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Review

Opening the lid on piano-stool complexes: An account of ruthenium(II)–arene complexes with medicinal applications

Alexey A. Nazarov [a], Christian G. Hartinger [b], Paul J. Dyson [c, *]

[a] Department of Organic Chemistry, Moscow State University, Leninskie Gory, 119991 Moscow, Russia
[b] School of Chemical Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand
[c] Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), EPFL–BCH, CH-1015 Lausanne, Switzerland

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ABSTRACT

Interest in the medicinal properties of ruthenium(II)–arene compounds has grown rapidly over the last decade. In this account we describe the origins of the field and subsequently highlight developments in the field, including the design of compounds that inhibit enzymes, the application of multinuclear systems to act as drug delivery vehicles, and the development of bioanalytical and biophysical methods to help elucidate the mechanisms by which these compounds function. The conducive properties and reasons for the rapid growth in interest in these and related compounds for their medicinal applications, especially in the treatment of solid tumours, are identified.

Contents

1. Introduction

The discovery of the anticancer properties of cisplatin, *cis*-$Pt(NH_3)_2Cl_2$, in 1965 is arguably *the* most significant and life-changing breakthrough in bioinorganic chemistry [1]. Cisplatin rapidly became, and today remains, one of the most widely used anticancer drugs and it is estimated that today 50–70% of all cancer patients are treated with cisplatin [2]. The landmark discovery of cisplatin initiated the search for other coordination complexes with anticancer properties, since cisplatin is not without problems [3–7], and two other platinum compounds, namely oxaliplatin and carboplatin, are in worldwide clinical use (Fig. 1) [7]. A vast number of complexes centred on metals other than platinum have also been evaluated as anticancer chemotherapeutics and the most advanced compounds include two palladium(II) porphyrin compounds, TOOKAD® and TOOKAD® Soluble, that are in phase III clinical trials as sensitizers in photodynamic therapy [8], and two ruthenium(III)

* Corresponding author.
E-mail addresses: alexey.nazarov@me.com (A.A. Nazarov), c.hartinger@auckland.ac.nz (C.G. Hartinger), paul.dyson@epfl.ch (P.J. Dyson).

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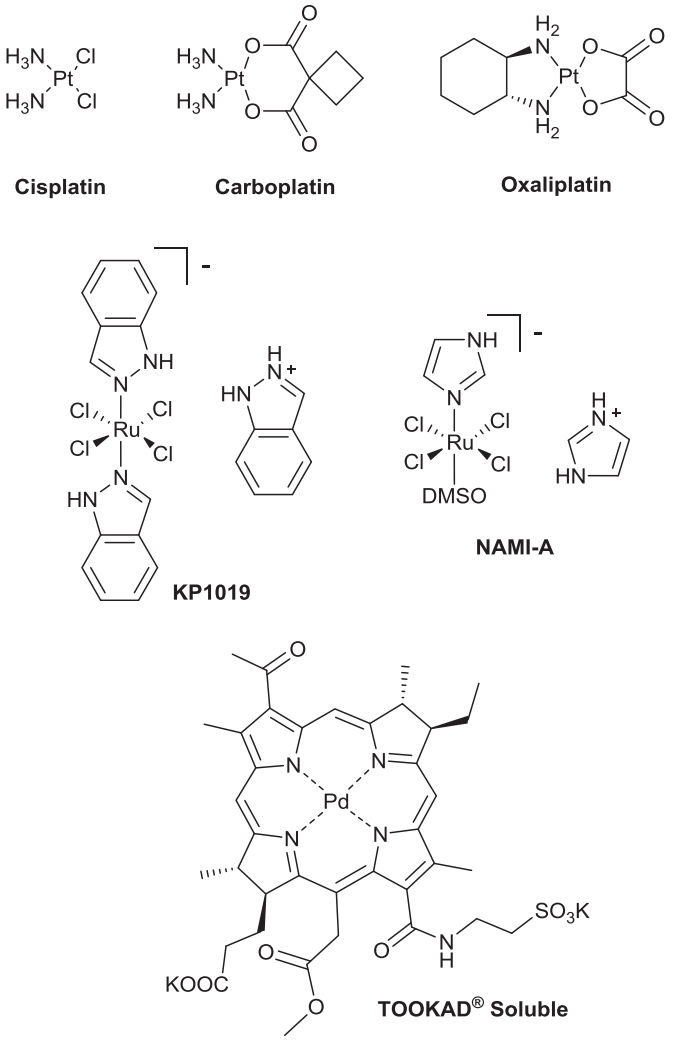

Fig. 1. The structures of cisplatin, carboplatin, oxaliplatin, KP1019, NAMI-A and Tookad® Soluble (the first three compounds are extensively used in the clinic to treat a wide range of different cancers and the last three compounds are undergoing clinical evaluation).

complexes, indazolium [*trans*-tetrachloridobis(1*H*-indazole)ruthenate(III)], KP1019 [9,10], and imidazolium trans-[tetrachlorido(dimethylsulfoxide-κ*S*)(1*H*-imidazole)ruthenate(III)], NAMI-A [11,12], that are currently undergoing phase II clinical trials (Fig. 1).

