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Ru (II) Arene Complexes: Structural Characteristics for Anticancer Activity

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Abstract - There is a family of complexes defined by the generic formula, and the arene moiety is considered the most important component of this family. By controlling the concentration of electrons in the central atoms and keeping Ru in its 2+ oxidation state, it serves a crucial role in ensuring the complexes' stability. RuII drug transport across cell membrane and interactions with potential targets may be facilitated by hydrophobic faces offered by more prolonged coordinated arenes such as biphenyl or tetrahydroanthracene. Experiments have demonstrated that larger arenes in RuIIarene ***complexes have more cytotoxic action. In this paper review the structural characteristics for anticancer activity of ru (ii) arene complexes.***

Keywords - Ru(ii) arenecomplexes, drug, DNA binding, ligand.

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INTRODUCTION

The arene moiety is the most crucial part of the generic formula, which defines a family of complexes. Ru's presence in the 2+ oxidation state is essential to the stability of the complexes, and it plays this function by regulating the concentration of electrons in the core atoms. Hydrophobic faces provided by longer extended coordinated arenes, such as biphenyl or tetrahydroanthracene, may promote RuII drug trafficking through the cell membrane and contacts with potential targets. The cytotoxic activity of complexes containing bigger arenes has been experimentally established. The IC50 values for just a series of Ru(II) - arene- ethylenediamine(en) compounds were as follows, as determined by testing on the human ovarian cancer cell line A2780: benzene (17M) >para-cymene (10M) > biphenyl (5M) >dihydroanthracene (2M) >tetrahydroanthracene (0.5 M) (0.5 M). It is hypothesized that a-arene intercalation into DNA contributes to the increased cytotoxicity of these compounds and similar extended arene complexes. This happens because the arenes have -stacking interactions with DNA that are moderate to strong, severely altering its structure. This demonstrates that the effect of isomeric of the terphenyl ligand on cytotoxicity or DNA binding in Ru (II)compounds has been studied.

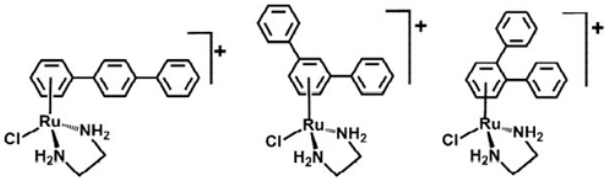


Figure 1: [(6-arene)Ru(en)Cl]+complex structure. Para-terphenyl, meta-terphenyl, and ortho-terphenyl are shown from left to right.

As one of the arene ligand, ara-terphenyl has been found to increase cytotoxicity in many cisplatin-resistant human cancer cell lines. While cytotoxic, meta- or ortho-terphenyl substances are much safer. Results also showed that the intercalative and belch - belch coordination DNA-binding method of a RuIIpara-terphenyl complex may be responsible for its particularly high cytotoxicity. It turns out that the ortho-terphenyl receptor forms a complex with DNA by a mechanism requiring just a single kind of coordination to a DNA base.

- **The monodentate ligands X and Y**

Creating Ru(II) arene complexes with bi - functional reactivity requires the synthesis of derivatives of the type [(6-arene)Ru(X)(Y)(Z)]n+. In the same vein as cisplatin, this strategy aims to enhance interactions with possible targets like DNA. Researchers have focused on the production and properties of the complex [(6-p-cym)Ru(NH3)2Cl]+. Despite sharing a chemical structure like cisplatin, the complex is far less cytotoxic, with an IC50 value that is almost

500 times higher under the same circumstances. Probably less action is seen since it is unstable in solutions. On the other hand, it was found that the cytotoxicity of $[(6\text{- p-cym})Ru(en)Cl]^{+}$is larger than a factor of one hundred greater than that of its structural isomer. These compounds have substitutions at one or more of the NH3 positions with sterically less demanding ligands including heterocyclic amines, pyridines, and phosphines. Compounds may be represented using the RAPTA notation.These compounds are soluble in water because a hydrophilic pta ligand surrounds the metal center and is preferentially protonated at low pH. Two-chloride-liganded RAPTA compounds were more vulnerable to hydrolysis in reduced environments.

