METALLI IN MEDICINA

A.A. 2016-2017

PARTE 7

Enzo Alessio

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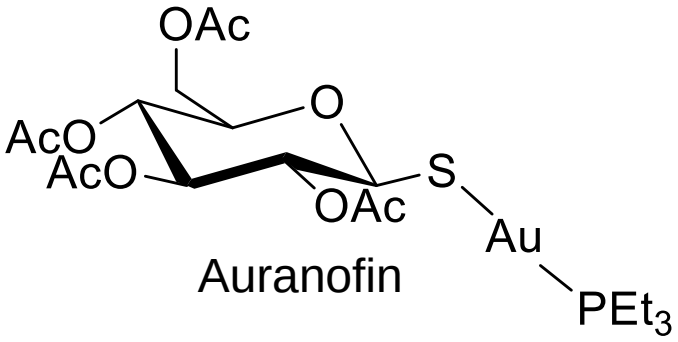
Metal-based Inhibitors of Enzymes

Auranofin: a serendipitous enzyme inhibitor

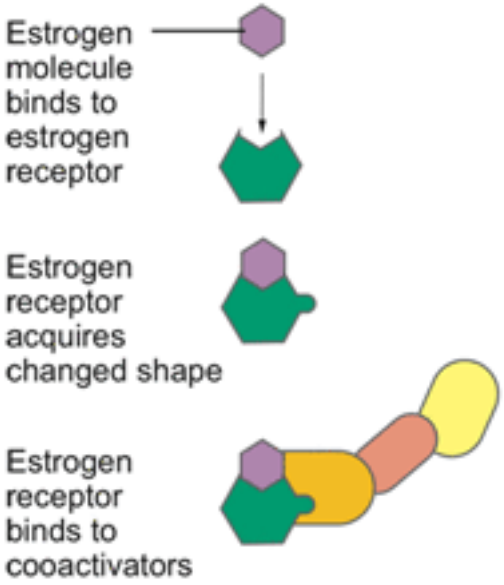


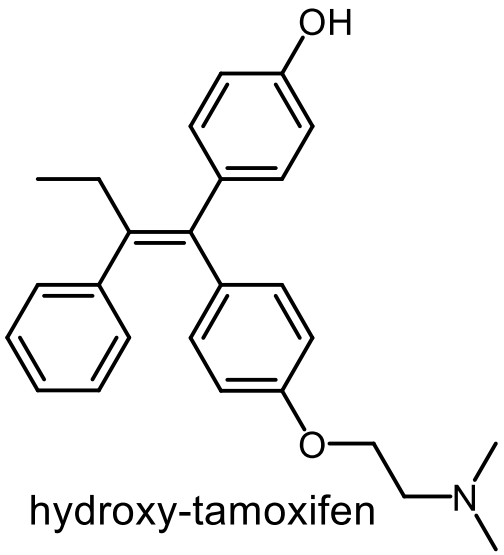
Auranofin

- 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).

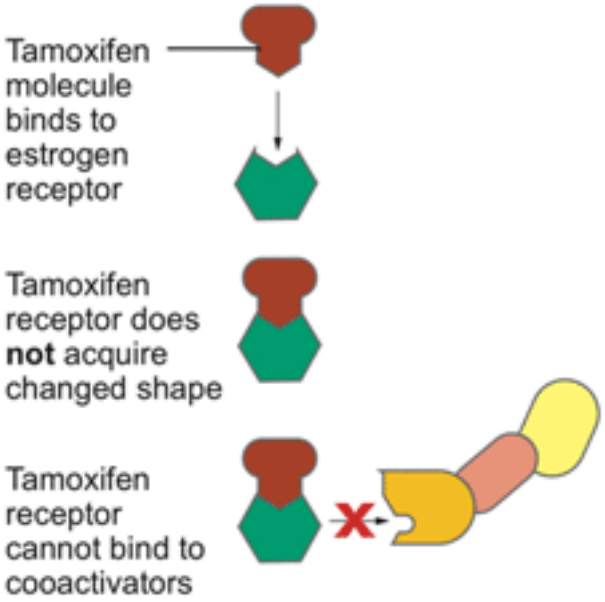
Au(I) from Auranofin strongly inhibits *in vitro* the seleno-cysteine enzymes *Thioredoxin reductase* and *Glutatione peroxidase*

