Transition Metal-Based Anti-cancer Agents: From Cytotoxic to Targeted Chemotherapy

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Michigan State University
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Outline

- Platinum-based Cytotoxic Chemotherapy
- Platinum-based Targeted Chemotherapy
- Ruthenium-based Targeted Chemotherapy
- The Challenges for Transition Metal-based Anti-cancer Drug Discovery

Chemotherapy: Cytotoxic vs Targeted

- Cytotoxic Therapy - “Cluster Bomb”
  - Targets general features of cells (DNA).
  - Associated with side effects.
- Targeted Therapy - “Smart Bomb”
  - Targets specific features of cancer cells.
  - Less side effects.

US National Cancer Institute: www.cancer.org

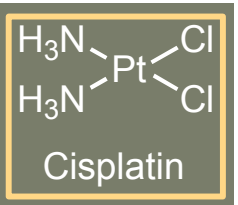
Outline

- Platinum-based Cytotoxic Chemotharepy
  - Drugs Approved by FDA
  - Drugs in Pending Approval / Clinical Trial
  - Drugs in Development
- Platinum-based Targeted Chemotharepy
- Ruthenium-based Targeted Chemotherapy
- The Challenges for Transition Metal-based Anti-cancer Drug Discovery

Outline

- Platinum-based Cytotoxic Chemotherapy
  - Drugs Approved by FDA
    - *Cisplatin*
    - *Carboplatin*
    - *Oxaliplatin*
  - Drugs in Pending Approval / Clinical Trial
  - Drugs in Development
- Platinum-based Targeted Chemotharepy
- Ruthenium-based Targeted Chemotherapy
- The Challenges for Transition Metal-based Anti-cancer Drug Discovery

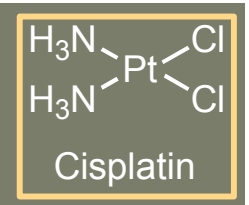
Cisplatin: A Chance Discovery to a Drug



- 1845 Peyrone's chloride
- 1893 Structure deduced by Werner
- 1968 Anti-cancer activity observed by Rosenberg in MSU
- 1971 The first patient treated
- 1978 Approved by FDA
- 2008 Still in use

Timeline for Cisplatin

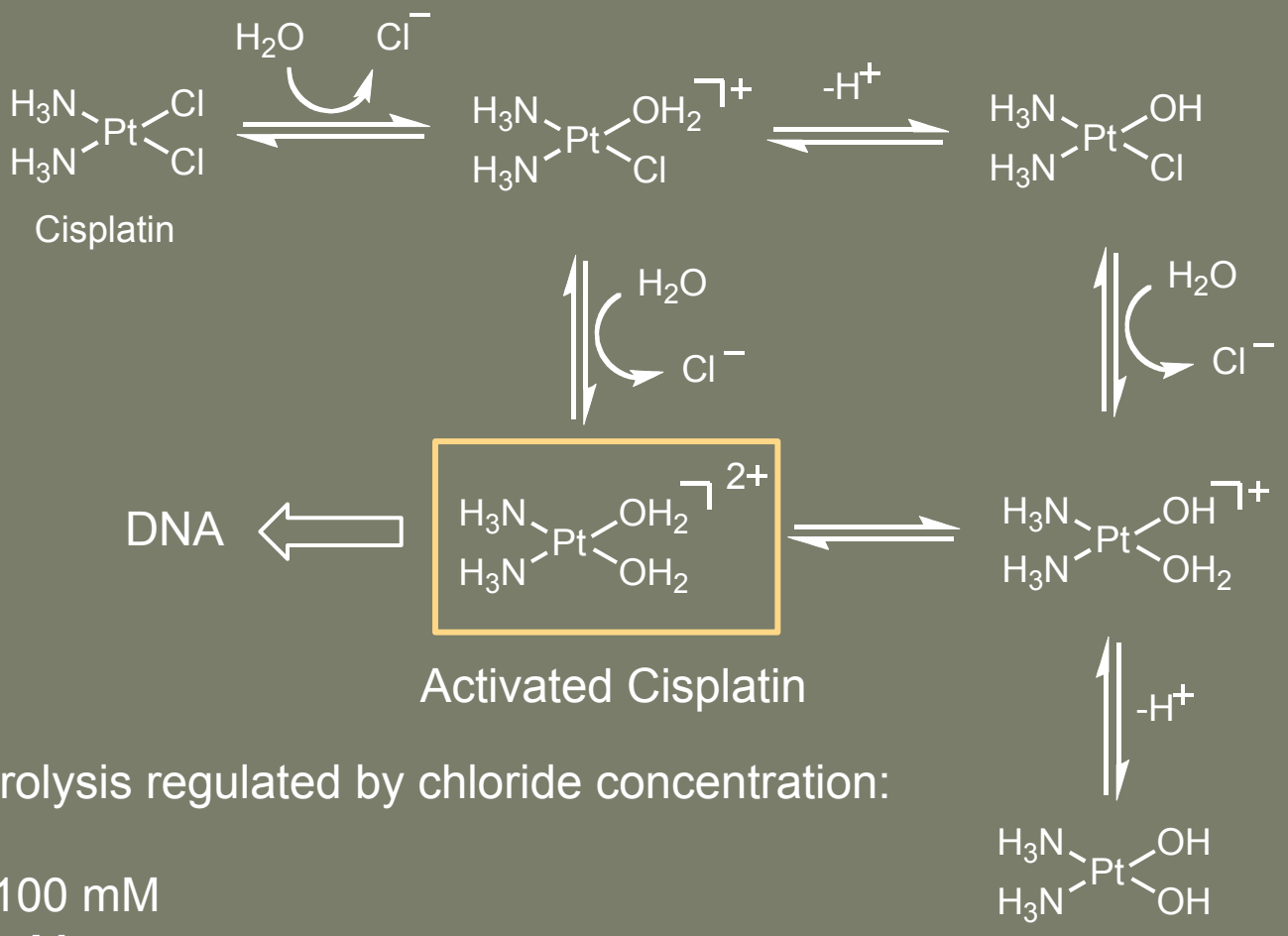
Cisplatin



- Brand Name: Platinol-AQ
- Each mL contains
  - Cisplatin 1 mg
  - Sodium Chloride 9 mg
  - Water for Injection
- Cisplatin could be used to treat:
  - Metastatic Testicular Tumors
  - Metastatic Ovarian Tumors
  - Advanced Bladder Cancer
- 50 mg/50 mL $18.50
- Marketed by Bristol-Myers Squibb

www.bms.com/products/data/index.html
www.bedfordlabs.com/products/ViewProductDetails?productID=47&item=3
US National Cancer Institute: www.cancer.org

Mechanism of Action of Cisplatin

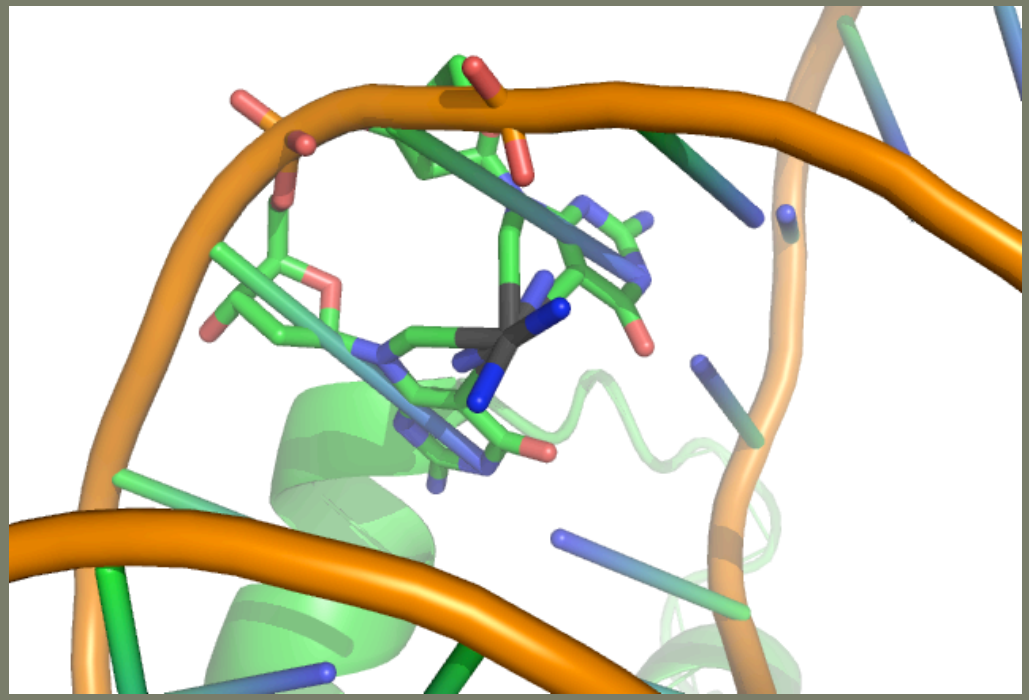


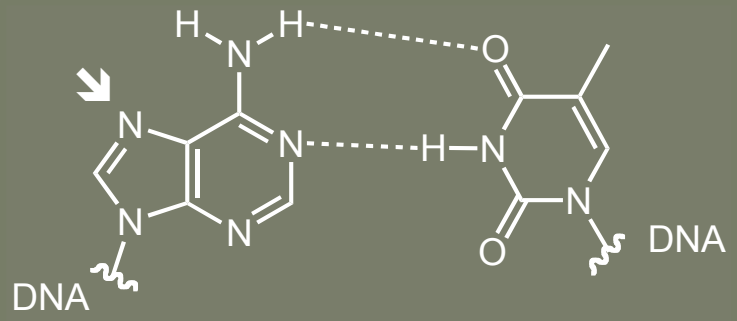
Cisplatin hydrolysis regulated by chloride concentration:

[Cl-Blood] = 100 mM
[Cl-Cell] = 3 mM

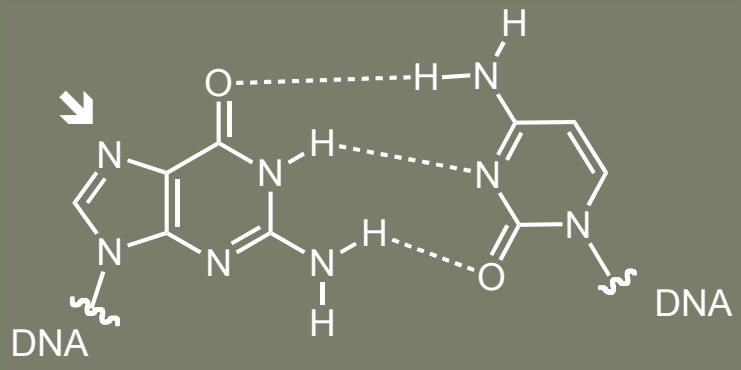
Hartinger, C. G.; Zorbas-Seifried, S.; Keppler, B. K. *J. Inorg. Biochem*. **2006**, *100*, 891.

Crystal Structure of Cisplatin & DNA Intrastrand Adduct





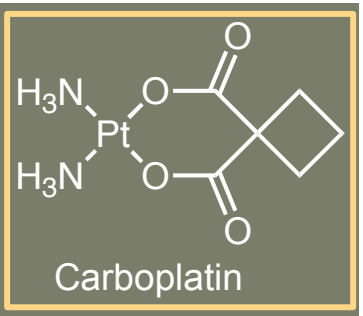
Adenine Thymine



Guanine Cytosine

Lippard, S. J. et al. *Nature*, **1999**, *399,* 708 -712.

