



Review

# The Development of Ru(II)-Based Photoactivated Chemotherapy Agents

Yongjie Chen <sup>1,\*</sup> , Lijuan Bai <sup>1</sup>, Pu Zhang <sup>1</sup>, Hua Zhao <sup>1</sup> and Qianxiong Zhou <sup>2,\*</sup> 

<sup>1</sup> Research Center for Pharmacodynamic Evaluation Engineering Technology of Chongqing, College of Pharmacy, Chongqing Medical University, Chongqing 400016, China; bailijua88@126.com (L.B.); zhangpu51@hotmail.com (P.Z.); 100923@cqmu.edu.cn (H.Z.)

<sup>2</sup> Key Laboratory of Photochemical Conversion and Optoelectronic Materials, Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing 100190, China

\* Correspondence: Jessicalchenyong@126.com (Y.C.); zhouqianxiong@mail.ipc.ac.cn (Q.Z.); Tel.: +86-23-68485161 (Y.C.); +86-10-82543592 (Q.Z.)

**Abstract:** Photoactivated chemotherapy (PACT) is a novel cancer treatment method that has drawn increasing attention due to its high selectivity and low side effects by spatio-temporal control of irradiation. Compared with photodynamic therapy (PDT), oxygen-independent PACT is more suitable for treating hypoxic tumors. By finely tuning ligand structures and coordination configurations, many Ru(II) complexes can undergo photoinduced ligand dissociation, and the resulting Ru(II) aqua species and/or free ligands may have anticancer activity, showing their potential as PACT agents. In this mini-review, we summarized the progress in Ru(II)-based PACT agents, as well as challenges that researchers in this field still face.

**Keywords:** photoactivated chemotherapy (PACT); Ru(II) complexes; photoinduced ligand dissociation



**Citation:** Chen, Y.; Bai, L.; Zhang, P.; Zhao, H.; Zhou, Q. The Development of Ru(II)-Based Photoactivated Chemotherapy Agents. *Molecules* **2021**, *26*, 5679. <https://doi.org/10.3390/molecules26185679>

Academic Editor: Julia Romanova

Received: 18 August 2021

Accepted: 13 September 2021

Published: 18 September 2021

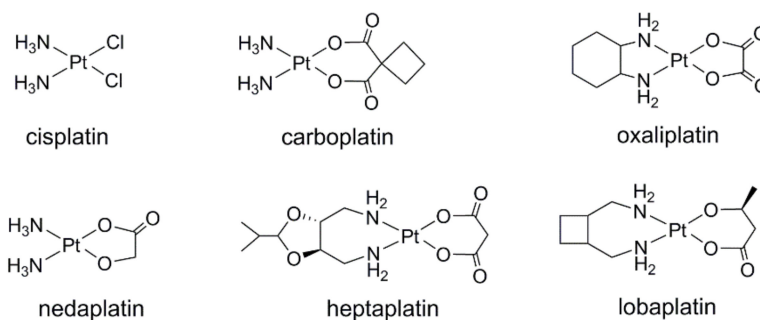
**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

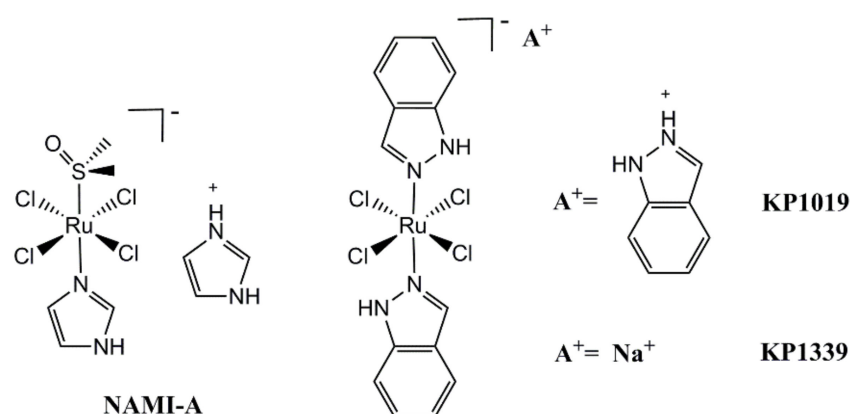
The research of new chemotherapeutic drugs for cancer treatment has been the focus in medicine and related fields for many years. Among them, the development of transition-metal-based agents has always been one of the hotspots [1–7], which obviously benefits from the long-term and wide clinical application of cisplatin [*cis*-Pt(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>]. The unexpected discovery by Rosenberg and his co-workers revealed the antitumor activity of cisplatin in the 1960s [8,9]; subsequently, cisplatin and its analogs (Figure 1) have been successfully used in the clinical treatment of many cancers [10]. Although cisplatin and its derivatives are efficacious against the vast majority of cancers, their selectivity to tumor tissues and normal tissues is poor [11]. This leads to the production of non-cancer cell toxicity; thereby, severe adverse effects are caused, including hair loss, peripheral neuropathy, and myelotoxicity in patients [12–14].



**Figure 1.** Clinically approved Pt (II) anticancer drugs.

Many strategies have been used for solving the above problems, for example, using targeting drug delivery systems and developing reduction responsive Pt(IV) prodrugs [15,16]. In addition, many photoactivated Pt(IV) agents have been reported, which are nontoxic in the dark but can release cytotoxic Pt(II) species upon light irradiation [17,18]. These kinds of prodrugs are commonly known as photoactivated chemotherapy (PACT) agents, which can trigger and limit the drug activity within the tumor tissues by spatio-temporal control of irradiation, thus achieving fewer side effects [19–21]. Compared with traditional photodynamic therapy (PDT) [22,23], another phototherapy that is generally oxygen-dependent, PACT offers an oxygen-independent mechanism, and is therefore more suitable for hypoxic tumors, where the concentration of oxygen is remarkably low [24,25].

Inspired by the success of Pt complexes as antitumor drugs, other transition metal complexes, especially Ruthenium (Ru) complexes, have drawn great attention owing to their potential anticancer properties and selective cytotoxic activity [26]. Investigating new Ru-based complexes as anticancer drugs is an important trend in modern medicinal inorganic chemistry [27–30]. Up till now, several Ru(III) complexes as chemotherapeutic agents have already entered clinical trials, such as NAMI-A, KP1019, and KP1339 (Figure 2) [31–35]. As the first approved Ru complex to reach clinical investigations, NAMI-A showed success in phase I clinical studies but showed only limited efficacy in the phase II stage, which resulted in the failure of the clinical investigations [27,36]. Afterward, another Ru therapeutic KP1019 showed solubility limited in phase I, but in its place, a more soluble sodium salt, KP1339, is currently undergoing clinical trials [27]. Different from focusing on the chemotherapeutic activity of Ru(III) complexes, more attentions has been paid to the photoactivation of Ru(II) complexes. TLD1433, the first Ru(II)-based photosensitizer for PDT, has already entered human clinical trials [37]. Moreover, studies have also indicated that Ru(II) complexes may possess potential as PACT agents [38–41]. Through proper structure design, they can undergo photoinduced ligand dissociation; then, the resulting Ru(II) aqua species can covalently bind to DNA in a manner similar to cisplatin. Compared with Pt(IV) complexes, Ru(II)-based PACT agents have some promising advantages. They possess diverse and easy-modified structures, rich photophysical and photochemical properties, and furthermore, the octahedral structures different from that of cisplatin may endow them with good activity against cisplatin-resistant cancer cells [42–44].



**Figure 2.** Three ruthenium(III) complexes in clinical trials.

The lowest energy absorption band of Ru(II) complexes usually comes from <sup>1</sup>MLCT (Metal-to-Ligand Charge Transfer) transitions. When irradiated by appropriate light, Ru(II) complexes first achieve the <sup>1</sup>MLCT state and then reach the <sup>3</sup>MLCT state through ultra-fast intersystem crossing (Figure 3) [19]. The <sup>3</sup>MLCT state of Ru(II) complexes can return to the ground state through non-radiative inactivation or luminescence pathways [45,46] or can interact with other molecules such as O<sub>2</sub> to generate singlet oxygen (<sup>1</sup>O<sub>2</sub>), showing potential as photodynamic agents [47–49]. This paper focuses on another photochemical process: the <sup>3</sup>MLCT excited state of Ru(II) complexes may populate the <sup>3</sup>MC state (metal-

centered state or ligand-field state) by thermal activation. The  $^3\text{MC}$  state has M-L ( $\sigma^*$ ) character, which may lead to ligand dissociation and generate Ru(II) aqua species with DNA-binding ability, showing potential in photoactivated chemotherapy. This mini-review aims to present the latest progress in photoinduced ligand dissociation related Ru(II)-based PACT agents for cancer treatment. By reading this article, we hope to not only let our peers know about the all-around development of Ru(II)-based PACT drugs but also inspire more researchers to enter this interesting field.

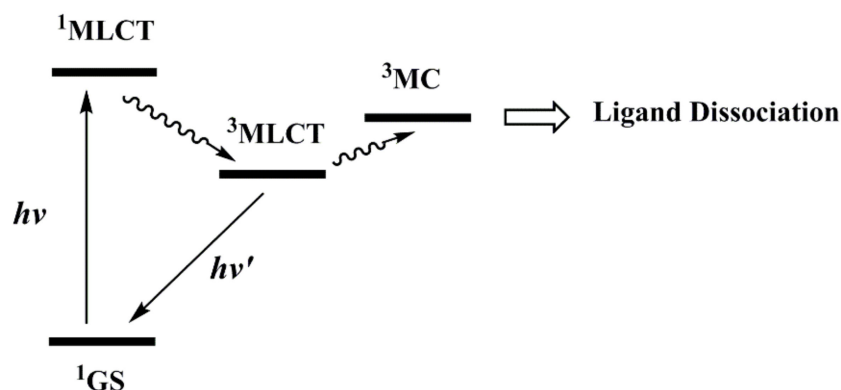


Figure 3. Jablonski diagram of Ru(II) complexes with photolabile ligands.

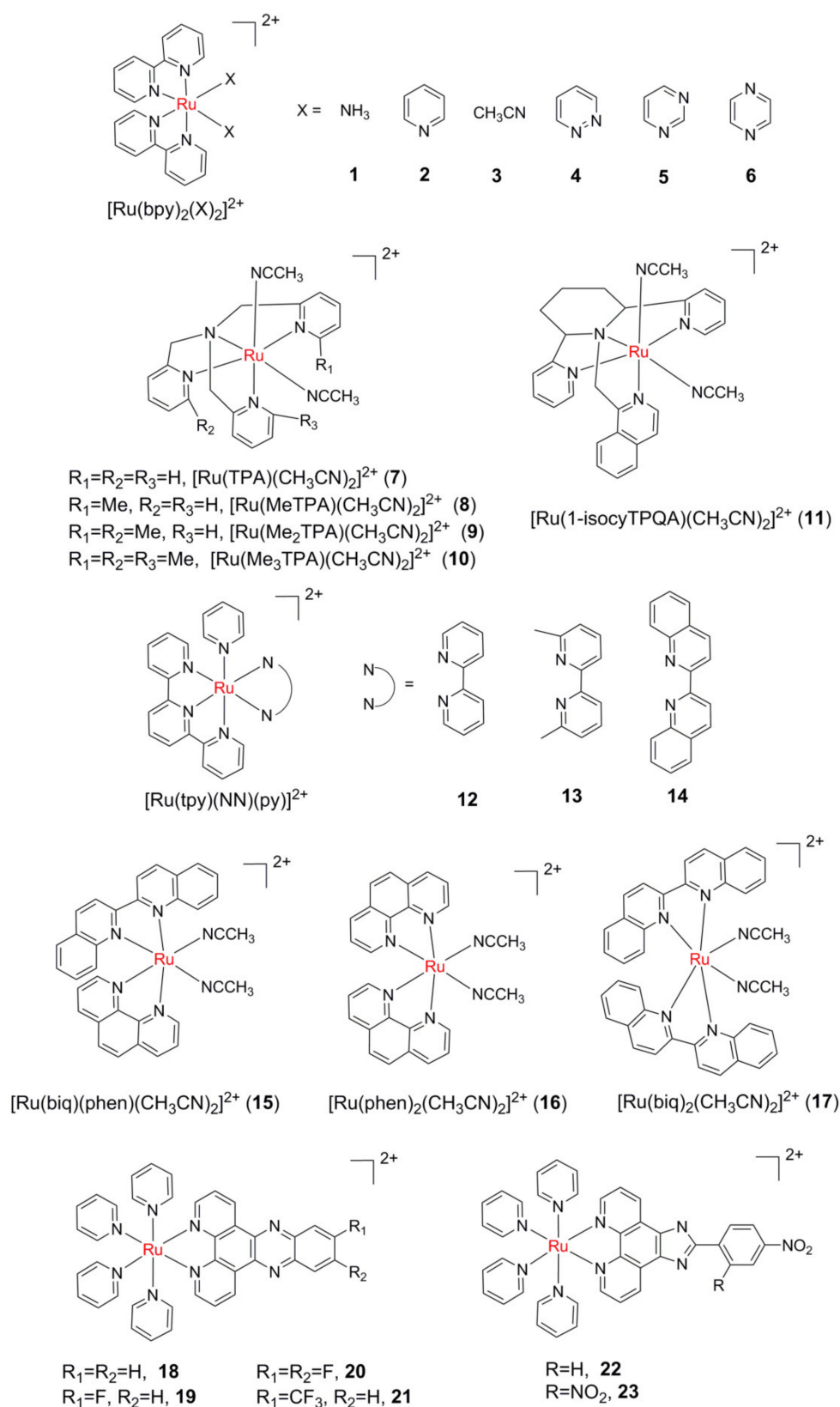
## 2. Ligand Photodissociation of Ru(II) Polypyridyl Complexes