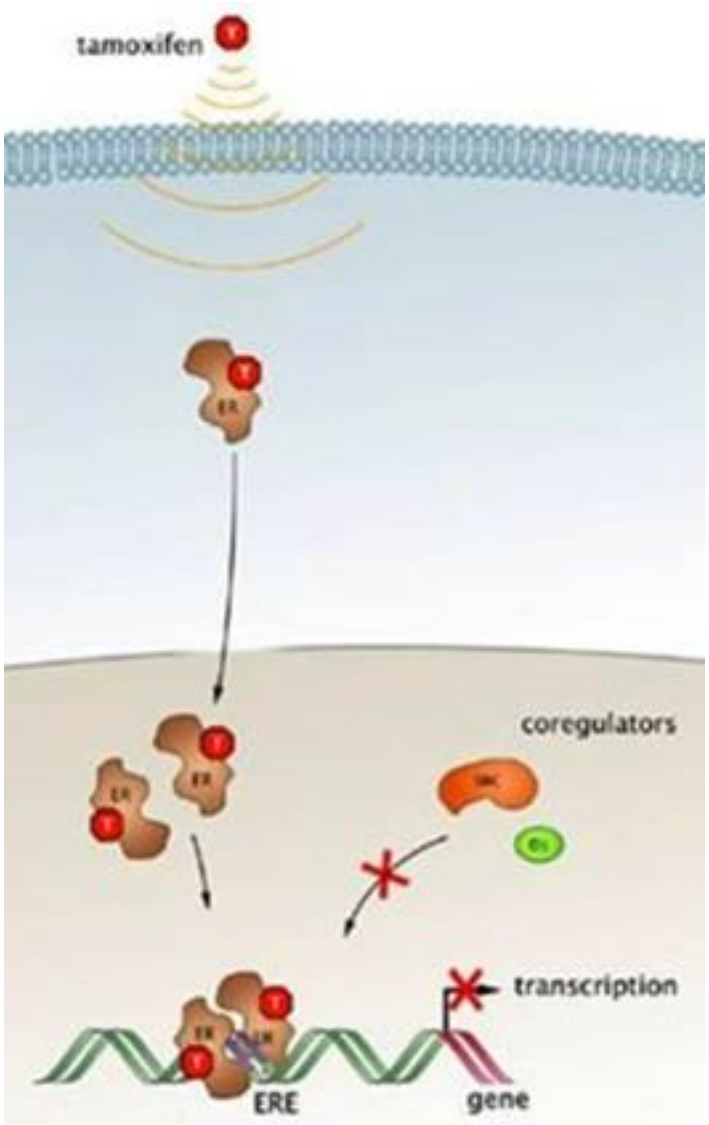
Estrogen Receptor Inhibitors



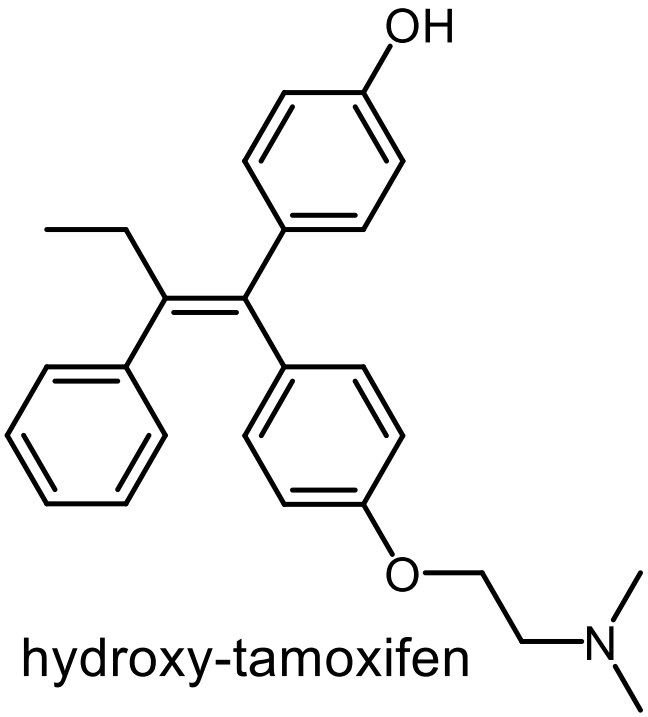


hydroxy-tamoxifen





ERE = estrogen response elements

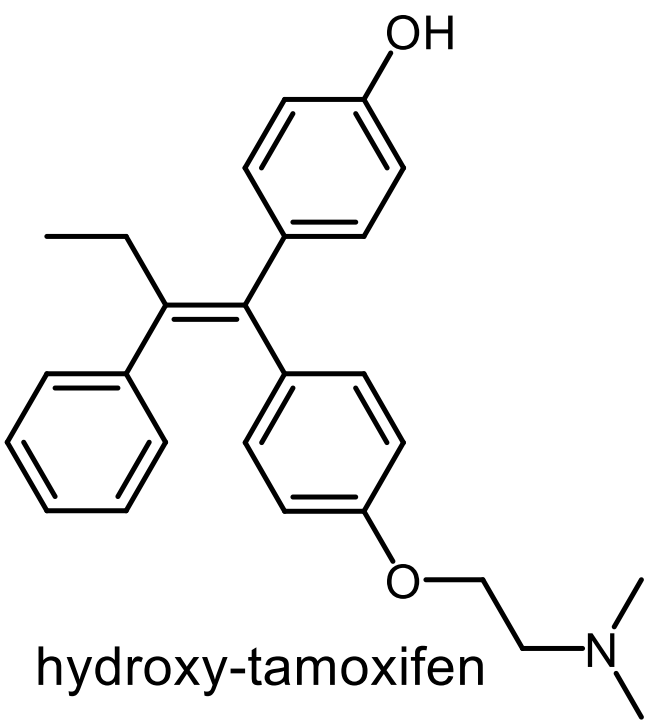


hydroxy-tamoxifen

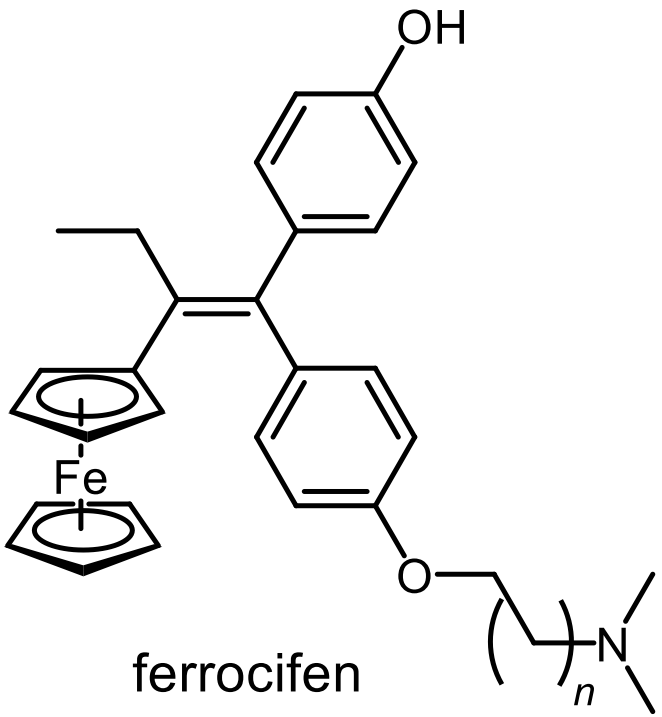
Tamoxifen binds selectively to estrogen receptor α subtype (ERα) in tumor cells, repressing estradiol-mediated DNA transcription.

