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Synthesis Methods, Characterization Techniques and Properties of Some Diruthenium Complexes

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SYNTHESIS METHODS, CHARACTERIZATION TECHNIQUES AND PROPERTIES OF SOME DIRUTHENIUM COMPLEXES

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This review provides an overview of some diruthenium complexes with respect to their synthesis methods, physical, and chemical properties. Diruthenium complexes discussed in this thesis play a part an important role in various fields, including medicine, catalysis, biology, nanoscience, redox and photoactive materials. Some synthesis methods will be discussed, which help researchers to enhance experimental conditions. Diruthenium complexes are able to bind to DNA and inhibit its replication and protein synthesis, an important property in cancer treatment. A review of synthesis methods and properties of some diruthenium complexes, $[Ru_2(ibp)_4Cl]$, $[Ru_2(asp)_4Cl]$, $[Ru_2(npx)_4(H_2O)_2]PF_6$, and $[Ru_2(ind)_4(H_2O)_2]PF_6$, that exhibited biological activities is presented in this thesis.

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LIST OF SYMBOLS

Symbols	Meaning
%	percent
°C	degrees celcius
Ar	aryl
BuLi	n-Butyllithium
cm^{-1}	wavenumber
COX	cyclooxygenase
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EDTA	ethylenediaminetetraacetic acid
$g•cm^{-3}$	density
Hasp	2-(acetyloxy)benzoic acid)
Hibp	α-methyl-4-(isobutyl)phenylacetic acid
Hind	[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl] acetic acid
Hpnx	2-(6-methoxy-2-naphthyl)propanoic acid
IR	infared spectroscopy
L-	ligand
M-M	metal-metal
mol L^{-1}	moles per liter
mg	milligram
mL	milliliter

mmol	millimole
M	meter
min	minute
mRNA	messenger RNA
MTT	colorimetric assay
nm	nanometer
NSAID	nonsteroidal anti-inflammatory drug
PBS	phosphate-buffered saline
PCR	polymerase chain reaction
PTGS	prostaglandin-endoperoxide synthase
R-	ligand
Ru	ruthenium
Ru_2	diruthenium
$Ru_2(RCO_2)_4Cl$	tetra carboxylate diruthenium

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CHAPTER 1

INTRODUCTION

Discovery

In 1844, Karl Karlovich Klaus at the University of Kazan extracted and purified a new metal, ruthenium (Ru) element 44, by way of its discovery from a Russian chemist named, Gottfried Osann. Its discovery manifested while investigating the platinum metal from ores in the Ural Mountains in Russia [1].

Nature

Being one of the earth's uncommon metals, it is found uncombined but commonly found in the minerals pentlandite and pyroxenite and also acquired commercially from the wastes of nickel refining [1].

Electron Configuration

Ruthenium is a platinum group metal along with rhodium (Rh), palladium (PD), osmium (Os), iridium (Ir), and platinum (Pt). It's positioned in group 8, period 5, and block d on the periodic table. Being element number 44, it has 44 electrons circulated in atomic orbitals. The electrons circulated in atomic orbitals lead to the electron configuration. Ruthenium has only one electron in its outermost shell, while its nucleus contains 44 protons and 57 neutrons giving it the electron configuration of $1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^6\ 4s^2\ 3d^{10}\ 4p^6\ 4d^7\ 5s^1$.

Isotopes

Ruthenium has seven stable isotopes (^{96}Ru, ^{98}Ru, ^{99}Ru, ^{100}Ru, ^{101}Ru, ^{102}Ru, ^{104}Ru) and many radioactive isotopes. The most stable radioactive isotopes are ^{106}Ru, ^{103}Ru, and ^{97}Ru with a half-life of 373.59, 39.26, 2.9 days [3].

Properties

Ruthenium is shiny and silvery in appearance. It has an atomic mass of 101.1 $g.mol^{-1}$ and a density of 12.2 $g.cm^{-3}$ at 20°C. The melting and boiling points are 2250 °C and 4150 °C, respectively. Its electronegativity according to Pauling is, 2.2. Ruthenium is a hard, white metal. It does not tarnish at room temperature but oxidizes in the air at about 800°C [4]. The metal does not dissolve in acids or aqua regia, but when potassium chlorate is added to the solution, it oxidizes explosively forming ruthenium oxide [4].

Uses and Applications

The uses for ruthenium and its compounds are developing tremendously. Currently, it is customarily used in the electronics industry for chip resistors and electrical contacts [1]. Contrariwise, in the chemical industry, ruthenium oxide is used in the anodes of electrochemical cells for the production of chlorine. The catalysts used in the production of acetic acid from methanol and ammonia from natural gas production contain ruthenium, similarly in catalysts that are used to remove hydrogen sulfide (H_2S) from industrial processes. Its compounds are used in solar cells, which turn light energy into electrical energy [1], and also to color ceramics or glass because it can adsorb light of the visible spectrum. This has led to the research of its complexes being used in other solar energy technologies. Ruthenium is used as a hardener for platinum and palladium,

it's then alloyed with these metals to make electrical contacts which improve the resistance of corrosion of titanium. It is used in some jewelry as an alloy. ^{106}Ru is used in the radiotherapy of malignant cells of the eye [5]. RuO_4 is used in forensic chemistry. Of all uses and applications, its in-vitro studies have led to the most common and significant research of ruthenium to discover their diruthenium complexes use in biomedical science for the diagnosis of some diseases and in anticancer activity as they demonstrate a promising capability to break down tumor cells.

CHAPTER 2

DIRUTHENIUM COMPLEXES IN LITERATURE

Although biomedical research of diruthenium complexes is soaring; synthesis, spectroscopic, structural, and electrochemical properties of common Ru-Ru complexes can be discussed [9]. Metal-metal (M-M) bonded compounds have captivated chemists for more than five decades. Dating back to 1966, Stephenson and Wilkinson synthesized the first tetra-carboxylate Diruthenium complex, $Ru_2(RCO_2)_4Cl$, where R in the ligand is an alkyl group, [8] (Figure 1) demonstrated in a paddlewheel structure. The ligand is equatorial and the chloro ligand in axial position. This unsymmetrical assembly permits several possible positions, where any bridging ligands across the metal-metal centers. Following, Bear and co-workers discovered that different variations of the ligand produce different products. Oxidation states of diruthenium complexes and their Ru core center, bridged by specific ligands, vary.

Figure 1. First Tetra-Carboxylate Diruthenium Complex, Paddlewheel Structure [9].

Diruthenium complexes containing mixed bridging ligands have also been reported. Since the clarification of the quadruple bond by, Cotton, many compounds containing an M-M bond have experimented. The dinuclear units that include four bidentate ligands, forming the paddlewheel structure, exhibit distinctive molecular, electronic structures, and beneficial electrochemical and magnetic properties [60]. Some laboratories focus on diruthenium paddlewheel complexes because of their ease of preparation, intense electrochemical properties, and notable stability. Diruthenium alkynyls, specifically, in various multiple oxidation states, with different equatorial ligand systems and their molecular and electronic structures have been studied. The Ru-Ru core and poly alkynyl ligand provide a great advantage. This has caused the expansion of Ru_2 complexes with Ru aryl linkages [60]. During experimentation, the aryl anion's pKa, has a magnitude twenty fold more basic than analogous acetylide. As a result, the dinuclear core is more electron rich which provides new electronic structures. Metal aryls are more kinetically reactive than metal alkynyls but are more stable than metal-alkyls. Ruthenium, being a second-row transition metal, has kinetic instability issues that are overlooked compared to first-row metals. Since metal-aryl complexes are known to exhibit great stability, synthesis, characterization, and analysis, molecular and electronic structures of diruthenium aryls are explored. This is done by way of lithium-halogen exchange reactions, resulting in the isolation of both mono and bis aryl diruthenium complexes [60]. Also, two oxidation states of diruthenium, Ru_2(II,III) and

