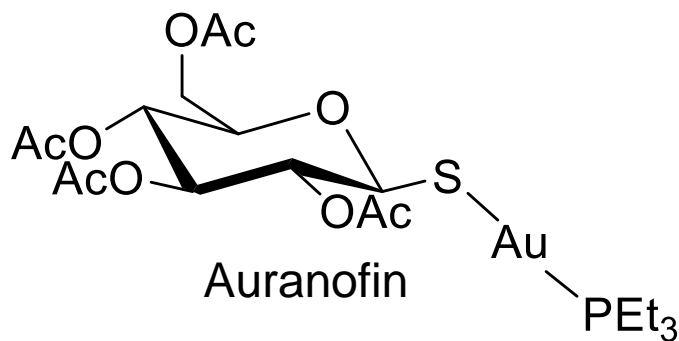


Metal-based Inhibitors of Enzymes

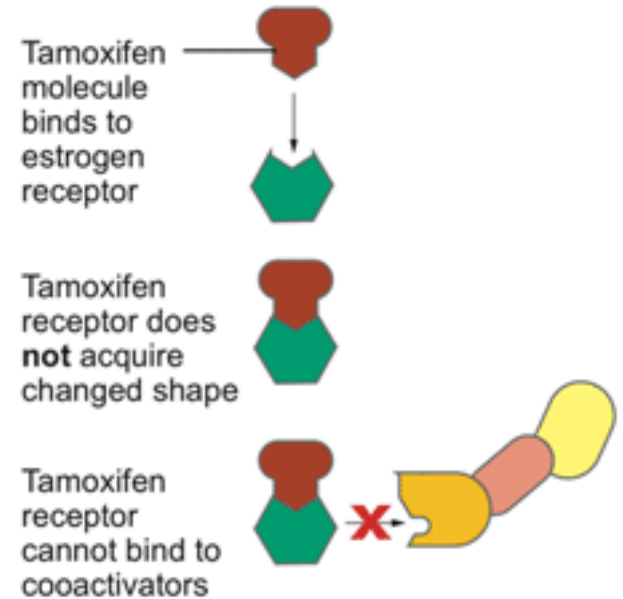
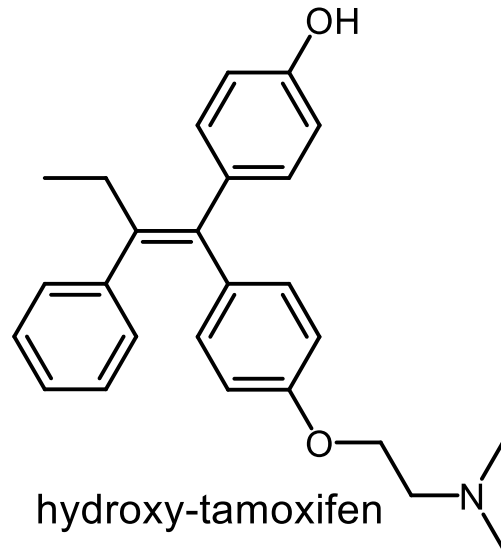
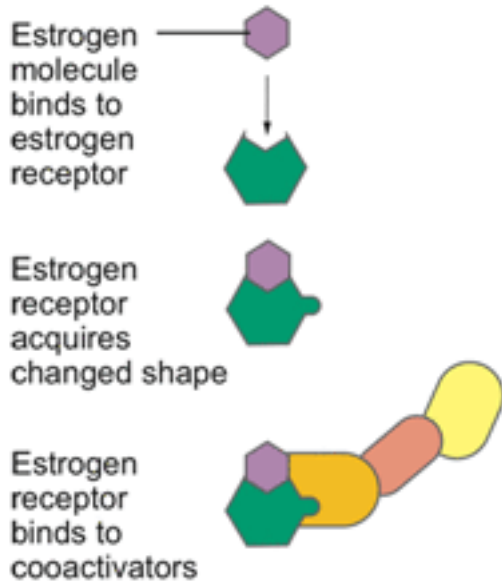
Auranofin: a serendipitous enzyme inhibitor



- Introduced in the late 1970s as oral substitute of gold anti-arthritic agents (developed on the wrong assumption that arthritis was caused by a bacterial infection).

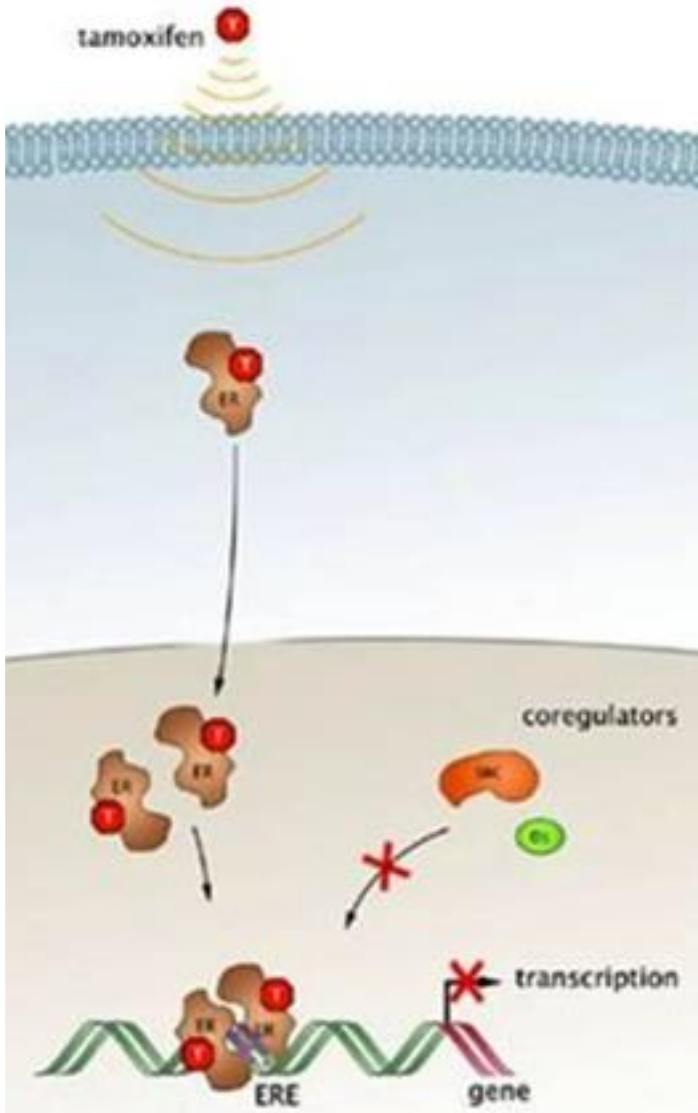
Au(I) from Auranofin strongly inhibits *in vitro* the seleno-cysteine enzymes *Thioredoxin reductase* and *Glutathione peroxidase*

Estrogen Receptor Inhibitors



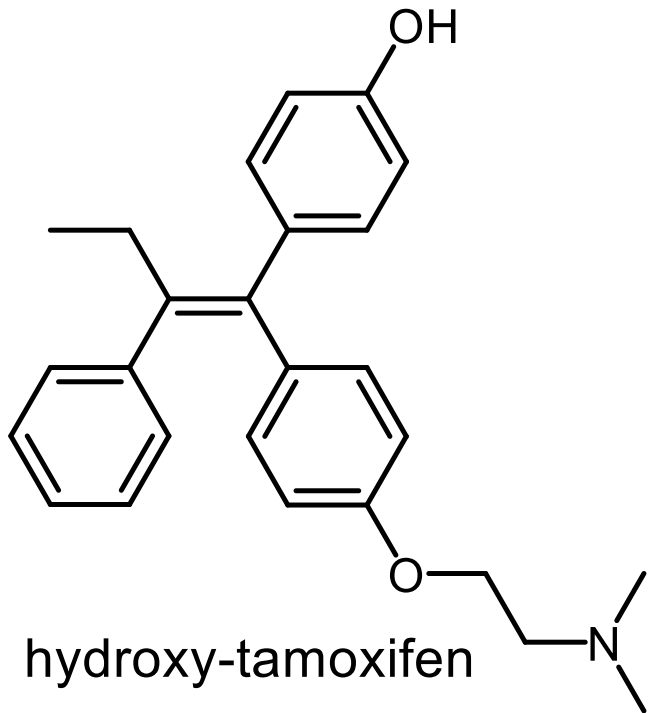
Proliferazione delle cellule tumorali

Inibizione delle cellule tumorali



ERE = estrogen response elements

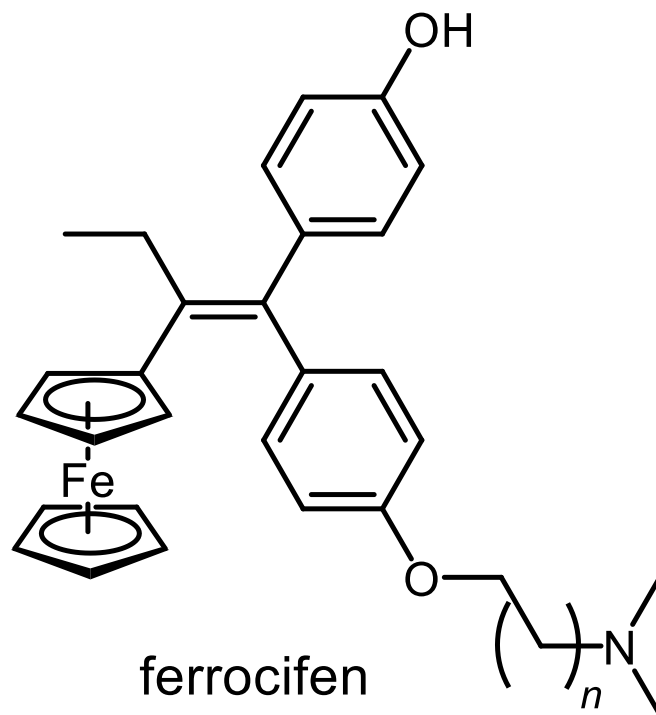
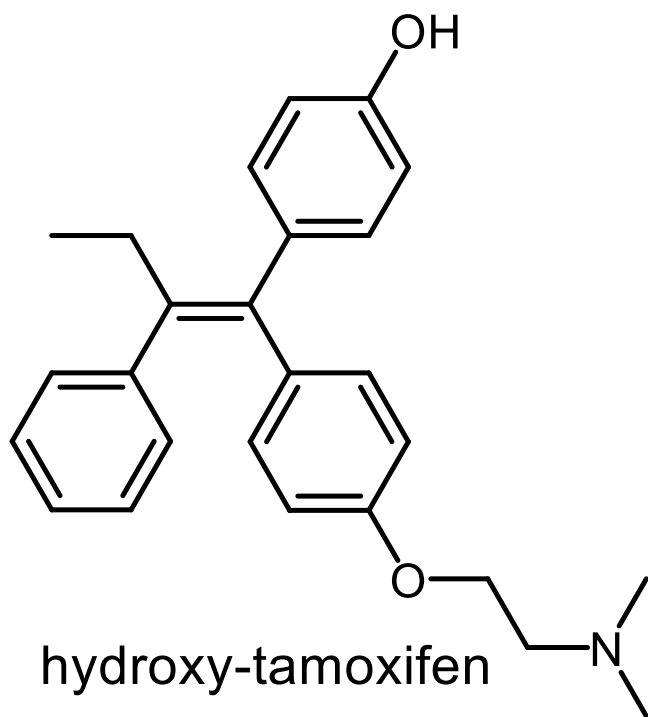
modulazione epigenetica



