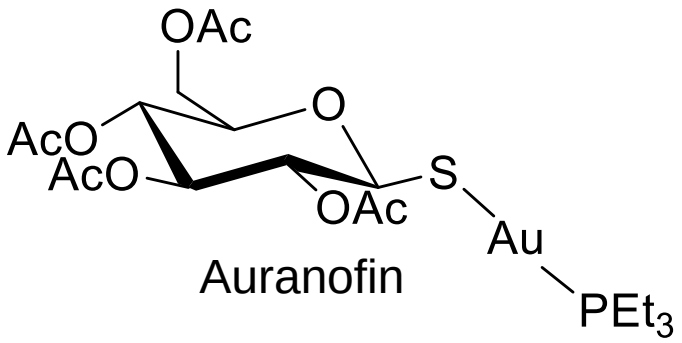
Metal-based Inhibitors of Enzymes

Auranofin: a serendipitous enzyme inhibitor

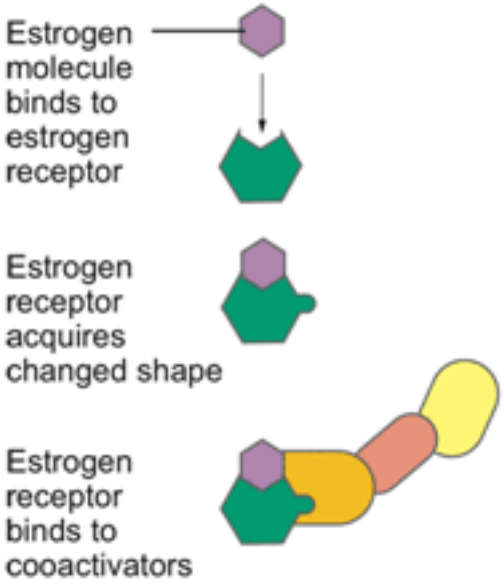


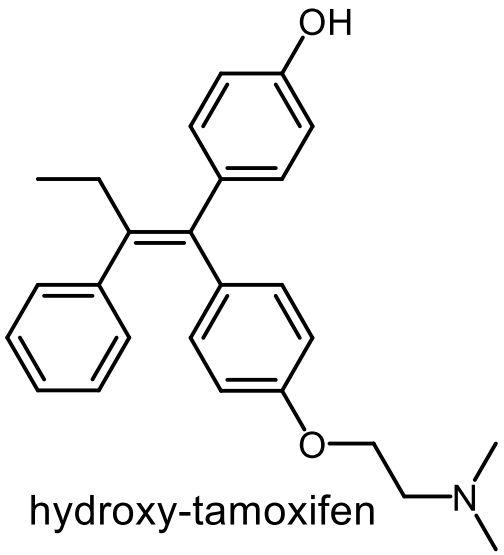
Auranofin

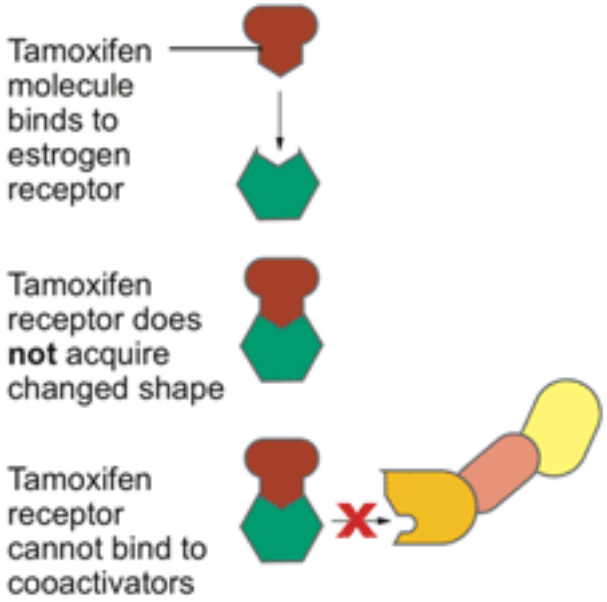
- Introduced in the late 1970s as oral substitute of gold anti-arthritic agents (developed on the wrong assumption that arthritis was caused by a bacterial infection).

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

Estrogen Receptor Inhibitors

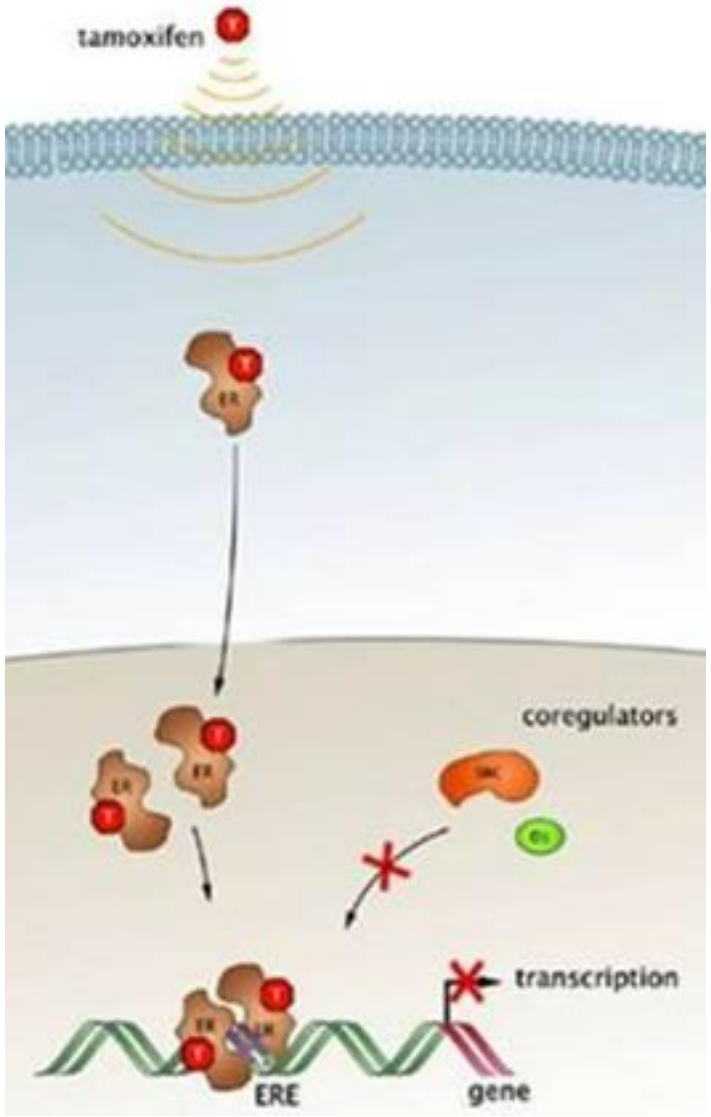






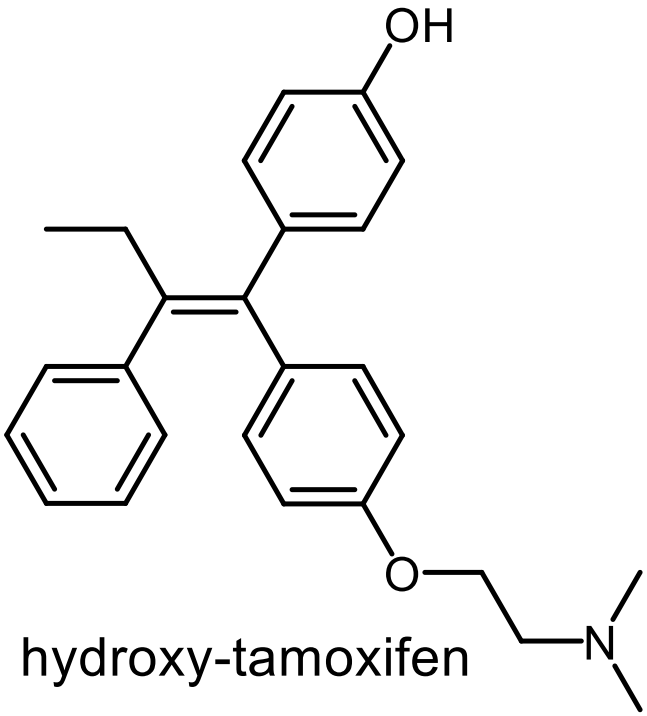
Proliferazione delle cellule tumorali

Inibizione delle cellule tumorali



ERE = estrogen response elements

modulazione epigenetica

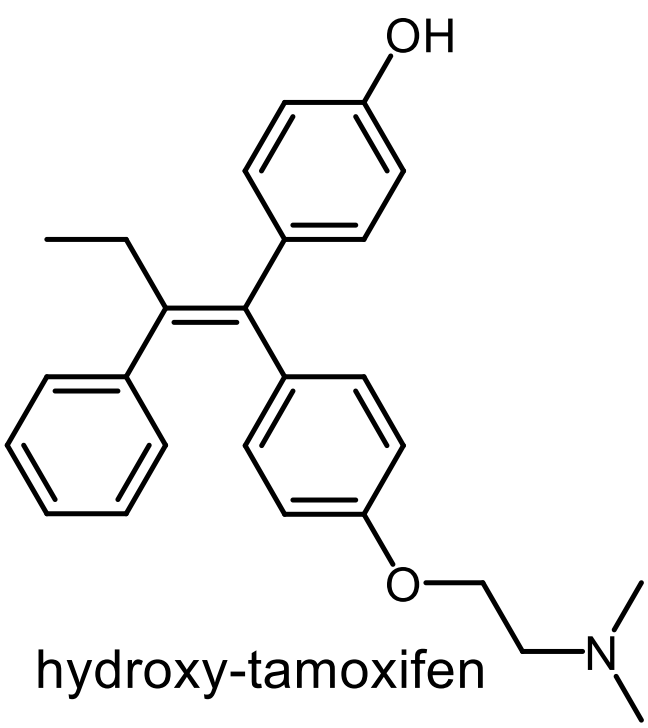


hydroxy-tamoxifen

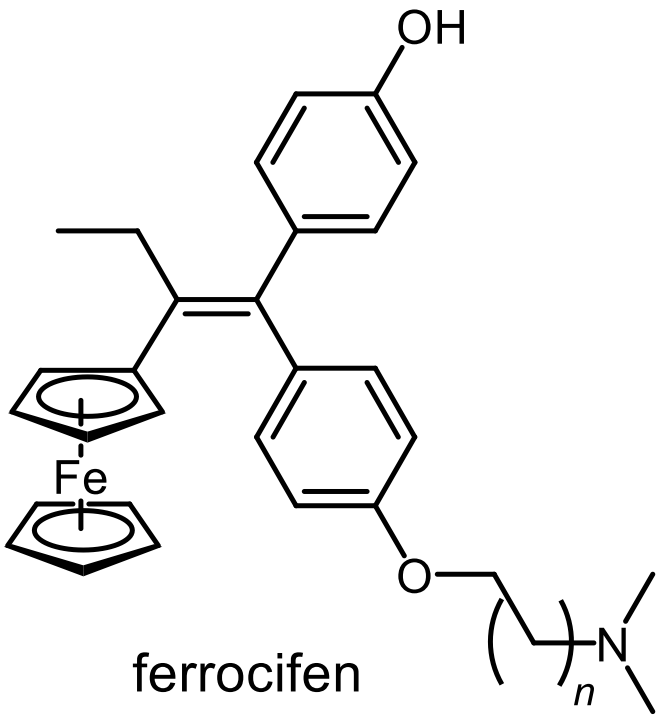
Tamoxifen binds selectively to estrogen receptor α subtype (ERα) in tumor cells, repressing estradiol-mediated DNA transcription.

