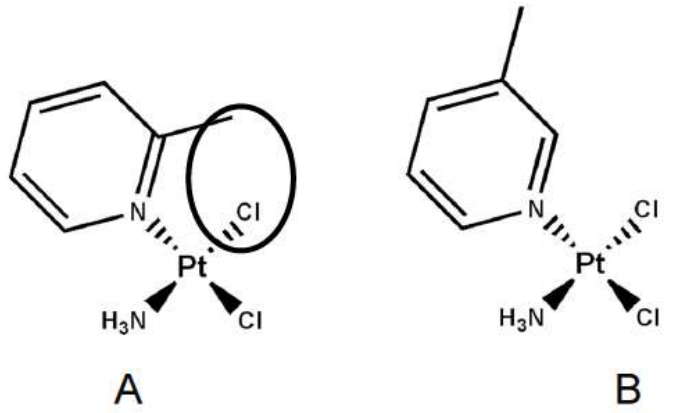
Slowing down hydrolysis of cisplatin: Consequences!

- The hydroxo / water ligands are much more reactive to substitution than the chloride ligands
- The hydrolysis rate is mainly determined by the *trans* effect of the ligands *trans* to Cl^-
- Steric hindrance can also slow rates of ligand substitution



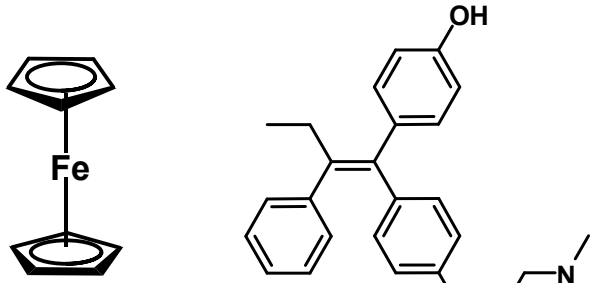
A undergoes hydrolysis 6x slower than **B**

The general order in bond strength is Pt-C (sp) > Pt-O > Pt-N > Pt-C (sp^3)

Role of metal : adding targets to existing organic drugs

Jaouen and coworkers:

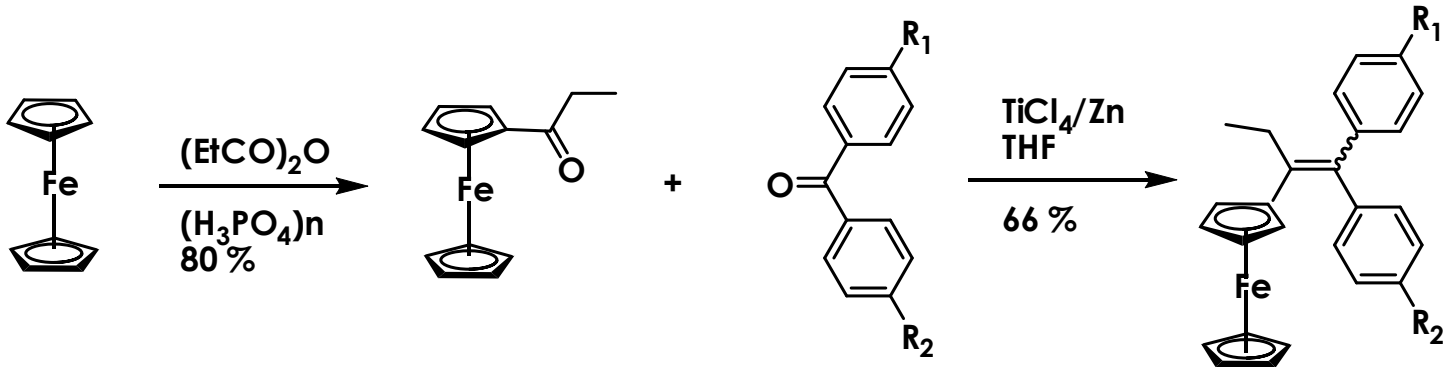
S. Top et al. *Chem. Comm. 1996, 955*
S. Top et al. *J. Organometal. Chem. 1997, 541, 355*



