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A REVIEW ON THERAPEUTIC APPLICATION OF RUTHENIUM COMPLEXES

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***Abstract*:** To create a comprehensive treatment for cancer, the compound of cis-platin, a platinum compound, is particularly effective against malignancies and need to evolve a drug with minimum side effects. They have harmful effects on normal cells. As a result, the potential for additional components to act as anti-cancer agents was widely examined. Metal complexes such as Ru and Au demonstrated anti-cancer activity. Ru-complexes, in particular, were far more effective against cancer cells and had less adverse effects. Several Ru complexes, including Ru-Hydrazone complexes, Ru-Arene complexes, and Organo-Ru complexes, have been discovered to be highly effective against cancer cell development. NAMI-A (Trans-[RuCl4(DMSO)(Im)) and (KP1019)21 Indazolium trans-[tetrachlorobis(1H-indazole) ruthenate(III)] are two significant Ru complexes that have entered clinical trials, showing good tumour inhibition and minimal damage to normal cells. This is a brief overview of the various forms of Ru- complexes that operate as anticancer agents.

Key words: Ru complexes - Ru-Hydrazone complexes - anticancer agents – Metal complexes - chemotherapeutic medicines.

I. INTRODUCTION

INTRODUCTION

Metal-based compounds were frequently employed in the past to treat many medical problems, but it was very difficult to distinguish between the therapeutic and lethal levels. A major breakthrough in the field was made with Barnett Rosenberg's discovery of cisplatin in 1960 for the treatment of Cancer[1]. Not only for the treatment of cancer but metal complexes could also be employed as HIV and TB chemotherapeutics[2]. Metal complexes can have unique characteristics and employ different ways of actions[3].The use of metal ions in biological systems for either therapeutic or diagnostic purposes is included in the field of medicinal inorganic chemistry, but it is not restricted to these objectives. An important property of metals is that they form positively charged ions in an aqueous solution that can bind to negatively charged biological molecules. Thus, the charge can be fine-tuned depending on the coordination environment involved[4].

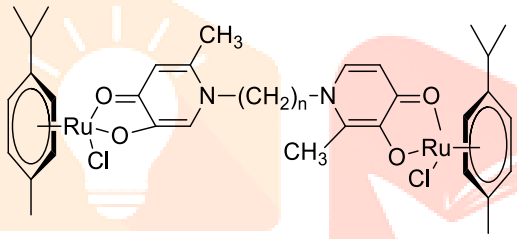
Current cancer chemotherapy has greatly benefited from the development of metal complexes with platinum center atoms, such as cisplatin and carboplatin. However, the range of malignancies that can be treated with platinum drugs is constrained and the efficacy of the treatment is hindered by side effects and resistance concerns. These dilemmas with platinum-based cancer treatment have spurred an increase in research toward novel non-platinum metal species as cytostatic agents[5]. Due to their potent inhibition of tumorigenesis, numerous gold (III) and ruthenium (III) complexes have drawn particular attention among the non-platinum antitumor drugs[6].Anticancer medications based on ruthenium have shown to be cytotoxic against a variety of cancer cells with few adverse effects on normal cells. Additionally, ruthenium can cause cancer cells to undergo apoptosis by using its strong nucleotide coordination affinity. Trans-[RuCl4(DMSO)(Im)](ImH) (ImH = protonated imidazole) (NAMI-A) for example, is a prominent contender for ruthenium chemotherapeutic medicines, are Pro-drugs that are activated upon hydrolysis[7].However, the majority of Ru complexes under investigation inanticancerresearch, function at least partially through ligand exchange to suppress cancer cell proliferation. In recent years, polypyridyl Ru(II) compounds that are

coordinatively saturated and substitutionally inert have become prospects for anticancer medications. Imidazolium trans-[tetrachloro- (dimethylsulfoxide)-(1H-imidazole)-ruthenate(III) (NAMIA) and Indazolium trans-[tetrachlorobis(1H-indazole)-ruthenate(III)] (KP1019)21 being two Ru(III) possibilities that haveeven entered clinical trials . Despite sharing a similar molecular makeup, the two Ru complexes function in distinct cytotoxic ways[8].

