Platinum complexes as potential prodrug in cancer therapy

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INTRODUCTION & AIM

Current platinum-based anticancer therapies are often hindered by severe side effects, drug resistance (including efflux transporter mechanisms), and poor cellular targeting. To address these challenges, this research focuses on the design of multifunctional Platinum(IV) prodrugs. By utilizing a platinum(IV) scaffold—obtained through the oxidation of precursors like cisplatin or oxaliplatin—we have developed a strategy to conjugate bioactive inhibitors via carbonate or carboxylate bridges. These complexes are designed to remain stable until they encounter intracellular reductants, which trigger the release of both the cytotoxic Platinum(II) species and the synergistic bioactive inhibitor.

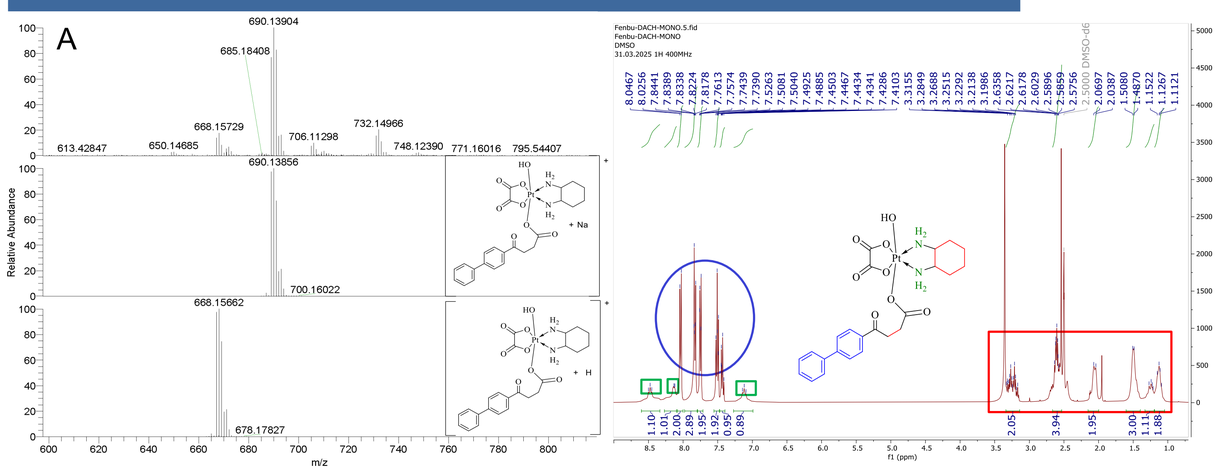
The primary aims of this study are:

To synthesize and characterize a series of novel Pt(IV) complexes using NMR, mass spectrometry, XRD, and electrochemical techniques.

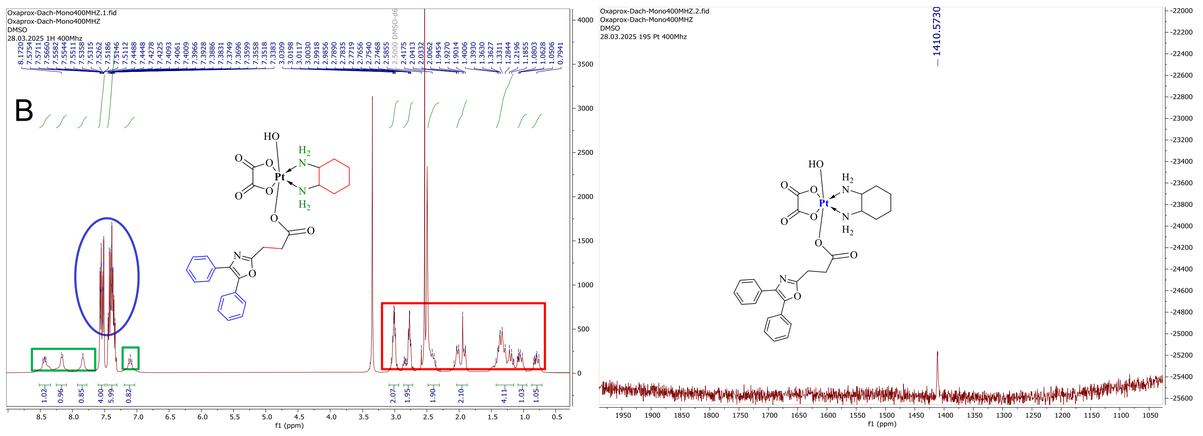
To evaluate the dual-action mechanism where the metal-ligand bonds are cleaved within the cellular environment.