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

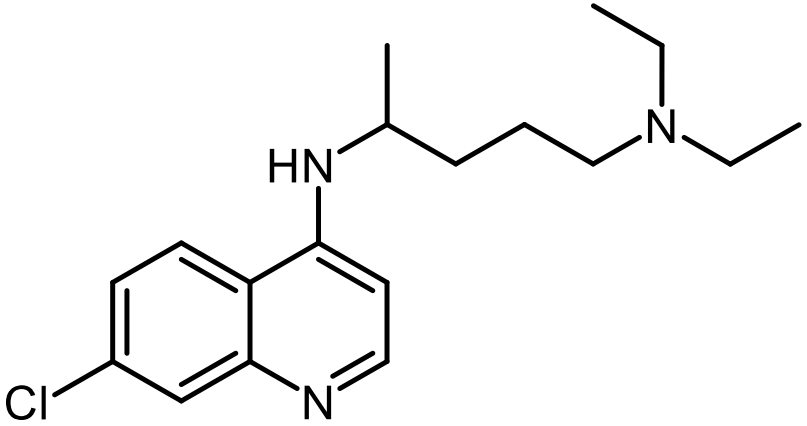


hydroxy-tamoxifen

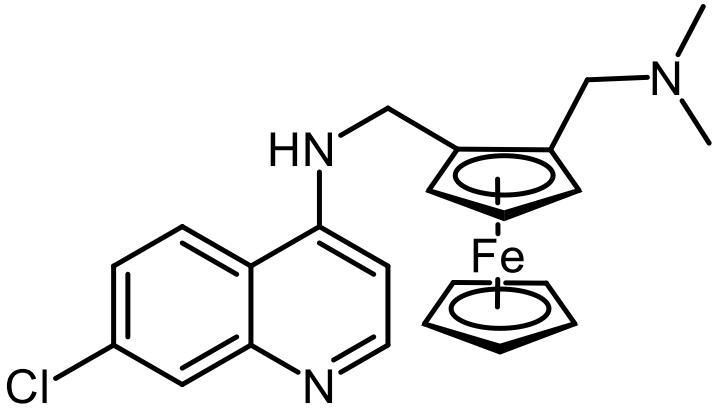


ferrocifen

Bio-isosteric replacement applied to antimalarial drugs



