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Metallodrugs and their various impacts on disorders and diseases

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Metallodrugs are drugs that contain a metal, and are usually seen with anticancer treatments. However, there has been significant development over years that have progressed the use of metallodrugs. These drugs can be seen in either an oral form or an injection/infusion. Metals have been used throughout the ages in medical applications. We see this in the 16th century with syphilis, which was treated with mercury. However, it wasn't until the 20th century when metals really caught the spot light. The first therapeutic metallodrug compound was developed in 1909, which was Salvarsan, also used to treat syphilis. Salvarsan, arsenic based, was the best option for treating syphilis until penicillin was discovered in 1928 [1,4,14].

In 1964 Barnett Rosenberg, discovered that platinum compounds hinder the growth of cells. From Rosenberg's studies the compound cisplatin, a platinum compound, was developed in the treatment of cancer cells. This drug was specifically used for ovarian and testicular cancer in the late 1970's. The application of cisplatin provoked an interest in other metal compound use in drugs. The problem with metallodrugs is that they have been tricky to develop; a lot of metal based drugs have been discovered by chance [1,4,7,14].

Looking at the 21th century, Medical inorganic chemists wanted to change the development of metallodrugs from chance to a rational discovery. When it comes to designing metal based drugs the first step is to identify the disease target and the specific molecular target associated with the cause of the disease. It is about knowing the disease or disorder of choice and then targeting the cause of that disease or disorder. Understanding metals in biology is a key base to start from when looking to develop metallodrugs. Knowing a metal's

uptake, trafficking, function and excretion is important. Looking at the characteristics of a metal within a cell and/or tissues is a step in development as well as a metals interactions with genes and proteins. The majority of drug development comes with the interactions of targeting DNA or proteins [1,17,18].

Understanding how to detect any disease or disorder is crucial. Radiopharmaceuticals is a primary way for medical diagnostics and therapy. Radiopharmaceuticals help with diagnosing cancer, cardiological disorders, infections, kidney or liver abnormalities and neurological disorders [1]. It is possible to find and differentiate between healthy tissue and carcinogenic tissue in image analysis before the tissue has ever been taken. The quality of medical scans has improved with the help of metallodrugs. A dominant as well as a majority used isotope, for radiopharmaceuticals, is technetium-99m (figure 1). There is a total of 28 FDA approved technetium-99m imaging agents. Technetium-99m is a dominant isotope used in radiopharmaceuticals because its gamma radiation is easily detected at 140.4KeV, where optimal gamma energy range is about 100 to 200keV. Technetium -99m has a wide range of oxidation numbers and coordination numbers. Oxidation states ranged from -1 to +7 and coordination numbers ranged from 4 to 9. The different properties of technetium -99m has led to an open target platform for the development of radiopharmaceuticals. There is a disadvantage to technetium -99m and that is that it is in short production. There is an alternative to technetium -99m; the isotopes Gallium-67m and gallium-68m. The gallium isotopes are used for SPECT and PET scans [1,9] .

