Tutora

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Treball Final de Grau

Cyclometallated platinum compounds with optically active ligands.
Compostos cicloplatinats amb lligands òpticament actius.

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B:KC Barcelona Knowledge Campus
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Emocionante y divertido.

Anònim

Primer de tot, agrair a la Dra. Margarita Crespo per tota l'ajuda, la paciència i dedicació durant la realització d'aquest treball que ha durat tant i que ha estat realitzat en unes condicions tan especials. Per altra banda, també m'agradaria agrair a l'Ari per utilitzar part del seu temps en ajudar-me sempre que ho he necessitat, a més del bon ambient que hi ha tant a dins com a fora del laboratori conjuntament amb l'Andrea, l'Araceli, en Fran, i la Rosa. Finalment també m'agradaria agrair el suport per part de la meva família i els meus amics. Gràcies a tots vosaltres ha sigut possible la realització d'aquest treball.

REPORT

CONTENTS

1. SUMMARY

In this work, the synthesis of several platinum (II) cyclometallated compounds with bidentate ligands type [C,N] has been reported.

In order to carry out this synthesis, compound $K_2[PtCl_4]$ has been used to prepare the metal agent (**1a**) used in all cyclometallation reactions. One amine (**2a**) and three different imines (**2b-2c**), previously synthesized from amine **2a** and the corresponding aldehyde, have been used as ligands.

These ligands have been reacted with compound **1a** in toluene or in methanol to inquire which of these solvents is more optimal for the cyclometallation, thus obtaining cyclometallated compounds (**3a-3d**). The expected isomer for this synthesis is the *endo* configuration but depending on the solvent and the imine used different isomers such as *exo* configuration or even cyclometallated compounds with metallacycles containing more than five members might be obtained.

The latter were subsequently reacted with triphenylphosphane to form the corresponding derivatives (**4a-4d**) where the number of isomers has been reduced due to the stability given to the compound by triphenylphosphane.

The nature of the synthesised compounds has been studied by proton nuclear magnetic resonance spectroscopy and for some compounds also by mass spectrometry.

Keywords: Cyclometallated compounds, platinum, bidentate ligands, nuclear magnetic resonance spectroscopy, mass spectrometry, synthesis.

2. RESUM

En aquest treball s'ha dut a terme la síntesi de diversos compostos ciclometal·lats de platí(II) amb lligands bidentats de tipus [C,N].

Per tal de dur a terme aquesta síntesi, s'ha utilitzat el compost $K_2[PtCl_4]$ per a formar l'agent metal·lant (**1a**) utilitzat en totes les reaccions de ciclometal·lació. Com a lligands s'han utilitzat una amina (**2a**) i tres imines diferents (**2b**-**2d**) preparades a partir de l'amina **2a** i l'aldehid corresponent.

Aquests lligands s'han fet reaccionar amb el compost **1a** en toluè i en metanol per tal de distingir quin d'aquests dissolvents és més òptim per a la ciclometal·lació, obtenint així els compostos ciclometal·lats (**3a**-**3d**). L'isòmer esperat per a aquesta síntesi és la configuració *endo*, però segons el dissolvent i la imina utilitzats es poden obtenir diferents isòmers com la configuració *exo* o anells de més de 5 àtoms.

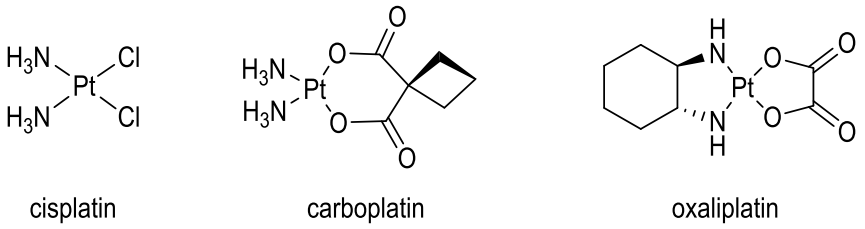
Posteriorment, aquests últims s'han fet reaccionar amb trifenilfosfana formant els corresponents derivats (**4a**-**4d**) on la quantitat d'isòmers s'ha vist reduïda per l'estabilitat que la trifenilfosfana dona al compost.

S'ha comprovat la naturalesa dels compostos formats mitjançant espectroscòpia de ressonància magnètica nuclear de protó i alguns compostos també s'han estudiat per espectrometria de masses.

Paraules clau: Compostos ciclometal·lats, platí, lligands bidentats, espectroscòpia de ressonància magnètica nuclear, espectrometria de masses, síntesi.

3. INTRODUCTION

In the 1960s, a new platinum(II) compound with anticancer properties was discovered, cisplatin.[1] Cisplatin is useful for the treatment of testicular cancer, among others.[2] Other compounds that are usually used for clinical application are carboplatin and oxaliplatin.[1–3] These compounds kill cancer cells by cross-linking DNA and inhibiting transcription. When one of these compounds enters a cell it loses one or both chloride ligands, forming an aqua-complex that is very electrophilic. This complex can react easily with the purine bases of nucleic acids, which are strongly nucleophilic. The reaction of the complex with the purine base forms a Pt-adduct that is capable of distorting and bending the DNA structure.[2,3] However, it induces some toxic side effects such as nephrotoxicity, neurotoxicity and, sometimes, it can induce a resistance against the anticancer effect under a long-term treatment due to the toxic nature of platinum.[4–6]



cisplatin carboplatin oxaliplatin

Figure 1. Chemical structure of clinically approved platinum antitumor complexes.

These kind of potential anticancer compounds need to have some different types of ligands in their own structure to achieve their function. First, ligands L are non-leaving groups, which are generally nitrogen donors. Their function is to be retained in the final platinum-DNA adduct. Secondly, ligands X are leaving groups. They are lost when the complex enters the cell to allow coordination to DNA. Finally, ligands R, which are only present in the axial position of platinum (IV) compounds, can modulate the properties of this compounds.[2,6,7]

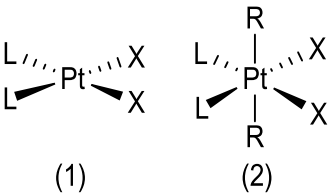


Figure 2. General structure of platinum(II) (1) or platinum(IV) (2) anticancer complexes.

Cyclometallated compounds have also been studied as potential anticancer agents, where the cyclometallated moiety will be retained as indicated above for ligands L. These platinum cyclometallated compounds contain a σ(C-Pt) bond, which increases the stability of the complex, thus being able to reach the cell without modifications in their structure and behaviour.[7,8] In the preparation of cyclometallated compounds it is common to use a [C,N] bidentate ligand as a non-leaving group (L). These are of great interest and the most studied ones, but also some others compounds with [C,N,N'] or [N,C,N] tridentate ligands exist, whose stability is increased due to the presence of another N-donor atom.[7–9]

3.1. MECHANISMS OF THE CYCLOMETALLATION

The cyclometallation reaction can be described in two consecutive steps; i) coordination of the ligand to the metal, ii) intramolecular activation of one *ortho* C-H bond.

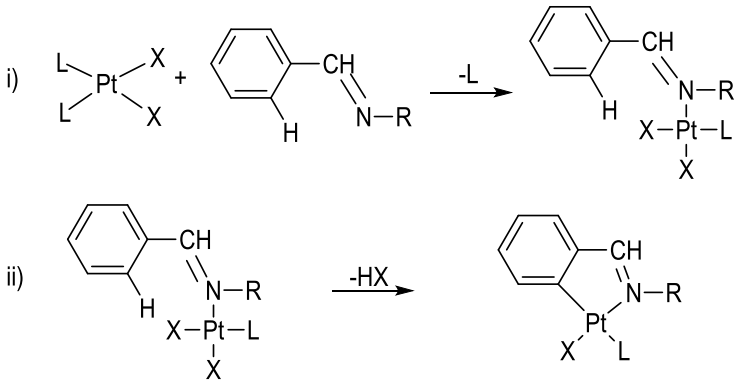


Figure 3. Electrophilic substitution mechanism for C-H activation.

The second step can happen through two different mechanisms: 1) oxidative addition, where the oxidation of platinum(II) to platinum(IV) is followed by an immediate reductive elimination to the initial oxidation state 2) electrophilic substitution, where an aromatic carbon goes through an electrophilic aromatic substitution of the H for a platinum atom, forming a C-Pt bond. The presence of a base is necessary for the elimination of the aromatic protons.[2,7] The latter is the mechanism taking place in the reactions studied in this work.

3.2. ISOMERISM STUDY

This project is focused on finding procedures that allow the synthesis of new cyclometallated platinum(II) compounds that contain imine ligands and are potentially useful for anticancer therapy. The most widely studied examples are platinum(II) compounds where C-H activation takes places at phenyl *ortho* positions to produce five-membered cyclometallated compounds. It is possible that, occasionally, a six-membered cyclometallated or even a seven-membered cyclometallated compound in the case of a toluene insertion are produced, but these results are uncommon. The most stable compounds are the five-membered metallacycles.[10]

Within five-member metallacycles, several isomers such as *endo-*/*exo-* exist. When the metallacycles contain the C=N moiety it is called as *endo-* and when it does not contain the C=N moiety it is called as *exo-*. In addition, switching the X and Y ligands that act as a leaving group gives rise to configurational isomers. It is known that for several cycloplatinated compounds the *endo-* isomer is more stable than the *exo-*.[11–13]

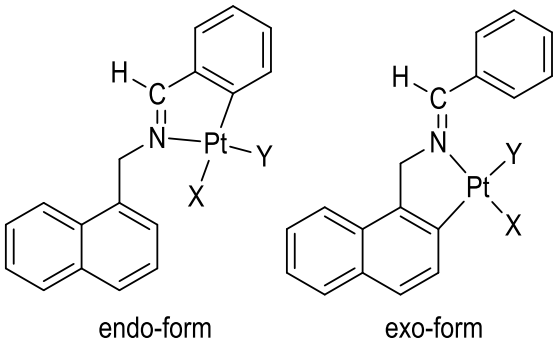


Figure 4. *Endo-* and *exo-* isomers, X = Y = Cl, $SOMe_2$.

In addition, when the exo isomer is obtained, the imine ligand can be present in either *Z* or *E* configuration. It depends on the position of the aromatic cycle attached to the C=N bond regarding the platinum atom.

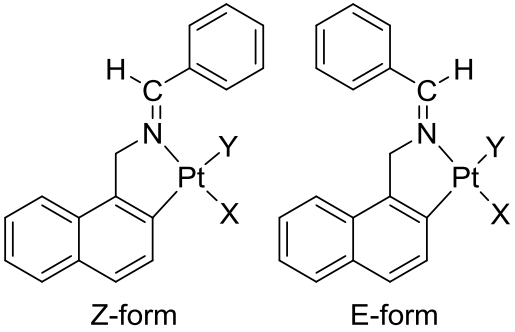


Figure 5. *Cis*- (Z) and trans- (E) isomers, X = Y = Cl, $SOMe_2$

Since several cyclometallated platinum(II) compounds derived from optically active amines were found to be effective against several cancer cell lines, this work was carried out with the aim of exploring the possibility to expand this family of potential antitumor agents.[3] The reaction of each compound with a platinum substrate was carried out following two different procedures by using as a reaction solvent toluene or methanol.

