Fe-11**) and vanadium(IV) (**V-51**) showed an octahedral geometry. Homobimetallic compounds of copper(II) (**Co-09**) and nickel(II) (**Ni-13**) exhibited tetrahedral geometries. Moreover, the homobimetallic derivatives of zinc(II) (**Zn-21**) and uranium(VI) (**U-01** and **U-02**) are diamagnetic, for which the authors did not determine the geometry around the metal centre. Regarding the heterobimetallic derivatives, it was only possible to determine the geometry of the transition metal different from uranium(VI), obtaining a planar square geometry

Table 18. Summary of zinc(II) complexes coordinated to ONN ligands with better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [μg]	Main feature	Ref.
Zn-16	Square planar	–	HCT-116	6.13[a]	The anticancer activity depends on the metal used in the synthesis of the coordination complex	[150]

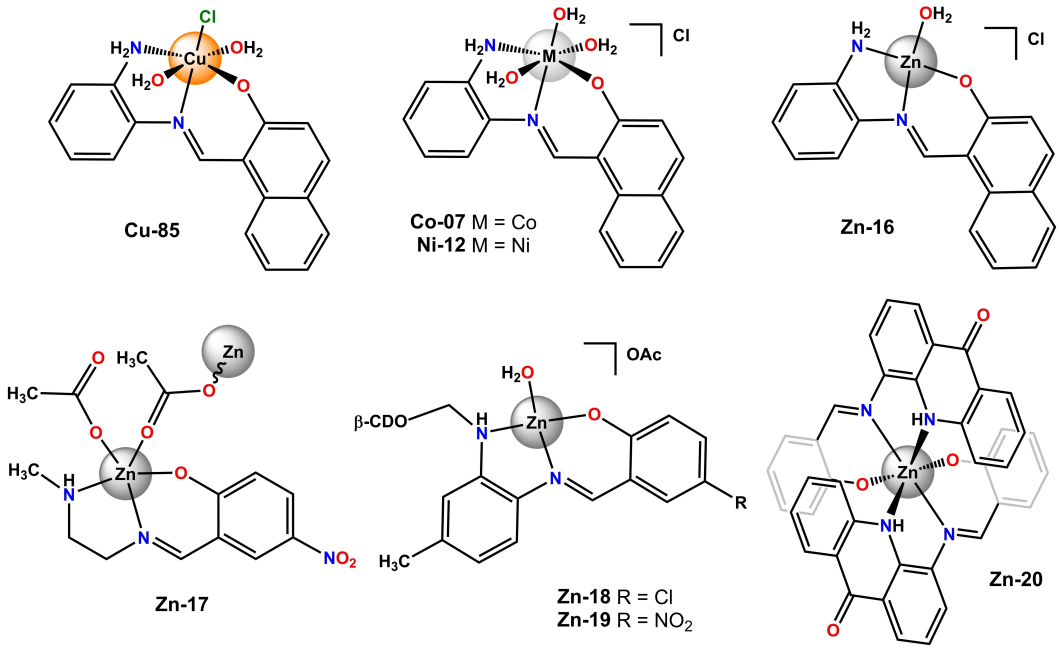

Figure 19. Zinc(IV) and other transition metal complexes (**Zn-16**–**Zn-20**) obtained from tridentate Schiff bases ONN.

for **U-Cu-01** and **U-Co-01**, as well as an octahedral geometry for **U-Ni-01** and **U-Fe-01**. The bimetallic compounds generally showed higher IC_{50} (μM) values than monometallic compounds in DPPH free radical inhibition, which indicates a lower antioxidant activity. This was attributed to the coordination of the second metal with the second OH group of the ligand, which avoids the proton donation to DPPH, converting it into an unstable free radical. The anticancer activity of all compounds including the ligand and cisplatin as the reference drug was evaluated against the EAC cell line. The coordination complexes showed considerably lower IC_{50} values ($mg\,mL^{-1}$) than the free ligand, which was attributed to the chelating effect that reduces the ligand polarity, promoting its insertion into the lipid membrane. Nevertheless, they did not find significant differences between monometallic and bimetallic compounds. The compounds with the highest anticancer activity were **Co-09**, **V-51** and **U-01**, since they presented the closest IC_{50} values to cisplatin (15.73, 16.22, 15.38 *versus* 5.0 $mg\,mL^{-1}$, respectively)[157] (Figure 20).