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

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

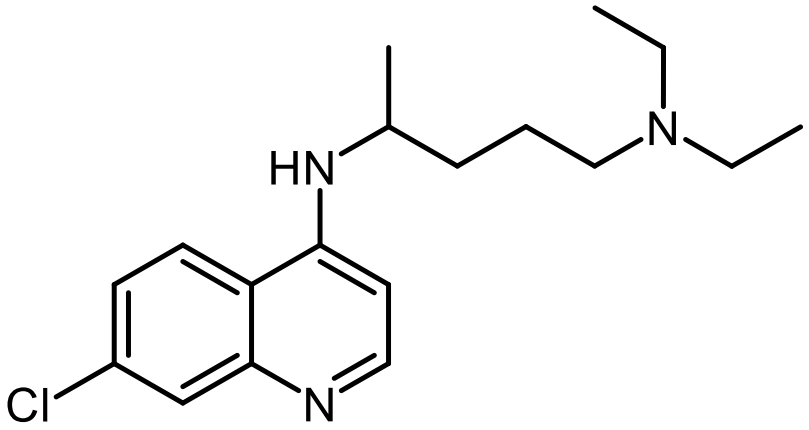


hydroxy-tamoxifen

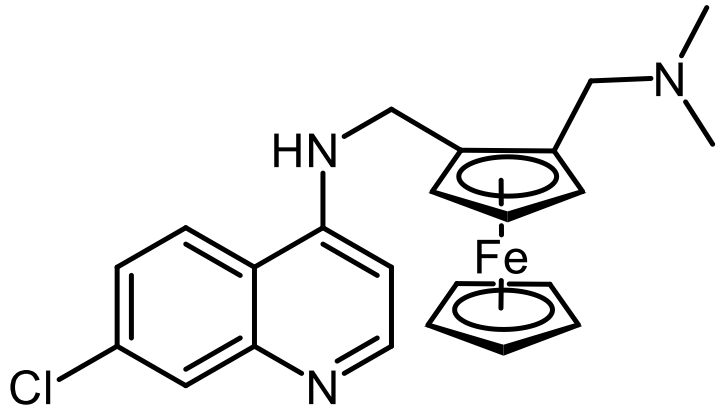


ferrocifen

Bio-isosteric replacement applied to antimalarial drugs



chloroquine

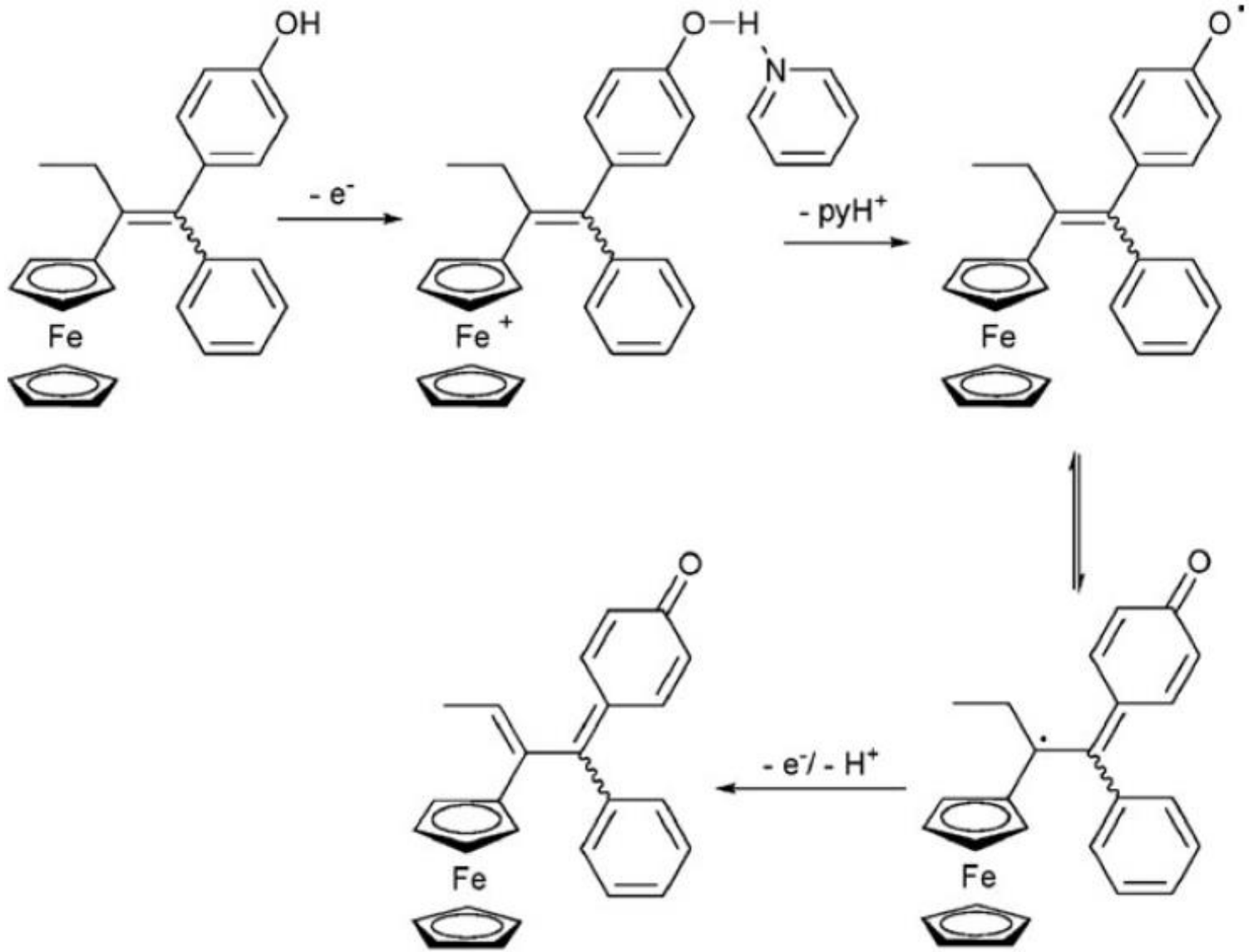


ferroquine

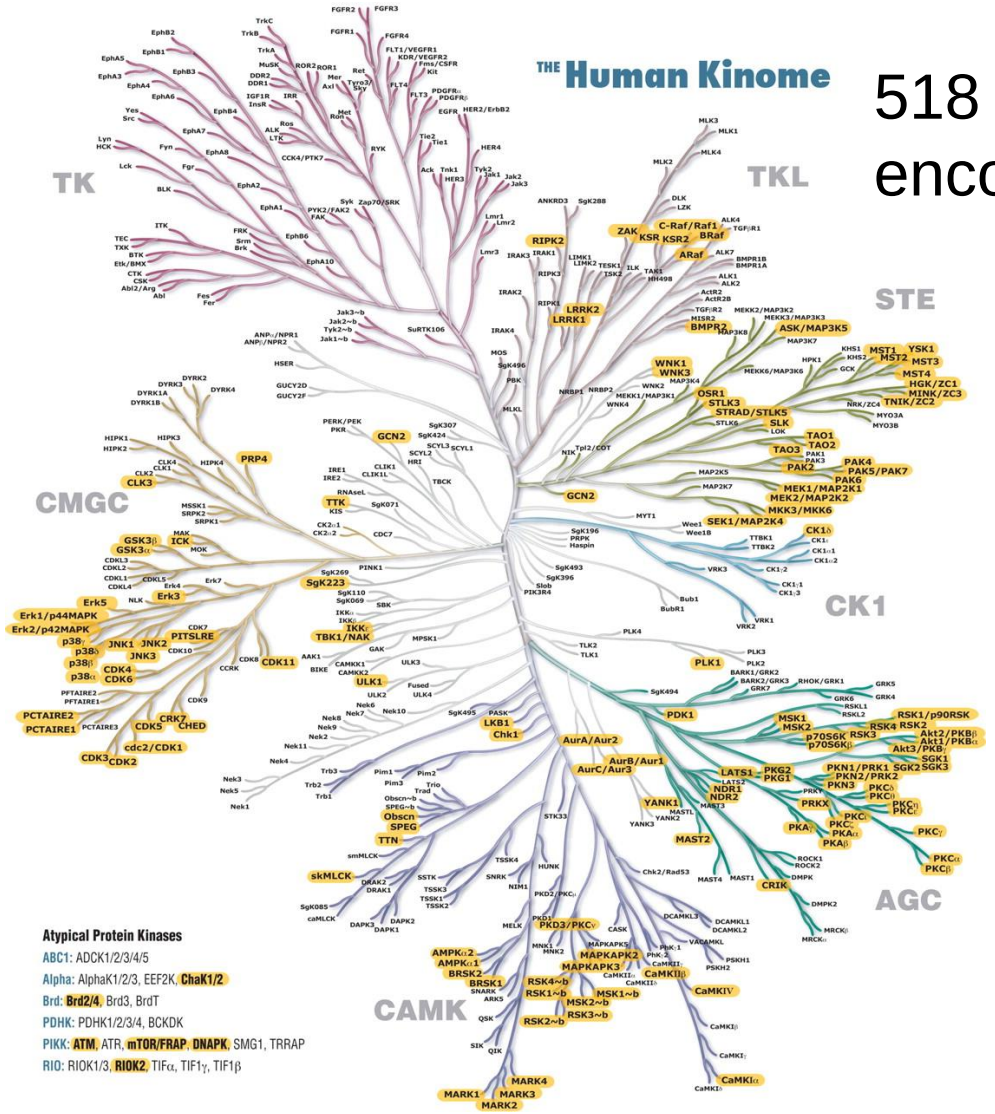
- Ferroquine is the ferrocenyl analogue of chloroquine, an established antimalarial drug.
- Ferroquine is active also against chloroquine-resistant strains and is due to enter clinical phase III trials.

