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Dinuclear Rhenium(I) Tricarbonyl Complexes as Anticancer Drug Candidates

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Cancer is one of the deadliest diseases worldwide. Chemotherapy remains one of the most dominant forms for anticancer treatment. Despite their clinical success, the used chemotherapeutic agents are associated with severe side effect and pharmacological limitations. To overcome these drawbacks there is a need for the development of new types of chemotherapeutic agents. Herein, the chemical synthesis and biological evaluation of dinuclear rhenium(I) complexes as potential chemotherapeutic drug candidates are proposed. The metal complexes were found to be internalized by an energy dependent endocytosis pathway, primary accumulating in the mitochondria. The rhenium(I) complexes demonstrated to induce cell death against a variety of cancer cells in the micromolar range through apoptosis. The lead compound showed to eradicate a pancreatic carcinoma multicellular tumor spheroid at micromolar concentrations.

Introduction

Despite the progress made in treating cancer in recent decades, it continues to be one of deadliest diseases globally.[1] According to the World Health Organization, almost 10 million individuals have died from cancer in 2020, and projections suggest that cancer-related death will increase to 16.4 million by 2040.[2] Currently, platinum complexes (i.e., cisplatin, oxaliplatin, and carboplatin) rank among the most widely utilized chemotherapy drugs worldwide. Despite their widespread clinical application, these compounds come with significant side effects such as nerve and kidney damage, nausea, vomiting, and bone marrow suppression, limiting their application.[3] To overcome these drawbacks, there is a need for the development of new types of anticancer agents with different mechanism of action.

Among the most promising anticancer drug candidates, increasing research efforts have been devoted towards the application of rhenium(I) tricarbonyl complexes.[4] The kinetically inert nature of this compound class, attributed to its octahedral geometry, low-spin d^6 electron configuration, and the influence of potent ligands, enhances its utility in biological applications.[5] Re(I) tricarbonyl complexes typically operate through distinct mechanisms. Mao *et al.* demonstrated the irreversible induction of oxidative stress and disruption of glutathione metabolism through rhenium(I) tricarbonyl complexes, which accumulate in mitochondria.[6] The same authors presented a rhenium(I)-based histone deacetylase inhibitor that targets mitochondria and suppresses histone deacetylase activity.[7] Massi *et al.* designed rhenium(I) complexes that induce cell death by inhibiting the phosphorylation of Aurora-A kinase.[8] Wilson *et al.* reported on an isonitrile rhenium(I) complex that induced apoptosis using the unfolded protein response pathway and exhibiting anticancer effects against ovarian cancer cells and tumor-bearing mouse models.[9] These findings highlight the ability of rhenium(I) complexes to interact through mechanisms different from traditional platinum-based chemotherapeutics.

Due to the valuable therapeutic attributes of the rhenium(I) tricarbonyl core, there has been considerable interest in incorporating this fragment in combination with other metal centers. Multimetallic complexes have proven to be beneficial in various biological applications by harnessing the unique properties of different metal centers simultaneously. Within the realm of rhenium(I) tricarbonyl complexes, there are reports of both homonuclear complexes and heteronuclear complexes, which has been recently reviewed.[10] Mao *et al.* reported on dinuclear rhenium(I) tricarbonyl complexes with different ancillary ligands. While the phenanthroline coordinated compound with lower lipophilicity, localized in the lysosomes and triggered caspase-independent apoptosis, the bathophenanthroline coordinated compound accumulated in the mitochondria, inducing caspase-independent paraptosis. Importantly, both compounds exhibited a higher cytotoxicity compared to their mononuclear counterparts.[11] Yan *et al.* demonstrated that dinuclear rhenium(I) tricarbonyl complexes, that were bridged with phosphines, were cytotoxic against various cancer cell lines in the low micromolar range.[12] Hall *et al.* reported on alkoxy/hydroxyl bridged dinuclear rhenium(I) tricarbonyl complexes as