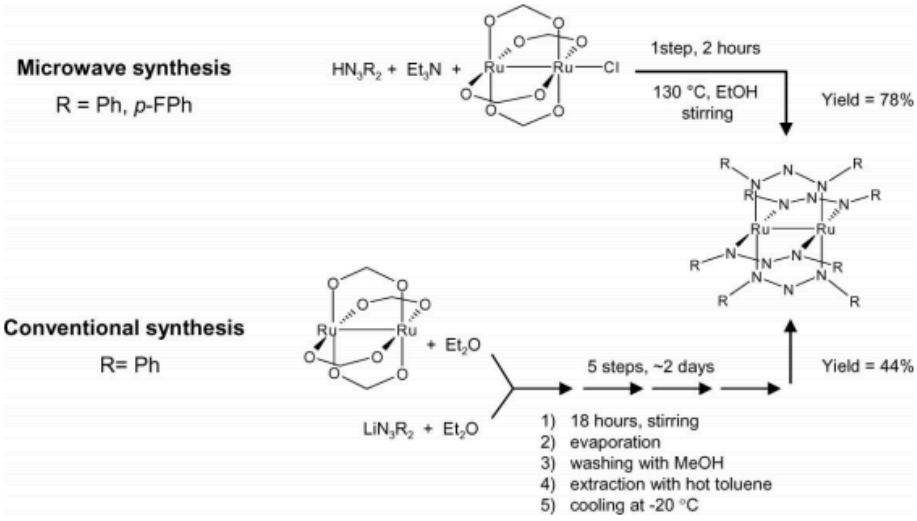
Ru_2(III,III) can be made by altering the ligands. Following, studies of Ru_2(II,III) mono aryls of the form $Ru_2(ap)_4Ar$ are completed. The conclusion of this was that diruthenium aryl interaction is a model of M-M-ligand interaction, bringing reactivity to the distal metal site [60]. Additionally, small changes in axial ligands can cause disruptions in electronic structure. The electronic structure can be inspected computationally but has some difficulty due to the complexity of the system. Mixing of the M-M and M-ligand valance diversity is easily isolated into simple structures such as mono aryls, like $Ru_2(II,III)_4Ar$. Electronic structure calculations also face difficulties due to unclear axially di-substituted mono and bis aryls, $(X)Ru_2(III,III)L_4Ar$ (X=CCH, CN, CO, etc) and $Ru_2(III,III)L_4Ar_2$. The compound $(X)Ru_2(III,III)L_4Ar$ poses even greater computational challenges, such as low-lying excited states, spin-admixed ground states, and isolation. Diruthenium aryls display unusual structures and complex bonding patterns, which has made researchers aware of the importance of M-M-ligand interactions more significantly than the sum of M-M and M-ligand parts.

Some scientists have also studied the electrochemical properties of the first tetra-carboxylate diruthenium complex, $Ru_2(RCO_2)_4Cl$. For example, the oxidation state of the Ru-Ru core is Ru_2^{5+}. Initial electrochemical experiments involved restricted media for the reason that the solubility of the compounds studied, exhibited poor solubility in organic solvents, restricting the number of reduction electrochemical processes. Experimentation with acetate buffer and the bridging ligand to be substituted with longer alkyl chains, caused the intensification of the solubility in organic solvents, which lead to new studies

to be experimented in nonaqueous solvents such as, CH_2Cl_2 [61]. This allowed additional redox processes to be observed within the solvent potential window [61]. The solvent potential window can be described as the maximum and minimum potentials that the reaction can occur before the solvent begins to get reduced or oxidized. Replacing the Cl axial ligand with CO or NO caused stabilization of lower oxidation states, as a result permitting more oxidation states of the compounds. Electrochemical data of various nonaqueous solvents, with CH_2Cl_2 and tetrahydrofuran (THF) being most common is now accessible. Both provide an enlarged cathodic and anodic potential range window. This allows for the assessment of several redox reactions of given compounds [61].
In addition to the studies of diruthenium paddlewheel complexes in nonaqueous solvents, organic tetraalkylammonium salts have been used as an electrolyte (tetrabutylammonium perchlorate or tetrabutylammonium hexafluorophosphate salts), while aqueous solvents use alkali metal salts or organic buffers. The concentration is significant for specific values of half-wave potentials [61].

In other studies, microwave irradiation has been used to help promote the synthesis of diruthenium and other coordination complexes, although is not as commonly used in their preparation as it is in the synthesis of many organic compounds. It's said to conquer difficulties encountered in other synthesis methods practiced. Complexes with N,N-donor ligands (anilinopyridinate, aminopyridinate, formamidinate, etc.) are widespread in the literature, but their preparation usually involves some complications [62]. Included in the N,N-ligand derivatives, triazenido complexes are rare, even though the 1,3-diaryltriazenide species has been known and used for many years [62]. After

more than a decade, the only models of low spin Ru_2 5+ complexes are tetrakis(diaryltriazenido) derivatives. This is due to the complexity of the synthesis. Specifically, tetrakis(triazenido)Diruthenium(II) compounds have been formerly synthesized by way of wearying multistep methods [62]. These methods included extensive reaction times and extraction steps, low temperatures, and closed systems. Some reagents and solvents such as BuLi are harmful and the final yield was relatively low. This is illustrated in Figure 2 [62]. Microwave irradiation results in higher reaction rates and yield, improved purity, and did not require harsh reaction conditions.



Scheme 1 Procedure schemes from microwave and conventional synthesis.

Figure 2. Microwave vs conventional method of synthesis of N,N-ligand derivative Diruthenium compound [62].

The characterization of diruthenium involve several technique methods. Characterization is the procedure used to determine a compounds structure and properties. A few of the common techniques are termed NMR, FT-IR, and ESI spectroscopy. After a crystal structure has been synthesized, the spectra of the new complex compared to its free ligands to investigate their vibration frequencies. In some cases, thermal studies are conducted to determine the stability of the complexes. Redox potentials can also be used to verify functional groups of the complex, an anodic or cathodic shift to will occur dependent upon the specific group.

Diruthenium Complexes in Anticancer Activity

Furthermore, Diruthenium complexes and their physical properties in research as possible cancer chemotherapeutics is becoming more noticed. The anti-cancer activity of tetra-carboxylate compounds became acknowledged in the 1970s considering the possible cellular targets, and among the recognized non-platinum antitumor agents are dinuclear carboxylate species of rhodium (Rh), rhenium (Re), and ruthenium. Modification of the R group (R= -CH3, -CH2CH3, or -CH2CH2CH3) on the equatorial bridging ligands also exposed structure-activity relationship effects of anticancer activity. Diruthenium compounds are less studied than dirhodium compounds although their biological mechanism of action is similar. It is also reported that biological activity is greatly enhanced for highly water-soluble diruthenium complexes, highlighting the importance of solubility in increasing the biological activity of these potential anticancer activities [9].

Ruthenium in general has been greatly researched throughout the years in cancer, including anti-cancer activity and its practices of therapy. Cancer is defined by the uncontrollable growth of cells within or a specific part of the body. To successfully cure cancer, the drug of design must inhibit DNA replication and protein synthesis. Presently, in the market, a vast majority of anti-cancer drugs use platinum metal as their anticancer agent. Overall, platinum has shown positive results in cancer treatment, although not in all natures of cancer. This limitation of platinum allowed for the expansion of ruthenium as a competitor in the treatment of cancer. Ruthenium equally inhibits DNA replication and protein synthesis of cancer cells causing apoptosis, death of cells at a controlled rate. A small downside, ruthenium has low aqueous solubility. This is rectified by using the dialkyl sulfoxide derivative of ruthenium [5]. Likewise, radiation therapy is used in cancer treatment with radio sensitizer agents. Radiotherapy must only be used in proximity to cancerous cells. It is accomplished by using radio sensitizers' complexes with ruthenium for the reason Ru binds to DNA effortlessly. Photodynamic therapy is also used in cancer treatment. This therapy involves the use of chemicals and electromagnetic radiation. The chemicals target cancer cells and become cytotoxic when interaction with electromagnetic radiation takes place [5]. The use of ruthenium aids in the access of these chemicals to cancerous cells. Being that the mitochondria are the most momentous component of any cell, it makes for a probable target for anticancer therapy of cancerous cells.

Current Organometallic Drugs Used As Anticancer Chemotherapeautics

The first ruthenium based compound to be researched is, NAMI-A. NAMI-A prevents metastasis by disrupting angiogenesis and with metalloprotease activity in cancer cells [21].

