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Synthesis of Cyclometalated Platinum(II) Complex in a Green Solvent: Biological Evolutions

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ABSTRACT

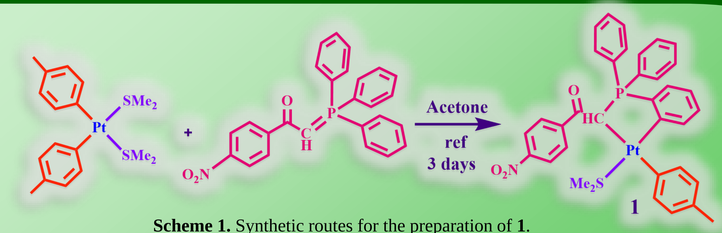
Cancer remains a major global health concern, leading to extensive research on new treatment options, including platinum-based chemotherapy drugs. This study focuses on the synthesis and characterization of a cyclometalated Pt(II) complex, demonstrating promising anticancer activity with selectivity towards cancer cells, particularly in breast cancer. The use of eco-friendly synthesis practices and the induction of apoptosis further highlight the potential of this complex as an effective anticancer agent.

INTRODUCTION

Cyclometalated Platinum(II) complexes are a class of organometallic compounds that have gained attention for their potential applications in cancer treatment. These complexes consist of a central platinum atom coordinated to organic ligands. The unique structure and properties of these complexes make them promising candidates for use as anticancer drugs[1]. When it comes to the synthesis of cyclometalated Platinum(II) complexes, the use of green chemistry solvents is becoming increasingly popular[2]. Green solvents are environmentally benign alternatives to traditional organic solvents, typically derived from renewable resources and designed to minimize waste and reduce the impact on human health and the environment. By employing green solvents in the synthesis process, researchers can carry out the reactions in a more sustainable and eco-friendly manner. The development of cyclometalated Platinum(II) complexes in green solvents holds great potential for the field of medicinal chemistry, as it not only offers a more sustainable approach to drug development but also has the potential to enhance the biological activity and efficacy of these compounds[3]. In this study, we present a novel approach to the synthesis of cyclometalated platinum(II) complexes using a green solvent, highlighting the importance of sustainable practices in chemical synthesis. The biological evolutions of these complexes are also explored, shedding light on their potential applications in anticancer systems.

EXPERIMENTAL

To synthesize a cyclometalated Pt(II) complex, [Pt(p-MeC_6H_4)(YPN)(SMe_2)] (**1**), 0.05 g (0.13 mmol) of [Pt(p-MeC_6H_4)$_2$(SMe_2)$_2$] complex was dissolved in 20 ml of acetone. Then, 0.055 g (0.13 mmol) of phosphonium ylide ligand[4], YPN, $Ph_3PC(H)C(O)C_6H_4NO_2$, was added to the solution (1:1) and stirred magnetically for 72 hours. The solvent was evaporated, and the product was dried and weighed at room temperature. The sample was analyzed using ^{1}H NMR and ^{31}P{H} NMR spectroscopy (Scheme 1).



Scheme 1. Synthetic routes for the preparation of **1**.

RESULT AND DISCUSSION

The complexes were completely identified by NMR (^{1}H, ^{31}P {^{1}H}, and ^{195}Pt{^{1}H}) spectroscopy, and single crystal X-ray crystallography. All the ^{1}H, ^{31}P {^{1}H}, and ^{195}Pt{^{1}H} NMR spectra are shown in **Figure 1**. In the ^{1}H NMR spectrum of [Pt(p-MeC_6H_4)(YPN)(SMe_2)], the aromatic protons appear as two and multiplets with Pt satellites at δ= 6.99-8.69 ppm, indicating chelate coordination of the YPN ligand with the Pt(II) center. The hydrogen doublet signal for the CH of the YPN ligand, related to the coupling of a phosphorus atom with $^2J_{PH}$= 14.0 Hz, is observed at δ= 4.58 ppm, along with satellites due to platinum with $^2J_{PtH}$= 99.5 Hz. The hydrogens of the methyl groups of SMe_2 and p-MeC_6H_4 are seen at δ= 2.27, 2.32, and 2.39 ppm. In the ^{31}P{^{1}H} NMR spectra, only one signal is present for the complex, flanked by Pt satellites with $^2J_{PtP}$= 2.9 Hz. The ^{195}Pt{^{1}H} NMR spectra show a doublet signal attributed to the coupling of the Pt center with the phosphorus atom.

