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Bibliographic project: Platinum(II) compounds with tetradentate ligands: Synthesis and applications.

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UNIVERSITAT DE BARCELONA

B:KC Barcelona Knowledge Campus
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Habla poco de lo que sabes y nada de lo que ignores.

Sadi Carnot

Me gustaría dedicar este trabajo a mis dos mejores amigos, Cristina y Carlos por el apoyo recibido y por estar presentes día a día.

También me gustaría dedicar este trabajo a mi tutora, Margarita Crespo, por cómo me ha ayudado a orientar la memoria y por toda su preocupación durante todo el tiempo.

REPORT

CONTENTS

1. SUMMARY

In the mid-20th century, early studies of platinum (II) complexes with tetradentate ligands began. Although it began many years ago, no conclusive results were observed with regards to its field of application until recently, that two interesting fields are being developed. There is still continuous research in these areas which have a promising future.

In this report, information has been collected about the two fields that have been discovered, on the one hand, it has been found that platinum (II) complexes with tetradentate ligands offer interesting luminescence properties and may even improve their predecessors, the octahedral complexes of Ir(III). On the other hand, they have also been found to possess antitumor properties in different trials to combat various tumors and to extend their application to other types of tumors.

Keywords: platinum, tetradentate ligands, photoluminescent, antitumoral activity, OLEDs.

2. RESUMEN

A mitad del siglo XX se iniciaron los primeros estudios con respecto a los compuestos de platino (II) con ligandos tetradentados. A pesar de haber empezado hace muchos años no se llegaron a observar resultados concluyentes respecto a su campo de aplicación hasta hace bien poco, que se están desarrollando dos áreas interesantes. Estas siguen en continua investigación y presentan un futuro prometedor.

En esta memoria se ha recopilado información sobre los dos campos que se han descubierto, por un lado se ha comprobado que los complejos de platino (II) con ligandos tetradentados ofrecen unas propiedades lumínicas interesantes y pueden incluso mejorar a sus antecesores, los complejos octaédricos del Ir (III). Por otro lado también se ha comprobado que posee unas propiedades antitumorales en diferentes ensayos para combatir diversos tumores y extender su aplicación a otros tipos de tumores.

Palabras clave: platino, ligandos tetradentados, fotoluminiscencia, actividad antitumoral, OLEDs.

3. INTRODUCTION

First of all, Platinum was discovered in America 1557 thanks to the writer Giulio Cesare, but no one knows about it in Europe until 1735, thanks to the writer and scientist Antonio de Ulloa, who brings a sample of this material to Europe. However, Ulloa hasn't the chemistry knowledge's to study it. His name seems to be related with the similar appearance to Silver. One of the most important properties of platinum is his resistance, furthermore it's ductile, malleable and has good electrical properties. It can be used from jewellery's from to vehicles catalysts. In the nature, it's rare to find the metal pure, usually it is united together with nickel, copper and impurities of gold.

The platinum (II) is a transition metal (noble metal) of group 10, it has an electronic configuration d^8 and the complexes adopt a square-planar geometry.

Platinum complexes have played an important role in the development of several areas of chemistry. For instance, cis and trans isomerism in square-planar complexes was described for square-planar platinum (II) compounds, and these compounds, were also useful for mechanistic studies of substitution reactions. Moreover, Zeise's salt $K[PtCl_3(C_2H_4)]$ was the first complex with an alkene coordinated to a metal and cisplatin cis-$[PtCl_2(NH_3)_2]$ was the first approved metal-based anticancer drug. Other interesting features of platinum include the possibility of forming stable compounds with oxidations states other than II, such as 0 or IV, and with different coordination numbers and geometries. The presence of NMR active nucleus (^{195}Pt, natural abundance 33.8%, I=1/2) facilitates the spectroscopic characterization of the compounds. Recently, the luminescence properties of the platinum complexes are attracting great interest, and nowadays the main applications of platinum compounds are related to the development of both anticancer drugs and efficient phosphorescent materials.

4. OBJECTIVES

This project aims to search the properties and applications of the platinum (II) compounds with tetradentate ligands. First of all, it will be focused on collecting information from the different databases like Scifinder, Reaxys, Scopus…

In the last 20 years, two different fields of investigation concerning Pt(II) compounds with tetradentate ligands have awaken a great deal of interest. The first one is related with their luminescence properties that could be useful to develop devices that emit light for long periods.

Furthermore, the second field is involved in medicine, since Pt(II) compounds are useful for the treatment of different types of tumors. Along the years many Pt(II) complexes, including those containing tetradentate ligands, have been tested and developed in the search of more efficient antitumor drugs.

5. METHODS

The investigation on the topic “Platinum(II) compounds with tetradentate ligands: Synthesis and applications” carried out in his project is based in the search of three database:

- Scifinder, the chemistry database of the American society, Chemical Abstracts Service (CAS).
- Reaxys, a chemistry database provided by Elsevier.
- Scopus., a science database provided by Elsevier.

The research have focused on the years from 2000s until present, because a thorough analysis of the number of papers in 5 years interval showed that the number of articles start to grow at the end of 90’s beginning of 2000. For this reason, I considered that the most relevant investigations would be included in the period of the years 2000-2021.

An initial search carried out using Scifinder and using the keywords “platinum tetradentate ligands” gave a high number of articles (near 7000). After filtered, this number was notably reduced by the years (since the first article was written until 2000, the number of articles removed are nearly of 1500).

When filters to consider only the years 2000-2021, as indicated above, and the articles written in English were used, the numbers of articles had reduced notably.

To find each document, the following steps were carried out:

Click in the tittle of the article, go to (Consulta'l UB), and then in services of papers online I choose one of the options that I can click that takes to the the full article.

Once the document is downloaded in pdf format, it is added to the reference manager Mendeley. The downloaded articles can be classified in function of the type of ligands, or the properties of the compounds, mainly luminescence and antitumoral activity.

Reviews summarize previously published research, because it's more detailed information than a simple article on a particular topic, and have a lot of references that can be used to find more information. For these reasons, a search filtered by reviews was also carried out, but it was found that very few reviews (approximately 10) have been published on this subject.

Since different databases may give different sets of articles, it is considered necessary to run the search in more than one database. For this reason, searches were carried out in databases Scopus and Reaxys using the same keywords used in Scifinder. Interestingly, the search in Scopus and Reaxys led to much less articles than in Scifinder, although the filters of Scopus and Reaxys are more accurate than in Scifinder. In fact, the search in Scifinder even if including the keyword platinum gave many results that contain other metals, indicating some failure in the filters. Nevertheless, the most part of the documents could be found in the three dataases and some new documents that were not found in Scifinder, were found in Scopus and Reaxys databases, confirming a higher quality of the filters of these two databases.

6. RESULTS AND DISCUSSION

6.1. Types of ligand

The platinum (II) complexes may have a variety of coordination with the ligands.

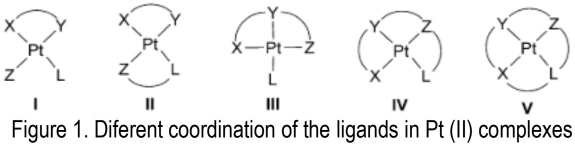


Figure 1. Diferent coordination of the ligands in Pt (II) complexes *(figure extracted from S.Huo et al. Asian J.Org.Chem. **2015**,4, 1210-1245)*

Like it shows in the Figure 1, the complex (I) corresponds to a bidentate and two single monodentate ligands, (II) to two bidentate ligands, (III) to a tridentate and monodentate ligand. Both types of IV and V are based on a single tetradentate ligand, but changes the form of closing the ligand, the structure (IV) is of open chain and (V) are closed chain. Depending on the nature of the ligands, the platinum complexes can be either neutral or ionic.[1]

6.1.1 Cyclometalated ligands

Cyclometalated platinum complexes have been the focus of considerable research, driven in large part by the potential use as sensitizers, photocatalysts, and chemosensors. Cyclometalation commonly refers to the coordination of a polydentate ligand to a metal center through covalent metal-carbon bond. The anionic carbon atom that coordinates to the metal center is a very strong σ-donor that gives rise to a very high energy ligand field splitting, which facilitate the luminescence of the complex system. The planar and rigid structure of the cyclometalating ligands can suppress the non-radiative decay pathway via molecular distortion. These metal complexes have also attracted strong interest as luminescent materials for use in organic light emitting diode (OLED) based display and lighting applications due to their ability to harvest both electro-generated singlet and triplet excitons, resulting in a theoretical 100% electron-to-photon conversion efficiency.