Various of $[Ru_2(O_2CR)_4L_2]PF_6$ complexes, where L = imidazole, 1-methylimidazole and water when R = CH_3; L = ethanol when R = Fc (ferrocenyl) or Fc–CH = CH–; and $M_3[Ru_2(O_2CR)_4(H_2O)_2]$ compounds, with M = Na^+ when R = *m*-C_6H_4SO3- and M = K^+ when R = *p*-C_6H_4SO3-, has been tested for cytotoxicity against HeLa and multidrug resistant CoLo 320DM human cancer cells [28].

Today, a great interest in metal–metal bonded complexes NSAIDs, has surfaced [29]. NSAID medications, also known as a nonsteroidal anti-inflammatory drug, are well known and commonly used to decrease inflammation and pain in the human body, but more recently it has caught notice because of its chemopreventive effect in diverse tumors [31]. Although the mechanism of action has not yet been determined, the pharmacological properties of certain NSAIDs differ depending upon their inhibitory effects in COX1 and COX2 [34]. Cyclooxygenase has also known as, COX, also known as, prostaglandin-endoperoxide synthase (PTGS), is responsible for the formation of prostanoids. The COX1 isozyme located on chromosome 9 is expressed while the COX2 isoenzyme located on chromosome 1, is induced during the inflammatory processes. Recently, clinical research is happening to study the COX2 inhibitor effects on tumor evolution in patients with glioblastoma multiforme, known as GBM, a brain

glioma [42]. GMB has not responded to current surgical techniques and treatment protocols. This is mainly due to their aggressive character and resistance to current chemotherapy and radiotherapy [44]. A 50% reduction in the mortality rate from certain cancers in patients being observed consuming NSAIDs, leads to examine cyclooxygenase in neoplasia [45]. Some recent studies determined certain NSAIDs cause antiproliferative effects independent of the cyclooxygenase activity. The effects of some NSAIDs on the proliferation of glioma cell lines have also been investigated. Following, studies between diruthenium centered and NSAIDs along with studies of antitumor properties of diruthenium–dNSAID complexes (dNSAID = deprotonated NSAID derived from: ibuprofen (Hibp), aspirin (Hasp), naproxen (Hnpx) and indomethacin (Hind) Figure 3 [10]. The antitumor effects for C6 rat glioma cell line (used as a model for GBM) and two human tumor cell lines (Hep2 larynx and T24/83 bladder) were investigated [10].

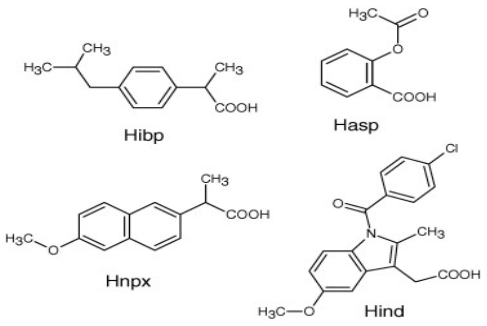


Figure 3. Structures of Hibp (α-methyl-4-(isobutyl)phenylacetic acid), Hasp (2-(acetyloxy)benzoic acid), Hnpx (2-(6-methoxy-2-naphthyl)propanoic acid), and Hind ([1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl] acetic acid). [10].

CHAPTER 3

EXPERIMENTATION AND METHODOLOGY

Materials Used

The following experiment was carried out by a group of scientists to determine the effects of tumor cell proliferation of several synthesized diruthenium complexes of NSAIDs. In the recent study, researchers used materials used for the experiment supplied by Aldrich or Merck and used as purchased. Aspirin was purchased from Aldrich, ibuprofen, from Natural Pharma; naproxen, from Purifarma; and indomethacin, from Henrifarma. An elemental and spectroscopic analysis was done to confirm purity. The diruthenium(II, III) precursor compounds, $[Ru_2(O_2CCH_3)_4Cl]$ (chloroacetate) and $[Ru_2(O_2CCH_3)_4(H_2O)_2]PF_6$ (aquaacetate) [48], were synthesized from the starting compound $RuCl_3 \cdot nH_2O$ (Aldrich) according literature [10].

Physical Measurements

An elemental analyses was performed on a Perkin–Elmer CHN 2004 Elemental Analyzer. Electronic absorption spectra of ruthenium compounds in solutions, at 200–700 nm UV–Vis, was done with a Shimadzu UV-1650 PC spectrophotometer. The solid reflectance spectra at 350–1400 nm UV–Vis/NIR, were measured on a Guided Wave model 260 spectrophotometer. Fourier-Transform Infrared (FTIR) spectra of solid samples dispersed in KBr, at 4000–400 cm^{-1} and FTIR transmittance spectra of samples in Nujol mulls between CsI pellets, at 400–200 cm^{-1}, were recorded on a Bomen MB-102 spectrophotometer. Raman spectra of solid samples were carried out on a Micro-Raman

RENISHAW System 3000 (laser line = 632.8 nm). The molar magnetic susceptibilities were measured on powdered samples at room temperature by the Faraday method using an electrobalance Cahn DTL 7500, then any diamagnetic corrections were made via Pascal's constants and $Hg[Co(SCN)_4]$ for calibration. Molar conductance measurements for $\sim 1 \times 10^{-3}$ mol L^{-1} acetonitrile solutions of the compounds were carried out with a Digimed DM-31 equipment, at 25.0 ± 0.5 °C; KCl aqueous solution, 146.9 μS cm^{-1} at 25 °C, cell constant = 0.1 cm^{-1}, was used for calibration [10].

Synthesis of Four Diruthenium Compounds With NSAIDs

$[Ru_2(ibp)_4Cl]$ Synthesis (Compound 1)

First, 300 mg at 0.63 mmol of $[Ru_2(O_2CCH_3)_4Cl]$ was dissolved in 200 mL of water. It was then evaporated by rotary evaporation to 40 mL. 660 mg at 3.20 mmol of ibuprofen in 40 mL of ethanol and 370 mg LiCl in 5 mL of water were added to the 40 mL of solution separately. Following, the mixture was stirred under nitrogen for 3 hours, at 60 °C. A precipitate (product) formed on the bottom of the flask. It was collected, washed with water then dissolved in ethanol. Next it was filtrated, and the resulting solution was evaporated under nitrogen stream and the dark-brown product was dried in a vacuum desiccator over phosphorus pentoxide [10]. Yield = 74%. *Anal.* Calc. for $C_{52}H_{68}O_8ClRu_2 \cdot 12H_2O$: C, 58.71; H, 6.16. Found: C, 58.39; H, 6.24%. Electronic absorptions at λ_{max} (nm): 483 and 1125 nm (solid phase); 428 nm (in methanol); μ_{eff} = 3.9 B.M.; FTIR major bands, ν (cm^{-1}): 3053sh ($\nu(CH)_{aromatic}$); 2955ms, 2923sh, 2867m ($\nu(CH)_{aliphatic}$); 1513m ($\nu(CC)_{ring}$); 1465s ($\nu_a(COO^-)$); 1409s ($\nu_s(COO^-)$); 1372m ($\delta_s(CH_3)$); 1286m, 1071m, 1019w (region of $\delta_s(CH_3)$, $\delta_{ring\ in\ plane}$, $\rho(CH_3)$); 849m

($\delta_s(CH_3)$, $\delta_{ring\ out\ plane}$); 740 m ($\delta$(OCO)); 555m, 492m ($\nu$(Ru–O)); molar conductance = 2.6 S cm^2 mol^{-1} in acetonitrile [10].

$[Ru_2(asp)_4Cl]$ Synthesis (Compound 2)

300 mg at 0.63 mmol $[Ru_2(O_2CCH_3)_4Cl]$ was dissolved in 200 mL of water. It was then evaporated by rotary evaporation to 65 mL. Next, 35 mL of ethanol and solutions of 640 mg at 3.56 mmol aspirin in 50 mL of ethanol and 270 mg of LiCl in 5 mL of water were added separately. The mix was stirred under nitrogen for 2 hours, at 60 °C. Following, it was filtered then washed with water and ethanol, the solid product was dried in a vacuum desiccator over phosphorus pentoxide. Yield = 65%. *Anal.* Calc. for $C_{36}H_{28}O_{16}ClRu_2$: C, 45.31; H, 2.96. Found: C, 45.03; H, 2.96% [10].