Vanadium-based drugs usually present a potent pharmacological activity. Nevertheless, such metal also shows high toxicity. In this way, reducing toxicity through the use of specific ligands is an exciting approach to producing vanadium drugs with fewer potential side effects. In 2010, Xie *et al.* studied the anticancer activity of the novel complex **V-52** against Caco-2 cells (MTT assay and 24 h of incubation). **V-52** presented two octahedral centres of vanadium(V) doubly bridged by oxygen atoms (V_2O_2 diamond core). According to the authors, **V-52** is a lipophilic drug, probably due to the symmetry of the compound, which reduces its dipole moment. Since lipophilic drugs present high cell permeability and absorption profiles, **V-52** can be administered orally. In addition, experimental evidence suggests that **V-52** inserted across the cell membrane through passive diffusion, which is a desirable feature in oral drug delivery. **V-52** presented extremely high anticancer activity, since the IC_{50} value determined was 0.0279 μM. Nevertheless, selective studies with healthy cells or comparative analyses with reference drugs were not carried out; therefore, there is no certainty about potentially dangerous side effects.[158]

In 2017, Majumder *et al.* synthesized dimeric molybdenum(V) complexes with square pyramidal geometry from tridentate Schiff bases ONN. The ligands were prepared by condensing *o*-phenylenediamine with four different aldehydes, whose main difference was the substituents in the aromatic ring (**Mo-03**, R_1=R_2=H; **Mo-04**, R_1=OCH_3, R_2=H and **Mo-05**, R_1=H, R_2=Br). In the fourth compound (**Mo-06**), the benzene-based aromatic system was replaced by naphthalene. The interaction between DNA (calf thymus) and coordination complexes was studied using different spectroscopy techniques, revealing a groove binding mode. Cytotoxicity was evaluated against HaCaT, MCF-7 and HCT-15 cells using the MTT assay. ONN tridentate ligands showed lower cytotoxicity than their coordination complexes. The authors mentioned that the coordination of Schiff bases with molybdenum(V) reduces the polarity of ligands, enhancing their transport through the non-polar lipid membrane, which increases anticancer activity. **Mo-03** showed the closest IC_{50} values (μM) to cisplatin after 48 h of treatment, making it a promising anticancer drug (**Mo-03**, 11.13 ± 0.65 in MCF-7 and 32.20 ± 0.92 in HCT-15; cisplatin, 7.80 in MCF-7 and 12.20 in HCT-15). The anticancer activity of **Mo-03** depends on its ability to bind with DNA and this, in turn, is influenced by the absence of substituents in the ligand. This was demonstrated by the K_b value since the **Mo-04** and **Mo-05**

