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Review

Ruthenium coordination compounds of biological and biomedical significance. DNA binding agents

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ABSTRACT

Ruthenium complexes exhibit a broad variety of biological and biomedical activities including anticancer efficiency. The reason is that the octahedral bonding of both Ru(II) and Ru(III) complexes affords an extensive repertoire of three-dimensional architectures, giving the potential for a high degree of site selectivity for binding to their biological targets. The mechanism of biological and biomedical action of ruthenium compounds is connected with their interactions with biomacromolecules. A lot of mechanistic studies revealed disposition of many ruthenium complexes to operate via mechanisms of action involving interactions with DNA, but distinctly different from those of the approved platinum anticancer drugs. In this Review, we discuss major DNA binding modes hitherto identified for ruthenium complexes of biological or biomedical significance and provide some typical examples. The introduction provides the reader with a brief overview of the approaches in the search for the new, transition metal-based agents of biological or biomedical significance to provide the context in which more recent research of DNA binding of ruthenium complexes has been evolved. We then describe main categories of binding modes between DNA and ruthenium compounds, such as coordinative, intercalative, minor groove binding, sequence specificity of DNA binding, the ability of ruthenium compounds to condense and cleave DNA, binding to A- and Z-DNA, DNA quadruplexes and other unusual DNA structures. A number of complexes based on ruthenium(II) centers have been reported to have excellent photophysical and radiosensitizing properties so that DNA photocleavage and synergistic enhancement of DNA damage due to a combined action of ruthenium complexes and ionizing radiation is also discussed. Finally, inhibition of DNA processing enzymes is reviewed as well. We believe that such a synthesis of disparate DNA binding modes of ruthenium complexes will help to generate new ruthenium complexes of improved biological and biomedical significance.

Contents

Abbreviations: 2,3-dpp, 2,3-bis(2-pyridyl)pyrazine; 2-appt, 2-amino-4-phenylamino-6-(2-pyridyl)-1,3,5-triazine; apip, 2-(2-aminophenyl)imidazo[4,5-*f*][1,10]phenanthroline; bnbp, 2,6-bis-(6-nitrobenzimidazol-2-yl)pyridine; bpm, 2,2′-bipyrimidine; bpy, 2,2′-bipyridine; dppz, dipyrido[3,2-*a*:2′,3′-*c*]phenazine; dppb, 1,4-bis(diphenylphosphino)butane; dpq, dipyrido[3,2-*d*:2′,3-*f*]quinoxaline; en, ethylenediamine; EtBr, ethidium bromide; iip, isoindolylimidazo[4,5,*f*][1,10]phenanthroline; Im, imidazole; hpip, 2-(2-hydroxyl-5-aminophenyl)imidazo[4,5-*f*][1,10]phenanthroline; Ind, indazole; ip, imidazo[4,5-*f*][1,10]phenanthroline; Me_2bpy, 4,4′-dimethyl-2,2′-bipyridine; NAMI, Na[*trans*-Ru(III)((DMSO)Cl_4(Im)]; NAMI-A, (H_2Im)[*trans*-Ru(DMSO)Cl_4(Im)]; nip, benzo[*f*]isoindole[4,5,*f*][1,10]phenanthroline; PARP, poly ADP ribose polymerase; phen, 1,10-phenanthroline; pip, 2-phenylimidazo[4,5-*f*][1,10]phenanthroline; pipsh, 2-(4-benzothiazolyl)phenylimidazo[4,5-*f*][1,10]phenanthroline; *p*-terp, paraterphenyl; RAPTA-C, [(η^6-*p*-cymene)Ru(1,3,5-triaza-7-phosphaadamantane)Cl_2]; ROS, reactive oxygen species; Ru-CYM, [(η^6-arene)Ru(II)(en)(Cl)]$^+$ (arene = *p*-cymene); Ru-THA, [(η^6-arene)Ru(II)(en)(Cl)]$^+$ (arene = tetrahydroanthracene); $SpymMe_2$, 4,6-dimethyl-2-mercaptopyrimidine anion; tatpp, 9,11,20,22-tetraazatetrapyrido[3,2-*a*:2′,3′-*c*:3″,2″-1:2″,3‴-*n*]-pentacene; ^{t}Bu_2bpy, 4,4′-di-*tert*-butyl-2,2′-bipyridine; tpphz, tetrapyridophenazine.

