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Treball Final de Grau

Activation of CH bonds of imines by ruthenium compounds.

Activació de l'enllaç CH d'imines amb compostos de ruteni.

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Success is the ability to go from one failure to another with no loss of enthusiasm".

Winston Churchill

Als meus yayos.

Agraeixo al meu tutor, Jaume Granell Sanvicente, per tot l'assessorament i ajuda rebuda al llarg del treball, per deixar-me innovar i explorar nous camps de la recerca que no m'havia plantejat mai. Agraeixo a tots els docents que m'han acompanyat al llarg de la carrera i m'han ensenyat els coneixements que he adquirit, especialment a la Montserrat Sofia Ferrer Garcia per l'acompanyament realitzat des de finals de tercer fins a l'actualitat. Agrair també a tots els amics que m'enduc de la carrera, sense ells aquest camí hagués estat molt més complicat.

Finalment voldria agrair a la meva família per tot el suport que m'han donat des de que vaig prendre la decisió d'estudiar una carrera universitària i totes les ajudes que m'han donat.

REPORT

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1. SUMMARY

The synthesis of different Schiff's bases has been described in order to use them as ligand for the subsequent cyclometallation reaction. The cyclometallation reaction has been described starting with a half sandwich ruthenium complex, $[RuCl_2(p\text{-}cymene)_2]_2$, and different benzylimines via *ortho* – CH activation. The reaction takes place at room temperature in methanol and in a short period of time (4 hours), using 2 equivalents of potassium acetate as deprotonation agent.

This cyclometallation reaction leads the *endo* cyclometallated ruthenium product. The resultant N – Ru – C metallocycle compound is formed by a five-member ring containing the C = N bond.

The molecular structures of each compound have been characterised by different spectroscopic techniques (IR, NMR and Mass) showing that the obtained product is in agreement with the proposed structures.

Keywords: Ruthenium, Imines, Metallocycles, Cycloruthenates, C – H bond activation, organometallic complexes.

2. RESUM

La síntesi de diferents bases de Shiff han estat descrites per poder ser utilitzades posteriorment en la reacció de ciclometal·lació. La reacció de ciclometal·lació ha estat realitzada utilitzant un compost de ruteni, $[RuCl_2(p\text{-}cymene)_2]_2$, amb diferents benzilimines mitjançant l'activació directa de l'enllaç C – H en posició *orto*. La reacció té lloc a temperatura ambient en metanol i amb una durada de quatre hores, utilitzant dos equivalents d'acetat de potassi com a agent desprotonant.

La reacció de ciclometal·lació permet obtenir el compost *endo* ciclometal·lat de ruteni. El compost final N – Ru – C està format per un anell de cinc vàlues que conté l'enllaç C = N.

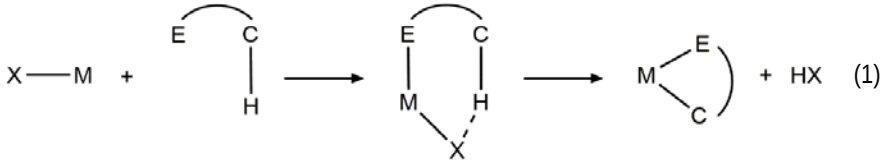
Les diferents estructures moleculars han estat caracteritzades mitjançant diferents tècniques espectroscòpiques (IR, RMN i Masses) demostrant que els productes obtinguts són els esperats.

Paraules clau: Ruteni, Iminas, Metal·locicles, compostos cíclics de ruteni, activació de l'enllaç C – H, compostos organometal·lics.

3. INTRODUCTION

3.1. CYCLOMETALLATION CHEMISTRY

Cyclometallated chemistry is one of the most active areas in organometallic chemistry and has been studied from the seventies to nowadays. The cyclometallation reaction is based in an aromatic or aliphatic substitution reaction where an aryl or alkyl C – H bond of the ligand of a transition metal complex reacts with the metal with the formation a sigma metal – carbon bond and the additional formation of HX species. The reaction generally occurs by an intramolecular pathway and it involves an *ortho* carbon – hydrogen bond of a nitrogen or phosphorous ligand donor. [1,2,3] The reaction takes place in two different steps (Equation 1): in the first step the coordination of the heteroatom of the ligand occurs and in the second step then the activation of the C – H bond of the ligand takes place obtaining the metallocycle and a new HX specie formed by the leaving proton. [2,3]



(1)

Cyclometallated compounds are the resultant product of cyclometallation reaction. This term was introduced by *Trofimenko* in 1972, he carried a reaction with a palladium (II) compound and different amines in aqueous solution in order to precipitate the cyclopalladation compounds, each reaction needed 1 – 3 days [4]. The work was the beginning of this field of organometallic chemistry.

Cyclometallated compounds can be prepared in different pathways in order to form a metal – carbon sigma bond. The easiest way to prepare a cyclometallated compound is the direct activation of C – H bond, this activation can be proceeded in many different mechanisms, but it generally occurs by an electrophilic aromatic substitution pathway and usually obtaining cycles of five- or six-membered ring (Scheme 1.a). [5]

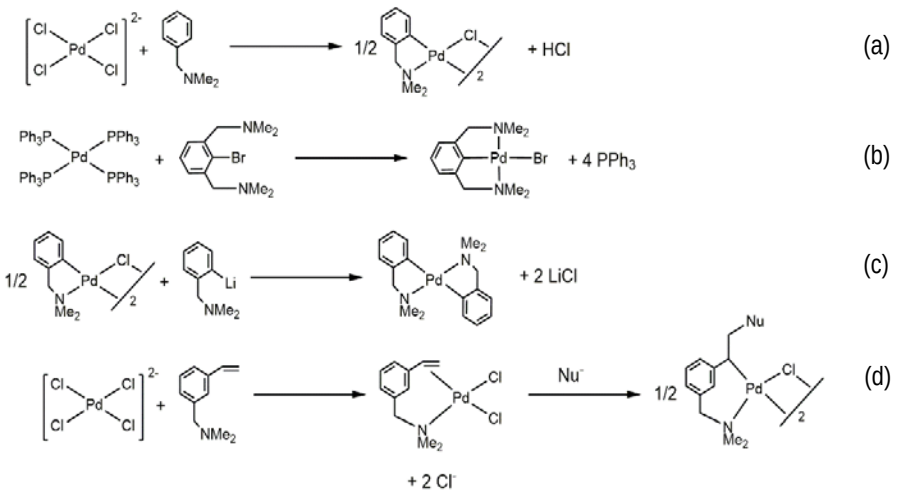
An oxidative activation can be another method to obtain metallocycles that cannot be obtained by C – H bond activation, indeed the procedure is successful in order to obtain three- or

four-membered ring. Starting with monomeric or dimeric neutral palladium (0) compounds and obtaining cyclopalladated compounds of palladium (II) (Scheme 1.b). [5]

Transmetalation could be another way to obtain cyclometallated compounds by using transmetalating agents like organolithiums or organomercurial reagents. [5] The transmetalation reaction key factor is the strength of a metal – carbon bond. Lithium – carbon and mercury – carbon bonds are weaker than a transition metal – carbon bond, and this factor deals the exchange of ligand and can generate cylometallated compounds (Scheme 1.c).

Another pathway in order to obtain metallocycles is by alkoxy- and carbometallation of alkenes and halometallation of alkenes. The reaction begins with a coordination of a C = C ligand to a metallic centre and it is followed by a nucleophilic addition to the carbon double bond leading a stable metallocycle (Scheme 1.d). [5]

In the study done during this research the cyclometallation procedure had been carried by a direct activation of the C – H bond assisted by acetate which leads the metallocycle of ruthenium.



Scheme 1. Different methods to prepare cyclometallation. (a) activation of C – H bond; (b) oxidative activation; (c) Transmetalation; (d) alkoxy- and carbometallation of alkenes and halometallation of alkenes.

Cyclometallation has been carried by different metallic centres, even though the most studied cyclometallation reaction is with palladium. We can easily find literature talking about palladium, platinum, rhodium, iridium cyclometallated complexes but it is rare to find reports talking about ruthenium cyclometallated compounds. The most common ligands used in order to create a metallocycles are P – donor (phosphines and derivates) or N – donor (amines, azo compound, etc.) ligands which contains an aryl or alkyl group making easier that cyclometallation takes place. In the following figure (Figure 1) we can find some reported examples of different metallocycles with different ligands and different metallic centres.

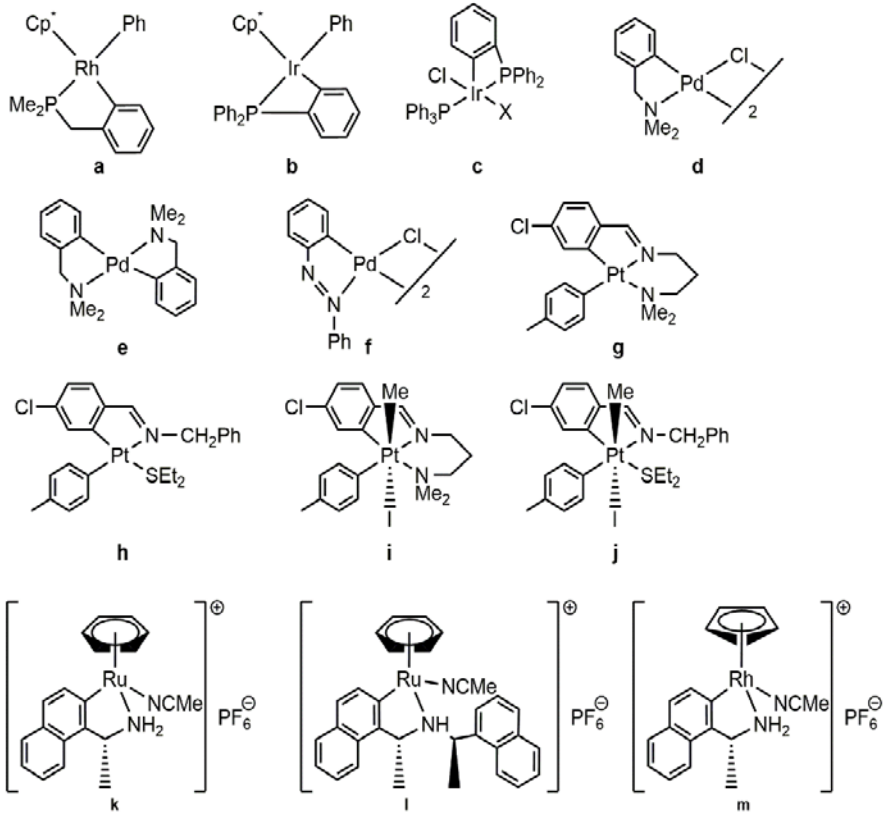


Figure 1. Different cyclometallated compounds with different ligands and metallic core. Compounds a, b and c described by Alexander Ryabov [2]; Compounds d, e and f described by Jairton Dupont *et al.* [5]; Compounds g, h, i and j reported by Margarita Crespo [6]; Compounds k, l and m described by Nicolas Pennetier *et al.* [7]

In our research group, cyclometallated ruthenium complexes with P – stereogenic phosphines have been described. The synthesis method used is similar that the method reported in this work: Introducing the ligand, the $[RuCl_2(p\text{-}cymene)]_2$ and potassium acetate in 80 mL of methanol was stirred for four hours at room temperature. The solvent was removed under vacuum and the solid product was chromatographed on silica gel column three times: first with CH_2Cl_2, second with CH_2Cl_2/Et_2O and third with methanol. The title product was obtained as an orange/brown solid with different yields depending upon the nature of the reactants (Figure 2)[3]

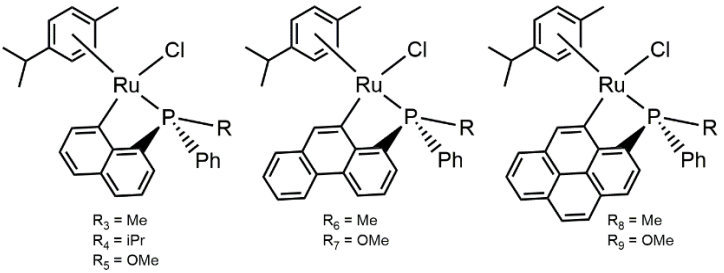


Figure 2. Ruthenium cyclometallated compounds previous studied in our research group with P – stereogenic ligands.

Other studies have described other cyclometallated ruthenium compounds with different ligands such as amines and some imines.

Nicolas Pannetier and co-workers have described the synthesis of $[(\eta^6\text{-}C_6H_6)Ru(C_6H_4\text{-}2\text{-}(R)\text{-}CH(iPr)NH_2)(NCCH_3)](PF_6)$ (Figure 1.k) starting from a suspension of $[Ru(\eta^6\text{-}C_6H_6)Cl_2]_2$ with (*R*)-1-phenyl-2-methylpropylamine, a fold excess of NaOH and a four-excess of KPF_6 in 15 mL of CH_3CN was stirred at 20ºC during 72 hours under argon atmosphere. The resultant suspension was filtered over celite, concentrated under vacuum and filtered over Al_2O_3 using CH_3CN as eluent. The light green fraction collected and concentrated under vacuum and vigorously stirred during 2 hours with 20 mL of hexane. The resultant solid was redissolved with the minimum volume of CH_2Cl_2 and the final product was obtained as a yellow precipitated compound.[7]

Few ruthenium metallocycle compounds with imines had been described by Bin Lin *et al.* following this experimental procedure: A mixture of $[RuCl_2(p\text{-}cymene)]_2$, 2 equivalents of different imines and 4 equivalents potassium acetate in 5 mL of methanol was stirred for twenty hours at room temperature. The resultant solid was filtered and dried under vacuum and the product was purified by chromatography column on silica gel with a mixture of petrol ether/ethyl acetate as

eluent (Figure 3.a, 3.b, 3.c, 3.d). Besides, other five components with different ligands have been described using the same experimental procedure (Figure 3.e, 3.f, 3.g, 3.h).[8]

Previously to the study carried by Bin Lin *et al.*, the compounds presented in figure 3 (3.e and 3.f) were described by Yousef Boutadla and co-workers. The experimental procedure followed by Yousef Boutadla and co-workers was different that the one used by Bin Lin *et al.* They started with a mixture of $[RuCl_2(p\text{-}cymene)]_2$, 1-phenylpyrazole and sodium acetate in 5 mL of dichloromethane was stirred during four hours at room temperature. The solution was filtered over celite and dried under vacuum, then the solid was washed with hexane and recrystalised with a mixture of CH_2Cl_2/hexane for compound 3.f in figure 3.[9]

In order to obtain the product described in figure 3.e Yousef and co-workers started with a mixture of $[RuCl_2(p\text{-}cymene)]_2$, 4(*S*)-isopropyl-2-oxazolinylbenzene and sodium acetate in 5 mL of dichloromethane was stirred during overnight at room temperature. The mixture was filtered over celite and dried under vacuum obtaining an oily residue which was recrystalised by slow diffusion of pentene into a dichloromethane solution to give the final product.[9]

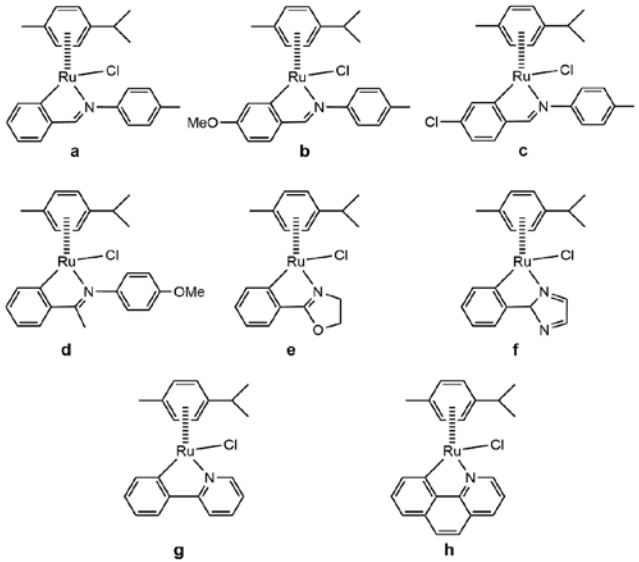


Figure 3. Examples of some ruthenium compounds with different N – donor ligands described by Bin Lin *et al.* and Yousef Boutadla *et al.*[8,9]

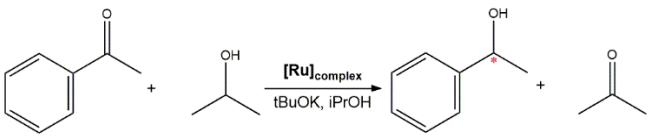
The synthesis of cyclometallated ruthenium compounds is not very usual in literature and also is rare to find literature talking about cyclorutenated imines. These cyclometallated ruthenium compounds with imines have not been tested in different applications that others cyclometallated compound had, so here could start a new research field.

3.2. APPLICATIONS OF RUTHENIUM CYCLOMETALLATED COMPOUNDS

The cyclometallated compounds have many plausible applications in different study fields, such as organic chemistry, homogeneous catalysis, asymmetric chemistry, photochemistry and medicine.[2]

In previous studies in our research group the cyclometallation reaction with ruthenium compounds have been archived with P – donor ligands and the compounds obtained have been used as a catalysts in ketone hydrogenation processes.[3,10] The hydrogenation reaction is useful in chemical industry in order to obtain stereocentres of chiral organic compounds, such as ketones or reduction of imines.[7] The reduction reaction can occur in two different pathways: by using hydrogen gas or by using a hydrogen donor carrying a transfer hydrogenation. The catalyst used by transfer hydrogenation contains a metallic chiral center obtained by cyclometallation reaction and leads an enantiomeric final product (alcohol, amine).