chloroquine

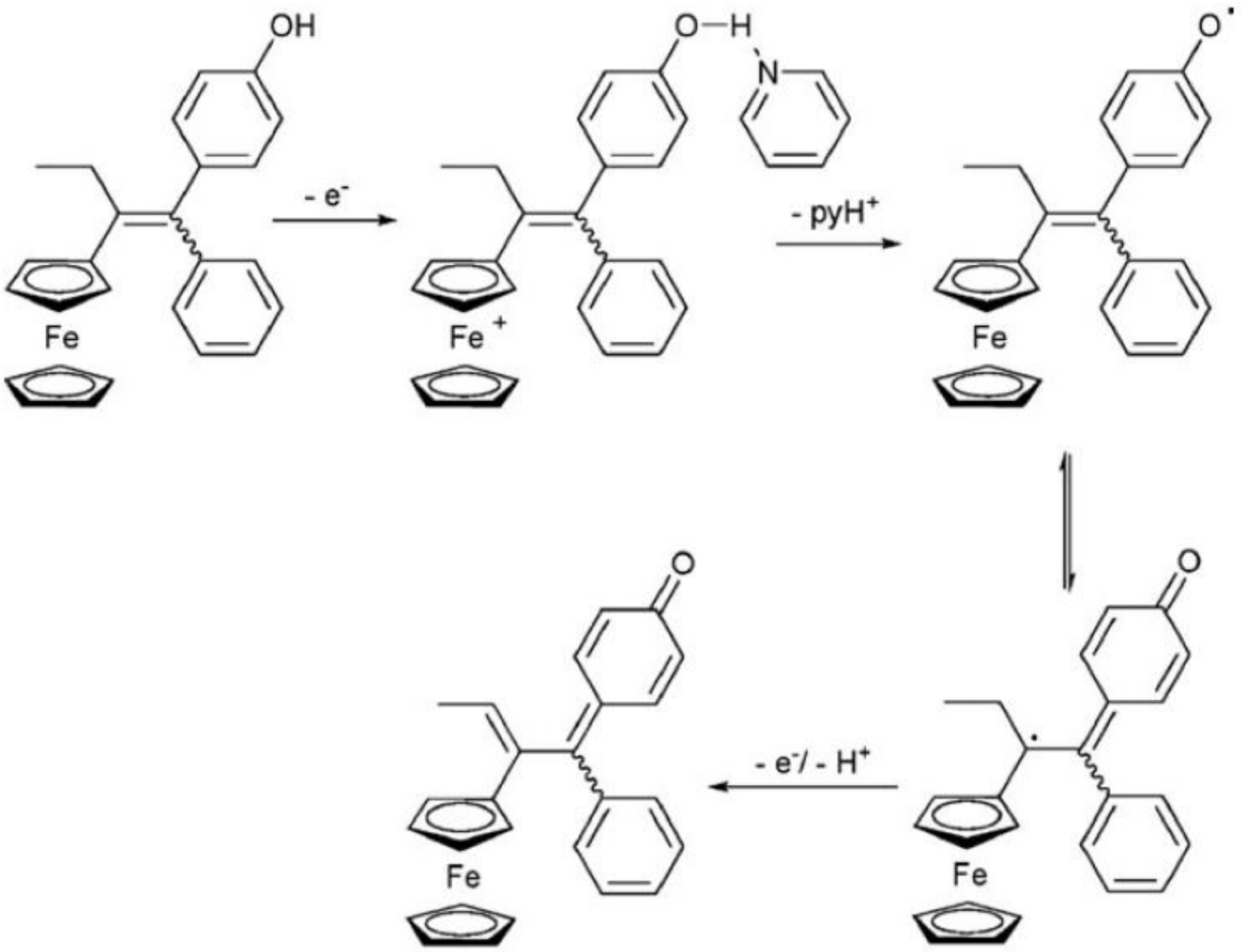


ferroquine

- 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
O
- e⁻/ - H⁺
Fe
Fe

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