4. OBJECTIVES

The aims of this work are:

- The synthesis of new cyclometallated platinum(II) compounds containing a bidentate [C,N] ligand:
  $[PtCl\{NH_2CH(CH_3)C_{10}H_6\}\{SOMe_2\}]$ (**3a**)
  $[PtCl\{(4\text{-}ClC_6H_3)CHNCH(CH_3)C_{10}H_7\}\{SOMe_2\}]$ (**3b**)
  $[PtCl\{(2,6\text{-}Cl_2C_6H_3)CHNCH(CH_3)C_{10}H_6\}\{SOMe_2\}]$ (**3c**)
  $[PtCl\{(C_{10}H_6)CH(CH_3)NCHC_{10}H_7\}\{SOMe_2\}]$ (**3d**)
- The study of the obtained isomers for all the compounds synthesized depending on the solvent used in the cyclometallation reaction.
- The study of the reactivity of the obtained cyclometallated compounds in front of triphenylphosphane ligand.
- The characterization of the new cyclometallated platinum(II) compounds by mass spectrometry and nuclear magnetic resonance spectroscopy.
- The comparison of the obtained results to determine which solvent is the most favorable in each case.

5. RESULTS AND DISCUSSION

Due to the multiple possible isomers that can be obtained as result of the performed reactions, they were tagged following the table below.

Type of compound	Number according to the type of compound	Letter to list the compounds	*Endo*- (A) or *exo*- (B)	*Cis*- (Z) or *trans*- (E) in ligand or in *exo*- isomers
Metal agent	1	a	-	-
Ligand	2	a, b, c, d	-	Z/E
Cycloplatinated compounds	3	a, b, c, d	A/B	Z/E
Phosphane derivates	4	a, b, c, d	A/B	Z/E

Table 1. Scheme for tagging compounds.

5.1. SYNTHESIS OF STARTING MATERIALS

5.1.1. Synthesis of platinum (II) precursor

Cis-$[PtCl_2\{SO(Me)_2\}_2]$ (**1a**) was synthesized following the method reported in the literature.[14] $K_2[PtCl_4]$ is commonly used as an initial reagent for the synthesis of **1a.**[15] The reaction of several neutral ligands L with **1a** gives the platinum(II) compounds $[PtCl_2L_2]$. In this project only DMSO ($SOMe_2$) was used as ligand L. The obtained cis-$[PtCl_2\{SO(Me)_2\}_2]$ was used as a metallating agent to prepare compounds **3a**, **3b**, **3c** and **3d**. Compound **1a** was characterized by ^{1}H-NMR spectroscopy and compared to that previously reported in the literature.[14]

$$K_2[PtCl_4] + 2\ SO(Me)_2 \xrightarrow{(1)} \text{cis-}[PtCl_2\{SO(Me)_2\}_2] + 2\ KCl$$

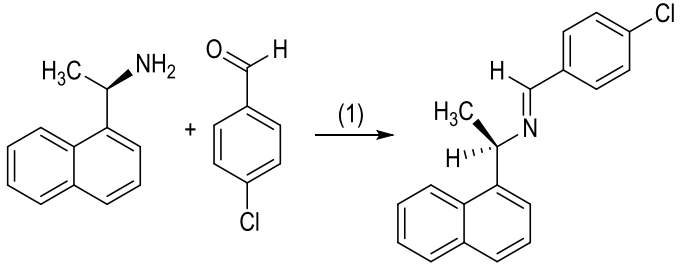
Figure 6. Synthesis of the metalling agent cis-$[PtCl_2\{SO(Me)_2\}_2]$:

(1) water, 3 h, r.t..

5.2. SYNTHESIS OF IMINES

5.2.1. Synthesis of (4-ClC_6H_4)CHNCH(CH_3)$C_{10}H_7$ (2b)

The synthesis of (R)-1-(4-chlorophenyl)-*N*-(1-(naphthalen-1-yl)ethyl)methanimine (**2b**) was carried out following the method reported in the literature.[13,16] This ligand was synthesized from R-(+)-1-(1-naphtyl) ethyl)amine (**2a**) and 4-chlorobenzaldehyde in refluxing ethanol for 2 hours. Compound **2b** was characterized by ^{1}H-NMR spectroscopy. The sharpness of the ^{1}H-NMR spectroscopy allowed to assume that only the more stable isomer of the imine was obtained, which displays an *E*- configuration around the C=N bond.[15] It could be observed the appearance of the characteristic iminic peak which proves its correct synthesis. It could also be clearly observed a quadruplet from CH(CH_3) due to coupling with the CH_3 group which appears as a doublet, which is in concordance with previously reported data.[12]



2a **2b**

Figure 7. Synthesis of imine **2b**: (1) ethanol, refluxing 3h.

5.2.2. Synthesis of (2,6-$Cl_2C_6H_3$)CHNCH(CH_3)$C_{10}H_7$ (2c)

The synthesis of (R)-1-(2,6-dichlorophenyl)-*N*-(1-(napthalen-1-yl)ethyl)methanimine (**2c**) was carried out following the literature.[13,17] This ligand was synthesized from amine **2a** and 2,6-dichlorobenzaldehyde in refluxing ethanol for 2 hours. Characterisation by ^{1}H-NMR spectroscopy resulted in concordance with the literature.[17] Imine **2c** was obtained as a single isomer, for which the most stable is *E*-configuration around the C=N bond. As in imine **2b** it could be observed the same characteristic peaks of the iminic proton and the CH(CH_3) quadruplet.

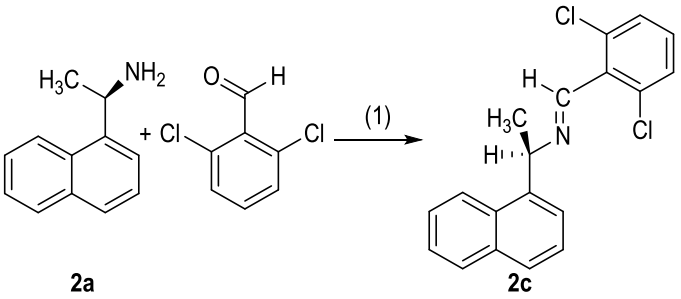


Figure 8. Synthesis of imine **2c**: (1) ethanol, refluxing 3h.

5.2.3. Synthesis of $(C_{10}H_7)CHNCH(CH_3)C_{10}H_7$ (2d)

The synthesis of (R)-1-(napthalen-1-yl)-*N*-(1-(napthalen-1-yl)ethyl)methanimine (**2d**) has been previously reported and it was carried out following the literature.[13] This ligand was synthesized from **2a** and 1-naphtaldehyde in refluxing ethanol for 2 hours. Compound **2d** was characterized by ^{1}H-NMR spectroscopy and compared with the literature.[13] It was obtained as the most stable isomer with an *E*-configuration around the iminic bond. As well as for imines **2b** and **2c** it could be observed the same characteristic peaks for the iminic proton and the $CH(CH_3)$ quadruplet.

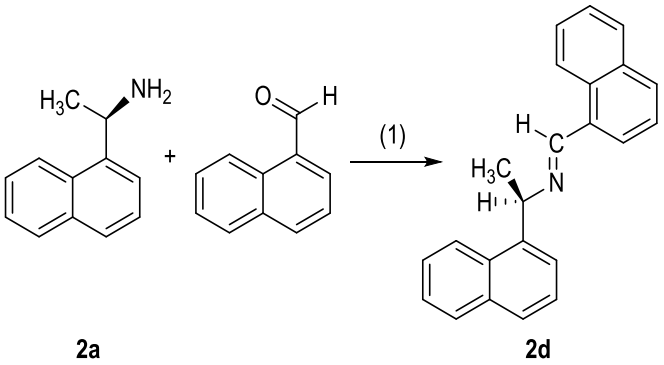


Figure 9. Synthesis of imine **2d**: (1) ethanol, refluxing 3h.

5.3. SYNTHESIS OF CYCLOPLATINATED COMPOUNDS

5.3.1. Synthesis of [PtCl{$NH_2CH(CH_3)C_{10}H_6$}{$SOMe_2$}] (3a)

The synthesis of compound **3a** has been previously reported.[16] For the study of the reaction of amine **2a**, compound **1a** and sodium acetate two different procedures were used. Toluene with a small amount of methanol at 90 ºC was used as a solvent in one procedure (1) and only methanol at 65 ºC was used in the other (2). Then, the first procedure was performed over the boiling point for the small amount of methanol but not at enough temperature for the reflux of toluene, as the metal agent **1a** may be reduced to metallic platinum at temperatures above 90ºC. Even so, quite platinum precipitated due to its reduction. Compound **3a** was characterized by ^{1}H-NMR spectroscopy and compared with that previously reported in the literature.[16]

(1): It could be observed the characteristic peaks of the $CH(CH_3)$ quadruplet, in addition to the extra peaks of $SOMe_2$ with Pt satellites.

(2): It could be observed approximately the same ^{1}H-NMR spectra as in procedure (1).

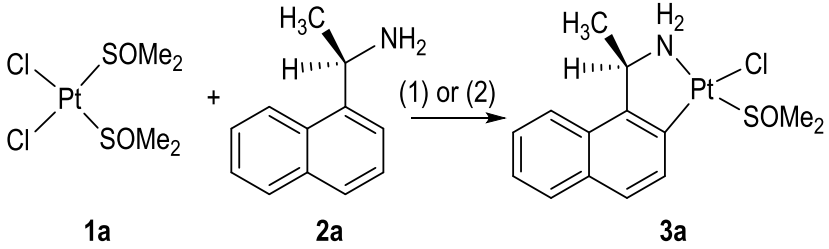


Figure 10. Synthesis of compound **3a**:
(1) toluene/MeOH, CH_3COONa , 48h, 90 ºC.
(2) MeOH, CH_3COONa, 48h, 65 ºC.

5.3.2. Synthesis of [PtCl{(4-ClC_6H_3)$CHNCH(CH_3)C_{10}H_7$}{$SOMe_2$}] (3b)

For the synthesis of cyclometallated compound **3b** the metal agent **1a**, the ligand **2b**, and sodium acetate were used. To try to avoid the platinum reduction, the temperature in the first procedure was decreased to 85 ºC, while the other conditions remained unchanged. Compound **3b** was characterised by ^{1}H-NMR spectroscopy and mass spectrometry.

(1): It could be observed a mixture of compounds even though, as previously said, the most stable isomer for cyclometallated compounds is the *endo*- form (**3bA**).[11–13] Firstly, the characteristic peak of an aldehyde at approximately 10 ppm at the ^{1}H-NMR spectra was observed. It was confirmed by mass spectrometry, where it showed clearly a peak with the exact mass of **2b**. This is due to the hydrolysis of imine to aldehyde and resulting to the synthesis of **3a** instead. The ^{1}H-NMR spectra of **3b** was compared with **3a** and observed approximately the same spectra in addition to the aldehyde protons.

The synthesis was repeated in freshly distilled toluene. Thanks to the spectrum results and compared with the literature it was determined that the major compound was the *endo*- isomer, (**3bA**). This is due to the presence of two signals in the 6.99-6.89 ppm range that can be assigned to (H^i) and ($H^{i'}$) coupling in an A-B system. The signal of ($H^{i'}$) corresponds to a doublet of doublet as it is coupled with the iminic proton (H^h) in cis position, while (H^i) displays only a doublet.

(2): It was also observed the hydrolysis of imine to aldehyde in this procedure. It appeared the characteristic peak of the aldehyde at approximately 10 ppm at the ^{1}H-NMR spectra. It was also confirmed by mass spectrometry, where it showed clearly the mass of **2b**. The ^{1}H-NMR spectra confirmed the hydrolysis by comparison with **3a**. The synthesis was repeated, and it was observed that the compound was hydrolysed again.

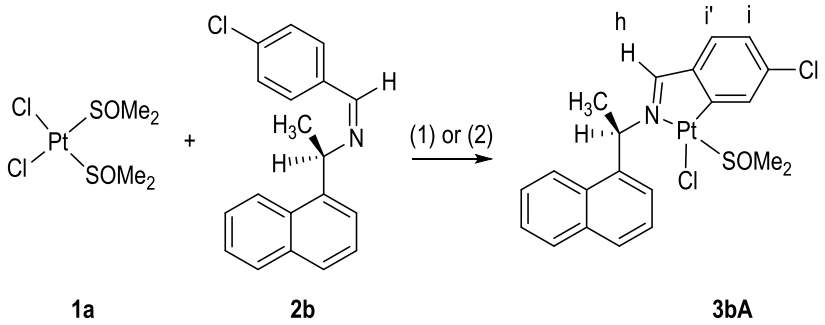


Figure 11. Synthesis of compound **3b**:
(1) toluene with MeOH, CH_3COONa, 48h, 85 ºC.
(2) MeOH, CH_3COONa, 48h, 65 ºC.