Scheme: 1

Chloro-ammine complexes were the first ruthenium compounds investigated for cancer action[9].There are two potential ruthenium-based families: Ru(III)-indazole/imidazole and Ru(II)-arene, both of which have exhibited antitumor efficacy while exhibiting low toxicity. The [RuCl2(arene)(PTA)] (RAPTA) class of complexes, which comprise a Ru(II) centre, a selected arene ligand, and the phosphine ligand 1,3,5-triaza-7-phosphaadamantane, is the second set of anti-cancer therapies (PTA)[10].Several Ru(II) arene complexes with the 1,3,5-triaza-7-phosphaadamantane ligand, dubbed RAPTA complexes, have been explored for their anticancer activity. They, like the NAMI-A complex, are ineffective against primary tumors but are beneficial against tumor metastases[11]. Zelonka et al reported the first stable monomeric benzene-Ru complexes in 1972, and the development of anticancer arene-Ru complexes was triggered by Tocher et al's(1992) observation that the cytotoxicity of metronidazole, an antibiotic agent, increased when coordinating with a benzene-Ru dichloro complex[12].

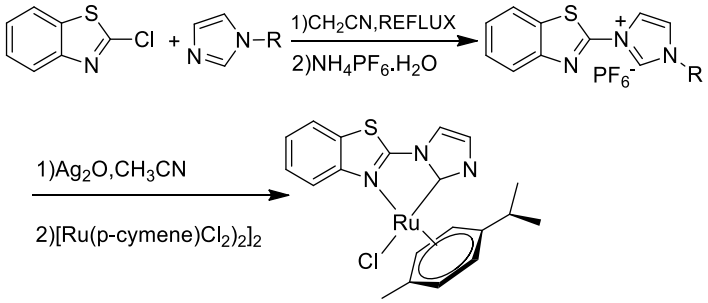
The majority of cytotoxicity investigations using arene ruthenium compounds have focused on mononuclear complexes. Complexes of dinuclear arene and ruthenium (pi PrC6H4Me),The pyridone-derived linker Ru(O,OC6H5O2N(CH2)nNC6H5O2-O,O)Ru(piPrC6H4Me) described by Hartinger hasmeaningful cytotoxic effects against human ovarian (A2780) and colon (SW480) cancer cell lines[13].



Cytotoxic dinuclear arene ruthenium Complexs.

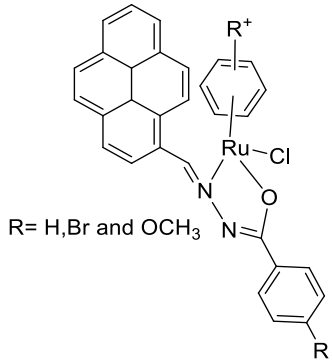
Ruthenium Hydrazone Complex in Anti-Cancer Treatments, Uncoordinated phenolic oxygen in Ru(III) hydrazone complexes was proposed as a better therapeutic candidate than Ru(II) complexes with the same ligands. Recent research has demonstrated that Ru(III) complexes suppress tumor cell proliferation by triggering apoptosis, which is defined as genetically determined programmed cell death and is essential for normal tissue homeostasis[14].

Scheme: 2 In the ongoing investigation of Ru(II) arene complexes, novel Ru(II) arene complexes coordinated with N-heterocyclic carbene (NHC) ligands were generated and their potency as metallodrugs against cancer cells was explored. A small panel of benzothiazole-functionalized NHC-Ru(II) arene complexes (Ru1-Ru6) with varying substituentswere synthesized in this study. In vitro cytotoxicity experiments revealed that Ru4 with n-octyl and Ru6 with pentamethylbenzyl had the highest potent cytotoxicity. Ru4 and Ru6 were less harmful in animals than clinically used cisplatin at the same doses[15].



