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Role of metallomic strategies in developing ruthenium anticancer drugs

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ABSTRACT

There is still high anticipation among oncology metallodrug developers that a real breakthrough can be gained due to substituting platinum, as a principal component of all approved metal-based chemotherapeutics, with another metal such as arguably second in importance ruthenium. Such expectations have directed research activities to improvements in the molecular design, with varying the ruthenium oxidation state and bonding type, and to the better understanding of the basic underlying chemistry and biochemical mechanisms of cytotoxicity. It is the latter issue where the metallomic approaches have received growing attention as indispensable to decipher the metabolic pathways, to shed light on modes of delivery and action, and to identify active, toxic species and potential cell targets of metallodrugs. Therefore, there is obviously a need to critically evaluate recent progress due to using metallomic strategies and techniques to advance the preclinical development of anticancer ruthenium agents. Being aware that the rate of failure for ruthenium compounds is no less than for other molecular entities tested and tending to be overwhelming, the author places the focus of this review on merely $(H_2ind)[Ru^{III}Cl_4(Hind)_2]$ (Hind = 1H-indazole) and $Na[Ru^{III}Cl_4(Hind)_2]$, often referred to as KP1019 and NKP-1339, respectively, the only ruthenium drug candidates presently in clinical trials, $(H_2im)[Ru^{III}Cl_4(DMSO)(Him)]$ (Him = 1H-imidazole), NAMI-A, which has though been recently suspended of clinical testing, as well as on $Ru(\eta^6\text{-toluene})(pta)Cl_2$ and $Ru^{II}(\eta^6\text{-p-cymene})(pta)Cl_2$ (pta = 1,3,5-triaza-7-phosphaadamantane), or RAPTA-T and RAPTA-C, respectively, the lead investigational compounds of the RAPTA family.

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1. Introduction

As time goes by after the approval for world-wide clinical use of the latest of metal-based anticancer drugs, oxaliplatin (in 2002), the feeling is coming to the fore that there is something off beam in the state of metallodrug discovery and development. Taking into account over 40 years of intense research and spending that is difficult to assess numerically, even with cisplatin and carboplatin that formerly reached patients, 'the three swallows do not make a summer.' Yet more discouraging is the fact that in the meantime on average ten new organic drugs for oncology are introduced each year [1]. Certainly, a much bigger number of organic chemists in drug development as compared to metallodrug researchers can constitute justification but to what degree acceptable?

Lack of developmental productivity did not pass round ruthenium coordination and organometallic compounds, none of which

Abbreviations: CE, Capillary electrophoresis; ESI-MS, Electrospray ionization mass spectrometry; GSH, Glutathione; HMW, high molecular weight; HPLC, High-performance liquid chromatography; ICP-MS, Inductively coupled plasma mass spectrometry; LMW, Low molecular weight; SEC, Size-exclusion chromatography; TOF, Time-of-flight; XAS, X-ray absorption spectroscopy; XRF, X-ray fluorescence.

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has found its way to market. For instance, more than 25 years passed since the antitumor properties of (H_2ind)[$Ru^{III}Cl_4$(Hind)$_2$] (**I**), perhaps the most potent Ru compound, were discovered. This is twice longer than it averagely requires for a successful medicine to be introduced to clinics. In this regard, it seems to be of immediate interest to discuss root causes of metallodrug development inefficiency and in particular, the challenges over the course of discovery and development for ruthenium-based would-be drugs. Given the scope of this journal and author's expertise, this review will rather highlight the state-of-the-art of analytical methodology used to identify, characterize and quantify metal species originating from the Ru drugs and to map their interactions with biomolecules in human body, as well as its potential role in improving the drug development process. Indeed, only such speciation information can mind the gaps in understanding the processes of drug delivery, uptake, and cell processing, including activation and targeting, at the molecular level. This comprehension has forced metallodrug developers to seek support of analytical chemists in order to revise the arsenal and design of techniques and methodologies in use. Their joint efforts over the last decade have resulted in adopting a variety of powerful, mostly mass spectrometry (MS)-based analytical tools from the armory of biospeciation analysis. This favorable situation has been reflected in recent review literature, including the most relevant to the subject of the present review in-depth surveys of metallomic and proteomic approaches to study the mode of action of anticancer metallodrugs by Messori and coworkers [2], Timerbaev and coauthors [3], Groessl and Hartinger [4], and Wang et al. [5]. Several more specialized review papers are available which provide coverage of contributions dealing with a specific method or a group of methods employed in the development of metal-based drugs [6–9]. However, none of the metallomics-oriented reviews focuses on anticancer ruthenium compounds, albeit with respect to progress in their preclinical and early clinical examinations the topic is well covered [10–16]. Written by bioinorganic or medicinal chemists, these issues though often miss the point of ever-growing importance of analytical methodology in putting ruthenium drug candidates on the map of modern cancer chemotherapy and in general are of a little overoptimistic style.