Figure 1: FDA-approved metalloradiopharmaceuticals

radioisotope	radiation	active ingredient	trade name	diagnostic imaging
^{67}Ga	γ	Ga-67 citrate		Hodgkin's disease, lymphoma, bronchogenic carcinoma
^{82}Rb	β^+	Rb-82 chloride	Cardiogen-82	myocardium
^{99m}Tc	γ	Tc-99m bicisate	Neurolite	stroke
^{99m}Tc	γ	Tc-99m disofenin	Hepatolite	cholecystitis
^{99m}Tc	γ	Tc-99m exametazime	Ceretec	stroke, abdominal infection
^{99m}Tc	γ	Tc-99m macroaggregated albumin		pulmonary perfusion, shunt patency
^{99m}Tc	γ	Tc-99m mebrofenin	Choletec	hepatobiliary system
^{99m}Tc	γ	Tc-99m medronate	MDP-Bracco	bone
^{99m}Tc	γ	Tc-99m mertiatide	Technescan MAG3	kidney
^{99m}Tc	γ	Tc-99m oxidronate	Technescan HDP	bone
^{99m}Tc	γ	Tc-99m pentetate		brain, kidney
^{99m}Tc	γ	Tc-99m pyrophosphate	Technescan, PYP	bone, myocardium, blood pool
^{99m}Tc	γ	Tc-99m red blood cells	UltraTag	blood pool
^{99m}Tc	γ	Tc-99m sestamibi	Cardiolite	myocardium, breast
^{99m}Tc	γ	Tc-99m sodium pertechnetate	Technelite	brain, thyroid, blood pool, urinary tract, nasolacrimal drainage system
^{99m}Tc	γ	Tc-99m succimer		kidney
^{99m}Tc	γ	Tc-99m sulfur colloid		lymphatic system, liver
^{99m}Tc	γ	Tc-99m tetrofosmin	Myoview	myocardium
^{99m}Tc	γ	Tc-99m tilmanocept	Lymphoseek	lymphatic system
^{111}In	γ	In-111 capromab pendetide	ProstaScint	prostate cancer
^{111}In	γ	In-111 chloride	Indiclor	radiolabeling of ProstaScint
^{111}In	γ	In-111 oxyquinoline		leukocytes, inflammation
^{111}In	γ	In-111 pentetate		brain, spinal canal
^{111}In	γ	In-111 pentetreotide	Ocetreoscan	neuroendocrine tumors
^{201}Tl	γ	Tl-201 chloride		myocardium, thyroid

Mjos, K. D.; Orvig, C. Metallodrugs in Medicinal Inorganic Chemistry. *Chemical Reviews* **2014**, *114*(8), 4540–4563.

There is a variety of metals that have been used or are in clinical trials as a metallodrug. Some metals in particular are gold, vanadium, copper, silver, bismuth and platinum. The uses that metals can play in biological conditions is outstanding. They can help a plethora of treatments for multiple disorders and diseases. Some of the disorders and diseases they can help in treating is arthritis, diabetes, Alzheimer's, wound healing and vaccines. Three metals in

particular, that play a part in helping the treatment of wounds are copper, silver and bismuth. Silver helps in the treatment of infections, such as burns as well as treating cysts and abscesses. Bismuth assists in treating antimicrobial treatments. One treatment in particular is in treating chronic wounds, such as diabetic foot ulcers [1,14,19].

Metallodrugs can also play a role in the treatment of psychiatric disorders. Lithium based drugs in the 1950's became a very recognizable treatment for bipolar disorders or disorders that have strong mood swings. In 1979 there was an oral lithium carbonate drug that was approved by the FDA. This drug was useful because it reduced suicide rises and mood swings. However, the mechanism for how lithium works is relatively unknown. It is thought to protect the nerves system from injury and damage, targeting the amygdala, part of the brain that processes negative emotion. It is also thought to regulate neurotransmissions and control cellular and intracellular changes in the second messenger system [1].

One disorder metallodrugs can add in is rheumatoid arthritis. Rheumatoid arthritis is an inflammatory autoimmune disorder that is painful and incurable. This disorder affects roughly one to two percent of people in the world and can cause a total loss of joint movement. There are two classifications for drugs to use for this disorder. One is called "first-line" drugs, which consist of aspirin and ibuprofen. These drugs are mainly just a way to alleviate pain and swelling, nothing more. The second class is "second-line" drugs, which includes methotrexate, D-penicillamine and various gold salts. The "second-line" drugs are used for more severe cases and can slow the progression of arthritis. Gold salts are considered second line drugs because they help on the treatment of slowing the advancement of arthritis. They act as immunosuppressants, and are antirejection drugs, preventing the body from rejection