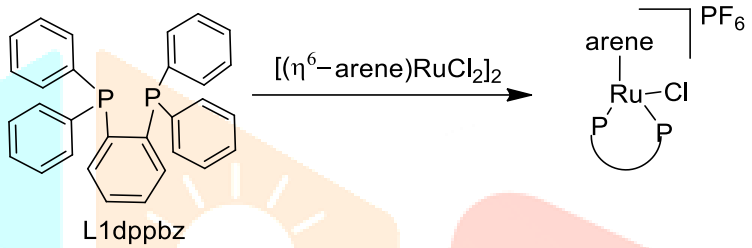
Synthetic cheme for benzothiazole functionalized N-hetrocyclic carbene ligands and the corresponding Ru-NHC complex (Ru1-Ru6)

Scheme: 3 Ru(II)-arene compounds have recently gained popularity as potential anticancer drugs. The development of arene-ruthenium complexes as prospective anticancer medications due to the amphiphilic features of the arene ruthenium unit provided by the combination of the hydrophobic arene ligand and the hydrophilic metal center[16].



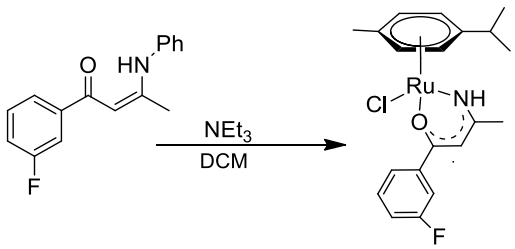
Scheme: 4 Ruthenium complexes have a six-coordination octahedron mode and a greater variety of oxidation states than platinum, resulting in plentiful complex structures. Ruthenium complexes may be used to treat tumors that are resistant to cisplatin. Ruthenium complexes have excellent photophysical and photochemical characteristics, making photodynamic therapy (PDT) and photothermal therapy (PTT)promising cancer treatment approaches[17].

Anticancer activities of Ru II compounds containing P^P ligands are particularly promising. Ru(II) compounds incorporating P^P chelating ligands considerably improved their anticancer efficacy[18]



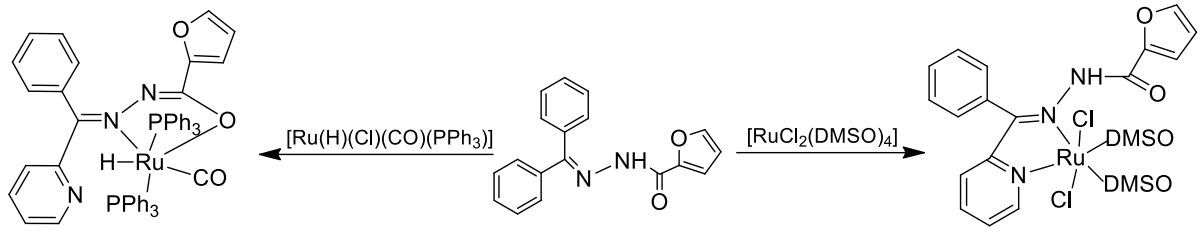
Some ruthenium compounds link more tightly than others, resulting in adducts that are more resistant to cell repair mechanisms. Ruthenium medicines kill cancer cells by interfering with human serum proteins and/or mitochondria. The Ru(III) prodrugs NAMI-A (used as an anti-metastatic medication) and KP1019 (for colon carcinomas) have reached phase two clinical trials because these complexes target both DNA and proteins, they may act via many or distinct pathways.The reactions of [RuIIICl3(PPh3)3] with thiophene-2-carboxylic acid (2-hydroxylbenzylidene)-hydrazide (H2L) resulted in the formation of a new set of hydrazone complexes containing trivalent and bivalent ruthenium ions [RuIII(HL)Cl2(PPh3)2] **(1)** and [RuII(L)(CO)(PPh3**)(2)** in presence of Methanol. Both complexes demonstrated a significant ability to cleave supercoiled DNA, even at low concentrations and in the absence of any oxidant or reductant[19].

