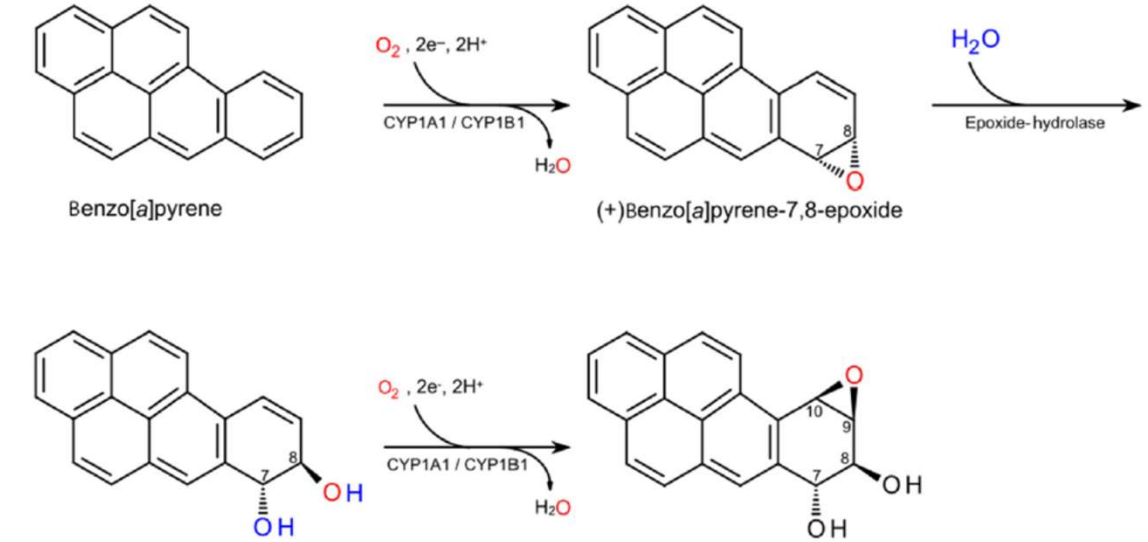
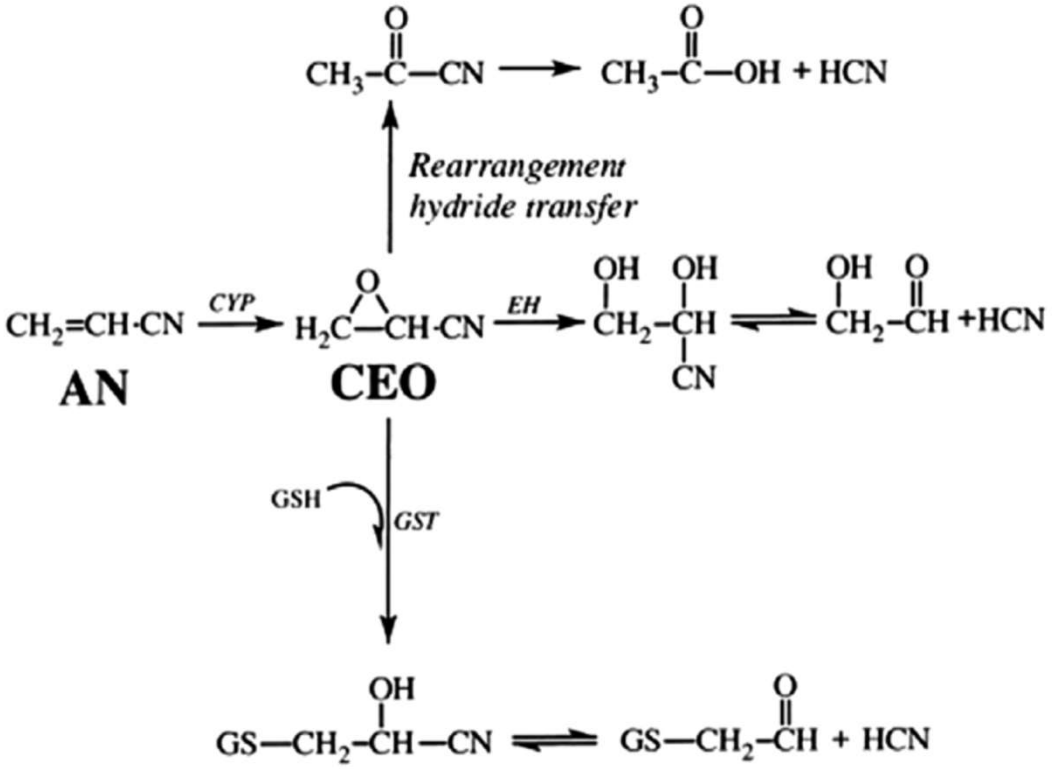