$[Ru_2(npx)_4(H_2O)_2]PF_6$ Synthesis (Compound 3)

76 mg at 0.12 mmol of $[Ru_2(O_2CCH_3)_4(H_2O)_2]PF_6$ was dissolved in 10 mL of water and then 15 mL of ethanol. Following, 140 mg at 0.61 mmol naproxen in 10 mL of ethanol and 230 mg of NH_4PF_6 in 3 mL of water were added. The mixture was stirred under nitrogen for 3 hours, at 60 °C, then continuously stirred under nitrogenous atmosphere for 18 hours, at room temperature. The solid (precipitate) formed was washed with water and dissolved in ethanol. After the product was filtrated, the resulting solution was evaporated under nitrogen stream and the dark-brown product was dried in a vacuum desiccator over phosphorus pentoxide. Yield = 62%. *Anal.* Calc. for $C_{56}H_{56}F_6O_{14}PRu_2$: C, 51.73; H, 4.34; Found: C, 52.10; H, 4.41% [10].

$[Ru_2(ind)_4(H_2O)_2]PF_6$ Synthesis (Compound 4)

80 mg at 0.13 mmol $[Ru_2(O_2CCH_3)_4(H_2O)_2]PF_6$ was dissolved in 10 mL of water and, then 15 mL of ethanol. This was followed by adding, 240 mg at 0.67 mmol indomethacin in 20 mL of ethanol and 240 mg NH_4PF_6 in 3 mL of water. The mixture was stirred under nitrogen for 4 hours, at 60 °C, in absence of light [10], then continuously stirred under stirring under nitrogenous atmosphere for 18 hours, at room temperature. Afterward, the mixture was centrifuge. The solid product formed and collected was washed with water and ethanol then, dried in a vacuum desiccator over phosphorus pentoxide. Yield = 26%. *Anal.* Calc. for $C_{76}H_{64}F_6N_4O_{18}PCl_4Ru_2$: C, 50.41; H, 3.57; N, 3.10. Found: C, 50.54; H, 3.87; N, 2.91% [10].

Cell Culture

The C6 rat glioma cells were acquired from the ATCC (American Type Culture Collection), while Hep2 cells and T24/83 cells were obtained from the ECACC (The European Collection of Authenticated Cell Cultures). Cells were kept frozen in liquid nitrogen in Dulbecco's Modified Eagle's Medium (DMEM), added with 10% fetal calf serum and 20% glycerol. Stock cells were grown in DMEM containing 10% fetal calf serum and antibiotics (penicillin 50 U mL^{-1} and streptomycin 50 μg mL^{-1}) [10]. The cells that were grown during the exponential phase of growth were used, growing in 75 cm^2 flasks in a humidified atmosphere of 5% CO_2: 95% air at 37 °C [10].

MTT Assay

The cells were placed into 96-well plates at a density of 1–2 × 10^4 cells per well. They were incubated overnight then subjected to Ru_2-dNSAIDs at concentrations of 1, 10, 100 and 1000 μmol L^{-1} for 24–72 hours (changing of the medium and drug every 24 hours). After, 25 μg of MTT was added to each well and incubated for another 2–4 hours. The medium was aspirated out and the cells were re-suspended in 100 μL of 0.04 mol L^{-1} HCl in isopropanol. The product formed was spect at the wavelength of 595 nm. The organic NSAIDs followed the same procedural process [10].

Cell Proliferation and Viability Assay

The cells were placed into 24-well plates at a density of 1–2 × 10^5 cells per well. After 24, 48 or 72 hours of incubation time, the cells were collected by trypsinization (trypsin 0.025%/EDTA 0.02%) before incubating with 0.2% trypan blue solution in PBS for 2 min [10]. Cells were counted with an Neubauer counter for apoptosis.

mRNA Expression Analysis of COX-2 By RT-PCR

The C6 cells grown in vitro and in vivo were used for total RNA extraction with Trizol. The first strand of complementary DNA (cDNA) was formed from 1 μg of RNA, using 2 μL of random hexamer primer at a concentration of 3 μg μL^{-1}, 1 μL of 10 U RNase inhibitor, 2 μL of deoxynucleoside triphosphate mix (dNTP mix) at a concentration of 10 m mol L^{-1}, and 2 μL moloney murine leukemia virus (M-MLV) reverse transcriptase at a concentration of 200 U μL^{-1}, in a total volume of 20 μL [10]. The reaction mixture was incubated at 21 °C for 10 min, at 42 °C for 50 min, and at 99 °C for 10 min in a GeneAmp®PCR System 9700 respectively. For amplification of the

COX-2 sequence, cDNA was amplified in a 50 μL volume using 0.5 μL (5 U μL^{-1}) platinum Taq DNA polymerase, 1 μL DNTP mix 10 mmol L^{-1}, 1.5 μL $MgCl_2$ 50 mmol L^{-1}, 5 μL PCR buffer 10× and 6 μL of specific primers (3 μL sense + 3 μL antisense) [10]. Rat ribosomal L19 (RPL19) gene was amplified and used a control. The oligonucleotide sequences used for COX-2 and RPL19 were: COX2 sense: 5′-TCAAGACAGATCAGAAGCGA-3′ antisense: 5′-TACCTGAGTGTCTTTGATTG-3′ and RPL19 sense: 5′-TCTCATGGAACACATCCACAA-3′ antisense: 5′-TGGTCAGCCAGGAGCTTCTT-3′ [10]. PCR amplification included cycles which denatured for 1 min at 94 °C, annealing for 1 min at 58 °C and extension for 1 min at 72 °C. The number of PCR cycles was verified for COX-2 as 38 cycles and RPL19 as 36 cycles to determine exponential growth. The PCR products were collected, aliquoted and placed on a 1% agarose gel containing 0.05% ethidium bromide. The resulting picture was captured using, Foto-Analyst. mRNA expression numbers were calculated mRNA/RPL19 density ratio [10].

CHAPTER 4

RESULTS AND DISCUSSION

Diruthenium Compounds Characterization

The following results were obtained after their methodology was concluded. Compounds, 1 and 2 were prepared by way of close reaction between $[Ru_2(O_2CCH_3)_4Cl]$ and the correspondent acidic drug ligands under comparable conditions. The $[Ru_2(ibp)_4Cl]$ complex was obtained by a way of a different method, but the characterization data is consistent with the literature, stated previously [29]. $[Ru_2(asp)_4Cl]$ has previously been prepared but no complete characterization was found in the literature [50]. It was synthesized and its spectroscopic data are presented. Compounds, 3 and 4 were made by a reaction between $[Ru_2(O_2CCH_3)_4(H_2O)_2]PF_6$ with the specific correspondent acidic drug ligands. A carboxylate exchange reaction happened for all products made, their elemental analyses confirms this. The four acetate anions from the precursors chloroacetate and aquaacetate are substituted by dNSAID ligands, resulting the derivatives $[Ru_2(dNSAID)_4Cl]$, with ibp and asp, and $[Ru_2(dNSAID)_4(H_2O)_2]PF_6$, for npx and ind, respectively [10]. Physicochemical data for compounds 2**,** 3 and 4 are shown in Table 1**.**

Table 1. Physicochemical Data For Diruthenium(II, III) compounds 2**,** 3 and 4 [10]

Compound	**$[Ru_2(asp)_4Cl]$**	**$[Ru_2(npx)_4(H_2O)_2]PF_6$**	**$[Ru_2(ind)_4(H_2O)_2]PF_6$**
Electronic absorption transitions; λ (nm); ε (mol^{-1} L cm^{-1})			
π(Ru–O, Ru_2) → π^* (Ru_2) (solvent)	439; 976 (in methanol)	429; 770 (in methanol)	430; sh (in methanol)
$\delta(Ru_2) \rightarrow \delta^*$ (Ru_2)	1140 (solid)	1112 (solid)	1110 (solid)
Effective magnetic moment per Ru_2; μ_{eff} (B.M.)			
	3.9	4.1	3.7
FTIR major bands; ν (cm^{-1})			
$\nu(CH)_{aromatic}$	3070w	3055vw	3092w
$\nu(CH)_{aliphatic}$	2990w, 2928w, 2882w	2975w, 2939w, 2904sh, 2845w	2993sh, 2962w, 2936w, 2834w
$\nu(C{=}O)_{esther}$	1761ms		
$\nu(C{=}O)_{amide}$			1683s
$\nu(CC)_{ring}$	1606m, 1583sh	1637m, 1604m	1593m
$\nu_a(COO^-)$[a]	1476ms	1459ms	1473s
$\nu_s(COO^-)$[a]	1409s	1410s	1410s, br
$\delta_s(CH_3)$	1374sh	1372m	1360s, br
$\nu(C_{ring}OC)$		1270ms	1227s
$\nu_a(OCC)$; $\nu(CC(O)O)$	1191ms		
Region of $\delta_s(CH_3)$; $\delta_{ring\ in\ plane}$; $\rho(CH_3)$	1161sh	1230m, 1214m, 1175m, 1160m, 1069m	1177m, 1147m, 1087m, 1067m, 1033m, 1013m
$\nu_s(COC)$		1029m	
$\delta(CH_3)$; $\delta_{ring\ out\ plane}$	817mw	*	*
ν(PF6−)		849vs, br	848vs, br
δ(FPF)		559s	559s
δ(OCO)	712m	711w	718m