something, it normally would. The FDA has approved several gold (I) arthritis metallodrugs. One type of gold salt that is the most common treatment, is gold sodium thiomalate. Gold sodium thiomalate did receive negative connotations because of the harmful side effects. As a result, methotrexate, an anticancer drug, became a treatment for arthritis. There are positive attributes to methotrexate such as having a smaller dosage than gold salts. At 7.5 mg per week, an improvement may be seen in three to six weeks. Where gold sodium thiomalate, on the other hand, has a dosage between 25 and 50 mg per week and it may take three to six months for improvement to be detected. Another advantage of methotrexate is its shorter half-life of 3 to 10 hours, while gold sodium thiomalate can be left in the body from 3 to 27 days. These are positive attributes of methotrexate, but methotrexate has just as many or more harmful side effects as gold sodium thiomalate. [1,11].

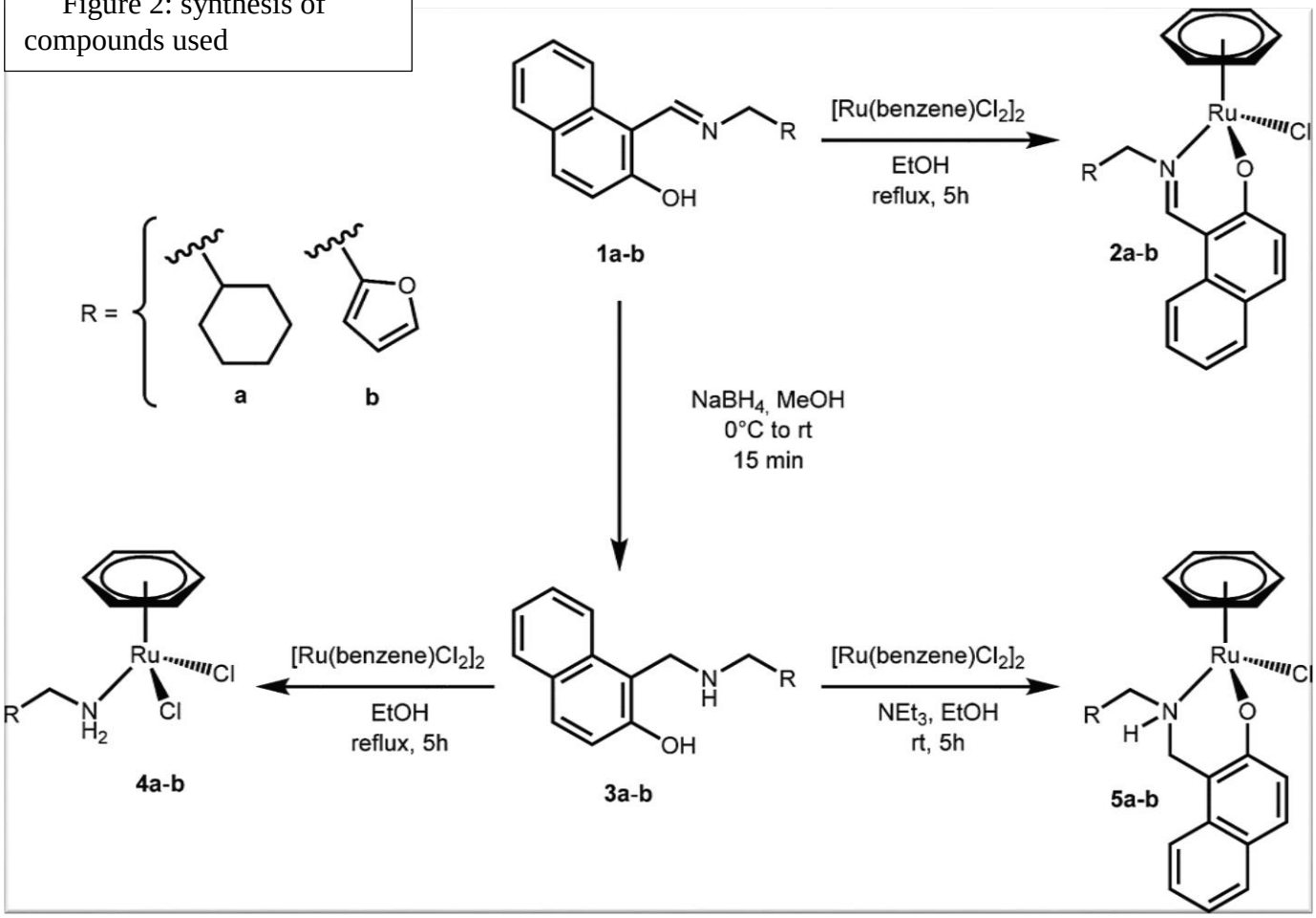
Diabetes is another disease that metallodrugs can help in treating. Throughout the world it is estimated that about 347 million people have diabetes. Diabetes can be grouped into two types. Type one is insulin dependent and is caused by a destruction of beta cells, these cells help in the creation of insulin. Type two is noninsulin-dependent and is caused by aging and obesity [12]. Antidiabetic treatments can be seen in vanadium salts and coordination compounds. They demonstrated insulin enhancing effects. In 1899, sodium vanadate was given to patients of Lyonnet ‘s, and he observed a positive effect on their health. Vanadate was also studied in 1977 by Josephson. In his research he saw inhibitory effects towered phosphatases. Later research studies involved diabetic rats and showed that sodium orthovanadate with drinking water could reverse a majority of diabetic symptoms. This provoked an increased interest in the biological functions of vanadium. First generation vanadium complexes had a bit