To check if the hydrolysis is due to the presence of platinum or to the solvents, a blank experiment was performed. Imine **2b** was kept stirring in the same reaction conditions without adding the metal agent. Then the imine was characterized by ^{1}H-NMR spectroscopy and it was observed that it had not hydrolysed. So, it was determined that the solvent was not the problem, but it is the coordination of the imine ligand to platinum which facilitates the hydrolysis with adventitious water contained in the solvent.

5.3.3. Synthesis of [PtCl{(2,6-$Cl_2C_6H_3$)CHNCH(CH_3)$C_{10}H_6$}{$SOMe_2$}] (3c)

For the synthesis of cyclometallated compound **3c**, compound **1a**, ligand **2c** and sodium acetate were used. In this reaction, the same conditions as for compound **3b** were used in both procedures. Compound **3c** was characterized by ^{1}H-NMR spectroscopy and mass spectrometry. For this five-membered cyclometallated compound only the *exo*- isomer (**3cBE**) can be synthetized because it is impossible to obtain the *endo*- form due to both *ortho*- positions being occupied by chloride atoms.

(1): It could be observed a mixture of compounds due to the large number of signals appearing in the ^{1}H-NMR spectrum. Thanks to the mass spectrum it could be determined that a toluene insertion had happened, thus synthesizing, along with other compounds including **3cBE**, a seven-member cyclometallated compound which includes the *endo*- form (**3cA'**), that is more stable.[11–13]

(2): Compound **3cBE** was characterized by ^{1}H-NMR spectroscopy. It could be observed the characteristic iminic peak with satellites due to the coupling with platinum, which proves the correct synthesis of this compound. It could also be clearly observed a quadruplet from CH(CH_3) due to coupling with the CH_3 group which appears as a doublet. It was compared with those compounds previously reported in the literature.[17]

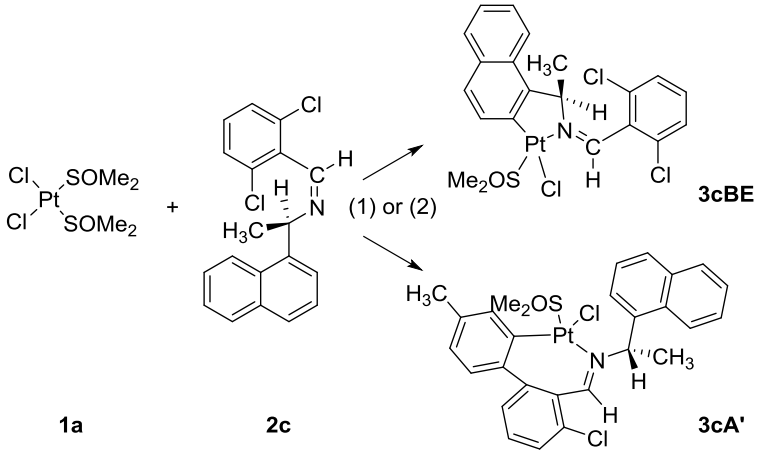


Figure 12. Synthesis of compounds **3c**:
(1) toluene with MeOH, CH_3COONa, 48h, 85 ºC.
(2) MeOH, CH_3COONa, 48h, 65 ºC.

5.3.4. Synthesis of [PtCl{($C_{10}H_6$)CH(CH_3)NCH$C_{10}H_7$}{$SOMe_2$}] (3d)

For the synthesis of cyclometallated compound **3d** compound **1a**, ligand **2d** and sodium acetate were used. To try to avoid the hydrolysis of the imine, dry freshly distilled toluene was used. All the other conditions were the same for both procedures as previously described. Compound **3d** was characterized by ^{1}H-NMR spectroscopy and mass spectrometry and compared with literature[13]. To try to understand the ^{1}H-NMR spectra of (1) it was necessary to determine first the (2) ^{1}H-NMR spectra.

(2): A mixture of compounds could be observed, where the two major compounds had a ratio of 3:1 (**3dBZ**:**3dBE**). It was possible to determine the nature of these compounds thanks to the ^{1}H-NMR spectra, where the coupling constants of the iminic satellites by coupling with platinum were approximately 50 ppm. That means the two major compounds are the *exo*-isomers. The range where the iminic proton appears in the ^{1}H-NMR spectra was useful to identify which *exo*- isomer was the more abundant. It is known that in the *trans*- isomer, the iminic proton is much more downfield-shifted and it can appear in the 10 ppm range. Meanwhile, the iminic proton of the *cis*- isomer is upfield-shifted. It can even appear in the aromatic zone overlapping other protons but identifiable by its characteristic satellite peaks from coupling with platinum.[12]

(1): It was a mixture of compounds. It was observed a major compound that matches with the minor compound of (2) comparing the ^{1}H-NMR spectra. It is known that the most stable isomer should be formed at the highest temperature. So, it was possible to determine that the major compound in this procedure was (**3dBE**).

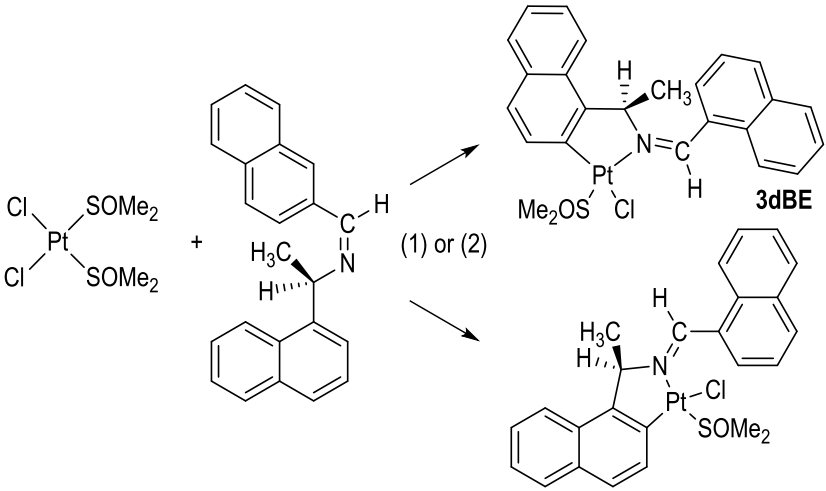


Figure 13. Synthesis of compound **3d** major isomers:
(1) toluene with MeOH, CH_3COONa, 48h, 85 ºC.
(2) MeOH, CH_3COONa, 48h, 65 ºC.

5.4. SYNTHESIS OF TRIPHENYLPHOSPHANE DERIVATIVES

5.4.1. Synthesis of [PtCl{$NH_2CH(CH_3)C_{10}H_6$}{PPh_3}] (4a)

For the synthesis of [PtCl{$NH_2CH(CH_3)C_{10}H_6$}{PPh_3}] (**4a**) the cyclometallated compound **3a** and triphenylphosphane were reacted in acetone for 2 hours at room temperature. Compound **4a** was characterized by ^{1}H-NMR and ^{31}P-NMR spectroscopy and mass spectrometry and compared with the literature.[18,19] Thanks to the ^{1}H-NMR it could be observed the characteristic quadruplet peak of $CH(CH_3)$. It could be observed too that the $SOMe_2$ had disappeared and a lot of signals in the aromatic zone that belong to the protons form triphenylphosphane appeared. Thanks to the mass spectrum it could be determined that the aimed compound was synthesized.

An assay was done with an excess of triphenylphosphane and the expected product [Pt{$NH_2CH(CH_3)C_{10}H_6$}{PPh_3}$_2$]Cl (**4a'**) was characterized by ^{1}H-NMR and ^{31}P-NMR

spectroscopy and mass spectrometry. Although the ^{1}H-NMR it was not useful due to the low quality of the spectra it could be determined that two triphenylphosphane molecules instead of one had reacted thanks to the ^{31}P-NMR spectrum. It is known that the phosphorus in *trans*-position to the N-donor has a coupling constant of approximately 4000 Hz and the one in *cis*-position has a coupling constant of approximately 2000 Hz.[16,18,19]

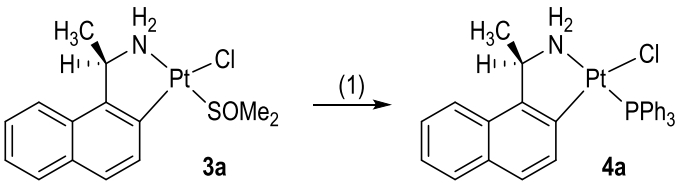


Figure 14. Synthesis of compound **4a**:
(1) PPh_3, acetone, 2h, r.t.

5.4.2. Synthesis of [PtCl{(4-ClC$_6$H$_3$)CHNCH(CH$_3$)C$_{10}$H$_7$}{PPh$_3$}] (4b)

For the synthesis of [PtCl{(4-ClC$_6$H$_3$)CHNCH(CH$_3$)C$_{10}$H$_7$}{PPh$_3$}] (4b) the cyclometallated compound 3b and triphenylphosphane were reacted in acetone for 2 hours at room temperature. Compound 4b was characterized by ^{1}H-NMR and ^{31}P-NMR spectroscopy and mass spectrometry and compared with the literature.[18,19] Only ^{31}P-NMR was useful to determine the compound, where it could be observed a minor compound (**4b**) at 23.20 ppm and a major compound at 14.29 ppm identified as [PtCl$_2$(PPh$_3$)$_2$].[18] The de-coordination of the cyclometallated ligand explains the complexity of the ^{1}H-NMR spectrum and the impossibility to assign peaks in the mass spectra.

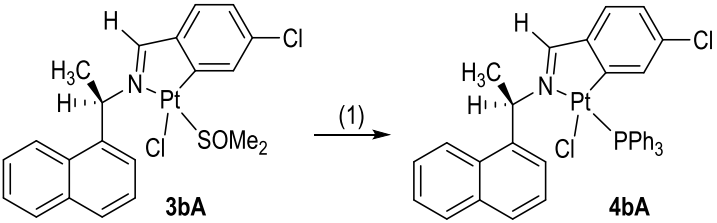
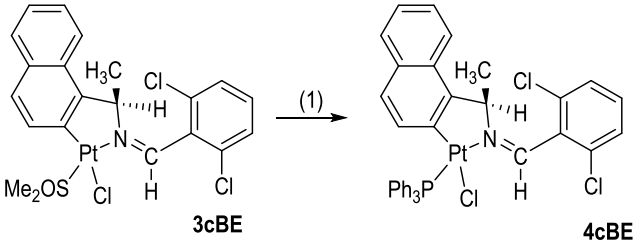


Figure 15. Synthesis of compound **4b**:
(1) PPh_3, acetone, 2h, r.t.

5.4.3. Synthesis of [PtCl{(2,6-$Cl_2C_6H_3$)CHNCH(CH_3)$C_{10}H_6$}{PPh_3}] (4c)

For the synthesis of **[PtCl{(2,6-$Cl_2C_6H_3$)CHNCH(CH_3)$C_{10}H_6$}{PPh_3}]** (**4c**) the cyclometallated compound **3c** and triphenylphosphane were reacted in acetone for 2 hours at room temperature. Compound **4c** was characterized by ^{1}H-NMR and ^{31}P-NMR spectroscopy and mass spectrometry and compared with the literature.[18,19] It could be observed the iminic peak and the characteristic quadruplet in the ^{1}H-NMR spectra which means the aim product has formed. By ^{31}P-NMR spectra it could be observed a mixture of compounds where the aimed product appears at 21.83 ppm as the major compound followed by [$PtCl_2(PPh_3)_2$], which suggests the de-coordination of the cyclometallated ligand.