Previous studies in our research group described the hydrogenation by transfer hydrogenation using ruthenium cyclometalated compounds with P-stereogenic phosphines and ruthenium complexes with P-stereogenic phosphines starting with acetophenone and 2-propanol, which is used as solvent and as hydrogen donor reactant (Scheme 2). The reaction takes place under nitrogen atmosphere conditions, using in both studies a 1% of ruthenium precursor and a 5% of potassium terc-butoxide, then the solids were dissolved in 25 mL of 2-propanol and stirred 15 at reflux in order to active the catalyst. Then the acetophenone is added to the flask and starts the catalytic run. The reaction is controlled by aliquots extracted in a regular time and analysed by gas chromatography.[3,10]

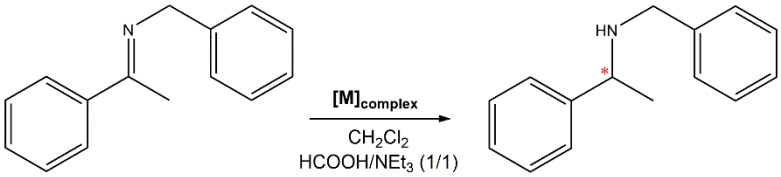


Scheme 2. Hydrogenation by transfer hydrogenation of acetophenone using a ruthenium complex in figure 2.

Similar studies have been reported by Pannetier *et al.* using acetophenone and cyclometalated catalyst with ruthenium, rhodium and iridium metallic centres. In this case the hydrogenation reaction was carried in similar conditions of our group even though they used different metallic centre, N-stereogenic ligands and not refluxing.[7]

They studied the catalysis using rhodium and iridium cyclometalated complexes, which had an imine ligand in order to create the metallacycle, this imine ligand was formed by the dehydrogenation of benzylamine ligands under the cyclometallation conditions. It is remarkable that the corresponding derivatives with ruthenium containing imine ligands were not obtained.[7]

The catalytic results were not significant at 20 ºC but heating the mixture to 60 ºC was observed a poor activity of the iridium catalyst obtaining an 8% of enantiomeric excess. The transfer hydrogenation reaction also has been studied in order to obtain optically active amines by asymmetric hydrogenation of imines with cyclometallated complexes. Excellent yields and enantioselectivities where obtained (Scheme 3). It should be noted that for this process is very important that the solution does not contain water because the imine could hydrolyse.[7]



Scheme 3. Hydrogenation by transfer hydrogenation of imine using a metallic complex of ruthenium (II), rhodium (III) or iridium (III).

Another useful application of cyclometallated ruthenium (II) compound is their use as redox mediators in peroxidase catalyst. A studied carried using plant peroxidases shows that a cyclometalated ruthenium (II) compound with an N-donor ligand were oxidized by hydrogen peroxide catalysed by plant peroxidases leading the ruthenium (III) complexes. The cyclometallated ruthenium compounds were also confirmed to be as efficient mediators for peroxidase process. The co-oxidation of the ruthenium compound and catechol, which is a poor peroxidase substrate, shows that oxidation of catechol increases more than 10.000-fold with the cyclometalated compound.[11]

One of the most extended application for ruthenium compounds is their study as antitumoral agents. Since 1980 numerous studies appear explaining the advantages using ruthenium-based drugs instead of platinum-based drugs. Platinum-based drugs have been used in cancer therapy for 40 years. The main platinum anticancer agent is cisplatin (*cis*-[$Pt(Cl)_2(NH_3)_2$]) (Figure 4.a) which is really effective for testicular and ovarian cancer and also used in therapies for bladder, cervical, head and neck, esophageal, and small cell lung cancer. Even though, platinum agents have three remarkable disadvantages: severe toxicity, a small activity range and resistance after treatment; that is why non-platinum anticancer complexes have been developing.[12]

Ruthenium compounds are situated at the top of the list in order to exchange platinum-based drugs for cancer therapy. Ruthenium complexes also have similarities with platinum compounds like the good affinity that both have for N-donor and S-donor ligands and similar kinetic for ligands exchange. Both compounds need to have labile ligands in order to interact with different physiological systems.[12]

Besides this, ruthenium-based drugs present relevant advantages respect the platinum-based drugs that make them interesting for this concrete application, such as: two oxidation state species are accessible in biological media: Ru (II) and Ru (III) which present different magnetic properties, Ru (II) (d^6, diamagnetic) and Ru (III) (d^5, paramagnetic). Ruthenium (II and III) ions have an octahedral geometry like most of first raw transition metals. Ruthenium (II) species cannot be oxidized to the corresponding ruthenium (III) species in air, so they are more stable than platinum (II) complexes. The main advantage that ruthenium presents over platinum is the similarities to iron, making it easy to interact with biological systems like transferrin and albumin. All these advantages make the ruthenium complexes less toxic, easy to move in the organism and also, they can be active against platinum resistant tumours.[12,13]

The cancer cells often have an over-expression of transferrin receptors because they require more iron, the possibility that iron and ruthenium atom interchange in transferrin makes the evidence that ruthenium-based drugs can easily arrive to cancer cells, cross the cell membrane and destroy the malignant cell.[12]

Another difference between ruthenium-based drugs and platinum-based drugs is the actuation mechanism in the therapy. Cisplatin attack to the primary tumour but ruthenium-based drugs reduces the metastasis prolongation. Nowadays the main tumour can be easily removed with a surgical procedure, but with metastasis the cells move around the organism to multiple

locations which make difficult access for surgery and/or radiotherapy and that is the main cause of death.[12]

The first reported experiment with ruthenium compounds was at earlies 80s, when the group of M.J. Clarke *et al.* Theses researches recreate the cisplatin with the ruthenium complexes *fac*-$[Ru(Cl)_3\ (NH_3)_3]$ and *cis*-$[Ru(Cl)_3\ (NH_3)_3]$ (Figure 4.b and 4.c, respectively), but their poor solubility makes them useless for cancer treatments.[12]

Subsequent studies during the 80s realized by Mestroni group compared two isomers of ruthenium (II) complexes (*cis*-$[RuCl_2(dmso)_4]$ and *trans*-$[RuCl_2(dmso)_4]$) (Figure 4.d and 4.e, respectively) with cisplatin with lab mice, the results showed that ruthenium compounds had less host toxicity, were more selective in metastasis and showed a prolonged postsurgical survival time of the mice.[12]

By the same time, Keppler group studied two isostructural ionic ruthenium (III) complexes: [ImH]*trans*-$[RuCl_4(Im)_2]$ (Im = Imidazole; ICR) and [IndH]*trans*-$[RuCl_4(Ind)_2]$ (Ind = Indazole; KP1019) (Figure 4.f and 4.g, respectively). These compounds showed an excellent activity against differents tumour including the platinum-resistant tumours.[12]

Subsequent studies in 90s discovered [Na]*trans*-$[RuCl_4(Im)(dmso\text{-}S)]$ called NAMI which presents an specific activity against metastasis process in mice. Further studies after NAMI replaced the sodium salt for a imidazolium salt creating the NAMI-A ([ImH]*trans*-$[RuCl_4(Im)(dmso\text{-}S)]$) (Figure 4.h), both compounds present the same antimetastatic properties but NAMI-A is easier to be synthetized and presents a remarkable less toxicity than cisplatin.[12]

Nowadays two ruthenium compounds KP1019 and NAMI-A are at phase I in cancer therapies. Even though, the two compounds interact with malignant cells in different pathways: NAMI-A interacts with cell DNA modifying the cell invasion and metastasis, making the cancer cells less malignant; KP1019 is the responsible of the cell apoptosis in a mitochondrial pathway, even though the mechanism of KP1019 inside the cell is unknown.[13]

Given the success of the previous studies, in 2001 Dixon group studied the anticancer effects of an arene ruthenium (II) complex $[(\eta^6\text{-}p\text{-}MeC_6H_4Pr^i)Ru(P\text{-pta})Cl_2]$, (pta = 1,3,5-triaza-7-phospha-tricyclo-[3.3.1.1]decane) named RAPTA – C (Figure 4.i), and they found that it presents a high activity inhibiting lung metastasis in mice and lower general toxicity, even though it presents a low activity *in vitro* experiments. Arene ligands give amphiphilic properties to ruthenium-based drugs,

the arene-ruthenium bond is very strong so the ruthenium complex can split chloride ligands in order to interact with the biological structures.[14]

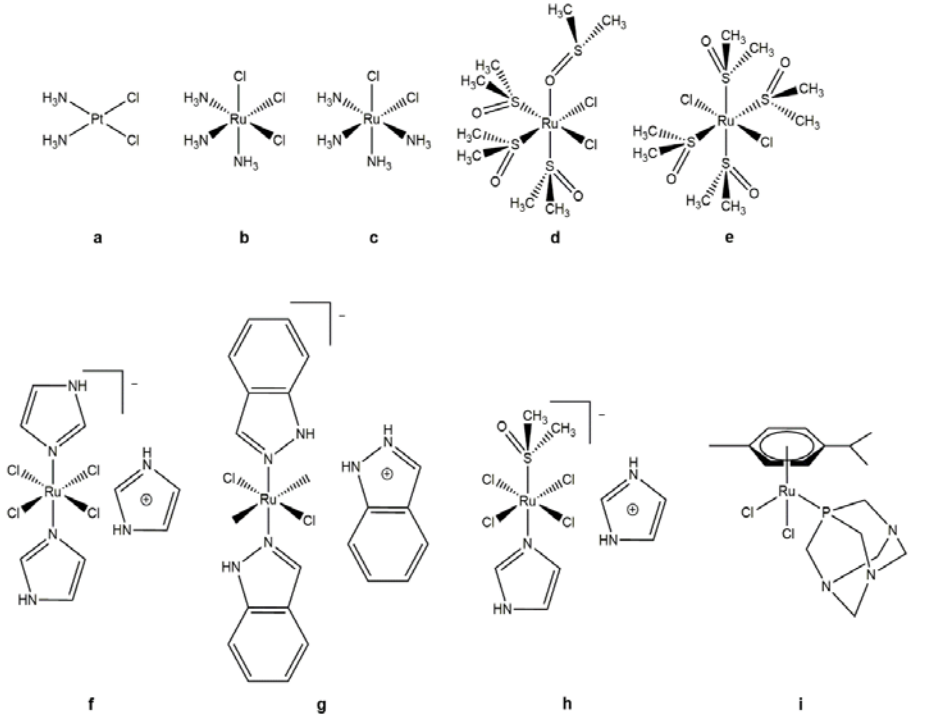


Figure 4. a) Cisplatin: b) *fac*-[Ru(Cl_3)(NH_3)$_3$]; c) *cis*-[Ru(Cl_3)(NH_3)$_3$]; d) *cis*-[$RuCl_2$(dmso)$_4$]; e) *trans*-[$RuCl_2$(dmso)$_4$]; f) ICR (ImH]*trans*-[$RuCl_4$(Im)$_2$]); g) KP1019 ([IndH]*trans*-[$RuCl_4$(Ind)$_2$]); h) NAMI-A ([ImH]*trans*-[Ru Cl_4(Im)(dmso-S)]); i) RAPTA-C ([(η^6-*p*-$MeC_6H_4Pr^i$)Ru(*P*-pta)Cl_2]).

4. OBJECTIVES

The main objective of this project was carrying the cyclometallation reaction with imine ligands to a ruthenium metallic core and describe the synthesis, stablishing a set conditions, and characterization of each compound using different spectroscopic techniques (NMR, IR and Mass) and elemental analysis for compounds C1 – C3. The synthesis of these compounds has hardly been explored until for ruthenium metallocycles with imine as cyclometallation agents. It is possible to prepare a huge diversity depending of the initial reactants, so the possible combinations of different aldehydes and amines could give to new cycloruthenate compounds showing a great variety of chemical structures.

This cyclometallated compounds (Figure 5) can be useful in many different fields and future studies will investigate them as a catalyst for the different transfer hydrogenation reactions with ketones and imines and in vitro tests to prove if they have potential as ruthenium-based drugs for anticancer treatments. These new compounds contain an arene ligand which gives them amphiphilic properties and also contains two labile positions (chloride and the cyclometalated bond, this last one can be regenerated), so here appears a wide investigation field for these compounds that it has not been explored yet.

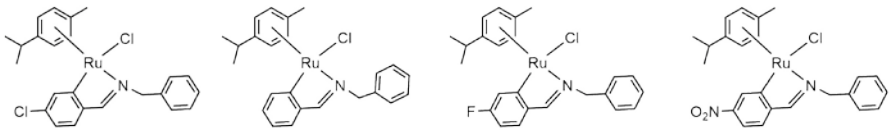
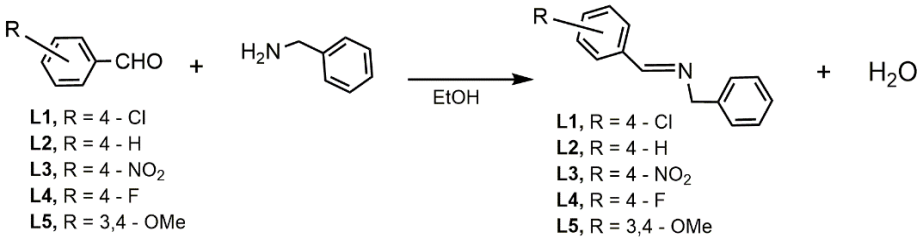


Figure 5. Ruthenium metallocycles compounds synthetized and characterized in this study.

5. RESULTS AND DISCUSSION

5.1. SYNTHESIS AND CHARACTERISATION OF IMINES, L1 – L5

The imines, used as a ligands, and also known as Schiff's bases, were synthesised by a condensation reaction. Imines are usually formed by the reaction of a primary amine and organic derivatives containing carbonyl groups (aldehyde or ketone), in the process involving a C=N double bond formation and the loss of a molecule of H_2O (Scheme 4). The addition of water or acid at the imine leads the hydrolysis affording the initial reactants so that is why the reaction is driven in an ethanolic solution and typically by heated until reflux to boost the reaction [15].



Scheme 4. Synthesis of imine compounds

Imine nitrogen is sp^2 hybridized, two of its sp^2 orbitals are forming σ bonds, one with imine carbon and the other with the substituent, and the third orbital contains the nitrogen electrons lone pair, this lone pair of electrons will coordinate with ruthenium in cyclometallation reaction. The *p* orbital of nitrogen and the *p* orbital of carbon overlap to form a π bond (Figure 6) [16].

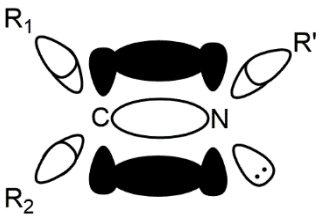
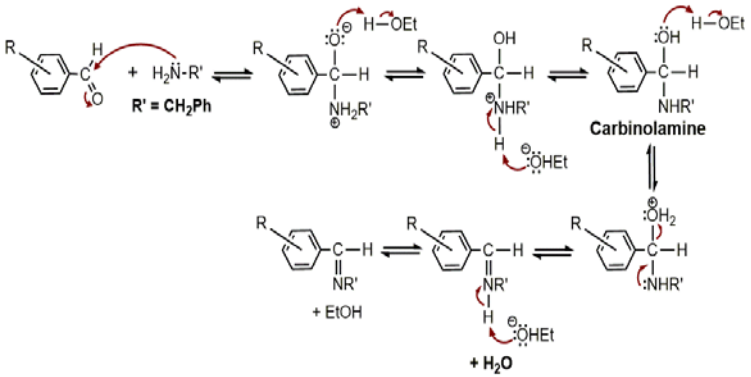


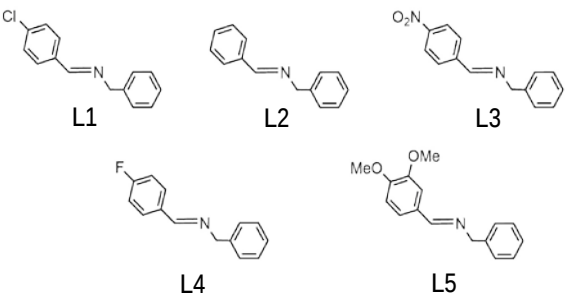
Figure 6. Molecular orbitals of imine bond.

The synthesis of imine proceeds by nucleophile addition – elimination process: the nucleophilic attack of the primary amine and the elimination of water. The process (Scheme 5) starts with a nucleophile addition of the amine to the carbonyl group, in a second step the protonation of alkoxide group takes place by a proton from ethanol. Then, the ammonium ion formed is deprotonated by ethoxy group to obtain a neutral tetrahedral intermediate (carbinolamine). Finally, water is eliminated from carbinolamine by the nucleophilic attack of the lone pair of nitrogen leading the protonated imine which proton is removed by the ethoxy to form the imine. This reaction is catalysed by ethanol which acts as an acid catalyst donating a proton to initial reactants and recovering it at the end of reaction.



Scheme 5. Mechanism of imine formation.

A procedure to obtain imines starts with a mixture of different benzaldehyde and benzylamine in relation 1:1 solved in 20 mL of ethanol and heated in a silicon bath at 85 ºC with stirring for an hour and a half. The ethanol was removed under vacuum leading to an oil which corresponds to the different imines. The yields of synthesis of imines were very high.



Schiff base	
Product	Isolated yield (%)
L1	100
L2	87
L3	98
L4	99
L5	100

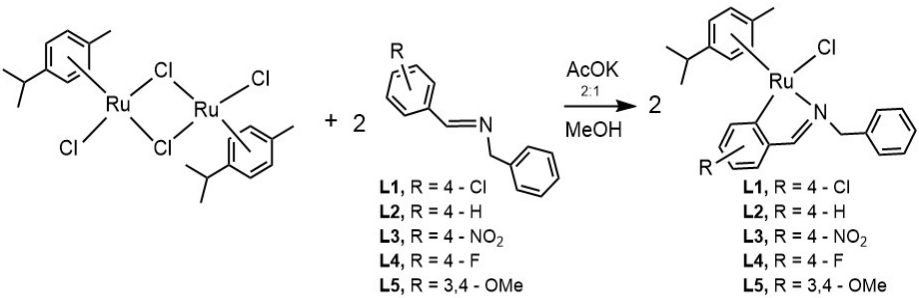
The imines were characterised by ^{1}H NMR and IR spectroscopy. Those two techniques, show that reaction was successful and that only exist imine in the resultant product.