Theoretically, the activity of Ru(II)-based PACT agents is closely related to their photoinduced ligand dissociation efficiency. Therefore, the research on ligand dissociation efficiency is the focus of developing potential Ru(II)-based PACT drugs.

### 2.1. Photodissociation of Monodentate Ligands

The development of photoinduced ligand dissociation and consequently DNA binding of Ru(II) complexes began with a report by Turro and colleagues in 2004 [50]. The photolysis of  $\text{cis-}[\text{Ru}(\text{bpy})_2(\text{NH}_3)_2]^{2+}$  (bpy = 2,2'-bipyridine, complex **1** in Figure 4) in water was investigated. Irradiation of **1** resulted in the sequential loss of the  $\text{NH}_3$  ligands and the formation of the corresponding bis-aqua complex  $\text{cis-}[\text{Ru}(\text{bpy})_2(\text{H}_2\text{O})_2]^{2+}$ . The photodissociation of ligands was dependent on the excitation wavelength. Under 350 nm and 400 nm light, the ligand exchange quantum yields were 0.024 and 0.018, respectively. Upon irradiation, **1** can form covalent binding with 9-methylguanine, 9-ethylguanine single-stranded and double-stranded DNA.

The photodissociation efficiency of the monodentate ligand is closely related to its coordination ability. Compared with **1**, the photoinduced ligand exchange quantum yield for  $\text{cis-}[\text{Ru}(\text{bpy})_2(\text{py})_2]^{2+}$  (py = pyridine, **2**) between pyridine and  $\text{Cl}^-$  was only 0.0059 [51], while the quantum yield of  $\text{cis-}[\text{Ru}(\text{bpy})_2(\text{H}_2\text{O})_2]^{2+}$  formed by illumination of  $\text{cis-}[\text{Ru}(\text{bpy})_2(\text{CH}_3\text{CN})_2]^{2+}$  (**3**) in water was as high as 0.38 (350 nm) and 0.22 (450 nm) [52]. The photoinduced ligand exchange reaction of **1** and **3** in an aqueous solution was studied using the density functional theory (DFT) by Kayanuma and co-workers [53]. The  $^3\text{MC}$  structure was lower in energy than the  $^3\text{MLCT}$  structure for **3**; in contrast, the  $^3\text{MLCT}$  structure was lower in energy than the  $^3\text{MC}$  structure for **1**. Such a difference would correlate with the higher photoinduced ligand dissociation quantum yield of **3** compared to **1**.



**Figure 4.** Ru(II) polypyridyl complexes with photolabile monodentate ligands.

Glazer et al., reported three Ru(II) polypyridyl complexes 4–6 [54] with isomeric diazine ligands, and their photochemical properties were compared to 2. It was found that unlike 2, which photodissociated only one monodentate ligand in water, 4–6 released

both monodentate ligands, with the quantum yields of the second phase varying from the ligand pKa and medium pH. These results suggest that the photochemistry of these complexes can be tuned by simple electronic effects.

The photodissociation efficiency of the monodentate ligand is also related to the distortion degree of octahedral Ru(II) complexes. Thus, the steric bulk is introduced to distort the octahedral field to lower the energy of the  $^3\text{MC}$  state and reduce the energy gap between the  $^3\text{MC}$  state and  $^3\text{MLCT}$  state, which will finally result in greater yields of ligand photodissociation. The photochemical behavior of a series of complexes  $[\text{Ru}(\text{TPA})(\text{CH}_3\text{CN})_2]$  (TPA = tris[(pyridin-2-yl)methyl]amine, 7–10) reflects the steric effect very well [55]. The quantum yield of photosubstitution in 7 was measured as 0.009 (400 nm) in water, while that of 8 was 0.011 under the same conditions. Due to the large steric crowding of 9 and 10, the  $\text{CH}_3\text{CN}$  ligand can be released even in dark conditions. Lately, complex  $[\text{Ru}(\text{1-isocyTPQA})(\text{CH}_3\text{CN})_2]^{2+}$  (1-isocyTPQA = 1-(((2R,6S)-2,6-bis(pyridin-2-yl)piperidin-1-yl)-methyl)isoquinoline, 11) was designed and synthesized by Kodanko and co-workers, which exhibited unique photochemical properties distinct from 7–10 [56]. It was found that the greatly enhanced quantum efficiency ( $\Phi_{400} = 0.033$  in water) of photodissociation in 11 can be explained by a *trans*-type effect in the  $^3\text{MLCT}$  state. DFT calculations and ultrafast transient spectroscopy revealed that a highly mixed  $^3\text{MLCT}/^3\pi\pi^*$  excited state instead of  $^3\text{MC}$  is the lowest-energy triplet state of 11. This research validated that orbital mixing and steric effects can have a strong influence on photoinduced ligand exchange.

The steric bulk effect is also found in complexes 12–14 [57]. The pyridine dissociation quantum yield upon 500 nm irradiation in  $\text{CH}_3\text{CN}$  was 0.16 and 0.033 for 13 and 14, respectively. While under the same conditions, ligand exchange was not observed in 12, which lacks steric strain. The ligand photodissociation behavior of *cis*- $[\text{Ru}(\text{biq})(\text{phen})(\text{CH}_3\text{CN})_2]^{2+}$  (biq = 2,2'-biquinoline, phen = 1,10-phenanthroline, 15) is very unique [58]. Upon irradiation with low energy light ( $\geq 550$  nm), only one  $\text{CH}_3\text{CN}$  ligand can exchange with the solvent molecule, but both ligands exchanged with the solvent molecule upon irradiation with high energy light ( $\geq 420$  nm). In contrast, two  $\text{CH}_3\text{CN}$  ligands of 16 and 17 were able to exchange with solvent molecules under both light conditions. The theoretical calculations gave a certain explanation for these results. The photodissociation of the ligand of 15 may occur through a so-called “dissociative” mechanism, in which the ligand leaves first to produce five-coordination intermediates. DFT calculations showed that the coordination vacancy of the five-coordination intermediate with the lowest energy forms a *trans* configuration with phen, which means that the  $\text{CH}_3\text{CN}$  ligand *trans* to phen leaves preferentially.

Recently, Glazer’s group investigated the interplay of steric and electronic features that impact the photodissociation efficiency of monodentate ligand for Ru(II) complexes [59]. The experimental results showed that rationally varying the ligand components and structures of the metal complex could result in a better photodissociation efficiency.

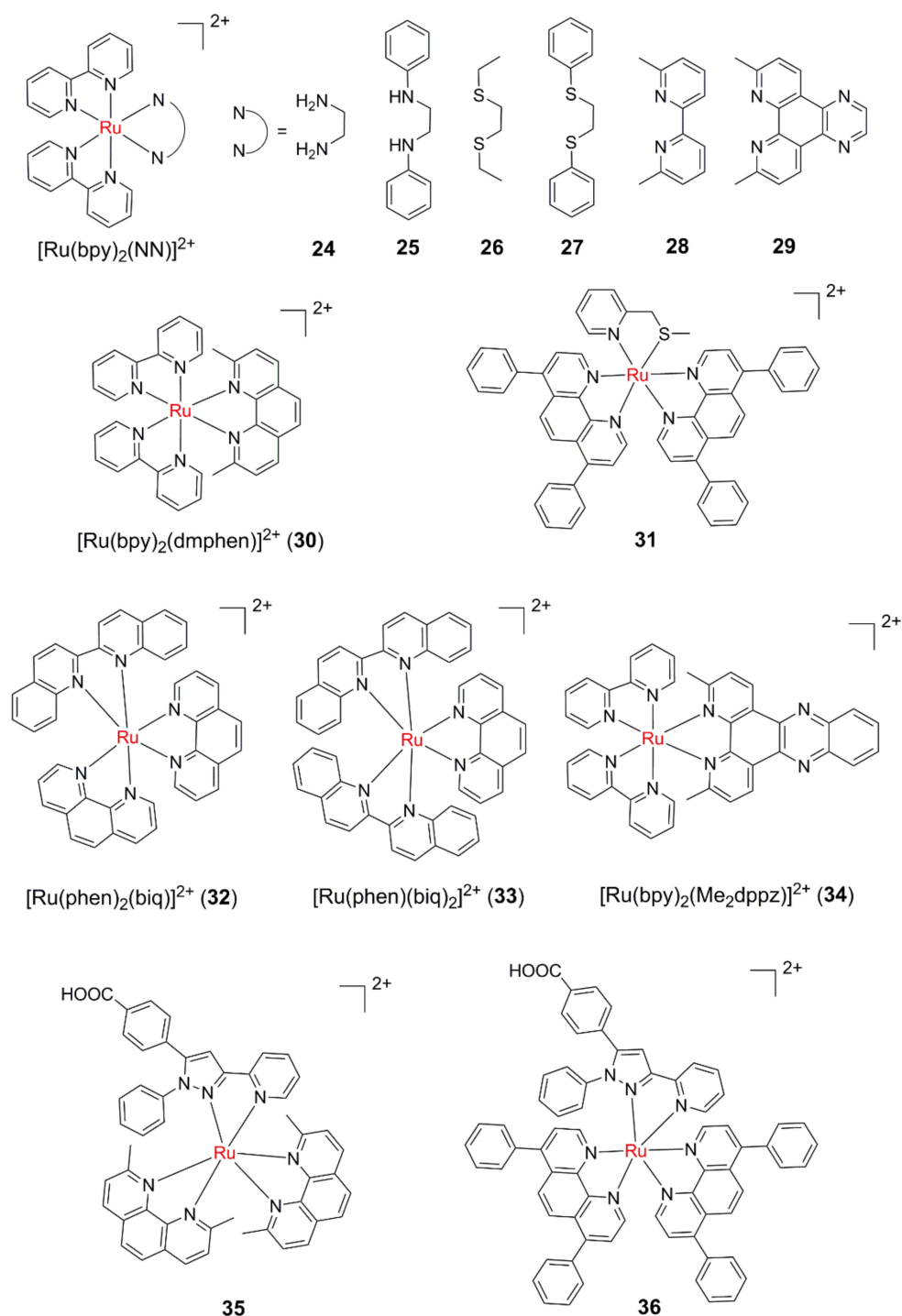
Additionally, to explore the role of modification on the retaining ligands in the anticancer activity of Ru(II) PACT agents, Zhou et al. reported complexes 18–21, which can photorelease one pyridine ligand and covalently bind to DNA [60]. The study found that compared with 18, the fluorinated complexes 19–21 exhibited enhanced phototoxicity, yet diminished dark cytotoxicity, more favorable for PACT applications. Lately, by introducing the strong electron-withdrawing  $-\text{NO}_2$  groups, two mitochondria-localized complexes 22–23 were designed and synthesized [61]. These two complexes can photocatalyze NADH ( $\beta$ -nicotinamide adenine dinucleotide) depletion and photoinduce ligand dissociation to damage the mitochondrial DNA simultaneously, thus display good activity towards cisplatin-resistant cancer cells.