Scheme: 5 Anti-cancer activity of ruthenium arene picolinamide complexes,the production and application of Ru(II) complexes with the generic structure [Ru(p-cymene)(XY)Cl], where XY is a bidentate ligand that binds to the metal via (N,N), (N,O), or (O,O) coordination.Complexes 1-5, in combination with cisplatin, [Ru(p-cymene)2Cl2]2, were examined for cytotoxicity against HT-29 and MCF-7 cell lines, and the IC50 value was determined[20].

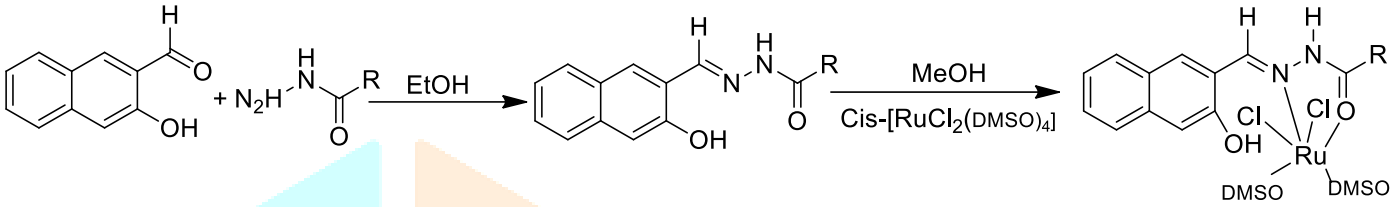


Synthesis if the Ruthenium p-cymene ketoiminate complex

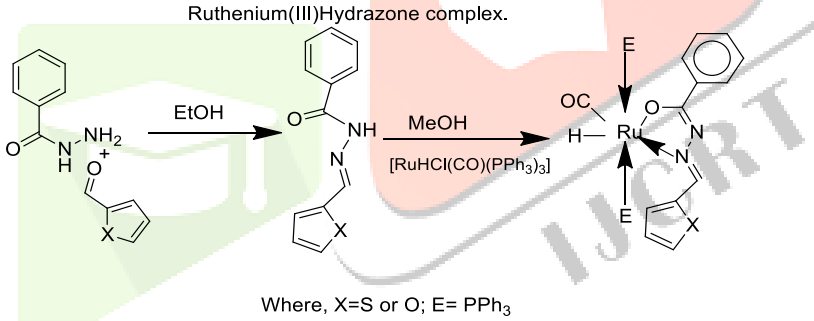
Scheme: 6 Because of their selectivity for solid tumor metastases and low toxicity in vivo, ruthenium-DMSO complexes are thought to have the greatest therapeutic potential of all ruthenium-based anticancer medicines. There is no report that precisely correlates Ru's co-ligand triphenyl phosphine and DMSO precursor complexes (II). As a result, the primary focus of this paper is to investigate the outcome of anticancer actions. Different Ru complexes with triphenyl phosphene and DMSO as co-ligands, as well as their structure, binding characteristics, and anticancer properties[21]



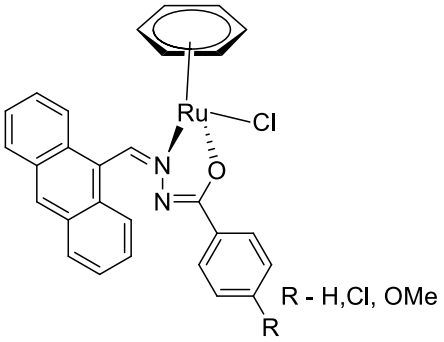
Scheme: 7 The metabolic alterations that occur as a result of cancer progression modify the physiological milieu, allowing ruthenium complexes to be selectively activated in cancer tissues. Dimethyl sulfoxide coordinated ruthenium complexes have a strong affinity for nitrogen donor ligands and have demonstrated a variety of biological actions, including anticancer activity, both in vitro and in vivo. The heteroaromatic ligands stabilise cis-[RuCl2(DMSO)4], a proven antitumor medication, as well as other anticancer-active ruthenium-DMSO complexes such NAMI, NAMI-A, KP1019, and RAPTA. Ruthenium hydrazone complexes, on the other hand, demonstrated excellent efficacy in various tumour types. The activities of ruthenium complexes on cancer cells are thought to occur through DNA binding or cleavage, resulting in cell death[22].