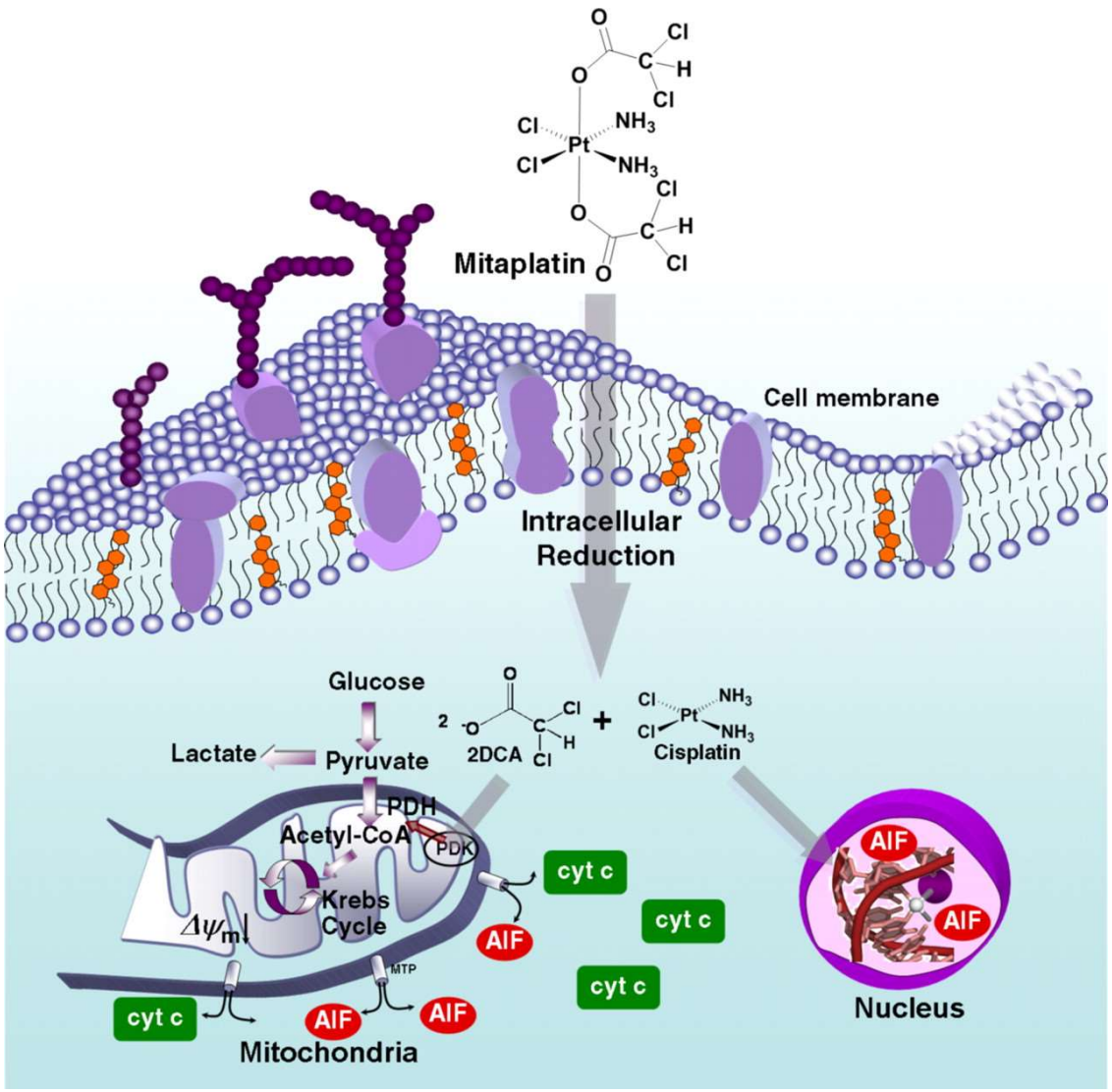
Glutathione: A cellular thiol detoxifying agent in synergy with $CytP_{450}$

