Ruthenium(II)

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The two Ru(III) and Ru(II) complexes, namely, BOLD-100 and RAPTA-C, are presently being studied in a clinical trial and preclinical studies evaluation, respectively, as anticancer agents. Ruthenium N-heterocyclic carbene (Ru-NHC) complexes show interesting properties in medicinal chemistry, exhibiting multiple biological activities, among them anticancer, antimicrobial, antioxidant, and anti-inflammatory. Among the newly synthesized complexes, RANHC-V and RANHC-VI are the most active against triple-negative human breast cancer cell lines MDA-MB-231. These compounds were selective in vitro inhibitors of the human topoisomerase I activity and triggered cell death by apoptosis. Furthermore, the Ru-NHC complexes' antimicrobial activity was studied against Gram-positive and -negative bacteria, revealing that all the complexes possessed the best antibacterial activity against the Gram-positive Staphylococcus aureus, at a concentration of 0,025 mg/mL. Finally, the antioxidant effect was assessed by DPPH and ABTS radicals scavenging assays, resulting in a higher ability for inhibiting the ABTS+, with respect to the well-known antioxidant Trolox. Thus, this work provides encouraging insights for further development of novel Ru-NHC complexes as potent chemotherapeutic agents endowed with multiple biological properties.

Keywords: ruthenium(II) complexes ; dual antitumor/antiviral agents ; p-cymene

1. Introduction

For many years, numerous researchers have actively worked in the field of inorganic drugs developing several metal complexes with diverse biological activities [1], such as anticancer [2][3][4][5][6][7][8] antibacterial [9], antioxidant [10], and antiviral [11][12][13]. During the COVID-19 pandemic [14], numerous studies have addressed using metal complexes in the hope of finding new strategies to cure the disease [15][16][17]. A comprehensive survey of the anti-COVID-19 options available using metal complexes has been recently reported by Gopal et al. (2023) [18]. Among the precious metals, ruthenium (Ru) has singular physicochemical properties, which makes it particularly useful in drug design [19]. Ru complexes represent an important class of metallo-organic compounds with numerous applications, and they are currently used in the fields of catalysis [20][21][22][23], including homogeneous, heterogeneous, and photocatalysis [24]. Moreover, numerous biological activities, such as antifungal [25], antibacterial [26], and anticarcinogenic [27][28][29][30][31][32], have been described for the complexes of Ru, as well as their uses in neurodegenerative diseases [33]. Several complexes with Ru(II) have been reported, including those with benzoic acid and their analogues [34], naphthoquinones, flavonoids, curcumins [35], *N*-heterocyclic carbenes (NHCs) [36], polypyridyl [37], phenanthroline [38], thiazole [39], Schiff bases [40][41][42][43], and half-sandwiched arene complexes [44]. Specifically, Ru complexes are widely studied in colorectal cancer [45], breast cancer [46], lung cancer [47], and prostate cancer [48]. Thota et al. (2018) recently described the importance of Ru(II) complexes as anticancer agents [49]. Ru(II) complexes show several advantages over traditional platinum-based chemotherapeutics, such as stability in biological media due to their higher redox potentials, which allows for longer circulation times in the body, thereby increasing the amount of time that the complexes have to target tumor cells [50]; selectivity towards tumor cells and minimal side effects, which are probably due to differences in the redox potentials or metal ion binding properties of tumor cells versus healthy cells [51]; easier accessibility for synthetic routes; low costs associated with the overall process; and, finally, Ru(II) complexes can be administered through a variety of routes, including oral, intravenous, and intraperitoneal. It is strongly believed that Ru(III) species act as prodrugs, and they are converted into Ru(II) species due to the hypoxic environment within the cancer cells [52][53][54]. Ru complexes are also studied in photodynamic therapy, photochemotherapy, and photothermal therapy [55]. With these activities, Ru can help to trigger antitumor activity only in desirable areas of the body or in cancer cells, apart from classical chemotherapeutic action [56][57]. Over the last two decades, the complexes of ruthenium have been also studied for their antioxidant [58], antimicrobial [59], and antiviral activities [60][61]. Moreover, the modulation activity of amyloid-β aggregation has been described, which can be useful in the treatment of Alzheimer's disease [62][63]. Ru(II) and Ru(III) complexes are currently objects of great attention in the field of medicinal chemistry as antitumor agents with selective antimetastatic properties and low systemic toxicity [64][65][66][67]. The pharmacological activity of metal complexes can be attributed to either the

