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Short Communication
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Ruthenium: The Platinum Substitute as the Best Cytotoxic Metal?

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Short Communication

For years, cancer has been known to be one of the most aggressive diseases in the current panorama, since it is one of the most frequent causes of death worldwide. If we try to find a theoretical definition of what this disease is, we should look at the one established by the World Health Organization (WHO), which enunciates the term cancer as "a group of related diseases in which, due to mutations in genetic information, a group of cells or tissues reproduce in an uncontrolled manner, even after the stimulus that leads to cell division has ceased" [1]. On the other hand, and with all the data that is currently known, it seems obvious that we should ask ourselves how this disease can be produced, because it can be caused by external carcinogens or by failures in DNA replication, which are never corrected. Furthermore, it can affect people of all ages and conditions indiscriminately, and its treatment is complicated; in some cases, it is impossible to cure some of the most aggressive types, or in more advanced states, despite the technological means we have today. That is why, as already mentioned, cancer is so high risk, because it does not discriminate and its appearance is, in popular jargon, practically random.

Nevertheless, if diagnosed in time, those patients suffering from this disease can be completely cured by undergoing different treatments which, nowadays, are quite painful and difficult to bear. And this is where we find the "kit of the question", since the study and development of new drugs that act as anti-tumor agents is one of the areas of greatest interest and importance in our society, and the aim, which is becoming more and more insistent, is to ensure that all possible treatments for this pathology are less and less invasive and harmful to the patient [1].

There are many metal complexes that are intended to act as anti-tumor drugs, and among all of them, some platinum complexes such as cis-platinum, carboplatinum and oxaliplatin (Figure 1), have been used as anti-cancer drugs [2] which, being very efficient, have undesirable side effects for the patients who undergo them.

Later, when the behavior of platinum as an anti-tumor agent became known, complexes with other metals with properties similar to those of platinum began to be studied in a similar way. Specifically, it was observed that some ruthenium compounds could act in a similar way.

Before continuing, it should be said that, in physiological conditions, ruthenium presents basically two oxidation states: Ruthenium (II) (d6, diamagnetic), and ruthenium (III) (d5, paramagnetic). Ruthenium (IV) complexes are also known, although the presence of acid, oxo, or Sulphur ligands is necessary for their stabilization. Ruthenium presents hexacoordination with octahedral geometry, while platinum (II) is always flat-squared. Similarly, Pt (II) and Ru (II) or Ru (III), show great affinity for nitrogen and Sulphur. Ruthenium (II) compounds are stable in air in the presence of acceptor ligands Π and give rise to an exchange of ligands through a dissociation mechanism similar to that which occurs in Pt (II) species. It is also a general fact that the Ru (II) complexes are less inert than those of Ru (III); the so-called "activation-reduction" hypothesis was initially proposed by Clarke, who was the first to investigate the antitumor capacity of some Ru (II) compounds [3,4]. Another fact sometimes used to explain the selectivity of ruthenium complexes against cancer cells is their low toxicity - similar to that of platinum compounds - So, as well as their ability to behave like iron in their binding to biological molecules such as transferrin and albumin.

Among all the ruthenium complexes synthesized so far, three different types with antitumor activity *in vivo* are especially remarkable, being these: Those containing the Ru (II)-DMSO fragment, the Ru (III) "Kepler type" compounds and the organometallic complexes containing the Ru (II)- sand unit [5,6]. The former are ruthenium (III) complexes containing nitrogen-dependent heterocyclic ligands with the general formula trans-[$RuCl_4L_2$]. Within this type of compounds,

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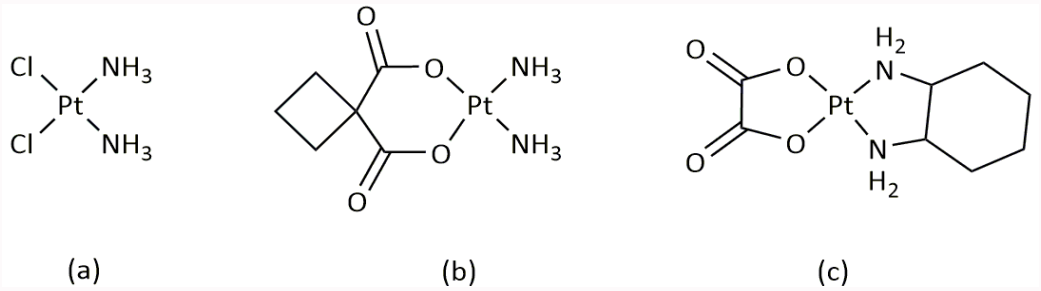

Figure 1: Molecular structures of (a) Cisplatin, (b) Carboplatin and (c) Oxaliplatin.