Imines can be easily characterised by infrared spectroscopy showing a band frequency at 1690 – 1590 cm^{-1} which fits to C = N bond. The absence of the bands in the infrared spectra at 3400 – 3380 and 1740 – 1725 cm^{-1}, which refers to primary amine N – H stretch and C = O stretch of aldehydes respectively [17] confirm the purity of the imines obtained.

The absence of a signal at 9 – 10 ppm which correspond to aldehyde proton and of a broad signal between 1.5 – 4 ppm which can be assigned as amine proton, in the proton NMR spectra also confirm that reaction is complete and the compounds are pure [16].

5.2. SYNTHESIS AND CHARACTERISATION OF COMPOUNDS C1 – C4

With the aim of obtaining cyclometallated complexes, the organometallic precursor $[Ru(Cl)_2(p\text{-}cymene)_2]_2$ was reacted with different imines in 1:1 relation and in the presence of two equivalents of potassium acetate in methanol. The expected metallacycle was obtained by removing the hydrogen atom from the aromatic carbon atom at the 2-position (Scheme 6).



Scheme 6. Synthesis of Ruthenium compounds

In order to set the optimal reaction conditions, the synthesis had been done changing different variables such as time or solvent volume, the results of those conditions are shown in table 1.

Table 1. Reaction conditions for cyclometallation.

Time (h)	Solvent volume (mL)	Yield (%)
24	15	47
24	10	62
4	10	67
1	10	38

These experiments permit to establish the reaction conditions in four hours and ten millilitres of methanol.

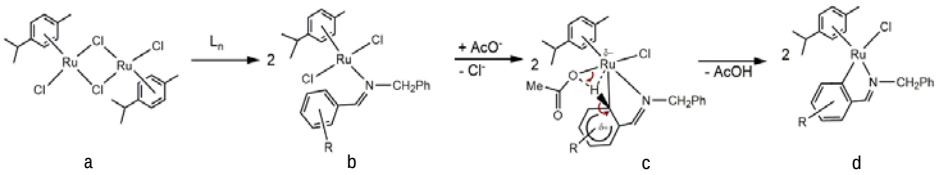
It seems that the reaction is driven by precipitation of the final product so that was why one-hour conditions did not permit that the precipitation conclude. Otherwise, overnight reaction (24 hours) shows that part of the product could be dissolved again.

In addition the effect of the presence of oxygen in solvent in the process had been studied comparing the yield obtained for the reaction with purged solvent and non-purged solvent, the results for C1 were 47% and 62% respectively for an overnight reaction, so there is not necessary for this cyclometallation reaction use purged solvent, in fact better yields were obtained with non-purged solvent.

Computational studies of the mechanism of cyclometallation using imines [18] show that the presence of acetate is needed to carry out the reaction, acetate helps to deprotonate *ortho* – CH bond by forming the cyclic compound in methanol solution. Subsequent studies on imine cyclometallation of palladium compounds suggested the formation of a highly ordered four-center transition state, which seems to be very sensitive to the flexibility and steric hindrance of the imines and do not affect to C – H bonds [19]. At this transition state, proton interacts with metallic center and with the acetato ligand weakening the hydrogen – carbon bond and favouring the cyclometallation [18].

According to these results for cyclopalladation of imines, we can propose a mechanism to explain the cyclorutenation reaction. The process (Scheme 7) starts with a dimeric ruthenium compound (a) which coordinates to the imine ligand (L_n) involving a bridge-splitting reaction and leading a monomeric compound (b), imine coordination takes place like a Lewis base association, through the electronic donation of the lone pair of electrons of the imine bond. Immediately thereafter, a ligand substitution of chloride for an acetate takes place. This acetato

group acts as a proton acceptor, in the transition state (c) where the cyclometallation takes place by C – H bond activation [5], to produce acetic acid as a leaving group and finally obtaining the cyclometallated compound (d).



Scheme 7. Mechanism of cyclometallation reaction

Kinetic and Activation parameters and computational studies performed with palladium compounds reach the conclusion that it is an associative process where the metal coordinates with carbon atom and then the deprotonation take place [18,19].

To prove the importance of acetate in solution, the cyclometallation reaction was attempted in the same optimized conditions but without potassium acetate. An orange solution has obtained after four hours and no precipitate was observed. The methanol was removed under vacuum leading to an orange solid which was characterised by ^{1}H NMR (Figure 7).

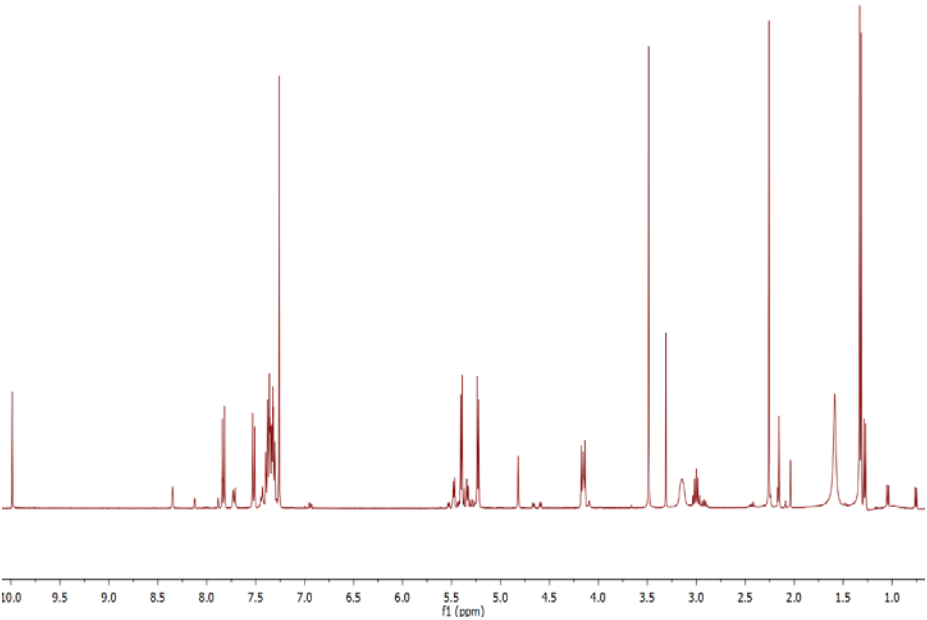


Figure 7. NMR proton shifts (ppm) of product obtained without acetate in solution in $CDCl_3$.

This spectrum shows that the hydrolysis of the imine ligand has occurred, with formation of the corresponding aldehyde, and the ruthenium coordination complex with a primary amine has been formed. This study confirms the proposed mechanism for the reaction.

This proton NMR spectrum shows two important facts: the presence of free aldehyde with the shift at 10 ppm, that confirms the hydrolysis of imine ligand, and the broad band at 3.15 ppm corresponding to the amine group after the hydrolysis. Even though, we can see a small fraction of cyclometalated compound but it only represents a 7 % respect the ruthenium coordinated to amine.

After this result, free aldehyde was separated from amino – ruthenium compound removing the aldehyde with diethyl ether leading the ruthenium compound insoluble and the solid was filtered and dried under vacuum to obtain the product Cx (Figure 8) was obtained as an orange solid, which can be considerate the intermediate of the cyclometallation reaction.

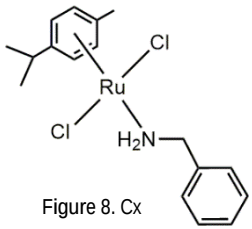


Figure 8. Cx

The cyclometalated derivatives can be easily characterised by IR spectroscopy and proton NMR spectroscopy, remarking that ruthenium is an inactive metal at NMR spectroscopy. Those two techniques, show that reaction was successful and that only exist the cyclometallated complex in the resultant product.

Cyclometallated compounds can be easily characterised by infrared spectroscopy showing a displacement of the C = N band frequency to lower wavenumbers. The formation of new Ru – N bond with the lone electron pair of imine bond remove electronic density from the double bond weakening it, so the force constant decreases as the vibrational frequency. The absence of the bands in the infrared spectra at 3400 – 3380 and 1740 – 1725 cm^{-1}, which refers to primary amine N – H stretch and C = O stretch of aldehydes respectively [17] confirm the purity of the cycloruthenium compounds obtained and that the hydrolysis of imine did not take place.

In figure 9, shows the two overlapped spectra of L1 (black) and C1 (red) where the difference between each C = N band can be noted in order to confirm that cyclometallation reaction takes place. The C = N band for L1 appears at 1643 cm^{-1} and the corresponding band for C1 appears at 1603 cm^{-1}. Those difference were noted equally with the other pair of compounds and ligands.

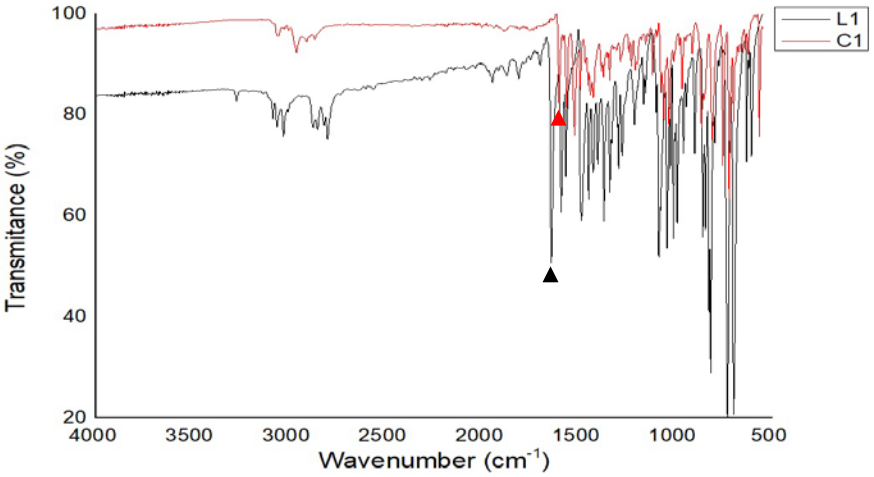


Figure 9. IR spectra recorded with ATR of L1 (black) and C1 (red).

When the cyclometallation reaction takes place, the ruthenium becomes an estrogenic center showing up four different proton shifts corresponding to four protons of the benzene in *p-cymene* group (figure 10). Besides, the absence of a signal at 9 – 10 ppm which correspond to aldehyde proton and of a broad signal between 1.5 – 4 ppm which can be assigned to the amine proton confirms that hydrolysis reaction did not take place. This figure (figure 10) shows the difference between the group *p-cymene* coordinated to the organometallic precursor $[Ru(Cl)_2(p\text{-}cymene)_2]_2$ (red) and the compound C1 (green). When the metallocycle has been obtained successfully and an estrogenic ruthenium center has been formed the proton NMR spectra shows four shifts which appears at 5.53, 5.43, 4.66 and 4.60 ppm from C1 (green) were significant different in relation to signals of the ruthenium precursor complex (red) where the corresponding protons appears at 5.47, 5.33 ppm respectively. Besides that, substituents groups of aromatic ring of *p-cymene* also shows differences, the methyl group and the iso-propyl group appears at low ppm and the methyl group of iso-propyl group can be distinguish in the spectra of metallocycle compound. Those difference were noted equally with the other pair of compounds and ligands.

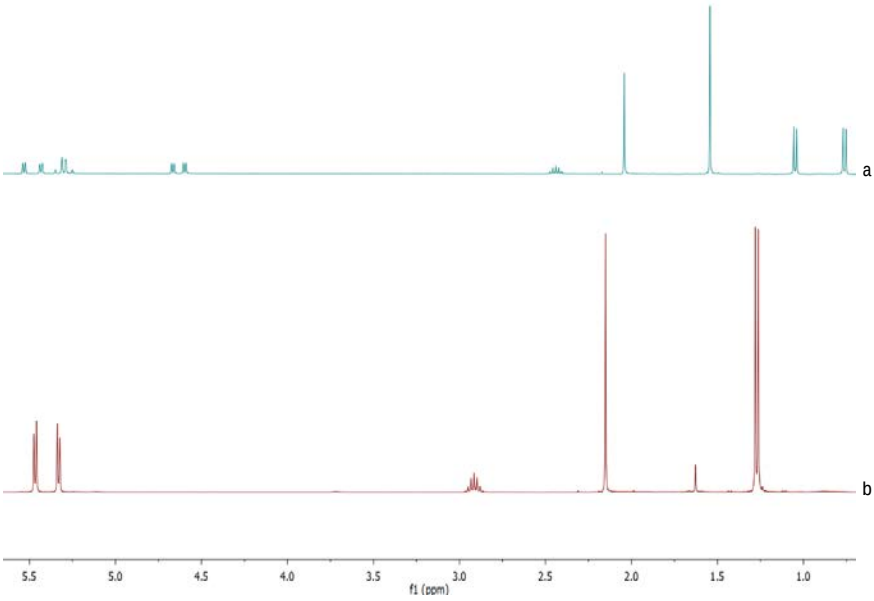


Figure 10. NMR proton shifts (ppm) of C1 (9.a) and $[Ru(Cl)_2(p\text{-}cymene)_2]_2$ (9.b) in *p-cymene* region overleaped.

For the characterisation of Cx, which corresponds to N-coordinate ruthenium compound, the presence of a broad band at 3.12 ppm confirms the existence of the intermedium of the reaction after hydrolysis and also shows that the pair of protons in group *p-cymene* are equivalent.

To show the difference between the free ligand and the cyclometallated compound, NMR spectra records of both compounds are overleaped in figure 11, where shifts at 8.35, 7.73 – 7.71, 4,82 ppm from L1 (red) were significant different in relation to signals of the C1 ruthenium complex (green) where the corresponding protons appears at 7.89, 7.32, 5.31 – 5.22 ppm respectively. Besides this, the apparition of two shifts at 8.12 and 6.95 ppm of the cyclometalated ring, shows that the cyclometallation reaction had taken place. Those difference were noted equally with the other pair of compounds and ligands.

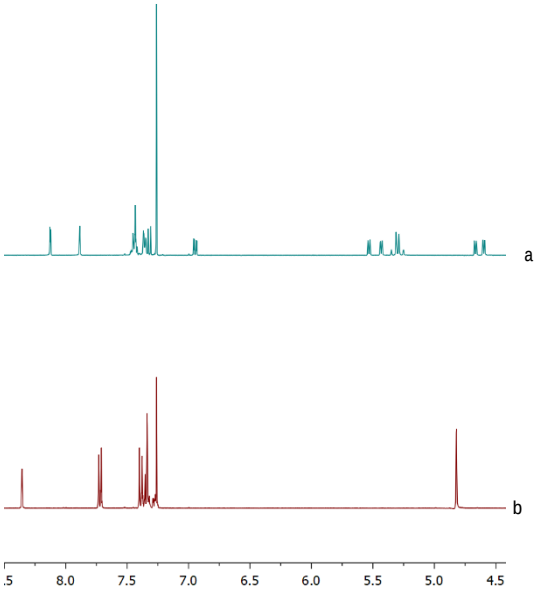


Figure 11. NMR proton shifts (ppm) of C1 (10.a) and L1 (10.b)

Furthermore, compounds C1 – C4 were characterised by HRMS. All the measures taken have less than ± 5 ppm error. The principal expecting picks are shown in each spectrum with a similar molecular weight and with the expected isotropic distribution. Besides, the observed compounds are the result of severe conditions of ionization, showing dimeric ruthenium compounds which are rarely observed in palladium metallocycles.

The following figures shows the HRMS spectrum of C1 of the most relevant specking picks: $[M\text{-}Cl]^+$ (figure12) and $[M+H]^+$ (figure 13), last one assigned as the molecular pick, and compared with the predicted spectra of the compound. Besides, figure 14 shows the pick assigned to the dimeric ruthenium metallocycle compound $[2M\text{-}Cl]^+$.

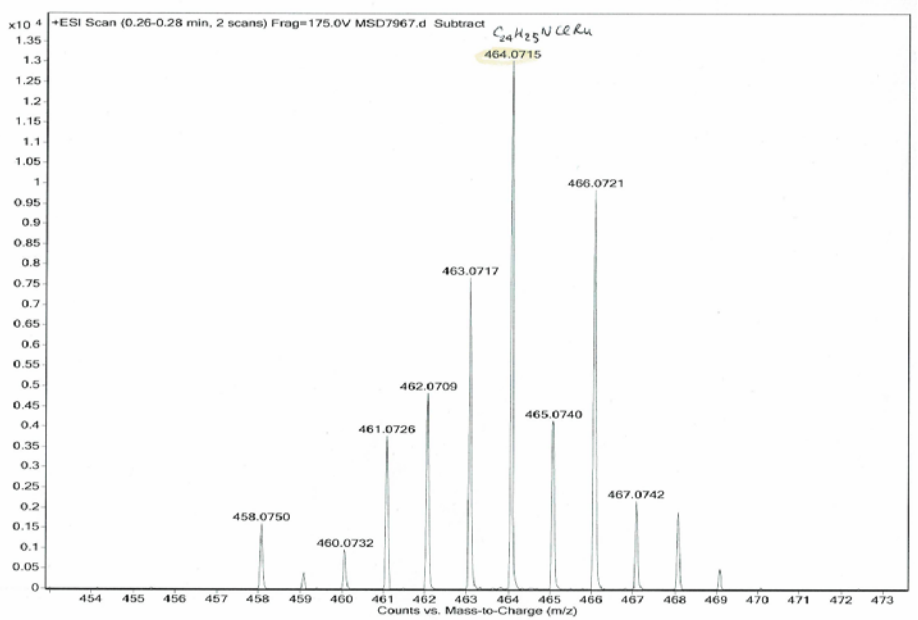


Figure 12. HRMS (ESI +) spectra of C1 utilizing a mixture of H_2O:CH_3CN (1:1, v/v) as the eluent and fragmenting potential 175 V, showing pick $[M\text{-}Cl]^+$

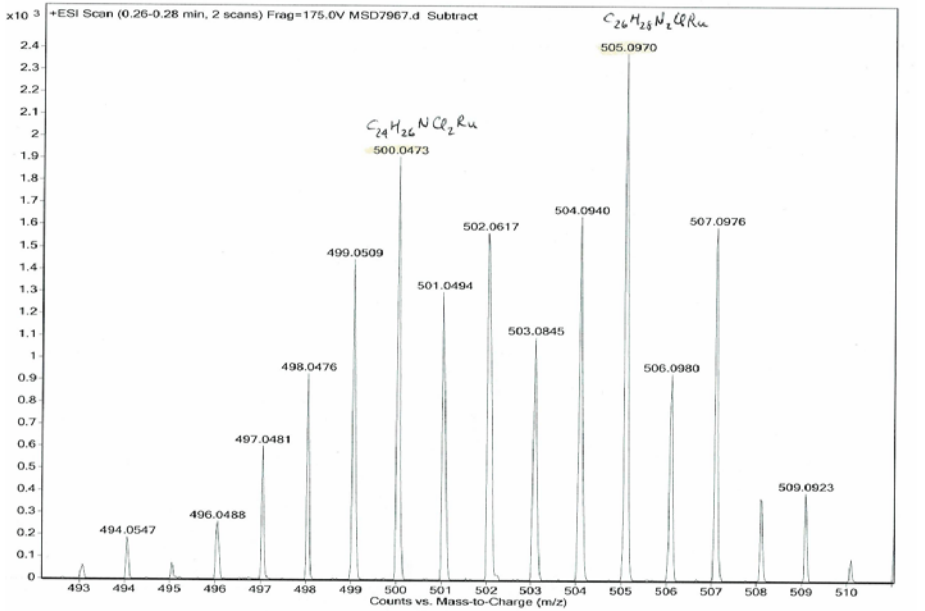


Figure 13. HRMS (ESI +) spectra of C1 utilizing a mixture of H_2O:CH_3CN (1:1, v/v) as the eluent and fragmenting potential 175 V, showing pick $[M+H]^+$ overlapped with $[M\text{-}Cl+CH_3CN]^+$ respectively.

