Università del Piemonte Orientale "Amedeo Avogadro"
Dipartimento di Scienze e Innovazione Tecnologica
Viale Teresa Michel 11, 15121 Alessandria (Italy)

stefano.tinello@mfn.unipmn.it

A versatile method for the oxidation of Pt(II) antitumour drugs

Stefano TINELLO, Mauro RAVERA, Elisabetta GABANO,

Federico FREGONESE, Giorgio PELOSI, Domenico OSELLA

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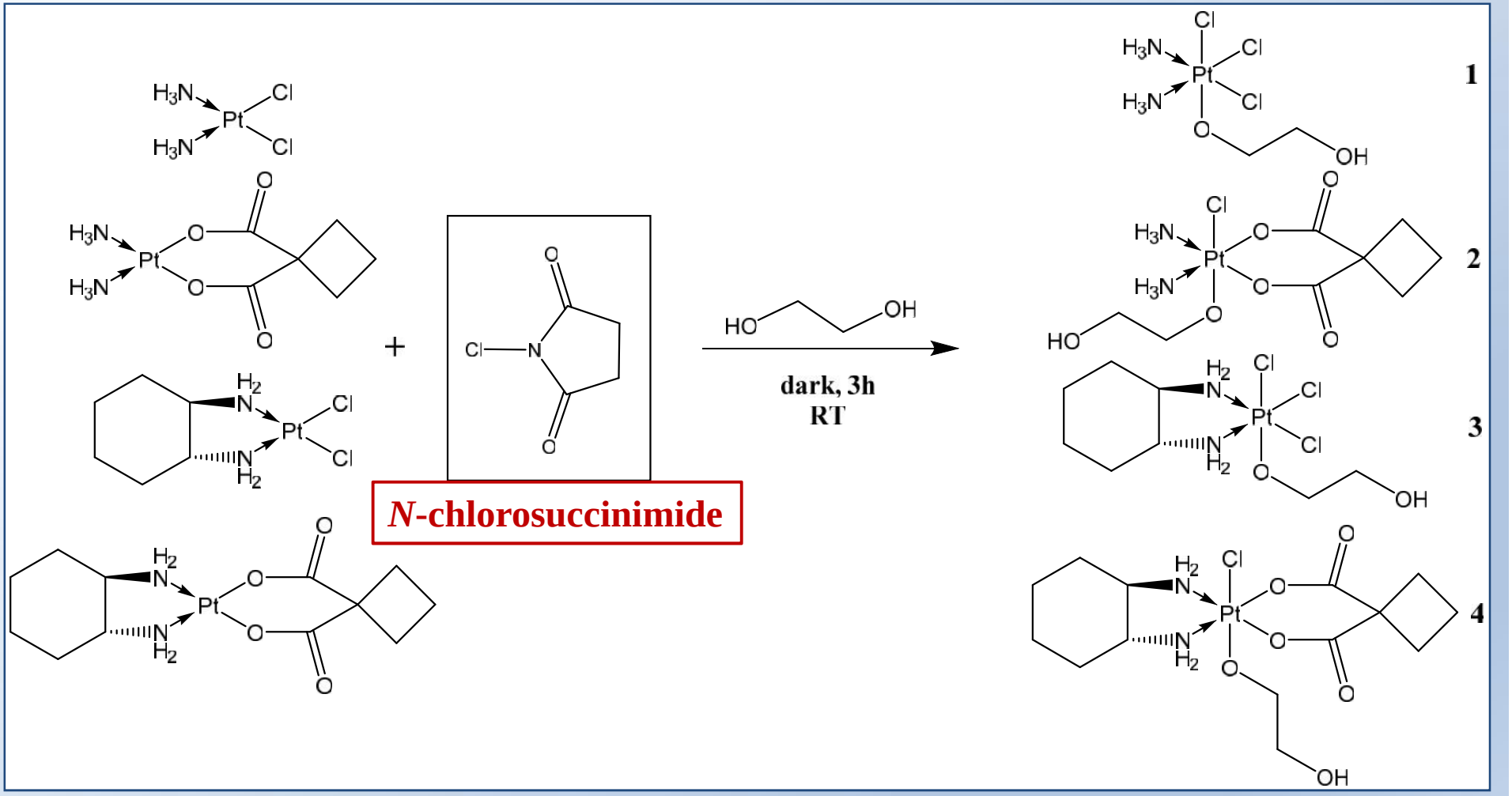
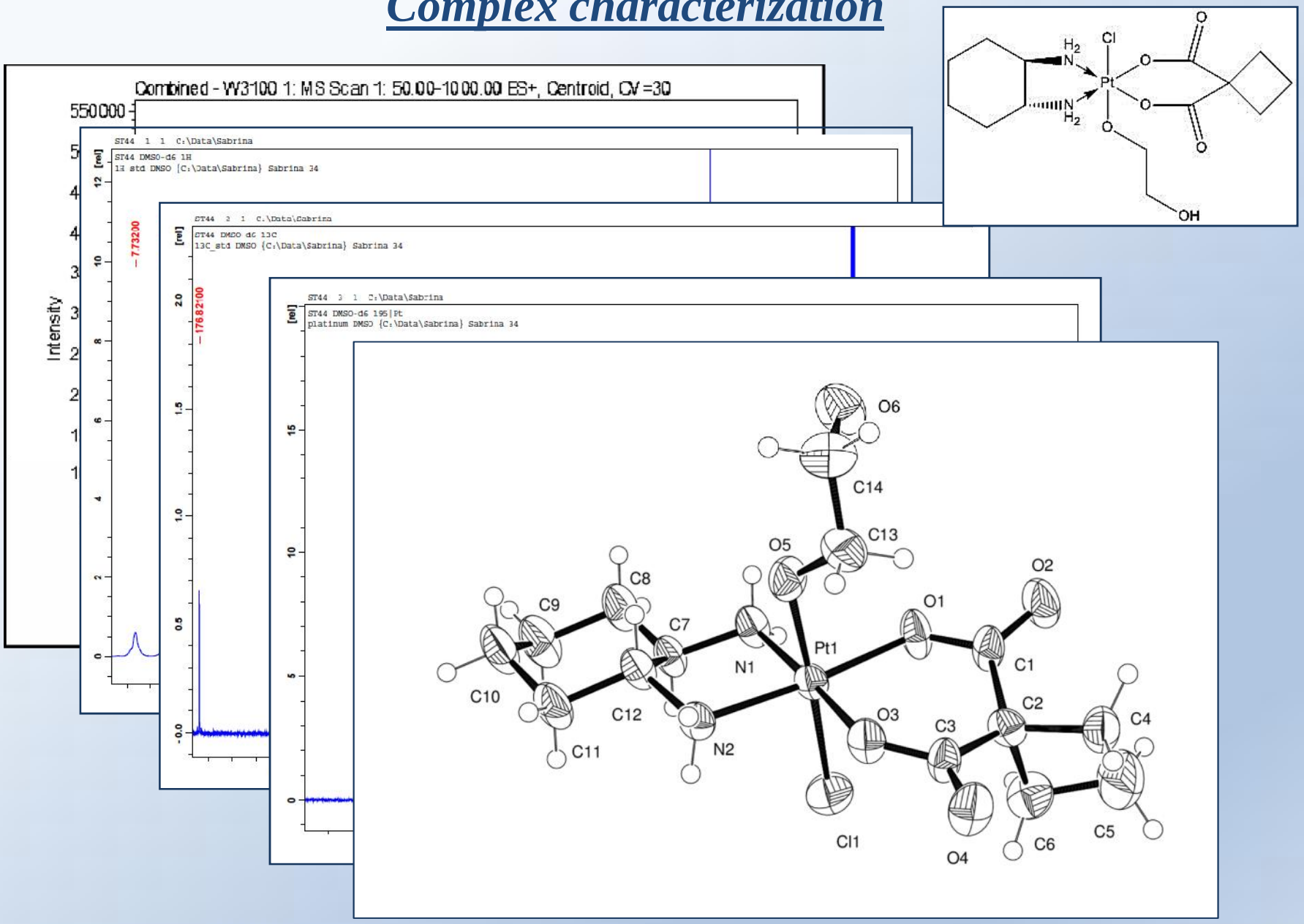
N-chlorosuccinimide as oxidizing agent for Pt(II) complexes