Carboplatin: Overcome Toxicity

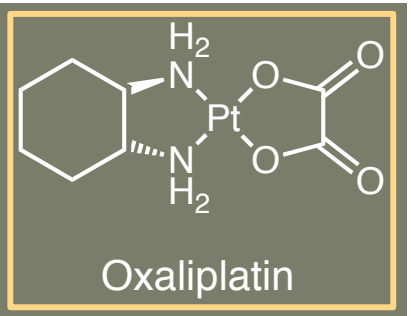


Carboplatin

- Approved by FDA in 2004
- Brand Name: Paraplatin
- Each mL Contains
  - Carboplatin 10 mg
  - Water for Injection.
- Carboplatin could be used to treat:
  - Ovarian cancer that recurred after earlier chemotherapy
- 450 mg/45 mL $90.00
- Marketed by Bristol-Myers Squibb

www.bms.com/products/data/index.html
www.bedfordlabs.com/products/ViewProductDetails?productID=47&item=3
US National Cancer Institute: www.cancer.org

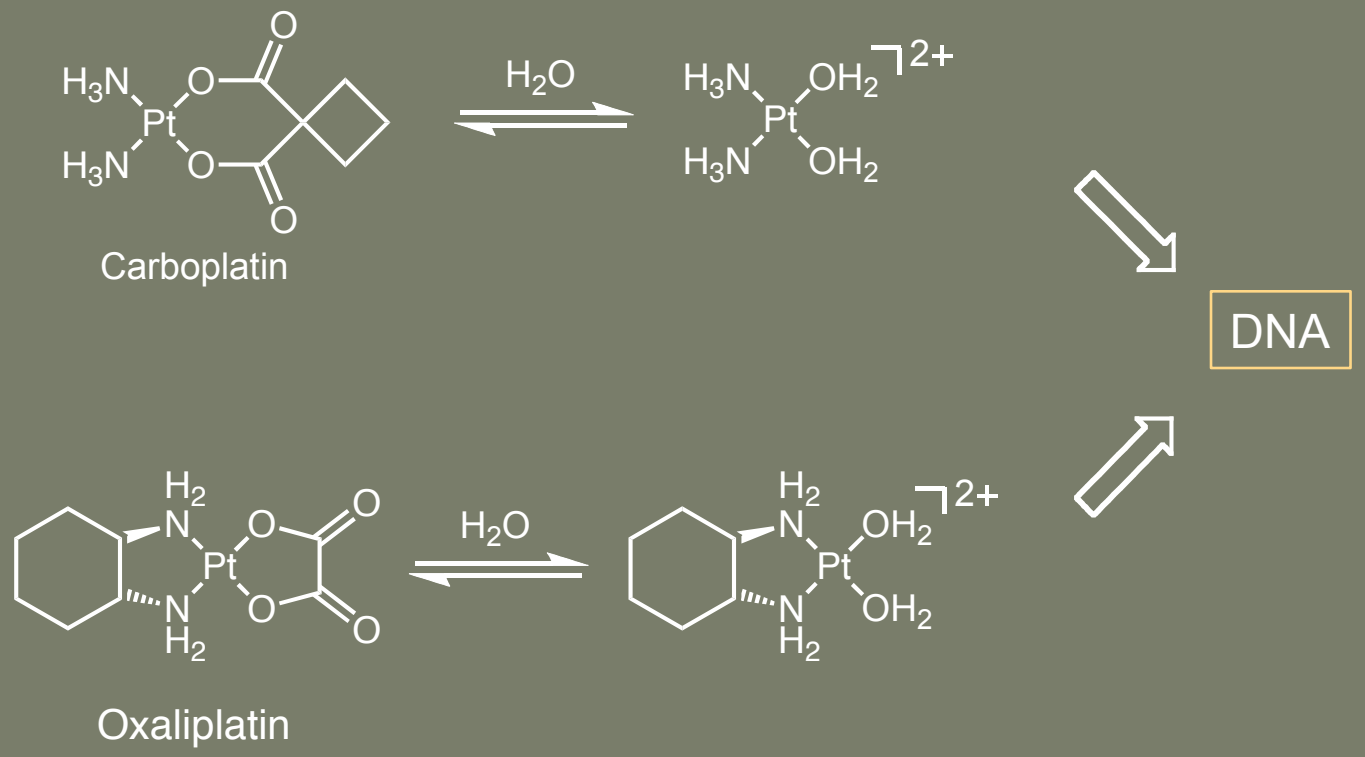
Oxaliplatin



Oxaliplatin

- Approved by FDA in 2004
- Brand Name: Eloxatin
- Each mL Contains
  - Oxaliplatin 5 mg
  - Water for Injection.
- Eloxatin could be used for:
  - Initial therapy of advanced colorectal cancer
  - Adjuvant therapy for stage III colorectal cancer
- 50 mg/10 mL $510
- Marketed by Sanofi-Aventis

Mechanism of Action of Carboplatin and Oxaliplatin



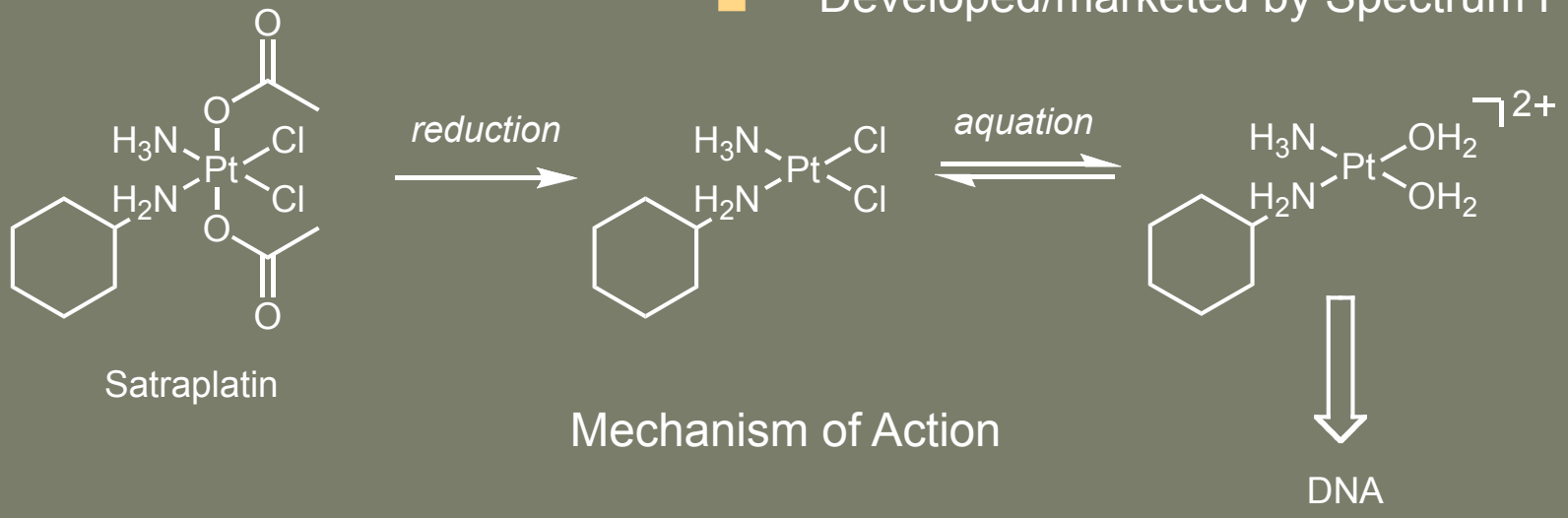
Hartinger, C. G.; Zorbas-Seifried, S.; Keppler, B. K. *J. Inorg. Biochem*. **2006**, *100*, 891.

Outline

- Platinum-based Cytotoxic Chemotharepy
  - Drugs Approved by FDA
  - Drugs in Pending Approval / Clinical Trial
    - *Satraplatin*
    - *Picoplatin*
  - Drugs in Development
- Platinum-based Targeted Chemotharepy
- Ruthenium-based Targeted Chemotherapy
- The Challenges for Transition Metal-based Anti-cancer Drug Discovery

Satraplatin: The First Oral Platinum Drug

- Under consideration for approval by FDA
- Brand Name: Orplatna
- Satraplatin could be used for:
  - Non-small cell lung cancer
  - Hormone refractory prostate cancer
- Developed/marketed by Spectrum Pharm.

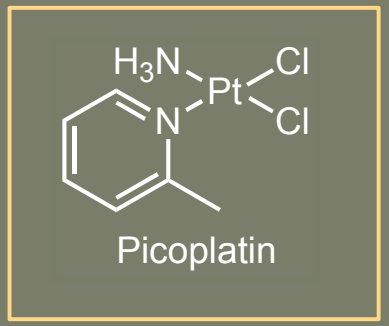


Satraplatin

Mechanism of Action

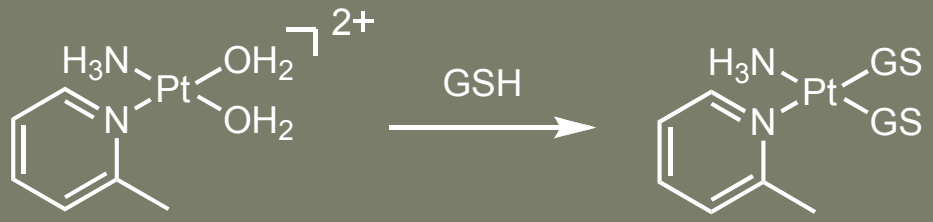
www.spectrumpharm.com/satraplatin.html

Picoplatin: Overcoming Drug Resistance



- Phase III trial about to begin
- Picoplatin could be used to treat:
  - Small-cell lung cancer
- Developed/marketed by PONIARD

Cisplatin: Associative Mechanism ⟹ Fast ⟹ Drug Resistance



Picoplatin: Dissociative Mechanism ⟹ Slow ⟹ Less Drug Resistance

Raynaud, F. I.; Kelland, L. R. *Clinical Cancer Research* **1997**, *3*, 2063-2074.

Outline

- Platinum-based Cytotoxic Chemotharepy
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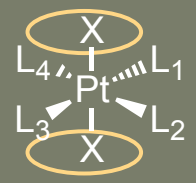
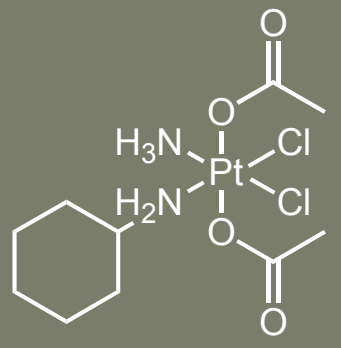
  - Drugs in Pending Approval / Clinical Trial
  - Drugs in Development
    - *Rational Design of Ethacraplatin*
- Platinum-based Targeted Chemotharepy
- Ruthenium-based Targeted Chemotherapy
- The Challenges for Transition Metal-based Anti-cancer Drug Discovery

Design of Pt(IV) Active Complex



Pt (IV)

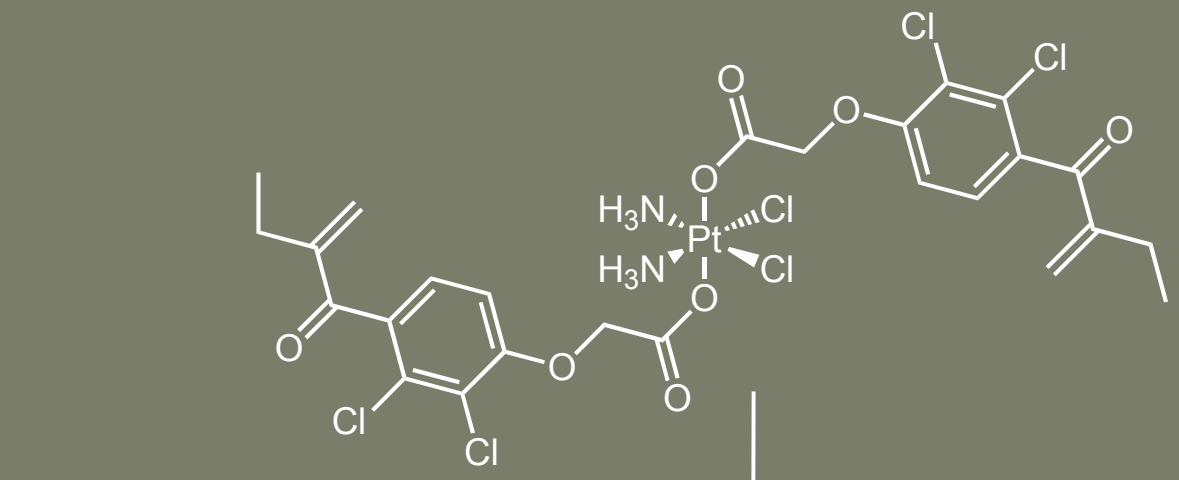
- Modifying the Axial Ligand
  - Tuning the activity of Pt (IV) Complexes
  - Molecular targeting
- Kinetically Inert
  - Reducing side reactions

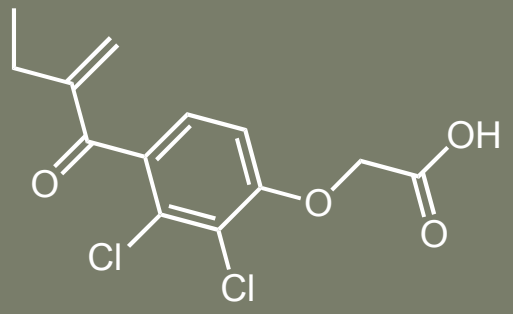


Satraplatin

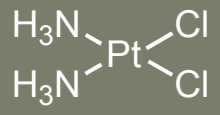
Ang, W. H.; Khalaila, I.; Allardyce, C. S.; Juillerat, L; Dyson, P. *J. Am. Chem. Soc*. **2005**, *127*, 1382-1383.

