Structural Studies of Platinum Complexes with Thioureas

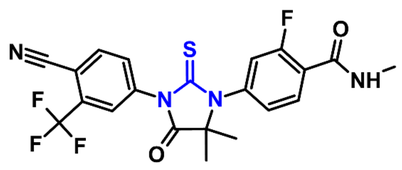
Aleksandra Drzewiecka-Antonik,[1,*] Anna Wolska,[1] Paweł Rejmak,[1] Daniel Szulczyk,[2]
Alexey Maximenko,[3] and Marcin T. Klepka[1]

[1]Institute of Physics Polish Academy of Sciences, 02-668 Warsaw, Poland
[2]Medical University of Warsaw, 02-097 Warsaw, Poland
[3]SOLARIS National Synchrotron Radiation Centre, 30-392 Krakow, Poland
*e-mail: adrzew@ifpan.edu.pl

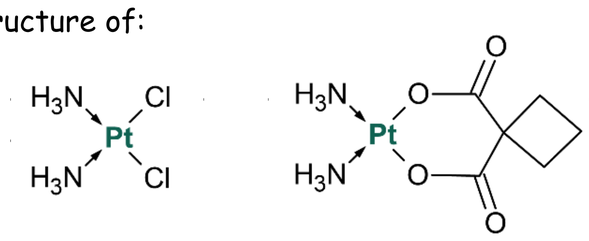
Motivation

The most approved therapeutics are organic compounds, however, metal complexes have the potential to offer more diverse properties that can be tuned in order to achieve specific functions.

The molecular structure of:



enzalutamide, a hormonal therapy organic drug used to treat prostate cancer;

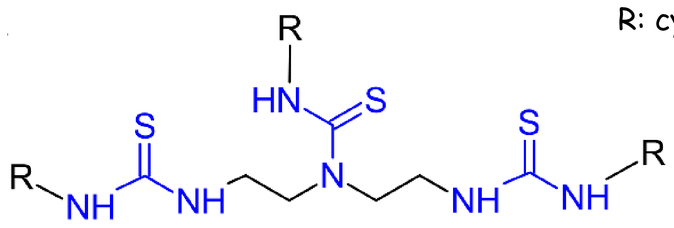


platinum-based drugs: cisplatin and carboplatin used to treat gynaecological cancers, germ cell tumours, head and neck cancer, thoracic cancers and bladder cancer.

Over the last three decades, there has been increasing interest in platinum complexes with *N,S*-donor ligands as thiourea derivatives. Such complexes may exhibit either higher anticancer activity or reduced toxicity compared to known metal containing drugs, such as cisplatin or carboplatin.

Purpose of the project

Two platinum complexes with compounds: **XDS2** and **XDS3**, containing three thiourea moieties in their structure, were synthesized in order to compare their cytotoxic activities with those of initial ligands and reference drugs.



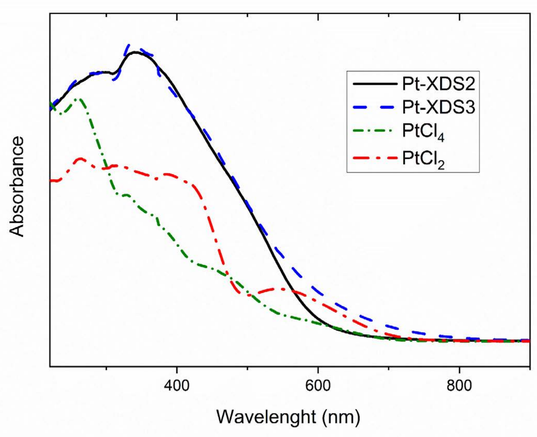
R: cyclohexyl (**XDS2**)
phenyl (**XDS3**)

All compounds were screened for their in vitro cytotoxic activity against a panel of human cancer cell lines, namely colorectal adenocarcinoma (CaCo-2), epithelial lung carcinoma (A549), and melanoma (HTB-140), by using the MTT method. Preliminary studies showed higher activity of the complexes in comparison to the starting ligands.

Structural characterization

The synthesized platinum complexes, **Pt-XDS2** and **Pt-XDS3**, have been structurally characterized by elemental analysis, ATR-IR and UV-Vis spectroscopies. More detailed information about the metal-thiourea ligand interaction has been obtained by applying the X-ray absorption spectroscopy (the ASTRA beamline) and calculations based on density functional theory (DFT).

UV-Vis



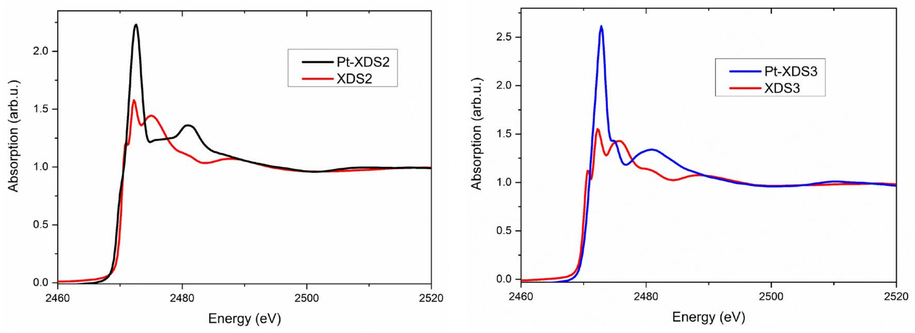
UV-Vis spectra of analysed complexes are typical for platinum compounds in the +4 oxidation state.