(Z)-4-Hydroxytamoxifen

Ferrocifen : Both effects coexist together

Anti-tumor and Anti-oestrogen properties

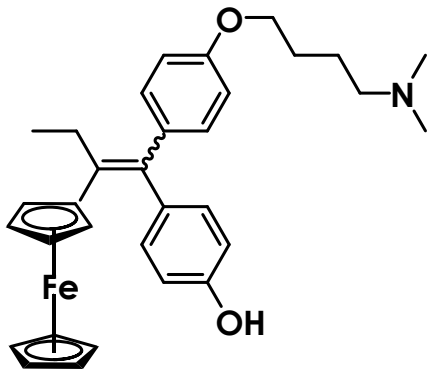


McMurry coupling

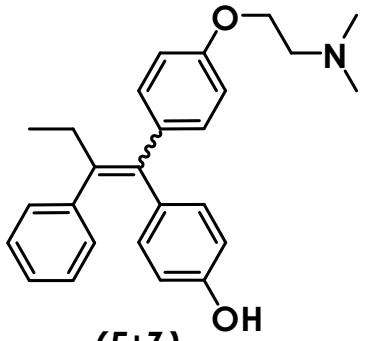
1:
R_1 = OH, R_2 = $O(CH_2)_4Br$

2 (Z+E) :
R_1 = OH, R_2 = $O(CH_2)_4Br$

Role of metal is adding targets to existing organic drugs



3 *(Z+E)*



(E+Z)

4-Hydroxytamoxifen

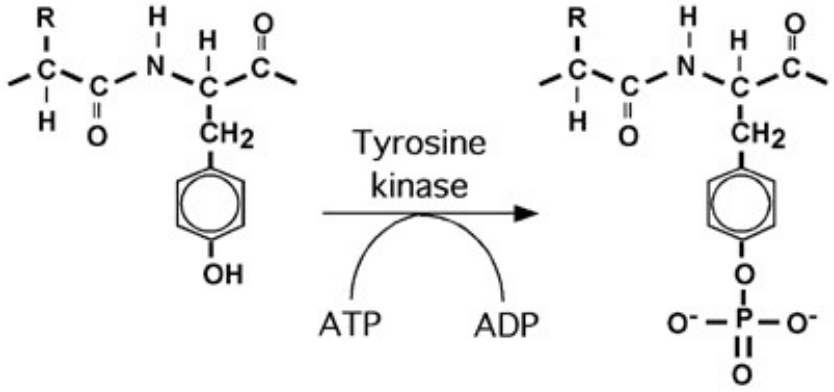
- Binding affinity < hydroxytamoxifen for 3 (sterics of ferrocinyl moiety)
- 3 > lipophilic
- Antiproliferative activity on breast cancer cells : 3 = OH-TAM for ER(+)
- Ferrocifen show remarkable **antiproliferative behaviour even against ER- tumors**

S. Top et al. *J.* Organometal. Chem. 2001, 637, 500
S. Top et al. *Chem. Eur. J*. 2003, *9*, 5223

Protein Kinases

Protein Kinases:

- Phosphorylation of proteins : turn them on or off



- Due to their involvement in various forms of cancers, PTKs have become prominent targets for therapeutics