Scheme: 8 Ruthenium hydrazone complexes [RuH(CO)(L1) (PPh3)2]**(1)** and [RuH(CO)(L2)(PPh3)2]**(2)**which was being produced by reacting [RuHCl(CO)(PPh3)3] with benzoic acid[(thiophene-2-yl)methylene] hydrazide (HL1) or benzoic acid[1-(furan-2-yl)methylene] (HL2).Both complexes interacted preferentially with BSA's tryptophan. The complexes' in vitro cytotoxicity against HeLa and MCF-7 cell lines confirmed that the one with sulphur in its hydrazone performed better than the two with oxygen. The observed cytotoxic potentials of **1** and **2** outperform other ruthenium(II) complexes and the common anticancer agent cisplatin[23].

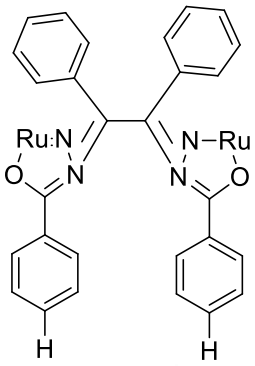


Scheme: 9 The design and synthesis of a new family of binucleated benzil bis(benzoyl hydrazone) ligands and associated ruthenium(II) complexes, taking advantage of the synthetic plasticity of benzoyl hydrazone derivatives and their intriguing biological activity. In three human cancer cell lines, cytotoxic activity investigations found that complexes possessing p-cymene as an arene had significantly higher cytotoxic activity than those comprising a benzene group or cisplatin. The observed enhanced potency could be attributed to stronger hydrophobic contacts between the ruthenium p-cymene complex and the biomolecule targets. The combination of Ru(II) arene moieties with binucleated benzil bis(benzhydrazone) ligands is a promising strategy for the creation of molecular targeted metal-based anticancer medicines that circumvent cisplatin resistance[24].



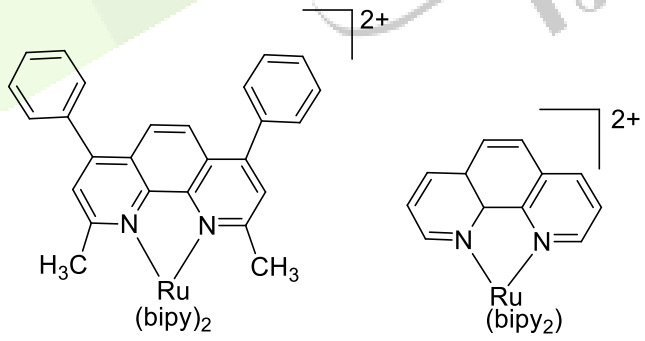
Design of Ru(III) arene 9- anthraldehyde benzhydrazone complexs.

Scheme: 10 Anthracene and its derivatives are among the most important groups of ligands with high intrinsic fluorescence, and they have been investigated as potential chemotherapeutic drugs. Anthracene has been discovered to be beneficial in the treatment of psoriasis. Anthracyclines' anticancer actions can be related to their substantial suppression of topoisomerase II activity and DNA damage. Bisantrene is a novel anthracycline derivative synthesised organically for cancer treatment. Kasim and his colleague used the synthetic plasticity of hydrazone derivatives and their promise biological activity to create a series of organometallic compounds with substantial anticancer activity.The complex's cytotoxic capabilities against the cancer cell lines examined were much superior to those of the well-known anticancer medication cisplatin. Thus, ruthenium-arene-based benzhydrazone complexes are appealing molecules for the development of future anticancer therapies for human tumours that rely on the combination of chemopreventive and chemotherapeutic drugs[25].

