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ORGANOMETALLIC COMPOUNDS OF RUTHENIUM AND THEIR ANTI-CANCER PROPERTIES

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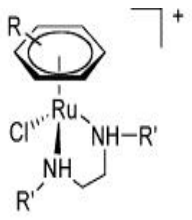
ABSTRACT
In this context, organometallic compounds, which are defined as metal complexes containing at least one direct, covalent metal−carbon bond, have recently been found to be promising anticancer drug candidates. Organometallics have a great structural variety (ranging from linear to octahedral and even beyond), have far more diverse stereochemistry than organic compounds (for an octahedral complex with six different ligands, 30 stereoisomers exist!) and by rational ligand design, provide control over key kinetic properties (such as hydrolysis rate of ligands). Furthermore, they are kinetically stable, usually uncharged, and relatively lipophilic and their metal atom is in a low oxidation state. Because of these fundamental differences compared to ―classical coordination metal complexes‖, organometallics offer ample opportunities in the design of novel classes of medicinal compounds, potentially with new metal-specific modes of action. Interestingly, all the typical classes of organometallics such as metallocenes, half-sandwich, carbene-, CO-, or π-ligands, which have been widely used for catalysis or biosensing purposes, have now also found application in medicinal chemistry.

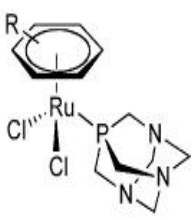
KEYWORDS: In this context, metallocenes, half-sandwich, carbene-, CO-, or π-ligands, biosensing purposes, chemistry.

INTRODUCTIONS
The idea of using ruthenium-containing organometallics as anticancer agents was first developed by Tochter et al.[1] before being intensively investigated in the Sadler and Dyson research groups. It was initially anticipated that the binding of *all* ruthenium compounds to DNA was the main reason for their anticancer effect, similar to the platinum derivatives; i.e., the coordination of the metal center to DNA causes structural modifications, which would ultimately lead to the induction of apoptosis. Indeed, the ability of ruthenium complexes to bind to DNA or model compounds has been amply demonstrated,[2] although it was found that the actual DNA binding of certain ruthenium compounds was weaker than or/and different from the one observed for platinum derivatives.[3-5] But recent studies for a series of ruthenium anticancer compounds revealed that DNA is not always the primary target and that these species were actually binding more strongly to proteins than to DNA.[7-9] These findings clearly indicated the occurrence of significantly different modes of action, depending on the type of ruthenium complexes. However, the exact mechanism by which these metallo drugs exert their effects has not (yet) been fully understood. Nonetheless, in this section, we will highlight recent developments on the elucidation of the mechanism of action of anticancer ruthenium half-sandwich organometallic compounds, as well as the exact role of the metal center. A non-exhaustive catalogue of ruthenium organometallic antitumor agents can be found in recent reviews or book chapters.[11-12] We will use structure comparisons to explicit the mechanism differences/analogies of these compounds.

At a first glance, the structural similarity of the half-sandwich "piano stool" type organometallics presented in Figure 1 might suggest an analoguous mechanism of cytotoxic action. However, to the best of our current knowledge, they appear to be much different.



Ru^{II} arene ethylenediamine derivatives

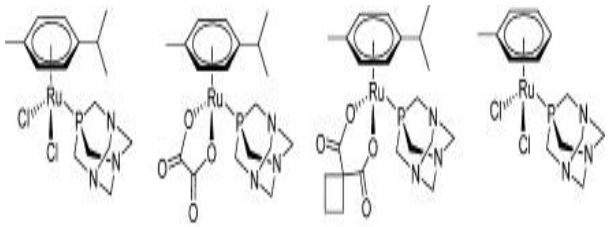


RAPTA Derivatives

Salder et al. established that the mechanism of action of their compounds $[(\eta^6\text{-arene})Ru(en)(Cl)]^+$ (en = ethylenediamine) (Figure (Figure7,7, left) has many of

