universität wien

MASTERARBEIT

„Tumorhemmende Metallkomplexe von Naphthochinonderivaten“

Mario Kubanik B.Sc.

angestrebter akademischer Grad

Master of Science (MSc)

Wien, 2011

Studienkennzahl lt. Studienblatt:	A 066 862
Studienrichtung lt. Studienblatt:	Masterstudium Chemie
Betreuerin / Betreuer:	PD. Mag. Dr. Christian Hartinger

universität wien

MASTER THESIS

„Tumor - inhibiting Metal Complexes with Naphthoquinone - derived Ligands“

Mario Kubanik B.Sc.

Submitted in part fulfilment of the requirements for the degree

Master of Science (MSc)

Supervisor

PD Mag. Dr. Christian Hartinger

Vienna, October 2011

First of all, I would like to give a glimpse of what I think of chemistry and the work on my master thesis, each supplemented with a quote.

Chemistry is a challenging field of science, with a wide variety of research directions, but in my opinion, bioinorganic chemistry is one of the most important research fields.

„Der wahre Zweck der Chemie besteht nicht darin, Gold zu machen, sondern Medizin herzustellen.“

(Paracelsus)

Research leads to better drugs and an increased lifespan.

„Früher starben die Menschen mit 35 Jahren, heute schimpfen sie bis 95 auf die Chemie.“

(Carl H. Krauch)

For this aim a lot of work in the laboratory is required, which isn`t always unproblematic.

„Diese Alchimisten sind immer nur damit beschäftigt, irgendwelches Zeug zu mischen und sich zu fragen, "He, was passiert, wenn wir einen Tropfen von diesem gelben Zeug hinzutun?" Und dann laufen sie zwei Wochen lang ohne Augenbrauen herum.“

(Terry Pratchett)

But after some time the practical part has to be finished and the writing part has to start.

"So eine Arbeit wird eigentlich nie fertig, man muss sie für fertig erklären, wenn man nach der Zeit und den Umständen das Möglichste getan hat."

(Johann Wolfgang von Goethe)

Finally, all I have to say is:

“Ich habe fertig!”

(Giovanni Trapattoni)

Acknowledgements

I would like to thank the following people:

I would like to thank O. Univ.-Prof. Dr. Dr. Keppler for the opportunity to perform my Master thesis at the Institute of Inorganic Chemistry of the University of Vienna.

Many thanks to my supervisors PD Mag. Dr. Christian Hartinger and DI Dr. Wolfgang Kandioller, who had the idea for my topic and supported me in every (chemical) matter.

I would like to thank Mag. Sergey Abramkin, Dr. Wolfgang Kandioller, Dipl.-Chem. Paul-Steffen Kuhn, Mag. Verena Pichler, Mag. Michael Primik and Prof. Dr. Markus Galanski for all the NMR measurements.

Ing. Alexander Roller and Prof. Dr. Vladimir Arion for X-ray data collection and structure refinement. Without them I would not know how my complexes really look like.

My Lab 6 colleagues Andrea, Leo, Martina, Masha, Sabine and Sam for the fun in the laboratory even if the chemistry sometimes did not work.

I furthermore would like to thank all my colleagues from the working group especially Verena, Sam, Lukas, Michi, Paul, Amitava, Sabine, Lindi, Christian, Wolfgang, Alex, Andrea and Elfi for the inspiring chats during the coffee breaks.

Since chemistry is not a study in which you can be successful on your own, I would like to thank my fellow students and friends Chrissi, Claudia, Kathi and Manu, who helped me through the studies.

A big **THANK YOU** goes to my parents and my whole family, which had to suffer during my examination periods (so the last five years) and supported me (with good advices and more importantly financially) through all the time of my life.

Furthermore I´d like to thank my good friends Kandi, Wolfi, Tanja and Harti, Lisi S., Lisi R. and Martin for the fun and the “sophisticated” talks in my spare time.

For financial support:

universität wien

Abstract

Metal containing cytostatics are very important in cancer treatment. The most prominent compounds of this kind are the platinum drugs cisplatin, carboplatin and oxaliplatin. A big disadvantage of these complexes is a broad spectrum of side effects, like nephrotoxicity, vomiting, nausea, neurotoxicity and so on. To avoid these adverse effects, the research for new chemotherapeutics focused on metal complexes with other central atoms than platinum(II). The ruthenium(III) complexes NAMI-A and KP1019 are under clinical trials and show promising results. It is assumed, that the reactive species are generated through intracellular reduction from Ru(III) to Ru(II) (“activation by reduction-hypothesis” by Clarke). The transport occurs through binding to plasma proteins after intravenous application. Since a few years, organometallic chemotherapeutics are under intensive investigation. Such Ru(II) compounds have a so called “piano-stool” configuration and the influence of the arene moiety on the biological activity was already extensively studied. For the remaining three binding sites bidentate ligands and one halido ligand are most frequently used. This type of coordination compound allows to tune the properties of the substance. This includes biophysical properties such as solubility and lipophilicity, but also the reactivity against biomolecules, or interaction with different biomolecules through binding to enzyme binding sites.

2-Hydroxy-[1,4]-naphthoquinone ligands exhibit the same first coordination sphere as the well-studied (thio)pyr(id)one-based metal complexes (4-pyrone, kojic acid, maltol, allomaltol, *etc.*).. Due to the quinonoid system, reactive oxygen species may be generated, which could lead to compounds with new properties and improved antitumor activity. Furthermore it is known, that some naphthoquinone derivatives inhibit enzymes of the cdc25 family, which could be another mode of action for improved cytostatic properties.

In my master thesis Ru(II) and Os(II) arene-complexes with different 2-hydroxy-[1,4]-naphthoquinones as chelating ligands were synthesized and characterized.

Zusammenfassung

Metallhältige Zytostatika sind in der Chemotherapie von großer Bedeutung. Die bekanntesten Verbindungen dieser Art sind die Platinkomplexe Cisplatin, Carboplatin und Oxaliplatin, welche jedoch ein breites Spektrum an Nebenwirkungen (Nephrotoxizität, Übelkeit, Erbrechen, Nervenschäden, *etc.*) aufweisen. Um diese nachteiligen Effekte zu umgehen, wird an der Entwicklung von neuen Krebstherapeutika geforscht, wobei Komplexverbindungen mit Ruthenium als Zentralatom von großem Interesse sind. Die Ruthenium(III)-Komplexe NAMI-A und KP1019 sind in klinischen Studien und in ihrer Entwicklung am weitesten vorangeschritten. Man nimmt an, dass die aktive Spezies erst durch intrazelluläre Reduktion von Ru(III) zu Ru(II) generiert wird („Activation by Reduction – Hypothese“ von Clarke), und dass der Transport im wesentlichen durch Plasmaproteine nach intravenöser Administration erfolgt. Seit einigen Jahren schreitet die Entwicklung in Richtung organometallischer Chemotherapeutika stark voran. Solche Ru(II) Verbindungen weisen eine sog. „piano-stool“ – Konfiguration auf, wobei der Einfluss des Arenliganden bereits eingehend untersucht wurde. Für die restlichen drei Bindungsstellen werden überwiegend zweizähnige Chelatliganden und ein Halogenidoligand verwendet. Diese Art von Verbindung ermöglicht ein sehr genaues Design von Substanzen mit spezifischen Eigenschaften. Diese umschließen sowohl biophysikalische Eigenschaften, wie die Löslichkeit und Lipophilie, aber auch die Reaktivität zu Biomolekülen oder auch die Wechselwirkung mit Biomolekülen durch Bindung in spezifische Enzymbindungsstellen. 2-Hydroxy-1,4-naphthochinonliganden sind eine Weiterentwicklung der bereits bekannten Pyron-basierten Chelatliganden (4-Pyron, Kojisäure, Maltol, Allomatol, *etc.*). Bei Koordination an Metallzentren bleibt die erste Koordinationssphäre unverändert. Aufgrund des chinoiden Systems könnten jedoch intrazellulär reaktive Sauerstoffspezies generiert und damit Verbindungen mit neuen Eigenschaften und verbesserter Antitumoraktivität erzielt werden. Weiters ist bekannt, dass einige Naphthochinonderivate Enzyme der Cdc25 Familie inhibieren können. So könnten möglicherweise auch über diesen Weg, verbesserte zytostatische Eigenschaften der Substanzen erreicht werden. Im Rahmen meiner Masterarbeit wurden nun Aren-Komplexe mit verschiedenen 2-Hydroxy-1,4-naphthochinon Liganden hergestellt und charakterisiert.

1 Table of contents

2 Introduction

2.1 Cancer – preface

In 2010, 19.757 people died of malignant growths (cancer) in Austria. Cancer is in Austria (and the developed countries) therefore the second most common cause of death after the cardiovascular diseases of which 33.196 people died in 2010.[1]

Due to the fact that cancer is not a single, well defined disease which can affect every tissue and organ in the human body, the malignant growths are classified after the WHO guidelines in accordance to Chapter II, C00-97 of the "International Statistical Classification of Diseases and Related Health Problems" (ICD-10). [2]

C00-C97	Malignant neoplasms		
	C00-C75	Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, haematopoietic and related tissue	
		C00-C14	Malignant neoplasms of lip, oral cavity and pharynx
		C15-C26	Malignant neoplasms of digestive organs
		C30-C39	Malignant neoplasms of respiratory and intrathoracic organs
		C40, C41	Malignant neoplasms of bone and articular cartilage
		C43, C44	Melanoma and other malignant neoplasms of skin
		C45-C49	Malignant neoplasms of mesothelial and soft tissue
		C50	Malignant neoplasm of breast
		C51-C58	Malignant neoplasms of female genital organs
		C60-C63	Malignant neoplasms of male genital organs
		C64-C68	Malignant neoplasms of urinary tract
		C69-C72	Malignant neoplasms of eye, brain and other parts of central nervous system
		C73-C75	Malignant neoplasms of thyroid and other endocrine glands
	C76-C80	Malignant neoplasms of ill-defined, secondary and unspecified sites	
	C81-C96	Malignant neoplasms of lymphoid, haematopoietic and related tissue	
	C97	Malignant neoplasms of independent (primary) multiple sites	

Table 1: Chapter II, C00 - 97 (ICD-10)

[1] http://www.statistik.at/web_de/statistiken/gesundheit/todesursachen/todesursachen_im_ueberblick/index.html, accessed September 20, 2011.
[2] http://www.who.int/classifications/icd/en/, accessed September 20, 2011.

As shown in Table 1, there is a broad variety of malignant neoplasms. This diversity is also reflected in Figure 1. Figure 1 shows the cancer incidence and mortality in Austria in 2008 for both genders. The most common types of cancer, which lead to death, are for women breast (C50), lung (C33-C34) and colorectal cancer (C18 – C21) and for men lung (C33-C34), colorectal (C18 –C21) and prostate cancer (C61).

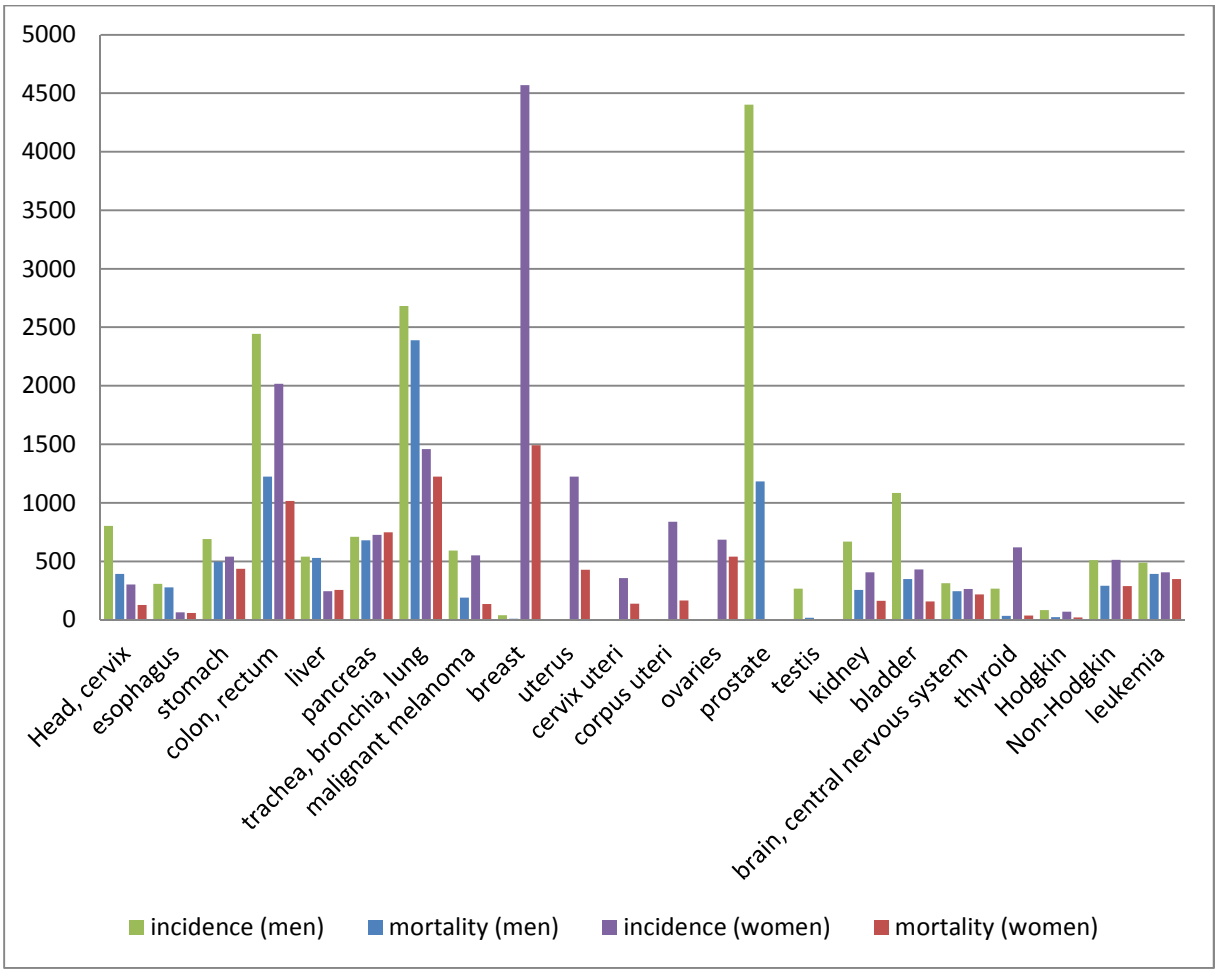


Figure 1: Cancer incidence and mortality in austria (2008)[3]

2.2 Carcinogenesis

Although there are about one hundred different tumor types (Table 1), the transformation from normal into malignant cells is usually described with a three step model of carcinogenesis (Figure 2).[4]

[3] Based on data from Statistik Austria; http://www.statistik.at/web_de/statistiken/gesundheit/krebserkrankungen/index.html, accessed October 11, 2011.

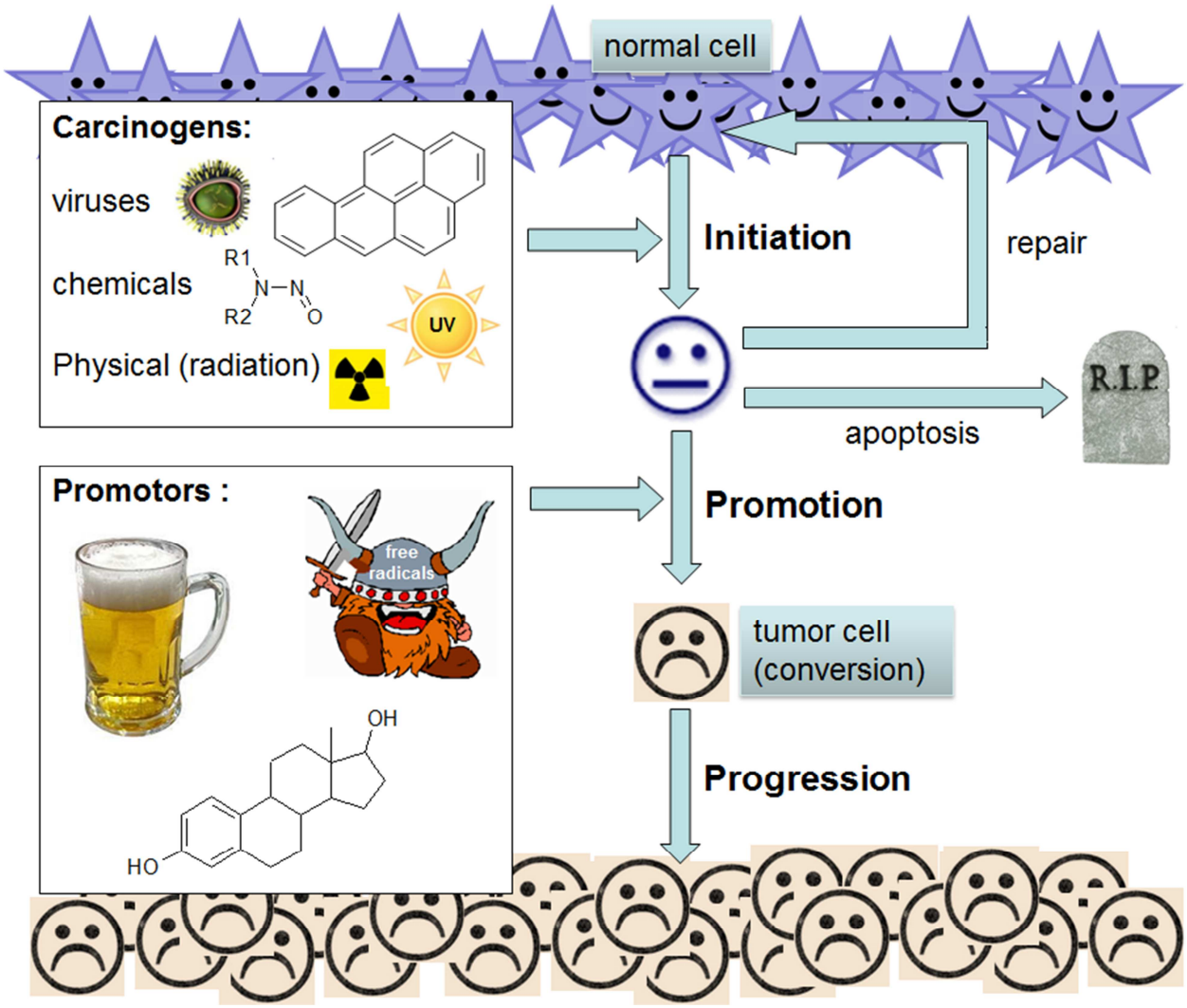


Figure 2: Carcinogenesis

In the first step of this model (Initiation), a single cell's DNA is altered through a carcinogen. A carcinogen can be a chemical substance (e.g. halogenated aliphatic hydrocarbons, nitrosamine, polycyclic aromatic hydrocarbons; metals like cadmium, cobalt, lead, *etc.*), radiation (UV-light, radioactivity and X-rays), or viruses (human papilloma virus, hepatitis B virus). Usually the damage can be removed by different repair mechanisms, or the cell undergoes the programmed cell death (apoptosis). However, cumulative mutations can lead to a loss of this function. If these mutations affect proto-oncogenes or anti-oncogenes (mainly genes which play an important role in signal transduction in there unaltered form), tumorigenesis is more likely.[5]

[4] J. Koolman, K. Röhm, Taschenatlas der Biochemie, Georg-Thieme-Verlag, Stuttgart **2002**, *3. edition*, 400.

[5] Löffler, Petrides, Heinrich, Biochemie & Pathobiochemie, Springer Verlag, Heidelberg, **2007**, *8. edition*, 1142 – 1161.

In the next step, which is the promotion, the altered cell starts to proliferate. This process is very slow and can take a few years. Endogenous or exogenous substances (hormones, ethanol, cigarette smoke, *etc.*) can accelerate the growth and lead to a preneoplastic focus. If this benign tumor is further exposed to carcinogenic substances the last step occurs, *i. e.*, the progression.

Malignant tumors proliferate uncontrolled and invade the surrounding tissue. At a certain size it builds a network of blood vessels to satisfy its increased nutrient demand (angiogenesis). Eventually, metastases occur in different parts of the body.

2.3 Cancer therapy

Due to the fact, that cancer is a family of diseases and the pathogenesis differs from person to person, there are different treatment methods. The classic therapies are surgery, radiation therapy and chemotherapy. The choice which treatment form is used depends on the health and age of the patient, on the one side and the tumor (location, class, state) on the other side.

Surgery is used in case of different (localized) carcinomas in an early stage and localized metastases.

Radiation therapy uses high energetic X-rays, γ-rays or radioactive radiation to damage tumor cells. It can be distinguished between curative- (for healing), adjuvant- (after surgery) and palliative radiotherapy (pain relief, life extension). Radiation therapy can be used for primary carcinomas or localized metastases. Due to the fact that this treatment also harms normal cells in the surrounding, several side effects like diarrhea, mucosal inflammation, urinary tract infections and thyroid hypofunction occur.

Chemotherapy uses drugs (synthetic or naturally occurring) to kill tumor cells. It can be distinguished between cytostatics (inhibit the cell proliferation by intercalation or binding to DNA, or inhibition of enzymes) or cytotoxics (direct damage to the cancer cell).[6] The cytostatics again can be classified whether they inhibit the DNA duplication direct or indirectly.

[6] http://www.krebshilfe-wien.at, accessed September 20, 2011.

The first group comprises alkylating and intercalating agents, which alter the structure of the cellular DNA by covalent binding and therefore inhibit transcription and replication (Figure 3).

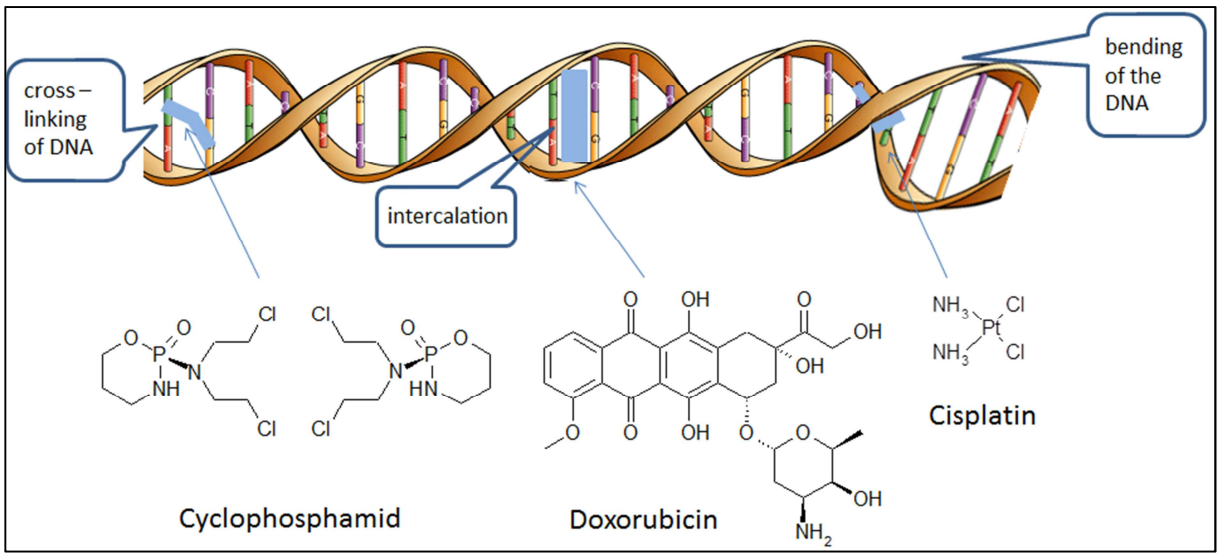


Figure 3: Alkylating and intercalating agents

The second group contains drugs which block the cell proliferation indirectly. Antimetabolites are inhibitors of enzymes, which are necessary for the nucleotide biosynthesis, by mimicking nucleobases (e.g. 6-*mercaptopurine, hydroxyurea, 5-fluorouracil, methotrexate*).[7]

In addition, there are many other types of chemotherapeutics known, which are based on a variety of concepts. Cytotoxic antibiotics (*e.g. anthracycline*, *bleomycine, mitoxantrone*), topoisomerase inhibitors (*e.g.* topotecan, etoposide), antibodies (*e.g.* bevacizumab), enzyme inhibitors, mitosis inhibitors, hormone and signal transduction inhibitors are examples for other chemotherapeutic drugs.

In most cases a combination of all three treatment forms is used in cancer therapy.

[7] J. Koolman, K. Röhm, Taschenatlas der Biochemie, **2002**, *3. Auflage*, 402.

2.4 Metal-based compounds for cancer treatment

In the 1960ies, an experiment by Barnett Rosenberg led to the rediscovery of *cis*-diamminedichloridoplatinum(II) (cisplatin) (Figure 4), which was first synthesized and published by Michele Peyrone in 1844.

The original goal of the experiment was to explore the impact of an electromagnetic field on the cell division. For his test he used *E. coli* bacteria, glucose and magnesium chloride enriched medium and platinum electrodes, which were known for their chemical inertness. Rosenberg observed a filamentous growth of the bacteria which is the case, if the cell division is blocked, but not the cell growth.

Through systematic research he soon found out, that this affect was caused by cisplatin, which was formed by oxidation of the platinum electrodes to Pt(IV) and the chloride and ammonium ions in the medium, and not by the electromagnetic field.[8]

The success of cisplatin in cancer treatment was the starting point of intensive research for new platinum-based drugs. From the multitude of synthesized compounds in the last 40 years, only carboplatin (*cis*-diammine(1,1-cyclobutanedicarboxylato)platinum(II)) and oxaliplatin ([(1R,2R)-diaminocyclohexane]oxalatoplatinum(II)) (Figure 4) have achieved approval for worldwide clinical use besides cisplatin.[9]

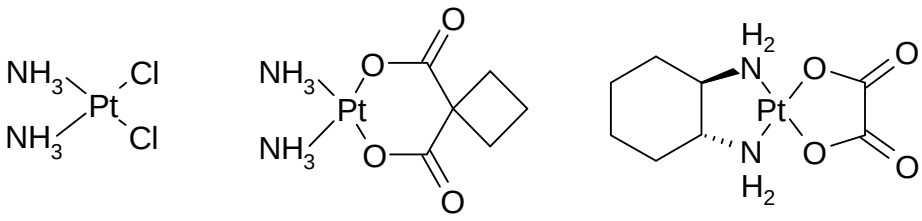


Figure 4: Platinum drugs in clinical use; cisplatin, carboplatin, oxaliplatin (from left to right)

The spectrum of activity of cisplatin is broad but the success of chemotherapy depends on the type of cancer. In combination with other cytostatics, a synergistic effect can be achieved (combination therapy) and decreased, for example, the mortality of patients suffering from testicular or bladder cancer to less than 10%.[10] Furthermore, cisplatin shows activity against lung, oesophageal, ovarian, cervical, head and neck cancer and plays an important role in the treatment of these diseases.

[8] M. Galanski, B. K. Keppler; *Pharm. Unserer Zeit*, **2006** (35)
[9] F. Muggia, *Gynecol Oncol*, **2009**, 275-281
[10] W. Kaim, B. Schwederski, *Bioanorganische Chemie*,**2005**, 4. Auflage

Carboplatin and its DNA adducts are very similar to cisplatin and covers therefore the same application areas. The advantage of this cytostatic is the bis(carboxylate) ligand. Due to the slower hydrolysis, the adverse side effects are less pronounced (*e.g.* ototoxicity, neurotoxicity, nephrotoxicity).

For the treatment of colorectal cancer, an oxaliplatin/5-fluorouracil combination therapy is used.[11]

Beside the curative or live extending advantages, which are achieved with tumor-inhibiting platinum complexes, there are still some major problems in the cancer treatment to overcome. The above mentioned coordination compounds cause a broad variety of adverse effects, for example tinnitus, ototoxicity, neurotoxicity, nausea, nephrotoxicity and vomiting. Another problem, are acquired or intrinsic resistances occurring during chemotherapy.[11,12] Due to these facts, research on non-platinum based drugs increased in the past few years. [13]

Besides Pt(II) compounds, ruthenium complexes are the most promising compounds in the research for new cytostatics. They show benefits with regard to side effects, resistance development and activity spectrum. Furthermore, coordination chemistry with compounds with an octahedral coordination sphere can be done, which provide access to different oxidation states (II, III, IV) under physiological conditions but maintain ligand exchange kinetics comparable to Pt(II) drugs.[14]

Another advantage of ruthenium compounds is a lower general toxicity, compared to platinum drugs, which can be explained by their supposed mode of action (Figure 5). Due to the similarity of Ru(III) and Fe(III), it is supposed that the complexes bind to transferrin (two binding sits per transport protein) and other biomolecules such as albumin after intravenous administration. Because of an increased iron uptake of cancerous cells this leads to an accumulation of Ru(III) at the target. After endocytosis and release in the reductive intracellular milieu, the Ru(III) prodrug might be activated

[11] M. A. Jakupec, M. Galanski, B. K. Keppler*, Rev. Physiol. Biochem. Pharmacol*., **2003**, 146, 1-53
[12] P. Heffeter, U. Jungwirth, M. Jakupec, C. Hartinger, M. Galanski, L. Elbling, M. Micksche, B. Keppler, W. Berger, *Drug Resistance Updates*, **2008**, 11, 1-16
[13] C. S. Allyardyce, A. Dorcier, C. Scolaro, P. J. Dyson, *Appl. Organometal. Chem*., **2005**, 19: 1-10
[14] M. A. Jakupec, M. Galanski, V.B. Arion, C. G. Hartinger, B. K. Keppler*, Dalton Trans.*, **2008**, 183-184

by reduction.[15] This active Ru(II) species can now induce apoptosis (programmed cell death) either by direct interaction with DNA or through the intrinsic mitochondrial pathway.[13,16]

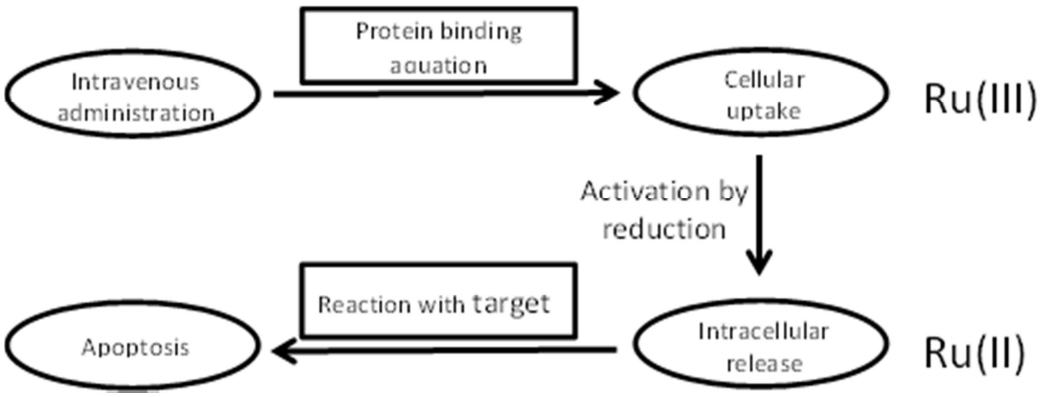


Figure 5: Proposed mode of action of Ru(III) drugs.