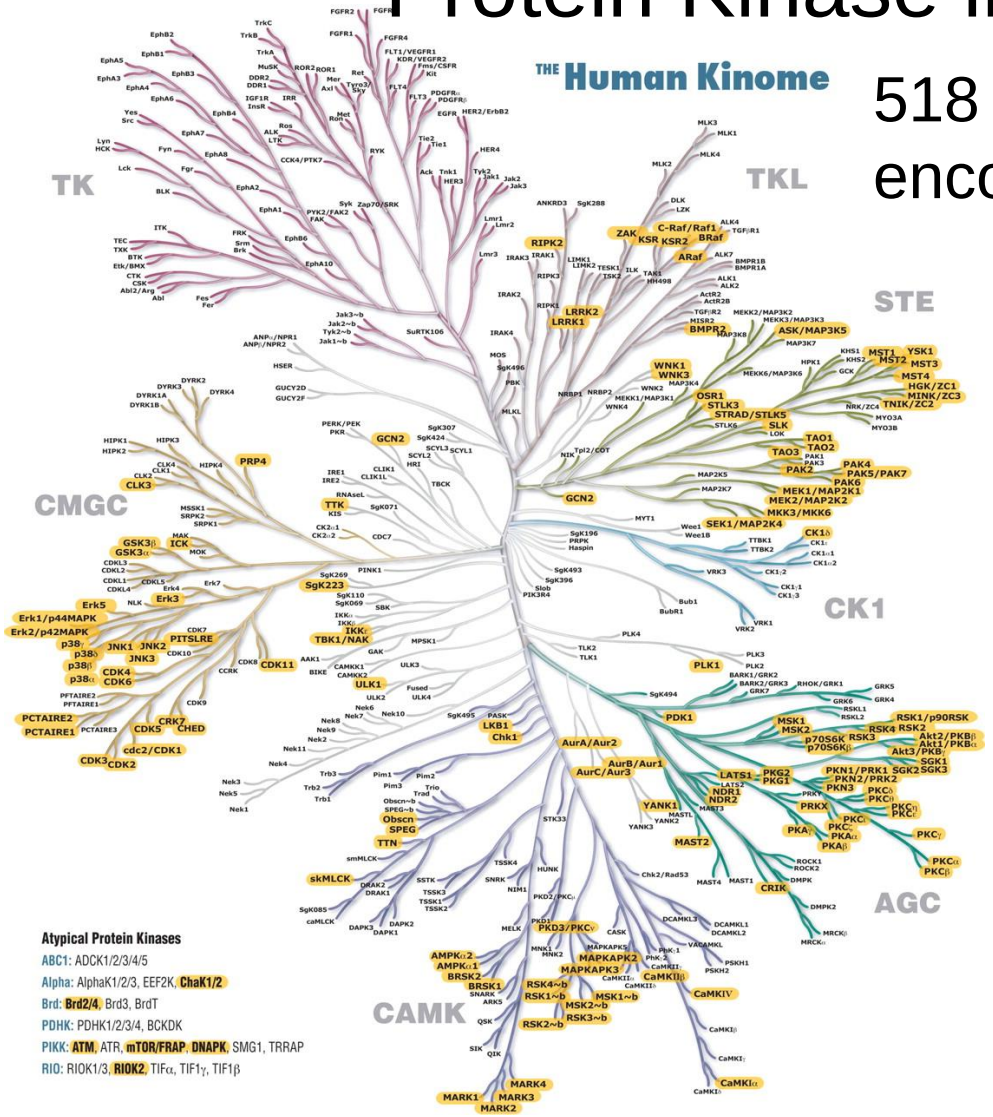
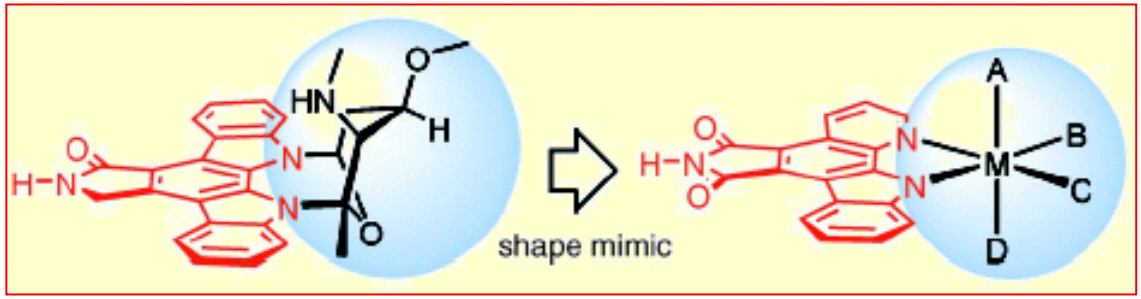
Protein Kinase inhibitors



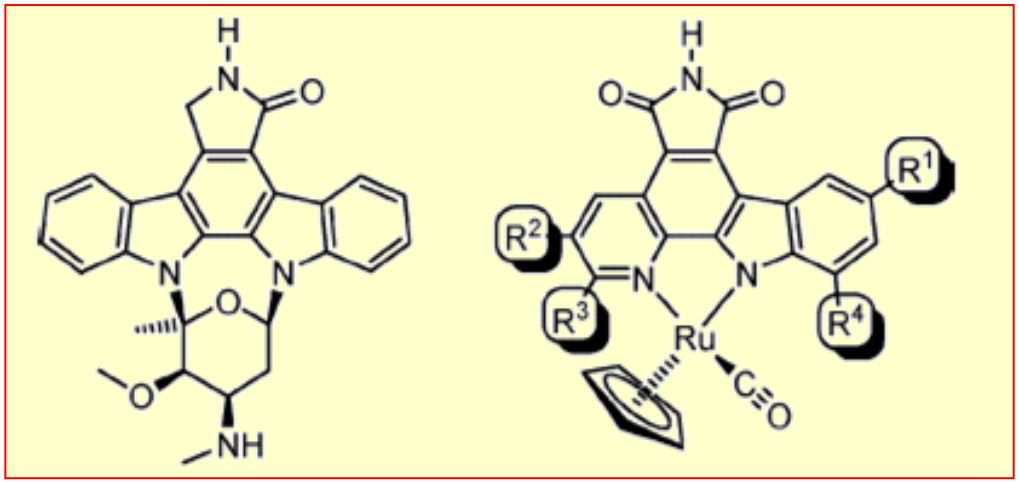
518 different kinases are encoded in the human genome