3cBE **4cBE**

Figure 16. Synthesis of compound **4c**:
(1) PPh_3, acetone, 2h, r.t.

5.4.4. Synthesis of [PtCl{($C_{10}H_6$)CH(CH_3)NCH$C_{10}H_7$}{PPh_3}] (4d)

For the synthesis of **[PtCl{($C_{10}H_6$)CH(CH_3)NCH$C_{10}H_7$}{PPh_3}]** (**4d**) the cyclometallated compound **3d** and triphenylphosphane were reacted in acetone for 2 hours at room temperature. Compound **4d** was characterized by ^{1}H-NMR and ^{31}P-NMR spectroscopy and mass spectrometry and compared with the literature.[18,19] The solid obtained was yellow although these phosphane derivatives are usually white. In the ^{31}P-NMR it could be observed that the aimed product was not formed, only $OPPh_3$ and [$PtCl_2(PPh_3)_2$] arising from the de-coordination of the cyclometallated ligand were observed. The formation of $OPPh_3$ probably is due to an excess of triphenylphosphane that was oxidized under the reaction conditions. Thanks to the mass spectra it could be observed that the aimed product was formed, but it was not possible to determine by NMR due to its low yield.

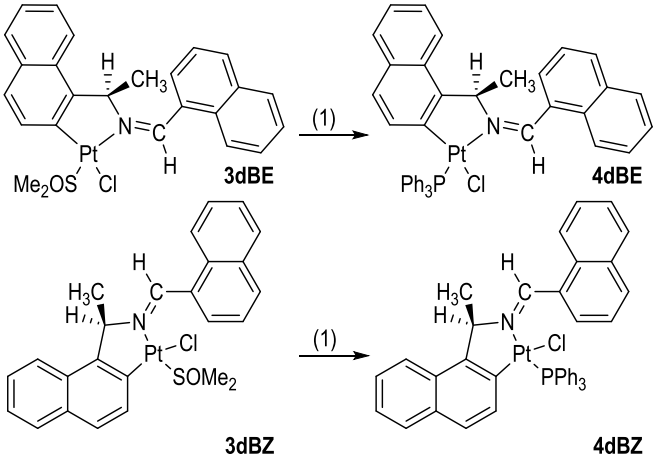


Figure 17. Synthesis of compound **4d**:
(1) PPh_3, acetone, 2h, r.t.

6. EXPERIMENTAL SECTION

6.1. REAGENTS AND SOLVENTS

All reagents and solvents that have been used are from a commercial origin. Dry toluene was obtained from a Pure Solv. solvent dispenser.

6.2. EQUIPMENT AND TECHNIQUES

The techniques and equipment used to characterize all compounds were:

- NMR spectra were registered at the "Unitat de RMN" of Universitat de Barcelona, by using the spectrometers Mercury (^{1}H, 400.0 MHz) and Bruker 400 (^{31}P-{^{1}H}, 161.95MHz). The values of coupling constants (J) are given in Hz, and the chemical shift (δ) values are given in ppm relative to TMS for ^{1}H and 85% H_3PO_4 for ^{31}P.
- ESI(+)-MS spectra were carried out at "Unitat d'Espectrometria de Masses de la Facultat de Química, Centres Científics i Tecnològics de la Universitat de Barcelona (CCiTUB)" by using an LC/MSD-TOF spectrometer and H_2O:CH_3CN (1:1) as solvent.

6.3. PREPARATION AND CHARACTERIZATION OF COMPOUNDS

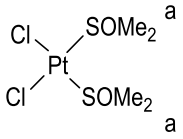
The reported compounds were synthesized following the procedures reported in the literature, and were checked by ^{1}H-NMR spectroscopy and MS spectrometry. Compounds **2b, 2c, 2d, 3a, 3b, 3c, 3d, 4a, 4b, 4c and 4d**, were prepared as detailed below.

Characterization data are given for the major compounds obtained.

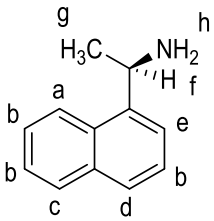
6.3.1. Preparation of the precursors

Cis-[$PtCl_2${$SOMe_2$}]$_2$ (**1a**)[3,14] was obtained from 2.47 g (6.0 mmol) of $K_2[PtCl_4]$ in 20 mL of water and 3 mL (42.2 mmol) of dimethylsulfoxide (DMSO). The mixture was stirred at room temperature for 4 hours. During the stirring a pale-yellow precipitate was formed. The solid was

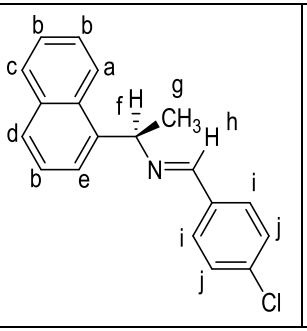
filtered and dried under vacuum and washed several times with 5 mL of water, 5 mL of ethanol and 5 mL of diethyl ether. Yield: 2.36 g (94%).

	Pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 [d, ^3J (H^a-Pt) = 20.6 Hz, 1H^a].

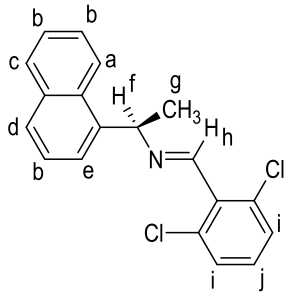
R-(+)-1-(1-naphtyl) ethyl)amine (**2a**) was commercially available.

	Orange liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 [d, ^3J (H^d-H^b) = 8.3 Hz, 1H^d]; 7.85 [dd, ^3J (H^e-H^b) = 8.0, ^3J (H^e-H^d) = 2.0 Hz, 1H^e]; 7.73 [d, ^3J (H^a-H^b) = 8.2 Hz, 1H^a]; 7.63 [d, ^3J (H^c-H^b) = 7.1 Hz, 1H^c]; 7.56 – 7.42 [m, 3H^b]; 4.93 [q, ^3J (H^f-H^g) = 6.6 Hz, 1H^f]; 1.53 [d, ^3J (H^g-H^f) = 6.6 Hz, 3H^g].

(R)-1-(4-chlorophenyl)-*N*-(1-(naphthalen-1-yl)ethyl)methanimine (**2b**)[13,20,21] was obtained from 0.51 g (3.55 mmol) of 4-chloro-benzaldehyde and 0.61 g (3.55 mmol) of R-(+)-1-(1-naphtyl) ethylamine (**2a**) in 30 mL of ethanol. The mixture was stirred under reflux for 3 hours to give an orange solution. The solvents were removed using a rotatory evaporator and a brown solid was formed. To remove the solvents completely the solid was dried under vacuum. Yield: 0.73 g (70%).

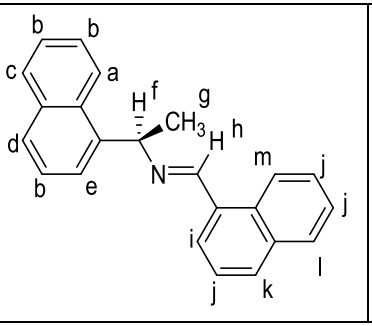
	White solid. **2bE** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 [s, 1H^h]; 8.23 [d, 3J (H^d-H^b) = 8.4 Hz, 1H^d]; 7.91 – 7.84 [d, ^3J (H^e-H^b) = 8.0 Hz, 1H^e]; 7.78 [d, ^3J (H^a-H^b) = 7.6 Hz, 1H^a]; 7.74 [m, 3$H^{j,c}$], 7.57 – 7.43 [m, 3H^b], 7.38 [d, ^3J (H^i-H^j) = 8.6 Hz, 2H^i], 5.35 [q, ^3J (H^f-H^g) = 6.6 Hz, 1H^f], 1.73 [d, ^3J (H^g-H^f) = 6.7 Hz, 3H^g].

(R)-1-(2,6-dichlorophenyl)-*N*-(1-(napthalen-1-yl)ethyl)methanimine (**2c**)[13,17,20,21] was obtained from 0.51 g (2.86 mmol) of 2,6-dichloro-benzaldehyde and 0.49 g (2.86 mmol) of **2a** in 30 mL of ethanol. The mixture was stirred under reflux for 3 hours to give an orange solution. The solvents were removed with a rotatory evaporator and an orange solid was formed. To remove the solvents completely the solid was dried under vacuum. Yield: 0.50 g (53%).



Orange solid. **2cE**
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 [s, 1H^h], 8.22 [d, ^3J(H^d-H^b) = 8.6 Hz, 1H^d], 7.88 [d, ^3J (H^e-H^b) = 8.55 Hz, 1H^e], 7.84 [d, ^3J (H^a-H^b) = 7.3 Hz, 1H^a], 7.78 [d, ^3J (H^c-H^b) = 8.2 Hz, 1H^c], 7.58 – 7.43 [m, 3H^b], 7.36 – 7.16 [m, 3H^{j,i}], 5.51 [q, ^3J (H^f-H^g) = 6.7 Hz, 1H^f], 1.80 [d, ^3J (H^g-H^f) = 6.7 Hz, 3H^g].

(R)-1-(napthalen-1-yl)-*N*-(1-(napthalen-1-yl)ethyl)methanimine (**2d**)[13,20,21] was obtained from 0.49 g (3.2 mmol) of 1-napthaldehyde and 0.55 g (3.2 mmol) of **2a** in 30 mL of ethanol. The mixture was stirred at reflux for 3 hours to give an orange solution. The solvents were removed with a rotatory evaporator and a brown solid was formed. To remove the solvents completely the solid was dried under vacuum. Yield: 0.71 g (71%).



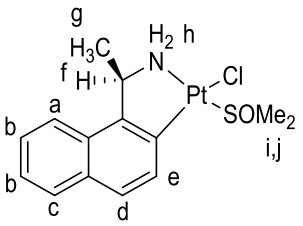
Brown solid. **2dE**
^{1}H NMR (400 MHz $CDCl_3$) δ 9.09 [s, 1H^h], 9.03 [d, ^3J (H^k-H^j) = 8.6Hz, 1H^k], 8.36 [d, ^3J (H^d-H^b) = 8.5 Hz, 1H^d], 7.97 – 7.86 [m, 5H^{a,e,i,l,m}], 7.79 [d, ^3J (H^c-H^b) = 8.3Hz, 1H^c], 7.65 – 7.46 [m, 6H^{b,j}], 5.46 [q, ^3J (H^f-H^g) = 6.7 Hz, 1H^f], 1.85 [d, ^3J (H^g-H^f) = 6.6 Hz, 3H^g].

6.3.2. Preparation of cyclometallated platinum (II) compounds

[PtCl{$NH_2CH(CH_3)C_{10}H_6$}{$SOMe_2$}] (**3a**)[12,16] was obtained by different procedures, following the literature.

Procedure (1): Compound **3a** was obtained from 150 mg (0.355 mmol) of compound **1a**, 61 mg (0.356 mmol) of compound **2a** and 29 mg (0.36 mmol) of sodium acetate previously dissolved in 2 mL of MeOH and 25 mL of toluene as solvent. The mixture was firstly purged under nitrogen. In the same atmosphere the mixture was heated and stirred at 90 ºC for 48 hours, using a magnetic stirrer equipped with a digital thermometer to control the temperature. The obtained mixture was filtered, and the solvent was removed in a rotatory evaporator. The solid obtained was dissolved in 1 mL of 1:1 MeOH/CH_2Cl_2 and the solution was kept for 24 hours in the freezer. The obtained precipitate was filtered and dried under vacuum. Yield: 80 mg (47%).

