

12th International School of Organometallic Chemistry (ISOC 2019)

“Exploiting organometallic chemistry for biomedical applications”

Angela Casini

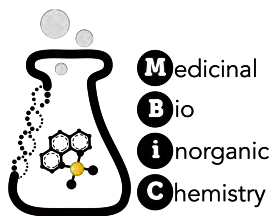
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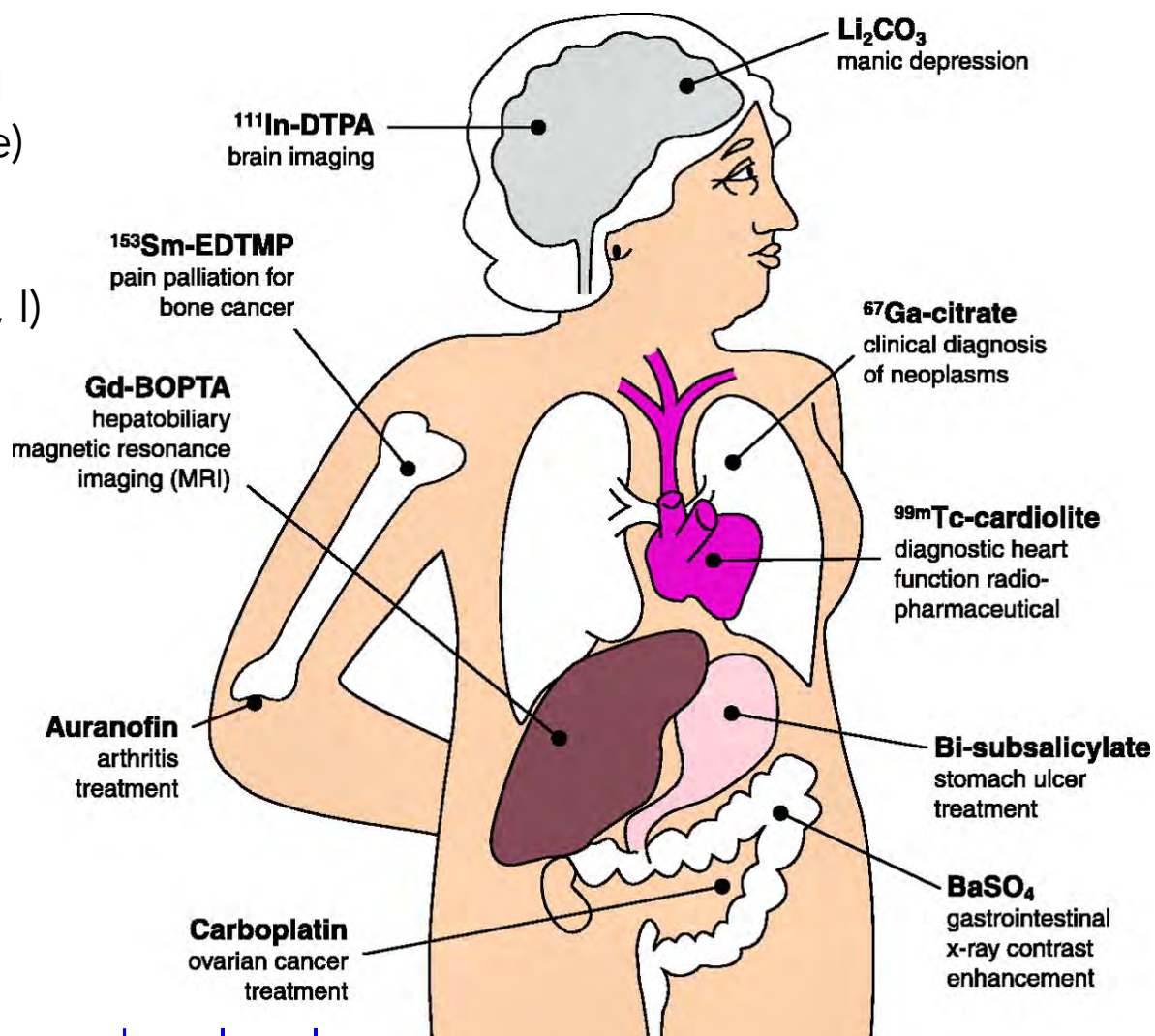
MedBioinorgChem



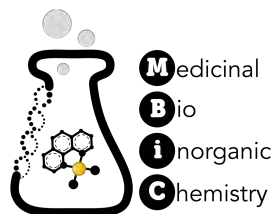


Medicinal Inorganic Chemistry

- ❑ Essential elements (Mineral supplements, e.g. Fe, Zn, Se)
- ❑ Diagnostic Agents (MRI e.g. Gd, Mn) (X-ray e.g. Ba, I)
- ❑ Radiopharmaceuticals as Diagnostic (^{99m}Tc) and Therapeutic (^{186}Re) agents
- ❑ Therapeutic Agents (e.g. Pt, Au, V, Bi, Li)
- ❑ Chelation Therapy (metal sequestering agents)
- ❑ Inorganic nanoparticle
- ❑ Supramolecular metal-based molecules

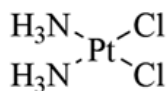


Thompson & Orvig, Science 2003

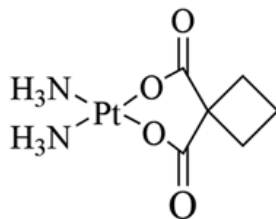


Pt(II) anticancer compounds

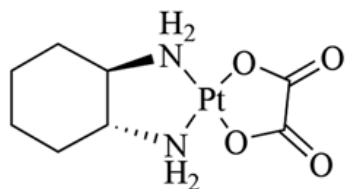
Platinum(II) drugs used globally



Cisplatin (1)
(1978)

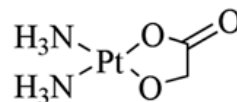


Carboplatin (2)
(1989)

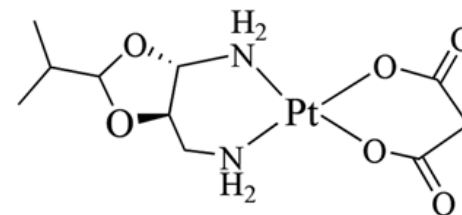


Oxaliplatin (3)
(2002)

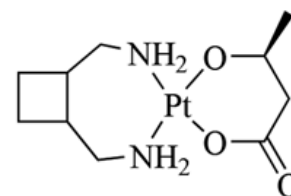
Platinum(II) drugs used in Japan (4), South Korea (5) and China (6)



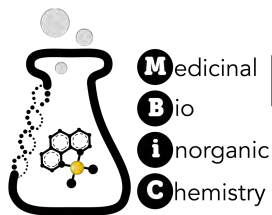
Nedaplatin (4)
(1995)



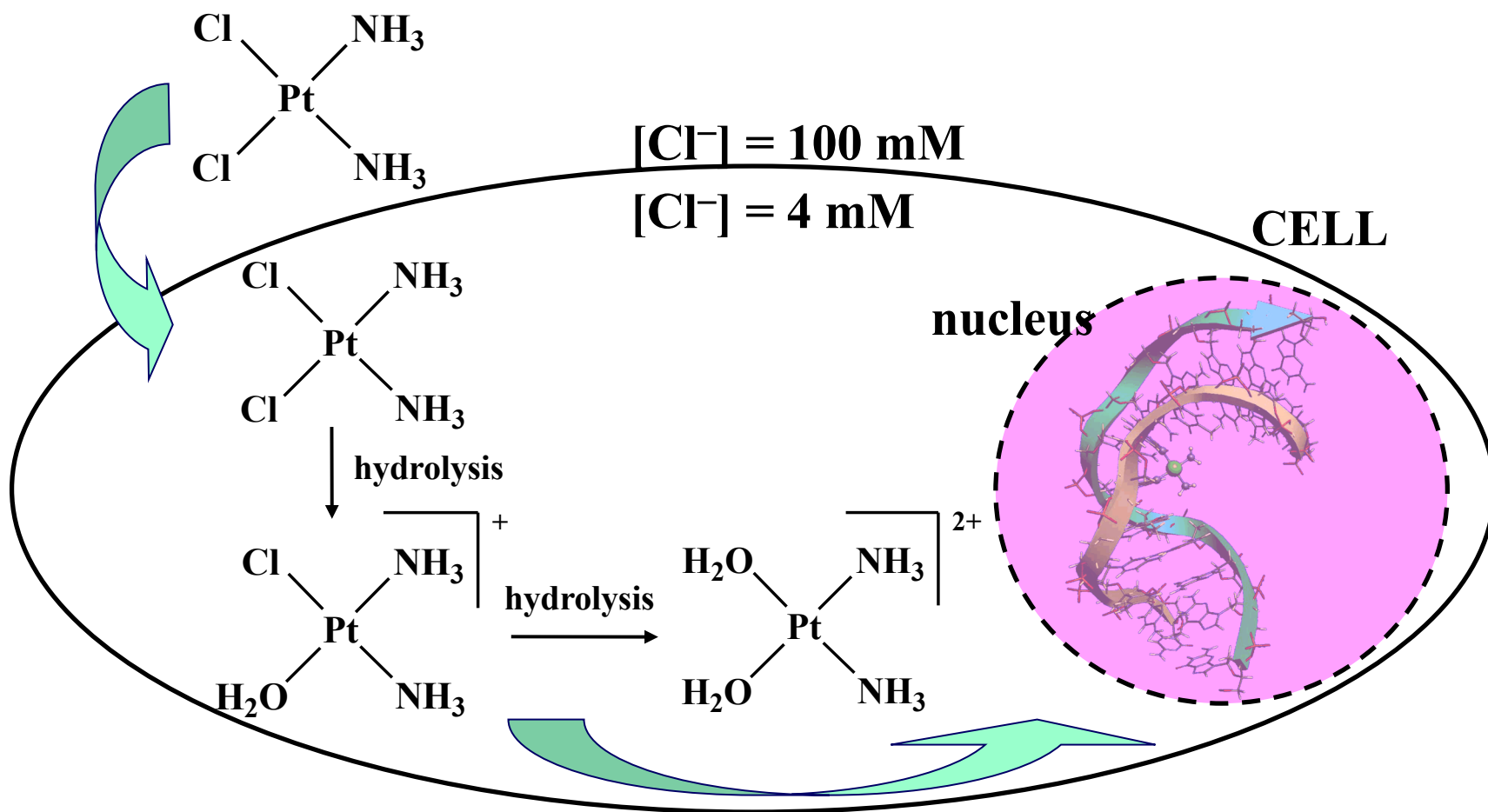
Heptaplatin (5)
(1999)

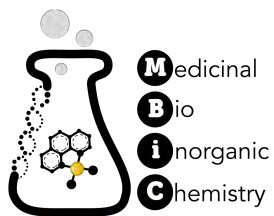


Lobaplatin (6)
(2010)



Mechanisms of action of Pt(II) complexes: a simplified view



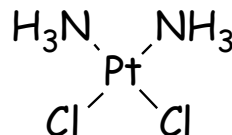


Historic development

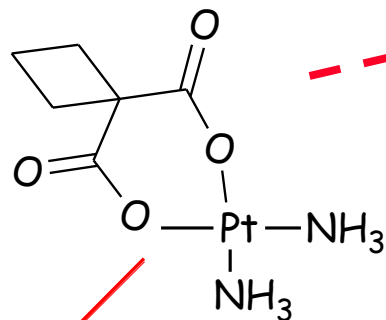
Japan: nedaplatin

China: lobaplatin

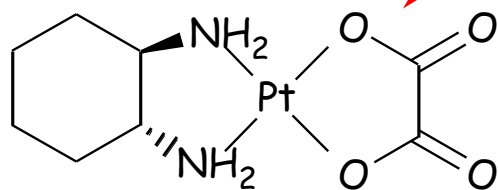
Korea: heptaplatin



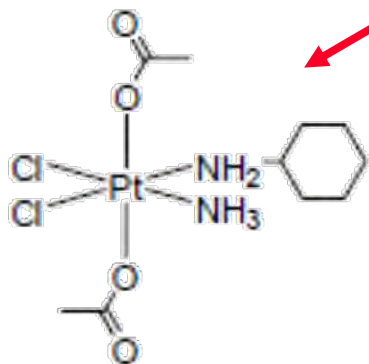
Second generation:
Changing chlorides



Third generation:
Changing amines

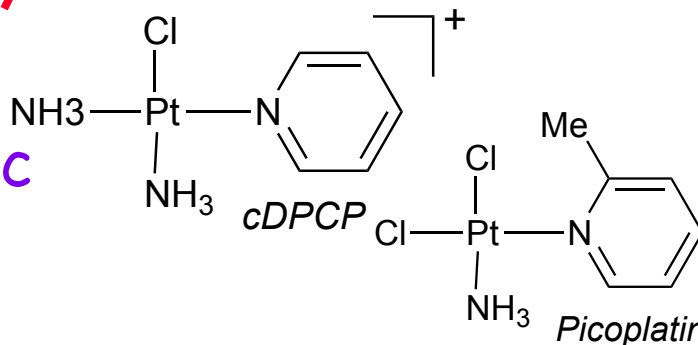


Pt(IV)
complexes



satraplatin

cationic
steric

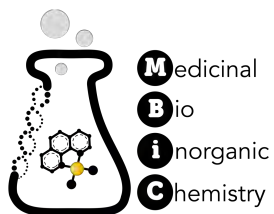


cDPCP

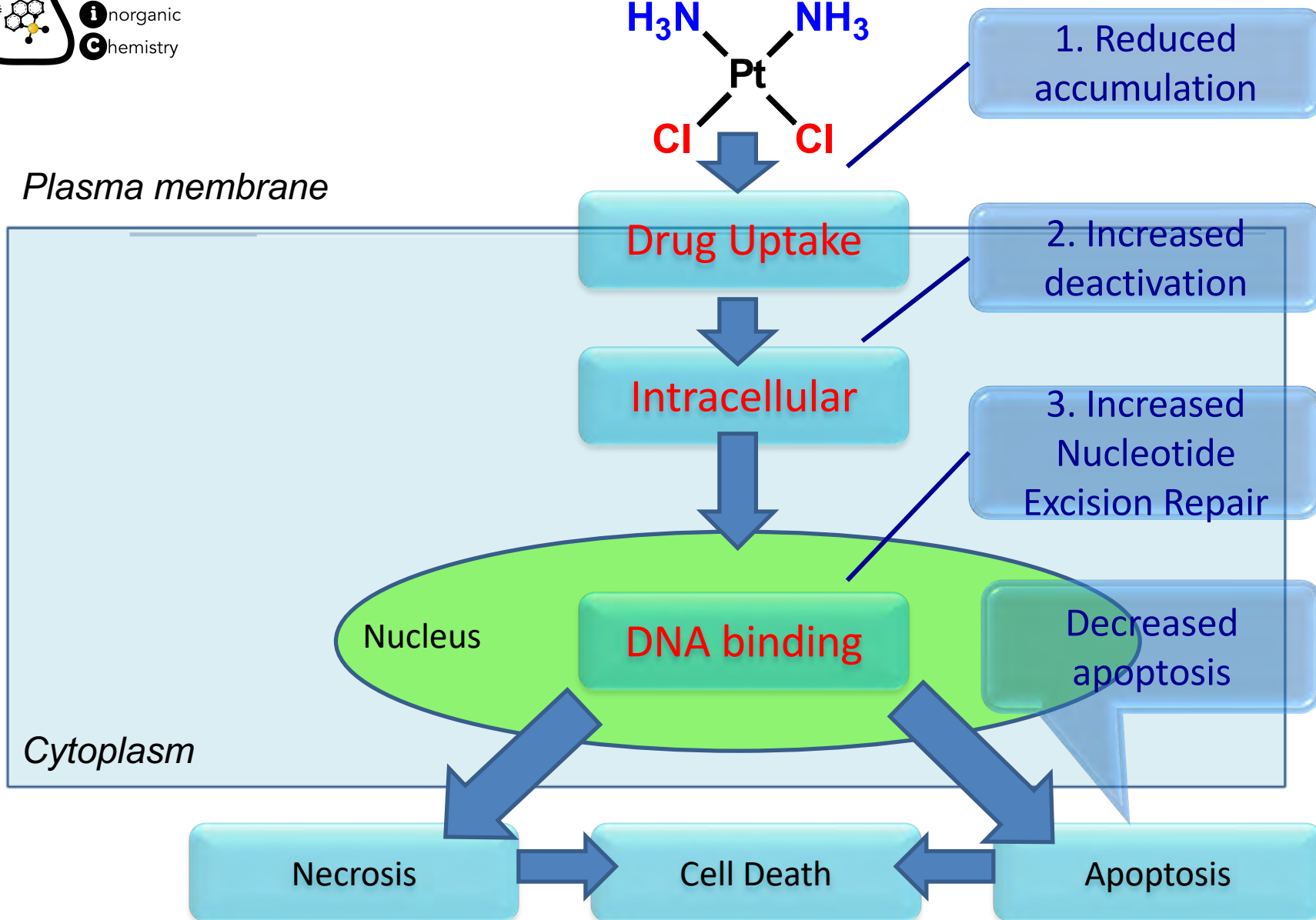
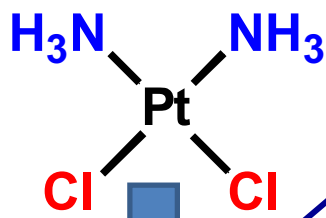
Picoplatin

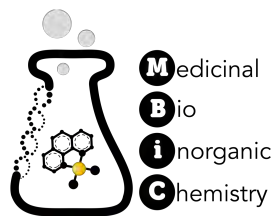
Transplatin
isomers

Dinuclear and
Trinuclear compounds

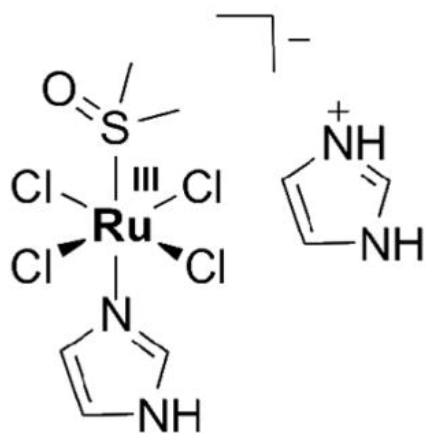


Resistance mechanisms



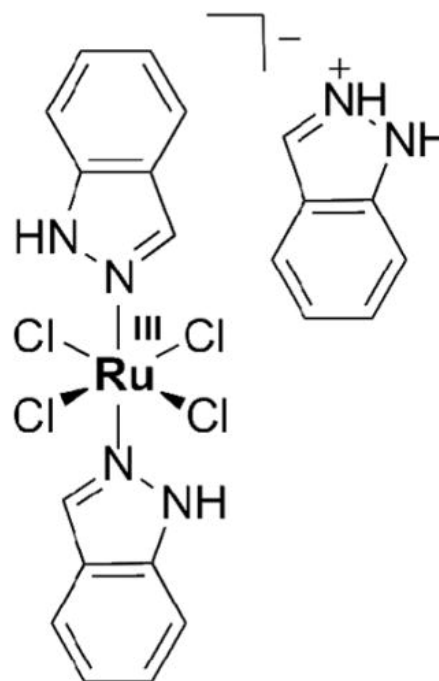


Ruthenium(III) complexes



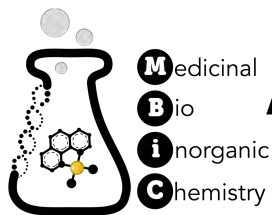
NAMI-A

Alessio, Mestroni, Sava

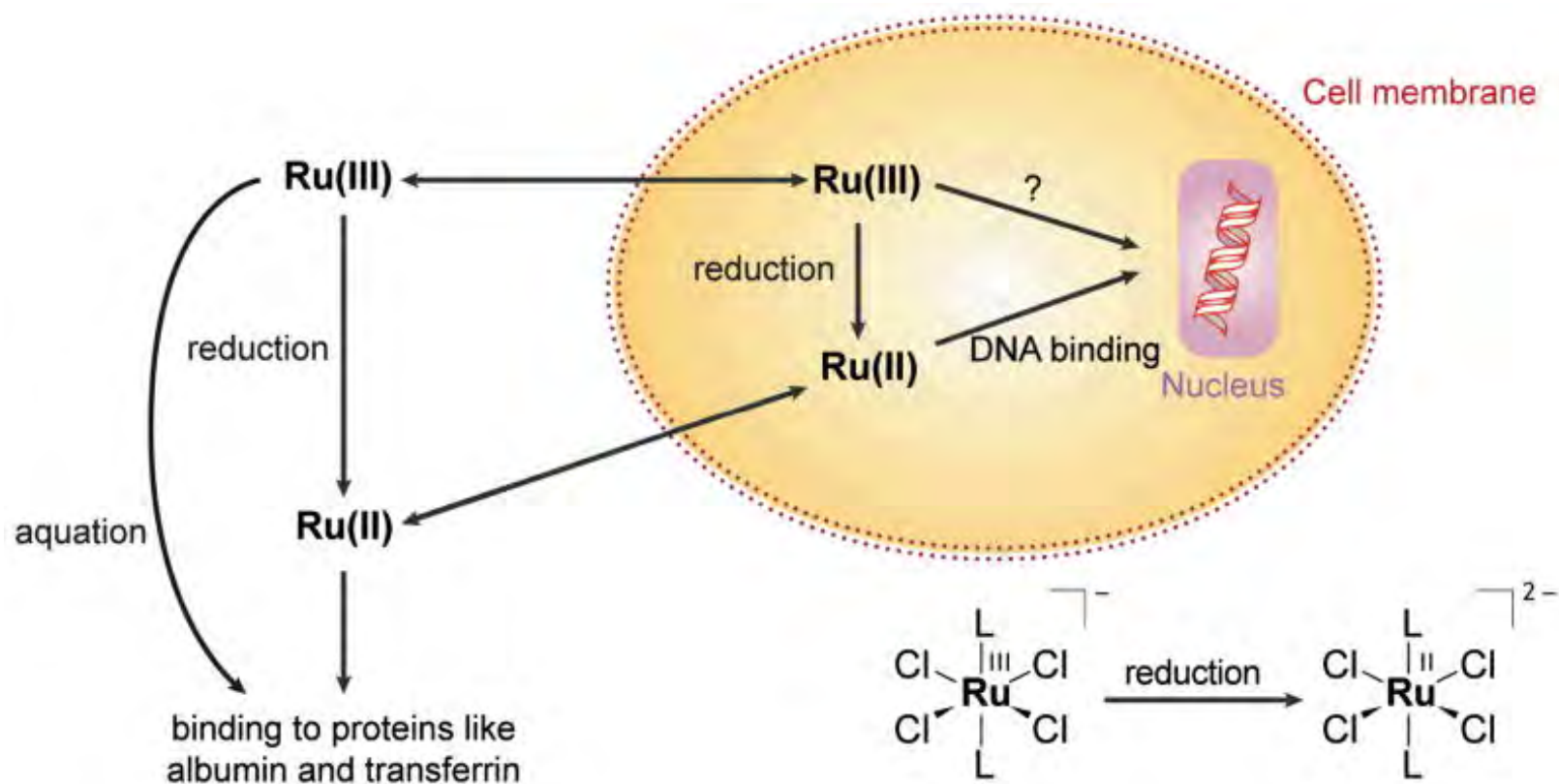


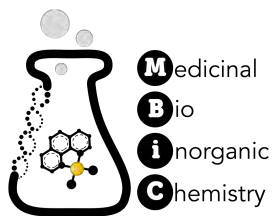
KP1019

Keppler

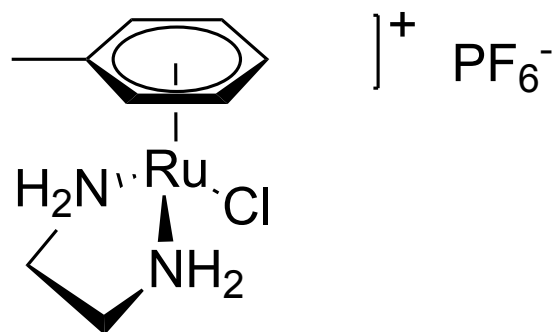


"Activation by reduction" mechanism

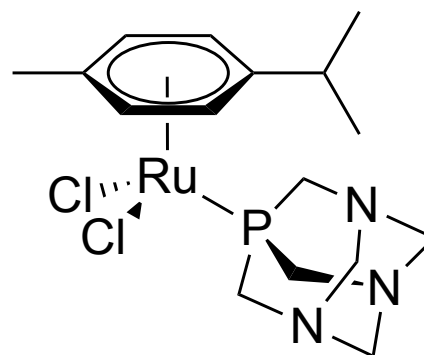




Ru(II) organometallic complexes

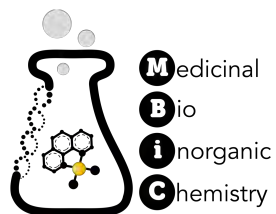


Sadler PJ
cytotoxic

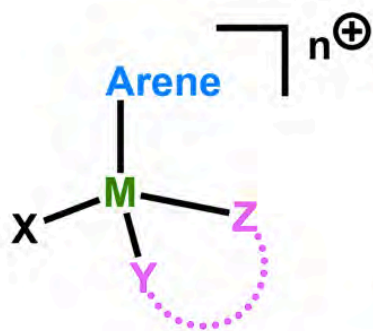


RAPTA-C

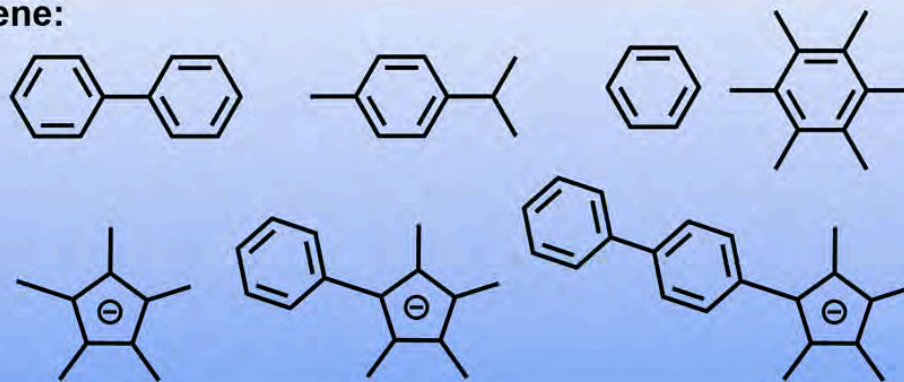
Dyson PJ
antimetastatic
non-cytotoxic



Sadler type 'piano-stool' complexes



Arene:

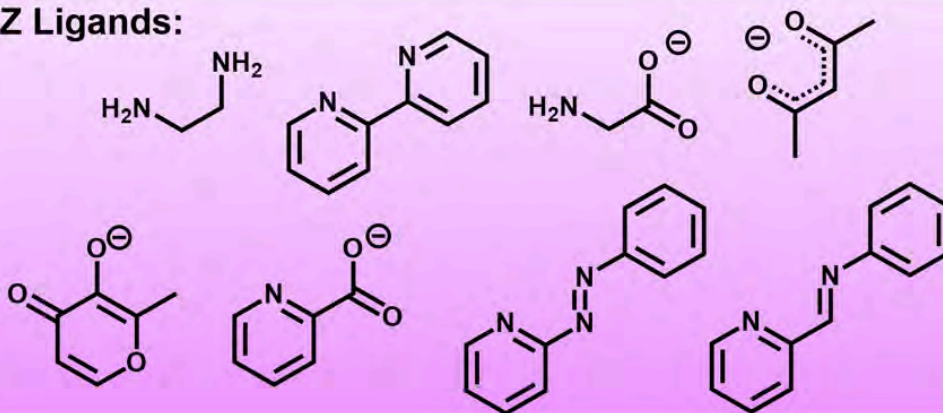


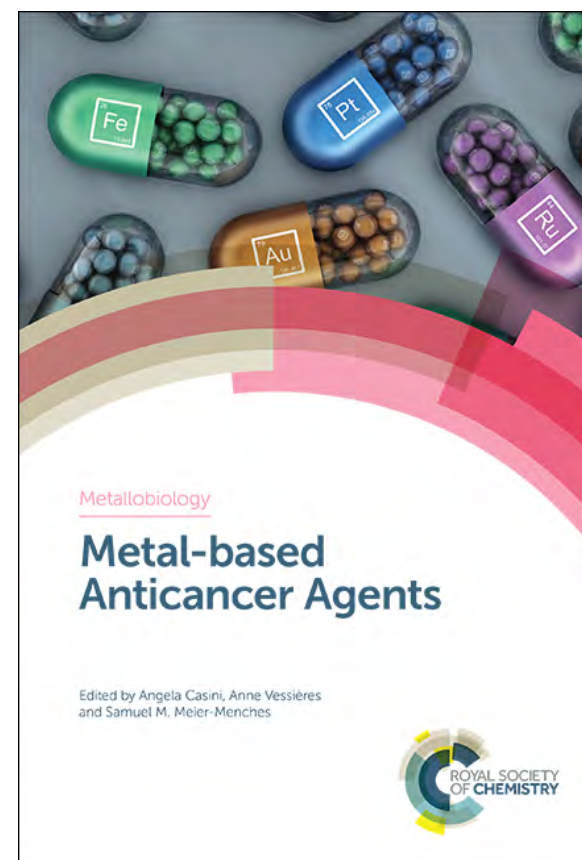
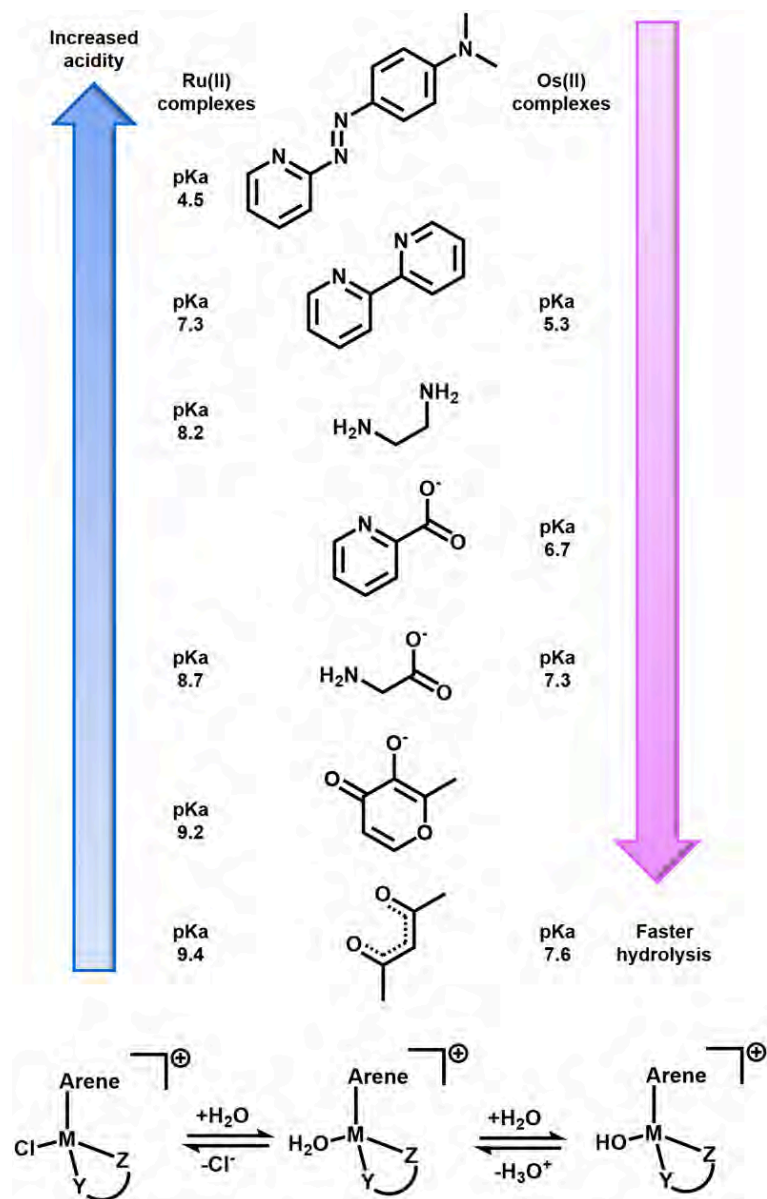
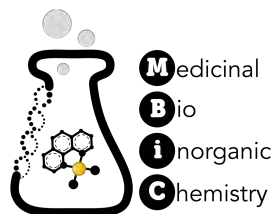
Metal centre: Ru(II),
Os(II) and Ir(III)

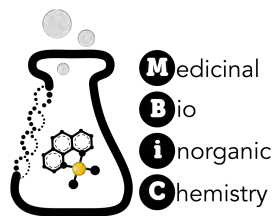
X Ligand: Halogens Cl, I
-CO, -CN, -SH



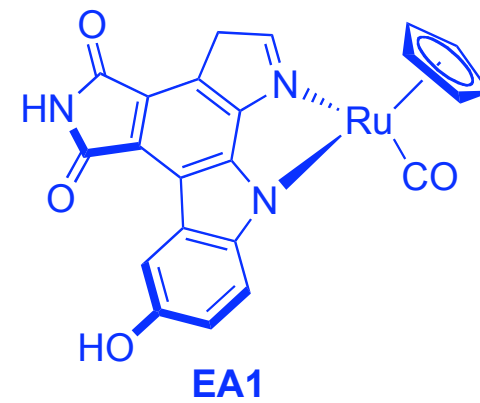
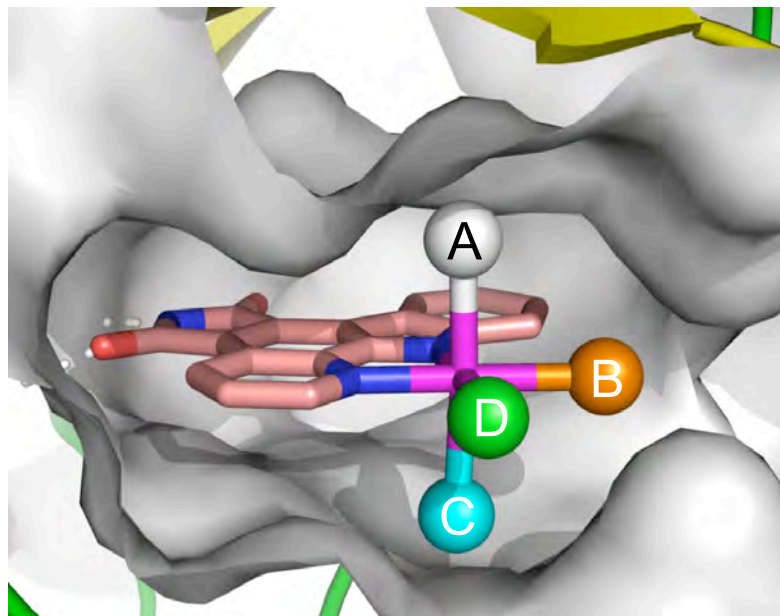
Y, Z Ligands:







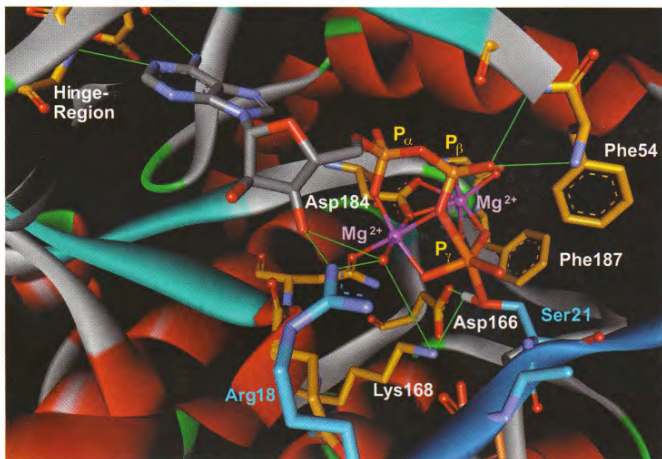
"Structural" metallodrugs



Courtesy of Eric Meggers

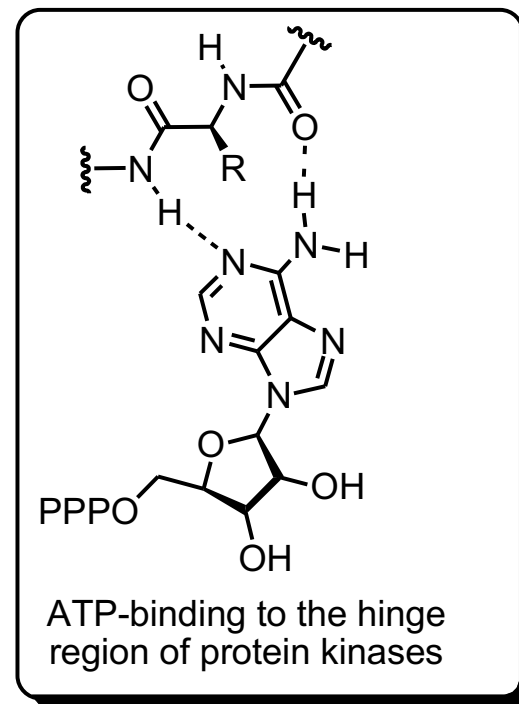
ATP-Recognition by Protein Kinases and the Design of Metal-Based Protein Kinase Inhibitors

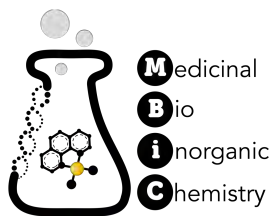
- ❑ Protein kinases involved in a large range of diseases
- ❑ Protein kinase inhibitors for cancer therapy: Gleevec (Novartis)
- ❑ 500 Protein kinases encoded in human genome
- ❑ Unsolved challenge: How to design selective inhibitors for each individual kinase?



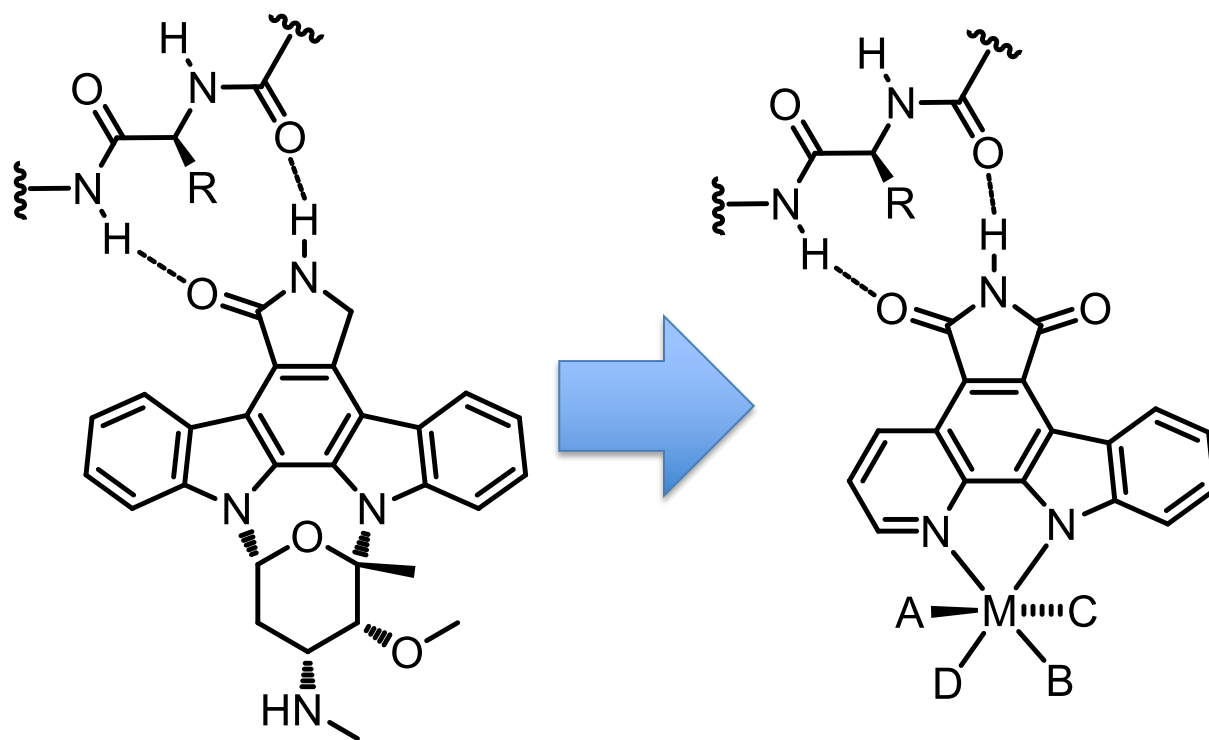
Klebe, *Wirkstoffdesign*, Spektrum, 2nd Ed.

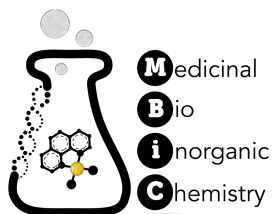
Noble & Endicott, *Pharmacol. Ther.* **1999**, 82, 269-278





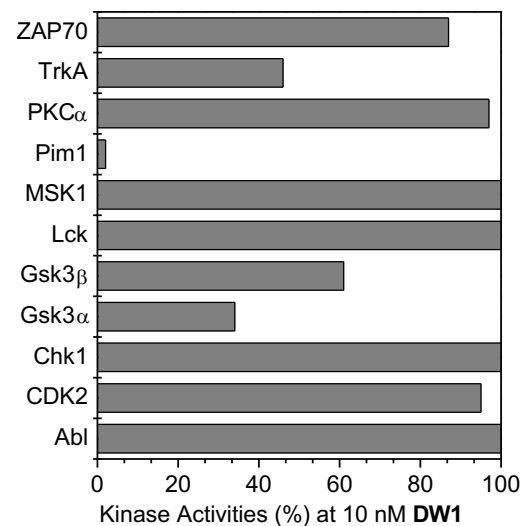
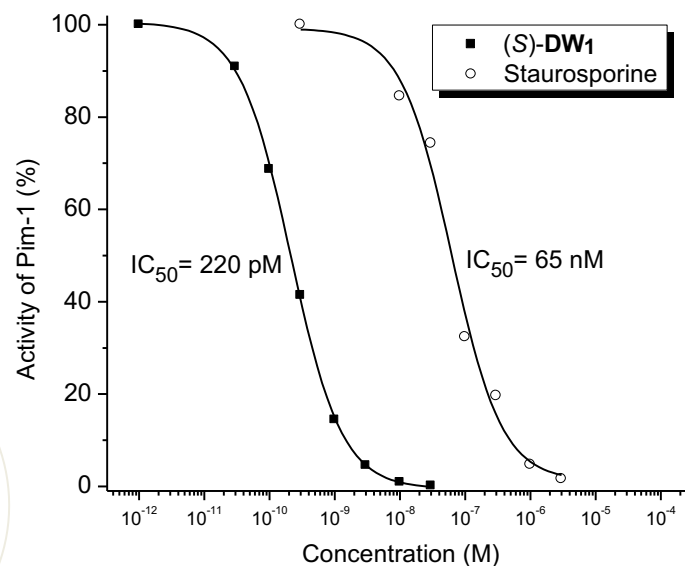
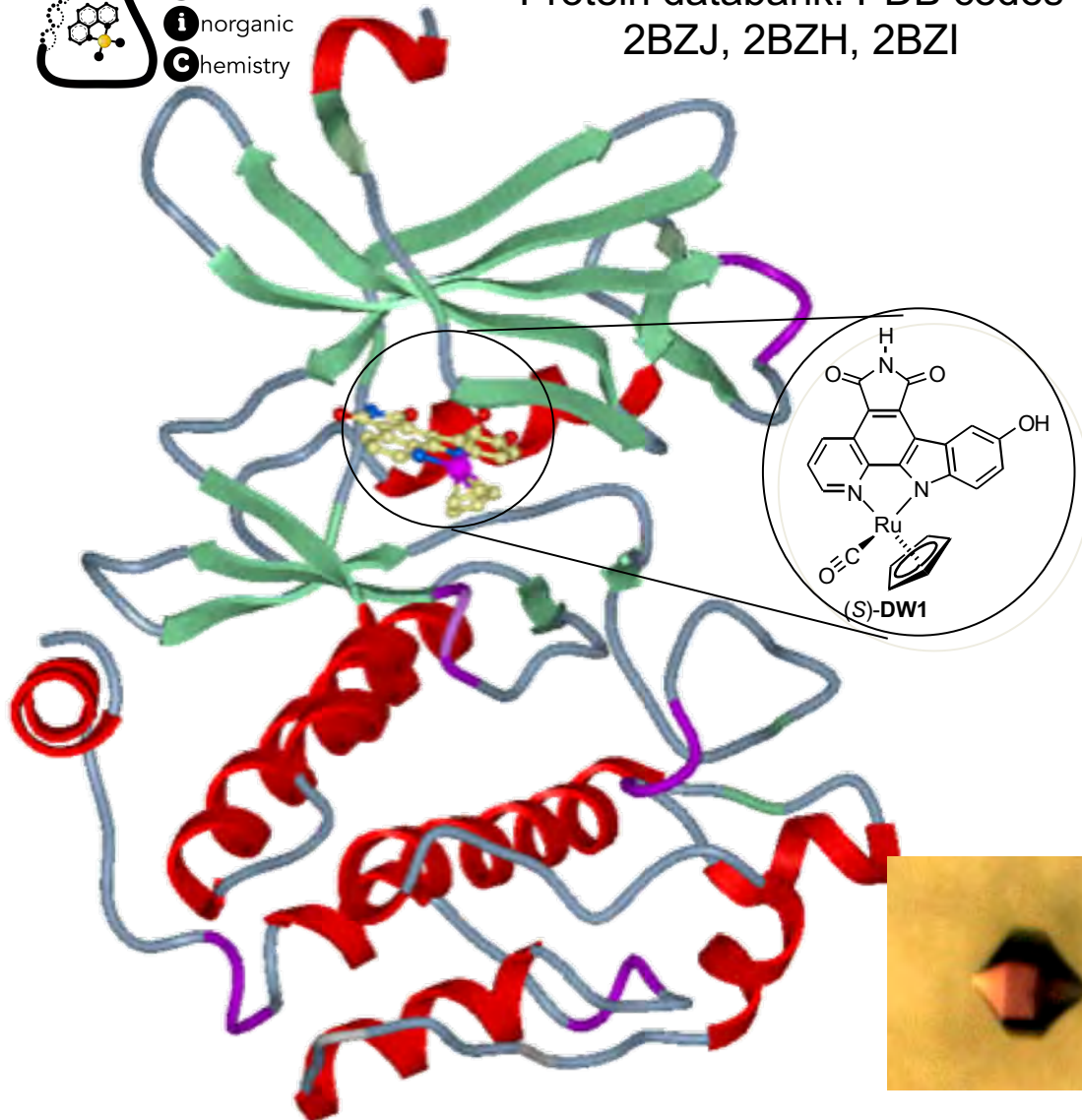
Inspiration.....



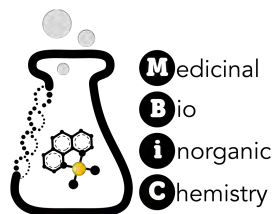


Ruthenium Half Sandwich Complex Bound to Pim-1

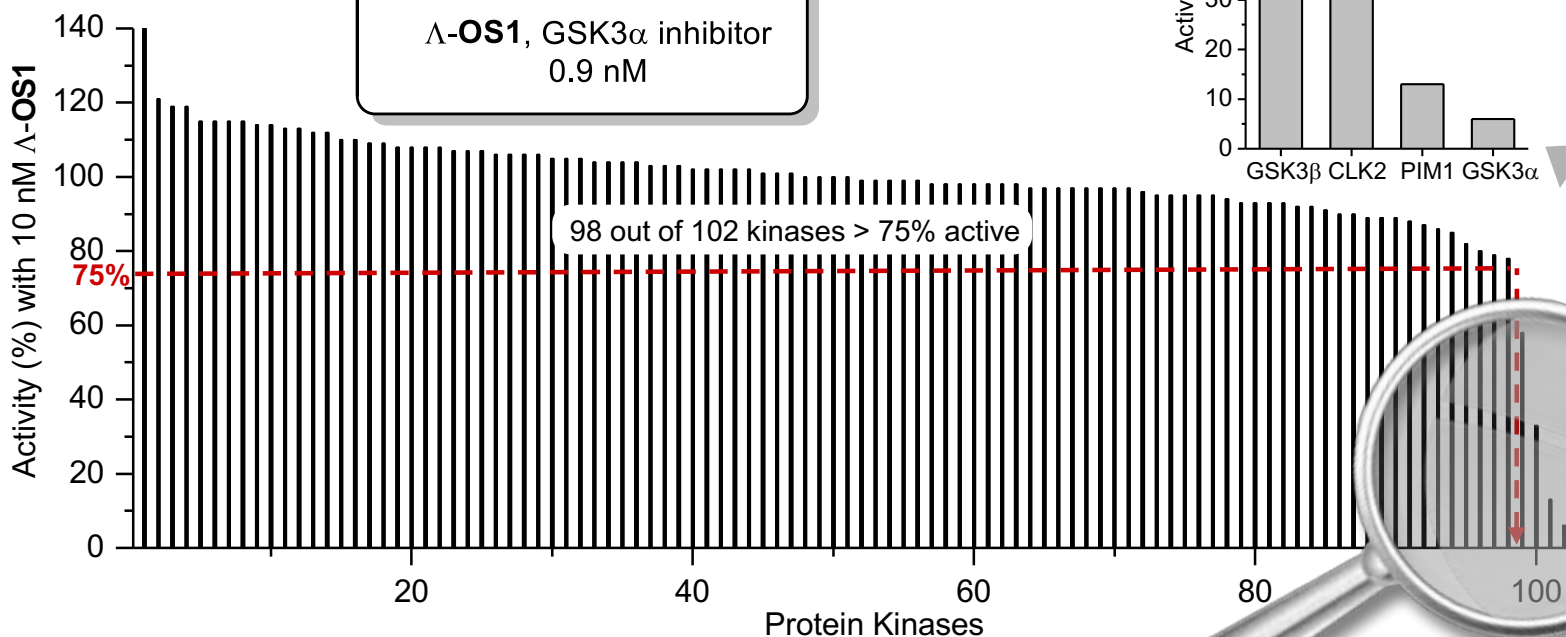
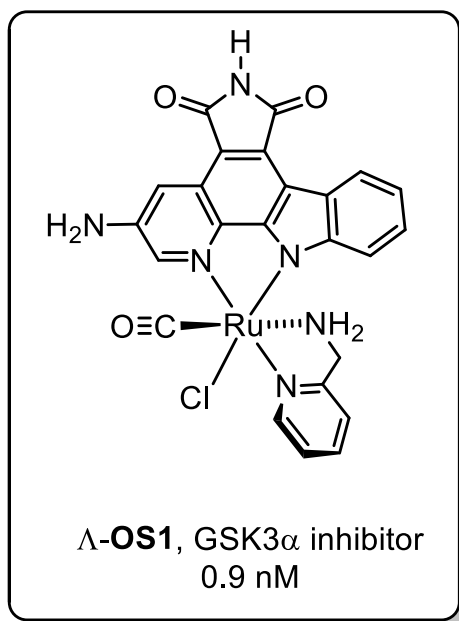
Protein databank: PDB codes
2BZJ, 2BZH, 2BZI



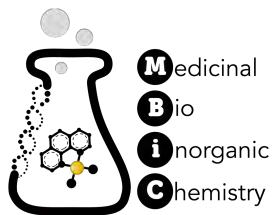
Meggers E. and co-workers, *Angew. Chem. Int. Ed.* **2006**, 45, 1580



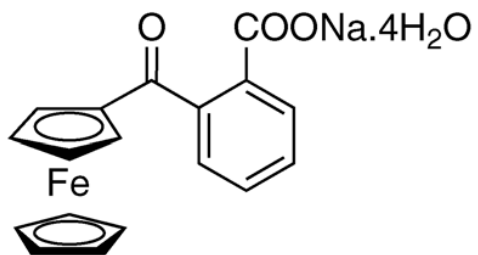
Selectivity of Λ -OS1 in a Panel of 102 Protein Kinases



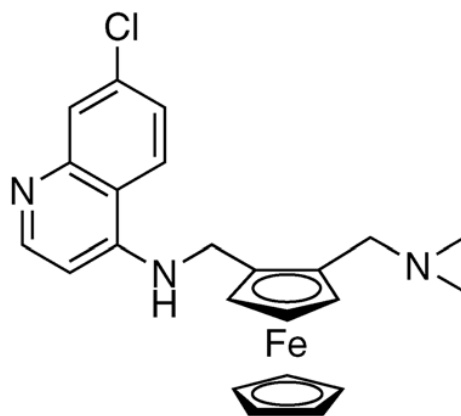
Screening against panels of human wild type protein kinases. Each bar represents the activity of one individual protein kinase. Protein kinases in each panel (Millipore KinaseProfiler) were solely selected on the basis that their concentration was equal to or lower than the concentration used of the screened compound. All assays were performed with 10 μ M ATP.