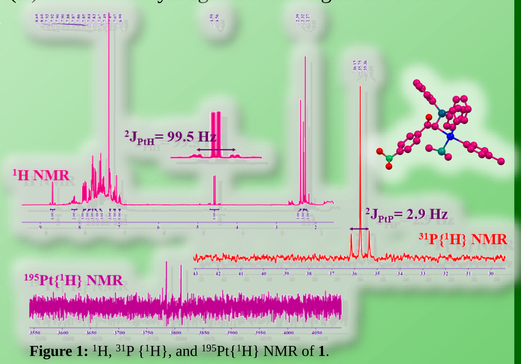


Figure 1: ^{1}H, ^{31}P {^{1}H}, and ^{195}Pt{^{1}H} NMR of **1**.

Complex 1 was explored by DFT and TD-DFT calculation methods. The ground states (S_0) of the complexes were optimized in both the gas phase and CH_2Cl_2 solution while the geometrical. parameters were in good agreement with those of crystal structures. Using the optimized structures of the complex, frontier molecular orbitals (MO) involving "HOMO" and "LUMO" were obtained. The visual plots of the mentioned MOs are depicted in **Figure 2** and their corresponding numerical details including the energy levels and component percentages (in terms of metal and ligands) are listed in **Table 1**. **Figure 2** depicts the comparative energy level diagram for the calculated MOs, HOMO, and LUMO plots of the complex. This complex exhibit a HOMO mainly localized on p-MeC_6H_4 ligand and Pt center. On the other hand, their higher LUMO is distributed over the YPN moiety.

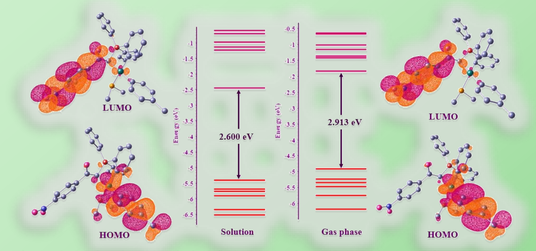


Figure 2: Molecular orbital plots for optimized structure and energy diagram of **1**.

Table 1: The energies of HOMO and LUMO of **1** with their compositions in gas phase and CH_2Cl_2 solution.

	MO	Energy (eV)	Components (%)			
			Pt	L_1=YPN	L_2=SMe_2	L_3=p-MeC_6H_4
Gas phase	LUMO	-2.465	3	96	0	1
	HOMO	-5.066	26	7	6	61
Solution	LUMO	-2.437	2	97	0	1
	HOMO	-5.350	30	6	4	60

Through the MTT assay, complex **1** showed high cytotoxic activity against lung, breast, and cervical cancer cells, as well as lung fibroblast cells, with the highest inhibition percentage. It was most effective against A549 lung cancer cells with an IC50 of 20.77 μM, outperforming cisplatin. While it also exhibited good cytotoxic effects against MCF-7 and HeLa cancer cells, there was no statistically significant difference in IC50 compared to cisplatin for these cell lines (**Table 2**).

Table 2. Cytotoxicity of the complex 1 against both cancerous and noncancerous cell lines when tested in vitro.

Compound	(IC_{50} ± SD) μM[a]				
	A549	MCF-7	HeLa	MRC-5	Selectivity Index[b]
1	20.77 ± 1.18	21.69± 0.26	19.04± 1.67	67.36±1.27	3.24
Cisplatin	9.82±1.93	16.67±1.49	18.35±1.16	15.74±2.08	1.60

a The MTT assay was performed for 72 h.
b IC50 for MRC-5 cell line/IC50 for A549 cell line.

CONCLUSION

In conclusion, the cyclometalated Pt(II) complex synthesized in this study demonstrates promising anticancer activity, particularly in breast cancer cells. The use of eco-friendly synthesis practices and the induction of apoptosis underscore the potential of this complex as an effective anticancer agent. Furthermore, the complex showed high cytotoxic activity against lung, breast, and cervical cancer cells, outperforming cisplatin in some cases. These findings highlight the importance of sustainable practices in drug development and the potential of cyclometalated Platinum(II) complexes as effective anticancer agents. Future research in this area holds great promise for the field of medicinal chemistry.

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