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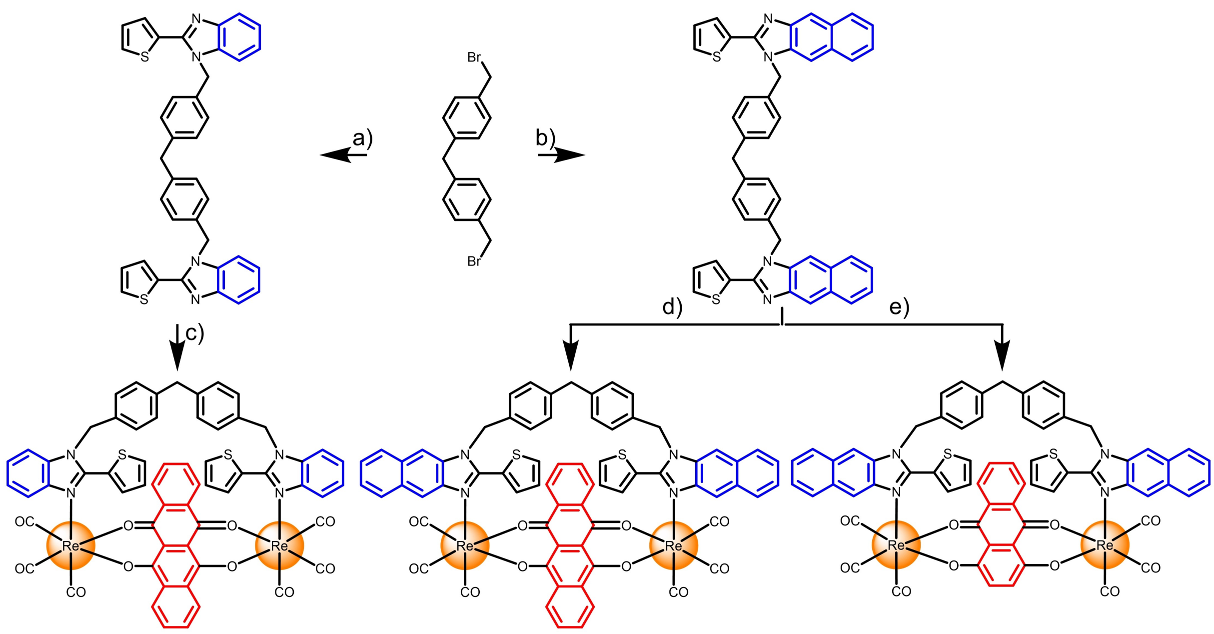
Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202400217 cytotoxic agents against a variety of cancer cell lines. The lead compounds were found to therapeutically intervene through involving DNA strand scission and impactful interference with nucleic acid metabolism through enzymes such as dihydrofolate reductase, PRPP-amido transferase, and thymidine kinases.[13] These research studies demonstrated the application of dinuclear rhenium(I) tricarbonyl complexes as anticancer drug candidates.

Herein, the chemical synthesis and biological evaluation of dinuclear rhenium(I) tricarbonyl complexes, that were dually linked through coordination to a monomeric linker as well as bridged through 1,4-dihydroxyanthraquinone, are reported. The metal complexes were found to efficiently taken up by the cancerous cells through an energy dependent endocytosis pathway. The rhenium(I) tricarbonyl complexes primarily localized in the mitochondria, triggering cell death by apoptosis. The lead compound demonstrated a strong tumor growth inhibition effect against breast cancer multicellular tumor spheroids.

Results and Discussion

In this study, the synthesis of dinuclear rhenium(I) complexes is pursued. Previous studies have indicated that the formation of a dinuclear metal complex could be achieved by an aliphatic linker that coordinates monodentate to the metal center[14] or through bridging ligands that coordinate to both metal centers in a bidentate fashion.[15] Herein, the combination of both synthetic strategies allowed the one-pot preparation of a series of new double-linked dinuclear rhenium(I) tricarbonyl complexes, which are distinct to previously reported anticancer dinuclear rhenium(I) tricarbonyl complexes.[4a,10–11,14c] 2-(2-thienyl)-1H-benzimidazole or 2-(2-thienyl)-1H-naphth[2,3-d]imidazole was deprotonated with sodium hydride in tetrahydrofuran. Afterwards, bis(4-(bromomethyl)phenyl)methane was added and mixture stirred at room temperature for two days. The product was precipitated from solution and the desired aliphatic linkers were obtained in high yields. The dirheniumdecacarbonyl precursor, the respective aliphatic linker as well as 6,11-dihydroxy-5,12-naphthacenedione or 1,4-dihydroxyanthraquinone as the bridging ligand were dissolved in p-xylene and sealed in a stainless-steel bomb. The vessel was heated at 160 °C for 48 h to obtain the desired metal complexes **1**–**3** as racemic mixtures (Figure 1). The compounds were characterized by NMR spectroscopy and high-resolution mass spectrometry (Figure S1–S6). Notably, we have recently reported the crystal structure of the metal complexes.[16] The purity was confirmed by elemental analysis. Remarkably, the herein described double-linked dinuclear rhenium(I) tricarbonyl complexes were easily obtained via one-pot synthesis while other reported dinuclear rhenium(I) tricarbonyl complexes often require several synthetic and purification steps to be obtained.