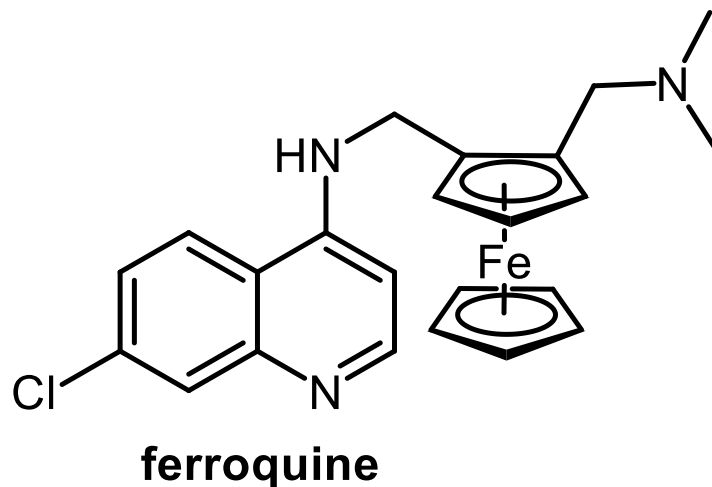
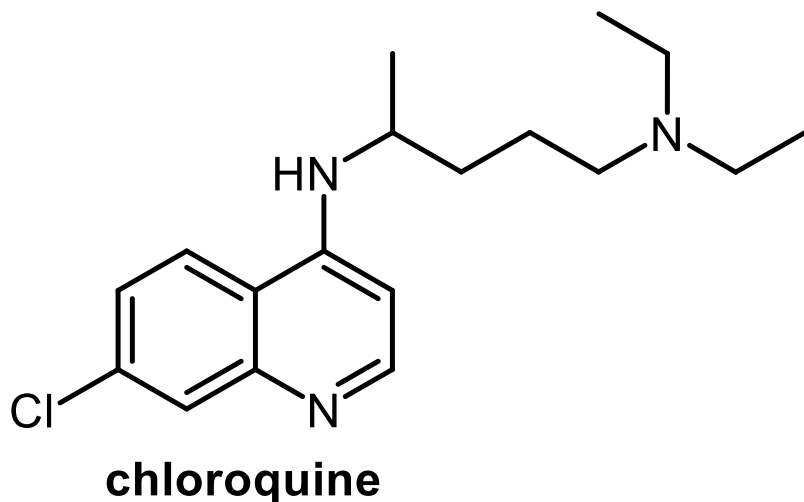
Tamoxifen binds selectively to estrogen receptor α subtype ($ER\alpha$) in tumor cells, repressing estradiol-mediated DNA transcription.

Thus tamoxifen is active only against those type of breast cancer that overexpress the $ER\alpha$ ($ER\alpha+$, ca. 2/3 of total).

Bio-isosteric replacement of phenyl rings with metallocene fragments in bioactive molecules



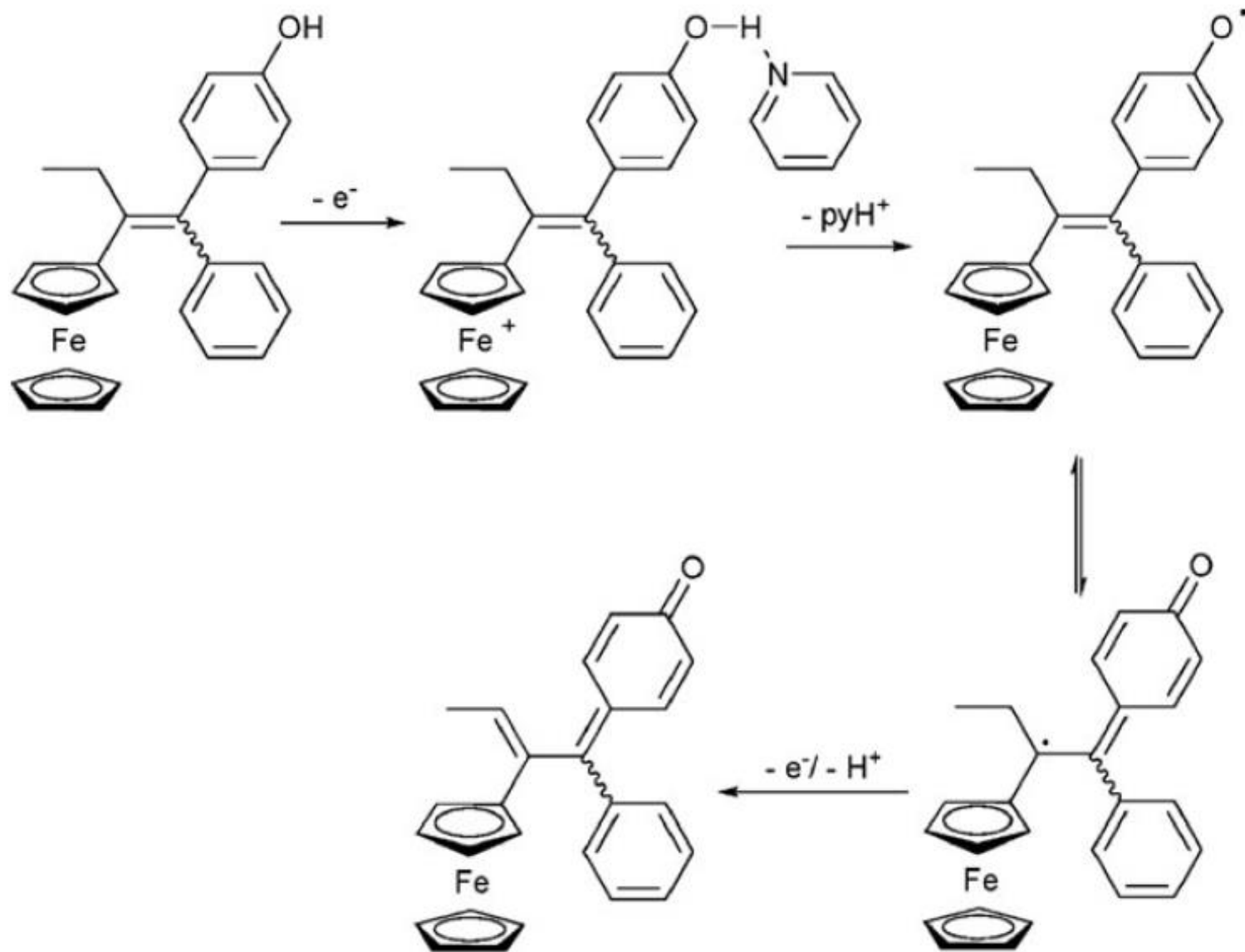
Bio-isosteric replacement applied to antimalarial drugs



- Ferroquine is the ferrocenyl analogue of chloroquine, an established antimalarial drug.
- Ferroquine is active also against chloroquine-resistant strains and is due to enter clinical phase III trials.

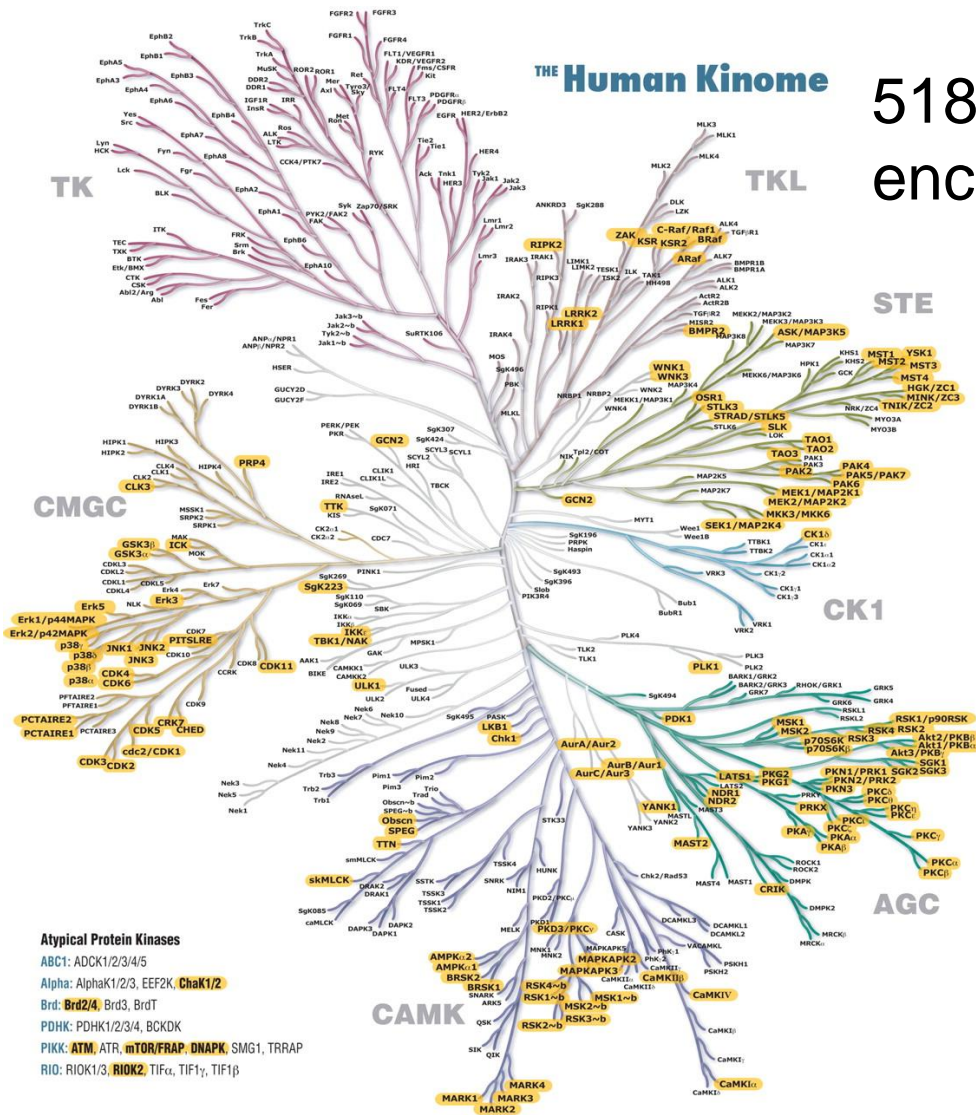
The metal fragment may lead to unexpected behaviors

