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Review

Anticancer and Antimicrobial Activity of Copper(II) Complexes with Fluorine-Functionalized Schiff Bases: A Mini-Review

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Academic Editor: Isabel Correia

Received: 23 November 2024
Revised: 21 January 2025
Accepted: 23 January 2025
Published: 26 January 2025

Citation: Moreno-Narváez, M.E.; González-Sebastián, L.; Colorado-Peralta, R.; Reyes-Márquez, V.; Franco-Sandoval, L.O.; Romo-Pérez, A.; Cruz-Navarro, J.A.; Mañozca-Dosman, I.V.; Aragón-Muriel, A.; Morales-Morales, D. Anticancer and Antimicrobial Activity of Copper(II) Complexes with Fluorine-Functionalized Schiff Bases: A Mini-Review. *Inorganics* **2025**, *13*, 38. https://doi.org/10.3390/inorganics13020038

Abstract: In recent years, metallodrugs have emerged as captivating and promising compounds in the fields of cancer therapy and antimicrobial agents. While noble metals have shown remarkable biological activity, increasing interest lies in utilizing more abundant and cost-effective metals in medicinal chemistry. This is primarily due to their pivotal role in biological processes and their lower cost compared to precious metals. Among these, copper(II) complexes have emerged with promising applications in medicine. Notably, copper compounds bearing Schiff bases stand out as innovative metallodrugs. They exhibit intriguing cytotoxic properties against a wide range of cancer cell lines, while also demonstrating inhibitory effects on prevalent bacterial and fungal strains. Nevertheless, research into Cu(II) complexes with Schiff bases remains of paramount interest. One strategic avenue to bolster their biological activity involves the introduction of fluorine groups into the ligands. This approach has demonstrated a significant augmentation in efficacy and selectivity, particularly in targeting cancer cells and microbial pathogens, because fluorine incorporation can improve metabolic stability and cellular uptake. This further reinforces the therapeutic potential of these metallodrugs. Thanks to these promising outcomes, research into the development of Cu(II) complexes with fluorinated Schiff bases is advancing significantly. This holds immense potential for progressing the field of medicinal chemistry, with the aim of addressing unmet clinical needs in both cancer therapy and antimicrobial treatment. This review comprehensively explores the latest advancements in Cu(II) complexes bearing fluorinated Schiff bases, encompassing diverse coordination modes. It delves into their scope and applications in cytotoxic evaluations, as well as their efficacy as antimicrobial and antifungal agents.

Keywords: Schiff base complexes; cytotoxicity; antibacterial/antifungal activity; fluorinated complexes; copper complexes; metallodrugs

1. Introduction

Throughout the annals of human history, the relentless pursuit of health and well-being has remained an enduring and formidable challenge. One particularly fascinating chapter in this narrative revolves around ancient civilizations' early utilization of inorganic compounds as medicine [1]. In this regard, both Egyptians and Greeks were pioneers in recognizing the therapeutic potential of specific metal compounds. They utilized substances containing copper, iron, or mercury in "potions" to treat a diverse range of diseases [2,3]. These early practitioners, often guided by empirical observations, established the groundwork for the subsequent exploration of metallodrugs in medicine.

A significant milestone in the history of metallodrugs was marked by the introduction of "Salvarsan" by Paul Ehrlich in the early 20th century. Salvarsan, an organoarsenic compound, represented the inaugural triumph in targeted therapy for syphilis [4]. Ehrlich's groundbreaking work exemplified the potential of metallodrugs to specifically target pathogens while sparing healthy cells, a principle that continues guiding drug design [5]. In the modern era, coordination complexes have witnessed resurgence in the field of medicine, particularly in the context of cancer therapy. Platinum-based metallodrugs, notably cisplatin, and its derivatives have emerged as powerful tools in the battle against cancer [6]. These compounds form coordination complexes with DNA, disrupting its structure and halting cell division, thereby inhibiting the proliferation of cancerous cells [7,8]. However, despite the success of cisplatin and its analogous complexes in combating cancer, several side effects have been observed, including nephrotoxicity [9] and ototoxicity [10]. Additionally, cancer cells may develop resistance to these compounds over time [11]. The constraints posed by these limitations have sparked a renewed interest in the development of novel and selective metallodrugs for cancer therapy. Researchers are delving into innovative coordination complexes designed to specifically target cancer cells while sparing healthy ones. This pursuit of precision in metallodrug design is aimed at minimizing side effects and enhancing overall treatment outcomes.

On the other hand, antimicrobial resistance has arisen as a crucial global health concern, undermining the efficacy of traditional antibiotics and antimicrobial agents. The extensive utilization and misuse of antibiotics in healthcare, agriculture, and animal husbandry have expedited the emergence of resistant bacterial strains, rendering numerous conventional treatments ineffectual. This trend has resulted in a notable upsurge in the prevalence of untreatable infections, prolonged hospitalizations, elevated healthcare expenditures, and heightened mortality rates worldwide. Furthermore, the ongoing evolution of resistant microbial strains poses a formidable obstacle to the development of new antimicrobial therapies, necessitating innovative approaches and strategies to address this escalating crisis. In response to the escalating threat of antimicrobial resistance, researchers have intensified efforts to explore alternative therapeutic options, including the development of novel copper-based drugs [12–14].

Among the various ligands employed in coordination chemistry with medicinal properties, Schiff bases stand out. Characterized by possessing an imine functional group (C=N), they are recognized as privileged ligands capable of coordinating diverse metal ions to form stable and structurally diverse complexes. This versatile chemistry enables the meticulous design and synthesis of Schiff base complexes with tailored properties to selectively and effectively target cancer [15–17]. In this context, selectivity is crucial in

oncology, as it tackles a primary challenge in cancer treatment: minimizing harm to healthy tissues while eliminating malignant cells.

In particular, Schiff base copper complexes have notably showcased remarkable and selective biological activity, garnering attention as promising anticancer metallodrugs [18]. Their potential in this regard arises from their multifaceted mechanisms of action, wherein they interact with various cellular components and critical processes to impact cell survival and proliferation. These mechanisms include DNA binding, enzyme inhibition, the generation of reactive oxygen species (ROS), and interference with cellular signaling pathways [19–22]. By virtue of their inherent reactivity and adaptability, copper can disrupt the delicate balance of cancer cell homeostasis, leading to cytotoxicity and apoptosis [23], all while preserving normal cells to a considerable extent. Furthermore, copper, as an essential trace element in the human body, adds another layer of complexity to the anticancer potential of these metallodrugs [24]. Copper Schiff base complexes capitalize on the body's natural uptake and distribution mechanisms for copper, enabling them to penetrate tumor tissues more effectively [25]. This intrinsic property, combined with the tailored selectivity of Schiff base ligands, holds promise for applications as anticancer agents and antimicrobial compounds.

In the field of drug development, the ability to fine-tune the properties of metallodrugs by incorporating fluorine groups has emerged as a powerful strategy, opening up new avenues for drug design. Figure 1 presents short synthetic routes to obtain this class of compounds, where in most cases, the fluorine group (or that contains fluorine) is attached to an aromatic ring. This approach harnesses the unique properties of fluorine, particularly its high electronegativity [26], to enhance the interactions between the resulting coordination complexes and diverse biological systems, such as enzyme-active sites and receptor-recognition sites, and pharmacokinetic and pharmacodynamic properties [27]. Moreover, fluorine has the capacity to increase the acidity of many compounds, which enhances their lipophilicity, facilitating their permeation through biological membranes [28–30]. As a result, in recent years, there has been a notable increase in the use of fluorinated ligands in coordination chemistry and their applications as antibiotics, antimycotics, and anticancer agents. In this review, we summarize the recent advances in fluorinated Schiff base copper complexes with significant biological properties, focusing on papers published in the last seven years. The selected molecules are shown in Figure 2, which presents a comprehensive overview of Cu(II) complexes incorporating Schiff bases substituted with diverse fluorinated moieties, as reported between 2018 and 2024 [31–45]. We explore coordination geometry, potential advantages, and recent discoveries. As we journey through this innovative intersection of chemistry and medicine, we gain a deeper understanding of how these remarkable compounds are reshaping the landscape of cancer therapy.