To assess biological efficacy in vitro against the MDA-MB231 breast cancer cell line, providing a basis for overcoming conventional platinum drug limitations.

RESULTS & DISCUSSION



^{1}H (400 MHz, DMSO-*d6*) δppm 8.47 (t, 1H, NH), 8.11 (t, 1H, NH), 8.03 (d, *J* = 8,2 Hz, 2H), 7.83 (d, *J* = 8,5 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.50 (t, *J* = 8.2 Hz, *J* = 7.5 Hz, 2H), 7,44 (d, *J* = 7.5 Hz, 1H), 7.11 (t, 1H, NH), 3.33-3.16 (m, 2H), 2.63 – 2.57 (m, 2H), 2.06 - 2.03 (m, 2H), 1.50 – 1.48 (m, 3H), 1.27-1.09 (m, 3H). ^{13}C RMN (100 MHz, DMSO-*d6*) δppm 198.4, 181.1,163.9, 163.8, 144.4, 138.9, 135.4, 129.1, 128.58, 128.55, 128.3, 126.99, 126.90, 61.2, 60.0, 34.1, 30.8, 30.7, 30.6, 23.7, 23.5. ^{195}Pt RMN (128 MHz, DMSO-*d6*) δppm 1410. HRMS (ESI+) m/z: $[M + H]^+$ calc. for $C_{24}H_{32}N_2O_8Pt$: 668.15662 measured 668.15729; [M+Na] 690.13904



^{1}H (400 MHz, DMSO-*d6*) δppm 8.42 (t, 1H, NH), 8.16 (t, 1H, NH), 7.83 (t, 1H, NH), 7.57 – 7.51 (m, 4H), 7.44 – 7.33 (m, 6H), 7.10 (t, 1H, NH), 3.05 -2.98 (m, 2H), 2.85 – 2.74 (m, 2H), 2.47 – 2.36 (m, 2H), 2.07 -1.90 (m, 2H), 1.42 – 1.14 (m, 4H), 1.09 – 1.01 (m, 1H), 0.84 – 0.76 (m, 1H).
^{13}C RMN (100 MHz, DMSO-*d6*) δppm 191.8, 176.0, 164.2, 163.4, 132.1, 130.2, 115.5, 66.6, 61.8, 60.6, 40.9, 31.3, 31.1, 24.1, 24.0. ^{195}Pt RMN (128 MHz, DMSO-*d6*) δppm 1410.5 HRMS (ESI+) m/z: $[M + H]^+$ calc. for $C_{26}H_{30}N_3O_8Pt$: 707.1603 measured 707.1662.

Fig.1. Structural characterization of novel Pt(IV) complexes with Fenbufen (A – ^{1}H NMR (400 MHz, DMSO-*d6* and HRMS spectra ESI+) and Oxaprozin (B- ^{1}H NMR (400 MHz, DMSO-*d6)*, and ^{195}Pt RMN (128 MHz, DMSO-*d6*)) NSAID moieties

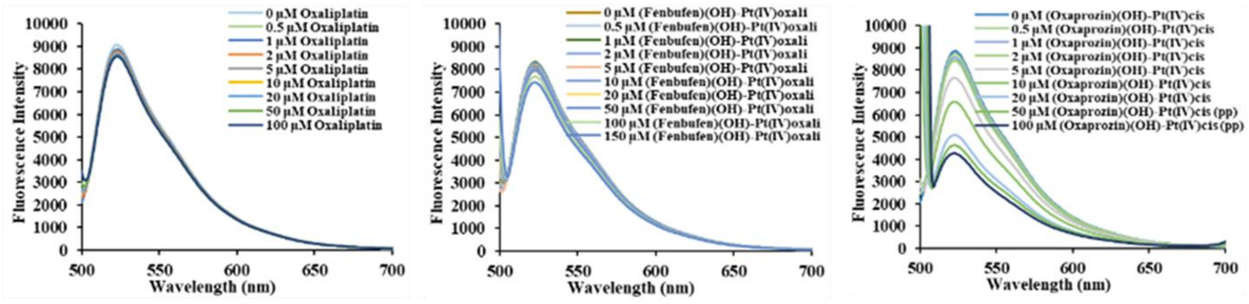


Fig. 2. Fluorescence emission spectra of DNA with SYBR Green, collected using an excitation wavelength of 495 nm in the presence of varying concentrations of complexes. Conditions: 2 µM calf thymus DNA, Tris-HCl buffer (pH 7.4), room temperature. Ligand concentrations are indicated in the figure legend.

