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Review

Thiolato-bridged dinuclear arene ruthenium complexes and their potential as anticancer drugs

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ABSTRACT

Water-soluble arene ruthenium complexes have been intensively studied as cytotoxic compounds for the last fifteen years, notably owing to the promising *in vitro* and *in vivo* evaluations of, respectively, RAPTA-C (η^6-*p*-$MeC_6H_4Pr^i$)Ru(*P*-pta)Cl_2 (pta = 1,3,5-triaza-7-phospha-tricyclo-[3.3.1.1]decane) from Dyson's laboratory, and the (η^6-arene)Ru(en)Cl]$^+$ (en = ethylenediamine, RAED) family of compounds from Sadler's laboratory. In this account we describe the discovery of thiolato-bridged dinuclear arene ruthenium complexes and highlight subsequent developments in the field, including their syntheses, structures, and the recent strategies for the design of thiolato-bridged dinuclear arene ruthenium bioconjugates.

1. Introduction

The properties of ruthenium have been intensely evaluated by many research groups worldwide for some 40 years. Ruthenium is a fantastic catalyzer, illustrated by the Nobel prizes 2001 (Noyori, enantio selective hydrogenation reactions catalyzed by chiral ruthenium complexes) [1] and 2005 (Grubbs, olefin metathesis reactions catalyzed by ruthenium carbene complexes) [2]. More recently, light-harvesting properties of ruthenium have also been recognized, when Grätzel won the Millennium prize 2010 for the development of dye-sensitized solar cells based on ruthenium complexes [3].

Ruthenium also turned out to be the most promising metal for replacing platinum in a future cancer therapy. Most ruthenium compounds have a low systemic toxicity, and most ruthenium(II) and ruthenium(III) complexes exhibit slow ligand exchange

Abbreviations: bip, biphenyl; cyt *c*, cytochrome-*c*; CD, circular dichroism; DNA, 2-deoxynucleic acid; en, ethylenediamine; ESI–MS, electrospray ionization mass spectrometry; GSH, glutathione; GSSG, oxidized glutathione; hmb, hexamethylbenzene; HsA, human serum albumin; IC_{50}, half maximal inhibitory concentration; ICP-MS, inductively coupled plasma mass spectrometry; i.p., intraperitoneal injection; IR, infrared spectroscopy; KP1019, indazolium trans-[tetrachloridobis(1*H*-indazole)ruthenate(III)]; log, *P*partition coefficient coefficient; Mb, myoglobin; MS, mass spectrometry; MTD, maximum tolerated dose; NAMI-A, imidazolium trans-[tetrachlorido(1*H*-imidazole)(S-dimethylsulfoxide)ruthenate(III)]; NKP1339, sodium trans-[tetrachloridobis(1*H*-indazole)ruthenate(III)]; NMR, nuclear magnetic resonance; PTA, 1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane; RAED, [(η^6-arene)Ru(en)Cl]$^+$; RAPTA-C, (η^6-*p*-cymene)$RuCl_2$(PTA); thn, tetrahydrohaphthalene; TOF_{50}, turnover frequency after 50% conversion; Tf, transferrin; Ub, ubiquitin.

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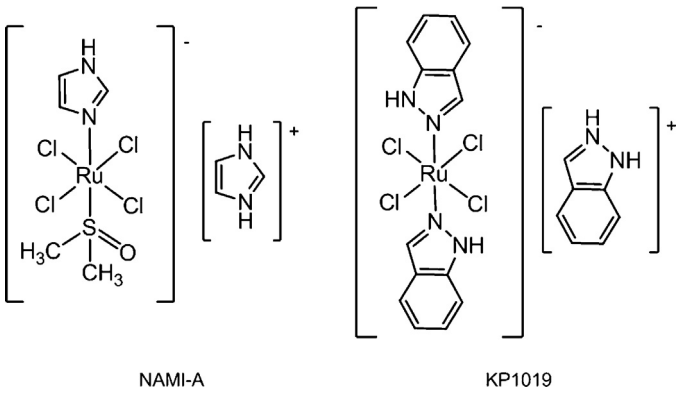