Selective protein kinase inhibitors

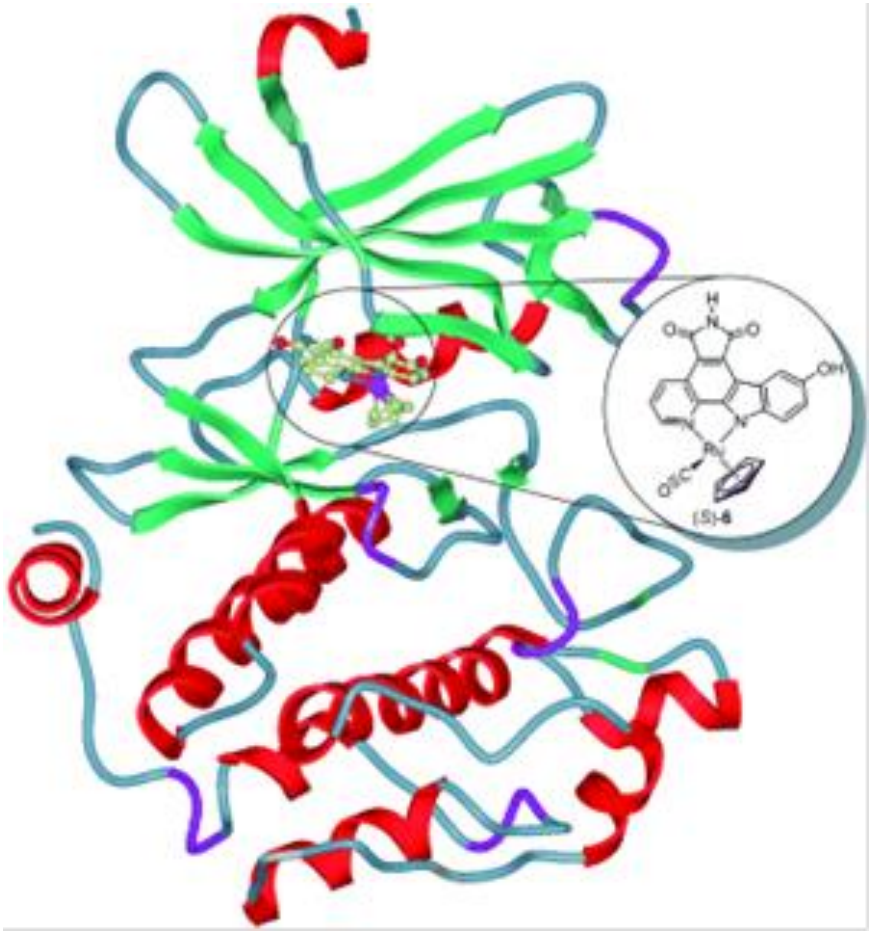


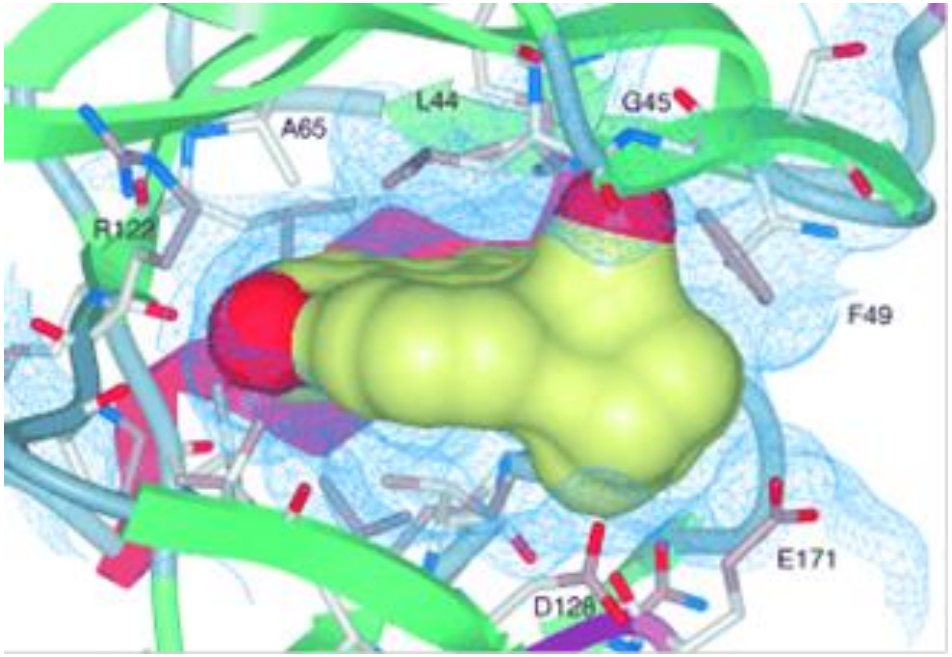
Staurosporine, unselective protein kinase inhibitor (ATP binding site)