2.4.1 Ruthenium(III)-based drugs

The most prominent and best studied ruthenium(III) compounds are NAMI-A (imidazolium [*trans*-tetrachlorido(dimethylsulfoxide)(1*H*-imidazole)ruthenate(III)]) and KP1019 (indazolium [*trans*-tetrachlorobis(1*H*-indazole)ruthenate(III)]) (Figure 6).

These two drugs have octahedral coordination geometry with ruthenium as the central atom in oxidation state +III and were the first ruthenium(III) complexes in clinical trials. Today both are in clinical phase II studies (KP1019 in a new formulation as the respective sodium salt KP1339). Although KP1019 and NAMI-A have structural similarities, they exhibit quite different biological effects and chemical properties.

KP1019 proved activity against different resistant tumors (gastrinoma non-pancreatic neuroendocrine-, carcinoid tumor, colorectal- and non-small cell lung cancers).[17]

In contrast, NAMI-A shows no or little activity against primary tumors in animal models, but an antimetastatic effect.[18,19]

[15] M. J. Clarke, Met. Ions Biol. Syst., 1980, 11,231.
[16] C. G. Hartinger, M. A. Jakupec, S. Zorbas-Seifried, M. Groessl, A. Egger, W. Berger, H. Zorbas, P.J. Dyson, B. K. Keppler, *Chem. Biodiv.*, **2008**, Vol.5, 2140-2155
[17] http://www.niikipharma.com/newsandevents.html, accessed September 20, **2011**.
[18] I. Bratsos, S. Jedner, T. Gianferrara, E. Alessio, *CHIMIA*, **2007**, 61, No. 11.
[19] A. Levina, A. Mitra, P. A. Lay, *Metallomics*, **2009**, 1, 458-470.

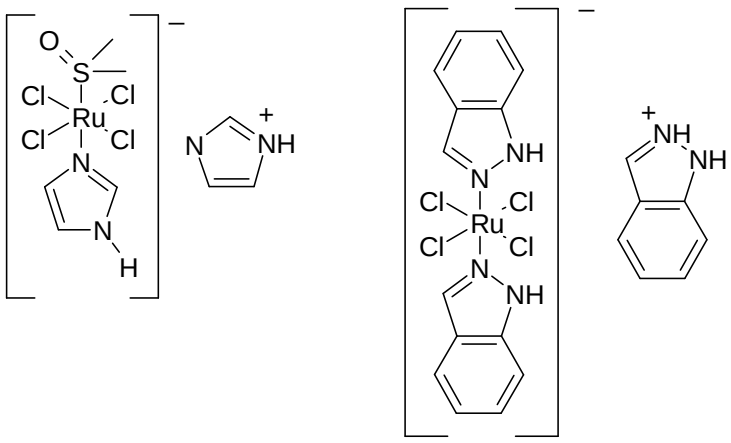


Figure 6: Structures of NAMI-A (left) and KP1019 (right)

The mode of action of KP1019 is still not fully understood. Although the complex interacts with the DNA after reduction to Ru(II), DNA does not seem to be the main target which leads to cell death. The intrinsic mitochondrial pathway or generation of reactive oxygen species (ROS) may also play a role in the mode of action of KP1019.[14]

Ruthenium(II)-arene based drug candidates

Ruthenium(II)-arene complexes belong to the most studied organoruthenium compounds. The “aromatic seat” in the so called “piano-stool configuration” (Figure 7) stabilizes the Ru(II) central atom and provides a hydrophobic side, which facilitates passive transport through the cell membrane. The ligands x, y and z are the legs of the chair.

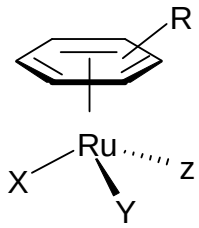
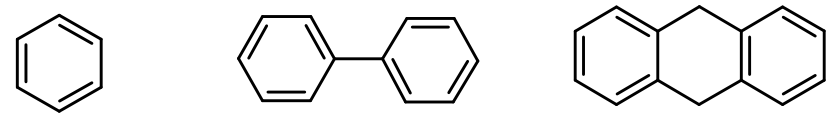


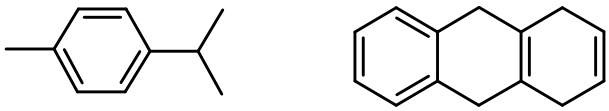
Figure 7: Ru(II) complex with "piano-stool" configuration

Sadler *et al*. studied the influence of different arene ligands (Figure 8) on the biological

activity of ruthenium(II) complexes with the general form [Ru(η^6-arene)(en)(X)] (en= ethylenediamine, X= Cl, Br, I).



benzene biphenyl dihydroanthracene



p-cymene tetrahydroanthracene

Figure 8: Arene ligands studied by Sadler and colleagues

The results revealed an increase of cytotoxic activity in A2780 cells (human ovarian carcinoma cell line), with an increase in lipophilicity of the arene ligand in the order benzene < *p*-cymene < biphenyl < dihydroanthracene < tetrahydroanthracene. Although tetrahydroanthracene shows the best results, often *p*-cymene is chosen, which is a compromise, between lipophilicity and cytotoxic activity.[20]

The possible mode of action, of Ru(II)-arene compounds differs from those of Ru(III) complexes. The first step includes hydrolysis to the more reactive aqua species which can in a next step react with nucleobases. The leaving group is in most cases a halide ligand. Since monodentate ligands are not as stable as bidentate ones, they can react with different biomolecules in the human body, which leads to loss of activity against certain cancer cells (e. g. A2780 ovarian cancer). Therefore, in most cases, the remaining two binding sites are occupied by chelating ligands.[21]

RAPTA-C (Figure 9) ([Ru(η^6-*p*-cymene)Cl_2(PTA)]) a member of the ruthenium-PTA-arene-compounds (PTA = 1,3,5-triaza-7-phosphaadamantane) shows antimetastatic activity compare able to that of NAMI-A with low general toxicity.[22] Modification of the PTA group led to DAPTA complexes (DAPTA = 3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane). Recent investigations of the RAPTA and DAPTA

[20] R. E. Aird, J. Cummings, A. A. Ritchie, M. Muir, R. E. Morris, H. Chen, P. J. Sadler, D. I. Jodrell, *Br. J. Cancer*, **2002**, 86, 1652-1657.
[21] R. E. Morris, R. E. Aird, P. Murdoch, H. Chen, J. Cummings, N. D. Hughes, S. Parsons, A. Parkin, G. Boyd, D. I. Jodrell, P. J. Sadler, *J. Med. Chem.,* **2001**, 44 (22), 3616-3621.
[22] A. Casini, C. G. Hartinger, A. A. Nazarov, P. J. Dyson, *Organomet. Chem*., **2010**, 32:57-80

compounds indicate antiangiogenic activity. Especially for RAPTA-T and DAPTA-C, inhibition of CAM (chicken chorioallantoic membrane) was shown.[23]

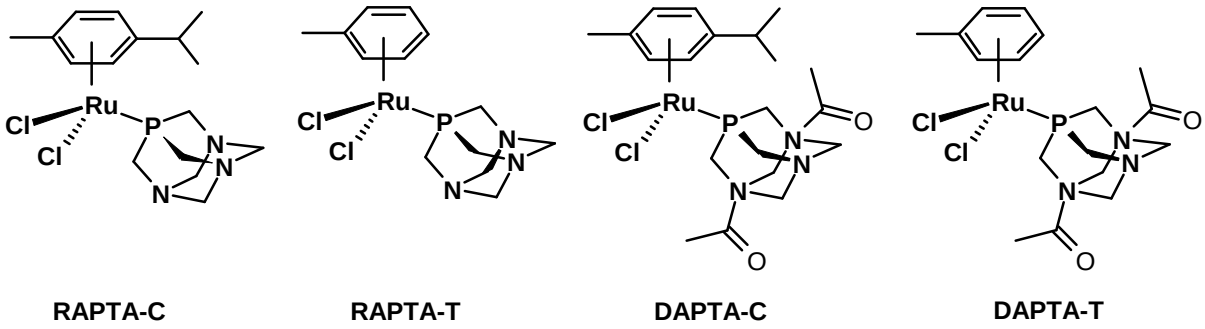


Figure 9: The chemical structure of different RAPTA and DAPTA complexes.

For a long time chelating ligands were kept relatively simple and derivatization occurred through modification of the arene moiety. Since a few years, ligands with more complex structures are under investigation. Figure 10 shows some examples of 4-pyrone-derived chelating ligands.[24,25,26,27,28]

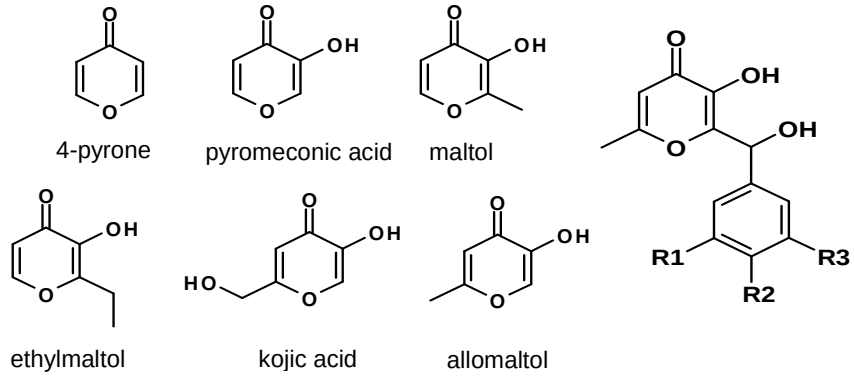


Figure 10: Examples of pyrone-derived chelating ligands

[23] P. Nowak-Sliwinska, J. R. van Beijnum, A. Casini, A. A. Nazarov, G. Wagnières, H. van den Bergh, P. J. Dyson, A.W. Griffioen, *J. Med. Chem*., **2011**, 54, 3895-3902.

[24] A. F. A. Peacock, M. Melchart, R. j. Deeth, A. Habtemariam, S. Parsons, P. J. Sadler, *Chem. Eur. J.*, **2007**, 13, 2601-2613.

[25] W. Kandioller, C. G. Hartinger, A. A. Nazarov, J. Kasser, R. John, M. A. Jakupec, V. B. Arion, P. J. Dyson, B. K. Keppler, *J. Organomet. Chem.,* **2008**.

[26] W. Kandioller, C. G. Hartinger, A. A. Nazarov, C. Bartel, M. Skocic, M. A. Jakupec, V. B. Arion, B. K. Keppler, *Chem. Eur. J*., **2009**, 15, 12283-12291.

[27] W. Kandioller, C. G. Hartinger, A. A. Nazarov, M. L. Kuznetsov, R. O. John, C. Bartel, M. A. Jakupec, V. B. Arion, B. K. Keppler, *Organometallics*, **2009**, 28, 4249-4251.

[28] W. Kandioller, A. Kurzwernhart, M. Hanif, S. M. Meier, H. Henke, B. K. Keppler, C. G. Hartinger, *J. Organomet. Chem.,* **2010**.

A further development of ruthenium-arene complexes with maltol derived chelating ligands are dinuclear ruthenium complexes (Figure 11). In vitro tests of these substances showed an increase in cytotoxic activity correlated with the spacer length between the metal centers. The best results showed the most lipophilic complex (n=12) and features a synergistic behavior of the two metal centers. [29,30,31]

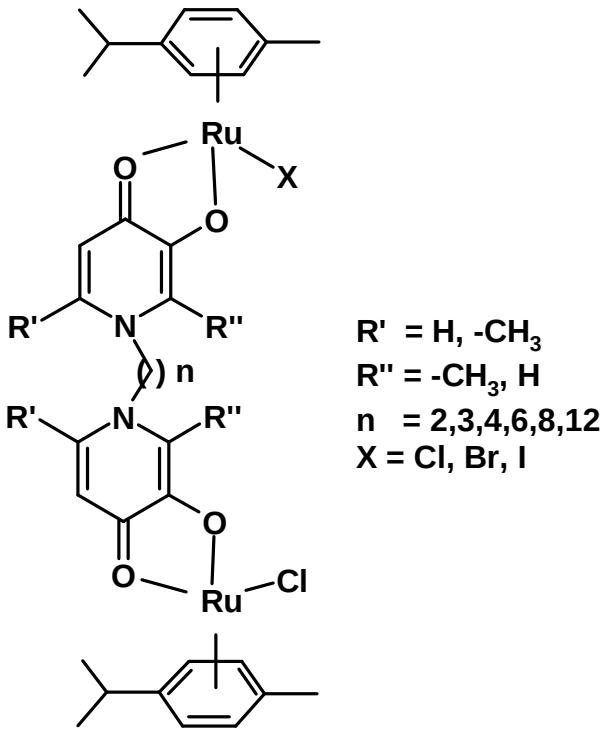


Figure 11: $PyrRu_2^n$

A more recent approach is the use of chelating ligands with biological activity. This can result in an enhanced cellular uptake of the biologically active ligand, or an increase in solubility. Synergistic effects from metal and ligands or different modes of action can also be achieved by complexation.[14]

Examples for such compounds are ruthenium arene complexes with indoloquinoline derivatives as chelators (Figure 12). These ligands were developed from paullones which are known cyclin dependent kinase (CDK) inhibitors. Antiproliferative activities of

[29] M. Mendoza-Ferri, C. G. Hartinger, R. E. Eichinger, N. Stolyarova, K. Severin, M. A. Jakupec, A. A. Nazarov, B. K. Keppler, *Organometallics*, **2008**, 27, 2405-2407.
[30] S. M. Ashraf, W. Kandioller, M. Mendoza-Ferri, A. A. Nazarov, C. G. Hartinger, B. K. Keppler, *Chem. Biodiv.*, **2008**, Vol. 5, 2060-2066.
[31] M. Mendoza-Ferri, C. G. Hartinger, A. A. Nazarov, W. Kandioller, K. Severin, B. K. Keppler, *Appl. Organometal. Chem.*, **2008**, 22, 326-332.

these complexes were remarkably good, whereas the indoloquinolines shows an insufficient solubility and could not be tested on their antitumor activity.[32]

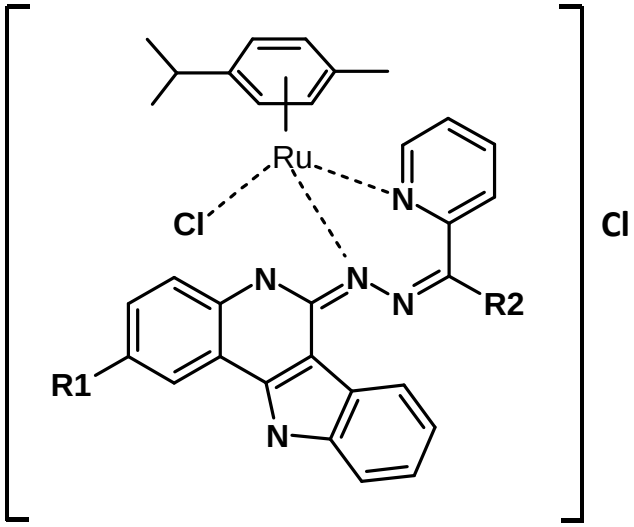


Figure 12: Ruthenium(II)-arene complex with a modified indoloquinoline ligand.

2.4.2 Os(II)-based drugs

Osmium is another heavy metal of the platinum group, with oxidation states from –II to +VIII. The most important oxidation states of osmium in bioinorganic coordination chemistry are +II and +III. Although it is on the first sight quite similar to ruthenium, for example with regard to the synthesis, the ligand exchange kinetic is totally different. Osmium half-sandwich complexes have been under investigation only since a few years. The hydrolysis rates for osmium compounds can be altered by choosing the appropriate chelating ligand. With an N,N-chelating ligand, the ligand exchange rates of Os-arene complexes were 40-100 times lower than for the ruthenium analogue. This behavior changes if the chelating ligand is replaced with an O,O-chelate (e.g. acetylacetone), which leads to an increase in the rate of water exchange.[33] However, the first Os-arene complex with *in vivo* activity against human colon cancer (HCT116, xenografts in mice) was an Os(II)arene-azopyridine complex (Figure 13) in 2011.[34]

[32] L. K. Filak, G. Mühlgassner, F. Bacher, A. Roller, M. Galanski, M. A. Jakupec, B. K. Keppler, V. B. Arion, *Organometallics*, **2011**, 30, 273-283.
[33] A. F. A. Peacock, P. J. Sadler, *Chem. Asian J.*, **2008**, 3, 1890-1899.
[34] S. D. Shnyder, Y. Fu, A. Habtemariam, S. H. van Rijt, P. A. Cooper, P. M. Loadman, P. J. Sadler, *Med. Chem. Commun.*, **2011**, 2, 666-668.

Other examples of osmium arene complexes are Os(II)-p-cymene complexes with paullone- and indoquinoline derived ligands. These are examples of targeted compounds, having probably CDK inhibitor properties.[32,35] (figure 13)

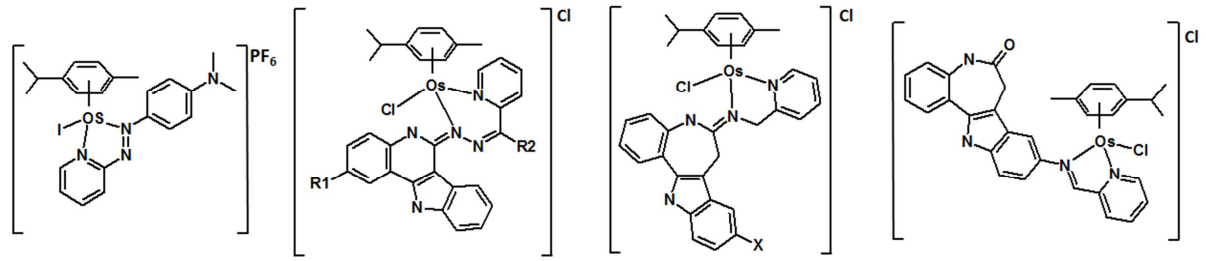


Figure 13: Examples of Os(II)-arene complexes.

2.5 Cyclin-dependent kinases

The cell cycle is a complex process which is divided into mitosis and interphase (consisting of G_1-, S and G_2- phases). Disturbances in this process can lead to diseases (e.g. cancer), and this is why regulation mechanisms are very important. A main regulating mechanism consists of cyclins and cyclin dependent kinases (CDKs).[36] Since the concentration of the cyclins oscillates during specific times of the cell cycle, this group of proteins are responsible of the time dependent activation of the CDKs. Another requirement for the kinase activity of cyclin/cdk complexes is the phosphorylation/dephosphorylation through the CDC25 phosphatases (cell division cycle 25). Three isoforms have been identified (CDC25A, CDC25B and CDC25C) which are responsible for progression through different cell cycle checkpoints. Through dephosphorylation, CDC25A activates cdk2/cyclinE and cdk2/cyclinA complexes and is therefore responsible for the G_1 to S transition. CDC25B is responsible for the G_2 to M transition by activation of the cdk1/cyclinB complex.

An overexpression of CDC25A and CDC25B is often found in cancers. Due to that fact, development of targeted cytostatics, which inhibit the CDC25 activity are currently under investigation.[37]

[35] W. F. Schmid, R. O. John, G. Mühlgassner, P. Heffeter, M. A. Jakupec, M. Galanski, W. Berger, V. B. Arion, B. K. Keppler, *J. Med. Chem.*, **2007**, 50, 6343-6355.
[36] Löffler, Petrides, Heinrich, Biochemie & Pathobiochemie, Springer Verlag, Heidelberg, **2007**, *8. edition*, 220 – 251.
[37] R. Boutros, V. Lobjois, B. Ducommun, *Nat. Rev. Canc.*, **2007**, Vol.7, 495 - 507

The CDC25 inhibitors can be divided into six different groups:

→ natural products (e.g.: sulfricins, dnacins and dysiolides)

→ lipophilic acids

→ electrophiles (fascaplysin)

→ phosphate mimics (e.g. xenicane diterpenoids)

→ peptides and peptide analogues

→ quinones (menadione)[38]

In my work, I focused on 2-hydroxy-1,4-naphthoquinones as chelating ligands of Ru(II)- and Os(II)-cymene complexes.

2.6 Naphthoquinones

Naphthoquinones belong to the family of secondary metabolites (in actinomycetes, fungi, lichens and algae) and occur in most important families of the higher plants in reduced and glycosidic form. They are derivatives of naphthalene with substitution in different positions. Most common are keto groups in positions C_1 and C_2 (1,2-naphthoquinones) or C_1 and C_4 (1,4-naphthoquinones), with a variety of other substituents on the remaining positions. Figure 14 shows different 1,4-naphthoquinones with their trivial names.[39]

Naphthoquinones have a broad variety on pharmacological properties, such as anticancer,[40,41] antimicrobial,[4243] antiparasitic,[44] antiviral[45] and molluscicidal[46] activity.

[38] J. S. Lazo, P. Wipf, *Anticancer Agents Med. Chem.,* **2008**, 8(8): 837–842.
[39] P. Babula, V. Adam, L. Havel, R. Kizek, *Curr. Pharm. Anal.*, **2009**, Vol. 5, No.1.
[40] I. Gomez-Monterrey, P. Campiglia, C. Aquino, A. Bertamino, I. Granata, A. Carotenuto, D. Brancaccio, P. Stiuso, I. Scognamiglio, M. R. Rusciano, A. S. Maione, M. Illario, P. Grieco, B. Maresca, E. Novellino, *J. Med. Chem.*, **2011**, 54, 4077-4091.
[41] J. M. M. del Corral, M. A. Castro, A. B. Oliveira, S. A. Gualberto, C. Cuevas, A. S. Feliciano, *Bioorg. Med. Chem*., **2006**, 14, 7231-7240.
[42] J. S. Mossa, F. S. El-Feraly, I. Muhammad, *Phytother. Res.,* **2004**, 18, 934–937.
[43] A. Riffel, L. F. Medina, V. Stefani, R. C. Santos, D. Bizani, A. Brandelli, *Braz J Med Biol Res*, **2002**, 35: 811-818.
[44] A. V. Pinto, S. L. de Castro, *Molecules*, **2009**, 14, 4570-4590.
[45] M. R. Fesen, K. W. Kohn, F. Leteurtre, Y. Pommier, *Proc. Natl. Acad. Sci. USA*, **1993**, Vol. 90,2399-2403.

Furthermore, substances of these natural occurring metabolites show antileukemic activity. Especially the glycosides of juglone demonstrate activity in HL-60 cells (human promyelocytic leukemia cells).[47]

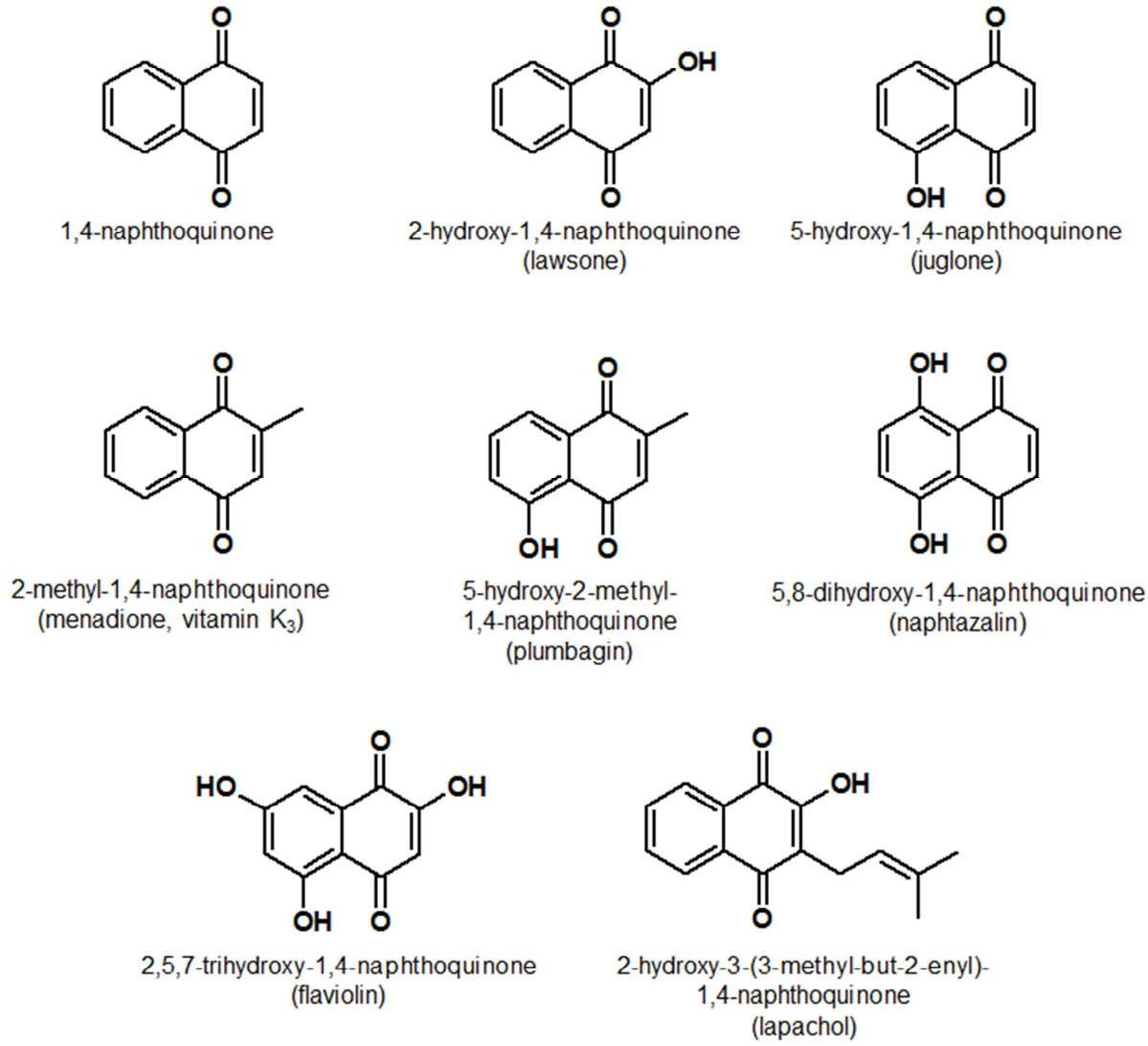
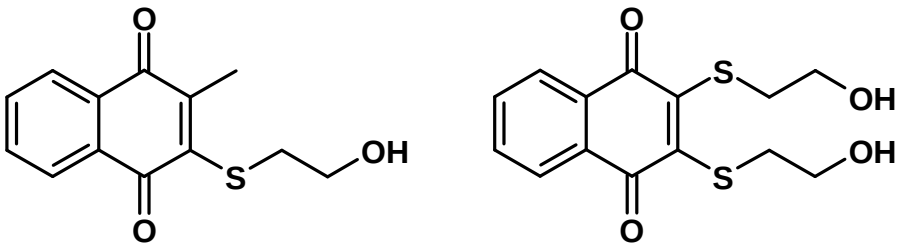


Figure 14: Examples of different 1,4-naphthoquinones

The cytostatic effects which are induced through naphthoquinone derivatives are based on different biological properties of this substance family. Quinones are redox active compounds and therefore able to generate ROS (reactive oxygen species) such as the superoxide anion radical ($O_2^{\bullet-}$), H_2O_2 and the hydroxyl radical ($^{\bullet}OH$).[48] This increased level of reactive species can lead to apoptosis via the extrinsic and intrinsic

[46] T. M. S. Silva, C. A. Camara, T. P. Barbosa, A. Z. Soares, *Bioorg. Med. Chem.*, **2005**, 13, 193–196.
[47] S.N. Fedorov, L.K. Shubina, A. Kuzmich, S.G. Polonik, *Open Glycoscience*, **2011**, Volume 4.
[48] N. V. de Witte, A. O.M. Stoppaniz, M. Dubin, *Arch. Biochem. Biophys*, **2004**, 432, 129-133.

mitochondrial pathways. [49,50] Another mode of action as known for doxorubicin and mitoxantrone, is the inhibition of DNA topoisomerase II.[51] As mentioned in the last chapter, CDC25 phosphatase is also a target of different naphthoquinone derivatives. The menadione thio analogue NSC 95397 (2,3-bis[2-hydroxyethylthio]-1,4-naphthoquinone) and Cpd 5 (2-(2-mercaptoethanol)-3-methyl-1,4-naphthoquinone) are two examples of CDC25 inhibitors with IC_{50} values in the µM range for Cpd 5 (found in the human hepatoma cell line Hep3B)[52] and in the nanomolar range for NSC 95397. [53]



Cpd 5 **NSC 95397**

Figure 15: Chemical structures of the CDC 25 phosphatase inhibitors Cpd 5 and NSC 95397

2.6.1 Synthesis of Naphthoquinones

Some of the 1,4-naphthoquinones shown in Figure 14, are obtainable through different biosynthetic pathways. For example lawsone is prepared *via* the shikimate/succinyl CoA combined pathway, plumbagin *via* acetate and malonate pathways and alkannin *via* the shikimate/mevalonate pathway. The fat soluble vitamins of the K group, phylloquinone (K_1) and menaquinone (K_2) are synthesized via the isochorismate pathway.[39]

There are theoretically several different methods to synthesis alkyl derivatives of lawsone reported in the literature. One example is the radical alkylation of lawsone with

[49] K. H. Xu, D. P. Lu, *Leuk. Res*., **2010**, 34, 658-665.
[50] R. J. McKallip, C. Lombard, J. Sun, R. Ramakrishnan, *Toxicol. Appl. Pharmacol.,* **2010**, 247, 41-52.
[51] B. Wang, Z. W. Miao, J. Wang, R. Y. Chen, X. D. Zhang, *Amino Acids*, **2008**, 35, 463–468.
[52] Y. Nishikawa, B. I. Carr, M. Wang, S. Kar, F. Finn, P. Dowdi, Z. B. Zhengi, J. Kernsi, S. Naganathani, *J. Biol*. *Chem.,* **1995**, 270, 28304-28310.
[53] J. S. Lazo, K. Nemoto, K. E. Pestell, K. Cooley, E. C. Southwick, D. A. Mitchell, W. Furey, R. Gussio, D. W. Zaharevitz, B. Joo, P. Wipf, *Mol. Pharmacol.*, **2002**, 61, 720-728.

acyl peroxide (Figure 16).[54] In this reaction acyl peroxide undergoes thermal decomposition, releases CO_2 and alkylates 2-hydroxy-1,4-naphthoquinone in position 3.