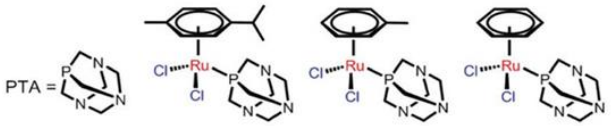


Figure 2: RAPTA complexes' structural. (RAPTA-C), (RAPTA-T), and (RAPTA-C) from left to right (RAPTA-B)

Both the $Ru(II)(pta)Cl2(RAPTA\text{-}C)$ & $Ru(II)(pta)Cl2(RAPTA\text{-}T)$complexes and CBA mice with MCa breast cancer demonstrated a reduction in lung metastases in vivo. RAPTA derivatives are still assumed to preferentially target host-cell DNA, as was previously believed. It has been hypothesised that RAPTA-Cis responsible for the maximum amount of DNA damage at a certain pH value, and this value mostly corresponds to the pH of cancerous cells. Recent research has shown that RAPTA-Tand auranofin have synergistic actions against cancer cells. While RAPTA complexes have been shown to quickly react with proteins and block enzymes like glutathione transaminase, there is little evidence that this activity translates to toxicity in cancer cells. Diverse hypotheses have been put up to explain how RAPTA derivatives destroy cancer cells.

- **A Cheating Ligand called XY**

The anticancer activity & aqueous solution durability of $[(6\text{-arene})Ru(X)(Y)(Z)]n+$complexes have been shown to be greatly improved by the substitution of bidentate XY cytotoxic groups for monodentate X and Y ligands. Complex activity is often improved by the addition of chelating ligands rather than monodentate ligands. Numerous structure-activity relationship (SAR) analyses have been performed to determine the effects of varying the centre atom of the XY cytotoxic ligand. The chelate ligand has been shown to slow down the binding rate to nitrogenous bases in DNA and, more importantly, alter the selectivity for these molecules. As far as I can tell, the tetradentate ligand's stabilising function is crucial for Ru(II)-arene complexes.

Sadler and coworkers have done substantial research on ruthenium arene compounds having N,N-chelating ligands, as well as $Ru(II)$ complexeswith N,O, O,O, S,O, C,N, or N,Schelating ligands. Neither large nor small alterations to the alkyne ring, an N,N-chelating ligand, or even the leaving group were found to significantly alter the compounds' chemical or biological activity. Improvements in hydrolysis of the leaving group (Z) were shown by switching from the cationic O,O-chelating ethylenediamine (en)ligand to the anionic O,O-chelating acetylacetonate (acac). The binding affinities or kinetics of chelate ligands to DNA nucleobases are related. Overall, it seems that acac prefers adenine nucleotides (A) over guanine bases (G) over en. This shows the significance of N-H groups in stabilising adducts with G bases through H-bonding, despite the likelihood of advantageous H-bonds between the oxygens in acac and the C6NH2 group of A bases. Plus, cisplatin is thought to recognise DNA via H-bonding. SAR analyses of RuIIarene compounds with N, N' cation - exchange ligands have also shown that species containing en exhibited higher cytotoxicity than TMEDA complexes. Researchers have hypothesised that the inertness of the TMEDA derivative is due to the steric effects of methyl groups and the absence of H-bonding. Substituting aromatic amines such 1, 2-diaminobenzene (dab) for en results in substantial cytotoxic action, with IC50 values for different RuII complexes ranging from 7 to 32 M. Furthermore, 2,2'-bipyridine (bpy) compounds have been found to be less cytotoxic towards A2780 than some other non-amine N,N'-chelating ligands.

It has been shown that ruthenium (II) arene complexesmay condense with a wide range of diamine moiety types. Other strategies include incorporating ruthenium scaffolds with together the like paullones or staurosporine.

Due to the recent synthesis of organoruthenium structures with 1,10-phenantroline-derived complexation aromatic ligands, researchers have been able to investigate the structure-activity relationship and gain insight into how the slight structural differences between the four Ru(II)complexes lead to significant differences in biological activity. The IC50values show that the biological activity of complexes containing the dppz ligand was not considerably altered by making small alterations to the ligand, such as by adding a substantially particle -NO2 or even a moderately particle -Cl substituent.