metal itself, its ligands, or both, depending on the structure of the complex. The ruthenate anion itself may interact with cellular targets or simply act as a scaffold to carry bioactive ligands to a target site [26][68]. Ru-based compounds, as well as other metal complexes, act via a myriad of mechanisms, which usually involve interactions with DNA or various proteins such as enzymes and transcription factors [68]. Ru complexes, as well as platinum complexes, are generally defined as “multitargeted”, since they not only target DNA, but also contain either a vector to enable them to target cancer cells selectively and/or moieties that target enzymes, peptides, and intracellular proteins [69]. Several studies are addressed here to understand the mechanism of action of Ru(II) complexes. Recently, a probable mechanism of transfer hydrogenation catalysis with respect to anticancer activity has been described for Ru–arene complexes [70]. Moreover, a recent review on Ru(II) complexes suggested that metal-based candidate drugs are promising modulators of cytoskeletal and cytoskeleton-associated proteins [71]. Recently, Ru and rhodium complexes have been suggested as promising agents for metalloimmunotherapy [72].

In the fight against cancer, three Ru(III) coordination complexes (NAMI-A, KP1019, and BOLD-100) and one Ru(II) coordination complex (TLD1433) have advanced to clinical trials (**Figure 1**) [73]. Inside the tumor, Ru(III) is proposed to be activated by its reduction to Ru(II) due to prevalent reductive conditions. The Ru(III) complexes are tetrachloride complexes with axial N-heterocyclic ligands. NAMI-A exhibited strong inhibitory effectiveness against tumor malignancy and metastasis, thereby preventing the development of the growth of tumors. It entered phase II trials, but due to limited efficacy and acute side effects in many patients, it could not proceed further for clinical development [74]. The Ru(III) complex sodium BOLD-100 is among the most widely investigated nonplatinum metal-based anticancer drugs [75]. It was studied as a substitution of the Ru complex KP1019, which entered phase I trials for colorectal tumors, but its further development was halted due to its low solubility [76]. KP1019 is known to be active against primary tumors, while NAMI-A is active against secondary tumors *via* antiangiogenic and antimetastatic activities [6]. NAMI-A and KP1019 have been shown to bind to DNA, RNA, and proteins [77]. The octahedral polypyridyl Ru(II) complex TLD1433 has potential as a photosensitizer for photodynamic therapy in the treatment of bladder cancer [78].