Ethacraplatin: Two Birds with One Stone





Ethacrynic Acid



Cisplatin

GST

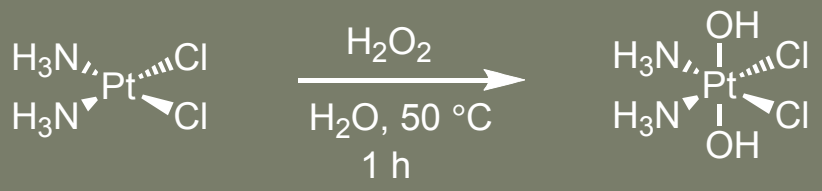
DNA

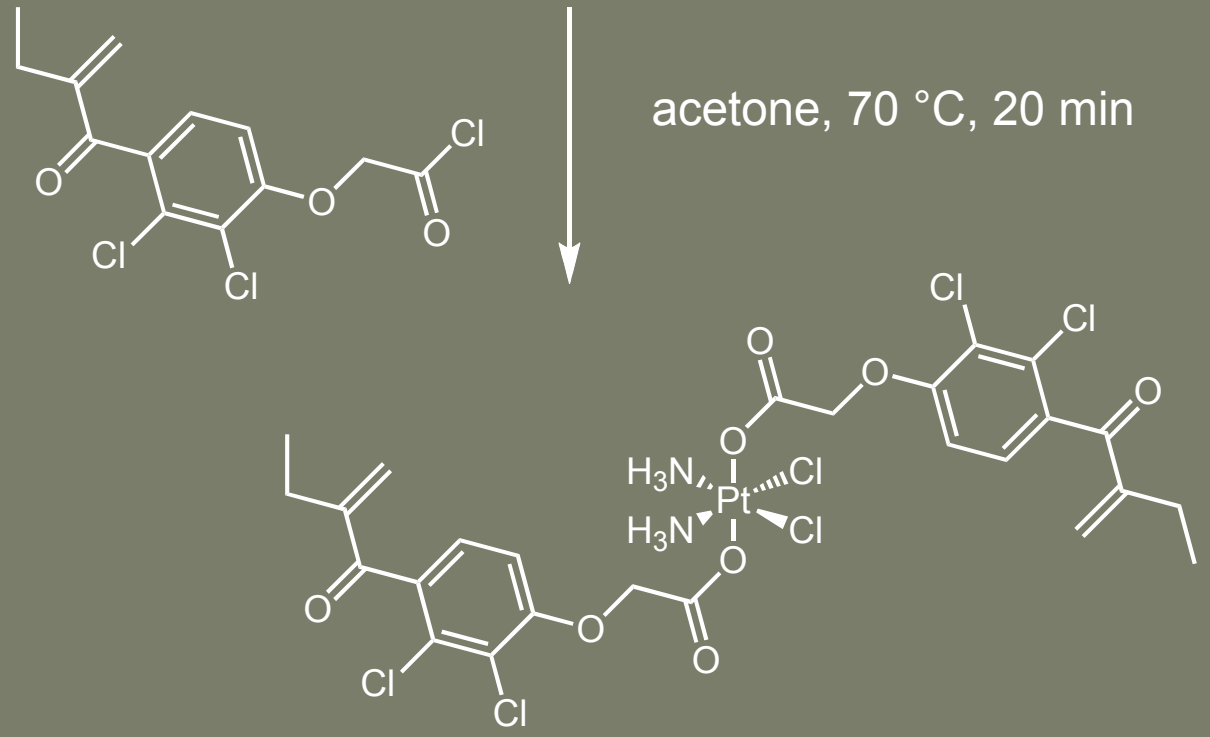
Overcome drug resistance

Apoptosis of Cancer cell

Ang, W. H.; Khalaila, I.; Allardyce, C. S.; Juillerat, L; Dyson, P. *J. Am. Chem. Soc*. **2005**, *127*, 1382-1383.

Preparation of Ethacraplatin





Ang, W. H.; Khalaila, I.; Allardyce, C. S.; Juillerat, L; Dyson, P. *J. Am. Chem. Soc*. **2005**, *127*, 1382-1383.

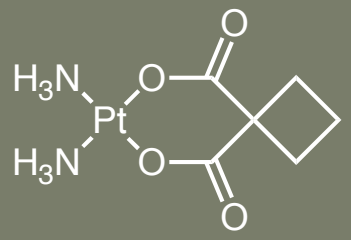
Cisplatin vs Ethacraplatin

	IC_{50} (μM)			
	MCF7	T47D	HT29	A549
	24 h	24 h	24 h	24 h
Cisplatin	>80	>80	>80	>80
Ethacraplatin	31.85	31.56	32.63	78.59

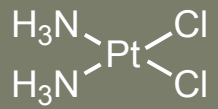
MCF7: Breast tumor cell line
T47D: Breast tumor cell line
HT29: Colon cancer cell line
A549: Lung adenocarcinoma epithelial cell line

Ang, W. H.; Khalaila, I.; Allardyce, C. S.; Juillerat, L; Dyson, P. *J. Am. Chem. Soc*. **2005**, *127*, 1382-1383.

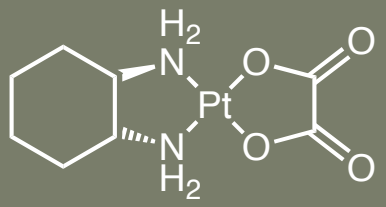
Family of Cytotoxic Platinum Drugs



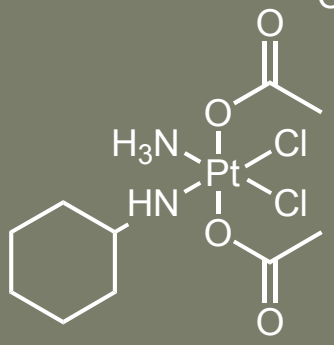
Carboplatin



Cisplatin

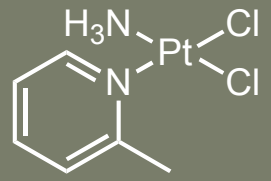


Oxaliplatin

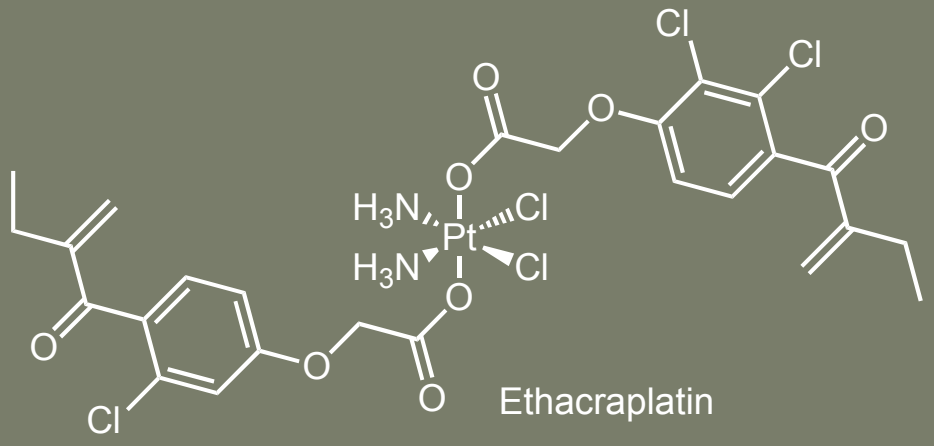


Satraplatin

DNA

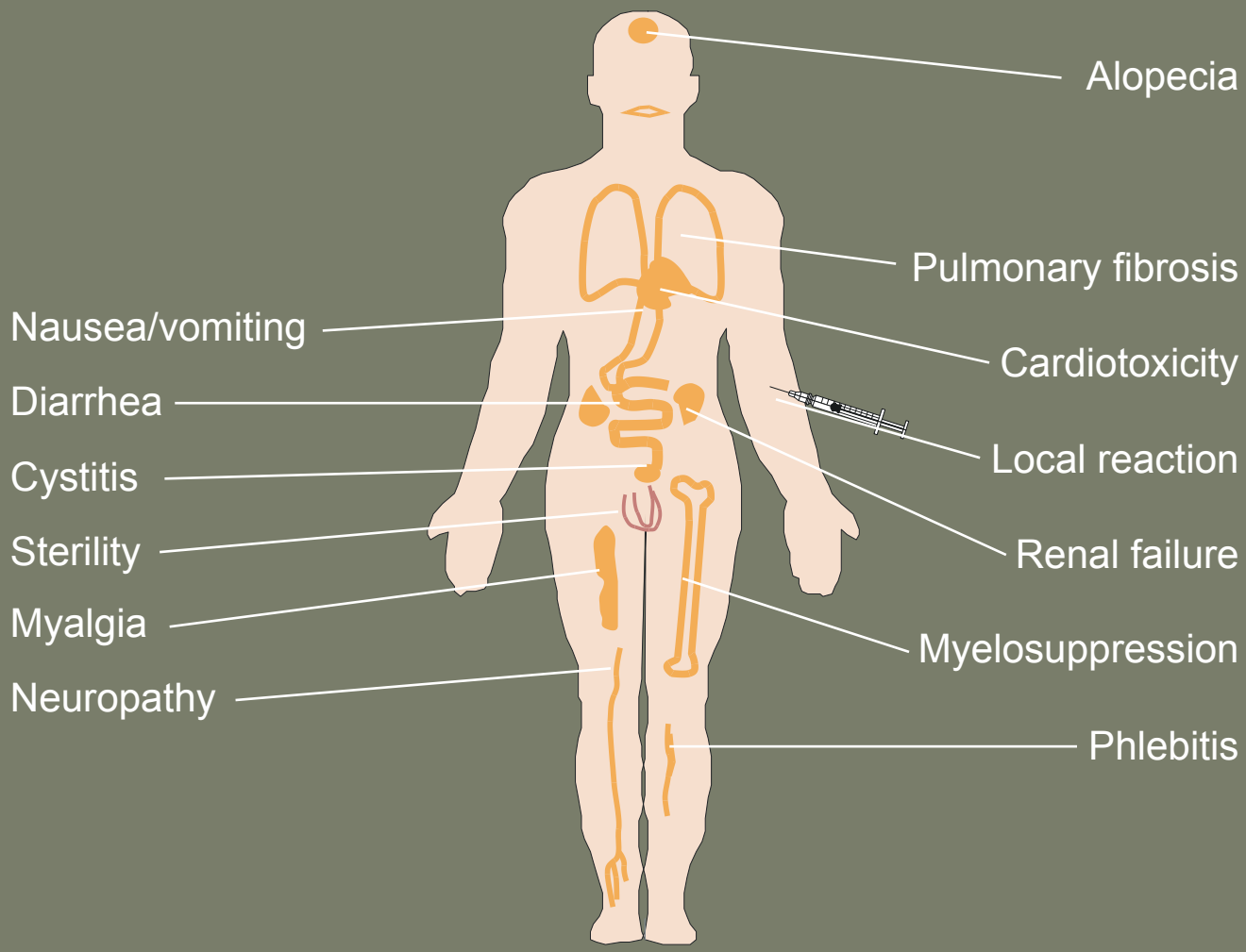


Picoplatin



Ethacraplatin

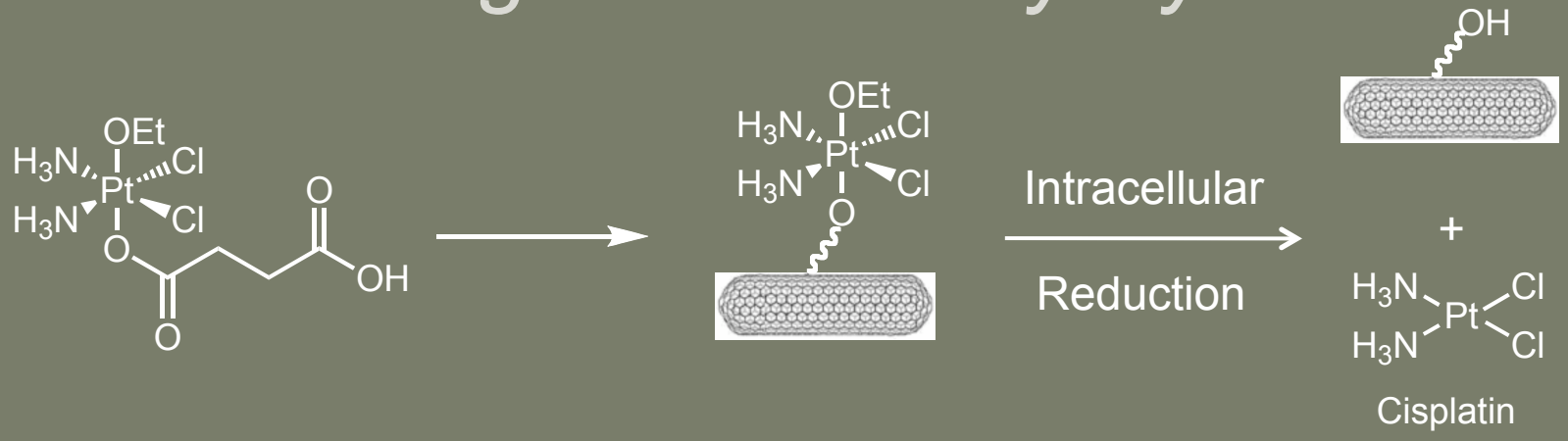
Side Effects of Cytotoxic Platinum Drugs

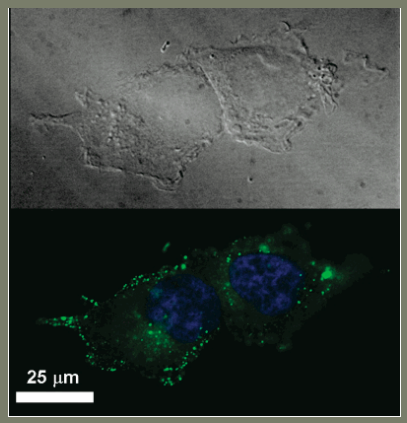


Outline

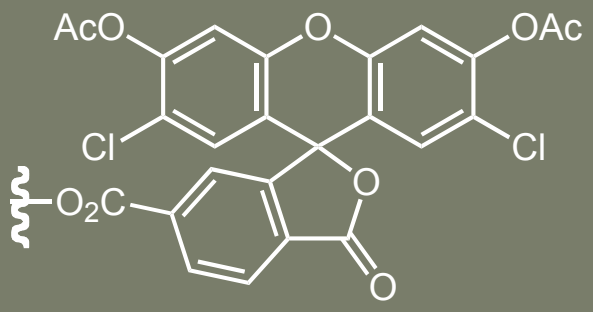
- Platinum-based Cytotoxic Chemotharepy
- Platinum-based Targeted Chemotharepy
  - *Soluble Single-Walled Carbon Nanotubes as Delivery Systems*
- Ruthenium-based Targeted Chemotherapy
- The Challenges for Transition Metal-based Anti-cancer Drug Discovery