P. Mailliet, B. Bourrie, A. Normand, French Patent FR 2 954 321 A1, **2010**
M. Ravera, E. Gabano, G. Pelosi, F. Fregonese, S. Tinello, D. Osella, *Inorg. Chem.*, in press, doi:10.1021/ic501446b

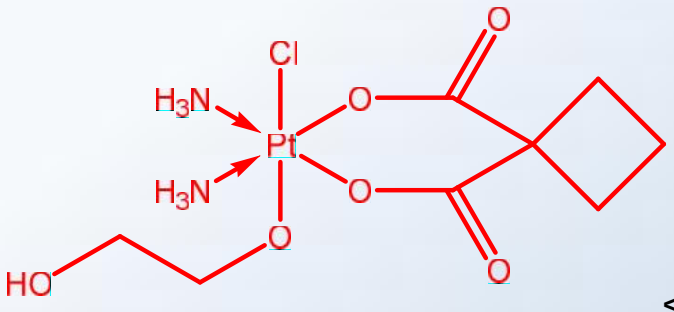
Complex characterization

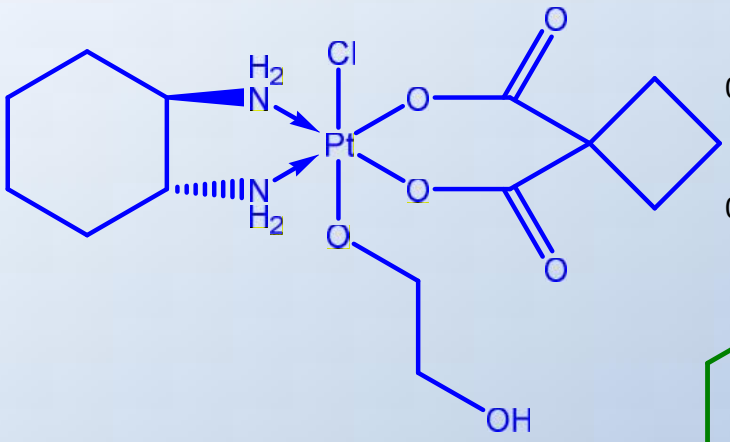


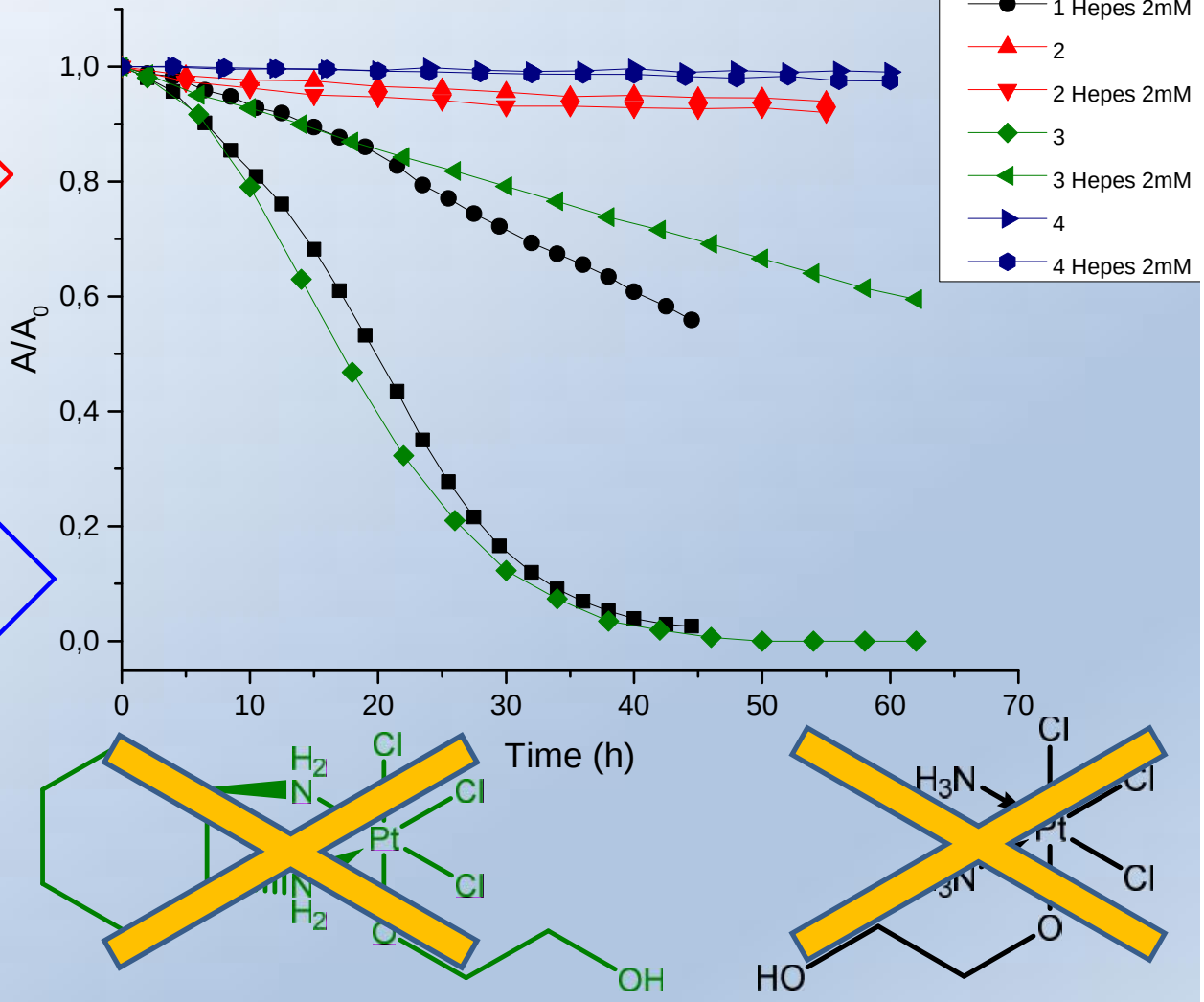
M. Ravera, E. Gabano, G. Pelosi, F. Fregonese, S. Tinello, D. Osella, *Inorg. Chem.*, in press, doi:10.1021/ic501446b