Fig. 1. Imidazolium and indazolium salts of ruthenium(III) complexes in clinical trials for cancer treatment [5,6].

kinetics, similar to those of platinum(II) complexes, which seems to be essential for anticancer activity. Moreover, ruthenium can accumulate in cancer cells better than platinum does [4]. This field has been pioneered by Alessio, Sava and Keppler, who developed ruthenium(III) imidazole and indazole complexes, the imidazolium or indazolium salts of which (termed NAMI-A and KP1019, see Fig. 1) went into clinical evaluation [5–7]. The sodium analog of KP-1019, termed NKP-1339, seems to be on the edge of clinical application [8]. Remarkably, the clinical studies revealed promising anticancer activity accompanied by only modest side-effects [8], which represent exactly the desired properties of an ideal anticancer drug. Despite the differences in their antitumor activities, a common feature of NAMI-A and NKP-1339 is that they are presumably activated by reduction to more active ruthenium(II) species in the low oxygen environment of solid tumors, according to the activation by reduction assumption [9].

More recently, the development of organometallic ruthenium (II)-arene compounds, stabilized in the +2 oxidation state by the η^6-coordinated arene ligand, have introduced a different metallodrug scaffold to that of the coordination compounds that have entered clinical studies so far. Arene ruthenium(II) complexes go back to the nineteen sixties: Winkhaus and Singer and subsequently Zelonka and Baird had obtained a precipitate by reacting ruthenium trichloride hydrate with 1,3-cyclohexadiene in dry ethanol with gentle warming (35 °C, 5 h), a solid which was isolated by decantation, washed with methanol and dried in high vacuum. The elemental analysis of this material suggested first the composition $[(\eta^6\text{-}C_6H_6)RuCl_2]$ [10], but turned out to be $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$ or $[(\eta^6\text{-}C_6H_6)Ru(\mu_2\text{-}Cl)Cl]_2$ (Fig. 2) on the basis of a detailed analysis of the infrared spectrum in 1972 [11,12].

Bennett and Smith subsequently synthesized a large number of derivatives $[(\eta^6\text{-arene})Ru(\mu_2\text{-}Cl)Cl]_2$ and $[(arene)RuCl_2(L)]$ [14] and showed the more soluble *p*-cymene derivative $[(\eta^6\text{-}p\text{-}MeC_6H_4Pr^i)Ru(\mu_2\text{-}Cl)Cl]_2$ to be dimeric in chloroform solution by osmometry [15]. While the molecular structures of various derivatives $[(\eta^6\text{-arene})Ru(\mu_2\text{-}Cl)Cl]_2$ (arene being hexamethylbenzene [16,17], indane [18,19], ethylbenzoate [20], 1,2,3,4-tetrahydronaphthalene [21], *o*-toluene methylcarboxylate [22], and *p*-cymene [23]) have been solved by X-ray structure analysis

Fig. 2. Synthesis of benzene ruthenium dichloride considered to be a polymer [10], until its dimeric nature, $[(\eta^6\text{-}C_6H_6)Ru(\mu_2\text{-}Cl)Cl]_2$, was established [11–14].