of a challenge attached with them in that they were needed in high dosages. Further generation development of vanadium complexes showed half toxicity as that of the first generation complexes, as well as the lower dosage need. There has been much progression in the development of treating diabetes with vanadium containing drugs [1,12].

As stated before, one widely known metallodrug is Cisplatin. While Cisplatin is well-known and commonly used for anticancer treatment for various cancers; there is a metal that has the potential to out shine cisplatin. Finding that particular metal had to be a smart choice. One paper takes this challenge head on in looking for that right metal. Looking into other ways to attack cancerous cells, other than what has been done before. They looked at metals with catalytic potential. Why catalytic drugs? Catalytic drugs were chosen for various purposes. These reasons were because catalytic drugs are used in small doses, there is low toxicity levels, and there is a well-known potential of cell death from redox reactions. Going down a new path to treat cancers, will inevitably help lower the resistance levels that are becoming present within cancerous cells, from current treatments. From there it led to the metal compound ruthenium and its catalytic potential. Ruthenium has the ability to be a successful catalyst. We see this in Ru oxidizing glutathione to its disulfide bond, which eventually leads to cell death [1,4,7]. This paper ended up synthesizing several different Ru complexes. The four complexes used consisted of either a cyclohexane ring or a furan ring (Figure 2: a- cyclohexane, b- furan). Cyclohexane ring and a furan ring were used as substitute ligands because they are used in other drug designs. They also have the potential for dissolving in fats, oils, lipids and non-polar solvents. Complex 2a-b (figure 2) contains a Schiff base and complex 5a-b (figure 2) contended to contain an amine liganded. Both complex 2a-b and 5a-b were the desired product. Past

research has shown that shiff base ligands has played a large role in antiproliferative activity. Knowing that a shiff base has potential to hinder cell growth, this research was done in hopes of seeing if another complex would hinder cell growth. The goal of complex 5a-b was to see if a simple change would affect the treatment of cancer cells[4].