## 2.2. Photodissociation of Bidentate Ligands

Compared with monodentate ligands, the photodissociation of bidentate ligands is much more difficult due to the chelation effect. Although the two  $\text{NH}_3$  ligands of *cis*- $[\text{Ru}(\text{bpy})_2(\text{NH}_3)_2]^{2+}$  (1) can be readily photoreleased, the quantum yield of ethanediamine



(en) ligand exchange with  $\text{Cl}^-$  for  $[\text{Ru}(\text{bpy})_2(\text{en})]^{2+}$  (**24**, Figure 5) is only 0.002 [62]. Similar to **24**, the quantum yield of ligand exchange for **25** is only 0.003.



**Figure 5.** Ru(II) polypyridyl complexes with photolabile bidentate ligands.

By taking some effective strategies, bidentate ligands can also serve as photolabile ones to expose two active sites at the same time. An effective strategy to improve the dissociation efficiency of bidentate ligands is to weaken the coordination ability of the coordination atoms. For example, compared with **24** and **25**, the photodissociation quantum efficiency of weaker bis-thioether ligands in **26** and **27** increase significantly, which are 0.019 and 0.016, respectively [62]. These two complexes can effectively reduce the mobility

of linearized pUC18 plasmid DNA in electrophoresis upon irradiation, indicating that they can covalently bind to DNA and show potential in PACT.

Another effective strategy to improve the dissociation efficiency of bidentate ligands is to utilize steric bulk. Glazer and co-workers designed two new complexes **28** and **29** [63]. Through the substitution of two methyl groups on the 6 and 6' positions of bpy, and **2** and **9** positions of dpq (dpq = dipyrdo [3,2-*f*:2',3'-*h*]-quinoxaline), steric bulk was successfully introduced into **28** and **29**. When the two complexes are illuminated, Me<sub>2</sub>bpy and Me<sub>2</sub>dpq can be effectively dissociated, and the resulting hydrate can covalently bind to plasmid DNA, reducing the DNA mobility on agarose gels electrophoresis. Interestingly, **29** can photocleave and photobind DNA at the same time, which indicates that photosensitization of singlet oxygen can compete with the ligand dissociation decay pathway. It was worth mentioning that the photo-cytotoxicity increased by 2 orders of magnitude for **28** and **29**. According to the same idea, a series of Ru(II) complexes with steric bulk have been studied in depth [64–68].

Khayzer et al., reported a sterically crowded complex **30**, which can release either bpy or dmphen (2,9-dimethyl-1,10-phenanthroline) ligands upon visible light irradiation in water [65]. It is noteworthy that the phototoxicity of **30** towards the ML-2 Acute Myeloid Leukemia cell line appears to come from dmphen rather than the bis-aqua photoproduct [Ru(bpy)<sub>2</sub>(H<sub>2</sub>O)<sub>2</sub>]<sup>2+</sup>. In another study, by comparing the ligand toxicity, lipophilicity, and cellular uptake of complexes **28** and **31**, Bonnet et al. found that the phototoxicity of **28** comes from the photoreleased dmbpy ligand, whereas the only phototoxicity species is the bis-aqua photoproduct in **31** [69]. A series of Ru polypyridyl complexes based on the nontoxic 3-(methylthio)propylamine ligand were reported. It was found that by fine-tuning the lipophilicity and steric strain, the Ru-based PACT prodrugs can be phototoxic [70].

2,2'-biquinoline ligand (biq) not only has steric bulk but also extends the absorption wavelength of the Ru(II) complexes due to its conjugated structure. In accordance with this expectation, the MLCT absorption maximums of complexes **32** and **33** were extended to 525 nm and 550 nm, respectively [66]. Complexes **32** and **33** could release the biq ligand, which resulted in the retarded electrophoresis rate of plasmid DNA and phototoxicity towards HL60 cells under red light irradiation. In addition, Glazer's group used cross-linked polymeric assemblies to load the strained Ru(II) complexes for the treatment of cancer and found that using polymeric nanoassemblies is a promising method to improve the pharmacological properties of Ru(II) complexes [67].

The Ruthenium complex [Ru(bpy)<sub>2</sub>(dppz)]<sup>2+</sup> (dppz = dipyrldylphenazine) displays the property of "DNA light switch"; that is, the emission of [Ru(bpy)<sub>2</sub>(dppz)]<sup>2+</sup> is quite low in aqueous solution, and can be switched on in the presence of DNA. The dppz ligand can intercalate into DNA base pairs; thus, the hydrogen bond between two N atoms in the phenazine ring and water molecule is inhibited [71]. Although the Me<sub>2</sub>dppz ligand can cause steric clashes, the ligand photodissociation efficiency of [Ru(bpy)<sub>2</sub>(Me<sub>2</sub>dppz)]<sup>2+</sup> (**34**) is very low. Meanwhile, the photodissociation process of the Me<sub>2</sub>dppz ligand is activated after DNA insertion, resulting in covalent binding of the complex to DNA after ligand photodissociation [72]. Further studies revealed that the ligand photodissociation of **34** is through the so-called "associative" mechanism; that is, the complex first coordinates with the exchange ligand to form seven coordination intermediates and then loses the coordination hindrance ligand Me<sub>2</sub>dppz [73].

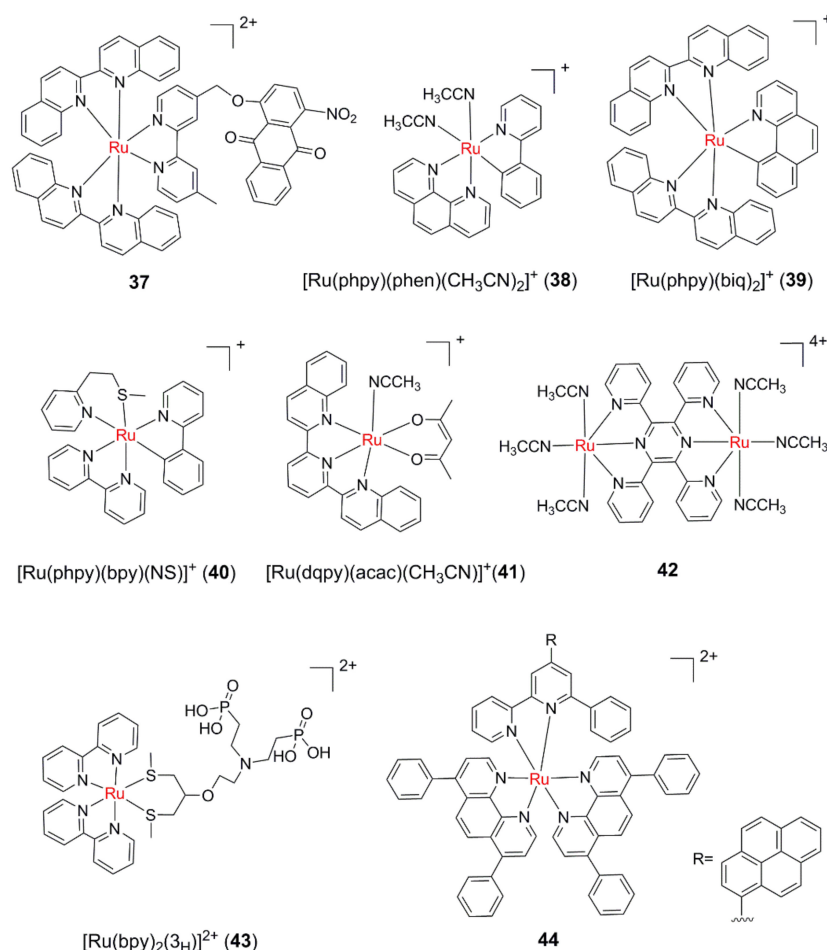
Recently, to expand the applications of sterically congested Ru(II) polypyridyl complexes in PACT, Glazer et al. investigated the photochemical and biological properties of a series of Ru(II) complexes with photolabile pyridyl-pyrazol(in)e ligands [74]. Due to the introduction of a carboxylic, complexes **35** and **36** exhibited the largest PI values of 146 and 59, respectively, by a remarkable reduction of dark cytotoxicity.

### 3. Extending the Photoactivation Wavelength

Similar to other phototherapies, the wavelength of photoactivation for PACT agents is important for clinical applications. The ideal phototherapy window is between 650

and 850 nm [75], while photoactivating most Ru(II) complexes mentioned above requires high-energy visible light (< 500 nm), which may be harmful to normal tissues [76] and has poor tissue penetration [77]. How to extend the photoactivation wavelength to the ideal phototherapy window has become one of the important problems to be solved.

As mentioned above, the large conjugated structure of the biq ligand obviously extends the photoactivation wavelengths of complexes **32** and **33**. On the one hand, the large conjugate system reduces the  $\pi^*$  orbital energy of the biq ligand, thus reducing the energy of  $^1\text{MLCT}$  [ $t_{2g}(\text{Ru})$  to  $\pi^*(\text{biq})$ ]. On the other hand, it causes steric hindrance, which reduces the  $^3\text{MC}$  energy through the distortion of the coordination field, and consequently ensures that efficient ligand dissociation can still occur upon low photon energy excitation. Recently, a nitro-anthraquinone group was attached to a biq-ligand-based Ru(II) complex by Wang and colleagues, endowing the resultant complex **37** (Figure 6) with multiple anticancer mechanisms upon irradiation in the phototherapy window [78]. It was found that **37** can release a biq ligand upon 600 nm irradiation, along with generating  $\text{O}_2^{\bullet-}$  and oxidizing NADH/NADPH ( $\beta$ -nicotinamide adenine dinucleotide phosphate).



**Figure 6.** Photoactivatable Ru(II) polypyridyl complexes upon long-wavelength light irradiation.

When the ring-metalized-ligands (such as 2-phenylpyridine, phpy) coordinate with Ru, the strong electron-donating capacity of carbon anions can significantly increase the  $t_{2g}$  orbital energy of Ru(II), thus greatly prolongs the MLCT absorption wavelength. Using this strategy, Turro's group designed and synthesized the complex *cis*- $[\text{Ru}(\text{phpy})(\text{phen})(\text{CH}_3\text{CN})_2]^+$  (**38**) [79]. The MLCT absorption peak of Ru(II) to phen ligand was at 490 nm, and the tail band extended to the phototherapy window. The quantum efficiency of ligand exchange between  $\text{CH}_3\text{CN}$  and  $\text{Cl}^-$  was up to 0.25 upon 450 nm excitation. Different from the wave-



length dependence of photoinduced ligand dissociation mentioned above, under 400 nm light irradiation, the ligand exchange efficiency of **38** decreased to 0.08. It is believed that the MLCT transition at 400 nm is mainly from Ru(II) to phpy ligand. Since the absorption band at 400 nm also contains too much of the  $\pi\pi^*$  transition component of the phpy ligand, the ligand photodissociation efficiency decreases instead of increasing. Turro's group further designed and synthesized the complex  $[\text{Ru}(\text{biq})_2(\text{phpy})]^+$  (**39**) by combining the phpy and biq ligands [45]. Cyclometallation results in a redshift of the MLCT absorption maximum of **39** by about 100 nm relative to that of **32** and **33**. Although **39** exhibited a distorted octahedral geometry, photoinduced ligand exchange did not occur. DFT calculations indicated that the difference of reactivity in **39** was ascribed to increased energy of  $^3\text{MC}$  states resulting from the bonding of the strong  $\sigma$ -donor phpy ligand. Bonnet et al. investigated the cyclometalated Ru complex **40**, which contained photolabile N,S bidentate ligand and found that **40** can be active under 521 nm irradiation in  $\text{CH}_3\text{CN}$ , which makes it the first cyclometalated Ru complex capable of undergoing photosubstitution of a bidentate ligand [80].

