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New Pt(IV) antitumour prodrugs for drug targeting and delivery strategies

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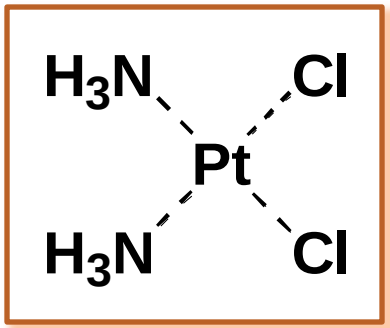
Some milestones in the development of Pt drugs



1965 — Discovery of the biological properties of cisplatin

1978 — Approval of cisplatin (testicular and bladder cancer)

1985 — Description of Pt-DNA adducts

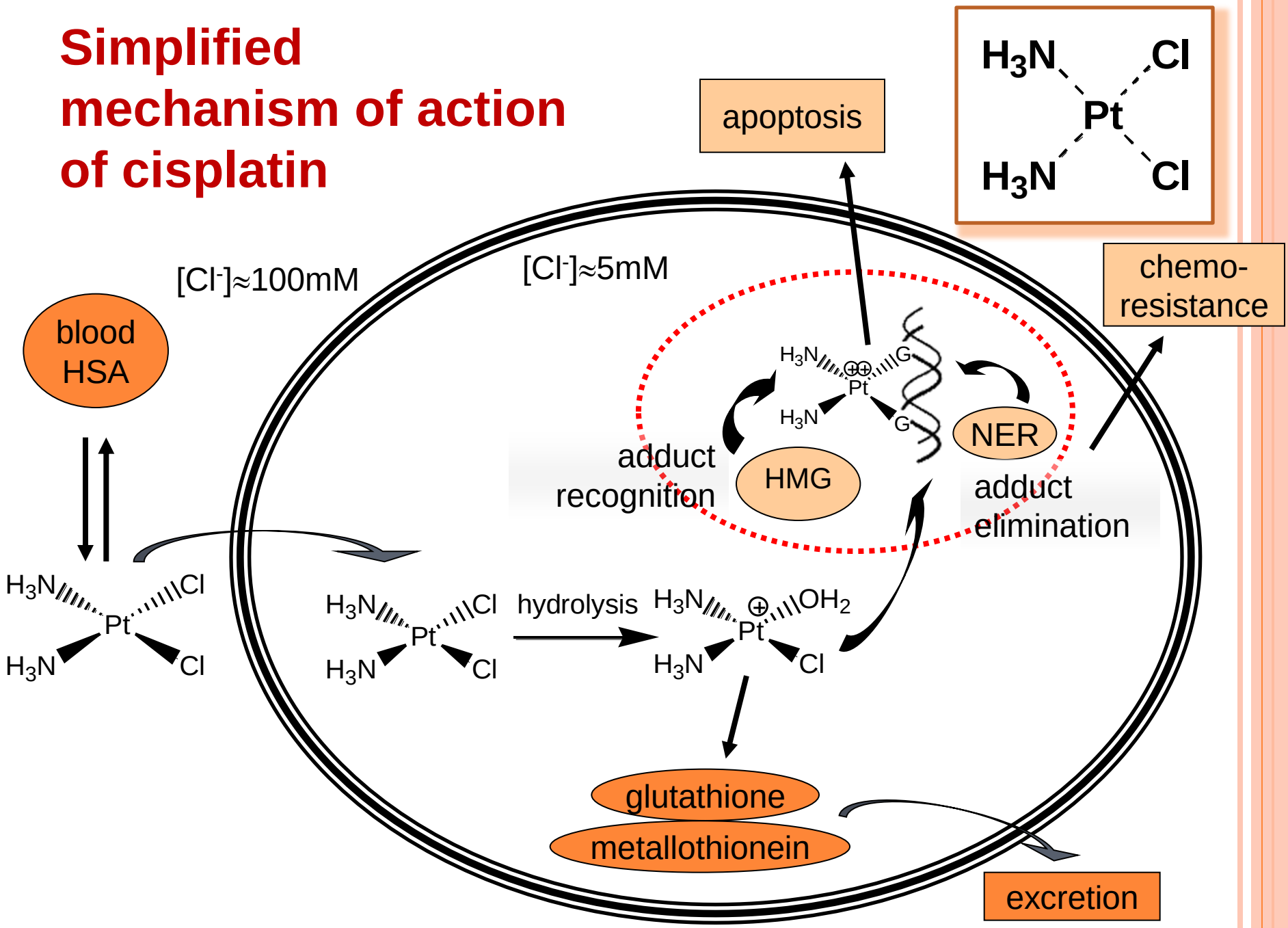
1989 — Approval of carboplatin (ovarian cancer)

1991 1992 — The role of GSH in the resistance to cisplatin; The role of NER in the low response to cisplatin

2002 — Approval of oxaliplatin (colorectal cancer)

2007 — Satraplatin Pt(IV) under approval (hormone-refractory prostate cancer)

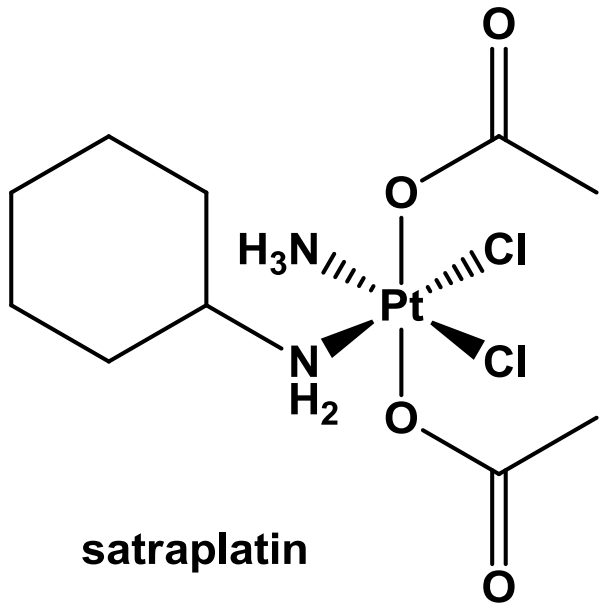
Simplified mechanism of action of cisplatin



Pt(IV)-based anticancer prodrugs

Pt(IV) complexes (d^6 low-spin electronic configuration) are quite inert towards ligand substitution:

- they give less side-reactions (less systemic toxicity);
- they are not deactivated by gastric juices and therefore are orally viable.