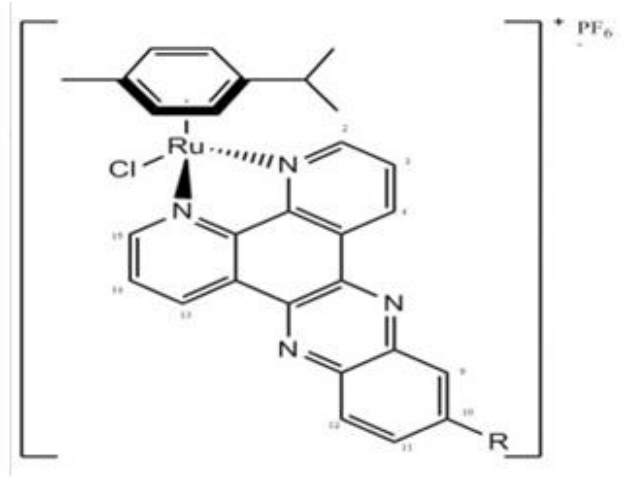


Figure 3: Substitutes for 1,10-phenantroline in ruthenium (II) cymene complexes

When the arene Ru(II) complex [(p- cym)Ru(bpm)(py)][PF6]is exposed to visible light, the monodentate ligand (py) may undergo selective photodissociation. The photoactivity and structure of Ru(II) pyridineor pyridinium complexes with N were also investigated. Research shows that adding more electron-donating substituents to the 4-position of the py ring only marginally boosts the rate of photo - induced hydrolysis, but adding more to the arene ring increases the extent or pace of photoinduced hydrolysis. Photoinduced hydrolysis of N, N-cytotoxic ligands was not slowed by aromaticity, however the amount of hydrolysis was reduced.

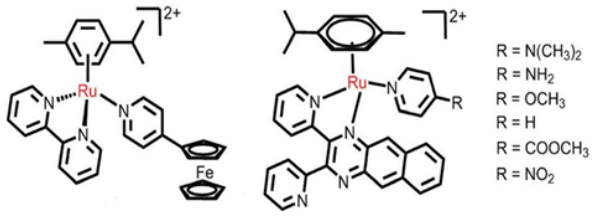


Figure 4: The highly photoactive N, N-ligand areneRu(II) compounds

Several areneRu(II) complexes with 1,2,3,4- tetrahydroisoquinoline amino alcoholligands were tested for anticancer efficacy . using human MCF-7, A549, or MDAMB-231 cancer cell lines. Among the N, O-Chelating ligands examined are tetrahydroisoquinoline& a few other amino acids; O, O-ligands include the more common -diketonate and pyrone.

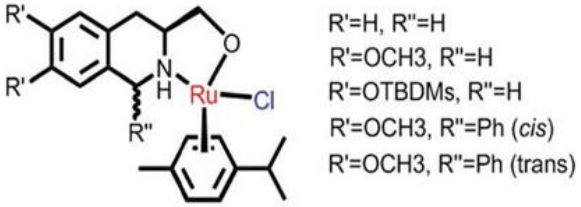


Figure 5: Ru(II) arene complexes with N,O-chelating ligands: structural formula

There is evidence that thiopyrones (S, O) are more lipid-friendly than pyrones. Thiopyrone complexes have been demonstrated to be more successful than pyrone molecules in reducing the growth of cancer cell lines, including SW480 from colon cancer or CH1 from ovarian cancer, in in vitro tests. Donor atoms have been demonstrated to affect in vitro anticancer properties, with DFT simulations indicating a higher affinity for ruthenium in thiopyrones compared to pyrones.