Figure 2: synthesis of compounds used



Anticancer Activity and Catalytic Potential of Ruthenium(II)–Arene Complexes with N,O-Donor Ligands Mohammad Mehdi Haghdoost, Juliette Guard, Golara Golbaghi, and Annie Castonguay *Inorganic Chemistry* **2018** *57* (13), 7558-7567 DOI: 10.1021/acs.inorgchem.8b00346

A variety of tests were performed on the four complexes such as: NMR, high-resolution electrospray ionization mass spectrometry (HR-ESI-MS) and elemental analysis, X-ray crystallography: on 4a and 5a-b, Hydrolysis, UV−vis. Different spectra were used to help confirm

the composition of the compounds and allow for a clearer understanding for what they were working with. When the compounds were originally analyzed, after refluxing in ethanol for 5 hours, by H-NMR it was discovered that their desired products were not present. However, unexpected product was produced, complex 4a-b (figure 2). They ended up discovering complex 5a-b when the reaction was performed at room temperature, with an excess amount of triethylamine. NMR and ESI-MS were also usual for concluding that complex 5a-b were more stable then complex 2a-b, this was seen when they were exposed to air for several weeks. Also, a hydrolysis was preformed, which concluded that 5 complexes had a hydrolysis rate that was 10 times slower than 2a-b complexes [4].

In this research they wanted to look into the complexes ability to hinder cell grow and that was done through an MTS assay. Where they tested each complex as well as cis-platin against human ovarian cancer cells (A2780), human neuroblastoma (SH-SY5Y), breast carcinoma (MCF-7), resistant cis-platin cancerous human breast cell line (T47D), and non-cancerous breast cells (MCF-12A) (figure 3). From this test they saw that cis-platin for A2780, SH-SY5y, and MCF-7 was the best inhibitor. It wasn't until they looked at T47D where they saw a great resistance to cis-platin and 5a in this case was the best option for the resistant cancer cell. Leading to the conclusion that this Ru complex (5a) has a high potential in treating someone who is resistant to cis-platin [4].

Figure 3: Antiproliferative activity

	IC_{50} (μM)[a]				
	A2780[b]	SH-SY5Y[b]	MCF-7[b]	T47D[b]	MCF-12A[c]
2a	30.4 ± 2.8[d]	67.1 ± 0.7[d]	88.7 ± 5.9[d]	21.4 ± 0.8	37.9 ± 0.8
2b	135 ± 4[d]	>150[d]	>150[d]	113 ± 11	105 ± 7
5a	8.9 ± 0.8	13.6 ± 3.6	49.8 ± 6.3	22.8 ± 4.3	59.3 ± 7.4
5b	50.1 ± 7.1	59.4 ± 7.3	108 ± 5	100 ± 6	111 ± 12
cis-platin	1.3 ± 0.4	4.1 ± 0.1	27.2 ± 3.3	>150	26.7 ± 3.0

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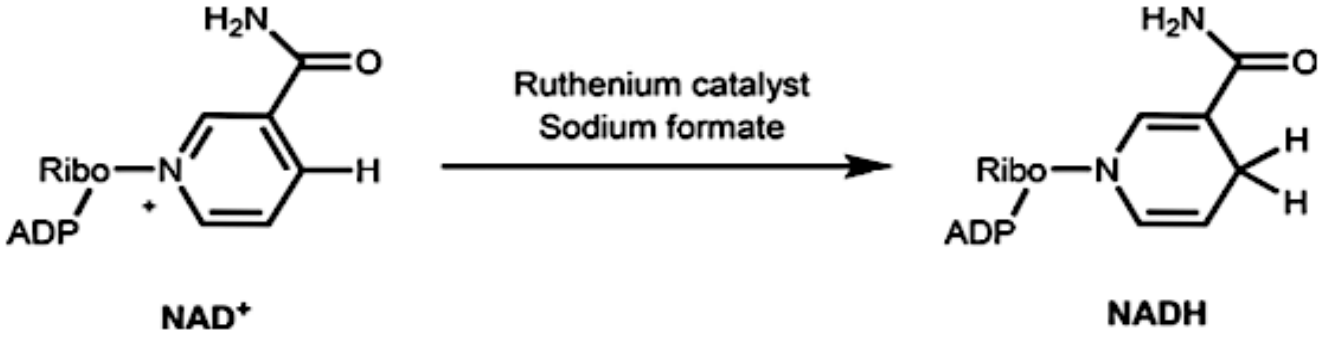
When looking into Ru ability to be an effective catalyst, they looked at NAD+ to its reduced form NADH. They wanted to see if Ru could be a catalyst for this well know coenzyme, known for critical cellular functions. So, they used Ruthenium as a catalyst and sodium formate as the hydrogen donor (figure 4).