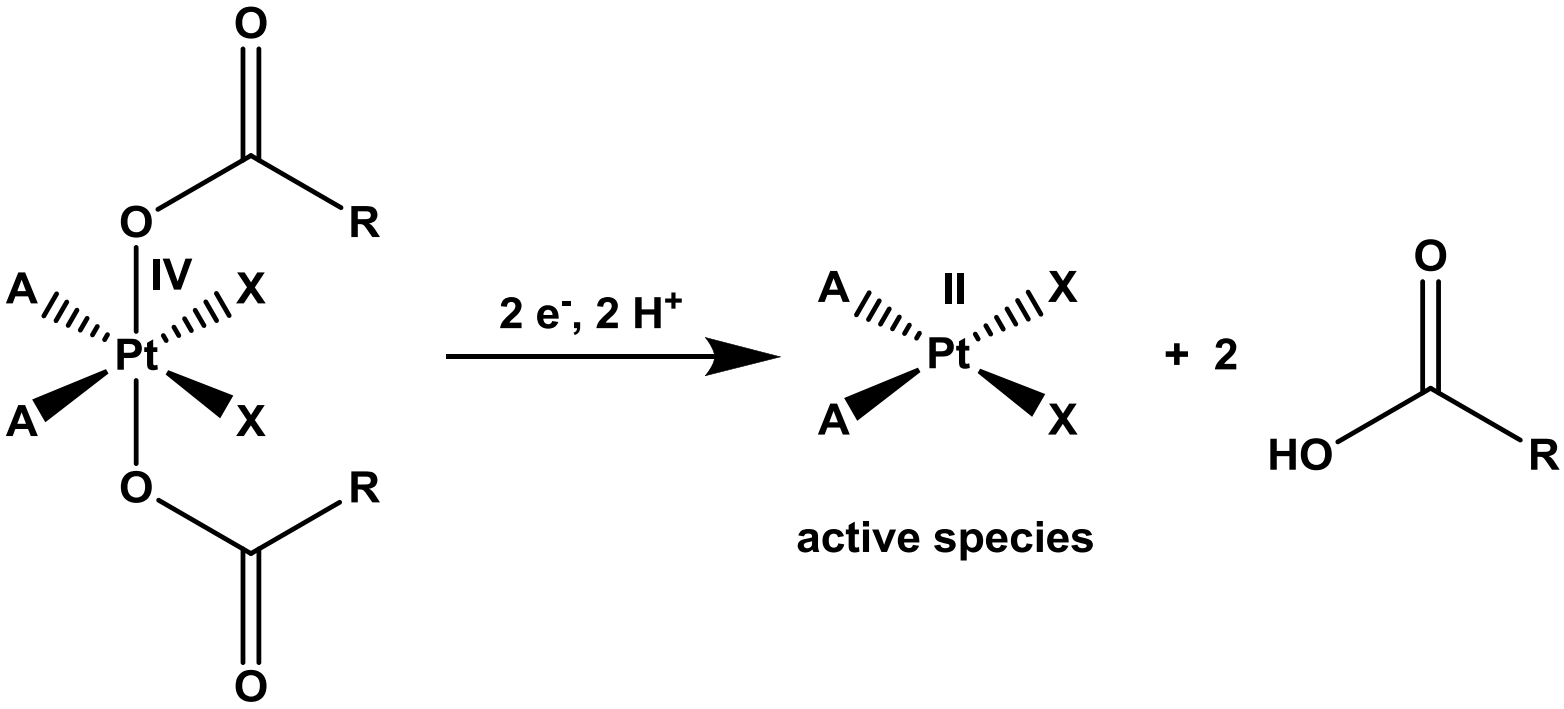
satraplatin

JM216 (satraplatin): after phase III, under approval for the cure of hormone-refractory prostate cancer.