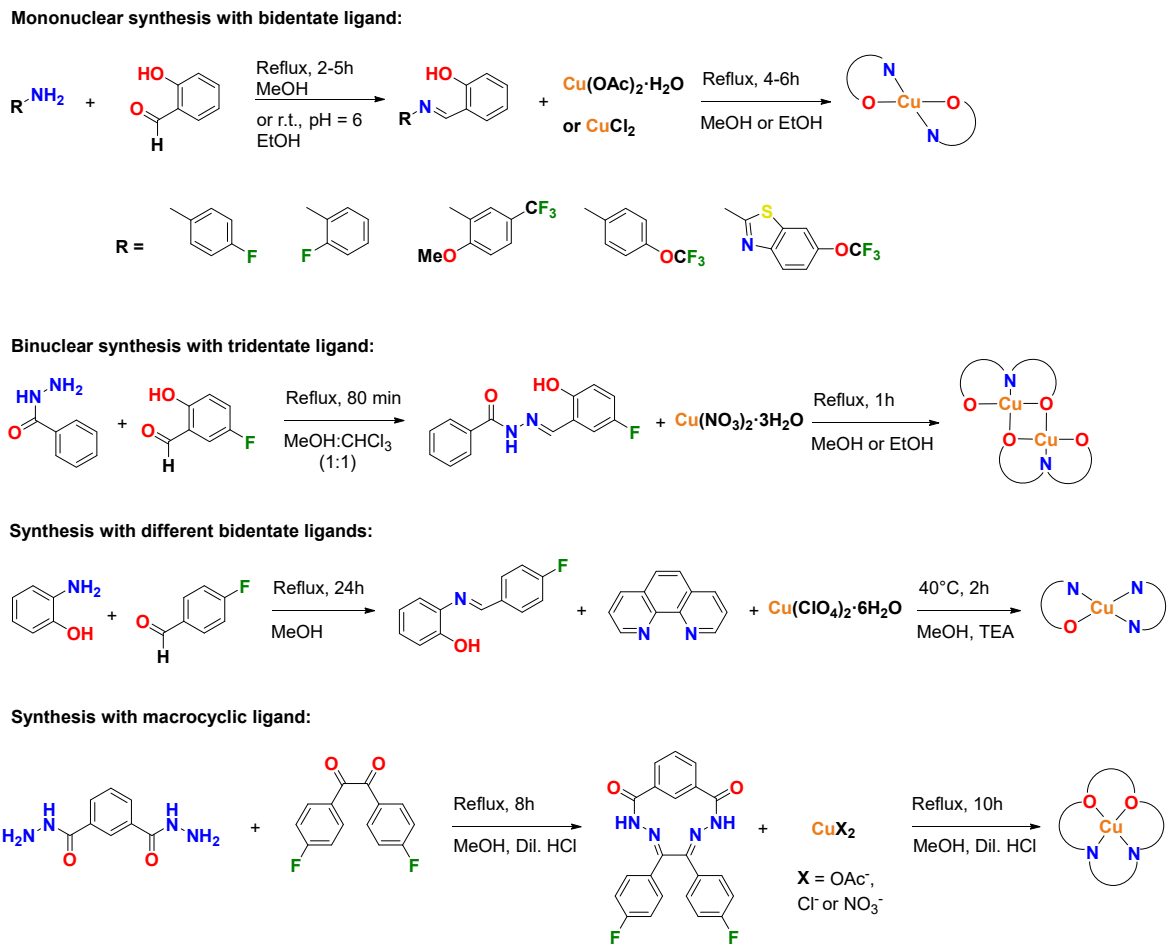

Figure 1. Main synthetic routes for obtaining fluorinated Schiff base Cu(II) complexes.

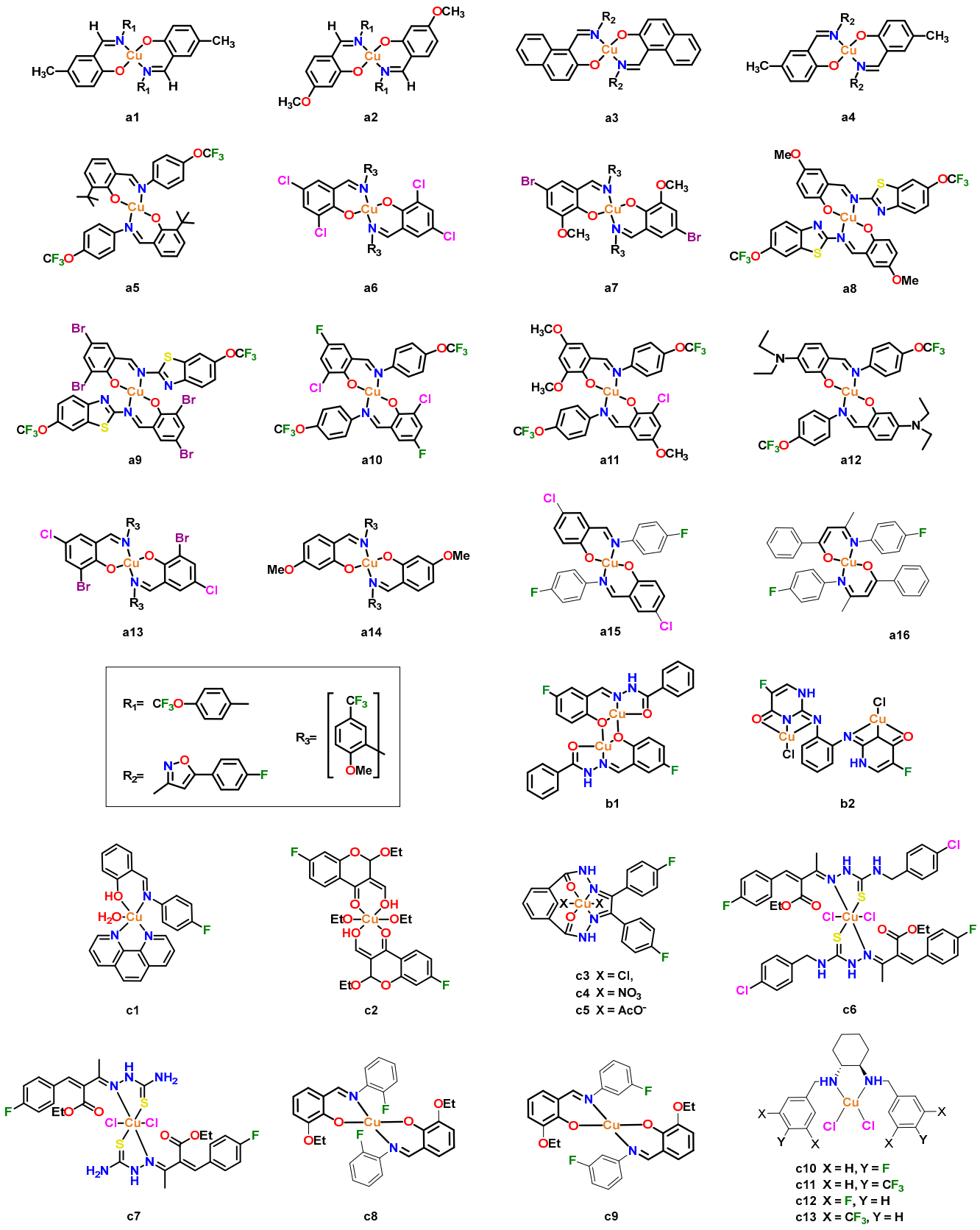

Figure 2. Structures of selected fluorinated Schiff base Cu(II) complexes.

