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Extended Abstract

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Targeting cancer with selective and potent ruthenium compounds

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Statement of the Problem: The discovery of new active and selective anticancer agents, able to reduce the noxious side effects of the chemotherapeutics in clinical use, and able to overcome resistance mechanisms, is the main goal for the research in this field.
Methodology & Theoretical Orientation: We have been developing new of [Ru(η5-C5H5) (2,2′-bipyridine-R)(PPh3)]+ based compounds through structure-activity studies, endowed with specific targeting components to take advantage of the singular characteristics of tumor cells and tissues, such as their permeability to macromolecules and overexpression of several receptors. Thus, when in the structure of our compounds R is a biodegradable and biocompatible polymer and/or a biomolecule recognized by cancer cells, passive and/ or active targeting can be achieved, respectively. Through a wide set of biological assays that involved spectroscopic, imaging and proteomic techniques, we show that this family of ruthenium metallodrugs possess very attractive features.
Conclusion & Significance: These compounds show high cytotoxicity against several cancer cell lines with different degrees of aggressiveness (hormone dependent vs triple negative breast cancer) and strong inhibition of key proteins known for their role in mechanisms of cell resistance. Their targets seem to be the proteins that regulate the microtubule or actin dynamics leading to cell death by apoptosis. In vivo studies in a zebrafish model revealed that the compounds are well tolerated. Thus, in this presentation the potential of new ruthenium (II) compounds for the targeted therapy of metastatic and resistant cancers is disclosed. Cancer is rapidly becoming the top killer in the world. Most of the FDA approved anticancer drugs are organic molecules, while metallodrugs are very scarce. The advent of first metal based therapeutic agent, cisplatin, launched a new era in the application of transition metal complexes for therapeutic design. Due to their unique and versatile biochemical properties, ruthenium-based compounds have emerged as promising anti-cancer agents that serve as alternatives to cisplatin and its derivertives. The ruthenium (III) complexes have successfully been used in clinical research and their mechanisms of anticancer action have been reported in large volumes over the past few decades. Ruthenium (II) complexes have also attracted significant attention as anticancer candidates; however, only few of them have been reported comprehensively. In this review, we discuss the development of ruthenium (II) complexes as anticancer candidates and biocatalysts, including arene ruthenium complexes, polypyridyl ruthenium complexes, and ruthenium nanomaterial complexes. This review focuses on the likely mechanisms of action of ruthenium (II)-based anticancer drugs and the relationship between their chemical structures and biological properties. This review also highlights the catalytic activity and the photoinduced activation of ruthenium (II) complexes, their targeted delivery, and their activity in nanomaterial systems. Due to a rapid increase in cancer cases worldwide, there is an indispensable need for the development and screening of potential anticancer agents. In this regard, metal complexes hold potential as novel anticancer agents against a wide majority of cancer types. Cisplatin or cis-diamminedichloroplatinum (II) is the most widely known metal-based anticancer drug. Cisplatin has been shown to have efficacy against lung, head, ovarian, neck, and esophageal cancers. Although cisplatin and its derivatives are efficacious against the vast majority of cancers, they also produce non-cancer cell toxicity, thereby causing severe adverse effects, including peripheral neuropathy, hair loss and myelotoxicity in patients. The resistance of tumors to platinum decreases the efficacy of platinum-based or even renders them ineffective, causing treatment failure. In the design of new anticancer drugs, the ruthenium complexes have raised great interest and have been tested against a number of cancer cell lines, and are regarded as promising candidates for alternative drugs to cisplatin and its derivatives. Ruthenium is a transition metal, the same chemical group as iron. Ruthenium has two main oxidation states, Ru (II) and Ru (III). Ruthenium (IV) compounds are also possible, but they are generally unstable due to their higher oxidation states. The ruthenium ion is typically hexa- coordinated with octahedral coordination geometries. Generally, the thermodynamic and kinetic stability of Ru (III) complexes are lower than that of Ru (II) complexes, and the kinetics of the hydration of Ru (II/III) compounds depends significantly on the nature of their ligands and net charge. Many Ru (III) compounds contain exchangeable ligands and require activation by the tumor microenvironment. The antitumor properties of the Ru (III) complexes occur when they are reduced to their corresponding Ru (II) counterparts *in vivo*. Under biological circumstances of low oxygen concentration, acidic pH and high levels of glutathione, the Ru (II/III) redox potential can be altered, and thus, Ru (III) complexes can be readily reduced to Ru (II) complexes. As the first approved ruthenium complex in clinical trials, NAMI-A, [ImH][trans-$RuCl_4$(DMSO)(Im)] (Im = imidazole, DMSO = imethylsulfoxide has low potency in terms of direct cytotoxicity towards cancer cells *in vitro*; however, *in vivo*, it has significant efficacy in inhibiting tumor metastasis. The mechanism of action of NAMI-A remains to be elucidated. There are data suggesting that NAMI-A is capable of binding to DNA and RNA. It can bind to the histidine residues of serum albumin (has or bsA) under physiological conditions. However, the low therapeutic efficiency, the progressive disease in the clinical studies (phase I) and partial response (phase I/II) limited the further clinical use of NAMI-A and resulted in the failure of the clinical investigations. The main reason of the failure is more philosophical, but nevertheless fundamental. Subsequently, the KP1019 [trans-tetrachlorobis -(1H-indazole) ruthenate (III)] designed by the Keppler group entered clinical trial. But its low solubility limits its further development and its better soluble sodium salt KP1339 is currently undergoing clinical trials.