Soluble Single-Walled Nanotubes (SWNT) as Longboat Delivery Systems



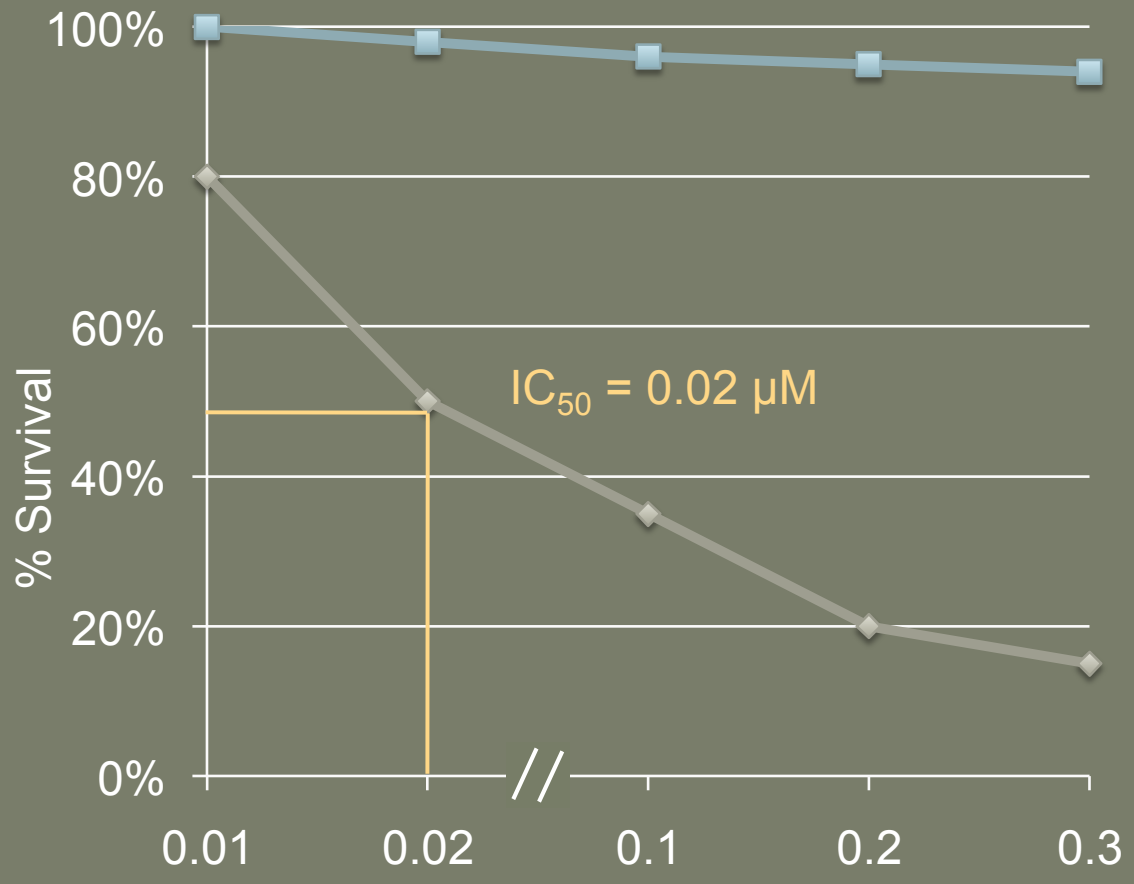


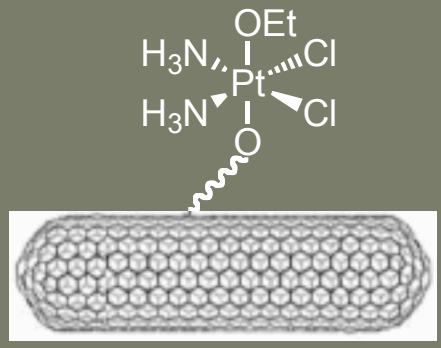
Tethered with Fluorescence



Feazell, R. P.; Ratchford, N.; Dai, H.; Lippard, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 8438.

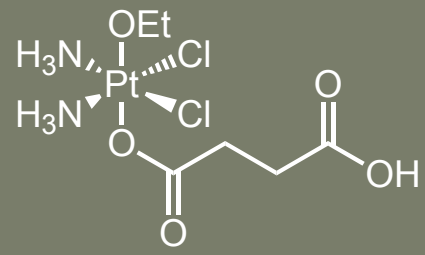
SWNT-Pt (IV) vs Parent Pt (IV)





SWNT-Pt (IV)

Pt (IV)



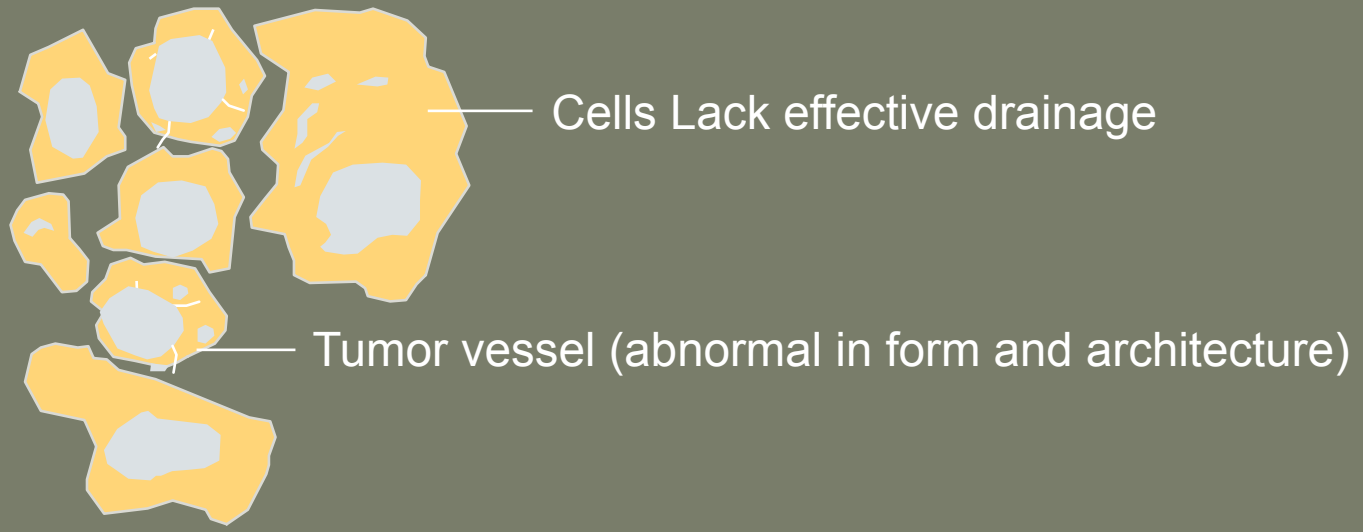
(Cisplatin: IC_{50} = 0.05 μM)

Feazell, R. P.; Ratchford, N.; Dai, H.; Lippard, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 8438.

Mechanism of Action of SWNT-Pt (IV)

- SWNT-Pt (IV) has EPR effect.

- *Enhanced Permeability and Retention (EPR) effect*:
  Macromolecular drugs accumulate in tumor tissues much more than they do in normal tissues.

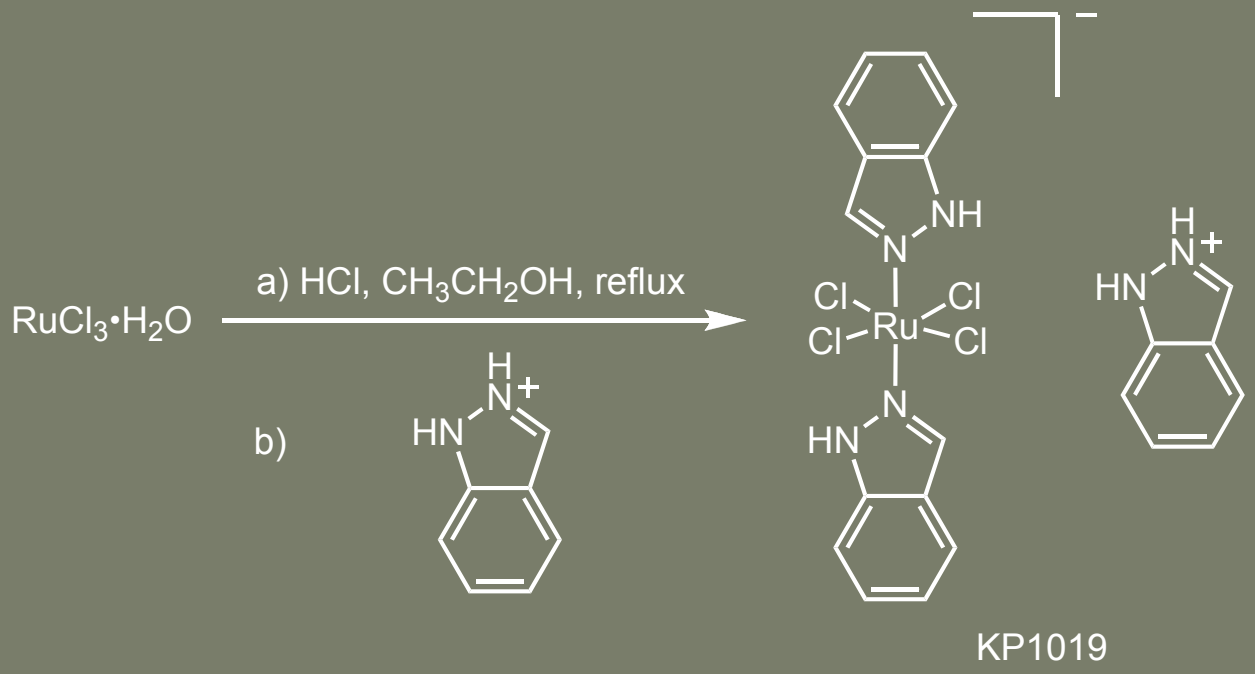


Feazell, R. P.; Ratchford, N.; Dai, H.; Lippard, S. J. *J. Am. Chem. Soc*. **2007**, *129*, 8438.
Iyer, A. K.; Khaled, G.; Fang, J.; Maeda, H. *Drug Discov. Today* **2006**, *11*, 812-818.

Outline

- Platinum-based Cytotoxic Chemotherapy
- Platinum-based Targeted Chemotharepy
- Ruthenium-based Targeted Chemotherapy
  - Ruthenium Drugs in Clinical Trial
    - *KP1019*
  - Ruthenium Drugs in Development
- The Challenges for Transition Metal-based Anti-cancer Drug Discovery

KP1019



KP1019

- Phase II clinical trial about to begin.
- KP1019 could be used to treat autochthonous colorectal tumors.

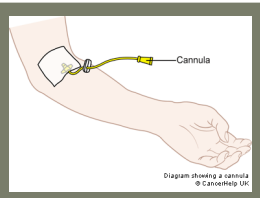
Hartinger, C. G. *J. Chem. Biol*. **2006**, *100*, 891-904.
Lipponer, K. G.; Vogel, E.; Keppler, B. K. *Metal-Based Drugs* **1996**, *3*, 243–260.