Turro et al. introduced new ancillary ligand platforms that consist of anionic acetylacetonate-based ligand along with tridentate 2,6-di(quinolin-2-yl)pyridine (dqpy) ligand into complex **41** [81]. Acetylacetonate ligands are strong  $\pi$ -donor ligands that used to destabilize the HOMO (highest occupied molecular orbital), whereas the dqpy ligand with its extended conjugation lowers the LUMO (lowest unoccupied molecular orbital) energy; both effects make the ligand substitution of **41** accessible with near-infrared (NIR) light ( $\geq 715$  nm).

The MLCT absorption band of binuclear or polynuclear Ru(II) complexes constructed with bridged ligands tends to be significantly redshifted compared with that of corresponding mononuclear complexes [82–84]. As a result, the bridging concept was utilized to design the first dinuclear Ru(II) complex (**42**) capable of undergoing ligand dissociation at both metal centers upon  $\geq 610$  nm irradiation in  $\text{H}_2\text{O}$  [85]. To further explore the effect of the bridging ligand on Ru(II)-based PACT agents, Dunbar et al. used quinoxaline-functionalized bridging ligand platforms to prepare corresponding binuclear complexes [86]. These complexes were capable of absorbing green light with tails extending beyond 650 nm, which is a promising feature for applications in PACT.

In recent years, upconversion nanoparticles (UCNPs), which produce high-energy light under NIR excitation, were successfully used to extend the photoactivation wavelength of Ru-based PACT drugs [87–91]. More recently, Bonnet et al. reported the synthesis and photochemistry of the Ru(II) polypyridyl complex  $[\text{Ru}(\text{bpy})_2(3_{\text{H}})]^{2+}$  (**43**) [92], where  $3_{\text{H}}$  is a photolabile bis(thioether) ligand. Complex **43** was bound to the surface of Lanthanoid-doped UCNPs through its bis(phosphonate) group, thereby creating an  $\text{H}_2\text{O}$ -dispersible, thermally stable nanoconjugate. The incorporation of the neodymium-doped shell allowed for activation of **43** by 796 nm irradiation, which prevents the undesired heating seen with conventional UCNPs activated at 980 nm.

Additionally, two-photon absorption has been utilized for photoactivation of Ru(II) complexes, in which the prodrugs are activated by radiation in the PDT window [93–96]. Recently, by simply using a pyrene-modified-terpyridine (tpy-Py) as the labile bidentate ligand, Zhou et al. designed and synthesized a promising Ru(II) polypyridine complex **44**, which shows dual PACT and PDT activity upon efficient two-photon excitation in the NIR region [97]. Complex **44** can potentially inactivate hypoxic and cisplatin-resistant cancer cells upon two-photon excitation at 800 nm.

#### 4. Ru(II) PACT Agents with Multiple Functions

As previously described, photoinduced ligand dissociation of the Ru(II) polypyridine complex was achieved by the thermal population of  $^3\text{MC}$  states from the lower-lying  $^3\text{MLCT}$  states. Therefore, the rational and precise regulation of the energy levels of MLCT, MC, and LC states can theoretically regulate the ratio of each decay pathway, which may endue the complexes with multiple functions.

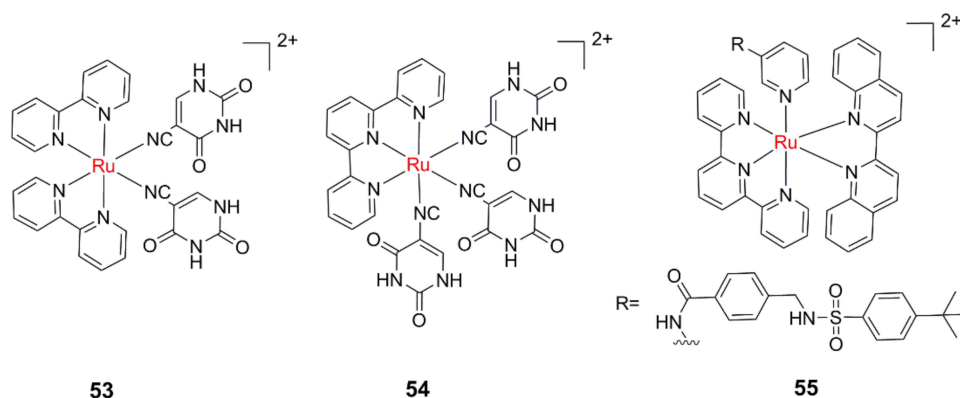


lung adenocarcinoma cells (A549). Detailed studies indicated that the high cytotoxicity of **52** may be attributed to its enhanced cell uptake and nuclear accumulation levels. Patra et al. designed and synthesized two Ru complexes of saccharin with dipyridoquinoxaline and dipyridophenazine. Upon irradiation with UV-A light of 365 nm, both complexes can undergo photoinduced dissociation of saccharin ligand and generate reactive oxygen species, showing dual PDT and PACT activities [107].

#### 4.2. The Combination of Ru(II)-Based PACT and Bioactive Ligands

By replacing the photolabile ligands in Ru-based PACT drugs with bioactive molecules, such as small molecule drugs and enzyme inhibitors, the resulting Ru(II) complexes may possess dual activity. Upon light activation, these complexes can release active ligands that may directly kill cancer cells, while the Ru(II) aqua species are able to damage DNA simultaneously.

Dunbar's and Turro's groups designed and synthesized **53** and **54** (Figure 8) using 5-cyano uracil (5CNU), a derivative of the chemotherapeutic drug 5-fluorouracil (5FU), as the leaving ligand [108,109]. The results of the cytotoxicity experiment showed that **54** showed similar cytotoxicity to the free 5CNU ligand at the same concentration under 400 nm illumination. Bonnet et al. reported a water-soluble Ru(II) complexes **55**, which can photorelease a cytotoxic nicotinamide phosphoribosyltransferase (NAMPT) inhibitor in an oxygen-independent manner [110]. A 3–4-fold increase in cytotoxicity was found upon red-light irradiation for **55**, whether the cells were cultured with 1% or 21% O<sub>2</sub>.



**Figure 8.** Ru(II) PACT agents with photolabile bioactive molecules.

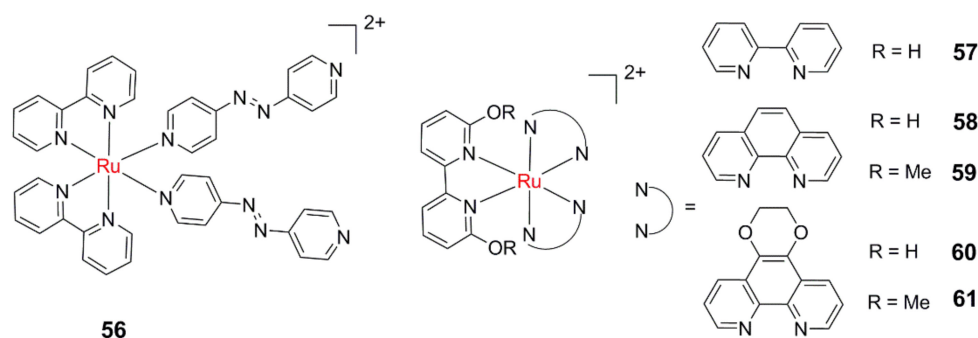
Until now, the anticancer agent CHS-828 [111], the imidazole-based cytotoxic drug econazole [112], the anti-tuberculosis drug isoniazid [113], the inhibitor of cathepsin K [114], cytochromes P450 [115] and CYP17A1 [116], etc. successfully photoreleased from Ru-based PACT agents were reported.

Due to the dual PACT and PDT activity presented by **46**, [Ru(tpy)(Me<sub>2</sub>dppn)] fragment was used to cage bioactive molecules for the purpose of achieving triple functions. Epoxysuccinyl-based inhibitors of cathepsin B (CTSB), a cysteine protease strongly associated with invasive and metastatic behavior, was conjugated to [Ru(tpy)(Me<sub>2</sub>dppn)] fragment by Kodanko et al. The study confirmed that the conjugate was capable of releasing ligand to form Ru(II) active center, generating <sup>1</sup>O<sub>2</sub> under light conditions, and irreversibly inhibiting CTSB, eventually causing efficient cell death [102].

#### 4.3. Dual-Activatable Ru(II) PACT Agents

Although the photoactivation process has been effective in increasing drug selectivity, unnecessary light irradiation, such as sunlight, may still activate the prodrugs in normal tissues (such as skin), resulting in side effects. The introduction of other tumor-microenvironment-related activation factors, such as high-level GSH (glutathione), low pH values, etc., may improve the selectivity of Ru(II) PACT agents further.

Wang et al. designed and synthesized a potential GSH—responsive Ru(II) PACT agent  $[\text{Ru}(\text{bpy})_2(\text{py}-\text{N}=\text{N}-\text{py})]^{2+}$  ( $\text{py}-\text{N}=\text{N}-\text{py} = 4,4'$ -azopyridine, **56**, Figure 9) by tethering a redox-active azo group on the leaving ligand [117]. The azo group can effectively quench the  $^3\text{MLCT}$  state and prevent the population of the  $^3\text{MC}$  state, which makes the target complex very stable under illumination. The DNA covalent binding capability of **56** can only be activated after GSH reduction and visible light irradiation. The concentration of GSH in tumor tissue is usually several times higher than that in normal tissue, which is also considered as a potential target of tumor tissue. This kind of GSH responsive PACT agent is expected to have a higher selectivity for tumor cells.



**Figure 9.** Dual-activatable Ru(II) PACT agents.

Considering the inherent acidity surrounding cancer cells, Papish and co-workers reported a series of pH-activated PACT agents, which can be activated by light- and pH-triggered ligand dissociation [118–120]. At a low pH value ( $\text{pH} = 5$ ), complexes **57–61** existed in their acidic form, and the quantum yields for photodissociation were higher than in deprotonated form. Further studies validated that these complexes can produce  $^1\text{O}_2$  under illumination. Thus, they investigated how synthetic changes to ligands and ligand protonation states can influence the quantum yields for  $^1\text{O}_2$  and photodissociation. Cytotoxicity studies showed that  $^1\text{O}_2$  formation is a more plausible cause of photocytotoxicity [120].

Recently, a CO/light dual-activatable Ru(II)-oligo-(thiophene ethynylene) (Ru-OTE) agent for lysosome-targeted multimodal cancer therapeutics was reported [121]. Upon the dual-triggering of CO and light, Ru-OTE can undergo ligand substitution and generate  $^1\text{O}_2$ . Importantly, Ru-OTE can be directly photoactivated using a two-photon laser (800 nm) and inhibit tumor growth in a breast tumor model.

## 5. Ruthenium(II) Arene Complexes

The above-mentioned Ru-based PACT agents are all Ru(II) polypyridyl complexes; in fact, another large family of Ru(II) complexes, i.e., Ru(II) arene complexes, show attractive prospects in chemotherapy [122,123]. They have the general formula  $[(\eta^6\text{-arene})\text{Ru}(\text{L})(\text{X})]^{n+}$  (where L is a bidentate ligand and X is a leaving ligand (usually halogen), and exhibit a spatial “piano stool” structure. The antitumor activity of these complexes is usually attributed to the formation of hydrates following the dissociation of the X ligand. When X is a halogen, the dissociation of the X ligand is spontaneous and uncontrollable. By replacing the X ligand with another monodentate ligand, such as pyridine and its derivatives, and optimizing the bidentate ligand and aromatic ring, Ru(II)-arene-based PACT agents can also be obtained.

Sadler’s group reported a series of ruthenium arene binuclear complexes (**62**, Figure 10) in 2007 [124]. The binuclear complexes with indene or benzene as aromatic ligands can dissociate aromatic ligands under UVA light, and the resultant hydrate can form cross-linking with DNA.





The introduction of the ferrocene group makes **66** have a long-wavelength absorption band extending to 600 nm. Moreover, **66** can generate both hydroxyl radicals ( $\cdot\text{OH}$ ) and  $^1\text{O}_2$  along with photoinduced monodentate ligand dissociation, leading to phototoxicity against SKOV3 and A549.