2. Characterization and Coordination Geometry of Cu(II) Complexes

The reported Cu(II) complexes have been characterized by different spectroscopic characterization techniques. FT-IR spectroscopy analyses allow the identification of common functional groups in this type of complexes and confirm the coordination of nitrogen

and oxygen atoms to the metal: the stretching band corresponding to the azomethine group (-HC=N) near 1600 cm^{-1} shifts to lower frequencies when nitrogen binds to Cu(II), while the vibration band of the phenolic C-O bond shifts between 60 and 70 cm^{-1} below 1280 cm^{-1}, confirming the coordination through these groups. Also reported are the bands attributed to the Cu-N and Cu-O bonds between 450 and 550 cm^{-1} and strong bands in the region between 1100 and 1350 cm^{-1}, characteristic of C-F stretching. On the other hand, UV-Vis spectra mainly show absorption bands corresponding to π-π* transitions of aromatic rings, n-π* or π-π* of the azomethine group (-HC=N) and charge transfer absorption bands between 300 and 550 nm. Bands corresponding to d-d transitions are also reported between 350 and 650 nm, which allow us to suggest the type of geometry; for example, Rambabu et al. reported that, according to the results of absorption and magnetic moment spectroscopy, the **a5** complex presents a square planar geometry [34], which is confirmed by X-ray crystallographic analysis, indicating a coordination to two deprotonated 2-((E)-(4-trifluoromethoxy)phenylimino)methyl)-6-tert-butylphenol ligands in the *trans* orientation (Figure 3a); this distorted square planar geometry indicates coordination of the monobasic bidentate ligands through two oxygens and two nitrogens. In the same year, S. Jiang and co-workers reported compound **b1**, which under the conditions presented in Figure 1 gives a bimetallic complex, X-ray study indicates that the Schiff base fraction containing O-phenolate atoms connects two Cu(II) units by means of two μ-O bridges to form binuclear structures [39], in this case the coordination geometry is distorted square pyramidal (Figure 3b).

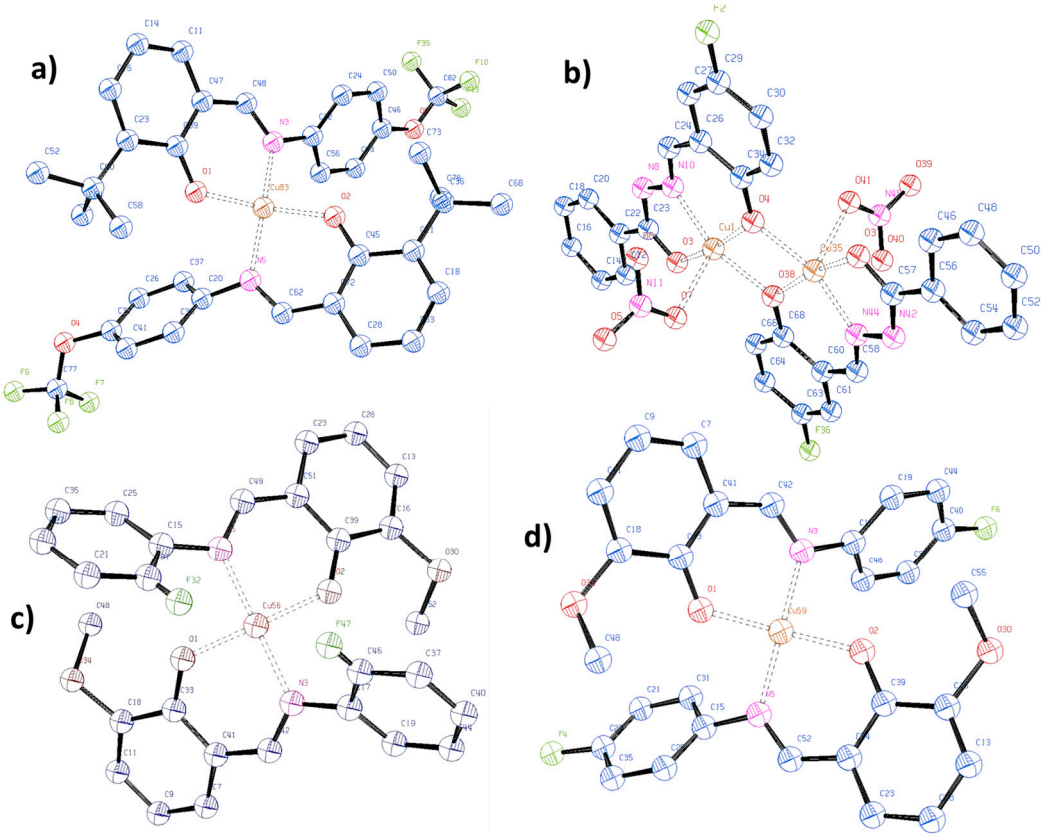

Figure 3. X-ray crystal structure of complex **a5** (readapted from Ref. [34]; Copyright© 2020 Elsevier Ltd.) (**a**), molecular structure of complex **b1** (readapted from Ref. [39]; Copyright© 2020 Elsevier Ltd.), (**b**) and molecular structure of complexes **c8** (**c**) and **c9** (**d**).

In the recent work of Kaştaş and co-workers, the molecular structures of complexes **c8** and **c9** are reported; crystallographic study indicates that the polyhedra around Cu(II) ions can be best described as a seesaw coordination geometry, where atoms in axial

positions lie along a common axis and atoms in equatorial positions are in a plane orthogonal to the axis defined by the axial atoms [44]. Based on the bond angles with the Cu(II) ion reported in this study, CuN_2O_2 kernels are proposed in the **c8** and **c9** complexes with seesaw coordination geometry (Figure 3c).

3. Anticancer Activity of Cu(II) Complexes

Cancer remains one of the most significant challenges in modern medicine, demanding innovative approaches to develop effective treatments. In this pursuit, square planar Cu(II) complexes have attracted attention due to their geometrical similarity to platinum-based metallodrugs. These complexes exhibit unique features such as antioxidant and anti-inflammatory properties that make them promising candidates for targeted cancer therapy [46]. In addition, their square planar geometry has been associated with better interaction with DNA, facilitating cleavage and non-covalent interactions [47]. Furthermore, it is well known that the introduction of lipophilic groups in copper complexes, particularly fluorinated moieties like F, CF_3, and OCF_3, increases their lipophilic nature, favoring in vivo uptake and transport in biological systems, thereby enhancing their biological activity. In the literature, several kinds of Cu(II) Schiff base complexes have been reported. Notably, these can be categorized into two main subgroups: mononuclear and binuclear copper Schiff base complexes, each offering unique benefits in cancer therapy. Therefore, this review section is structured based on the number of metal ions present in the complex. Table 1 presents the results of the cytotoxic activity reported for the selected complexes against different cancer cell lines, including both mononuclear planar square complexes (type a) and binuclear complexes (type b), as well as others with different coordination geometries (type c).