Therefore, the aim of this review is to offer critical analysis of metallomic strategies that can promote the elucidation of the molecular mechanisms underlying the mode of action of anticancer or antimetastatic drug candidates based on ruthenium. Special emphasis is placed here on those lead compounds that are specified above (see the abstract; structural formulas are shown in Fig. 1). No consideration is thus given to other promising Ru agents regardless of how high their potential is valued by their developers. This is not only consistent with author's long-term research strategy, avoiding the use of rather expensive metallomic techniques in investigations of each compound in early stages of preclinical development ('take not a musket to kill a butterfly!'). More broadly speaking, if a novel cytotoxic agent coming from an academic lab does not exhibit druglike properties and pass pharmacological screening tests, often competing with structurally similar compounds, how one could convince the analyst that there is another use of the data acquired than to publish another paper with a catchy title? This issue is particularly critical in the light of the significant resources being put into generating such data. Also, with regard to expertise of this journal readership, basics and instrumental

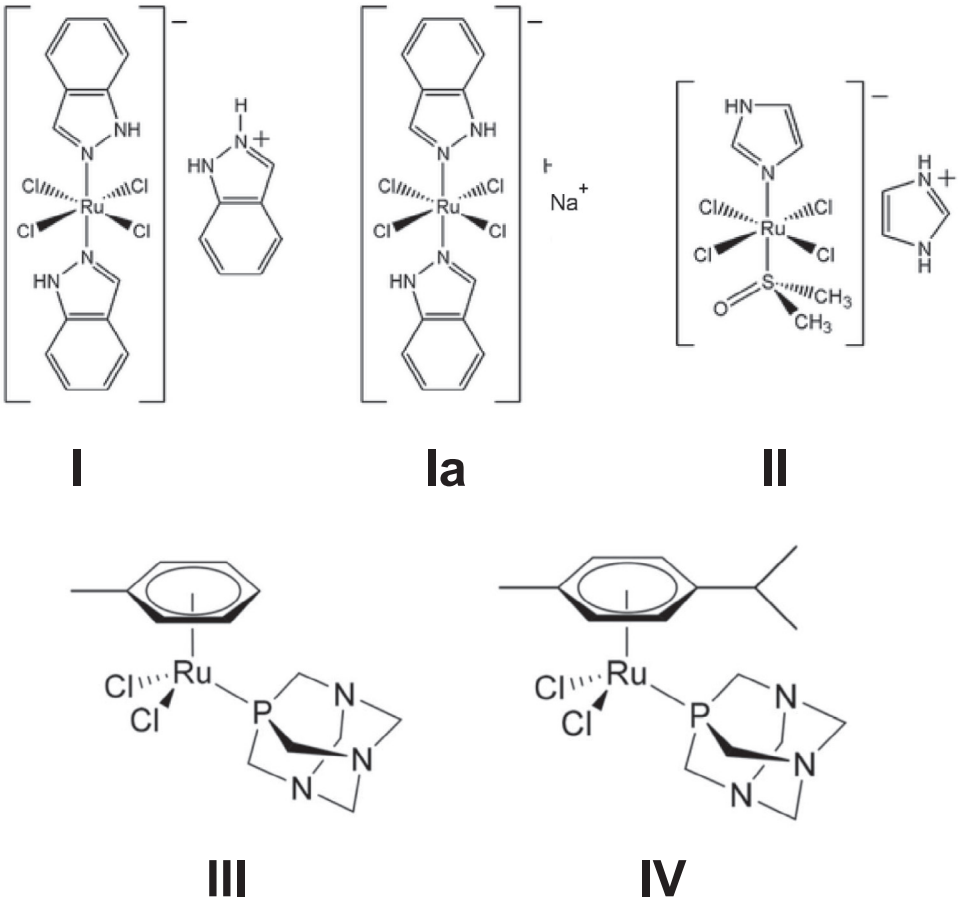

Fig. 1. Structural formulas of selected ruthenium anticancer drugs.