ONCN ligands. [2] New series of cyclometalated platinum(II) complexes supported by a rigid tetradentate ligand O^N^C^N (O^N^C^N=5,5-dibutyl-2-(3-(pyridin-2-yl)- phenyl)-5H-indeno [1,2-b]pyridin-9-olate and its derivatives; 1–5(Figure 1) have been reported. The substitution pattern of the O^N^C^N ligand was found significantly affect the properties of the excimeric emissive excited states.

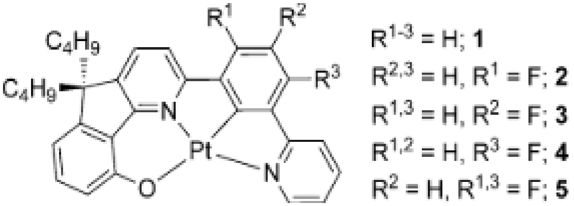
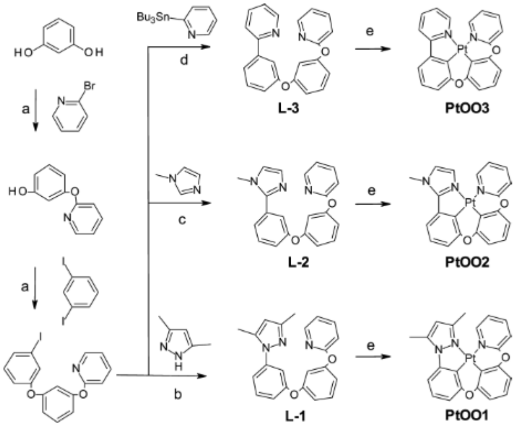


Figure 2.Chemical structure of complexes 1-5 (*figure extracted from S.C.F. Kui et al. Chem.-A Eur.J, 2013,19,69-73)*

NC-O-LL ligands. [3] A class of complexes was developed in which a portion of the ligand could be freely modified with the cyclometalating (N^C) and coupled to shared ancillary portion(L^L) that would not directly contribute to the radiative decay process. This ancillary portion should be relatively easy to reduce and form an additional Pt-C bond to destabilize the well-known metal center quenching states found in platinum complexes.



^{a}Reagents and conditions: (a) 1-methylimidazole (0.5 equiv), K_2CO_3 (2 equiv), CuI (10%), pyridine/toluene (1:1), 120 °C. (b) Cu_2O (10%), syn-2-pyridinealdoxime (20%), Cs_2CO_3 (2.5 equiv), acetonitrile, reflux. (c) CuI (2 equiv), $Pd(OAc)_2$ (10%), 1-methylimidazole (1.5 equiv), DMF, microwave, 150 W, 160 °C. (d) tetrakis(triphenylphosphine)palladium(0) (5%), KF (1.2 equiv), toluene, reflux. (e) K_2PtCl_4 (1 equiv), AcOH, reflux.

Figure 3.Synthesis of tetradentate platinum complexes of the type N^C-O-LL *(figure extracted from E.Turner et al. Inorg. Chem, 2013, 52, 7344-7351)*

6.1.2 Macrocyclic ligands

Macrocyclic ligands are also of theoretical interest since they are capable of furnishing an environment of controlled geometry and ligand field strength. Metal complexes with macrocyclic ligands have generated much research in recent years because of their potential applications in fundamental, applied sciences and coordination chemistry useful in industrial and synthetic process such as catalysis, photochemistry and biological systems. In addition, the study of metal complexes of macrocyclic ligands appears to be interesting in view of the possibility of obtaining coordinating compounds of unusual structure and stability. The formation of macrocyclic complexes depends on the size of the macrocycles, on the nature of its donor atoms and on the complexing behaviour of the anions involved in coordination.

N,N,N,N ligand.[4]

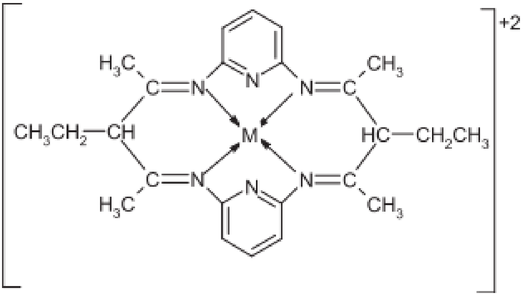


Figure 4. Structure of complex with ligand [N,N,N,N], M= Pt(II), Pd(II) *(figure extracted from S.Rani et al. Spectrochim.Acta-Part A Mol.Biomol.Spectrosc, 2011,78,1507-1514)*

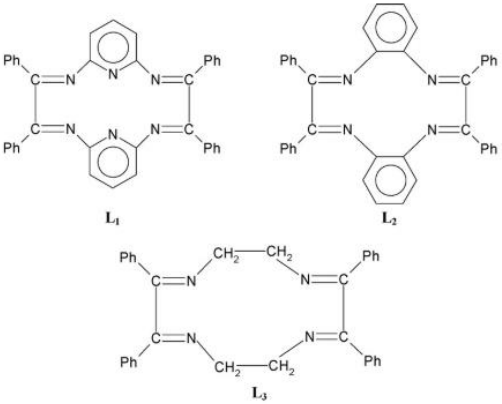


Figure 5. Structure of ligands N^N^N^N (*figure extracted from S.Rani et al. Spectrochim.Acta-Part A Mol.Biomol.Spectrosc, 2011,78,1507-1514)*

Transition metal complexes with macrocyclic ligands have been useful in the study of metal reduction-oxidation (redox) behaviour in well-defined coordination environments and often generating metals in relatively rare oxidation states. Some investigations of the redox behaviour indicate that ligand stereochemistry does play a very important role.[5]

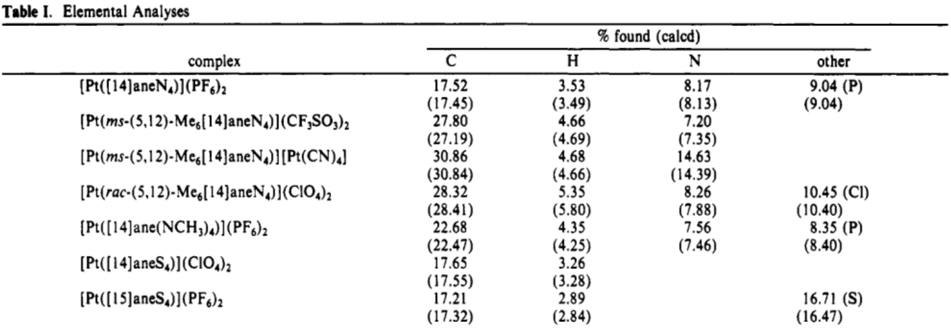


Table I. Elemental Analyses

complex	% found (calcd) C	 H	 N	 other
$[Pt([14]aneN_4)](PF_6)_2$	17.52 (17.45)	3.53 (3.49)	8.17 (8.13)	9.04 (P) (9.04)
$[Pt(\mathit{ms}\text{-}(5,12)\text{-}Me_6[14]aneN_4)](CF_3SO_3)_2$	27.80 (27.19)	4.66 (4.69)	7.20 (7.35)	
$[Pt(\mathit{ms}\text{-}(5,12)\text{-}Me_6[14]aneN_4)][Pt(CN)_4]$	30.86 (30.84)	4.68 (4.66)	14.63 (14.39)	
$[Pt(\mathit{rac}\text{-}(5,12)\text{-}Me_6[14]aneN_4)](ClO_4)_2$	28.32 (28.41)	5.35 (5.80)	8.26 (7.88)	10.45 (Cl) (10.40)
$[Pt([14]ane(NCH_3)_4)](PF_6)_2$	22.68 (22.47)	4.35 (4.25)	7.56 (7.46)	8.35 (P) (8.40)
$[Pt([14]aneS_4)](ClO_4)_2$	17.65 (17.55)	3.26 (3.28)		
$[Pt([15]aneS_4)](PF_6)_2$	17.21 (17.32)	2.89 (2.84)		16.71 (S) (16.47)

Table 1. Some types of Pt(II) with macrocyclic ligands (*figure extracted from D.Waknine et al. Inorg.Chem. , 1991,30,3691-3700)*

6.1.3 Schiff bases

Schiff bases[6] are compounds of general formula $R^1R^2C{=}NR^3$ used as substrates in the preparation of a lot of industrial compounds via ring closure, cycloaddition and replacement reactions. Schiff bases are also important class of compounds in medicinal and pharmaceutical fields such as antimicrobial, antifungal and antitumor activity.