- Some ferrocifens are active against **both** ER α + **and** ER α - breast cancer cell lines
- The activity is linked to reversible redox behavior of the iron center
- Ru(II) analogues are active against ER α + breast cancer cell lines only

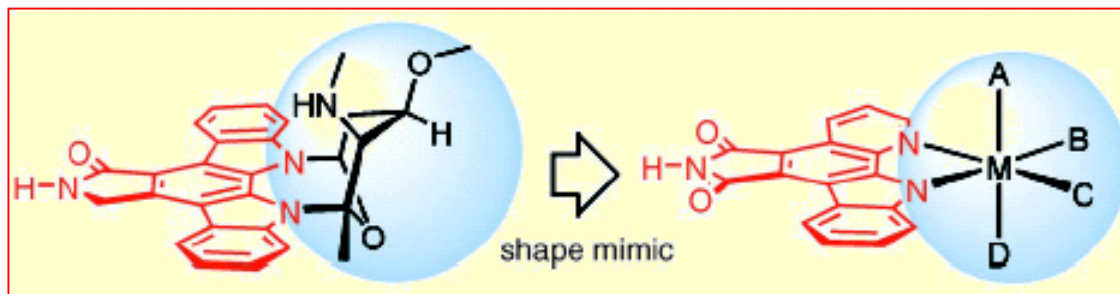


Protein Kinase inhibitors

518 different kinases are encoded in the human genome

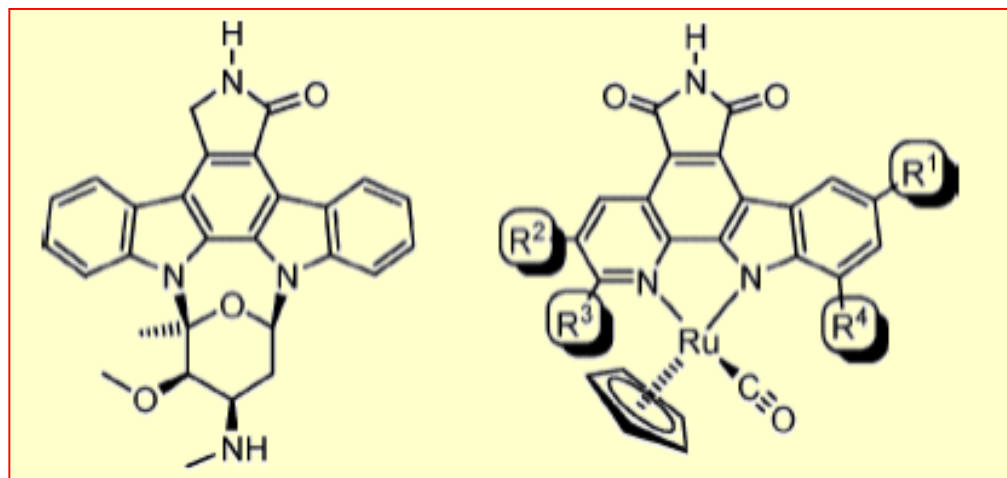


Selective protein kinase inhibitors

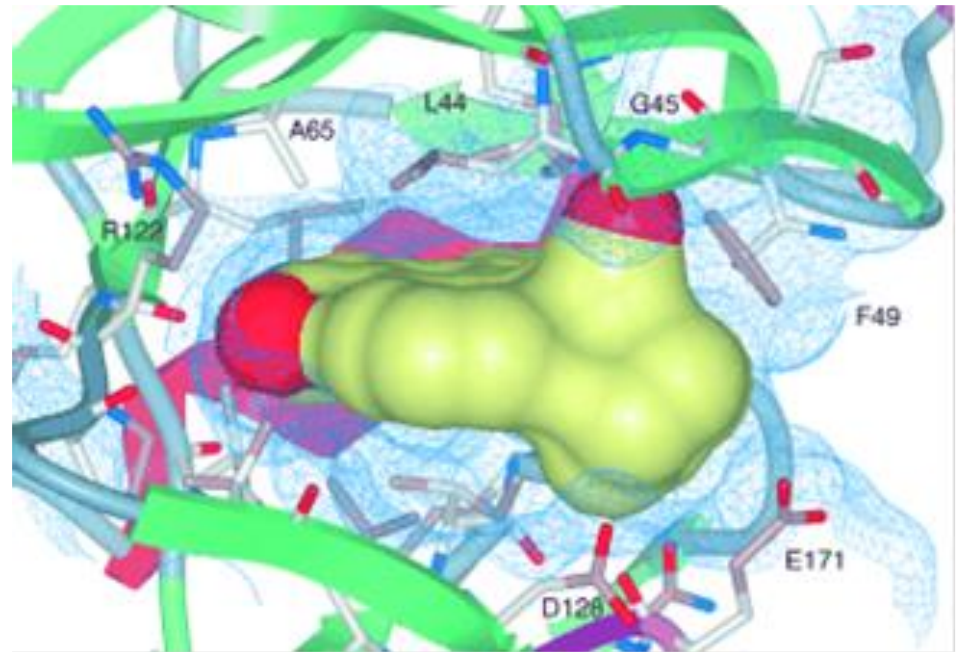
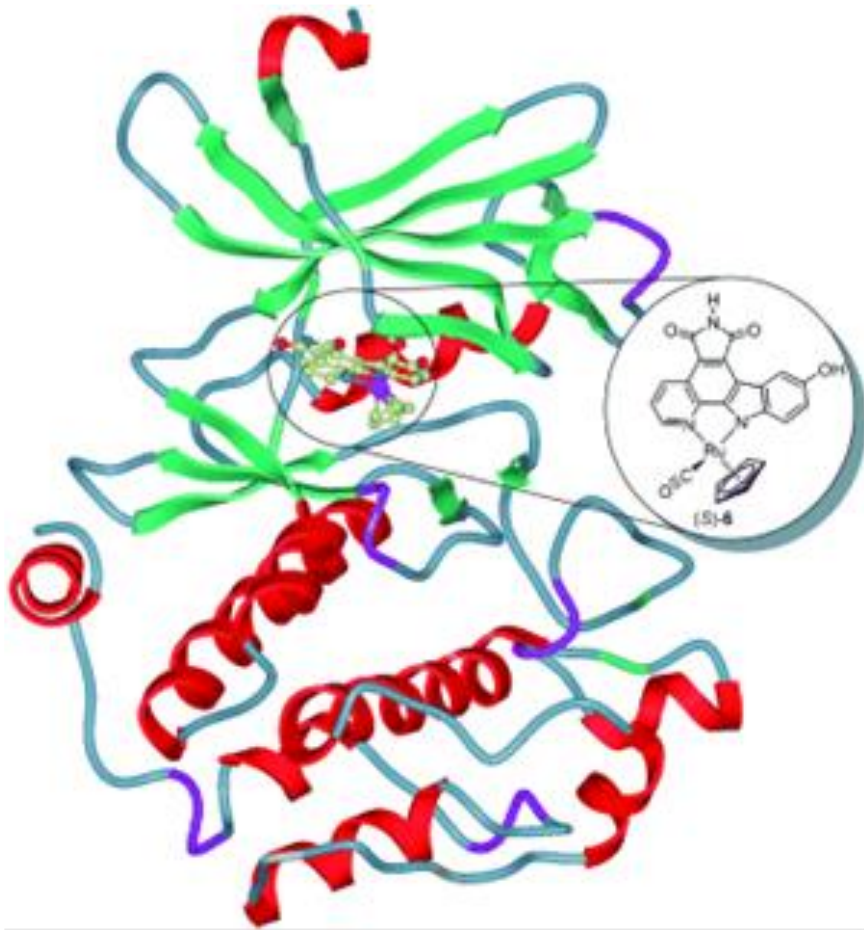


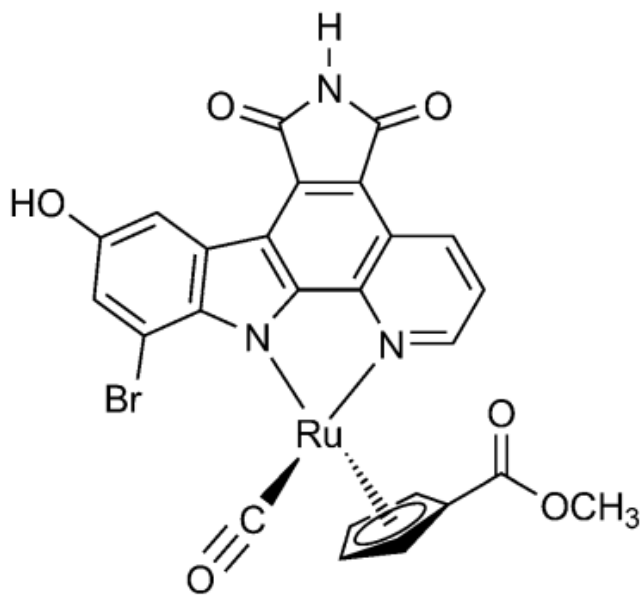
Staurosporine, unselective protein kinase inhibitor (ATP binding site)

- Great structural variety (geometry)
- Stereochemistry far more diverse than organic compounds
- Rational ligand design