Stability Test

The stability of complexes **1**-**4** was studied both in carbonated water (pH = 6.4) and in HEPES buffer (pH = 7.5) at 37°C, by monitoring the decrease of the area of the Pt(IV) HPLC peaks as function of time.

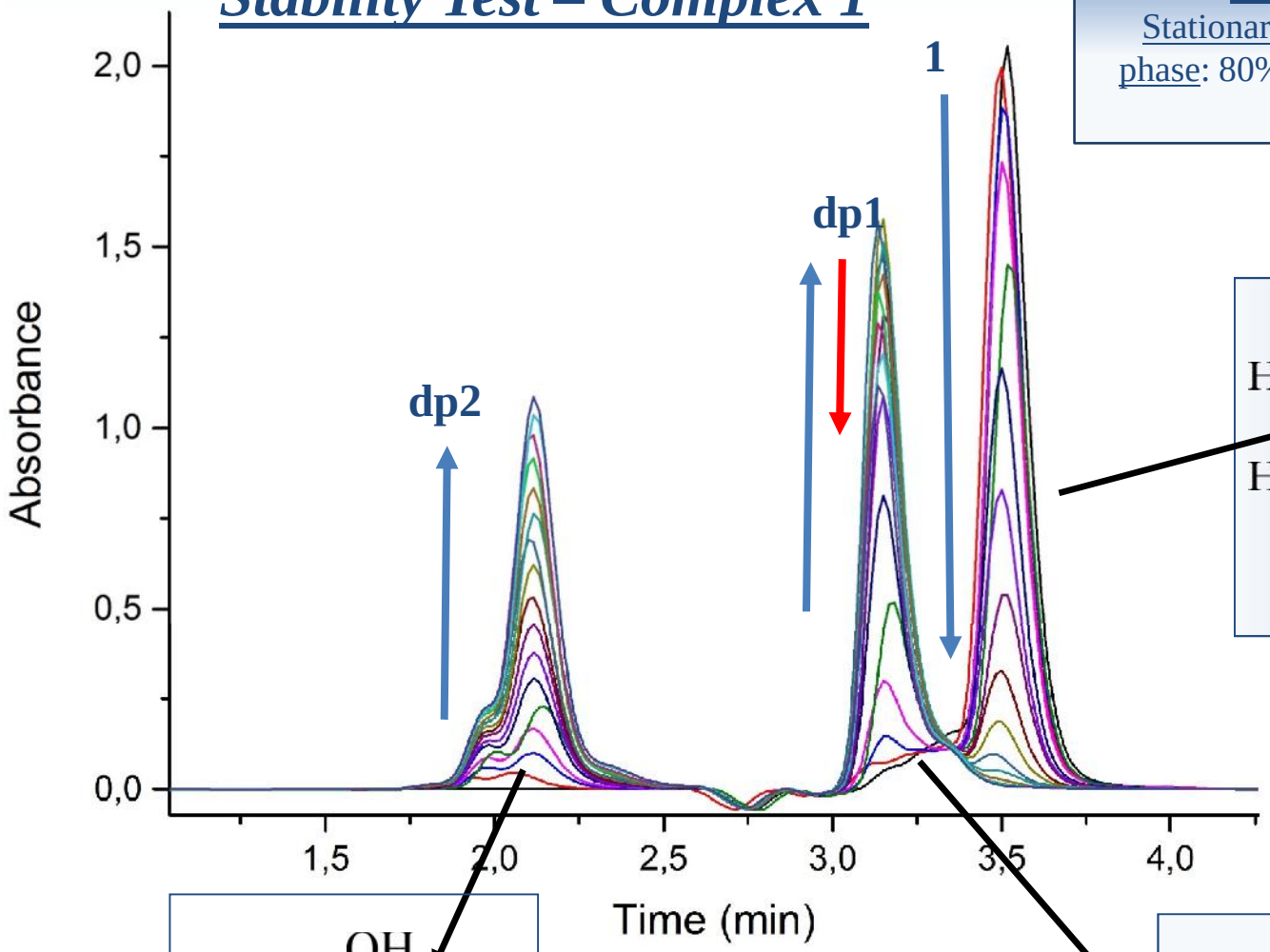


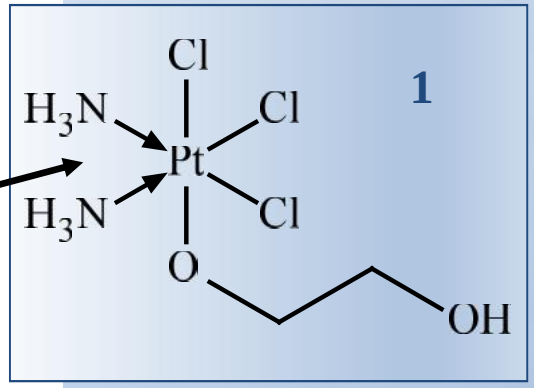


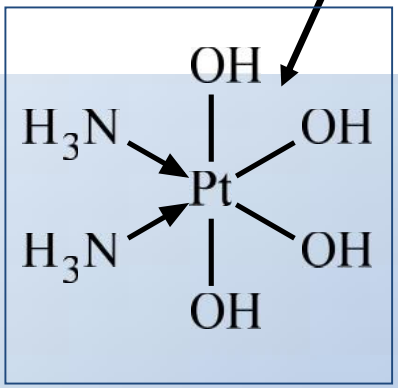


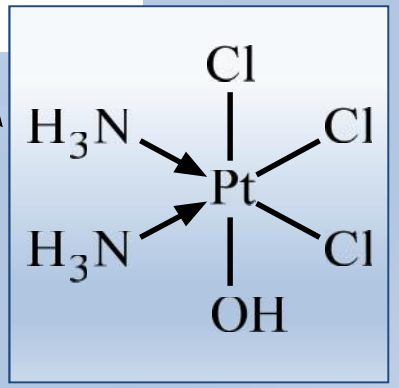