Procedure (2): Compound **3a** was obtained from 151 mg (0.357 mmol) of compound **1a**, 61 mg (0.356 mmol) of compound **2a** and 29 mg (0.365 mmol) of sodium acetate previously dissolved in 25 mL of MeOH. The mixture was firstly purged in nitrogen atmosphere. In the same atmosphere the mixture was heated and stirred at 65 ºC for 48 hours, using a magnetic stirrer equipped with a digital thermometer to control the temperature. The obtained mixture was filtered, and the solvent was removed with a rotatory evaporator. The solid was dissolved in 1mL of CH_2Cl_2 and kept in the freezer for 24 hours. The obtained precipitated was filtered and dried under vacuum. Yield: 34 mg (17%).

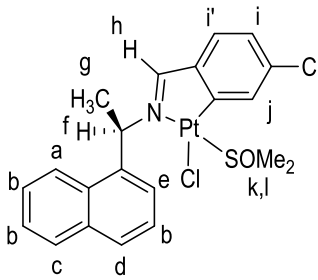
	White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 [d, ^3J (H^h-H^f) = 8.6 Hz, ^3J (H^h-Pt) = 42.20 Hz, 1H^h], 7.79 – 7.71 [m, 2H^{d,e}], 7.53 [d, J (H^a-H^b) = 8.6 Hz, 1H^a], 7.51– 7.44 [m, 1H^c], 7.39 – 7.28 [m, 2H^b], 5.10 [p, J (H^g-H^f) = 6.3 Hz, 1H^g], 3.47 [s, ^3J (H^i-Pt) = 23.92 Hz, 3H^i], 3.41 [s, ^3J (H^j-Pt) = 22.4 Hz, 3H^j], 1.77 [d, J (H^f-H^g) = 6.5 Hz, 3H^f].

[PtCl{(4-ClC$_6$H$_3$)CHNCH(CH$_3$)C$_{10}$H$_7$}{SOMe$_2$}] (**3b**)[12,16] was obtained by two different procedures, following the literature methods for analogous compounds.

Procedure (1): Compound **3b** was obtained from 150 mg (0.355mmol) of compound **1a**,105 mg (0.357mmol) of compound **2b** and 31 mg (0.378mmol) of sodium acetate previously dissolved in 2 mL of MeOH and 25 mL of toluene as solvent. The mixture was firstly purged under nitrogen. In the same atmosphere the mixture was heated and stirred at 90 ºC for 48 hours, using a magnetic stirrer equipped with a digital thermometer to control the temperature.

The obtained mixture was filtered, and the solvent was removed in a rotatory evaporator. The solid obtained was dissolved in 1 mL of 1:1 MeOH/CH_2Cl_2 and the solution was kept for 24 hours in the freezer. The obtained precipitate was filtered and dried under vacuum. Yield: 52 mg (24%).

Procedure (2): Compound **3b** was obtained from 150 mg (0.355 mmol) of compound **1a**, 104 mg (0.354 mmol) of compound **2b** and 32 mg (0.39 mmol) of sodium acetate previously dissolved in 25 mL of MeOH. The mixture was firstly purged in nitrogen atmosphere. In the same atmosphere the mixture was heated and stirred at 65 ºC for 48 hours, using a magnetic stirrer equipped with a digital thermometer to control the temperature. The obtained mixture was filtered, and the solvent was removed in a rotatory evaporator. The solid was dissolved in 1mL of CH_2Cl_2 and kept in the freezer for 24 hours. The obtained precipitated was filtered and dried under vacuum. Yield: 37 mg (17%).

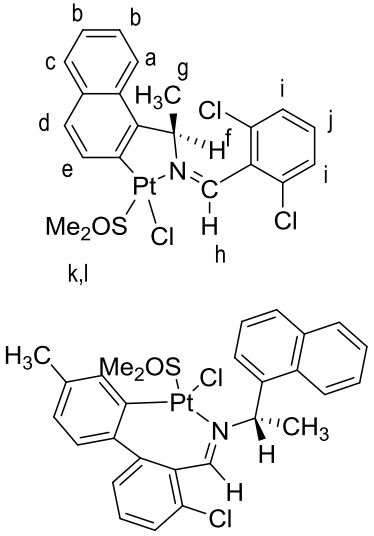


White solid. **3bA** obtained using procedure (1)
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 [d, ^4J (H^h-$H^{i'}$) = 2.0 Hz, 1H^h], 8.18 [d, ^3J (H^d-H^b) = 8.5 Hz, 1H^d], 7.89 [t, J ($H^{a,e}$-H^b) = 7.7 Hz, 2$H^{a,e}$], 7.66 [d, ^3J (H^c-H^b) = 7.2 Hz, 1H^c], 7.62 – 7.50 [m, 4$H^{b,j}$], 6.99 [dd, ^3J ($H^{i'}$-H^i) = 8.0, ^4J ($H^{i'}$-H^h) = 1.9 Hz, 1$H^{i'}$], 6.90 [d, ^3J (H^i-$H^{i'}$) = 8.0 Hz, 1H^i], 6.76 [q, ^3J (H^f-H^g) = 6.7 Hz, 1H^f], 3.67 [s,^{3} J (H^k-Pt) = 22.45 Hz, 3H^k], 3.66 [d, ^3J (H^l-Pt) = 19.57 Hz, 3H^l], 1.90 [d, ^3J (H^g-H^f) = 6.7 Hz, 3H^g].
ESI – (+) {H_2O:CH_3CN (1:1)} m/z: 607.09 [M-Cl+CH_3CN]$^+$, 566.07 [M-Cl]$^+$, 529.08 [M-Cl-DMSO+CH_3CN]$^+$.

[PtCl{(2,6-$Cl_2C_6H_3$)CHNCH(CH_3)$C_{10}H_6$}{$SOMe_2$}] (**3c**)[12,16] was obtained by two procedures.

Procedure (1): Compound **3c** was obtained from 151 mg (0.355 mmol) of compound **1a**, 116 mg (0.355 mmol) of compound **2c** and 29 mg (0.355 mmol) of sodium acetate previously dissolved in 2 mL of MeOH and 25 mL of toluene as solvent. The mixture was firstly purged under nitrogen. In the same atmosphere the mixture was heated and stirred at 90 ºC for 48 hours, using a magnetic stirrer equipped with a digital thermometer to control the temperature. The obtained mixture was filtered, and the solvent was removed in a rotatory evaporator. The solid obtained was dissolved in 1 mL of 1:1 MeOH/CH_2Cl_2 and the solution was kept for 24 hours in the freezer. The obtained precipitate was filtered and dried under vacuum. Yield: 60 mg (28%).

Procedure (2): Compound **3c** was obtained from 151 mg (0.355 mmol) of compound **1a**, 115 mg (0.354 mmol) of compound **2c**, 31 mg (0.37 mmol) of sodium acetate previously dissolved in 25 mL of MeOH. The mixture was firstly purged in nitrogen atmosphere. In the same atmosphere the mixture was heated and stirred at 65 ºC for 48 hours, using a magnetic stirrer equipped with a digital thermometer to control the temperature. The obtained mixture was filtered, and the solvent was removed in a rotatory evaporator. The solid was dissolved in 1mL of CH_2Cl_2 and kept in the freezer for 24 hours. The obtained precipitated was filtered and dried under vacuum. Yield: 76 mg (34%).



Orange solid. **3cBE** Obtained using procedure (2)
Major product:
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 [s, $^3J(H^h\text{-Pt})$ = 75.66, $1H^h$], 8.27 [d, ^3J (H^e-H^d) = 8.7 Hz, $^3J(H^e\text{-Pt})$ = 67.0 Hz, $1H^e$], 7.96 – 7.72 [m, $2H^{a,d}$], 7.59 [d, ^3J (H^c-H^b) = 8.7 Hz, $1H^c$], 7.52 – 7.43 [m, $3H^{i,j}$], 7.35 [m, $2H^b$], 5.68 [q, ^3J (H^f-H^g) = 6.4 Hz, ^3J (H^f-Pt) = 67.0 Hz, $1H^f$], 3.68 [s, $3H^k$], 3.65 [s, $3H^l$], 1.70 [d, J (H^g-H^f) = 6.4 Hz, $3H^g$].
ESI – (+) {H_2O:CH_3CN (1:1)} m/z: 641.05 [M-Cl+CH_3CN]$^+$, 600.02 [M-Cl]$^+$.

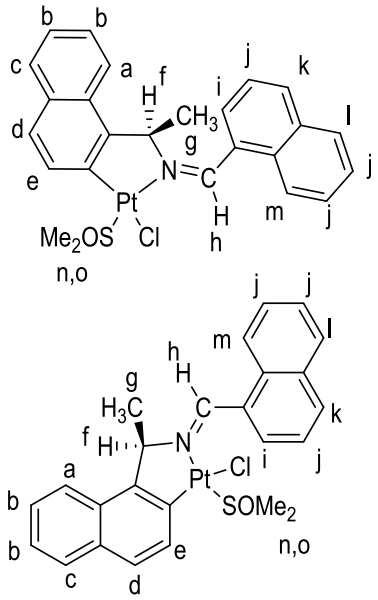
Additional compound obtained using procedure (1) **3cA'**
ESI – (+) {H_2O:CH_3CN (1:1)} m/z: 697.14 [M+toluene-2Cl+CH_3CN]$^+$, 656.11 [M+toluene-2Cl]$^+$, 641.05 [M-Cl+CH_3CN]$^+$, 600.02 [M-Cl]$^+$.

[PtCl{($C_{10}H_6$)CHNCH(CH_3)$C_{10}H_7$}{$SOMe_2$}] (**3d**)[12,16] was obtained by two procedures.

Procedure (1): Compound **3d** was obtained from 154 mg (0.364 mmol) of compound **1a**, 114 mg (0.368 mmol) of compound **2d** and 29 mg (0.355 mmol) of sodium acetate previously dissolved in 2 mL of MeOH and 25 mL of toluene as dissolvent. The mixture was firstly purged under nitrogen. In the same atmosphere the mixture was heated and stirred at 90 ºC for 48 hours, using a magnetic stirrer equipped with a digital thermometer to control the temperature. The obtained mixture was filtered, and the solvent was removed in a rotatory evaporator. The solid obtained was dissolved in 1 mL of 1:1 MeOH/CH_2Cl_2 and the solution was kept for 24

hours in the freezer. The obtained precipitate was filtered and dried under vacuum. Yield: 53 mg (27%).

Procedure (2): Compound **3d** was obtained from 154 mg (0.364 mmol) of compound **1a**, 115 mg (0.372 mmol) of compound **2d** and 33 mg (0.40 mmol) of sodium acetate previously dissolved in 25 mL of MeOH. The mixture was firstly purged in nitrogen atmosphere. In the same atmosphere the mixture was heated and stirred at 65 ºC for 48 hours, using a magnetic stirrer equipped with a digital thermometer to control the temperature. The obtained mixture was filtered, and the solvent was removed in a rotatory evaporator. The obtained solid was dissolved in 1mL of CH_2Cl_2 and kept in the freezer for 24 hours. The obtained precipitated was filtered and dried under vacuum. Yield: 64 mg (29%).



Brown solid.

Major compound using procedure (1) (**3dBE**):

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 [d, ^3J (H^d-H^b) = 7.2 Hz, 1H^d], 8.63 [d, ^3J (H^e-H^b) = 8.9 Hz, 2H^{e,h}], 6.31 [q, ^3J (H^f-H^g) = 6.4 Hz, 1H^f], 3.28 [s, 3H^n], 3.26 [s, 3H^o], 2.54 [d, ^3J (H^g-H^f) = 7.0 Hz, 3H^g].