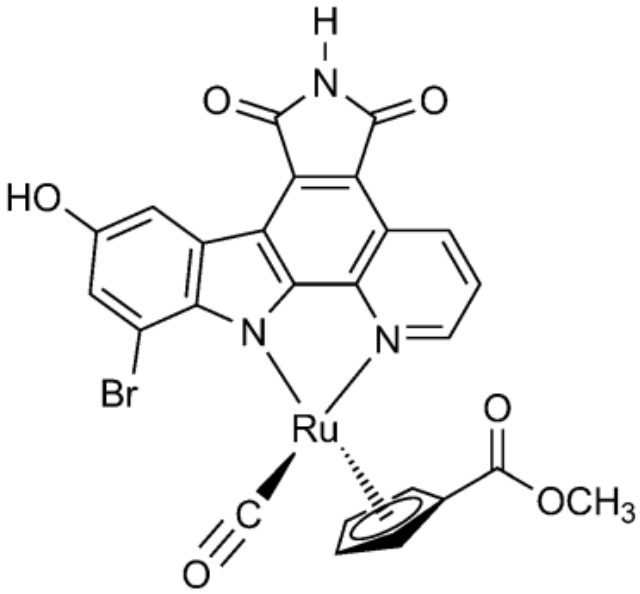
- Great structural variety (geometry)
- Stereochemistry far more diverse than organic compounds
- Rational ligand design



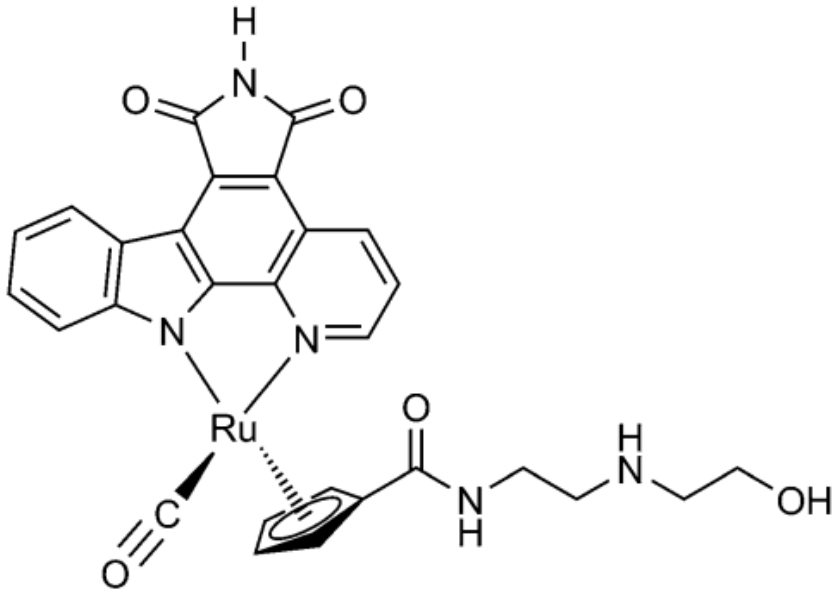
The binding of an organometallic ruthenium inhibitor to the ATP binding site of protein kinase Pim-1