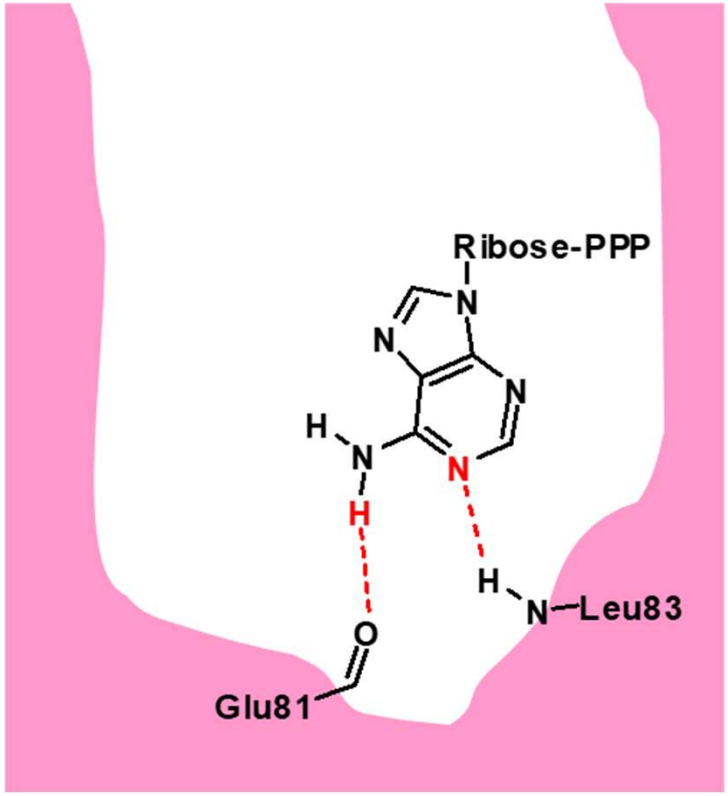
- Regulate the majority of cellular pathways e.g DNA replication, cell growth
- Most kinases contain a 250-300 amino acid domain with a conserved core structure, compromising a binding pocket for ATP

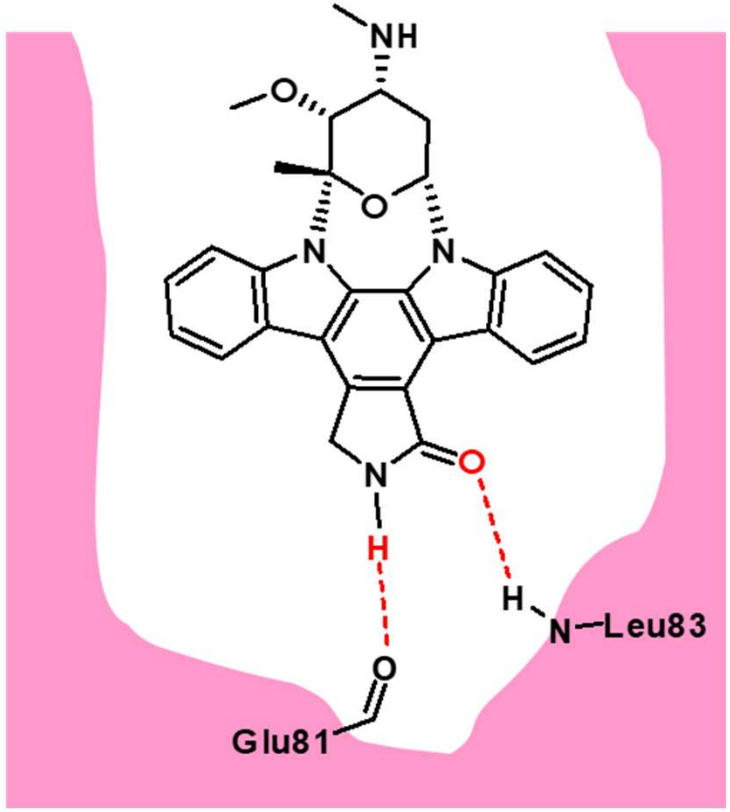
Blume-Jensen. P.; Hunter, T. *Nature*, 2002, *411*, 355
Fischer, P.M. *Curr. Med. Chem.* 2004, *11,* 1583

- These domains are more or less homologous

ATP Binding

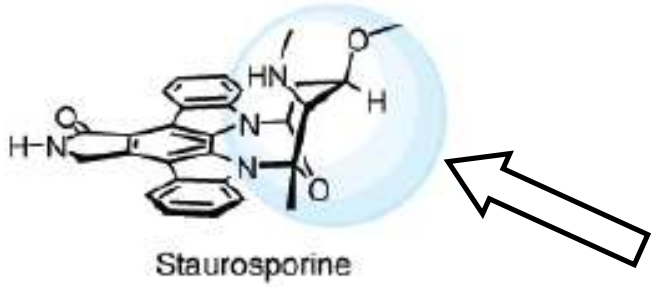
- ATP-binding site is an ubiquitous “receptor” in nature
- Most kinase inhibitors mimic mainly the adenine portion of ATP
- Approach is limited in terms of selectivity