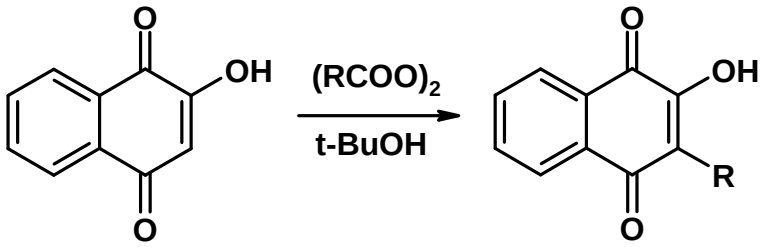


Figure 16: Radical alkylation of lawsone

Another synthetic pathway which leads to an alkyl derivative of lawsone is a palladium(0) catalysed reaction.[55] In this reaction the coupling of lawsone and an allyl alcohol (or its acetate) take place in the presence of tetrakis(triphenylphosphine)palladium(0) and AcOH as catalyst under neat conditions.

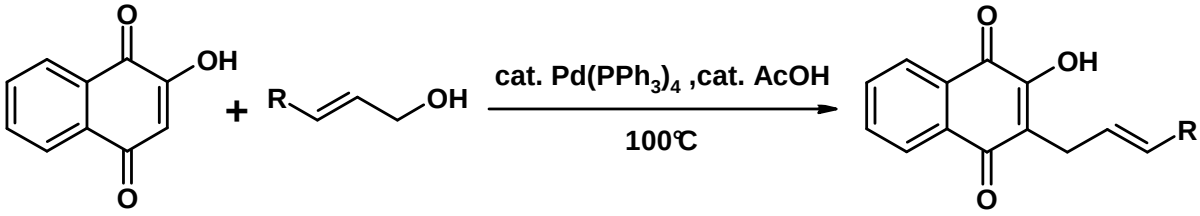


Figure 17: Pd(0) catalysed alkylation of lawsone

2-Hydroxy-3-methyl-1,4-naphthoquinone can be synthesized *via* epoxidation and acid catalyzed ring opening of menadione.[56]

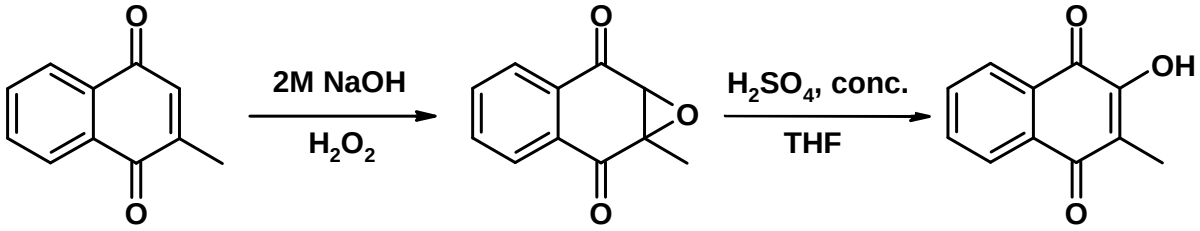


Figure 18: Derivatisation of menadione

[54] A. Y. Yakubovskaya, T. Y. Kochergina, V. A. Denisenko, D. V. Berdyshev, V. P. Glazunov, V. P. Anufriev, *Russ. Chem. Bull., Int. Ed.*, **2006**, Vol. 55, 301-305.
[55] G. Kazantzi, E. Malamidou-Xenikaki, S. Spyroudis, *Synlett,* **2007**, No.3, 427-430.
[56] R. Zhu, L. Xing, X. Wang, C. Cheng, B. Liu, Y. Hu, *Synlett,* **2007**, No. 14,2267–2271.

3 Results and Discussion

3.1 Synthesis and characterization of p-cymene complexes with 2-hydroxy-[1,4]-naphthoquinones as ligands.

Several different synthetic strategies were applied for the preparation of ligands **1a-6a**. Ligand **1a** (2-hydroxy-3-methyl-[1,4]-naphthoquinone) was synthesized *via* epoxidation of menadione, followed by an acid-catalyzed ring opening (Figure 19). Treating of lawsone (2-hydroxy-[1,4]-naphthoquinone) with diacyl peroxide led to the ligands **2a-5a**. 2-Hydroxy-3-propyl-[1,4]-naphthoquinone **(3a)** and 2-butyl-3-hydroxy-[1,4]-naphthoquinone **(4a)** were also synthesized *via* a Pd(0) catalyzed reaction, using tetrakis(triphenylphosphine)palladium(0) as catalyst. After cross-coupling, the allyic double bond was hydrogenated yielding **3a** and **4a**. Comparison between Pd(0) and the peroxide reaction are summarized in Table 2. Ligand **6a** was obtained by Pd(0)-catalyzed cross coupling with allyl alcohol.

	Steps	**Time (h)**[57]	**Yield (%)**	**Cost per gram product**
Pd(0)	2	3.5	31 **(3a)** 28 **(4a)**	23.50 € 26.39 €
peroxide	2	12 **(3a)** 14 **(4a)**	24 **(3a)** 16 **(4a)**	4.82 € 12.37 €

Table 2: Comparison between Pd(0) catalyzed and peroxide-based synthesis of the ligands

The acyl peroxide synthetic pathway seemed to be the better route for the ligand synthesis, because of the price and versatility of the educts although the yield is lower and the reaction time is significantly longer. The costs per gram, which are listed in Table 2 are calculated without solvents. The costs of the palladium coupled compounds is based on the used allyl alcohol, 2-hydroxy-1,4-naphthoquinone and tetrakis(triphenylphosphine)palladium(0). For the compounds synthesized *via* the

[57] Overall reaction time, without purification.

peroxide route, the calculation takes 2-hydroxy-1,4-naphthoquinone and the anhydride into account. It also should be mentioned that peroxides are labile compounds and therefore careful handling is necessary.

The ligands were characterized by 1D and 2D NMR (**3a**) spectroscopy, melting point and elemental analysis.

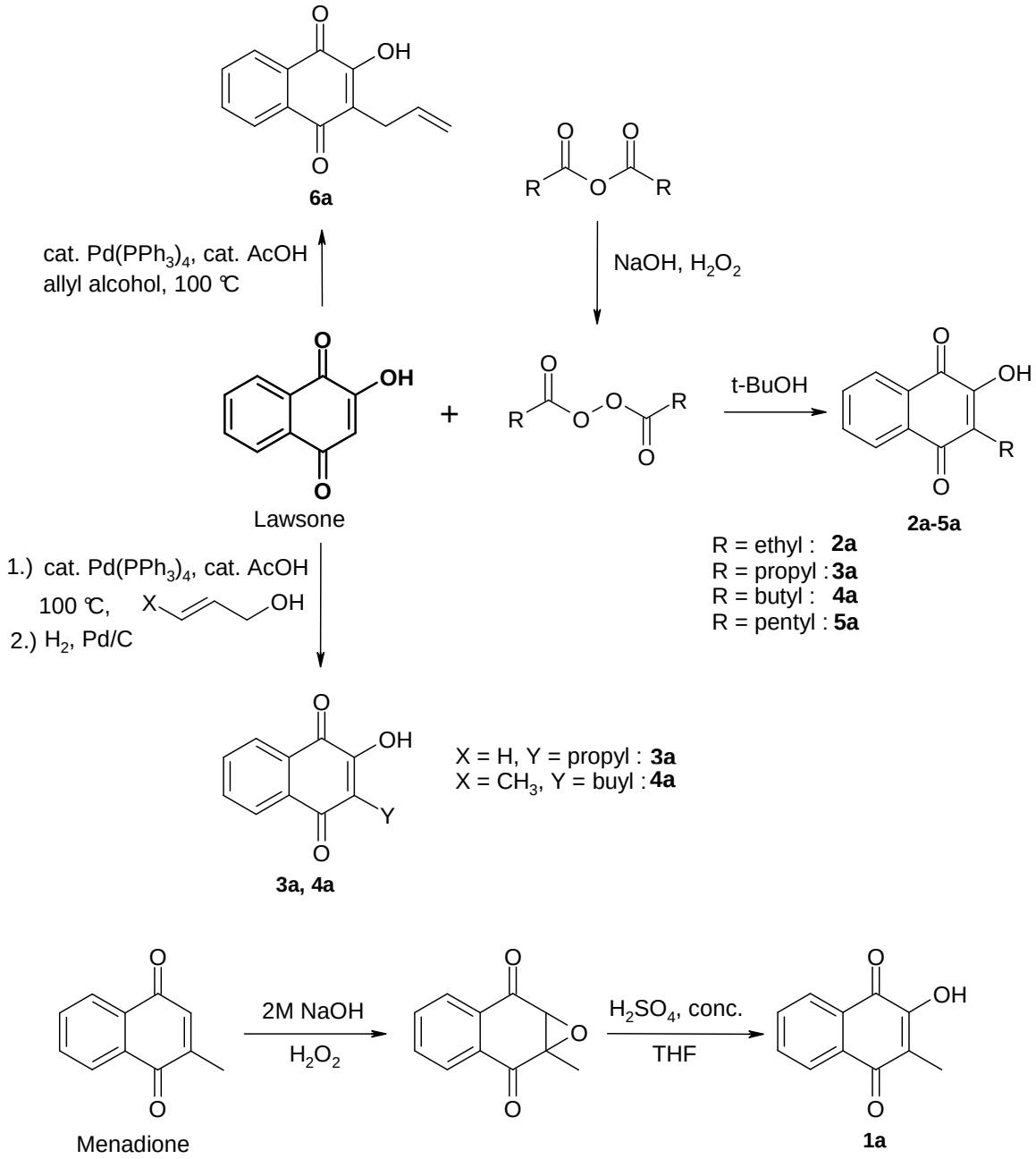


Figure 19: Synthesis of naphthoquinone ligands

Ligands **1a–6a** were converted into the corresponding Ru(II)-arene complexes **1b-6b** under alkaline conditions with bis[chlorido(μ-chlorido)(η^6-*p*-cymene)ruthenium(II)] in moderate to good yields (Figure 20). Conversion of **1a** with bis[chlorido(μ-chlorido)(η^6-*p*-cymene)osmium(II)] yielded the analogous osmium complex **13b**. The reactions were performed under argon atmosphere with a slight excess of the ligand to facilitate the purification step. The reaction times and yields are summarized in Table 3.

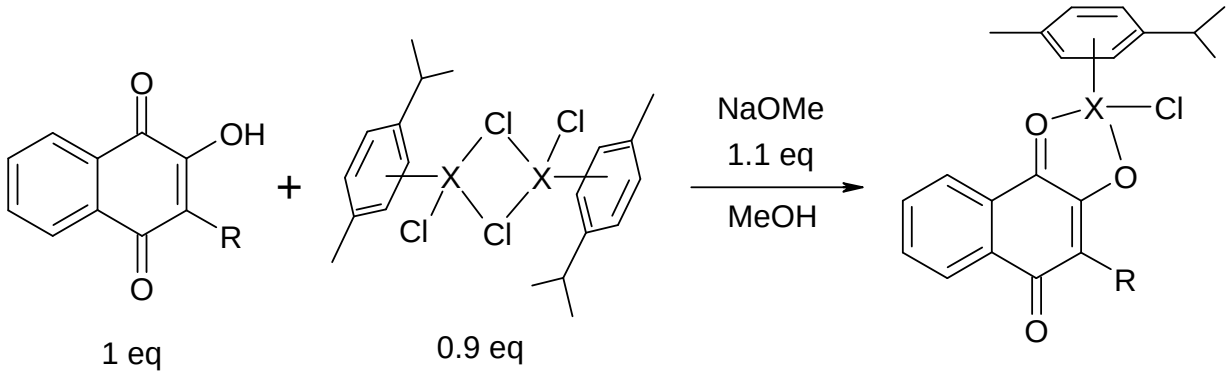


Figure 20: Synthesis of arene complexes

Complex	Ligand	X	R	Time (h)	Yield (%)
1b	1a	Ru	-methyl	6	66
2b	2a	Ru	-ethyl	6	40
3b	3a	Ru	-propyl	6	55
4b	4a	Ru	-butyl	7	65
5b	5a	Ru	-pentyl	4	66
6b	6a	Ru	-allyl	7	77
13b	1a	Os	-methyl	3	70

Table 3: Complexation of naphtoquinone ligands

The complexes were characterized by 1D NMR spectroscopy and elemental analysis. Compound **2b** was also analyzed by 2D NMR methods.

Crystal structures

Single crystals suitable for X-ray diffraction analysis were obtained from n-hexane/chloroform for **4b** and **6b.** Both structures show a pseudo octahedral configuration which is known as “piano-stool configuration”, with ruthenium as central atom. This type of structure is common for Ru(II)-arene complexes. In both molecules the naphthoquinone derivative acts as bidentate chelating ligand via the oxygen atoms. The ruthenium-oxygen bond length varies in both complexes, which is in accordance with the literature.[29] Complex **6b** shows slightly longer Ru-O bonds [2.0799(1) (Ru-O1) and 2.1305(1) Å (Ru-O2)] than complex **4b** [2.0554(3) (Ru-O1) and 2.1220(3) Å (Ru-O2)]. The aryl side chain in complex **6b** is twisted out of plane with a torsion angle of -88.84°. **4b** shows an almost similar torsion angle between the naphthoquinone moiety and the butyl side chain with a value of 88.95°. Fu rthermore, it should be mentioned that the X-ray structure of **4b** shows unidentified spots of electron density. Elemental and thermogravimetric analysis indicate that residual solvent molecules are embedded in the crystal structure.

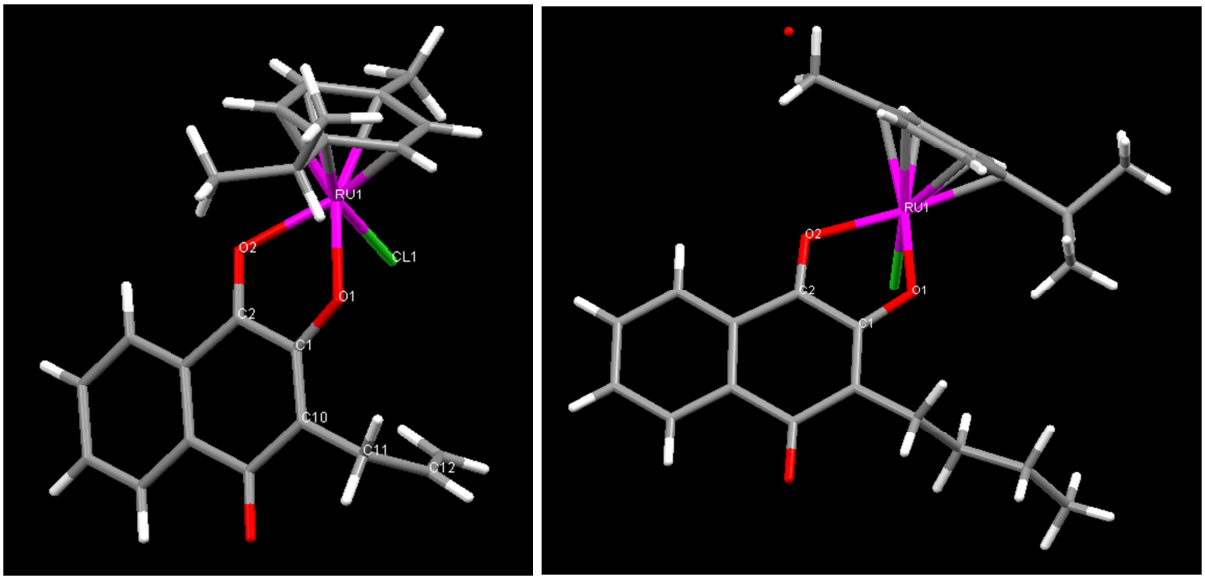


Figure 21: Molecular structures of 6b (left) and 4b (right)

3.2 Synthesis and characterization of p-cymene complexes with 2-hydroxy-[1,4]-naphthoquinone-oximes as ligands.

Ligands **1a-6a** were treated with hydroxylamine under alkaline conditions to obtain compounds **7a–12a** (Figure 22).

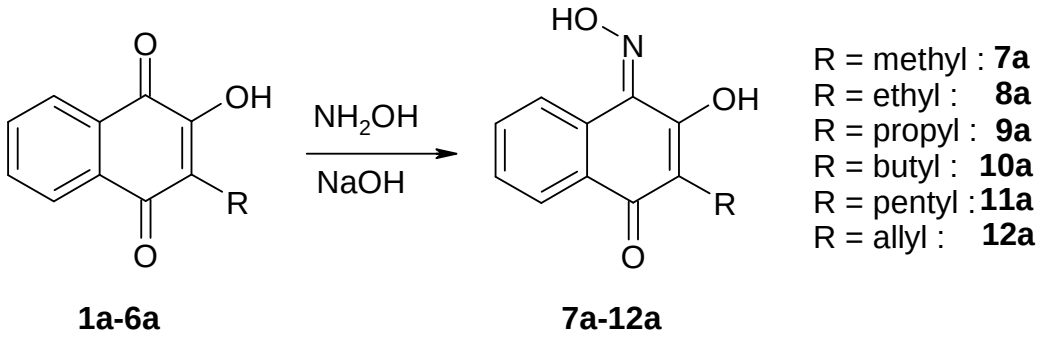


Figure 22: Synthesis of 2-hydroxy-1,4-naphthoquinone-oxime ligands

The reaction led to the formation of *E* and *Z* isomers of the oximes, as shown in Figure 23.

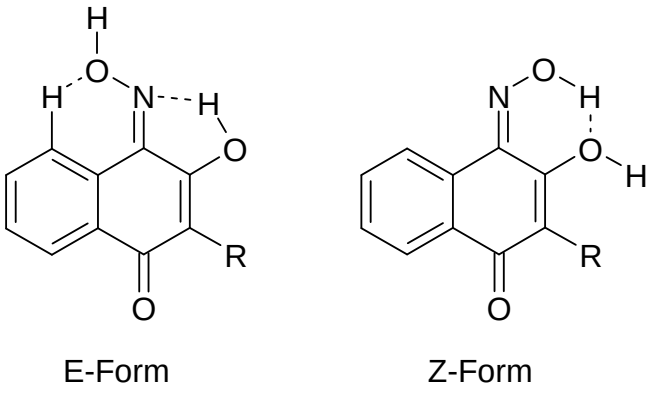


Figure 23: E and Z iosmers of 2-hydroxy-1,4-naphthoquinone.

The formation was confirmed by 1H-NMR spectroscopy of compounds **7a–12a.** The spectra showed two sets of signals for the aromatic protons (Figure 24). The ratio of the signal sets is equivalent to the ratio of the isomers and differs from reaction to reaction. Furthermore, the signal of the hydroxyl group is shifted to higher fields by about 1 ppm. Also one H_{Ar} showed a significant low field shift by approximately 1 ppm, which could be

explained with an intramolecular hydrogen bond of the –OH group to the oxime oxygen.

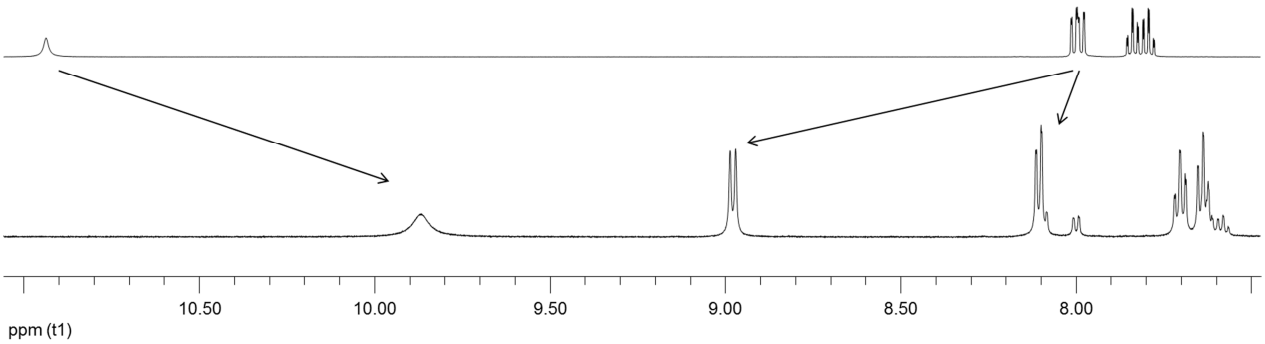


Figure 24: ^{1}H-NMR spectra of aromatic protons for 1a (top) and 7a (bottom)

The characterization of the oxime ligands was performed by NMR spectroscopy, elemental analysis and by determination of the melting point. Interpretation of the ^{13}C NMR spectra of some compounds was difficult due to the weak signals of the quaternary carbon atoms.

The oxime complexes **7b-12b** were obtained by converting **7a–12a** with bis[chlorido(μ-chlorido)(η^6-*p*-cymene)ruthenium(II)] under alkaline conditions. Moreover, compound **7a** was also treated with bis[chlorido(μ-chlorido)(η^6-*p*-cymene)osmium(II)] to afford the osmium complex **14b**. The reactions were performed under argon atmosphere with a slight excess of the ligand. The results are summarized in Table 4.

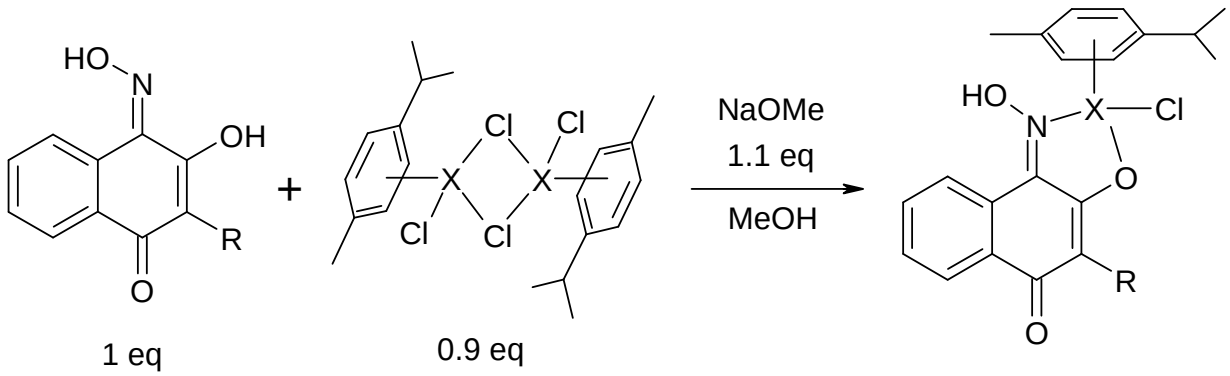


Figure 25: Synthesis of the oxime-p-cymene complexes

Complex	Ligand	X	R	Time (h)	Yield (%)
7b	7a	Ru	-methyl	5	31
8b	8a	Ru	-ethyl	5	23
9b	9a	Ru	-propyl	5	45
10b	10a	Ru	-butyl	5	67
11b	11a	Ru	-pentyl	5	46
12b	12a	Ru	-allyl	5	53
14b	14a	Os	-methyl	3	70

Table 4: Complexation of naphthoquinone-oxime ligands

Characterization of the oxime complexes was done by NMR spectroscopy, elemental analysis and determination of the melting points. A $^{13}C\{^{1}H\}$ NMR spectra was recorded for only one compound (**8b**) due to the long duration of the measurement. It took three days till the quaternary carbon atoms were clearly detectable for an assignment. After complexation of the oximes to Ru(cymene) or Os(cymene) moieties, the NMR spectra show only one isomer (E-form). The shifts of the aromatic cymene-CH protons of the oxime complexes in the ^{1}H NMR spectrum are in the same range as for the naphthoquinone analogues but with an overall trend to lower fields. In the oxime spectra the two symmetry equivalent protons of Hc and of Hd are detected as two doublets, yielding in total four doublets, which are slightly shifted to higher field than in the naphthoquinones.

3.3 Cyclic voltammetry

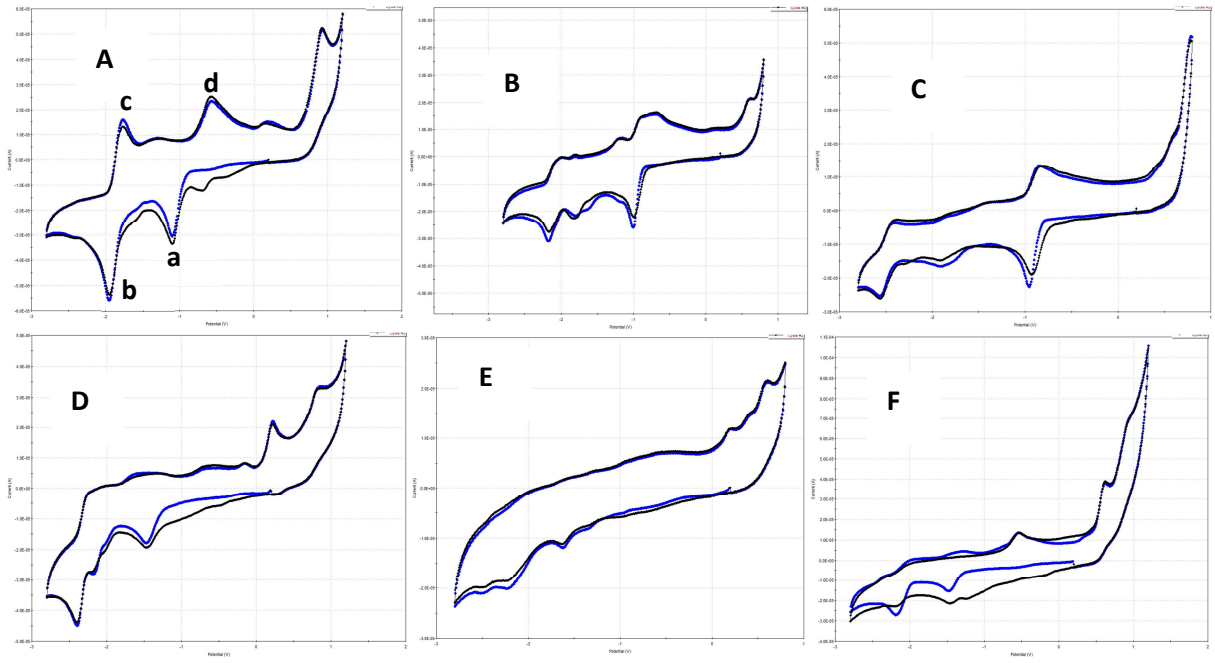


Figure 26: CV in acetonitrile with 0.1 M tetrabutylammonium tetrafluoroborate. Scan rate 200mV/s. naphthoquinone ligand (A), naphthoquinone-ruthenium complex (B), naphthoquinone-osmium complex (C), oxime ligand (D), oxime-ruthenium complex (E), oxime-osmium complex (F)

The electrochemical properties of the ligands and complexes were studied using an EG&G PARC 273A potentiostat/galvanostat (at room temperature).