The metal fragment may lead to unexpected behaviors

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

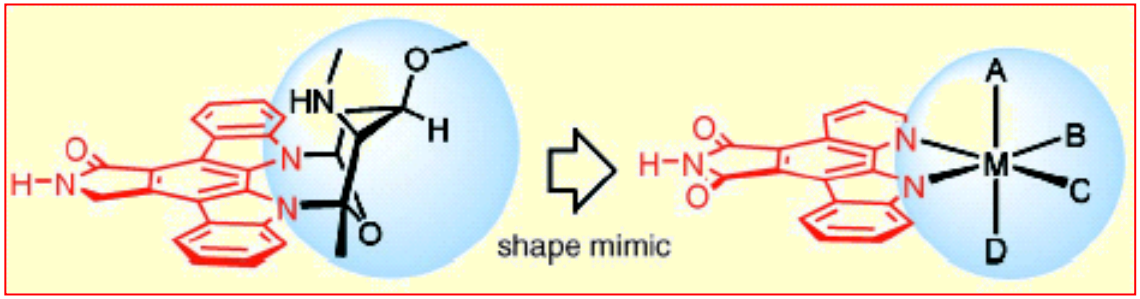

OH
- e⁻
O—H
N
- pyH⁺
O•
Fe
Fe⁺
Fe
O
- e⁻/ - H⁺
O
Fe
Fe

Protein Kinase inhibitors



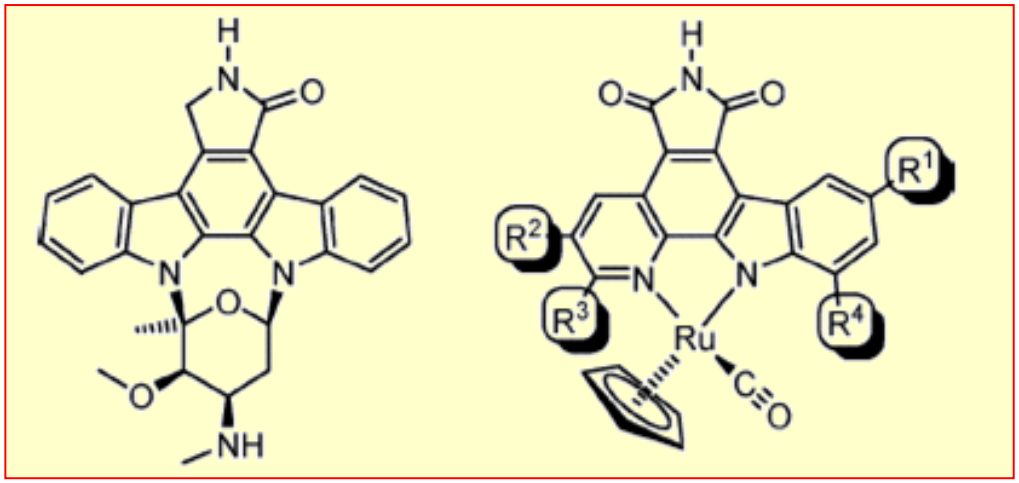
518 different kinases are encoded in the human genome

Selective protein kinase inhibitors

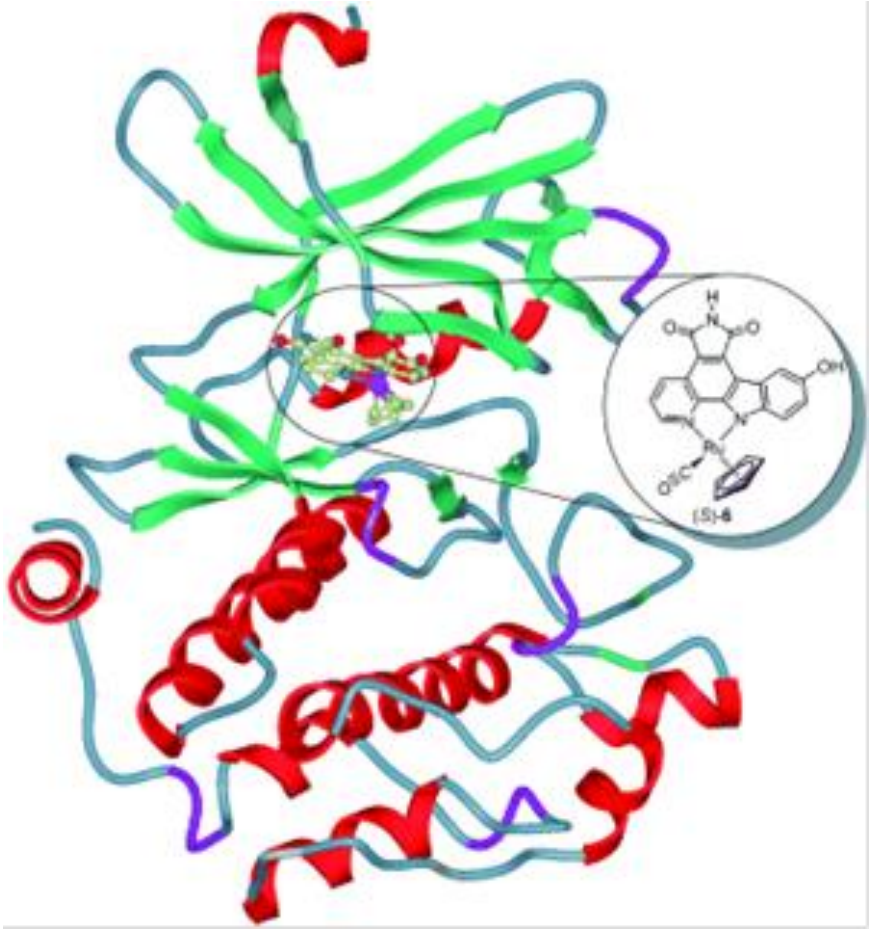


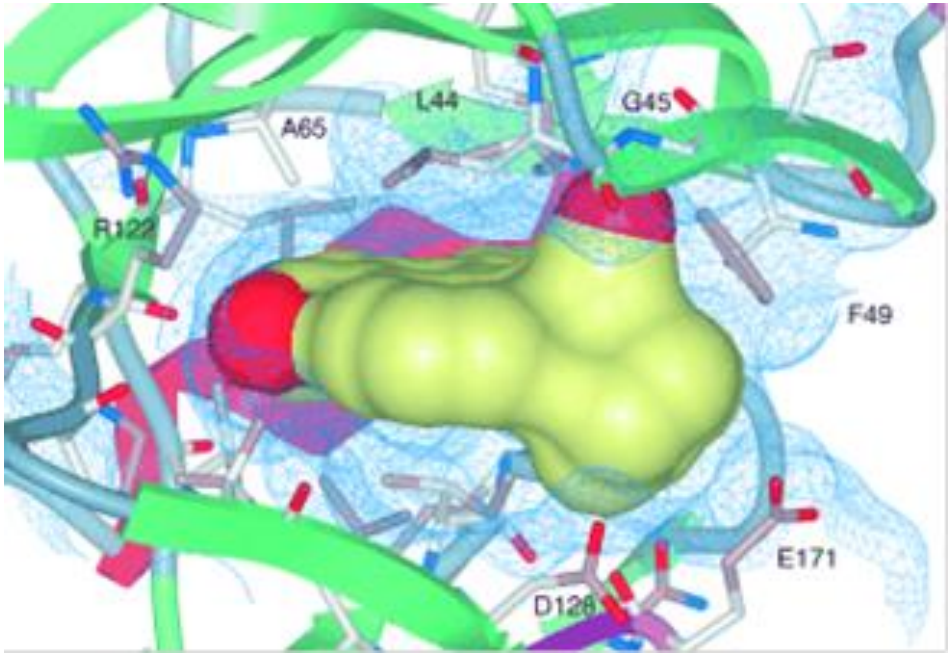
Staurosporine, unselective protein kinase inhibitor (ATP binding site)

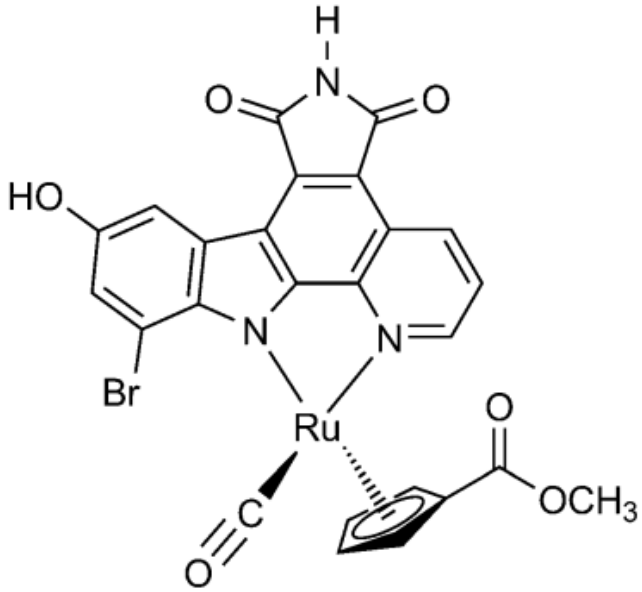
- Great structural variety (geometry)
- Stereochemistry far more diverse than organic compounds
- Rational ligand design