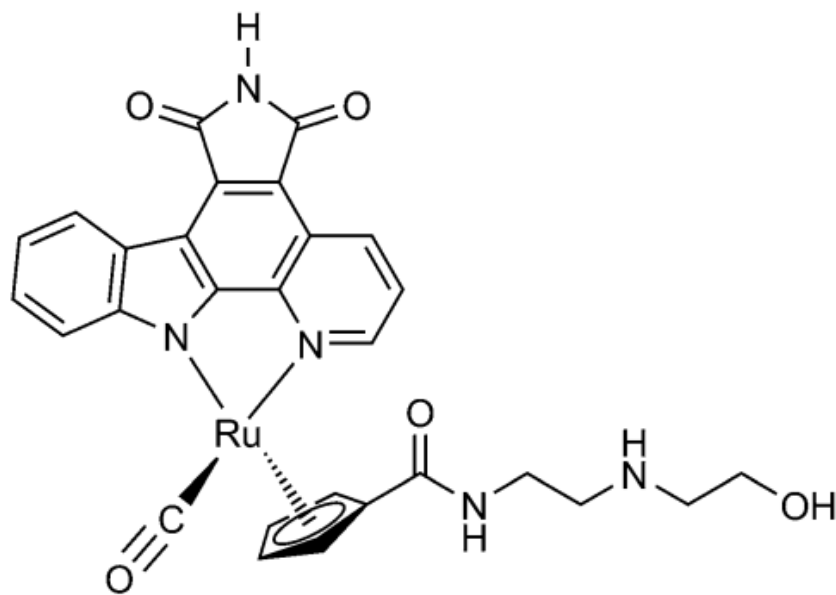


The binding of an organometallic ruthenium inhibitor to the ATP binding site of protein kinase Pim-1