An intriguing mononuclear Ru(II) arene complex  $[(p\text{-cym})\text{Ru}(\text{dpb})(\text{py})]^{2+}$  (**67**) [130] with a dpb (2,3-bis(2-pyridyl)-benzoquinoline) ligand was synthesized and scrutinized by the same research group. The bulky features of the dpb ligand result in a strained coordination sphere of **67**, which leads to the photodissociation of both monodentate and bidentate ligands. The highly delocalized nature of dpb provides **67** with long-wavelength-absorbing properties and the ability to generate  $^1\text{O}_2$ . The cytotoxicity test showed that the complex could effectively kill A549 cells under light conditions with a PI value of 6.9. Subsequently, a series of  $[(p\text{-cym})\text{Ru}(\text{dpb})(\text{py-R})]^{2+}$  complexes (**68–72**) were synthesized and compared to disclose the substituent effect on the py ligand [131]. It seems that the electron-withdrawing groups facilitate both  $^1\text{O}_2$  generation and ligand photodissociation.

García et al. investigated a neutral Ru(II) arene complex **73** bearing a benzothiazole ligand (HL2) as the bidentate ligand [132]. The results of this study indicated that the arene ligand is released after irradiation with UV light even in the absence of oxygen and leads to cytotoxicity enhancement, thus revealing the potential of **73** as a prodrug for PACT.

## 6. Conclusions and Future Perspectives

The research on Ru(II)-based PACT agents has been a hotspot in the field of metal anticancer drugs in recent years. Thanks to the efforts of many groups, continuous progress has been achieved in recent years. However, there is still a long way to realize the clinical applications of these Ru(II)-based PACT agents.

First, the photoactivation wavelength needs to be further extended. However, prolonging the MLCT absorption wavelength will increase the energy gap between the  $^3\text{MLCT}$  state and the  $^3\text{MC}$  state, which will, unfortunately, reduce the ligand dissociation efficiency. How to prolong the activation wavelength without sacrificing the ligand dissociation efficiency is full of challenges.

Second, most of the current studies focus on the ligand photodissociation-related photophysical and photochemical properties, while less attention is paid to the structure–activity relationship of antitumor activity. Many Ru(II) complexes displayed efficient photoinduced ligand dissociation; however, little anticancer activity was observed. Therefore, in addition to the ligand photodissociation, more efforts are needed to disclose how the other factors (such as DNA binding, cellular uptake, subcellular localization, etc.) influence the anticancer activity of Ru(II) PACT agents.

Third, the real cellular anticancer targets of Ru(II) PACT agents are still unknown. DNA is proposed as the potential target, and indeed many studies have verified that Ru(II) complexes with photolabile ligands can form Ru–DNA covalent binding in solutions after photoinduced ligand dissociation. However, some of the reported Ru(II) complexes with efficient PACT activity cannot attend the nucleus, which may hint to us that DNA should not be the only target. To disclose the real anticancer mechanism can undoubtedly promote the rational design of efficient Ru(II) PACT agents.

Fourth, among the existing reports on Ru(II)-based PACT agents, only a few studies were conducted at the living animal level. Although some promising results in vitro have been achieved so far, the lack of research in vivo is not conducive to promoting the clinical application of these complexes. Obviously, Ru(II) PACT agents may not be suitable to treat all kinds of cancers; thus, finding the possible indications of Ru(II) PACT is meaningful.

The research of Ru(II)-based PACT agents may still be at the early stage. We hope the current review can inspire more researchers with different backgrounds to enter this interesting field.

**Author Contributions:** Conceptualization, Y.C. and Q.Z.; investigation, L.B., P.Z., and H.Z.; writing—original draft preparation, Y.C.; writing—review and editing, Y.C. and Q.Z. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by the National Natural Science Foundation of China (21701018, 21571181, 21773277), the Science and Technology Planning Project of Yuzhong District of Chongqing City (Grant No. 20200125), and the discipline talent training program of the College of Pharmacy (YXY2020SDTR01).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Acknowledgments:** We also thank the College of Pharmacy, Chongqing Medical University, for partial financial support.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. Romero-Canelón, I.; Sadler, P.J. Next-generation metal anticancer complexes: Multitargeting via redox modulation. *Inorg. Chem.* **2013**, *52*, 12276–12291. [[CrossRef](#)]
2. Mjos, K.D.; Orvig, C. Metallodrugs in Medicinal Inorganic Chemistry. *Chem. Rev.* **2014**, *114*, 4540–4563. [[CrossRef](#)]
3. Das, U.; Kar, B.; Pete, S.; Paira, P. Ru(II), Ir(III), Re(I) and Rh(III) based complexes as next generation anticancer metallopharmaceuticals. *Dalton Trans.* **2021**, *50*, 11259–11290. [[CrossRef](#)]
4. Ma, D.L.; He, H.Z.; Leung, K.H.; Chan, D.S.; Leung, C.H. Bioactive luminescent transition-metal complexes for biomedical applications. *Angew. Chem. Int. Ed.* **2013**, *52*, 7666–7682. [[CrossRef](#)] [[PubMed](#)]
5. Ohata, J.; Ball, Z.T. Rhodium at the chemistry-biology interface. *Dalton Trans.* **2018**, *47*, 14855–14860. [[CrossRef](#)]
6. Ma, D.L.; Wu, C.; Wu, K.J.; Leung, C.H. Iridium(III) Complexes Targeting Apoptotic Cell Death in Cancer Cells. *Molecules* **2019**, *24*, 2739. [[CrossRef](#)]
7. Omondi, R.O.; Ojwach, S.O.; Jaganyi, D. Review of comparative studies of cytotoxic activities of Pt(II), Pd(II), Ru(II)/(III) and Au(III) complexes, their kinetics of ligand substitution reactions and DNA/BSA interactions. *Inorg. Chim. Acta.* **2020**, *512*, 119883. [[CrossRef](#)]
8. Rosenberg, B.; Vancamp, L.; Krigas, T. Inhibition of Cell Division in Escherichia coli by Electrolysis Products from a Platinum Electrode. *Nature* **1965**, *205*, 698–699. [[CrossRef](#)] [[PubMed](#)]
9. Rosenberg, B.; VanCamp, L.; Trosko, J.E.; Mansour, V.H. Platinum Compounds: A new class of potent antitumor agents. *Nature* **1969**, *222*, 385–386. [[CrossRef](#)] [[PubMed](#)]
10. Wheate, N.J.; Walker, S.; Craig, G.E.; Oun, R. The status of platinum anticancer drugs in the clinic and in clinical trials. *Dalton Trans.* **2010**, *39*, 8113–8127. [[CrossRef](#)] [[PubMed](#)]
11. Galanski, M.; Jakupec, M.A.; Keppler, B.K. Update of the Preclinical Situation of Anticancer Platinum Complexes: Novel Design Strategies and Innovative Analytical Approaches. *Curr. Med. Chem.* **2005**, *12*, 2075–2098. [[CrossRef](#)] [[PubMed](#)]
12. Zheng, Y.R.; Suntharalingam, K.; Johnstone, T.C.; Yoo, H.; Lin, W.; Brooks, J.G.; Lippard, S.J. Pt(IV) Prodrugs Designed to Bind Non-Covalently to Human Serum Albumin for Drug Delivery. *J. Am. Chem. Soc.* **2014**, *136*, 8790–8798. [[CrossRef](#)]
13. Graf, N.; Bielenberg, D.R.; Kolishetti, N.; Muus, C.; Banyard, J.; Farokhzad, O.C.; Lippard, S.J.  $\alpha$ V $\beta$ 3 Integrin-Targeted PLGA-PEG Nanoparticles for Enhanced Anti-tumor Efficacy of a Pt(IV) Prodrug. *ACS Nano.* **2012**, *6*, 4530–4539. [[CrossRef](#)]
14. Suntharalingam, K.; Song, Y.; Lippard, S.J. Conjugation of vitamin E analog  $\alpha$ -TOS to Pt(IV) complexes for dual-targeting anticancer therapy. *Chem. Commun.* **2014**, *50*, 2465–2468. [[CrossRef](#)]
15. Johnstone, T.C.; Suntharalingam, K.; Lippard, S.J. The Next Generation of Platinum Drugs: Targeted Pt(II) Agents, Nanoparticle Delivery, and Pt(IV) Prodrugs. *Chem. Rev.* **2016**, *116*, 3436–3486. [[CrossRef](#)] [[PubMed](#)]
16. Fanelli, M.; Formica, M.; Fusi, V.; Giorgi, L.; Micheloni, M.; Paoli, P. New trends in platinum and palladium complexes as antineoplastic agents. *Coord. Chem. Rev.* **2016**, *310*, 41–79. [[CrossRef](#)]
17. Farrer, N.J.; Woods, J.A.; Salassa, L.; Zhao, Y.; Robinson, K.S.; Clarkson, G.; Mackay, F.S.; Sadler, P.J. A Potent Trans-Diimine Platinum Anticancer Complex Photoactivated by Visible Light. *Angew. Chem. Int. Ed.* **2010**, *49*, 8905–8908. [[CrossRef](#)]
18. Kasparkova, J.; Kosthunova, H.; Novakova, O.; Křikavová, R.; Vaňo, J.; Trávníček, Z.; Brabec, V. A Photoactivatable Platinum(IV) Complex Targeting Genomic DNA and Histone Deacetylases. *Angew. Chem. Int. Ed.* **2015**, *54*, 14478–14482. [[CrossRef](#)]
19. Farrer, N.J.; Salassa, L.; Sadler, P.J. Photoactivated chemotherapy (PACT): The potential of excited-state d-block metals in medicine. *Dalton Trans.* **2009**, 10690–10701. [[CrossRef](#)]
20. Imberti, C.; Zhang, P.; Huang, H.; Sadler, P.J. New Designs for Phototherapeutic Transition Metal Complexes. *Angew. Chem. Int. Ed.* **2020**, *59*, 61–73. [[CrossRef](#)] [[PubMed](#)]
21. Bonnet, S. Why develop photoactivated chemotherapy? *Dalton Trans.* **2018**, *47*, 10330–10343. [[CrossRef](#)]
22. Detty, M.R.; Gibson, S.L.; Wagner, S.J. Current Clinical and Preclinical Photosensitizers for Use in Photodynamic Therapy. *J. Med. Chem.* **2004**, *47*, 3897–3915. [[CrossRef](#)]
23. Fan, W.; Huang, P.; Chen, X. Overcoming the Achilles' heel of photodynamic therapy. *Chem. Soc. Rev.* **2016**, *45*, 6488–6519. [[CrossRef](#)]