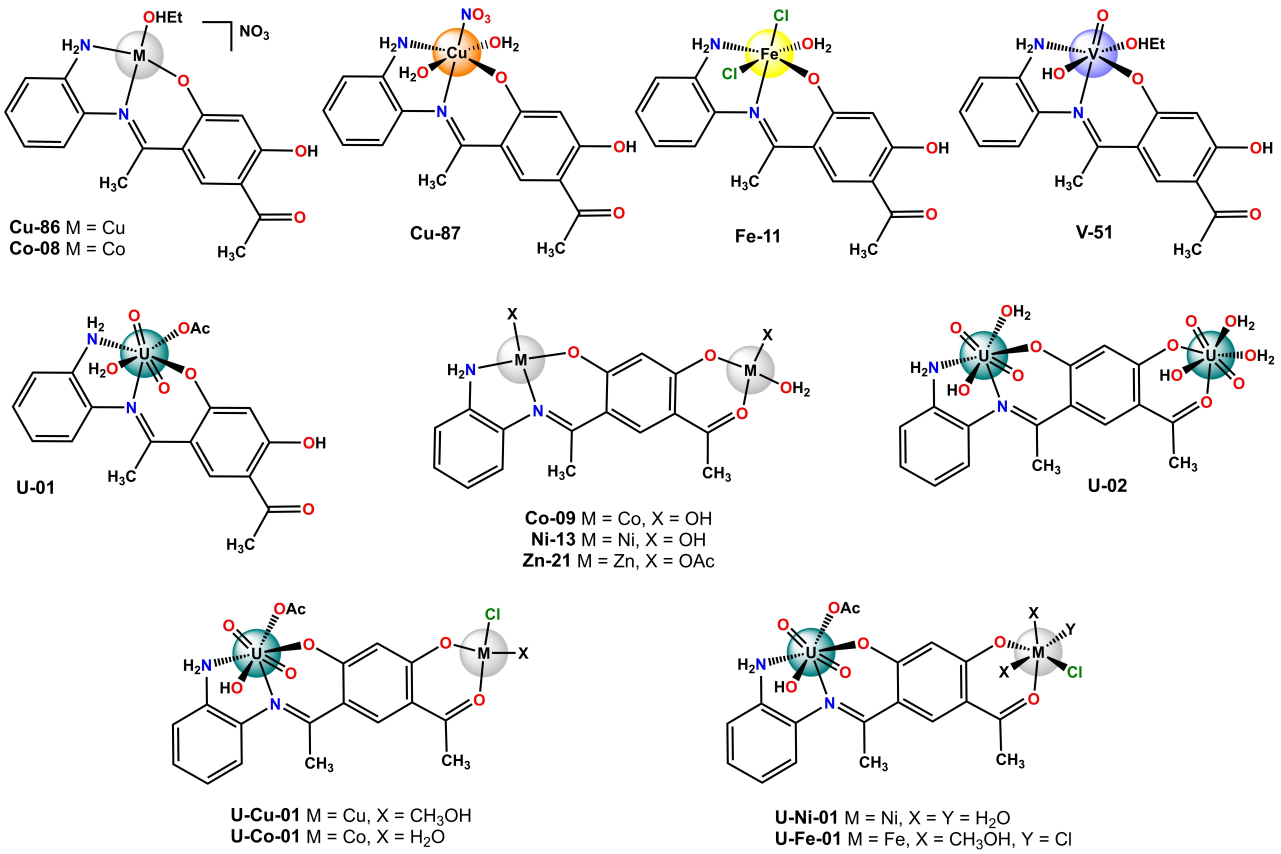

Figure 20. Coordination complexes with different transition metals obtained from tridentate Schiff bases ONN.

compounds with substituents $-OCH_3$ and -Br had a lower affinity for DNA compared to the **Mo-03** and **Mo-06** compounds without substituents. Finally, **Mo-03** demonstrated a high selectivity in the presence of the healthy cell line HaCaT ($IC_{50} = 200.74 \pm 0.12$ μM).[159]

Historically, ruthenium has been proposed as an alternative metal to platinum, since coordination complexes based on this metal have shown anticancer activity similar to that of cisplatin, even with lower toxicity. In 2016, Kirubavathy *et al.* studied a series of four novel octahedral complexes of ruthenium(III) with mercaptopyrimidine-based Schiff bases against MCF-7 cancer cells by MTT assay. The compounds studied differ in the functional groups binding to the ligand: **Ru-03** (R_1=R_2=R_3=H), **Ru-04** (R_1=Br, R_2=R_3=H), **Ru-05** (R_1=H, R_2=NO_2, R_3 =OCH_3). In the case of **Ru-06**, the benzene-based Schiff base aromatic system was replaced by its naphthalene analogue. The drug-DNA interaction was elucidated by absorption and emission spectral measurements, and later was confirmed by docking studies, exhibiting an intercalative interaction. All four compounds showed IC_{50} values indicating moderate anticancer activity; however, reference drugs and treatment times were not reported. The free ligands did not show anticancer activity, confirming that chelation is responsible for the observed cytotoxicity. The two most active compounds were **Ru-06** ($IC_{50} = 21.68$ μg mL^{-1}) and **Ru-05** ($IC_{50} = 25.85$ μg mL^{-1}). This result can be attributed to the higher number of non-covalent interactions with DNA caused by the availability of electrons in the additional ring for **Ru-06**, or to the presence of the -NO_2 group for **Ru-05**. In addition, the electron-donating or electron-withdrawing functional groups in **Ru-04** and **Ru-05** should produce a higher dipole moment than in **Ru-06**, which should obstruct the complex insertion through the lipid membrane[160] (Figure 21, Table 19).