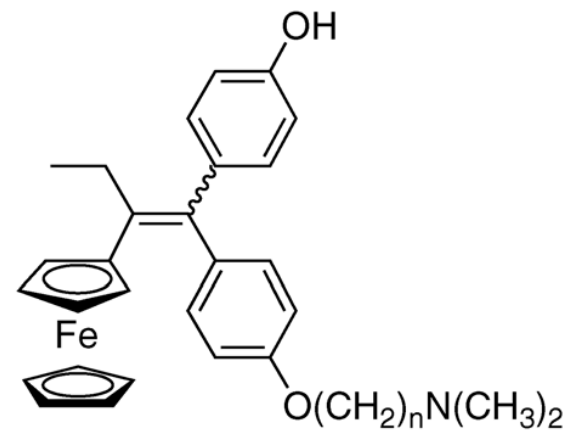
Ferrocene-based complexes



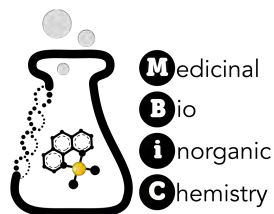
Ferrocerone



Ferroquine



Ferrocifens
Fc-OH-Tam with n= 2-5, 8

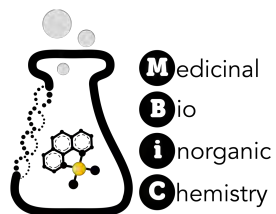


Gold compounds in therapy

❑ Gold used medicinally for centuries

Chrysotherapy

- ❑ Arabian, Chinese and Indians 2500 BC
- ❑ Medieval Europe: *aurum potabile*. This mixture was an alcoholic solution that contained various herb extracts and essential oils, along with gold, as a powder or as small flakes
- ❑ Europe 17th century: Nicholas Culpeper treated melancholy
- ❑ Bartholomäus Kretschmar made his recipe for “aurum vitae” public, which he advertised to be an efficient remedy against syphilis, dropsy, madness, epilepsy, malaria, icterus, leprosy, lupus, cancer (ulcers), skin rashes, fistulae, and cysts. He considered it also as a preservative (i.e., prophylactic medicine) against poisoning, magic and plague
- ❑ 1890 Robert Koch discovered the bactericidal properties of gold cyanide and in 1920 it was used to treat tuberculosis
- ❑ 20th century *Ridaura* (auranofin) – arthritis

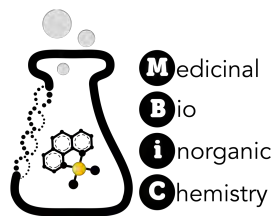


J Biol Inorg Chem (2014) 19:961–965
DOI 10.1007/s00775-014-1135-4

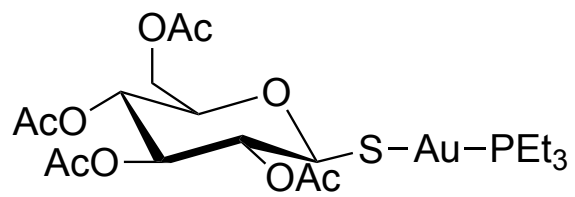
ORIGINAL PAPER

Historical and biochemical aspects of a seventeenth century gold-based aurum vitae recipe

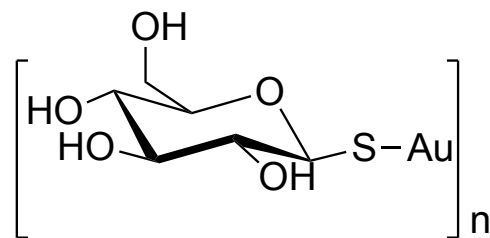
Riccardo Rubbiani · Bettina Wahrig ·
Ingo Ott



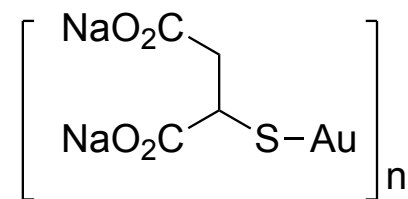
Au(I) anti-arthritis drugs



auranofin

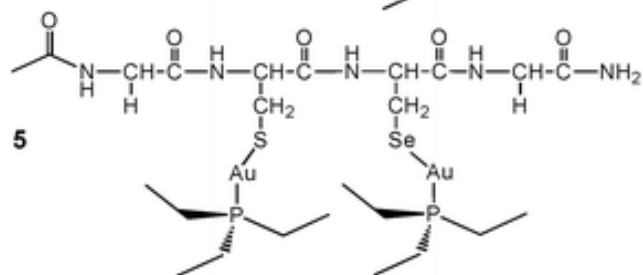
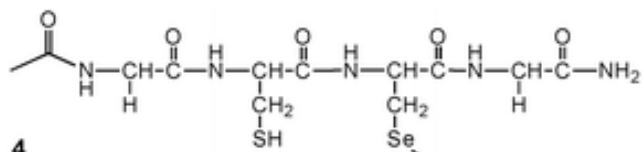


aurothioglucose

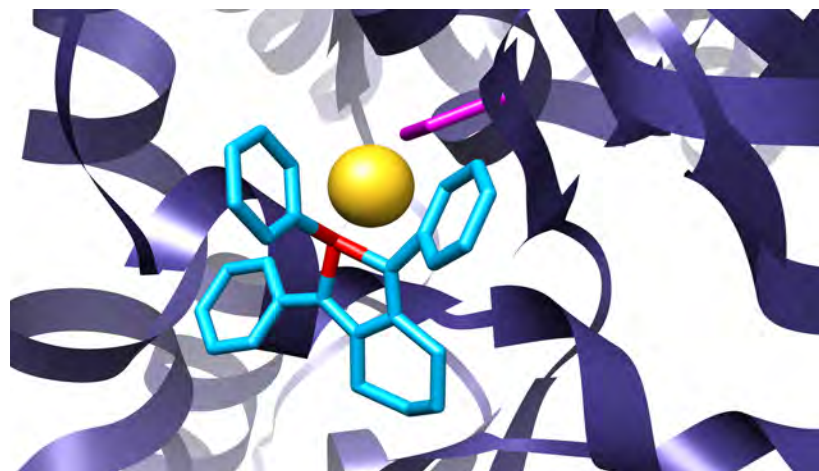
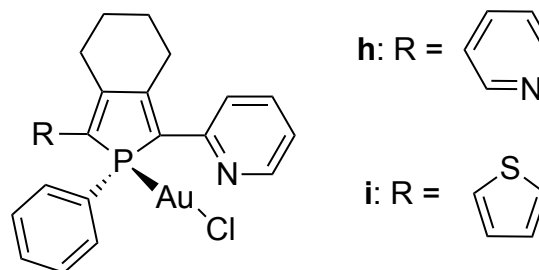


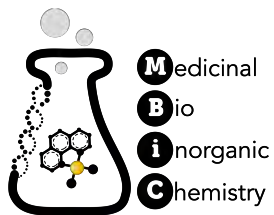
aurothiomalate

Au(I)-protein adducts

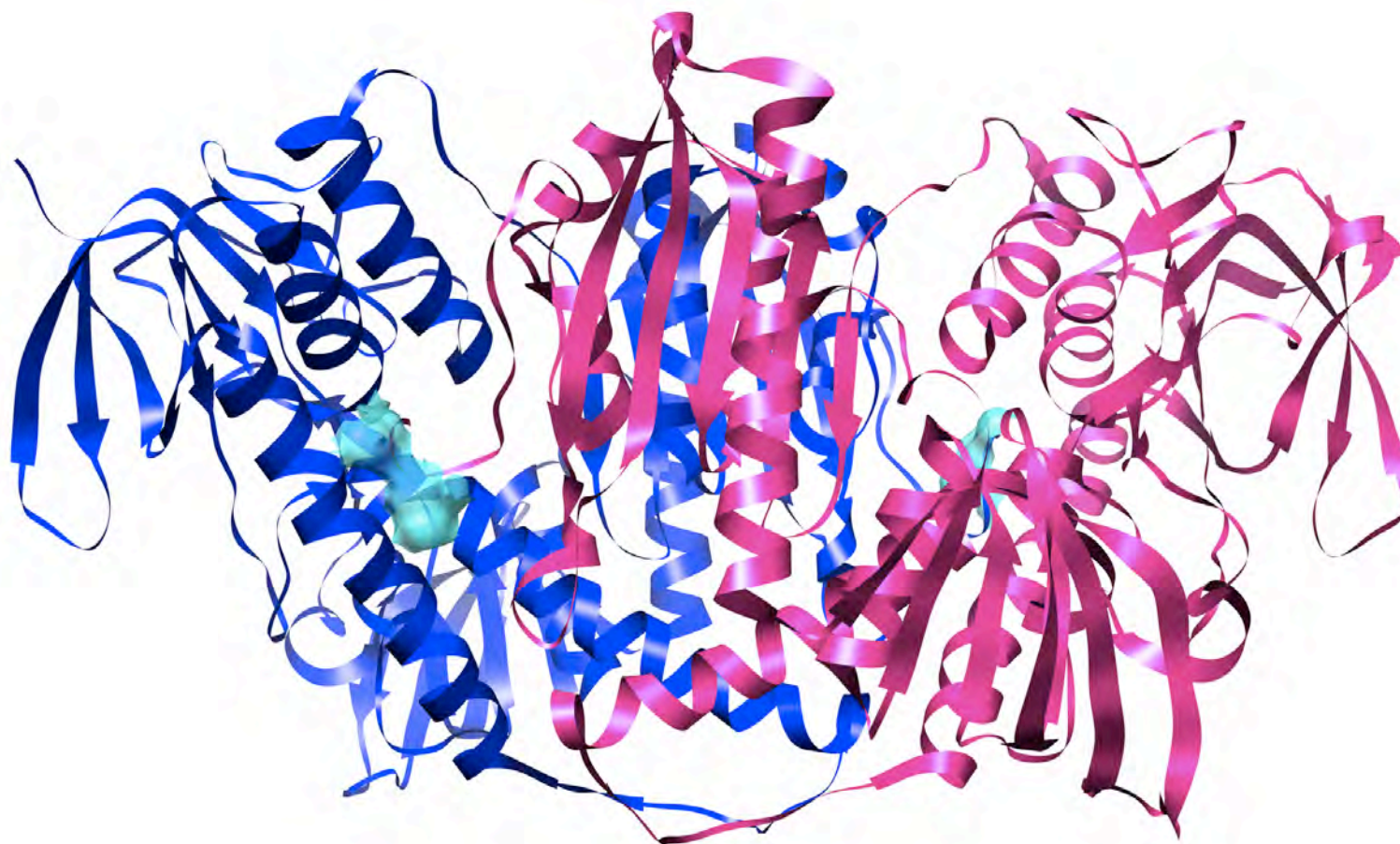


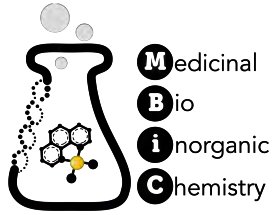
Au(I) phosphole-GR adduct



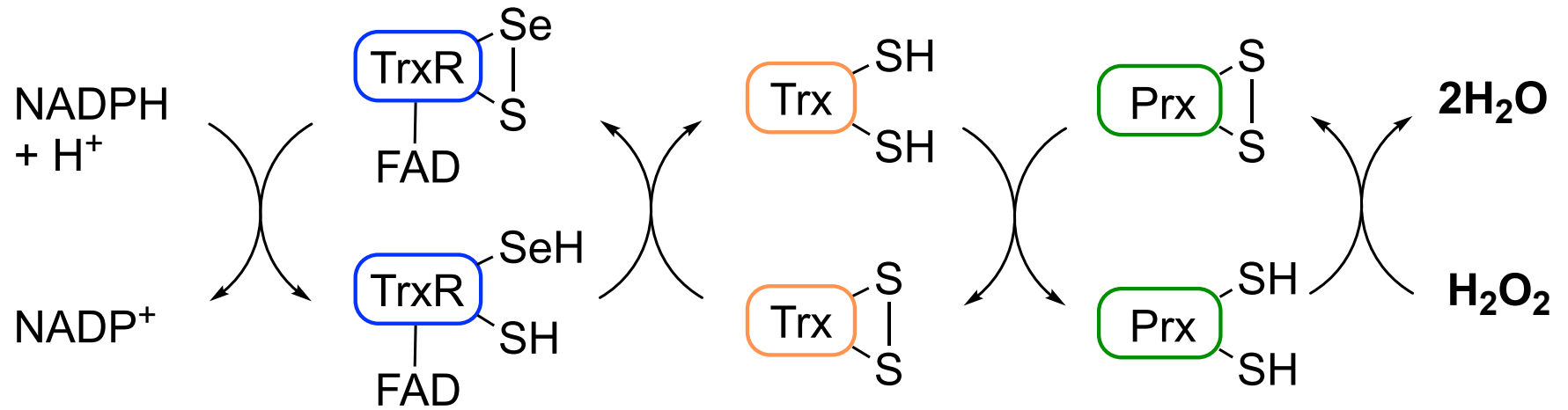


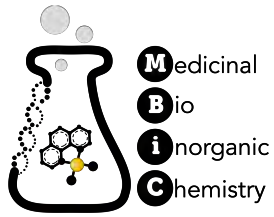
Thioredoxin Reductase (TrxR) structure a seleno-enzyme





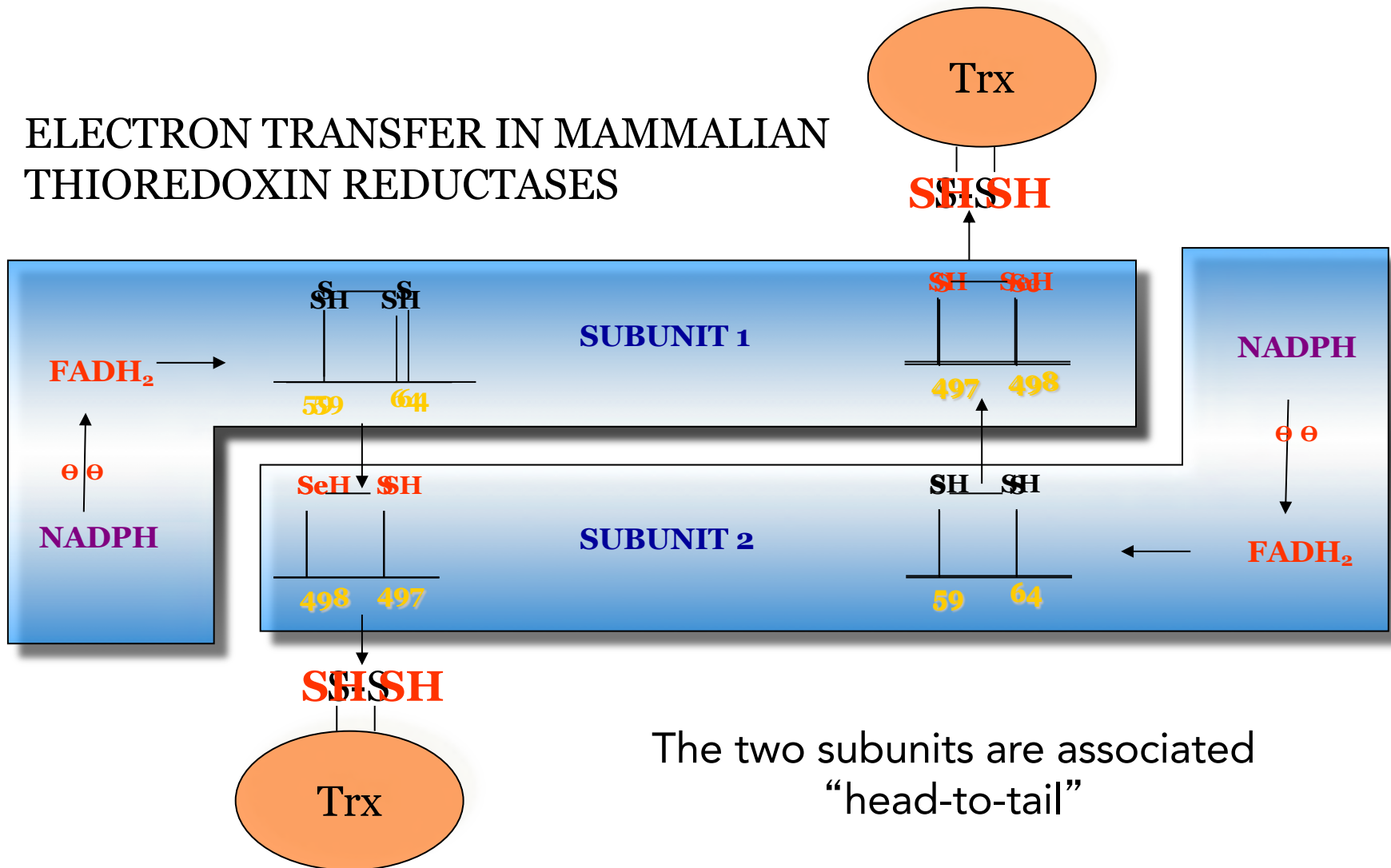
Thioredoxin pathways mediate the reduction of hydrogen peroxide



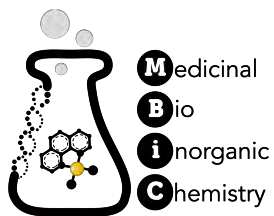


Thioredoxin/Thioredoxin Reductase (Trx/TrxR) system

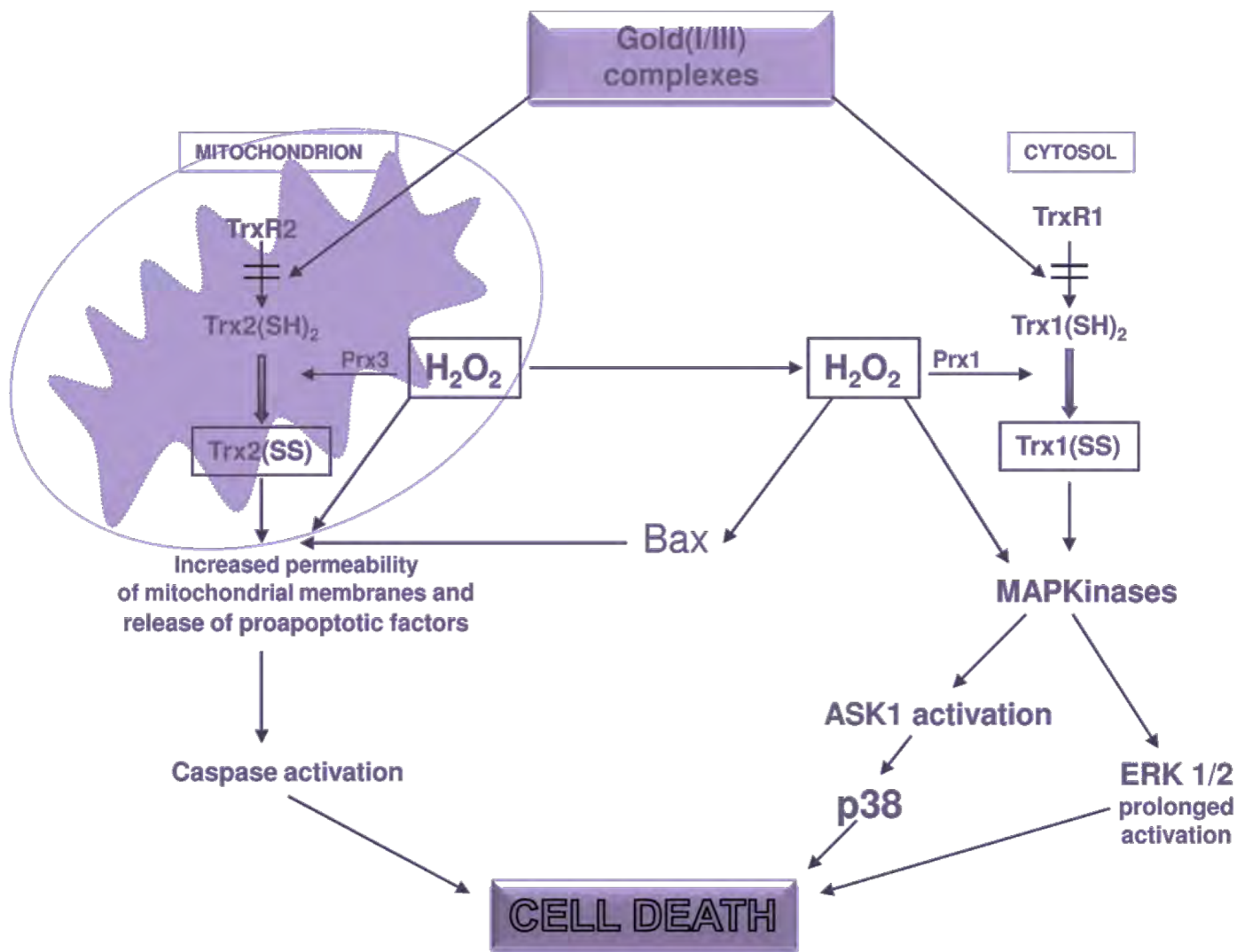
ELECTRON TRANSFER IN MAMMALIAN THIOREDOXIN REDUCTASES



The two subunits are associated "head-to-tail"



Au(I) complexes as TrxR inhibitors



Au(I) complexes as TrxR inhibitors

CHEMMEDCHEM
 CHEMISTRY ENABLING DRUG DISCOVERY

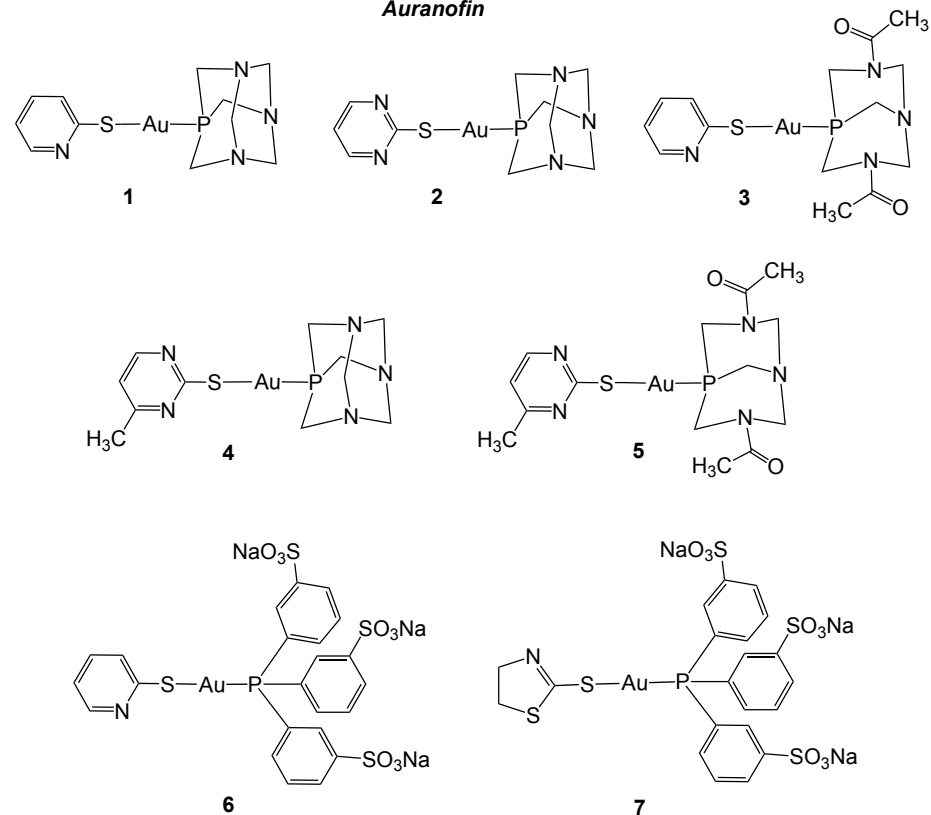
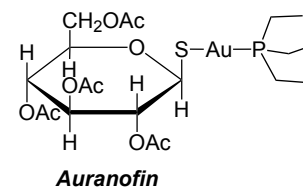
Thioredoxin Reductase Inhibition

A Journal of
1/2010
 ChemPubSoc Europe

The inside cover picture shows the X-ray structure of human thioredoxin reductase dimer (TrxR; PDB: 2I3N; ribbon representation), with the catalytic site residues Sec and Cys highlighted (cyan surface). Enzyme activity assays and biochemical studies identified the Sec-Cys dyad as essential for TrxR inhibition by water-soluble Au^I-phosphine complexes. For more details, see the Full Paper by M. Laguna, P. J. Dyson, et al. on p. 96 ff.

