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Review

Biological applications of Ru(II) polypyridyl complexes

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ABSTRACT

Ru(II) polypyridyl complexes are of great interest for their unique biological, photophysical, optical, catalytic and electronic properties. This class of complexes demonstrates a number of potential therapeutic applications via interactions with DNA, enzymes and cell membranes, leading to cell death. Metal-based drugs have many common mechanisms of action when acting against cancer and bacterial cells. Even though it was discovered over 50 years ago, the best-known anticancer agent is still cisplatin and the high toxicity and potentially serious complications point to the need for improved drug treatments. Similarly, the first antibiotics introduced in the 1930s against bacterial infection started "the golden age of antibiotics", but the increased number of antibiotic-resistant bacteria has become a global health problem. Recent research has shown that Ru(II) polypyridyl complexes have the potential to be used for the treatment of both cancer and bacterial infections, and in this review the most promising complexes are presented with their anticancer and antimicrobial properties discussed in detail.

Contents

Abbreviations: FDA, United States Food and Drug Administration; PDT, photodynamic therapy; PS, photosensitizer; ROS, reactive oxygen species; PACT, photodynamic antimicrobial chemotherapy; NKP-1339, sodium salt of indazolium trans-[tetrachlorobis(1H-indazole)ruthenate(III)]; KP-1019, trans-[tetrachlorobis(1H-indazole)ruthenate (III)]; NAMI-A, (imidazolium trans-[tetrachloro(dimethylsulfoxide)(1H-imidazole)ruthenate(III)]; TLD-1433, [Ru(II)(4,4′-dimethyl-2,2′-bipyridine(dmb))2-(2-(2′,2″:5″,2‴-terthiophene)-imidazo[4,5f][1,10]phenanthroline)]$^{2+}$; dppz, dipyridophenazine; bpy, bipyridines; phen, phenanthroline; MRSA, methicillin-resistant *Staphylococcus aureus*; MIC, minimum inhibitory concentration; MBC, minimum bactericidal concentration; HepG2, human hepatocellular liver carcinoma cell; MDA-MB-231, invasive human breast cancer; MCF-7, non-invasive human breast cancer; MCF-10, non-tumorigenic epithelial cells; CCL228, colorectal adenocarcinoma cells; H358, bronchioalveolar carcinoma non-small cell lung cancer; LNCaP, androgen-sensitive human prostate adenocarcinoma cells; DLD-1, colorectal adenocarcinoma cells; HeLa, cervical cancer cells; DU-145, prostate cancer cells; A2780S, human ovarian carcinoma sensitive; A2780R, cisplatin-resistant human ovarian carcinoma cells; A375, melanoma cells; SW620, colorectal adenocarcinoma cells; L929, mouse fibroblast; HS68, fibroblast; HK-2, kidney cells; HL60, leukemia cells; A549, lung human carcinoma cells; MRC-5, non-tumorigenic lung cells; AGS, gastric human carcinoma cells; HCT116, human colorectal carcinoma cells; CT26, murine colon carcinoma cells; TNBC, triple-negative breast cancer; IC_{50}, the half maximal inhibitory concentration; HAS, human serum albumin.

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1. Introduction

There is a long-standing interest in the use of transition metal complexes for the diagnosis and therapy of diseases [1]. Medicinal Inorganic Chemistry reached the mainstream in the 1960s when cisplatin (*cis*-$Pt(NH_3)_2Cl_2$) was successfully applied in cancer treatment for the first time [2]. Thereafter, other Pt(II)-based drugs were approved for cancer therapy by the United States Food and Drug Administration (FDA) (e.g., oxaliplatin, carboplatin) (Fig. 1) [3].

Despite its potent anticancer properties, cisplatin exhibits a large number of side-effects, including nerve damage and/or renal toxicity [4,5]. In addition, certain cancer types exhibit drug-resistance towards Pt(II)-based drugs [6], and the biological reducing agent glutathione (GSH) is known to inactivate platinum-based drugs [7]. The covalent interaction between cisplatin and DNA is the primary mechanism of action, causing cell apoptosis [105]. However, recent work has shown that other biological targets are more important, depending on the Pt complex [8]. Many researchers have focused on the design of new complexes containing metal ions, such as Cr(III) [9], Ru(II, III) and Rh(II, III) [10], that interact with DNA.

Bacterial infections are a huge global health concern due to the increase in multidrug-resistant pathogens [80]. Significant effort has been dedicated to designing new compounds, and improving existing antibiotics, to expand antimicrobial activity. Bacterial and eukaryotic DNA exhibit very similar features, limiting the feasibility of selective targeting of bacterial DNA. However, ribosomal RNA (rRNA) constitutes a much better target for antibacterial drugs due to (i) the different features of rRNA in bacterial and eukaryotic cells [11], (ii) rRNA is the most abundant form of RNA, and (iii) the non-duplex structure type provides a three-dimensional structure containing bulges, loops, turns and pseudo-knots for selective drug targeting [12]. Moreover, clinically-approved antibiotics also target (i) inhibition of cell wall synthesis (e.g., vancomycin, penicillin), (ii) the cell membrane (e.g., gramicidin) or (iii) inhibition of the synthesis proteins essential for bacterial growth (e.g., streptomycin). Complexes of bioactive agents with silver, copper or zinc oxide, also demonstrate good antimicrobial properties [13]. Cisplatin exhibits antimicrobial properties, however, it has never been used as an antimicrobial agent due to its very high toxicity to eukaryotic cells [14].

