Targeted Tumor Therapy with Multifunctional Platinum (IV) Drug Conjugates

NEMZETKÖZI VEGYÉSZKONFERENCIA
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SYNTHESIS, STRUCTURAL INSIGHTS, AND COMPUTATIONAL STUDIES OF NEW PLATINUM(IV) COMPLEXES WITH CARBOXYLIC OR PHENOLIC LIGANDS

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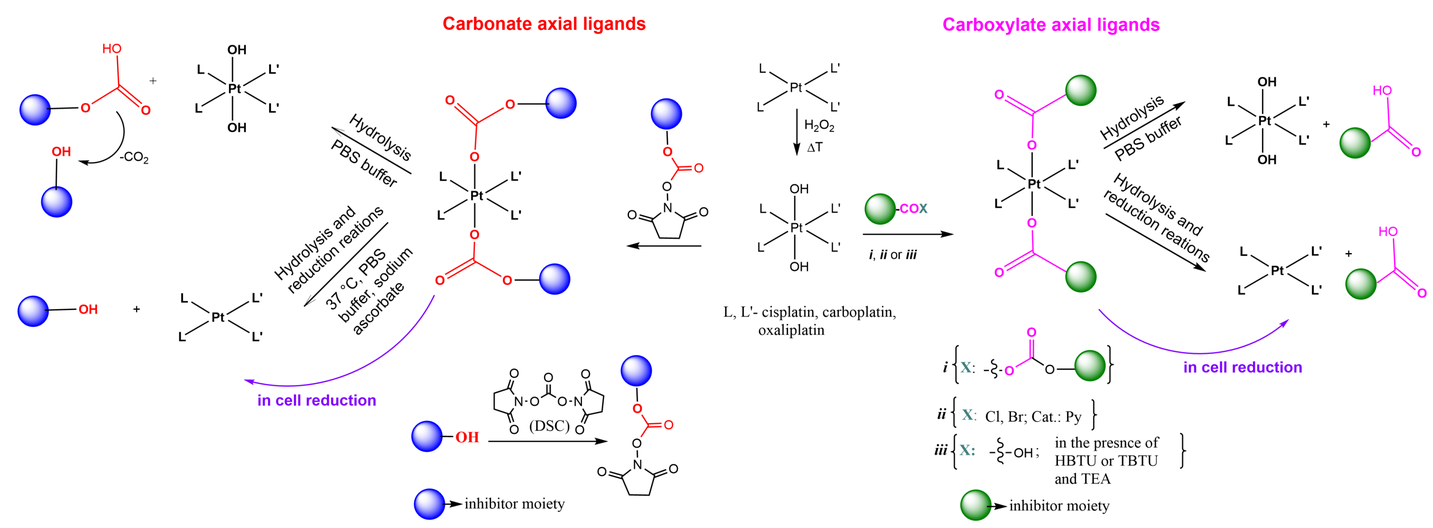
Abstract

Platinum-based anticancer treatments include side effects, drug efflux transporter resistance, and restricted cellular mechanism targeting [1]. In this study, new platinum(IV) complexes with carboxylic or phenolic ligands were synthesized and characterized in the attempt to overcome these issues. The platinum(IV) complexes were synthesized from platinum(II) cisplatin-type scaffolds by incorporating therapeutic agents as ligands. This made it possible to make multipurpose therapeutic agents that could be used as pro-drugs to improve selectivity while limiting toxicity. The axial ligand coordination through carbonate or carboxylate units at platinum(IV) (obtained by oxidation of cisplatin raw material) allows intracellular reductants to cleave metal-ligand bonds and release the bioactive inhibitor and cytotoxic platinum(II) species.
DFT calculations assisted the stages preceding the synthesis, leading to the final design of the desired complexes. For all platinum(IV) complexes axially functionalized with carboxylic or phenolic ligands, the assignment of the structural formula was carried out by NMR spectroscopy and mass spectrometry (HRMS).

The platinum(IV) strategy



Scheme 1. The Pt(IV) complexes strategy.

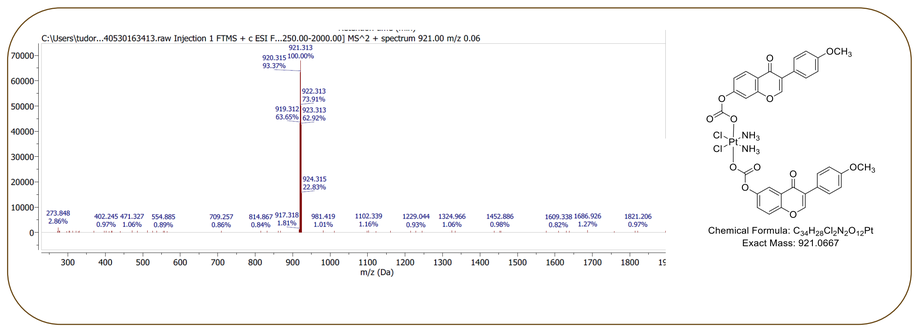
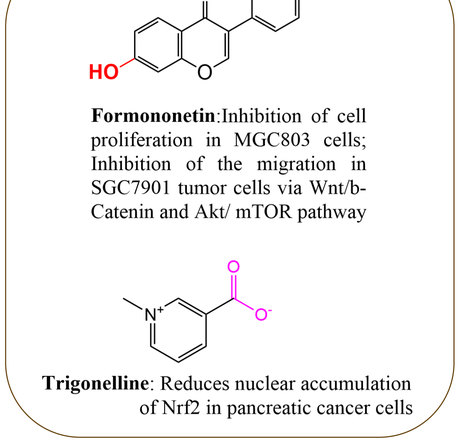


