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Ruthenium Based Anticancer Compounds and Their Importance

Rahul Kanaoujiya[*1], Mukta Singh[1], Jyoti Singh[1], and Shekhar Srivastava[1]

[1]Department of Chemistry, University of Allahabad, Prayagraj-211002, India
kanaoujiyarahul@gmail.com

Abstract:**Ruthenium has numerous properties, while platinum-based compounds , have served as very successful anti-cancer drugs, they have several limitations including their side effects as well as ineffectiveness against certain types of cancer. Though most ruthenium complexes are only in the beginning stages of the approval process for anti-cancer drugs, many of their properties may give them advantages over many platinum-based drugs now in use. Herein, the recent literature is reviewed critically to ascertain likely mechanisms of action of Ru-based anticancer drugs, with the emphasis on their reactions with biological media. This diversity of modes of action of Ru anticancer drugs is also likely to enhance their anticancer activities and to reduce the potential for them to develop tumour resistance. Ruthenium have several chemical properties, these chemical properties are very useful for anticancer drug design. Ruthenium compounds have various type of advantages as metallodrugs because of lower toxicity emerging as a new and different therapeutic alternatives to platinum drugs. Ruthenium has unique properties which make it particularly useful in drug design. In this overall review we discuss ruthenium from a clinical stance and anticancer drug design uses of ruthenium-based compounds.**

Index Terms:**Anticancer activity, KP1019, NAMI-A, NKP-1339, RAPTA-T.**

I. INTRODUCTION

After clinical success of platinum anticancer agents, complexes of other metals such as gallium, gold, titanium, iron, rhodium and ruthenium have been considered for the development of metal-based cancer chemotherapeutics[1]. Ruthenium anti-cancer drugs are coordination complexes of ruthenium complexes that have anticancer properties. They promise to provide alternatives to platinum-based drugs for anticancer therapy. No ruthenium anti-cancer drug has been commercialized. Since 1979, when Cisplatin entered clinical trials, there has been continuing interest in alternative metal-based drugs. The leading ruthenium-based candidates are NAMI-A and KP1019. The first one to enter was NAMI-A. More ruthenium drugs are still under development. Ruthenium complexes as anticancer drugs are almost always designed to mimic platinum drugs, for targeting DNA. Due to a rapid increase in cancer cases worldwide, there is an indispensable need for the development and screening of potential anticancer agents. In this regard, metal complexes hold potential as novel anticancer agents against a wide majority of cancer types. Cisplatin or cis-diamminedichloroplatinum(II) is the most widely known metal-based anticancer drug. Cisplatin has been shown to have efficacy against lung, head, ovarian, neck, and esophageal cancers. Although cisplatin and its derivatives are efficacious against the vast majority of cancers, they also produce non-cancer cell toxicity, thereby causing severe adverse effects, including peripheral neuropathy, hair loss and myelotoxicity in patients. The resistance of tumors to platinum decreases the efficacy of platinum-based or even renders them ineffective, causing treatment failure. In the design of new anticancer drugs, the ruthenium complexes have raised great interest and have been tested against a number of cancer cell lines, and are regarded as promising candidates for alternative drugs to cisplatin and its derivatives.

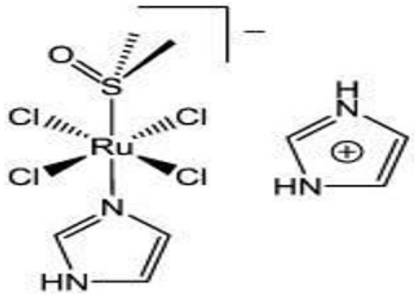
Ruthenium has a specific chemical properties which make it an ideal choice over than other metals for design of therapeutic agents.[2,3] Among the transition metal complexes studied so for the anticancer activity, ruthenium based complexes are most promising. The Ru(III) complexes NAMI-A and Cis-[Rucl4(Indazole)2] or KP1019/NKP-1339 were developed to clinical trials.[4,5]Like all metal drugs, the activity of the ruthenium based compounds depends on both the oxidation state and the ligands. These features are manipulating ruthenium centered are anticancerous drugs have been made metal complexes remain an important resource for the generation of chemical diversity in the search for novel therapeutic and

diagnostic agents, especially in the area of anticancer drug development.[6] Ruthenium compounds have several types of advantages as metalldrugs because of lower toxicity emerging a new anticancerous drug have been made. This is in part due to the ability of ruthenium to mimic the binding of iron to biomolecules, exploting the mechanisms that the body has evolved for nontoxic transport of iron.