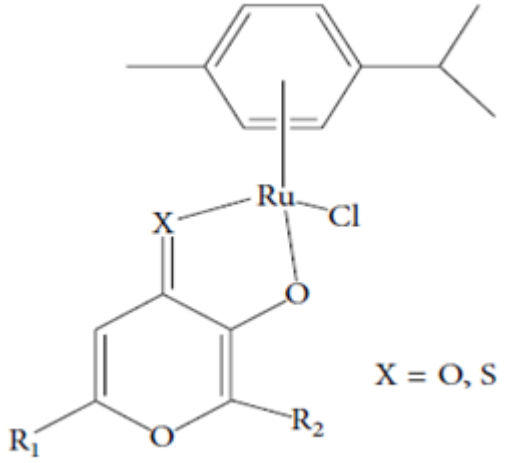


Figure 6: Synthesis and characterization ofrethenium(ii)-cymene complexeswithpyrone and thiopyrone.

The results demonstrated that the conjugate's porphyrin component was unaffected by either white or red light. Tests in living organisms show that the compound is both an efficient photosensitizer and an anticancer drug, blocking the development of cancer cells even in the dark as well as at relatively low doses and incubation durations.

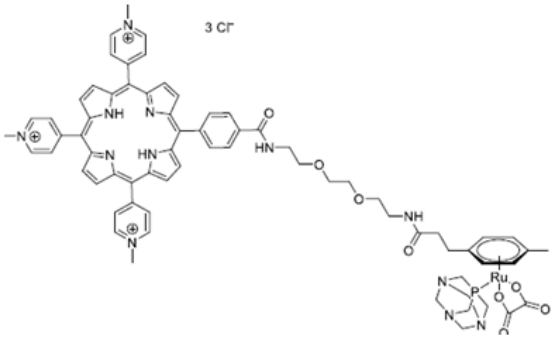


Figure **7: RAPTA-Porphyrin Conjugate, a Cationic Conjugate**

Different Ru (II) iminophosphoranecompounds were created by Frik et al. that are soluble in water. Studies on a variety of cancer cell lines showed that the complexes were more lethal than cisplatin. Better anticancer effects than cisplatin have been shown using areneRu (II) complexes using C, N-cyclometalated ligands. Many different C, N-cyclometalated areneRu (II) compounds were synthesised by Yellol and colleagues, and they were proven to be effective in killing HT29, T47D, A2780, and A2780cisRcancer cell lines. Then, Yellol et al. investigated how changing the substituent on the phenyl ring's C-4 position in the 2-phenylbenzimidazolecationic ligand affected the complexes' anticancer efficacy.

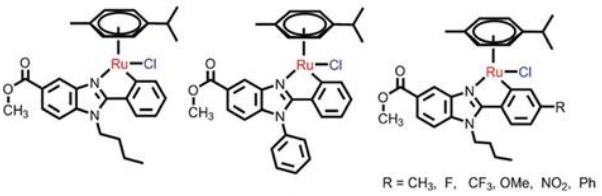


Figure 8: Complexes of ruthenium(II) that are cyclo(2,4)nitride(6,p-cymene)

A Ru(II)-benzene complex with a pyrrolidine moiety showed the lowest IC50 values among the drugs evaluated against the cancer cells. The generated Ru(II)-arene complexeswere further probed for their interaction with DNA/HSA using absorption and emission spectroscopy methods. Through a process called intercalation, the complexes strongly bind to DNA.

- **The People Leaving in Z**

As the removal of the leaving group (Z), often a halide ion, from the metal centre activates Ru(II)arene complexes, this site becomes available for coordination by potential biomolecules. Based on preliminary investigations, it seems that switching out the chloride leaving group for another halide, such iodide, has a little effect on cytotoxicity. The rate of Ru-Z bond hydrolysis may be affected by either the pH of the surrounding media or the amount of Z. AreneRu(II) complexes' anticancer efficacy may be affected by the chelating ligand's water solubility or the size of the leaving group. A thiophenolate leaving group, rather than a halide, was found to be an exception to the norm. This compound is efficient against A2780 human ovary cancer cells and is resistant to hydrolysis. Many monodentate ligands (Cl, CH3OH, pta) and a 4-(biphenyl-4-carbonyl)-3- methyl-1-phenyl-5-pyrazolonate ligand were included in an analysis of the anticancer effects of areneRu(II)complexes. There was a clear hierarchy in the DNA-binding affinities of the Ru(II)complexes, with the pta analogues being the most potent followed by the CH3OH counterparts and then the chloride analogues.