The octanol-phosphate buffered saline partition coefficient (log*P*) was determined using the shake-flask method by absorption spectroscopy. As expected, **1**–**3** were found to be strongly lipophilic with log*P* values ranging from +0.7 to +0.9 (Table S1). The biological evaluation of the metal complexes was assessed against pancreatic carcinoma (PT-45) cells. The cellular uptake was time-dependently determined upon determination of metal content inside the cancer cells by inductively coupled plasma mass spectrometry (ICP-MS). The results



1 **2** **3**

Figure 1. Synthesis of dinuclear Re(I) tricarbonyl complexes investigated in this study. a) 2-(2-thienyl)-1H-benzimidazole, NaH, THF, 51 h, RT, 96%; b) 2-(2-thienyl)-1H-naphth[2,3-d]imidazole, NaH, THF, 51 h, RT, 78%; c) dirheniumdecacarbonyl, 6,11-dihydroxy-5,12-naphthacenedione, p-xylene, 48 h, 160 °C, 70%; d) dirheniumdecacarbonyl, 6,11-dihydroxy-5,12-naphthacenedione, p-xylene, 48 h, 160 °C, 70%; e) dirheniumdecacarbonyl, 1,4-dihydroxyanthraquinone, p-xylene, 48 h, 160 °C, 87%. All the compounds were isolated as racemic mixtures.

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showed that the maximal cellular uptake was reached for all compounds after incubation for 4 h (Figure S1). Followingly, all cellular experiments were performed upon incubation of the cancer cells with the metal complexes for 4 h. The uptake mechanism of the compounds was studied by blocking various pathways by preincubation with a metabolic (2-deoxy-*D*-glucose and oligomycin), cationic transporter (tetraethylammonium chloride), and endocytotic inhibitors (ammonium chloride or chloroquine) as well as at reduced temperature (4° C). As the preincubation with tetraethylammonium chloride did not change the internalization of the metal complexes, the cellular uptake by the cationic transporter was ruled out. The preincubation with 2-deoxy-*D*-glucose and oligomycin as well as the reduced temperature demonstrated to reduce the internalization of compounds, indicative of the energy dependence of the cellular uptake of the metal complexes. As the preincubation with ammonium chloride or chloroquine drastically decreased the cellular uptake, the cellular uptake mechanism of **1**–**3** by an energy dependent endocytosis pathway is suggested (Figure S2–S4).

The cytotoxicity of the compounds **1**–**3** in comparison to the chemotherapeutic anticancer drug cisplatin was investigated against cancerous PT-45, human cervical carcinoma (HeLa), breast cancer (MCF-7) as well as non-cancerous non-cancerous human fibroblast (GM-5657) cells using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The compounds **1**–**3** were found to be cytotoxic in the micromolar range against all tested cell lines with a ~2–14 times higher therapeutic effect than cisplatin. Promisingly, the metal complexes **1**–**3** were found to be more cytotoxic against the cancerous cells than the non-cancerous cells. Among all studied metal complexes, compound **1** showed the highest cytotoxicity with an IC_{50} value of 2.3 ± 0.7 μM against PT-45 cells (Table 1). Following mechanistic experiments were performed with **1** in PT-45 cells.

Table 1. IC_{50} values (in μM) of the compounds **1**–**3** and the anticancer drug cisplatin against cancerous pancreatic carcinoma (PT-45), human cervical carcinoma (HeLa), and breast cancer (MCF-7) as well as non-cancerous non-cancerous human fibroblast (GM-5657) cells. The error bars correspond to the standard deviation of the three replicates.

Compound	PT-45	HeLa	MCF-7	GM-5657
1	2.3 ± 0.7	7.1 ± 1.4	6.3 ± 0.8	12.5 ± 2.8
2	5.8 ± 1.2	9.6 ± 1.7	8.4 ± 1.1	15.7 ± 3.1
3	8.3 ± 1.3	12.7 ± 1.5	9.7 ± 1.2	14.3 ± 2.4
cisplatin	31.6 ± 3.3	24.5 ± 2.8	32.1 ± 2.7	39.3 ± 4.2

For a deeper understanding of the therapeutic effect, the subcellular localization of **1** in PT-45 cells was determined. The cancer cells were incubated with 10 μM of the metal complex for 4 h, the cell organelles carefully extracted, and metal content determined by ICP-MS. The results showed that **1** was found primarily in the mitochondria and secondarily in the lysosomes (Figure 2).