Preliminary data collated for the naphthoquinone ligands are in accordance with literature.[58] The cyclic voltammograms of 1a–6a revealed only minor differences in their electrochemical behavior (Figure 26A). The first reduction band can be assigned to the formation of a radical anion. The proton transfer to this species from another naphthoquinone molecule leads to a naphthoquinone radical and the conjugated base, which is responsible for the non-reversible nature of band a in Figure 26A. The signals b and c may be generated by the $Q^{-}/Q^{\bullet 2-}$ couple. The oxime ligands showed a significantly different redox behavior (Figure 28D), due to only one keto functionality. Furthermore, the cyclic voltammograms of the ruthenium complexes of the *O,O* chelates (**1b-6b**) (Figure 26B), the oxime analogues (Figure 26E) and the corresponding osmium complexes (**13b, 14b**; Figure 26C and 26F) were recorded. No reduction of the metal center was observed in the cyclic voltammograms. However, the mentioned observations are to be considered premliminary and have to be confirmed in future.

[58] C. R. Solorio-Alvarado, E. Pena-Cabrera, J. Garcia-Soto, Juana Lòpez-Godinez, F. J. Gonzàlez, A. Àlvarez-Hernàndez, *ARKIVOC*, **2009**, (ii), 239-257.

4 Conclusions

Targeted metal complexes equipped with biologically active ligands represent a new, very promising alternative design strategy for the development of new anticancer chemotherapeutics. Such compounds may exert a variety of different modes of action comprising enzyme inhibition, DNA binding, ROS production and also bimodal effects. Therefore, they have the potential to overcome current limitations of chemotherapeutics in general. Especially bimodal compounds, which can interact with more than one biological target, could overcome acquired and/or intrinsic resistance of tumors to small molecule drugs.

The aim of my Master thesis was the synthesis and characterization of 2-hydroxy-[1,4]-naphthoquinone-based ligands and their *p*-cymene complexes of different metals. 2-Hydroxy-[1,4]-naphthoquinones are known for their biological properties *e. g*. for their ability to generate reactive oxygen species and some representatives are also able to inhibit cdc25 enzymes. In this thesis, Ru(II) and Os(II) were selected for complexation to these ligands and such compounds are expected exhibit such bimodal activity as described above: synergistic effects due to the presence of a bioactive ligand and a metal complex may result in improved drug-like properties (solubility, lower toxicity to normal tissue, *etc.*) with different biological activity than the chosen elements. Within this master thesis, 12 naphthoquinone ligands with an aliphatic chain in position three were synthesized, *i.e.*, 6 with an O,O-donor system and 6 based on an N,O-chelating ligand (Scheme 27). The synthesis of the ligands was performed via different synthetic pathways comparing a Pd(0)-catalyzed cross coupling reaction with a strategy using acyl peroxide, with the latter having been shown to be the best option. Complexation of the ligands with bis[chlorido(μ-chlorido)(η^6-*p*-cymene)ruthenium(II)] worked very well especially with the naphthoquinone derivates with yields ranging from 40 to 77%, whereas the complexation to 2-hydroxy-[1,4]-naphthoquinone-oxime ligands yielded 23-70% of the desired product. A similar trend was observed in the preparation of two analogous osmium complexes. This trend can be explained by different solubility in the solvents used for purification.

All compounds were characterized by NMR spectroscopy, elemental analysis and

determination of the melting point. The molecular structures of the two compounds were determined by X-ray diffraction analysis. In case of the oxime complexes, ^{13}C-NMR was not used to confirm the structure, due to the long measurement time to detect the quaternary carbon atoms.

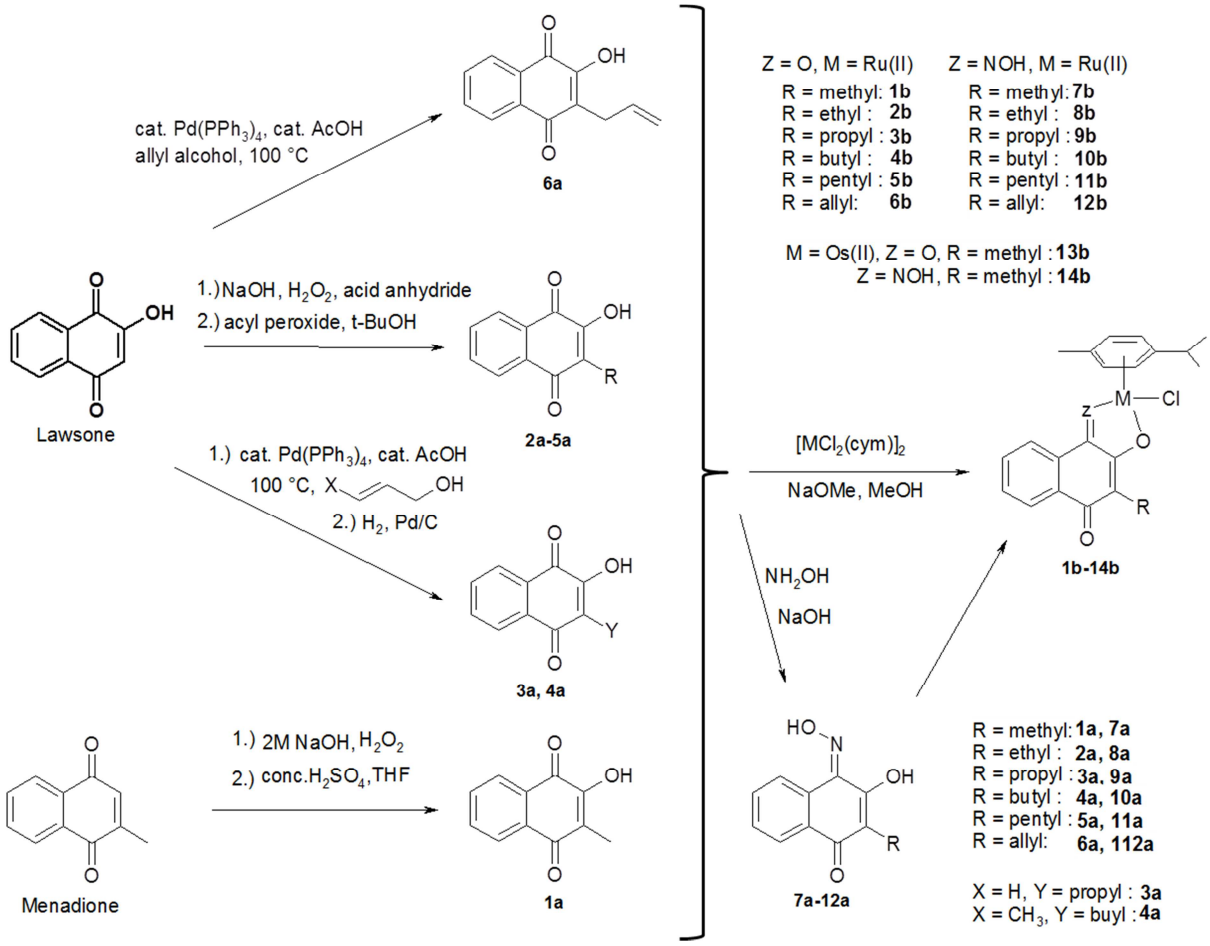


Figure 27 Summary of synthetic pathways and prepared ligands and metal complexes.

In summary, a series of naphthoquinone-derived complexes was prepared and characterized by different physicochemical methods. Future studies on the biological activity of the complexes will enlighten their potential as anticancer agents. These experiments should be complemented by efforts to determine their modes of action, in particular the potential bimodal properties of the compound class need to be demonstrated by biological and physicochemical methods.

5 Experimental Part

5.1 Equipment and Methods

Elemental Analysis

The determination of the elements carbon, hydrogen and nitrogen was performed by the Microanalytical Laboratory of the University of Vienna with a Perkin Elmer 2400 CHN Elemental Analyzer.

NMR spectra

NMR spectra were recorded with a BRUKER FT-NMR spectrometer Avance III 500 MHz with an UltraShieldPlus magnet at 25 °C. The me asurement frequency for proton NMR (^{1}H) was 500.10 MHz and for carbon NMR ($^{13}C\{^{1}H\}$) 125.75 MHz [D_6]-DMSO, $CDCl_3$ or [D_4]CH_3OH were used as solvents. The Gradient-enhanced mode was used for the 2D NMR spectra measurement.

Melting points

A Büchi Melting Point B-540 was used for the determination of the melting points.

X-ray structures

The X-ray diffraction measurement was performed with single crystals of **4b** and **6b** on a Bruker X8 APEX II CCD diffractometer at 100 K.

5.2 Chemicals

All solvents were dried and distilled prior to use.

Chemicals for the synthesis of the ligands

2-Methyl-[1,4]-naphthoqunione (Menadione) (Fisher), hydrogen peroxide (30%) (Aldrich), sulfuric acid (Merck), hydroxylamine hydrochloride (Fluka), 2-hydroxy-[1,4]-naphthoquinone (Lawsone) (Fisher), propionic anhydride (Fisher), butyric anhydride (Sigma-Aldrich), valeric anhydride (Sigma-Aldrich), hexanoic anhydride (Sigma-Aldrich), allyl alcohol (Sigma-Aldrich), crotyl alcohol, *cis*/*trans* (Aldrich), tetrakis(triphenylphosphine)palladium(0) (Sigma-Aldrich), acetic acid (Merck) and palladium on activated charcoal (10% Pd) (Fluka) were purchased and used without further purification.

Chemicals for the synthesis of the complexes

Sodium methoxide (Aldrich) as purchased and used without further purification.

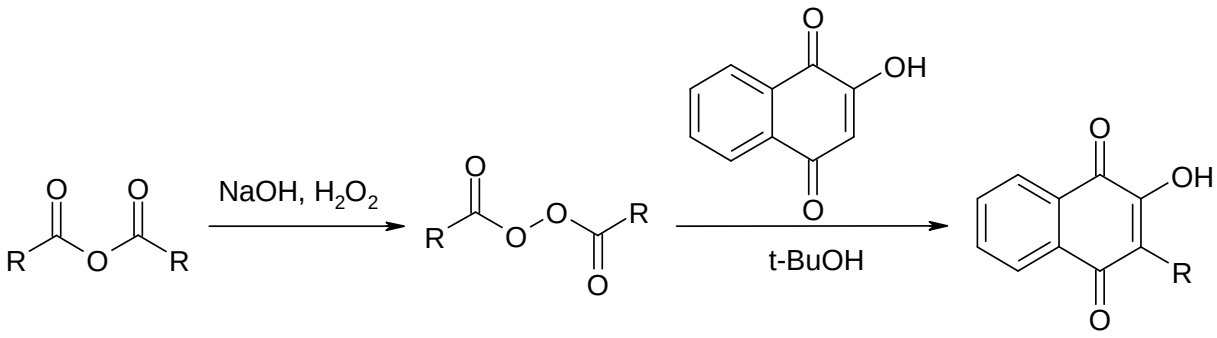
Bis[dichlorido(η^6-*p*-cymene)ruthenium(II)][59] and bis[chlorido(μ-chlorido)(η^6-*p*-cymene)osmium(II)][60] were synthesized as described in literature.

[59] M. A. Bennett, A. K. Smith, *J. Chem. Soc., Dalton Trans.,* **1974,** 233-241.
[60] W. A. Kiel, G. Ball, A. G. Graham, *J. Organomet. Chem.,* **1990**, 383, 481-496.

5.3 Synthesis of the naphthoquinone ligands

5.3.1 General procedures

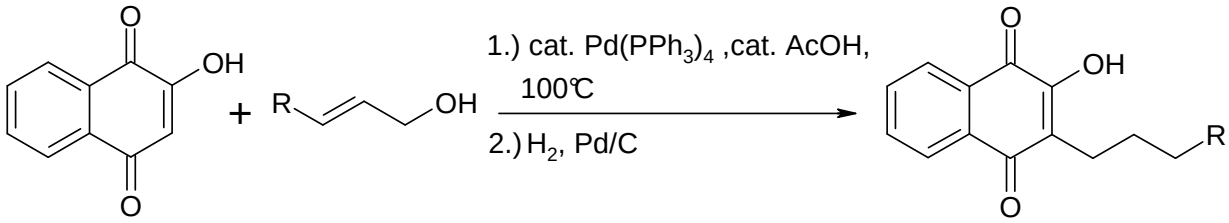
Derivatisation of lawsone by diacyl peroxide



An aliphatic acid anhydride (1.5 eq) was slowly added to a solution of NaOH (1.5 eq in H_2O) and H_2O_2 (1 eq) at 0° C and stirred for 3-5 h at 0° C. The reaction mixture was extracted with diethyl ether and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure.

The obtained diacyl peroxide was added dropwise to a boiling solution of t-BuOH (250 mL) and Lawsone (3.00 g, 17.22 mmol). After 6-9 hours at 90 ℃ the solution was concentrated under reduced pressure, the residue was dissolved in CH_2Cl_2 and extracted with saturated Na_2CO_3 solution. The aqueous layer was acidified to pH 2, the color of the solution changed from red to yellow and a yellow precipitate was formed. Finally, the obtained solid was filtered, washed with water and dried in vacuum.

Derivatization of lawsone by Pd(0) cross coupling reaction and general hydrogenation protocol

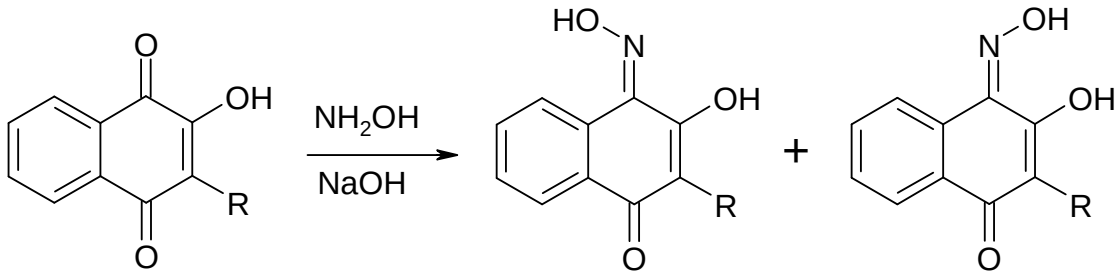


A reaction mixture of lawsone (1 eq), $Pd(PPh_3)_4$ (0.05 eq), allylic alcohol (1.6 eq) and AcOH (0.1 eq) was stirred under argon atmosphere at 100℃. After 35 min the highly viscous material was purified by column chromatography (silica gel 60, n-hexane-EtOAc, 5:1).

The obtained product was dissolved in methanol (10mL per 100 mg) and the allylic double bond was reduced in the presence of palladium on activated char coal (10% w/w) and H_2 (5 bar). After full conversion (3h), the catalyst was separated by filtration and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel 60, n-hexane-EtOAc, 5:1).

The yellow product was dissolved in CH_2Cl_2 and extracted with saturated Na_2CO_3 solution. The aqueous layer was acidified to pH 2, the color of the solution changed from red to yellow and precipitation occurred. The precipitate was filtered, washed with water and dried in vacuum.

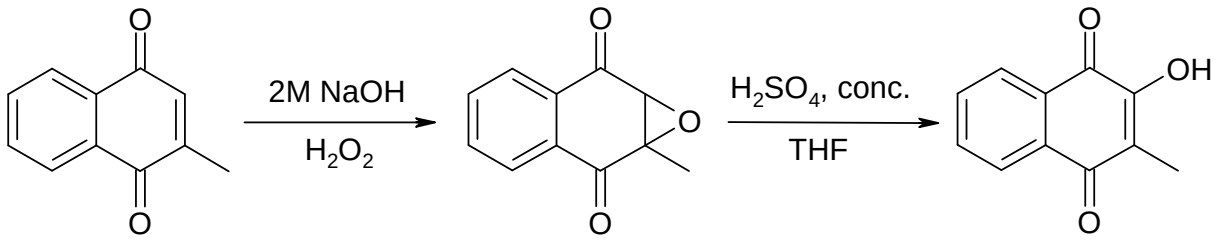
General protocol for the synthesis of oximes



Hydroxylamine hydrochloride (1 eq) was added to a solution of naphthoquinone (1 eq) in 1M NaOH (10mL per 100mg naphthoquinone) and stirred for 2 h at room temperature.

Afterwards the reaction mixture was acidified to pH 2, the color of the solution changed from red to yellow and a yellow precipitate was formed. The product was separated by filtration, washed with water and dried in vacuum.

5.3.2 2-Hydroxy-3-methyl-[1,4]-naphthoquinone (1a)



[172.18] [188.18] [188.18] **1a**

Synthesis:

Menadione (3.00g, 17.4 mmol, 1 eq) was dissolved in water (120 mL) and cooled to 0° C. NaOH (2 M, 4.4 mL, 8.7 mmol, 0.5 eq) was added and the mixture was stirred for 10 minutes, followed by dropwise addition of hydrogen peroxide (30%) (1.7 mL, 26.1 mmol, 1.5 eq). After 10 minutes the ice bath was removed and the suspension was diluted with methanol (480 mL). The reaction was continued for further 2 h and the formed precipitate was separated by filtration and dried *in vacuo*.

The obtained epoxide (1.50 g, 7.97 mmol, 1 eq), H_2SO_4 (3 mL, 55.8 mmol, 7 eq), THF (21 mL) and silica gel (12 g) were reacted at 70 ℃ on the rotary evaporator. After removal of the solvent the reaction was continued for 3 min. The residue was extracted several times with CH_2Cl_2 and the organic layers were washed with $NaHCO_3$, filtered, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The solid product was recrystallized from methanol.

Yield: 1.55 g (64 %) yellow solid

Characterization:

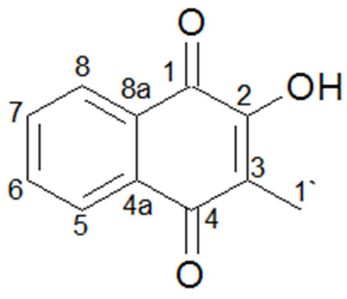
Melting point: 167 – 170 ℃

Elemental analysis:

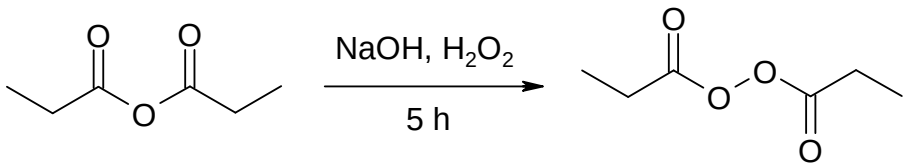
		C [%]	H [%]	N [%]	O [%]
1a	calculated	70.21	4.29	0.00	25.51
$C_{11}H_8O_3$	measured	69.93	4.06	0.11	25.86
	Δ	0.28	0.23	0.11	0.35

^{1}H-NMR (500.10 MHz, DMSO-d_6) δ: 1.96 (s, 3H, H1`), 7.79 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.84 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 7.98 (d, ^{3}J = 8 Hz, 1H, H5), 8.01 (d, ^{3}J = 8 Hz, 1H, H8), 10.94 (s, 1H, OH).

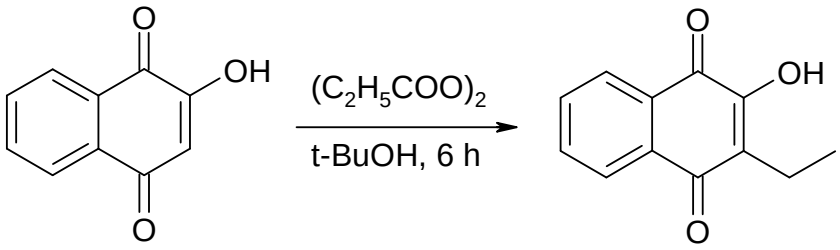
^{13}C-NMR (125.75 MHz, DMSO-d_6) δ: 9.0 (C1`), 120.4 (C3), 126.1 (C5, C8), 130.5 (C4a), 132.5 (C8a), 133.6 (C7), 134.9 (C6), 155.9 (C2), 181.1 (C1), 185.1 (C4).



5.3.3 2-Ethyl-3-hydroxy-[1,4]-naphthoquinone (2a)



[130.14] [146.14]



[174.15] [202.21] **2a**

Synthesis:

The synthesis was performed according to the general “Derivatization of lawsone by diacyl peroxide” procedure, using propionic anhydride (10.00 g, 76.8 mmol), NaOH (3.17 g in 9.6 mL, 79.3 mmol), hydrogen peroxide (35%, 5.3 mL, 51.8 mmol) and 2-hydroxy-[1,4]-naphthoquinone (3.00 g, 17.2 mmol).

Yield: 1.07 g (31%), yellow solid

Characterization:

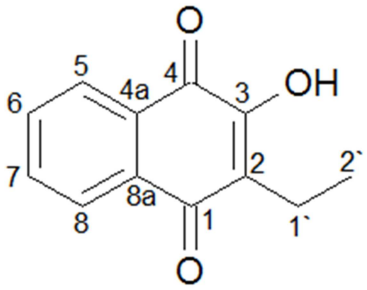
Melting point: 132 – 135 °C

Elemental analysis:

		C [%]	H [%]	N [%]
2a	calculated	70.65	5.04	0.00
$C_{12}H_{10}O_3$*0.1H_2O	measured	70.62	4.71	0.11
	Δ	0.03	0.33	0.11

^{1}H-NMR (500.10 MHz, DMSO-d_6) δ: 1.04 (t, ^{3}J = 8 Hz, 3H, H2`), 2.49 (q, $^{3}$J = 8 Hz, 2H, H1`), 7.79 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz , 1H, H6), 7.84 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.98 (dd, ^{3}J = 8 Hz, 2H, H5,H8),10.93 (s, 1H, OH).

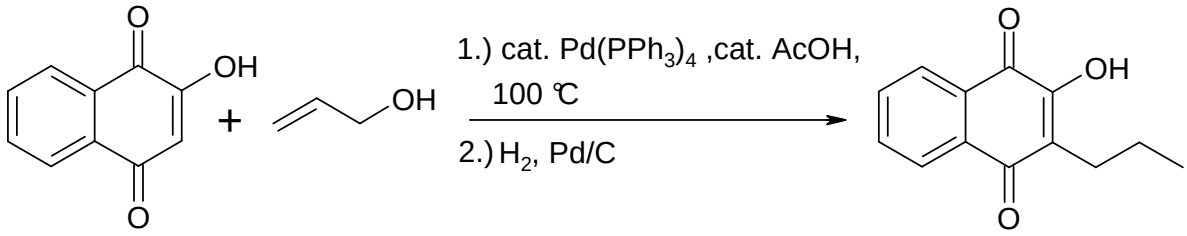
^{13}C-NMR (125.75 MHz, DMSO-d_6) δ: 13.1 (C2`), 16.6 (C1`), 125.8 (C2), 126.1 (C5, C8), 130.5 (C8a), 132.5 (C4a), 133.6 (C6), 134.9 (C7), 155.5 (C3), 181.5 (C4), 184.7 (C1).



5.3.4 2-Hydroxy-3-propyl-[1,4]-naphthoquinone (3a)

Ligand **3a** was synthesized following two different methods

a) *Via* palladium catalyzed reaction:



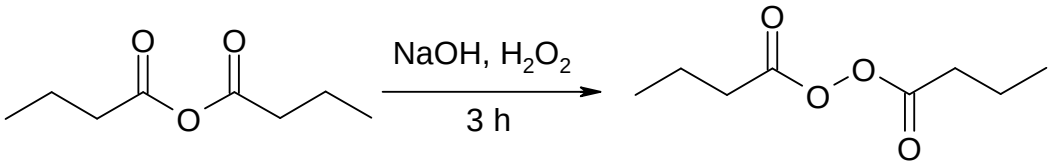
[175.16] [58.08] [216.23] **3a**

Synthesis:

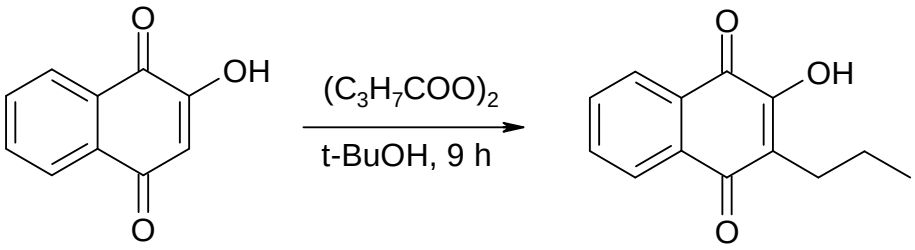
The synthesis was performed according to the general Pd(0) coupling procedure, using 2-hydroxy-[1,4]-naphthoquinone (1.00 g, 5.7 mmol), allyl alcohol (0.53 g, 9.2 mmol), tetrakis(triphenylphosphine)palladium(0) (0.33 g, 0.3 mmol) and AcOH (34.5 mg, 0.6 mmol).

Yield: 0.39 g (31%), yellow-orange solid

b) *Via* peroxide reaction



[158.19] [174.19]



[174.15] [216.23] **3a**

Synthesis:

The synthesis was performed according to the general “Derivatization of lawsone by diacyl peroxide” procedure, using butyric anhydride (10.00 g, 63.2 mmol), NaOH (2.53 g in 7.6 mL, 63.2 mmol), hydrogen peroxide (35%, 4.3 mL, 42.1 mmol) and 2-hydroxy-[1,4]-naphthoquinone (3.00 g, 17.2 mmol).

Yield: 0.89 g (24%), yellow-orange solid

Characterization:

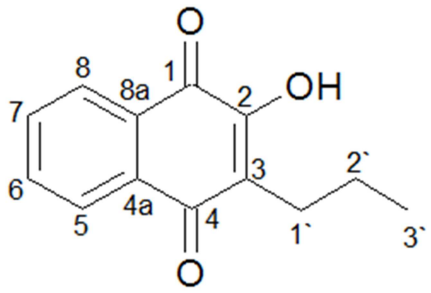
Melting point: 99 – 100℃

Elemental analysis:

		C [%]	H [%]	N [%]
3a	calculated	72.21	5.59	0.00
$C_{13}H_{12}O_3$	measured	72.01	5.41	0.09
	Δ	0.20	0.18	0.09

^{1}H-NMR (500.10 MHz, DMSO-d_6) δ: 0.91 (t, ^{3}J = 8 Hz, 3H, H3`), 1.48 (q, $^{3}$J = 8 Hz, 2H, H2`), 1.45 (t, ^{3}J = 8 Hz, 2H, H1`), 7.79 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.84 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 7.98 (d, ^{3}J = 8 Hz, 1H, H5), 8.00 (d, ^{3}J = 8 Hz, 1H, H8), 10.90 (s, 1H, OH).

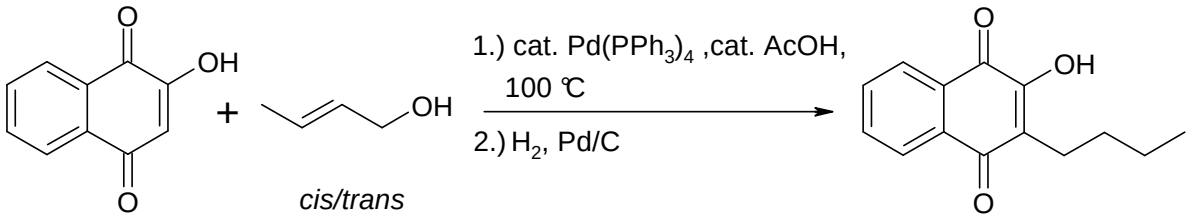
^{13}HC-NMR (125.75 MHz, DMSO-d_6) δ: 14.5 (C3`), 21.6 (C2`), 25.2 (C1`), 124.3 (C3), 126.1 (C5), 126.2 (C8), 130.5 (C4a), 132.5 (C8a), 133.6 (C7), 134.9 (C6), 155.9 (C2), 181.4 (C1), 184.9 (C4).



5.3.5 2-Butyl-3-hydroxy-[1,4]-naphthoquinone (4a)

Ligand **4a** was synthesized following two different methods

a) *Via* palladium catalyzed reaction:



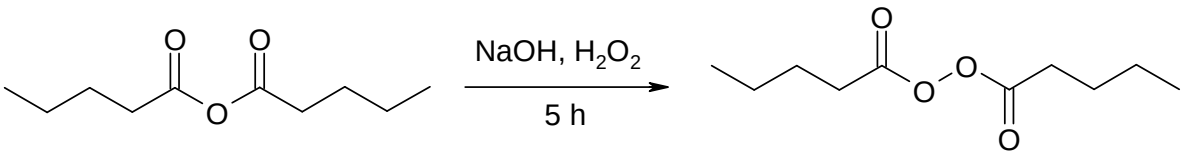
[174.15] [72.11] [230.26] **4a**

Synthesis:

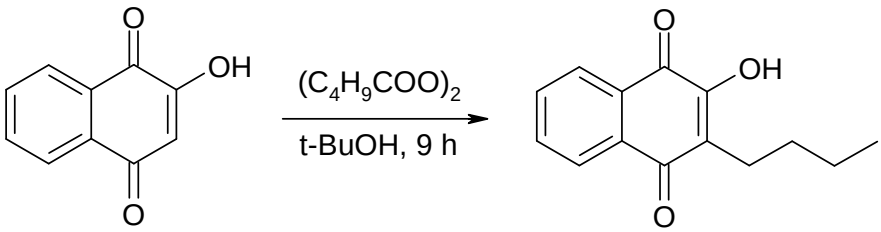
The synthesis was performed according to the general Pd(0) coupling procedure, using 2-hydroxy-[1,4]-naphthoquinone (2.00 g, 11.5 mmol), crotyl alcohol (1.32 g, 18.4 mmol), tetrakis(triphenylphosphine)palladium(0) (0.66 g, 0.6 mmol) and AcOH (69 mg, 1.1 mmol).

Yield: 0.74 g (28%), yellow solid

b) *Via* peroxide reaction:



[186.25] [202.25]



[174.15] [230.26] **4a**

Synthesis:

The synthesis was performed according to the general “Derivatization of lawsone by diacyl peroxide” procedure, using valeric anhydride (10.00 g, 53.7 mmol), NaOH (2.15 g in 7 mL, 53.7 mmol), hydrogen peroxide (35%, 3.7 mL, 35.8 mmol) and 2-hydroxy-[1,4]-naphthoquinone (3.00 g, 17.2 mmol).