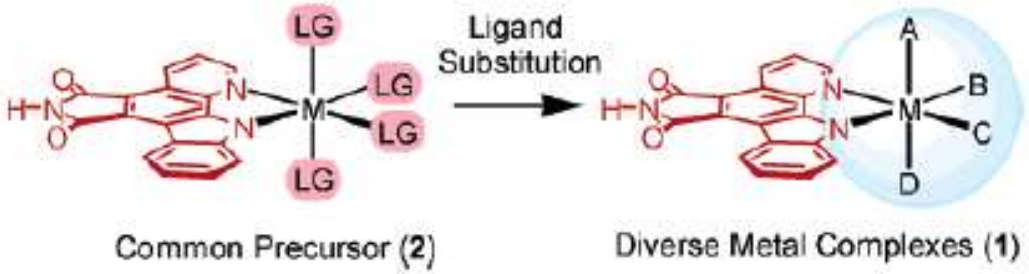


Fischer, P.M. *Curr. Med. Chem.* 2004, *11,* 1583

Staurosporine metal complexes



Defined globular shape



- copying the structural features of small organic molecule inhibitors
- metal plays solely a structural role
- access to new areas of chemical space

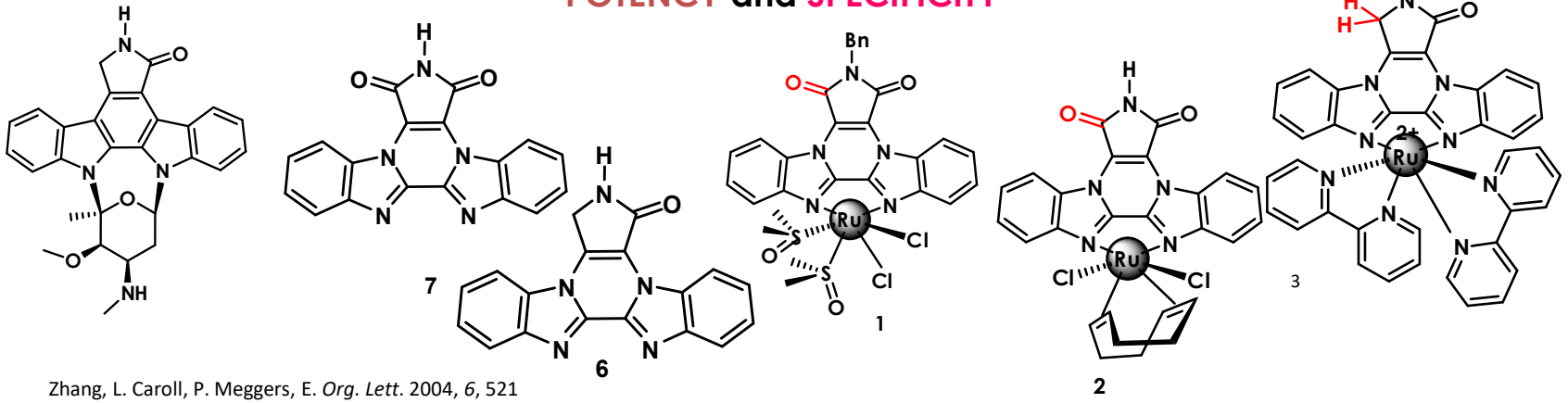
Zhang, L. Caroll, P. Meggers, E.; *Org. Lett*. 2004, *6*, 521
Bregman, H. Williams, G. S. Meggers, E.; *Synthesis,* 2005, *9*, 1521
Bregman, H, Caroll, P.J. Meggers, E. *J. Am. Chem. Soc.* 2006, *128*, 877

Analysis of IC_{50} values: Ruthenium worsening kinase inhibition or enhancing selectivity

Inhibition of some protein kinases with the various compounds (in µM)