For a deeper understanding of the therapeutic effect, the cell death mechanism **1** was studied in PT-45 cells upon preincubation with specific cell death inhibitors Z-VAD-FMK (apoptosis inhibitor), cycloheximide (paraptosis inhibitor), 3-methyladenine (autophagy inhibitor), and necrostatin-1 (necrosis inhibitor), the cancer cells treated with **1**, and afterward the cell viability assessed by a MTT assay. As the preincubation with cycloheximide, 3-methyladenine, and necrostatin-1 did not strongly influence the cell survival, the cell death mechanisms by paraptosis, autophagy, or necrosis were ruled out. In contrast, the preincubation with Z-VAD-FMK increased the survival of the cancer cells, suggestive that **1** induced cell death by apoptosis (Figure 3). For further insight into the apoptosis cell death mechanism its dependency on the caspase 3/7

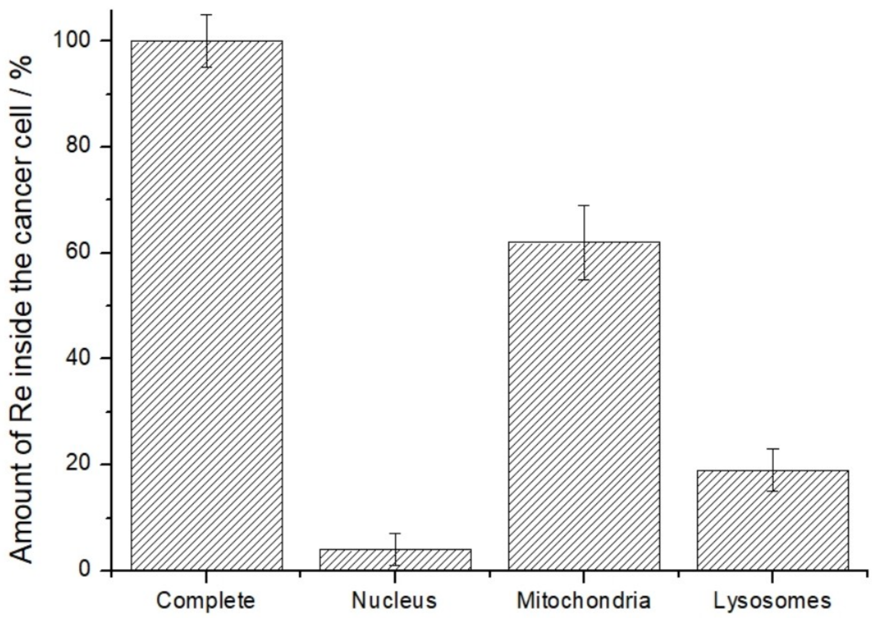

Figure 2. Subcellular distribution of **1** (10 μM) in PT-45 cells determined by ICP. The error bars correspond to the standard deviation of the three replicates.