Yield: 0.63 g (16%), brown solid

Characterization:

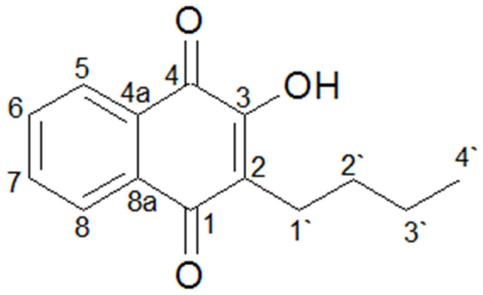
Melting point: 94 – 97 ℃

Elemental analysis:

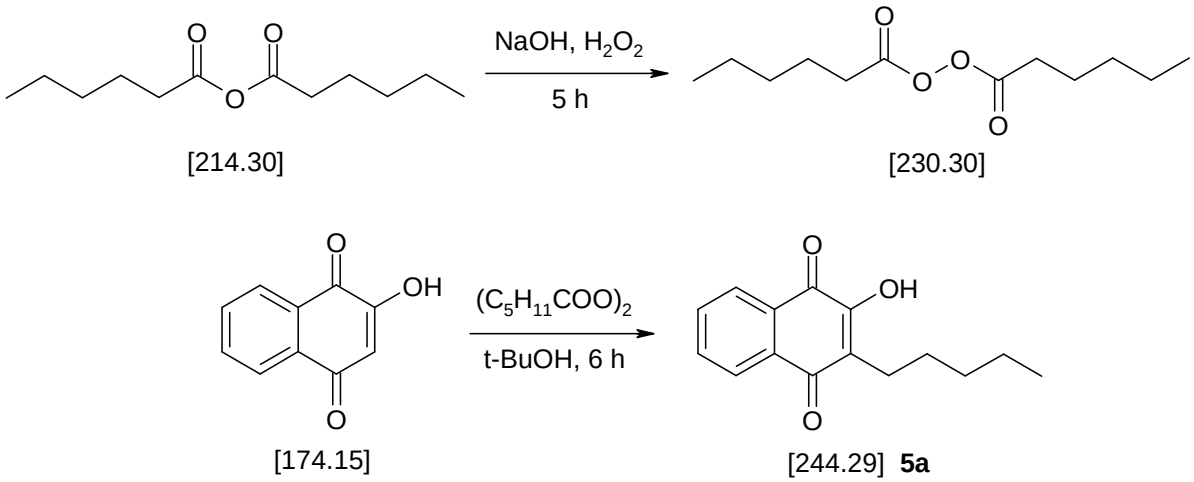
		C [%]	H [%]	N [%]
4a	calculated	72.46	6.17	0.00
$C_{14}H_{14}O_3$*0.1H_2O	measured	72.51	5.87	0.09
	Δ	0.05	0.30	0.09

^{1}H-NMR (500.10 MHz, DMSO-d_6) δ: 0.90 (t, ^{3}J = 8 Hz, 3H, H4`), 1.33 (sext, $^{3}$J = 7 Hz, 2H, H3`), 1.43 (quint, ^{3}J = 8 Hz, 2H, H2`), 2.50 (t, $^{3}$J = 8 Hz, 2H, H1`), 7.79 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 7.84 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.99 (d, ^{3}J = 8 Hz, 1H, H8), 8.01 (d, ^{3}J = 8 Hz, 1H, H5), 10.90 (s, 1H, OH).

^{13}HC-NMR (125.75 MHz, DMSO-d_6) δ: 14.3 (C4`), 22.8 (C3`), 22.9 (C2`), 30.4 (C1`), 124.5 (C2), 126.1 (C8), 126.2 (C5), 130.5 (C8a), 132.5 (C4a), 133.6 (C6), 134.9 (C7), 155.8 (C3), 181.4 (C4), 184.9 (C1).



5.3.6 2-Hydroxy-3-pentyl-[1,4]naphthoquinone (5a)



Synthesis:

The synthesis was performed according to the general “Derivatization of lawsone by diacyl peroxide” procedure, using hexanoic anhydride (10.00 g, 46.7 mmol), NaOH (1.87 g in 7 mL, 46.7 mmol), hydrogenperoxide (35%, 3.2 mL, 31.1 mmol) and 2-hydroxy-[1,4]-naphthoquinone (3.00 g, 17.2 mmol).

Yield: 1.64 g (39%), yellow solid

Characterization:

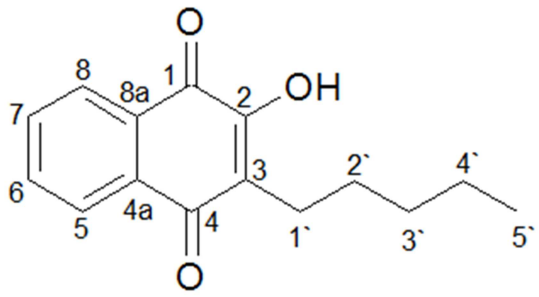
Melting point: 103 – 104 °C

Elemental analysis:

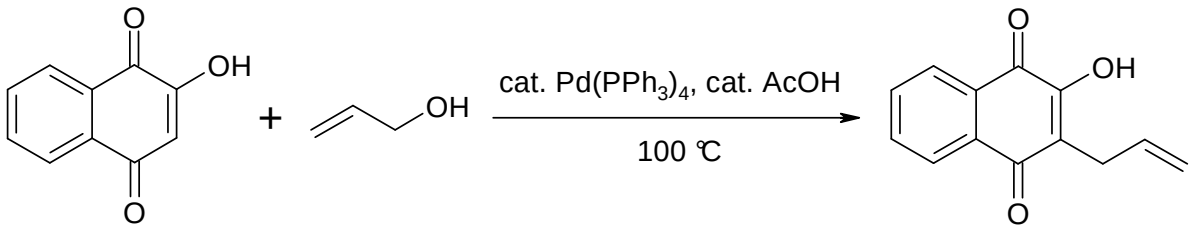
		C [%]	H [%]	N [%]
5a	calculated	73.75	6.60	0.00
$C_{15}H_{16}O_3$	measured	73.90	6.50	0.13
	Δ	0.15	0.10	0.13

^{1}H-NMR (500.10 MHz, DMSO-d_6) δ: 0.87 (t, ^{3}J = 7 Hz, 3H, H5`), 1.28–1.34 (m, 4H, H4`, H3`), 1.45 (quin, $^{3}$J = 8 Hz, 2H, H2`), 2.47 (t, ^{3}J = 8 Hz, 2H, H1`) 7.79 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.84 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 7.98 (d, ^{3}J = 8 Hz, 1H, H5), 8.00 (d, ^{3}J = 8 Hz, 1H, H8), 10.94 (s, 1H, OH).

^{13}C-NMR (125.75 MHz, DMSO-d_6) δ: 14.3 (C5`), 22.4 (C4`), 23.1 (C3`), 27.9 (C2`), 31.8 (C1`), 124.6 (C3), 126.1 (C5, C8), 130.5 (C4a), 132.5 (C8a), 133.6 (C7), 134.9 (C6), 155.8 (C2), 181.4 (C1), 184.9 (C4).



5.3.7 2-Allyl-3-hydroxy-[1,4]-naphthoquinone (6a)



[174.16] [58.08] [214.22] **6a**

Synthesis:

A reaction mixture of lawsone (4.00 g, 22.9 mmol, 1 eq), $Pd(PPh_3)_4$ (1.32 g, 1.1 mmol, 0.05 eq), allylic alcohol (2.13 g, 36.8 mmol, 1.6 eq) and AcOH (138 mg, 2.3 mmol, 0.1 eq) was stirred under argon atmosphere at 100 °C. A fter 35 min the highly viscous material was purified by column chromatography (silica gel 60, n-hexane-EtOAc, 5:1)

The yellow product was dissolved in CH_2Cl_2 and extracted with saturated Na_2CO_3 solution. The aqueous layer was acidified to pH 2, the color of the solution changed from red to yellow and a yellow precipitate was formed. Finally the precipitate was filtered, washed with water and dried in vacuum.

Yield: 1.08 g (22%), yellow solid

Characterization:

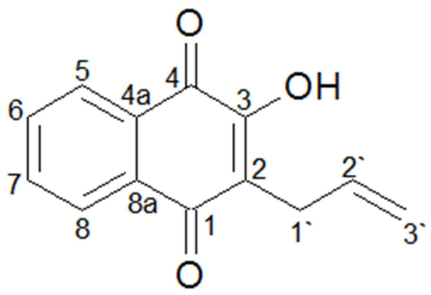
Melting point: 114 – 115 °C

Elemental analysis:

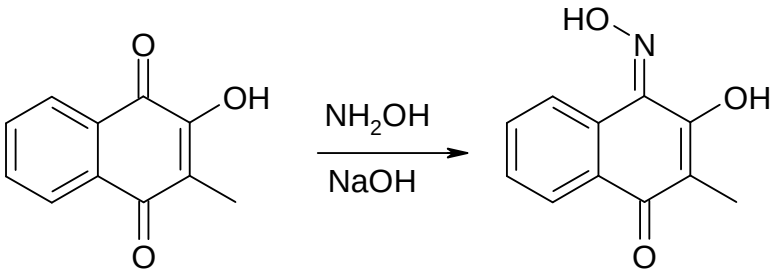
		C [%]	H [%]	N [%]
6a	calculated	72.28	4.76	0.00
$C_{13}H_{10}O_3$*0.1H_2O	measured	72.43	4.49	0.09
	Δ	0.15	0.27	0.09

^{1}H-NMR (500.10 MHz, DMSO-d_6) δ: 3.23 (d, ^{3}J = 6 Hz, 2H, H1`), 4.98 (d, $^{3}$J = 10 Hz, 1H, H3`), 5.06 (d, ^{3}J = 17 Hz, 1H, H3`), 5.80–5.88 (m, 1H, H2`), 7.80 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz,, 1H, H6), 7.85 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz,, 1H, H7), 7.99 (d, ^{3}J = 8 Hz, 1H, H8), 8.02 (d, ^{3}J = 8 Hz, 1H, H5), 11.11 (s, 1H, OH).

^{13}C-NMR (125.75 MHz, DMSO-d_6) δ: 27.4 (C1`), 116.1 (C2`), 121.6 (C2), 126.2 (C5, C8), 130.5 (C8a), 132.4 (C4a), 133.7 (C6), 134.9 (C7), 135.0 (C3`), 156.1 (C3), 181.5 (C4), 184.4 (C1).



5.3.8 2-Hydroxy-3-methyl-[1,4]-naphthoquinone-1-oxime (7a)



[188.18] **1a** [203.19] **7a**

E/Z (5:1)

Synthesis:

The synthesis was performed according to the general oxime preparation procedure, using naphthoquinone **1a** (0.70 g, 3.7 mmol) and hydroxylamine hydrochloride (0.26 g, 3.72 mmol).

Yield: 0.36 g (47%), yellow-brown solid

Characterization:

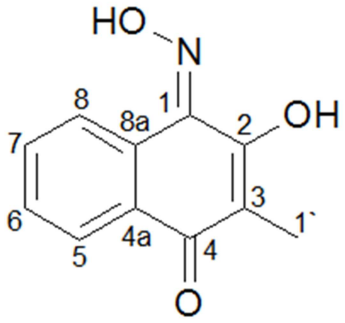
Melting point: 172 – 174 ℃

Elemental analysis:

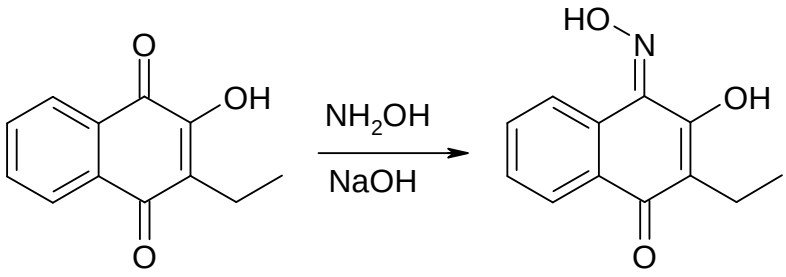
		C [%]	H [%]	N [%]
7a	calculated	64.45	4.52	6.83
$C_{11}H_9NO_3$*0.1H_2O	measured	64.27	4.27	6.71
	Δ	0.18	0.25	0.12

^{1}H-NMR (500.10 MHz, DMSO-d_6) δ: 1.96 (s, 3H, H1`), 7.64 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.70 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 8.11 (d, ^{3}J = 8 Hz, 1H, H5), 8.98 (d, ^{3}J = 8 Hz, 1H, H8), 9.87 (s, 1H, OH), 13.62 (s, 1 H, N-OH).

^{13}C-NMR (125.75 MHz, DMSO-d_6) δ: 8.9 (C1`), 113.2 (C3), 126.3 (C5), 129.9 (C8), 130.9 (C7), 131.1 (C8a, C4a), 132.7 (C6), 140.4 (C1), 159.0 (C2), 184.0 (C4).



5.3.9 2-Ethyl-3-hydroxy-[1,4]-naphthoquinone-4-oxime (8a)



[202.21] **2a** [217.22] **8a**

E/Z (5:1)

Synthesis:

The synthesis was performed according to the general oxime preparation procedure, using naphthoquinone **2a** (1.00 g, 4.9 mmol) and hydroxylamine hydrochloride (344 mg, 4.9 mmol).

Yield: 0.67 g (62%), green solid

Characterization:

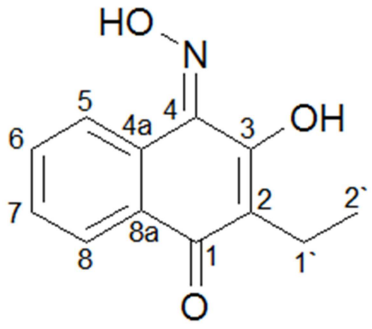
Melting point: 159 – 160 ℃

Elemental analysis:

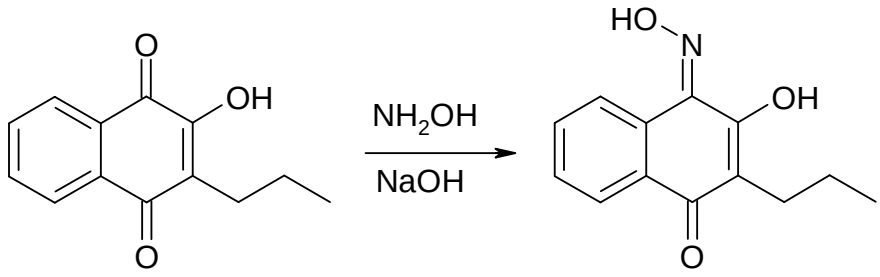
		C [%]	H [%]	N [%]
8a	calculated	65.81	5.15	6.40
$C_{12}H_{11}NO_3$*0.1H_2O	measured	65.63	5.05	6.20
	Δ	0.18	0.10	0.20

^{1}H-NMR (500.10 MHz, DMSO-d_6) δ: 1.02 (t, ^{3}J = 7 Hz, 3H, H2`), 2.50 (q, $^{3}$J = 7 Hz, 2H, H1`), 7.64 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 7.70 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 8.11 (d, ^{3}J = 8 Hz, 1H, H8), 8.98 (d, ^{3}J = 8 Hz, 1H, H5), 9.82 (s, 1H, OH), 13.63 (s, 1 H, N-OH).

^{13}C-NMR (125.75 MHz, DMSO-d_6) δ: 13.5 (C2`), 16.4 (C1`), 119.2 (C2), 126.3 (C8), 129.8 (C5), 130.9 (C6), 131.1 (C4a, C8a), 132.7 (C7), 140.4 (C4), 158.6 (C3), 183.5 (C1).



5.3.10 2-Hydroxy-3-propyl-[1,4]-naphthoquinone-1-oxime (9a)



[216.23] **3a** [231.25] **9a**

E/Z (10:3)

Synthesis:

The synthesis was performed according to the general oxime preparation procedure, using naphthoquinone **3a** (1.00 g, 4.6 mmol) and hydroxylamine hydrochloride (0.32 g, 4.6 mmol).

Yield: 0.78 g (73%), brown solid

Characterization:

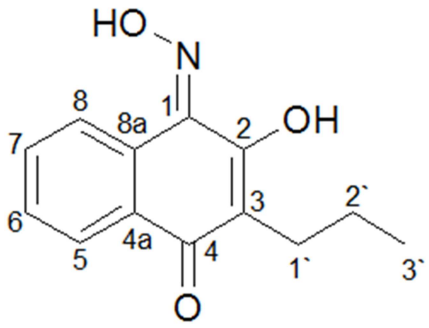
Melting point: 145 – 147 ℃

Elemental analysis:

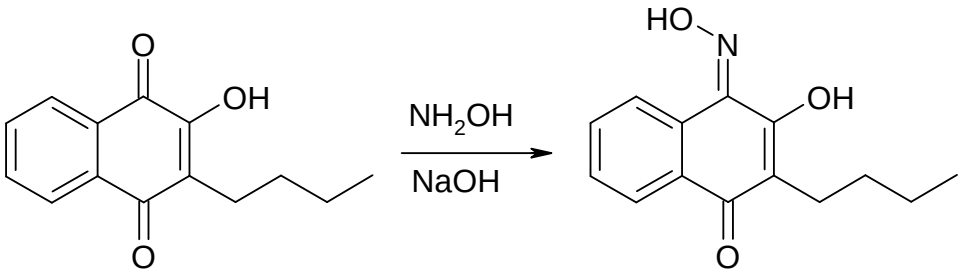
		C [%]	H [%]	N [%]
9a	calculated	66.23	5.77	5.49
$C_{13}H_{13}NO_3$*0.25H_2O	measured	66.37	5.53	5.59
	Δ	0.14	0.24	0.10

^{1}H-NMR (500.10 MHz, DMSO-d_6) δ: 0.90 (t, ^{3}J = 8 Hz, 3H, H3`), 1.43–1.50 (m, 2H, H2`), 2.47 (t, ^{3}J = 8 Hz, 2H, H1`), 7.64 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.70 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 8.11 (d, ^{3}J = 8 Hz, 1H, H5), 8.97 (d, ^{3}J = 8 Hz, 1H, H8), 9.79 (s, 1H, OH), 13.63 (s, 1 H, N-OH).

^{13}C-NMR (125.75 MHz, DMSO-d_6) δ: 14.5 (C3`), 21.8 (C2`), 25.1 (C1`), 117.7 (C3), 126.4 (C5), 129.8 (C8), 130.9 (C7), 131.2 (C4a, C8a), 132.7 (C6), 140.4 (C1), 159.0 (C2), 184.0 (C4).



5.3.11 2-Butyl-3-hydroxy-[1,4]-naphthoquinone-4-oxime (10a)



[230.26] **4a** [245.27] **10a**

E/Z (5:1)

Synthesis:

The synthesis was performed according to the general oxime preparation procedure, using naphthoquinone **4a** (1.00 g, 4.3 mmol) and hydroxylamine hydrochloride (0.30 g, 4.3 mmol).

Yield: 0.99 g (99%), yellow solid

Characterization:

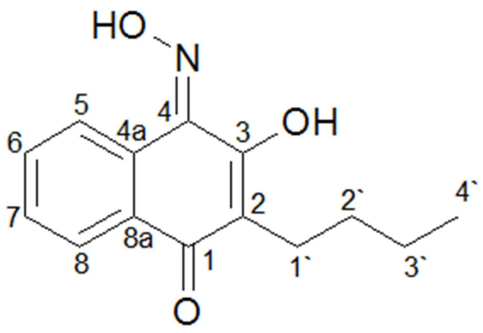
Melting point: 164 – 166 ℃

Elemental analysis:

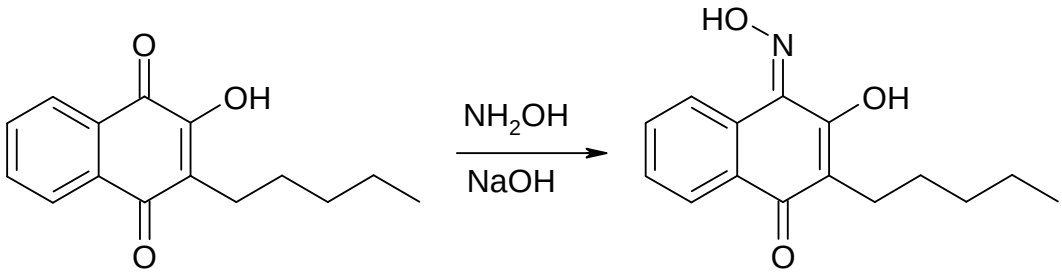
		C [%]	H [%]	N [%]
10a	calculated	68.56	6.16	5.71
$C_{14}H_{15}NO_3$	measured	68.21	5.80	5.51
	Δ	0.35	0.36	0.20

^{1}H-NMR (500.10 MHz, DMSO-d_6) δ: 1.02 (t, ^{3}J = 8 Hz, 3H, H4`), 1.32 (sext, $^{3}$J = 8 Hz, 2H, H3`), 1.39–1.45 (m, 2H, H2`), 2.50 (t, $^{3}$J = 8 Hz, 2H, H1`), 7.63 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 7.70 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 8.10 (d, ^{3}J = 8 Hz, 1H, H8), 8.97 (d, ^{3}J = 8 Hz, 1H, H5), 9.77 (s, 1H, OH), 13.62 (s, 1H, N-OH).

^{13}C-NMR (125.75 MHz, DMSO-d_6) δ: 14.4 (C4`), 2 x 22.8 (C3`, C2`), 30.7 (C1`), 117.9 (C2), 126.4 (C8), 129.8 (C5), 130.9 (C6), 131.2 (C4a, C8a), 132.6 (C7), 140.4 (C4), 158.6 (C3), 183.5 (C1).



5.3.12 2-Hydroxy-3-pentyl-[1,4]-naphthoquinone-1-oxime (11a)



[244.29] **5a** [259.30] **11a**

E/Z (10:3)

Synthesis:

The synthesis was performed according to the general oxime preparation procedure, using naphthoquinone **5a** (0.80 g, 3.3 mmol) and hydroxylamine hydrochloride (0.30 g, 4.3 mmol).

Yield: 0.83 g (97%), yellow solid

Characterization:

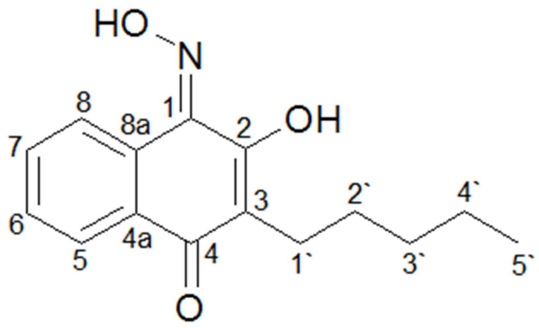
Melting point: 154 – 155 °C

Elemental analysis:

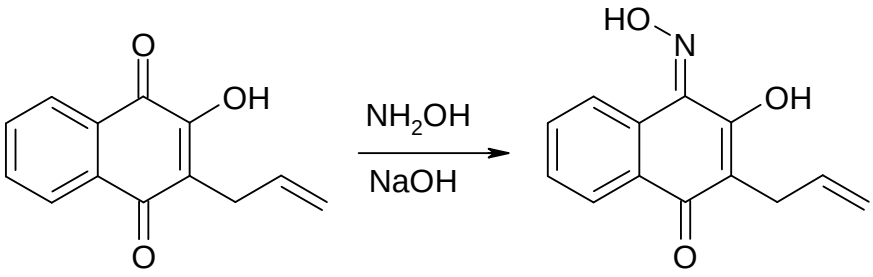
		C [%]	H [%]	N [%]
11a	calculated	69.48	6.61	5.40
$C_{15}H_{17}NO_3$	measured	69.27	6.38	5.11
	Δ	0.21	0.23	0.29

^{1}H-NMR (500.10 MHz, DMSO-d_6) δ: 0.87 (t, ^{3}J = 7 Hz, 3H, H5`), 1.28–1.34 (m, 4H, H4`, H3`), 1.41–1.47 (m, 2H, H2`), 2.47 (t, ^{3}J = 8 Hz, 2H, H1`), 7.64 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.70 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 8.10(d, ^{3}J = 8 Hz, 1H, H5), 8.97 (d, ^{3}J = 8 Hz, 1H, H8), 9.77 (s, 1H, OH), 13.62 (s, 1 H, N-OH).

^{13}C-NMR (125.75 MHz, DMSO-d_6) δ: 14.4 (C5`), 22.5 (C4`), 23.0 (C3`), 28.1 (C2`), 31.8 (C1`), 117.9 (C3), 126.4 (C5), 129.8 (C8), 130.9 (C7), 131.2 (C4a, C8a), 132.7 (C6), 140.4 (C1), 159.0 (C2), 183.6 (C4).



5.3.13 2-Allyl-3-hydroxy-[1,4]-naphthoquinone-4-oxime (12a)



[214.22] **6a** [229.23] **12a**

E/Z (5:1)

Synthesis:

The synthesis was performed according to the general oxime preparation procedure, using naphthoquinone **6a** (0.44 g, 2.0 mmol) and hydroxylamine hydrochloride (0.14 g, 2.0 mmol).

Yield: 0.21 g (45%), beige solid

Characterization:

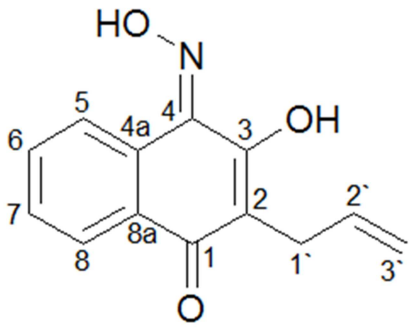
Melting point: 147 – 149 °C

Elemental analysis:

		C [%]	H [%]	N [%]
12a	calculated	67.58	4.89	6.06
$C_{13}H_{11}NO_3$*0.1H_2O	measured	67.56	4.66	6.00
	Δ	0.02	0.23	0.06

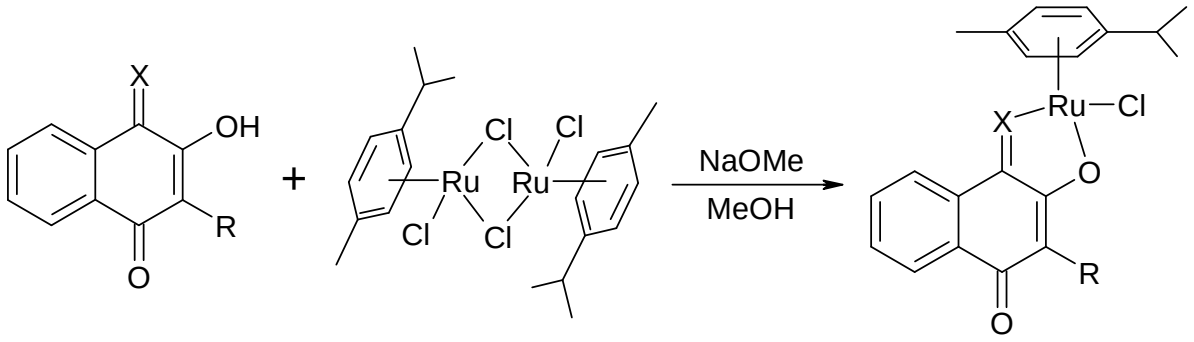
^{1}H-NMR (500.10 MHz, DMSO-d_6) δ: 3.23 (d, ^{3}J = 7 Hz, 2H, H1`), 4.94 (d, $^{3}$J = 10 Hz, 1H, H3`), 5.01 (d, ^{3}J = 17 Hz, 1H, H3`), 5.80–5.89 (m, 1H, H2`), 7.65 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 7.71 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 8.11 (d, ^{3}J = 8 Hz, 1H, H8), 8.98 (d, ^{3}J = 8 Hz, 1H, H5), 9.99 (s, 1H, OH), 13.69 (s,1H, N-OH).

^{13}C-NMR (125.75 MHz, DMSO-d_6) δ: 27.3 (C1`), 115.2 (C2`), 126.4 (C2), 129.9 (C8), 130.8 (C8a), 130.9 (C5), 130.8 (C4a), 130.9 (C6), 132.8 (C7), 136.1 (C3`), 140.4 (C4), 158.6 (C3), 184.4 (C1).



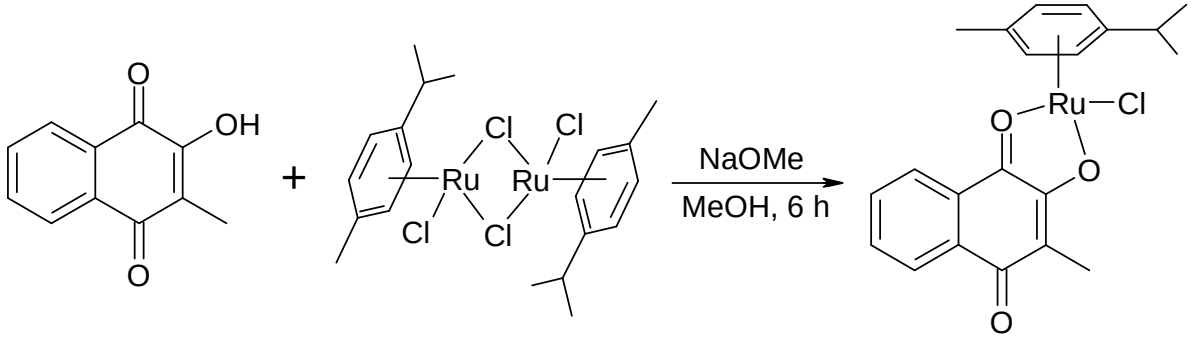
5.4 Synthesis of the Ru(II)-cymene complexes

5.4.1 General complexation procedure



Bis[chlorido(μ-chlorido)(η^6-*p*-cymene)ruthenium(II)] (0.9 eq) was added to a solution of naphthoquinone (1 eq) and sodium methoxide (1.1 eq) in methanol (80 mL). The reaction mixture was stirred at room temperature under argon atmosphere for 4-8 h. The solvent was evaporated under reduced pressure, the residue was dissolved in dichloromethane and filtered. The filtrate was reduced in vacuum to ~ 2 mL, n-hexane was added and the mixture was stored in the fridge at 4 ℃ over night. The obtained solid was separated by filtration, washed with n-hexane (3 x 10 mL) and dried in vacuum.