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1. Introduction

Medicinal coordination chemistry is now established as an acknowledged area of the interdisciplinary research. A key theme of this research has been to develop the fundamental principles that enable the design of effective anticancer metal-containing chemotherapeutic agents. Early research work on anticancer coordination compounds was concerned with the most widely used anticancer chemotherapeutics and successful platinum drugs, cisplatin, carboplatin, and oxaliplatin, approved worldwide for treating human tumors and additional three, heptaplatin, lobaplatin and nedaplatin approved for clinical use to treat cancer in humans in specific countries. However, there are several clinical problems relating to current platinum anticancer drugs which demand improvements in design. The first is drug resistance which can develop after repeated treatment, second, poor activity against some types of cancer (e.g., colon, lung and pancreatic cancer) and thirdly the occurrence of side-effects. These drawbacks have been the impetus for the development of improved anticancer drugs derived from not only platinum complexes but also other transition metal-based complexes. Notably, despite the intense research activity into new metal-based antitumor compounds, a new transition-metal based compound has not been hitherto approved.

Broadening the spectrum of antitumor metallodrugs depends on understanding the mechanism of action of existing and new candidate antitumor agents with a view toward developing new modes of attack. It is therefore of great interest to understand details of molecular and biochemical mechanisms underlying the biological efficacy of the platinum compounds and other transition metal-based complexes. There is good evidence [1] that the preferential pharmacological target for platinum diammine drugs such as cisplatin and its clinically used derivatives in cancer cells is nuclear DNA, which is a molecule that contains the instructions an organism needs to develop, live and reproduce. The nitrogen N7 atom of the guanine residue is the most electron-dense site in DNA and is accessible in its major groove. Cross-linking of two adjacent purines leads to kinking of the DNA, recognition by high mobility group and other proteins, triggering apoptosis and cell death. In addition, it has been shown that: (i) there is a correlation between the antitumor activity of platinum compounds and their capability to induce in DNA a certain sort of conformational and other alterations; (ii) this correlation may be exploited for simple screening of new platinum complexes for antitumor activity in the search for new antitumor platinum drugs; (iii) this concept has already led to the synthesis of several new platinum antitumor compounds that violate the original structure–activity relationships.

One approach in the search for the new, metal-based anticancer agent which would exhibit antitumor activity markedly different from that of cisplatin and its direct analogs is to examine complexes that would contain another transition metal. Possible advantages in using transition-metal ions other than platinum may involve additional coordination sites, alterations in ligand affinity and substitution kinetics, changes in oxidation state and photodynamic approaches to therapy [2]. In the design of these new drugs, ruthenium complexes have raised great interest [2–4]. The octahedral bonding of both Ru(II) and Ru(III) complexes affords an extensive repertoire of three-dimensional architectures, giving the potential for a high degree of site selectivity and implementation of favorable pharmacological attributes [5]. The pharmacological target for many antitumor ruthenium compounds has not been univocally identified although a number of antitumor ruthenium compounds have been found to inhibit DNA replication, exhibit mutagenic activity, induce SOS repair mechanism, bind to nuclear DNA including unusual DNA structures and reduce RNA synthesis, which is consistent with DNA binding of these compounds *in vivo*. Moreover, several ruthenium complexes have unequivocally been shown to have genomic DNA as their pharmacological target [6–9], and many ruthenium compounds are known to have high selectivity for binding to DNA [10–13]. Thus, also by analogy with platinum antitumor drugs DNA interactions of antitumor ruthenium agents are of great interest as well because understanding the cellular DNA damage responses to lesions generated by ruthenium complexes may considerably contribute to design and development of DNA-binding ruthenium agents. Since several review articles appeared recently [9,14–19] in which pharmacological properties of antitumor ruthenium compounds have been discussed, the present article is mainly focused on variety of DNA interactions of ruthenium complexes of biological or biomedical significance which result in novel lesions in DNA so that their origin may be connected with their biological (antitumor) effects or their use as new probes, and imaging or diagnostic agents. In this Review, we discuss major DNA binding modes