Macrocyclic Schiff base[7] nitrogen donor ligands have received special attention because of their mixed hard-soft donor character and versatile coordination behaviour. Platinum complexes of some Schiff base ligands derived from S-alkyl esters of dithiocarbazic acid have been found to exhibit marked cytotoxicity against leukaemia and the human ovarian cancer cell lines.

ONNO ligands.

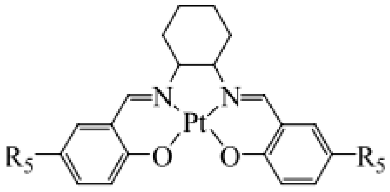


Figure 6. Structure of ONNO ligands *(figure extracted from S.Chandra et al. Spectrochim.Acta-Part A Mol. Biomol. Spectrosc, 2008, 71, 720-724)*

6.1.4 Dinuclear platinum compounds

Furthermore, there were developed a new type of complex that is different of the others because there are two metal centers that coordinate with the tetradentate ligand. This ligand was the first one developed for treatments of various cancers - that reacts in vitro, joining to the DNA, avoiding the replication of the DNA in the cell and causing the apoptosis of the cell. It shows that multinuclear platinum complexes with two or more metal centers in close proximity can effectively deliver drugs to a tumor and possibly form mutable-binding with tumor cell to block DNA replication. [8]

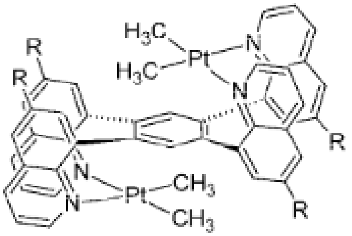
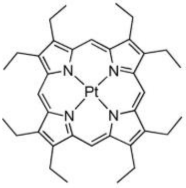


Figure 7. Structure of dinuclear Pt (II) *(figure extracted from R. Tan et al. Organometallics, 2008, 27, 6614-6622)*

6.2 Photoluminescence studies

Since the first organic electroluminescent diode with a low driving voltage and promising luminescence efficiency was demonstrated by Tang and VanSlyke in 1987, much efforts have been devoted to the development of OLEDs in order to achieve high luminescence efficiency, long device lifetime, low manufacturing cost and good color purity. Nowadays OLED technology has been extensively used in flat panel displays for portable or wearable devices such as cameras, cellular phones and watches, and recently, found applications in the market of large screen TVs. [9] In 1998, Baldo used a platinum octaethylporphyrn (PtOEP) as emissive material with encouraging results.



PtOEP

1

Figure 8. The first Pt(II) complex investigated *(figure extracted from J.A. Gareth Williams et al. Coord. Chem. Rev, 2008,252, 2596-2611)*

OLEDs (organic light emitting devices) are like a sandwich between two electrodes (cathode and anode). The organic layer at the cathode is reduced and the anode oxidized to give electron and hole carriers, respectively. When the latter occurs, the two carriers combine to produce one ground state molecule and an exciton, this is comparable to the excited state produced by the transfer of an electron between HOMO to LUMO.[10]

In the investigation for the improvement parameters of OLEDs, previously the photo-physics properties of the complexes of Pt (II) are studied by different methods to calculate the frontier orbitals HOMO (higher occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) that are the responsible for the transitions of energy emissions. These studies are carried by methods like DFT and TADF[11]. Furthermore, electronic spectroscopy can excite electrons since the ground state to excited states without ionizing the complex. The UV-visible spectroscopy is a method who is employed a lot to determine the behavior of the ligands with the metallic center, the wavelengths range between 200-400 nm correspond to high energy transitions and are correlated with interactions between the ligand orbitals. Between 400-700 nm there are transitions of standard energy that can be attributed to the d orbitals of the metal. These types of bands are nominated like transferring charge and there are different types that give different information, the transitions d-d are the causing of the color of complex. There are other ones like the LMCT (ligand-to- metal charge transfer) and MLCT(metal-to- ligand charge transfer),and both indicate the intensity of the color, when more higher is the band more intensity have the color of the complex.

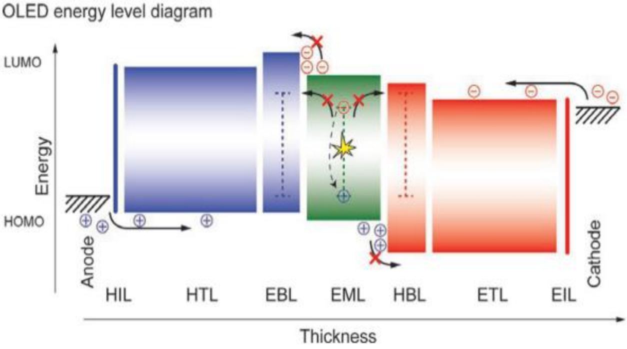


Figure 9. Energy-level diagram of a multilayer OLED *(figure extracted from P.Will et al. Elsevier Ltd, 2019, 2nd edition)*

As shown in figure 9, from anode to cathode, there are different functional layers in an OLED. From anode to cathode, the functional layers are: hole injection layer (HIL), hole transport layer (HTL), electron blocking layer (EBL), emission layer (EML), hole blocking layer (HBL), electron transport layer (ETL) and electron injection layer (EIL). To achieve a high efficiency the device has to pass the following characteristics, the HIL have to facilitate the injection of holes since the anode to the HTL. This can be made if the energetic level of HOMO of HIL is between the HOMO of HTL and the ionization potential of anode. The HTL should present a higher hole mobility and stop the electrons arriving to the anode. The HOMO and LUMO of the EML, should be facilitate the pass of holes and electrons in the EIL, for this usually are employed a metal like Mg o Ca. Also it requires that one of the electrodes is transparent to the light, in most cases an oxide of tin-indium (ITO) or a fluorine doped in oxide (FTO) are used. [12][13]

The d^8 square planar compounds have opened up the design of white OLEDs (WOLEDs) by the combination of three primary colors red, green and blue (RGB) or based on single emitter. For example, square planar Pt complexes may form excimers so that is possible to generate blue emission from the molecule and yellow to red emission from the excimer resulting in white light from a single compound. There are more techniques for the design of WOLEDs, one of them consists in one mixture of co-polimers, another one it's a structure dopped with diferent colorants, and also there are developed another technique based in bimolecular complexes that can produce exciplex states for increase the emission spectrum. Independently of the use of each technique, all of these have to reach a necessary requirement, the emission spectrum have to cover all the wavelengths of all the visible region to generate white light. [14][15]

One of the disadvantages of the WOLEDs are the device lifetime, to be useful, it has to exceed 1000h over a luminescence close to 800cd/m^2 and it's a little close of this value. [16]

Furthermore, there are developed PHOLEDs, a type of OLED that use the phosphorescence instead of fluorescence. With phosphorescence higher internal efficiency (IQE) than in fluorescent OLEDs have been reported. There's a difference between fluorescence and phosphorescence and it is the different form to keep the energy. The fluorescence absorbs the energy of UV and immediately emit the illuminated radiation. On the other side, phosphorescence starts like the fluorescence, but retain the time of the emission, being able to emit the illuminated radiation slowly during hours after the beginning excited radiation.[17]

Since then, organometallic compounds based on transition metal centers, have attracted extensive attention in the past decades, considering attractive candidates for full-color display technologies and energy-saving solid-state lighting. It has been shown that the presence of a heavy metal center with a high spin-orbit coupling constant can effectively promote rapid intersystem crossing from the singlet excited state to the lower-energy triplet excited state at room temperature.

Second and third row transition metals with d^8 electronic configuration prefer square-planar coordination, which[18] allows the formation of excimer and the linear stacking of these square species via axial coordination.

Platinum (II) complexes, have been proved to be potential materials for optoelectronic devices, including organic solar cells and OLEDs. The square planar geometry of platinum (II) complexes can accommodate tetradentate ligands, containing nitrogen donor ligands with interesting luminescence properties. This coordinative insaturation nature of platinum (II) has been found to show unique spectroscopic and luminescence functionality as a consequence of their propensity to form aggregates, excimers and exciplexes via non-covalent metal-metal interactions in the solid state thin films.

6.2.1 Photophysicals and luminescence properties

Several parameters currently used to report the efficiency of OLEDS are summarized below.

EQE, the external quantum efficiency of a device gives the ratio of the number of useful light particles to the number of injected charge particles. Is the most representative performance indicator quantity when differents OLEDs are comparing due that gives the ratio of extracted photons over injected charges.

IQE, internal quantum efficiency, is defined as the ratio of the number of photons emitted from active region per second respect to the number of electrons injected per second, within the active layers of the device. The IQE is the value most comparable to the PLQY, photoluminescence quantum yield, is the ratio of the number of photons emitted to the number of photons absorbed.[10]

PE, power efficiency, is defined as the ratio of output light power to input electric power.