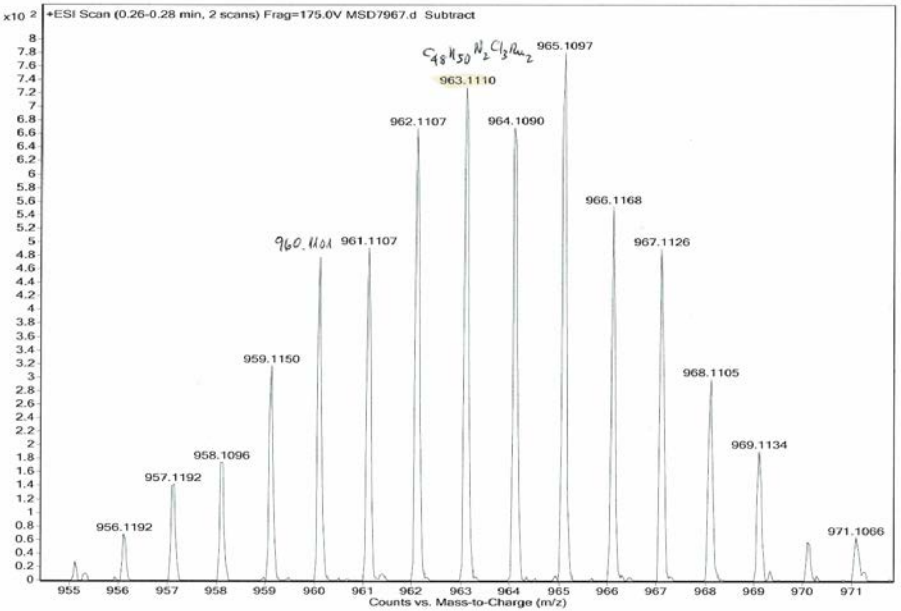
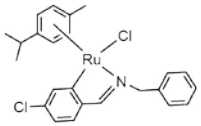
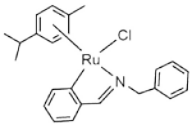


Figure 14. HRMS (ESI +) spectra of C1 utilizing a mixture of H_2O:CH_3CN (1:1, v/v) as the eluent and fragmenting potential 175 V, showing pick $[2M\text{-}Cl]^+$

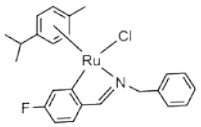
The cyclometalated compounds obtained were isolated as pure compounds and with high yields.



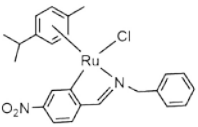
C1



C2



C3



C4

Cyclorutheniated compound	
Product	Isolated yield (%)
C1	67
C2	72
C3	42
C4	82

Compounds C1 – C3 were characterised by elemental analysis of C, H and N (See the experimental section).

6. EXPERIMENTAL SECTION

6.1. GENERAL CONSIDERATIONS

NMR spectra were recorded in $CDCl_3$ at 298 K with Mercury 400 (^1H) spectrometer. Chemical shifts are given in δ values (ppm) relative to $SiMe_4$. Coupling constants are given in Hz and the multiplicity is expressed as: s (singlet), d (doublet), t (triplet), hept (heptuplet), m (multiplet) and br (broad signal). The IR spectra was recorded in a Nicolet iS5 spectrophotometer equipped with iD7 ATR accessory, and the main absorption bands are expressed in cm^{-1}. High – resolution mass spectrometry analyses were performed with electrospray ionisation. ESI (+) spectra were acquired either on an LC/MSD – TOF instrument (Agilent Technologies, 2006.), utilizing a mixture of H_2O:CH_3CN (1:1, v/v) as the eluent and fragmenting potential 175 V. Elemental analysis C, H and N analyses were performed with an Eager 1108 microanalyzer.

6.2. SYNTHESIS OF LIGANDS

6.2.1. Synthesis of L1, N-benzyl-1-(4-chlorophenyl)methanimine

A mixture of 4-chlorobenzaldehyde (171 mg, 1.2 mmol) and benzylamine (129 mg, 1.2 mmol) was solved in 20 mL of ethanol and heated in a silicon bath at 85 ºC with stirring for an hour and a half. The ethanol was removed under vacuum leading to a colourless oil. Yield: 100% (220 mg).

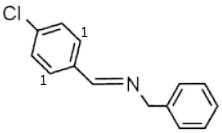


Figure 15. L1

^1H NMR ($CDCl_3$, 400 MHz): δ 8.36 (s, *H*CN), 7.73 – 7.71 (d, 2H, J = 8.5 Hz, *H1*), 7.41 – 7.27 (m, 7H, *aromatic*), 4.82 (d, C*H*$_2$N, J = 1.4 Hz).
IR: 3272, 3063, 2853, 1643, 1486, 1370, 1100, 827, 731, 699.

6.2.2. Synthesis of L2, N-benzyl-1-phenylmethanimine

The procedure was the same as the one followed to prepare L1. Starting from benzylamine (101 mg, 0.94 mmol) and benzaldehyde (99 mg, 0.93 mmol) the title product was a colourless oil. Yield: 87 % (158 mg).

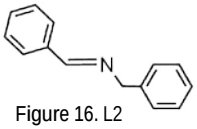


Figure 16. L2

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33 (s,1H, *H*CN), 7.73 – 7.67 (m, 2H), 7.37 – 7.18 (m, 8H, *aromatic*), 4.75 (d, 2H, C*H*$_2$N, J = 1.4 Hz).

IR, ν = 3026, 2837, 1641, 1450, 1025, 749, 690 cm^{-1}.

6.2.3. Synthesis of L3, N-benzyl-1-(4-nitrophenyl)methanimine

The procedure was the same as the one followed to prepare L1. Starting from benzylamine (119 mg, 1.11 mmol) and 4-nitro-benzaldehyde (169 mg, 1.12 mmol) the title product was a yellowish oil. Yield: 98 % (261 mg).

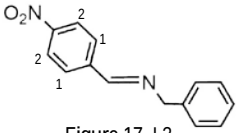


Figure 17. L3

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.37 (s, 1H, *H*CN), 8.18 – 8.16 (d, 2H, J = 8.8 Hz, *H2*), 7.86 – 7.84 (d, 2H, J = 8.8 Hz, *H1*), 7.38 – 7.11 (m, 5H, *aromatic*), 4.75 (d, 2H, C*H*$_2$N, J = 1.4 Hz).

IR, ν = 3053, 2852, 1600, 1513, 1341, 852, 739, 698 cm^{-1}.

6.2.4. Synthesis of L4, N-benzyl-1-(4-fluorophenyl)methanimine

The procedure was the same as the one followed to prepare L1. Starting from benzylamine (107 mg, 1.00 mmol) and 4 - fluorobenzaldehyde (141 mg, 1.13 mmol) the title product was a colourless oil. Yield: 99% (211 mg).

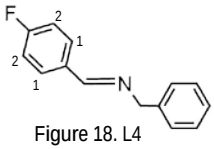


Figure 18. L4

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36 (s, 1H, *H*CN), 7.80 – 7.76 (dd, 2H, J_{HH} = 8.7 Hz, J_{HF} 5.6 Hz, *H1*), 7.39 – 7.27 (m, 5H, *aromatic*), 7.12 – 7.08 (t, 2H, J_{HF} = J_{HH} = 8.6 Hz, *H2*), 4.81 (br.s, 2H, C*H*$_2$N).

IR, ν = 3028, 2838, 1642, 1596, 1507, 1226, 1150, 834, 731, 695 cm^{-1}.

6.2.5. Synthesis of L5, N-benzyl-1-(3,4-dimethoxyphenyl)methanimine

The procedure was the same as the one followed to prepare L1. Starting from benzylamine (115 mg, 1.07 mmol) and 3,4 - dimethoxybenzaldehyde (176 mg, 1.06 mmol) the title product was a brownish oil. Yield: 100% (280 mg).

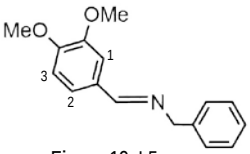


Figure 19. L5

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (br. t, 1H, *H*CN), 7.41 (d, 1H, J = 1.9 Hz, *H1*), 7.30 – 7.17 (m, 5H, *aromatic*), 7.12 (dd, 1H, J = 8.1, 1.9 Hz, *H3*), 6.81 (d, 1H, J = 8.2 Hz, *H2*), 4.73 (s, 2H, C*H*$_2$N), 3.86 (s, 3H, O*Me*), 3.85 (s, 3H, O*Me*).

IR, ν = 3001, 2933, 2834, 1639, 1584, 1508, 1136, 1021, 752, 697 cm^{-1}.

6.3. SYNTHESIS OF COMPLEXES

6.3.1. Synthesis of C1

A mixture of **L1** (100 mg, 0.44 mmol), [$RuCl_2$(*p-cymene*)]$_2$ (133 mg, 0.22 mmol) and potassium acetate (86 mg, 0.88 mmol) in 10 mL of methanol was stirred for four hours at room temperature. The resultant solid was filtered and dried under vacuum and the product **C1** was obtained as an orange solid. Yield: 67 % (146 mg). The compound can be recrystalised with a mixture of CH_2Cl_2 : Diethyl ether (v/v, 1:1).

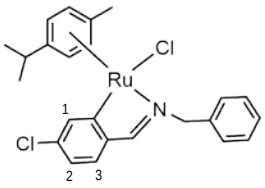


Figure 20. C1

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (d, 1H, J = 2.0 Hz, *H1*), 7.89 (br.t., 1H, *H*CN), 7.45 – 7.34 (m, 5H, *aromatic*), 7.32 (d, 1H, J = 8.0 Hz, *H3*), 6.95 (ddd, 1H, J = 8.1, 2.0. 0.6 Hz, *H2*), 5.53 (d, 1H, J = 5.9 Hz, η^6- C_6H_4), 5.43 (d, 1H, J = 5.9 Hz, η^6- C_6H_4), 5.31 – 5.22 (m, 2H, C*H*$_2$N), 4.66 (d, 1H, J = 5.9 Hz, η^6- C_6H_4), 4.60 (d, 1H, J = 5.9 Hz, η^6- C_6H_4), 2.43 (hept, 1H, J = 6.9 Hz, C*H*Me$_2$), 2.04 (s, 3H, *Me*), 1.05 (d, 3H, J = 6.9 Hz, CH*Me*$_2$), 0.76 (d, 3H, J = 6.9 Hz, CH*Me*$_2$).

IR, ν =: 3054, 2961, 2909, 1603, 1522, 1035, 864, 811, 755, 722, 581 cm^{-1}.

HRMS (ESI): m/z calc. for $C_{24}H_{25}NClRu^+$ [M-Cl]$^+$ 464.0713; found 464.0715 (ppm error: 0.3196), for $C_{24}H_{26}NCl_2Ru^+$ [M+H]$^+$ 500.0480; found 500.0473 (ppm error: -1.4587), for $C_{26}H_{28}N_2ClRu^+$ [M-Cl+CH_3CN]$^+$ 505.0979; found 505.0790 (ppm error: -1.7833), for $C_{24}H_{29}N_2Cl_2Ru^+$ [M+NH_4]$^+$ 517.0745; found 517.0741 (ppm error: -0.9255), for $C_{48}H_{50}N_2Cl_3Ru_2^+$ [2M-Cl]$^+$ 963.1121; found 963.1110 (ppm error: -1.1469), for $C_{48}H_{54}N_3Cl_4Ru_2^+$ [2M+ NH_4]$^+$ 1016.1153; found 1016.1136 (ppm error: -1.7040).

Elemental analysis (calc. for $C_{24}H_{25}Cl_2NRu$): C: 56.7% (57.72 %); H: 5.2 % (5,05 %) and N: 2.7 % (2.80 %).

6.3.2. Synthesis of C2

Onepot synthesis procedure was followed to prepare C2. A mixture of L2 (90 mg, 0.46 mmol), $[RuCl_2(p\text{-}cymene)]_2$ (141 mg, 0.23 mmol) and potassium acetate (90 mg, 0.92 mmol) in 10 mL of methanol was stirred for four hours at room temperature. The resultant solid was filtered and dried under vacuum and the product C2 was obtained as an orange solid. Yield: 72% (153 mg).

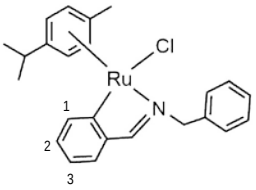


Figure 21. C2

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (d, 1H, J = 7.6 Hz, *H1*), 7.93 (s, 1H, *H*CN), 7.45 – 7.36 (m, 6H, *aromatic*), 7.12 (t, 1H, J = 7.4 Hz, *H2*), 6.96 (t, 1H, J = 7.4 Hz, *H3*), 5.53 (d, 1H, J = 5.9 Hz, η^6- C_6H_4), 5.42 (d, 1H, J = 5.9 Hz, η^6- C_6H_4), 5.36 – 5.21 (m, 2H, C*H*$_2$N), 4.61 (d, 1H, J = 5.9 Hz, η^6- C_6H_4), 4.54 (d, 1H, J = 5.9 Hz, η^6- C_6H_4), 2.43 (hept, 1H, J = 6.9 Hz, C*H*Me$_2$), 2.02 (s, 3H, *Me*), 1.04 (d, 3H, J = 6.9 Hz, CH*Me*$_2$), 0.75 (d, 3H, J = 6.9 Hz, CH*Me*$_2$).

IR, ν = 3030, 2958, 2908, 1601, 1541, 858, 745, 728, 699 cm^{-1}.

HRMS (ESI): m/z calc. for $C_{24}H_{26}NRu^+$ $[M\text{-}Cl]^+$ 430.1103; found 430.1114 (ppm error: 2.5015), for $C_{24}H_{27}NClRu^+$ $[M+H]^+$ 466.0870; found 466.0862 (ppm error: -1.7201), for $C_{24}H_{30}N_2ClRu^+$ $[M+NH_4]^+$ 483.1135; found 483.1145 (ppm error: 1.9646), for $C_{48}H_{56}N_3Cl_2Ru_2^+$ $[2M+ NH_4]^+$ 948.1932; found 948.1926 (ppm error: -0.7130).

Elemental analysis (calc. for $C_{24}H_{26}ClNRu$): C: 59.6% (61.99 %); H: 5.6 % (5,64 %) and N: 2.9 % (3.01 %).

6.3.3. Synthesis of C3

The procedure was the same as the one followed to prepare C1. Starting from L3 (100 mg, 0.42 mmol), the title product was obtained as a red solid. Yield: 42% (88 mg).

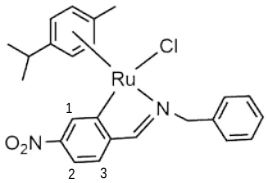


Figure 22. C3

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.97 (d, 1H, J = 2.2 Hz, *H1*), 8.01 (s, 1H, *H*CN), 7.81 (dd, 1H, J = 8.3, 2.2 Hz, *H3*), 7.52 – 7.50 (d, 1H, J = 8.30 Hz, *H2*), 7.49 – 7.35 (m, 5H, *aromatic*), 5.65 (d, 1H, J = 6.4 Hz, η^6- C_6H_4), 5.54 (d, 1H, J = 6.0 Hz, η^6- C_6H_4), 5.46 – 5.31 (m, 2H, C*H*$_2$N), 4.80 (d, 1H, J = 6.0 Hz, η^6- C_6H_4), 4.70 (d, 1H, J = 6.0 Hz, η^6- C_6H_4), 2.44 (hept, 1H, J = 7.0 Hz, C*H*Me$_2$), 2.07 (s, 3H, *Me*), 1.05 (d, 3H, J = 6.9 Hz, CH*Me*$_2$), 0.75 (d, 3H, J = 6.9 Hz, CH*Me*$_2$).

IR, ν = 3055, 2965, 1507, 1442, 1371, 1304, 843, 746, 711 cm^{-1}.