ESI – (+) {H_2O:CH_3CN (1:1)} m/z: 671.10 [M+HCl+NH_4]$^+$, 622.15 [M-Cl+CH_3CN]$^+$, 581.12 [M-Cl]$^+$, 544.14 [M-Cl-DMSO+CH_3CN]$^+$.

Major compound using procedure (2) (**3dBZ**):

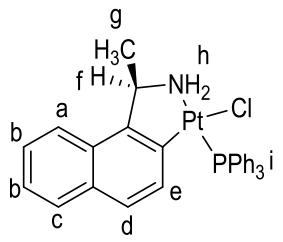
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 [s, 1H^h], 6.86 [q, ^3J (H^f-H^g) = 6.7 Hz, 1H^f], 3.75 – 3.67 [m, 6H^{n,o}], 3.58 – 3.43 [m, 3H^g] .

ESI – (+) {H_2O:CH_3CN (1:1)} m/z: 1329.13 2M+2Cl+Na]$^+$, 676.06 [M+HCl+Na]$^+$, 671.10 [M+HCl+NH_4]$^+$, 622.15 [M-Cl+CH_3CN]$^+$, 618.10 [M+H]$^+$, 581.12 [M-Cl]$^+$, 544.14 [M-Cl-DMSO+CH_3CN]$^+$.

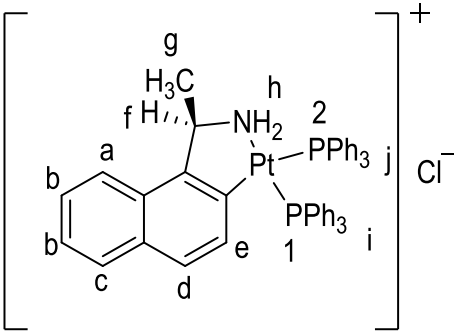
6.3.3. Preparation of triphenylphosphane compounds

[PtCl{$NH_2CH(CH_3)C_{10}H_6$}{PPh_3}] (**4a**)[12,16] was obtained from 19 mg (0.040 mmol) of compound **3a** and 11 mg (0.042 mmol) of triphenylphosphane which were allowed to react in acetone at room temperature for 2 hours. The solvent was removed with a rotatory evaporator

and a white solid was obtained. The solid was washed with diethyl ether, dried under vacuum and recrystallized in 1 mL of 1:1 MeOH/CH_2Cl_2. The solution was kept for 24 hours in the freezer. The precipitate obtained was filtered and dried under vacuum. Yield: 8 mg (29%).

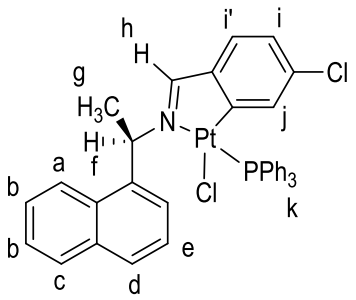
	^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.72 [m, 4H^{b,d,e}], 7.68 [d, ^3J(H^a-H^b) = 8.3 Hz, 1H^a], 7.58 [d, ^3J(H^c-H^b) = 8.2 Hz, 1H^c], 7.44 – 7.28 [m, 15H^i], 6.89 [d, ^3J (H^h-H$^{h'}$) = 8.6 Hz, 1H^h], 6.73 [dd, ^2J (H$^{h'}$-H^h) = 8.6, ^3J (H$^{h'}$-H^f) = 2.9 Hz, 1H$^{h'}$], 5.47 [q, ^3J(H^f-H^g) = 6.5 Hz, 1H^f], 1.92 [d, ^eJ (H^g-H^f) = 6.4 Hz, 3H^g]. ^{31}P-{^{1}H}-NMR (161.95 MHz, $CDCl_3$) δ 23.20 [s, ^1J (P-Pt) = 4336.95 Hz, P] ESI – (+) {H_2O:CH_3CN (1:1)} m/z: 668.18 [M-Cl+CH_3CN]$^+$, 627.15 [M-Cl]$^+$, 279.09 [PPh_3O]$^+$.

[PtCl{$NH_2CH(CH_3)C_{10}H_6$}{PPh_3}] (**4a'**)[12,16] was obtained from 19 mg (0.040 mmol) of compound **3a** and 30 mg (0.11mmol) of triphenylphosphane which were allowed to react in acetone at room temperature for 2 hours. The solvent was removed with a rotatory evaporator and a white solid was obtained. The solid was washed with diethyl ether, dried under vacuum and recrystallized in 1 mL of 1:1 MeOH/CH_2Cl_2. The solution was kept for 24 hours in the freezer. The precipitate obtained was filtered and dried under vacuum.

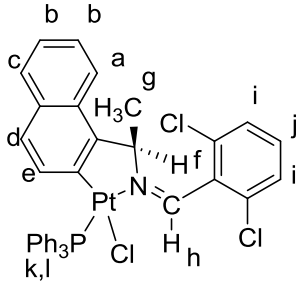
	^{31}P-{^{1}H}-NMR (161.95 MHz, $CDCl_3$) δ 23.54 [d, ^2J (P^1-P^2)= 18.15 Hz, ^1J (P^1-Pt) = 1809.06 Hz, P^1], 21.36 [d, ^2J (P^2-P^1) = 18.36 Hz, ^1J (P^2-Pt) = 3806.30 Hz, P^2]. ESI – (+) {H_2O:CH_3CN (1:1)} m/z: 668.18 [M-Cl+CH_3CN]$^+$, 627.15 [M-Cl]$^+$, 279.09 [PPh_3O]$^+$.

[PtCl{(4-ClC_6H_3)CHNCH(CH_3)$C_{10}H_7$}{PPh_3}] (**4b**)[12,16] was obtained from 60 mg (0.10 mmol) of compound **3b** and 26 mg (0.099 mmol) of triphenylphosphane which were allowed to react in acetone at room temperature for 2 hours. The solvent was removed with a rotatory evaporator and a white solid was obtained. The solid was washed with diethyl ether, dried under vacuum

and recrystallized in 1 mL of 1:1 MeOH/CH_2Cl_2. The solution was kept for 24 hours in the freezer. The precipitate obtained was filtered and dried under vacuum. Yield: 29 mg (37%).

	^{31}P-{^{1}H}-NMR (161.95 MHz, $CDCl_3$) δ 23.20 [s, ^{1}J (P-Pt) = 4332.85 Hz, P],

[PtCl{(2,6-$Cl_2C_6H_3$)CHNCH(CH_3)$C_{10}H_6$}{PPh_3}] (**4c**)[12,16] was obtained from 17 mg (0.0.27 mmol) of compound **3c** and 26 mg (0.030 mmol) of triphenylphosphane which were allowed to react in acetone at room temperature for 2 hours. The solvent was removed with a rotatory evaporator and a white solid was obtained. The solid was washed with diethyl ether, dried under vacuum and recrystallized in 1 mL of 1:1 MeOH/CH_2Cl_2. The solution was kept for 24 hours in the freezer. The precipitate obtained was filtered and dried under vacuum. Yield: 13 mg (59%).

	^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (d, J = 1.2 Hz, 1H), 5.84 [q, ^{3}J(H^f-H^g) = 6.5 Hz, 1H^f], 1.79 (d, J (H^g-H^f)= 6.4 Hz, 3H^g). ^{31}P-{^{1}H}-NMR (161.95 MHz, $CDCl_3$) δ 21.83 [s, ^{1}J (P-Pt) = 4340.26 Hz, P], 14.29. ESI – (+) {H_2O:CH_3CN (1:1)} m/z: 825.13 $[M\text{-}Cl+CH_3CN]^+$, 784.10 $[M\text{-}Cl]^+$.

[PtCl{($C_{10}H_6$)CHNCH(CH_3)$C_{10}H_7$}{PPh_3}] (**4d**)[12,16] was obtained from 12 mg (0.019 mmol) of compound **3d** and 9 mg (0.034 mmol) of triphenylphosphane which were allowed to react in acetone at room temperature for 2 hours. The solvent was removed by rotatory evaporator and a yellow solid was obtained. The solid was washed with diethyl ether and dried under vacuum and recrystallized in 1 mL of 1:1 MeOH/CH_2Cl_2. The solution was kept for 24 hours in the freezer. The obtained precipitate was filtered and dried under vacuum.

7. CONCLUSIONS

The reactions of three imine ligands $RCHNCH(CH_3)C_{10}H_7$ with cis-$[PtCl_2\{(SO(Me)_2\}_2]$ were studied using two different solvents (methanol or toluene) into the conditions previously reported for the corresponding amine $C_{10}H_7CH(CH_3)NH_2$.

These reactions lead to complex mixtures of cyclometallated platinum compounds that were analyzed by ^{1}H-NMR and mass spectrometry.

For the less bulky imine **2b** (R = 4-ClC_6H_4), the hydrolysis of the imine takes places easily under the reaction conditions, but by using high quality toluene, the endo-platinacycle could be obtained with a fair yield.

For imine **2c** (R = 2,6-$Cl_2C_6H_3$) an exo-platinacycle was obtained in a fair yield in methanol, while in toluene a more complex mixture was obtained due to the formation of seven-membered metallacycles arising from the toluene insertion.

The reactions of the imine **2d** (R = 1-$C_{10}H_7$) gave mixtures of E and Z exo-platinacycles in ratios depending on the solvent used.

The reactions of the obtained compounds with triphenylphosphane gave the corresponding derivatives from **3b** and **3c**, along with a certain amount of $[PtCl_2(PPh_3)_2]$ while only decomposition products were obtained for **3d**, which suggest a lower stability of these exo-platinacycles.

To sum up, the best conditions to carry out these reactions have been elucidated, in particular the endo-platinocycle **3b** is best obtained in toluene while the exo-platinocycle **3c** is best obtained in methanol.

Due to the presence of minor isomers in all cases, further purification of these compounds would be needed before testing them as possible anti-cancer agents.

8. REFERENCES AND NOTES

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9. ACRONYMS

CCiTUB: Centres Científics i Tecnològics de la Universitat de Barcelona

DMSO: dimethylsulfoxide

DNA: deoxyribonucleic acid

d: doublet

dd: doublet of doublets

ESI (+): electrospray mass spectrometry

^{n}J(A-B): coupling constants with n bonds, between A and B atoms

LC/MSD-TOF: liquid chromatography coupled to mass spectroscopy detector with time of flight as analyser