Compound	**$[Ru_2(asp)_4Cl]$**	**$[Ru_2(npx)_4(H_2O)_2]PF_6$**	**$[Ru_2(ind)_4(H_2O)_2]PF_6$**
ν(Ru–O)	560m, 458m	557m, 474m	557m, 481mw
Raman major bands at low frequency; ν (cm^{-1})			
ν(Ru–Ru)	342s	360m	347s
ν(Ru–O)	367w		
ν(PF6−)		760s	749s

Tentative attributions for major bands observed at the correspondent vibrational FTIR and Raman spectra [10].

a $\delta(CH_3)$ is overlapped with these bands; ∗ not identified, overlapped with $\nu_s(PF_6)$; s = strong; m = medium; mw = medium-weak; ms = medium-strong; w = weak; br = broad; sh = shoulder [10].

Diruthenium compounds mixed in methanol show absorption bands at about 430 nm which can be ascribed to $\pi(Ru–O, Ru_2) \rightarrow \pi^*(Ru_2)$ electronic transitions. Compounds 1 and 2 show a comparable lowering of energy of Solid-state λ_{max} shifts to 470–500 nm with similar diruthenium-tetracarboxylates [41], [42], [43]. IR bands of $\delta(Ru_2) \rightarrow \delta^*(Ru_2)$ electronic transition involving dimetal core *δ* orbitals were observed of solid-state diruthenium compounds with an energy intensity around 1100 nm. The data of these bands is comparable with previously reported spectra for similar diruthenium carboxylates. The high effective magnetic moments (μ_{eff} = 3.7–4.1 B.M. per Ru_2 unit) link to the three unpaired electrons per di-nuclear unit, comparable to similar complexes. Compounds 1 and 2 display low molar conductance values, of 3.7 S cm^2mol^{-1}. This behavior, considered non-electrolyte, is result of the presence of its neutral species in acetonitrile mixtures. On the other hand, high conductance values of, 84 and 65 S cm^2 mol^{-1}, for compounds 3 and 4 correspond with 1:1 electrolytes which is

projected due to the presence of $[Ru_2(dNSAID)_4]^+$ cations and $PF6^-$ anions in their solutions.

After the NSAIDs bonded to their respective diruthenium cores, no sprectra changes were observed. The only significant spectra changes were energies related to the carboxylic (–COOH) groups [45], [46]. The carbonyl stretching, ν(C═O), of the parent acids Hibp, Hasp, Hnpx, and Hind disappeared in the correspondent metal complexes spectra [10]. Carboxylate ($–COO^-$) bands were found at the region of 1480–1400 cm^{-1}, distinctive values for carboxylate groups. The values for $\Delta\nu$ [ν_a(COO)–ν_s(COO)] are in the range of 40–70 cm^{-1}, this corresponds to the bridging of carboxylate ligands to their respective Diruthenium cores [10].

$PF6^-$ counter-ions appearing in compounds 3 and 4 are confirmed by the bands at ~850 cm^{-1} (ν(PF) stretching, ν_3) and 559 cm^{-1} (δ(FPF), ν_4) [46]. While intense bands at 556 cm^{-1} and 450–490 cm^{-1}, are detected for all complexes, due to ν(Ru–O) stretching modes with ruthenium–O(carboxylate) metal-ligand bonds [57]. The Raman bands at 336–357 cm^{-1} indicate ν(Ru–Ru) stretching of the two chloro complexes [57]. The frequencies for compound 1 at, 336 cm^{-1} and compound 2, at 342 cm^{-1} are shifted to higher energy indicating that the Ru–Ru bond in Ru_2-dNSAID derivatives are slightly shorter than that observed for Ru_2-acetate precursor (327 cm^{-1}) [10]. The aqua-complexes exhibit broad and overlapped bands due to the presence of axial water molecules. The ν(PF) stretching mode and ν_1 frequency, are detected around 750 cm^{-1} for both $[Ru_2(dNSAID)_4(H_2O)_2]PF_6$ compounds, compounds 3 and 4. $[Ru_2(dNSAID)_4Cl]$ and $[Ru_2(dNSAID)_4(H_2O)_2]PF_6$ show mixed valent Ru_2(II, III) cores

with Ru–Ru bonds in like-paddlewheel structures confirmed by experimental results, Figure 4**.** The electronic structure of the novel compounds compared to the diruthenium precursors showed no dissimilarities based upon large dNSAID anion attatchment. Compounds 1 and 2 display structures similar to other like chloro complexes while compounds 3 and 4 have two water molecules in axial position, providing appositive charge that causes a charge-balance by the $PF6^{-}$ counter-ions.

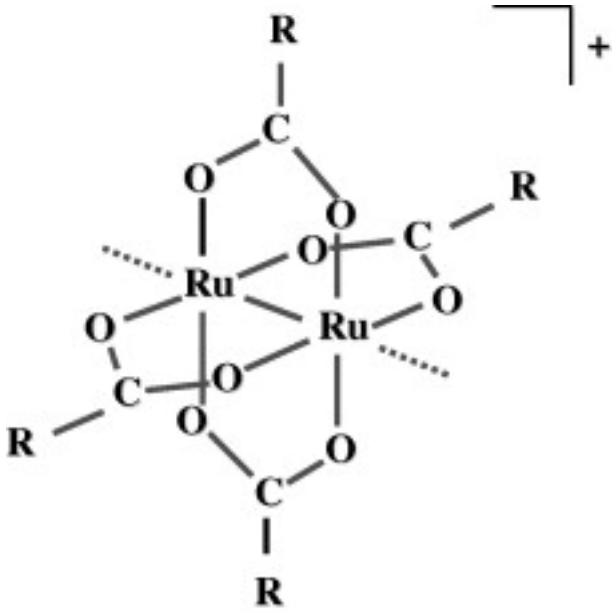


Figure 4. General Structure of the Ru_2-dNSAID Compound [10]

MTT Assays

They experimented the effects of the four Ru_2–dNSAID complexes and the parent NSAIDs in vitro in the human larynx tumor Hep2, the human bladder tumor T24/83 and the rat glioma C6 [10]. Preliminary experiments had no effect on any of the three cell lines at either concentration of 1 or 10 μmol L^{-1}. Furthermore, at 100 μmol L^{-1} the drugs

showed some preventative effects. Experiments carried out with 1 mmol L^{-1} were rejected because high concentrations of DMSO or ethanol were cytotoxic to all cell lines. Experiments performed at 100 μmol L^{-1}, showed no significant effect of the complexes in the Hep2 human larynx tumor or the T24/83 human bladder tumor after 24 hours of incubation, shown in Table 2. In the C6 rat glioma, some drugs showed antiproliferation activity by the MTT assay. The percentages of the control MTT value were: 85.9 ± 6.2 for Hind, 82.7 ± 3.4 for Hnpx, 77.4 ± 5.9 for compound 1 and 72.1 ± 5.5 for compound 3 [10]. Hasp 95.6 ± 4.6 and compound 2 96.3 ± 7.8 did not display noteworthy values [10]. High values for compound 4 at 93.1 ± 6.2 could not be explained through different experiments, until presently.