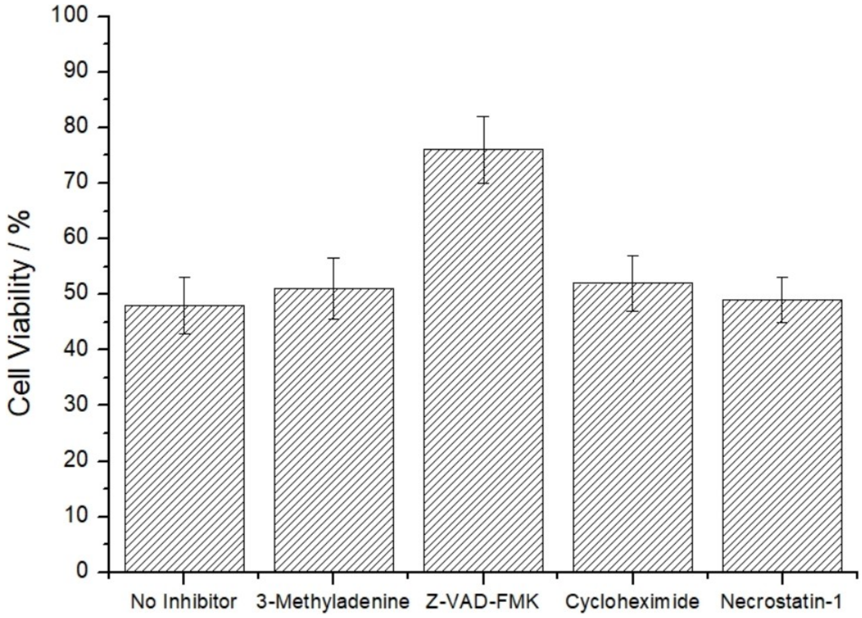

Figure 3. Determination of the cell death mechanism of **1** in PT-45 cells upon preincubation with different cell death inhibitors and treatment with the IC_{50} concentration of **1** (2.3 μM). Autophagy inhibitor: 3-Methyladenine (100 μM), apoptosis inhibitor: Z-VAD-FMK (20 μM), paraptosis inhibitor: Cycloheximide (0.1 μM), necrosis inhibitor: Necrostatin-1 (60 μM). The error bars correspond to the standard deviation of the three replicates.

pathway was investigated using a caspase 3/7 glo assay. The results demonstrated that the treatment **1** strongly elevated the caspase 3/7 activity (Figure S11). Combined these findings suggest that **1** induces cell death by apoptosis using the caspase 3/7 pathway.

After evaluating the cytotoxicity in two-dimensional cancer cells, the therapeutic effects against three-dimensional multicellular tumor spheroids were investigated. Multicellular tumor spheroids are a tissue culture model that mimics the histological and pathological conditions of solid tumors such as proliferation gradients, nutrition gradients, and a hypoxic center. Many preliminary investigated anticancer agents have failed the translation from two-dimensional cancer cells into animal models partially attributed to poor drug delivery into the tissue. Multicellular tumor spheroids are able to simulate three-dimensional cellular architecture of solid, clinical tumors.[17] In this study, PT-45 multicellular tumor spheroids with an average diameter of ~400 μm were grown and the therapeutic efficiency evaluated upon determination of the adenosine triphosphate concentration in a luciferase-based luminescence assay. The results demonstrated that **1** had a higher cytotoxicity ($IC_{50} = 9.4 \pm 2.5$ μM) than cisplatin ($IC_{50} >$ 100 μM) against PT-45 multicellular tumor spheroids (Figure 4). For a deeper understanding of the therapeutic effects, the size and morphology of the treated multicellular tumor spheroids was studied by light microscopy. The treatment with cisplatin was found not to influence the size or morphology of the tumor spheroid. In contrast, the treatment with **1** demonstrated a strong reduction of the tumor size as well as clear morphological damage (Figure 5). Combined these findings demonstrated the ability of the dinuclear rhenium complexes to eradicate multicellular tumor spheroids.

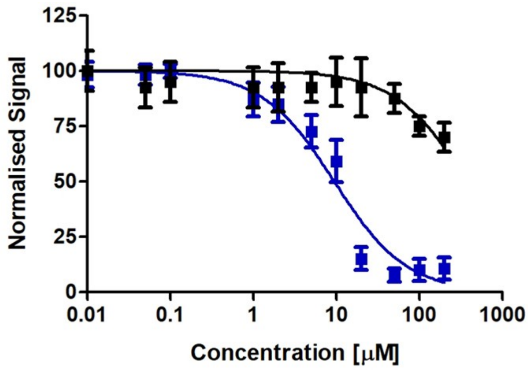

Figure 4. Drug-response curves upon treatment of PT-45 multicellular tumor spheroids with an average diameter of ~400 μm with **1** (blue) or cisplatin (black). The error bars correspond to the standard deviation of the three replicates.

Conclusions

This study reports on the chemical synthesis and biological evaluation of a series of dinuclear rhenium(I) complexes as potential chemotherapeutic agents. The metal complexes were dually linked through coordination to a monomeric linker as well as bridged through 1,4-dihydroxyanthraquinone moiety. Biological evaluation in pancreatic carcinoma cells demonstrated that the dinuclear rhenium(I) complexes were efficiently internalized by an energy dependent endocytosis pathway. After 4 h incubation, the majority of the metal complex localized in the mitochondria and a smaller portion inside the lysosomes of the cancerous cells. The rhenium(I) complexes demonstrated to be cytotoxic up to the very low micromolar range against a variety of cancer cells. Mechanistic insights