In a diode, the light emission is due to radiative decay of the excitons to produce the photons. The exciton could be in the singlet state or triplet state according to the global electronic spin. Only the singlet states can decay radiatively in common organic compounds. Since the probability to form excimers in the singlet state is 25%, it means that 75% of the excitons created have non-radiative decay.[13]

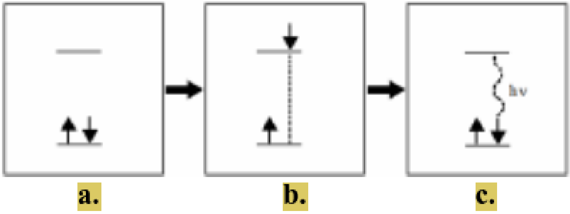


Figure 10. Steps of the radiation due that of singlet excimers *(figure extracted from O.Mauricio et al. Sci.Tech,2017,16,199-206)*

In the figure 10, the state of a) represents the ground state, in b) shows how one of the electrons absorb energy passing to a higher level, obtaining the excited singlet state, and in c) it shows when the electron decays to the ground state after the radiative emission. The quantity of radiative emission can be quantified and OLEDs with phosphorescent materials for which emission can occur from both singlet and triplet excitons can be made. The subsequent radiative decay of the triplet state, which is formally forbidden in organic systems, should be promoted by the high spin-orbit coupling of heavy metals. The extent to which this occurs depends on the contribution of metal orbitals to the lowest energy triplet excited state.

CE, current efficiency, is the ratio of the electrochemical equivalent current density for a specific reaction to the total applied current density (CD) and describes the efficiency with which electrons are transferred in a system facilitating an electrochemical reaction.[19]

CD, current density, refers to the density of current flow in some conductor and it's the measure of the flow of electric charge and gives a vector quantity due to be having the direction of the electrons flow.

CIE, Commission Internationale de L'Eclaraige (1931), is a chromatometry system to describe the hue, luminescence, and saturation of colors. To determinate the chromatometry coordinates (x,y) the value of three primary colors (blue,red and green) of a certain color were defined to tristimulus values of the color. The tristimulus values provide a reliable system that provides manufacturers and costumers a way to communicate color preferences in order to ensure precise color matching and product compatibility. [20] [21]

6.2.2 Application of Pt(II) compounds for OLEDs

Over the years Ir(III) octahedral complexes have been dominating, but in the past decade, recent developments have enabled square-planar Pt(II) and Pd(II) complexes to meet or exceed the performance of Ir complexes. Currently OLEDs are gaining on increasing share in the display market as small displays for portable and wearable electronics, and even as the next generation of high-definition and large screen televisions. Much of the success of this technology is the continued development of phosphorescent metal complexes that are capable of high efficiencies and high color quality across the visible spectrum. Despite of Pt complexes have been historically considered less satisfactory due to their relatively long luminescent lifetime and low photoluminescence, they are also comparable to its Ir analogs and are considered as an alternative for phosphorescent OLEDs applications.

Platinum (II) complexes[22] have exhibited blue to red emissions depending on both ligand frameworks and substituents. In comparison with green or red emissions in Pt(II) complexes, achieving blue emission is highly challenging and much research has been focused on it over the past two decades. Emission in platinum complexes predominately originates from intraligand charge transfer (ILCT) mixed with a metal to ligand charge transfer transition (MLCT).

Phosphorescent organic light-emitting diodes (PHOLEDs)[23][24] are leading candidates for next-generation displays and solid-state lighting technologies. Efficient phosphorescent metal complexes emitting in the green and red spectral regions have been well developed and incorporated into efficient and stable OLEDs. On the other hand, blue phosphorescent materials and their devices have demonstrated much less success, being progressively more challenging. There are many potential reasons for this deficiency, the most important of which is the competition between the population of desirable radiative excited states and nonradiative states that reduce emission efficiency and can result in molecular dissociation.

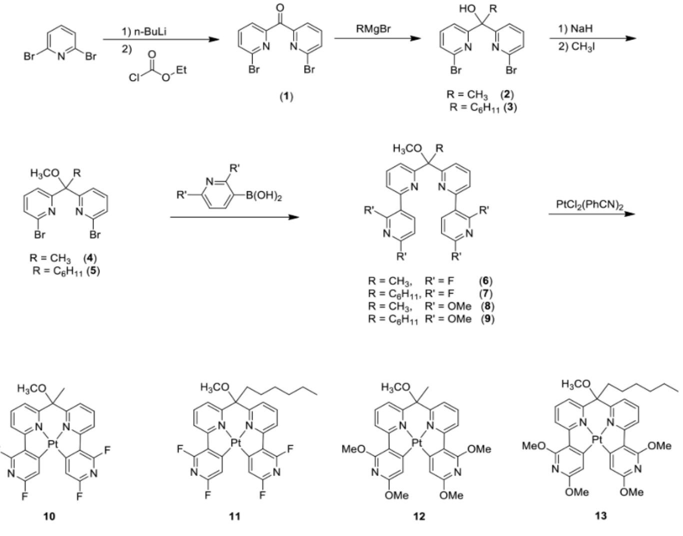


Figure 11. Synthesis of complexes with CN chelating ligands (10-13)
(figure extracted from C.Lee et al. Organometallics, 2018, 37,4639-4647)

Platinum (II) complexes containing N-donor and/or cyclometalated ligands have emerged to be important classes of phosphorescent materials with useful practical applications in molecular and bio-molecular sensing and in organic electronics.

A series[25] of cyclometalated platinum (II) complexes supported by a new tetradentate ligand O^N^C^N have been reported. These Pt(II) complexes shows high energy monomer emission (480-520nm) and low energy excimer emission (>600nm) enabling the fabrication of high-efficiency WOLEDs by using it as single emissive dopant. However, excimer emission is not desirable in achieving high performance red, green and blue OLEDs.

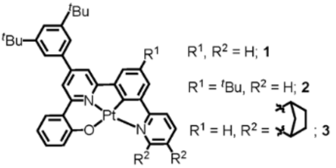


Figure 12. Pt(II) complexes electrophosphorescent with tetradentate ligands (1-3)
(figure extracted from S.C.F. Kui et al. Chem.Commun. ,2013,49,1497-1499)

It shows complex 3 has a high phosphorescence quantum yield, maybe because the bulkynorbornane group on the pyridine moiety can block intermolecular interactions thus disfavouring excimer formation in solutions.

Furthermore, the LUMO can be destabilized with isoelectronic azolyl rings. An additional pathway has been demonstrated recently, which raises the triplet energy through using the nonconjugated binding group in the cyclometalating ligand, forming 6-membered metal chelation ring, without containing any strong electron-withdrawing groups or azoyl rings, doing this strategy more compatible with the state of the art transporting and host materials.

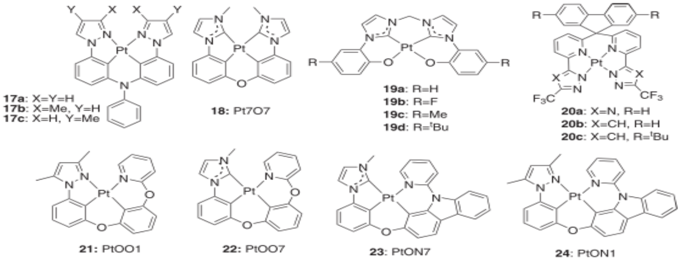


Figure 13. Molecular structures of selected blue-emitting tetradentate Pt complexes
(figure extracted from T. Fleetham et al. Adv.Matter, 2017,29,1-16)

Tetradentate ligands of Pt blue emitting, exhibit higher values in emission efficiency and much lower emission energies than bidentate analogs. The decrease of emission energies of these complexes can be attributed to extended pi conjugation through the amino bridging ligands.

One of the most successful strategies for OLEDs is the use for asymmetric tetradentate Pt complexes (21-24) which contain C^N cyclometalating ligands oxygen bridged to a high triplet energy “supporting-ligand”.

White OLEDs are the result to generate blue emission from individual molecules alongside broad yellow to red emission from excimers, resulting in a white-light generation based on a single emissive material. The achievement of broad white emission covering the visible spectrum poses several significant challenges, like achieving sufficient blue emission, turning the excimer emission energy, and the simultaneous optimization of both emission spectra to span a wide range of the visible spectrum.