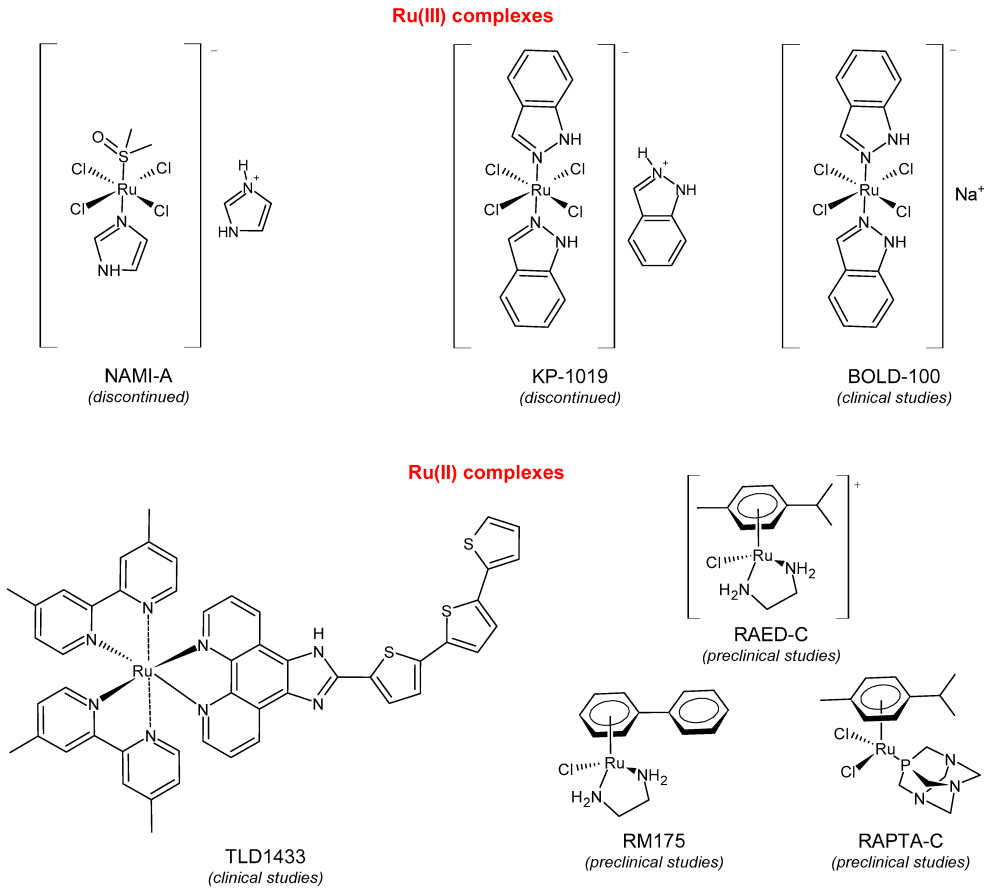

Figure 1. Structures of Ru(III) and Ru(II) complexes in clinical and preclinical trials.

Ru(II) complexes, namely RM175, RAED-C, and RAPTA-C, are 18-electron Ru–arene “piano-stool” complexes, in which an η^6-arene ring stabilizes the 2^+ oxidation state of the Ru metal center [73]. These complexes entered into preclinical studies because of their appealing anticancer properties [79]. RM175 was the first Ru(II) complex reported to have potential for anticancer activity. RM175 has undergone successful in vitro and in vivo cytotoxic assessment and has shown efficient cytotoxicity in vitro, with IC_{50} values similar to that of cisplatin [80]. RM175 shows a mechanism of action similar to cisplatin through its interaction with guanine. The possible mechanism of interaction has been recently

elucidated by Prathima et al. (2023) [6]. However, it differs from cisplatin, as it revealed no cross-resistance against cisplatin-resistant ovarian carcinoma cells (A2780cis); this is indicative of a distinctive mode of anticancer action and has also been reported to trigger p53-dependent cell-cycle arrest [81]. Ru(II)–arene RAED-type compounds (ED = ethylenediamine) and Ru(II)–arene RAPTA-type compounds (PTA = 1,3,5-triaza-7-phosphaadamantane or 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decanephosphine) were developed by the groups of Sadler [82] and Dyson [83], respectively. Both have the *p*-cymene moiety, that is, 1-methyl-4-(propan-2-yl)benzene. The RAED series was first reported in 2001 by Morris et al. [84], and these compounds are able to coordinate with DNA through the N7 of guanine residues and, when bearing an extended arene ligand such as biphenyl, dihydroanthracene, or tetrahydroanthracene, may concomitantly intercalate in DNA. These compounds are cytotoxic against diverse cancer cell lines, including cisplatin-resistant strains [85]. Swaminatan et al. (2022) [86] reported that RAED-C is highly active in primary tumors, whereas RAPTA-C is inactive in primary tumors but possesses antimetastatic and antiangiogenic properties. Moreover, the former preferentially forms adducts at the DNA sites with only one additional binding site at the histone level, while the latter preferably forms adducts at the histone protein sites residing on the surface of the nucleosome core. Hildebrandt et al. (2022) [87] have recently reported that both compounds, RAPTA-C and RM175, are being studied in advanced clinical studies. However, to our knowledge, no other research confirms this statement.

Moreover, the drug delivery forms of Ru complexes have also been studied as antitumor drugs for combination therapy [88]. Finally, and very importantly, dual-active drugs are a concept that has been noted as an imperative in future drug design. The development of novel drugs that can have double biological behavior (anticancer–antiviral, anticancer–antimicrobial, etc.), leading to the opportunity to treat two different diseases, has been recently widely addressed [89][90][91][92].