24. Eales, K.L.; Hollinshead, K.E.R.; Tennant, D.A. Hypoxia and metabolic adaptation of cancer cells. *Oncogenesis* **2016**, *5*, e190. [[CrossRef](#)] [[PubMed](#)]
25. Cosse, J.P.; Michiels, C. Tumour hypoxia affects the responsiveness of cancer cells to chemotherapy and promotes cancer progression. *Anticancer Agents Med. Chem.* **2008**, *8*, 790–797. [[CrossRef](#)]
26. Alagesan, M.; Sathyadevi, P.; Krishnamoorthy, P.; Bhuvanesh, N.S.; Dharmaraj, N. DMSO containing ruthenium(II) hydrazone complexes: In vitro evaluation of biomolecular interaction and anticancer activity. *Dalton Trans.* **2014**, *43*, 15829–15840. [[CrossRef](#)] [[PubMed](#)]
27. Thota, S.; Rodrigues, D.A.; Crans, D.C.; Barreiro, E.J. Ru(II) Compounds: Next-Generation Anticancer Metallotherapeutics? *J. Med. Chem.* **2018**, *61*, 5805–5821. [[CrossRef](#)]
28. Notaro, A.; Gasser, G. Monomeric and dimeric coordinatively saturated and substitutionally inert Ru(II) polypyridyl complexes as anticancer drug candidates. *Chem. Soc. Rev.* **2017**, *46*, 7317–7337. [[CrossRef](#)] [[PubMed](#)]
29. Sun, Q.; Li, Y.; Shi, H.; Wang, Y.; Zhang, J.; Zhang, Q. Ruthenium Complexes as Promising Candidates against Lung Cancer. *Molecules* **2021**, *26*, 4389. [[CrossRef](#)]
30. Poynton, F.E.; Bright, S.A.; Blasco, S.; Williams, D.C.; Kelly, J.M.; Gunnlaugsson, T. The development of ruthenium(II) polypyridyl-complexes and conjugates for in vitro cellular and in vivo applications. *Chem. Soc. Rev.* **2017**, *46*, 7706–7756. [[CrossRef](#)]
31. Bergamo, A.; Zorzet, S.; Gava, B.; Sorc, A.; Alessio, E.; Iengo, E.; Sava, G. Effects of NAMI-A and some related ruthenium complexes on cell viability after short exposure of tumor cells. *Anti-Cancer Drugs.* **2000**, *11*, 665–672. [[CrossRef](#)] [[PubMed](#)]
32. Bratsos, I.; Jedner, S.; Gianferrara, T.; Alessio, E. Ruthenium Anticancer Compounds: Challenges and Expectations. *CHIMIA* **2007**, *61*, 692–697. [[CrossRef](#)]
33. Rademaker-Lakhai, J.M.; van den Bongard, D.; Pluim, D.; Beijnen, J.H.; Schellens, J.H. A Phase I and Pharmacological Study with Imidazolium-trans-DMSO-imidazole-tetrachlororuthenate, a Novel Ruthenium Anticancer Agent. *Clin. Cancer Res.* **2004**, *10*, 3717–3727. [[CrossRef](#)] [[PubMed](#)]
34. Hartinger, C.G.; Zorbas-Seifried, S.; Jakupec, M.A.; Kynast, B.; Zorbas, H.; Keppler, B.K. From bench to bedside—preclinical and early clinical development of the anticancer agent indazolium trans-[tetrachlorobis(1H-indazole)ruthenate(III)] (KP1019 or FFC14A). *J. Inorg. Biochem.* **2006**, *100*, 891–904. [[CrossRef](#)] [[PubMed](#)]
35. Bytzek, A.K.; Koellensperger, G.; Keppler, B.K.; Hartinger, C.G. Biodistribution of the novel anticancer drug sodium trans-[tetrachloridobis(1H-indazole)ruthenate(III)] KP-1339/IT139 in nude BALB/c mice and implications on its mode of action. *J. Inorg. Biochem.* **2016**, *160*, 250–255. [[CrossRef](#)]
36. Leijen, S.; Burgers, S.A.; Baas, P.; Pluim, D.; Tibben, M.; Werkhoven, E.; Alessio, E.; Sava, G.; Beijnen, J.H.; Schellens, J.H.M. Phase I/II study with ruthenium compound NAMI-A and gemcitabine in patients with non-small cell lung cancer after first line therapy. *Investig. New Drugs.* **2015**, *33*, 201–214. [[CrossRef](#)] [[PubMed](#)]
37. Monro, S.; Colón, K.L.; Yin, H.; Roque, J.; Konda, P.; Gujar, S.; Thummel, R.P.; Lilge, L.; Gameron, C.G.; McFarland, S.A. Transition Metal Complexes and Photodynamic Therapy from a Tumor-Centered Approach: Challenges, Opportunities, and Highlights from the Development of TLD1433. *Chem. Rev.* **2019**, *119*, 797–828. [[CrossRef](#)]
38. Mari, C.; Pierroz, V.; Ferrari, S.; Gasser, G. Combination of Ru(II) complexes and light: New frontiers in cancer therapy. *Chem. Sci.* **2015**, *6*, 2660–2686. [[CrossRef](#)]
39. Knoll, J.D.; Turro, C. Control and utilization of ruthenium and rhodium metal complex excited states for photoactivated cancer therapy. *Coord. Chem. Rev.* **2015**, *282*, 110–126. [[CrossRef](#)]
40. Zeng, L.; Gupta, P.; Chen, Y.; Wang, E.; Ji, L.; Chao, H.; Chen, Z.S. The development of anticancer ruthenium(II) complexes: From single molecule compounds to nanomaterials. *Chem. Soc. Rev.* **2017**, *46*, 5771–5804. [[CrossRef](#)]
41. Li, A.; Turro, C.; Kodanko, J.J. Ru(II) polypyridyl complexes as photocages for bioactive compounds containing nitriles and aromatic heterocycles. *Chem. Commun.* **2018**, *54*, 1280–1290. [[CrossRef](#)] [[PubMed](#)]
42. Zhang, C.X.; Lippard, S.J. New metal complexes as potential therapeutics. *Curr. Opin. Chem. Biol.* **2003**, *7*, 481–489. [[CrossRef](#)]
43. Grover, N.; Welch, T.W.; Fairley, T.A.; Cory, M.; Thorp, H.H. Covalent Binding of Aquaruthenium complexes to DNA. *Inorg. Chem.* **1994**, *33*, 3544–3548. [[CrossRef](#)]
44. Gill, M.R.; Thomas, J.A. Ruthenium (II) polypyridyl complexes and DNA—from structural probes to cellular imaging and therapeutics. *Chem. Soc. Rev.* **2012**, *41*, 3179–3192. [[CrossRef](#)] [[PubMed](#)]
45. Albani, B.A.; Peña, B.; Dunbar, K.R.; Turro, C. New cyclometallated Ru(II) complex for potential application in photochemotherapy. *Photochem. Photobiol. Sci.* **2014**, *13*, 272–280. [[CrossRef](#)] [[PubMed](#)]
46. Durham, B.; Walsh, J.L.; Carter, C.L.; Meyer, T.J. Synthetic applications of photosubstitution reactions of poly(pyridyl) complexes of ruthenium(II). *Inorg. Chem.* **1980**, *19*, 860–865. [[CrossRef](#)]
47. Hu, X.; Liu, N.Y.; Deng, Y.Q.; Wang, S.; Liu, T.; Liu, X.W. Photoinduced DNA Cleavage and Photocytotoxic of Phenanthroline-Based Ligand Ruthenium Compounds. *Molecules* **2021**, *26*, 3471. [[CrossRef](#)]
48. Zhou, Q.X.; Lei, W.H.; Sun, Y.; Chen, J.R.; Li, C.; Hou, Y.J.; Wang, X.S.; Zhang, B.W. [Ru(bpy)<sub>3-n</sub>(dpb)<sub>n</sub>]<sup>2+</sup>: Unusual Photophysical Property and Efficient DNA Photocleavage Activity. *Inorg. Chem.* **2010**, *49*, 4729–4731. [[CrossRef](#)]
49. Jakubaszek, M.; Goud, B.; Ferrari, S.; Gasser, G. Mechanisms of action of Ru(II) polypyridyl complexes in living cells upon light irradiation. *Chem. Commun.* **2018**, *54*, 13040–13059. [[CrossRef](#)] [[PubMed](#)]
50. Singh, T.N.; Turro, C. Photoinitiated DNA Binding by cis-[Ru(bpy)<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>]<sup>2+</sup>. *Inorg. Chem.* **2004**, *43*, 7260–7362. [[CrossRef](#)]

51. Rillema, D.P.; Blanton, C.B.; Shaver, R.J.; Jackman, D.C.; Bolda-ji, M.; Bundy, S.; Worl, L.A.; Meyer, T.J. MLCT- $\pi$  Energy Gap in Pyridyl-Pyrimidine and Bis(pyridine) Complexes of Ruthenium(II). *Inorg. Chem.* **1992**, *31*, 1600–1606. [[CrossRef](#)]
52. Liu, Y.; Turner, D.B.; Singh, T.N.; Angeles-Boza, A.M.; Chouai, A.; Dunbar, K.R.; Turro, C. Ultrafast ligand exchange: Detection of a pentacoordinate Ru(II) intermediate and product formation. *J. Am. Chem. Soc.* **2009**, *131*, 26–27. [[CrossRef](#)]
53. Kayanuma, M.; Shoji, M.; Shigeta, Y. Photosubstitution Reaction of cis-[Ru(bpy)<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub>]<sup>2+</sup> and cis-[Ru(bpy)<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>]<sup>2+</sup> in Aqueous Solution via Monoaqua Intermediate. *J. Phys. Chem. A* **2019**, *123*, 2497–2502. [[CrossRef](#)]
54. Havrylyuk, D.; Deshpande, M.; Parkin, S.; Glazer, E.C. Ru(II) complexes with diazine ligands: Electronic modulation of the coordinating group is key to the design of “dual action” photoactivated agents. *Chem. Commun.* **2018**, *54*, 12487–12490. [[CrossRef](#)]
55. Arora, K.; White, J.K.; Sharma, R.; Mazumder, S.; Martin, P.D.; Schlegel, H.B.; Turro, C.; Kodanko, J.K. Effects of Methyl Substitution in Ruthenium Tris(2-pyridylmethyl)amine Photocaging Groups for Nitriles. *Inorg. Chem.* **2016**, *55*, 6968–6979. [[CrossRef](#)]
56. Li, A.; Turro, C.; Kodanko, J.J. Ru(II) Polypyridyl Complexes Derived from Tetradentate Ancillary Ligands for Effective Photocaging. *Acc. Chem. Res.* **2018**, *51*, 1415–1421. [[CrossRef](#)]
57. Knoll, J.D.; Albani, B.A.; Durr, C.B.; Turro, C. Unusually Efficient Pyridine Photodissociation from Ru(II) Complexes with Sterically Bulky Bidentate Ancillary Ligands. *J. Phys. Chem. A* **2014**, *118*, 10603–10610. [[CrossRef](#)]
58. Albani, B.A.; Durr, C.B.; Turro, C. Selective photoinduced ligand exchange in a new tris-heteroleptic Ru(II) complex. *J. Phys. Chem. A* **2013**, *117*, 13885–13892. [[CrossRef](#)]
59. Havrylyuk, D.; Stevens, K.; Parkin, S.; Glazer, E.C. Toward Optimal Ru(II) Photocages: Balancing Photochemistry, Stability, and Biocompatibility Through Fine Tuning of Steric, Electronic, and Physicochemical Features. *Inorg. Chem.* **2020**, *59*, 1006–1013. [[CrossRef](#)]
60. Boerhan, R.; Sun, W.; Tian, N.; Wang, Y.; Lu, J.; Li, C.; Cheng, X.; Wang, X.; Zhou, Q. Fluorination on non-photolabile dppz ligands for improving Ru(II) complex-based photoactivated chemotherapy. *Dalton Trans.* **2019**, *48*, 12177–12185. [[CrossRef](#)]
61. Qi, S.; Jin, Z.; Jian, Y.; Hou, Y.; Li, C.; Zhao, Y.; Wang, X.; Zhou, Q. Photo-induced mitochondrial DNA damage and NADH depletion by -NO<sub>2</sub> modified Ru(II) complexes. *Chem. Commun.* **2021**, *57*, 4162–4165. [[CrossRef](#)]
62. Garner, R.N.; Joyce, L.E.; Turro, C. Effect of electronic structure on the photoinduced ligand exchange of Ru(II) polypyridine complexes. *Inorg. Chem.* **2011**, *50*, 4384–4391. [[CrossRef](#)] [[PubMed](#)]
63. Howerton, B.S.; Heidary, D.K.; Glazer, E.C. Strained ruthenium complexes are potent light-activated anticancer agents. *J. Am. Chem. Soc.* **2012**, *134*, 8324–8327. [[CrossRef](#)]
64. Hidayatullah, A.N.; Wachter, E.; Heidary, D.K.; Parkin, S.; Glazer, E.C. Photoactive Ru(II) complexes with dioxinophenanthroline ligands are potent cytotoxic agents. *Inorg. Chem.* **2014**, *53*, 10030–10032. [[CrossRef](#)]
65. Azar, D.F.; Audi, H.; Farhat, S.; El-Sibai, M.; Abi-Habib, R.J.; Khnayzer, R.S. Phototoxicity of strained Ru(II) complexes: Is it the metal complex or the dissociating ligand? *Dalton Trans.* **2017**, *46*, 11529–11532. [[CrossRef](#)] [[PubMed](#)]
66. Wachter, E.; Heidary, D.K.; Howerton, B.S.; Parkin, S.; Glazer, E.C. Light-activated ruthenium complexes photobind DNA and are cytotoxic in the photodynamic therapy window. *Chem. Commun.* **2012**, *48*, 9649–9651. [[CrossRef](#)] [[PubMed](#)]
67. Dickerson, M.; Howerton, B.; Baeb, Y.; Glazer, E.C. Light-sensitive ruthenium complex-loaded cross-linked polymeric nanoassemblies for the treatment of cancer. *J. Mater. Chem. B* **2016**, *4*, 394–408. [[CrossRef](#)]
68. Bataglioli, J.C.; Gomes, L.M.F.; Maunoir, C.; Smith, J.R.; Cole, H.D.; McCain, J.; Sainuddin, T.; Cameron, C.G.; McFarland, S.A.; Storr, T. Modification of amyloid-beta peptide aggregation via photoactivation of strained Ru(II) polypyridyl complexes. *Chem. Sci.* **2021**, *12*, 7510–7520. [[CrossRef](#)]
69. Cuello-Garibo, J.; Meijer, M.S.; Bonnet, S. To cage or to be caged? The cytotoxic species in ruthenium-based photoactivated chemotherapy is not always the metal. *Chem. Commun.* **2017**, *53*, 6768–6771. [[CrossRef](#)]
70. Cuello-Garibo, J.A.; James, C.C.; Siegler, M.A.; Bonnet, S. Ruthenium-based PACT compounds based on an N,S non-toxic ligand: A delicate balance between photoactivation and thermal stability. *Chem. Sq.* **2017**, *1*, 2. [[CrossRef](#)]
71. Friedman, A.E.; Chambron, J.C.; Sauvage, J.P.; Turro, N.J.; Barton, J.K. A molecular light switch for DNA: Ru(bpy)<sub>2</sub>(dppz)<sup>2+</sup>. *J. Am. Chem. Soc.* **1990**, *112*, 4960–4962. [[CrossRef](#)]
72. Wachter, E.; Howerton, B.S.; Hall, E.C.; Parkin, S.; Glazer, E.C. A new type of DNA “light-switch”: A dual photochemical sensor and metalating agent for duplex and G-quadruplex DNA. *Chem. Commun.* **2014**, *50*, 311–313. [[CrossRef](#)]
73. Wachter, E.; Glazer, E.C. Mechanistic study on the photochemical “light switch” behavior of [Ru(bpy)<sub>2</sub>dmdppz]<sup>2+</sup>. *J. Phys. Chem. A* **2014**, *118*, 10474–10486. [[CrossRef](#)]
74. Havrylyuk, D.; Heidary, D.K.; Sun, Y.; Parkin, S.; Glazer, E.C. Photochemical and Photobiological Properties of Pyridyl-pyrazol(in)e-Based Ruthenium(II) Complexes with Sub-micromolar Cytotoxicity for Phototherapy. *ACS Omega* **2020**, *5*, 18894–18906. [[CrossRef](#)]
75. Dąbrowski, J.M.; Arnaut, L.G. Photodynamic therapy (PDT) of cancer: From local to systemic treatment. *Photochem. Photobiol. Sci.* **2015**, *14*, 1765–1780. [[CrossRef](#)] [[PubMed](#)]
76. Hopkins, S.L.; Siewert, B.; Askes, S.H.C.; Veldhuizen, P.; Zwier, R.; Heger, M.; Bonnet, S. An In Vitro Cell Irradiation Protocol for Testing Photopharmaceuticals and the Effect of Blue, Green, and Red Light on Human Cancer Cell Lines. *Photochem. Photobiol. Sci.* **2016**, *15*, 644–653. [[CrossRef](#)] [[PubMed](#)]
77. Vogel, A.; Venugopalan, V. Mechanisms of Pulsed Laser Ablation of Biological Tissues. *Chem. Rev.* **2003**, *103*, 577–644. [[CrossRef](#)] [[PubMed](#)]



