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Synthesis and Characterization of PT(II) Complexes for Anticancer Therapy

Mihaela A. Ciulei
University of Nevada, Las Vegas

Pradip K. Bhowmik Professor
University of Nevada, Las Vegas, pradip.bhowmik@unlv.edu

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Mihaela A. Ciulei, McNair Scholar, Nutrition Sciences Major
Dr. Pradip K. Bhowmik, Department of Chemistry and Biochemistry

Introduction

The first platinum-based drug was discovered and approved by Food and Drug Administration (FDA) in 1978 is *cis*-diamminedichloroplatinum (II) (cisplatin or CDDP). Cisplatin is used for about 50% of the chemotherapeutic cancer treatments along with its two analogues carboplatin and oxaliplatin. So far these drugs have been used extensively as treatment for ovarian, bladder, head and neck, and lung cancers. Although cisplatin has been used so often, it has toxic side effects and drug resistance.[1-4] Due to these limitations other compounds have been synthesized. Specifically, our lab in conjunction with a biochemistry lab has recently published one article in this area.[5] This project is a continuation to the development of anticancer drugs.

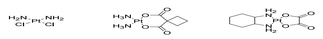


Figure 1. The chemical structures of cisplatin, carboplatin, and oxaliplatin.

Objective

•This project's objective is to synthesize a series of platinum Pt (II) complexes, **I-IV**, which will be targeted for testing in different cell lines for their therapeutic effects in biochemistry lab facilities.
•The structure-activity relationship will provide a rational basis for the discovery of novel platinum compounds with increased effectiveness and low toxic side effects.

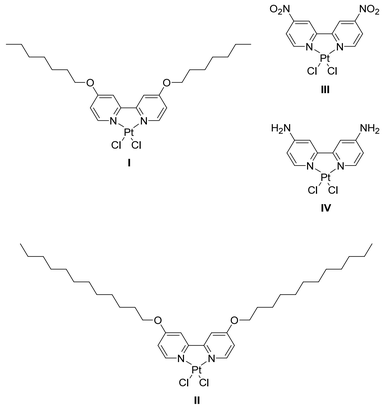
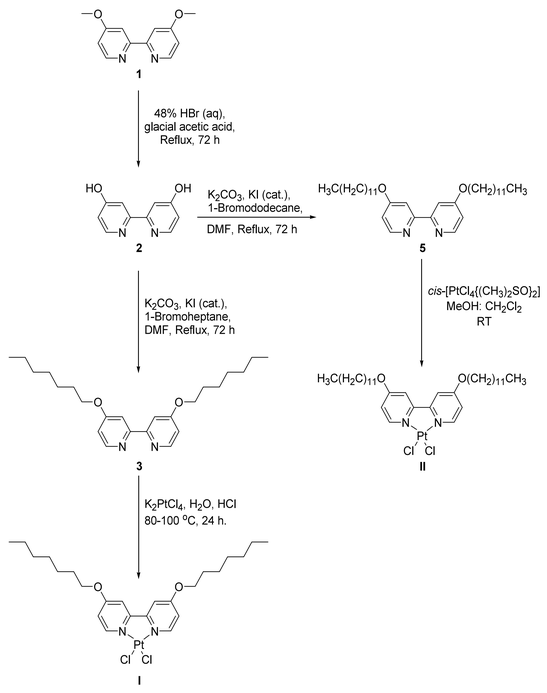
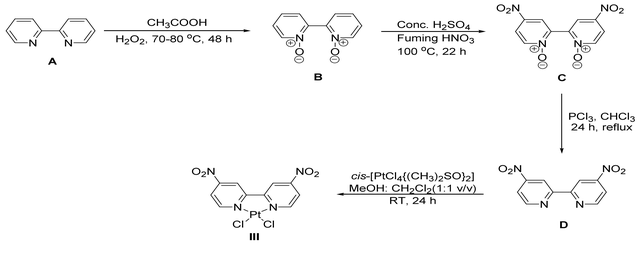


Figure 2. The proposed chemical structures of Pt(II) complexes to be synthesized and characterized.

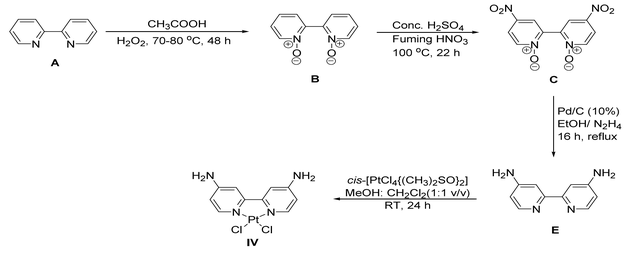
Methodology



Scheme 1. Synthesis routes for complexes **I** and **II** from 4,4′-dimethoxy-2,2′-bipyridine (**1**).



Scheme 2. Synthesis routes for complex **III** from 2,2′-bipyridine (**A**).



Scheme 3. Synthesis routes for complex **IV** from 2,2′-bipyridine (**A**).