GSK-3 inhibitor
 $IC_{50} \sim 0.5 \text{ nM}$

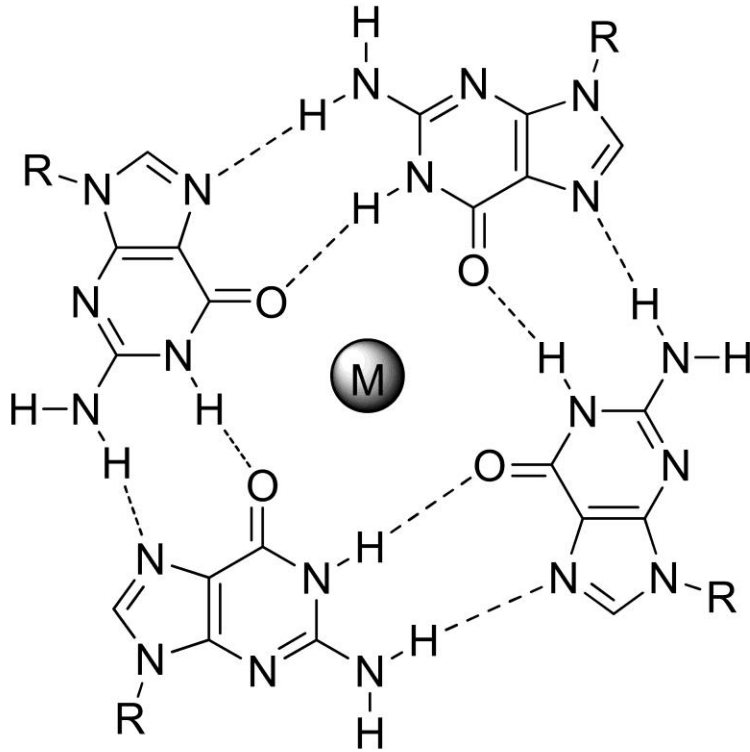


Pim1 inhibitor
 $IC_{50} \sim 2 \text{ nM}$

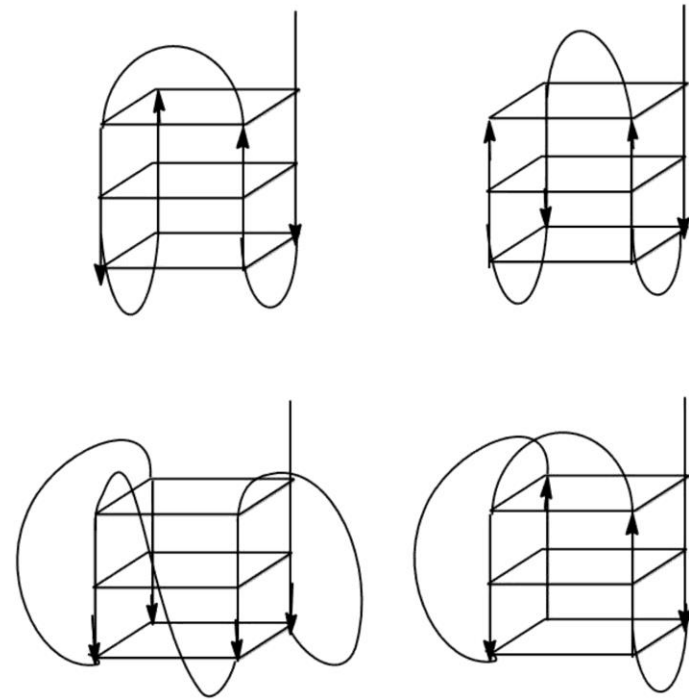
Commercially available

Telomerase

G quartet



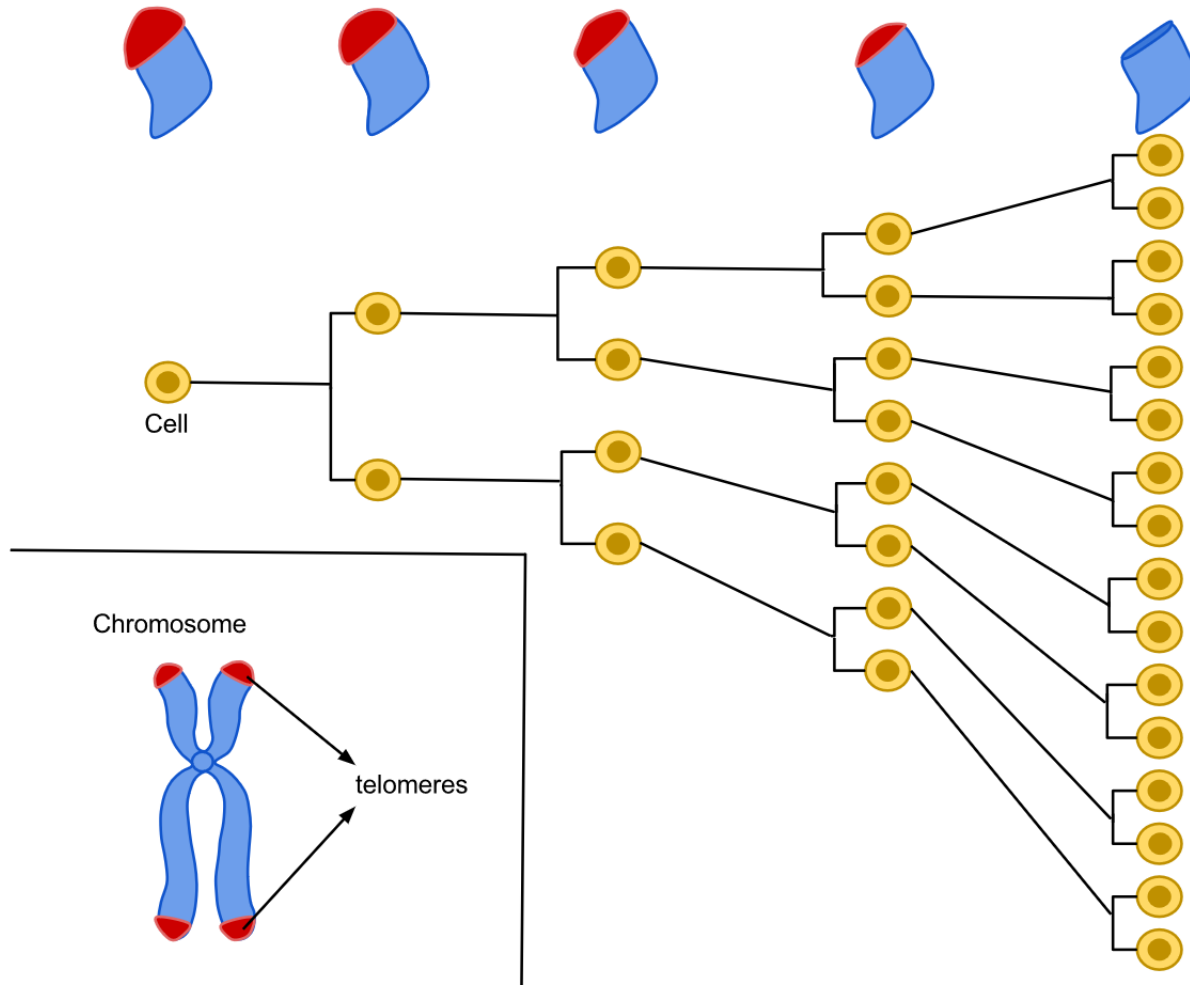
G quadruplexes

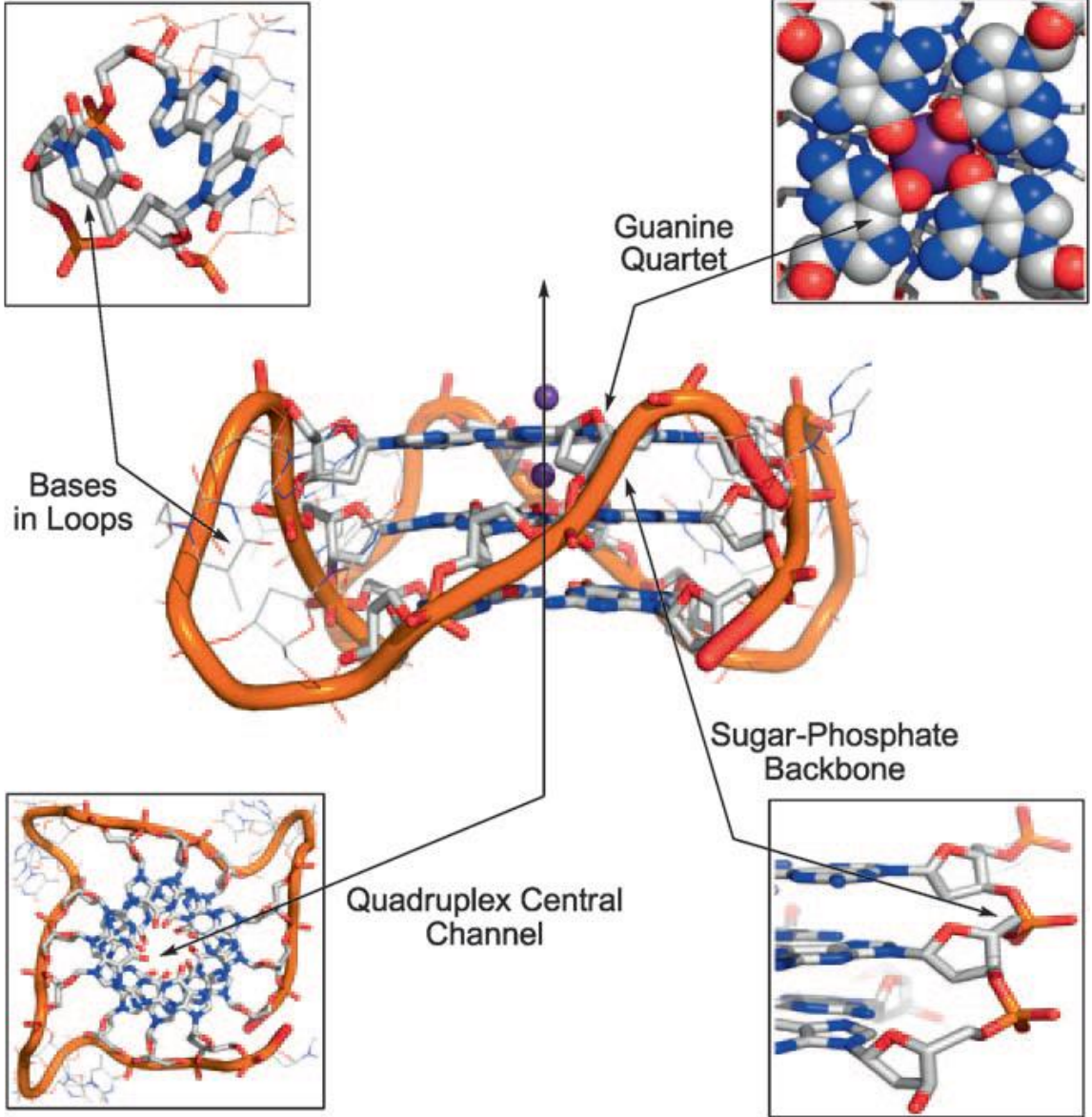


d(TTAGGG) sequences

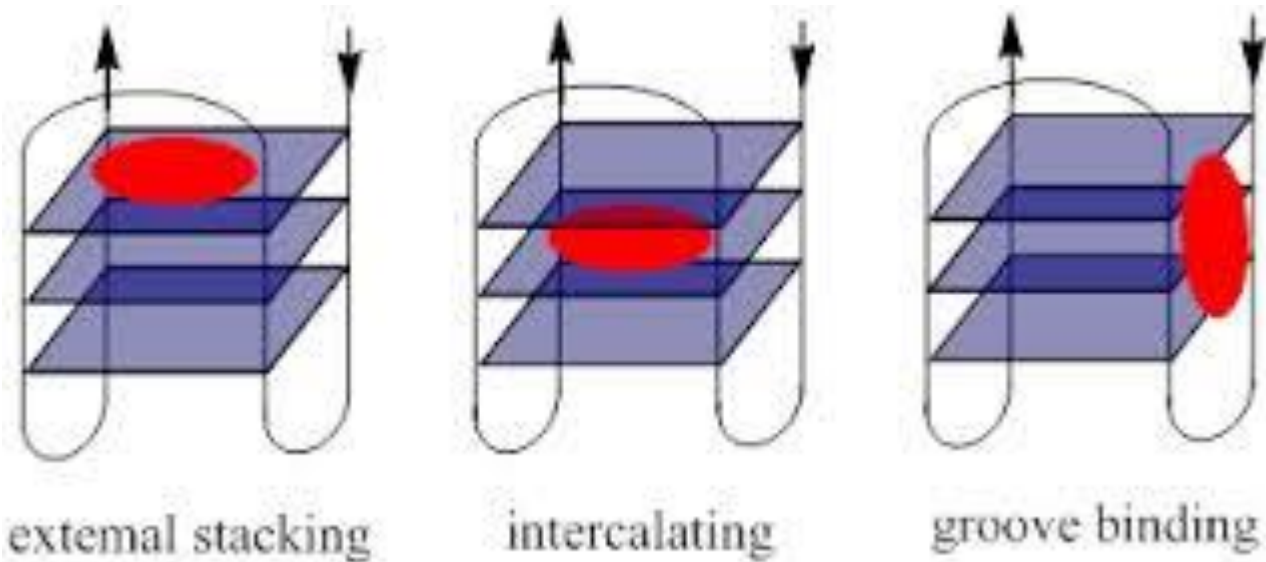
The Hayflick limit

(ca. 50 divisioni cellulari)

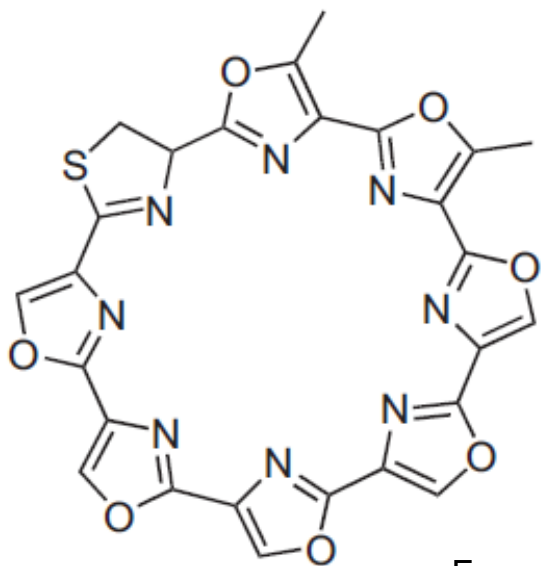




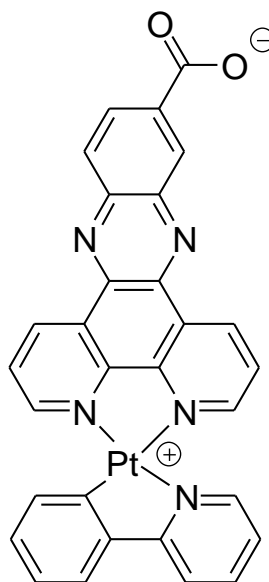
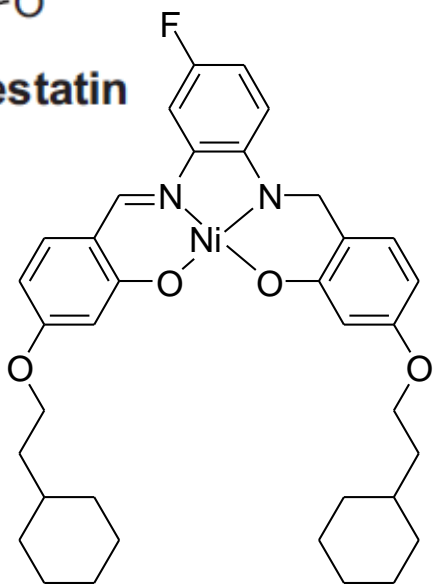
G-quadruplex stabilization for telomerase inhibition