Figure 4: Reduction of NAD+



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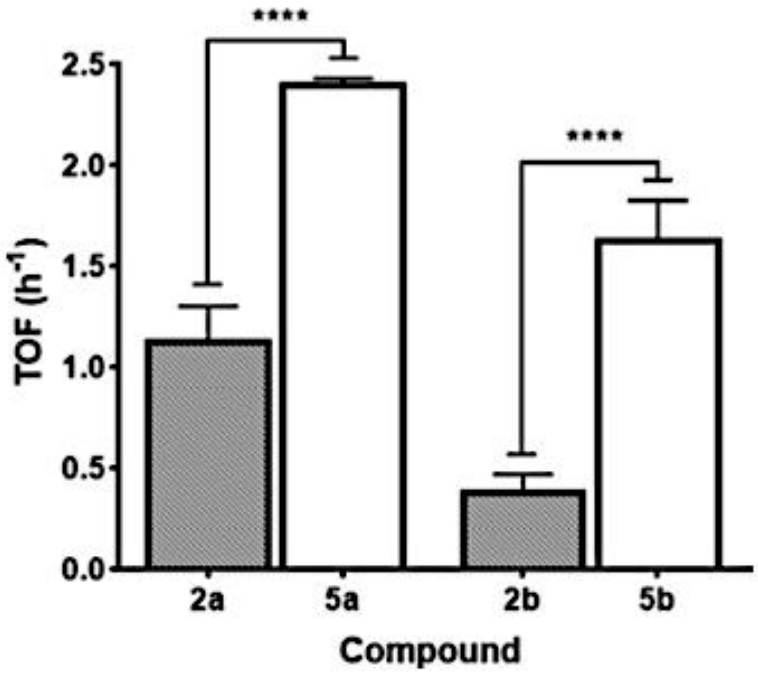
UV-vis spectra did confirm that 5a was a catalyst for NAD+ to NADH. They also obtained turnover frequency (TOF) of the complexes after they were in a water/methanol mixture, heated to 60°C. Turnover frequency is the number of moles transformed into the desired product/one mole of active site per hour, the larger the TOF, the higher the catalytic activity. Showing that 5a did have the higher TOF (figure 5), displaying that more NADH was

produced from 5a then the other complexes. While they did see Ru worked as a catalyst for this reduction, however, once this took place the compound could not operate within the cell environment. So, what they saw was Ru has a great cytotoxicity and catalytic potential, however the two could not work together. Which brought them to the concept of reactive oxygen species (ROS) generation. The over production of ROS would produce oxidative stress, which eventually leads to cell death[4].