5. Concluding remarks

Undoubtedly, cancer remains one of the main challenges to overcome in the future to come. As we have pointed out throughout this document, chemotherapy treatments continue to be one of our main weapons to combat cancer. Although platinum-based metallopharmaceuticals have an enormous advantage due to more than five decades of study, it is necessary to find some other compounds with more specific activity, capable of distinguishing between different types of cancer, but also more selective, capable of distinguishing between cancer cells and healthy cells. The foregoing, added to the large number of secondary effects conferred to platinum derivatives, lead us to suppose that sooner or later other metals, mainly *d*-block, will be able to offer better alternatives. Until now, only a few derivatives of ruthenium, copper, titanium, gold, and silver have made it to preclinical trials, but none are

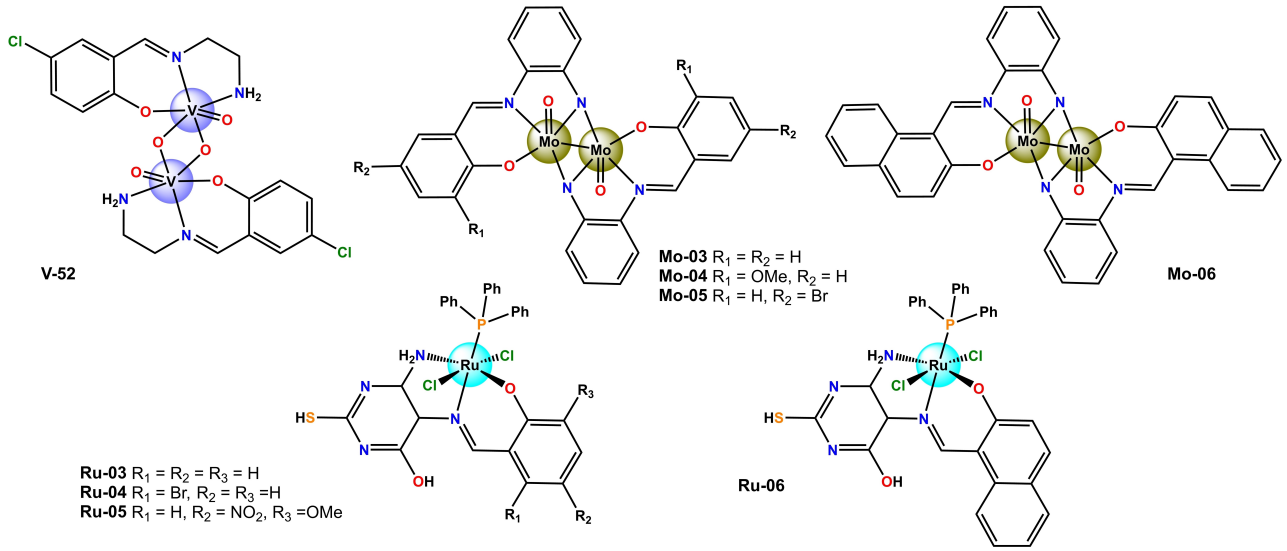

Figure 21. Vanadium(V), molybdenum(V) and ruthenium(II) complexes (**V-52**, **Mo-03**–**Mo-06** and **Ru-03**-**Ru-06**) obtained from tridentate Schiff bases ONN.

Table 19. Summary of vanadium(V) and molybdenum(V) complexes coordinated to ONN ligands with better IC_{50} values (μM) in different cell lines.