Table 1. IC_{50} values of fluorinated Schiff base Cu(II) complexes evaluated against different cancer cell lines and general mechanism of action reported.

Complex	IC_{50} (μM)	General Mechanism of Action	Ref.
a6	HeLa: 15.99; A549: 19.44	DNA intercalation binding	[35]
a7	HeLa: 18.47; A549: 21.04		[35]
a10	A549: 38.09; MCF-7: 34.07	DNA intercalation binding	[31]
a11	A549: 42.05; MCF-7: 39.04		[31]
a12	A549: 48.03; MCF-7: 45.01		[31]
a13	HeLa: 25.78; A549: 26.62	DNA intercalation binding	[36]
a14	HeLa: 28.63; A549: 30.58		[36]
b1	Bell-7402: 2.7; HeLa: 0.5; MCF-7: 0.8; MGC-803: 3.0; WI-38: 3.2	HSA interaction	[39]
b2	Caco-2: 31.8; L-929: 285	Not studied	[40]
c1	A549: 3.52	DNA cleavage	[41]
c3	SCC4: >100	EGFR Kinase receptor binding	[42]
c4	SCC4: 74.9		[42]
c5	SCC4: 54.3		[42]
c6	HeLa: 16.66; MCF-7: 8.9; TIB-71: 85.43	DNA intercalation binding	[43]
c7	HeLa: 13.39; MCF-7: 5.28; TIB-71: 95.33		[43]
c10	HepG2: 61.3	DNA intercalation binding	[45]
c11	HepG2: 28.7		[45]
c12	HepG2: 64.4		[45]
c13	HepG2: 189.1		[45]

The methods used for the biological evaluation of the selected copper complexes are summarized in the diagram presented in Figure 4. For the determination of IC_{50} values, the reported cytotoxicity assays mainly employ the 3-(4,5-dimethylthiazol-2-yl)-2,5-

diphenyltetrazolium bromide (MTT) assay after the interaction of the complexes with the cell lines between 24 and 48 h.

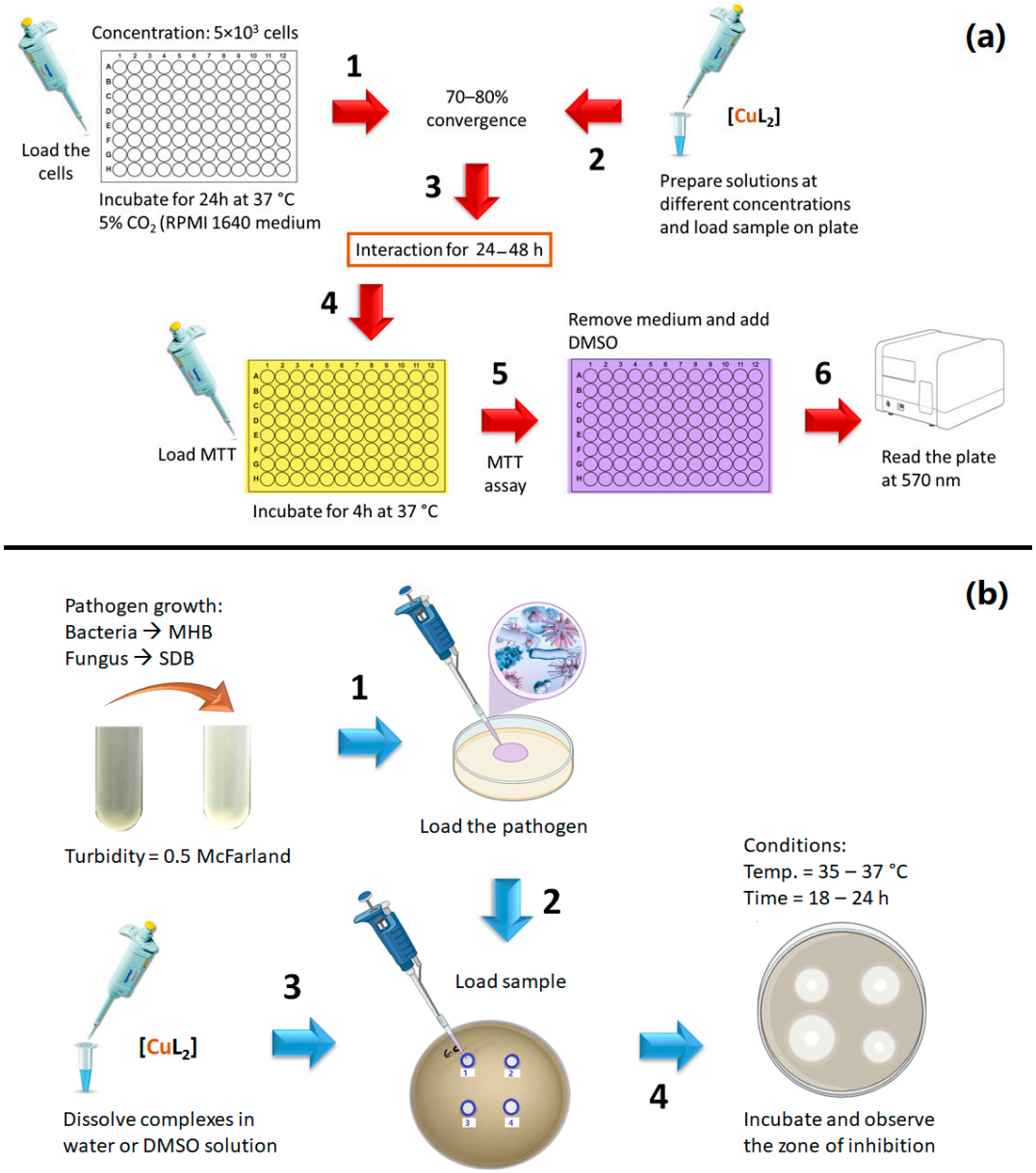

Figure 4. Schematic diagram of the methods used for cytotoxicity (**a**) and antimicrobial (**b**) activity studies. (MHB = Muller–Hinton Broth; SDB = Sabouraud Dextrose Broth).

The authors of the different works report additional studies that allow them to shed light on a possible mechanism of action; in this context, the mechanisms presented in Table 1 are proposed, which include interaction with DNA, HSA, and the EGFR Kinase receptor. The works of Shivaraj's group include electron absorption titrations for DNA binding studies, where the intensity of the M-L charge transfer band varies with the added amount of DNA when there is an interaction; the idea of an intercalative binding mode between the complex and the DNA base pairs is proposed due to the hypochromism with a slight red shift evidenced in the UV-Vis spectra [31,35,36]. On the other hand, S. Jiang et al. explored the interactions of the **b1** complex with the HSA protein through UV-Vis spectroscopy, finding that the bimetallic complex can interact with the cavity of the HSA subdomain IIA and cause a conformational change in the HSA protein [39]. Rajendiran et al. indicated that the mechanistic study allows us to infer that DNA cleavage is possibly

mediated by the phenoxyl radical bound to Cu(II) of the **c1** complex [41], while P. Jain et al. bet on relating the cytotoxic activity with the binding mode of the **c3**–**c5** complexes against the EGFR kinase receptor by analyzing several types of interactions such as hydrogen bonds, hydrophobic bonds, and electrostatic interactions through molecular docking studies. These interactions show a significant binding of the complexes with the EGFR kinase receptor that contributes to a favorable binding energy (−59.88 kcal/mol) [42].