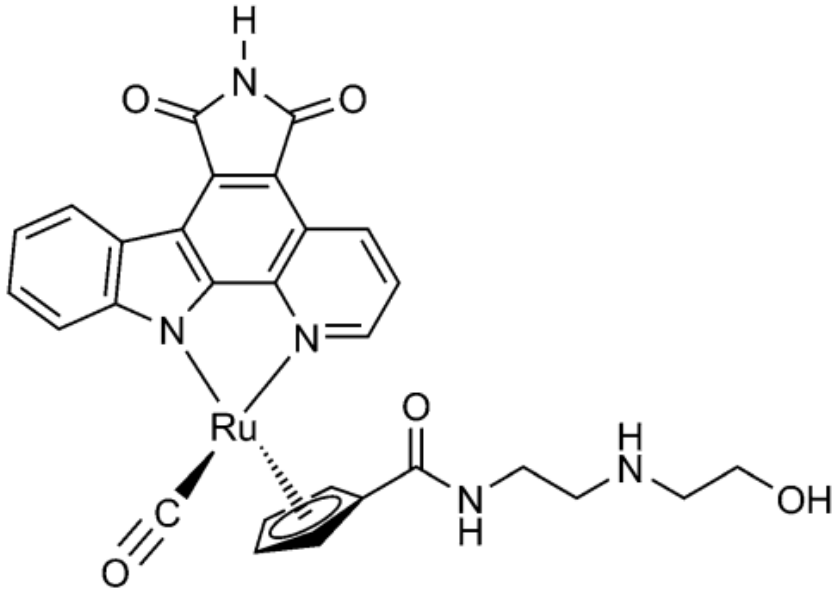
The binding of an organometallic ruthenium inhibitor to the ATP binding site of protein kinase Pim-1