Stability Test – Complex 1

Chromatographic conditions
Stationary phase: silica-based C18; Mobile phase: 80% formic acid 15 mM / 20% MeOH;
Flow rate = 0.5 mL min^{-1}



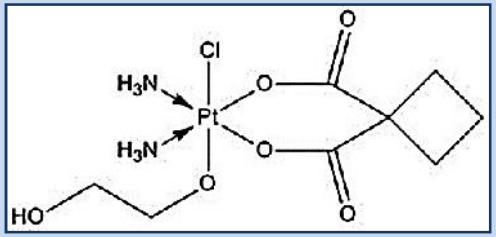
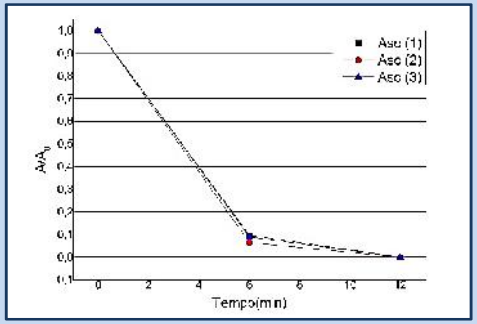
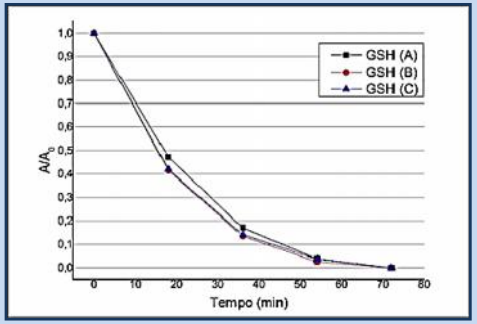
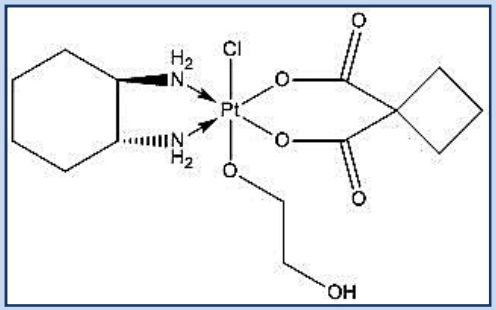
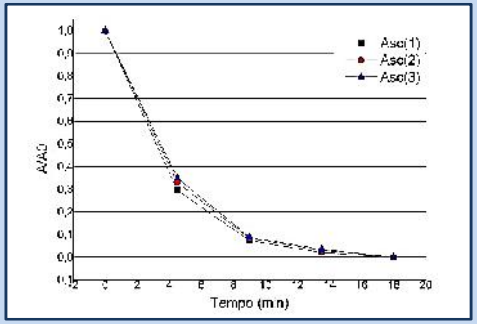
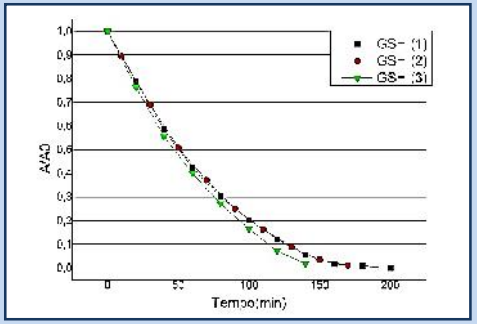