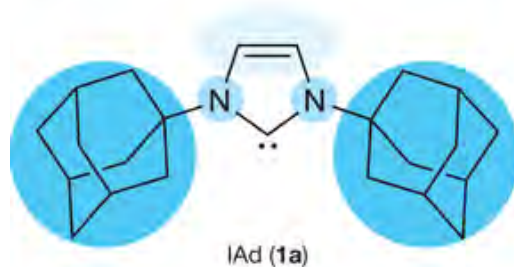
www.chemmedchem.org

WILEY-VCH



Au(I) N-heterocyclic carbenes (NHCs)

a



Backbone

- electronic stabilization from aromaticity
- substituents affect carbene electronics

N-substituent(s)

- kinetic stabilization from steric bulk
- electronic influence
- potential for asymmetric induction

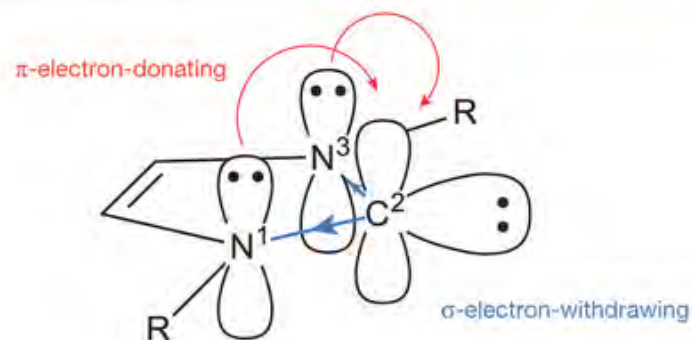
Nitrogen heteroatom(s)

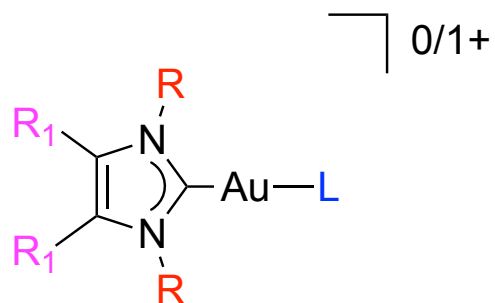
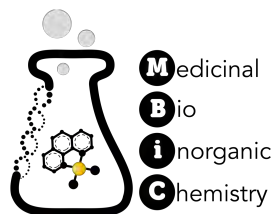
- σ -electron-withdrawing
- π -electron-donating
- inductive and mesomeric stabilization
- number and identity of heteroatoms affects carbene electronics

Ring size

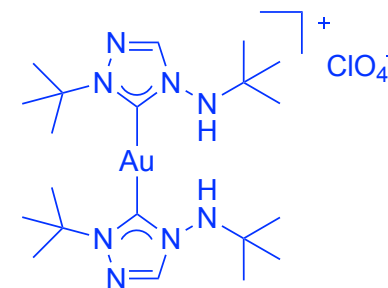
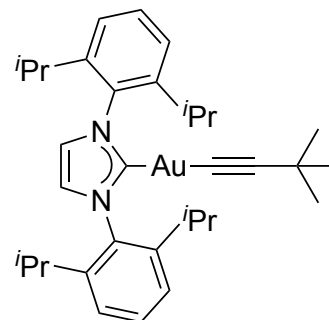
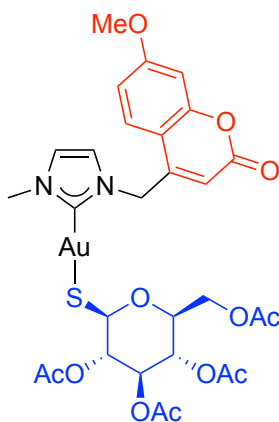
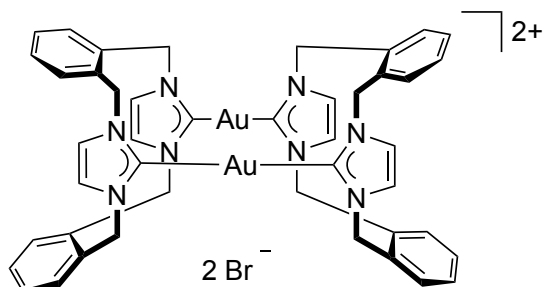
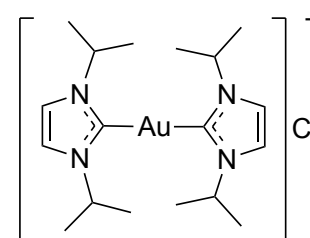
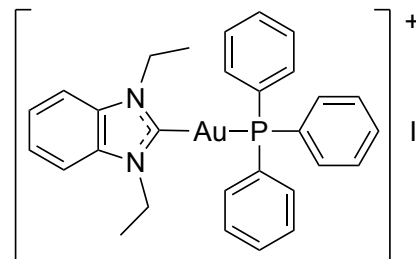
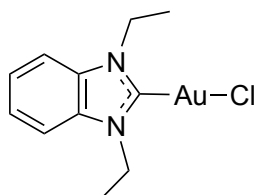
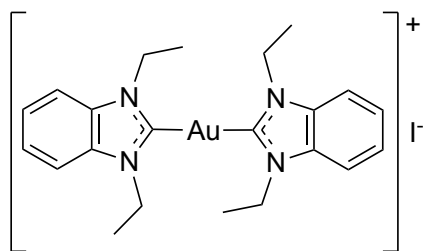
- cyclic structure favours bent singlet ground state
- ring geometry affects sterics and electronics

b

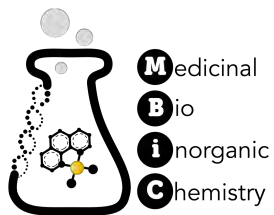




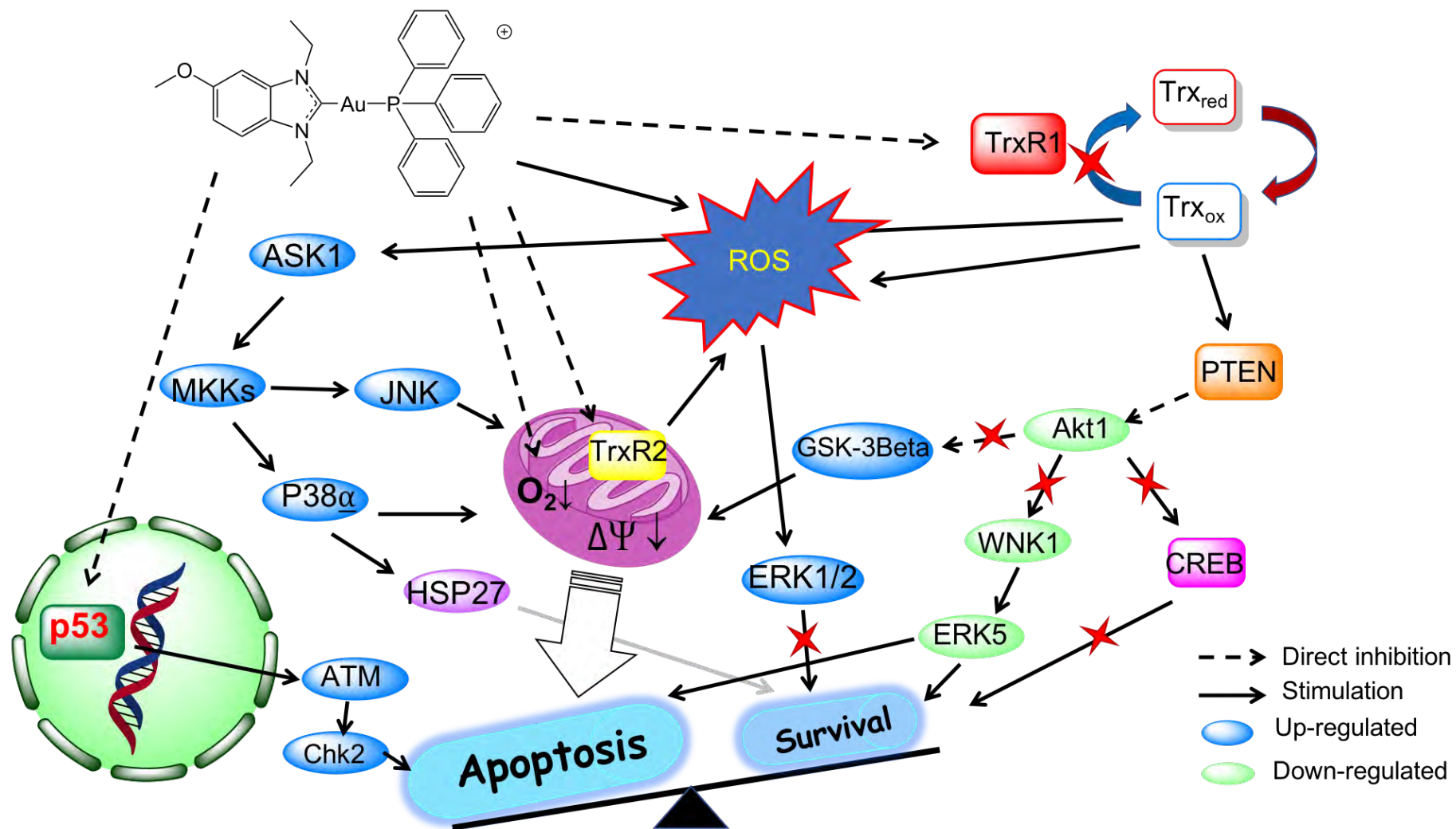
R = Wingtips substituents
 R₁ = Backbone substituents
 L = Ancillary ligand

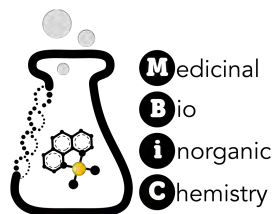


Casini, A., Bonsignore, R. and Oberkofler, J. **2018**. Organometallic gold-based anticancer therapeutics. In: *Reference module in chemistry, molecular sciences and chemical engineering*. Elsevier.

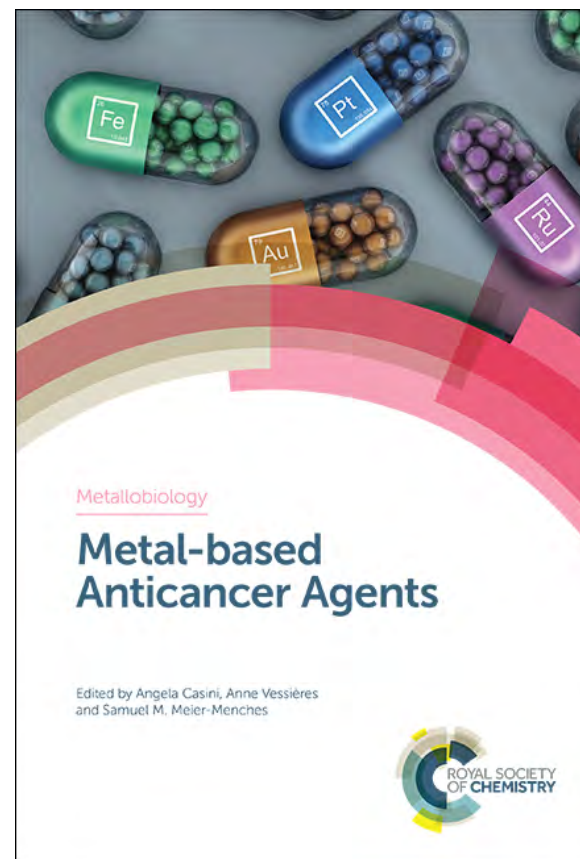
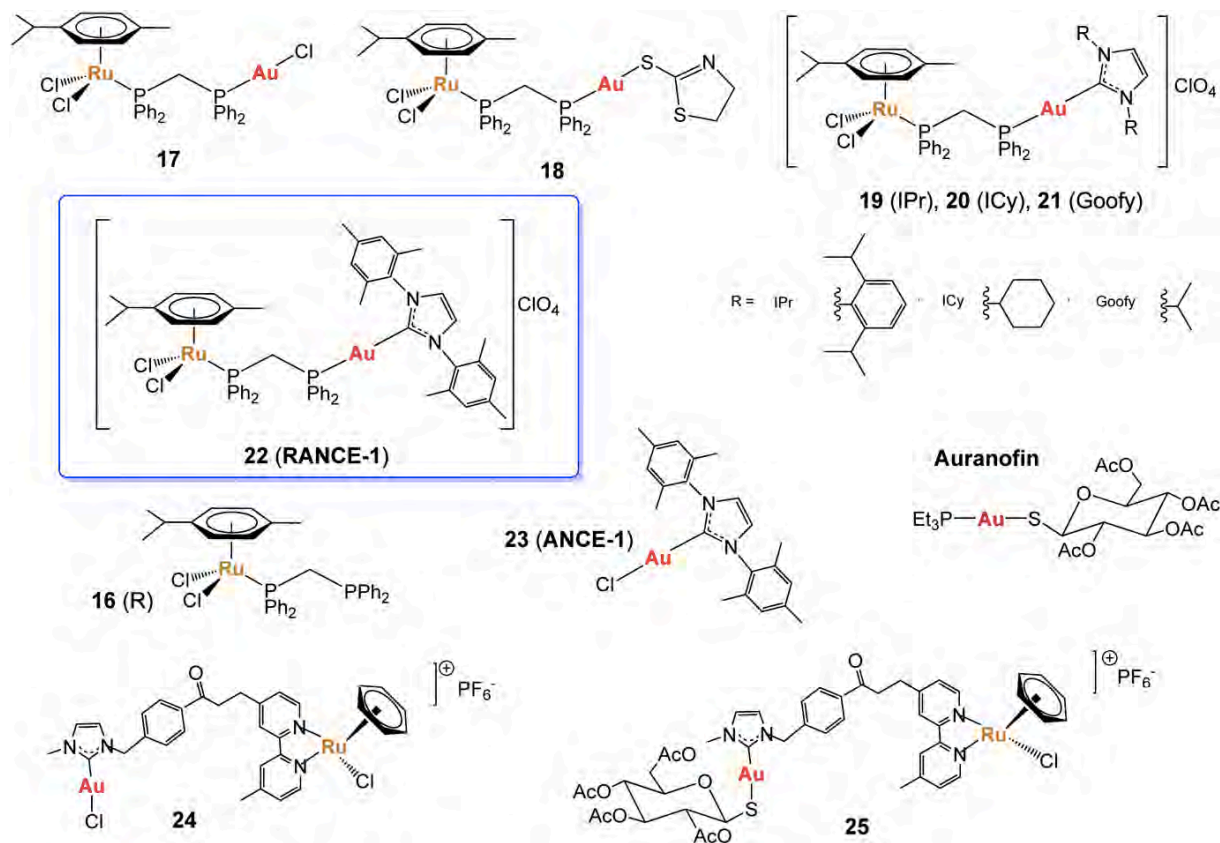


Mechanisms of action of Au(I) NHCs



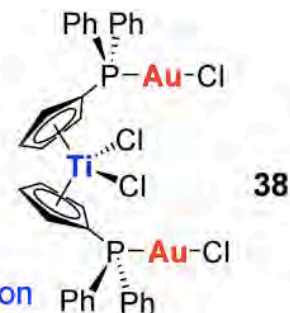
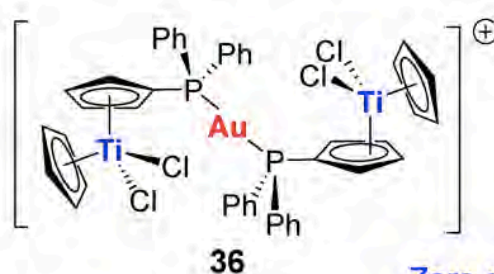
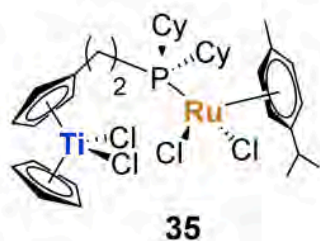
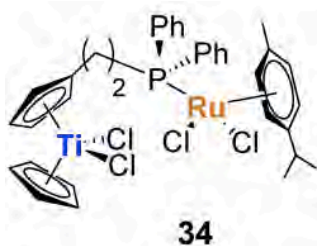


Heteronuclear Au⁺/Ru²⁺ complexes

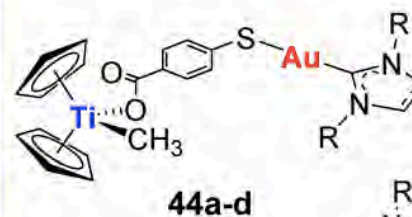
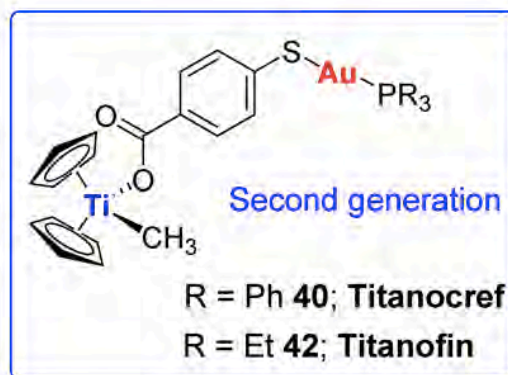
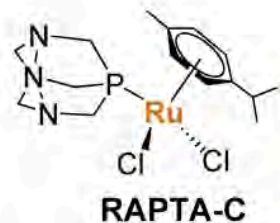
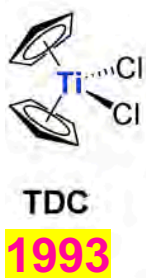


Maria Contel and co-workers, Chapter 6, RSC Book

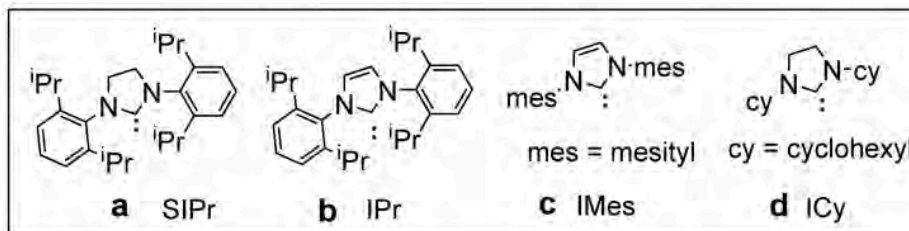
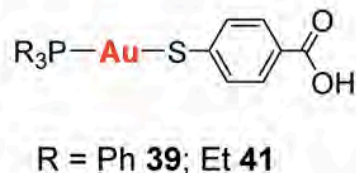
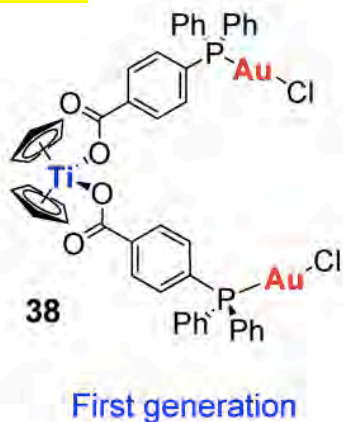
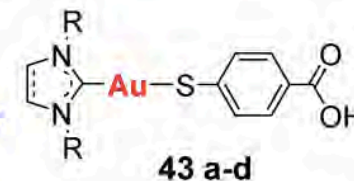
Heteronuclear Au⁺/Ti⁴⁺ complexes

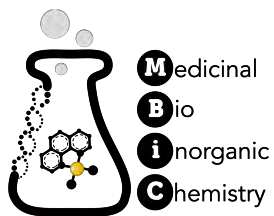


Zero generation

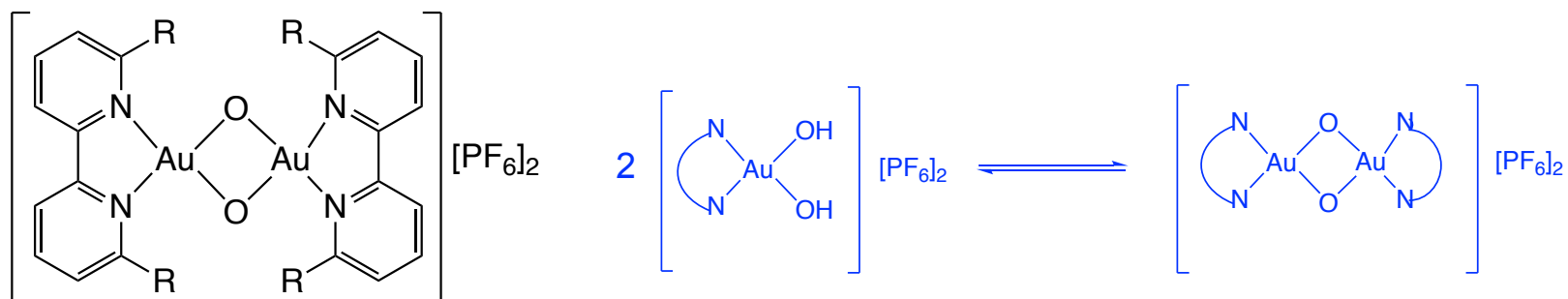


Third generation

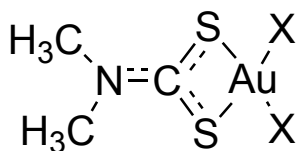




Au(III) coordination complexes

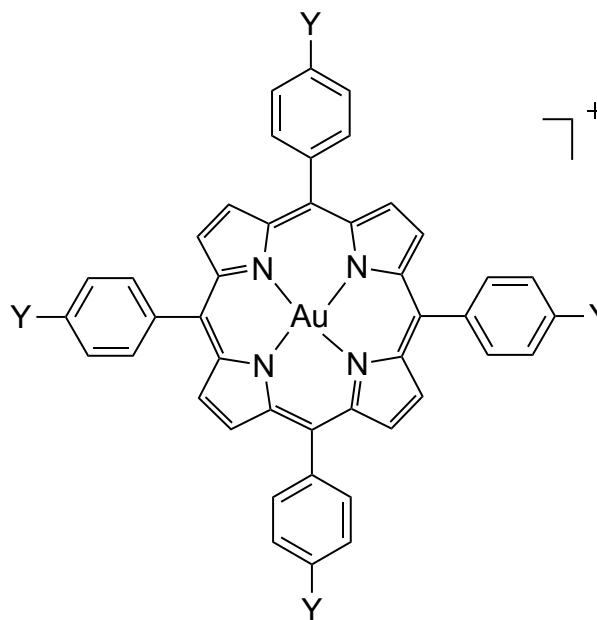


$[\text{Au}_2(\mu\text{-O})_2(\text{bipy})_2](\text{PF}_6)_2$ (**Auoxo1**)
 $[\text{Au}_2(\mu\text{-O})_2(6,6'\text{-Me}_2\text{bipy})_2](\text{PF}_6)_2$ (**Auoxo6**)



X = Cl, $[\text{AuCl}_2(\text{DMDT})]$ **AuL10**
 X = Br, $[\text{AuBr}_2(\text{DMDT})]$ **AuL14**

Fregona and coworkers



Y = H (**Gold 1a**)
 = Me
 = OMe
 = Br
 = Cl

Che and coworkers

Cyclometalated Au(III) complexes

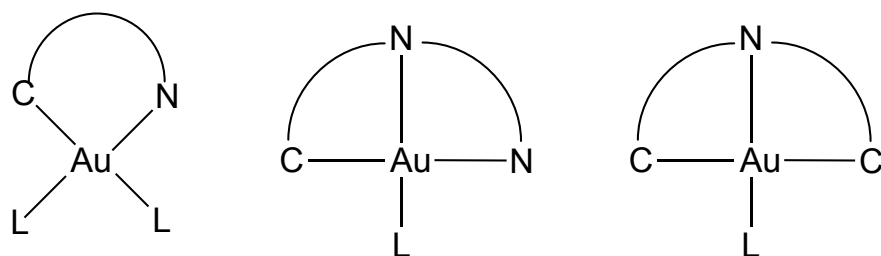
Gold(III)

International Edition: DOI: 10.1002/anie.201607225
 German Edition: DOI: 10.1002/ange.201607225

Cyclometalated Gold(III) Complexes: Synthesis, Reactivity, and Physicochemical Properties

*Roopender Kumar and Cristina Nevado**

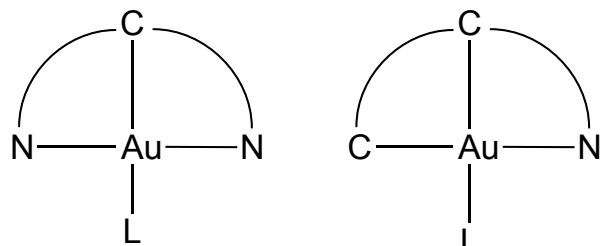
Keywords:
 coordination chemistry ·
 cyclometalation · gold