HRMS (ESI): m/z calc. for $C_{24}H_{25}N_2O_2Ru^+$ $[M\text{-}Cl]^+$ 475.0954; found 475.0967 (ppm error: 2.7316), for $C_{26}H_{28}N_3O_2Ru^+$ $[M\text{-}Cl+CH_3CN]^+$ 516.1219; found 516.1229 (ppm error: 1.8380), for $C_{24}H_{29}N_3O_2Cl_2Ru^+$ $[M+NH_4]^+$ 528.0986; found 528.0989 (ppm error: 0.5129), for $C_{48}H_{50}N_4O_4ClRu_2^+$ $[2M\text{-}Cl]^+$ 985.1602; found 985.1637 (ppm error: 3.5468), for $C_{48}H_{54}N_5O_4Cl_2Ru_2^+$ $[2M+ NH_4]^+$ 1038.1634; found 1038.1633 (ppm error: -0.1277).

Elemental analysis (calc. for $C_{24}H_{25}ClN_2O_2Ru$): C: 54.3% (56.52 %); H: 5.2 % (4.94 %) and N: 5.3 % (5.49 %).

6.3.4. Synthesis of C4

The procedure was the same as the one followed to prepare C1. Starting from L4 (0.099 mg, 0.46 mmol), the title product was obtained as an orange solid. Yield: 82 % (183 mg).

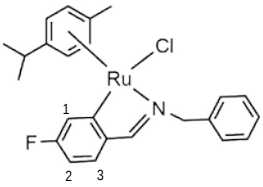


Figure 23. C4

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.88 (s, 1H, *H*CN), 7.84 (dd, 1H, J = 9.2, 2.5 Hz, *H1*), 7.49 – 7.32 (m, 6H, *aromàtic + H3*), 6.65 (td, 1H, J = 8.8, 2.3 Hz, *H2*), 5.50 (d, 1H, J = 5.9 Hz, η^6- C_6H_4), 5.41 (d, 1H, J = 6.3 Hz, η^6- C_6H_4), 5.36 – 5.22 (m, 2H, CH_2N), 4.65 (d, 1H, J = 5.7 Hz, η^6- C_6H_4), 4.57 (d, 1H, J = 5.9 Hz, η^6- C_6H_4), 2.45 (hept, 1H, J = 7.0 Hz, C*H*Me_2), 2.04 (s, 3H, *Me*), 1.05 (d, 3H, J = 6.9 Hz, CH*Me*$_2$), 0.75 (d, 3H, J = 6.9 Hz, CH*Me*$_2$).

IR, ν = 3044, 2958, 2915, 1607, 1551, 1438, 1233, 858, 810, 745, 728, 587 cm^{-1}.

HRMS (ESI): m/z calc. for $C_{24}H_{25}NFRu^+$ $[M\text{-}Cl]^+$ 448.1009; found 448.1011 (ppm error: 0.4414), for $C_{24}H_{26}NFClRu^+$ $[M+H]^+$ 484.0775; found 484.0776 (ppm error: 0.0414), for $C_{26}H_{28}N_2FRu^+$ $[M\text{-}Cl+CH_3CN]^+$ 489.1274; found 489.1271 (ppm error: -0.7182), for $C_{24}H_{29}N_2FClRu^+$ $[M+NH_4]^+$ 501.1041; found 501.1054 (ppm error: 2.5362), for $C_{48}H_{54}N_3F_2Cl_2Ru_2^+$ $[2M+ NH_4]^+$ 984.1744; found 984.1740 (ppm error: -0.4395).

6.3.5. Synthesis of Cx

A mixture of **L1** (100 mg, 0.44 mmol) and $[RuCl_2(p\text{-}cymene)]_2$ (133 mg, 0.22 mmol) in 10 mL of methanol was stirred for four hours at room temperature. The resultant solution was evaporated under vacuum. Proton NMR spectrum of the bulk shows the presence of aldehyde, suggesting that the hydrolysis of imine ligand occured. Aldehyde was removed solving the initial solid with diethyl ether leading the ruthenium compound insoluble and the solid was filtered and dried under vacuum to obtain the product **Cx** as an orange solid.

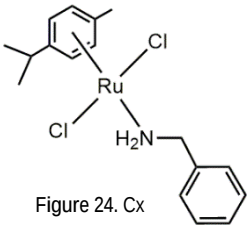


Figure 24. Cx

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44 – 7.39 (m, 5H, *aromatic*), 5.40 (d, 2H, J = 5.9 Hz, η^6- C_6H_4), 5.23 (d, 2H, J = 6.3 Hz, η^6- C_6H_4), 4.20 – 4.13 (m, 2H, C*H*$_2$N), 3.12 (br. s, 1H, *H*NCH$_2$), 3.01 (hept, 1H, J = 6.9 Hz, C*H*Me$_2$), 2.27 (s, 3H, *Me*), 1.33 (d, 6H, J = 6.9 Hz, CH*Me*$_2$).

7. CONCLUSIONS

It has been described an easy method for the synthesis for ruthenium (II) metallocycles with N – donor ligand via C – H direct activation using potassium acetate to deprotonate one of the *ortho* C – H bonds. The reaction takes place at room temperature and in a short period of time (four hours) in methanol solution. The synthesis of these ruthenium metallocycles, starting from $[RuCl_2(p\text{-}cymene)]_2$ with different benzylimines presents a successful result with high yields. The resultant products have been characterised by different techniques showing high purity and complete regioselectivity to form the *endo* metallocycle, the metallocycle that contains the C = N bond.

Infrared spectroscopy and nuclear magnetic resonance are good techniques to confirm that reaction has concluded and that the title product is the expected compound. Also, the mass spectrum is in agreement with the proposed structure.

The successful characterisation of one intermediate in the reaction shows that the process starts with the coordination of imines to the metal and in a second step the CH activation takes place, assisted by the acetato group that acts as internal base.

These new compounds present different properties in relation to the previously described ruthenium metallocycle obtained from imine ligands containing aniline group they may present good applications as catalysts and antitumoral agents, which is going to be tested in future studies.

8. REFERENCES AND NOTES

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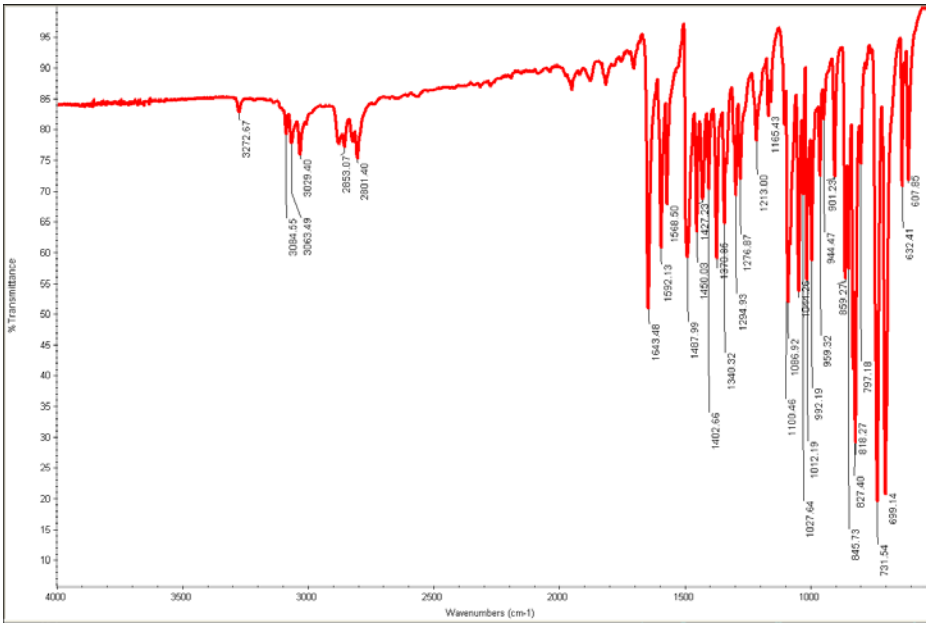
APPENDICES

APPENDIX 1: IR RECOMPILATIONS

In this appendix you can find the different infrared spectrum for each ligand and compound. Starting form ligands L1 to L5 and followed by compounds C1 to C4.

L1:



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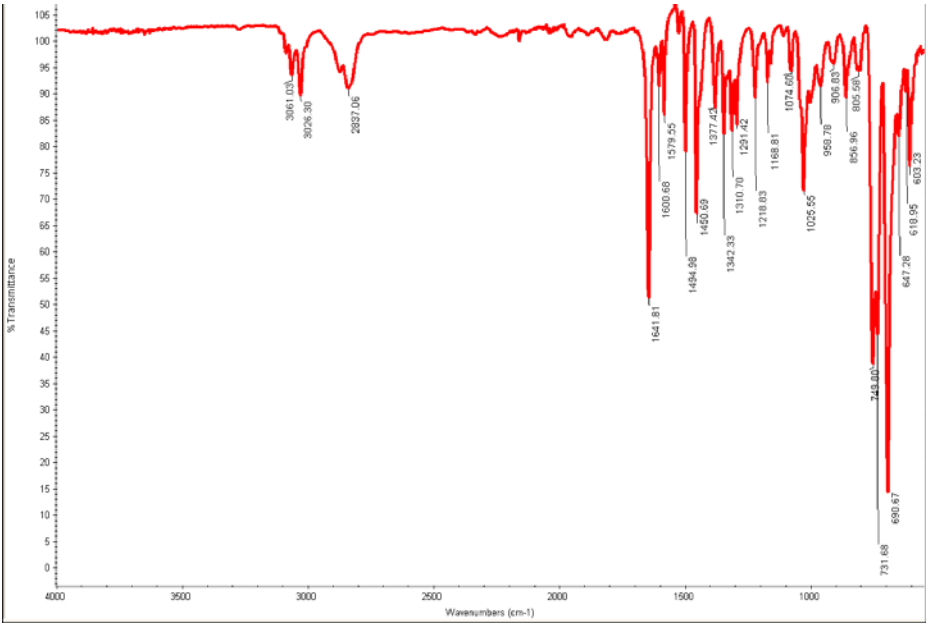
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Wavenumbers (cm-1)
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1579.55
1494.98
1450.69
1377.43
1342.33
1310.70
1291.42
1218.83
1168.81
1074.60
1025.55
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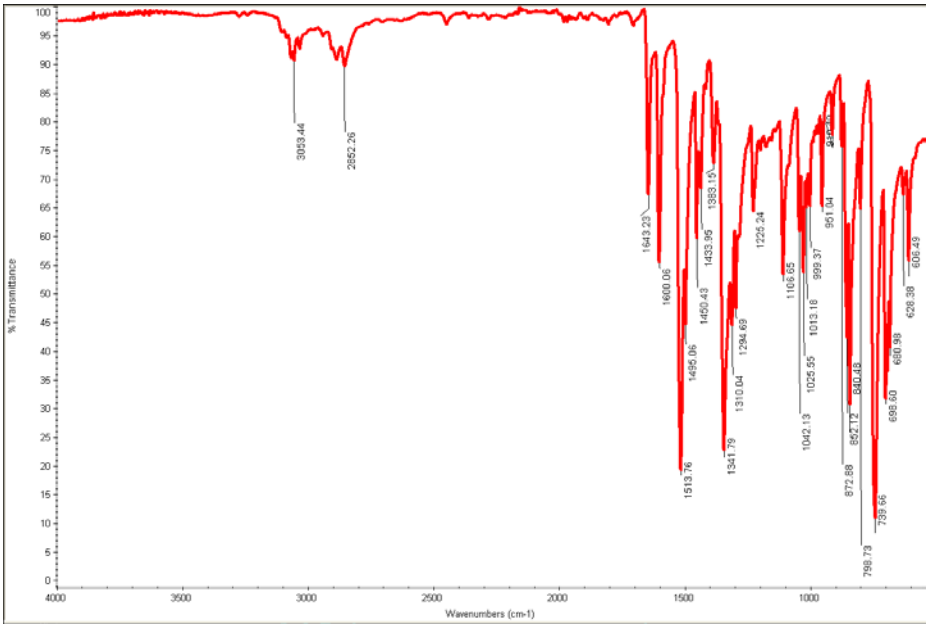
647.28
619.95
603.23

L3:


% Transmittance
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1450.43
1433.95
1383.19
1341.79
1310.04
1294.69
1226.24
1166.65
1042.13
1025.55
1013.18
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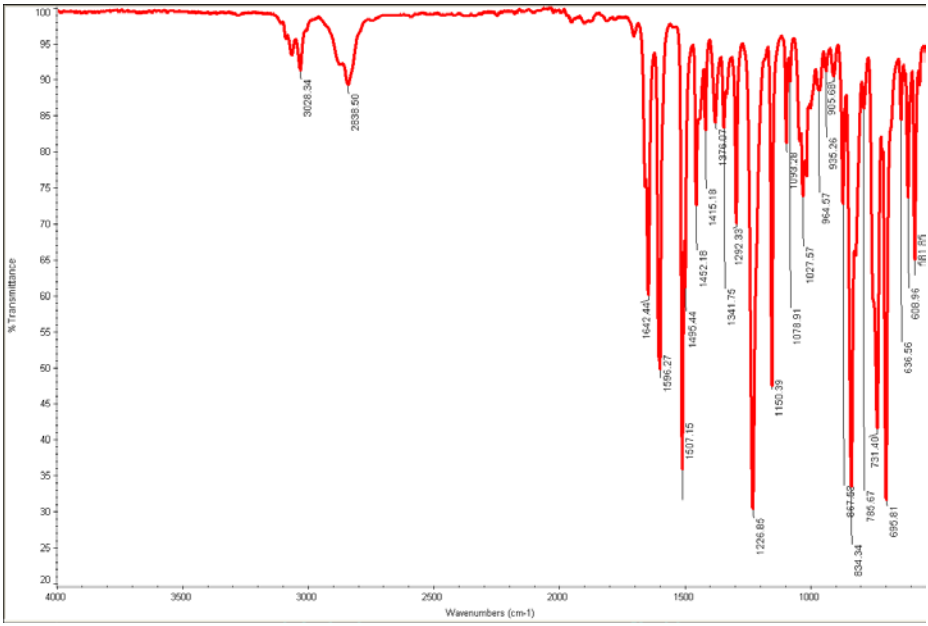
698.60
680.98
626.39
606.49

L4: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Wavenumbers (cm-1)
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1341.75
1292.33
1226.85
1150.39
1078.91
1027.57
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695.81
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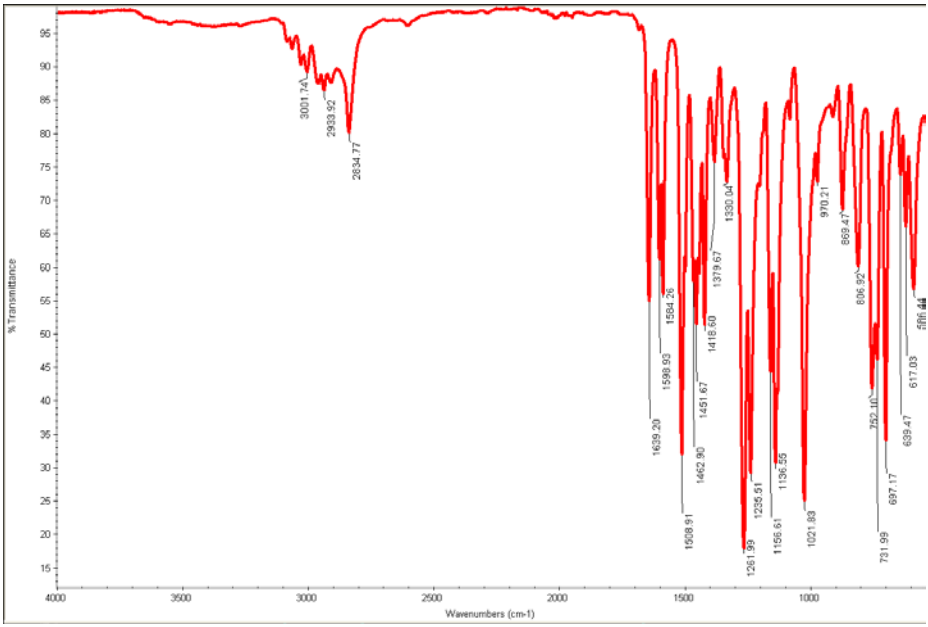
608.96
581.51

L5: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1451.67
1418.60
1379.67
1330.04
1261.99
1235.51
1156.61
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731.99
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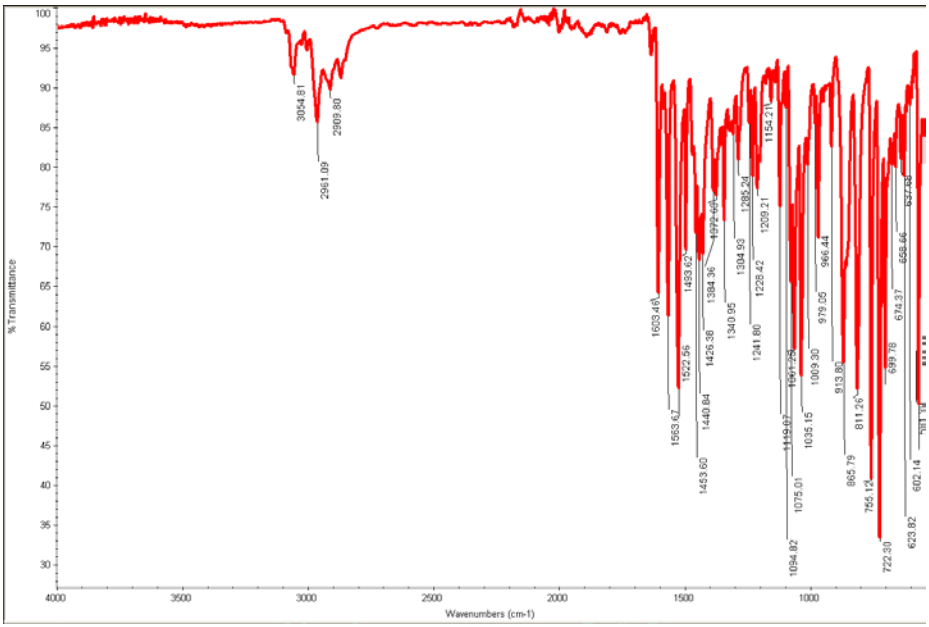
639.47
617.03