GSK-3 inhibitor
IC_{50} ~ 0.5 nM

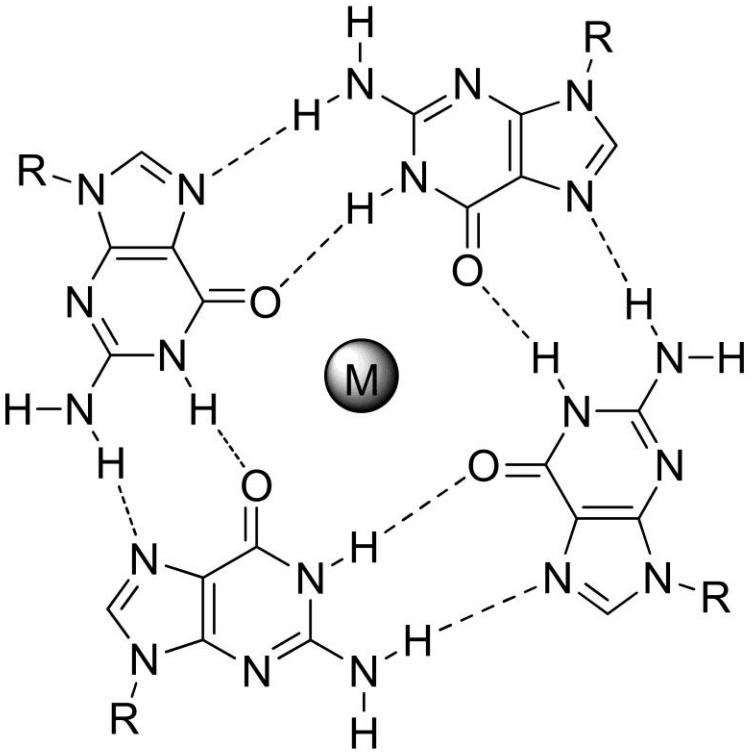


Pim1 inhibitor
IC_{50} ~ 2 nM

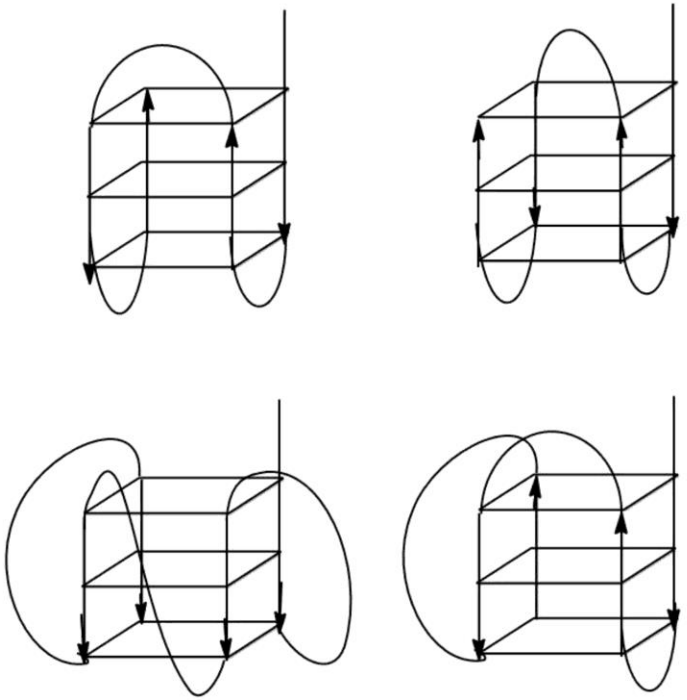
Commercially available

Telomerase

G quartet



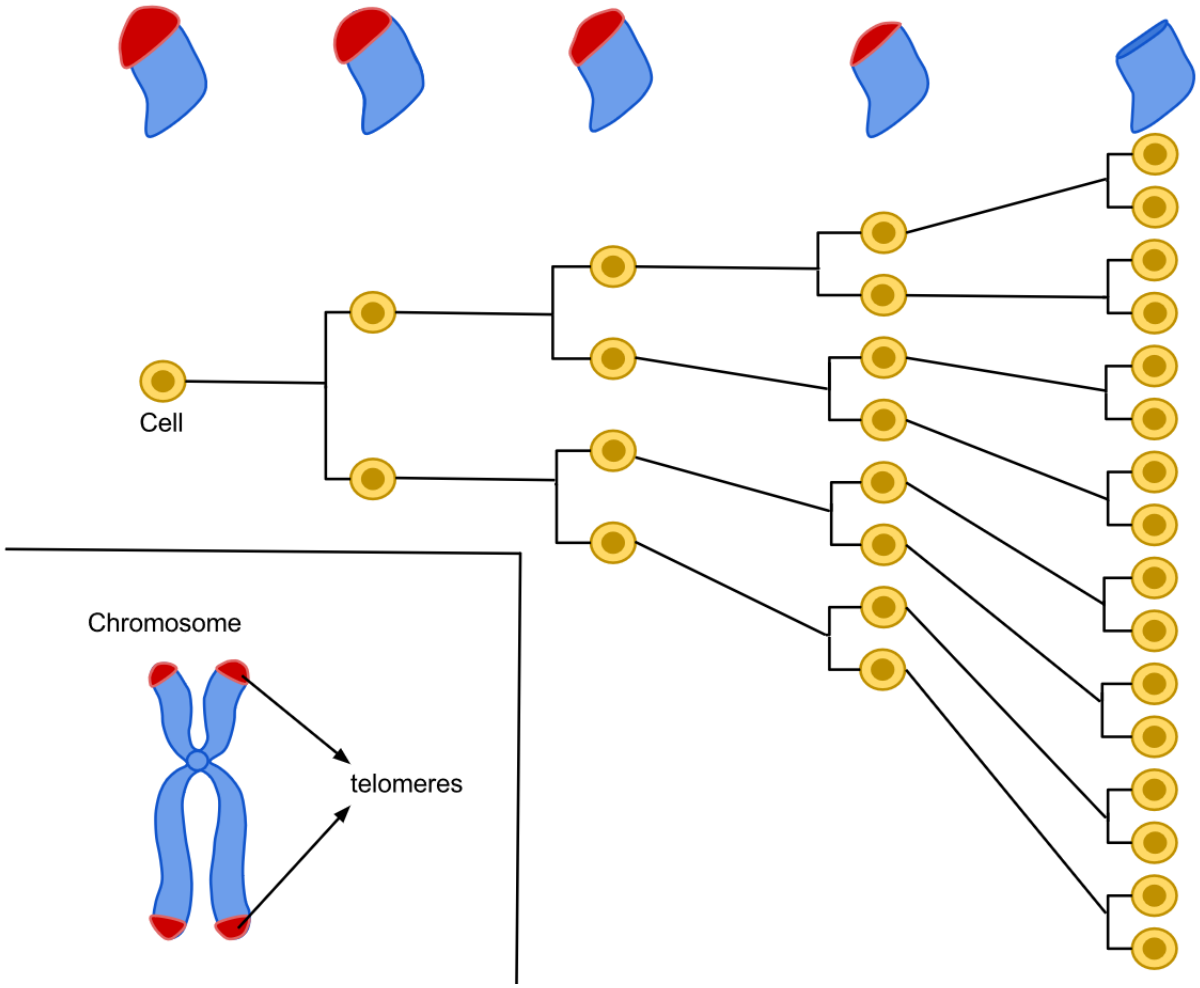
G quadruplexes

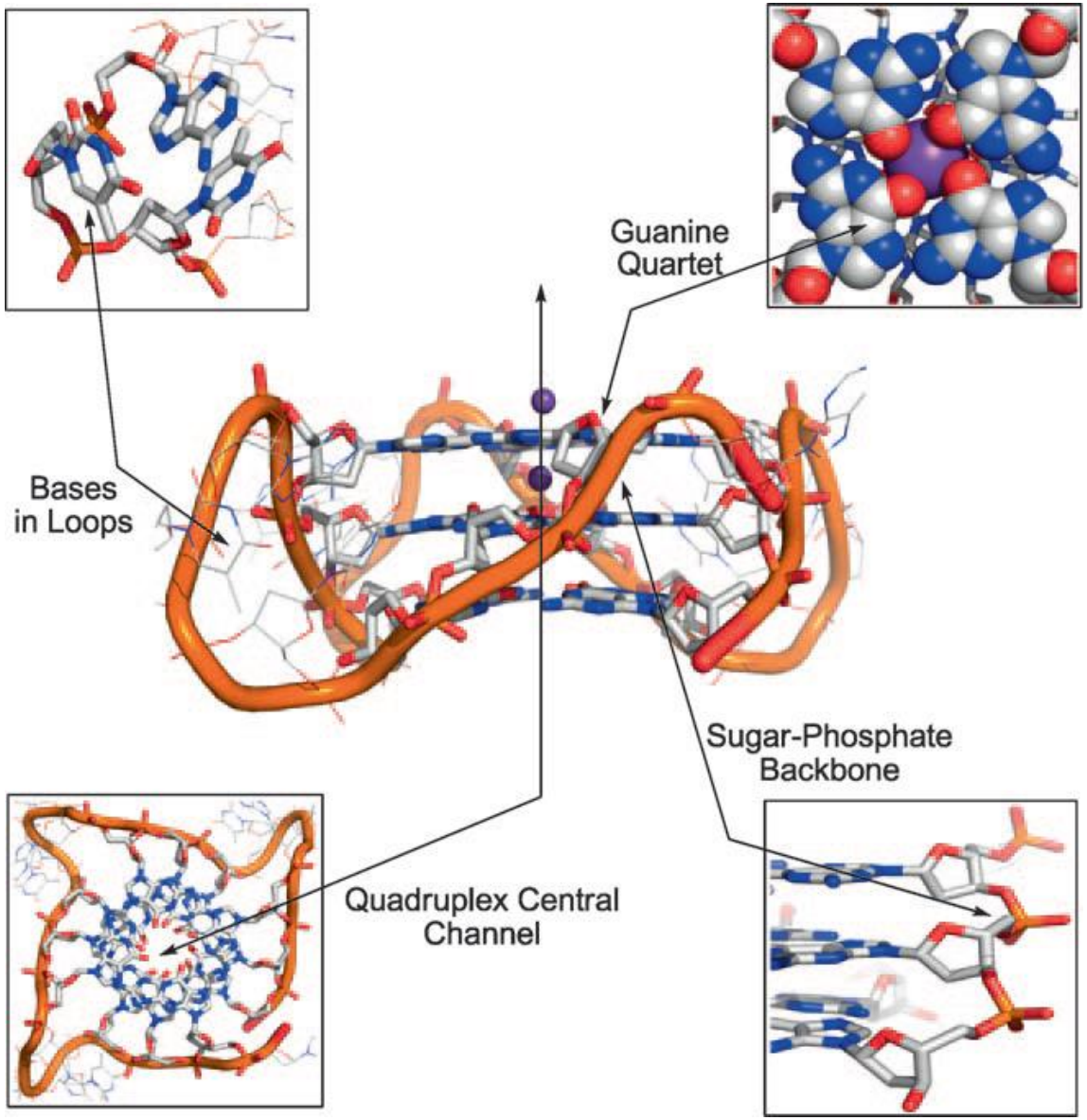


d(TTAGGG) sequences

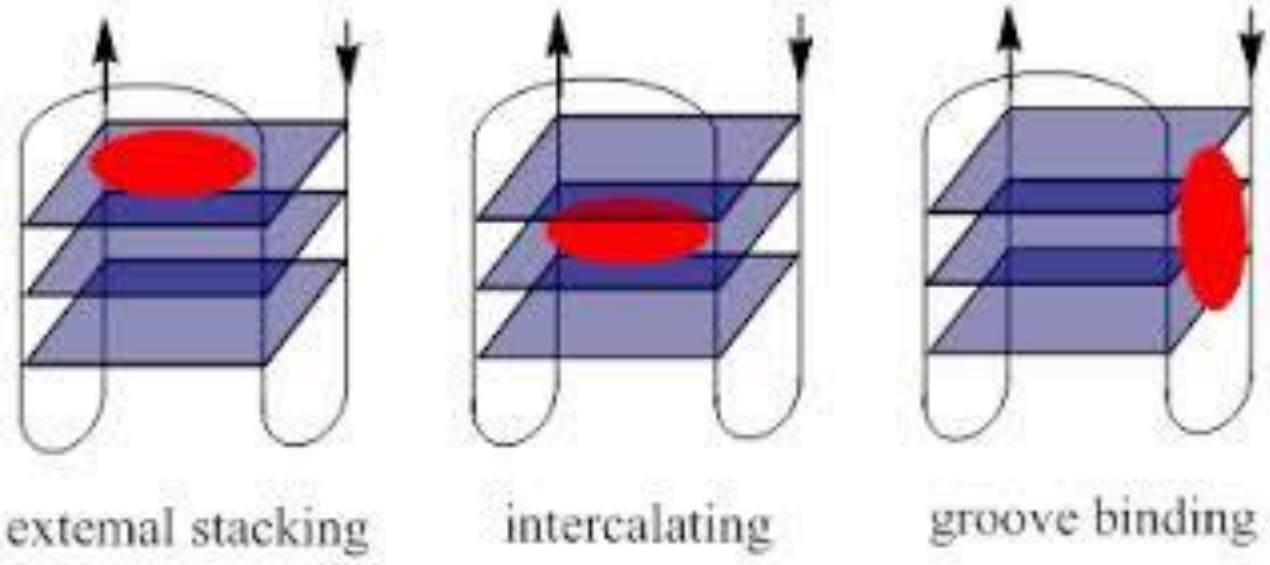
The Hayflick limit

(ca. 50 divisioni cellulari)

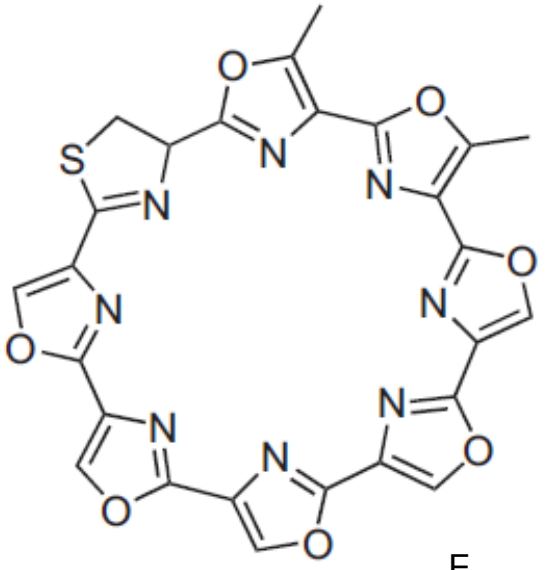



Guanine
Quartet
Bases
in Loops
Sugar-Phosphate
Backbone
Quadruplex Central
Channel