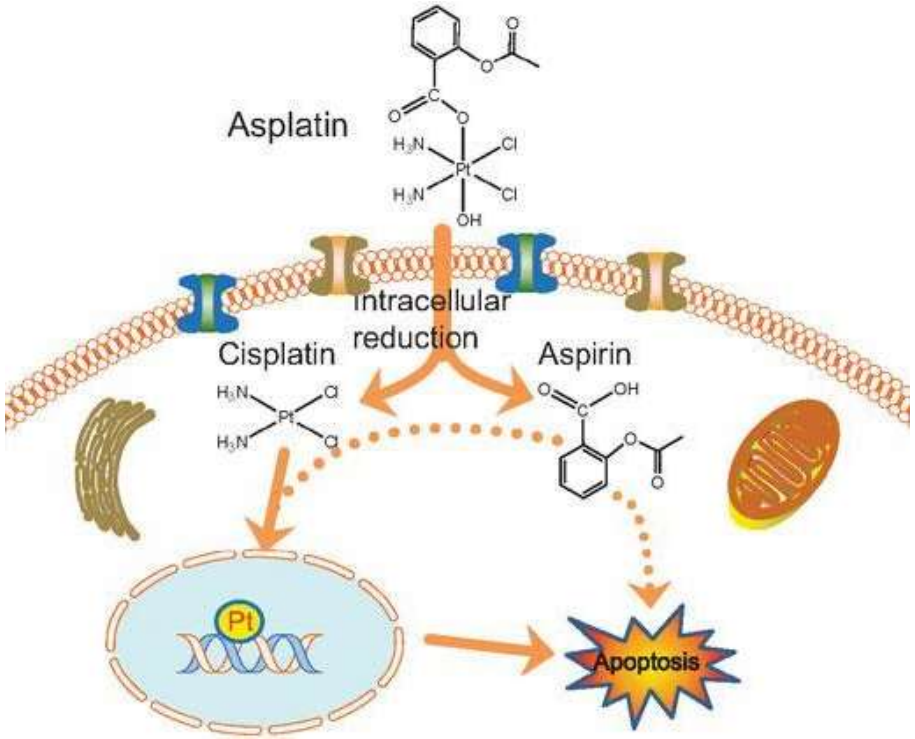


Metabolism of benzo(*a*)pyrene yielding benzo(*a*)pyren-7,8-diol-9,10-epoxide.