Mechanism of Action of KP1019

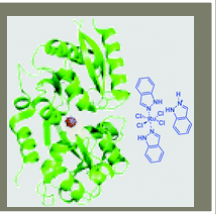
Infusion

KP1019

Blood

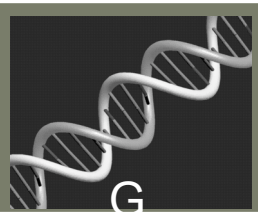


Ru III – Transferrin Adducts



Tumor

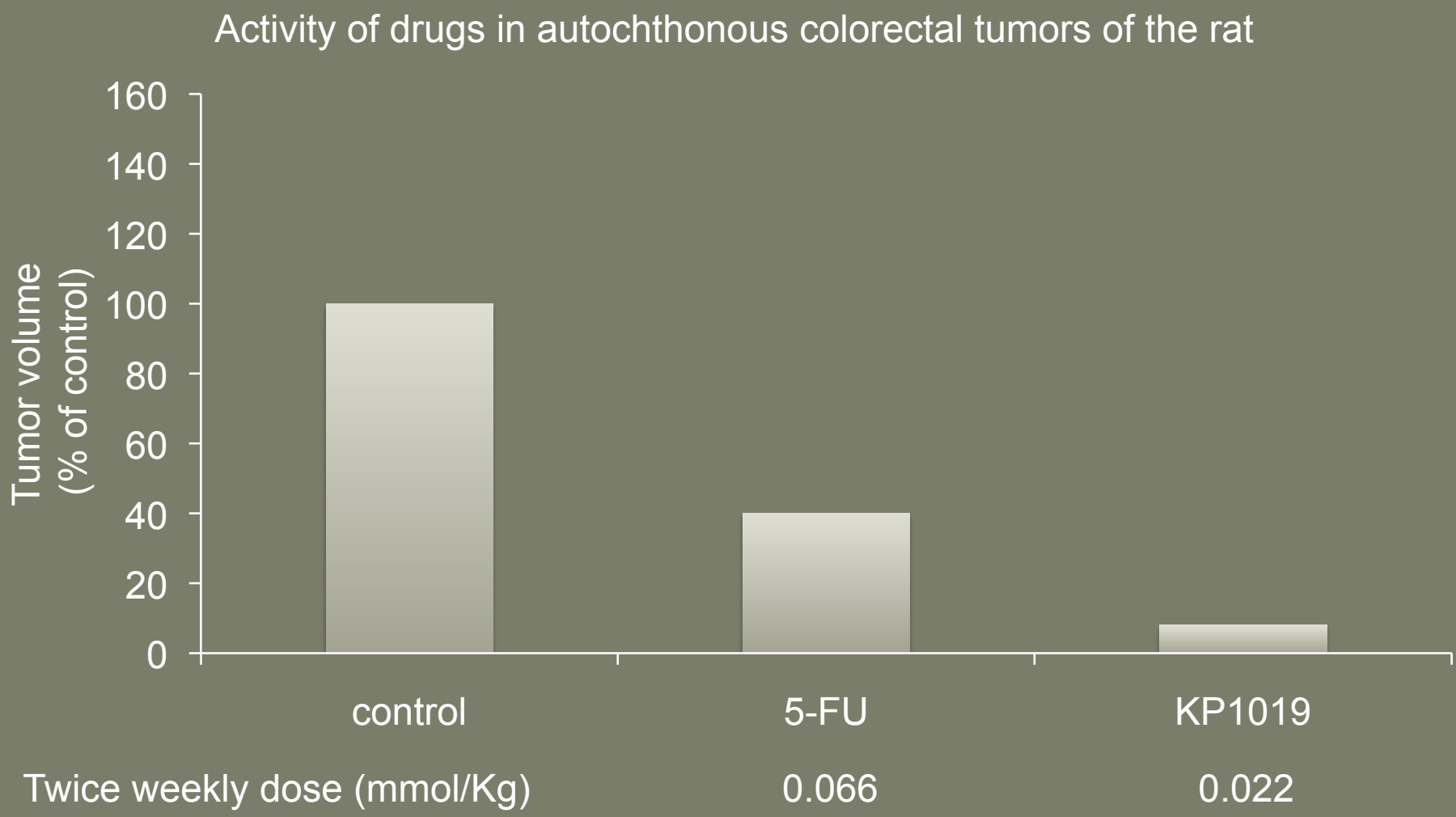
- Release of Ru III
- Reduction to Ru II
- Adducts with DNA



KP1019

Hartinger, C. G. *J. Chem. Biol*. **2006**, *100*, 891-904.

Activity of KP1019 in vivo



Hartinger, C. G. et al. *J. Chem. Biol.* **2006**, *100*, 891-904.

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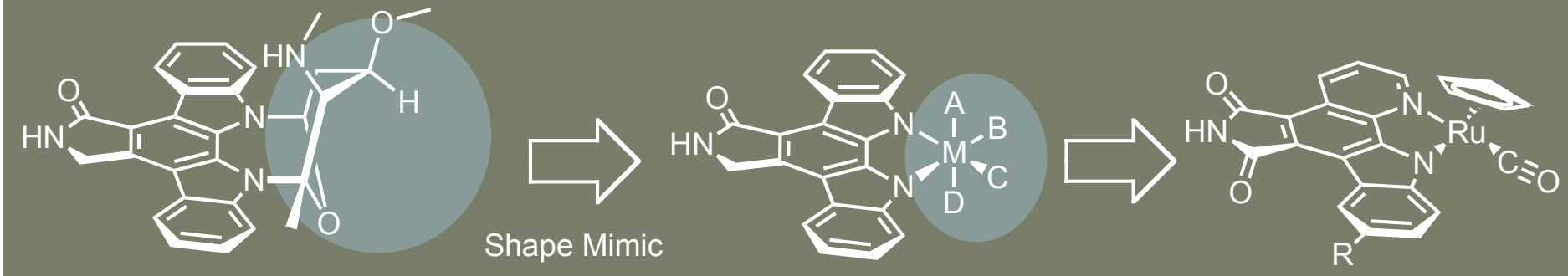
- Platinum-based Cytotoxic Chemotherapy
- Platinum-based Targeted Chemotharepy
- Ruthenium-based Targeted Chemotherapy
  - Ruthenium Drugs in Clinical Trial
  - Ruthenium Drugs in Development
    - *Design of Organo-Ruthenium Protein Kinase Inhibitor*
    - *Development of a Trojan Horse for Cancer Cells*
- The Challenges for Transition Metal-based Anti-cancer Drug Discovery

Design of Organo-Ruthenium Protein Kinase Inhibitor (Pim-1)



Staurosporine

Metal Complexes

R = H, OH

Pim-1 Kinase Inhibitor:

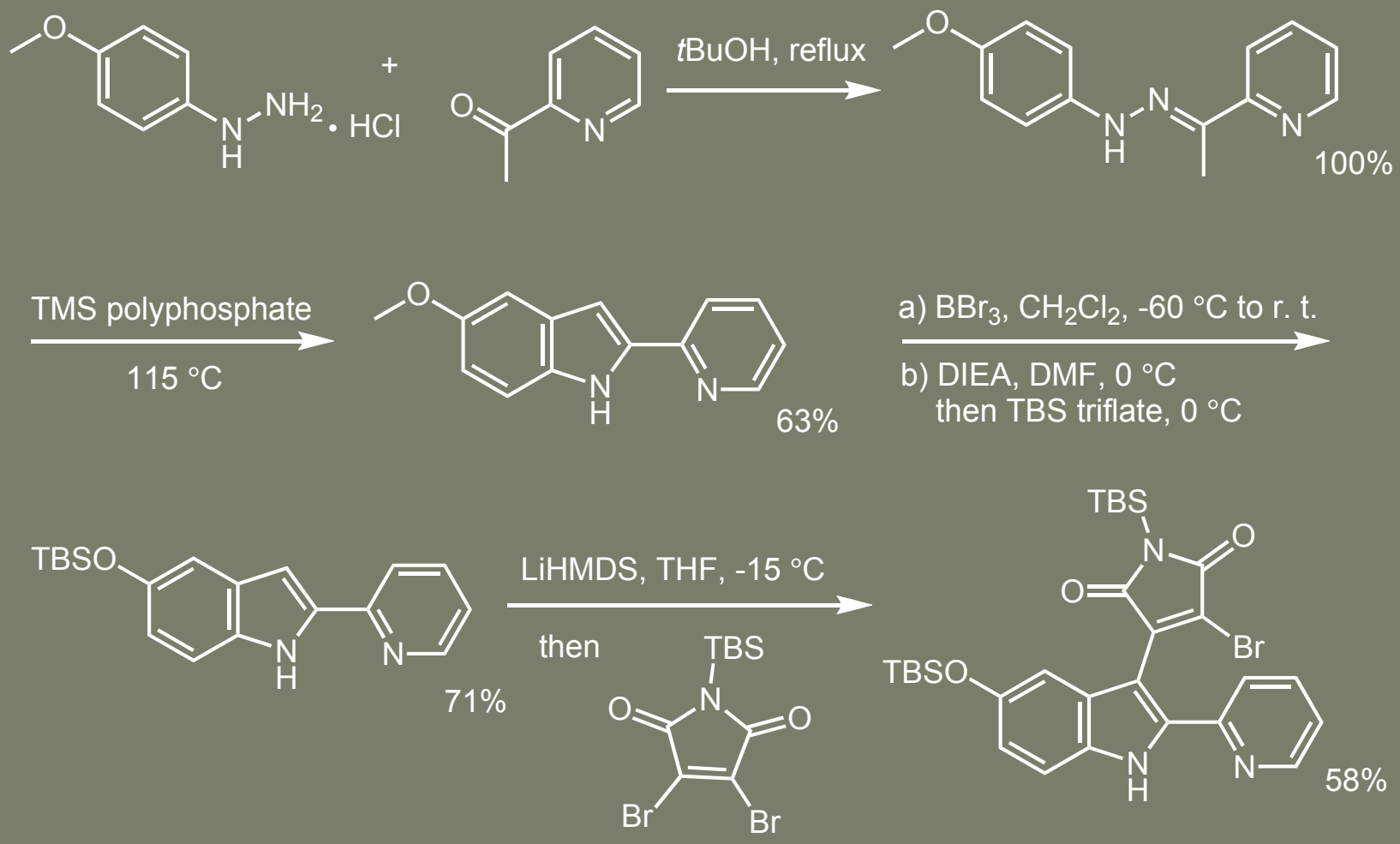
- Globular shape
- Lactam moiety

- Maintain the active moiety and globular shape
- Reduce the synthetic effort
- Stable metal complex

Debreczeni, J.; Bullock, A. N.; Atilla, G. E.; Williams, D. S.; Bregman, H.; Knapp, S.; Meggers, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 1580-1585.

Synthesis of Ruthenium Complex

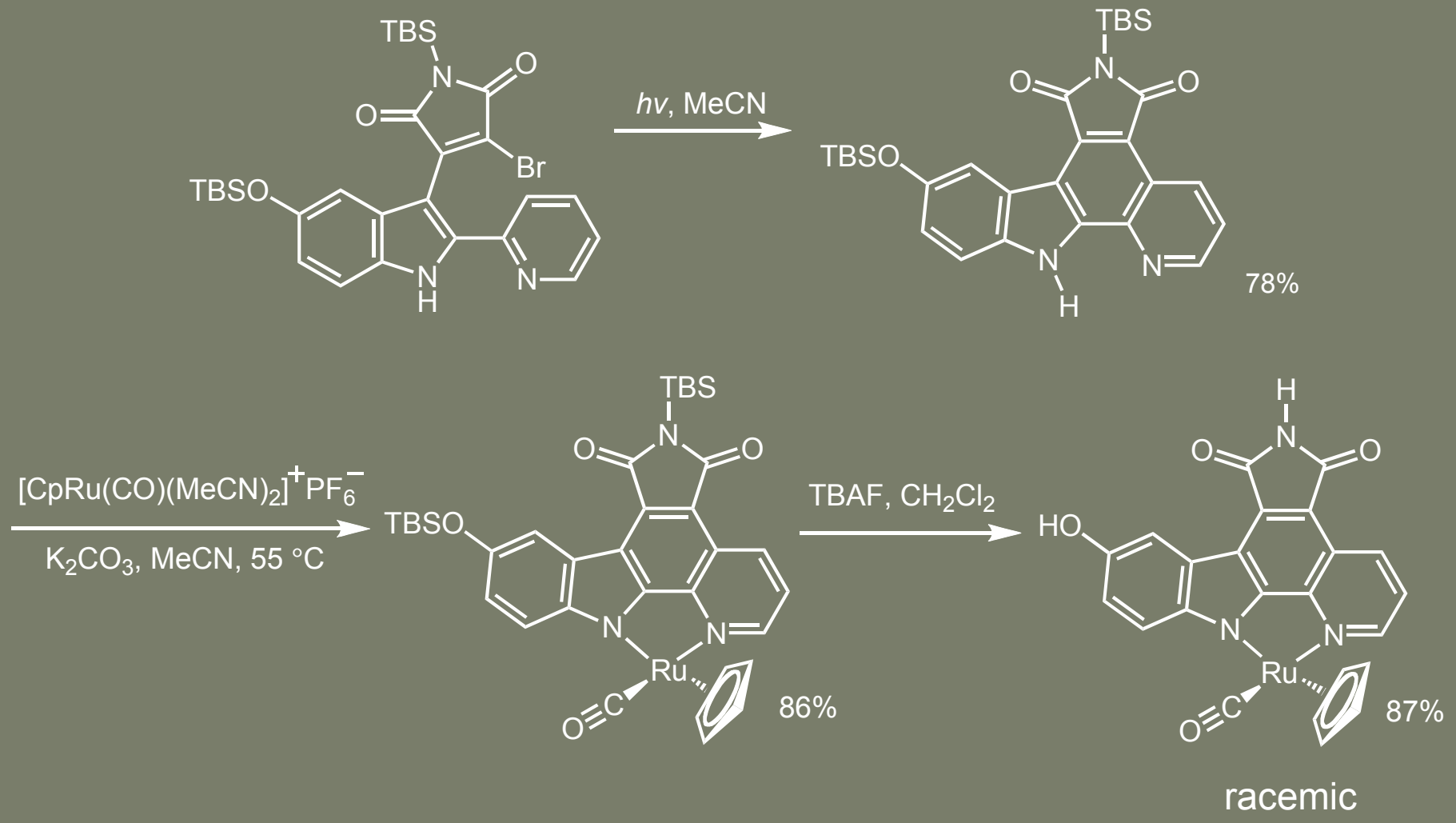
R = OH



Meggers, E. et al. *Angew. Chem. Int. Ed.* **2005**, *44*, 1984-1987.