Table 2. MTT Assay [10]

Compound	**Hep2**	**T24/83**	**C6**
$[Ru_2(ibp)_4Cl]$	84.0 ± 7.6	103 ± 9.3	77.4 ± 5.9[a]
Hibp	82.1 ± 5.4	94.3 ± 5.9	94.2 ± 5.3
$[Ru_2(asp)_4Cl]$	83.1 ± 3.9	n.d.	96.3 ± 7.8
Hasp	106 ± 4.3	n.d.	95.6 ± 4.6
$[Ru_2(npx)_4 (H_2O)_2]PF_6$	86.7 ± 3.3	138 ± 11.5	72.1 ± 5.5[a]
Hnpx	82.7 ± 8.1	112 ± 9.0	82.7± 3.4[b]
$[Ru_2(ind)_4 (H_2O)_2]PF_6$	115 ± 6.3	93.8 ± 6.5	93.1 ± 6.2
Hind	85.8 ± 1.6	94.1 ± 6.5	85.9 ± 6.2[b]

Data are expressed as percentage of optical density of control cells ± SEM, n.d., not determined. Representative data from two separate experiments with $n = 9–12$. Drugs were present at a final concentration of 100 μmol L^{-1}. Statistical analysis used 1-way ANOVA with Tukey's post test, [a]$p < 0.001$; [b]$p < 0.01$ [10].

Cell Proliferation and Viability Assay

To further evaluate the MTT data, additional experiments for Hibp, Hnpx and their diruthenium complexes were executed using cell counting methods and determination of cell viability using trypan blue. These experiments were carried out on C6 glioma cell lines in company of $[Ru_2(O_2CCH_3)_4Cl]$, Hibp, compound 1, Hnpx or compound 3 for 24, 48 or 72 hours, shown in Table 3. Ru_2–dNSAID incubated at 24 hours displayed only some inhibitory effects. Inhibition was absent at 48 hours of incubation but increased critically at 72 hours, although compound $[Ru_2(O_2CCH_3)_4Cl]$ does not exhibit inhibitory effect at 72 hours [10]. This explained data would assume the effects of compounds 1 and 3 are time dependent. A large percentage of cells held their capacity to exclude trypan blue, for example cell viability at 72 hours was: 98.5 ± 0.7% for compound 1; 100 ± 0.1% for compound 3; and 99.1 ± 0.5% for control, shown in Table 4 [10]. The inhibitory effects established after 72 hours exposure to the Hibp NSAID was examined. This cell line does not express COX2 under normal culture conditions or produce PGE_2, assuming the effects must be through a COX2-independent mechanism [10] Figure 5.

Table 3. Cell Number [10]

Compound	24 hours	48 hours	72 hours
$[Ru_2(O_2CCH_3)_4Cl]$	89.4 ± 4.8	96.2 ± 2.8	93.7 ± 2.4
$[Ru_2(ibp)_4Cl]$	85.5 ± 4.4	99.1 ± 5.7	$50.6 \pm 1.6^{a,b,c}$
Hibp	100 ± 3.2	89.8 ± 2.2	74.6 ± 1.7^{a}
$[Ru_2(npx)_4(H_2O)_2]PF_6$	88.6 ± 2.0	80.7 ± 6.4	$53.2 \pm 3.5^{a,b,c}$
Hnpx	95.6 ± 6.6	81.7 ± 9.5	82.9 ± 2.7^{a}

Data are expressed as percentage of control cell number ± SEM. Representative data from three separate experiments with $n = 4$. Drugs were present at a final concentration of 100 μmol L^{-1}. Statistical analysis used 1-way ANOVA with Tukey's post test, $p < 0.05$; [a]versus control; [b]versus ibuprofen; [c]versus naproxen [10].

Table 4. Cell Using Trypan Blue [10]

	24 hours	48 hours	72 hours
Control	99.5 ± 0.25	99.4 ± 0.39	99.1 ± 0.52
$[Ru_2(O_2CCH_3)_4Cl]$	99.9 ± 0.33	98.5 ± 0.72	98.0 ± 0.41
$[Ru_2(ibp)_4Cl]$	99.8 ± 0.13	98.2 ± 1.10	98.5 ± 0.73
Hibp	99.8 ± 0.11	98.6 ± 0.86	98.4 ± 1.00
$[Ru_2(npx)_4(H_2O)_2]PF_6$	99.8 ± 0.23	98.2 ± 0.84	100 ± 0.10
Hnpx	99.5 ± 0.26	98.3 ± 0.83	99.1 ± 0.45

Viable cell data are expressed as percentage of total cell population ±SEM. Drugs were present at a final concentration of 100 μmol L^{-1}. Cells were incubated with trypan blue prior to counting in a Neubauer chamber. Representative data from three separate experiments with $n = 4$ [10].

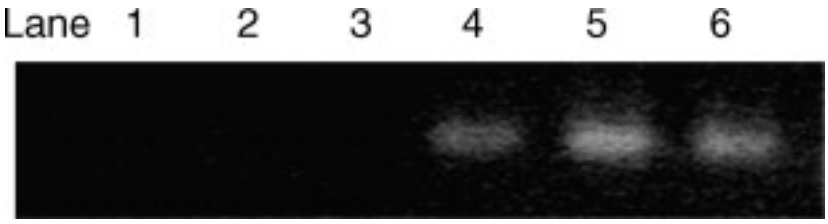


Figure 5. COX2 mRNA Expression In C6 Cells in vitro Lanes 1–3; C6 Cells in vivo Lanes 4–6 [10].

Compounds 1 and 3 inhibit C6 glioma cell proliferation in vitro, with effectiveness increasing with time of exposure to the complexes. C6 cell lines do not express COX2 in vitro, thus any effects of the NSAID component is via either COX1 or non-COX related mechanisms [10]. Ruthenium bonded to naproxen or ibuprofen improved their inhibitory properties, even though they each display antitumor properties in C6 cells single-handedly. It's said that these drugs possibly are more effective in vivo in gliomas where COX2 is expressed by tumor, endothelial and infiltrating microglial cells. Earlier studies with NAMI-A have reported anti-angiogenic and anti-matrix metalloprotease effects [21]. The probability that complexes of 1 and 3 could employ similar effects unlocks new opportunities for in vivo C6 glioma model.

CHAPTER 5

SUMMARY AND CONCLUSIONS

Ruthenium is silver, with a hard metal and shiny surface. Ru can form many oxidation states, which is a significant property related to its part in its applications. Ruthenium forms coordinate complexes. These complexes play a part in various fields such as medicine, catalysis, biology, nanoscience, redox and photoactive materials.

The electrochemical data and synthesis techniques are vital in enhancing the Diruthenium complexes. These methods lead to higher yields than the previously published one, and it could facilitate the access to a family of compounds with interesting redox properties.

In biology and medicine, Ru is used for diagnosis and treatment. Ruthenium complexes are able to bind to DNA and inhibit its replication and protein synthesis, an important property in cancer treatment.

Diruthenium compounds of Hipb, Hasp, Hnpx and Hind NSAID drugs antitumor activity was studied. No significant effects were found for the complexes and their parent NSAIDs in the Hep2 human larynx or the T24/83 human bladder tumor [10]. Yet, the coordination of the Ru_2(II, III) showed considerable effects in the C6 rat glioma cell antiproliferative activity of naproxen and ibuprofen drugs. Rising progression of novel drugs with positive effects on proliferation of glioma cells, also known as powerful inhibitors of COX2, is a valuable in future research of chemotherapy for glioma treatment. The Diruthenium complexes of ibuprofen and naproxen employ angiogenic and anti-matrix metalloprotease effects, which are comparable to those demonstrated by

NAMI-A, unlocks new opportunities for in vivo C6 glioma model studies.

Examining chemical and biological behavior to explain the antitumor properties of analogous compounds is part of imminent work. Insufficient information of the mechanism of action in ruthenium-based drug design is the most significant limitation during drug discovery. Different approaches to combat this hinderance could be used. First, creating a considerable number of different compounds to examine against a variety of cell lines and cancer targets could be helpful to conclude how rearrangement or different functional groups affect its activity. Research of current ruthenium-based compounds and how it acts in biological media is helpful for chemists in order to design a drug with the highest affinity for their cancer targets, while simultaneously have less side effects. Research in determination of the water-solubility of ruthenium and their complexes is lesser unknown. Additional research to determine its solubility must be known to produce new complexes, this is dependent upon the geometrical arrangement of the various complexes made.