3.1. Mononuclear Complexes

Mononuclear complexes, which contain a single copper atom at the center of the coordination sphere chelated by a Schiff base ligand, offer advantages as anticancer agents. For instance, many of these complexes present square planar geometries, allowing efficient binding to biological macromolecules such as DNA and proteins, which is crucial for interfering with cellular processes essential for cancer cell proliferation [48]. Additionally, the controlled release of copper ions from these complexes can induce oxidative stress within cancer cells, ultimately triggering apoptosis or programmed cell death [49].

In recent years, the Shivaraj group has extensively reported a series of fluorinated Schiff base complexes and the study of their DNA binding, cytotoxic, and antibacterial activities. The Shivaraj Group conducted a study investigating the interactions between Cu(II) Schiff complexes, and CT-DNA using methods such as UV-absorption, fluorescence, and viscosity measurements. Through these analyses, binding constants (K_b) and Stern–Volmer quenching constants (K_{SV}) were determined and compared with those of ethidium bromide ($K_b = 7 \times 10^7$ M^{-1}).

The calculated K_b and K_{SV} values for the Cu(II) complexes are summarized in Table 2. The results indicate that, in general, the binding affinity of the copper complexes to DNA was lower compared to ethidium bromide. Notably, among the various copper complexes examined, **a10**, **a11**, and **a12** exhibited the most promising activity. This trend was further confirmed by the K_{SV} values, with complex **a10** demonstrating the highest activity. These findings suggest that the presence of halogens in the ligand can effectively modulate the binding affinity of the metal complex towards DNA [31].

Table 2. Binding (K_b) and Stern–Volmer (K_{SV}) constants obtained for the mononuclear planar square copper(II) metal complexes.

Complex	K_b (M^{-1})	K_{SV} (M^{-1})	Ref.
a1	$1.41 \pm 0.02 \times 10^5$	---	[33]
a2	$1.34 \pm 0.02 \times 10^5$	---	[33]
a3	$2.33 \pm 0.02 \times 10^5$	$2.47 \pm 0.02 \times 10^4$	[33]
a4	$1.41 \pm 0.02 \times 10^5$	$2.01 \pm 0.01 \times 10^4$	[33]
a5	$4.92 \pm 0.04 \times 10^5$	$2.30 \pm 0.01 \times 10^4$	[34]
a6	$5.13 \pm 0.01 \times 10^5$	$4.26 \pm 0.02 \times 10^4$	[35]
a7	$4.62 \pm 0.01 \times 10^5$	$4.09 \pm 0.03 \times 10^4$	[35]
a8	$5.93 \pm 0.01 \times 10^5$	$6.85 \pm 0.02 \times 10^5$	[32]
a10	$7.25 \pm 0.01 \times 10^5$	$6.73 \pm 0.02 \times 10^4$	[31]
a11	$6.85 \pm 0.02 \times 10^5$	$5.89 \pm 0.02 \times 10^4$	[31]
a12	$6.25 \pm 0.03 \times 10^5$	$5.50 \pm 0.01 \times 10^4$	[31]
a13	$5.23 \pm 0.01 \times 10^5$	$5.36 \pm 0.02 \times 10^4$	[36]
a14	$4.13 \pm 0.01 \times 10^5$	$4.99 \pm 0.03 \times 10^4$	[36]
Ethidium bromide	7×10^7	---	

On the other hand, complexes **a5** and **a8** also exhibited good binding affinity. In contrast, complex **a9**, which differs from **a8** by the presence of bromine instead of a methoxy group, displayed poor binding affinity. Therefore, in complexes **a8** to **a10**, the presence of

other substituents such as the methoxy group also plays a crucial role in binding efficiency [32]. Further evaluation of complex DNA cleavage activity using the agarose gel electrophoresis method, employing supercoiled plasmid pBR322 DNA as the substrate in the presence and absence of activators (H_2O_2 and UV light), revealed that all copper complexes exhibited a more pronounced potential for cleavage than their precursor ligands. Generally, the metal complexes were capable of degrading supercoiled pBR322 in the presence of activators, but their activity decreased in the absence of external agents. This suggests that -OH groups play a significant role in DNA cleavage.

The authors proposed a mechanism of action where the central metal ion of Cu(II) acts as a Lewis acid, activating the phosphodiester bonds for nucleophilic attack. From the results obtained, it was confirmed that all reported complexes are capable of interacting with CT-DNA through an intercalative mode [31].

The cytotoxic activity of complexes **a6–a7** and **a10–a14** was evaluated against the HeLa, A549, and MCF-7 cell lines using the MTT assay, with cisplatin serving as the standard drug. Following incubation with each compound, a dose-dependent increase in cell mortality was observed across all cell lines.

Two distinct fluorinated Cu(II) complexes derived from the same ligand, containing either Cl or Br, along with their Ni(II) and Co(II) analogs, were investigated to demonstrate the impact of halogen moieties on ligands and the influence of metal centers on cytotoxic activity [35]. Notably, copper complexes **a6** and **a7** exhibited superior activity against the HeLa and A549 human cell lines compared to their Ni(II) and Co(II) analogs, both of which presented an IC_{50} around 22 μM for both cell lines. Despite the authors not discussing a plausible reason for the observed behavior in the series of different metal complexes, it is likely that the presence of different halogens induces a synergistic effect on the electronic properties of complexes. Moreover, the selection of an accurate metal center, in this case Cu(II), likely contributed to enhancing the cytotoxic activity.

Another comparative study reviewed the effect of fluorine moieties in combination with donor groups on the ligands of the **a10–a12** [31], and **a13–a14** [36] complexes. For the **a10–a12** series, it was observed that the presence of halogens in the same ligand increased cytotoxicity; however, the presence of donor groups (Me_2N-, MeO-) decreased activity. In contrast, for the **a13–a14** compounds, the presence of donor groups increased cytotoxic activity. Notably, all complexes presented superior cytotoxic activity compared to the free ligands, meaning that copper incorporation significantly affects the cytotoxic activity of the complexes. For these series of compounds, no selective behavior was observed against one cell line or another; however, all these copper complexes showed IC_{50} values similar to that of cisplatin (A549: 24.12 μM, MCF-7: 28.62 μM, HeLa: 14.98 μM), suggesting a promising advance in the field of fluorinated Schiff base complexes as anticancer drugs.

3.2. Binuclear Complexes

Binuclear Schiff base complexes are composed of two metal ions bridged by a Schiff base ligand. The presence of dual metal centers enhances DNA binding and increases catalytic activity, making these complexes particularly effective in damaging the genetic material of cancer cells [50]. The binuclear structure can result in synergistic effects, and modifications with fluorine moieties have been shown to significantly enhance cytotoxic activity and selectivity, as reported by Jiang and coworkers [39]. They synthesized a series of Cu(II) binuclear Schiff base complexes bearing different halogens, $[Cu_2(HLX)_2(C_2H_5OH)_2]\cdot 2NO_3$ (X = F, Br, Cl), **b1**, and these were evaluated against five cancer cell lines (Bel-7402, HeLa, MCF-7, MGC-803, and WI-38). In particular, the fluorinated complex presented better cytotoxic activity compared to the analogs containing Br and Cl substituents. Additionally, this fluorinated complex showed the ability to interact with human serum albumin and induce conformational changes. The in vitro screening

revealed two interesting observations: the presence of Cu(II) significantly increased cytotoxicity compared to their free ligands and cisplatin. According to the authors, all the different substituents (F, Cl, or Br) can induce a lipophilicity-dependent decline during in vitro evaluation, but the fluorinated complex presented the best cytotoxic activity. Furthermore, apoptosis and mitochondrial potential experiments conducted with the fluorinated complex indicated that its cytotoxicity is concentration-dependent, and its mechanism involves triggering the mitochondrion-mediated apoptosis pathway. Unfortunately, these series of complexes did not show selectivity and were completely cytotoxic to all cell lines, including the normal lung fibroblast cell line WI38 (non-cancer cells).