Synthesis of Ruthenium Complex

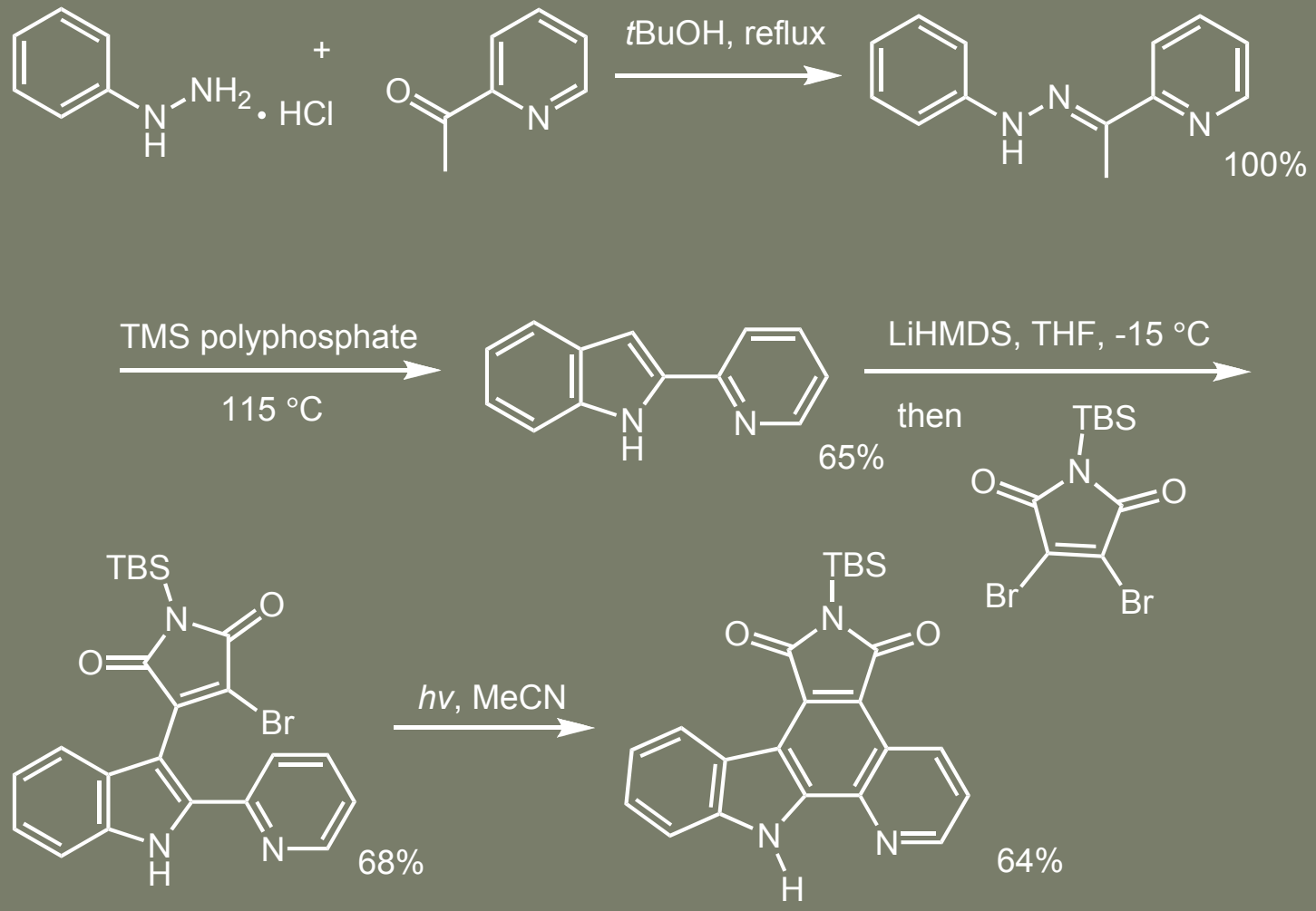
R = OH



Debreczeni, J.; Bullock, A. N.; Atilla, G. E.; Williams, D. S.; Bregman, H.; Knapp, S.; Meggers, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 1580-1585.

Synthesis of Ruthenium Complex

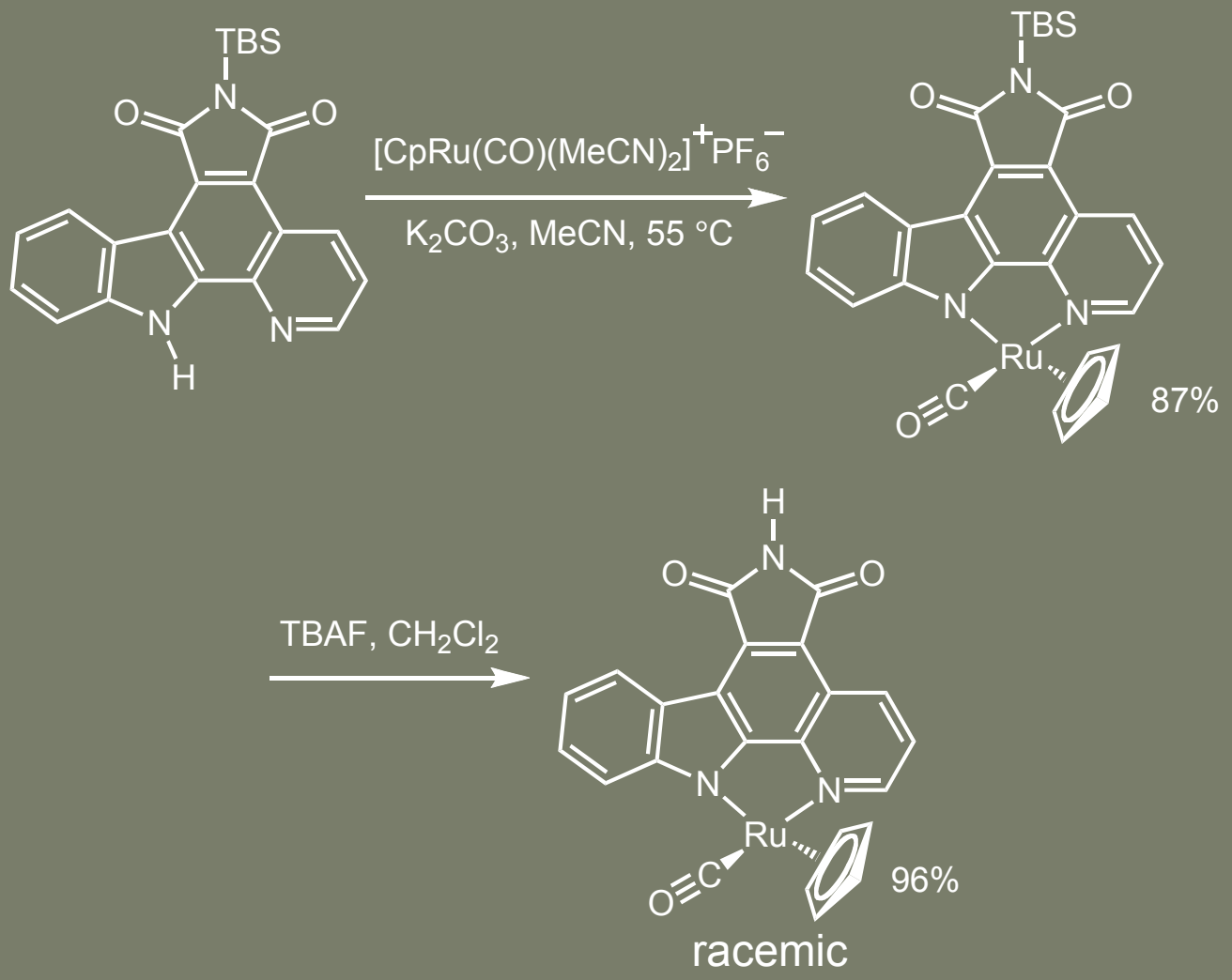
R = H



Bregman, H.; Williams, D. S.; Meggers, E. *Synthesis* **2005**, *9*, 1521-1527.

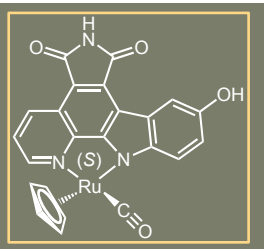
Synthesis of Ruthenium Complex

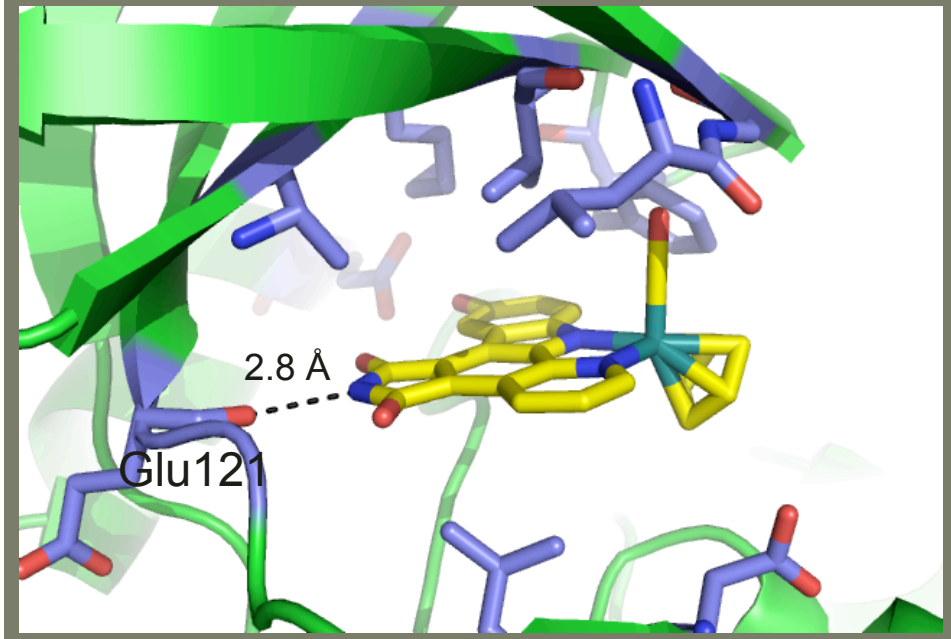
R = H

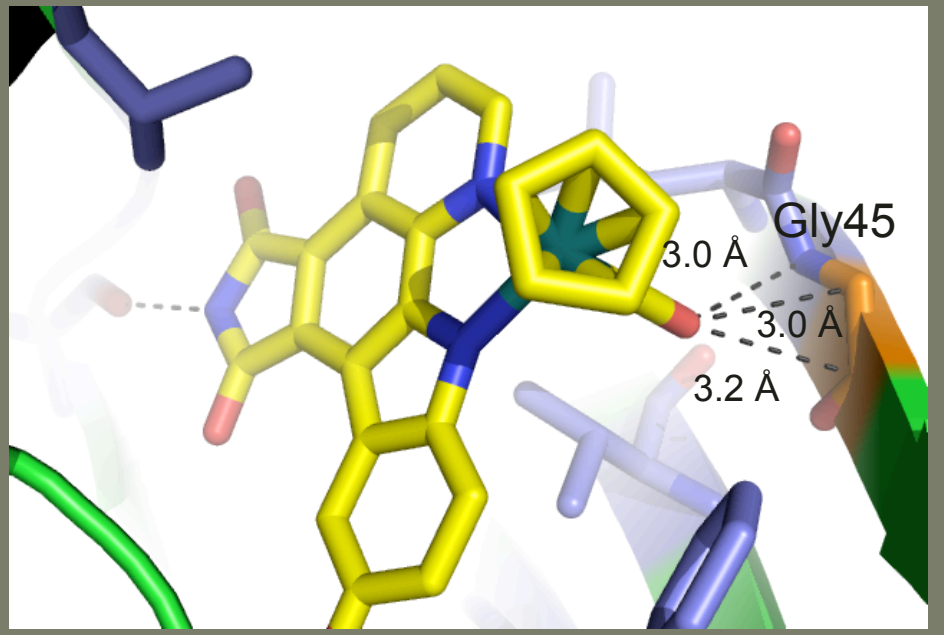


Bregman, H.; Williams, D. S.; Meggers, E. *Synthesis* **2005**, *9*, 1521-1527.