78. Zhang, C.; Guo, X.; Da, X.; Wang, Z.; Wang, X.; Zhou, Q. A Ru-anthraquinone dyad with triple functions of PACT, photoredox catalysis and PDT upon red light Irradiation. *Dalton Trans.* **2021**, *50*, 10845–10852. [[CrossRef](#)]
79. Sears, R.B.; Joyce, L.E.; Ojaimi, M.; Gallucci, J.C.; Thummel, R.P.; Turro, C. Photoinduced ligand exchange and DNA binding of cis-[Ru(phpy)(phen)(CH<sub>3</sub>CN)<sub>2</sub>]<sup>+</sup> with long wavelength visible light. *J. Inorg. Biochem.* **2013**, *121*, 77–78. [[CrossRef](#)] [[PubMed](#)]
80. Cuello-Garibo, J.A.; James, C.C.; Siegler, M.A.; Hopkins, S.L.; Bonnet, S. Selective Preparation of a Heteroleptic Cyclometallated Ruthenium Complex Capable of Undergoing Photosubstitution of a Bidentate Ligand. *Chem. Eur. J.* **2019**, *25*, 1260–1268. [[CrossRef](#)]
81. Al-Afyouni, M.H.; Rohrabough, T.N.; Al-Afyouni, K.F.; Turro, C. New Ru(ii) photocages operative with near-IR light: New platform for drug delivery in the PDT window. *Chem. Sci.* **2018**, *9*, 6711–6720. [[CrossRef](#)] [[PubMed](#)]
82. Wang, J.; Lu, Y.; McCarthy, W.; Conway-Kenny, R.; Twamley, B.; Zhao, J.Z.; Drapera, S.M. Novel ruthenium and iridium complexes of N-substituted carbazole as triplet photosensitisers. *Chem. Commun.* **2018**, *54*, 1073–1076. [[CrossRef](#)]
83. Wadman, S.H.; Havenith, R.W.A.; Hartl, F.; Lutz, M.; Spek, A.L.; van Klink, G.P.M.; van Koten, G. Redox Chemistry and Electronic Properties of 2,3,5,6-Tetrakis(2-pyridyl)pyrazine-Bridged Diruthenium Complexes Controlled by N,C,N'-BisCyclometalated Ligands. *Inorg. Chem.* **2009**, *48*, 5685–5696. [[CrossRef](#)] [[PubMed](#)]
84. Ruminski, R.R.; Degroff, C.; Smith, S.J. Synthesis and characterization of tetracarbonylmolybdenum(0) complexes bound to the novel bridging ligand dipyrido[2,3-a:2',3'-h]phenazine (DPOP). *Inorg. Chem.* **1992**, *31*, 3325–3328. [[CrossRef](#)]
85. Albani, B.A.; Peña, B.; Saha, S.; White, J.K.; Schaeffer, A.M.; Dunbar, K.R.; Turro, C. A dinuclear Ru(II) complex capable of photoinduced ligand exchange at both metal centers. *Chem. Commun.* **2015**, *51*, 16522–16525. [[CrossRef](#)]
86. Saha, S.; Peña, B.; Dunbar, K.R. Partially Solvated Dinuclear Ruthenium Compounds Bridged by Quinoxaline-Functionalized Ligands as Ru(II) Photocage Architectures for Low-Energy Light Absorption. *Inorg. Chem.* **2019**, *58*, 14568–14576. [[CrossRef](#)]
87. Chen, Z.; Thiramanas, R.; Schwendy, M.; Xie, C.; Parekh, S.H.; Mailänder, V.; Wu, S. Upconversion Nanocarriers Encapsulated with Photoactivatable Ru Complexes for Near-Infrared Light-Regulated Enzyme Activity. *Small* **2017**, *13*, 1700997. [[CrossRef](#)]
88. Ruggiero, E.; Habtemariam, A.; Yate, L.; Mareque-Rivas, J.C.; Salassa, L. Near Infrared Photolysis of a Ru Polypyridyl Complex by Upconverting Nanoparticles. *Chem. Commun.* **2014**, *50*, 1715–1718. [[CrossRef](#)] [[PubMed](#)]
89. Shi, H.; Fang, T.; Tian, Y.; Huang, H.; Liu, Y. A Dual-Fluorescent Nano-Carrier for Delivering Photoactive Ruthenium Polypyridyl Complexes. *J. Mater. Chem. B* **2016**, *4*, 4746–4753. [[CrossRef](#)] [[PubMed](#)]
90. Chen, Y.; Jiang, G.; Zhou, Q.; Zhang, Y.; Li, K.; Zheng, Y.; Zhang, B.; Wang, X. An upconversion nanoparticle/Ru(II) polypyridyl complex assembly for NIR-activated release of a DNA covalent-binding agent. *RSC Adv.* **2016**, *6*, 23804–23808. [[CrossRef](#)]
91. Zhang, C.; Guo, X.; Da, X.; Yao, Y.; Xiao, H.; Wang, X.; Zhou, Q. UCNPs@BSA@Ru nanoparticles with tumor-specific and NIR-triggered efficient PACT activity in vivo. *Dalton Trans.* **2021**, *50*, 7715–7724. [[CrossRef](#)]
92. Meijer, M.S.; Natile, M.M.; Bonnet, S. 796 nm Activation of a Photocleavable Ruthenium(II) Complex Conjugated to an Upconverting Nanoparticle through Two Phosphonate Groups. *Inorg. Chem.* **2020**, *59*, 14807–14818. [[CrossRef](#)]
93. Greenough, S.E.; Horbury, M.D.; Smith, N.A.; Sadler, P.J.; Pater-son, M.J.; Stavros, V.G. Excited-State Dynamics of a Two-Photon-Activatable Ruthenium Prodrug. *ChemPhysChem* **2016**, *17*, 221–224. [[CrossRef](#)] [[PubMed](#)]
94. Ávila, M.R.; León-Rojas, A.F.; Lacroix, P.G.; Malfant, I.; Farfán, N.; Mhanna, R.; Santillan, R.; Ramos-Ortiz, G.; Malval, J.P. Two-Photon-Triggered NO Release via a Ruthenium–Nitrosyl Complex with a Star-Shaped Architecture. *Phys. Chem. Lett.* **2020**, *11*, 6487–6491. [[CrossRef](#)]
95. Li, H.; Xie, C.; Lan, R.; Zha, S.; Chan, C.; Wong, W.; Ho, K.; Chan, B.D.; Luo, Y.; Zhang, J.; et al. A Smart Europium–Ruthenium Complex as Anticancer Prodrug: Controllable Drug Release and Real-Time Monitoring under Different Light Excitations. *J. Med. Chem.* **2017**, *60*, 8923–8932. [[CrossRef](#)] [[PubMed](#)]
96. Wang, Y.; Tian, N.; Sun, W.; Rena, B.; Guo, X.; Feng, Y.; Li, C.; Wang, X.; Zhou, Q. A Ru(II)-Based Nanoassembly Exhibiting Theranostic PACT Activity in NIR Region. *Part. Part. Syst. Charact.* **2020**, *37*, 2000045. [[CrossRef](#)]
97. Jin, Z.; Qi, S.; Guo, X.; Jian, Y.; Hou, Y.; Li, C.; Wang, X.; Zhou, Q. The modification of a pyrene group makes a Ru(II) complex versatile. *Chem. Commun.* **2021**, *57*, 3259–3262. [[CrossRef](#)] [[PubMed](#)]
98. Albani, B.A.; Peña, B.; Leed, N.A.; de Paula, N.A.B.G.; Pavani, C.; Baptista, M.S.; Dunbar, K.R.; Turro, C. Marked improvement in photoinduced cell death by a new tris-heteroleptic complex with dual action: Singlet oxygen sensitization and ligand dissociation. *J. Am. Chem. Soc.* **2014**, *136*, 17095–17101. [[CrossRef](#)]
99. Knoll, J.D.; Albani, B.A.; Turro, C. Excited state investigation of a new Ru(II) complex for dual reactivity with low energy light. *Chem. Commun.* **2015**, *51*, 8777–8780. [[CrossRef](#)]
100. Knoll, J.D.; Albani, B.A.; Turro, C. New Ru(II) Complexes for Dual Photoreactivity: Ligand Exchange and <sup>1</sup>O<sub>2</sub> Generation. *Acc. Chem. Res.* **2015**, *48*, 2280–2287. [[CrossRef](#)]
101. Loftus, L.M.; White, J.K.; Albani, B.A.; Kohler, L.; Kodanko, J.K.; Thummel, R.P.; Dunbar, K.R.; Turro, C. New Ru(II) Complex for Dual Activity: Photoinduced Ligand Release and <sup>1</sup>O<sub>2</sub> Production. *Chem. Eur. J.* **2016**, *22*, 3704–3708. [[CrossRef](#)] [[PubMed](#)]
102. Arora, K.; Herroon, M.; Al-Afyouni, M.H.; Toupin, N.P.; Rohrabough, T.N.; Loftus, L.M.; Podgorski, I.; Turro, C.; Kodanko, J.J. Catch and Release Photosensitizers: Combining Dual-Action Ruthenium Complexes with Protease Inactivation for Targeting Invasive Cancers. *J. Am. Chem. Soc.* **2018**, *140*, 14367–14380. [[CrossRef](#)] [[PubMed](#)]
103. Toupin, N.P.; Nadella, S.; Steinke, S.J.; Turro, C.; Kodanko, J.J. Dual-Action Ru(II) Complexes with Bulky π-Expansive Ligands: Phototoxicity without DNA Intercalation. *Inorg. Chem.* **2020**, *59*, 3919–3933. [[CrossRef](#)] [[PubMed](#)]