In spite of their structural similarity in these Ru(III) derivatives exhibit markedly different anticancer effects.[7,8] NAMI-A shows a remarkable and selective activity against cancer.

Metastases [9,10]mostly of solid lung tumours, but it not effective in the reduction of primary cancers. KP1010 is highly active against colorectal cancer cell lines both in vivo and vitro is shown in biological tests.[11,12] KP1019 is more readily taken by cancer cells than NAMI-A and is more stable toward hydrolysis.[13] Cisplatin platinum based drug, It is analogues.

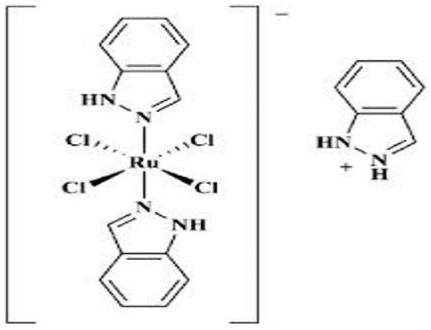
Carboplatin and oxaliplatin, are by the worldwide drugs being 50-70% of chemotherapy use for treatment of lung, bladder , testicular, ovarian cancers among others.Search for alternative metal –based anticancer agents with enhanced the efficiency, higher selectivity , reduced the toxicity especially against cancer resistant to platinum drugs.[14,15]



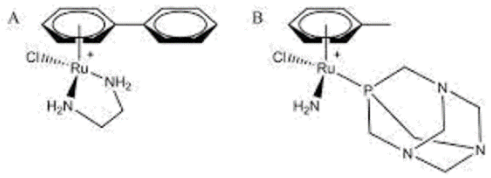
NAMI-A

In addition both of these RuIII complexes readily react with biological reductants, suggesting that the in situ reduction of RuIII to RuII species may be relevant for their biological activity, producing a more reactive from able to interact with protein and or to bind Nucleic acid.[16-19]

In the field of Research, ruthenium complexes used for cancer therapy has been quite and has been the subject of many reviews.[20-21] The Stabilizing scaffolds are relatively inert toward displacement under physiological conditions. The scope providing optimizing the design of anticancer complexes.[22,23-24]



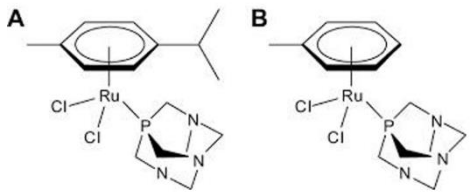
Cis-[Rucl4(Indazole)2] or KP1019



RM175(X=PF6)

ONCO4417(X=Cl)

The complexes with the "Ru(n6- arene)" scaffold are weakly cytotoxic against tumor cells are usually low toxicity or free of toxicity towards healthy cells, Importantly antimatastatic. Activity was reported in particular for [(n6-biphenyl)]-Ru(ethylenediamine) Cl]X (X=PF6- in RM175;X=Cl- ONCO 4417.[25]This is particularly true for NAMI-A and NAMI-A type complexes that share the capacity to modify important parameters of metastasis such as tumor invasion, and cell cycle progression.[26]



RAPTA-C (R_1=H,R_2=Me)

RAPTA-T(R_1=Me,R_2=i-Pr)

Ruthenium based compounds to shows anticancer activity

The Water-soluble RAPTA-C ([Ru(n6-p-cymene) (pta) Cl2] and RAPTA-T ([Ru(n6-p-toluene) (Pta)cl2] were found to exhibit antimetastatic properties in vivo.

The both type of activity has been shown in vitro and in vivo by these compounds supports hypothesis that numerous targets are involved in their mode of action, and the overall activity is the result of several extracellular and intracellular interactions.[27]

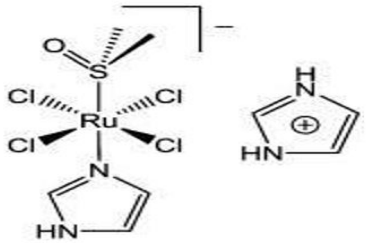
II. RUTHENIUM(III) COMPOUNDS

All the three ruthenium complexes that have been studied for clinical trials such as NAMI-A, KP1019, NKP-1339), are ruthenium (III) based drug development with an octahedral

geometry. While KP1019 and NKP-1339 are based on the same complex anion and though may be not exactly bioequivalent they most likely share the same purporte mechanism of action [28]involving interference with cellular responses to endoplasmic reticulam (ER) stress and with histone related processes.