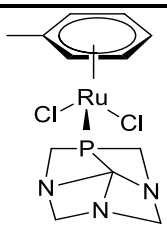


The tumour metastasis targeting ruthenium complex NAMI-A synergistically boosts the action of gemcitabine in combination therapy, Doxorubicin was identified as a hit compound and was so tested in vitro and in a preclinical in vivo model with NAMI-A. High-throughput screening discovered eight structurally varied drugs, including doxorubicin, that synergize with NAMI-A. NAMI-A, followed by doxorubicin, dramatically improved the efficacy of the individual drugs on metastases in MCa mammary cancer of CBA mice, with 70% of animals resulting free of macroscopically visible tumour nodules in the lungs at sacrifice. Unlike doxorubicin, NAMI-A healed 60% of the mice treated, although the combo therapy was harmful to the animals[26].

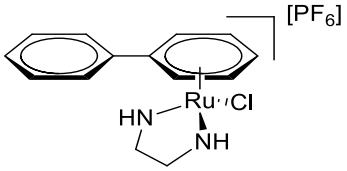
Scheme: 11 Sterically strained Ru(II) bipyridyl complex [Ru(bipy)2(BC)]Cl2**(1)** [where BC 14 bathocuproine] as well as an unstrained control [Ru(bipy)2(phen)]Cl2 **(2)**. The goal of introducing the BC ligand was to boost the lipophilicity of the medication by introducing phenyl groups at the 4,7-positions of the 1,10-phenanthroline ligand and to induce steric strain around the ruthenium core due to the methyl groups at the 2,9-positions. Complex 1 is a promising PACT candidate due to its high uptake and photochemical attributes[27].



Scheme: 12 This research provides the first glimpse into the use of cyclopentadienyl-ruthenium(II) complexes with bio-derivative moieties as CC chemotherapeutic agents. Organo-ruthenium(II) complexes appear to be promising therapeutic candidates. Ruthenium(II)-arene complexes, with the generic formula [(6-C6H6)Ru(L1)(L2)(L3)], are the most investigated class of ruthenium compounds, with promise anticancer action in vitro and in vivo. General formula compounds [Ru(5-C5H5)(PP)(L)] [X] (PP = mono- or bidentate phosphanes, L = N-donor ligand, X = counter-ion) and [Ru(5 -C5H5)(P)(N-N)] [X] (P= phosphane ligand; NN= bidentate ligand; X=counter-ion) exhibited significant toxicity against a number of cancer cell lines, including LoVo (human colon adenocarcinoma), MiaPaCa (pancreatic cancer), HL-60 (human leukaemia), A2780 and A2780CisR (human ovarian, cisplatin sensitive and cisplatin-resistant)[28].



RAPTA-T



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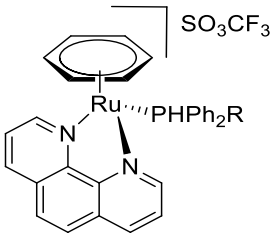

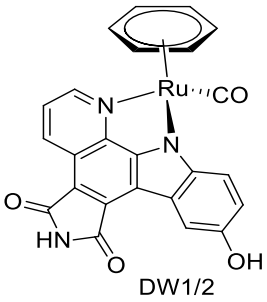

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Reference

[1] Ndagi, U. Mhlongo, N. and Soliman, M.E. 2017. Drug Design Development and Therapy, 11: 599-616.

[2] Yufanyi, D.M. Abbo, H.S. Titinchi, S.J. and Neville, T. 2020. Coordination Chem Review. 1(3): 293-414.

[3] Karges, J. Stokes, R.W. and Cohen, S.M. 2021. Trend in chemistry. 3: 523-534.

[4] Frezza, M. Hindo, S. Chen, D. Davenport, A. Schmitt, S. Tomco, D. and Dou, Q. P. 2010. Current Pharmacutical Design. 16: 1813-1825.

[5] Ott, I. and Gust, R. 2007. Arch Pharm Chem Life Sci. 340: 117-126.