5.4.2 Chlorido[3-methyl-(2-oxo-κO)-[1,4]-naphthoquinonato-κO](η^6-p-cymene)ruthenium(II) (1b)



[188.18] **1a** [612.39] [457.91] **1b**

Synthesis:

The synthesis was performed according to the general complexation procedure, using naphthoquinone **1a** (0.200 g, 1.1 mmol), sodium methoxide (0.063 g, 1.2 mmol) and bis[chlorido(μ-chlorido)(η^6-*p*-cymene)ruthenium(II)] (0.293 g, 0.5 mmol).

Yield: 0.287 g (66%) dark blue solid

Characterization:

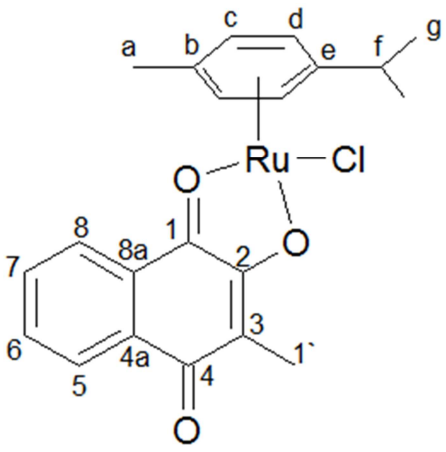
Melting point: 112 - 116 ℃ (decomposition)

Elemental analysis:

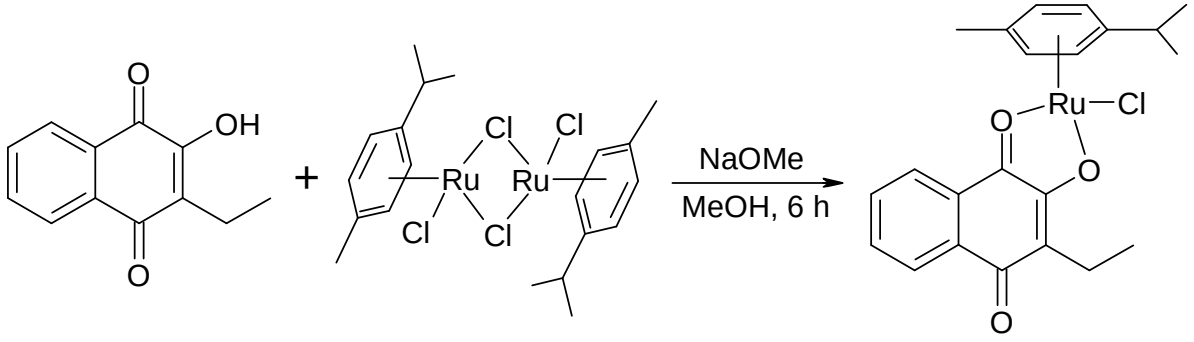
		C [%]	H [%]	N [%]	O [%]
1b	calculated	54.55	4.69	0.00	11.24
$C_{21}H_{21}ClO_3Ru*0.25H_2O$	measured	54.22	4.39	0.05	10.92
	Δ	0.33	0.30	0.05	0.32

^{1}H-NMR (500.10 MHz, [D_4]MeOH) δ: 1.45 (t, ^{3}J = 7 Hz, 6H, Hg), 2.04 (s, 3H, H1`), 2.39 (s, 3H, Ha), 2.97–3.03 (m, 1H, Hf), 5.69 (d, ^{3}J = 6 Hz, 2H, Hc), 5.96 (d, ^{3}J = 6 Hz, 2H, Hd), 7.68 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.81 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 7.95 (d, ^{3}J = 8 Hz, 1H, H5), 8.05 (d, ^{3}J = 8 Hz, 1H, H8).

^{13}C-NMR (125.75 MHz, [D_4]MeOH) δ: 7.2 (C1`), 17.3 (Ca), 21.2 (Cg), 31.3 (Cf), 78.6 (Cc), 79.5 (Cc), 81.0 (Cd), 81.9 (Cd), 96.8 (Cb), 100.7 (Ce), 121.8 (C3), 125.8 (C5), 126.2 (C8), 127.9 (C8a), 131.7 (C7), 132.6 (C4a), 136.1 (C6), 169.4 (C2), 183.3 (C4), 195.5 (C1).



5.4.3 Chlorido[2-ethyl-(3-oxo-κO)-[1,4]-naphthoquinonato-κO4](η^6-p-cymene)ruthenium(II) (2b)



[202.21] **2a** [612.39] [471.94] **2b**

Synthesis:

The synthesis was performed according to the general complexation procedure, using naphthoquinone **2a** (0.200 g, 0.1 mmol), sodium methoxide (0.059 g, 1.1 mmol) and bis[chlorido(μ-chlorido)(η^6-*p*-cymene)ruthenium(II)] (0.273 g, 0.4 mmol).

Yield: 0.169 g (40%) dark blue solid

Characterization:

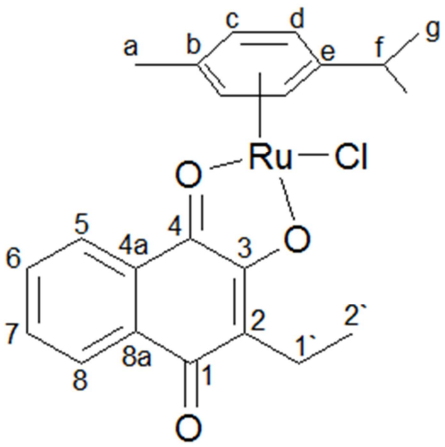
Melting point: 118 ℃ (decomposition)

Elemental analysis:

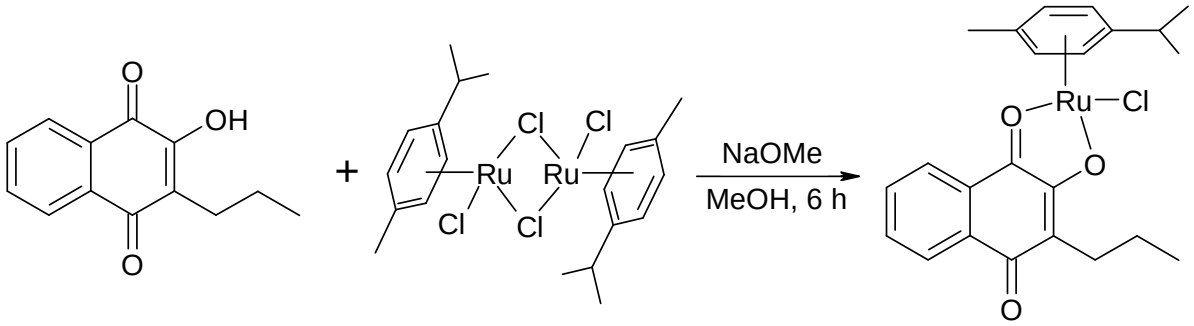
		C [%]	H [%]	N [%]
2b	calculated	54.19	4.80	0.00
$C_{22}H_{23}ClO_3Ru*0.25CH_2Cl_2$	measured	54.06	4.74	0.00
	Δ	0.13	0.06	0.00

^{1}H-NMR (500.10 MHz, [D_4]MeOH) δ: 1.09 (t, ^{3}J = 7 Hz, 3H, H2`), 1.43–1.47 (m, 6H, Hg), 2.39 (s, 3H, Ha), 2.58–2.60 (m, 2H, H1`), 2.97–3.03 (m, 1H, Hf), 5.67–5.70 (m, 2H, Hc), 5.96 (d, ^{3}J = 6 Hz, 2H, Hd), 7.68 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 7.82 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.95 (d, ^{3}J = 8 Hz, 1H, H8), 8.04 (d, ^{3}J = 8 Hz, 1H, H5).

^{13}C-NMR (125.75 MHz, [D_4]MeOH) δ: 11.9 (C2`), 15.9 (C1`), 17.3 (Ca), 21.2 (Cg), 31.3 (Cf), 78.4 (Cc), 79.5 (Cc), 80.9 (Cd), 82.1 (Cd), 97.0 (Cb), 100.7 (Ce), 125.8 (C8), 126.2 (C5), 127.6 (C2), 127.9 (C4a), 131.7 (C6), 132.6 (C8a), 136.1 (C7), 169.2 (C3), 182.7 (C1), 196.1 (C4).



5.4.4 Chlorido[(2-oxo-κO)-3-propyl- [1,4]-naphthoquinonato-κO](η^6-p-cymene)ruthenium(II) (3b)



[216.23] **3a** [612.39] [485.97] **3b**

Synthesis:

The synthesis was performed according to the general complexation procedure, using naphthoquinone **3a** (0.200 g, 0.9 mmol), sodium methoxide (0.055 g, 1.0 mmol) and bis[chlorido(μ-chlorido)(η^6-*p*-cymene)ruthenium(II)] (0.255 g, 0.4 mmol).

Yield: 0.221 g (55%) dark blue solid

Characterization:

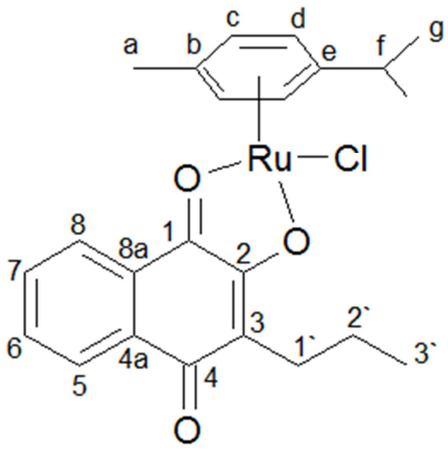
Melting point: 101 ℃ (decomposition)

Elemental analysis:

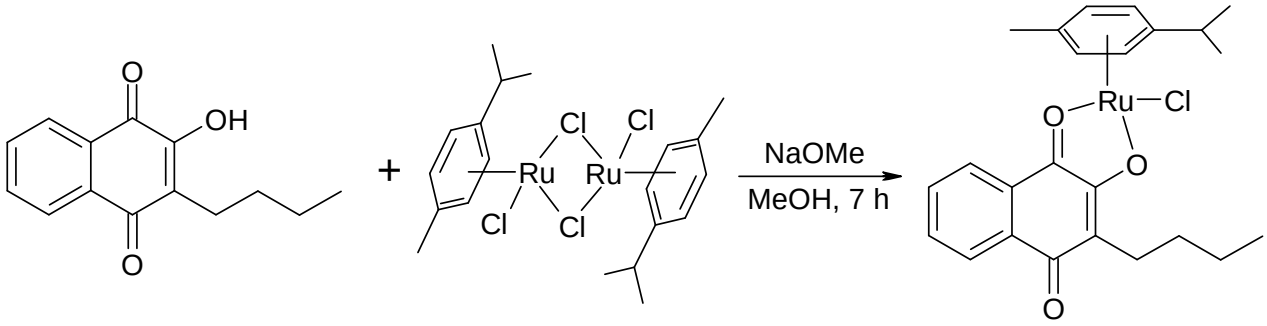
		C [%]	H [%]	N [%]	O [%]
3b	calculated	55.81	5.29	0.00	11.31
$C_{23}H_{25}ClO_3Ru*0.5H_2O$	measured	55.58	5.22	0.09	10.42
	Δ	0.23	0.07	0.09	0.89

^{1}H-NMR (500.10 MHz, [D_4]MeOH) δ: 0.97 (t, ^{3}J = 8 Hz, 3H, H3`), 1.43–1.47 (m, 6H, Hg), 1.51–1.56 (m, 2H, H2`), 2.39 (s, 3H, Ha), 2.56 (t, ^{3}J = 7 Hz, 2H, H1`), 2.96–3.02 (m, 1H, Hf), 5.67–5.69 (m, 2H, Hc), 5.95 (d, ^{3}J = 6 Hz, 2H, Hd), 7.68 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.81 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 7.95 (d, ^{3}J = 8 Hz, 1H, H5), 8.04 (d, ^{3}J = 8 Hz, 1H, H8).

^{13}C-NMR (125.75 MHz, [D_4]MeOH) δ: 13.3 (C3`), 17.4 (Ca), 21.3 (Cg), 21.4 (C2`), 24.7 (C1`), 31.4 (Cf), 78.4 (Cc), 79.6 (Cc), 80.9 (Cd), 82.2 (Cd), 97.0 (Cb), 100.6 (Ce), 124.1 (C3), 125.8 (C5), 126.2 (C8), 127.9 (C8a), 131.6 (C7), 132.6 (C4a), 136.1 (C6), 169.6 (C2), 182.9 (C4), 195.9 (C1).



5.4.5 Chlorido[2-butyl-(3-oxo-κO)-[1,4]-naphthoquinonato-κO4](η^6-p-cymene)ruthenium(II) (4b)



[230.26] **4a** [612.39] [499.99] **4b**

Synthesis:

The synthesis was performed according to the general complexation procedure, using naphthoquinone **4a** (0.200 g, 0.9 mmol), sodium methoxide (0.052 g, 1.0 mmol) and bis[chlorido(μ-chlorido)(η^6-*p*-cymene)ruthenium(II)] (0.239 g, 0.4 mmol).

Yield: 0.283 g (65%) dark violet solid

Characterization:

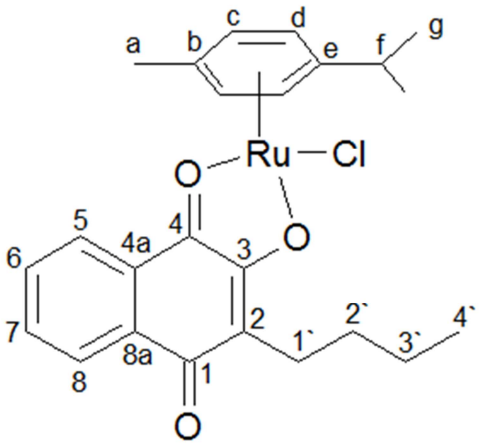
Melting point: 102 – 104 ℃ (decomposition)

Elemental analysis:

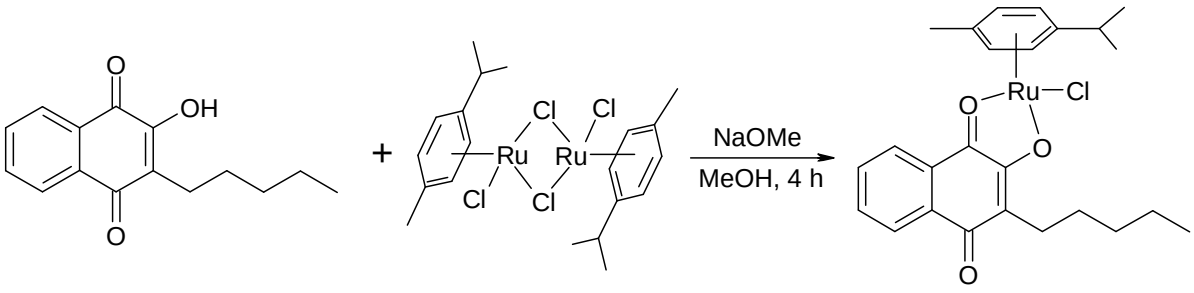
		C [%]	H [%]	N [%]	O [%]
4b	calculated	57.14	5.49	0.00	10.31
$C_{24}H_{27}O_3ClRu*0.25H_2O$	measured	56.95	5.28	0.10	10.15
	Δ	0.19	0.21	0.10	0.17

^{1}H-NMR (500.10 MHz, [D_4]MeOH) δ: 0.97 (t, ^{3}J = 7 Hz, 3H, H4`), 1.39–1.42 (m, 2H, H3`), 1.44–1.47 (m, 6H, Hg), 1.50–1.54 (m, 2H, H2`), 2.39 (s, 3H, Ha), 2.57–2.60 (m, 2H, H1`), 2.97–3.03 (m, 1H, Hf), 5.67–5.70 (m, 2H, Hc), 5.95 (d, ^{3}J = 6 Hz, 2H, Hd), 7.68 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 7.82 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.95 (d, ^{3}J = 8 Hz, 1H, H8), 8.05 (d, ^{3}J = 8 Hz, 1H, H5).

^{13}C-NMR (125.75 MHz, $CDCl_3$) δ: 14.1 (C4`), 18.8 (Ca), 17.3 (Ca), 22.2 (Cg), 23.0 (C3`), 30.0 (C2`), 30.7 (C1`), 31.5 (Cf), 78.2 (Cc), 79.6 (Cc), 80.9 (Cd), 82.2 (Cd), 96.7 (Cb), 100.4 (Ce), 126.3 (C8), 126.5 (C5), 127.9 (C2), 128.1 (C4a), 131.2 (C6), 133.0 (C8a), 135.9 (C7), 169.2 (C3), 182.8 (C1), 196.3 (C4).



5.4.6 Chlorido[(2-oxo-κO)-3-pentyl-[1,4]-naphthoquinonato-κO](η^6-p-cymene)ruthenium(II) (5b)



[244.29] **5a** [612.39] [514.02] **5b**

Synthesis:

The synthesis was performed according to the general complexation procedure, using naphthoquinone **5a** (0.200 g, 0.8 mmol), sodium methoxide (0.049 g, 0.9 mmol) and bis[chlorido(μ-chlorido)(η^6-*p*-cymene)ruthenium(II)] (0.225 g, 0.4 mmol).

Yield: 0.250 g (66%) dark violet solid

Characterization:

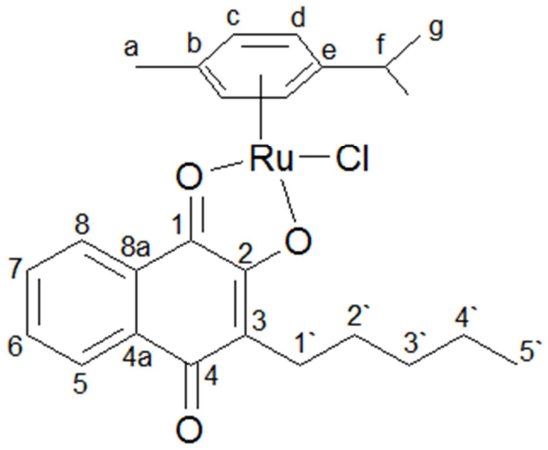
Melting point: 127 - 129℃ (decomposition)

Elemental analysis:

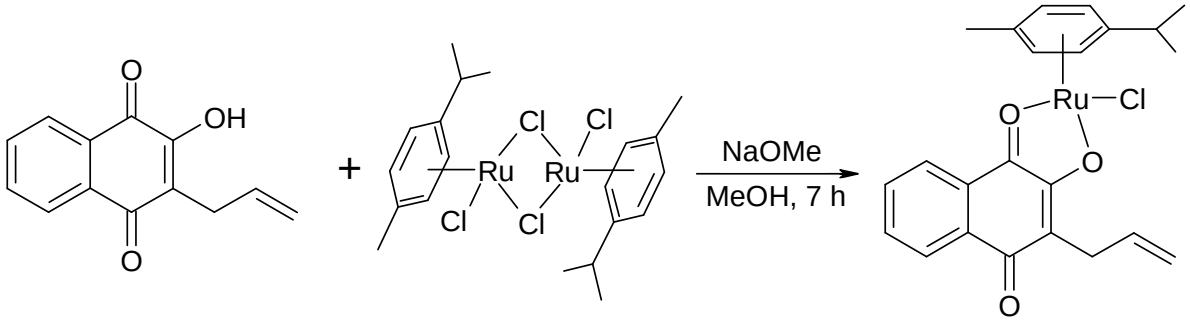
		C [%]	H [%]	N [%]	O [%]
5b	calculated	58.42	5.69	0.00	9.34
$C_{25}H_{29}ClO_3Ru$	measured	58.20	5.48	0.08	9.57
	Δ	0.23	0.21	0.08	0.23

^{1}H-NMR (500.10 MHz, [D$_4$]MeOH) δ: 0.94 (t, ^{3}J = 7 Hz, 3H, H5`), 1.34–1.40 (m, 4H, H3`, H4`), 1.43–1.47 (m, 6H, Hg), 1.51–1.53 (m, 2H, H2`), 2.39 (s, 3H, Ha), 2.57 (t, ^{3}J = 7 Hz, 2H, H1`), 2.97-3.02 (m, 1H, Hf), 5.66–5.70 (m, 2H, Hc), 5.95 (d, ^{3}J = 6 Hz, 2H, Hd), 7.68 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.82 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 7.95 (d, ^{3}J = 8 Hz, 1H, H5), 8.04 (d, ^{3}J = 8 Hz, 1H, H8).

^{13}C-NMR (125.75 MHz, [D$_4$]MeOH) δ: 13.1 (C5`), 17.4 (Ca), 21.3 (Cg), 22.3 (C4`), 22.6 (C3`), 27.8 (C2`), 31.8 (C1`), 31.5 (Cf), 78.4 (Cc), 79.6 (Cc), 80.9 (Cd), 82.2 (Cd), 97.0 (Cb), 100.5 (Ce), 124.4 (C3), 125.8 (C5), 126.2 (C8), 127.9 (C8a), 131.6 (C7), 132.6 (C4a), 136.1 (C6), 169.6 (C2), 182.9 (C4), 195.9 (C1).



5.4.7 Chlorido[2-allyl-(3-oxo-κO)-[1,4]-naphthoquinonato-κO4](η^6-p-cymene)ruthenium(II) (6b)



[214.22] **6a** [612.39] [483.95] **6b**

Synthesis:

The synthesis was performed according to the general complexation procedure, using naphthoquinone **6a** (0.200 g, 0.9 mmol), sodium methoxide (0.055 g, 1.0 mmol) and bis[chlorido(μ-chlorido)(η^6-*p*-cymene)ruthenium(II)] (0.257 g, 0.4 mmol).

Yield: 0.314 g (77%) dark violet solid

Characterization:

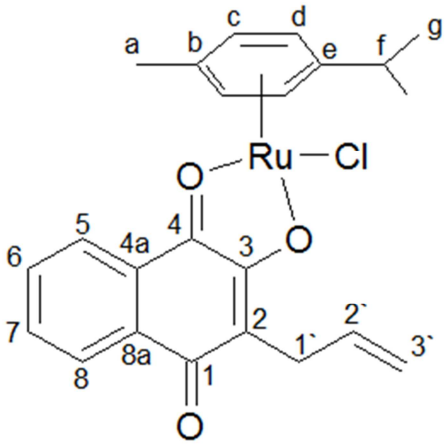
Melting point: 155.5 ℃ (decomposition)

Elemental analysis:

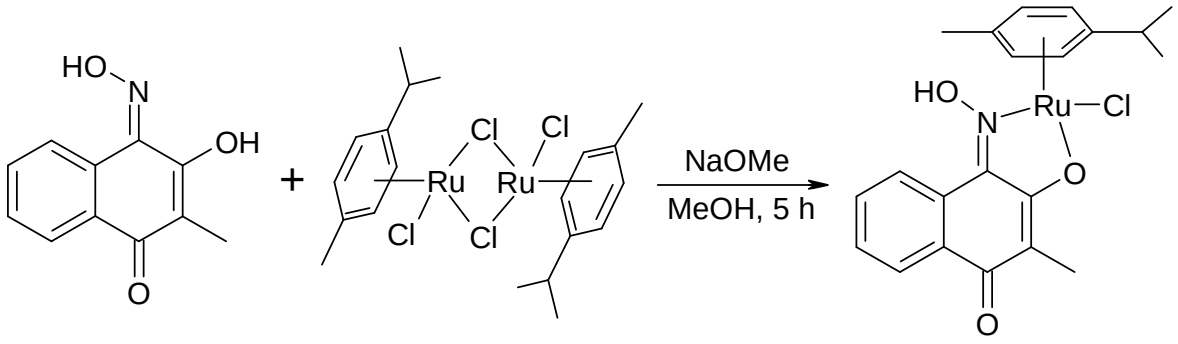
		C [%]	H [%]	N [%]
6b	calculated	55.28	4.69	0.00
$C_{23}H_{23}ClO_3Ru*0.25CH_2Cl_2$	measured	55.04	4.43	0.11
	Δ	0.24	0.27	0.11

^{1}H-NMR (500.10 MHz, $CDCl_3$) δ: 1.43–1.48 (m, 6H, Hg), 2.43 (s, 3H, Ha), 3.02 (m, 1H, Hf), 3.40 (d, ^{3}J = 7 Hz, 2H, H1`), 4.99 (d, $^{3}$J = 10 Hz, 1H, H3`), 5.17 (d, ^{3}J = 17 Hz, 1H, H3`), 5.49–5.51 (m, 2H, Hc), 5.76–5.78 (m, 2H, Hd), 5.93–6.01 (m, 1H, H2`), 7.55 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 7.71 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 8.00 (d, ^{3}J = 8 Hz, 1 H, H8) 8.02 (d, ^{3}J = 8 Hz, 1 H, H5).

^{13}C-NMR (125.75 MHz, $[D_4]$MeOH) δ: 17.4 (Ca), 21.2 (Cg), 26.8 (C3`), 31.3 (Cf), 56.0 (C1`), 72.7 (C2`), 78.3 (Cc), 79.7 (Cc), 80.9 (Cd), 82.3 (Cd), 97.0 (Cb), 100.7 (Ce), 123.2 (C2), 125.9 (C8), 126.3 (C5), 127.9 (C4a), 131.7 (C6), 132.6 (C8a), 136.2 (C7), 169.5 (C3), 182.4 (C1), 196.1 (C4).



5.4.8 Chlorido[3-methyl-(2-oxo-κO)-[1,4]-naphthoquinone-1-oximato-κN](η^6-p-cymene)ruthenium(II) (7b)



[203.19] **7a** [612.39] [472.93] **7b**

Synthesis:

The synthesis was performed according to the general complexation procedure, using **7a** (0.200 g, 1.0 mmol), sodium methoxide (0.058 g, 1.1 mmol) and bis[chlorido(μ-chlorido)(η^6-*p*-cymene)ruthenium(II)] (0.271 g, 0.4 mmol).

Yield: 0.129 g (31%) dark green solid

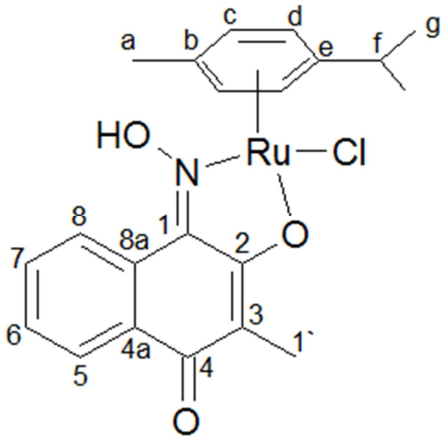
Characterization:

Melting point: 136 - 138 ℃ (decomposition)

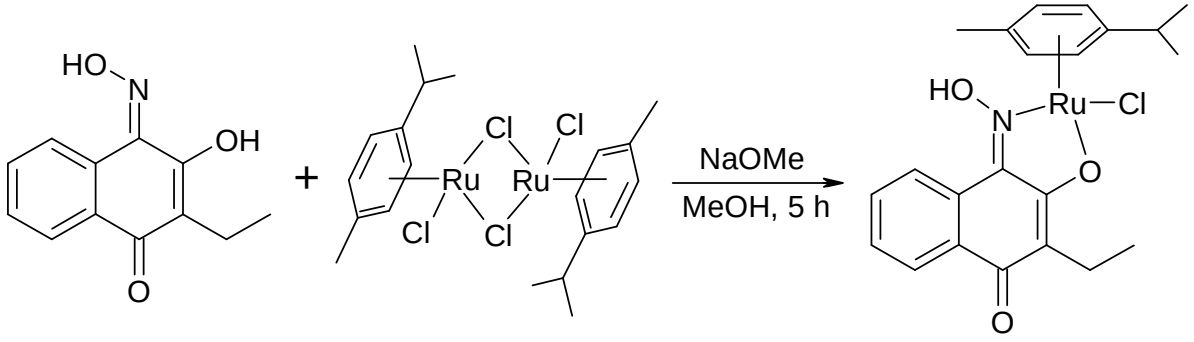
Elemental analysis:

		C [%]	H [%]	N [%]
7b	calculated	51.65	4.59	2.83
$C_{21}H_{22}ClNO_3Ru*0.25CH_2Cl_2$	measured	51.78	4.72	2.90
	Δ	0.13	0.13	0.06

^{1}H-NMR (500.10 MHz, [D_4]MeOH) δ: 1.30 (t, ^{3}J = 6 Hz, 6H, Hg), 2.25 (s, 3H, H1`), 2.30 (s, 3H, Ha), 2.88–2.94 (m, 1H, Hf), 5.49 (d, ^{3}J = 7 Hz, 1H, Hc), 5.54 (d, ^{3}J = 7 Hz, 1H, Hc), 5.66 (d, ^{3}J = 6 Hz, 1H, Hd), 5.76 (d, ^{3}J = 6 Hz, 1H, Hd), 7.46 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.58 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 8.08 (d, ^{3}J = 8 Hz, 1H, H5), 9.12 (d, ^{3}J = 8 Hz, 1H, H8).