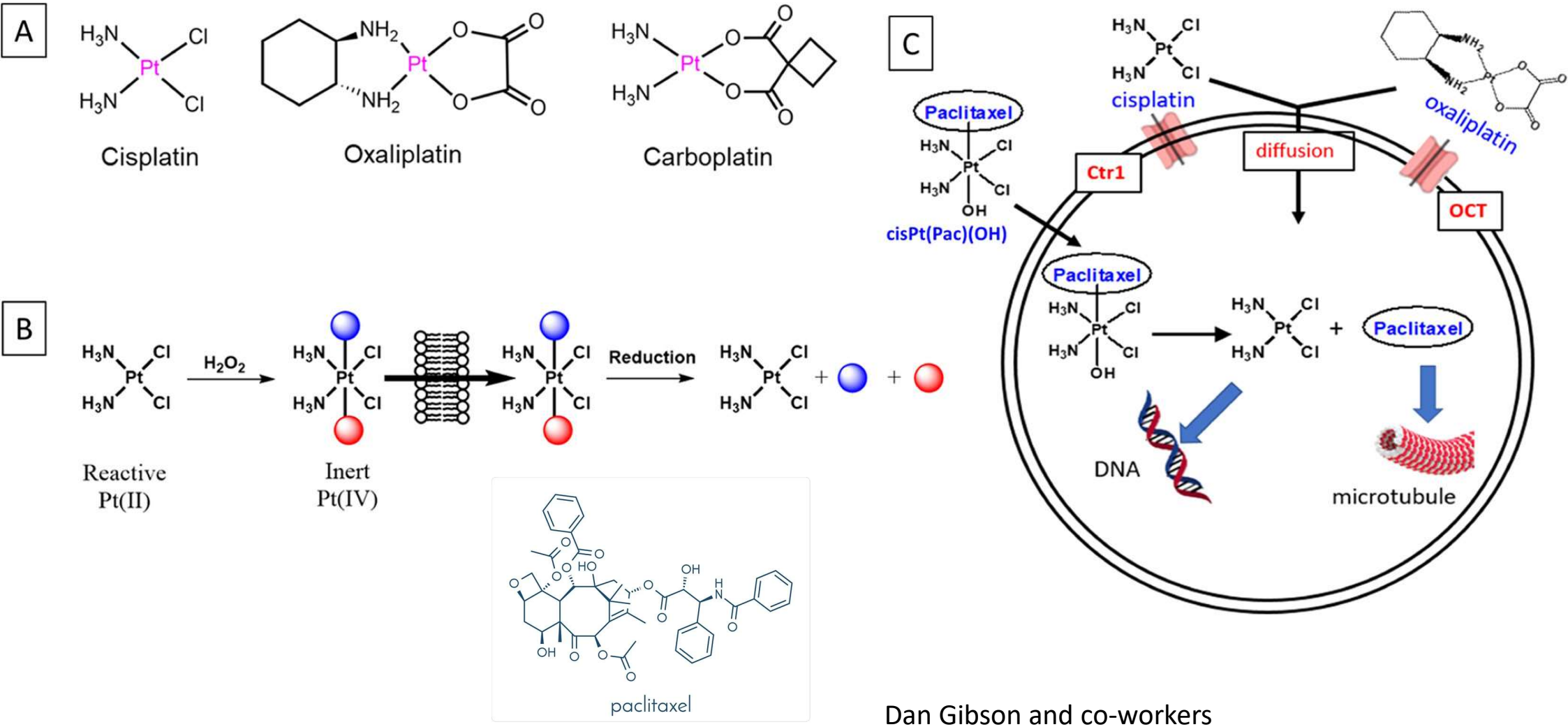
Moving from Pt(II) to Pt(IV): Limited Success??





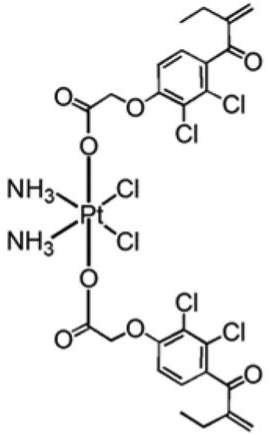
Lippard et al

Moving from Pt(II) to Pt(IV): Limited Success??



Dan Gibson and co-workers

Moving from Pt(II) to Pt(IV): Limited Success??