$C^{\wedge}N$

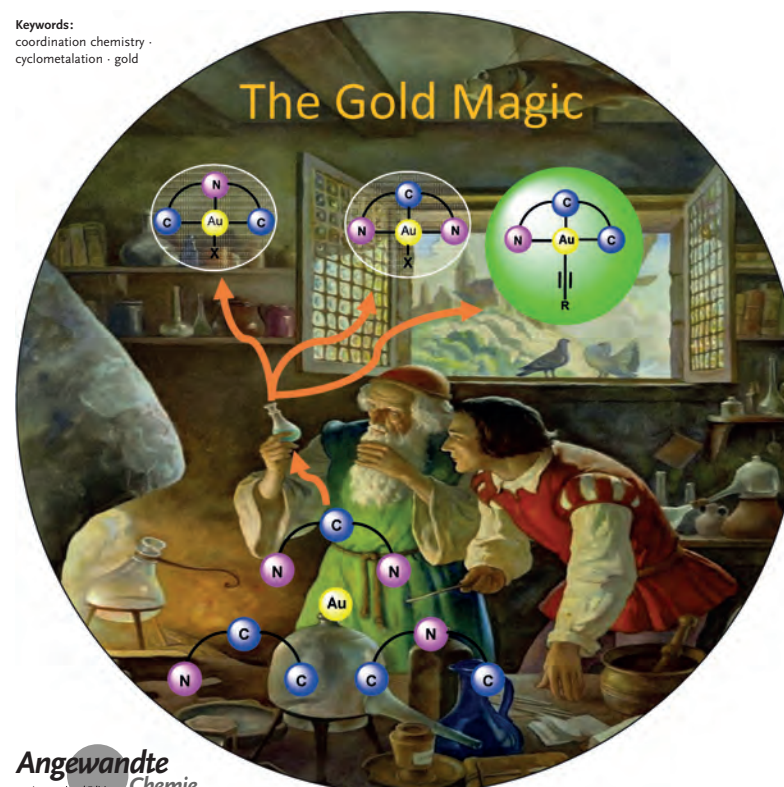
$C^{\wedge}N^{\wedge}N$

$C^{\wedge}N^{\wedge}C$



$N^{\wedge}C^{\wedge}N$

$C^{\wedge}C^{\wedge}N$

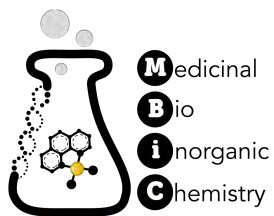


Angewandte
 International Edition
Chemie

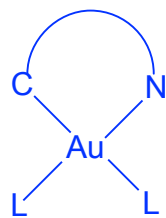
1994 www.angewandte.org

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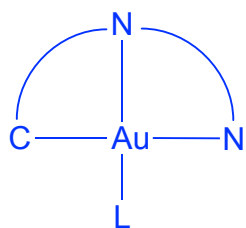
Angew. Chem. Int. Ed. 2017, 56, 1994–2015



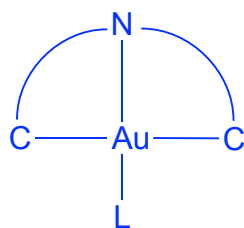
Cyclometalated Au(III) complexes



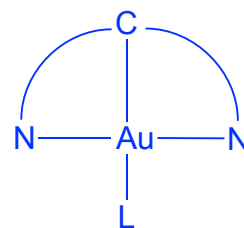
C^N



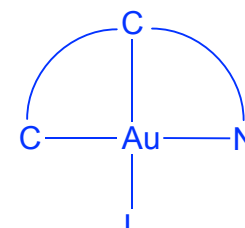
C^N^N



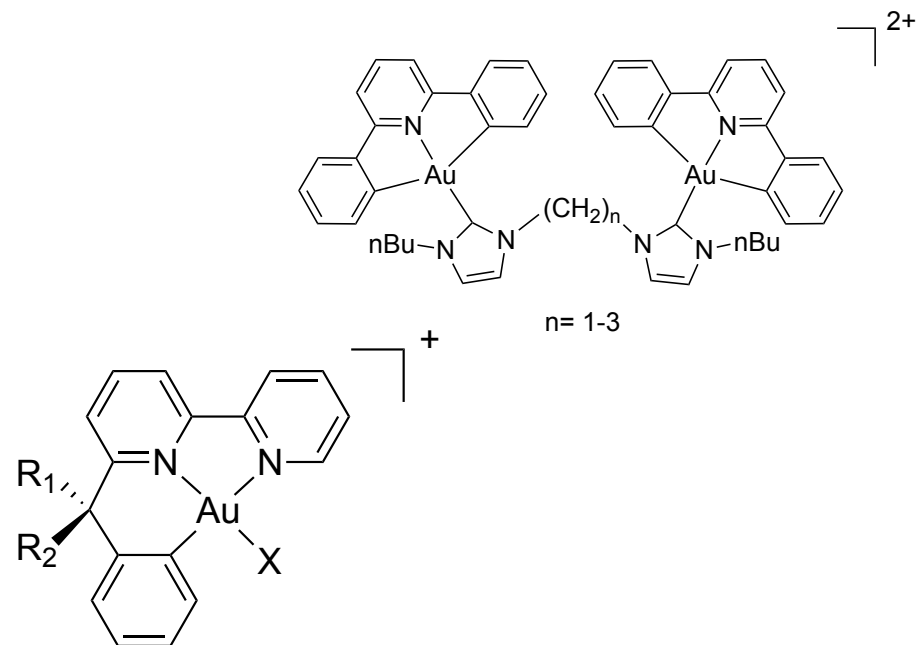
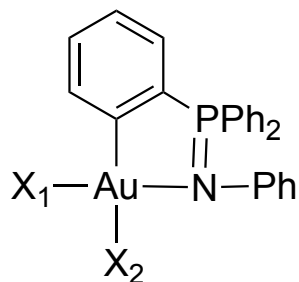
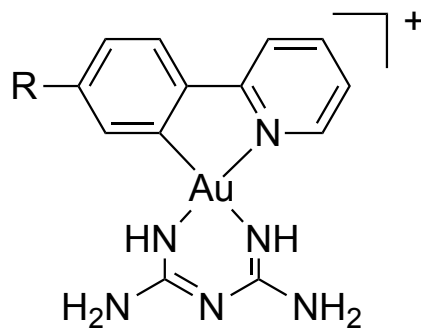
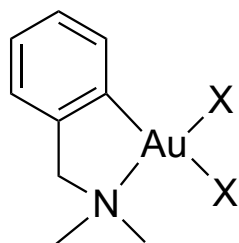
C^N^C



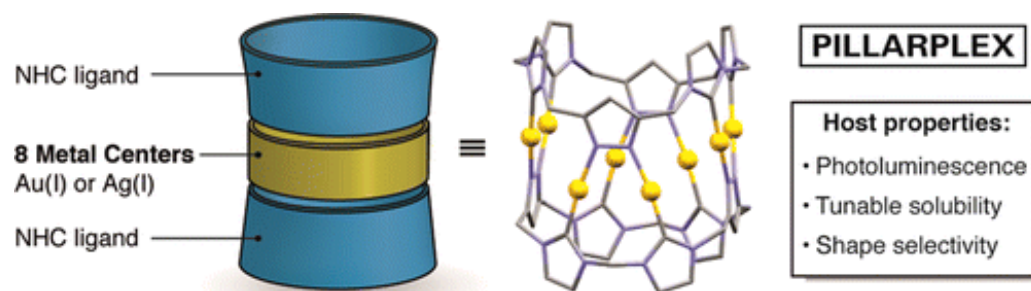
N^C^N



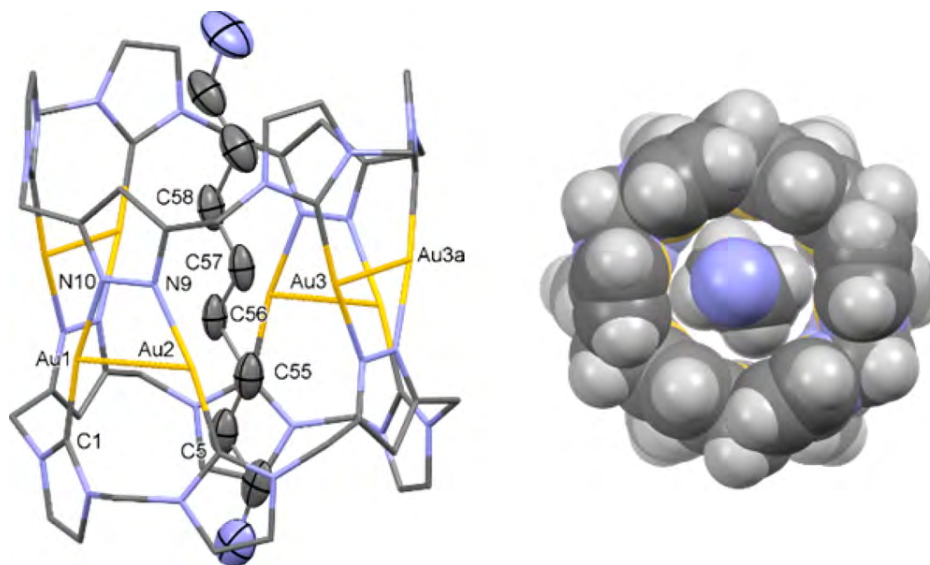
C^C^N



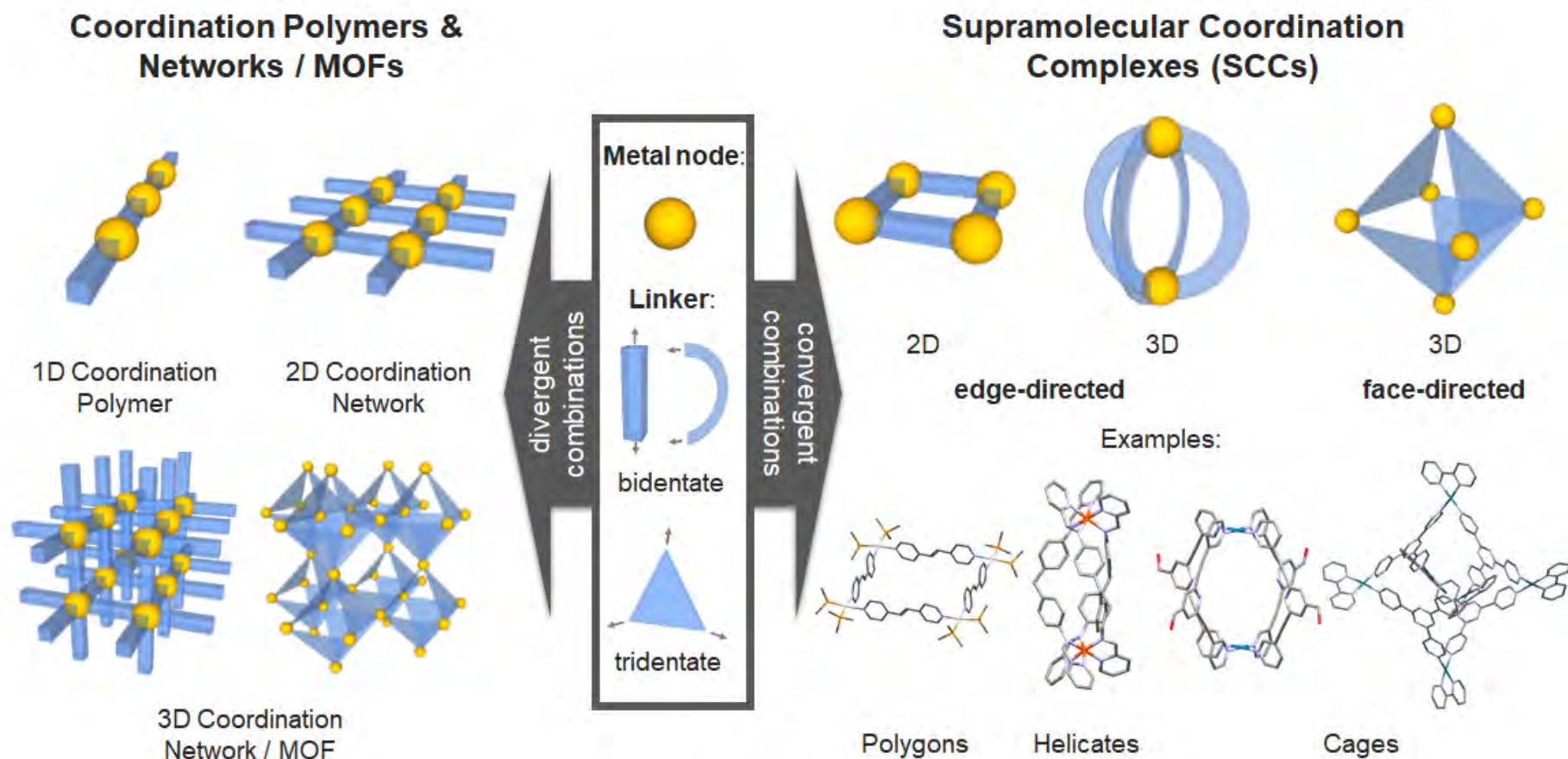
Supramolecular metal-based complexes



Metallocavitand with tubular cavity for supramolecular complexation



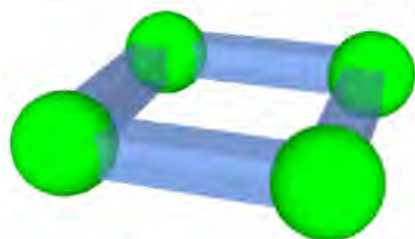
Supramolecular metal-based systems



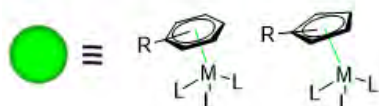
Theranostics, **2019**, 9, 3150-3169.
Inorg.Chem., **2017**, 56, 14715-14729.

Organometallic Supramolecular Coordination Complexes

Organometallic Node

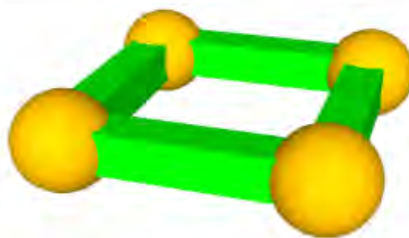


Examples:

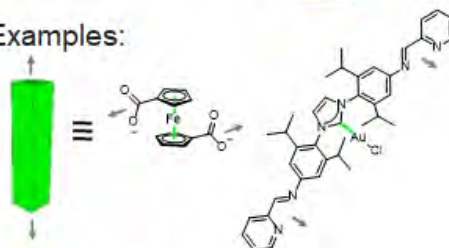


→ influence on
node directionality

Organometallic Linker

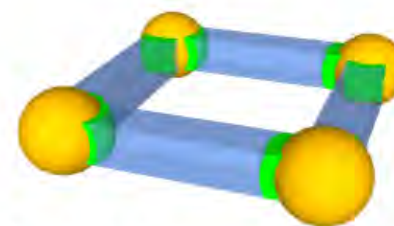


Examples:

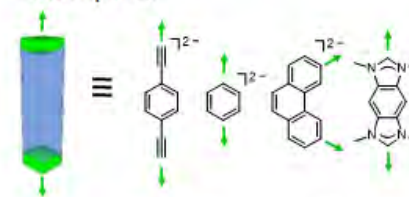


→ influence on
linker properties

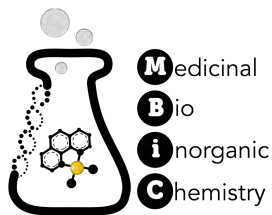
Organometallic Assembly



Examples:

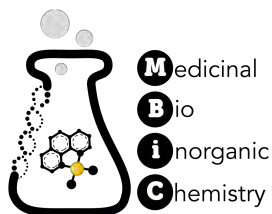


→ influence on
assembly

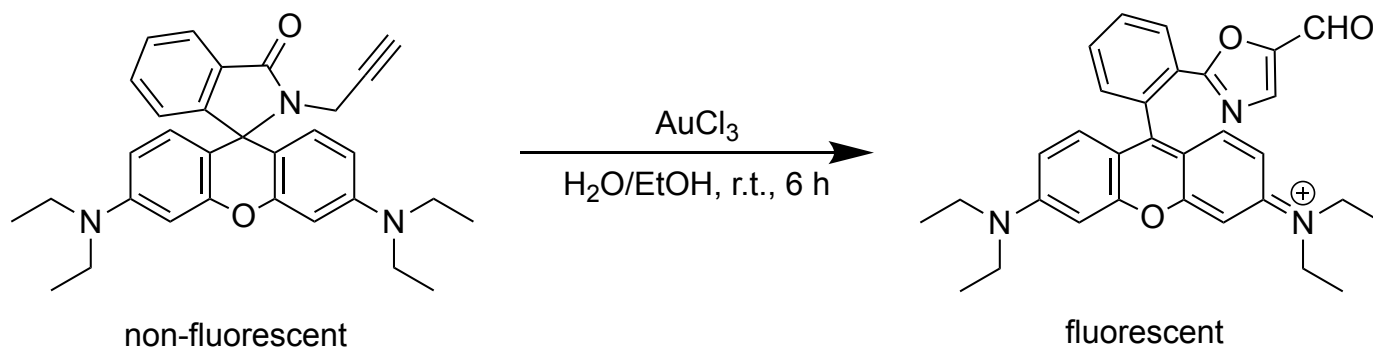


Can we use metal (gold) compounds as therapeutic catalysts in cells?

- Bio-orthogonal modifications of biomolecules
- Pro-drug activation

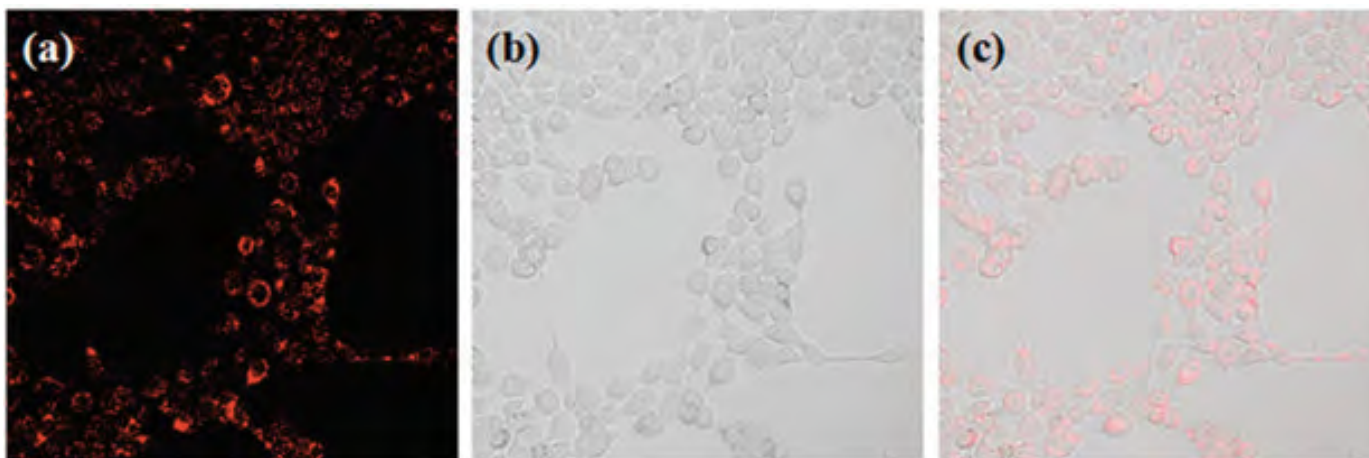


Sensors for Au(III) ions in biological environment



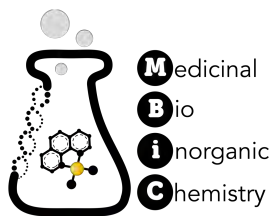
1 + Au³⁺

- Au(III)-induced intramolecular oxa-cyclization from propargylamide to oxazolecarbaldehyde.



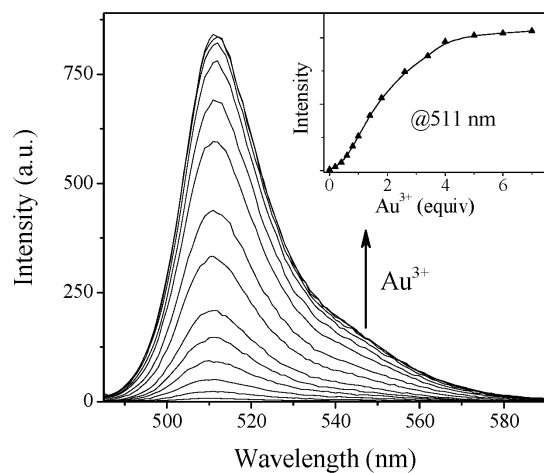
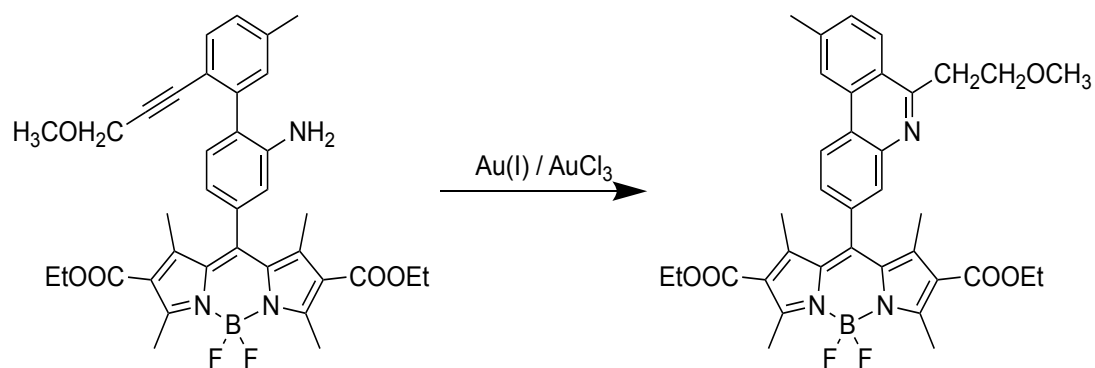
HaCaT
cells

Yoon J and co-workers, *Chem. Commun.* **2009**, 7218-7220.

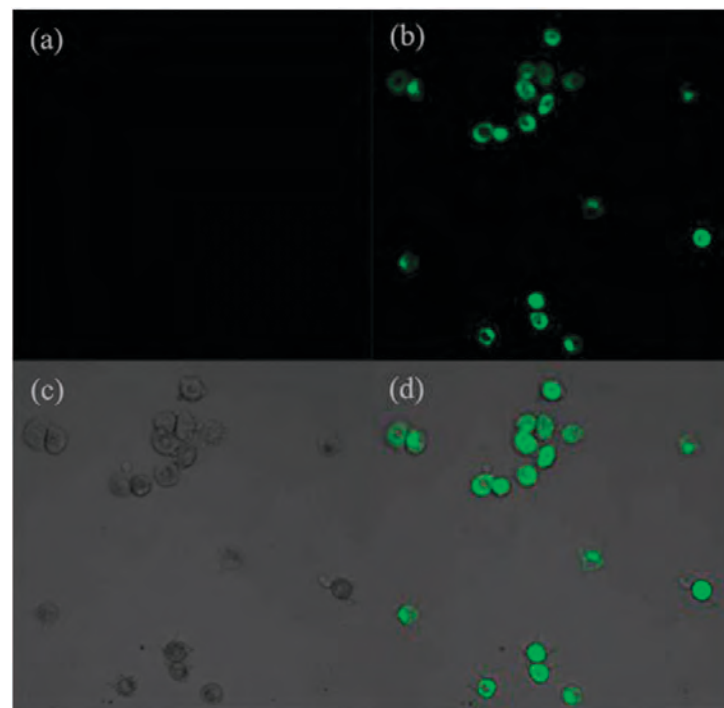


Sensors for Au(III)/Au(I) ions in biological environment

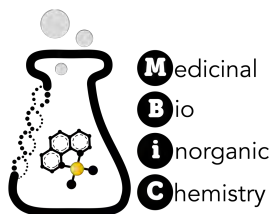
hydroamination



HeLa cells

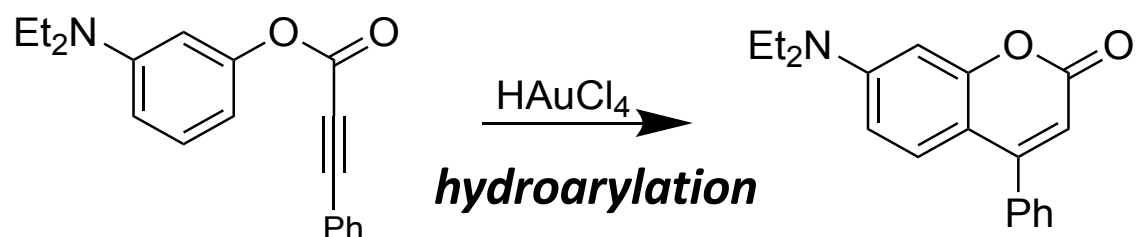


Song QH and co-workers, *Chem. Commun.* **2012**, 48:744–746.