Crystal Structure of Pim-1 with (S)-Ruthenium Complex

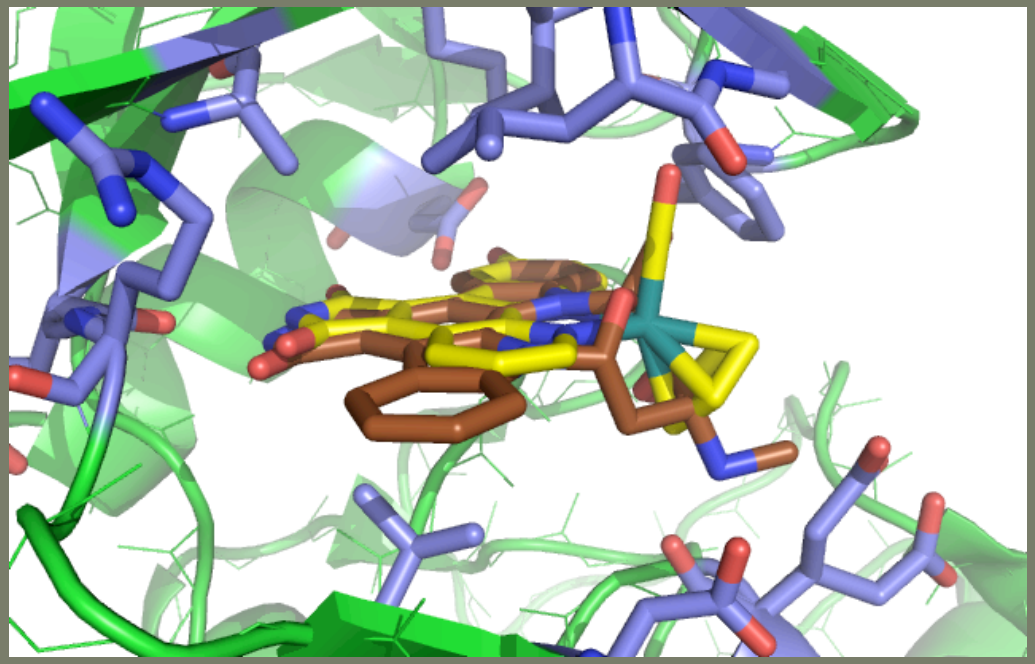


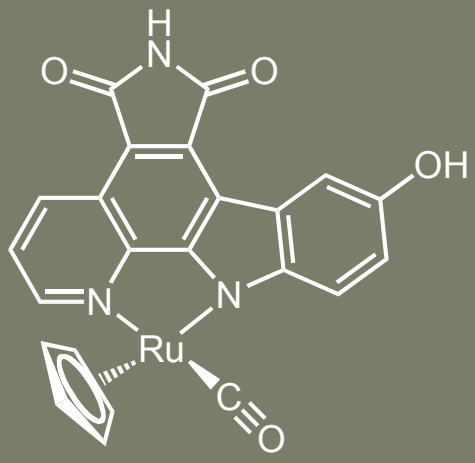




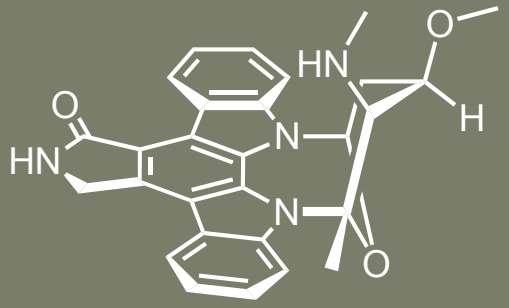
Debreczeni, J.; Bullock, A. N.; Atilla, G. E.; Williams, D. S.; Bregman, H.; Knapp, S.; Meggers, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 1580-1585.

Ruthenium Complex vs Staurosporine

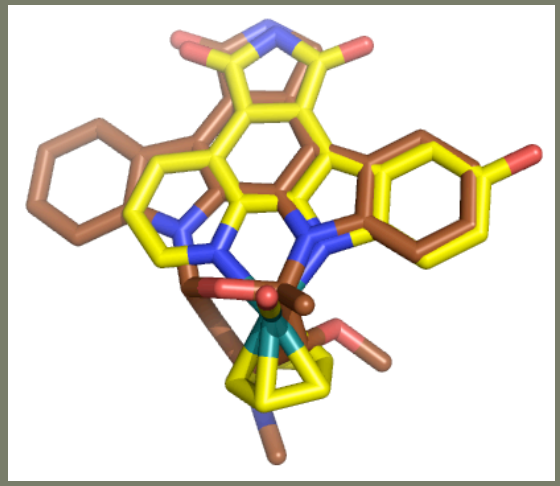




(*S*)-Isomer



Staurosporine



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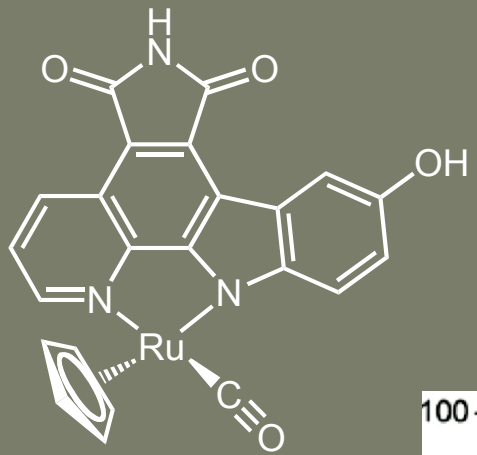
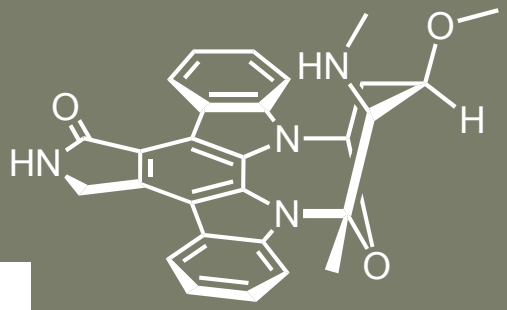
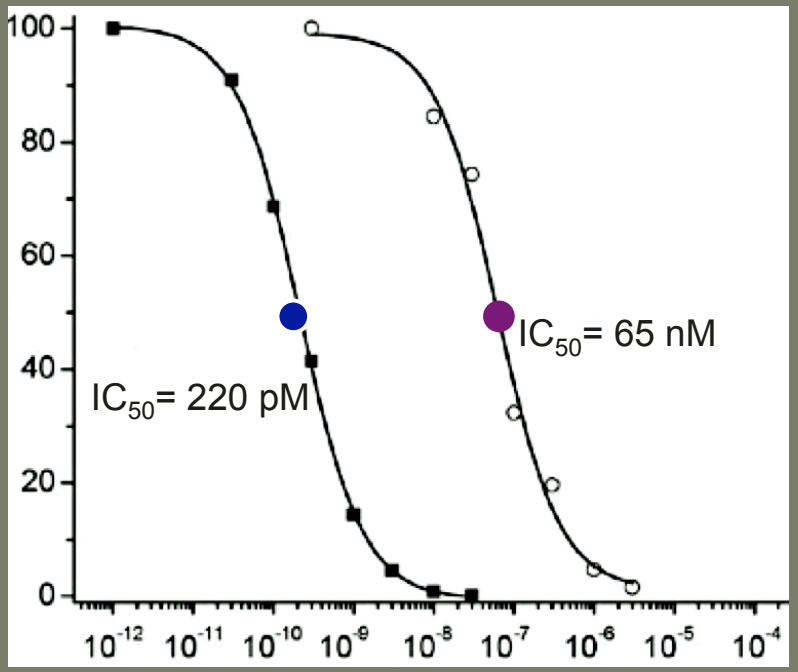
Ruthenium Complex vs Staurosporine



(*S*)-Isomer



Staurosporine



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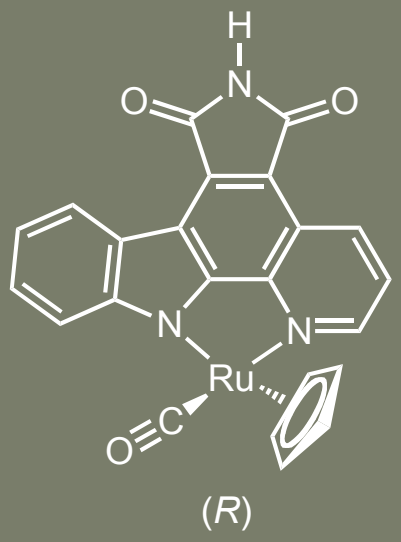
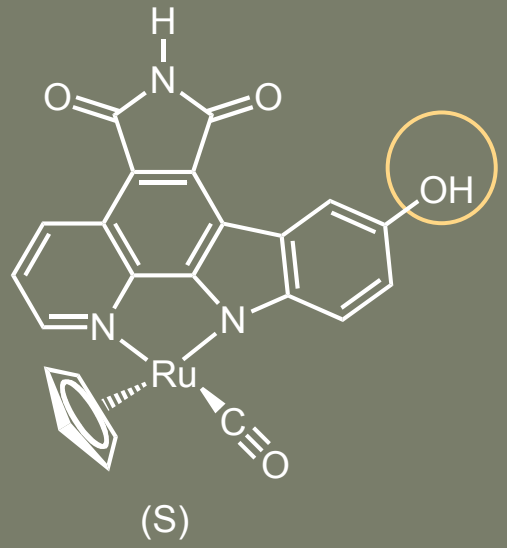
Differences Between Two "Isomers"



(*R*)

IC_{50} = 25 nM

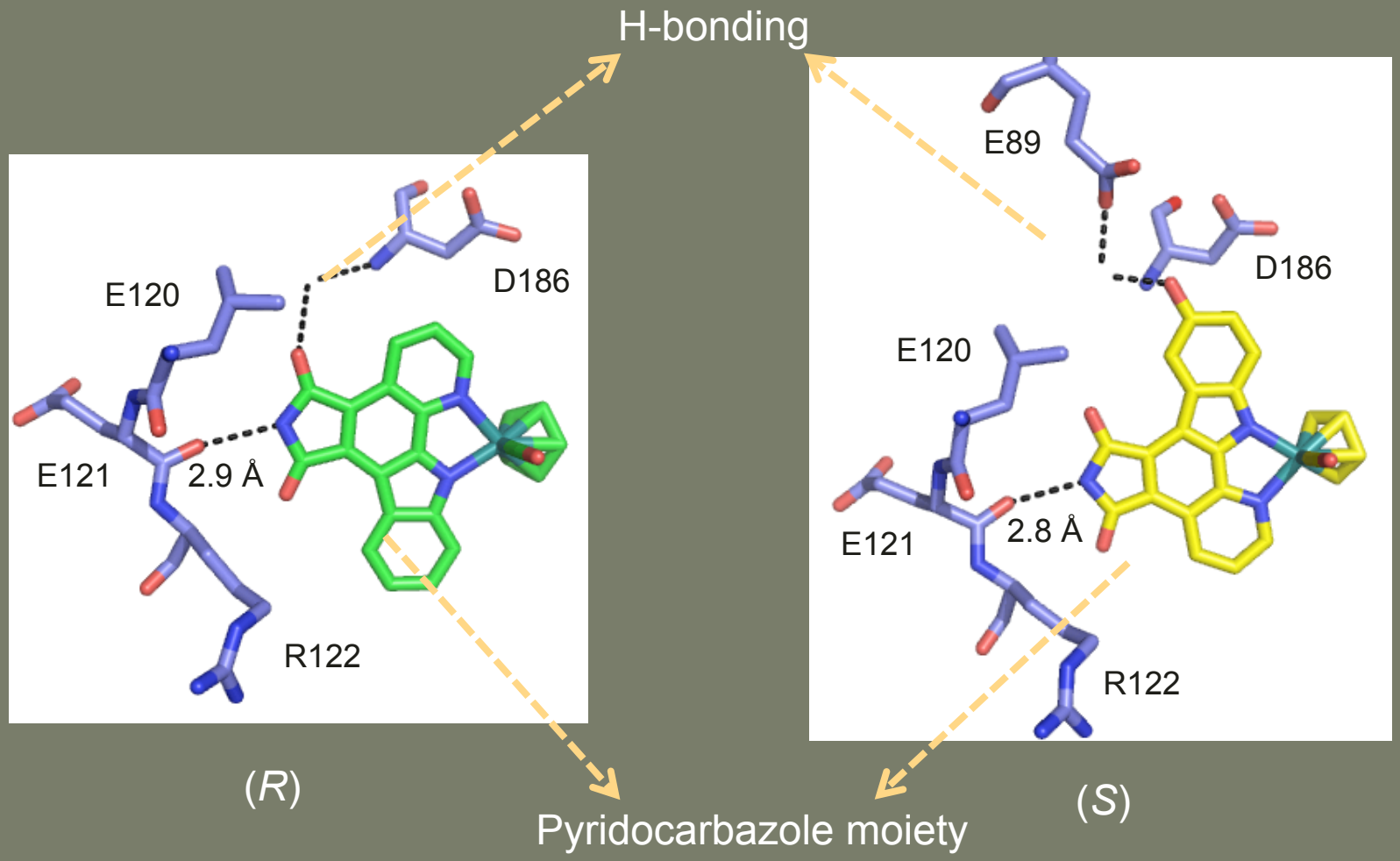


(S)

IC_{50} = 220 pM

Debreczeni, J.; Bullock, A. N.; Atilla, G. E.; Williams, D. S.; Bregman, H.; Knapp, S.; Meggers, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 1580-1585.