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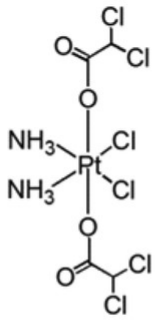

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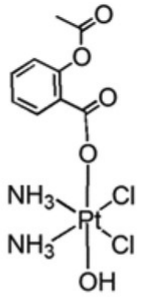

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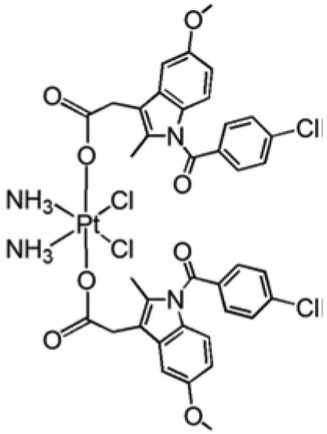

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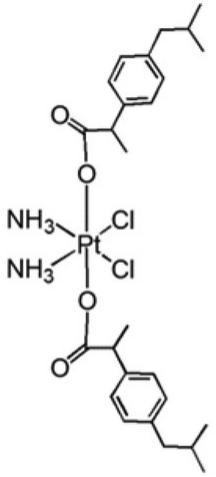

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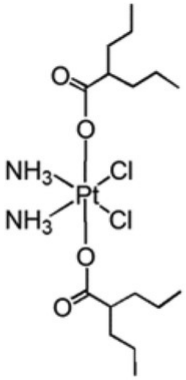

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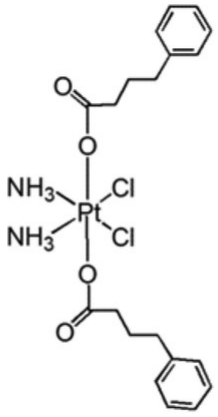

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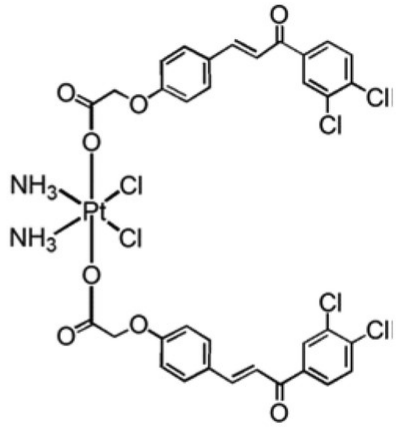


H

Moving from Pt(II) to Pt(IV): Limited Success -- Problem in Hypotheses???

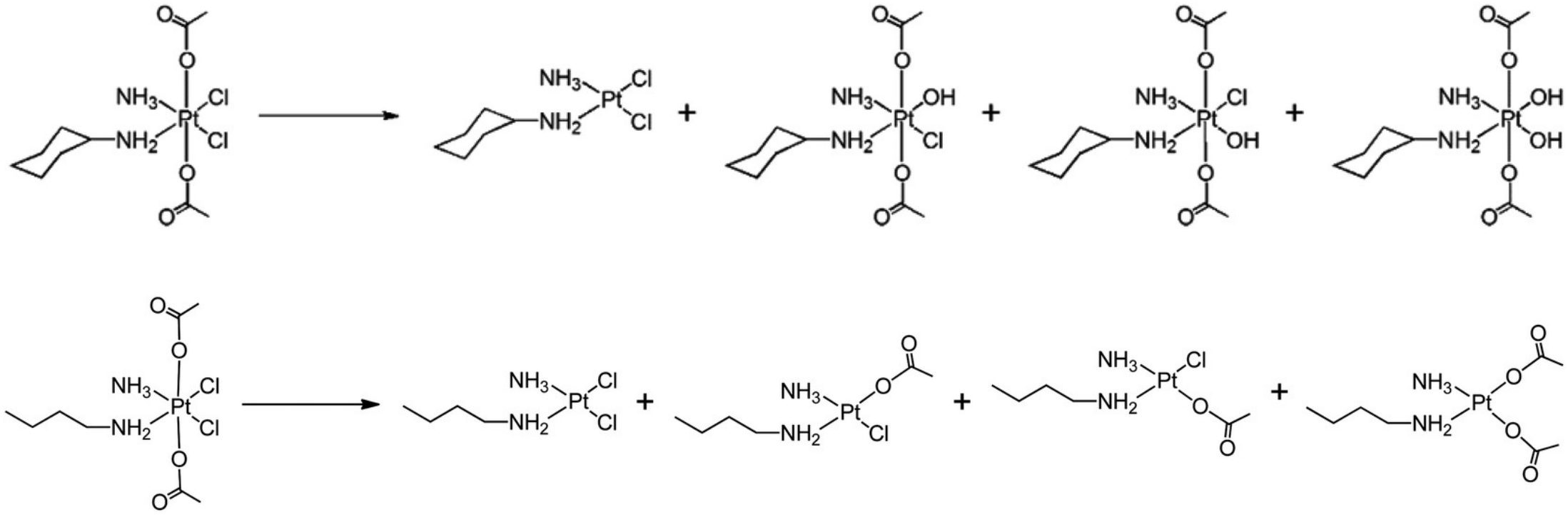
- **Hypothesis:** stable in extracellular biological fluids