dp = degradation product

Activation by reduction

Compound	Ascorbic Acid	Glutathione
 **2**	 $t_{½}$ = 1.6 ± 0.2 min	 $t_{½}$ = 13.1 ± 0.9 min
 **4**	 $t_{½}$ = 2.4 ± 0.2 min	 $t_{½}$ = 46.3 ± 3.1 min

Chromatographic conditions

Stationary phase: silica-based C18; Mobile phase: formic acid 15 mM/MeOH (70:30 (**2**) and 50:50 (**4**)); Flow rate = 0.5 mL min^{-1}

Drug targeting and delivery (DTD)

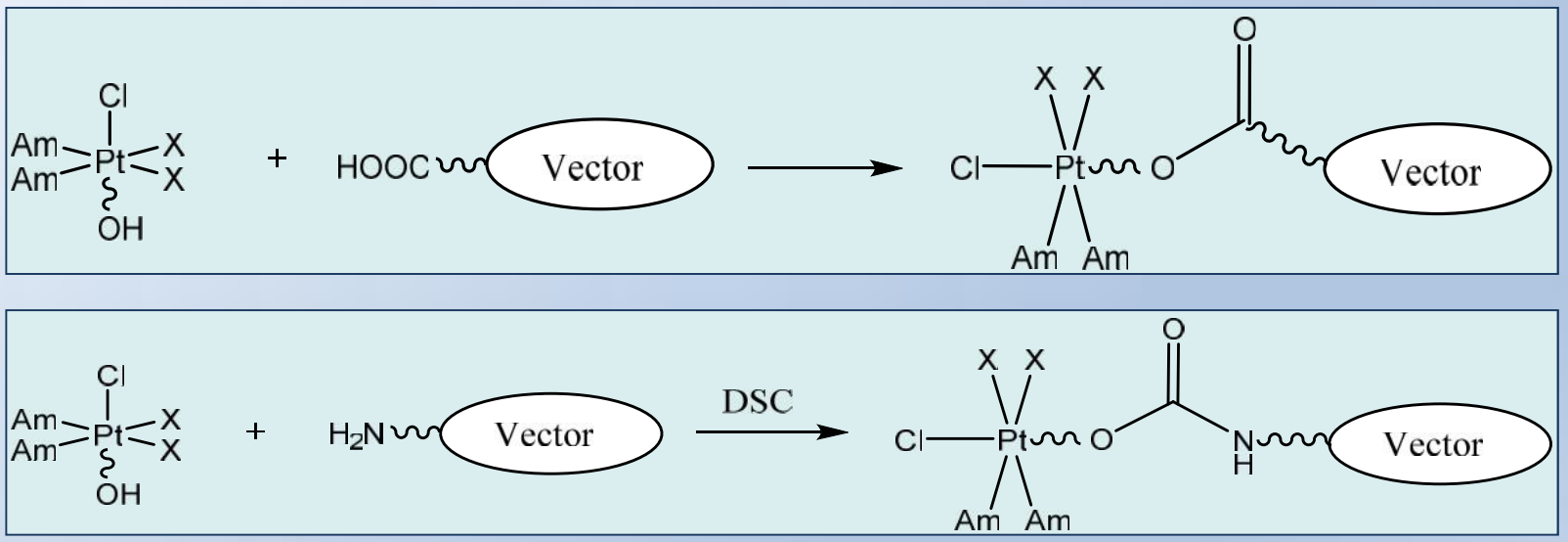
The concept of drug targeting and delivery (DTD) can be applied to tumours with biochemical differences from normal tissues.