The discovery of cisplatin and the exciting developments in the field of metal-based drugs for the treatment of cancer and other diseases were not ignored by the organometallic community. Indeed, shortly after the initial clinical success of cisplatin a series of metallocene complexes were evaluated for anticancer activity [13]. From the series of metallocenes studied titanocene dichloride, $Ti(\eta^5\text{-}C_5H_5)_2Cl_2$ (Fig. 2), was identified as a lead compound, and following extensive biological studies it entered clinical trials, although it was eventually abandoned following a phase III clinical trial [14]. Many titanocene derivatives have since been prepared and evaluated for their cytotoxicity against cancer cells and in animal models including more stable complexes that potentially overcome the problems associated with the limited aqueous stability of titanocene dichloride [15].

Increasing interest in organometallic pharmaceuticals has centred on the evaluation and application of Group 8 compounds. Notably, the quintessential organometallic sandwich compound ferrocene, $Fe(\eta^5\text{-}C_5H_5)_2$, is not particularly toxic whereas the ferrocenium cation, $[Fe(\eta^5\text{-}C_5H_5)_2]^+$, exhibits an anti-proliferative effect on various cancer cell lines [16–18]. Consequently, the delivery of a non-toxic ferrocene moiety to a cancer cell that is subsequently oxidized to a toxic ferrocinium ion is an attractive strategy assuming that the oxidation takes place selectively in tumours, which is not inconceivable given the different pharmacological features that distinguish rapidly growing cancer cells and healthy cells. Based on this hypothesis tamoxifen, a key chemotherapeutic agent used to treat hormone-dependent breast cancers (its active metabolite is hydroxy-tamoxifen), was modified with a ferrocenyl group in place of a phenyl ring affording ferrocifen (Fig. 2) [19,20].

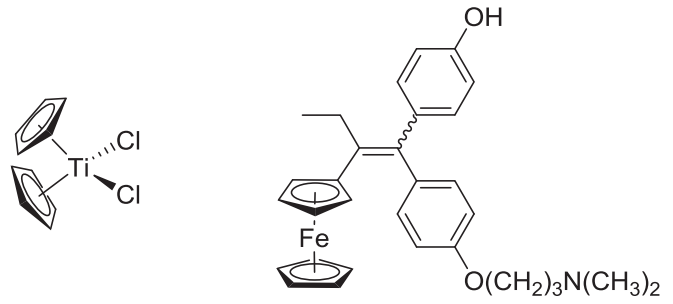

Fig. 2. The structures of titanocene dichloride (left) and ferrocifen (right). The former compound underwent clinical evaluation and the latter compound has been the subject of extensive biological studies.

In addition to ferrocene derivatives of tamoxifen both ruthenocene- and osmacene-based compounds have been prepared and evaluated in vitro for cytotoxicity, however, the iron-based compounds have the most relevant pharmacological properties [19,21]. A rhodium pentamethylcyclopentadienyl derivative of hydroxytamoxifen has also been reported [22]. Previously, rhodium(III)–pentamethylcyclopentadienyl aqua complexes had been shown to readily react with DNA model compounds indicating that under physiological conditions such compounds could be of therapeutic use [23–28].

2. Promising nascent studies

The first paper to describe a medicinal application of a ruthenium(II)–arene compound, to the best of our knowledge, was published in 1992 [29]. The known anticancer agent 1-β-hydroxyethyl-2-methyl-5-nitroimidazole (metronidazole) was coordinated to the ruthenium(II)–benzene fragment via a nitrogen donor atom (Fig. 3) giving a compound with superior, selective cytotoxicity compared to metronidazole. This paper went largely unnoticed at the time and further papers describing its biological properties in more detail were not forthcoming, indicating that the compound was not studied further or that further biological studies were disappointing. However, ruthenium(II)–arene chemistry underwent a considerable expansion over the next few years due to their utility in synthesis and catalysis [30–34]. Combined with the positive developments of ruthenium(III) complexes in cancer therapy, in the late 1990s/early 2000s three papers were published that described rather simple ruthenium(II)–arene complexes with interesting biological properties.

The rather unstable complex, $Ru(\eta^6\text{-benzene})(dmso)Cl_2$ (Fig. 3), unstable in the sense that the dmso and chloride ligands are all relatively labile and can undergo substitution by water, was shown to inhibit topoisomerase II activity although only at quite high concentrations [35,36]. The authors proposed that the ruthenium complex interacts with DNA as well as forms crosslinks with topoisomerase II. The prototype RAPTA compound, $Ru(\eta^6\text{-}p\text{-}$