First orally administrable Pt(IV) drug

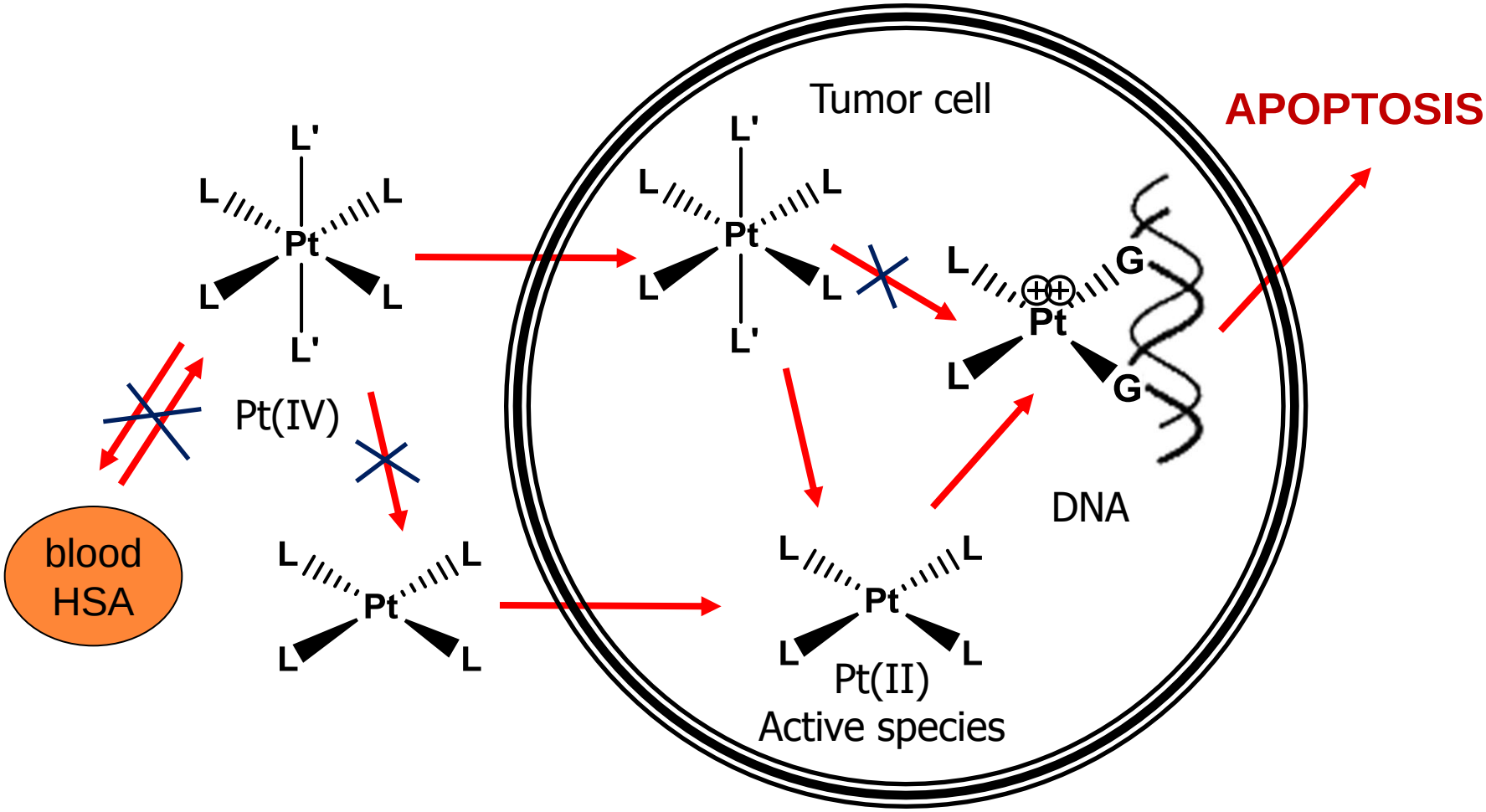
Activation by reduction

The Pt(IV) complexes are supposed to act as prodrugs being *reduced in vivo* to their active Pt(II) metabolites in the hypoxic and reducing conditions of the tumor tissue.



In the case of carboxylato ligands the Pt(IV)→Pt(II) reduction is further favored by low pH.

Activation by reduction



Key features of Pt(IV) prodrugs

A rational choice of the ligands is fundamental to modulate the key features of these drugs:

Structure of the active Pt(II) metabolite. The equatorial base of the complexes must be an active Pt(II) drug.

Reduction peak potential. The complexes must be reduced in vivo in the hypoxic and reducing tumor tissue: the easier is the reduction, the higher is the cytotoxicity. Too easy reduction implies systemic toxicity.

Lipophilicity. The complex must be able to enter the tumor cells by passive diffusion; too high lipophilicity is often associated to low solubility.

Drug targeting and delivery (DTD)

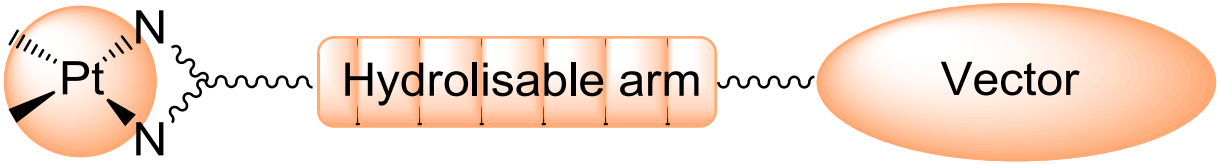
The concept of drug targeting and delivery (DTD) can be applied to tumours with biochemical differences from normal tissues.

Active targeting

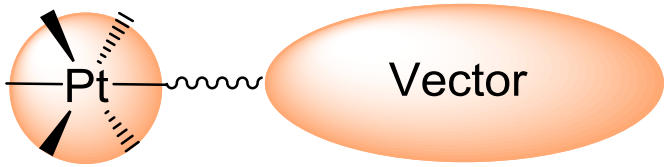
Active targeting exploits specific interactions between the vector and some cell elements. It involves, for example, ligands for tumour-related receptors.