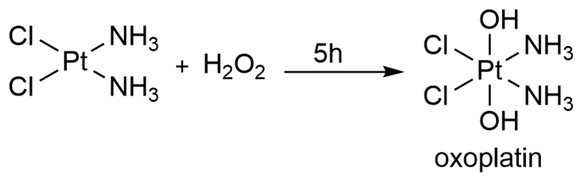
Figure 1. MS (ESI$^+$) spectrum of compound **1**.



Formononetin:Inhibition of cell proliferation in MGC803 cells; Inhibition of the migration in SGC7901 tumor cells via Wnt/b-Catenin and Akt/ mTOR pathway

Trigonelline: Reduces nuclear accumulation of Nrf2 in pancreatic cancer cells

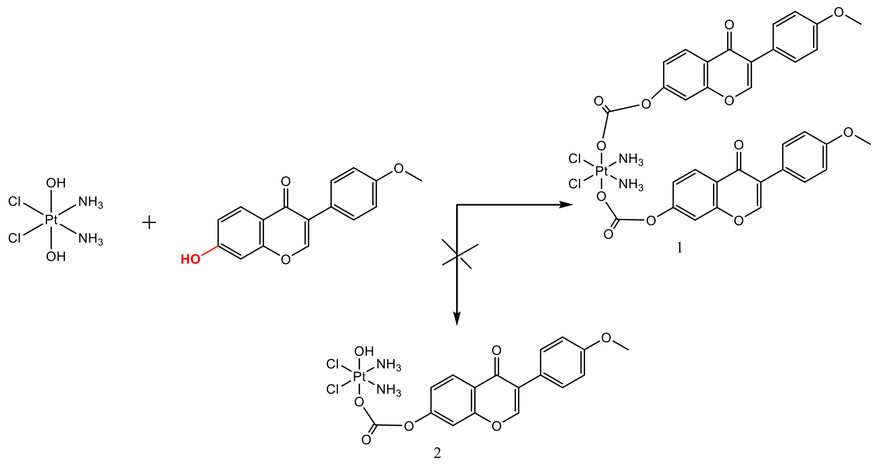
The Pt(IV) complexes synthesis



Scheme 2. The synthesis of oxoplatin.

Table 1. Optimization of oxoplatin synthesis conditions.

Temperature	% H_2O_2 (H_2O:H_2O_2 = 1/4, V/V)	Yield
75°C	30%	60%
40°C	35%	40%
50°C	35%	56%
65°C	35%	70%



Scheme 3. The synthesis of formononetin-Pt(IV)-derivative.

Table 2. The synthesis of compound **1**. For all the reaction – room temperature and inert (Ar) atmosphere, oxoplatin:ligand = 1:2 (v:v).

Time	Solvent	Catalyst	Product
24h (12h DSC+Ph-OH (1); 12h Oxoplatin + (1))	Acetonitrile Dry DMSO	DSC (N,N′-Disuccinimidyl carbonate), Pyridine	1
24h	Dry DMSO	TBTU, Et_3N	1
24h (12h succ.anh. +Ph-OH (1); 12h Oxoplatin + (1))	DCM Dry DMSO	4-DMAP, Et_3N TBTU, Et_3N	??