C1: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1428.38
1384.36
1340.95
1304.93
1285.24
1241.80
1228.42
1209.21
1154.21
1094.82
1075.01
1035.15
1009.30
979.05
966.44
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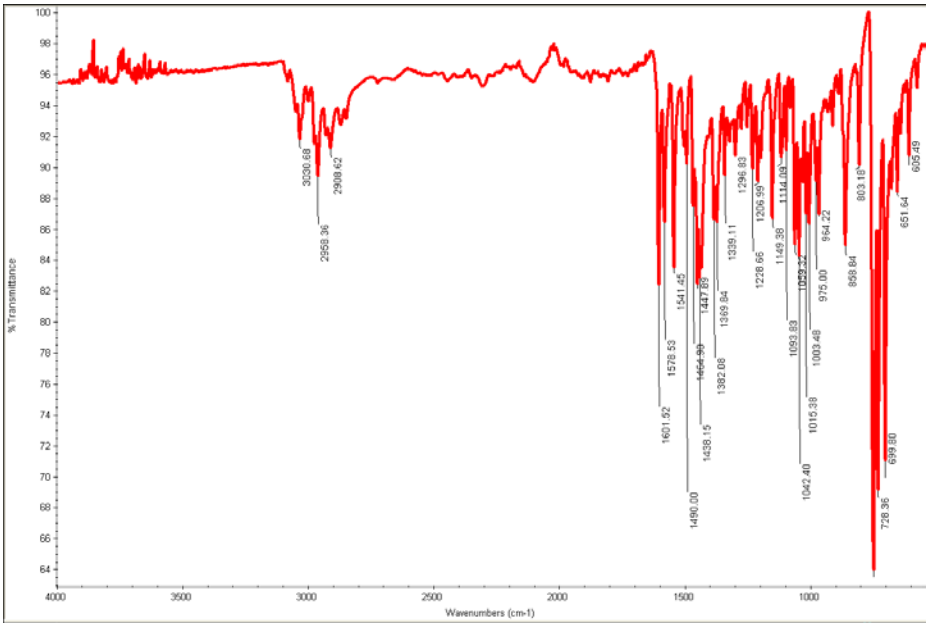
602.14

C2: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Wavenumbers (cm-1)
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1417.89
1399.84
1382.08
1339.11
1296.83
1276.99
1228.66
1149.38
1114.09
1093.83
1059.32
1042.40
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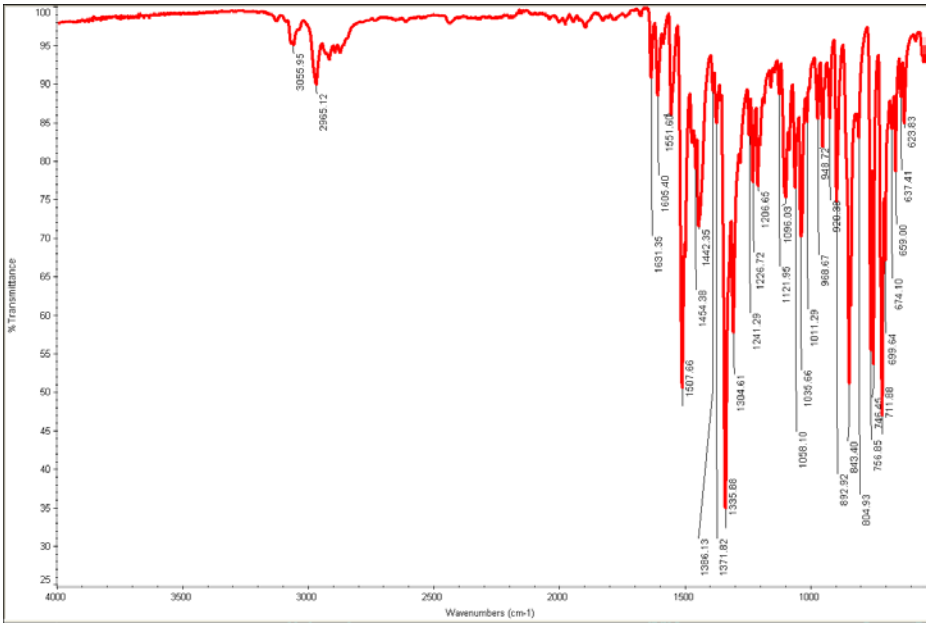
699.80
651.64
605.49

C3: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1371.82
1335.66
1304.61
1241.29
1226.72
1206.65
1121.95
1096.03
1058.10
1035.66
1011.29
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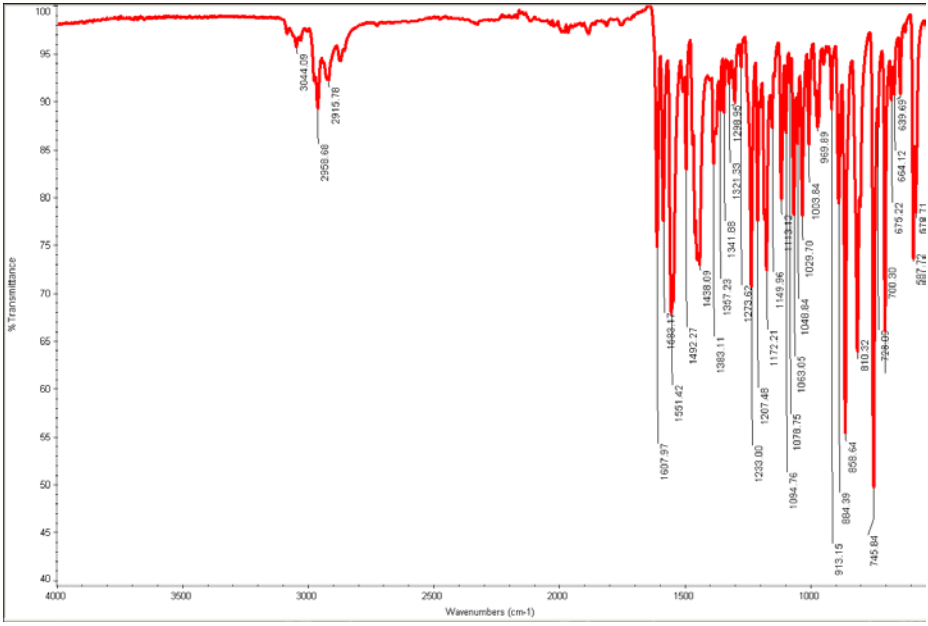
C4: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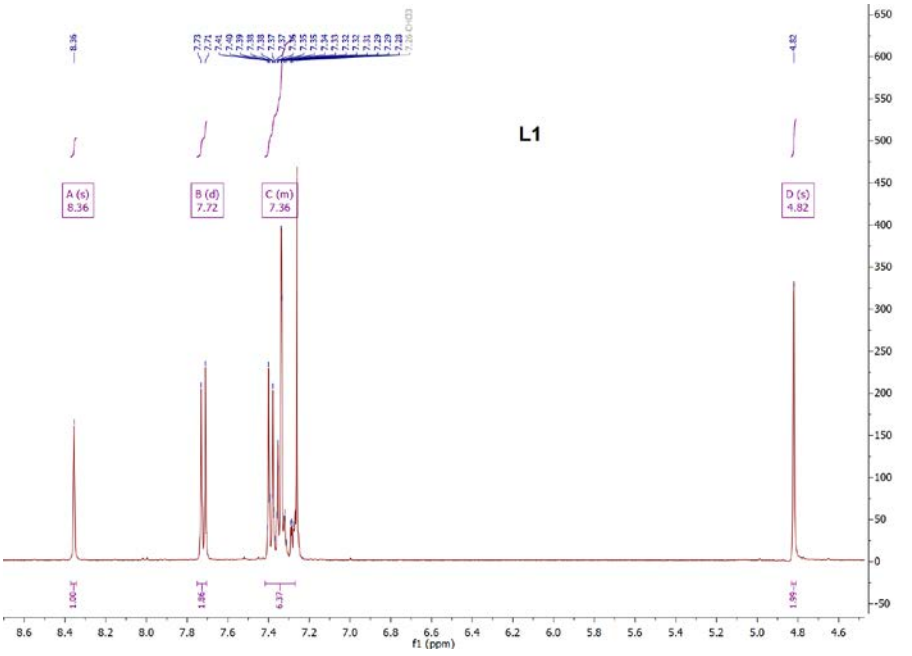
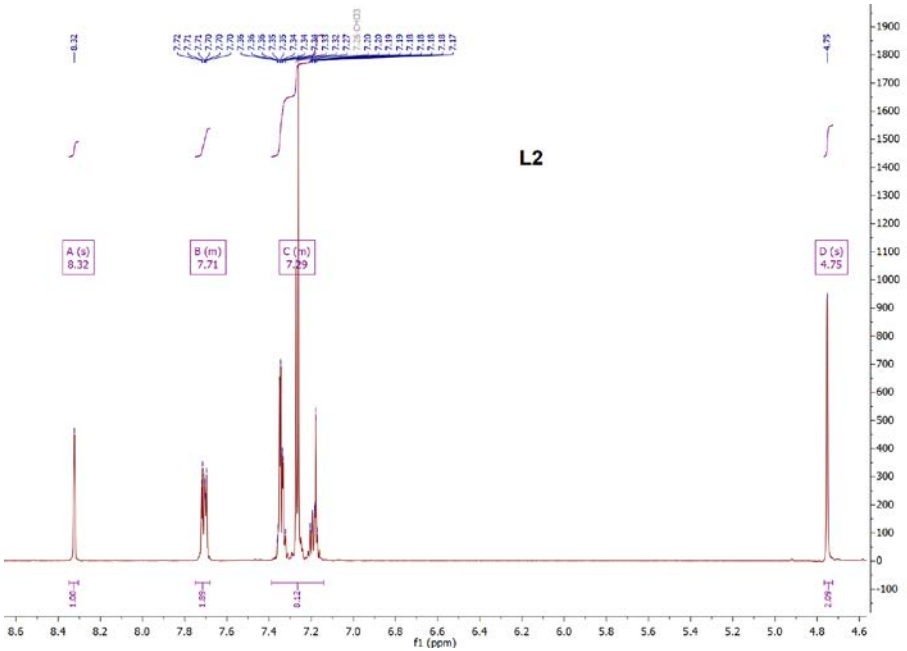
1321.33
1298.95
1273.62
1233.00
1207.48
1172.21
1149.96
1113.12
1094.76
1078.75
1063.65
1048.84
1029.70
1003.84
969.89
913.15
884.39
858.64
810.22
745.84
700.30
679.22
664.12
639.65
587.72

APPENDIX 2: NMR RECOMPILATIONS

In this appendix you can find the different NMR spectrum for each ligand and compound. Starting form ligands L1 to L5 and followed by compounds C1 to C4.




L2
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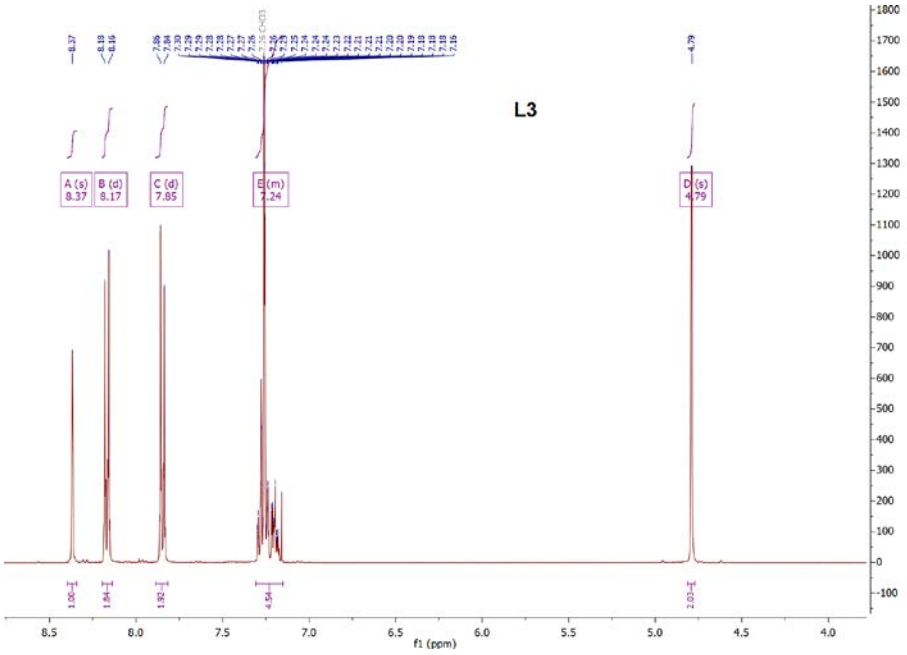
B (m) 7.71
C (m) 7.29
D (s) 4.75
f1 (ppm)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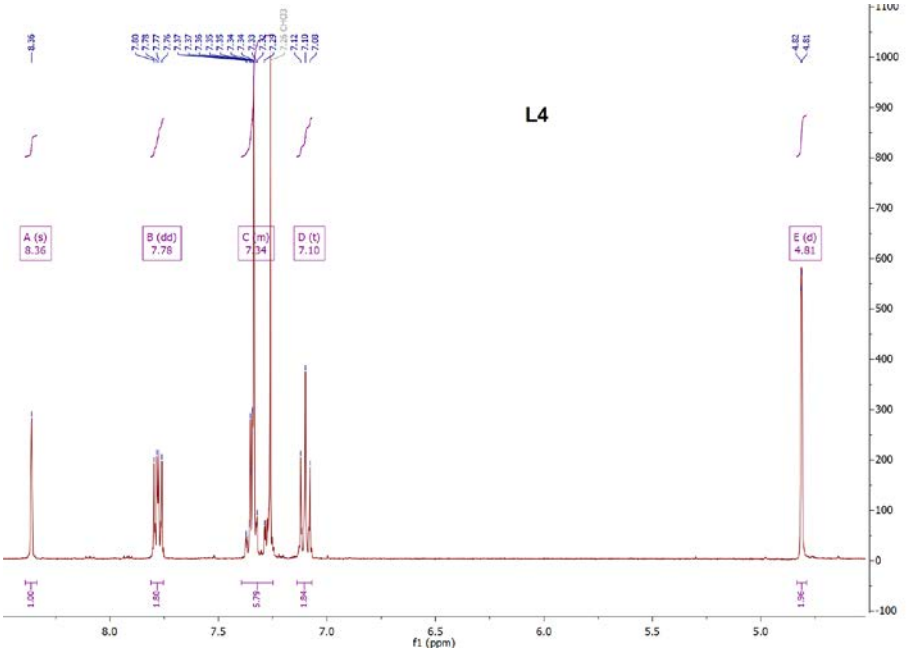
B (d) 8.17
C (d) 7.85
E (m) 7.24
D (s) 4.79
f1 (ppm)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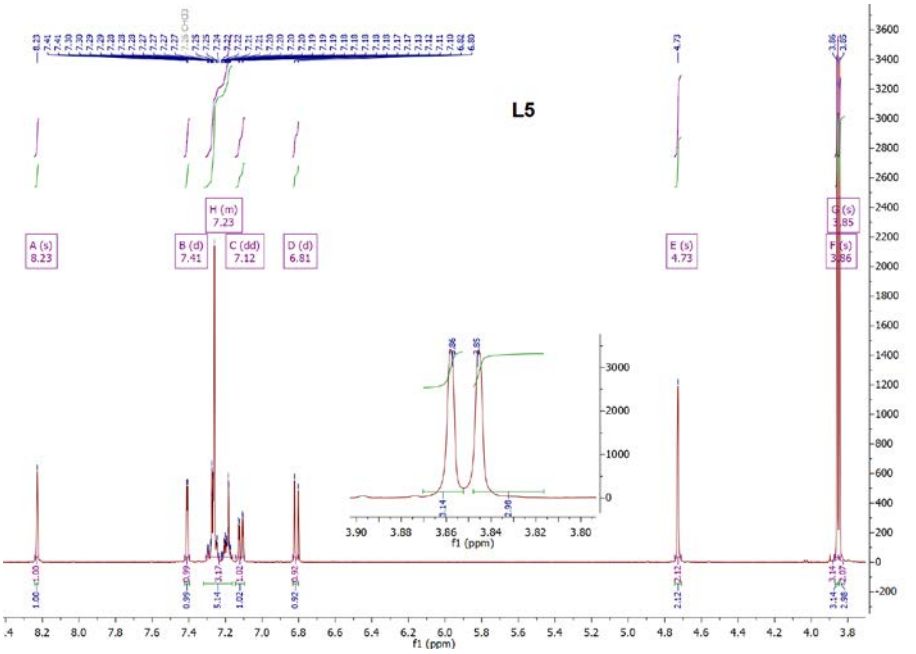
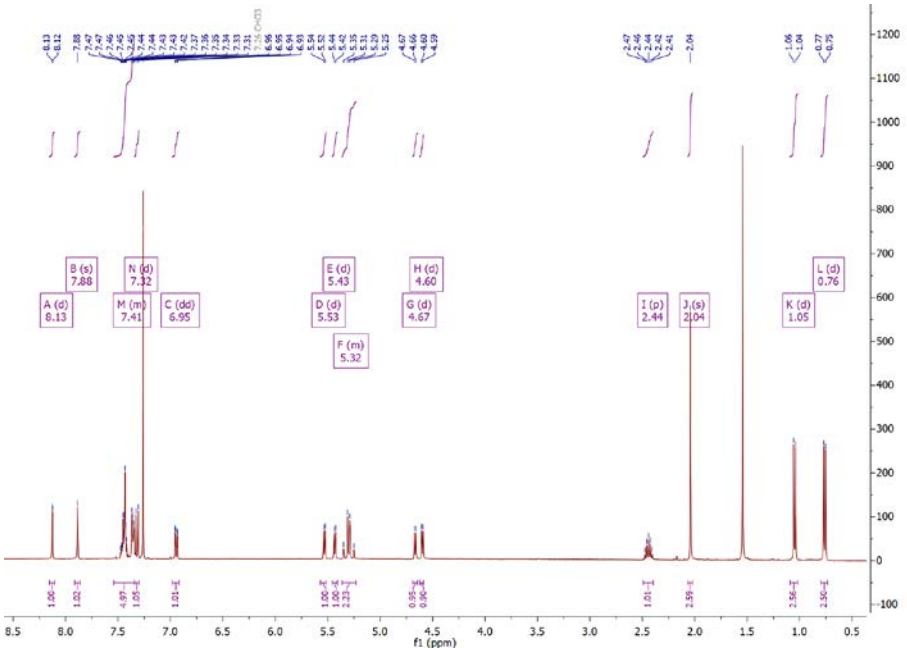
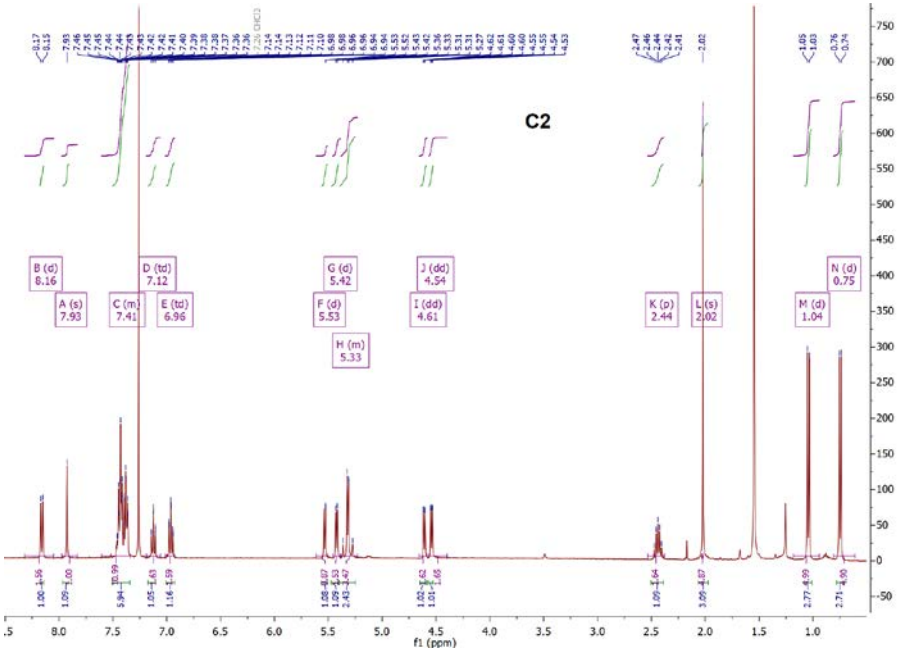
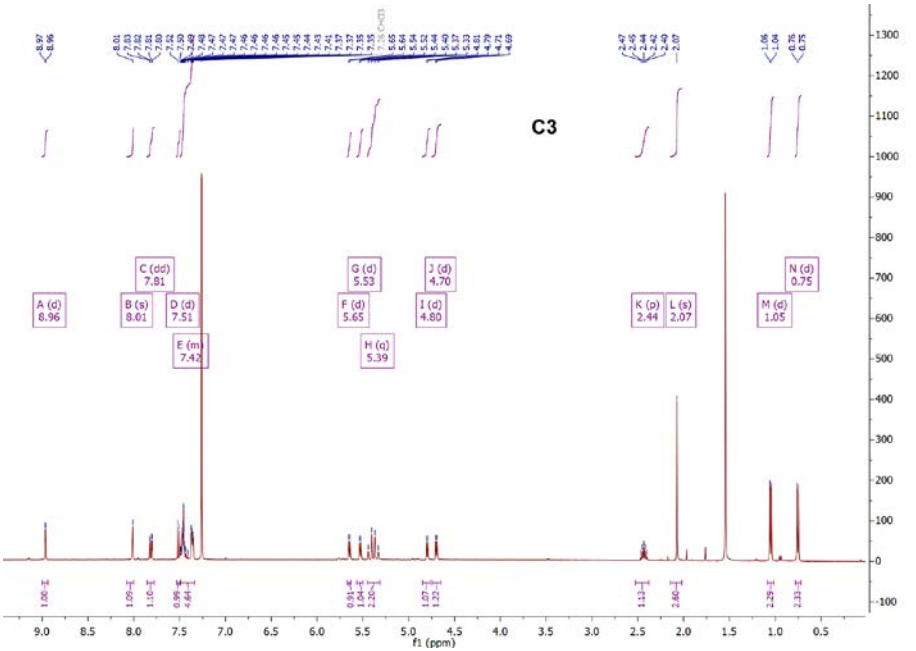
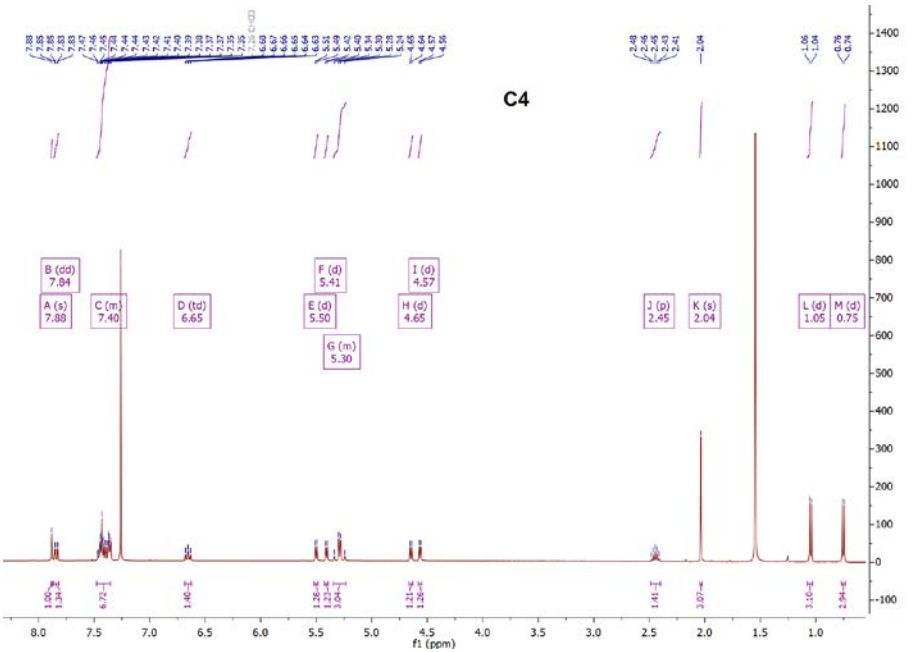
B (dd) 7.78
C (m) 7.34
D (t) 7.10
E (d) 4.81
f1 (ppm)