analogies to that of cisplatin. It first involves hydrolysis of the Ru−Cl bond of the prodrug to generate an active $[(\eta^6\text{-arene})Ru(en)(H_2O)]^{2+}$ species. Detailed kinetic studies showed that the Ru−Cl bond hydrolysis can be strongly influenced by the nature of the coligands as well as the nature of the metal ion (see also the section Organometallic Osmium Half-Sandwich Complexes below).[121,122] Importantly, this step is suppressed in the blood because of the high chloride concentrations enabling $[(\eta^6\text{-arene})Ru(en)(Cl)]^{+}$ to cross the cell and nuclear membranes. Once inside the cell, the hydrolysis of the chloro anion takes place because of the much lower chloride concentration (~25 times lower). It is then assumed that the aqua complex $[(\eta^6\text{-arene})Ru(en)(H_2O)]^{2+}$ binds to nuclear DNA with a high affinity for the N7 position of guanine bases as shown by NMR and X-ray crystallographic studies and transcription mapping experiments.[13-17] It must be pointed out that the analogy in the mode of action between $[(\eta^6\text{-arene})Ru(en)(Cl)]^{+}$ and cisplatin stops at this point. Indeed, the Ru arene compounds can only form monofunctional adducts compared to cisplatin which is known to form bifunctional adducts and DNA cross-links. Importantly also, $[(\eta^6\text{-arene})Ru(en)(Cl)]^{+}$ derivatives were found to be active against cisplatin-resistant cell lines, indicating that the detoxification mechanism is different from the one of cisplatin.(124) However, in silico calculations undertaken by Deubel et al. to compare the difference in selectivity of cisplatin to organometallic ruthenium complexes toward biological targets show that organometallic ruthenium anticancer complexes are more similar to cisplatin than to inorganic Ru(II) complexes.[18-21]

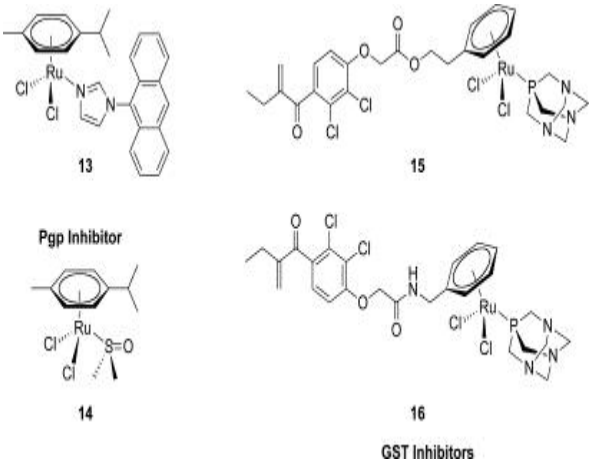
Ru-RAPTA derivatives were originally designed to improve the aqueous solubility (pta = 1,3,4-triaza-7-phosphatricyclo[3.3.1.1]decane, As for Ru(II) arene ethylenediamine compounds, RAPTA derivatives(22) containing two chloride ligands were also found to be susceptible to hydrolysis and it was first anticipated that DNA was a primary target.[23] Dyson et al. recently prepared RAPTA carboxylato derivatives (oxalo-RAPTA-C and carbo-RAPTA-C, Figure 2 This work was evidently inspired by the structures of carboplatin and oxaliplatin. In analogy to the Pt compounds, it was assumed that the carboxylato ligands would hydrolyze more slowly and in a more controllable way than the chloride ligands in the original RAPTA-C compound. These RAPTA derivatives have an in vitro activity similar to that of RAPTA-C. All evidence taken together, RAPTA compounds seem to operate by a different mode of action compared to cisplatin, Ru(II) arene ethylenediamine compounds and most of the known anticancer compounds in general. In vitro cytotoxicity studies showed that these compounds were much less cytotoxic than cisplatin. Indeed, many of the RAPTA compounds could not even be classified as cytotoxic and were also nontoxic to healthy cells. The extent of this nontoxicity was proven in an in vivo study when healthy mice were treated at quite high doses with RAPTA compounds without triggering toxic side effects[24] But the most striking result observed was that both RAPTA-C and RAPTA-T inhibited lung metastasis in CBA mice bearing the MCa mammary carcinoma (the number and weight of the metastases were reduced) while having only mild effects on the primary tumor. The only other metallo drug candidate displaying this outstanding behavior is imidazolium *trans*-[tetrachloro(dimethylsulfoxide)(1*H*-imidazole)ruthenate(III) (NAMI-A).[25-27] This discovery is of high practical interest, as the removal of the primary tumor by surgery is frequently an efficient procedure while the treatment options for metastases are quite limited.