Differences Between Two "Isomers"



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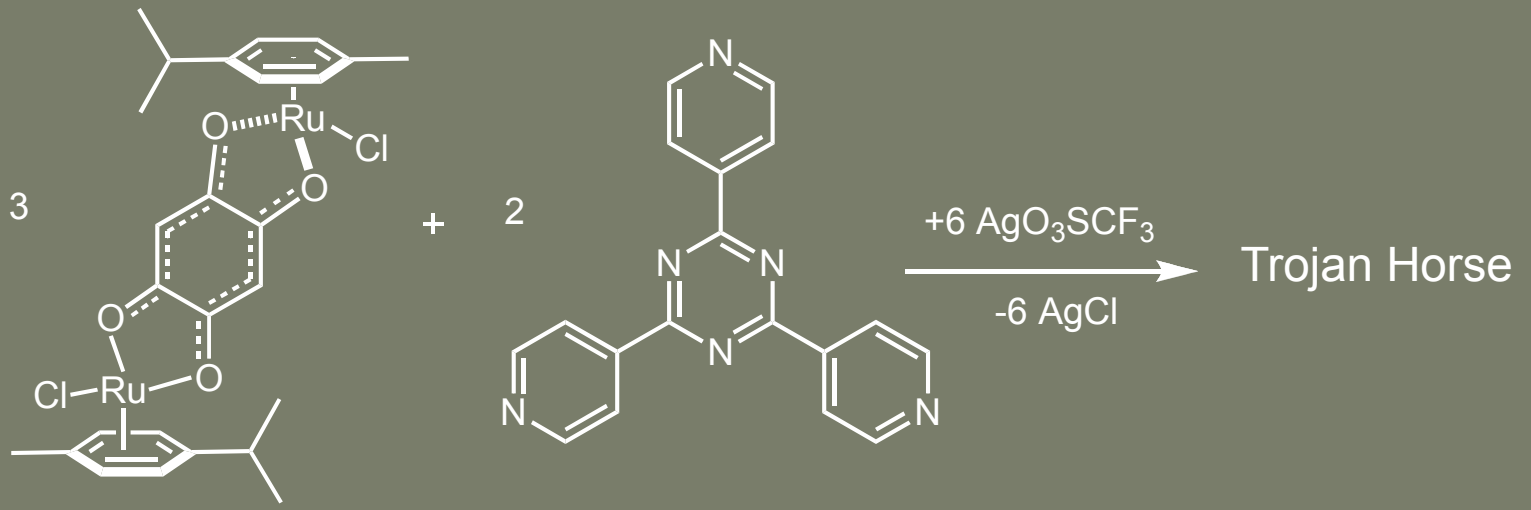
Development of a Trojan Horse for Cancer Cells



Therrien, B.; Süss-Fink, G.; Govindaswamy, P.; Renfrew, A. K.; Dyson, P. J. *Angew. Chem. Int. Ed*. **2008**, *47*, 3773

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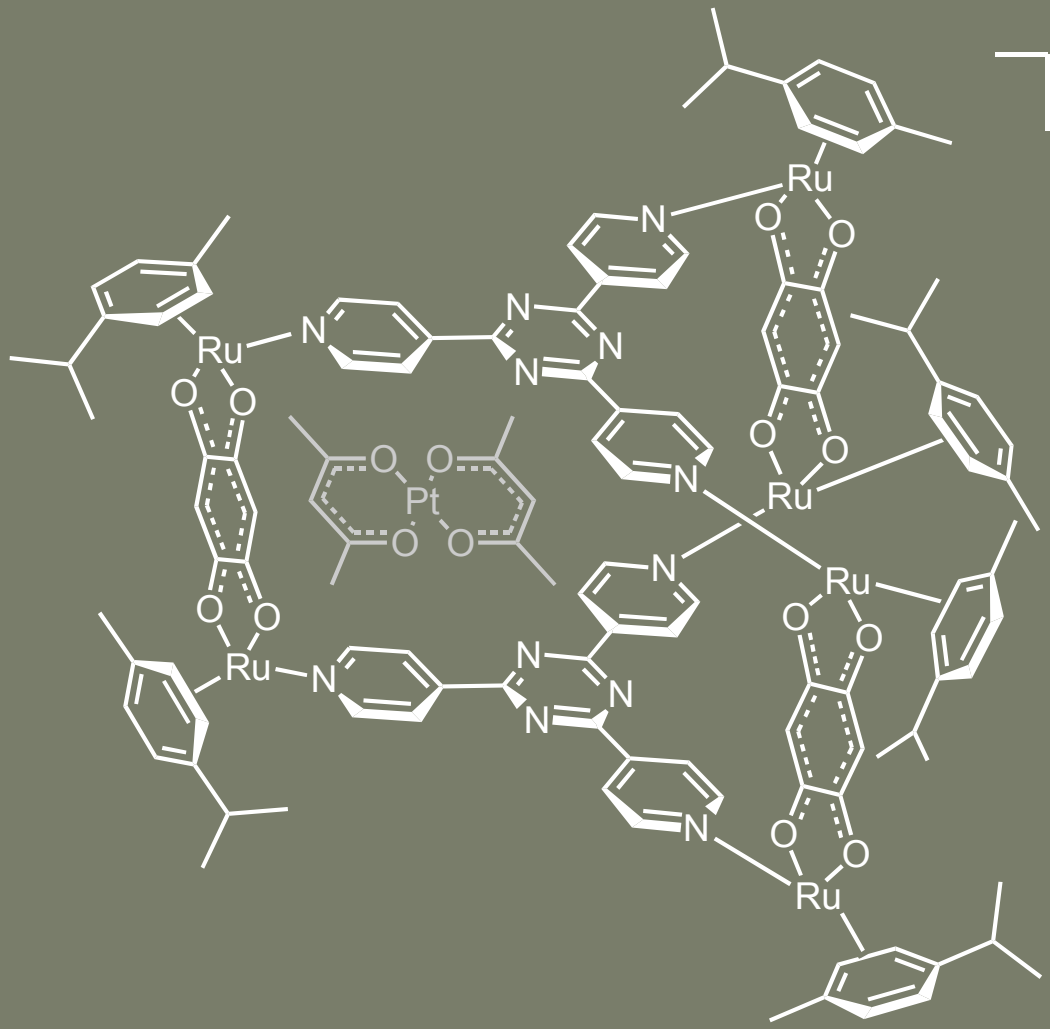
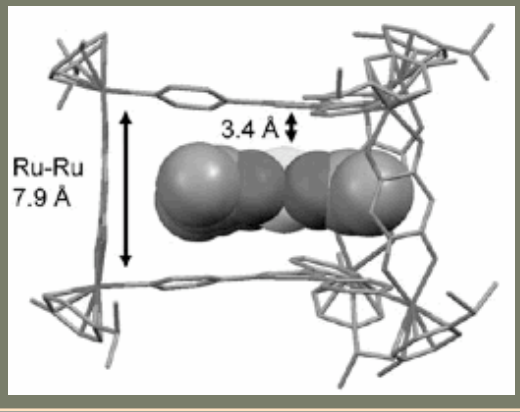


$6^{-}O_3SCF_3$

Side view



Therrien, B.; Süss-Fink, G.; Govindaswamy, P.; Renfrew, A. K.; Dyson, P. J. *Angew. Chem. Int. Ed*. **2008**, *47*, 3773

Activity of Trojan Horse Complex

Complex	IC_{50} [µM]
$[Pt(acac)_2]$	Inactive
Trojan Horse	23
Trojan Horse + $[Pt(acac)_2]$	12

Cytotoxicity in Human A2780 Ovarian Cancer Cells

- "Cisplatin rapidly leaches from the trojan horse."
- Mechanism of Action ?

  Enhanced Permeability and Retention Effect

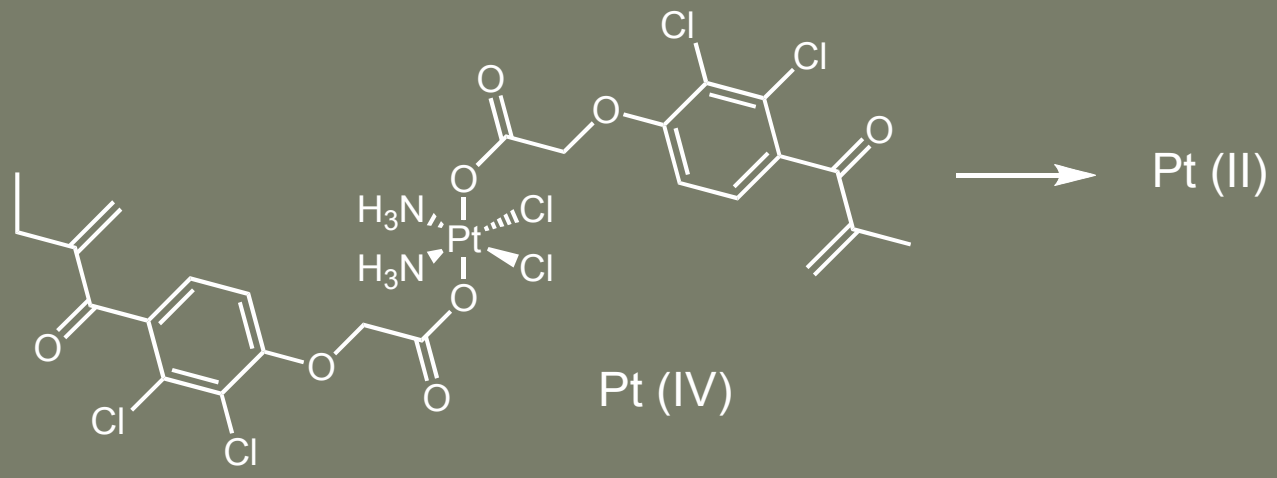
Therrien, B.; Süss-Fink, G.; Govindaswamy, P.; Renfrew, A. K.; Dyson, P. J. *Angew. Chem. Int. Ed*. **2008**, *47*, 3773

Outline

- Platinum-based Cytotoxic Chemotherapy
- Platinum-based Targeted Chemotharepy
- Ruthenium-based Targeted Chemotherapy
- The Challenges for Transition Metal-based Anti-cancer Drug Discovery

The Challenges

- Prodrug – Only fully activated in a living system.



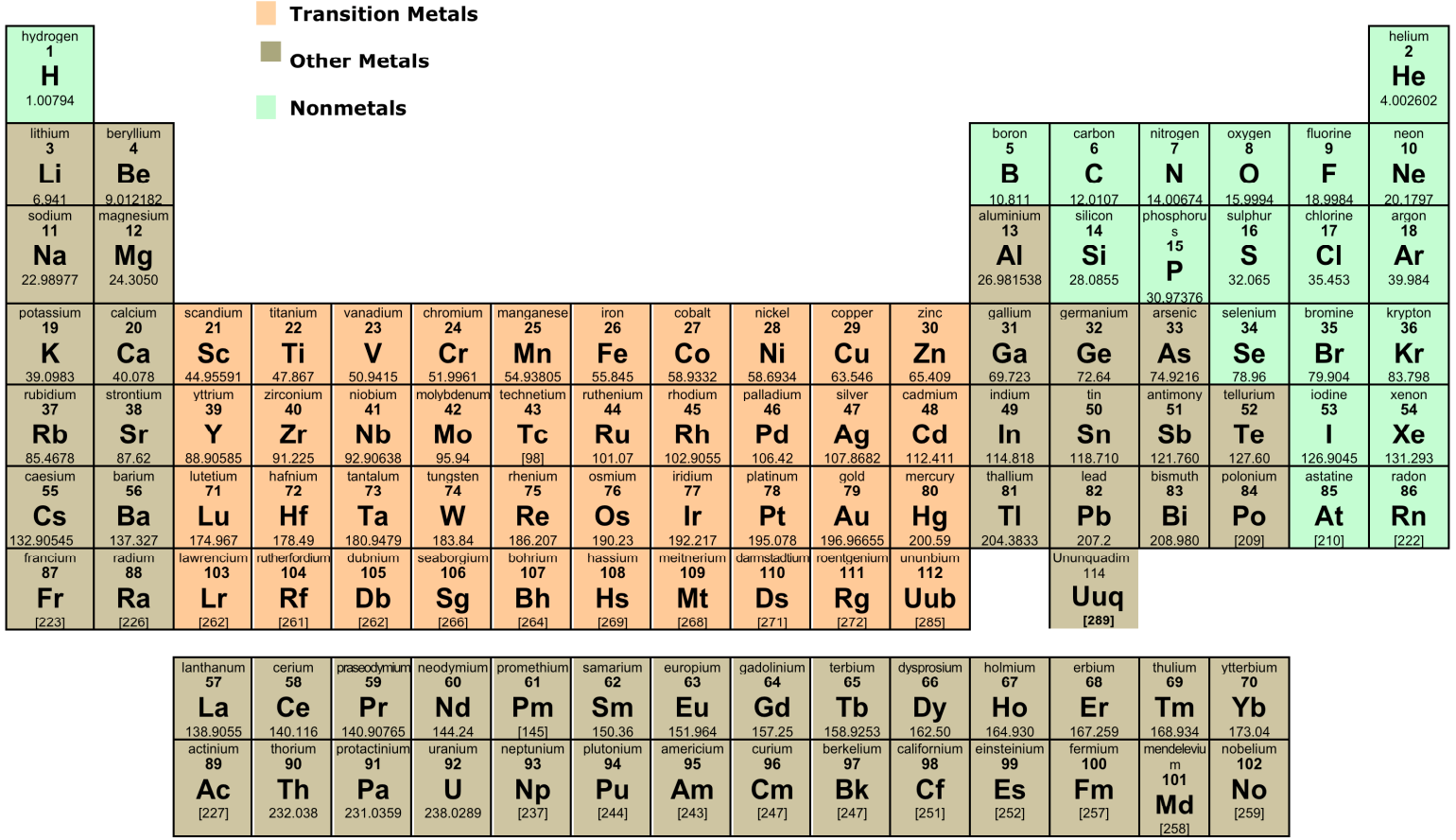
- Identification of new biological target beyond DNA.

- Prejudice against metal-based drugs based on their perceived toxicity.

Hambley, T. W.; *Dalton Trans*. **2007**, 4929-4937.

Total Elements: 114
Non-metal Elements: 22
Transition Metals: 40

Periodic Table of the Elements



Acknowledgement

Dr. Wulff

Dr. Borhan

Aman, Li, Anil, Munmun, Nilanjana, Yong, Dmytro ,
Wynter, Maria, Ding, Alex

Allison, Chrysoula, Mercy