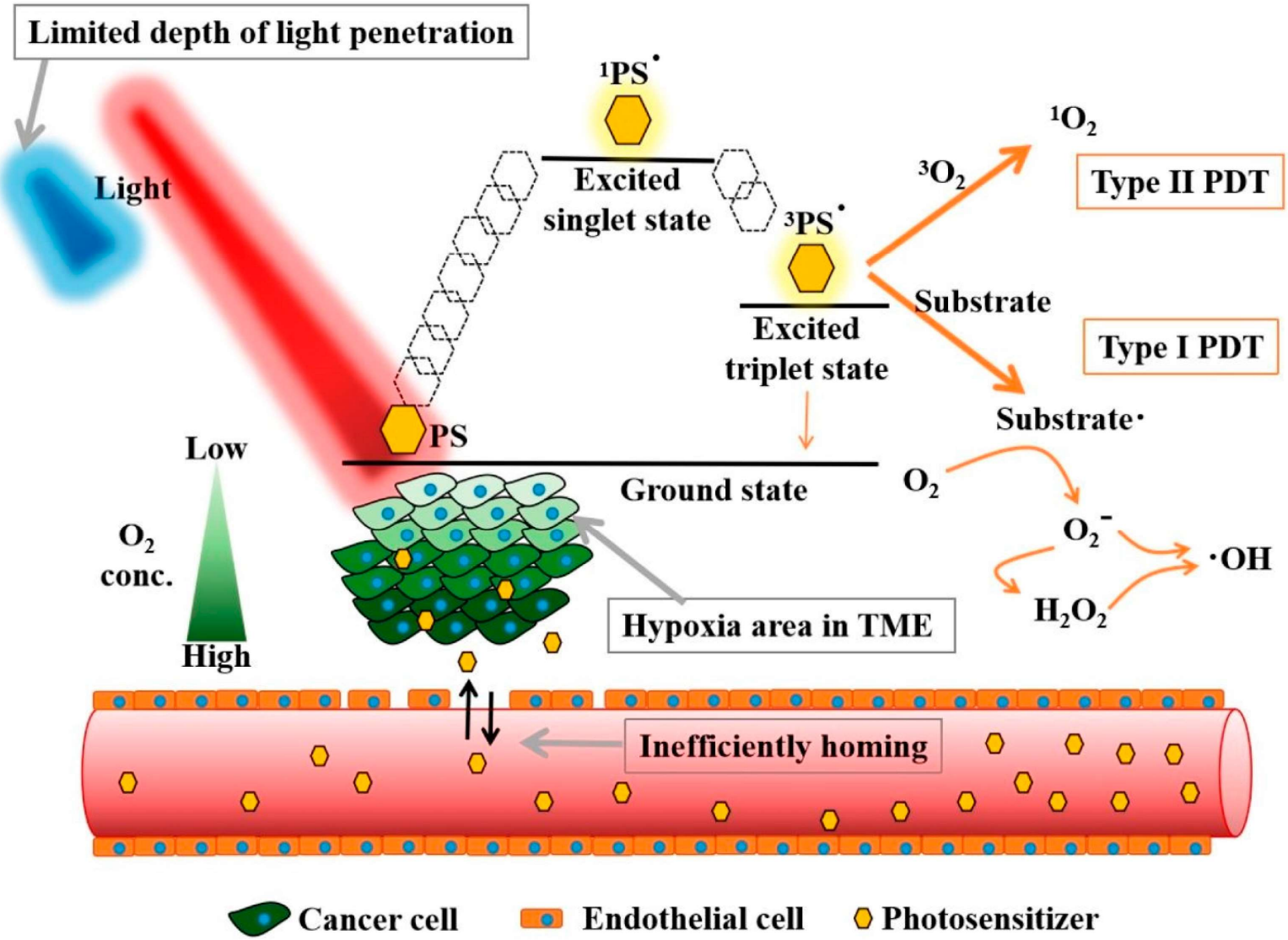
compound	Ab1	RSK1	Src	PKCa	ZAP70
staurosporine	2	<1	<1	<1	<1
7	25	30	>100	>100	>100
6	20	25	60	>100	50
1	10	8	30	>100	40
2	2	8	40	>100	30
3	5	8	30	50	40

POTENCY and SPECIFICITY



Zhang, L. Caroll, P. Meggers, E. *Org. Lett*. 2004, *6*, 521

What is PDT (Photodynamic Therapy)



TOOKAD: Padeliporfin