2. Ruthenium(II/III) Complexes in Clinic Trials and Advanced Preclinical Studies as Anticancer Agents

2.1. BOLD-100

The Ru(III) complex sodium *trans*-tetrachlorobis(1*H*-indazole)ruthenate(III) (BOLD-100, formerly known as NKP-1339, KP1339, and IT-139) is a double prodrug that undergoes hydrolysis via the ligand exchange of chloride ligands and subsequent reduction to Ru(II) [93][94]. BOLD-100 is a versatile small molecule with manifold intracellular modes of action, which were previously summarized by the research group that synthesized this molecule [95]. In clinical phase I evaluation, BOLD-100 therapy led to disease stabilization and even partial response in various types of advanced solid tumors, including colorectal cancer, non-small-cell lung cancer, and neuroendocrine tumors of carcinoid origin [96]. BOLD-100 was granted an orphan drug designation (ODD) in gastric and pancreatic cancers [97]. It is currently in a phase 2a clinical trial in combination with folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX regimen) for the treatment of advanced solid tumors, such as colorectal, pancreatic, and gastric cancers, as well as cholangiocarcinoma (NCT04421820) [98][99]. Moreover, BOLD-100 has also demonstrated increased activity in the cell lines from esophageal cancer, blood cancers, and bladder cancer [100]. BOLD-100 has also recently gained particular interest for its potential multiple activities. Earlier, the drug had won orphan drug titles for its indication of pancreatic cancer [98][100]. Besides its undiscussed anticancer activity, it has been recently demonstrated that this compound is also a potent inhibitor of the replication of human immunodeficiency virus type 1 (HIV-1), human adenovirus type 5, and SARS-CoV-2 in vitro [101]. Repression of the genes involved in DNA repair, the induction of reactive oxygen species (ROS), and interference with ribosomal proteins seem to be results of BOLD-100 activity [75]. Moreover, BOLD-100 is an inhibitor of glucose-regulated protein 78 kDa (GRP78) (WO/2017/151762), thus disrupting endoplasmic reticulum homeostasis, inducing endoplasmic reticulum stress, and eliciting an unfolded protein response [102]. This is reflected by the phosphorylation of the eukaryotic translation initiation factor 2A [103] and caspase-8-dependent cell death [104]. The suppression of Grp78 transcription is a mechanism described for antiviral activity, which has also been demonstrated against SARS-CoV-2 [105]. Moreover, in vitro studies have demonstrated that this compound triggers an immunogenic cell death (ICD) signature hallmarked by the phosphorylation of PERK, the eukaryotic translation initiation factor 2α (eIF2α) exposure of calreticulin on the cell membrane, the release of the high mobility group box 1, and the secretion of ATP [106]. Interestingly, Mucke (2022) [107] reported that BOLD-100 inhibited the cytopathic activity in an assay based on Vero-E6 cell lines infected with the Wuhan strain of the virus: the absolute EC_{50} value for preinfection protection by BOLD-100 was 1.9 µM, whereas postinfection treatment required 1.8 µM. This value is orders of magnitude lower than the 200–400 mM cytotoxicity limit for BOLD-100 in this cell line, and it is much lower than the respective values for the antiviral remdesivir [108]. At 200 µM, the cytopathy of 293T-ACE2 human kidney cells (which express the ACE2 receptor) infected with the ‘California variant’ of the B.1.1.7 viral strain was prevented by BOLD-100 [107]. Yet, a general limitation of systemic cancer therapy efficacy is the acquisition of treatment resistance [109]. The mechanism against solid tumors that has been recently suggested is related to its ability to inhibit glycolysis and render cells vulnerable to glucose-deficient metabolism [110]. It is known that, besides other

metabolic changes, including alterations in oxidative phosphorylation or glutaminolysis [111], several types of solid cancers show improved glycolysis to convert glucose to lactate, even under aerobic conditions: this effect is called the “Warburg effect” [112]. BOLD-100 demonstrated a significant glycolysis-blocking anti-Warburg effect as a novel mechanism of action. Thus, glycolysis inhibition has also been suggested as a potential strategy to overcome acquired BOLD-100 resistance and enhance BOLD-100 anticancer activity. Moreover, an upregulated glucose uptake was detected in combination with BOLD-100 exposure [110]. Baier et al. (2023) [113] recently identified BOLD-100 as an epigenetically active substance targeting several oncometabolic pathways. The authors suggested that acquired BOLD-100-resistant colon and pancreatic carcinoma cells may be related to lipid metabolism. BOLD-100 significantly reduced the production and release of lactate, which is a major immunosuppressive metabolite. The existence of crosstalk between BOLD-100 exposure, acquired resistance, and histone acetylation has been suggested.