ATR-IR

Compound	νC=S (cm^{-1})	
Pt-XDS2	1305 (w)	740 (w)
XDS2	1322 (w)	803 (w)
Pt-XDS3	1300 (w)	752 (m)
XDS3	1320 (m)	803 (w)

The shift of the bands corresponding to the vibrations of the C=S group within the ligand-complex pair indicates the coordination of the S atom to the Pt(IV).

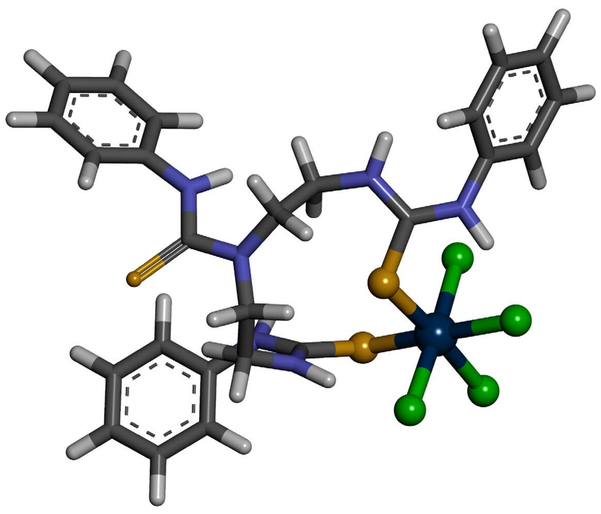
Sulfur K-edge XANES



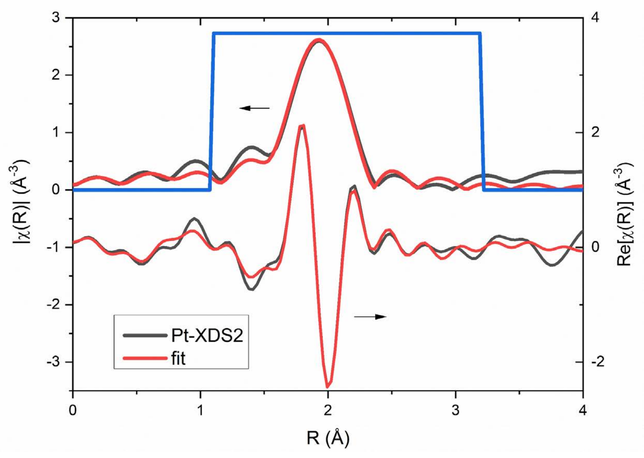
Comparison of spectra shape within the ligand-complex pairs confirms that ligands (XDS2, XDS3) coordinate to Pt(IV) via thiocarbonyl S atoms of thiourea moiety.

Platinum L_3-edge EXAFS & DFT calculations

The considered molecular structure of Pt(IV) complexes



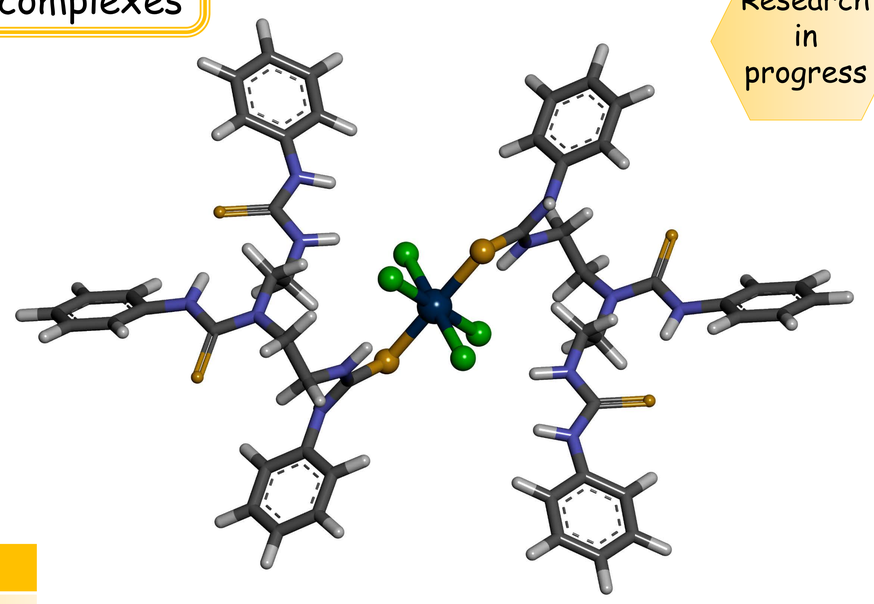
The bidentate thiourea ligand (L) coordinates Pt(IV) giving a monomeric complex, $PtLCl_4$, having an octahedral structure.



Atom type	N	R (Å)	σ^2 (Å^2)
Cl	4	2.32 (3)	0.002 (1)
S	2	2.34 (3)	0.002 (1)

The parameters of EXAFS fitting. N - number of atoms, R - the distance from central atom, σ2 - Debye-Waller factor describing local atomic disorder. The amplitude reduction factor S_0^2 was found to be 0.8 (1) and R-factor of the fit was 0.01.

Research in progress



The monometallic fragment of the polymeric structure of the complex $(PtLCl_4)_n$, in which two ligands (L) coordinate to Pt(IV) cation.