Passive targeting

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

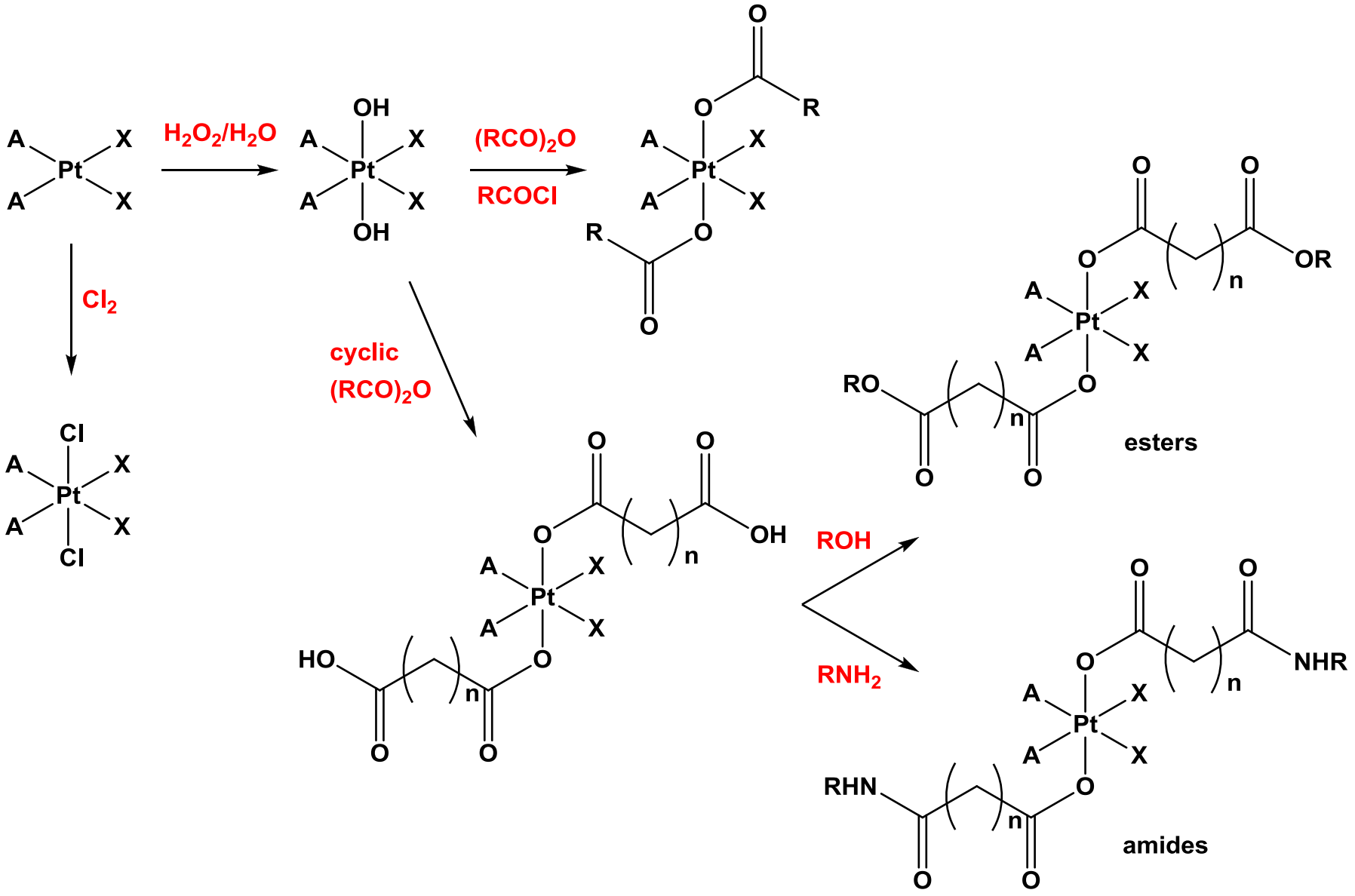


When a drug contains two different agents (i.e. a Pt(II) drug and a vector for DTD), a hydrolisable linking arm is necessary.