- **Satraplatin [$Pt(NH_3)$(c-hexylamine)$(OAc)_2Cl_2$]:** Only Pt(IV) drug advanced to Phase-III clinical trials in combination with prednisone, completed phase III clinical trials against Hormone Refractory Prostate Cancer (HRPC) by oral administration. Not approved by the FDA → overall survival was not significantly improved compared to existing treatment

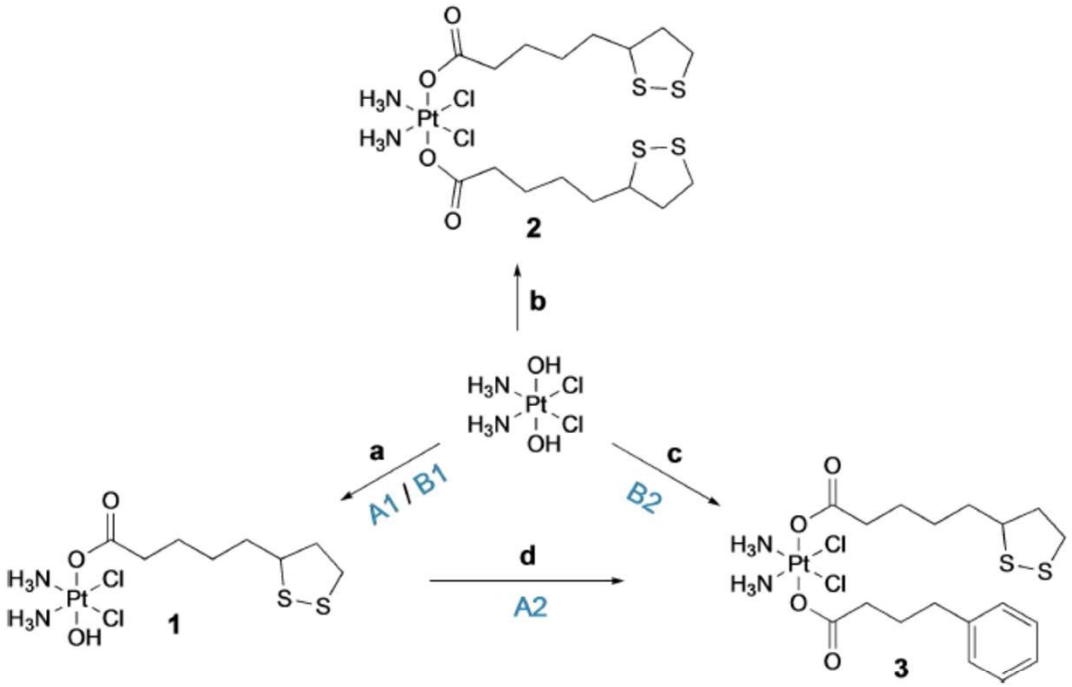
- Advancement to Phase-III in the clinical trials by oral administration suggests that Pt(iv) complexes are sufficiently stable to be used as oral drugs.