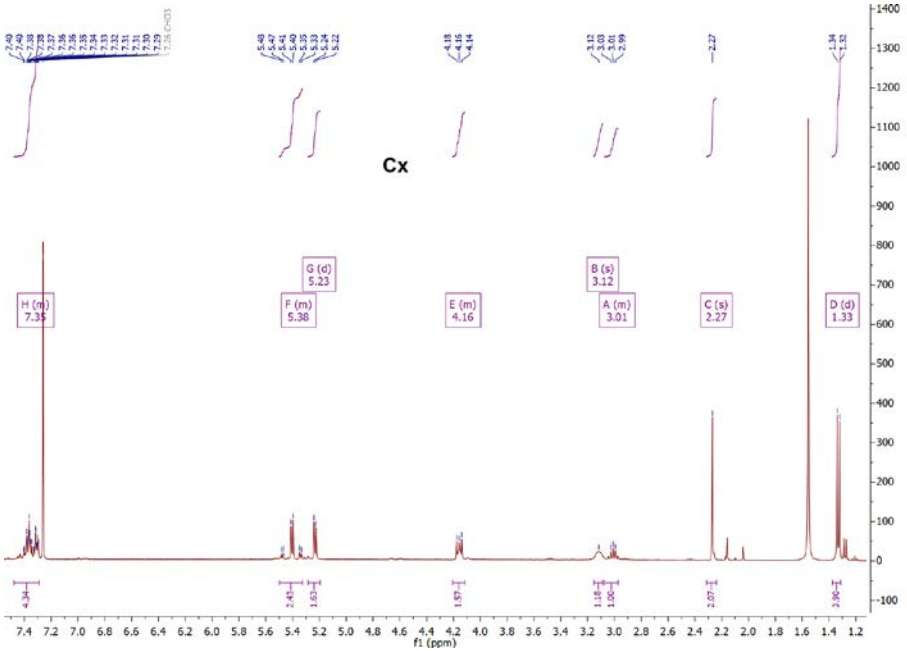

L5
A (s) 8.23
B (d) 7.41
H (m) 7.23
C (dd) 7.12
D (d) 6.81
E (s) 4.73
G (s) 3.85
F (s) 3.86
f1 (ppm)


B (s) 7.88
N (d) 7.32
E (d) 5.43
H (d) 4.60
L (d) 0.76
A (d) 8.13
M (m) 7.41
C (dd) 6.95
D (d) 5.53
G (d) 4.67
I (p) 2.44
J (s) 2.04
K (d) 1.05
F (m) 5.32
f1 (ppm)


C2
B (d) 8.16
D (td) 7.12
G (d) 5.42
J (dd) 4.54
N (d) 0.75
A (s) 7.93
C (m) 7.41
E (td) 6.96
F (d) 5.53
I (dd) 4.61
K (p) 2.44
L (s) 2.02
M (d) 1.04
H (m) 5.33
f1 (ppm)


C3
A (d) 8.96
B (s) 8.01
C (dd) 7.81
D (d) 7.51
E (m) 7.42
F (d) 5.65
G (d) 5.53
H (q) 5.39
I (d) 4.80
J (d) 4.70
K (p) 2.44
L (s) 2.07
M (d) 1.05
N (d) 0.75
f1 (ppm)

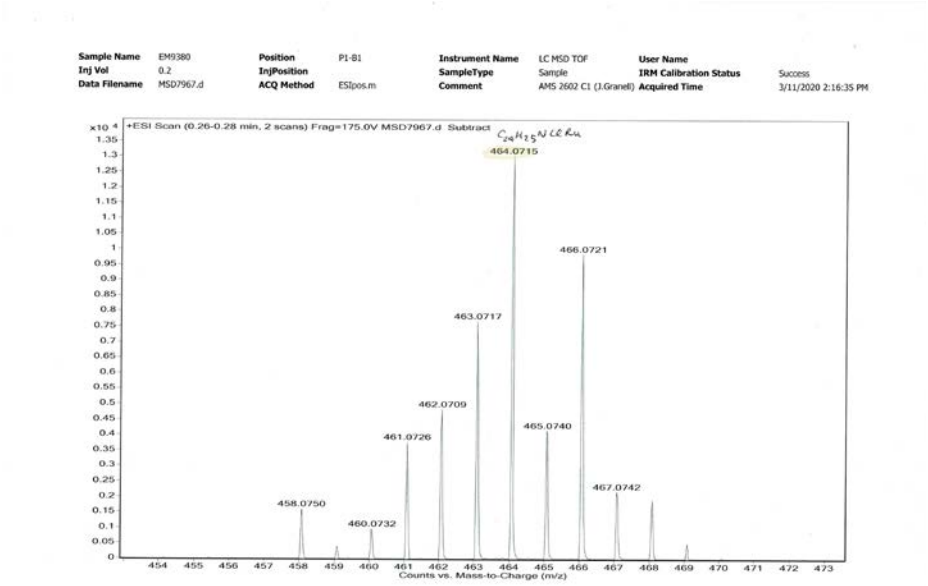

C4
A (s) 7.88
B (dd) 7.94
C (m) 7.40
D (td) 6.65
E (d) 5.50
F (d) 5.41
G (m) 5.30
H (d) 4.65
I (d) 4.57
J (p) 2.45
K (s) 2.04
L (d) 1.05
M (d) 0.75
f1 (ppm)


Cx
H (m)
7.35
G (d)
5.23
F (m)
5.38
E (m)
4.16
B (s)
3.12
A (m)
3.01
C (s)
2.27
D (d)
1.33
f1 (ppm)

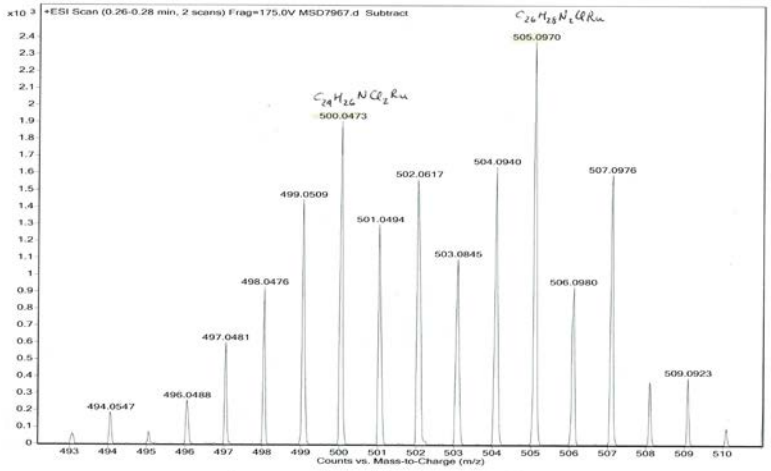
APPENDIX 3: MASS SPECTRUM RECOMPILATIONS

In this appendix you can find the different Mass spectrum for compounds C1 to C4.

C1:

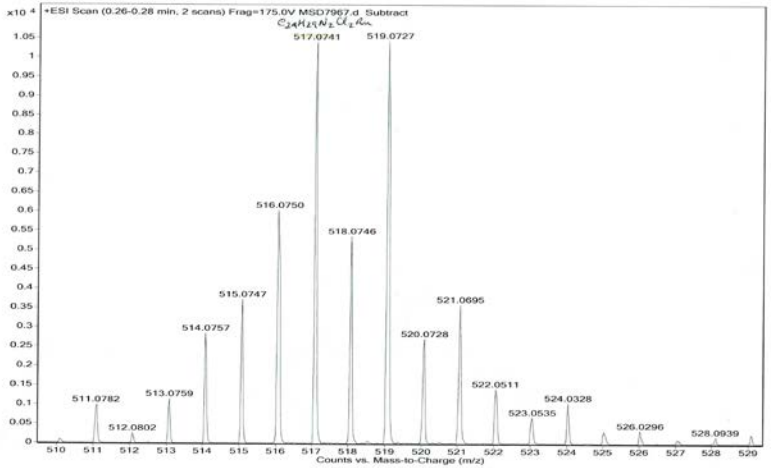


Sample Name	EM9380	**Position**	P1-B1	**Instrument Name**	LC MSD TOF	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	MSD7967.d	**ACQ Method**	ESIpos.m	**Comment**	AMS 2602 C1 (J.Granell)	**Acquired Time**	3/11/2020 2:16:35 PM

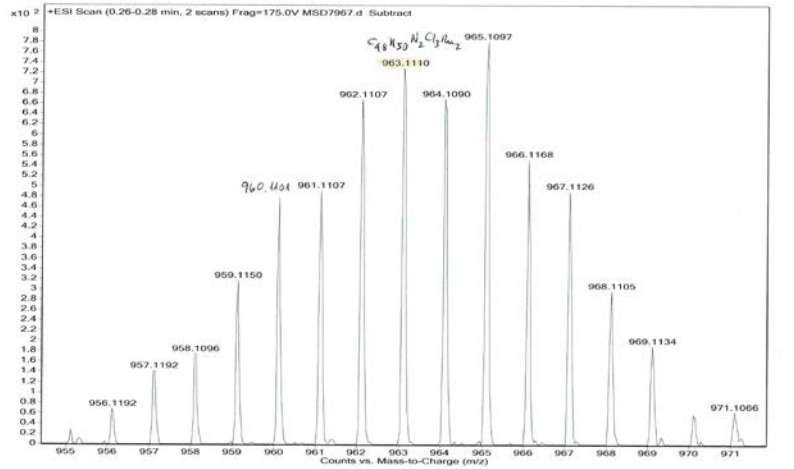


Solapados señales $[M+H]^+$ + $[M-Cl+CH_3CN]^+$

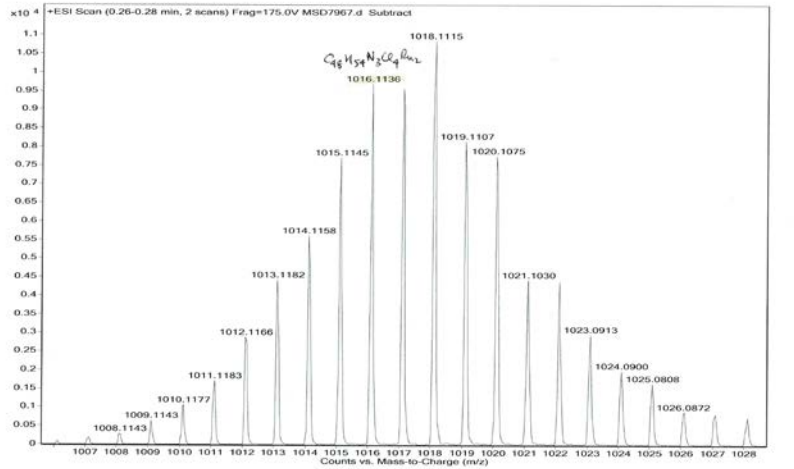
Sample Name	EM9380	**Position**	P1-B1	**Instrument Name**	LC MSD TOF	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	MSD7967.d	**ACQ Method**	ESIpos.m	**Comment**	AMS 2602 C1 (J.Granell)	**Acquired Time**	3/11/2020 2:16:35 PM