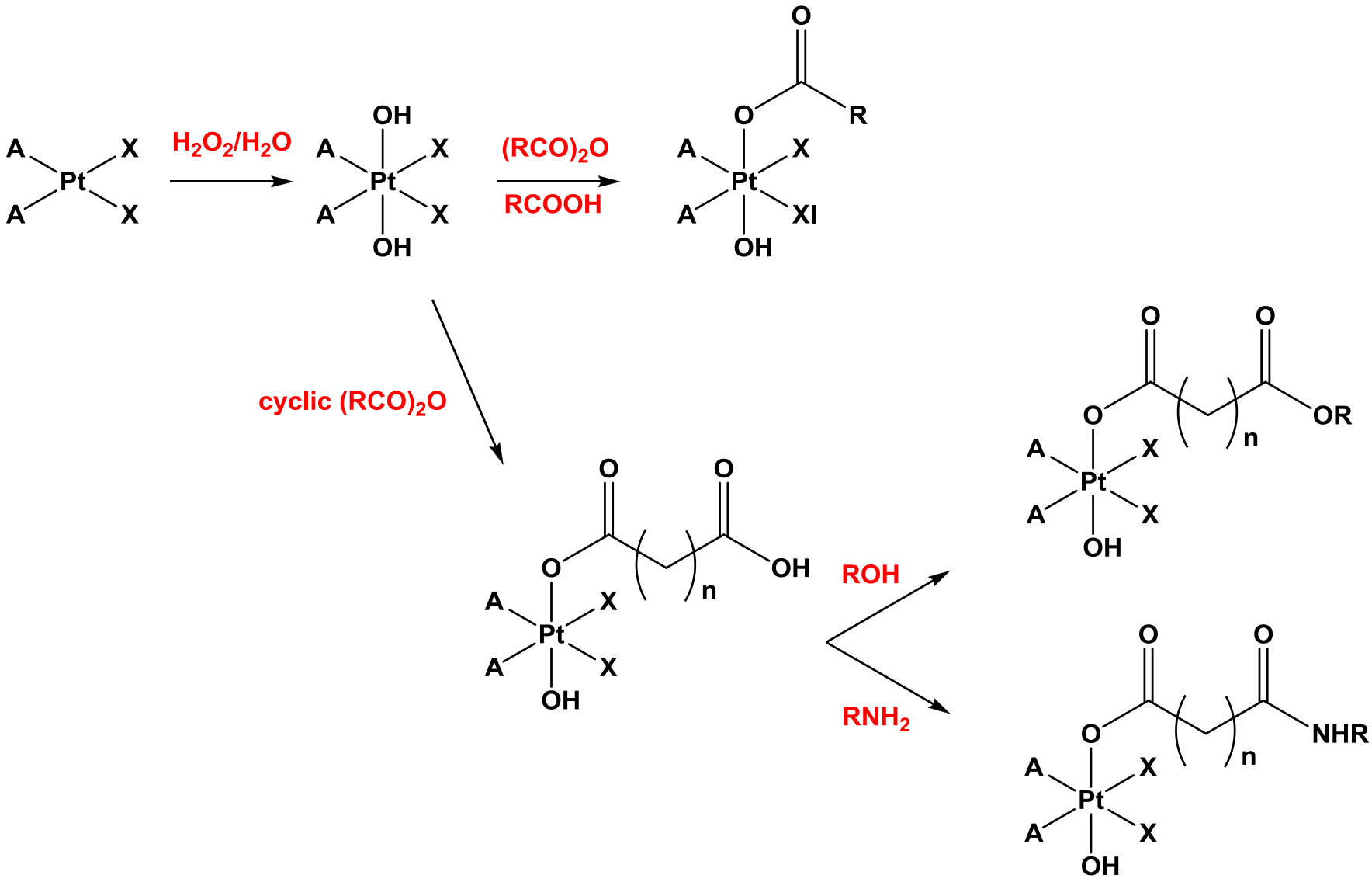


Using Pt(IV) compounds, the biologically active molecule or the passive DTD vector are linked in the axial position and the Pt metabolite is released by reduction.