REFERENCES

1. Royal Society of Chemistry, https://www.rsc.org/periodic-table/element/44/ruthenium
2. Ablialimov O, Kędziorek M, Malinska M, Wozniak K. Synthesis, structure, and catalytic activity of new ruthenium(II) indenylidene complexes bearing unsymmetrical N-heterocyclic carbenes. Organometallics. 2014;33:2160-2171. DOI: 10.1021/om4009197
3. Timo Hopp *, Mario Fischer-Gödde and Thorsten Kleine Ruthenium stable isotope measurements by double spike MC-ICPMS.) *J. Anal. At. Spectrom.*, 2016, 31, 1515-1526. DOI: 10.1039/CJA00041J
4. Lenntech Chemical Properties of Ruthenium, https://www.lenntech.com/periodic/elements/ru.htm#ixzz6ZBiFpZ1y
5. Singh SK, Pandey DS. Multifaceted half-sandwich arene-ruthenium complexes: Interactions with biomolecules, photoactivation, and multinuclearity approach. RSC Advances. 2014;4:1819-1840. DOI: 10.1039/C3RA44131H
6. Anil K. Sahu, Deepak K. Dash, Koushlesh Mishra, Saraswati P. Mishra, Rajni Yadav and Pankaj Kashyap (July 4th 2018). Properties and Applications of Ruthenium, Noble and Precious Metals - Properties, Nanoscale Effects and Applications, Mohindar Singh Seehra and Alan D. Bristow, IntechOpen, DOI: 10.5772/intechopen.76393.

7. Viktor, Brabec, Jana, Kasparkova Institute of Biophysics, Czech Academy of Sciences, Kralovopolska 135, CZ-61265 Brno, Czech Republic
Received 26 May 2018, Revised 6 July 2018, Accepted 15 July 2018, Available online 14 August 2018.

8. Manuel A.S. Aquino, Coordination Chemistry Reviews Volume 170, March 1998, p. 141-202 Diruthenium and Diosmium Tetracarboxylates: Synthesis, Physical Properties and Applications
DOI: 10.1016/S0010-8545(97)00079-9

9. Geise Ribeiro, Marcel Benadiba, Alison Colquhoun, Denise de Oliveira Silva Volume 27, Issue 3, 2008, Pages 1131-1137, ISSN 0277-5387, Diruthenium(II,III) complexes of ibuprofen, aspirin, naproxen and indomethacin non-steroidal anti-inflammatory drugs: Synthesis, characterization and their effects on tumor-cell proliferation, Polyhedron, https://doi.org/10.1016/j.poly.2007.12.011.

10. M.J. Clarke, Coord. Chem. Rev., Vol 236 (2003), p. 209, Ruthenium metallopharmaceuticals

11. P.J. Dyson, G. Sava, Dalton Trans. Issue 16 (2006), p. 1929, Metal-based antitumour drugs in the post genomic era

12. I. Kostova, Curr. Med. Chem., Vol 13 Issue 9 (2006), p. 1085
Ruthenium complexes as anticancer agents

13. C.X. Zhang, S.J. Lippard, Curr. Opi. Chem. Biol., Vol 7, Issue 4 Aug (2003), p. 481, New metal complexes as potential therapeutics

14. A. Habtemariam, M. Melchart, R. Fernadez, S. Parsons, I.D.H. Oswald, A. Parkin, F.P.A. Fabbiani, J.E. Davidson, A. Dawson, R.E. Aird, D.I. Jodrell, P.J. Sadle J. Med. Chem., Vol 49, Issue 23, 16 November (2006), p. 6858 Structure-activity relationships for cytotoxic ruthenium(II) arene complexes containing N,N-, N,O-, and O,O-chelating ligands

15. W.H. Ang, P.J. Dyson Eur. J. Inorg. Chem., 20 (2006), p. 4003

16. C.G. Hartinger, S.Z. Seifred, M.A. Jakupec, B. Kynast, H. Zorbas, B. Keppler J. Inorg. Biochem., Vol 100, Issue 5-6, May (2006), p. 891 From bench to bedside - preclinical and early clinical development of the anticancer agent indazolium trans-[tetrachlorobis(1H-indazole)ruthenate(III)] (KP1019 or FFC14A)

17. S.R. Grguric- Sipka, R.A. Vilaplana, J.M. Pérez, M.A. Fuertes, C. Alonso, Y. Alvarez, T.J. Sab o, F. Vílchez-González, J. Inorg. Biochem., Vol 97, Issue 2, October (2003), p. 215, Synthesis, characterization, interaction with DNA and cytotoxicity of the new potential antitumour drug cis-K[Ru(eddp)Cl_2]

18. A. Bergamo, G. Stocco, B. Gava, M. Cocchietto, E. Alessio, B. Serli, E. Iengo, G. "Distinct effects of dinuclear ruthenium(III) complexes on cell proliferation and on cell cycle regulation in human and murine tumor cell lines." *Sava J. Pharmacol. Expl. Ther*., Vol 305, Issue 2, May (2003), p. 725

19. V. Djinovíc, M. Momcilovíc, S. Grguric-
Sipka, V. Trajkovic, M.M. Stojkovic, D. Miljkovic, T. Sabo
J. Inorg. Biochem., Vol 98, Issue 12, December (2004), p. 2168
Novel ruthenium complex $K_2[Ru(dmgly)Cl_4] \cdot 2H_2O$ is toxic to C6 astrocytoma cell line, but not to primary rat astrocytes

20. S. Zorzet, A. Bergamo, M. Cocchietto, A. Sorc, B. Gava, E. Alessio, E. Iengo, G. Sava, J. Pharmacol. Expl. Ther., Vol 295, Issue 3 (2000), p. 927
Lack of in vitro cytotoxicity, associated to increased G_2-M cell fraction and inhibition of matrigel invasion, may predict in vivo-selective antimetastasis activity of ruthenium complexes

21. G. Sava, S. Zorzet, C. Turrin, F. Vita, M.R. Soranzo, G. Zabucchi, M. Cocchietto, A. Bergamo, S. DiGiovine, G. Pezzoni, L. Sartor, S. Garbisa
Clin. Cancer Res., Vol 9, Issue 5, May (2003), p. 1898
Dual action of NAMI-A in inhibition of solid tumor metastasis: Selective targeting of metastatic cells and binding to collagen

22. F.A. Cotton, C.A. Murillo, R.A. Walton (Eds.), Multiple Bonds Between Metal Atoms (3rd ed.), Springer Science and Business Media Inc., New York (2005)

23. M.A.S. Aquino, Coord. Chem. Rev., Vol 170, Issue 1, March (1998), p. 141
Diruthenium and diosmium tetracarboxylates: Synthesis, physical properties and applications

24. M.A.S. Aquino, Coord. Chem. Rev., Vol 248, Issue 11-12, June (2004), p. 1025
Recent developments in the synthesis and properties of diruthenium tetracarboxylates

25. B.K. Keppler, M. Henn, U.M. Juhl, M.R. Berger, R. Niebl, F.E. Wagner
Prog. Clin. Biochem. Med., 10 (1989), p. 41

26. B.K. Keppler, K. Lipponer, B. Stenzel, F. Kratz, B.K. Keppler (Ed.), Metal Complexes in Cancer Chemotherapy, VCH, New York (1993)

27. C.E.J. Van
Rensburg, E. Kreft, J.C. Swarts, S.R. Dalrymple, D.M. Macdonald, M.W. Cooke, M.A.S. Aquino, Anticancer Res., Vol 22, Issue 2A (2002), p. 889
Cytotoxicity of a series of water-soluble mixed valent diruthenium Tetracarboxylates

28. A. Andrade, S.F. Namora, R.G. Woisky, G. Wiezel, R. Najjar, J.A.A. Sertié, D. d e Oliveira Silva, J. Inorg. Biochem., Vol 81, Issue 1-2, 15 July (2000), p. 23
Synthesis and characterization of a diruthenium-ibuprofenato complex – Comparing its anti-inflammatory activity with that of a copper(II)- ibuprofenato complex

29. F.A. Cotton, D. de Oliveira Silva, Inorg. Chim. Acta, Vol 249, Issue1, August (1996), p. 57, Preparation and crystal structure of a dimolybdenum(II) complex with the drug Ibuprofen

30. M.J. Thun, S.J. Henley, C. Patrono
J. Nat. Cancer Inst., Vol 94, Issue 4, February (2002), p. 252
Nonsteroidal anti-inflammatory drugs as anticancer agents: Mechanistic, pharmacologic, and clinical issues