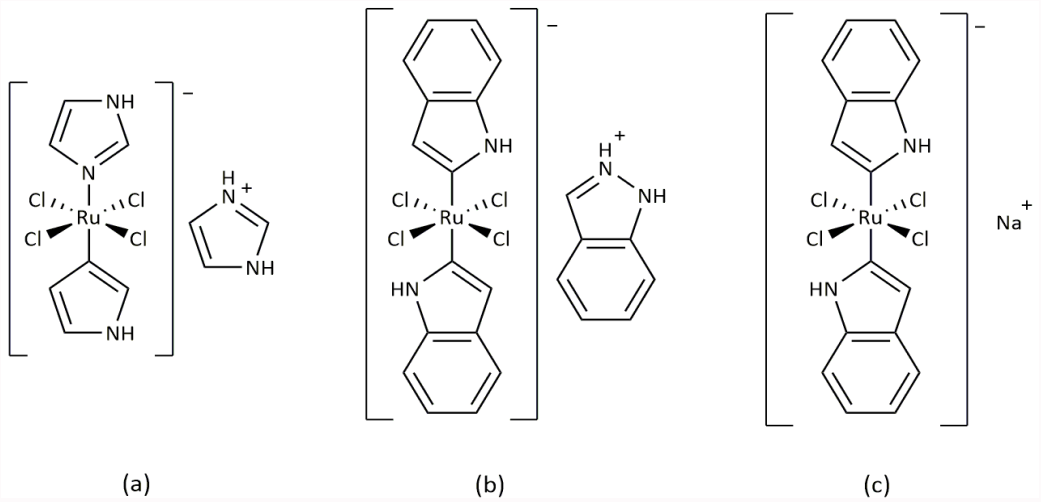

Figure 2: Ru (III) "Kepler type" structures with: (a) Imidazole, (b) Indazole and (c) Indazole with Na+.

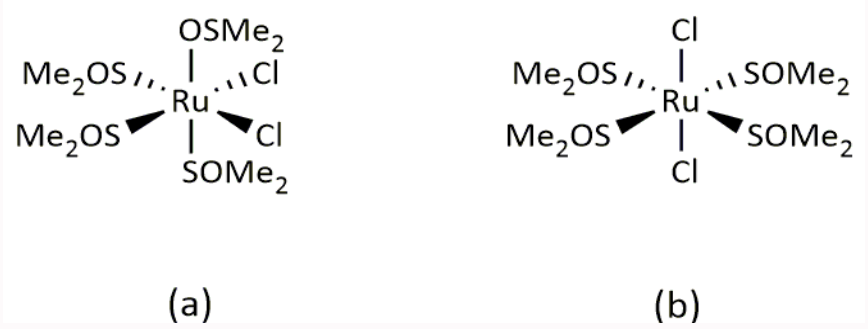

Figure 3: Structures of (a) Cis-[$RuCl_2(DMSO)_4$] and (b) Trans-[$RuCl_2(DMSO)_4$].

the most important are those that contain as ligand imidazole (a), indazole (b) or indazole with a sodium cation (c) (Figure 2). These were considered the most promising as antitumor agents after their discovery [2,7].

On the other hand, we find the ruthenium (II) complexes that have as binding agent the Dimethyl Sulfoxide (DMSO), with an interesting capacity of being able to coordinate to the central metal through oxygen or, through Sulphur. In this way, it is possible to speak of two different types of coordination, which will depend on electronic and steric factors. We highlight the cis-[$RuCl_2(DMSO)_4$] (a), which was quickly replaced by the trans-[$RuCl_2(DMSO)_4$] (b) (Figure 3), because the first one required too high concentrations to perform its anti-tumor capacity [8].

Finally, a wide group of ruthenium (II) compounds called "half-sandwich" has been described and they have a structure known as "piano tool": [η^6-(biphenyl)Ru(en)Cl] PF_6 [9-13] and [(η^6-p-cimene) $Ru(pta)Cl_2$] [14,15], which represent an interesting new class of complexes with anti-tumor activity (Figure 4). Moreover, recently, Ruiz et al. have described the synthesis of ruthenium (II) complexes containing p-cymene and ortho-metallic ligands of stoichiometry [(η^6-p-cymene) Ru(CN)X]0/+ (X=Cl, py or 4-NMe_2py), which contain a 2-ppy or 1-ppz cyclometallic with an uncoordinated -CHO group, which also present antitumor activity [16].