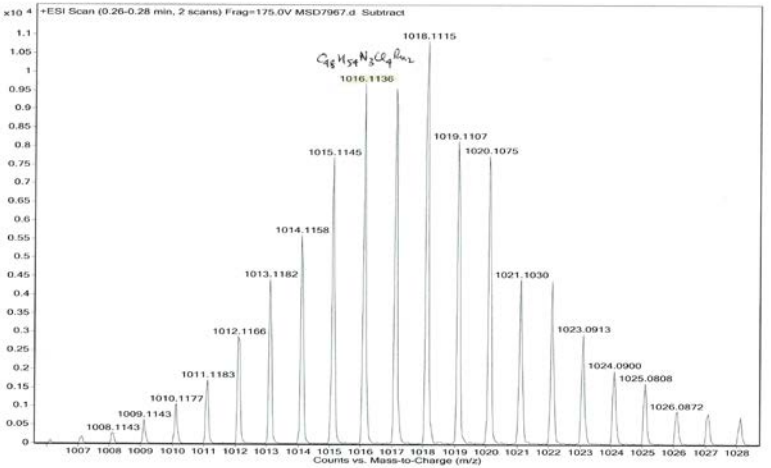
Sample Name	EM9380	**Position**	P1-B1	**Instrument Name**	LC MSD TOF	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	MSD7967.d	**ACQ Method**	ESIpos.m	**Comment**	AMS 2602 C1 (J.Granell)	**Acquired Time**	3/11/2020 2:16:35 PM



Sample Name	EM9380	**Position**	P1-B1	**Instrument Name**	LC MSD TOF	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	MSD7967.d	**ACQ Method**	ESIpos.m	**Comment**	AMS 2602 C1 (J.Granell)	**Acquired Time**	3/11/2020 2:16:35 PM

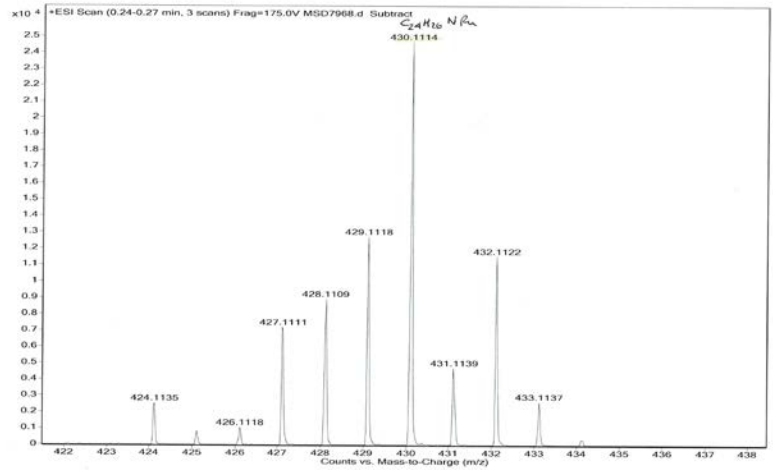


Sample Name	EM9380	**Position**	P1-B1	**Instrument Name**	LC MSD TOF	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	MSD7967.d	**ACQ Method**	ESIpos.m	**Comment**	AMS 2602 C1 (J.Granell)	**Acquired Time**	3/11/2020 2:16:35 PM

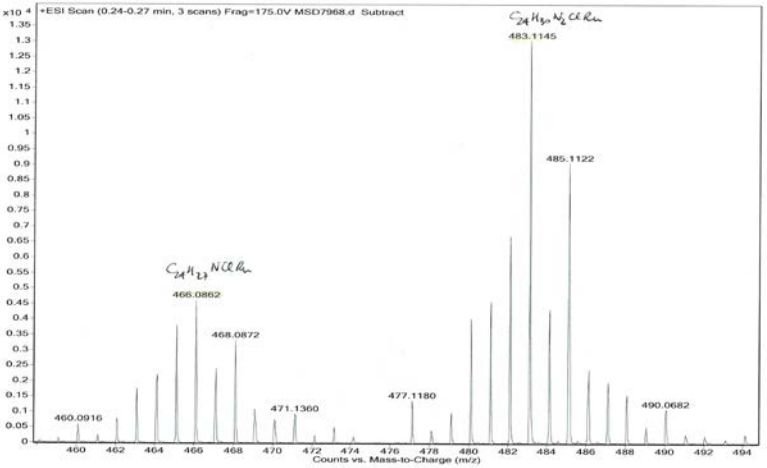


C2:

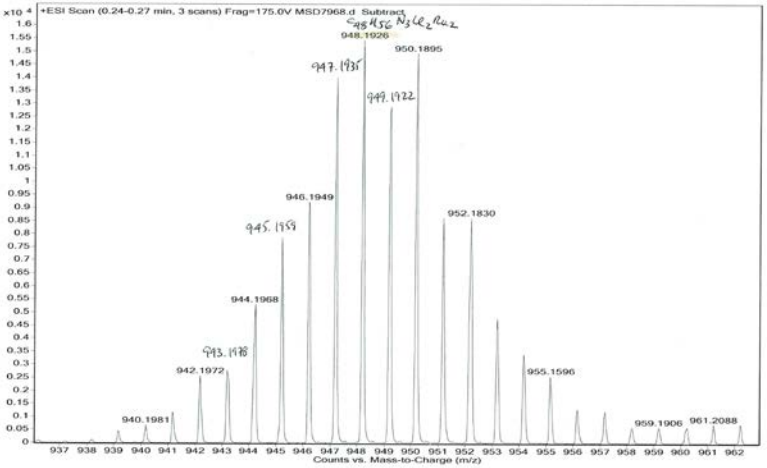
Sample Name	EM9381	**Position**	P1-B2	**Instrument Name**	LC MSD TOF	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	MSD7968.d	**ACQ Method**	ESIpos.m	**Comment**	AMS 0603 C2 (J.Granell)	**Acquired Time**	3/11/2020 2:40:52 PM



Sample Name	EM9381	**Position**	P1-B2	**Instrument Name**	LC MSD TOF	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	MSD7968.d	**ACQ Method**	ESIpos.m	**Comment**	AMS 0603 C2 (J.Granell)	**Acquired Time**	3/11/2020 2:40:52 PM

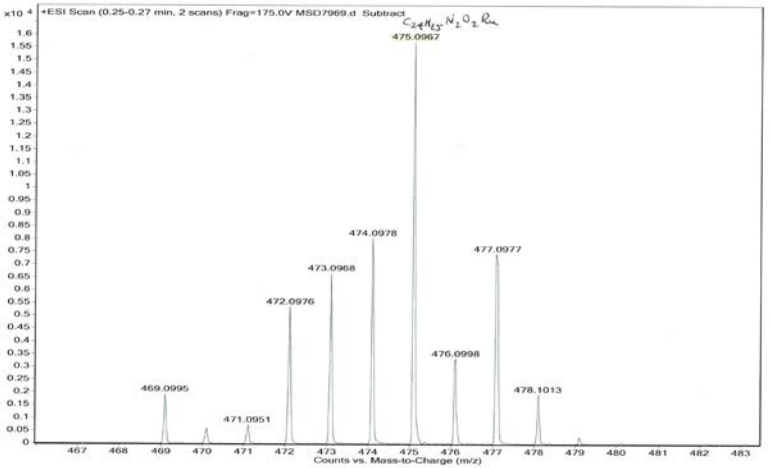


Sample Name	EM9381	**Position**	P1-B2	**Instrument Name**	LC MSD TOF	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	MSD7968.d	**ACQ Method**	ESIpos.m	**Comment**	AMS 0603 C2 (J.Granell)	**Acquired Time**	3/11/2020 2:40:52 PM

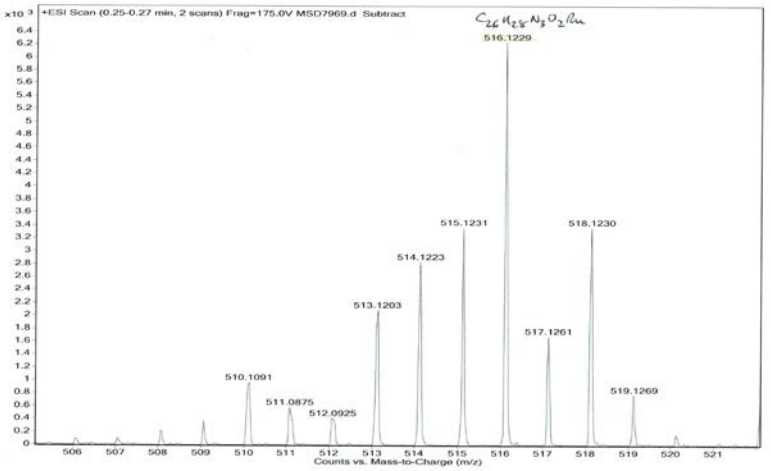


C3:

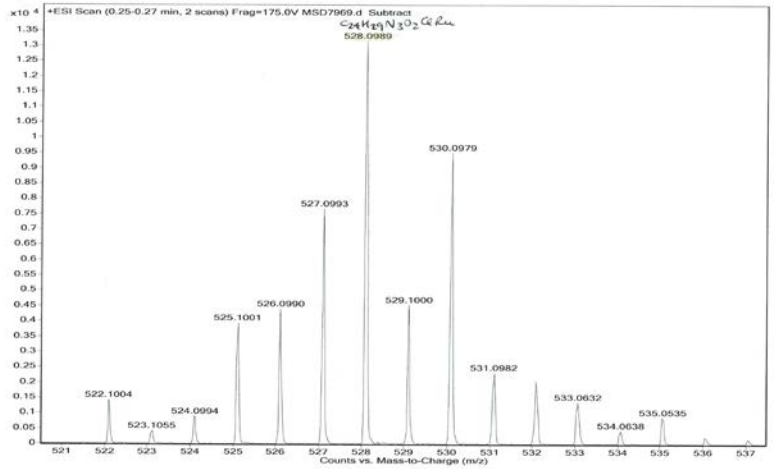
Sample Name	EM9382	**Position**	P1-B3	**Instrument Name**	LC MSD TOF	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	MSD7969.d	**ACQ Method**	ESIpos.m	**Comment**	AMS 0403 C3 (J.Granell)	**Acquired Time**	3/11/2020 2:51:08 PM



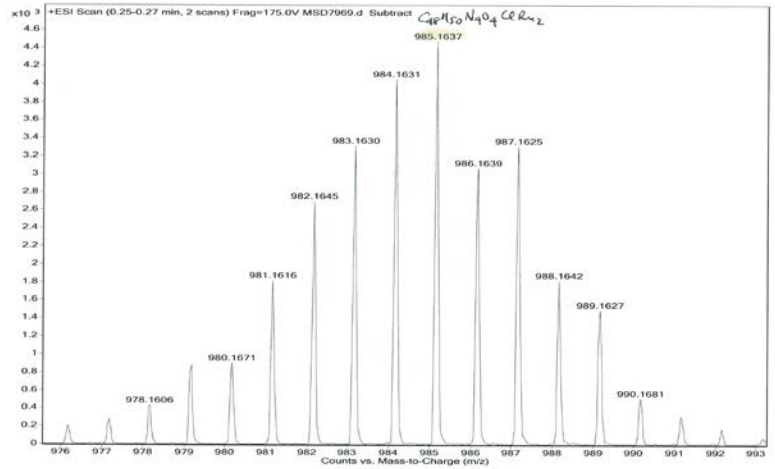
Sample Name	EM9382	**Position**	P1-B3	**Instrument Name**	LC MSD TOF	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	MSD7969.d	**ACQ Method**	ESIpos.m	**Comment**	AMS 0403 C3 (J.Granell)	**Acquired Time**	3/11/2020 2:51:08 PM



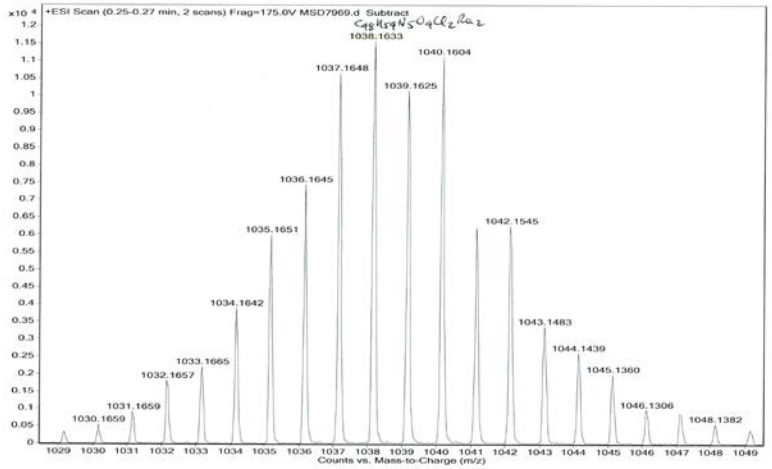
Sample Name	EM9382	**Position**	P1-B3	**Instrument Name**	LC MSD TOF	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	MSD7969.d	**ACQ Method**	ESIpos.m	**Comment**	AMS 0403 C3 (J.Granell)	**Acquired Time**	3/11/2020 2:51:08 PM



Sample Name	EM9382	**Position**	P1-B3	**Instrument Name**	LC MSD TOF	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	MSD7969.d	**ACQ Method**	ESIpos.m	**Comment**	AMS 0403 C3 (J.Granell)	**Acquired Time**	3/11/2020 2:51:08 PM

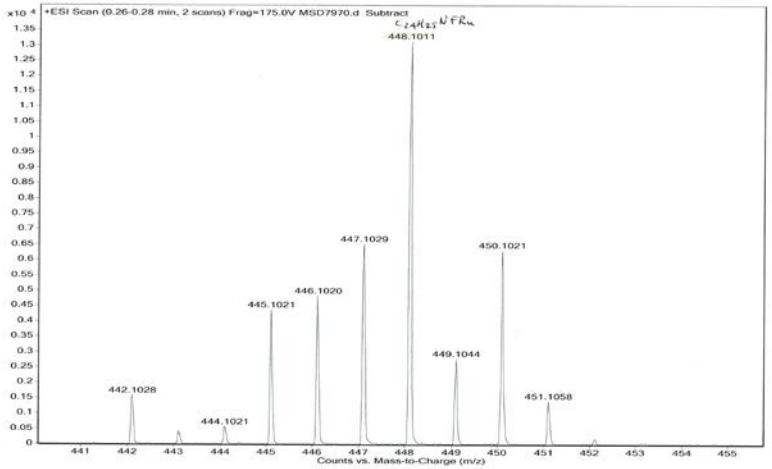


Sample Name	EM9382	**Position**	P1-B3	**Instrument Name**	LC MSD TOF	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	MSD7969.d	**ACQ Method**	ESIpos.m	**Comment**	AMS 0403 C3 (J.Granell)	**Acquired Time**	3/11/2020 2:51:08 PM

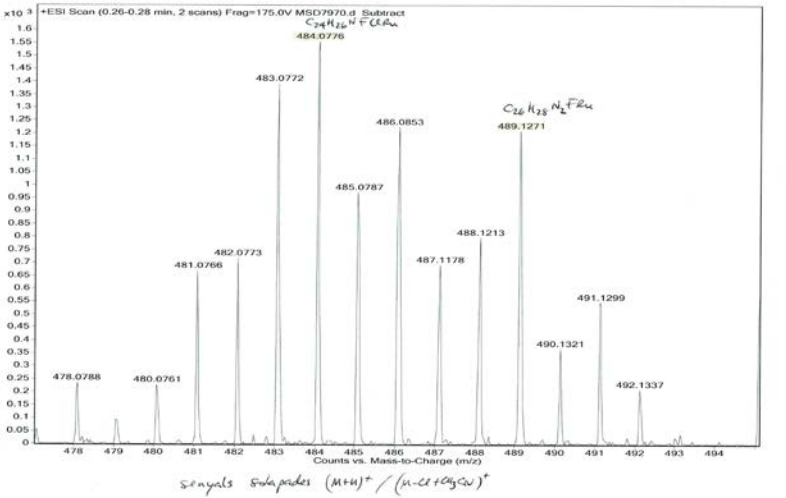


C4:

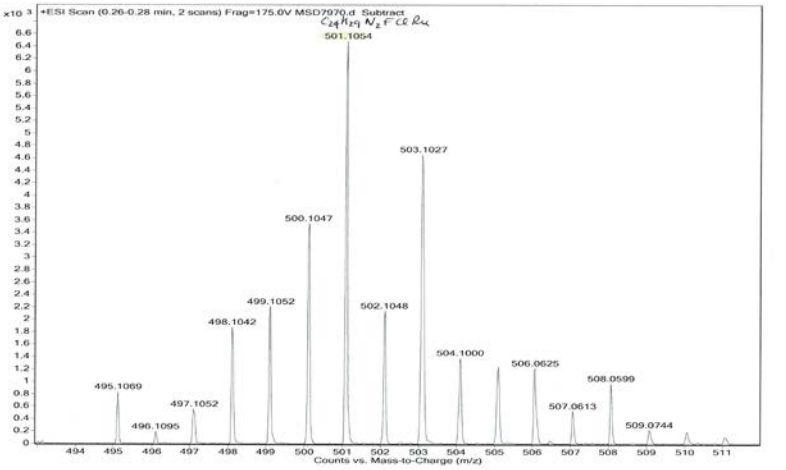
Sample Name	EM9383	**Position**	P1-B4	**Instrument Name**	LC MSD TOF	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	MSD7970.d	**ACQ Method**	ESIpos.m	**Comment**	AMS 0903 C4 (J.Granell)	**Acquired Time**	3/11/2020 3:02:14 PM



Sample Name	EM9383	**Position**	P1-B4	**Instrument Name**	LC MSD TOF	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	MSD7970.d	**ACQ Method**	ESIpos.m	**Comment**	AMS 0903 C4 (J.Granell)	**Acquired Time**	3/11/2020 3:02:14 PM



Sample Name	EM9383	**Position**	P1-B4	**Instrument Name**	LC MSD TOF	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	MSD7970.d	**ACQ Method**	ESIpos.m	**Comment**	AMS 0903 C4 (J.Granell)	**Acquired Time**	3/11/2020 3:02:14 PM



Sample Name	EM9383	**Position**	P1-B4	**Instrument Name**	LC MSD TOF	**User Name**	
Inj Vol	0.2	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	MSD7970.d	**ACQ Method**	ESIpos.m	**Comment**	AMS 0903 C4 (J.Granell)	**Acquired Time**	3/11/2020 3:02:14 PM