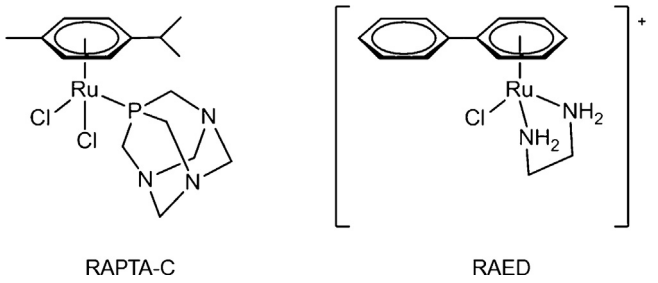

Fig. 3. Prototype anticancer arene ruthenium compounds reported by Dyson and by Sadler [26,27].

during the following years, the molecular structure of the parent benzene complex $[(\eta^6\text{-}C_6H_6)Ru(\mu_2\text{-}Cl)Cl]_2$ was only confirmed in 2005 by a single-crystal X-ray analysis of the chloroform disolvate [24]. The molecule has indeed the expected dimeric structure; the two halves of the molecule are related by a crystallographic inversion center. The Ru···Ru distance is 3.7099(8) Å, there is no metal-metal bond, in accordance with the electron count of 36 and the noble gas rule [24].

Tocher and co-workers observed in 1992 a cytotoxicity enhancement by coordinating the anticancer agent metronidazole [1-β-(hydroxyethyl)-2-methyl-5-nitro-imidazole] to a benzene ruthenium dichloro fragment [25]. Later on, it became obvious that water-soluble arene ruthenium complexes are in general cytotoxic, since they seem to have the right balance between lipophilicity and hydrophilicity, essential for cellular uptake. The field of antitumoural and antimetastatic arene ruthenium complexes was pioneered by Dyson and by Sadler [26,27]. Initially, the prototype arene ruthenium(II) complexes evaluated for anticancer properties in 2001 were $(\eta^6\text{-}p\text{-}MeC_6H_4Pr^i)Ru(P\text{-pta})Cl_2$ (pta = 1,3,5-triaza-7-phospha-tricyclo-[3.3.1.1]decane), termed RAPTA-C, from Dyson's laboratory [28] and the RAED family of compounds $[(\eta^6\text{-}C_6H_5Ph)Ru(N,N\text{-en})Cl]^+$ (en = 1,2-ethylenediamine) as hexafluorophosphate or chloride salt from Sadler's laboratory (Fig. 3) [29]. Although RAPTA-C exhibits only a low activity *in vitro*, it is very active *in vivo*, where it inhibits lung metastases in CBA mice. Therefore, RAPTA-C can be considered as an antimetastatic agent like NAMI-A [27,30]. RAED compounds are highly cytotoxic to a range of cancer cell lines [31], including cisplatin-resistant cell lines, and an *in vivo* study [32] established that RM175, $[(\eta^6\text{-}C_6H_5Ph)Ru(N,N\text{-en})Cl]PF_6$, is active against MCa mammary carcinoma and causes metastasis reduction. In addition to these two prototype compounds, numerous organometallic ruthenium(II) compounds have been prepared and their cytotoxicity to cancer cells examined [33–43].

This review focuses on the discovery of thiolato-bridged dinuclear arene ruthenium complexes and subsequently highlights developments in the field, including their syntheses, structures, and the recent strategies for the design of thiolato-bridged dinuclear arene ruthenium bioconjugates. Recent *in vitro* evaluations and a first *in vivo* evaluation show that thiolato-bridged dinuclear arene ruthenium complexes belong to the most promising ruthenium compounds to replace cisplatin in future cancer therapy.

2. Trithiolato complexes

After the synthesis of $[(\eta^6\text{-}C_6H_6)Ru(\mu_2\text{-}Cl)Cl]_2$ by Winkhaus and Singer in 1967 [10], the dimeric arene–ruthenium dichloride complexes $[(\eta^6\text{-arene})Ru(\mu_2\text{-}Cl)Cl]_2$ were found to react with thiols to give cationic trithiolato complexes of the type $[(\eta^6\text{-arene})_2Ru_2(\mu_2\text{-}SR)_3]^+$, the first examples being the hexamethylbenzene derivative $[(\eta^6\text{-}C_6Me_6)_2Ru_2(\mu_2\text{-}SPh)_3]^+$ reported by Rakowski DuBois and coworkers [44] and the *p*-cymene derivative