Additionally, Savci and coworkers explored the cytotoxic potential of a series of fluorinated binuclear complexes featuring three different metals: Ru(III), Pd(II), and Cu(II), **b2** [40]. This investigation targeted colorectal adenocarcinoma cells (Caco-2) and fibroblasts (L-929). Remarkably, the Cu(II) and Pd(II) complexes exhibited notable IC_{50} values (31.88 and 25.35 μM, respectively) against Caco-2 cells, while demonstrating limited activity against L-929 cells (IC_{50} = 285 μM). Conversely, the Ru(III) complex displayed the lowest cytotoxicity. These findings underscore the pivotal role of the metallic center in determining selectivity and cytotoxicity. Notably, the Cu(II) complex emerged as particularly promising, displaying excellent selectivity towards Caco-2 cells while sparing healthy cell lines.

3.3. Other Coordination Complexes

The pivotal role of coordination geometry in metallodrug design is widely recognized. Such geometries facilitate specific interactions with targets through coordination or metal-mediated transfer reactions [51]. Consequently, complexes with square planar geometry remain extensively investigated as anticancer metallodrugs [52]. However, other intriguing coordination geometries are also reported in the literature. For instance, Rajendiran and colleagues reported complex **c1** and a series of non-fluorinated derivatives (replacing fluorine with H, Cl, or NO_2) exhibiting a square pyramidal geometry [41]. Notably, these complexes demonstrated a unique property: the generation of phenoxyl radicals, with the fluorinated complex showing a stable generation compared to its analogs. This property holds significance in the active site modeling of the galactosidase enzyme. Complex **c1** and its chlorinated derivative displayed fluorescence quenching of DNA-EthBr adducts, with binding constants (K_{app}) of 3.70×10^{-5} and 1.78×10^{-5} M^{-1}, respectively. As anticipated, the cytotoxic evaluation of this series revealed that **c1** and its chloro derivative exhibited the highest cytotoxic activity against alveolar adenocarcinoma A549 (IC_{50} = 3.52 and 3.40 μM, respectively), while the other derivatives (H and NO_2) showed higher values (IC_{50} = 12.25 and 6.25 μM, respectively) even close to cisplatin (IC_{50} = 13.0 μM). According to the authors, the cytotoxic activity of halogenated complexes is possibly mediated via copper(II)-bound phenoxyl radicals, leading to successful DNA cleavage and apoptosis. To evaluate the selectivity in this study, the cytotoxicity of the chloro derivative complex was tested against normal human peripheral blood mononuclear cells (PBMCs); the IC_{50} during 24 h treatment was 160.1 μM, which is 47 times higher than the IC_{50} obtained with A549 cancer cells, suggesting high selectivity for cancer cells and no effect on healthy normal cells.

In 2020, Arjmand and colleagues also reported the synthesis of the fluorinated formylchromone Cu(II) complex **c2** and its brominated derivative [53]. These complexes exhibited DNA binding affinity, with K_b values of 7.58 and 6.46×10^{-4} M^{-1}, respectively. The authors found that both fluorinated and brominated **c2** bind to DNA nucleobases via π-π stacking, as evidenced by molecular docking studies using a dodecamer DNA sequence, as shown in Figure 5. The results indicated an intercalative behavior in the adenine–cytosine-rich region due to the interaction of the aromatic chromone ring motif with

the minor groove of ct-DNA, along with an interaction between the halogen moiety and nucleotides. The binding energies were determined to be −333.98 and 347.07 kJ/mol for **c2** and its brominated derivative, respectively, suggesting efficient DNA–drug interaction and a slight difference based on the electronegativity of the halogen substituent. These two complexes were assessed against prostate cancer (DU-145), human liver carcinoma (Huh-7), and normal prostate epithelial (PNT1) cell lines. The results indicated that both complexes exhibited dose-dependent inhibition activity and significant selectivity. In the presence of cancer cell lines, the complexes displayed identical inhibition rates (60%) at the higher concentration (4.0 μM) while showing a 30% inhibition for PNT1.

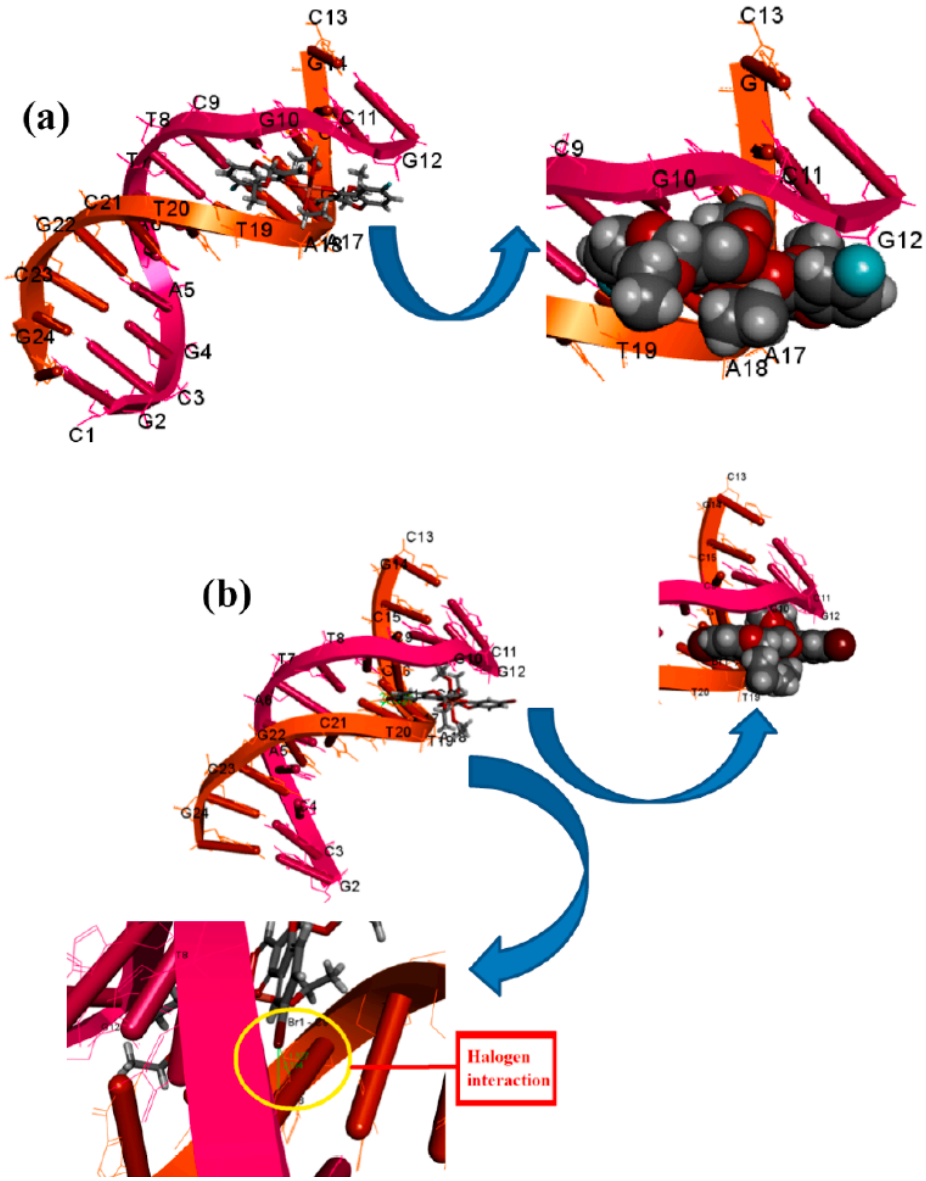

Figure 5. In silico evaluation of (**a**) complex **c2** and (**b**) its brominated derivative in the presence of (CGCGAATTCGCG)2 (PDF ID: 1BNA) dodecamer sequence of DNA helix (Adapted from Ref. [53] Copyright© 2020 Elsevier Inc.).