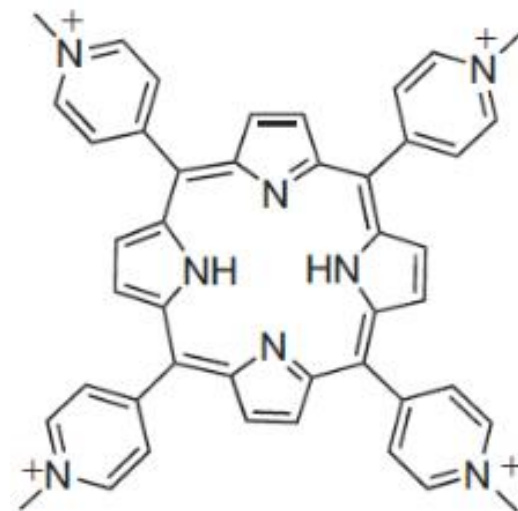
Telomerase Inhibitors



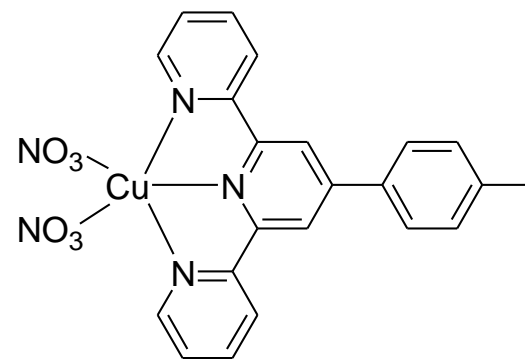
Telomestatin



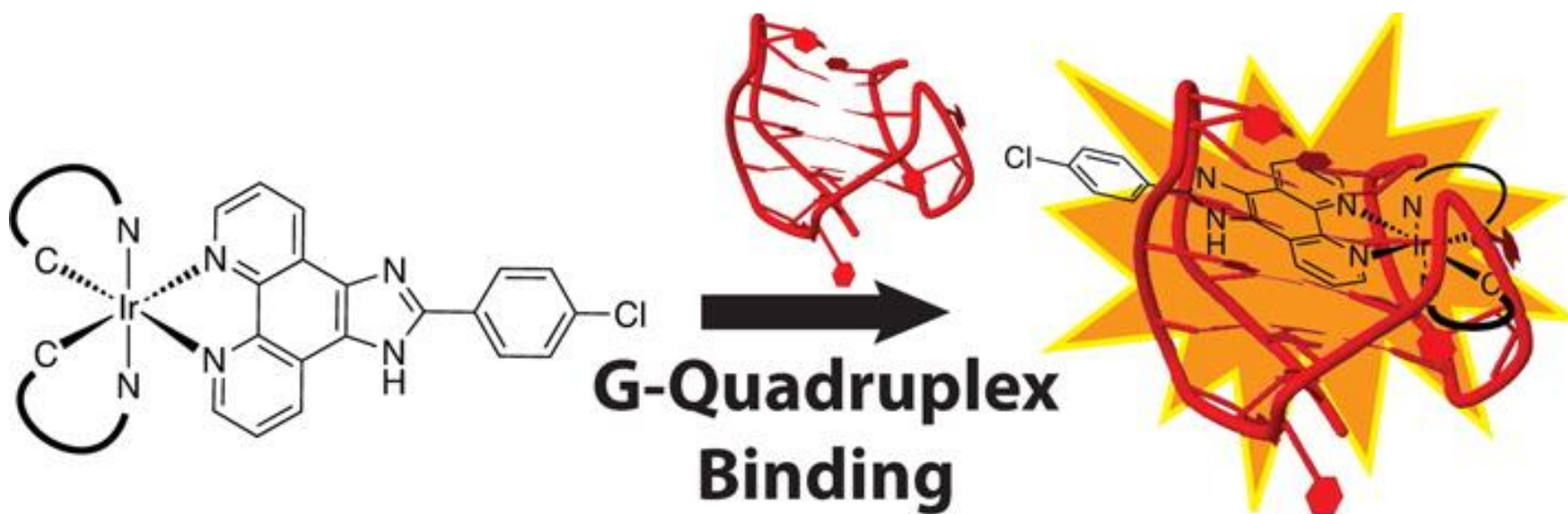
π stacking on G quartets

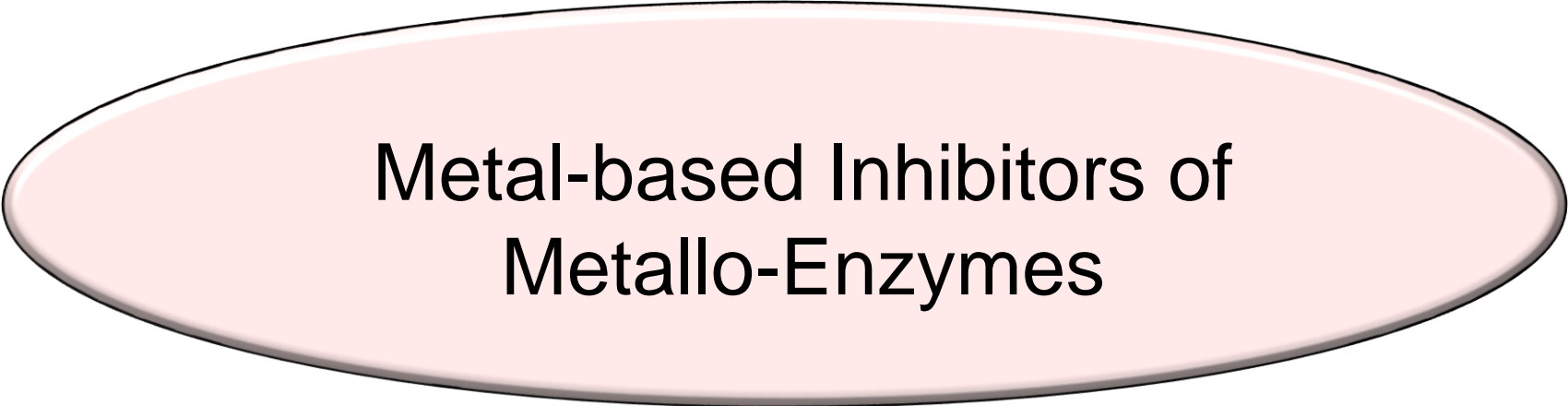


TmPyP4



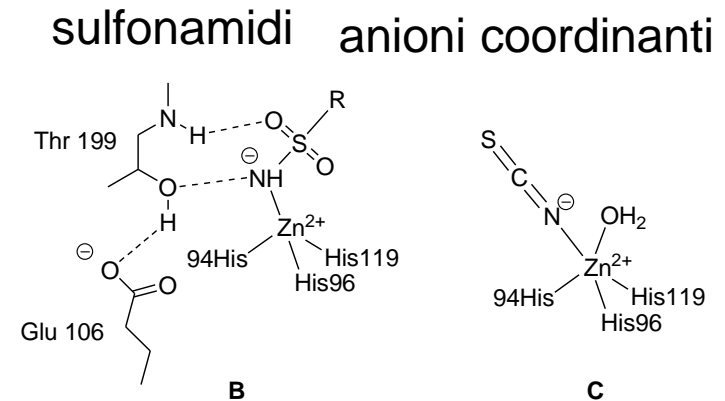
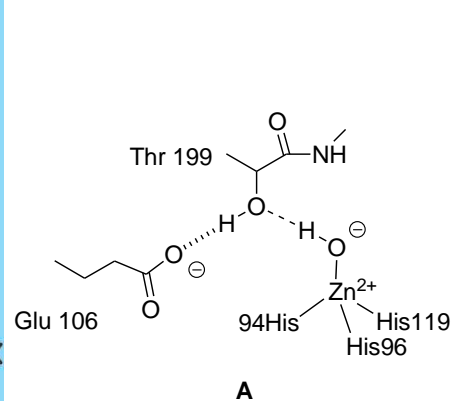
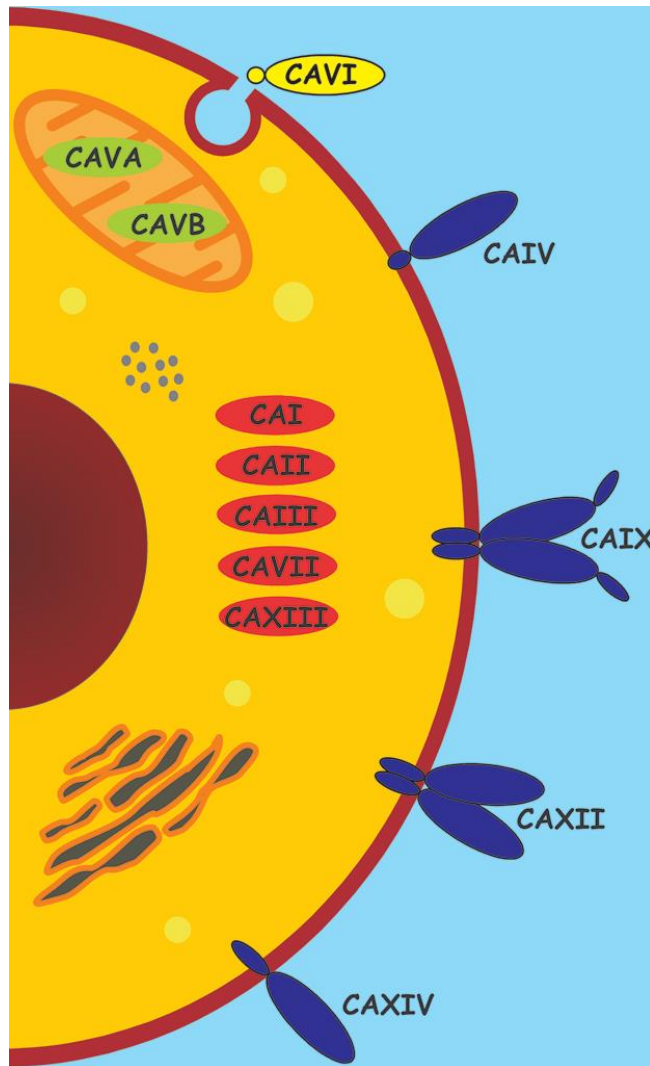
G-quadruplex sensing





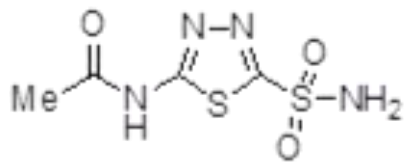
Metal-based Inhibitors of
Metallo-Enzymes

Human Carbonic Anhydrase (hCA) inhibitors

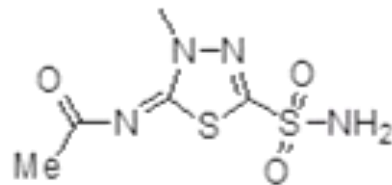


$$k \approx 10^{-1} \text{ s}^{-1} \rightarrow 10^6 \text{ s}^{-1}$$

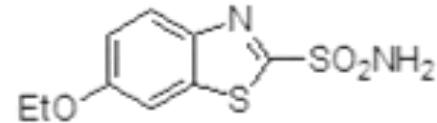
Sulfonamides as CA inhibitors



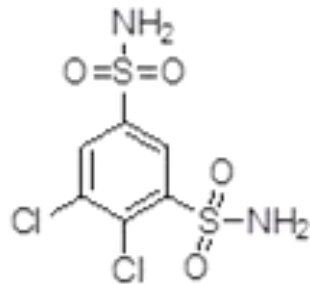
Acetazolamide (AAZ)



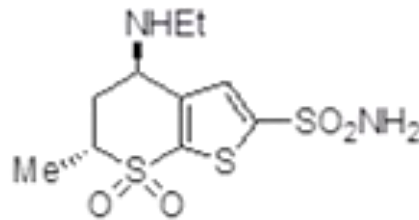
Methazolamide (MZA)



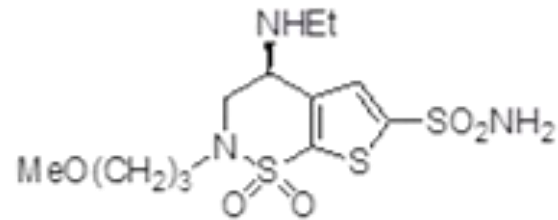
Ethoxzolamide (EZA)



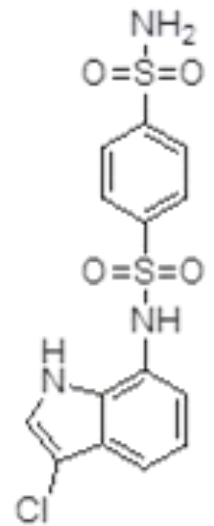
Dichlorophenamide (DCP)



Dorzolamide (DZA)