Nonetheless, these very exciting findings engendered naturally a new and obvious question: If DNA is not the target for these RAPTA derivatives, then what is the target? The final answer has not yet been determined, but at this stage of the research, enzyme binding is the most probable explanation. It was shown by mass spectrometry that RAPTA compounds form adducts with proteins[28-30] and that the reactivity of RAPTA-C and cisplatin in the presence of proteins was much different.[31-33] To get more insight, Messori et al. studied the inhibition activity of a series of RAPTA compounds to two proteins, i.e., cathepsin B (Cat B) and thioredoxin reductase (TrxR), which are possible targets for anticancer metallodrugs.[34-38] They found that all tested Ru compounds were inhibitors of Cat B while none of them, with the exception of RAPTA-C, was inhibiting TrxR. Computer docking experiments validated this finding. Assuming that one of the two chloride ligands of the RAPTA derivatives was first replaced by a water molecule, it was then found that the Ru(II) center coordinates to the active site cysteine residue. Furthermore, other atoms of RAPTA (chloride, nitrogen of pta, etc.) bind other amino acids of Cat B, thereby stabilizing the metallodrug−enzyme complex Interestingly, a good correlation was observed between the inhibiting potency of the RAPTA derivatives and the calculated stability of the corresponding Cat B/RAPTA adducts.[39-41]

Other proteins have been proposed as the target for Ru organometallics. P-Glycoprotein (Pgp) is a plasma membrane protein that is responsible for drug efflux from cells and is involved in multidrug resistance

(MDR). Inhibitors of Pgp, namely, phenoxazine and anthracene derivatives, were synthetically modified and coordinated to Ru organometallics. The aim was to obtain a synergistic effect by combining the selectivity of ruthenium complexes toward cancer cells and the ability of the phenoxazine and anthracene derivatives for Pgp inhibition. These newly formed complexes were found to be, in general, more cytotoxic and inhibited to a lesser extent the Pgp protein than the original Pgp inhibitor derivatives used as ligands. Interestingly, for one of these ruthenium derivatives (Figure 3), it was shown that the ruthenium coordination to the Pgp inhibitor derivative induced an even stronger protein inhibition. Furthermore, because of the presence of the fluorescent anthracene group, it was observed that was accumulating in cell nuclei, suggesting a DNA synthesis inhibition as the mechanism of cytotoxic action. Nonetheless, because of the strong increase in cytotoxicity upon ruthenium coordination, Dyson et al. believe that their organometallic compound not only inhibits the enzyme but also induces cell death via a second mechanism, implying a bifunctionality of this compound.[42]



In a similar line of thought, namely, a dual cytotoxic mode of action, ethacrynic acid (EA) was coupled to two RAPTA derivatives as well as to other Ru arene organometallics EA is an effective glutathione transferase (GST) inhibitor, which has been investigated as a potential anticancer drug. EA is known to bind competitively to the hydrophobic cosubstrate (H-site) of GST, while the RAPTA compounds are recognized to react with soft nucleophilic centers such as thiol groups (see above). **15** and **16** compounds were therefore thought to be able to bind not only to the enzyme at the H-site but also to interact with the reactive cysteine residues of GST P1-1 (this GST protein possesses two solvent-accessible cysteine residues that affect catalytic activity when modified). As assumed, these two new compounds were found to bind the catalytic H-site in a similar fashion as EA. Furthermore, the inhibition constants K_i of the complexes on GST P1-1 were 3 or 4 times lower than EA. The authors therefore concluded that the ruthenium centers were also involved in the inhibition of GST P1-1. Interestingly, it was demonstrated by X-ray crystallography and by ESI-MS that **16** decomposed, over a period of time, into a ruthenium derivative and EA. It is anticipated that the cleavage occurs, by virtue of a possible allosteric effect or simply over time, when the EA moiety of **16** is bound to the H-site. Importantly, this (selective?) release of the ruthenium moiety should enhance the toxic effect of the compound on cancer cells, which had already been sensitized by the EA moiety that inactivated GST(This feature could be used to specifically deliver a cytotoxic payload for targeted chemotherapy.

CONCLUSIONS

In this Perspective, we summarized recent developments toward the use of organometallic compounds as anticancer drug candidates. The general notion that organometallic compounds would be sensitive to air and water and therefore unstable under physiological conditions and unsuitable for medicinal purposes has been disproved. Rather, our above analysis demonstrates a broad range of classes of compounds that are stable and well characterized for biological applications. Organometallic compounds are frequently kinetically inert and amenable to (multiple) derivatization reactions. They are thus suitable for conventional structure-based drug design, including computer docking experiments similar to those for the more traditional organic drug candidates. The successful development of ruthenium kinase inhibitors by Meggers and co-workers impressively demonstrates this capacity.

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