Active targeting

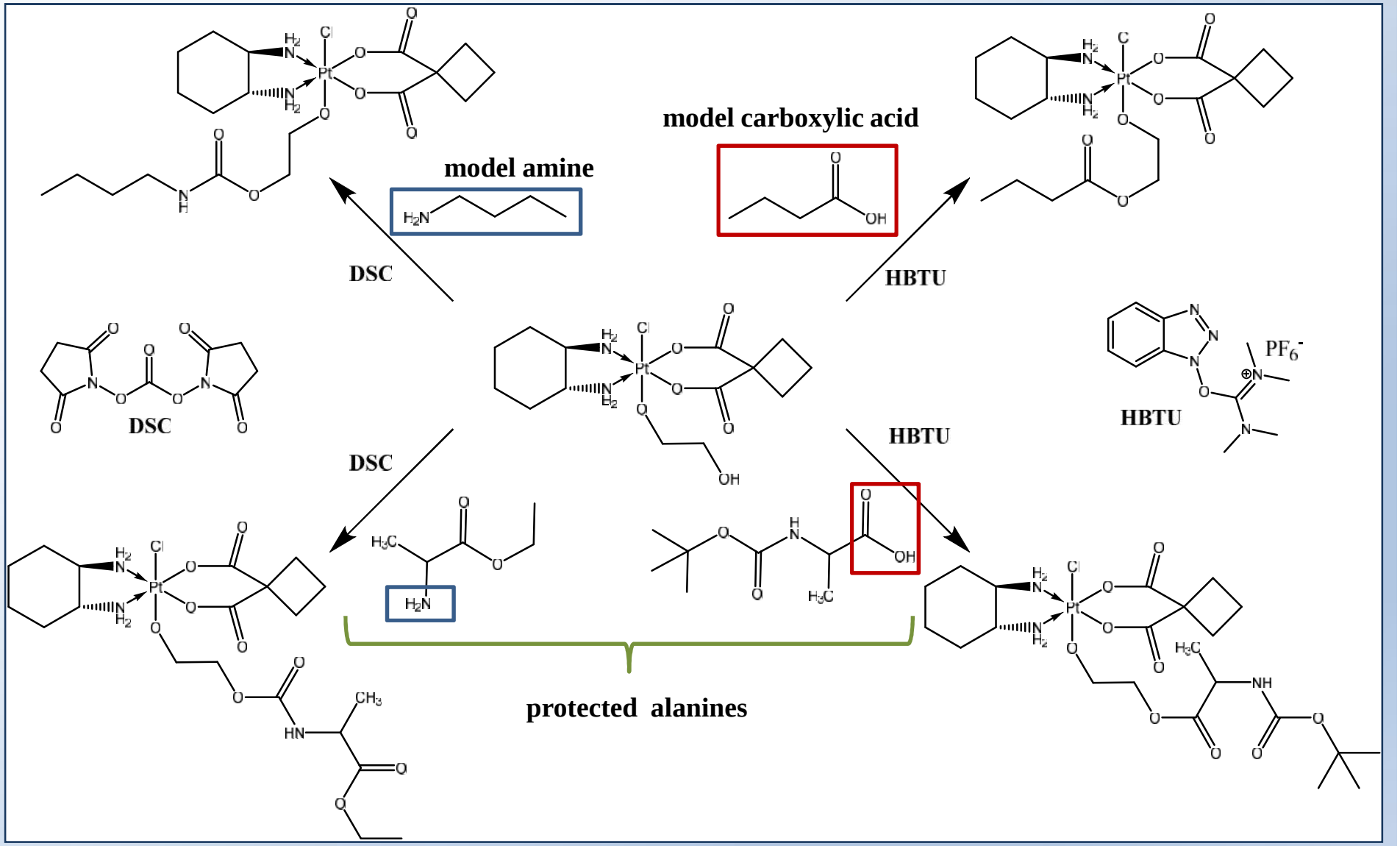
Active targeting exploits specific interactions between the vector and some cell elements. It involves, for example, ligands for tumour-related receptors.

Passive targeting

The “enhanced permeability and retention” effect in solid tumours allows macromolecules to diffuse out of tumour blood vessels and to be retained.