Compound	Metal geometry	Exposure time [h]	Cell lines	IC_{50} value [μM]	Main feature	Ref.
V-52	Octahedral	24	Caco-2	0.0279	The anticancer activity depends on the lipophilic character conferred by the symmetry of the compound	[158]
Mo-03	Square pyramidal	48	MCF-7 HCT-15 HaCaT	11.13 ± 0.65 32.20 ± 0.92 200.74 ± 0.12	The anticancer activity depends on the binding capacity of the complex with DNA, influenced by the absence of substituents in the ligand	[159]

yet for commercial sale. In this sense, the use of versatile organic ligands, such as Schiff bases, capable of forming stable coordination compounds, offers a real alternative, which has been extensively investigated by various research groups. In addition, the metals of the first transition row are the most studied, mainly copper since most of its commercial salts are cheap and the synthesis conditions are easy since they do not require the absence of moisture or an inert atmosphere.

The analysis of the articles cited in this review suggests that there is a large number of compounds that could attract the attention of the scientific community since in their first stage of analysis they have shown very good values of cytotoxic or antiproliferative activity, most of them these compounds were reported in the summary tables. In addition, some of the recommendations that groups investigating the SAR of coordination complexes obtained from tridentate Schiff bases with *d*-block metals could take are: (a) The nature of the metal centre, currently the derivatives of copper and ruthenium are the most studied; however, some other metals such as rhodium, iridium, gold and silver have not yet been explored, and it is known that with other ligands, they have also given promising results. (b) The geometry of the complex, currently most of the coordination complexes that offer good anticancer activity, preferably have square-planar or square-pyramidal geometries. It is important to note that geometry is intrinsically related to the type of metal and its oxidation state. (c) Nuclearity, in this review it was evidenced that the tetranuclear complexes of copper(II), mostly showed excellent IC_{50} values, which suggests that they are outstanding candidates for cancer therapy. (d) Chirality, various working groups use Schiff bases derived from chiral amino acids, conferring chirality to their coordination complexes, showing a direct relationship between the biological activity and the stereochemistry of the compound. (e) The nature of the ligand, some coordination complexes obtained from Schiff bases that have previously shown some biological activity also show anticancer activity. In addition, the use of functional groups in specific positions of the Schiff base potentiates its cytotoxic activity. (f) The use of co-ligands, it has been shown that polypyridyl derivatives favour DNA binding and excision, such is the case of aromatic derivatives of *phen* that increase anticancer activity.

Abbreviations

A-431	human epidermoid carcinoma cell line
A-498	human kidney adenocarcinoma cell line
A-549	human lung adenocarcinoma cell line
A-2780	human ovarian carcinoma cell line