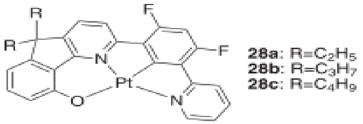


Figure 14. Pt (II) complexes (WOLEDs) *(figure extracted from T. Fleetham et al. Adv.Matter, 2017,29,1-16)*

Furthermore, there are yellow and red OLEDs of Pt(II) complexes as dopants for PHOLEDs.[18]

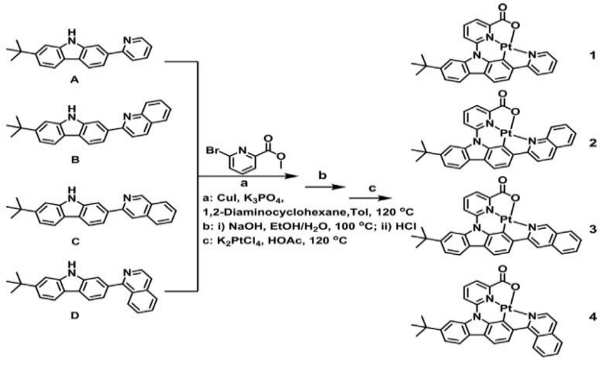


Figure 15. Synthetic routes of complexes 1,2,3,4 (*figure extracted from D.Zhao et al. Org.Electron, 2018, 62, 542-547)*

Complex 1 and 3 are yellow emitters in their PL spectra meanwhile 2 and 4 are red emitters. In order to achieve the large color gamut for the high quality display application, the dopant materials with saturated emission were highly desirable.

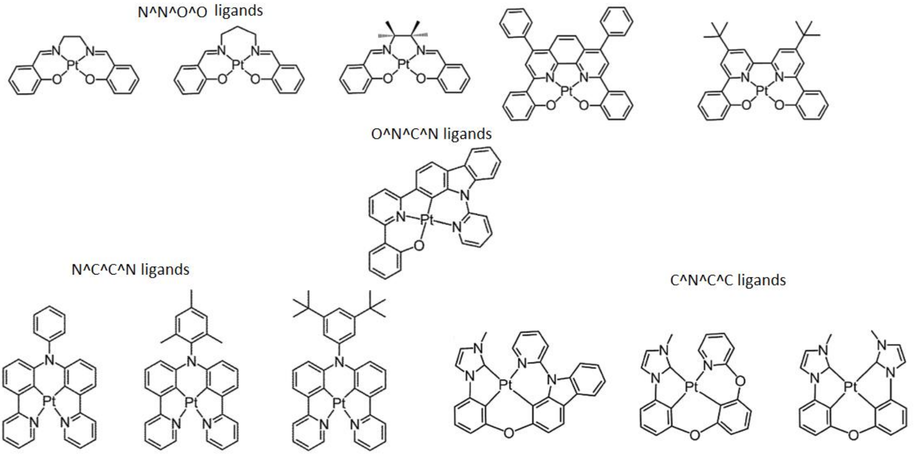
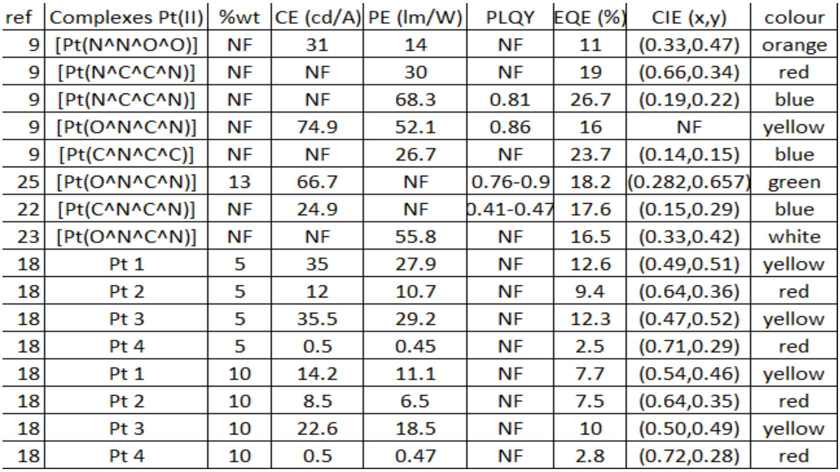


Figure 16. Complexes of Pt (II) with tetradentate ligands of the table 2. (*figure extracted from* M. C. Tang et al.,*Top. Curr. Chem, 2016,* 374, 1–43)

The parameters obtained for OLEDs containing a selection of platinum (II) compounds with different tetradentate ligands are collected in table 2



ref	Complexes Pt(II)	%wt	CE (cd/A)	PE (lm/W)	PLQY	EQE (%)	CIE (x,y)	colour
9	[Pt(N^N^O^O)]	NF	31	14	NF	11	(0.33,0.47)	orange
9	[Pt(N^C^C^N)]	NF	NF	30	NF	19	(0.66,0.34)	red
9	[Pt(N^C^C^N)]	NF	NF	68.3	0.81	26.7	(0.19,0.22)	blue
9	[Pt(O^N^C^N)]	NF	74.9	52.1	0.86	16	NF	yellow
9	[Pt(C^N^C^C)]	NF	NF	26.7	NF	23.7	(0.14,0.15)	blue
25	[Pt(O^N^C^N)]	13	66.7	NF	0.76-0.9	18.2	(0.282,0.657)	green
22	[Pt(C^N^C^N)]	NF	24.9	NF	0.41-0.47	17.6	(0.15,0.29)	blue
23	[Pt(O^N^C^N)]	NF	NF	55.8	NF	16.5	(0.33,0.42)	white
18	Pt 1	5	35	27.9	NF	12.6	(0.49,0.51)	yellow
18	Pt 2	5	12	10.7	NF	9.4	(0.64,0.36)	red
18	Pt 3	5	35.5	29.2	NF	12.3	(0.47,0.52)	yellow
18	Pt 4	5	0.5	0.45	NF	2.5	(0.71,0.29)	red
18	Pt 1	10	14.2	11.1	NF	7.7	(0.54,0.46)	yellow
18	Pt 2	10	8.5	6.5	NF	7.5	(0.64,0.35)	red
18	Pt 3	10	22.6	18.5	NF	10	(0.50,0.49)	yellow
18	Pt 4	10	0.5	0.47	NF	2.8	(0.72,0.28)	red

Table 2. Recopilation of different tetradentate ligands with their efficience in OLED, view figure 11,12,14,15 and 16 (NF means not found in the reference)

6.3 Biological properties

6.3.1 Antitumoral activity

Platinum metallo-drugs[26] are among the most effective agents for the treatment of cancer; however its clinical utility is restricted due to the frequent development of drug resistance. These disadvantages have driven the development of improved platinum-based anticancer drugs different from the traditional cisplatin structure and which could probably have different DNA-binding modes as well as exhibit different biological profiles.

Therefore, developing novel platinum complexes with reduced toxicity, improved clinical efficacy and a broader anticancer spectrum is an area of focus for anticancer drugs research. Following the classical structure-activity relationships of cisplatin and analogues, has offered thousands of platinum compounds, but the carboplatin and oxalplatin are the best representatives[27].

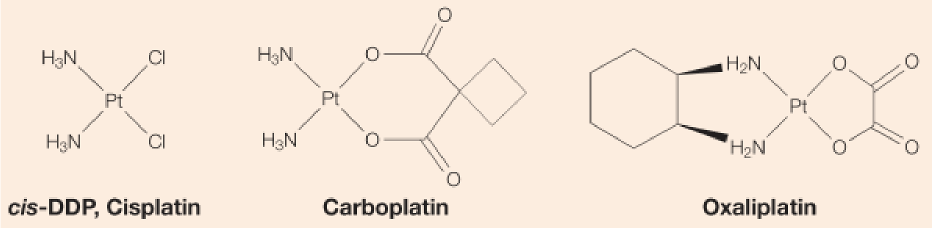


Figure 17. Platinum anticancer drugs used worlwide *(figure extracted of D.Wang et al. Rev.Drug Discov. 2005,4,307-320)*

Specific chemical and structural features can be incorporate into new Pt[6] compounds so that they are able to circumvent a specific drug resistance mechanism, such as sterically hindered Pt complexes. There also have been efforts directed at the design of unconventional complexes that violate the original structure-activity relationships, such as trans Pt compounds and binuclear Pt complexes. It is hoped that they will overcome Pt drug resistance in tumors and be applicable to a broader range of cancers. In recent years, there has been a gradually attempt in the application of electrochemical techniques, to understand interactions between

DNA and moleculers due to cheapness, simplicity, fast detection and small amount of sample required with respect to the generally used spectroscopic methods.