Despite significant research on metal complexes as therapeutic agents, there is still a need for the development of new compounds to improve the: (i) physico-chemical properties of complexes (e.g., water solubility), (ii) cellular uptake by changing the lipophilic properties or size of molecules, (iii) biological activity via a combination of strategies to obtain a synergistic effect (therapy with diagnosis; multitarget complexes), and (iv) specificity by incorporating photoactive groups into metal-based drugs for targeted activation.

1.1. The truth and scientific urban legends about Ru

Over the last forty years [15], Ru complexes have gained immense popularity in inorganic chemistry due to their unique biological, catalytic, optical and electronic properties [16]. In the context of drug development, a number of factors are beneficial including: (i) different accessible Ru oxidation states (II, III, IV) at physiological pH and the effect of the oxidation state on drug distribution [17], (ii) slow ligand-exchange kinetics, similar to Pt complexes [18], (iii) well-established coordination chemistry [19], (iv) lower toxicity in comparison to Pt-based drugs [20], and (v) similar coordination properties between Fe and Ru [21].

According to Alessio, who is the co-inventer of one of the Ru(III) complexes that has completed a clinical trial, all of the above properties are only postulated "scientific urban legends" and he critically discusses them in his review [22]. Fe and Ru differ from each other: (i) the Ru(III) crystal ionic radius (68 pm) is larger than that of Fe(III) in both spin states (55 pm low spin, 64.5 pm high spin) (ii) Ru is softer and in general results in more kinetically inert complexes in comparison to Fe. The next consideration is the behavior of Ru complexes *in vivo* in the bloodstream, where the interaction with transferrin and albumin proteins are important and may actively participate in transportation of therapeutic agents. Current research on cancer cells has shown the increased demand for Fe ions, resulting in overexpression of transferrin receptors (TfR). Taking advantage of transferrin-mediated drug delivery is a promising strategy in cancer research. Human serum albumin (HSA) also interacts with small molecules and is the dominant protein in plasma with a 15–20-fold higher concentration in comparison to transferrin. Thus, Ru complexes likely bind predominantly to HSA in plasma [23]. Pt-based drugs are characterized by slow ligands exchange behavior (cisplatin – 2.4 h; carboplatin – 268 h), which influences the anticancer activity. In the case of Ru complexes, compounds exhibiting both slow and rapid ligand exchanges have shown good anticancer activity, such as KP1339 or NAMI-A, respectively. One of the postulated features of Ru(III) complexes is "activation by reduction" with the Ru(III) ion being reduced to the Ru(II) ion in the tumor environment, however, recent studies have shown that the Ru(III) oxidation state may predominate *in vivo* [24–26].

An advantage of Ru(II) complexes is their tunable photophysical properties, desirable for photoactivated biological applications.

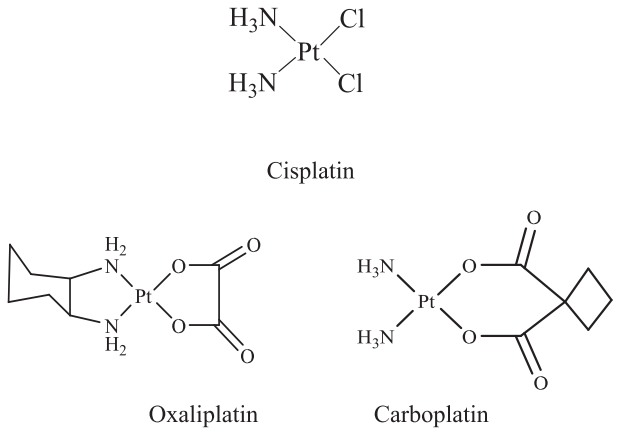

Fig. 1. FDA-approved Pt(II)-based drugs for cancer treatment.

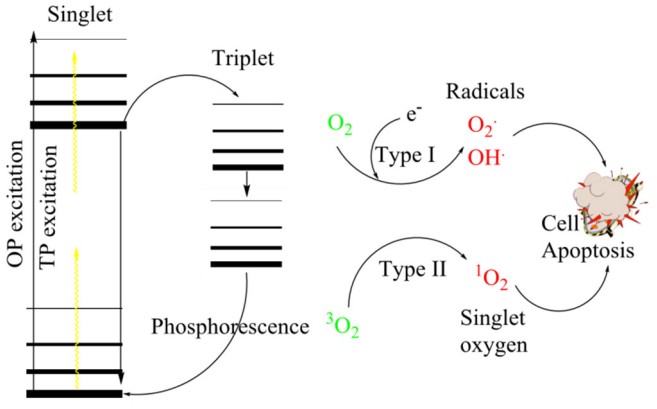

Fig. 2. Schematic energy level diagram presenting the activation of the photosensitizer during OP PDT and TP PDT leading to the production of a ROS or singlet oxygen, causing the cell death.

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