A-2780cisR or A-2780R	cisplatin-resistant human ovarian carcinoma cell line
Akt	protein kinase B
aminophen	5-amine-1,10-phenanthroline
BAX	BCl-2-associated X protein (apoptosis regulator)
BEL-7402	human hepatocellular carcinoma cell line
BEL-7404	human liver cancer cell line
BGC	human gastric carcinoma cell line
BODIPY	boron dipyrromethene
bpy	2,2′-bipyridine
BSA	bovine serum albumin
C33 A	human cervical squamous carcinoma cell line
Caco-2	human colon adenocarcinoma cell line
CCD18-Co	human noncancerous fibroblast cell line
CCK-8	cell counting kit-8
CCRF/CEM	drug sensitive human T-lymphoblastic leukemia cell line
CEM/ADR 5000	drug resistant human T-lymphoblastic leukemia cell line
β-CD	β-cyclodextrin
CNE	human nasopharyngeal carcinoma epithelioid cell line
diphphen	4,7-diphenyl-1,10-phenanthroline
DFT	density functional theory
DNA	deoxyribonucleic acid
dmephen	4,7-dimethyl-1,10-phenanthroline
DPPH	2,2-diphenyl-1-picrylhydrazyl
dppz	dipyrido[3,2-*a*:2′,3′-*c*]phenazine
dpq	dipyridoquinoxaline
EAC	Ehrlich ascites carcinoma cells
EAC/DOX	doxorubicin resistant Ehrlich ascites carcinoma
EAC/S	sensitive Ehrlich ascites carcinoma
epoxyphen	5,6-epoxy-5,6-dihydro-1,10-phenanthroline
Erk1/2	extracellular signal-regulated protein kinases 1 and 2
FT-IR	Fourier transform infrared spectroscopy
G_0/G_1	cell cycle phases (initial/growth)
GI_{50}	amount of drug to inhibit cell growth by fifty percent
GSH	glutathione
h	hour
HaCaT	immortalized human keratinocyte cell line
HASM-C1	non-cancer human aortic smooth muscle cell line 1
HASM-C2	non-cancer human aortic smooth muscle cell line 2
HCT-15	human colorectal adenocarcinoma cell line
HCT-116	human colorectal carcinoma cell line
HEK or HEK-293	human embryonic kidney cell line
HeLa	human cervical adenocarcinoma cell line
Hep-2	human laryngeal carcinoma cell line
Hep-G2	liver hepatocellular carcinoma cell line
HFF	human foreskin fibroblast cell line
His-242	histidine residue
HL-60	human acute promyelocytic leukaemia
HL-7702	normal human liver cell line
HOS	resistant human osteosarcoma cell line
HPL1D	human peripheral lung epithelial cell line
HT-29	human colorectal carcinoma cell line
HUH-7	human hepatocarcinoma cell line
HUVEC	human umbilical vein endothelial cell line
IC_{50}	concentration required to achieve fifty percent of maximal inhibition
K-562	human chronic myelogenous leukaemia cell line
K_b	binding constant
imdz	imidazole
L-02	human liver hepatocytes cell line
L-132	human lung embryonic normal cell line
L-929	murine fibroblast cell line
M	molar
μM	micromolar
μg/mL	microgram/millilitre
MCF-7	human breast adenocarcinoma cell line
MDA-MB-231	human breast adenocarcinoma cell line
MIA-PaCa-2	human pancreatic ductal adenocarcinoma cell line
MRC-5	normal human fetal lung fibroblast cell line
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NCI-H460 or H-460	human large lung carcinoma cells
NHAG	*N*-(2-hydroxyacetophenone)glycinate
NHDF	normal human dermal fibroblasts cell line
NIH-3T3	mouse embryonic fibroblast cell line
nM	nanomolar
nm	nanometer
$^1O_2$	singlet oxygen
pBR322	plasmid cloning vector in *E. coli*
PC-3	human prostate adenocarcinoma cell line
PDT	photodynamic therapy
PET	positron emission tomography
pH	hydrogen potential
phen	1,10-phenanthroline
ppm	parts per million
PI	photocytotoxicity index (IC_{50}(dark)/IC_{50}(light)
PBMC	healthy normal human peripheral blood mononuclear cell line
PS	photosensitizers
pUC19	plasmid cloning vector in *E. coli*

RMN	nuclear magnetic resonance
RNA	ribonucleic acid
RNS	reactive nitrogen species
ROS	reactive oxygen species
SAR	structure-activity relationship
SEM	scanning electron microscopy
SH-SY5Y	human neuroblastoma cell line
SOD	superoxide dismutase
SRB	sulforhodamine B
$T_{1/2}$	half-life time
TBARS	thiobarbituric acid reactive substances
tdzp	[1,2,5]thiadiazolo[3,4-*f*][1,10]phenanthroline
TGI	tumour growth inhibition
Trp-134, Trp-212, Trp-214	tryptophan residues
Topo I	topoisomerases I
U-87	human primary glioblastoma cell line
UV-Vis	ultraviolet-visible
V-79	Chinese hamster non-tumoral fibroblast cell line
VB_6	vitamin B_6
VB_{12}	vitamin B_{12}
VEGF	vascular endothelial growth factor
VEGFR2	vascular endothelial growth factor receptor 2
$VO(acac)_2$	vanadyl acetylacetonate
WHO	World Health Organization
XRD	X-ray diffraction

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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