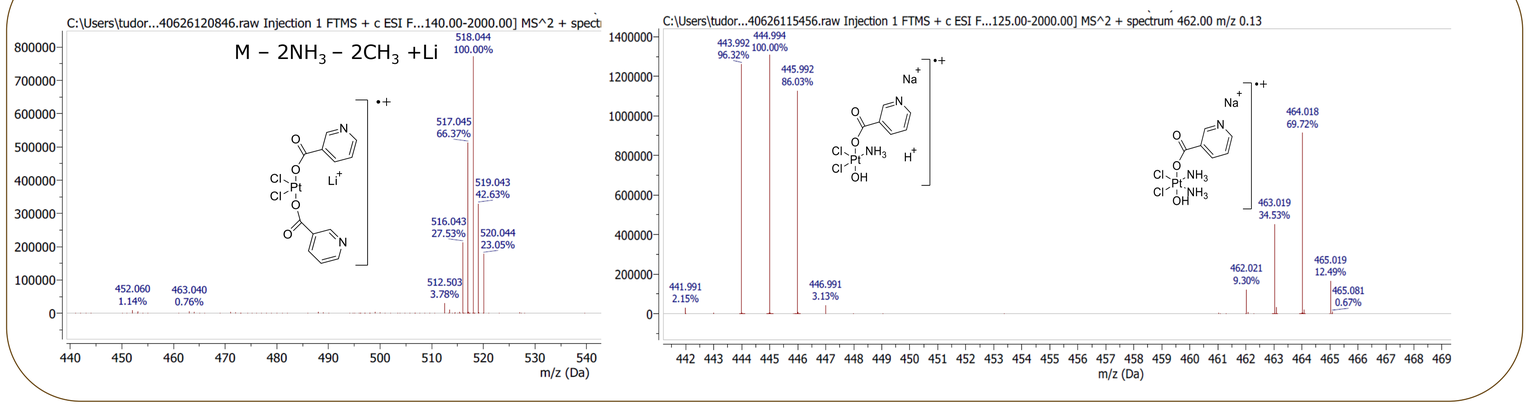
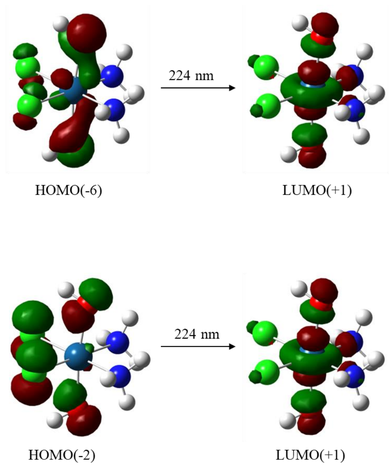
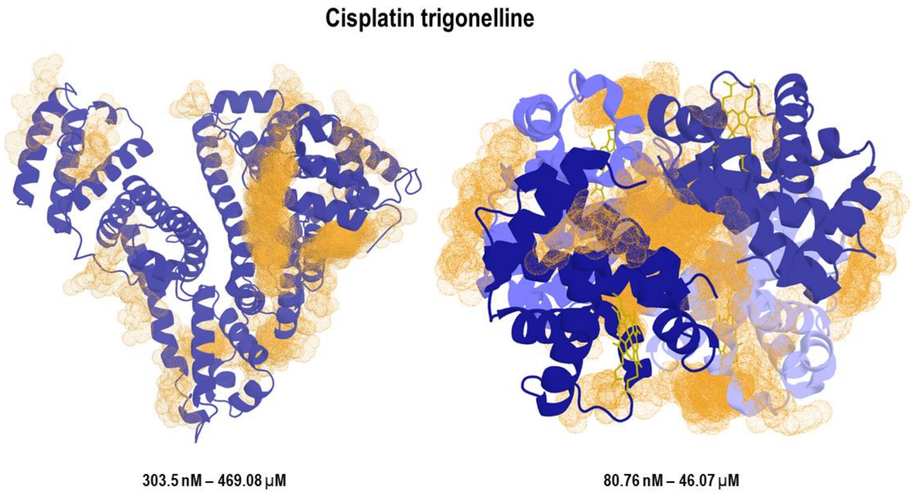


Figure 2. MS (ESI$^+$) spectrum of compound **2**.

DFT



Docking



Acknowledgments

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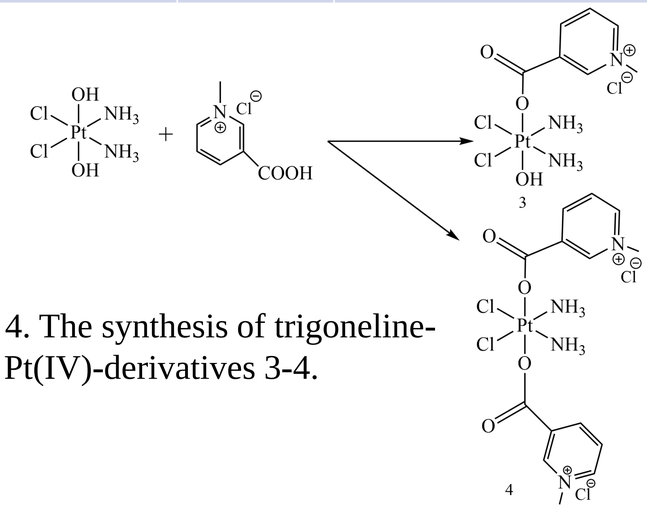
References:
[1] Z. Li, X.J. Ding, X. Qiao, X.M. Liu, C.Z. Xie, R.P. Liu, J.Y. Xu, Thalidomide-based Pt(IV) prodrugs designed to exert synergistic effect of immunomodulation and chemotherapy, J. Inorg. Biochem. 232 (2022) 111842.



Scheme 4. The synthesis of trigoneline-Pt(IV)-derivatives 3-4.

Table 3. The synthesis of compounds **3-4**.

Time	Temperature	Solvent	Catalyst	Product
36h	60°C	CH_2Cl_2	DCC, NHS	-
36h	60°C	Dry DMF	Et_3N, TBTU	4
24h	50°C	CH_3COOH Few drops of DMSO	-	3