Two years before, Singh and colleagues reported another intriguing series of fluorinated complexes derived from the condensation of 1,3-dicarbonyl-phenyl-dihydrazide with 4,40-difluorobenzil with Co(II), Ni(II), and Cu(II) [42]. The cytotoxic assessment of Cu(II) derivatives (**c3**, **c4**, **c5**) and their Co(II) and Ni(II) counterparts against squamous carcinoma SCC4 revealed a concentration-dependent activity. After 48 h, all complexes

displayed high IC_{50} values exceeding that of cisplatin (IC_{50} = 5.2 μM). Particularly noteworthy was the activity observed with copper complex **c5** (X = AcO-) and the Co(II) analog (X = NO_3^-), with IC_{50} values of 74.9 and 54.3 μM, respectively, whereas Cu(II) complexes with X = Cl- and NO_3^- did not exhibit significant activity; see Table 1. Although the authors did not discuss the influence of metal ions and substituents, it was evident that, under specific conditions, the biological activity of Cu(II) and Co(II) could be modulated by selecting appropriate moieties such as acetyl or nitrate groups. In this study, a discussion on selectivity cannot be made, since other cell lines were not tested.

Recently, thiosemicarbazide Cu(II) Schiff base complexes **c6** and **c7**, along with their Co(II) and Zn(II) analogs, were investigated by Ramani and coworkers [43]. Docking evaluations of **c6** and **c7** suggest that the presence of electronegative groups in the structure promotes electrostatic interactions between these complexes and DNA, leading to successful intercalation as observed in Figure 6. In this regard, complexes **c6** and **c7** showed higher binding activities (−11.98 and −11.21 kcal/mol, respectively) than their cobalt and zinc analogs. The cytotoxic evaluation of Cu(II), Co(II), and Zn(II) thiosemicarbazide complexes against MCF-7 and HeLa cell lines, along with macrophages (TIB-71), was also analyzed. As expected, copper complexes showed the highest cytotoxic activities against both cancer cells, with IC_{50} = 5.28 and 8.9 μM for **c6** and **c7**, respectively, in MCF-7, and IC_{50} = 8.9 and 5.28 μM in HeLa. On the other hand, the activity of Cu(II) complexes on macrophages resulted in IC_{50} values >80 μM, demonstrating considerable selectivity toward cancer cell lines. According to the authors, the observed cytotoxic activity is due to the reducing nature of copper ions and the presence of heteroatoms in the ligand, along with the planar conformation of the aromatic groups that increase the lipophilic nature of the complexes, allowing their permeability through the cells.

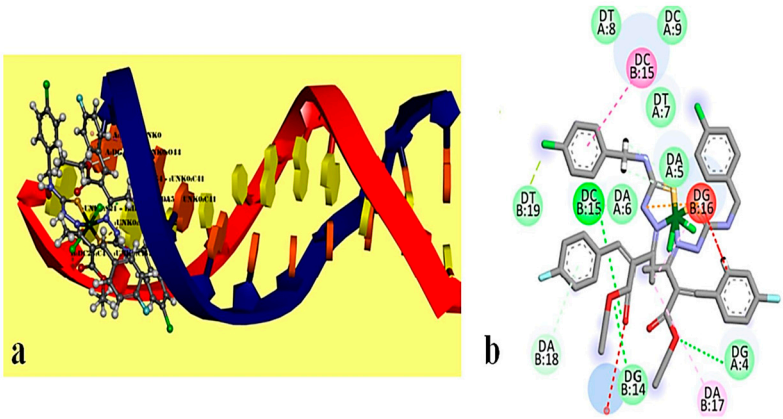

Figure 6. Three-dimensional (**a**) and two-dimensional (**b**) docking evaluation of complex c7 with CT-DNA (adapted from Ref. [43]; Copyright© 2023 Elsevier Ltd.).

Finally, in the work reported by Habala's group this year, the cytotoxic activity of four complexes of reduced Schiff bases containing fluoride substituents (**c10–c13**) was studied, showing a considerably high activity against the HepG2 hepatocellular carcinoma cell line compared to cisplatin (IC_{50} = 336.8 μM) [45]. The best activity was presented by the **c1** complex (IC_{50} 28.7 μM), but it is not possible to discuss its selectivity because it was only tested against one cell line.

4. Antibacterial and Antifungal Activity of Square Planar Cu(II) Complexes

In recent years, the rise of drug-resistant bacterial and fungal strains has become a significant global health concern, highlighting the urgent need for new antimicrobial agents. The search for effective antibacterial and antifungal compounds is critical due to the increasing prevalence of antibiotic resistance in key strains.

Metal complexes, particularly those derived from transition metals, have gained considerable attention for their promising biological activities, closely linked to their molecular structures. Among these, Schiff base complexes have shown remarkable antimicrobial properties, attributed to the synergistic effects of the biological activity of specific ligands and the ability of transition metals to disrupt essential cellular processes [54,55].

In this context, the Shivaraj group evaluated the antibacterial and antifungal properties of various fluorine-functionalized square planar Cu(II) Schiff base complexes. The aim was to understand the relationship between their molecular structure and biological activity [31–36]. The antifungal and antibacterial activities of complexes **a1–a16**, as well as their respective ligands, were assessed and compared with standard antibiotics (Ampicillin and Streptomycin for antibacterial activity) and antifungal agents (Ketoconazole and Mancozeb for antifungal activity); see Table 3. The general method reported to carry out the antimicrobial activity tests for the selected compounds can be seen in Figure 4b.

Table 3. Summary of antibacterial/antifungal activity of complexes **a1–a15** (evaluated at 500 μg/mL) and **a16** (evaluated at 40 μg/mL).