G-quadruplex stabilization for telomerase inhibition

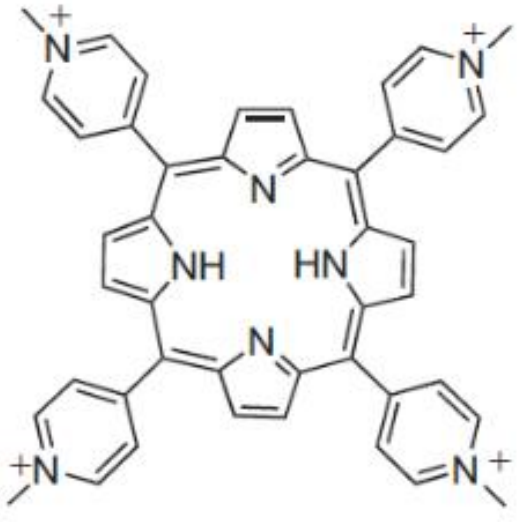


Telomerase Inhibitors

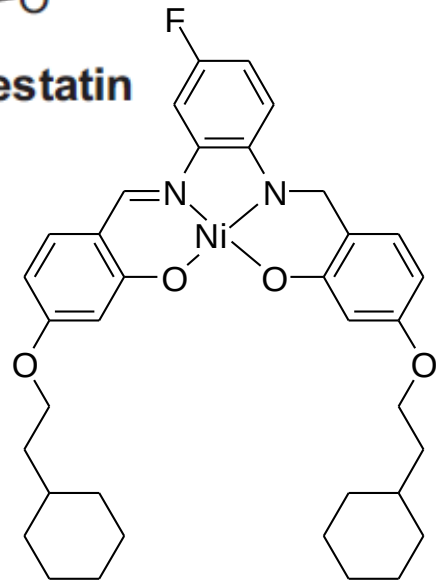


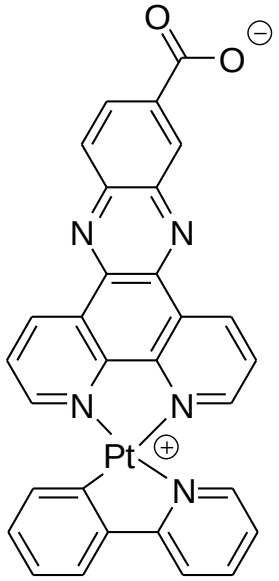
Telomestatin

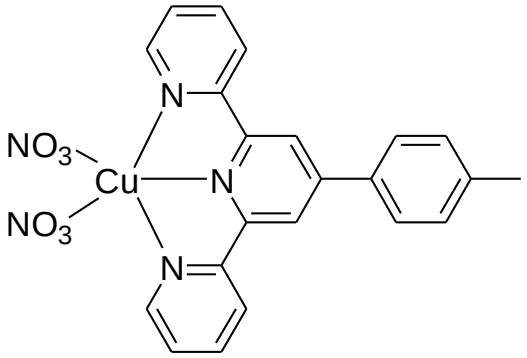
π stacking on G quartets



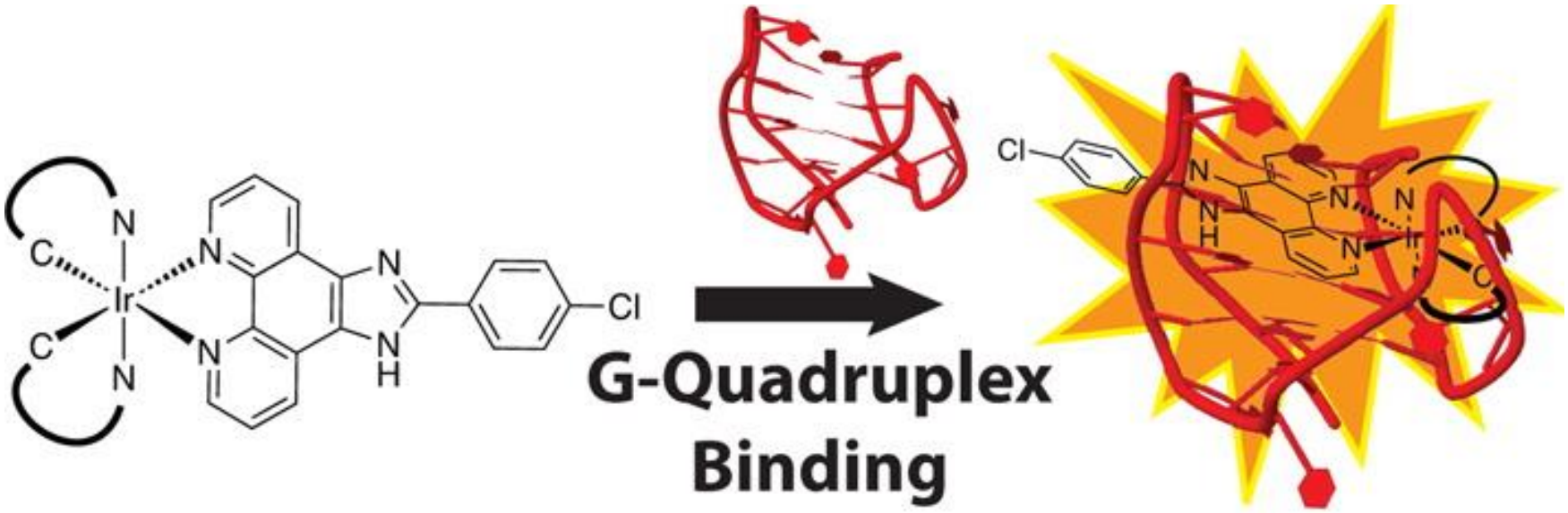
TmPyP4





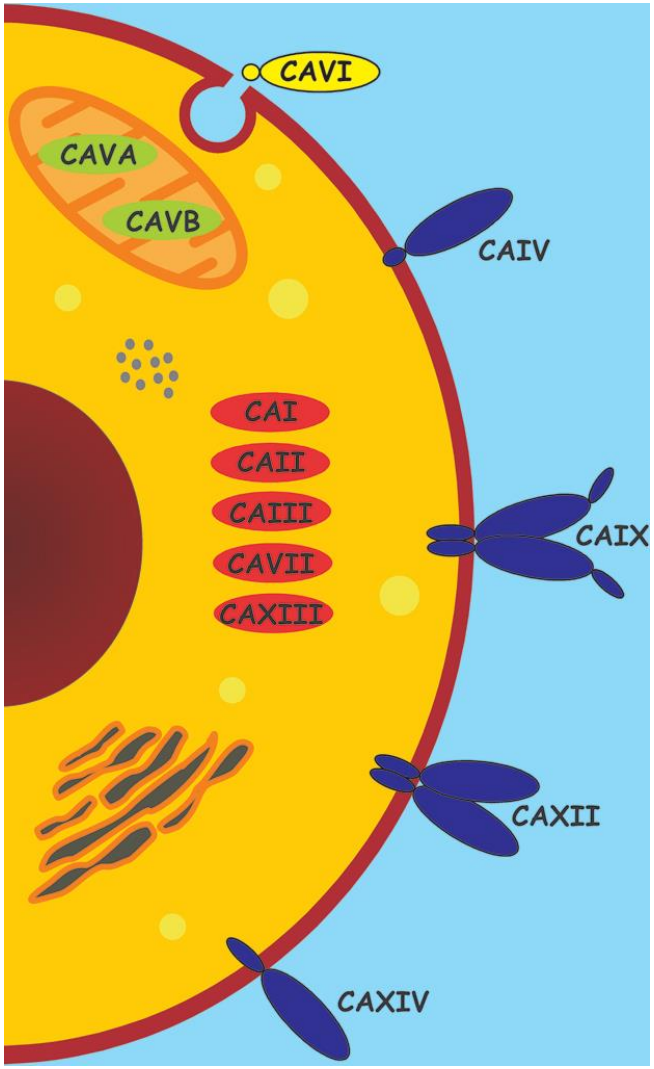


G-quadruplex sensing



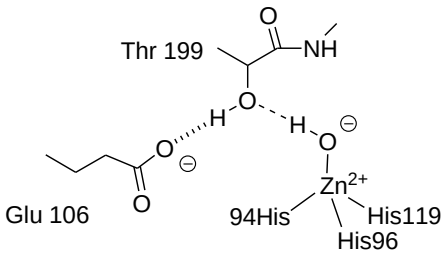
Metal-based Inhibitors of Metallo-Enzymes

Human Carbonic Anhydrase (hCA) inhibitors



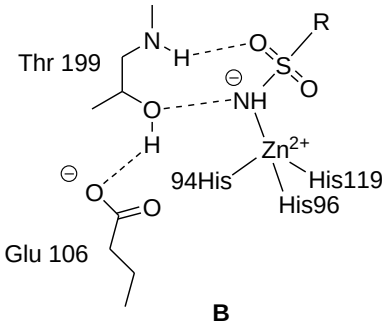
sulfonamidi

anioni coordinanti



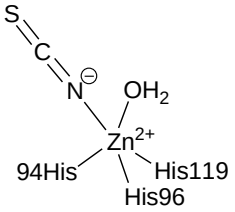
A

Zn(II) ion coordination in the hCA II active site



B

Tetrahedral adduct (sulfonamide)



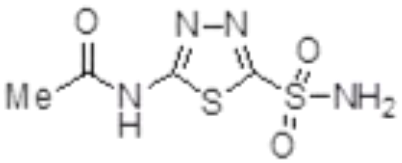
C

Trigonal-bipyramidal adduct (thiocyanate)

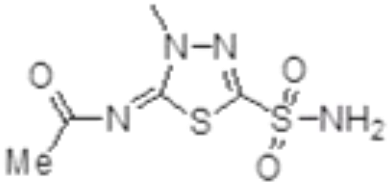
$$H_2O + CO_2 \rightleftharpoons HCO_3^- + H^+$$

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

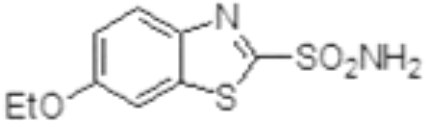
Sulfonamides as CA inhibitors



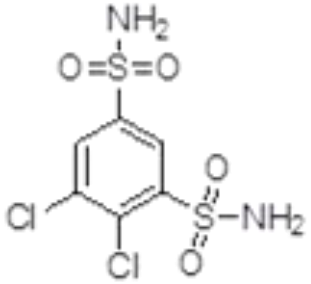
Acetazolamide (AAZ)



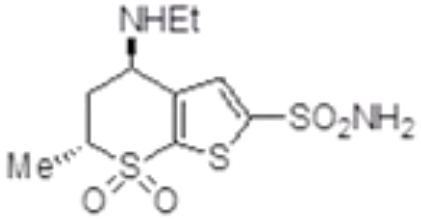
Methazolamide (MZA)



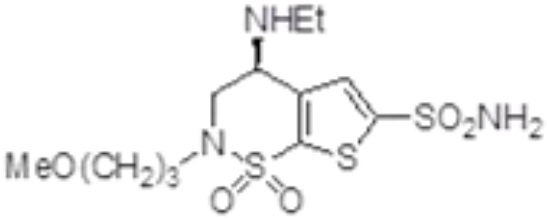
Ethoxzolamide (EZA)



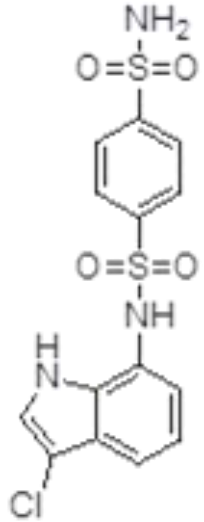
Dichlorophenamide (DCP)



Dorzolamide (DZA)

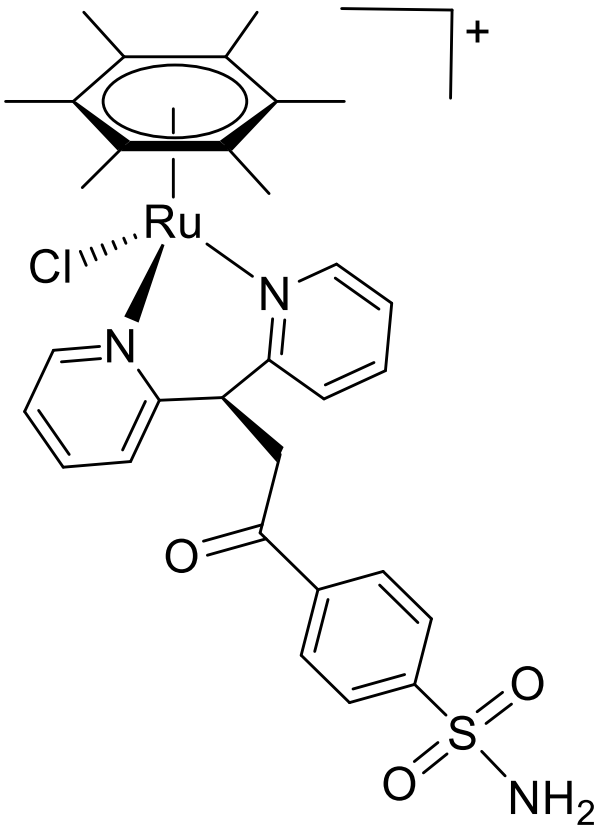


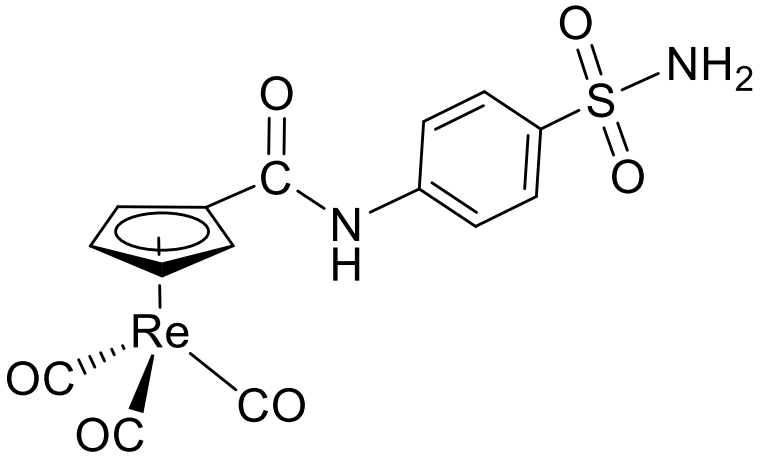
Brinzolamide (BRZ)