2.2. TLD1433

TLD1433 (also known as Ruvidar® and “Theralase®) was the first Ru(II)-based photosensitizer to enter clinical trials and successfully complete a phase 1b human clinical trial (NCT03053635). A phase 2 study is ongoing (NCT03945162) [114] [115] to evaluate TLD1433 in non-muscle-invasive bladder cancer patients. It has been recently suggested as a repositioning drug for the treatment of conjunctival melanoma, which is a rare but often deadly ocular cancer [116], and human lung adenocarcinoma [117]. Recently, Karges (2022) [118] reviewed the clinical development of TLD1433 and other metal-containing compounds, including rostaporfin (Purlytin®), motexafin lutetium (Lutrin®/Antrin®), and the sulfonated aluminium phthalocyanin (Photosens®), bearing the different metals Sn, Lu, and Al, respectively, as well as padeliporfin (WST09) and padeliporfin (WST11 or TOOKAD® soluble), which contain Pd, as photosensitizers for the photodynamic therapy of cancer.

2.3. RAPTA-C

The therapeutic potential of Ru(II)–arene RAPTA-type compounds (PTA = 1,3,5-triaza-7-phosphaadamantane or 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1]decanephosphine) has been thoroughly investigated, thus owing to the excellent antimetastatic property of the initial candidate RAPTA-C [Ru(η^6-*p*-cymene)Cl_2(PTA)] [119]. It is a multitargeting drug candidate that has demonstrated pH-dependent DNA damage, inhibited the enzyme activity of cathepsin-B and thioredoxin reductase, and showed selectivity towards the hypoxic environment of cancer cells [120]. It represents an innovative antitumor therapy and a better-tolerated alternative to Pt-based chemotherapeutic drugs in the treatment of tumors, as it exhibits antitumoral, antimetastatic, and antiangiogenic activities through protein and histone–deoxyribonucleic acid alterations [121]. RAPTA-C acts synergistically in association with other drugs, such as the EGFR inhibitor erlotinib, the tyrosine kinase inhibitor axitinib, PI3K, and the mTOR inhibitor BEZ-235, as demonstrated by in vivo models [122][123][124][125]. The study by Weiss et al. (2014) [126] demonstrated that RAPTA-C caused a reduction in the growth of primary tumors in preclinical models for ovarian (A2780 ovarian carcinoma transplanted onto a chicken chorioallantoic membrane model) and colorectal (in LS174T colorectal carcinoma in athymic mice) carcinomas. Moreover, the clearance rate of RAPTA-C from the organs and the bloodstream was studied using RAPTA-C that incorporated radio-labeled (^{103}Ru). Biodistribution studies with radio-labeled (^{103}Ru) RAPTA-C demonstrated that the compound is rapidly cleared from the organs and the bloodstream through excretion by the kidneys. Recently, the combination of RAPTA-C and paclitaxel based on fructose-coated nanoparticles has been suggested as a dual drug delivery system for the treatment of metastatic cancer. The dual drug delivery system was studied via in vitro tests using MDA-MB-231 breast cancer cells, and it was observed that RAPTA-C, in combination with paclitaxel, significantly enhanced antitumor and antimetastatic action [127].

3. Ruthenium Complexes Acting against Viruses

Several metal-based drugs have been described regarding their antiviral activities, thereby highlighting the potential for these metal-based drugs to be used in treating COVID-19 [17][128][129][130][131]. Although many studies have described the anticancer activity of Ru complexes, there are very few reports on their antiviral activity [129][132][133]. Recently, Gil-Moles and colleagues (2021) [134] described some metallodrugs, including Ru complexes, and their activity against SARS-CoV-2. Some complexes were potent inhibitors of essential SARS-CoV-2 targets, such as the SARS-CoV-2 spike protein/host ACE2 receptor interaction and the SARS-CoV-2 papain-like protease (PL^{pro}). Moreover, Janković et al. (2022) [135] reported other Ru complexes as potent antivirals against SARS-CoV-2, which target the papain-like proteases PL^{pro} and M^{pro}. They are shown in the next paragraphs. De Oliveira et al. (2020) [61] described their antiviral activity against other viruses, such as the Chikungunya virus, thereby highlighting the potential of Ru-based compounds as broad-acting antivirals.

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