104. Zheng, Y.; Zhou, Q.X.; Lei, W.H.; Hou, Y.J.; Li, K.; Chen, Y.J.; Zhang, B.W.; Wang, X.S. DNA photocleavage in anaerobic conditions by a Ru(II) complex: A new mechanism. *Chem. Commun.* **2015**, *51*, 428–430. [CrossRef]
105. Zheng, Y.; Zhou, Q.X.; Zhang, Y.Y.; Li, C.; Hou, Y.J.; Wang, X.S. Substituent effect and wavelength dependence of the photoinduced Ru-O homolysis in the [Ru(bpy)<sub>2</sub>(py-SO<sub>3</sub>)]<sup>+</sup>-type complexes. *Dalton Trans.* **2016**, *45*, 2897–2905. [CrossRef]
106. Tian, N.; Feng, Y.; Sun, W.; Lu, J.; Lu, S.; Yao, Y.; Li, C.; Wang, X.; Zhou, Q. A nuclear permeable Ru(II)-based photoactivated chemotherapeutic agent towards a series of cancer cells: In vitro and in vivo studies. *Dalton Trans.* **2019**, *48*, 6492–6500. [CrossRef] [PubMed]
107. Kumar, P.; Dasari, S.; Patra, A.K. Ruthenium(II) complexes of saccharin with dipyridoquinoxaline and dipyridophenazine: Structures, biological interactions and photoinduced DNA damage activity. *Eur. J. Med. Chem.* **2017**, *136*, 52–62. [CrossRef]
108. Gamer, B.N.; Gallucci, J.C.; Dunbar, K.R.; Turro, C. [Ru(bpy)<sub>2</sub>(5-cyanouracil)<sub>2</sub>]<sup>2+</sup> as a Potential Light-Activated Dual-Action Therapeutic Agent. *Inorg. Chem.* **2011**, *50*, 9213–9215.
109. Sgambellone, M.A.; David, A.; Garner, R.N.; Dunbar, K.R.; Turro, C. Cellular Toxicity Induced by the Photorelease of a Caged Bioactive Molecule: Design of a Potential Dual-Action Ru(II) Complex. *J. Am. Chem. Soc.* **2013**, *135*, 11274–11282. [CrossRef]
110. Lameijer, L.N.; Ernst, D.; Hopkins, S.L.; Meijer, M.S.; Askes, S.H.C.; Le Devedec, S.E.; Bonnet, S. A Red-Light-Activated Ruthenium-Caged NAMPT Inhibitor Remains Phototoxic in Hypoxic Cancer Cells. *Angew. Chem. Int. Ed.* **2017**, *56*, 11549–11553. [CrossRef]
111. Wei, J.H.; Renfrew, A.K. Photolabile Ruthenium Complexes to Cage and Release a Highly Cytotoxic Anticancer Agent. *J. Inorg. Biochem.* **2018**, *179*, 146–153. [CrossRef]
112. Karaoun, N.; Renfrew, A.K. A Luminescent Ruthenium(II) Complex for Light-Triggered Drug Release and Live Cell Imaging. *Chem. Commun.* **2015**, *51*, 14038–14041. [CrossRef]
113. Smith, N.A.; Zhang, P.Y.; Greenough, S.E.; Horbury, M.D.; Clarkson, G.J.; McFeely, D.; Habtemariam, A.; Salassa, L.; Stavros, V.G.; Dowson, C.G.; et al. Combatting AMR: Photoactivatable Ruthenium(II)-Isoniazid Complex Exhibits Rapid Selective Antimycobacterial Activity. *Chem. Sci.* **2017**, *8*, 395–404. [CrossRef]
114. Herroon, M.K.; Sharma, R.; Rajagurubandara, E.; Turro, C.; Kodanko, J.J.; Podgorski, I. Photoactivated Inhibition of Cathepsin K in a 3D Tumor Model. *Biol. Chem.* **2016**, *397*, 571–582. [CrossRef]
115. Zamora, A.; Denning, C.A.; Heidary, D.K.; Wachter, E.; Nease, L.A.; Ruiz, J.; Glazer, E.C. Ruthenium-Containing p450 Inhibitors for Dual Enzyme Inhibition and DNA Damage. *Dalton Trans.* **2017**, *46*, 2165–2173. [CrossRef] [PubMed]
116. Li, A.; Yadav, R.; White, J.K.; Herroon, M.K.; Callahan, B.P.; Podgorski, I.; Turro, C.; Scott, E.E.; Kodanko, J.J. Illuminating Cytochrome P450 Binding: Ru(II)-Caged Inhibitors of CYP17A1. *Chem. Commun.* **2017**, *53*, 3673–3676. [CrossRef] [PubMed]
117. Zhou, Q.X.; Zheng, Y.; Wang, T.J.; Chen, Y.J.; Li, K.; Zhang, Y.Y.; Li, C.; Hou, Y.J.; Wang, X.-S. A novel azopyridine-based Ru(ii) complex with GSH-responsive DNA photobinding ability. *Chem. Commun.* **2015**, *51*, 10684–10686. [CrossRef]
118. Qu, F.; Park, S.; Martinez, K.; Gray, J.L.; Thowfeik, F.S.; Lundeen, J.A.; Kuhn, A.E.; Charboneau, D.J.; Gerlach, D.L.; Lockart, M.M.; et al. Ruthenium Complexes are pH-Activated Metallo Prodrugs (pHAMPs) with Light-Triggered Selective Toxicity Toward Cancer Cells. *Inorg. Chem.* **2017**, *56*, 7519–7532. [CrossRef] [PubMed]
119. Qu, F.; Martinez, K.; Arcidiacono, A.M.; Park, S.; Zeller, M.; Schmehl, R.H.; Paul, J.J.; Kim, Y.; Papish, E.T. Sterically demanding methoxy and methyl groups in ruthenium complexes lead to enhanced quantum yields for blue light triggered photodissociation. *Dalton Trans.* **2018**, *47*, 15685–15693. [CrossRef] [PubMed]
120. Qu, F.; Lamb, R.W.; Cameron, C.G.; Park, S.; Oladipupo, O.; Gray, J.L.; Xu, Y.; Cole, H.D.; Bonizzoni, M.; Kim, Y.; et al. Singlet Oxygen Formation vs. Photodissociation for Light Responsive Protic Ruthenium Anticancer Compounds: The Oxygenated Substituent Determines Which Pathway Dominates. *Inorg. Chem.* **2021**, *60*, 2138–2148. [CrossRef]
121. Yang, M.; Zhao, H.; Zhang, Z.; Yuan, Q.; Feng, Q.; Duan, X.; Wang, S.; Tang, Y. CO/light dual-activatable Ru(II)-conjugated oligomer agent for lysosome-targeted multimodal cancer therapeutics. *Chem. Sci.* **2021**, *12*, 11515–11524, Advance Article. [CrossRef]
122. Suss-Fink, G. Arene ruthenium complexes as anticancer agents. *Dalton Trans.* **2010**, *39*, 1673–1688. [CrossRef]
123. Lee, S.Y.; Kim, C.Y.; Nam, T.G. Ruthenium Complexes as Anticancer Agents: A Brief History and Perspectives. *Drug Des. Devel Ther.* **2020**, *14*, 5375–5392. [CrossRef]
124. Magennis, S.W.; Habtemariam, A.; Novakova, O.; Henry, J.B.; Meier, S.; Parsons, S.; Oswald, L.D.H.; Brabec, V.; Sadler, P.J. Dual Triggering of DNA Binding and Fluorescence via Photoactivation of a Dinuclear Ruthenium(II) Arene Complex. *Inorg. Chem.* **2007**, *46*, 5059–5068. [CrossRef]
125. Betanzos-Lara, S.; Salassa, L.; Habtemariam, A.; Sadler, P.J. Photocontrolled nucleobase binding to an organometallic Ru<sup>II</sup> arene complex. *Chem. Commun.* **2009**, *43*, 6622–6624. [CrossRef] [PubMed]
126. Betanzos-Lara, S.; Salassa, L.; Habtemariam, A.; Novakova, O.; Pizarro, A.M.; Clarkson, G.J.; Liskova, B.; Brabec, V.; Sadler, P.J. Photoactivatable Organometallic Pyridyl Ruthenium(II) Arene Complexes. *Organometallics* **2012**, *31*, 3466–3479. [CrossRef]
127. Barragán, F.; López-Senín, P.; Salassa, L.; Betanzos-Lara, S.; Habtemariam, A.; Moreno, V.; Sadler, P.J.; Marchán, V. Photocontrolled DNA Binding of a Receptor-Targeted Organometallic Ruthenium(II) Complex. *J. Am. Chem. Soc.* **2011**, *133*, 14098–14108. [CrossRef] [PubMed]
128. Zhou, Q.X.; Lei, W.H.; Hou, Y.J.; Chen, Y.J.; Li, C.; Zhang, B.W.; Wang, X.S. BODIPY-modified Ru(II) arene complex—a new ligand dissociation mechanism and a novel strategy to red shift the photoactivation wavelength of anticancer Metallodrugs. *Dalton Trans.* **2013**, *42*, 2786–2791. [CrossRef]

129. Wang, T.J.; Zhou, Q.X.; Zhang, Y.Y.; Zheng, Y.; Wang, W.B.; Hou, Y.J.; Jiang, G.Y.; Cheng, X.X.; Wang, X.S. A ferrocenyl pyridine-based Ru(II) arene complex capable of generating  $\cdot\text{OH}$  and  $^1\text{O}_2$  along with photoinduced ligand dissociation. *RSC Adv.* **2016**, *6*, 45652–45659. [[CrossRef](#)]
130. Chen, Y.J.; Lei, W.H.; Jiang, G.Y.; Hou, Y.J.; Li, C.; Zhang, B.W.; Zhou, Q.X.; Wang, X.S. Fusion of photodynamic therapy and photoactivated chemotherapy: A novel Ru(II) arene complex with dual activities of photobinding and photocleavage toward DNA. *Dalton Trans.* **2014**, *43*, 15375–15384. [[CrossRef](#)]
131. Chen, Y.J.; Lei, W.H.; Hou, Y.J.; Li, C.; Jiang, G.Y.; Zhang, B.W.; Zhou, Q.X.; Wang, X.S. Fine control on the photochemical and photobiological properties of Ru(II) arene complexes. *Dalton Trans.* **2015**, *44*, 7347–7354. [[CrossRef](#)] [[PubMed](#)]
132. Lari, M.; Martínez-Alonso, M.; Busto, N.; Manzano, B.R.; Rodríguez, A.M.; Acuna, M.I.; Domínguez, F.; Albasanz, J.L.; Leal, J.M.; Espino, G.; et al. Strong Influence of Ancillary Ligands Containing Benzothiazole or Benzimidazole Rings on Cytotoxicity and Photoactivation of Ru(II) Arene Complexes. *Inorg. Chem.* **2018**, *57*, 14322–14336. [[CrossRef](#)] [[PubMed](#)]