5.4.9 Chlorido[2-ethyl-(3-oxo-κO)-[1,4]-naphthoquinone-4-oximato-κN](η^6-p-cymene)ruthenium(II) (8b)



[217.22] **8a** [612.39] [486.95] **8b**

Synthesis:

The synthesis was performed according to the general complexation procedure, using **8a** (0.200 g, 0.9 mmol), sodium methoxide (0.055 g, 1.0 mmol) and bis[chlorido(*μ*-chlorido)(*η*^{6}-*p*-cymene)ruthenium(II)] (0.254 g, 0.4 mmol).

Yield: 0.093 g (23%) brown solid

Characterization:

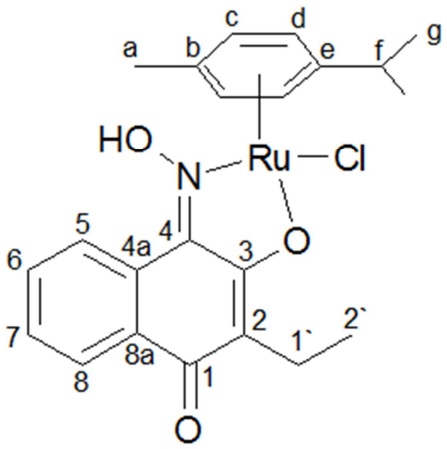
Melting point: 123 - 124℃ (decomposition)

Elemental analysis:

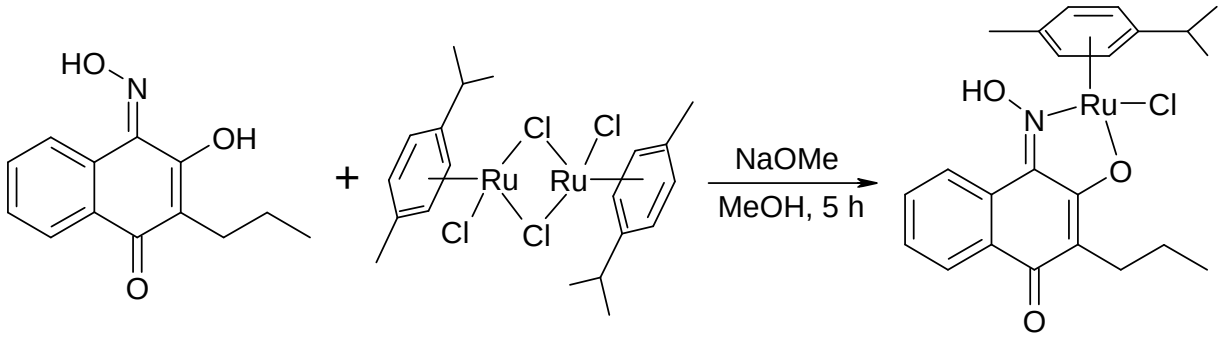
		C [%]	H [%]	N [%]
8b	calculated	53.28	5.08	2.82
$C_{22}H_{24}ClNO_3Ru*0.5H_2O$	measured	52.95	4.67	2.89
	Δ	0.33	0.41	0.07

^{1}H-NMR (500.10 MHz, [D$_4$]MeOH) δ: 1.19 (t, ^{3}J = 8 Hz, 3H, H2`), 1.28–1.32 (m, 6H, Hg), 2.30 (s, 3H, Ha), 2.81–2.87 (m, 2H, H1`), 2.88–2.92 (m, 1H, Hf), 5.49 (d, ^{3}J = 6 Hz, 1H, Hc), 5.55 (d, ^{3}J = 6 Hz, 1H, Hc), 5.66 (d, ^{3}J = 6 Hz, 1H, Hd), 5.78 (d, ^{3}J = 6 Hz, 1H, Hd), 7.46 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 7.58 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 8.08 (d, ^{3}J = 8 Hz, 1H, H8), 9.19 (d, ^{3}J = 8 Hz, 1H, H5).

^{13}C-NMR (125.75 MHz, [D$_4$]MeOH) δ: 12.3 (C2`), 15.5 (C1`), 17.2 (Ca), 20.8, 21.2 (Cg), 31.0 (Cf), 84.2 (Cc), 85.0 (Cc), 85.1 (Cd), 85.9 (Cd), 100.4 (Cb), 103.9 (Ce), 117.1 (C2), 122.6 (C8), 122.7 (C4a), 123.0 (C5), 123.9 (C8a), 126.7 (C6), 131.2 (C7), 148.0 (C4), 161.0 (C3), 187.3 (C1).



5.4.10 Chlorido[(2-oxo-κO)-3-propyl-[1,4]-naphthoquinone-1-oximato-κN](η^6-p-cymene)ruthenium(II) (9b)



[231.25] **9a** [612.39] [500.98] **9b**

Synthesis:

The synthesis was performed according to the general complexation procedure, using **9a** (0.200 g, 0.9 mmol), sodium methoxide (0.051 g, 1.0 mmol) and bis[chlorido(*μ*-chlorido)(*η*^{6}-*p*-cymene)ruthenium(II)] (0.238 g, 0.4 mmol).

Yield: 0.175 g (45%), dark green solid

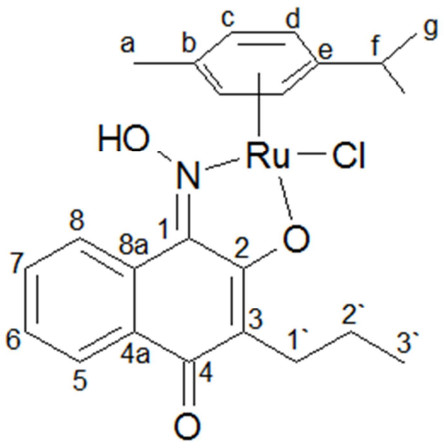
Characterization:

Melting point: 138 – 139 °C (decomposition)

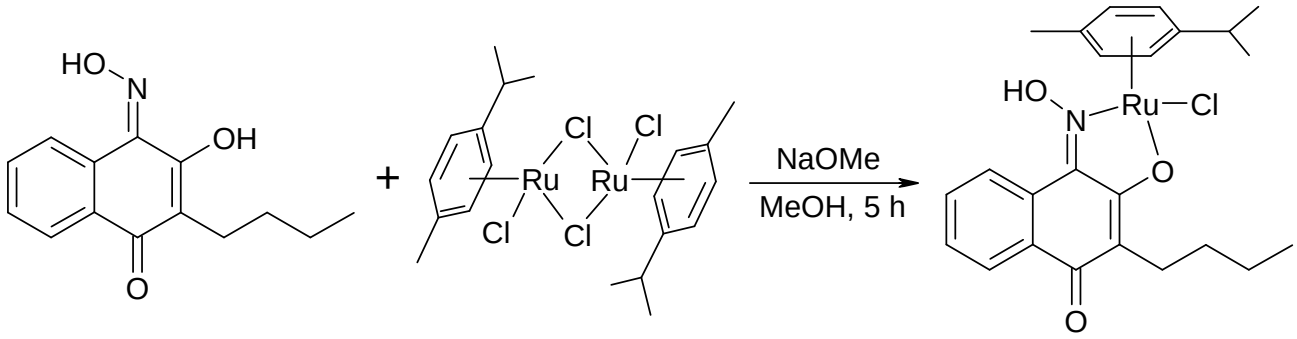
Elemental analysis:

		C [%]	H [%]	N [%]
9b	calculated	53.47	5.11	2.68
$C_{23}H_{26}ClNO_3Ru*0.25CH_2Cl_2$	measured	53.59	4.86	2.91
	Δ	0.12	0.26	0.23

^{1}H-NMR (500.10 MHz, [D$_4$]MeOH) δ: 1.04 (t, ^{3}J = 8 Hz, 3H, H3`), 1.28–1.33 (m, 6H, Hg), 1.61–1.66 (m, 2H, H2`), 2.30 (s, 3H, Ha), 2.74–2.83 (m, 2H, H1`), 2.87–2.93 (m, 1H, Hf), 5.48 (d, ^{3}J = 6 Hz, 1H, Hc), 5.54 (d, ^{3}J = 6 Hz, 1H, Hc), 5.64 (d, ^{3}J = 7 Hz, 1H, Hd), 5.76 (d, ^{3}J = 7 Hz, 1H, Hd), 7.46 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.58 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 8.08 (d, ^{3}J = 8 Hz, 1H, H5), 9.20 (d, ^{3}J = 8 Hz, 1H, H8).



5.4.11 Chlorido[2-butyl-(3-oxo-κO)-[1,4]-naphthoquinone-4-oximato-κN](η^6-p-cymene)ruthenium(II) (10b)



[245.27] **10a** [612.39] [515.01] **10b**

Synthesis:

The synthesis was performed according to the general complexation procedure, using **10a** (0.200 g, 0.8 mmol), sodium methoxide (0.048 g, 0.9 mmol) and bis[chlorido(*μ*-chlorido)(*η*^{6}-*p*-cymene)ruthenium(II)] (0.225 g, 0.4 mmol).

Yield: 0.253 g (67%), dark brown solid

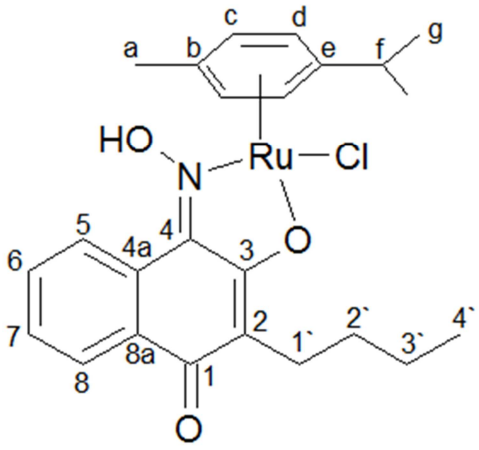
Characterization:

Melting point: 111 – 112 °C (decomposition)

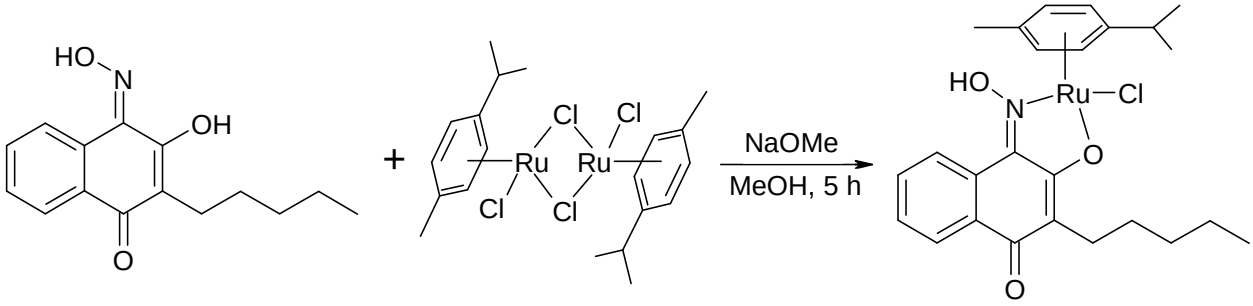
Elemental analysis:

		C [%]	H [%]	N [%]
10b	calculated	55.78	5.50	2.71
$C_{24}H_{28}ClNO_3Ru*0.1H_2O$	measured	55.44	5.14	2.73
	Δ	0.34	0.37	0.02

^{1}H-NMR (500.10 MHz, $CDCl_3$) δ: 0.97 (t, ^{3}J = 8 Hz, 3H, H4`), 1.29–1.36 (m, 6H, Hg), 1.29–1.36 (m, 2H, H3`), 1.35 – 1.48 (m, 2H, H2`), 2.35 (s, 3H, Ha), 2.86 – 2.98 (m, 2H, H1`), 2.92-2.98 (m, 1H, Hf), 5.43 (t, ^{3}J = 6 Hz, 2H, Hc), 5.53 (d, ^{3}J = 6 Hz, 1H, Hd), 5.65 (d, ^{3}J = 6 Hz, 1H, Hd), 7.34 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 7.52 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.86 (d, ^{3}J = 7 Hz, 1H, H8), 9.19 (d, ^{3}J = 8 Hz, 1H, H5).



5.4.12 Chlorido[(2-oxo-κO)-3-pentyl-[1,4]-naphthoquinone-1-oximato-κN](η^6-p-cymene)ruthenium(II) (11b)



[259.30] **11a** [612.39] [529.03] **11b**

Synthesis:

The synthesis was performed according to the general complexation procedure, using **11a** (0.200 g, 0.8 mmol), sodium methoxide (0.046 g, 0.8 mmol) and bis[chlorido(μ-chlorido)(η^6-*p*-cymene)ruthenium(II)] (0.213 g, 0.3 mmol).

Yield: 0.168 g (46%), dark brown solid

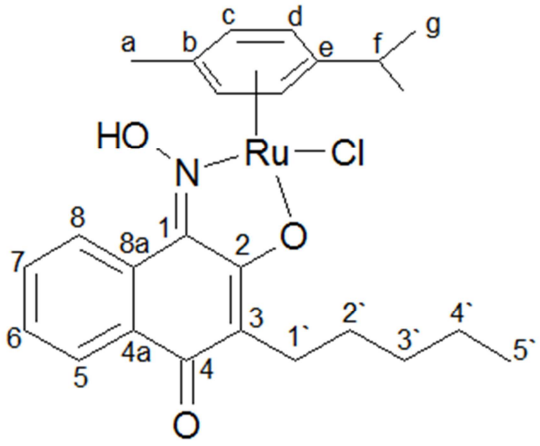
Characterization:

Melting point: 134 - 138℃ (decomposition)

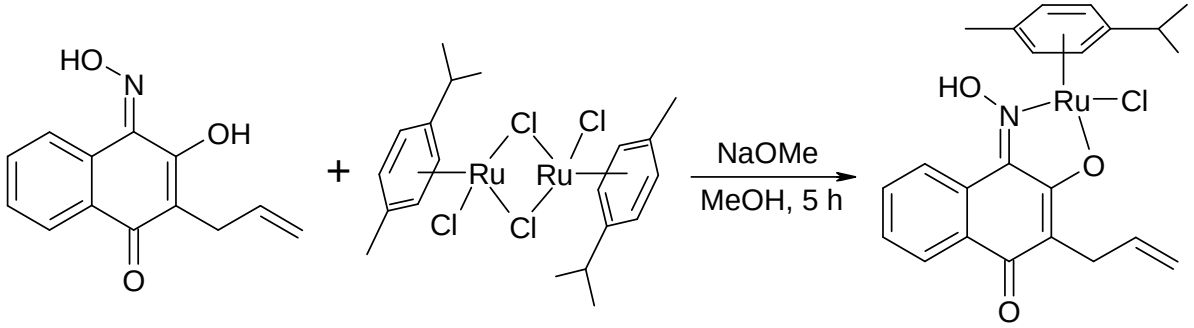
Elemental analysis:

		C [%]	H [%]	N [%]
11b	calculated	56.08	5.66	2.61
$C_{25}H_{30}ClNO_3Ru*0.1CH_2Cl_2$	measured	55.86	5.38	2.73
	Δ	0.22	0.28	0.12

^{1}H-NMR (500.10 MHz, [D$_4$]MeOH) δ: 0.96–0.99 (m, 3H, H5`), 1.29–1.34 (m, 6H, Hg), 1.40–1.48 (m, 4H, H3`, H4`), 1.58–1.64 (m, 2H, H2`), 2.31 (s, 3H, Ha), 2.75–2.86 (m, 2H, H1`), 2.88–2.94 (m, 1H, Hf), 5.49 (d, ^{3}J = 6 Hz, 1H, Hc), 5.54 (d, ^{3}J = 6 Hz, 1H, Hc), 5.64 (d, ^{3}J = 6 Hz, 1H, Hd), 5.76 (d, ^{3}J = 6 Hz, 1H, Hd), 7.46 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.57 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 8.07 (d, ^{3}J = 8 Hz, 1H, H5), 9.20 (d, ^{3}J = 8 Hz, 1H, H8).



5.4.13 Chlorido[2-allyl-(3-oxo-κO)-[1,4]-naphthoquinone-4-oximato-κN](η^6-p-cymene)ruthenium(II) (12b)



[229.22] **12a** [612.39] [498.96] **12b**

Synthesis:

The synthesis was performed according to the general complexation procedure, using **12a** (0.150 g, 0.7 mmol), sodium methoxide (0.039 g, 0.7 mmol) and bis[chlorido(*μ*-chlorido)(*η*^{6}-*p*-cymene)ruthenium(II)] (0.180 g, 0.3 mmol).

Yield: 0.157 g (53%), dark green solid

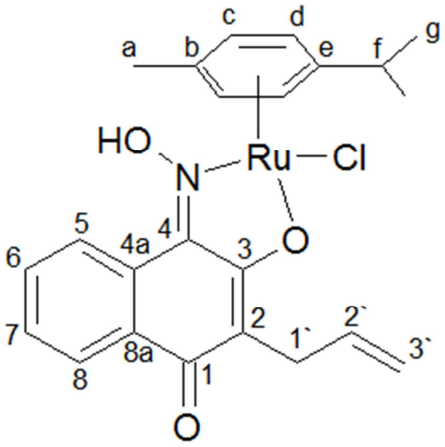
Characterization:

Melting point: 125 - 126℃ (decomposition)

Elemental analysis:

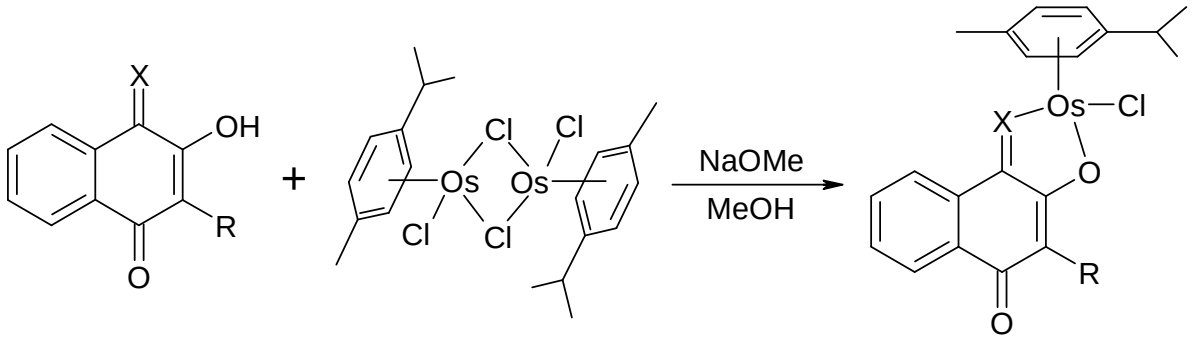
		C [%]	H [%]	N [%]
12b	calculated	54.38	4.96	2.76
$C_{23}H_{24}ClNO_3Ru*0.5H_2O$	measured	54.44	4.57	2.84
	Δ	0.06	0.39	0.8

^{1}H-NMR (500.10 MHz, [D_4]MeOH) δ: 1.26–1.31 (m, 6H, Hg), 2.29 (s, 3H, Ha), 2.86-2.92 (m, 1H, Hf), 3.51–3.56 (m, 1H, H1`), 3.62–3.67 (m, 1H, H1`), 5.01–5.03 (m, 1H, H3`), 5.04–5.08 (m, 1H, H3`), 5.48 (d, ^{3}J = 6 Hz, 1H, Hc), 5.52 (d, ^{3}J = 6 Hz, 1H, Hc), 5.65 (d, ^{3}J = 6 Hz, 1H, Hd), 5.76 (d, ^{3}J = 6 Hz, 1H, Hd), 5.98 – 6.06 (m, 1H, H2`), 7.47 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 7.60 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 8.09 (d, ^{3}J = 8 Hz, 1 H, H8) 9.21 (d, ^{3}J = 8 Hz, 1 H, H5).



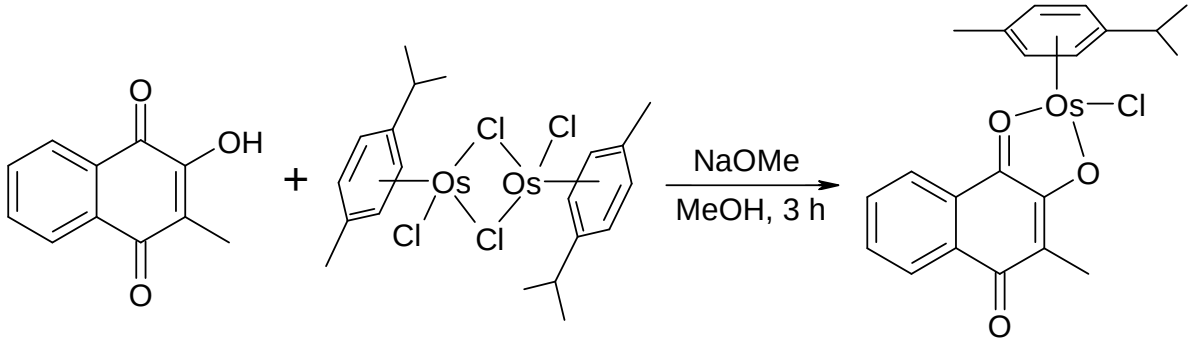
5.5 Synthesis of the Os(II)-cymene complexes

5.5.1 General complexation procedure



Bis[chlorido(μ-chlorido)(η^6-*p*-cymene)osmium(II)] (0.9 eq) was added to a solution of naphthoquinone (1 eq) and sodium methoxide (1.1 eq) in methanol (40 mL). The reaction mixture was stirred at room temperature under argon atmosphere for 3 h. The solvent was evaporated under reduced pressure, the residue was dissolved in dichloromethane and filtered. The filtrate was reduced to 2 mL in volume approximately, n-hexane was added and the mixture stored in the fridge at 4 ℃ overnight. The obtained solid was separated by filtration, washed with n-hexane (3 x 10 mL) and dried in vacuum.

5.5.2 Chlorido[3-methyl-(2-oxo-κO)-[1,4]-naphthoquinonato-κO](η^6-p-cymene)osmium(II) (13b)



[188.18] **1a** [612.39] [547.07] **13b**

Synthesis:

The synthesis was performed according to the general complexation procedure, using naphthoquinone **1a** (0.053 g, 0.3 mmol), sodium methoxide (0.017 g, 0.3 mmol) and bis[chlorido(*μ*-chlorido)(*η*^{6}-*p*-cymene)osmium(II)] (0.100 g, 0.1 mmol).

Yield: 0.097 g (70%), dark blue solid

Characterization:

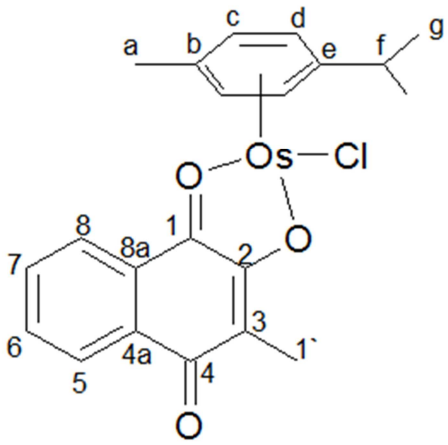
Melting point: 105 – 106 °C (decomposition)

Elemental analysis:

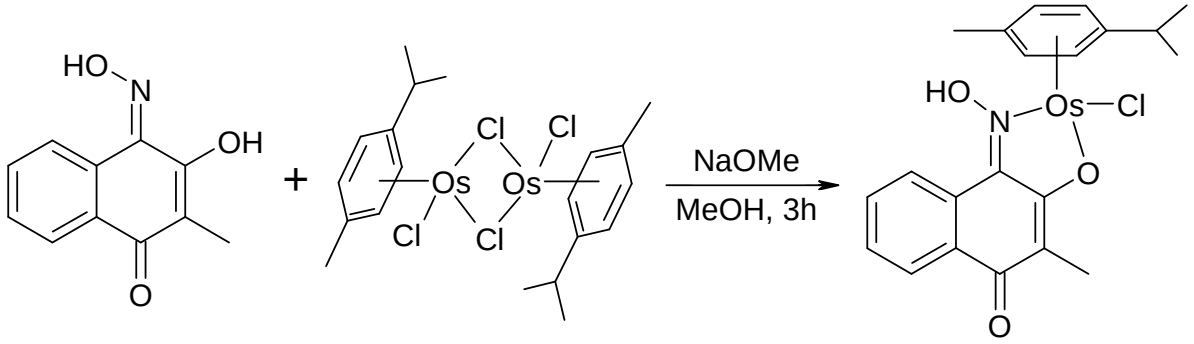
		C [%]	H [%]	N [%]
13b	calculated	45.36	3.99	0.00
$C_{21}H_{21}ClO_3Os*0.5H_2O$	measured	45.35	3.65	0.16
	Δ	0.01	0.34	0.16

^{1}H-NMR (500.10 MHz, [D_4]MeOH) δ: 1.41 (t, ^{3}J = 7 Hz, 6H, Hg), 2.09 (s, 3H, H1`), 2.42 (s, 3H, Ha), 2.82-2.88 (m, 1H, Hf), 5.12 (d, ^{3}J = 6 Hz, 1H, Hc), 6.12 (d, ^{3}J = 6 Hz, 1H, Hc), 6.14 (d, ^{3}J = 6 Hz, 1H, Hc), 6.41 (d, ^{3}J = 6 Hz, 1H, Hd), 6.44 (d, ^{3}J = 6 Hz, 1H, Hd), 7.71 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.87 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 8.01 (d, ^{3}J = 8 Hz, 1H, H5), 8.10 (d, ^{3}J = 8 Hz, 1H, H8).

^{13}C-NMR (125.75 MHz, [D_4]MeOH) δ: 7.2 (C1`), 17.7 (Ca), 21.6 (Cg), 32.0 (Cf), 69.5 (Cc), 70.5 (Cc), 72.7 (Cd), 73.7 (Cd), 88.1 (Cb), 91.3 (Ce), 122.4 (C3), 126.1 (C5), 126.4 (C8), 127.8 (C8a), 131.9 (C7), 132.6 (C4a), 136.4 (C6), 170.5 (C2), 183.4 (C4), 197.5 (C1).



5.5.3 Chlorido[3-methyl-(2-oxo-κO)-[1,4]-naphthoquinone-1-oximato-κN](η^6-p-cymene)osmium(II) (14b)



[203.19] **7a** [612.39] [562.09] **14b**

Synthesis:

The synthesis was performed according to the general complexation procedure, using **7a** (0.057 g, 0.3 mmol), sodium methoxide (0.017 g, 0.3 mmol) and bis[chlorido(*μ*-chlorido)(*η*^{6}-*p*-cymene)osmium(II)] (0.100 g, 0.1 mmol). In this case the remaining NaCl was removed by filtration (Kieselgur, MeOH). The filtrate was evaporated under reduced pressure, the residue was dissolved in dichloromethane and n-hexane was added. The mixture was stored in the fridge at 4 ℃ overnight. The obtained solid was separated by filtration, washed with n-hexane (3 x 10 mL) and dried in vacuum.

Yield: 0.054g (38%), brown solid

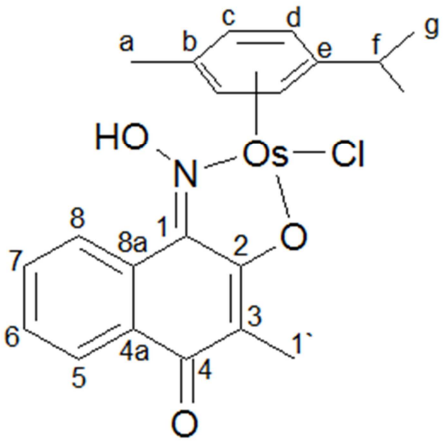
Characterization:

Melting point: 126 ℃ (decomposition)

Elemental analysis:

		C [%]	H [%]	N [%]
14b	calculated	36.97	3.25	2.05
$C_{21}H_{22}ClNO_3Os*2SiO_2$	measured	36.70	2.91	2.10
	Δ	0.27	0.34	0.05

^{1}H-NMR (500.10 MHz, [D_4]MeOH) δ: 1.26–1.27 (m, 6H, Hg), 2.27 (s, 3H, H1`), 2.38 (s, 3H, Ha), 2.77-2.83 (m, 1H, Hf), 5.71 (d, ^{3}J = 6 Hz, 2H, Hc), 5.92 (d, ^{3}J = 6 Hz, 1H, Hd), 6.05 (d, ^{3}J = 6 Hz, 1H, Hd), 7.51 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H7), 7.59 (ddd, ^{4}J = 2 Hz, ^{3}J = 8 Hz, ^{3}J = 8 Hz, 1H, H6), 8.13 (d, ^{3}J = 8 Hz, 1H, H5), 9.30 (d, ^{3}J = 8 Hz, 1H, H8).