Cisplatin[28] which was found to own great anticancer activity by Rosenberg B in 1965, known as a widely used chemotherapeutic agent, serves as one of the most effective antitumor agents in the treatment of testicular cancer, and is also used in combination regimens for a variety of other tumors, including ovarian, cervical, bladder, lung, and those of the head and neck.

The antitumoral activity of several types of platinum compounds with tetradentate ligands has been reported and will be summarised below. Pt (II) complexes with Schiff bases as ligands have more thermodynamic stability.

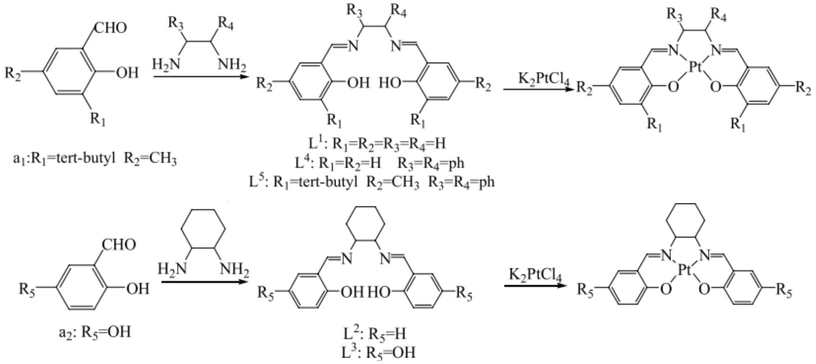


Figure 18. Synthesis of differents ligands with Schiff bases and their complexes of Pt(II) *(figure extracted from L.Li et al. E-Journal Chem, 2012, 9,1422-1430)*

Compounds were tested for their DNA interaction ability using differential pulse voltammetry. The determined DNA binding levels for platinum complexes showed that [Pt(L^1)] had the best interaction with DNA, substituents on ligands can effectively influence the interaction between Pt complexes and DNA, bulky substituents on ligands can effectually embarrass the coordination of Pt ion to guanine and adenine residues. It would be necessary more extensive observations in this study to assert that the complexes act as cleavage agents.

Another example are using bpy and terpy as ligands, because they have the ability to intercalate into DNA, that can give rise to anticancer activity for certain members of this class of compounds. The complex of platinum wears as a ligand a ***β***-diketiminate ligand (BDI^{QQ})$^-$.

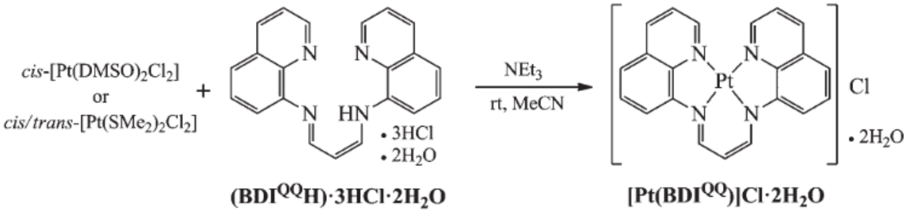


Figure 19. Synthesis of [Pt(BDI^{QQ})]Cl *(figure extracted of J.M.Hope et al. Dalt. Trans, 2013,42,3176-3180)*

Molecules that interact with DNA, including related platinum-terpy complexes, often exhibit cytotoxic properties, the cell killing ability of the BDI^{QQ} was assessed in human lung carcinoma (A549) and cervical cancer (HeLa) cell lines compared to that of the established anticancer drug cisplatin. The IC$_{50}$ values, determined by the colorimetric MTT assay, show that Pt BDI^{QQ} exhibits cytotoxicity in HeLa cells similar to that of cisplatin, where as in A549 cells it is approximately four times more potent. Although this research about Pt BDI^{QQ} compound showed that it is cytotoxic, the mechanism of this cytotoxicity is unknown right now. However, the emission turn-on may be useful for future cellular imaging studies, and also the complex exhibit better results than cisplatin in the two cell lines tested and it maybe expanded to cell lines in order to further evaluate the complex as a chemotherapeutic agent.[29]

Since the discovery of cisplatin as a clinically approved anticancer drug, many researchers have focused on the synthesis of new analogous platinum (II) coordination compounds to developed more potent drugs with low side effects. Carboplatin and oxaliplatin were developed to overcome the resistance observed in some type of cancers. The progress[30] in the new design of platinum (II) drugs has been recently reviewed. It has been suggested that in order to obtain high cytotoxic to Pt drug, the corresponding Pt(II) complex is supposed to be cationic and planar to increase the interaction with DNA and also should have a favourable chemical structure bearing significant functional groups such as NH moiety for H-bonding interactions toward DNA. In addition, the compound incorporating a large interacting aromatic moiety shows better interactions with DNA. As previously mentioned, they successfully showed that the calculated binding constants Kb, increase in the order upon increasing the aromatic planar surface extension as expected ($[Pt(bpy)(py)_2]^{2+}$ <$[Pt\text{-}(terpy)(py)]^{2+}$ < $[Pt(quaterpy)]^{2+}$). It's well-known that minor changes in the chemical structure can lead to pronounced differences in the biological activity of organometallic coordination compounds. This is confirmed by Pt(bpy)$_2$Cl$_2$ and analogous compounds with bpy, moieties which exhibit lower cytotoxic activity than cisplatin, but the cisplatinum (II) complex with 2'-pyridyl(benzimidazole) shows a remarkable cytotoxicity toward certain tumor cell lines. The new complex is a dicationic Pt(II) complex showing square-planar geometry and is very stable in the solid state and in solution. The ligand has a tetradentate binding pocket which makes the compund essentially planar.

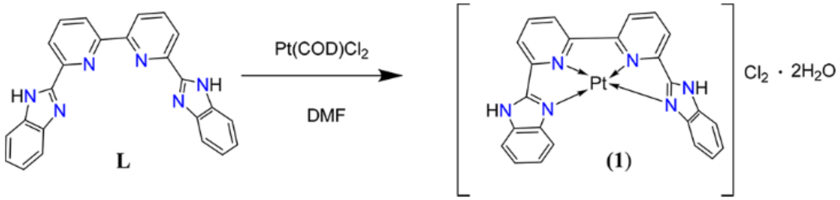


Figure 20. Synthesis of complex 1 [Pt(QP)] , QP= quaterpyridine, N4-donor ligand *(figure extracted from I.Yllmaz et al. ACS Med. Chem. Lett, 2020,11, 940-948)*

PC-3, A549, MDA-MB-231, HCT-116, and BEAS-2B cells were treated with varying concentrations of complex 1 to evaluate the antigrowth/cytotoxic effect via SRB cell viability assay and confirmed by ATP assay (ATP shows more sensibility than other cell viability tests). It was found that complex 1 decreased cell viability in a dose-dependent manner in all five cell lines as a result of SRB assay. Especially PC-3 and MDA-MB-231 were found more sensitive than HCT-116 and A549 cell lines, according to the ATP assay. On the other hand A549 shows resistance to complex 1. Although, the complex 1 has no cytotoxic effect to non-tumorigenic BEAS-2B cells.

Two different cell viability assays were done, the SRB assay reflects the amount of protein mass of alive cells. The ATP assay is done to confirm the results of SRB because is more sensitive. These two assays are biologically different but match each other very well. The cytotoxic activity of N4-donor ligand, is a component of complex 1, that was investigated by using SRB assay, whether cell death is caused by complex or ligand itself, generating a process of apoptosis.

In conclusion, complex 1 induced intrinsic apoptosis with the increased mitochondrial membrane depolarization level Bcl-2, and DNA damage in PC-3 and A549. The platinum (II) complex induced mitochondrial membrane depolarization in a time-dependent manner in BEAS-2B. Also it increased Bcl-2 inactivation and DNA damage. To sum up, the in vitro analysis showed that the cationic square-planar platinum(II) coordination compound with N4-donor ligand, that induces apoptosis with different mechanisms in cell lines. Also, platinum-based complex 1 caused cytotoxicity with less concentration compared to clinically used platinum-based drugs such as cisplatin. All these results supported the potential of use complex 1 as a drug in cancer treatment.

It has been shown that multinuclear platinum complexes with two or more metal centers in close proximity can effectively deliver drugs to a tumor and possibly form mutable-binding with tumor cell DNA, thereby increasing the ability of the drug to block DNA replication. Intercalative binding is a kind of noncovalent stacking interaction resulting from the insertion of planar aromatic rings into the grooves of the DNA double helix structure. Polynuclear platinum complexes with intercalative bindings are capable to intercalate between DNA bases while the metal coordinates directly to DNA bases that could lead DNA functional changes, such as inhibitions of transcription, replication and DNA repair processes, which make intercalators potent mutagens.