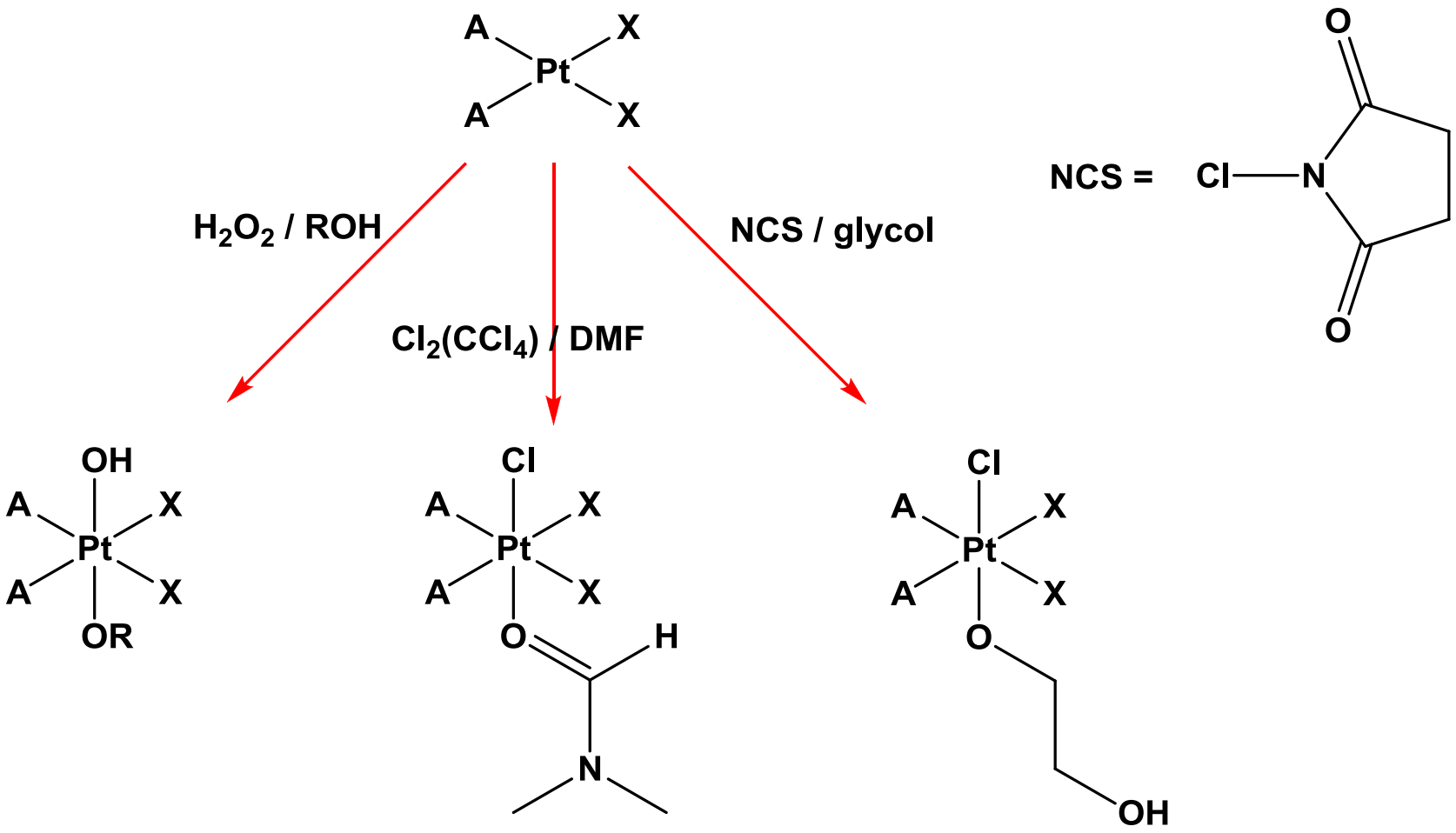
Traditional syntheses



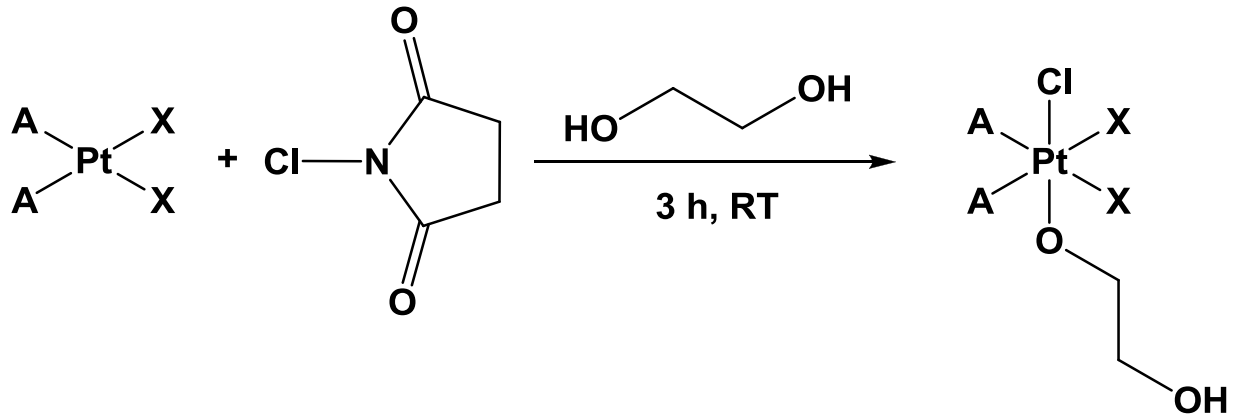
Traditional syntheses

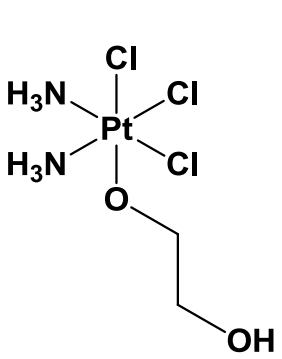


Axially mixed complexes



Glycol derivatives





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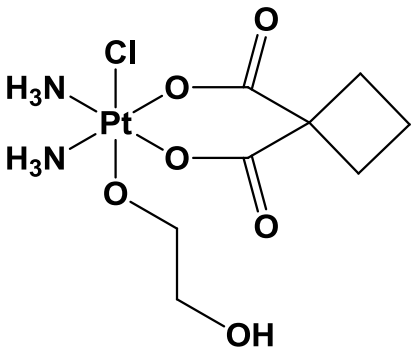

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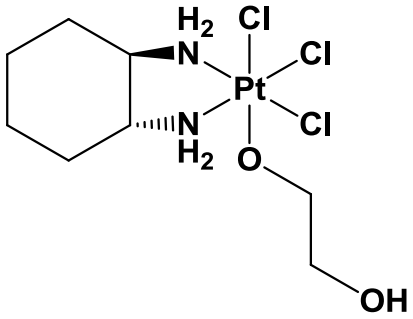

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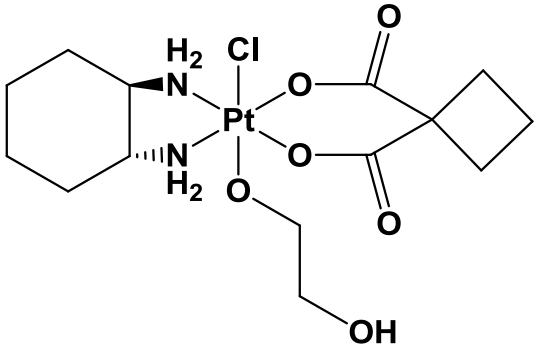
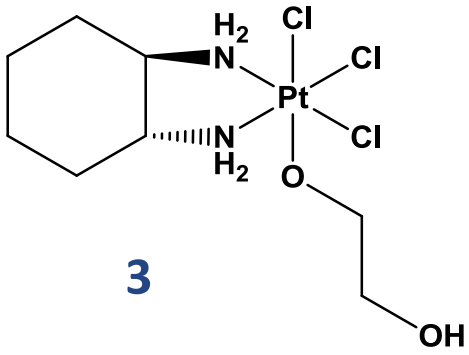


4

Stability in aqueous solutions



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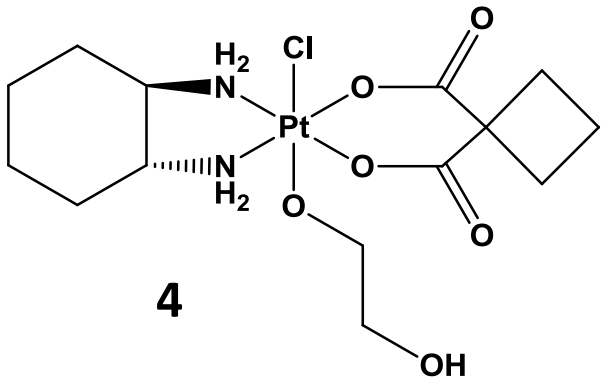

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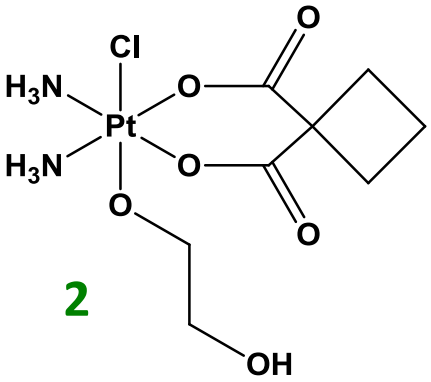

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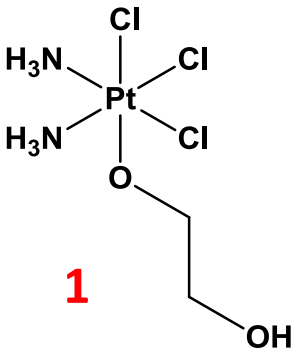