m: multiplet

Me: methyl

MS: mass spectrometry

NMR: Nuclear magnetic resonance spectroscopy

Ph: phenyl

PPh_3: triphenylphosphane

q: quadruplet

s: singlet

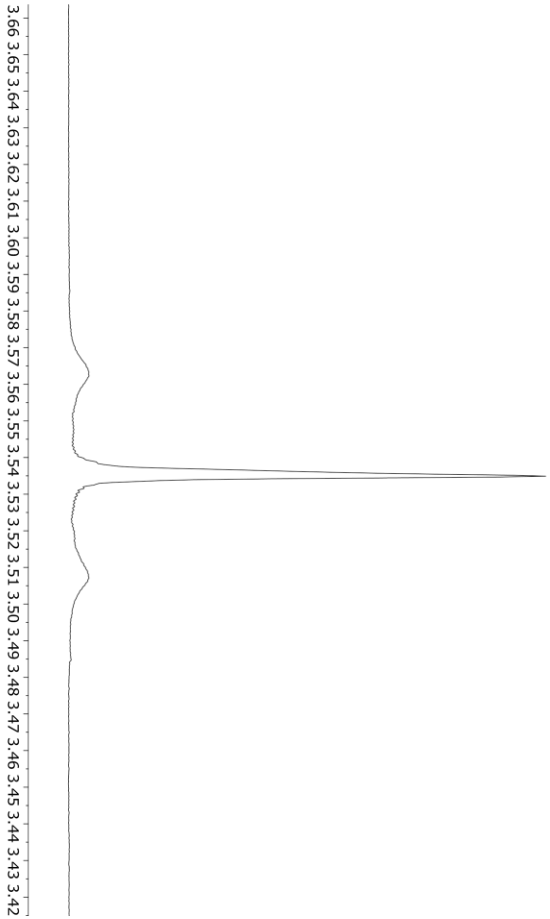
t: triplet

δ: chemical shift

APPENDICES

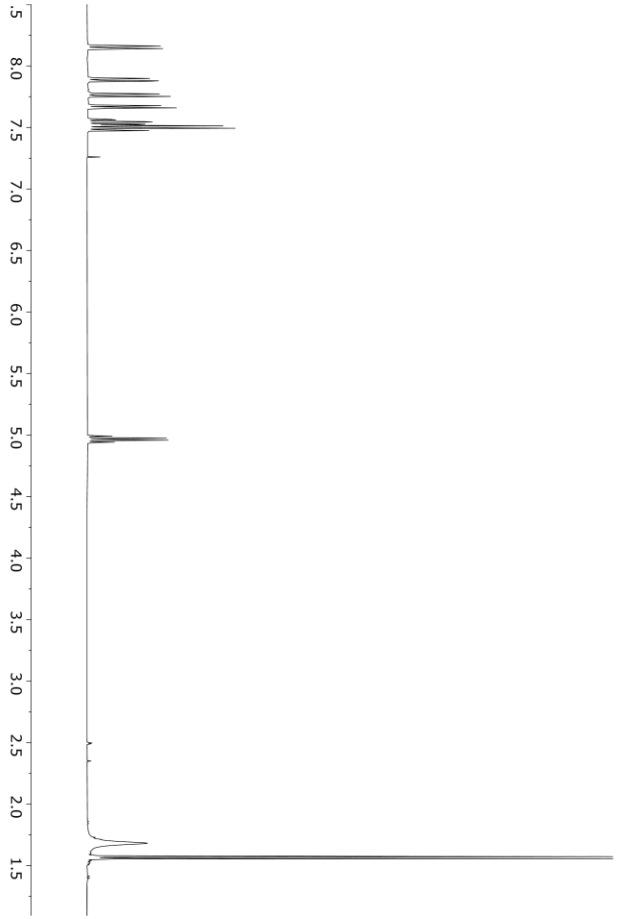
APPENDIX 1:

^{1}H-NMR spectra of **1a** in $CDCl_3$.



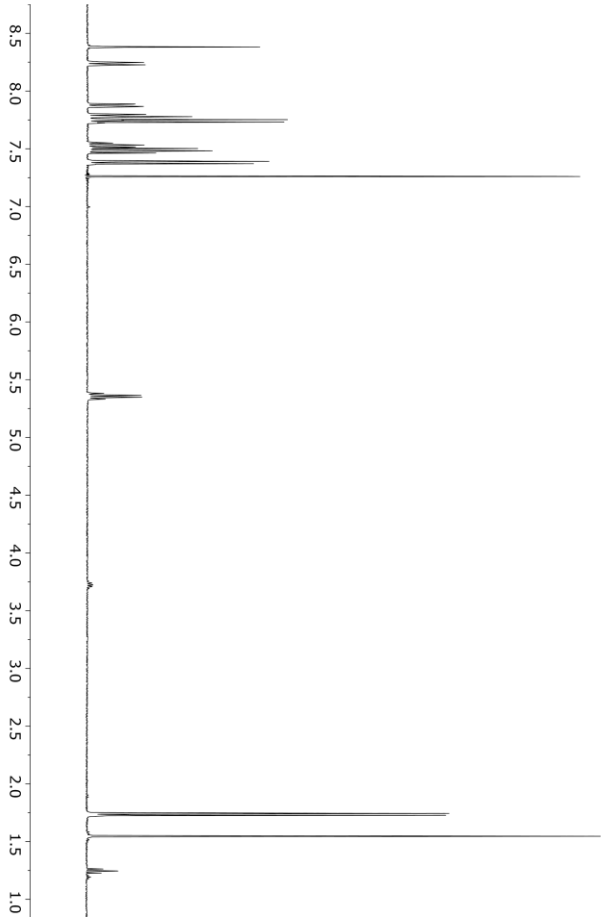
APPENDIX 2:

^{1}H-NMR spectra of **2a** in $CDCl_3$.



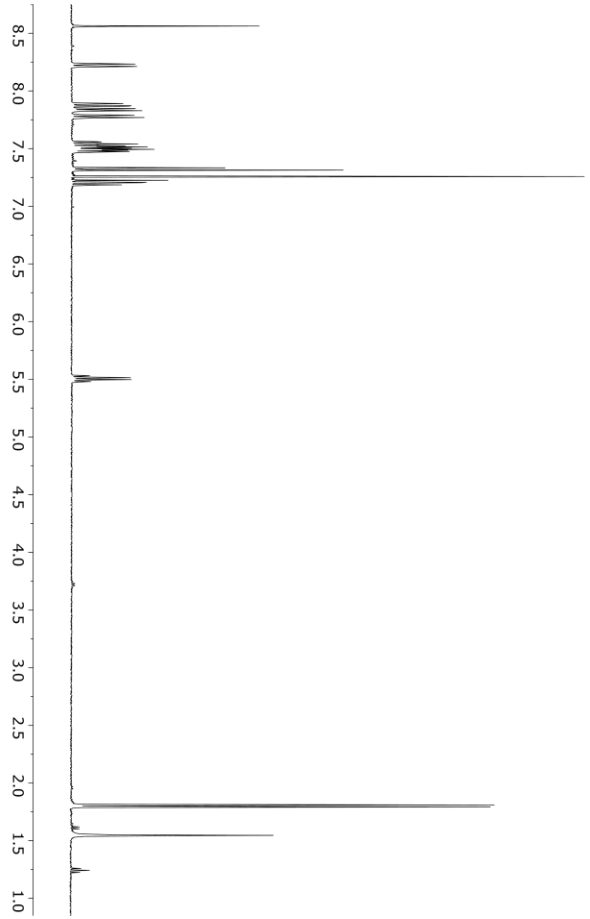
APPENDIX 3:

^{1}H-NMR spectra of **2b** in $CDCl_3$.



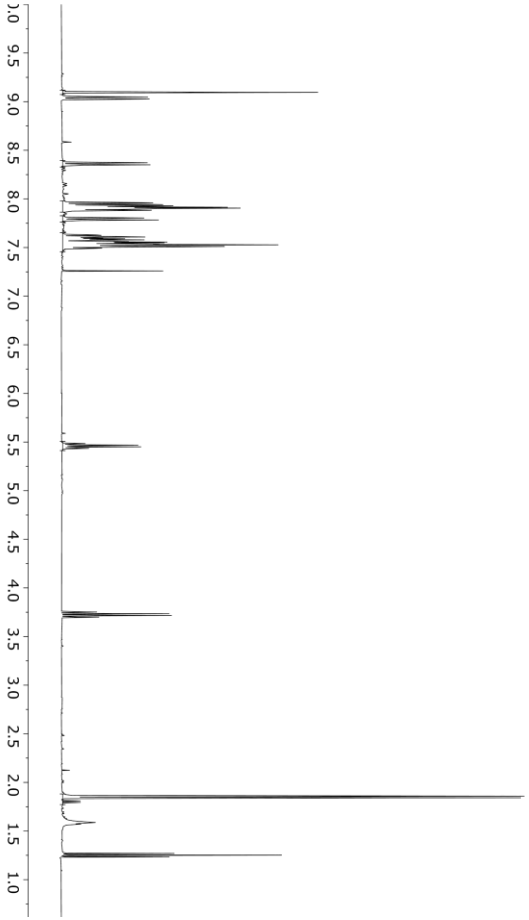
APPENDIX 4:

^{1}H-NMR spectra of **2c** in $CDCl_3$.



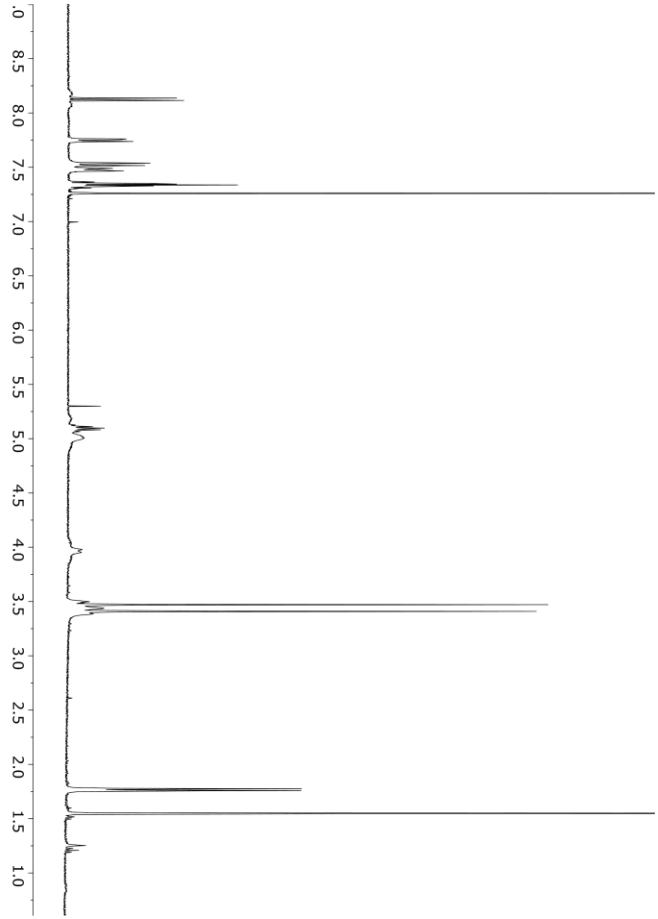
APPENDIX 5:

^{1}H-NMR spectra of **2d** in $CDCl_3$.



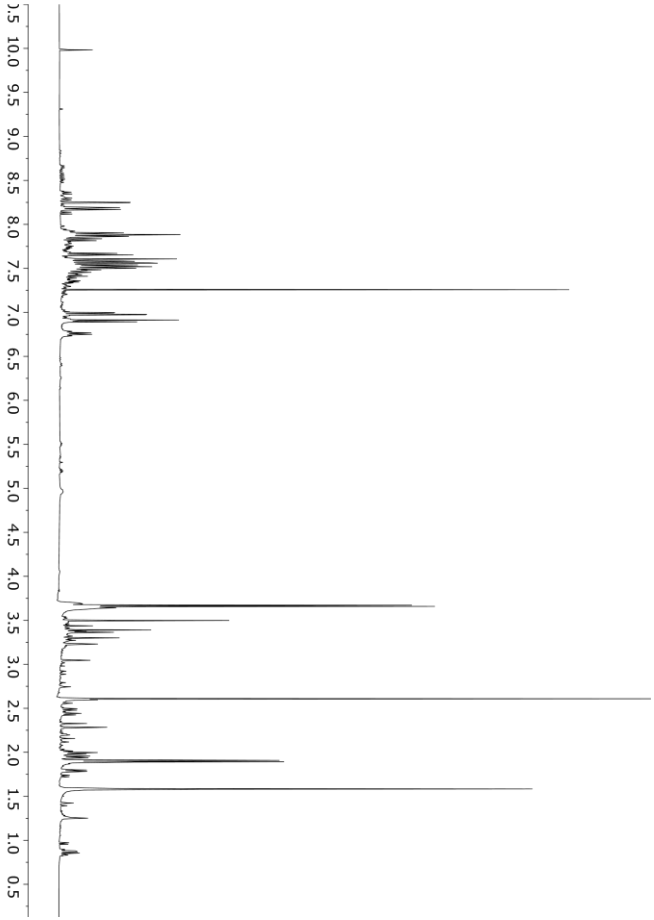
APPENDIX 6:

^{1}H-NMR spectra of **3a** in $CDCl_3$.