Coupling reactions



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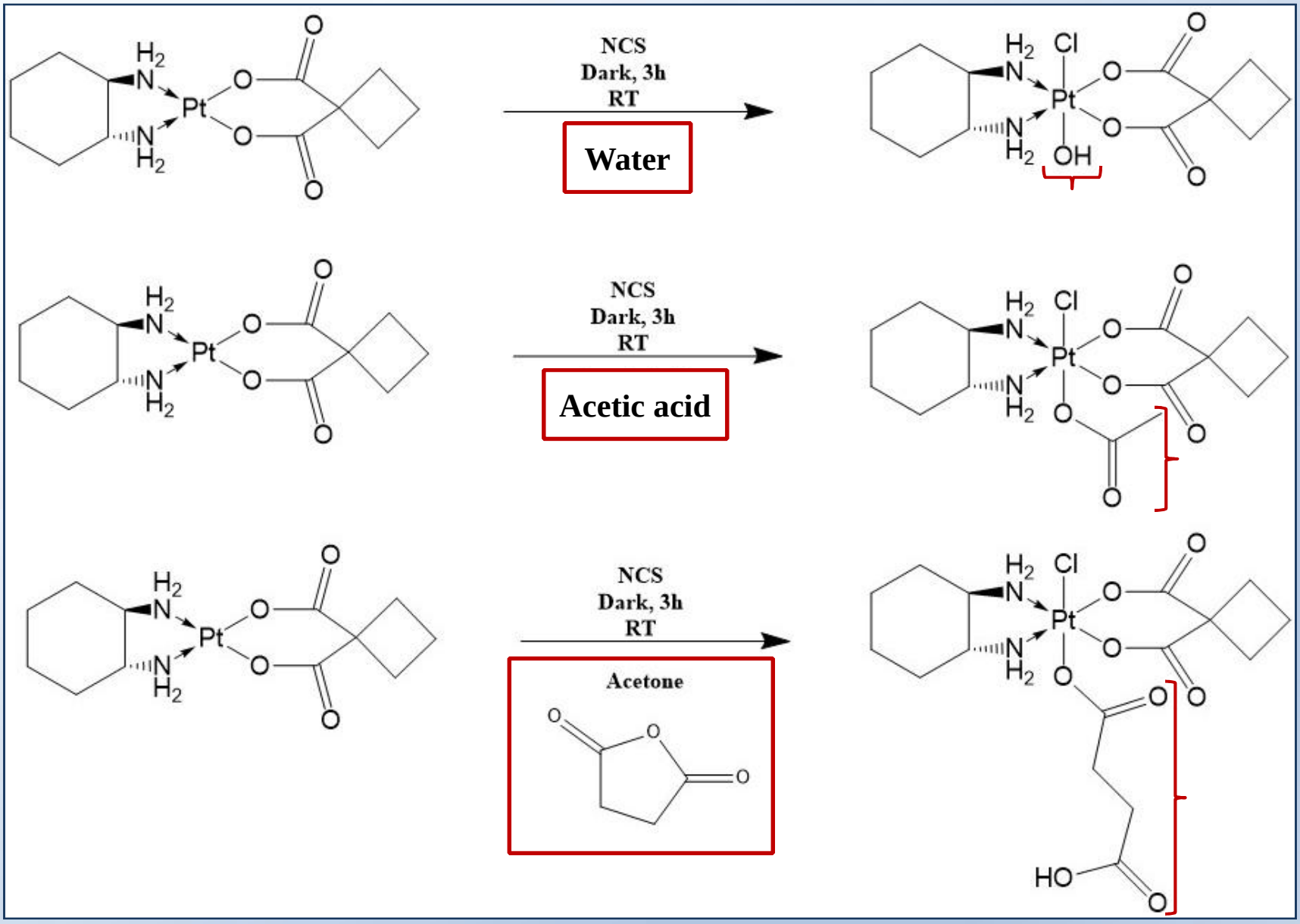
Other complexes obtained with similar procedure



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Conclusions

- Synthesis of several new Pt(IV) prodrugs
- Study of the stability in water and in hepes buffer
- Study of the reduction rate with the most common biological reducing agents
- Coupling with carboxylic acids and amine models for active or passive drug delivery vectors.

Acknowledgments

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- Federico Fregonese
- Giorgio Pelosi (*University of Parma, Italy*)

Acknowledgments

COST Action CM1105

Functional metal complexes that bind to biomolecules

***C**onsorzio **I**nteruniversitario di **R**icerca in **C**himica dei **M**etalli nei **S**istemi **B**iologici* (Bari)

Thank you for your attention!