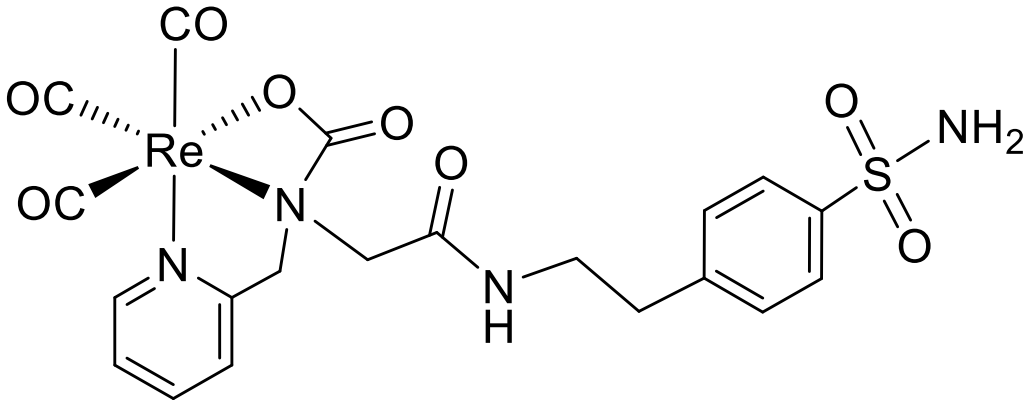


Indisulam (IND)

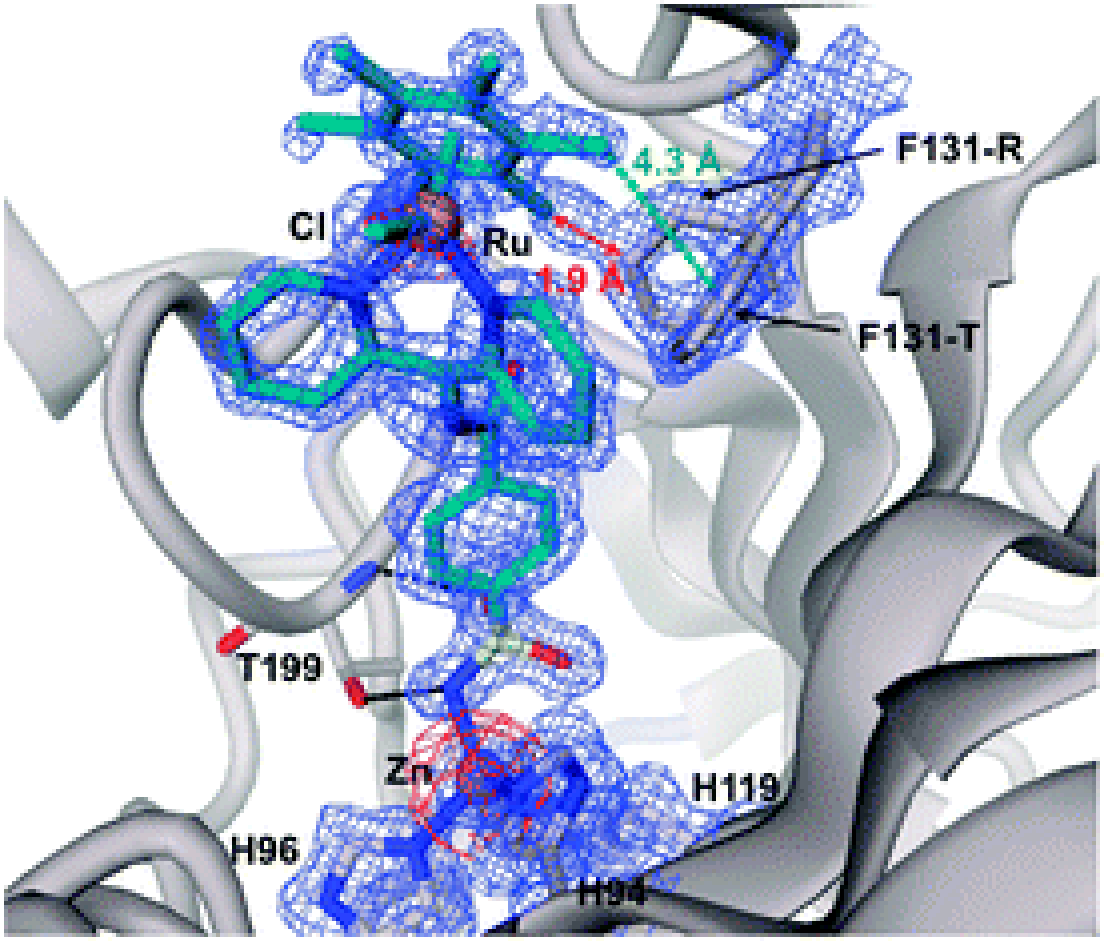
Inert organometallic compounds as hCA inhibitors