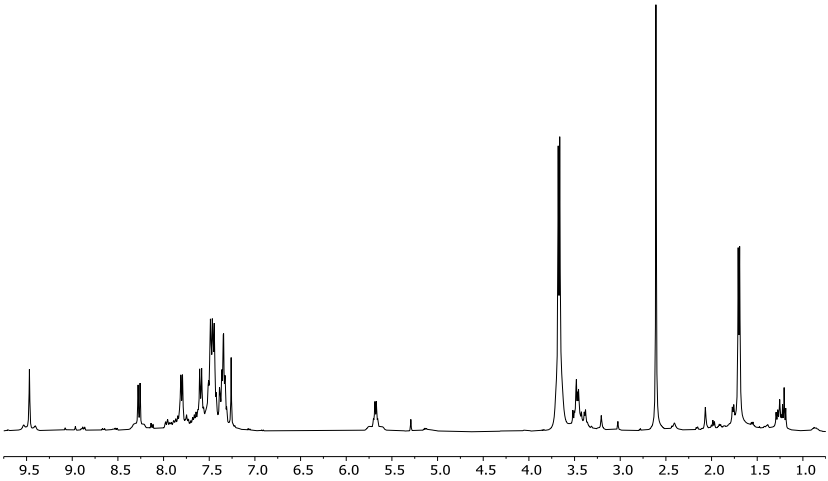
APPENDIX 7:

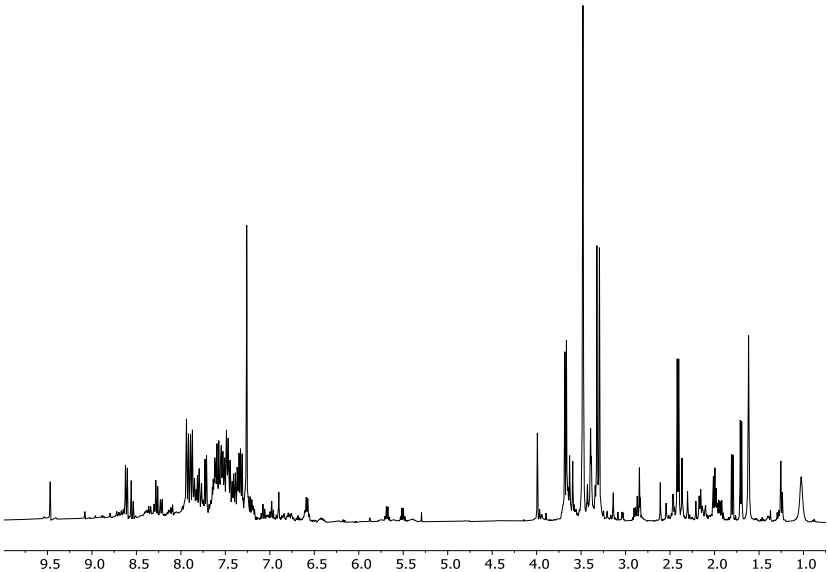
^{1}H-NMR spectra of **3b** in $CDCl_3$.



APPENDIX 8:

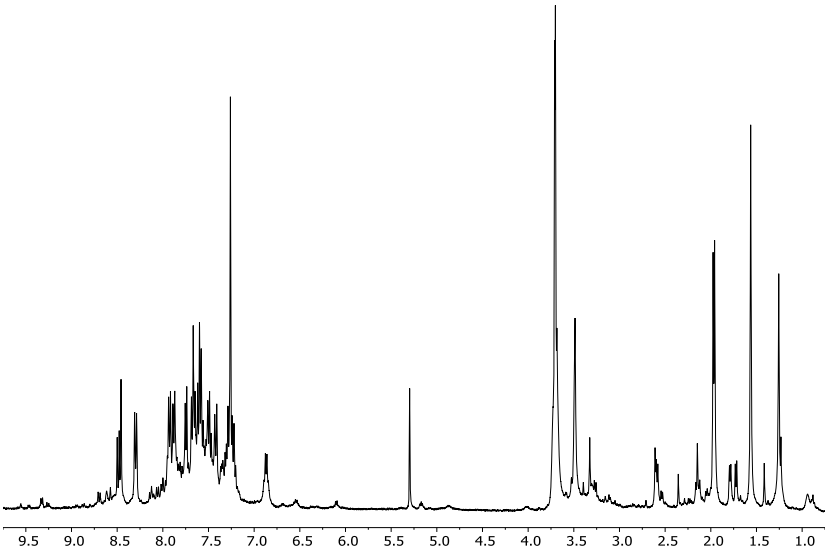
^{1}H-NMR spectra of **3cBE** and **3cA'** in $CDCl_3$.

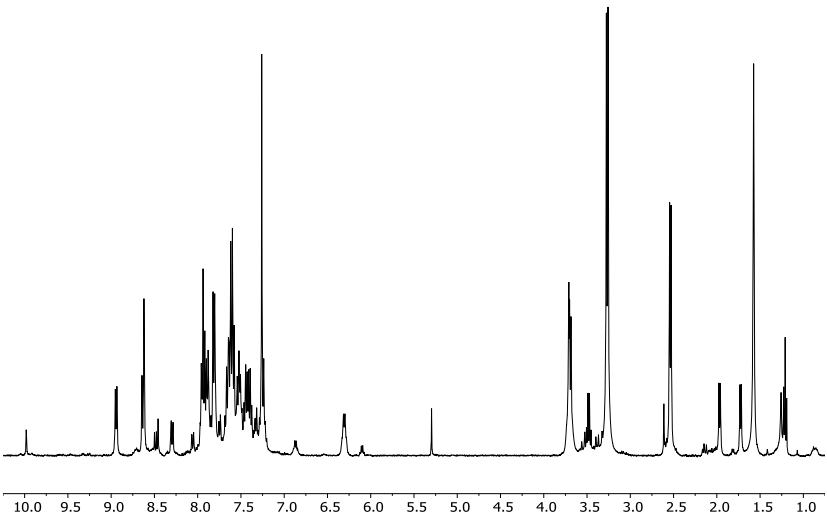




APPENDIX 9:

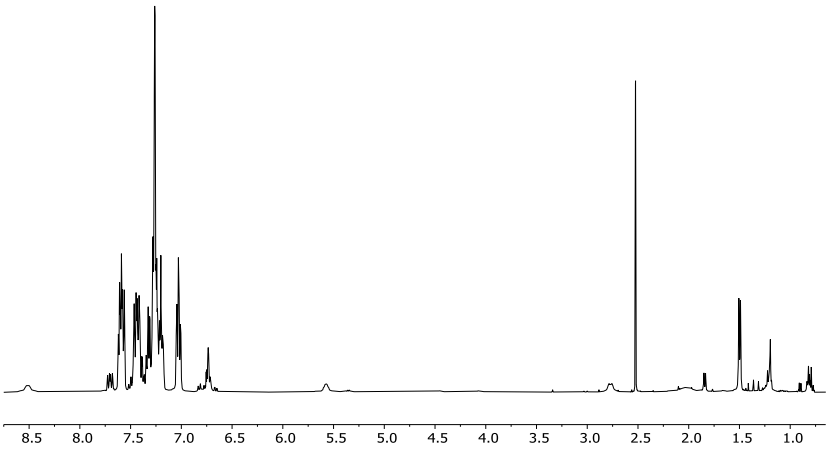
^{1}H-NMR spectra of **3dBE** and **3dBZ** in $CDCl_3$.

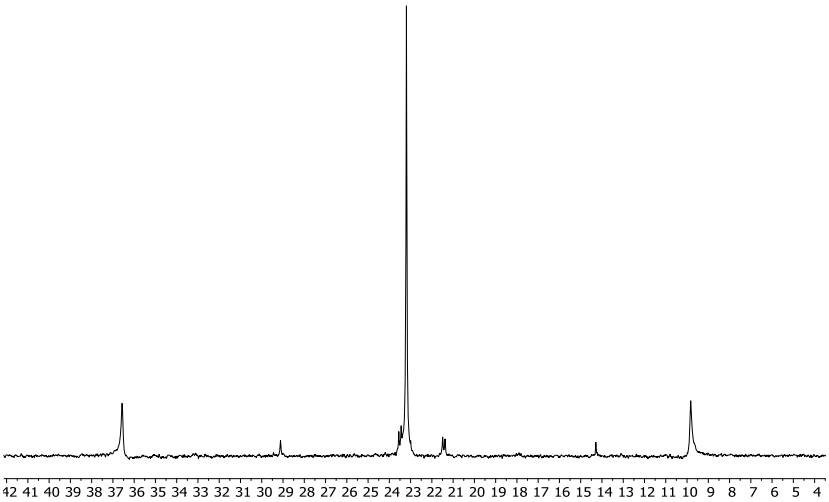




APPENDIX 10:

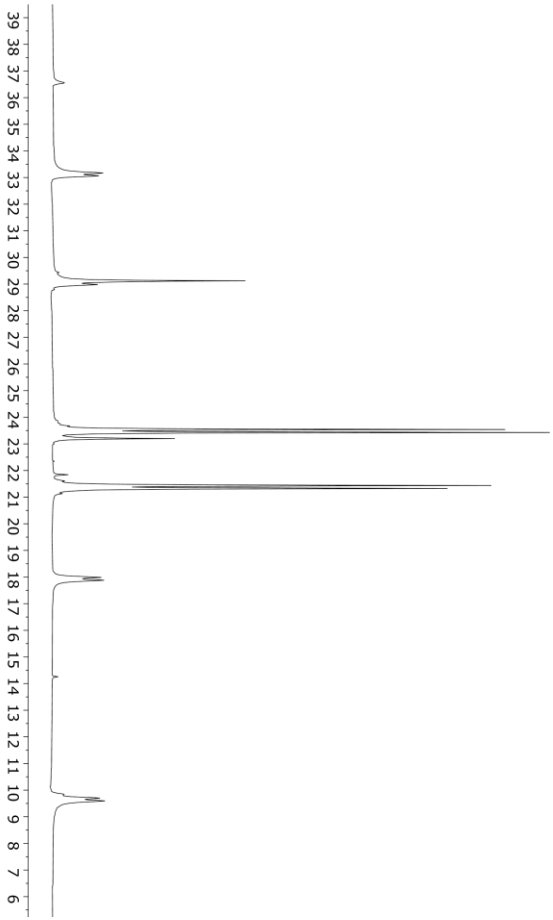
^{1}H-NMR and ^{31}P-NMR spectra of **4a** in $CDCl_3$.





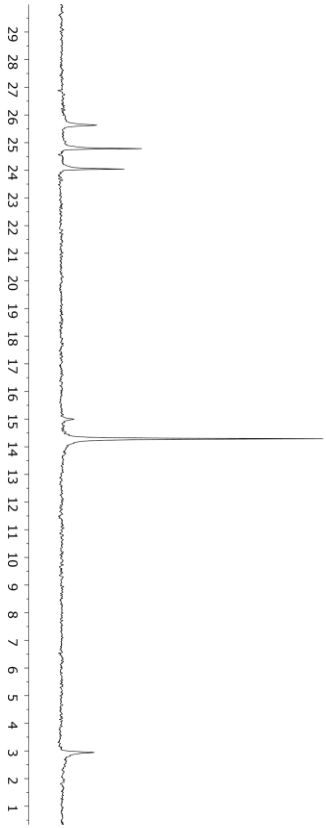
APPENDIX 11:

^{31}P-NMR spectra of **4a'** in $CDCl_3$.



APPENDIX 12:

^{31}P-NMR spectra of **4b** in $CDCl_3$.



APPENDIX 13:

^{1}H-NMR and ^{31}P-NMR spectra of **4c** in $CDCl_3$.