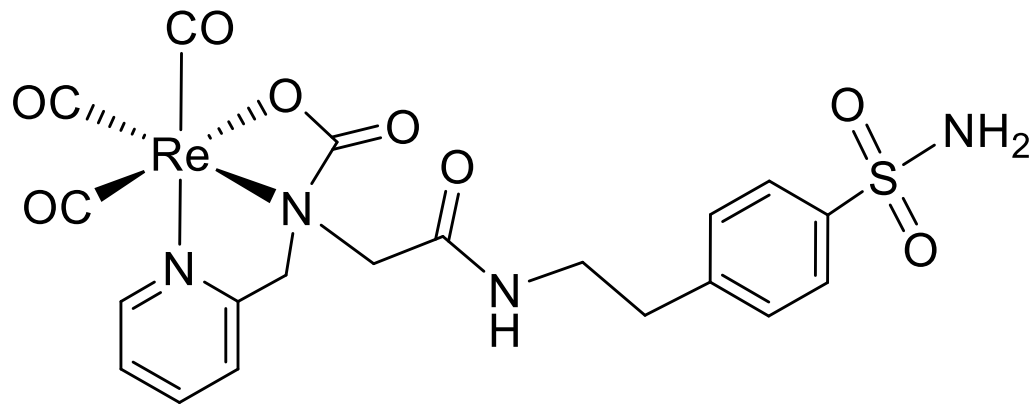
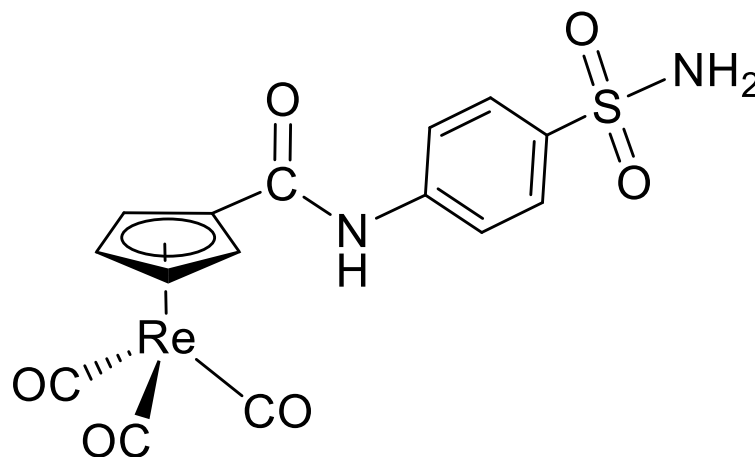
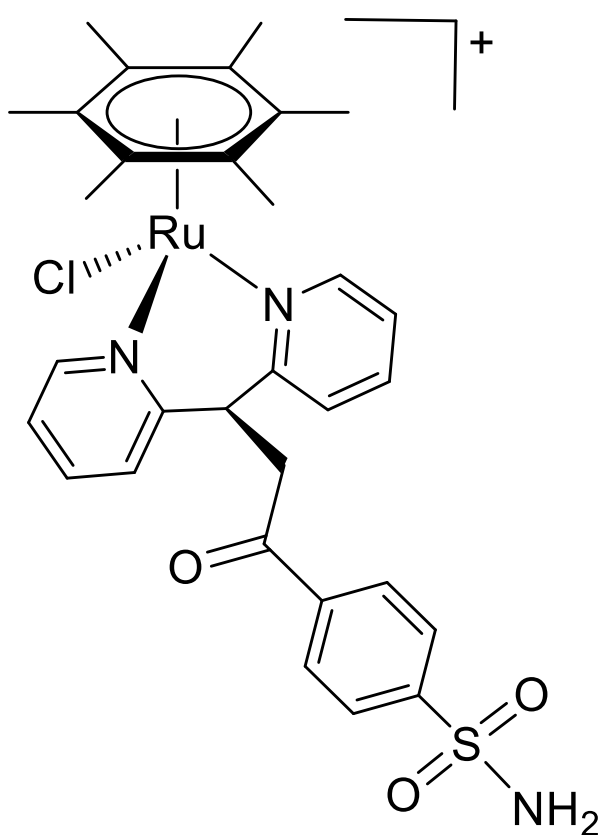


Brinzolamide (BRZ)

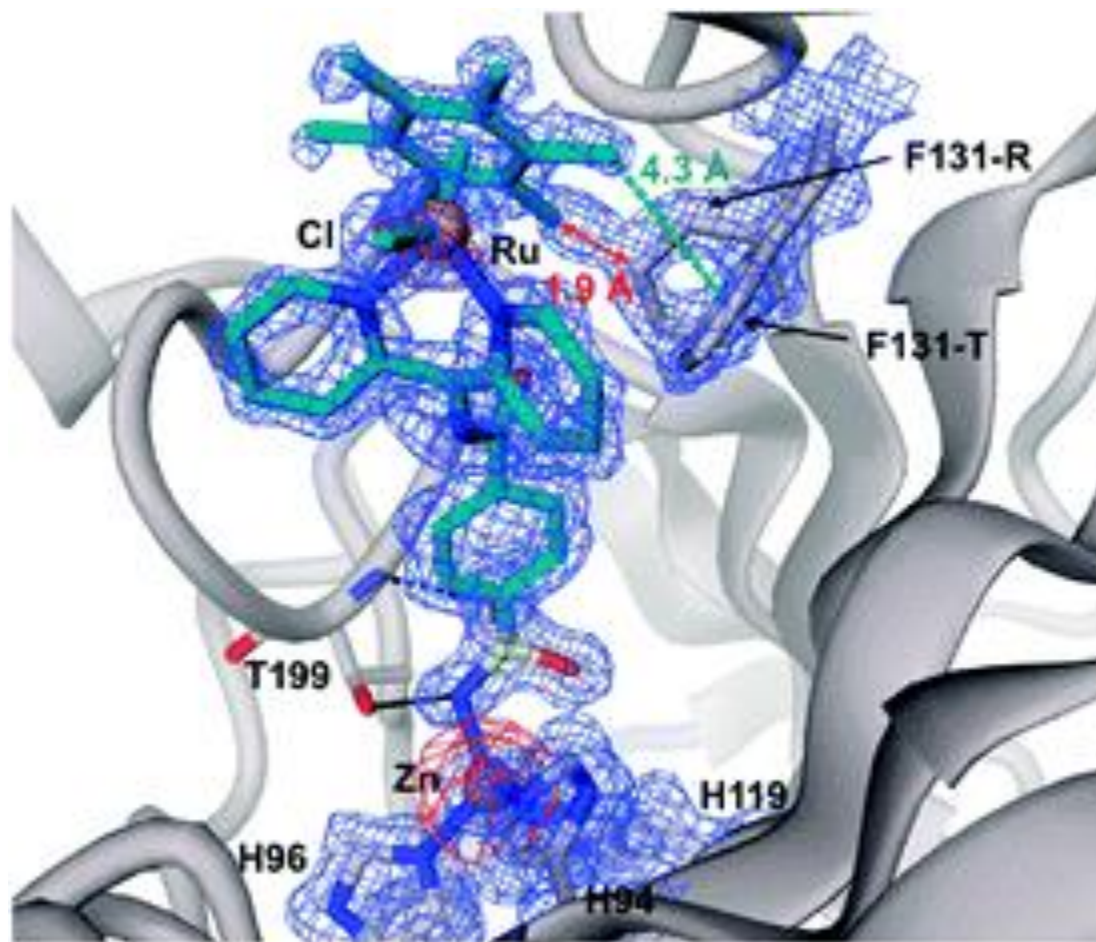


Indisulam (IND)

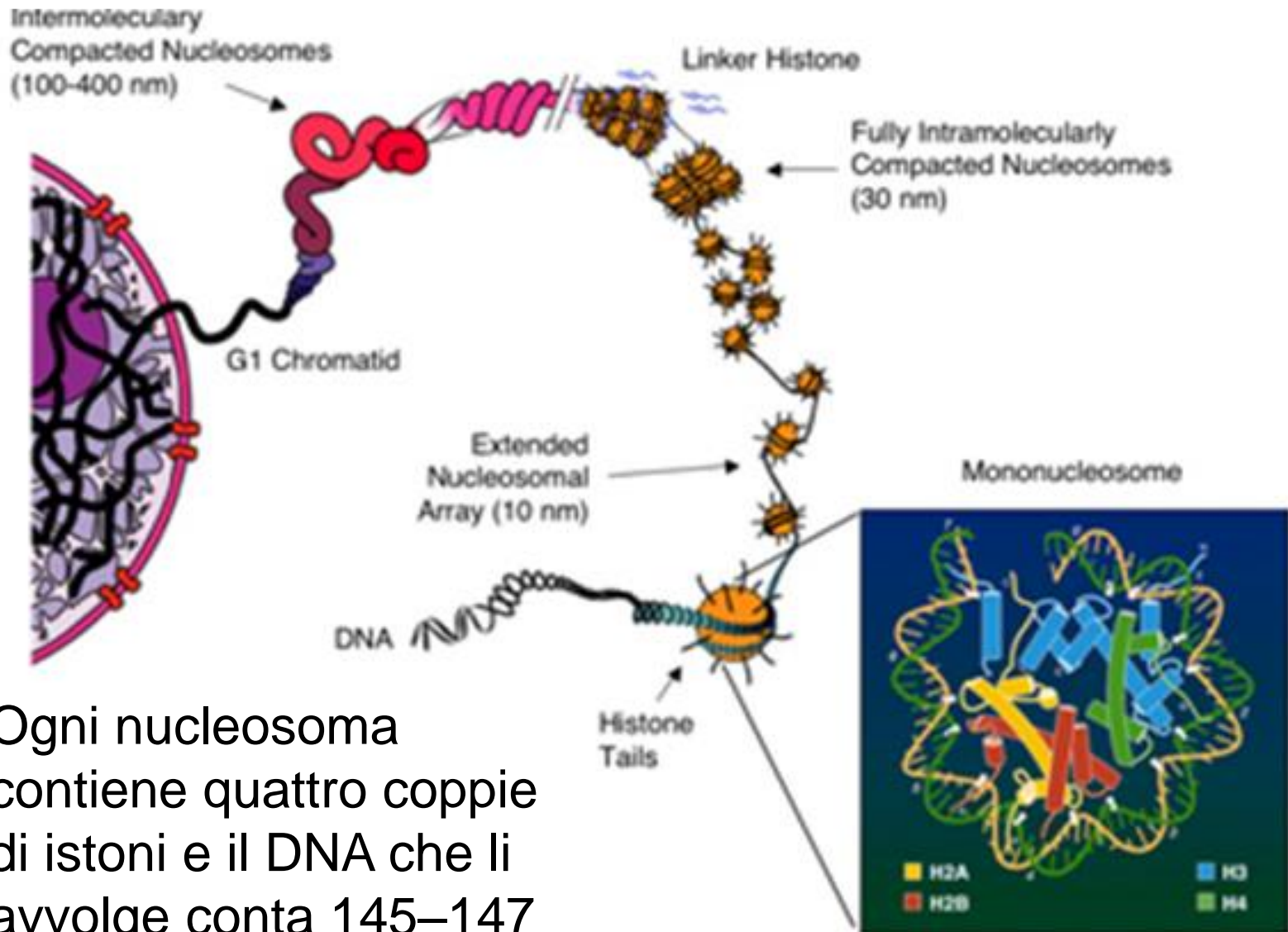
Inert organometallic compounds as hCA inhibitors