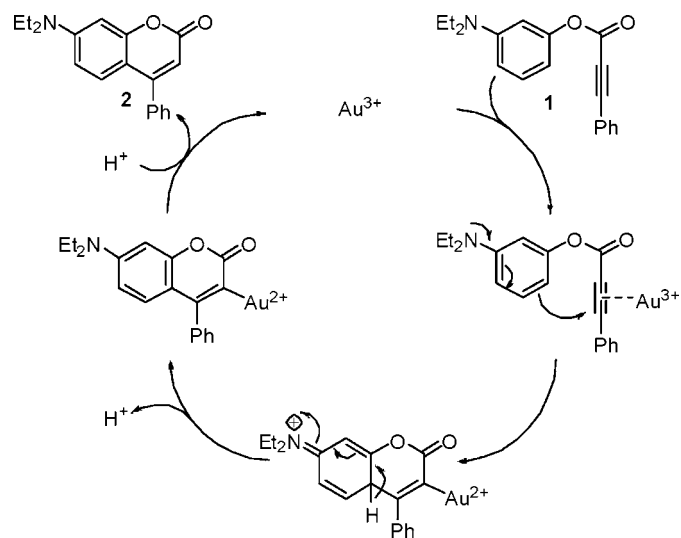


Sensors for Au(III) ions in biological environment

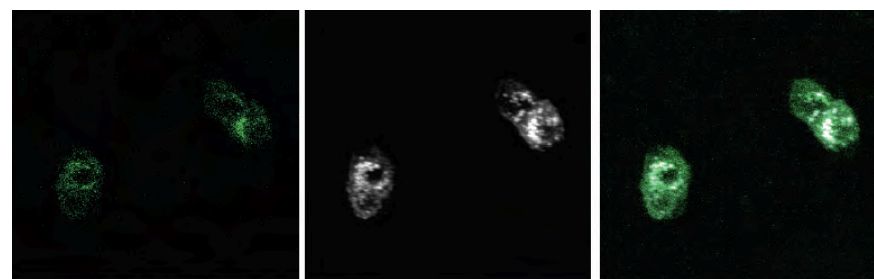
C-C cross coupling



fluorescent



HaCaT cells



A

B

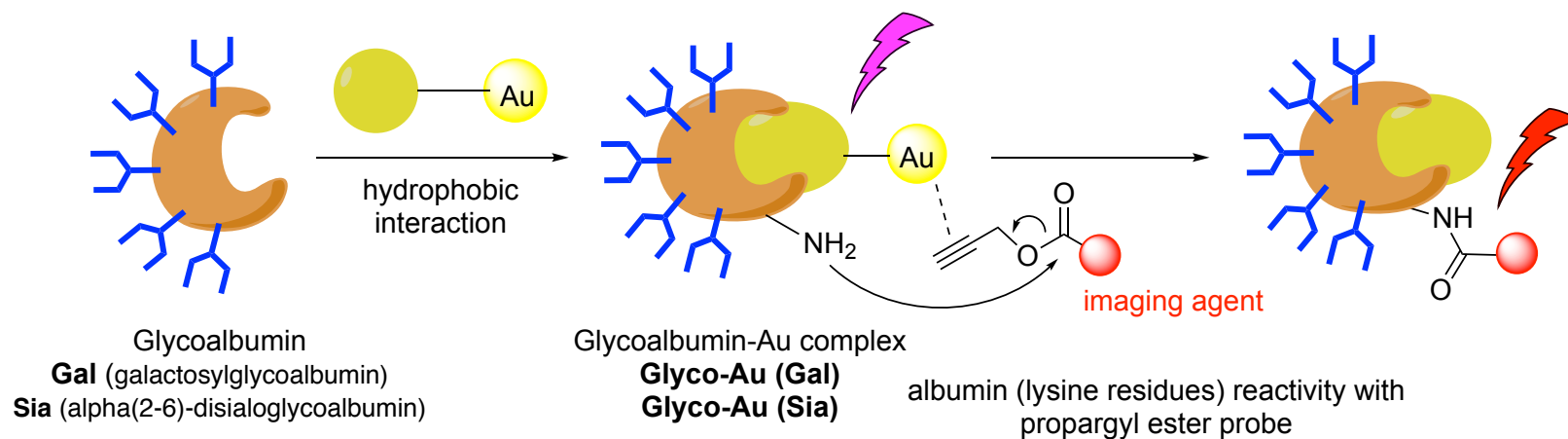
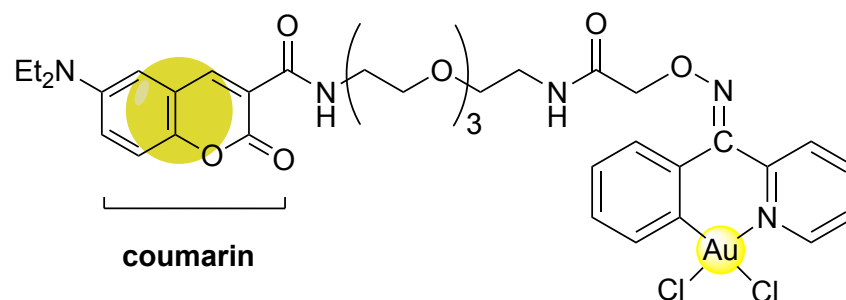
C

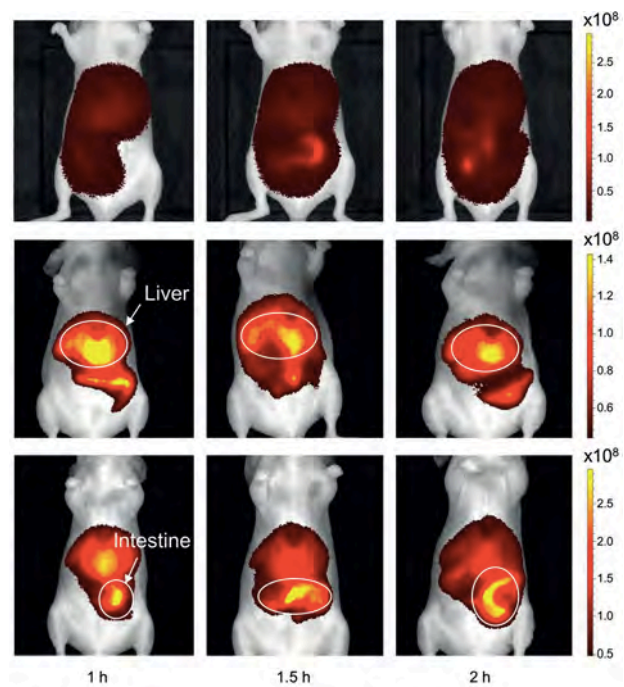
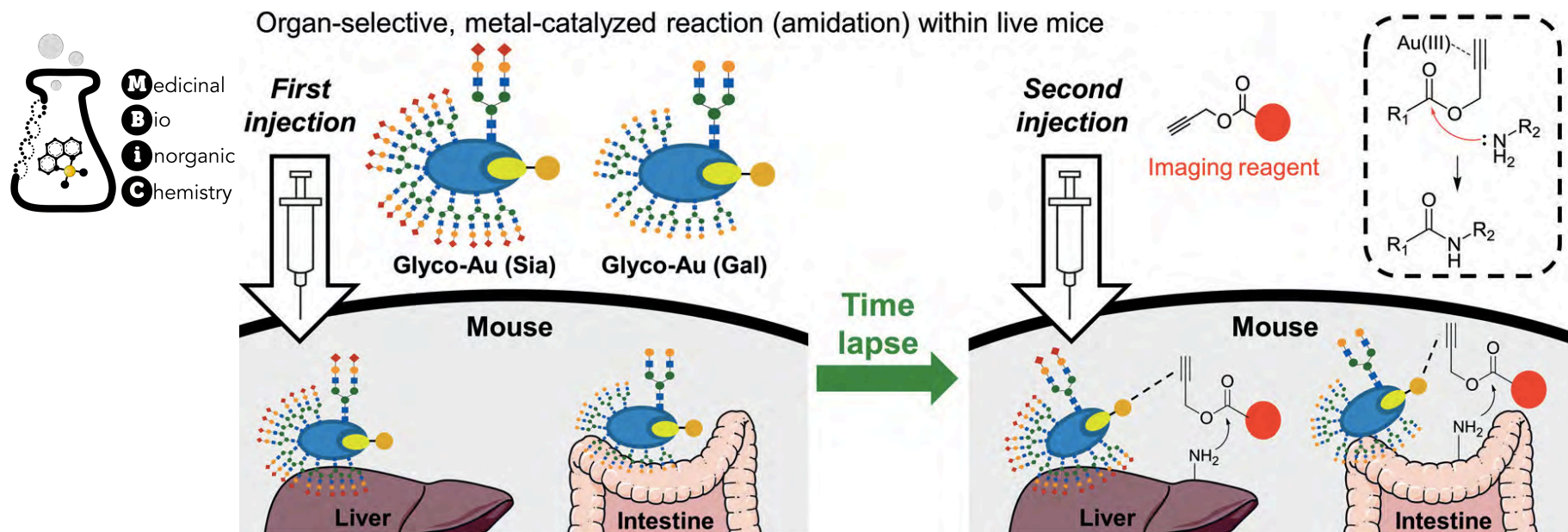
incubation with Au(III) ions (10 μM) and 10 min with substrate (50 μM) in PBS buffer

Kim H and coworkers, *Org Lett* **2010**, 12:932–934.

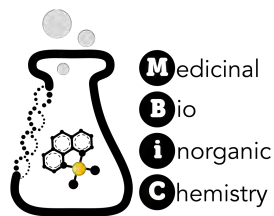
In Vivo Gold Complex Catalysis

Au(III)-mediated ester amidation





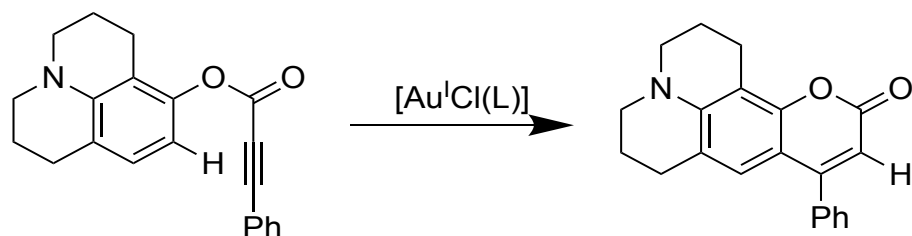
Tanaka and co-workers, *Angewandte Chemie Int Ed* **2017**, 56:3579–3584.



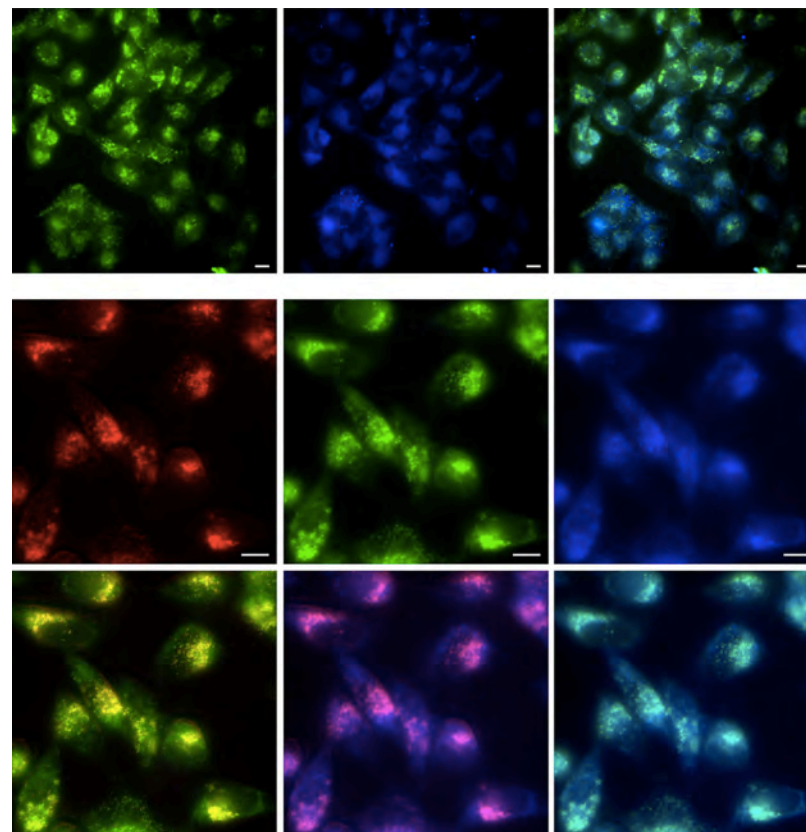
Au(I)-mediated biorthogonal reactions in cells

C-C cross coupling

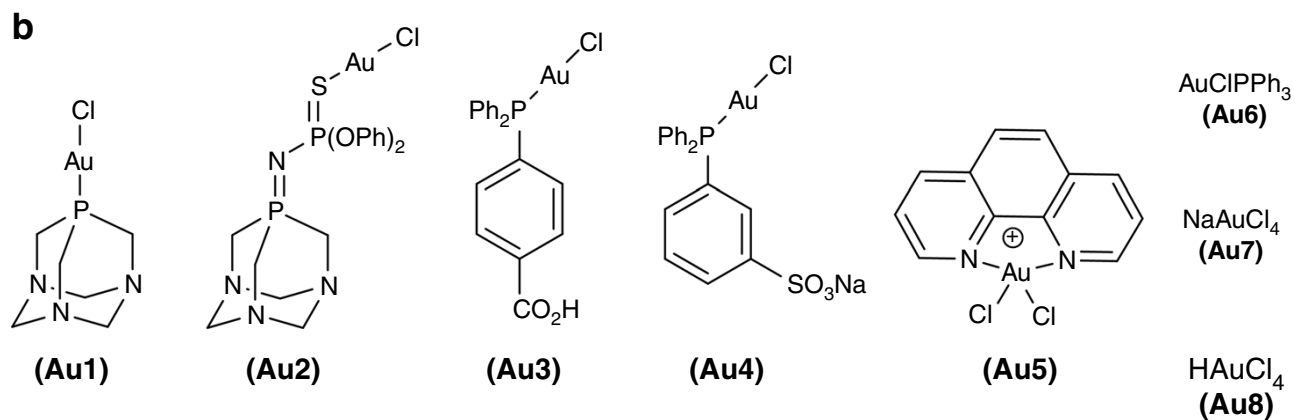
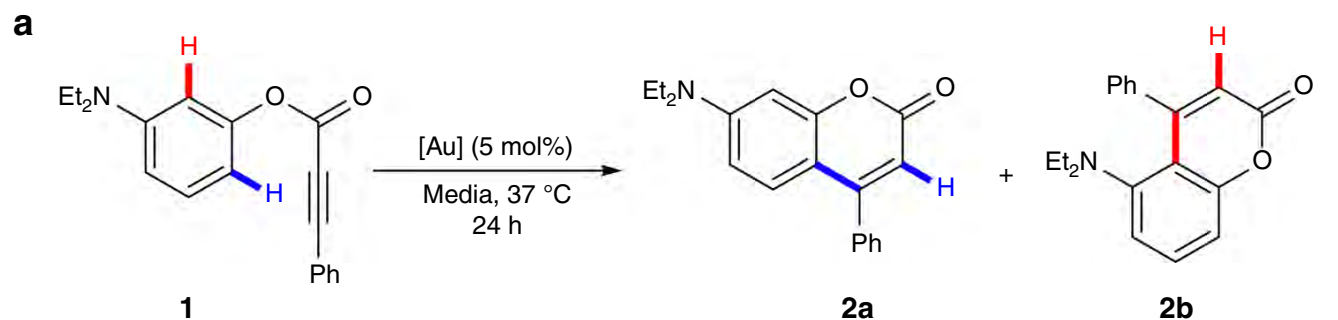
Au(I)-mediated hydroarylation

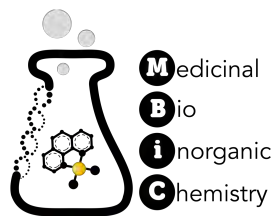


- Cells were incubated in DMEM with the gold complex (50 μM in DMSO) for 30 min, followed by two washings with DMEM and treatment with substrate (100 μM) for 6 h.

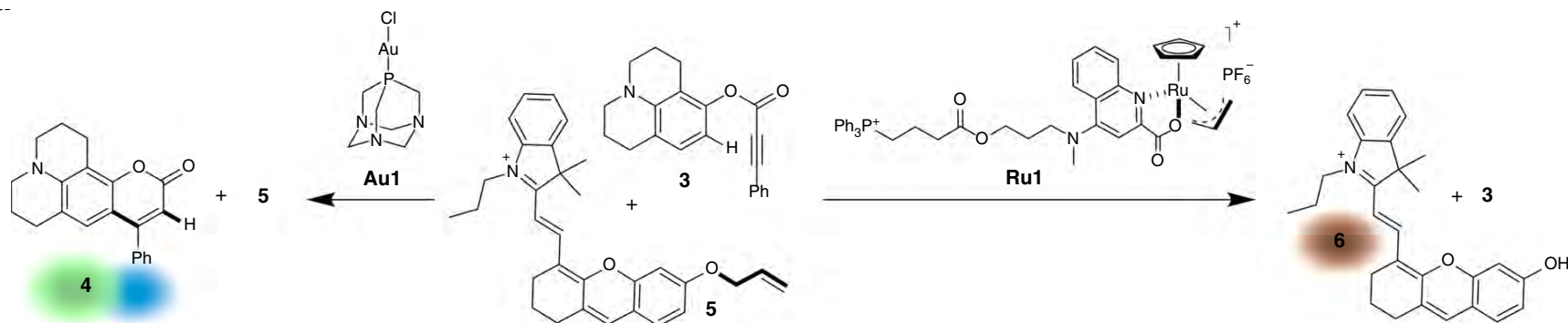
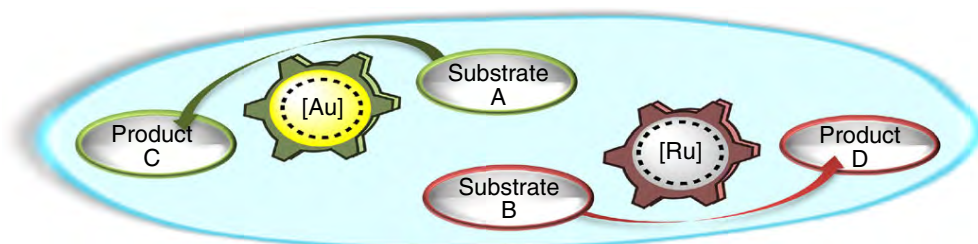


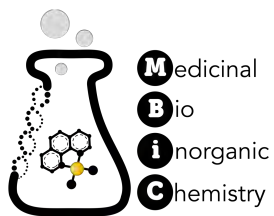
Some optimization....





Concurrent Au(I) and Ru(II) catalysis in cells

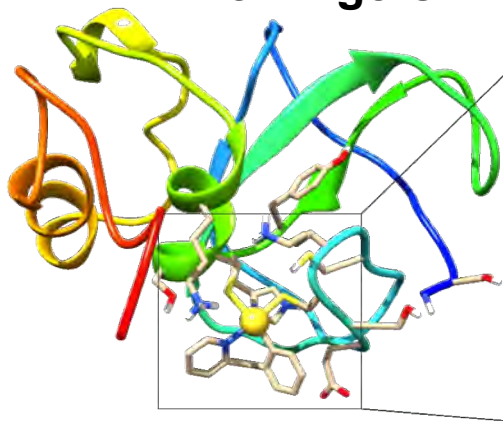




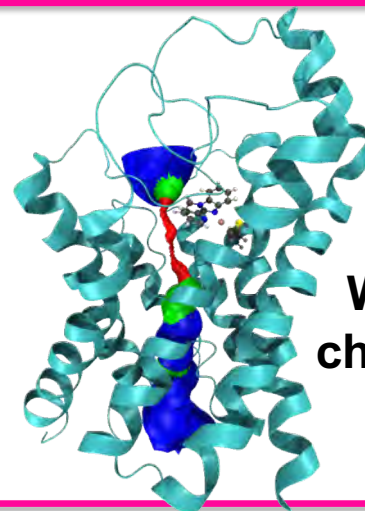
Targeted therapeutics

Chemical probes

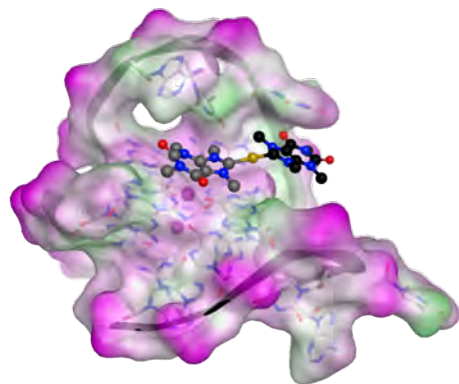
Zinc Fingers



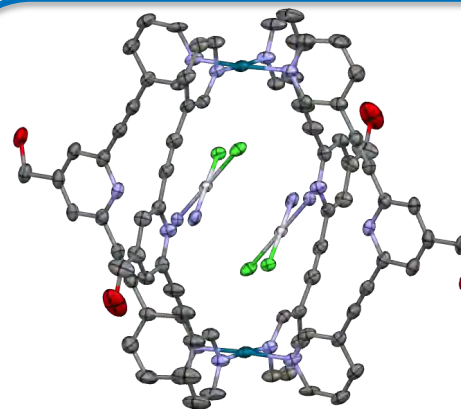
Water channels



DNA G-quadruplexes

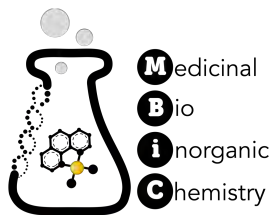


Metallacages

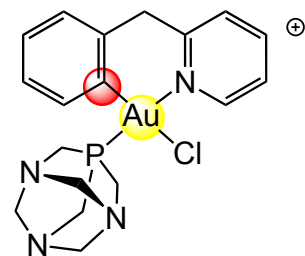
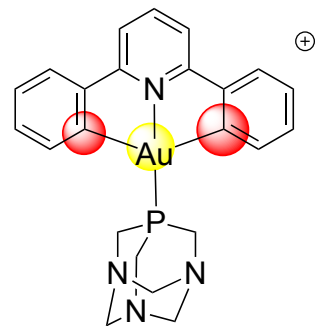
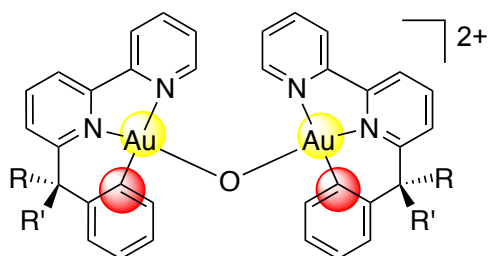
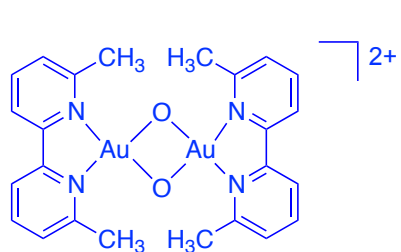


Drug delivery

Imaging agents



GOLD COMPOUNDS



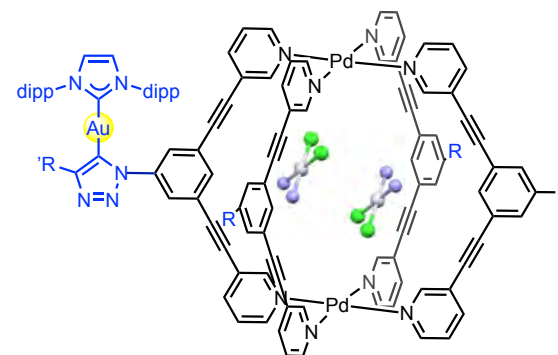
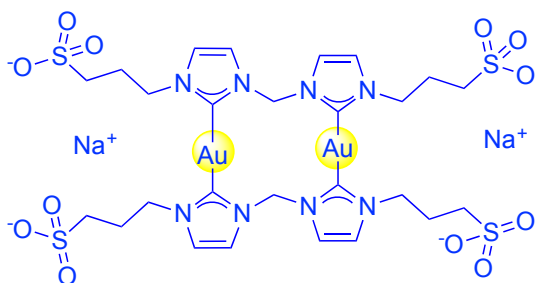
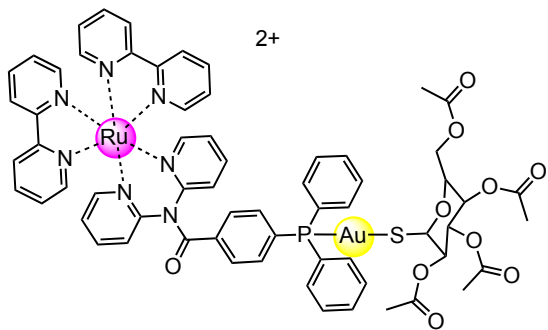
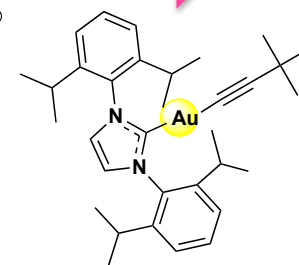
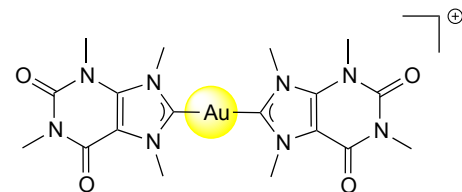
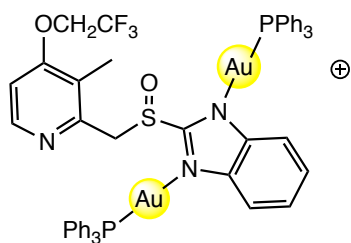
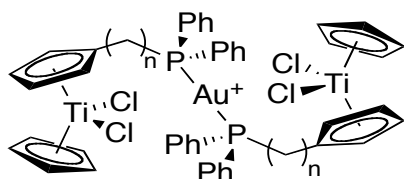
2006

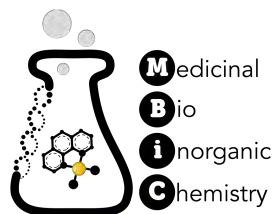
2008

2010

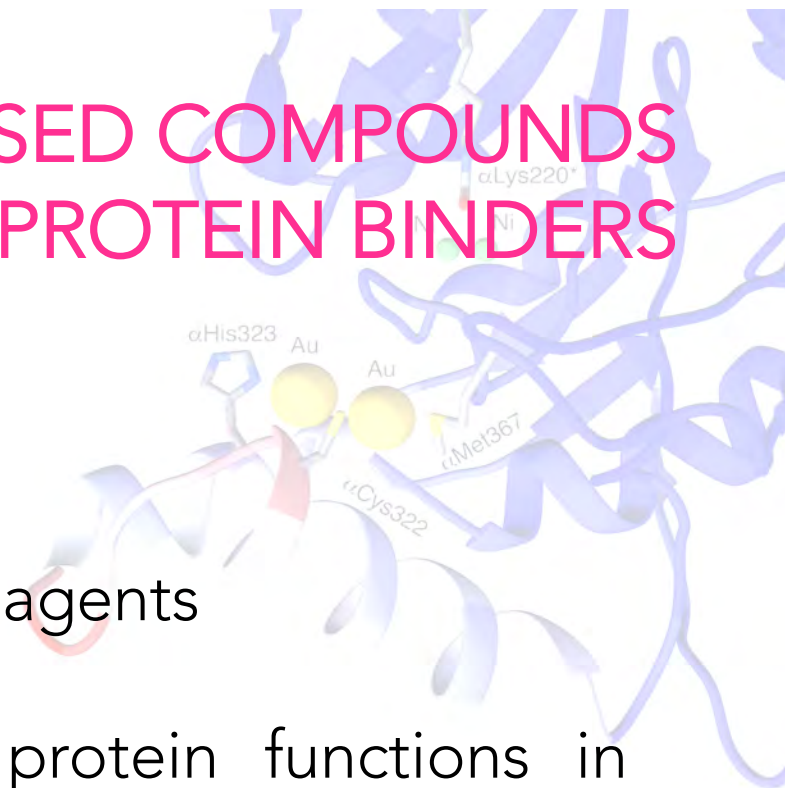
2014

2019

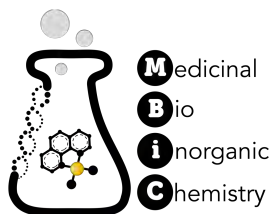




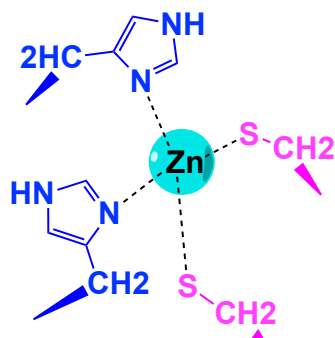
GOLD-BASED COMPOUNDS AS SELECTIVE PROTEIN BINDERS