A. NAMI-A

Among the valuable considerations for producing complexes with dimethyl sulfoxide (DMSO) ligand is a very high capacity for permeating membranes and very strong trans effect inducedby coordination through sulfur.



NAMI-A(a)

NAMI-A Is the favorable chemical properties including higher stability in the solid state with the toxicological properties are similar and least equal or equivalent efficiency in case of vivo.[29]

1) NAMI MODE OF ACTION

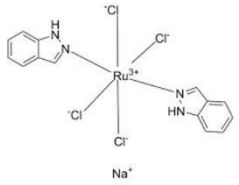
NAMI-A even seems to exert selection effects on a genomically heterogeneous tumor cell population(M Ca cells) , cell fraction are reduced with high ploidy, which suggests elimination of cell clones with high metastatic potential.[30]The affinity of ruthenium for nitric oxide , experimental evidence suggests that the antiangiogenic effects are caused by interference with no signaling.[31] Under the condition is like psysiological, NAMI-A seems to promote extravasation of peripheral blood lymphocytes and production of nitric oxide by tumor –infiltrating lymphoscytes[32-33].NAMI-A, in contrast to many classic anticancer drugs that are cytotoxic to immune cells , may be capable of activating tumor-suppressing properties in immune cells.[34] Sensitivity toward KP1019 treatment does not correlate with intracellular drug accumulation[35-36] cancer cells.[37-38] The studies of several views concerning the impact of KP1019/NKP-1339 DNAdamage might be secondary to massive redox disturbance.The ability of KP1019/NKP-1339 to bind proteins also offer new applications as has been recently demonstated by the modulation of a β-peptide aggregation in Alzheimer's diseasess.[39] In addition to its cytotoxic activity in malignant cells, KP1019/1339mightinterfare with the tumor-stroma interaction or compounds of the microenvironment.

B. KP1019/NKP-1339

The class of tetrachloride bisazoleruthenate(III) complexs, KP1019 was originally selected for clinical development because of efficancy in preclinical colorectal carcinoma models, but these development are replaced by the analogue of NKP-1339 (KP1339,IT-139), only differ by counter ion because of the higher solubility of the letter. NKP-1339 the pharmacological profile are distinctly different from known anticancer drugs.

1) KP1019/NKP-1339 MODE OF ACTION

There are several type of characteristics features of KP1019/NKP-1339 make the mode of action of these ruthenium compounds are challenging. KP1019/NKP -1339 is accumulated with in the malignant tissue due to the EPReffect, regulating the anticancer activity. Uptake of the drug from interstitium into tumor cells, chemical reduction and interaction with specific intracellular targets. For anexample, KP1019 was reduce the migration and invasion of mammary carcinsoma cells. [40]

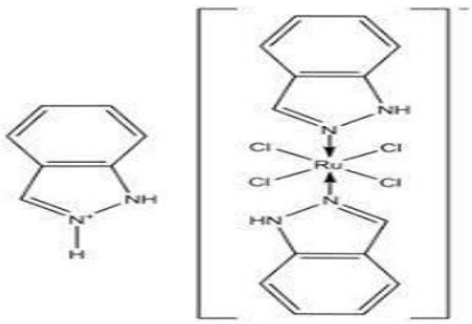


NKP-1339(c)

The Structural formulas of Ruthenium(III) Complexes NAMI-A (a) KP1019(b)and NKP-1339(C)

CONCLUSION

Cisplatin are the only metallodrugs these are platinum based anticancer drugs worldwide clinical use for cancer therapy regardless of their severe side effects. Ruthenium compounds have various type of advantages as metallodrugs, because of their lower toxicity and provide ability to overcome resistance. Platinum drug are mainly target in DNA, although more recent developments have identified other targets. This diversity of modes of action of Ru anticancer drugs is also likely to enhance their anticancer activities and to reduce the potential for them to develop tumour resistance. Ruthenium have several chemical properties, these chemical properties are very useful for anticancer drug design. Ruthenium compounds have various type of advantages as metallodrugs because of lower toxicity emerging as a new and different therapeutic alternatives to platinum drugs. The evidence from above literature it is proved that ruthenium compounds are anticancerous compounds but still more research works should be done in future specially in the compunds of ruthenium.



KP1019(b)

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