Results

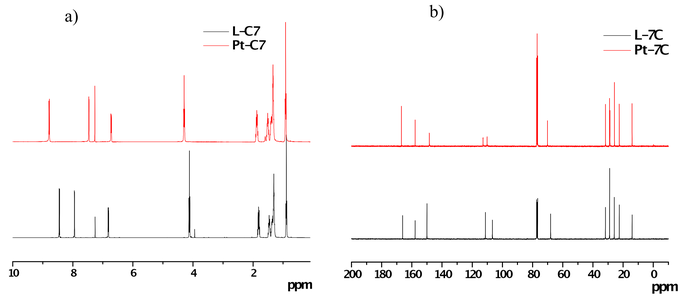


Figure 3. (a) ^{1}H NMR spectra of ligand **3** and Pt(II)-complex **I** recorded in $CDCl_3$ at room temperature. (b) ^{13}C NMR spectra of ligand **3** and Pt(II)-complex **I** recorded in $CDCl_3$ at room temperature.

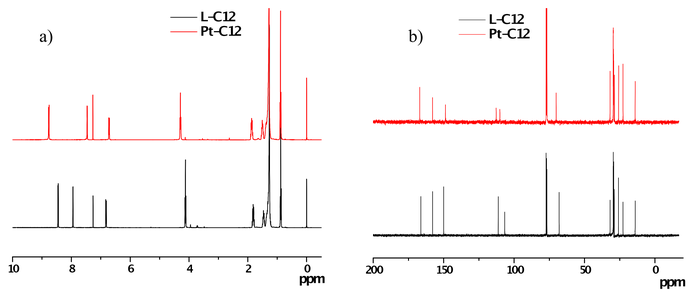


Figure 4. (a) ^{1}H NMR spectra of ligand **5** (L-C12) and Pt(II)-complex **II** (Pt-C12) recorded in $CDCl_3$ at room temperature. (b) ^{13}C NMR spectra of ligand **5** (L-C12) and Pt(II)-complex **II** (Pt-C12) recorded in $CDCl_3$ at room temperature.

Table 1. Elemental Analysis for Complex **I**

$C_{24}H_{36}Cl_2N_2O_2Pt$	C%	H%	Cl%	N%	O%	Pt%
Calc	44.31	5.58	10.90	4.31	4.92	29.99
Found	44.41	6.51	-	4.37	-	-
Δ	0.1	0.93	-	0.06	-	-

Table 2. Elemental Analysis for Complex **II**

$C_{34}H_{56}Cl_2N_2O_2Pt$	C%	H%	Cl%	N%	O%	Pt%
Calc	51.64	7.14	8.97	3.54	4.05	24.67
Found	51.24	7.10	-	3.80	-	-
Δ	0.4	0.04	-	0.26	-	-

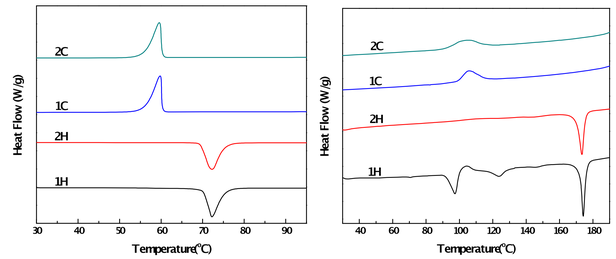


Figure 5. DSC thermograms of ligand **3** (left) and Pt(II)-complex **I** (right) obtained at heating and cooling rates of 10 °C/min in nitrogen.

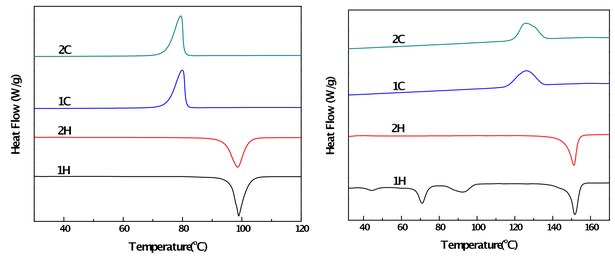


Figure 6. DSC thermograms of ligand **5** (left) and Pt(II)-complex **II** (right) obtained at heating and cooling rates of 10 °C/min in nitrogen.

Conclusions

- Platinum complexes **I** and **II** were synthesized via a three-step reaction: demethylation, S_N^2 (alkylation), and preparation of the platinum complex by coordination chemistry. The products were characterized by using ^{1}H, ^{13}C NMR, and elemental analysis.
- Unlike small organic compounds, ligands **3** and **5** showed broad melting endotherms at 72 and 99 °C, respectively. In contrast, **I** and **II** showed multiple endotherms in the first heating cycle, but in the second heating cycle they showed melting transitions at 174 and 152 °C, respectively.
- Ligand **E** was synthesized by a three-step reaction: oxidation, nitration, and reduction. Additionally, ligand **D** will be synthesized by a three-step synthesis: oxidation, nitration, and deoxygenation.
•All of these platinum complexes will be tested in different cell lines for anticancer properties.

Acknowledgments

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