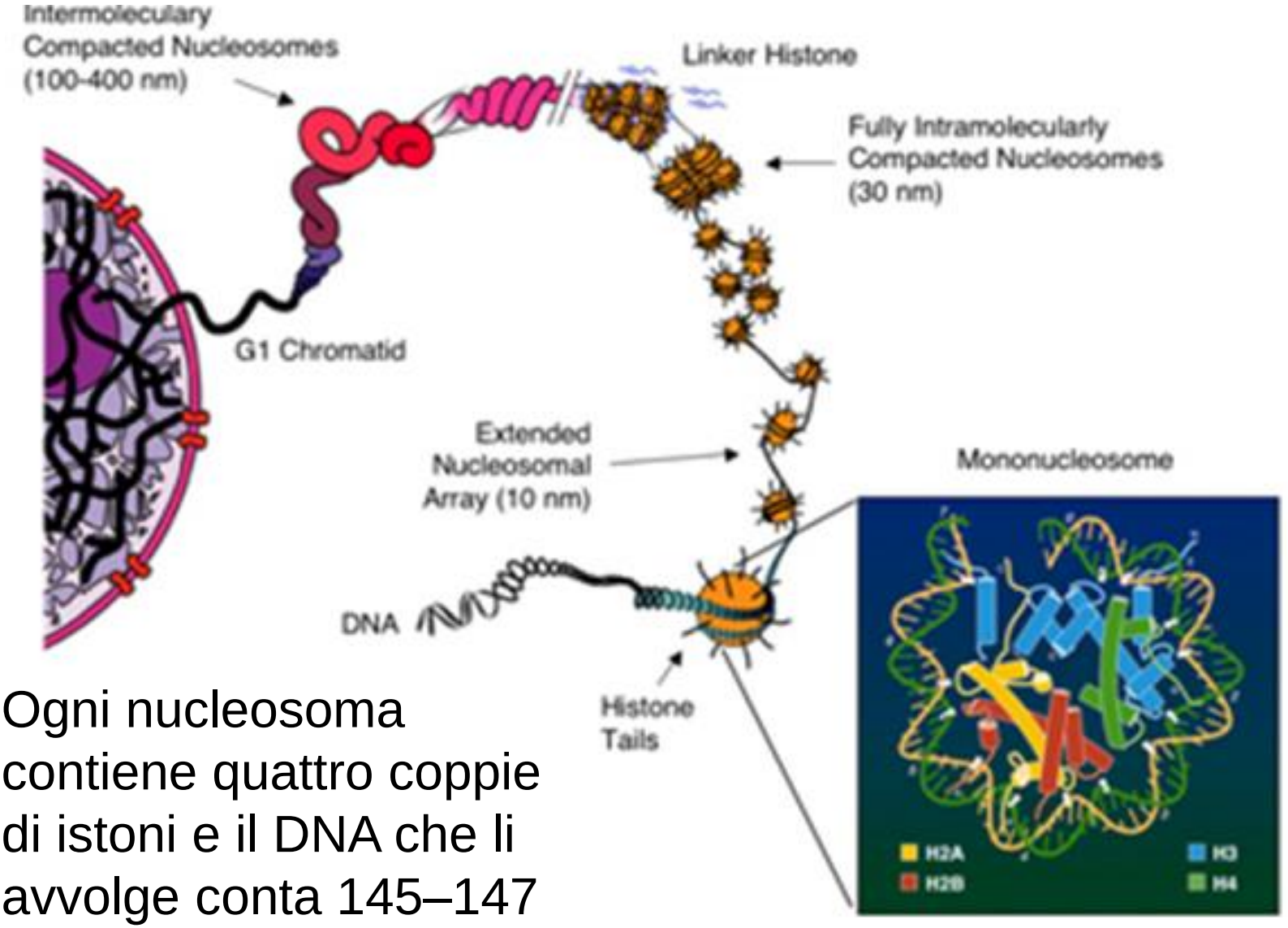




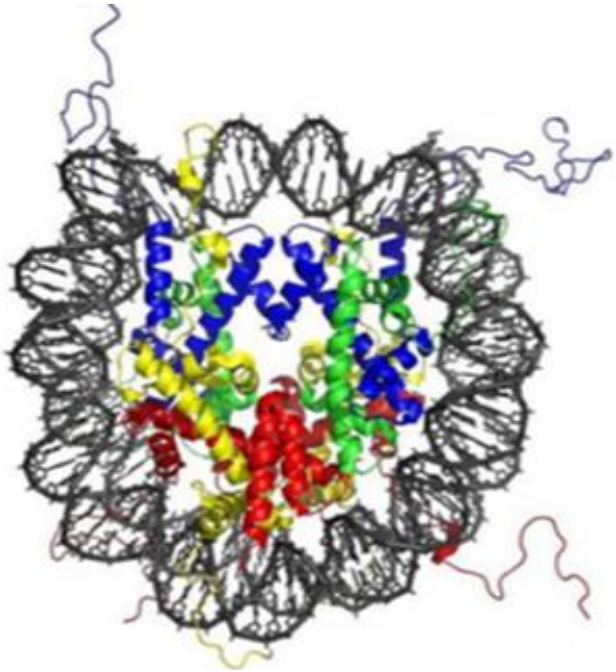
Ru-arene piano-stool complex @ hCA II

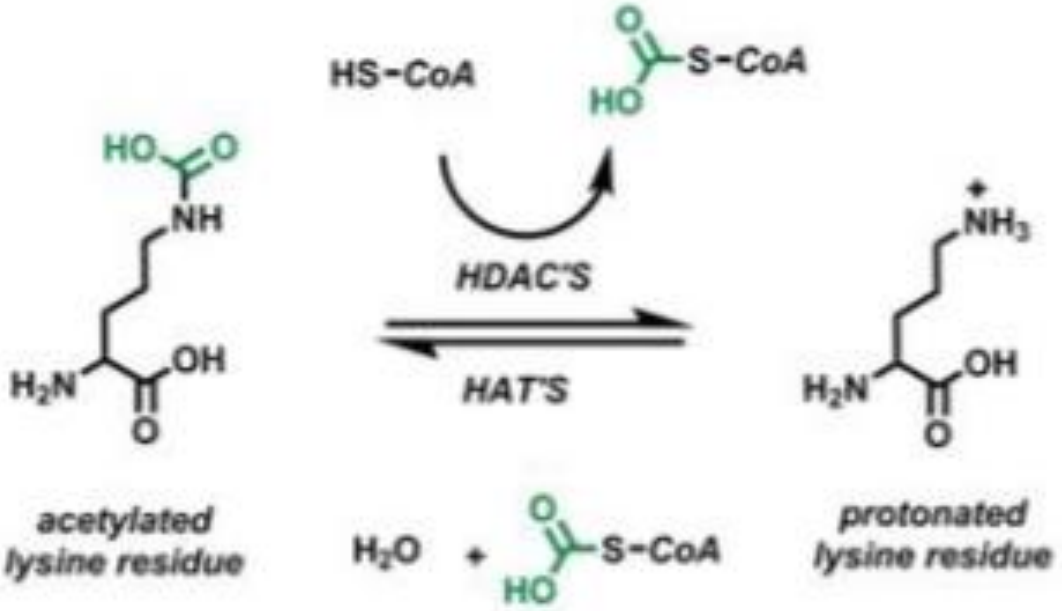


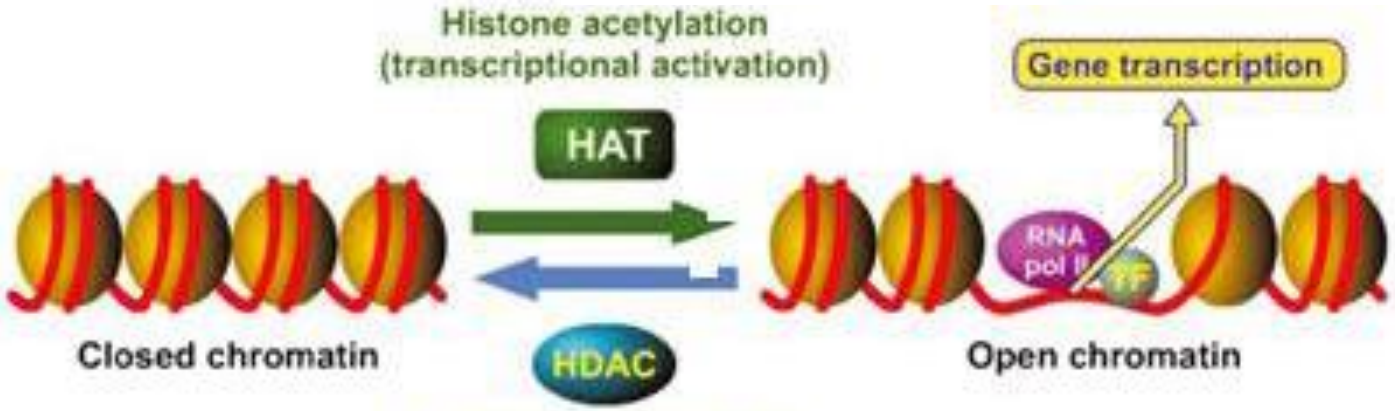
Cromatina, Nucleosomi e Istoni



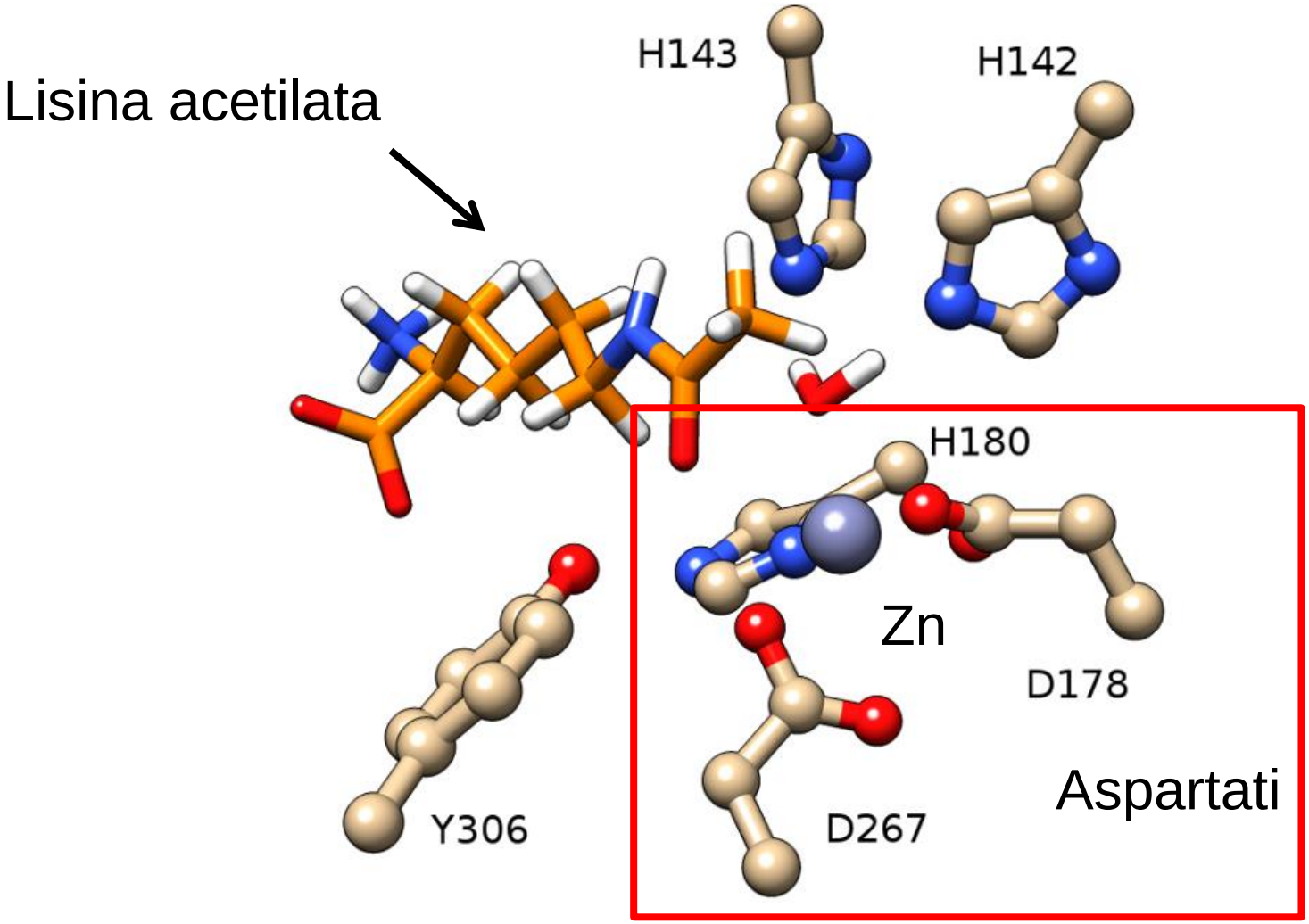
Ogni nucleosoma contiene quattro coppie di istoni e il DNA che li avvolge conta 145–147 coppie di basi



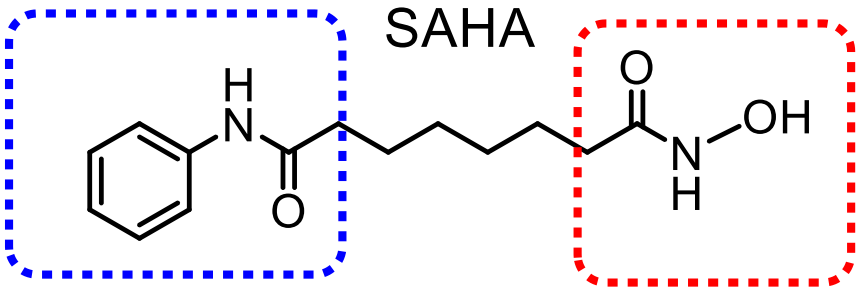

HS-CoA
S-CoA
HO
HDAC'S
HAT'S
NH
OH
H_2N
O
NH_3
acetylated
lysine residue
H_2O
protonated
lysine residue


Histone acetylation
(transcriptional activation)
HAT
Gene transcription
RNA
pol II
TF
Closed chromatin
HDAC
Open chromatin
Histone deacetylation
(gene silencing)

HDAC8 active site

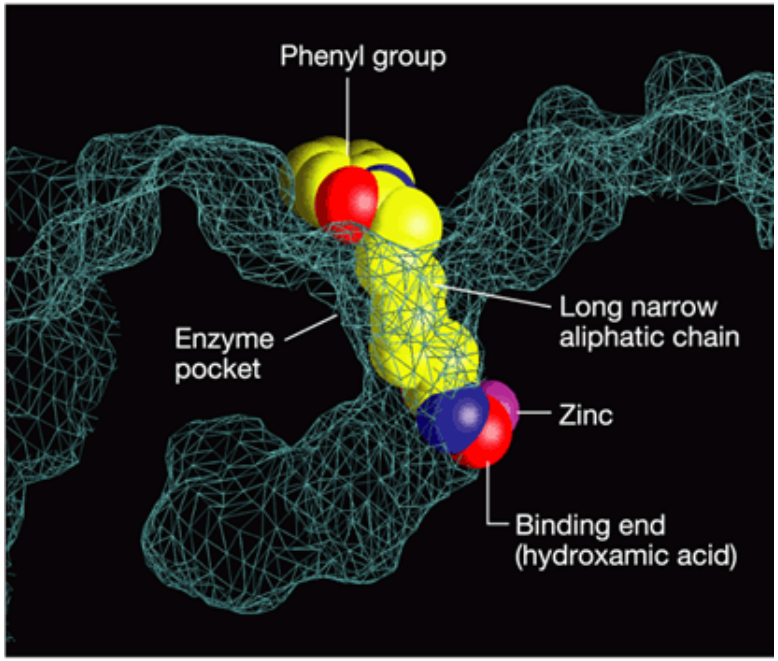


HDAC Inhibitors (HDACi) anticancer agents



aromatic protein recognition domain

hydroxamic acid Zn^{2+}binding site



Zolinza®

Treatment of *cutaneous T-cell lymphoma*

modulazione epigenetica

Metal-based HDAC Inhibitors