Recently, many organometallic Ru (II), inorganic Ru (II) and nanomaterial Ru (II) complexes have been designed and developed into anticancer drugs, with potent therapeutic properties. With the development of new technology, such as photodynamic therapy (PDT) and nanomaterials, Ru (II) complexes can be photophysical and bioactive, improving the efficacy and selectivity of Ru (II) complexes as anticancer drugs, as well as allowing for the elucidation of their mechanism of action. The Ru (II)-polypyridyl compound (TLD-1433) recently entered phase IB clinical trials as PDT agent in patients with bladder cancer at 2015. Therefore, the direct study of Ru (II) complexes for cancer therapy contributes to the design of new metal-based drugs. Generally speaking, the following options are viable in the design of ruthenium-based drugs: (i) constructing complexes with selective and specific targets; (ii) exploiting the potential targets and mechanisms; (iii) the evaluation of structure-activity relationships; (iv) exploiting prodrugs that can be activated by light; and (v) exploiting drug accumulation and activation at the tumour tissues with the nano drug-delivery system. This Review aims to present the reader with an impression of the latest progress of development of ruthenium complexes as anticancer agents as well as biocatalysts from single molecule compounds to nanomaterials. We present an overview of the field today, hoping that colleagues not only may taste a comprehensive development of ruthenium (II) complexes as metallodrugs, but that we can inspire more researchers to enter the charming field of metallodrugs. The uptake of ruthenium complexes by cancer cells or other cells is important for selective and effective cancer therapy. In order to move into living cells, molecules and atoms must cross or penetrate the cell membrane. The cell membrane contains diverse proteins and lipids, and it functions to regulate what substances enter into the cells. The general mechanisms of cellular uptake for small molecule drugs are shown in Ru (II) complexes are known to enter cells through multiple mechanisms, such as passive diffusion, active transport, and endocytosis. However, it is noted that most nanostructured ruthenium complexes enter cells by endocytosis. Confocal laser scanning fluorescence microscopy, inductively coupled plasma mass spectrometry (ICP-MS), flow cytometry and transmission electron microscopy are often used to determine the intracellular accumulation of ruthenium complexes. As the changes in ligands and hydrophobicity can modulate cellular uptake and cellular localization, the intracellular distribution of ruthenium complexes in cells have been discussed with regard to: (a) the net ionic charge, which can undergo change from anionic to cationic; (b) the degree of lipophilicity based on the octanol/water partition coefficient; (c) the structures and sizes of the ligands.

Bottom Note: *This work is partly presented at* 6th World Congress on NATURAL PRODUCT & SYNTHETIC CHEMISTRY June 24-25, 2019 | New York, USA.