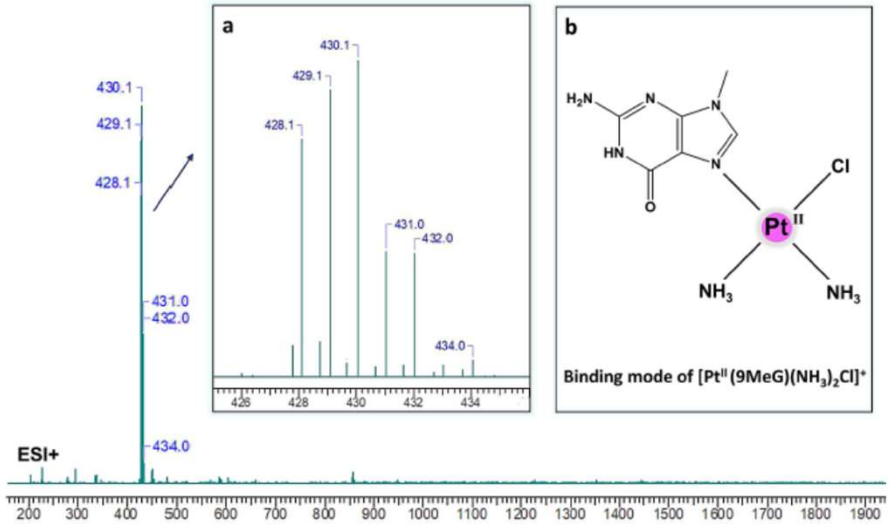
- **Problem with Hypotheses:** Yet, once in the bloodstream, satraplatin metabolized and several distinct platinum metabolites were identified in plasma ultrafiltrates of patients. The major metabolite was the expected reduction product cis-[$Pt(NH_3)$(c-hexylamine)Cl_2] obtained from the loss of the two axial acetate ligands.
- Surprisingly, the other metabolites were Pt(IV) complexes where one or two chloride ligands were replaced by hydroxides.

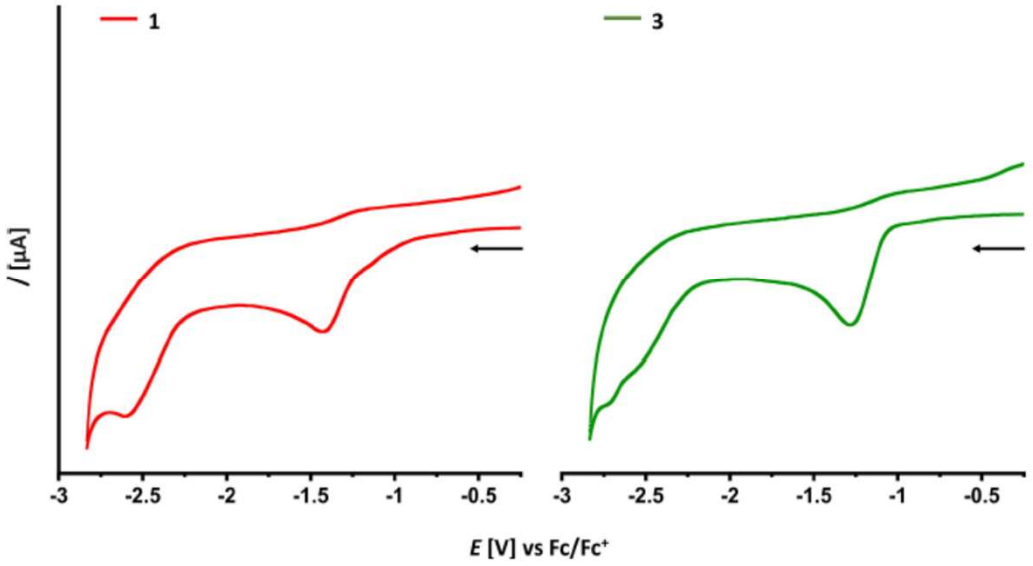
Moving from Pt(II) to Pt(IV): Limited Success -- Problem in Hypotheses???



Moving from Pt(II) to Pt(IV): Limited Success -- Problem in Hypotheses???







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