	Inhibition Zone (mm) Bacteria Strains						**Inhibition Zone (mm) Fungi Strains**				
	Gram-Positive			**Gram-Negative**							
Compound	***B. amyloliquefaciens***	***B. subtilis***	***S. aureus***	***E. coli***	***P. aeruginosa***	***K. pneumoniae***	***A. niger***	***C. albicans***	***M. phaseolina***	***S. rolfsii***	**Ref.**
a1	-	10 ± 0.1	8 ± 0.2	10 ± 0.1	9 ± 0.1	-	10 ± 0.1	11 ± 0.2	-	-	[33]
a2	-	8 ± 0.3	11 ± 0.1	12 ± 0.2	11 ± 0.1	-	12 ± 0.2	11 ± 0.2	-	-	[33]
a3	22 ± 0.3	-	24 ± 0.2	23 ± 0.1	21 ± 0.3	-	-	-	22 ± 0.1	23 ± 0.2	[33]
a4	20 ± 0.2	-	22 ± 0.2	21 ± 0.3	20 ± 0.1	-	-	-	20 ± 0.1	22 ± 0.1	[33]
a5	9 ± 0.38	-	-	10 ± 0.22	-	-	-	-	8 ± 0.26	3 ± 0.22	[34]
a6	26 ± 0.2	-	23 ± 0.4	21 ± 0.3	-	22 ± 0.2	-	-	21 ± 0.2	20 ± 0.2	[35]
a7	25 ± 0.3	-	23 ± 0.1	20 ± 0.2	-	21 ± 0.3	-	-	22 ± 0.2	20 ± 0.2	[35]
a8	7 ± 0.28	-	7 ± 0.18	9 ± 0.20	6 ± 0.18	-	-	-	8 ± 0.28	8 ± 0.26	[32]
a9	6 ± 0.30	-	7 ± 0.20	8 ± 0.20	6 ± 0.22	-	-	-	6 ± 0.24	7 ± 0.22	[32]
a10	20 ± 0.21	-	-	19 ± 0.16	-	-	-	-	18 ± 0.15	18 ± 0.18	[31]
a11	17 ± 0.14	-	-	16 ± 0.21	-	-	-	-	16 ± 0.16	15 ± 0.24	[31]
a12	16 ± 0.18	-	-	16 ± 0.15	-	-	-	-	15 ± 0.19	14 ± 0.15	[31]
a13	26 ± 0.2	-	24 ± 0.4	25 ± 0.3	-	22 ± 0.2	-	-	20 ± 0.2	21 ± 0.2	[36]
a14	24 ± 0.3	-	22 ± 0.3	23 ± 0.4	-	22 ± 0.2	-	-	20 ± 0.2	21 ± 0.2	[36]
a15	-	110.7 ± 0.5	-	8.9 ± 0.9	11.7 ± 1.2	-	-	-	-	-	[37]
a16	-	-	17	10	15	-	-	17	-	-	[38]
Ampicillin	30 ± 0.2	-	31 ± 0.2	30 ± 0.2	-	30 ± 0.2	-	-	-	-	
Streptomycin	15 ± 0.18	-	11.0 ± 0.14	10.0 ± 0.22	10.0 ± 0.26	-	-	-	-	-	

Ketoconazole	-	-	-	-	-	-	15 ± 0.2	16 ± 0.3	-	-
Mancozeb	-	-	-	-	-	-	-	-	31 ± 0.2	30 ± 0.2

According to the antibacterial screening results, the free Schiff base ligands did not exhibit significant activity; however, their corresponding complexes demonstrated substantial antibacterial inhibition, which varied based on the ligand's size and lipophilicity. The highest activity was observed in complexes **a6**, **a7**, **a13**, and **a14** against *B. amyloliquefaciens*, *S. aureus*, *P. aeruginosa*, and *K. pneumoniae*, with inhibition zones comparable to those of ampicillin. In contrast, the complexes with bulkier structures showed smaller inhibition halos. Similarly, in the antifungal screening, complexes **a3** and **a4** displayed notable inhibition zones, although their activities were lower than those of mancozeb.

The behavior observed in bacterial and fungal strains is primarily attributed to steric hindrance effects caused by substituents and the molecule's lipophilic nature. Introducing lipophilic moieties into the structure increases lipophilicity and thereby enhances antimicrobial activity. This increase is attributed to improved uptake across the cell membrane, as the lipidic nature of the membrane permits only lipid-soluble materials to penetrate the cell [56,57]. Additionally, the high lipophilicity of metal complexes results from chelation, which reduces the polarity of metal ions through partial sharing of their positive charge with donor atoms and π electron delocalization across the entire chelate ring. This characteristic further enhances the lipophilicity of metal complexes [33]. Therefore, liposolubility is considered a key factor in controlling antibacterial activity.

The most recent work presenting results of antimicrobial activity is that reported by Kaştaş et al. The **c8** and **c9** complexes containing fluorine improve the activity compared to the ethoxy-containing analog when tested against *S. aureus*, *B. cereus*, *E. coli*., *P. aeruginosa*, *C. parapsilosis*, and *C. krusei* [44]. In this study, the position of fluorine in the aromatic ring plays an important role in the activity, since **c9** (fluorine in the meta position) is more active (inhibition zone = 9 mm for *S. aureus* and 16 mm for *C. parapsilosis*) than the other compounds; however, the inhibition does not exceed the effect of commercial antibiotics. Finally, Habala et al. reported the antimicrobial activities of the copper complexes **c10–c13**, which were evaluated in vitro against Gram-negative (*E. coli*) and Gram-positive (*S. aureus*) bacterial strains and against the yeast *C. albicans* [45]. In this work, it is found that Cu(II) complexes are more active against bacterial strains than against fungi, and in general, there is no selectivity between Gram-positive and Gram-negative bacteria; however, a clear synergistic effect is observed, since the complexes are more active than the free ligands. This can be explained based on the Overtone concept and Tweedy's chelation theory, where lipophilic compounds are more likely to pass through the lipid membrane surrounding the cell while the chelation of a metal ion reduces its polarity, also increasing the lipophilicity of the compound.

5. Conclusions

Cu(II) complexes with fluorine-functionalized Schiff bases represent a significant advance in medicinal chemistry, given their ability to act as effective antitumor and antimicrobial agents. Through an in-depth analysis of the existing literature, this review provides valuable insights into the structural characteristics of fluorinated Schiff base Cu(II) complexes and their cytotoxic and antimicrobial properties. For instance, incorporating fluorine atoms into metal complexes has been shown to enhance the bioavailability and cellular uptake of these complexes, thereby increasing their potential as targeted anticancer agents and antimicrobial metallodrugs. Fluorine functionalization not only improves the metabolic stability and cellular uptake of these compounds, but also optimizes their interaction with biomolecules such as DNA, amplifying their therapeutic potential.

These advances underline the importance of continuing to investigate these systems as promising alternatives to current treatments. It is necessary to continue developing molecular modeling studies to explore specific interactions between Cu(II) complexes and target proteins or DNA, with the aim of identifying structures that maximize therapeutic efficacy and minimize side effects, as well as designing detailed studies that investigate the molecular mechanisms of cytotoxicity, including the generation of reactive oxygen species and the induction of apoptosis in cancer cells. The development of selective functionalization strategies in Cu(II) complexes with Schiff bases will allow exploring the incorporation of additional functional groups, such as electron donors or acceptors, that enhance selectivity toward specific tumor cells or microbial strains.

The results discussed in this review show that bimetallic complexes are an underexplored alternative but with promising results, so it would be interesting to investigate how the inclusion of a second metal could generate synergistic effects in biological activity, particularly in resistant bacterial strains or difficult-to-treat tumor cells. In conclusion, fluorine-functionalized Cu(II) complexes have the potential to revolutionize treatments in oncology and microbiology, standing out as a versatile and powerful tool in the development of new drugs.

Author Contributions: Conceptualization and investigation, L.G.-S., V.R.-M., A.R.-P. and L.O.F.-S.; Writing—original draft preparation, J.A.C.-N., M.E.M.-N., R.C.-P. and D.M.-M.; execution and drawing, J.A.C.-N., M.E.M.-N. and I.V.M.-D.; writing—review and editing, J.A.C.-N., R.C.-P., A.A.-M. and D.M.-M.; visualization and supervision, D.M.-M.; Funding acquisition, D.M.-M. All authors have read and agreed to the published version of the manuscript.

Funding: D.M.-M. would like to thank UNAM-DGAPA-PAPIIT IN223323 and CONAHCYT A1-S-033933 for their generous financial support.

Data Availability Statement: No new data were created or analyzed in this study.

Acknowledgments: This research was funded by the postdoctoral scholarship provided by Consejo Nacional de Humanidades, Ciencia y Tecnología (CONAHCyT)-Estancias Postdoctorales por México (3) granted to J.A.C.N. (CVU 824190), and the doctoral scholarship granted to M.E.M.N (CVU 815652).

Conflicts of Interest: Authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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