6 Appendix

6.1 Abbreviations

1D	one dimensional NMR
2D	two dimensional NMR
AcOH	acetic acid
℃	degree Celsius
CDK	cyclin-dependent kinase
CDC25	cell division cycle 25
cat.	catalytic
d	doublet (NMR)
DACH	1,2-diaminocyclohexane
$CDCl_3$	deuterated chloroform
δ	chemical shift (NMR)
[D6]-DMSO	deuterated dimethyl sulfoxide
[D4]-CH_3OH	deuterated methanol
e.g.	*exempli gratia* (for example)
eq	equivalent
EtOAc	ethyl acetate
g	gram
h	hour
Hind	indazole
H_2O_2	hydrogen peroxide
Hz	hertz
i. e.	id est (that is)
J	coupling constant (NMR)
M	molar
m	multiplet (NMR)
mg	milligram
min	minute
MeOH	methanol
mL	milliliter
mmol	millimol
nM	nanomolar
NaOMe	sodium methoxide
Na_2CO_3	sodium carbonate
Na_2SO_4	sodium sulfate
NMR	nuclear magnetic resonance
pH	pondus Hydrogenii (power of hydrogen)
ppm	parts per million
q	quartet (NMR)
quin	quintet (NMR)
s	singlet (NMR)
sext	sextet (NMR)
t	triplet (NMR)
t-BuOH	tert-butanol
UV	ultraviolet

6.2 Single crystal X-ray diffraction data for complex 6a

Empirical formula	$C_{23}H_{23}ClO_3Ru$	
Formula weight	483.93	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	triclinic, P-1	
Unit cell dimensions	a = 9.8719(3) Å	α = 94.806(2)°
	b = 10.8326(4) Å	β = 107.608(2)°
	c = 11.0802(4) Å	γ = 116.4760(10)°
Volume	977.17(6) $Å^3$	
Z, Calculated density	2, 1.645 mg/m^3	
Absorption coefficient	0.961 mm^{-1}	
F(000)	492	
Crystal size	0.20 x 0.13 x 0.04 mm	
Theta range for data collection	2.17 to 28.00 °	
Index ranges	-13<=h<=11, -14<=k<=14, -14<=l<=14	
Reflections collected / unique	27051 / 4645 [R(int) = 0.0413]	
Completeness to 2theta = 28.00	98.5%	
Max. and min. transmission	0.9626 and 0.8311	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4645 / 0 / 254	
Goodness-of-fit on F^2	1.052	
Final R indices [I>2σ(I)]	R1 = 0.0278, wR2 = 0.0672	
R indices (all data)	R1 = 0.0311, wR2 = 0.0688	
Largest diff. peak and hole	2.734 and -0.971 e. $Å^{-3}$	

Bond lengths [Å]

Ru(1)-O(1)	2.0799(15)	C(11)-C(12)	1.507(3)
Ru(1)-O(2)	2.1305(15)	C(11)-H(11A)	0.9900
Ru(1)-C(16)	2.156(2)	C(11)-H(11B)	0.9900
Ru(1)-C(18)	2.158(2)	C(12)-C(13)	1.312(4)
Ru(1)-C(19)	2.161(2)	C(12)-H(12)	0.9500
Ru(1)-C(17)	2.178(2)	C(13)-H(13A)	0.9500
Ru(1)-C(15)	2.189(2)	C(13)-H(13B)	0.9500
Ru(1)-C(14)	2.204(2)	C(14)-C(15)	1.401(3)
Ru(1)-Cl(1)	2.3888(5)	C(14)-C(19)	1.423(4)
O(1)-C(1)	1.301(3)	C(14)-C(20)	1.504(3)
O(2)-C(2)	1.246(3)	C(15)-C(16)	1.420(3)
O(3)-C(9)	1.233(3)	C(15)-H(15)	0.9500
C(1)-C(10)	1.374(3)	C(16)-C(17)	1.418(3)
C(1)-C(2)	1.483(3)	C(16)-H(16)	0.9500
C(2)-C(3)	1.457(3)	C(17)-C(18)	1.426(3)
C(3)-C(4)	1.394(3)	C(17)-C(21)	1.514(3)
C(3)-C(8)	1.403(3)	C(18)-C(19)	1.400(3)
C(4)-C(5)	1.385(3)	C(18)-H(18)	0.9500
C(4)-H(4)	0.9500	C(19)-H(19)	0.9500
C(5)-C(6)	1.388(3)	C(20)-H(20A)	0.9800
C(5)-H(5)	0.9500	C(20)-H(20B)	0.9800
C(6)-C(7)	1.388(3)	C(20)-H(20C)	0.9800
C(6)-H(6)	0.9500	C(21)-C(23)	1.518(4)
C(7)-C(8)	1.387(3)	C(21)-C(22)	1.530(3)
C(7)-H(7)	0.9500	C(21)-H(21)	1.0000
C(8)-C(9)	1.501(3)	C(22)-H(22A)	0.9800
C(9)-C(10)	1.447(3)	C(22)-H(22B)	0.9800
C(10)-C(11)	1.496(3)	C(22)-H(22C)	0.9800

C(23)-H(23A)	0.9800	C(23)-H(23C)	0.9800
C(23)-H(23B)	0.9800		

Bond angles [degree]

O(1)-Ru(1)-O(2)	76.19(6)	C(16)-Ru(1)-C(14)	68.48(9)
O(1)-Ru(1)-C(16)	121.77(8)	C(18)-Ru(1)-C(14)	68.69(9)
O(2)-Ru(1)-C(16)	94.31(7)	C(19)-Ru(1)-C(14)	38.04(9)
O(1)-Ru(1)-C(18)	93.89(8)	C(17)-Ru(1)-C(14)	82.17(9)
O(2)-Ru(1)-C(18)	151.99(8)	C(15)-Ru(1)-C(14)	37.18(9)
C(16)-Ru(1)-C(18)	68.41(8)	O(1)-Ru(1)-Cl(1)	84.47(5)
O(1)-Ru(1)-C(19)	118.63(8)	O(2)-Ru(1)-Cl(1)	84.08(4)
O(2)-Ru(1)-C(19)	164.80(8)	C(16)-Ru(1)-Cl(1)	152.65(7)
C(16)-Ru(1)-C(19)	80.80(9)	C(18)-Ru(1)-Cl(1)	121.51(6)
C(18)-Ru(1)-C(19)	37.84(9)	C(19)-Ru(1)-Cl(1)	93.66(6)
O(1)-Ru(1)-C(17)	94.43(7)	C(17)-Ru(1)-Cl(1)	159.86(6)
O(2)-Ru(1)-C(17)	115.27(7)	C(15)-Ru(1)-Cl(1)	115.11(7)
C(16)-Ru(1)-C(17)	38.19(9)	C(14)-Ru(1)-Cl(1)	90.64(6)
C(18)-Ru(1)-C(17)	38.39(8)	C(1)-O(1)-Ru(1)	114.24(14)
C(19)-Ru(1)-C(17)	69.17(9)	C(2)-O(2)-Ru(1)	113.62(14)
O(1)-Ru(1)-C(15)	159.76(8)	O(1)-C(1)-C(10)	124.9(2)
O(2)-Ru(1)-C(15)	99.71(8)	O(1)-C(1)-C(2)	114.39(18)
C(16)-Ru(1)-C(15)	38.14(9)	C(10)-C(1)-C(2)	120.71(19)
C(18)-Ru(1)-C(15)	80.49(9)	O(2)-C(2)-C(3)	121.7(2)
C(19)-Ru(1)-C(15)	67.61(9)	O(2)-C(2)-C(1)	117.46(19)
C(17)-Ru(1)-C(15)	69.08(9)	C(3)-C(2)-C(1)	120.87(19)
O(1)-Ru(1)-C(14)	155.93(8)	C(4)-C(3)-C(8)	120.3(2)
O(2)-Ru(1)-C(14)	126.82(8)	C(4)-C(3)-C(2)	121.6(2)

C(8)-C(3)-C(2)	118.0(2)	C(13)-C(12)-C(11)	126.7(2)
C(5)-C(4)-C(3)	120.0(2)	C(13)-C(12)-H(12)	116.6
C(5)-C(4)-H(4)	120.0	C(11)-C(12)-H(12)	116.6
C(3)-C(4)-H(4)	120.0	C(12)-C(13)-H(13A)	120.0
C(4)-C(5)-C(6)	119.7(2)	C(12)-C(13)-H(13B)	120.0
C(4)-C(5)-H(5)	120.1	H(13A)-C(13)-H(13B)	120.0
C(6)-C(5)-H(5)	120.1	C(15)-C(14)-C(19)	118.0(2)
C(5)-C(6)-C(7)	120.6(2)	C(15)-C(14)-C(20)	121.7(2)
C(5)-C(6)-H(6)	119.7	C(19)-C(14)-C(20)	120.2(2)
C(7)-C(6)-H(6)	119.7	C(15)-C(14)-Ru(1)	70.83(13)
C(8)-C(7)-C(6)	120.3(2)	C(19)-C(14)-Ru(1)	69.34(13)
C(8)-C(7)-H(7)	119.8	C(20)-C(14)-Ru(1)	128.07(17)
C(6)-C(7)-H(7)	119.8	C(14)-C(15)-C(16)	120.9(2)
C(7)-C(8)-C(3)	119.1(2)	C(14)-C(15)-Ru(1)	71.98(13)
C(7)-C(8)-C(9)	120.2(2)	C(16)-C(15)-Ru(1)	69.67(12)
C(3)-C(8)-C(9)	120.78(19)	C(14)-C(15)-H(15)	119.6
O(3)-C(9)-C(10)	121.5(2)	C(16)-C(15)-H(15)	119.6
O(3)-C(9)-C(8)	118.9(2)	Ru(1)-C(15)-H(15)	131.7
C(10)-C(9)-C(8)	119.58(19)	C(17)-C(16)-C(15)	121.5(2)
C(1)-C(10)-C(9)	120.0(2)	C(17)-C(16)-Ru(1)	71.73(12)
C(1)-C(10)-C(11)	121.5(2)	C(15)-C(16)-Ru(1)	72.19(13)
C(9)-C(10)-C(11)	118.52(19)	C(17)-C(16)-H(16)	119.3
C(10)-C(11)-C(12)	113.51(19)	C(15)-C(16)-H(16)	119.3
C(10)-C(11)-H(11A)	108.9	Ru(1)-C(16)-H(16)	129.3
C(12)-C(11)-H(11A)	108.9	C(16)-C(17)-C(18)	117.0(2)
C(10)-C(11)-H(11B)	108.9	C(16)-C(17)-C(21)	124.0(2)
C(12)-C(11)-H(11B)	108.9	C(18)-C(17)-C(21)	118.8(2)
H(11A)-C(11)-H(11B)	107.7	C(16)-C(17)-Ru(1)	70.07(12)

C(18)-C(17)-Ru(1)	70.04(13)	H(20B)-C(20)-H(20C)	109.5
C(21)-C(17)-Ru(1)	127.10(15)	C(17)-C(21)-C(23)	112.3(2)
C(19)-C(18)-C(17)	121.3(2)	C(17)-C(21)-C(22)	109.8(2)
C(19)-C(18)-Ru(1)	71.19(13)	C(23)-C(21)-C(22)	112.3(2)
C(17)-C(18)-Ru(1)	71.57(13)	C(17)-C(21)-H(21)	107.4
C(19)-C(18)-H(18)	119.4	C(23)-C(21)-H(21)	107.4
C(17)-C(18)-H(18)	119.4	C(22)-C(21)-H(21)	107.4
Ru(1)-C(18)-H(18)	130.6	C(21)-C(22)-H(22A)	109.5
C(18)-C(19)-C(14)	121.3(2)	C(21)-C(22)-H(22B)	109.5
C(18)-C(19)-Ru(1)	70.96(13)	H(22A)-C(22)-H(22B)	109.5
C(14)-C(19)-Ru(1)	72.63(13)	C(21)-C(22)-H(22C)	109.5
C(18)-C(19)-H(19)	119.3	H(22A)-C(22)-H(22C)	109.5
C(14)-C(19)-H(19)	119.3	H(22B)-C(22)-H(22C)	109.5
Ru(1)-C(19)-H(19)	129.6	C(21)-C(23)-H(23A)	109.5
C(14)-C(20)-H(20A)	109.5	C(21)-C(23)-H(23B)	109.5
C(14)-C(20)-H(20B)	109.5	H(23A)-C(23)-H(23B)	109.5
H(20A)-C(20)-H(20B)	109.5	C(21)-C(23)-H(23C)	109.5
C(14)-C(20)-H(20C)	109.5	H(23A)-C(23)-H(23C)	109.5
H(20A)-C(20)-H(20C)	109.5	H(23B)-C(23)-H(23C)	109.5

Torsion angles [degree]

O(2)-Ru(1)-O(1)-C(1)	18.13(14)	C(14)-Ru(1)-O(1)-C(1)	-146.22(19)
C(16)-Ru(1)-O(1)-C(1)	104.62(15)	Cl(1)-Ru(1)-O(1)-C(1)	-67.12(14)
C(18)-Ru(1)-O(1)-C(1)	171.57(15)	O(1)-Ru(1)-O(2)-C(2)	-15.36(14)
C(19)-Ru(1)-O(1)-C(1)	-158.27(14)	C(16)-Ru(1)-O(2)-C(2)	-137.04(16)
C(17)-Ru(1)-O(1)-C(1)	133.07(15)	C(18)-Ru(1)-O(2)-C(2)	-87.1(2)
C(15)-Ru(1)-O(1)-C(1)	98.7(2)	C(19)-Ru(1)-O(2)-C(2)	152.5(3)

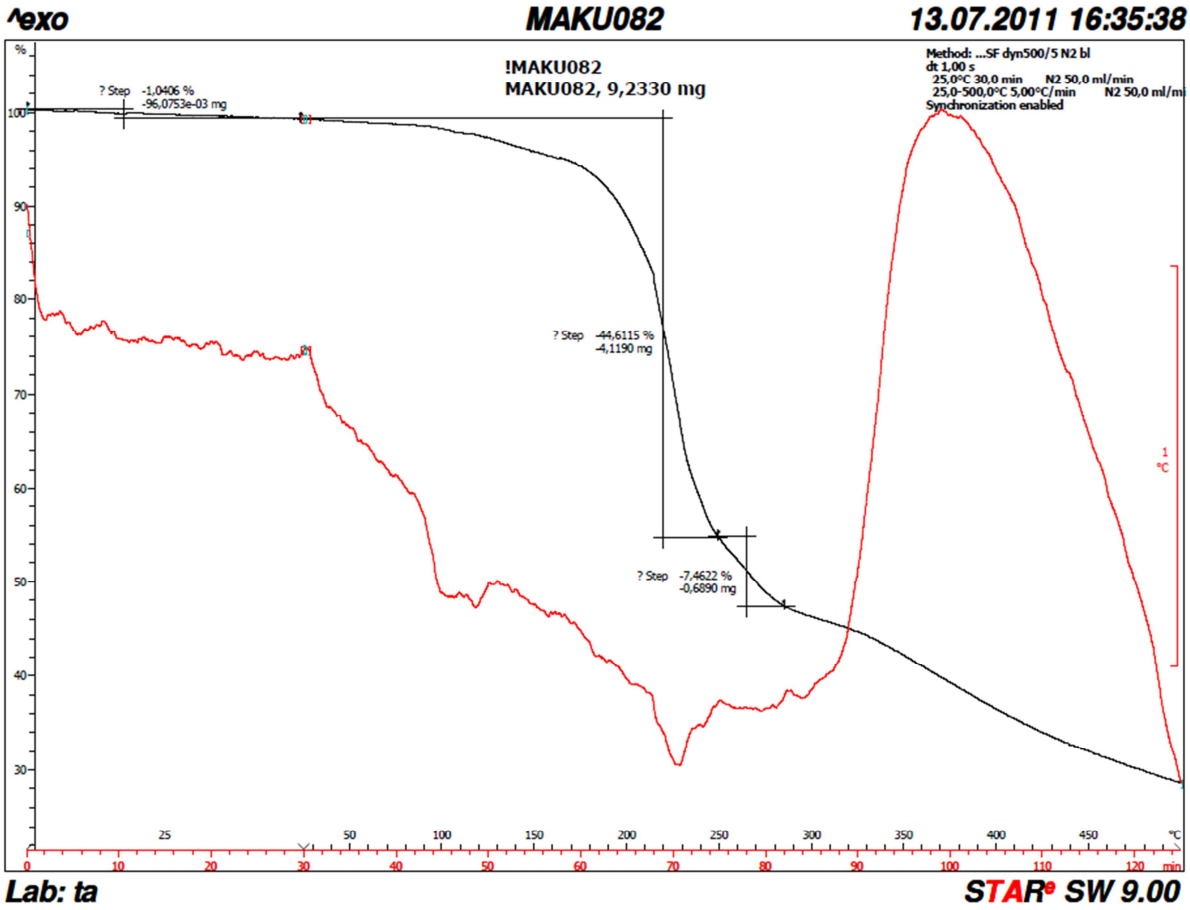
C(17)-Ru(1)-O(2)-C(2)	-103.75(16)
C(15)-Ru(1)-O(2)-C(2)	-175.10(15)
C(14)-Ru(1)-O(2)-C(2)	156.73(15)
Cl(1)-Ru(1)-O(2)-C(2)	70.38(14)
Ru(1)-O(1)-C(1)-C(10)	162.17(18)
Ru(1)-O(1)-C(1)-C(2)	-18.4(2)
Ru(1)-O(2)-C(2)-C(3)	-167.68(15)
Ru(1)-O(2)-C(2)-C(1)	10.7(2)
O(1)-C(1)-C(2)-O(2)	4.9(3)
C(10)-C(1)-C(2)-O(2)	-175.6(2)
O(1)-C(1)-C(2)-C(3)	-176.67(18)
C(10)-C(1)-C(2)-C(3)	2.8(3)
O(2)-C(2)-C(3)-C(4)	-0.8(3)
C(1)-C(2)-C(3)-C(4)	-179.1(2)
O(2)-C(2)-C(3)-C(8)	177.0(2)
C(1)-C(2)-C(3)-C(8)	-1.4(3)
C(8)-C(3)-C(4)-C(5)	-0.6(3)
C(2)-C(3)-C(4)-C(5)	177.1(2)
C(3)-C(4)-C(5)-C(6)	0.1(3)
C(4)-C(5)-C(6)-C(7)	0.6(4)
C(5)-C(6)-C(7)-C(8)	-0.9(4)
C(6)-C(7)-C(8)-C(3)	0.3(3)
C(6)-C(7)-C(8)-C(9)	-178.1(2)
C(4)-C(3)-C(8)-C(7)	0.4(3)
C(2)-C(3)-C(8)-C(7)	-177.4(2)
C(4)-C(3)-C(8)-C(9)	178.8(2)
C(2)-C(3)-C(8)-C(9)	1.1(3)
C(7)-C(8)-C(9)-O(3)	-3.4(3)
C(3)-C(8)-C(9)-O(3)	178.2(2)
C(7)-C(8)-C(9)-C(10)	176.4(2)
C(3)-C(8)-C(9)-C(10)	-2.1(3)
O(1)-C(1)-C(10)-C(9)	175.6(2)
C(2)-C(1)-C(10)-C(9)	-3.8(3)
O(1)-C(1)-C(10)-C(11)	-5.5(3)
C(2)-C(1)-C(10)-C(11)	175.02(19)
O(3)-C(9)-C(10)-C(1)	-176.8(2)
C(8)-C(9)-C(10)-C(1)	3.4(3)
O(3)-C(9)-C(10)-C(11)	4.3(3)
C(8)-C(9)-C(10)-C(11)	-175.43(19)
C(1)-C(10)-C(11)-C(12)	-88.8(3)
C(9)-C(10)-C(11)-C(12)	90.0(2)
C(10)-C(11)-C(12)-C(13)	6.3(4)
O(1)-Ru(1)-C(14)-C(15)	-148.78(17)
O(2)-Ru(1)-C(14)-C(15)	50.34(17)
C(16)-Ru(1)-C(14)-C(15)	-28.46(14)
C(18)-Ru(1)-C(14)-C(15)	-102.76(15)
C(19)-Ru(1)-C(14)-C(15)	-131.5(2)
C(17)-Ru(1)-C(14)-C(15)	-65.47(15)
Cl(1)-Ru(1)-C(14)-C(15)	133.42(14)
O(1)-Ru(1)-C(14)-C(19)	-17.3(3)
O(2)-Ru(1)-C(14)-C(19)	-178.20(12)
C(16)-Ru(1)-C(14)-C(19)	103.01(15)
C(18)-Ru(1)-C(14)-C(19)	28.71(13)
C(17)-Ru(1)-C(14)-C(19)	66.00(14)
C(15)-Ru(1)-C(14)-C(19)	131.5(2)
Cl(1)-Ru(1)-C(14)-C(19)	-95.11(13)

O(1)-Ru(1)-C(14)-C(20)	95.5(3)
O(2)-Ru(1)-C(14)-C(20)	-65.4(3)
C(16)-Ru(1)-C(14)-C(20)	-144.2(3)
C(18)-Ru(1)-C(14)-C(20)	141.5(3)
C(19)-Ru(1)-C(14)-C(20)	112.8(3)
C(17)-Ru(1)-C(14)-C(20)	178.8(2)
C(15)-Ru(1)-C(14)-C(20)	-115.7(3)
Cl(1)-Ru(1)-C(14)-C(20)	17.7(2)
C(19)-C(14)-C(15)-C(16)	-0.9(3)
C(20)-C(14)-C(15)-C(16)	175.2(2)
Ru(1)-C(14)-C(15)-C(16)	51.67(19)
C(19)-C(14)-C(15)-Ru(1)	-52.57(18)
C(20)-C(14)-C(15)-Ru(1)	123.6(2)
O(1)-Ru(1)-C(15)-C(14)	142.3(2)
O(2)-Ru(1)-C(15)-C(14)	-141.30(14)
C(16)-Ru(1)-C(15)-C(14)	134.1(2)
C(18)-Ru(1)-C(15)-C(14)	67.12(15)
C(19)-Ru(1)-C(15)-C(14)	29.96(14)
C(17)-Ru(1)-C(15)-C(14)	105.23(16)
Cl(1)-Ru(1)-C(15)-C(14)	-53.33(15)
O(1)-Ru(1)-C(15)-C(16)	8.2(3)
O(2)-Ru(1)-C(15)-C(16)	84.58(14)
C(18)-Ru(1)-C(15)-C(16)	-67.00(14)
C(19)-Ru(1)-C(15)-C(16)	-104.16(15)
C(17)-Ru(1)-C(15)-C(16)	-28.89(13)
C(14)-Ru(1)-C(15)-C(16)	-134.1(2)
Cl(1)-Ru(1)-C(15)-C(16)	172.55(11)
C(14)-C(15)-C(16)-C(17)	1.6(3)
Ru(1)-C(15)-C(16)-C(17)	54.35(18)
C(14)-C(15)-C(16)-Ru(1)	-52.70(19)
O(1)-Ru(1)-C(16)-C(17)	50.20(15)
O(2)-Ru(1)-C(16)-C(17)	126.62(13)
C(18)-Ru(1)-C(16)-C(17)	-30.65(13)
C(19)-Ru(1)-C(16)-C(17)	-67.88(14)
C(15)-Ru(1)-C(16)-C(17)	-133.1(2)
C(14)-Ru(1)-C(16)-C(17)	-105.33(15)
Cl(1)-Ru(1)-C(16)-C(17)	-147.94(12)
O(1)-Ru(1)-C(16)-C(15)	-176.67(12)
O(2)-Ru(1)-C(16)-C(15)	-100.25(14)
C(18)-Ru(1)-C(16)-C(15)	102.49(15)
C(19)-Ru(1)-C(16)-C(15)	65.26(14)
C(17)-Ru(1)-C(16)-C(15)	133.1(2)
C(14)-Ru(1)-C(16)-C(15)	27.80(14)
Cl(1)-Ru(1)-C(16)-C(15)	-14.8(2)
C(15)-C(16)-C(17)-C(18)	-0.9(3)
Ru(1)-C(16)-C(17)-C(18)	53.65(17)
C(15)-C(16)-C(17)-C(21)	-176.5(2)
Ru(1)-C(16)-C(17)-C(21)	-122.0(2)
C(15)-C(16)-C(17)-Ru(1)	-54.56(19)
O(1)-Ru(1)-C(17)-C(16)	-139.07(13)
O(2)-Ru(1)-C(17)-C(16)	-62.26(14)
C(18)-Ru(1)-C(17)-C(16)	130.2(2)
C(19)-Ru(1)-C(17)-C(16)	101.94(15)
C(15)-Ru(1)-C(17)-C(16)	28.85(13)
C(14)-Ru(1)-C(17)-C(16)	64.91(14)
Cl(1)-Ru(1)-C(17)-C(16)	134.93(16)

O(1)-Ru(1)-C(17)-C(18)	90.68(13)
O(2)-Ru(1)-C(17)-C(18)	167.49(12)
C(16)-Ru(1)-C(17)-C(18)	-130.2(2)
C(19)-Ru(1)-C(17)-C(18)	-28.31(14)
C(15)-Ru(1)-C(17)-C(18)	-101.40(15)
C(14)-Ru(1)-C(17)-C(18)	-65.34(14)
Cl(1)-Ru(1)-C(17)-C(18)	4.7(3)
O(1)-Ru(1)-C(17)-C(21)	-20.9(2)
O(2)-Ru(1)-C(17)-C(21)	55.9(2)
C(16)-Ru(1)-C(17)-C(21)	118.2(3)
C(18)-Ru(1)-C(17)-C(21)	-111.6(3)
C(19)-Ru(1)-C(17)-C(21)	-139.9(2)
C(15)-Ru(1)-C(17)-C(21)	147.0(2)
C(14)-Ru(1)-C(17)-C(21)	-176.9(2)
Cl(1)-Ru(1)-C(17)-C(21)	-106.9(2)
C(16)-C(17)-C(18)-C(19)	-0.5(3)
C(21)-C(17)-C(18)-C(19)	175.3(2)
Ru(1)-C(17)-C(18)-C(19)	53.14(19)
C(16)-C(17)-C(18)-Ru(1)	-53.67(17)
C(21)-C(17)-C(18)-Ru(1)	122.18(19)
O(1)-Ru(1)-C(18)-C(19)	134.04(13)
O(2)-Ru(1)-C(18)-C(19)	-158.38(14)
C(16)-Ru(1)-C(18)-C(19)	-103.24(15)
C(17)-Ru(1)-C(18)-C(19)	-133.7(2)
C(15)-Ru(1)-C(18)-C(19)	-65.55(14)
C(14)-Ru(1)-C(18)-C(19)	-28.85(14)
Cl(1)-Ru(1)-C(18)-C(19)	48.15(15)
O(1)-Ru(1)-C(18)-C(17)	-92.22(13)
O(2)-Ru(1)-C(18)-C(17)	-24.6(2)
C(16)-Ru(1)-C(18)-C(17)	30.50(13)
C(19)-Ru(1)-C(18)-C(17)	133.7(2)
C(15)-Ru(1)-C(18)-C(17)	68.19(14)
C(14)-Ru(1)-C(18)-C(17)	104.89(15)
Cl(1)-Ru(1)-C(18)-C(17)	-178.11(11)
C(17)-C(18)-C(19)-C(14)	1.3(3)
Ru(1)-C(18)-C(19)-C(14)	54.58(19)
C(17)-C(18)-C(19)-Ru(1)	-53.31(18)
C(15)-C(14)-C(19)-C(18)	-0.5(3)
C(20)-C(14)-C(19)-C(18)	-176.7(2)
Ru(1)-C(14)-C(19)-C(18)	-53.82(19)
C(15)-C(14)-C(19)-Ru(1)	53.28(18)
C(20)-C(14)-C(19)-Ru(1)	-122.9(2)
O(1)-Ru(1)-C(19)-C(18)	-54.79(15)
O(2)-Ru(1)-C(19)-C(18)	138.7(3)
C(16)-Ru(1)-C(19)-C(18)	66.49(14)
C(17)-Ru(1)-C(19)-C(18)	28.69(13)
C(15)-Ru(1)-C(19)-C(18)	103.83(15)
C(14)-Ru(1)-C(19)-C(18)	133.2(2)
Cl(1)-Ru(1)-C(19)-C(18)	-140.48(13)
O(1)-Ru(1)-C(19)-C(14)	172.05(12)
O(2)-Ru(1)-C(19)-C(14)	5.5(4)
C(16)-Ru(1)-C(19)-C(14)	-66.67(14)
C(18)-Ru(1)-C(19)-C(14)	-133.2(2)
C(17)-Ru(1)-C(19)-C(14)	-104.47(15)
C(15)-Ru(1)-C(19)-C(14)	-29.33(13)
Cl(1)-Ru(1)-C(19)-C(14)	86.36(13)

C(16)-C(17)-C(21)-C(23)	14.0(3)
C(18)-C(17)-C(21)-C(23)	-161.5(2)
Ru(1)-C(17)-C(21)-C(23)	-75.7(3)
C(16)-C(17)-C(21)-C(22)	-111.7(2)
C(18)-C(17)-C(21)-C(22)	72.8(3)
Ru(1)-C(17)-C(21)-C(22)	158.64(17)

6.3 Thermogravimetric analysis of complex 4b



Curriculum vitae

MARIO **K**UBANIK B.SC.

Brünnerstraße 54

2170 Poysdorf

Tel. +43 2552 3819

+43 699 11225912

Email: mario.kubanik@aon.at

Nationality:	Austria
Date of Birth:	14.06.1985
Marital status:	single

Education

2009 to date	Master's program Chemistry, University of Vienna
16.11.2009	Graduation with B.Sc.
2006 – 2009	Bachelor's program Chemistry, University of Vienna
22.06.2005	Vocational matriculation examination
2000 – 2004	training school (Berufsschule für Mechanik, Optik und Fertigungstechnik)
1999 – 2000	Polytechnische Schule in Poysdorf
1995 - 1999	Hauptschule Poysdorf
1991 - 1995	Elementary school Poysdorf

Professional Experience

01.03.2011 – 31.07.2011	Tutor at the Institute of Inorganic Chemistry, University Vienna
12.07.2010 – 30.09.2010	Mechanic at Gebauer&Griller
07.07.2008 - 30.09.2008	Mechanic at Gebauer&Griller
01.07.2007 - 30.09.2007	Mechanic at Gebauer&Griller
01.01.2006 - 29.09.2006	Mechanic at Gebauer&Griller
2004	Completion of apprenticeship as mechanic
2000 – 2004	Apprenticeship as a mechanic at ÖBB

Language skills

German (mother tongue)

English