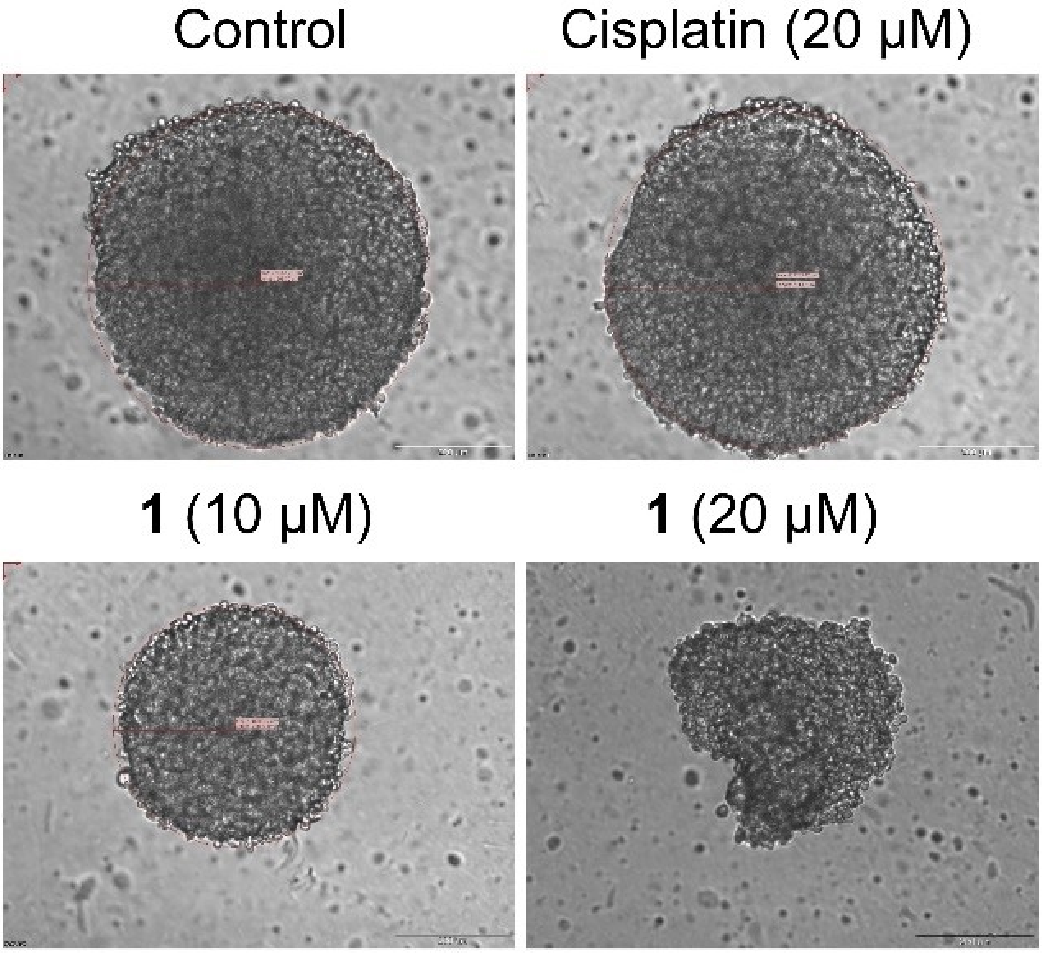

Figure 5. Representative light microscopy images of PT-45 multicellular tumor spheroids upon treatment with phosphate-buffered saline (control), cisplatin (20 μM), or **1** (10–20 μM). The scalebars represent 200 μm.

revealed that the metal complexes induced cell death by apoptosis. Based on these promising findings, the biological properties were further studied against multicellular tumor spheroids that represent a model system for clinical tumors. The lead compound demonstrated to eradicate the multicellular tumor spheroid upon treatment in the micromolar range. These findings highlight the potential application of multimetallic metal complexes and could open new avenues for the treatment of certain types of cancer. Future studies will focus on developing multimetallic compounds in which each metal center synergistically improves the therapeutic efficiency of the treatment.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Bioinorganic Chemistry · Chemotherapy · Medicinal Inorganic Chemistry · Metals in Medicine · Rhenium

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RESEARCH ARTICLE

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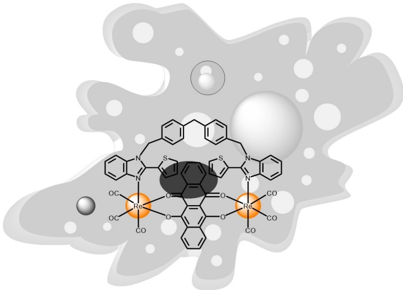

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