[6] Dalla Pozza, M. Orvain, C. Brustolin, L. Pettenuzzo, N. Nardon, C. Gaiddon, C. and Fregona, D. 2021. Molecules. 26(13): 4073.

[7] Maikoo, S. Chakraborty, A. Vukea, N. Dingle, L.M.K. Samson, W.J. de la Mare, J.A. Edkins, A.L. and Booysen, I.N. 2021. Journal of Biomolecular Structure and Dynamics. 39: 4077-4088.

[8] Pierroz, V. Joshi, T. Leonidova, A. Mari, C. Schur, J. Ott, I. Spiccia, L. Ferrari, S. and Gasser, G. 2012, Journal of the American Chemical Society. 134(50): 20376-87.

[9] Süss-Fink,G. 2010. Dalton Trans. 39: 1673–1688.

[10] Blunden, B.M. Thomas, D.S. and Stenzel, M.H. Stenzel, 2012. PolymChem. 3(10): 2964–2975.

[11] Lazarevic, T. Rilak, A. and Bugarcic, Z.D. 2017. European Journal of Medicinal Chem. 142: 8-31.

[12] Lee, S.Y.. Kim, C.Y and Nam, T.G. 2020, Development and Therapy. 14: 5375–5392.

[13] Gras, M. Therrien, B. Suss-Fink, G. Zava, O. and Dyson, P.J. 2010, Dalton Trans. 39: 10305–10313.

[14] Sun, Q. Li, Y. Shi, H. Wang, Y. Zhang, J. and Zhang, Q. 2021, Molecules. 26(15): 4389.

[15] Chen, C. Xu, C. Li, T. Lu, S. Luo, F. and Wang, H. 2020. European Journal of Medicinal Chem. 203: 112605.

[16] Kumar, R.R. Ramesh, R. and Małecki, J.G. 2018. Journal of Organometallic Chem. 862: 95-104.

[17] Lu, Y. Zhu, D. Le, Q.B.T. Wang, Y. and Wang, W. 2022. Nanoscale.1-69.

[18] Li, J. Tian, Z. Xu, Z. Zhang, S. Feng, Y. Zhang, L. and Liu, Z. 2018. Dalton Trans. 47: 15772–15782.

[19] Jayanthi, E. Venkataramana, M. Neethu, S. Bhuvanesh, N.S.P. and Dharmaraj, N. 2017. Polyhedron. 132: 39-52.

[20] Lucas, S.J. Lord, R.M. Wilson, R.L. Phillips, R.M. Sridharan, V. and McGowan, P.C. 2012. Dalton Trans. 41(45): 13800–13802.

[21] Alagesan, M., Bhuvanesh, N.S. and Dharmaraj, N. 2014. Dalton Trans, 43(16): 6087–6099

[22] Alagesan, M. Sathyadevi, P. Krishnamoorthy, P. Bhuvanesh, N.S.P. and Dharmaraj, N. 2014. Dalton Trans. 43: 15829-15840

[23] Jayanthi, E. Anusuya, M. Bhuvanesh, N.S.P. Khalil, K.A. and Dharmaraj, N. 2015. Journal of Coordination Chem. 68: 3551-3565.

[24] Subarkhan, M.K.M. and Ramesh, R. 2016. Inorg. Chem. Front. 3: 1245-1255.

[25] Kasim, M.S.M. Sundar, S. and Rengan, R. 2018. Inorg. Chem. Front. 5: 585-596.

[26] Bergamo, A. Riedel, T. Dyson, P.J. and Sava, G. 2015. Invest New Drugs. 33(1): 53–63.

[27] Mehanna, S. Mansour, N. Audi, H. Bodman-Smith, K. Mroueh, M.A. Taleb, R.I. Daher, C.F. and Khnayzer, R.S. 2019, RSC Adv. 9: 17254–17265.

[28] Florindo, P.R. Pereira, D.M. Borralho, P.M. Rodrigues, C.M. Piedade, M.F. and Fernandes, A.C. 2015, J. Med. Chem. 58 (10): 4339–4347.