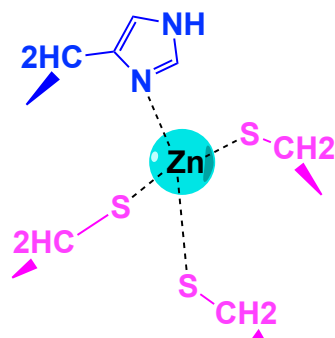
- ❑ New Therapeutic (anticancer) agents
- ❑ Chemical probes to study protein functions in biological systems
- ❑ Selective bio-orthogonal modification of proteins



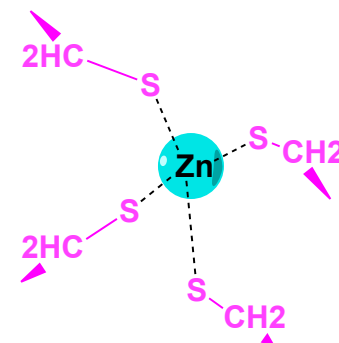
ZINC FINGER PROTEINS



Cys₂His₂

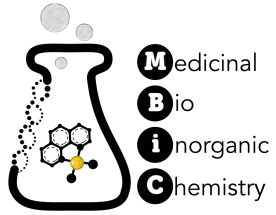


CysHisCys₂



Cys₄

- ❑ Functional ZFs recognize specific DNA, RNA, or protein targets
- ❑ Zinc finger structures are as diverse as their functions
- ❑ 14 classes of ZFs are differentiated by ligand set (number of Cys and His residues), spacing (number and type of amino acids between each Cys and His)

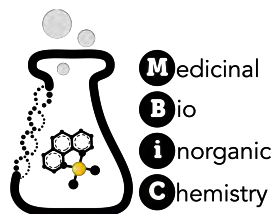


Fundamental cellular processes

Development

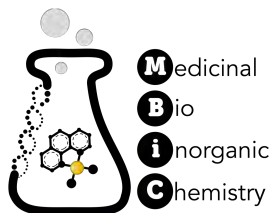
Differentiation

Tumor suppression



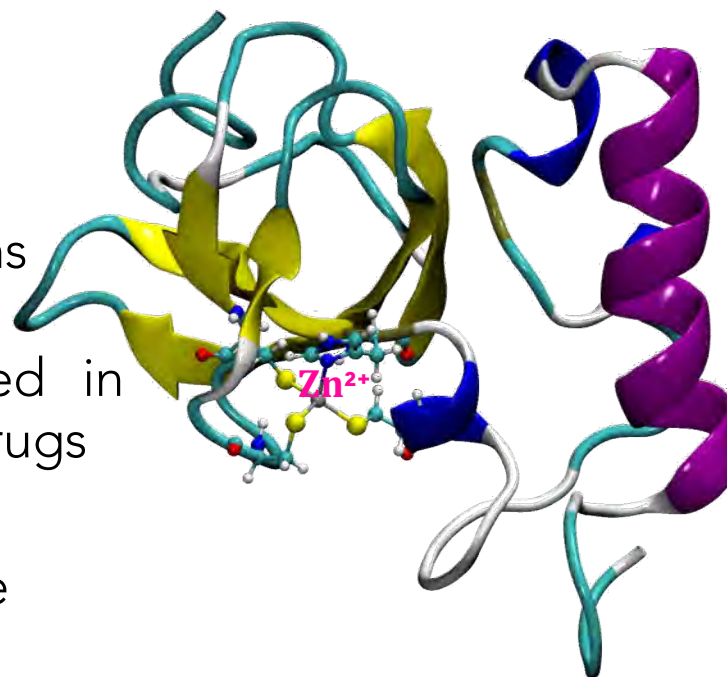
Zinc finger proteins

Zinc finger motif	Representative proteins	Biological Functions
Cys ₂ His ₂	Transcription factors (e.g. TFIIIA, Sp1, NGFI-A) WT1	Gene regulation Tumor suppressor protein
Cys ₄	Hormone receptors (e.g. ER, GR, TR, RAR, VDR) XPA, Fpg	Receptor proteins, gene regulation DNA repair
Cys ₃ His	Retroviral nucleocapsid proteins (e.g. NCp7) PARP-1	RNA packaging DNA repair, apoptosis
RING finger	BRCA-1, Mdm2	DNA repair Ubiquitin protein ligase, p53 regulation



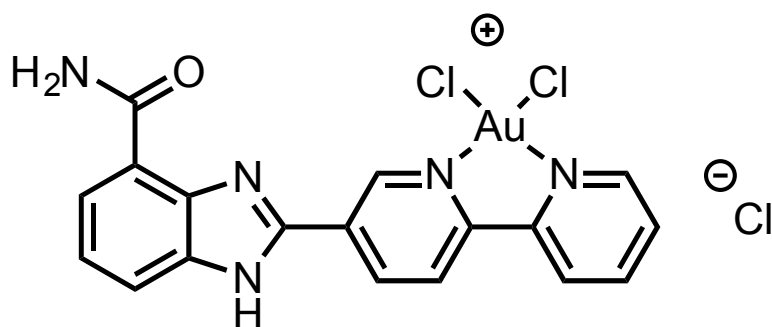
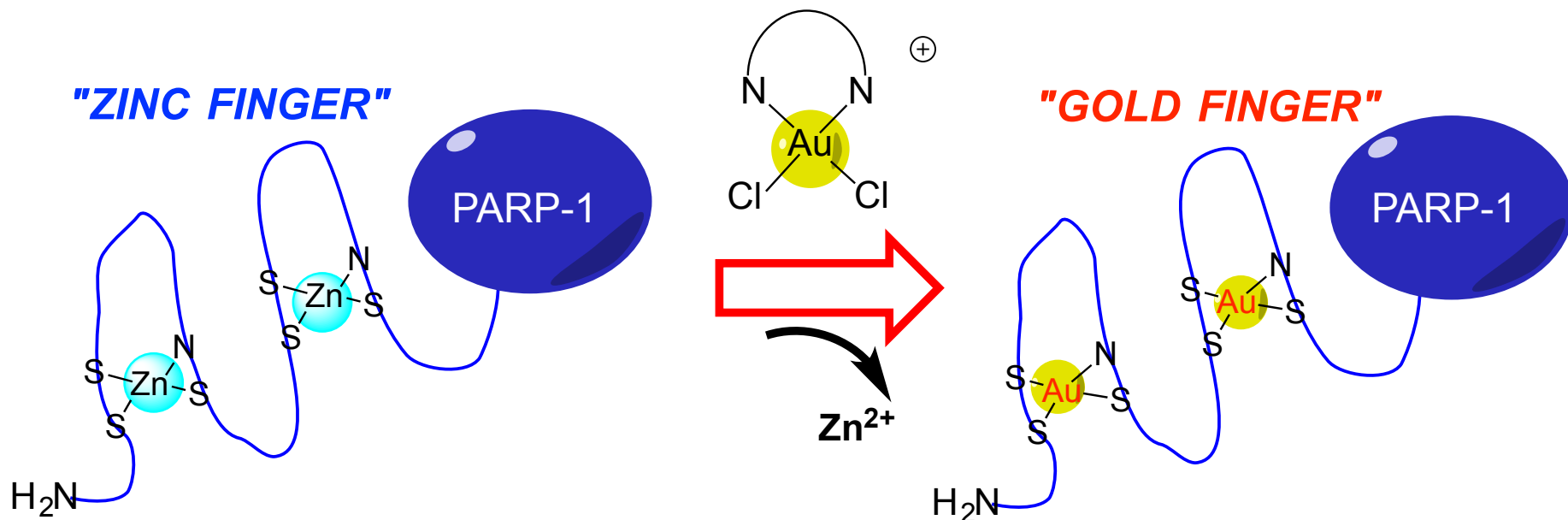
The “Guardian Angel” of DNA: PARP-1

- ❑ Playing an important role in DNA repair
- ❑ Involved in cisplatin resistance mechanisms
- ❑ PARP-1 inhibitors have been considered in combinatorial therapies with anticancer drugs
- ❑ Two N-terminal zinc finger domains of the type $\text{Cys}_2\text{HisCys}$

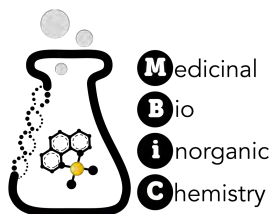


- ❑ *Au(III) compounds with N-donor ligands are potent PARP-1 inhibitors (IC_{50} nM level)*
- ❑ *Au(I) compounds are active but less effective than Au(III)*

What is the mechanism of inhibition?

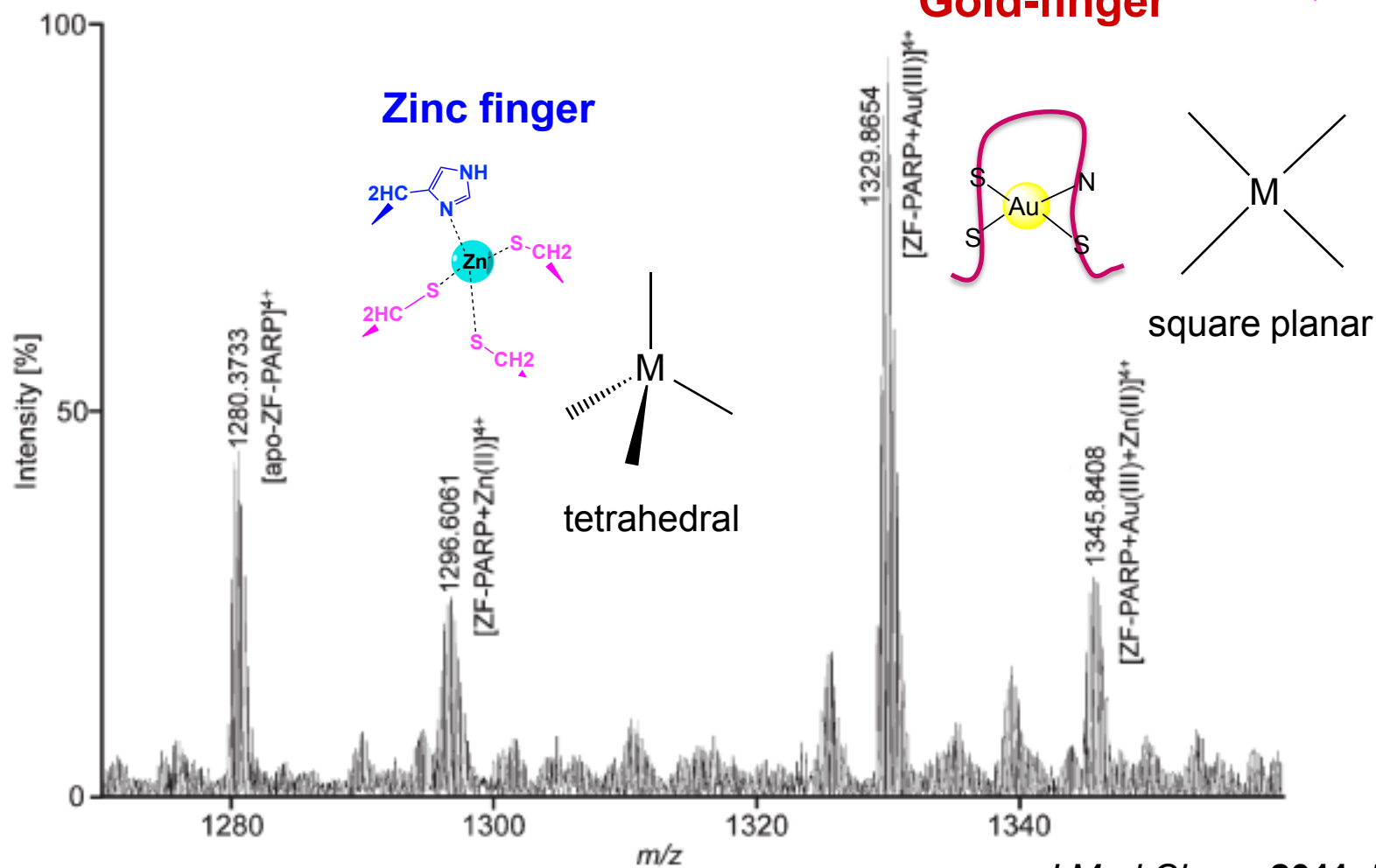
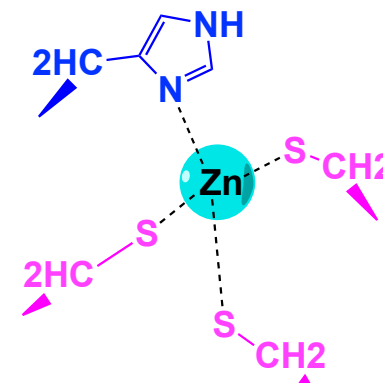


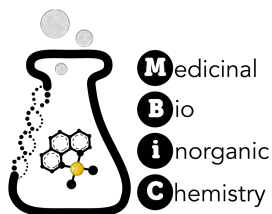
J. Med. Chem. **2011**, 54, 2196-2206.
RSC Adv., **2016**, 6, 79147-79152



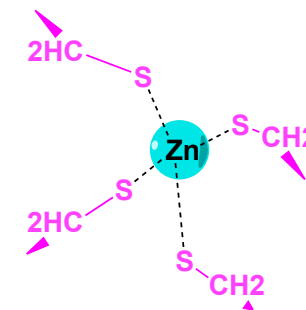
high-resolution FT-ICR MS

Au(III) complex vs ZF-PARP-1

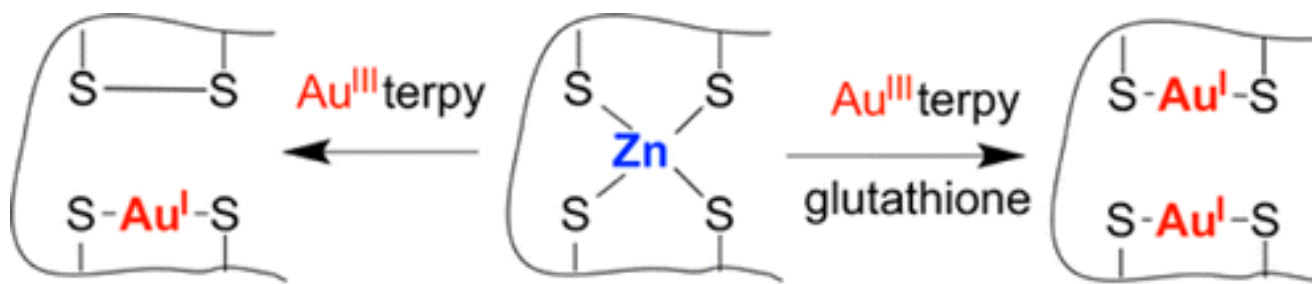
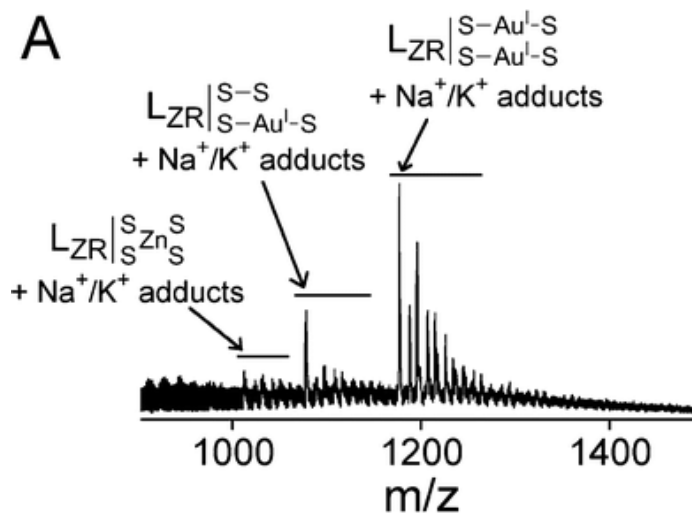
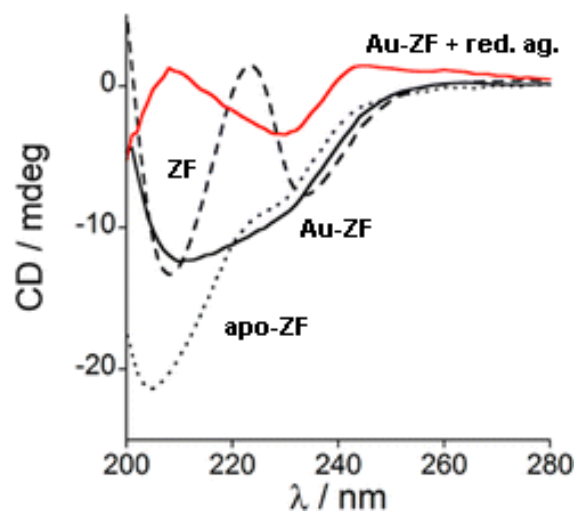
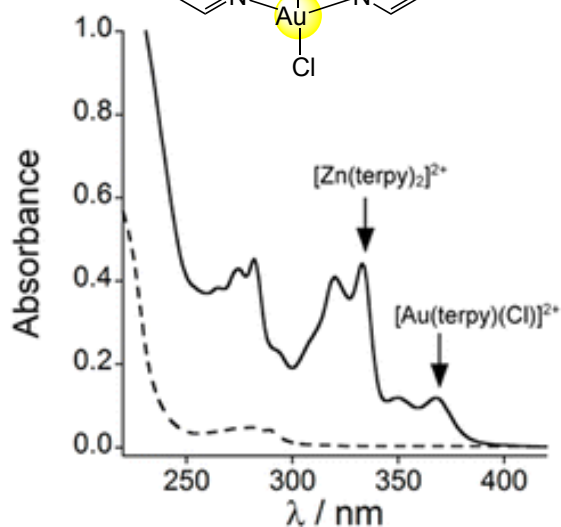
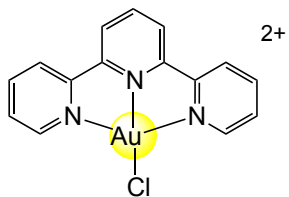


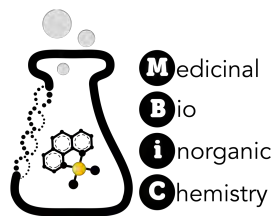


UV-vis, CD, HPLC, ESI-MS and XAS Au(III) complex vs Cys₄



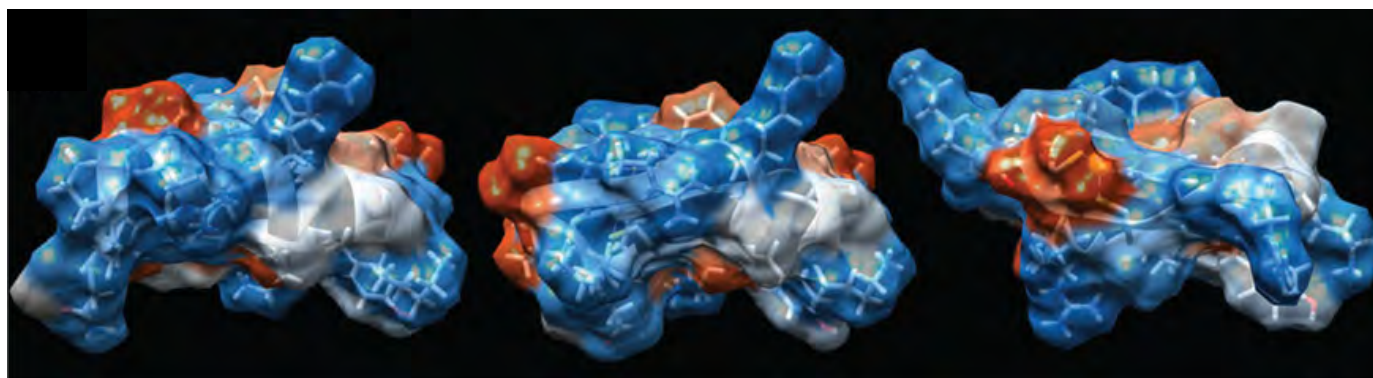
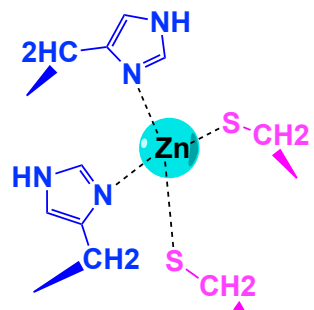
Collaboration with Prof. JM Latour - CNRS

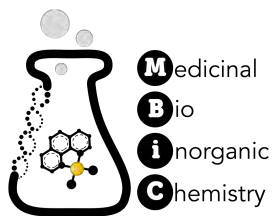




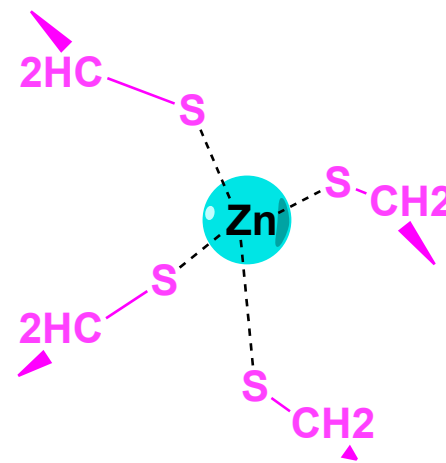
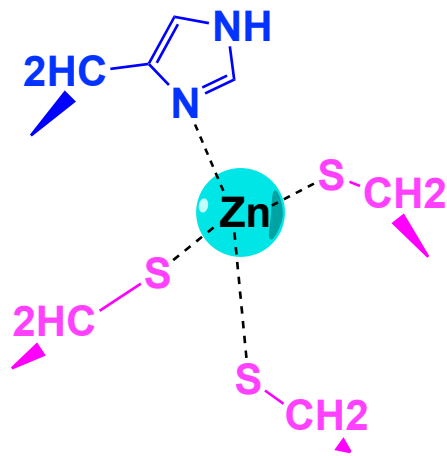
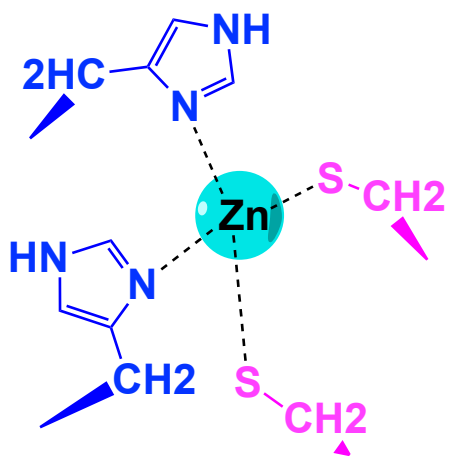
in silico: QM/MM

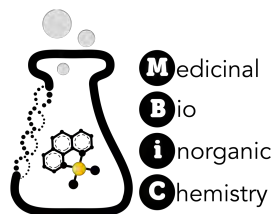
Au(III) vs Au(I)



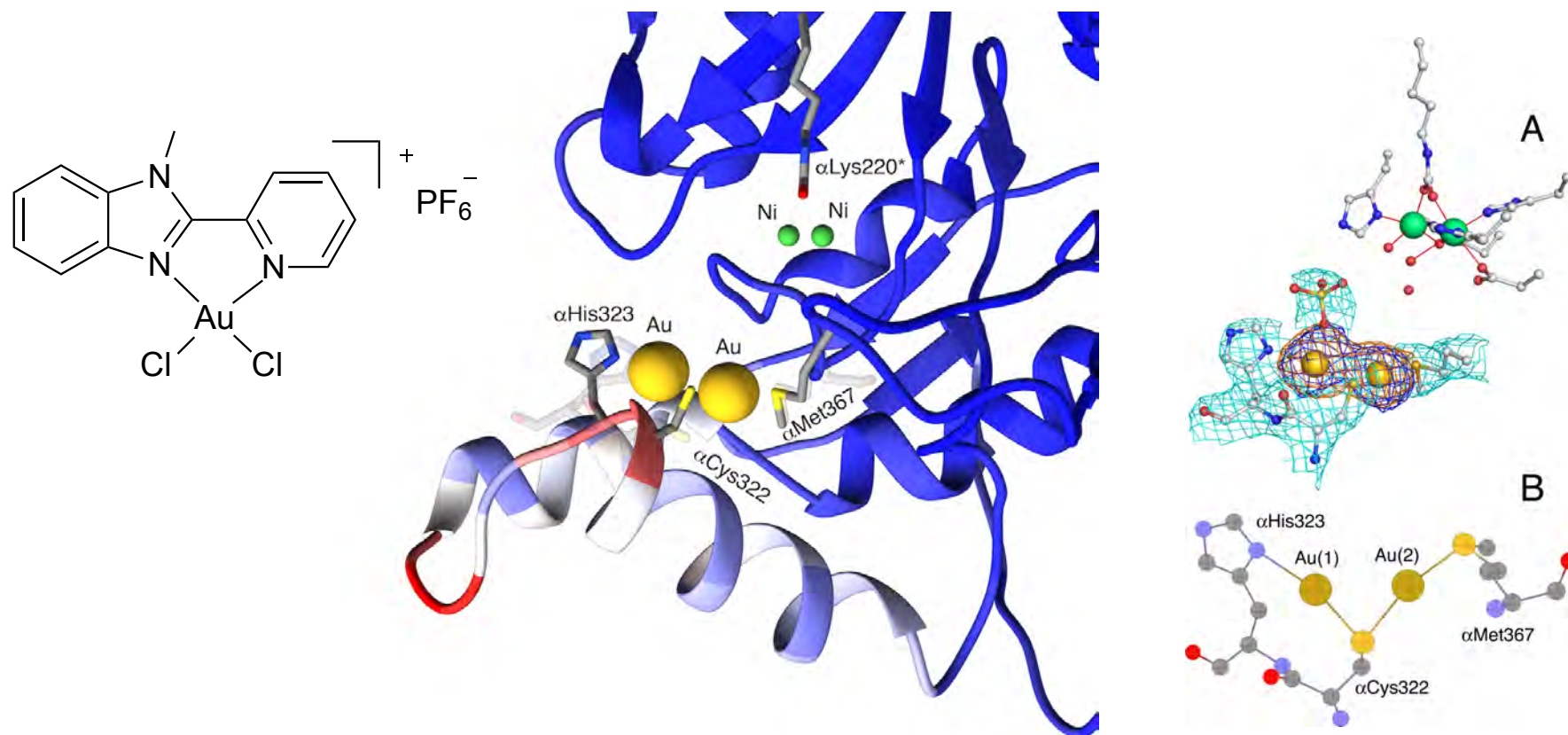


Can we target a specific zinc finger?