31. S.J. Shiff, M.I. Koutsos, L. Qiao, B. Rigas, Exptl. Cell Res., Vol 222, Issue 1, 10 January (1996), p. 179, Nonsteroidal antiinflammatory drugs inhibit the proliferation of colon adenocarcinoma cells: Effects on cell cycle and apoptosis

32. M.L. Smith, G. Hawcroft, M.A. Hull, Eur. J. Cancer, Vol 36, Issue 5, March (2000), p. 664, The effect of non-steroidal anti-inflammatory drugs on human colorectal cancer cellsevidence of different mechanisms of action

33. G.A. Fitzgerald, Nature Rev. Drug Discovery, Vol 2, Issue 11, November (2003), p. 879, COX-2 and beyond: Approaches to prostaglandin inhibition in human disease

34. M. Romano, J. Clària, FASEB J., Vol 17, Issue 14, November (2003), p. 1986 Cyclooxygenase-2 and 5-lipoxygenase converging functions on cell proliferation and tumor angiogenesis: Implications for cancer therapy

35. S. Zha, V. Yegnasubramanian, W.G. Nelson, W.B. Isaacs, A.M. De Marzo
Cancer Lett., Vol 215, Issue 1, 8 November (2004), p. 1
Cyclooxygenases in cancer: Progress and perspective

36. T. Shono, P.J. Tofilon, J.M. Bruner, O. Owolabi, F.F. Lang, Cancer Res., Vol 61, Issue 11, 1 June (2001), p. 4375, Cyclooxygenase-2 expression in human gliomas: Prognostic significance and molecular correlations

37. F. Kürzel, C. Hagel, S. Zapf, H. Meissner, M. Westphal, A. Geise
Acta Neurochir. (Wien), Vol 144, Issue 1, (2002), p. 71
Cyclo-oxygenase inhibitors and thromboxane synthase inhibitors differentially regulate migration arrest, growth inhibition and apoptosis in human glioma cells

38. N. Nathoo, G.H. Barnett, M. Golubic, J. Clin. Pathol., Vol 57, Issue 1, January (2004), p. 6, The eicosanoid cascade: Possible role in gliomas and meningiomas

39. P. New, Câncer Control, Vol 11, Issue 3, May/June (2004), p. 152
Cyclooxygenase in the treatment of glioma: Its complex role in signal transduction

40. M. Wang, D. Yoshida, S. Liu, A. Teramoto, J. Neuro-Oncol., Vol 72, (2005), p. 1
A novel technique of optical interference to generate equispaced fringe pattern of concentric ring

41. J. Drappatz, P. Wen, Curr. Opi. Neur., Vol 17, Issue 6, December (2004), p. 663
Non-cytotoxic drugs as potential treatments for gliomas

42. J. Tuettenberg, R. Grobholz, T. Korn, F. Wenz, R. Rever, P. Vajkoczy
J. Cancer Res. Clin. Oncol., Vol 131, Issue 1, January (2005), p. 31
Continuous low-dose chemotherapy plus inhibition of cyclooxygenase-2 as an antiangiogenic therapy of glioblastoma multiforme

43. F. Lefranc, J. Brotchi, R. Kiss, J. Clin. Oncol., Vol 23, Issue 10 (2005), p. 2411
Possible future issues in the treatment of glioblastomas: Special emphasis on cell migration and the resistance of migrating glioblastoma cells to apoptosis

44. N.R. Sivac-Sears, J.A. Schwartzbaum, R. Miike, M. Moghadassi, M. Wrensch
Am. J. Epidemiol., Vol 159 (2004), p. 113

45. M. Ishibashi, F.G. Bottone Jr., S. Taniura, H. Kamitani, T. Watanabe, T.E. Eling
Exp. Cell Res., Vol 302, Issue 2, 15 January (2005), p. 244
The cyclooxygenase inhibitor indomethacin modulates gene expression and represses the extracellular matrix protein laminin γ1 in human glioblastoma cells

46. A. Bernardi, M.C. Jaques-Silva, A. Delgado-Cañedo, G. Lenz, A.M.O. Battastini
Eur. J. Pharm., Vol 532, Issue 3, 27 February (2006), p. 214
Nonsteroidal anti-inflammatory drugs inhibit the growth of C6 and U138-MG glioma cell lines

47. R.W. Mitchell, A. Spencer, G. Wilkinson, J. Chem. Soc., Dalton Trans. Issue 8, (1973), p. 846, Carboxylato-triphenylphosphine complexes of ruthenium, cationic triphenylphosphine complexes derived from them, and their behaviour as homogeneous hydrogenation catalysts for alkenes

48. K.D. Drysdale, E.J. Beck, T.S. Cameron, K.N. Robertson, M.A.S. Aquino
Inorg. Chim. Acta, Vol 256, Issue 2, 31 March (1997), p. 243
Crystal structures and physico-chemical properties of a series of $[Ru_2(O_2CCH_3)_4L_2]$ (PF_6) adducts (L = H_2O, DMF, DMSO)

49. A. Carvill, P. Higgins, G.M. McCann, H. Ryan, A. Shiels
J. Chem. Soc., Dalton Trans. Issue 12, (1989), p. 2435
Synthesis, spectroscopic, electrochemical, and magnetic properties of dimolybdenum(II,II), diruthenium-(II,III) and -(II,II) complexes containing bridging aspirinate (2-acetoxybenzoate) ligands

50. J.G. Norman Jr., G.E. Renzoni, D.A. Case, J. Am. Chem. Soc., Vol 101, Issue 18, 1 February (1979), p. 5256, Electronic Structure of $Ru_2(O_2CR)_4$+ and $Rh_2(O_2CR)_4$+ Complexes

51. V.M. Miskowski, H.B. Gray, Inorg. Chem., Vol 27, Issue 14 (1988), p. 2501
Electronic Spectra of $Ru_2(carboxylate)_4^+$ Complexes. Higher Energy Electronic Excited State

52. G. Estiú, F.D. Cukiernik, P. Maldivi, O. Poizat, Inorg. Chem.,Vol 38, Issue 13, (1999), p. 3030, Electronic, magnetic, and spectroscopic properties of binuclear diruthenium tetracarboxylates: A theoretical and experimental study

53. W.J. Geary, Coord. Chem. Rev., Vol 7, Issue 1, October (1971), p. 81
The use of conductivity measurements in organic solvents for the characterisation of coordination compounds

54. R.A. Nyquist, C.L. Putzig, M.A. Leugers, Infrared and Raman Spectral Atlas of Inorganic Compounds and Organic Salts: Text and Explanations, Vol. 1, Academic Press, San Diego (1996)

55. K. Nakamoto, Infrared and Raman Spectra of Inorganic and Coordination Compounds. Parts A and B (5th ed.), John Wiley & Sons Inc., New York (1997)

56. V.M. Miskowski, T.M. Loehr, H.B. Gray, Inorg. Chem., Vol 26, Issue 7, 1 April (1987), p. 1098, Electronic and Vibrational Spectra of $Ru_2(carboxylate)_4^+$Complexes. Characterization of a High-Spin Metal-Metal Ground State

57. K.L. Ramos, A. Colquhoun, Glia, Vol 43, Issue 2, August (2003), p. 149 Protective role of glucose-6-phosphate dehydrogenase activity in the metabolic response of C6 rat glioma cells to polyunsaturated fatty acid exposure

58. Malinski, T.,Chang, D.,Feldmann, F.N.,Bear, J.L.,Kadish, K.M. Inorganic Chem, Vol 22, Issue 22, October (1983), p. 3225-3233 Electrochemical Studies of a Novel Ruthenium(II, III) Dimer, $Ru_2(HNOCCF_3)_4Cl$(Article)

59. Raghavan, Adharsh (2020): Diruthenium Aryls: Structure, Bonding, and Reactivity. Purdue University Graduate School. Thesis. https://doi.org/10.25394/PGS.12722087.v1

60. Eric VanCaemelbecke, Tuan Phan, W. Ryan Osterloh, Karl M. Kadish Coord Chemistry. Vol 434, 1 May 2021 Electrochemistry of metal-metal bonded diruthenium complexes

61. Herrero, Santiago & Jimenez-Aparicio, Reyes & Perles, Josefina & Priego, Jose & Urbanos, Francisco. (2010). First microwave synthesis of multiple metal-metal bond paddlewheel compounds. Green Chemistry - GREEN CHEM. 12. 10.1039/c003411h.