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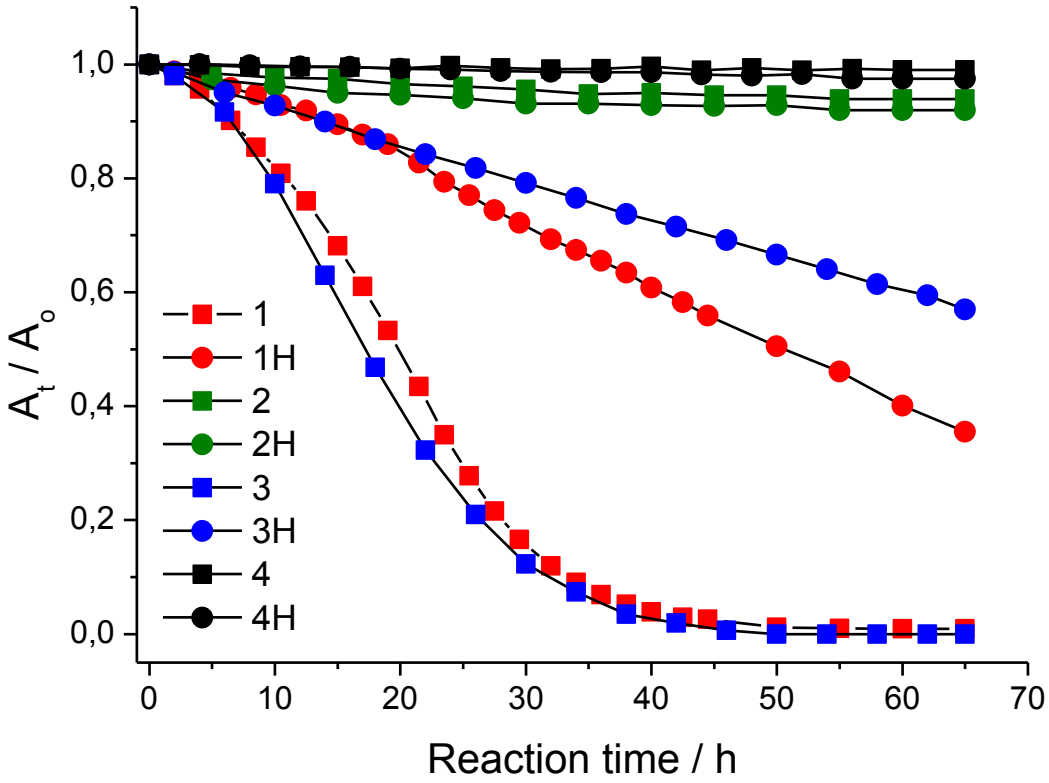
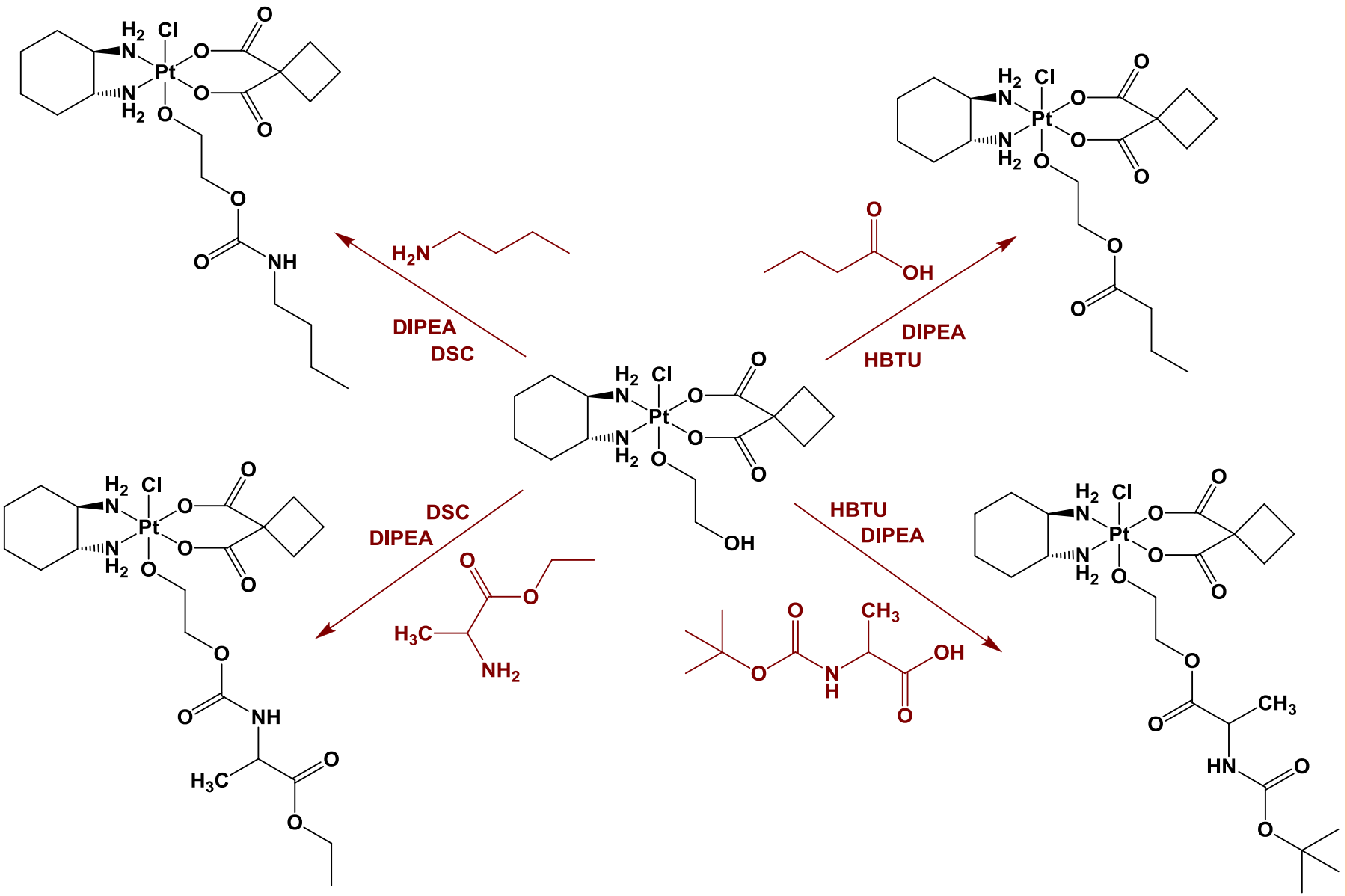
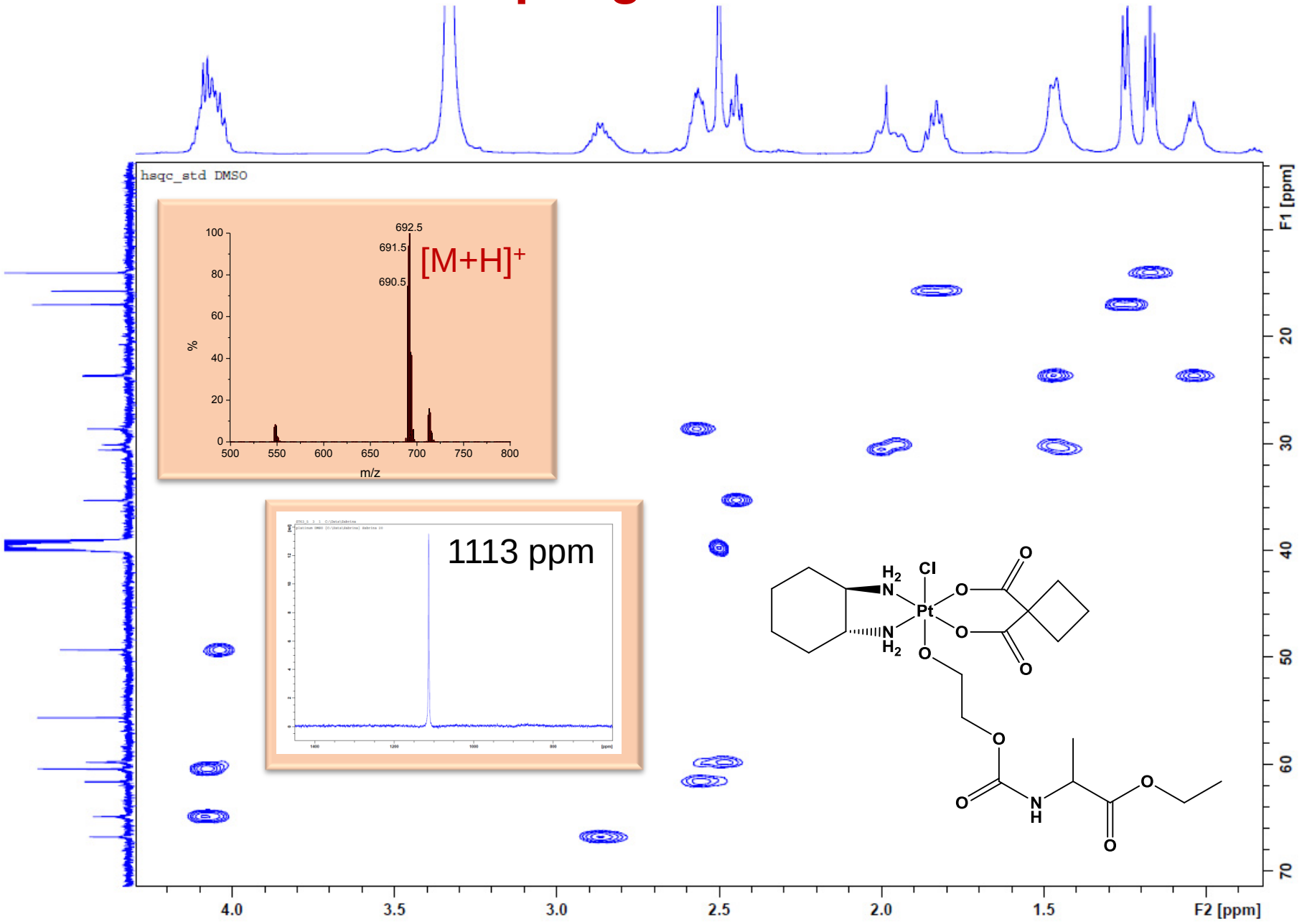


H = HEPES buffer (pH 7.5)

Coupling reactions



Coupling reactions



Concluding remarks

- Pt(IV) complexes have an enormous potential as anticancer prodrugs

- monofunctional glycol-Pt(IV) complexes are suitable for coupling with vectors for selective drug targeting to the tumour site

- more details on the syntheses are depicted in the poster of dr. S. Tinello

… and now?

- we need vectors for drug targeting

Acknowledgements

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COST Action CM1105
Functional metal complexes that bind to biomolecules

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FONDAZIONE CASSA DI RISPARMIO DI ALESSANDRIA

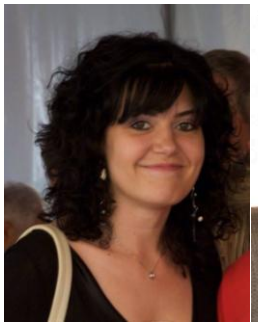
FONDAZIONE CRT Cassa di Risparmio di Torino

Thank you for your attention!

Thanks to:


D. Osella


E. Gabano


S. Bianco


I. Zanellato


I. Bonarrigo

Valentina Gandin
Cristina Marzano

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