Oxaliplatin is the first platinum based drug containing a chiral moiety, 1R,2R-diaminocyclohexane (DACH), as a carrier group, and is now a preferred drug in the treatment of advanced colorectal carcinoma. Although, oxaliplatin has replaced cisplatin as the largest selling platinum therapeutic, its dose-limiting toxicity in clinical practice is unacceptable, 90% of patients treated with oxaliplatin suffer from acute neurotoxicity and 15% suffer from cumulative sensitivity.

DACH is believed to play an important role in the success of oxiplatin. In this instance two chiral DACHs have been linked with a phenyl group as bridge to afford a novel chiral tetradentate ligand (HP) which can present four coordination sites to Pt(II) and provide a foundation for the preparation of a series of novel dinuclear platinum complexes.

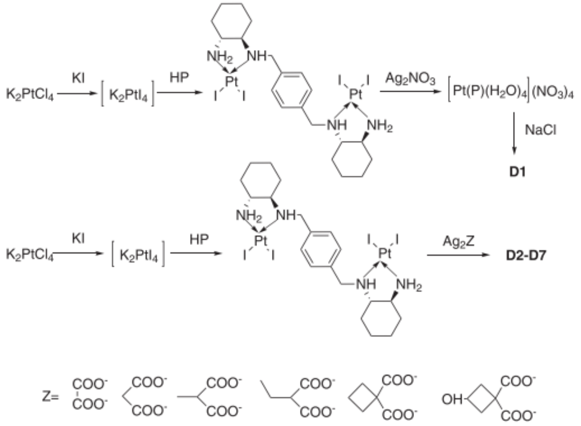


Figure 21. Stynthesis D1-D7 of dinuclear platinum (II) with DACH *(figure extracted from Y.Zhang et al., Appl.Organomet.Chem.,2015,29,481-486)*

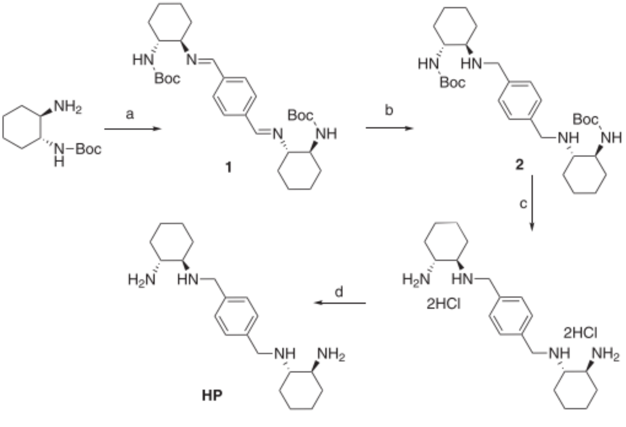
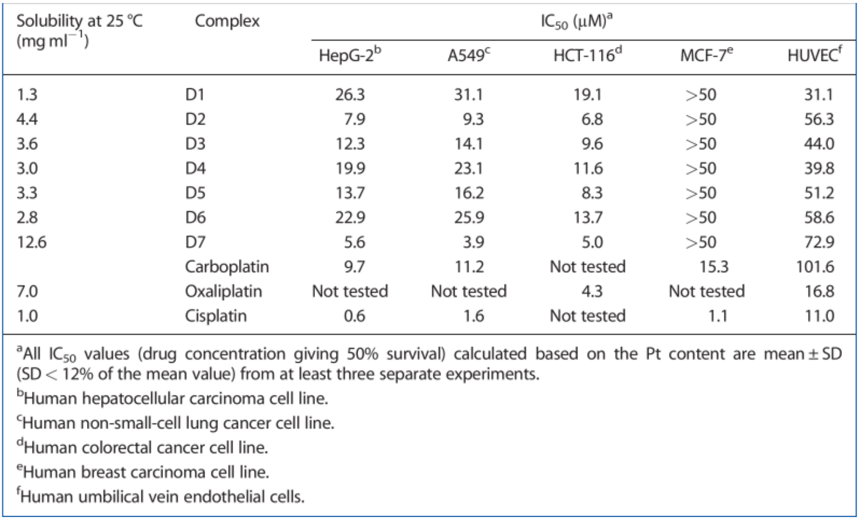


Figure 22. Preparation of ligand HP (a)p-phthalalaldehyde,toluene, refluxing; (b) $NaBH_4$; (c)HCl-EtOAc, Et_2O; (d) Na_2CO_3 (*figure extracted from Y.Zhang et al., Appl.Organomet.Chem.,2015,29,481-486)*



Solubility at 25 °C ($mg\ ml^{-1}$)	Complex	IC_{50} (µM)[a]				
		HepG-2[b]	A549[c]	HCT-116[d]	MCF-7[e]	HUVEC[f]
1.3	D1	26.3	31.1	19.1	>50	31.1
4.4	D2	7.9	9.3	6.8	>50	56.3
3.6	D3	12.3	14.1	9.6	>50	44.0
3.0	D4	19.9	23.1	11.6	>50	39.8
3.3	D5	13.7	16.2	8.3	>50	51.2
2.8	D6	22.9	25.9	13.7	>50	58.6
12.6	D7	5.6	3.9	5.0	>50	72.9
	Carboplatin	9.7	11.2	Not tested	15.3	101.6
7.0	Oxaliplatin	Not tested	Not tested	4.3	Not tested	16.8
1.0	Cisplatin	0.6	1.6	Not tested	1.1	11.0

[a] All IC_{50} values (drug concentration giving 50% survival) calculated based on the Pt content are mean ± SD (SD < 12% of the mean value) from at least three separate experiments.

[b] Human hepatocellular carcinoma cell line.

[c] Human non-small-cell lung cancer cell line.

[d] Human colorectal cancer cell line.

[e] Human breast carcinoma cell line.

[f] Human umbilical vein endothelial cells.

Table 3. Results with different Pt(II) complexes in different assays tumor cells *(figure extracted from Y.Zhang et al., Appl.Organomet.Chem.,2015,29,481-486)*

The in vitro cytotoxic activities of compounds D2-D7 against five human cell lines, were evaluated using the MTT assay. Cisplatin, carboplatin and oxaliplatin were used as positive controls.

The results show all dinuclear platinum complexes display cytotoxicity towards HepG-2, A549 and HCT-116 cell lines. However, none of the target platinum complexes display any appreciable activity (IC_{50}>50Um) towards MCF-7 cell line. This suggest that MCF-7 line is resistant to the dinuclear platinum complexes.

Compounds D2 and D7 show potent antitumor activity against HCT-116 cell line, in compared to activity of carboplatin, and show much better activity against HepG-2 and A549 cell lines (for the same compounds). In addition, cisplatin shows values for HUVEC three and four times less cytotoxic than oxaliplatin, that compared to oxaliplatin, D2 and D7 may be selectively cytotoxic for human cancer cell lines.

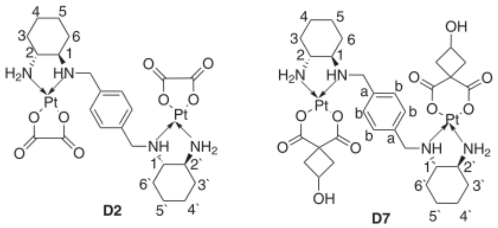


Figure 23. Compounds D2 and D7 dinuclear platinum (II) *(figure extracted from Y.Zhang et al., Appl.Organomet.Chem.,2015,29,481-486)*

Considering the favourable anticancer activities and relatively mild side effects of oxaliplatin, it has been synthetized six dinuclear platinum complexes based on the structure of oxaliplatin. The structure of DACH which has been believed to play an important role in the success of oxaliplatin was retained while a benzene-bridge was introduced as DNA insertion group to enhance the ability of DNA-bindings[31].