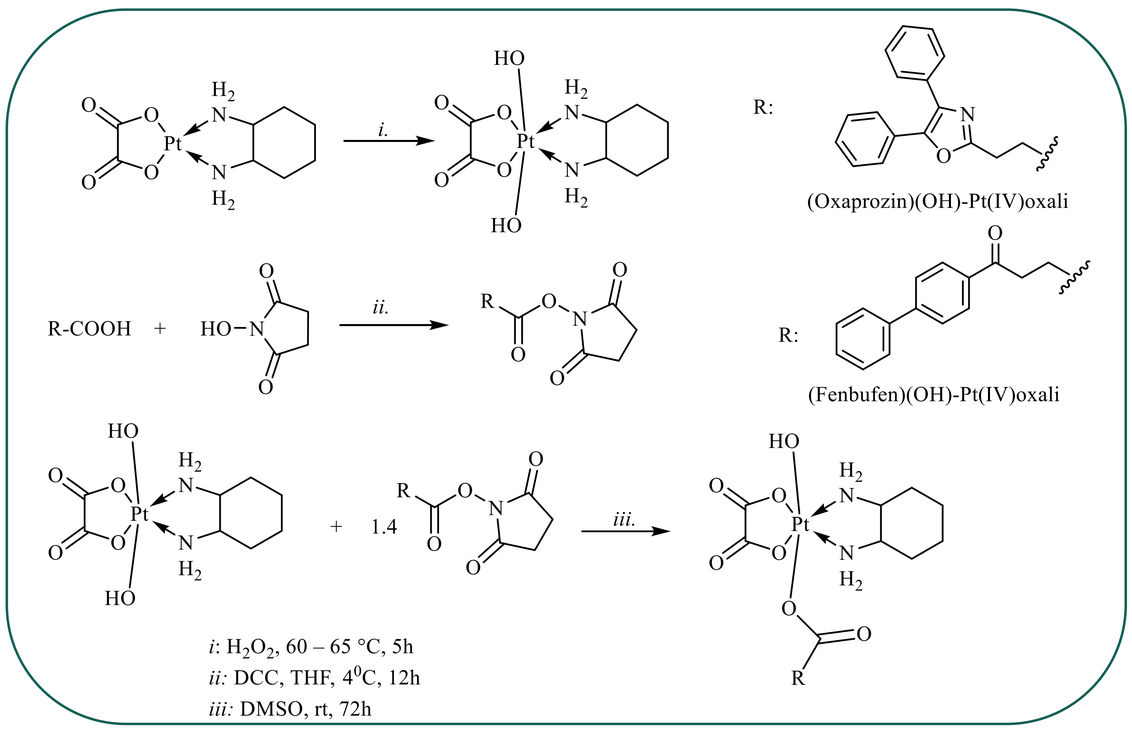
CONCLUSIONS

Novel axial mono-oxaliplatin-Pt(IV) prodrugs with Fenbufen and Oxaprozin moieties were successfully synthesized and confirmed via NMR and HRMS. Fluorescence assays showed that the complexes effectively interact with DNA, supporting their intracellular targeting mechanism. Cytotoxicity tests on BT549 and MDA-MB-231 breast cancer cell lines demonstrated distinct antiproliferative profiles, showing potential to overcome conventional platinum limitations. Integrating NSAID moieties into Pt(IV) scaffolds offers a promising strategy for targeted, synergistic chemo-anti-inflammatory therapy with reduced side effects.

SYNTHESIS OF OXALIPLATIN PT(IV) PRODRUGS WITH ANTI-INFLAMMATORY MOIETIES

The synthesis of these novel axial mono-oxaliplatin-platinum(IV) complexes was carried out through a streamlined three-step reaction sequence:

1. Oxidation: The initial oxaliplatin-Pt(II) precursor is oxidized to create a reactive oxaliplatin-Pt(IV) intermediate.
2. Activation of NSAID Moieties: The carboxylic acid groups of the anti-inflammatory agents are converted into reactive N-hydroxysuccinimide (NHS) esters via reaction with N-hydroxysuccinimide.
3. Esterification: The activated NSAID-NHS ester reacts with the oxaliplatin-Pt(IV) intermediate to yield the final axial mono-oxaliplatin-Pt(IV) complex.