Figure 5: TOF values



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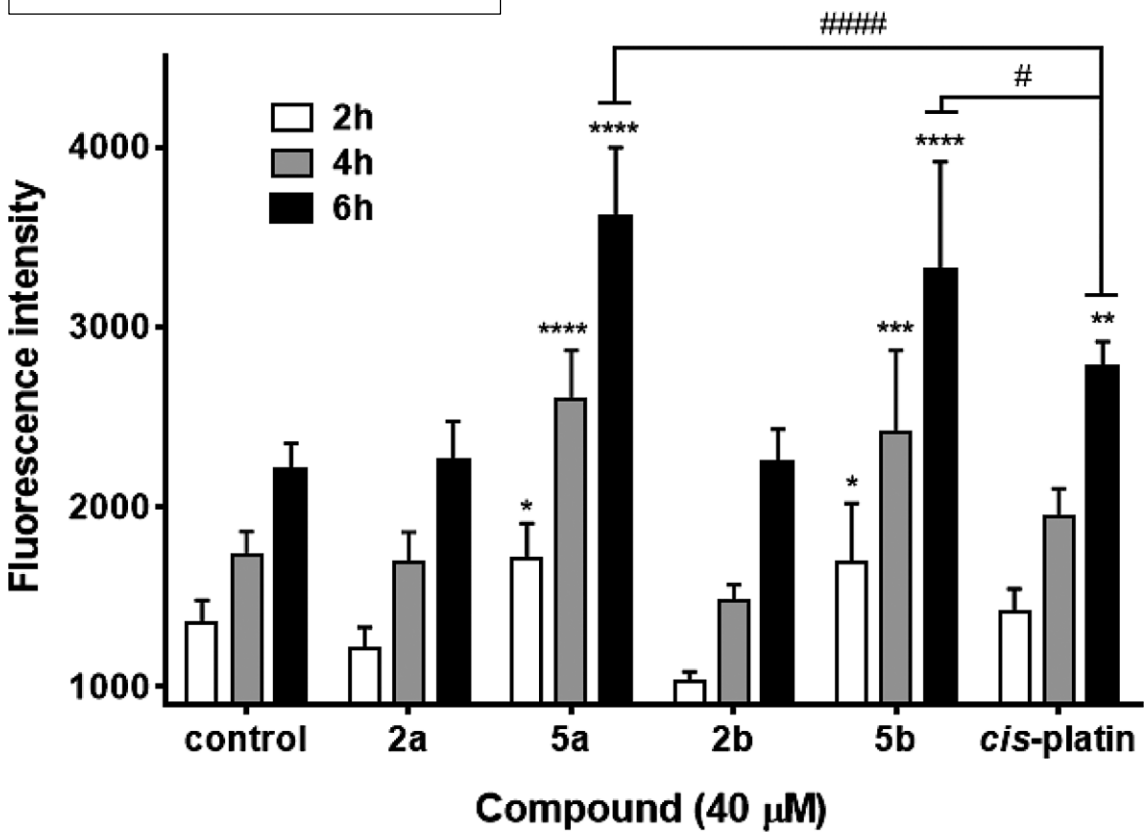
The main focus was seeing if the Ru complexes, could in fact, produce ROS. Hoping that a catalytic drug could select cancerous cells and then generate ROS, leading to cell death within

the cancer. There have been clinical trials in the area of ROS generation using two manganese porphyrin complexes treating metastatic colorectal cancer. Within this paper's research they used DCFDA (dichlorofluorescin diacetate) and fluorescence radiation for analysis. They test each complex against breast cancer cell line, seeing which complex resulted in a greater production. From the fluorescence they saw 5a-b complexes had the highest production. Complexes 2a-b had little to no production when compared to the control. Cis-platin did exhibit generation, however it was lower than 5a-b (figure 6) [4].

Figure 6: ROS production



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The overall research was assessing two different structural complexes, consisting of either a Schiff base or amine. They wanted to see the effects of a simple change, this change was the difference between the Schiff base and amine ligand and whether this change would have positive anticancer treatment potentials. This research group did see what they potentially wanted to see and that was Ru complexes had promise for antiproliferative activity as well as the ability to form ROS from catalyzing a redox reaction. When thinking about future research there is a high need for drugs that can reduce the resistance of cells. The problem found is that the tolerance for these drugs is growing and metallodrugs could provide an answer, as well as help our resistance to these drugs. Metallodrugs hold tremendous potential to help mankind overcome drug resistance and to find new cures in medicine. Further research into catalytic potential of complex 5a-b, in particular, and their ROS generation could be just what is needed in cancer treatments. Metallodrugs have a wide range yet to be explored. The simplest modification could end up having the greatest effect [4]. There are disorders and disease that could greatly benefit from a deeper understanding of metallodrugs. The hope is that people become open to the idea of metallodrugs and try not to only focus on the negative connotations. With any drug there is a range of side effects. Whether there is metal present in the drug or no metal present they all have their own kind of side effects. Metals can be a risk, but there is great potential with metals and drug research.

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