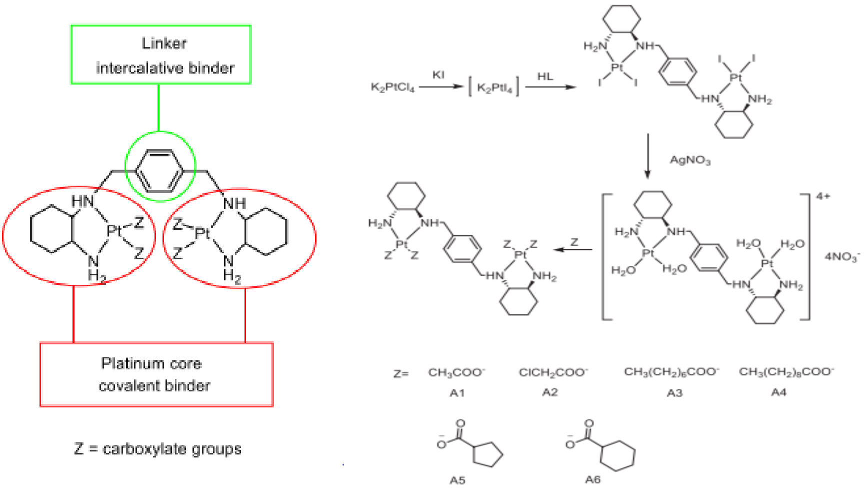


Figure 24. Dinuclear platinum complexes based on oxaliplatin with a benzene-bridge *(figure extracted from C. Yu et al. Bioorganic Med. Chem. Lett, 2017,27,481-486)*

With a chiral tetradentate ligand, six dinuclear platinum complexes (A1-A6) which owned several carboxylates as leaving groups have been designed and synthetized to evaluate antitumor bioactivity. All compounds showed positive antitumor activity to HepG2, HCT-116 and A549 cell lines. Compound A2 which has $ClCH_2COO^-$ as a leaving group not only showed better antitumor activity than carboplatin against the four tested cancer cell lines, also showed a comparable activity against HCT-116 and HepG2 to oxaliplatin and cisplatin.

6.3.2 Antimicrobial activity [4]

The chemical properties of macrocyclic complexes can be tuned to force metal ions to adopt unusual coordination geometry. Platinum complexes are of biological importance due to their carcinostatic activity and interest in biological chemistry. The characterization and biological activity of transition metal complexes, including Pt coordinated with the ligand (L) 3,5,13,15(tetramethyl4,14diethyl2,6,12,16,21,22hexaazatricyclodicosa1,(21),2,5,7,l9,11(22),12, 15,17,19-decaene) have been reported.

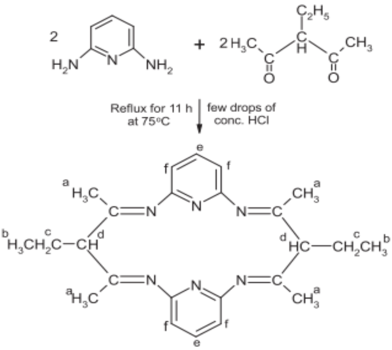
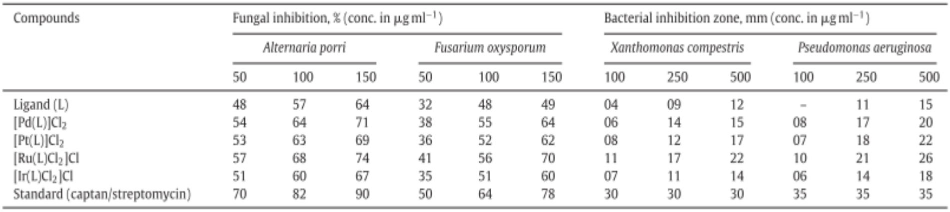


Figure 25. Synthesis of ligand "L" *(figure extracted from S.Rani et al. Spectrochim.Acta-Part A Mol. Biomol. Spectrosc., 2011,78,1507-1514)*

The antifungal and antibacterial screening of platinum (II) compounds, is carried out using Food Poison and Disc Diffusion Method against plant pathogenic fungi and bacteria Alternaria porri, Fusarium oxysproum, Xanthomas compestris and Pseudomonas aeruginosa, respectively.

The fungicidal activity of the ligand and complexes was determined in vitro by Food Poison Technique. The inhibition of fungal growth expressed in % terms was determined form the growth in the test plates compared to the respective control plates.

It has been found that the activity of the ligand was always less pronounced than those of its complexes, demonstrating that complexation with metals enhance the anti pathogenic activity of the ligand. The values obtained from the antifungal and antibacterial screening of the compounds indicate that the Pt(II) complex show moderate antimicrobial activity in comparison of the free ligand.



Compounds	Fungal inhibition, % (conc. in μg ml^{-1})						Bacterial inhibition zone, mm (conc. in μg ml^{-1})					
	Alternaria porri			*Fusarium oxysporum*			*Xanthomonas compestris*			*Pseudomonas aeruginosa*		
	50	100	150	50	100	150	100	250	500	100	250	500
Ligand (L)	48	57	64	32	48	49	04	09	12	–	11	15
$[Pd(L)]Cl_2$	54	64	71	38	55	64	06	14	15	08	17	20
$[Pt(L)]Cl_2$	53	63	69	36	52	62	08	12	17	07	18	22
$[Ru(L)Cl_2]Cl$	57	68	74	41	56	70	11	17	22	10	21	26
$[Ir(L)Cl_2]Cl$	51	60	67	35	51	60	07	11	14	06	14	18
Standard (captan/streptomycin)	70	82	90	50	64	78	30	30	30	35	35	35

Table 4. Antifungal and antibacterial activities of ligand (L) and its complexes *(figure extracted from S.Rani et al. Spectrochim.Acta-Part A Mol. Biomol. Spectrosc., 2011,78,1507-1514)*

7. CONCLUSIONS

The research of the Pt (II) complexes with tetradentate ligands has been focused on the last 20 years. At this moment, there is still a lot of work to develop in the two fields where the complexes of Pt(II) can be applied. Nevertheless great advances in the study of the Pt(II) compounds with tetradentate ligands have been obtained.

Concerning the luminescence properties, multiple tests have been carried out to achieve higher efficiency in the different Pt(II) compounds with tetradentate ligands. First of all, the energies of the orbitals HOMO and LUMO of the complexes are calculated thanks to methods like DFT. The energies of these orbitals influence the properties, which can be modulated in function of the type of ligands by stabilizing these orbitals and facilitating the transition of the electrons of the ground state (singlet) to the excited state (triplet), where the light emission is produced. Furthermore, UV-vis spectra are done to know and assign the absorption bands and a chromatogram that allows identifying the color of the emission is also studied.

Moreover, there are made different assays to improve the efficiency of the devices (OLEDs). For the consequent analysis, the Pt(II) complexes with tetradentate ligands are used as dopants dissolved in an organic polymer like DCM or PMMA...

This type of essay has a little inconvenient, there isn't a concrete methodology, since an insignificant variation in the type of ligand, the quantity of complex doped, or the disposition of the atoms in the space can produce drastical variations in the emission properties. For now, efficient results have been reported with the goal to achieve different types of lights, producing white light (WOLEDs) and improve the OLEDs with phosphorescence doing PHOLEDs which are more efficient than the OLEDs. There is a disadvantage with the time of luminescence of the devices, but there is a lot of research to upgrade this parameter and the forecast is optimistic.

Concurrently, another field has been developed in the ambit of medicine for the treatment of different types of tumors. The complexes of Pt(II) shows great activities in vitro against tumor cells and they have demonstrated their power to stop the reproduction of these cells and furthermore they coordinate with the DNA of the cell, to inhibit her replication and produce the apoptosis.

Looking to the future, higher efficiency is expected in both fields, making Pt(II) complexes more competitive and more versatile in order to be able to combine these different properties. For example, the luminescence ability of the complexes used as antitumor drugs allows their cellular localization using fluorescence microscopy and a better understanding on how the complex acts in the body of the patient, and on the behavior of the complex with the tumor cells.

8. REFERENCES AND NOTES

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9. ACRONYMS

A549: Lung Carcinoma Cell

A2780/A2780cisR: Epithelian ovarian cancer

BEAS-2B: Ephitelial cell line

Bpy: 2,2’-bipyridine

CIE: Comission Internationale de l’Eclairage

DACH: Diaminocyclohexane

DFT: Density Functional Theory

DNA: Deoxyribonucleic acid

HCT-116: Human Colon carcinoma

HepG2: Hepatocellular carcinoma

HOMO: High occupied molecular orbital

IC_{50}: Inhibitory concentration at 50%

ILCT: Intra ligand charge transfer

LUMO: Lower unoccupied molecular orbital

MCF-7: Breast cancer

MCLT: Metal to ligand charge transfer

MDA-MB-231: breast cancer cell lines

MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

NCI-H460: non-small cell lung cancer

OLED: Organic light-emitting diodes

PC-3: prostate cancer

Ph: phenyl

PHOLED: Phosphorescent organic light-emitting diodes

Py: pyridine

SRB: Sulforhodamine B

TADF:Thermally Activated Delayed Fluorescence

Terpy: terpyridine

WOLED: White organic light-emitting diodes