Scheme 1. Synthesis of novel Pt(IV) complexes with Oxaprozin and Fenbufen NSAID moieties

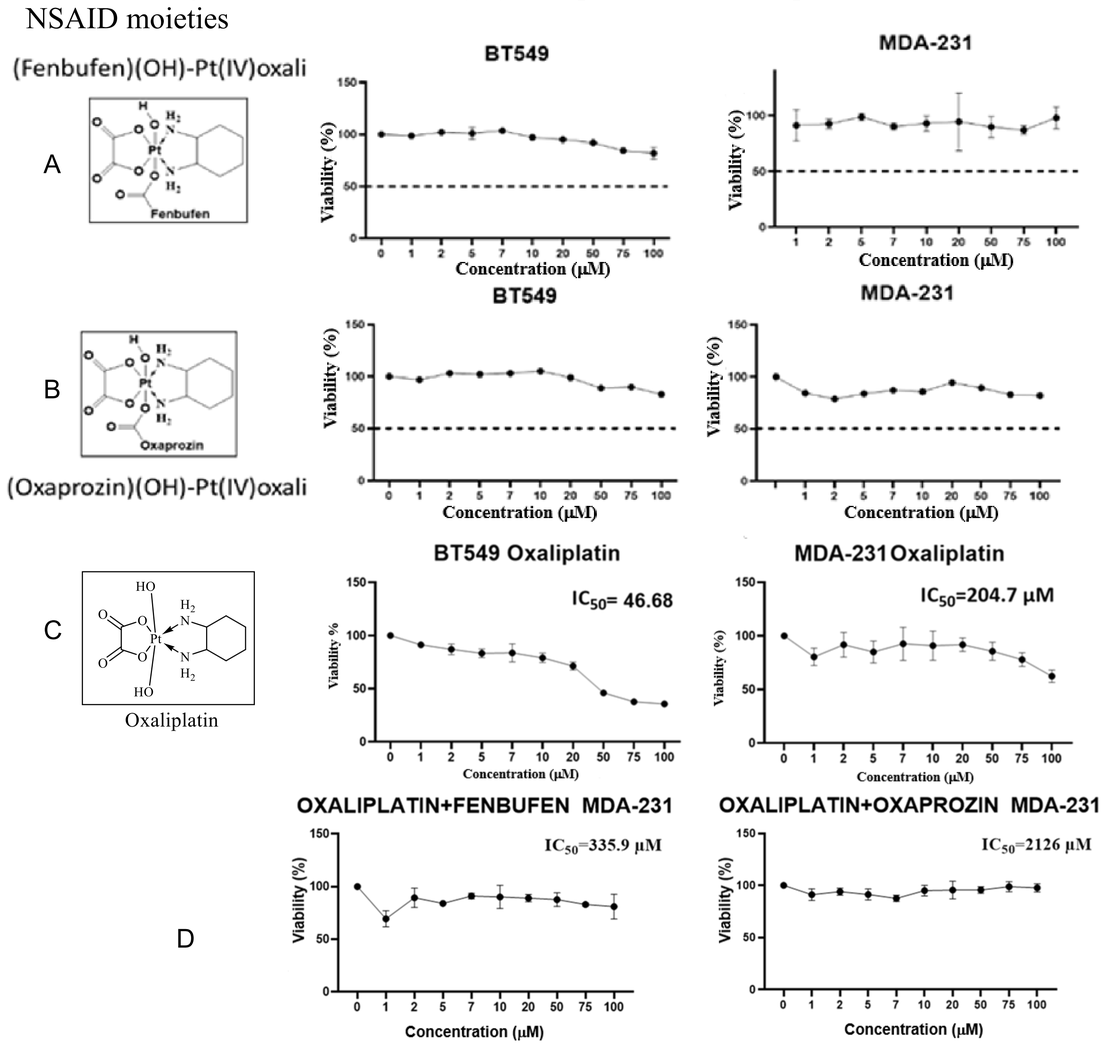


Fig.3. Cytotoxicity Evaluation of Pt(IV)-oxali Complexes in Breast Cancer Cell Lines:

A. Cytotoxicity evaluation of (Fenbufen)-(OH)-Pt(IV)oxali complex in the B9549 and MDA-MB-231 cell line
B. Cytotoxicity evaluation of (Oxaprozin)-(OH)-Pt(IV)oxali complex in the B9549 and MDA-MB-231 cell line
C. Cytotoxicity evaluation of Oxaliplatin in the B9549 and MDA-MB-231 cell line
D. Evaluation of the efficacy of combined treatment with oxaliplatin and free ligands (mixture) in the MDA-MB-231 cell line.

ACKNOWLEDGMENT

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