In 1994, Garcia and López, described the synthesis and characterization of ruthenium (II) complexes containing the fragment η^6-arene-Ru(II) (η^6-arene=benzene or p-cimene), and potentially bidentate ligands of stoichiometry [(η^6-p-cymene)

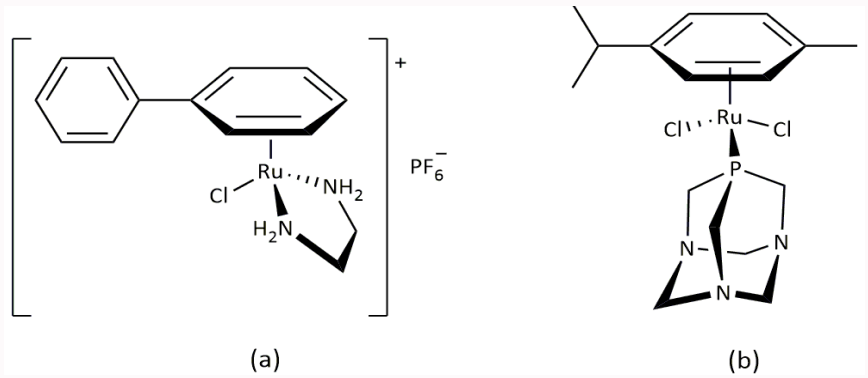

Figure 4: Complexes (a) $[\eta^6$-(bifenill)Ru(en)Cl$]PF_6$ and (b) $[(\eta^6$-p-cimene)Ru(pta)$Cl_2]$.

$RuCl_2L]$ (L=4-cyanopyridine (II) and 2-aminophenol (III)) and $[(\eta^6$-p-cimene)$RuClL_2]PF_6$ (L=4-cyanopyridine (IX)) [17]. At the same time, a similar work was done to obtain rhodium (III) compounds containing, in this case, the fragment Cp^*Rh ($Cp^*=C_5Me_5$) from the complex $[Cp^*RhCl(\mu\text{-}Cl)_2]_2$ [18]. Later, it has been demonstrated that the ruthenium (II) compound described in 1994, $[(\eta^6$-p-cymene) RuCl(o-phenylenediamine)$]PF_6$ [17], behaves as anti-tumor agent against different cancers [19,20].

Once the desired complexes have been synthesized and characterized, *in vitro* cytotoxicity tests have been performed, a topic of great relevance in recent years for ruthenium (II) compounds, which show reduced toxicity and have advantages over platinum complexes due to the different states of oxidation that they can have, the mechanism of action by which they take place and the different kinetics involved in the replacement of ligands. These advantages make ruthenium complexes suitable for biological applications. We have been able to see all this in several previous studies in which a series of organometallic complexes of sand-ruthenium (II) were developed, which exert antimetastatic activity with less activity in the growth of the primary tumor [21,22].

In recent years, another type of ruthenium compounds, with half- sandwich structure, obtained from the same precursor dimer that we use, $[Ru(p\text{-cimene})Cl(\mu\text{-}Cl)]_2$, have been evaluated against human tumor cells such as: Ovarian carcinoma A2780 and breast adenocarcinoma MCF7 and MDAMB231; and against normal primary fibroblasts, showing moderate cytotoxic activity [23]. In addition, the cytotoxic effects of some pyrazole-carbothioamide derivatives and their four sand-ruthenium complexes have been evaluated, using the MTT assay, against three cancer cell lines: HL-60, NALM-6, WM-115 and normal Human Foreskin Fibroblasts (HFF-1). The novel sand-ruthenium (II) compounds were found to inhibit cancer cell proliferation and protect patients against malignant wound infections due to their antimicrobial properties [24].

With this background, we considered to perform the synthesis of complexes similar to those previously described by us, which contain the fragment $Ru(\eta^6$-p-cimene), using the dimer $[Ru(\eta^6$-p-cimene)$Cl(\mu\text{-}Cl)l]_2$ as starting element [17], and different ligands to investigate the possible antitumor activity of these complexes. The compounds have been characterized by elemental analysis of C, H and N, infrared spectroscopy, proton nuclear magnetic resonance and high-resolution mass spectrometry and X-ray diffraction studies.

The cell lines chosen to evaluate the cytotoxic activity of the synthesized compounds are HeLa, MCF-7 and BGM cells, human carcinogens of cervical carcinoma and human breast cancer, and renal epithelial monkey cells, respectively. Cytotoxicity was determined by the 3 - (4, 5 - dimethylthiazole - 2 - yl) - 2, 5 - diphenyltetrazolium bromide assay (MTT). Thus, it is intended to know its potential anticarcinogenic activity and, in this way, to make a selection based on the data obtained from the complexes that present a greater efficacy against cancer cells that, in addition, are also little harmful to healthy cells and, therefore, to health [25,26]. The most outstanding characteristics of cytotoxicity tests are that they are profitable, both economically and in terms of time [27].

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