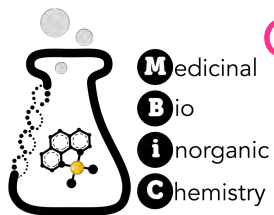




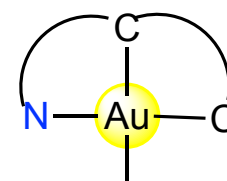
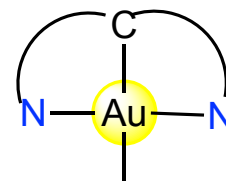
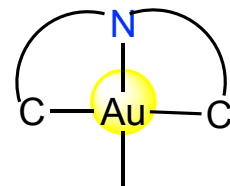
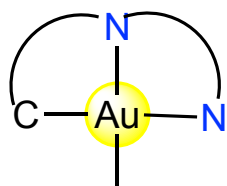
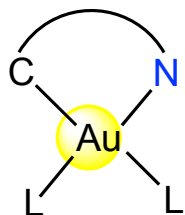
Inhibition mechanism of urease by Au(III) compounds with N-donor ligands



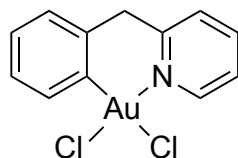
- The binding of the Au ions to these residues blocks the movement of a flap, located at the edge of the active site channel and essential for enzyme catalysis, completely obliterating the catalytic activity of urease.



Can we achieve selectivity with Au(III) cyclometallated complexes?



Margot Wenzel

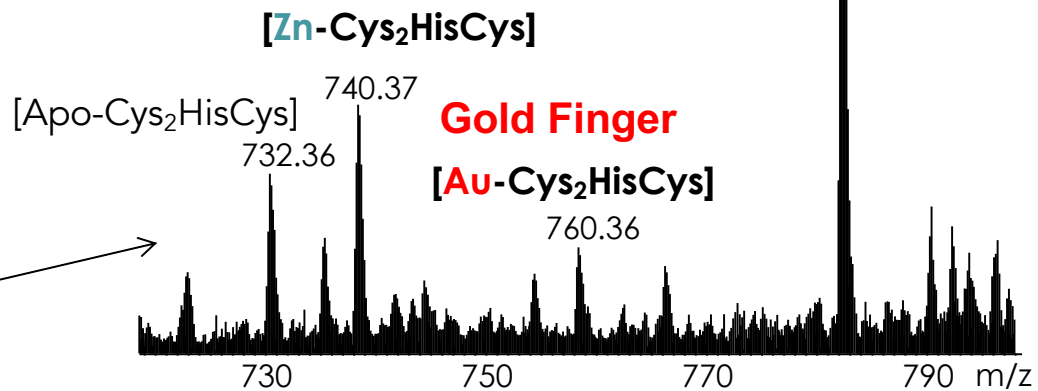
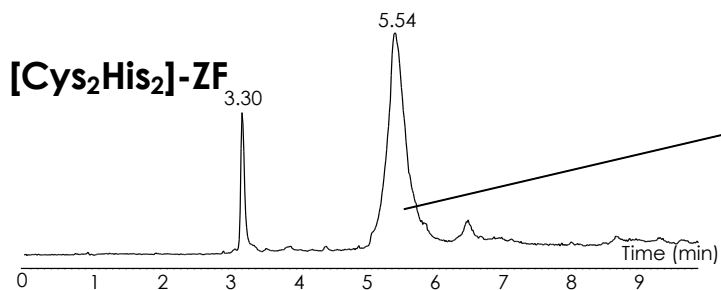
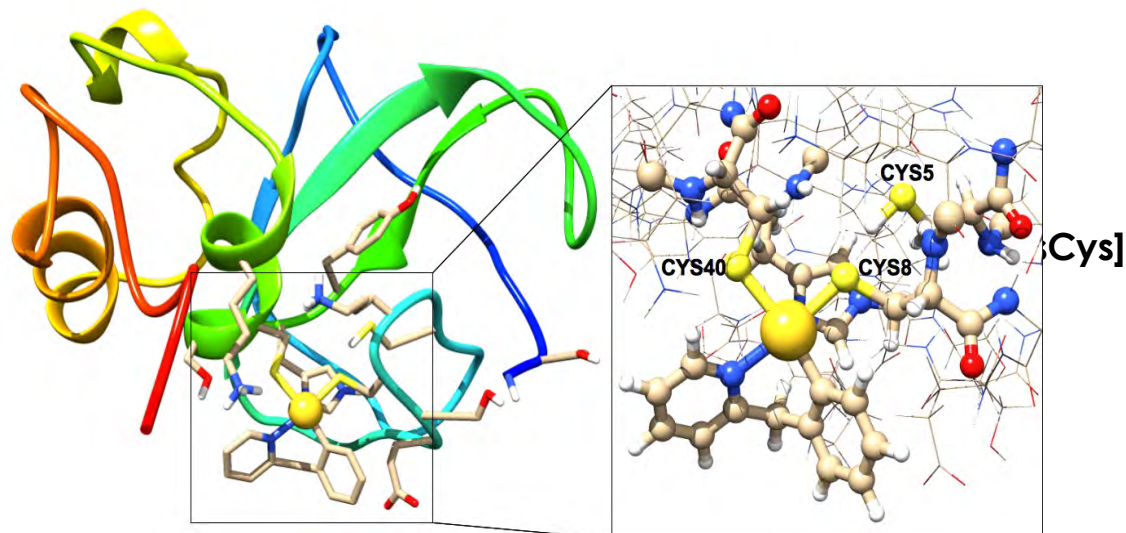


$\text{Au}(\text{C}^{\wedge}\text{N})\text{Cl}_2$

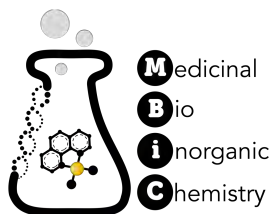


Sam Meier

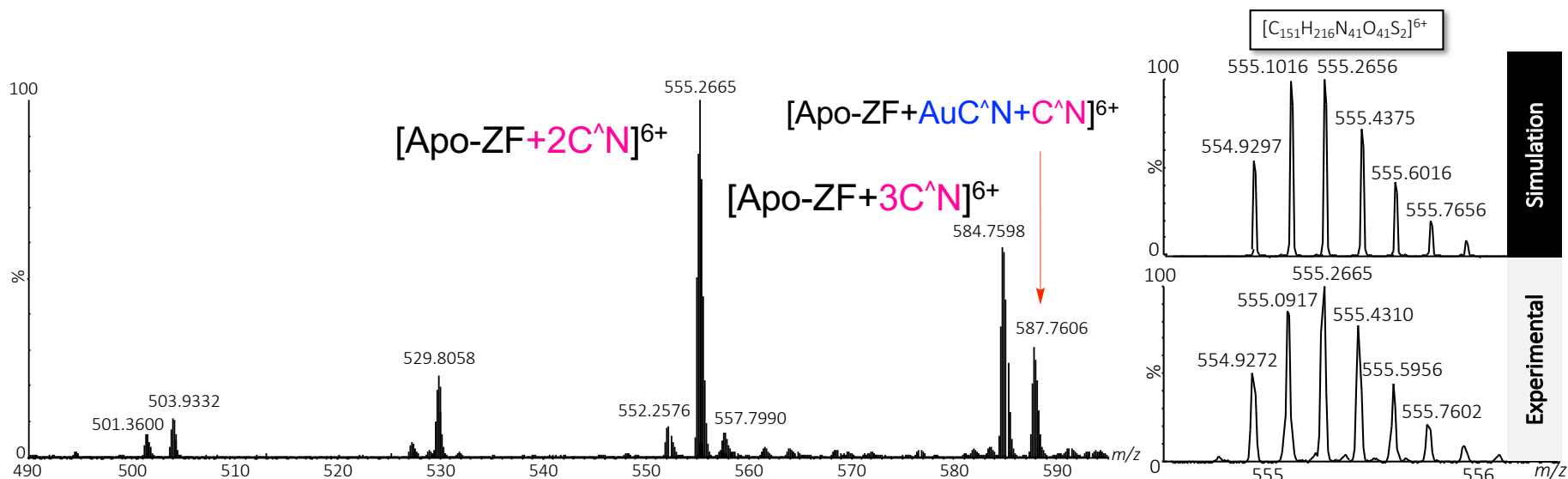
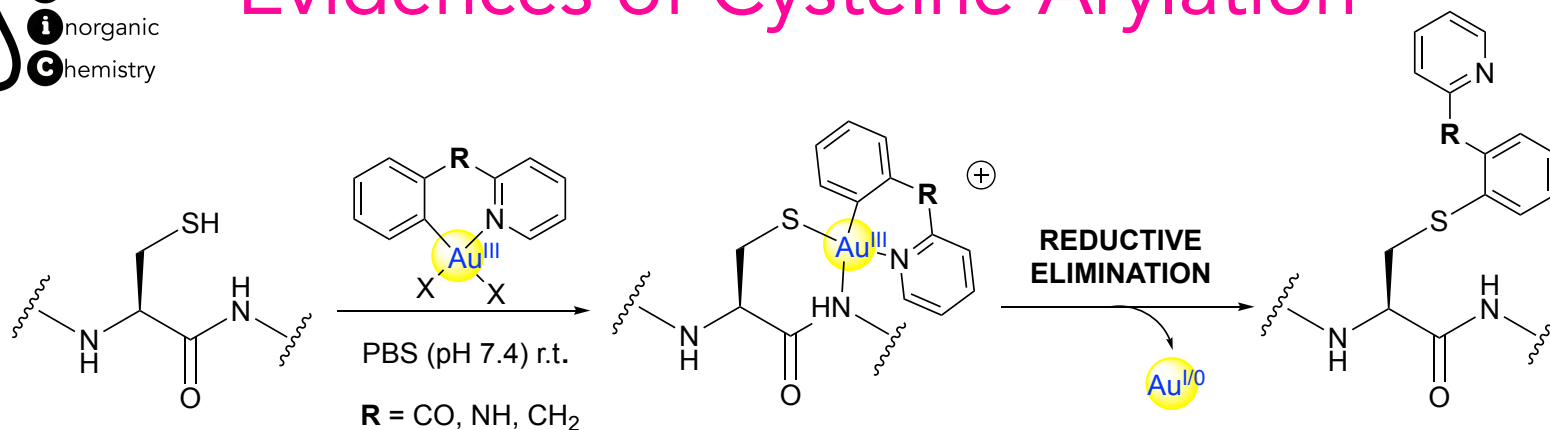
LC-MS approach
1 Au(III) compound
against a mixture of
 Cys_2His_2 and PARP-1
zinc fingers



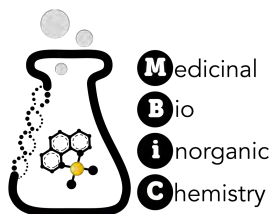
Chem. Commun., 2018, 54, 611-614.



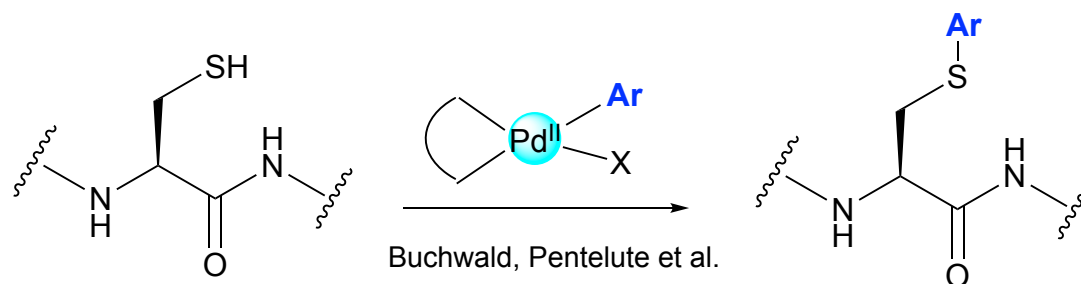
Evidences of Cysteine Arylation



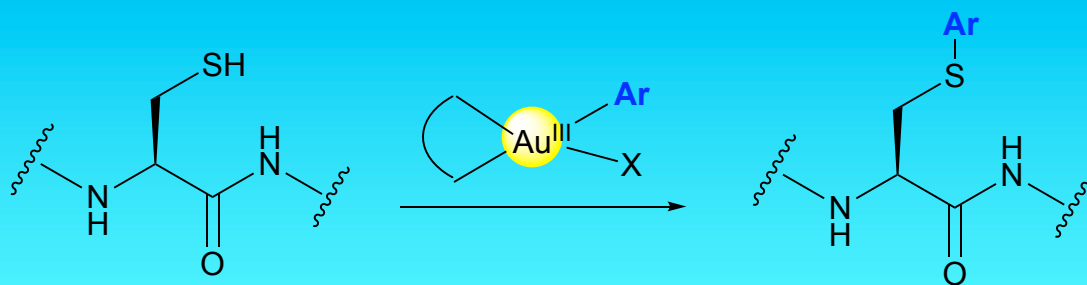
□ Opportunities for bio-orthogonal Cys modification
via Au-mediated C-S cross coupling



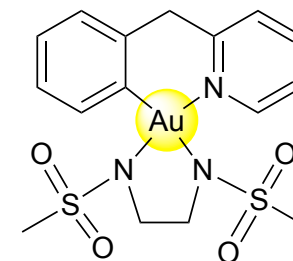
Metal-mediated Cysteine Arylation



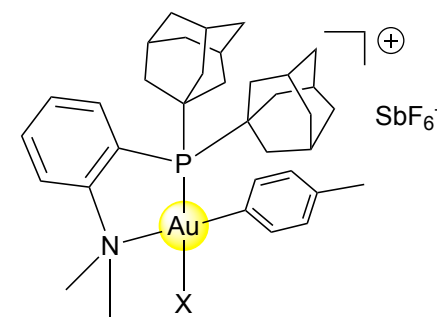
What about gold?



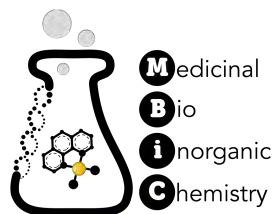
- **Wider pH range**
- **Faster kinetic**
- **Complementary chemoselectivity**



Wong et al,
Chem. Commun., **2014**, 50, 11899.



Spokoyny et al,
J. Am. Chem. Soc., **2018**, 140, 7065.



LC-HR-ESI-MS

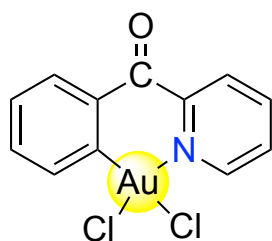
Au(III) complex vs ZF-Cys₂His₂



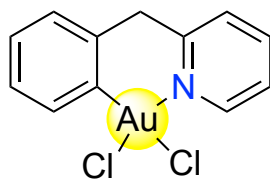
Sophie
Thomas



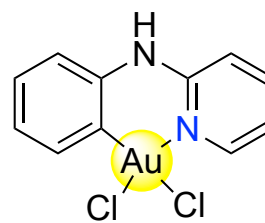
Riccardo
Bonsignore



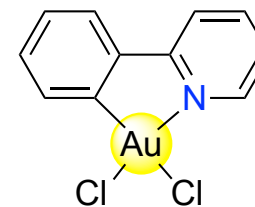
3



1



2

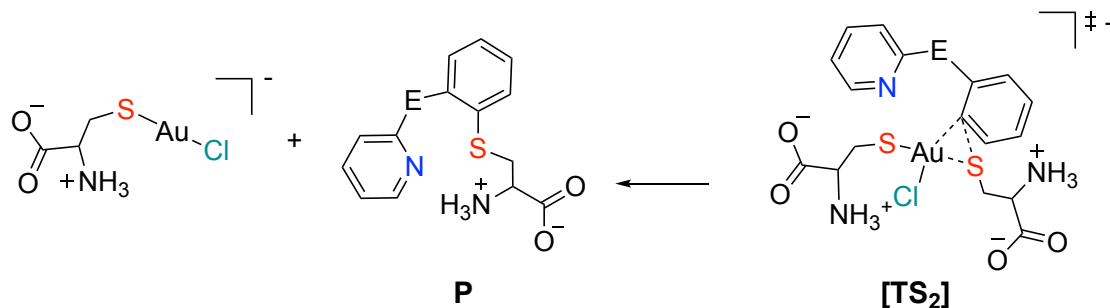
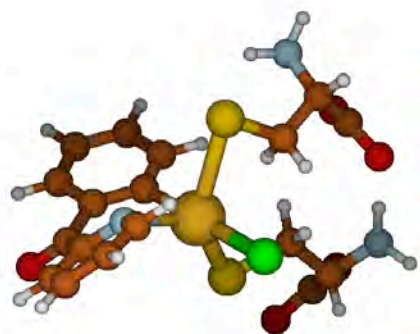
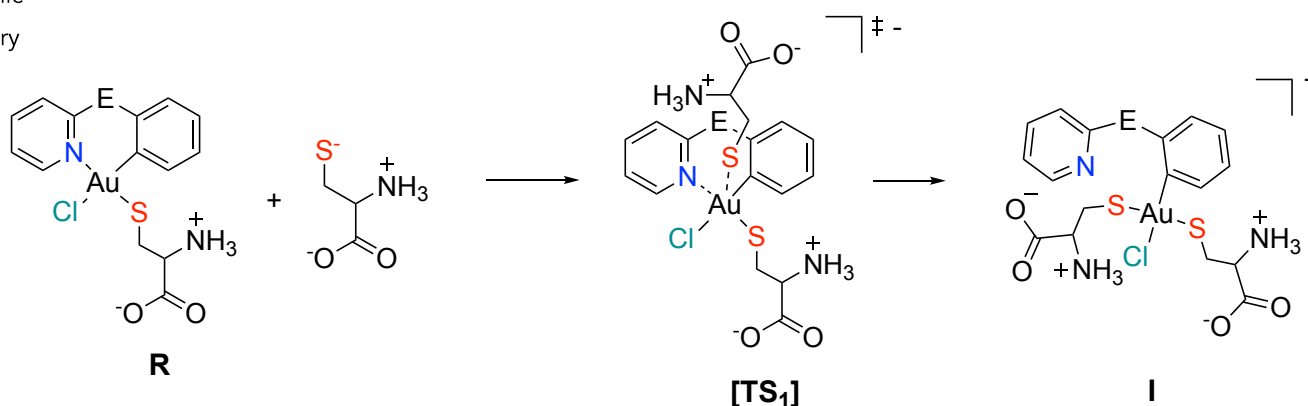


4

- ❑ Complex **3** mediates Cys arylation after 10 min incubation.
- ❑ **1** and **2** requires longer time to undergo Cys arylation (24 h).
- ❑ Complex **4** does not induce Cys arylation (forms only ZF-Au-C^N adducts).

Chemistry Eur. J., **2019**, *25*, 7628-7634.

Mechanistic hypothesis

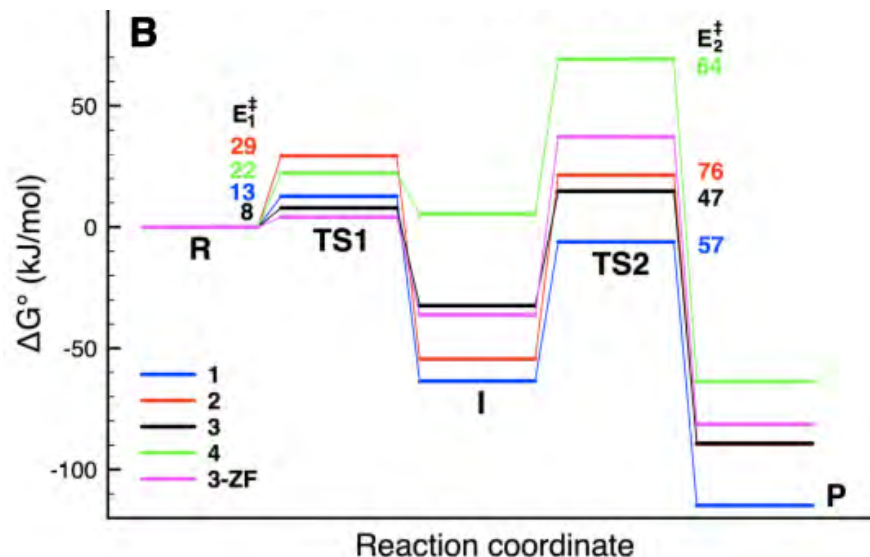
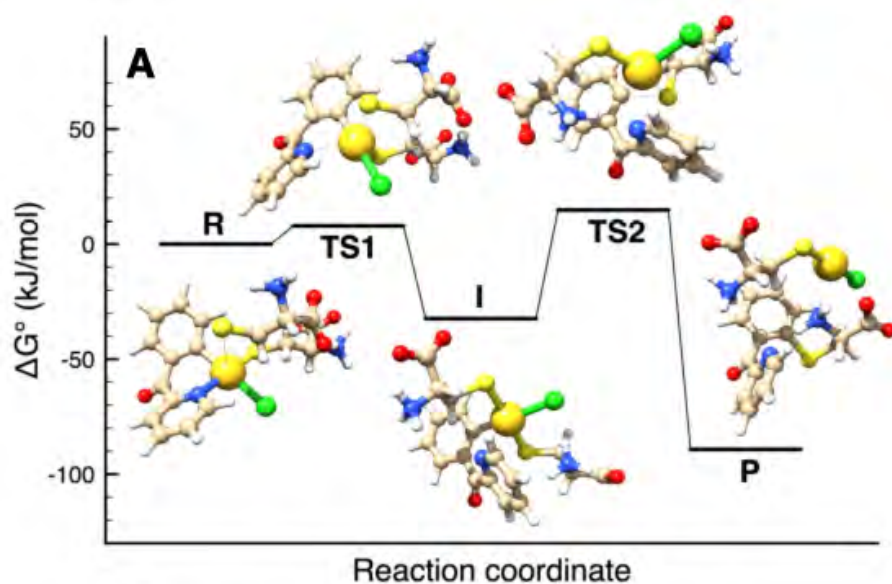


E = CH₂ (1), NH (2), CO (3)

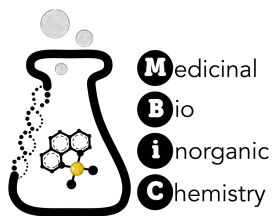
- The 1st cysteinatate adduct forms with S in *trans* position to N (and thus, *cis* to the aryl group) is more favored thermodynamically.
- Following the apical approach of the 2nd cysteinatate, the N atom decoordinates and the C[^]N chelate to opens.

DFT & QM/MM

Collaboration with Prof. G. Barone – Univ. Palermo



- ❑ The first reaction step is exergonic for **1-3**.
- ❑ The subsequent reductive elimination is favored thermodynamically and is the rate-determining step.
- ❑ The difference results from the stability of the bis-cysteinate intermediate **I** as compared to the starting complex **R**.
- ❑ The activation barrier for the C–S coupling (E_2^\ddagger) increases in the order CO (**3**) < CH₂ (**1**) < NH (**2**).



Medicinal
Bio
inorganic
Chemistry

Outlook



Structure-activity relationships

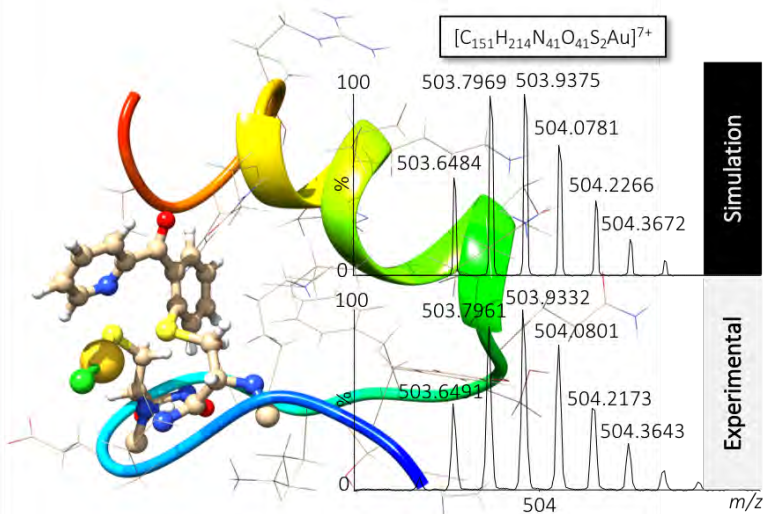
Steric vs Electronic effects

Implementation of computational approach

Peptide Sequence

H-bonding

Different C-X bond cross coupling



Therapeutic Catalysts