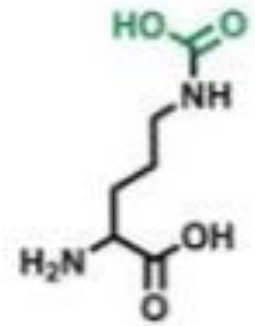
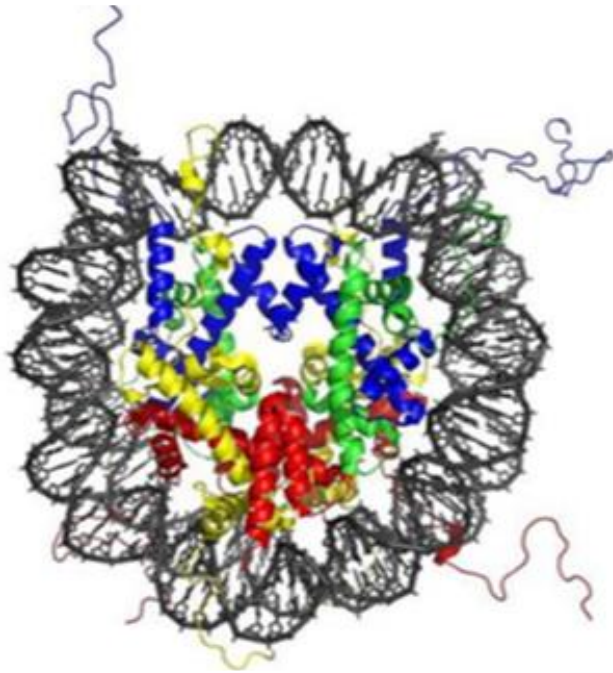
Ru-arene piano-stool complex @ hCA II



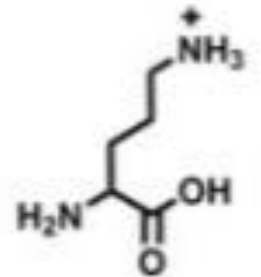
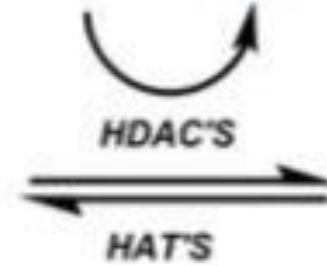
Cromatina, Nucleosomi e Istoni



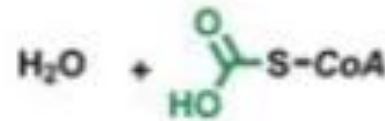
Ogni nucleosoma contiene quattro coppie di istoni e il DNA che li avvolge conta 145–147 coppie di basi



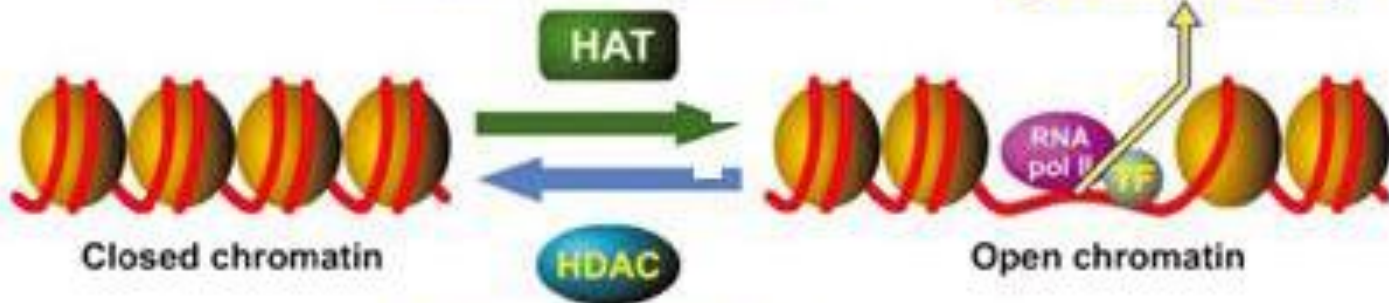
acetylated lysine residue



protonated lysine residue



Histone acetylation
(transcriptional activation)



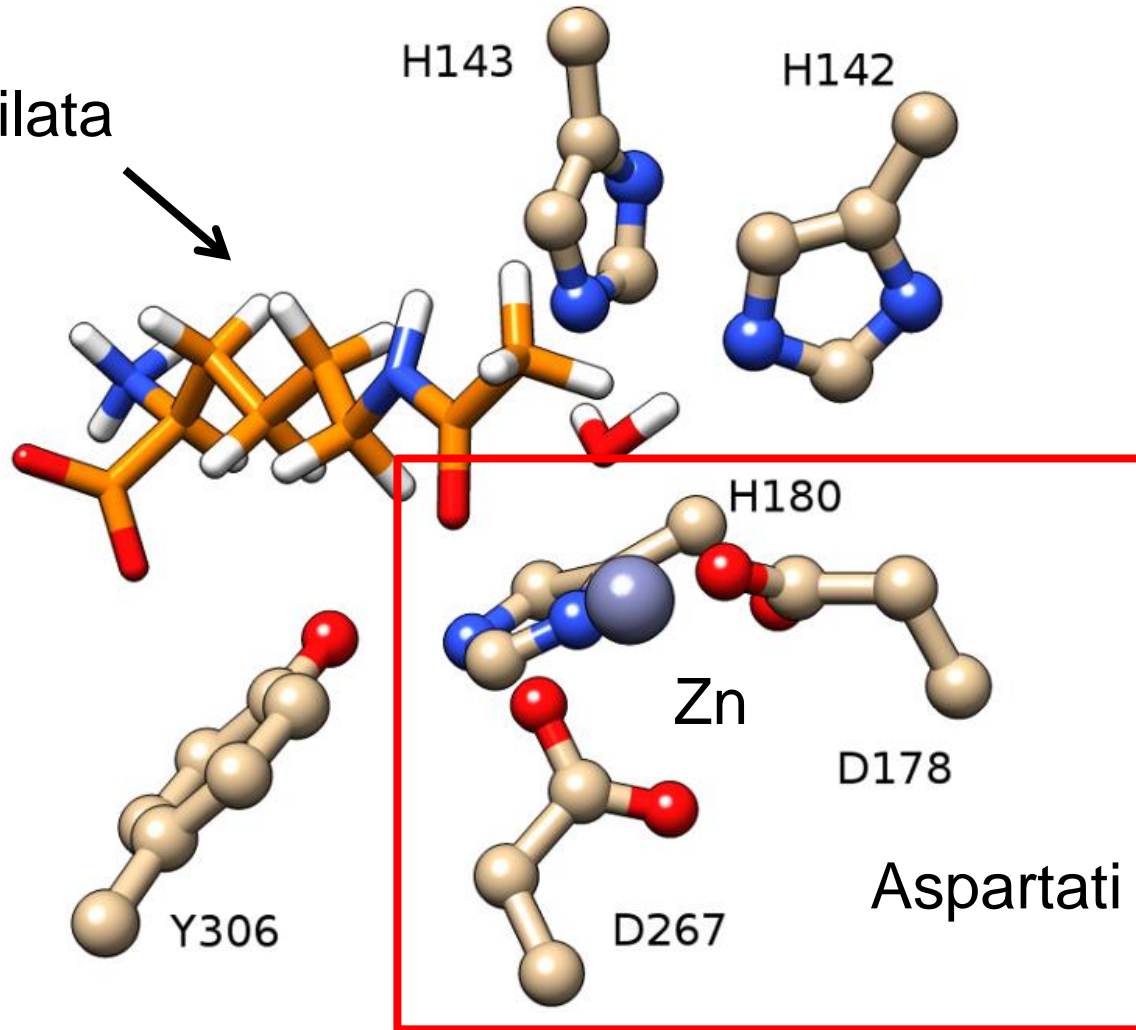
Closed chromatin

Open chromatin

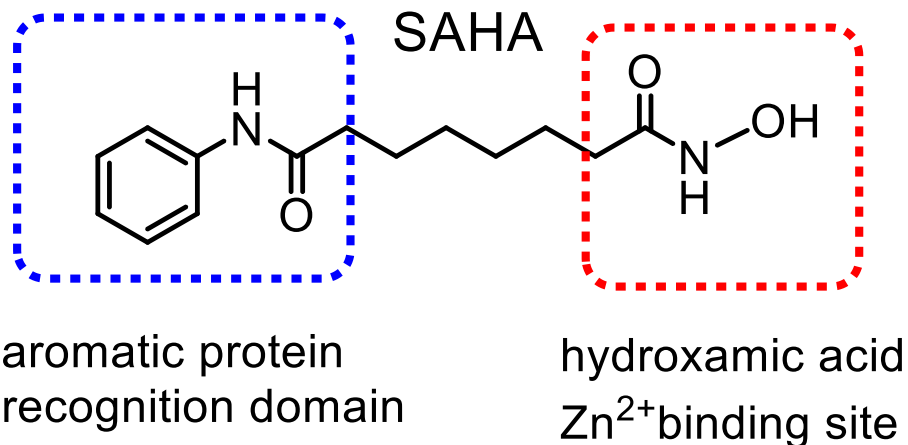
Histone deacetylation
(gene silencing)

HDAC8 active site

Lisina acetilata



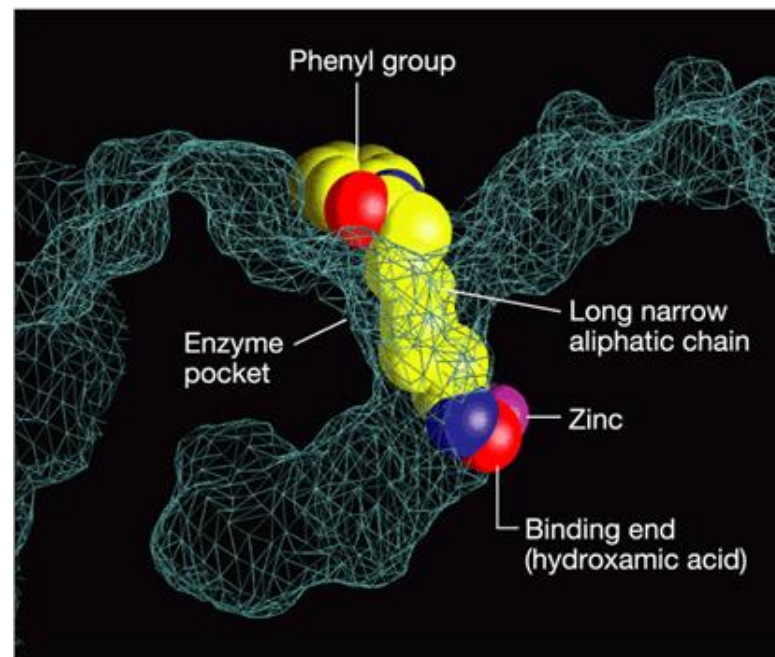
HDAC Inhibitors (HDACi) anticancer agents



Zolinza®

Treatment of *cutaneous T-cell lymphoma*

modulazione epigenetica



Metal-based HDAC Inhibitors