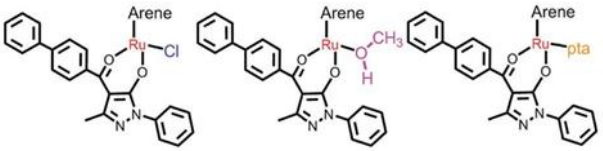


Figure 9: Several monodentate ligand complexes of the Ru(II) arene

In this work, we provide the isolation and characterisation of two new water-soluble Ru(II)arene complexes of the half-sandwich type. P-cymenecomplexes have enhanced DNA ligand binding because of hydrophobic interactions between both the DNA and the methyl or isopropyl groups of a arene ligand. In the conformational transition, the p-cymene complex binds to DNA and is stabilized by hydrogen bond interactions, as established by DNA docking experiments. Similar to the benzene compound, the P-cymenecomplex showed increased binding affinity to BSA inside the hydrophobic region. Researchers have shown that this compound is able to destroy human breast, lung, or ovarian cancer cells while having no impact on healthy kidney cells. Important players in cancer biology, guanine-rich quadruplex nucleic have only lately been recognised as a potential target for micro-sized treatments.According to the citations, Hager et al. Using 1,3-dioxoindan-2-carboxamidesas ligands with pendant naphthyl groups, the scientists have synthesised four distinct Ru(II) arene complexes that bind quadruplexes through complex formation and coordination. In vivo studies have shown that switching out the chlorido leaving ligand for pyridine increases cytotoxicity against ovarian cancer cells, improves hydrolytic stability, and modifies interaction with quadruplexes. As of late, it has been shown that phosphine ligands may be incorporated into ruthenium complexes (II). Multiple types of cancer, including colon, breast, or lung tumours, have been proven to be vulnerable to their antiproliferative effects. Two of the Ru(II) complexes had IC50 values below 2 mM. The kind of arene molecule coupled to a ruthenium core was shown to considerably affect the complexes' cytotoxicity.

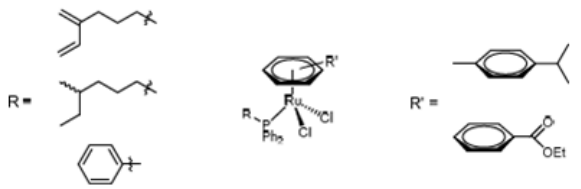
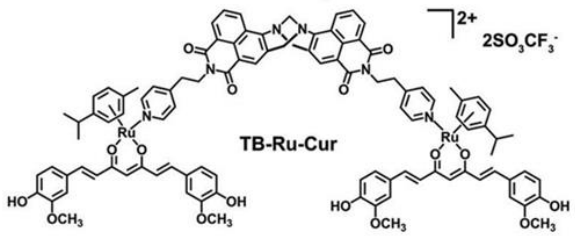


Figure 10: The analyzed structures of Ru(II)-based complexes

Tröger's base-Ru(II)-curcuminis a new luminous organometallic conjugate that has been shown to exhibit antiproliferativeeffect . As hypothesised, TB-Ru-anticancer Cur's efficacy was bolstered by the conjugation's cationic nature and the joining of 2 anticancer active structures . Compared to its predecessors, TBRuCurlocalised within cells faster and exhibited higher antiproliferative effect.



Figrue 11: The TB-Ru-Cur Structure

CONCLUSION

Literature review reveals that ruthenium medications, unlike platinum (II) compounds, show promising antitumor efficacy in in in vitro and in vivo studies while exhibiting low systemic toxicity. The coordination structure and ligand combination between ruthenium and its ligands govern ruthenium compound reactivity, hydrophobicity, adhesion, intracellular absorption, and intracellular distribution. Selectivity and targeting abilities have been shown in some Ru (II) compounds, making them more powerful against cancer cells while minimising their toxicity to healthy cells. The activity of these chemicals is quite different from that of conventional chemotherapies.

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