GSK-3 inhibitor
IC_{50} ~ 0.5 nM

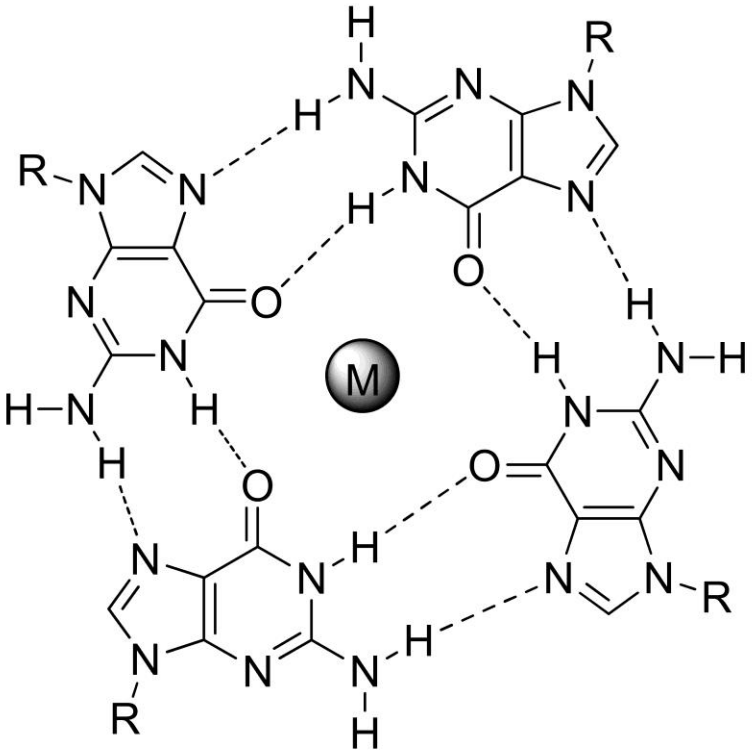


Pim1 inhibitor
IC_{50} ~ 2 nM

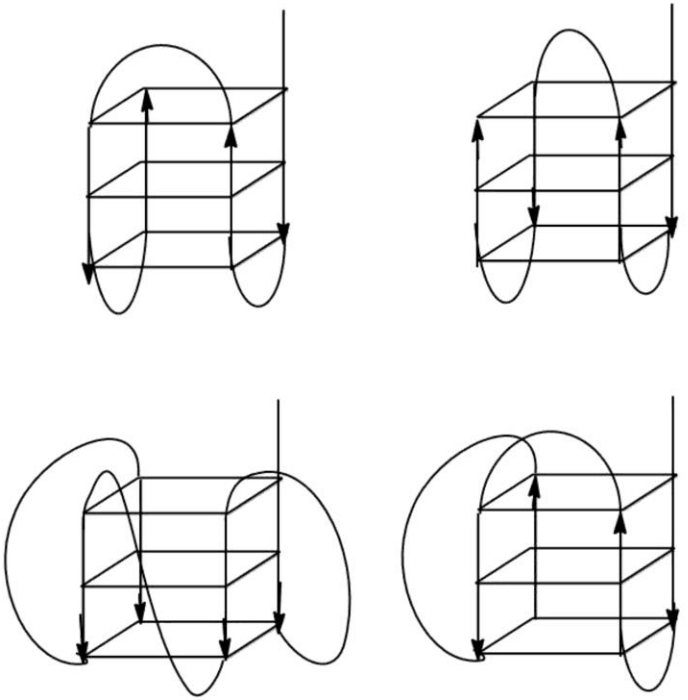
Commercially available

Telomerase

G quartet

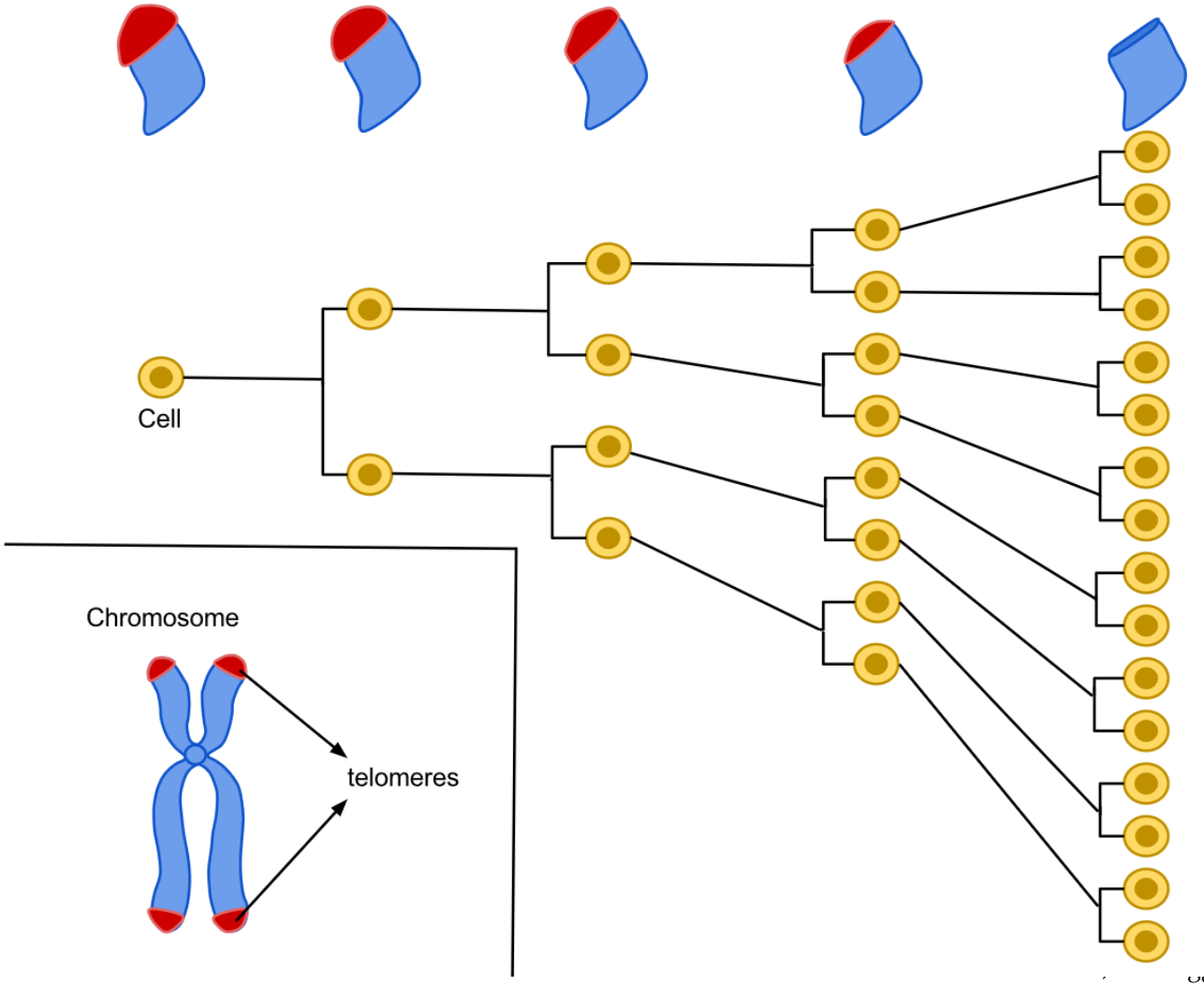


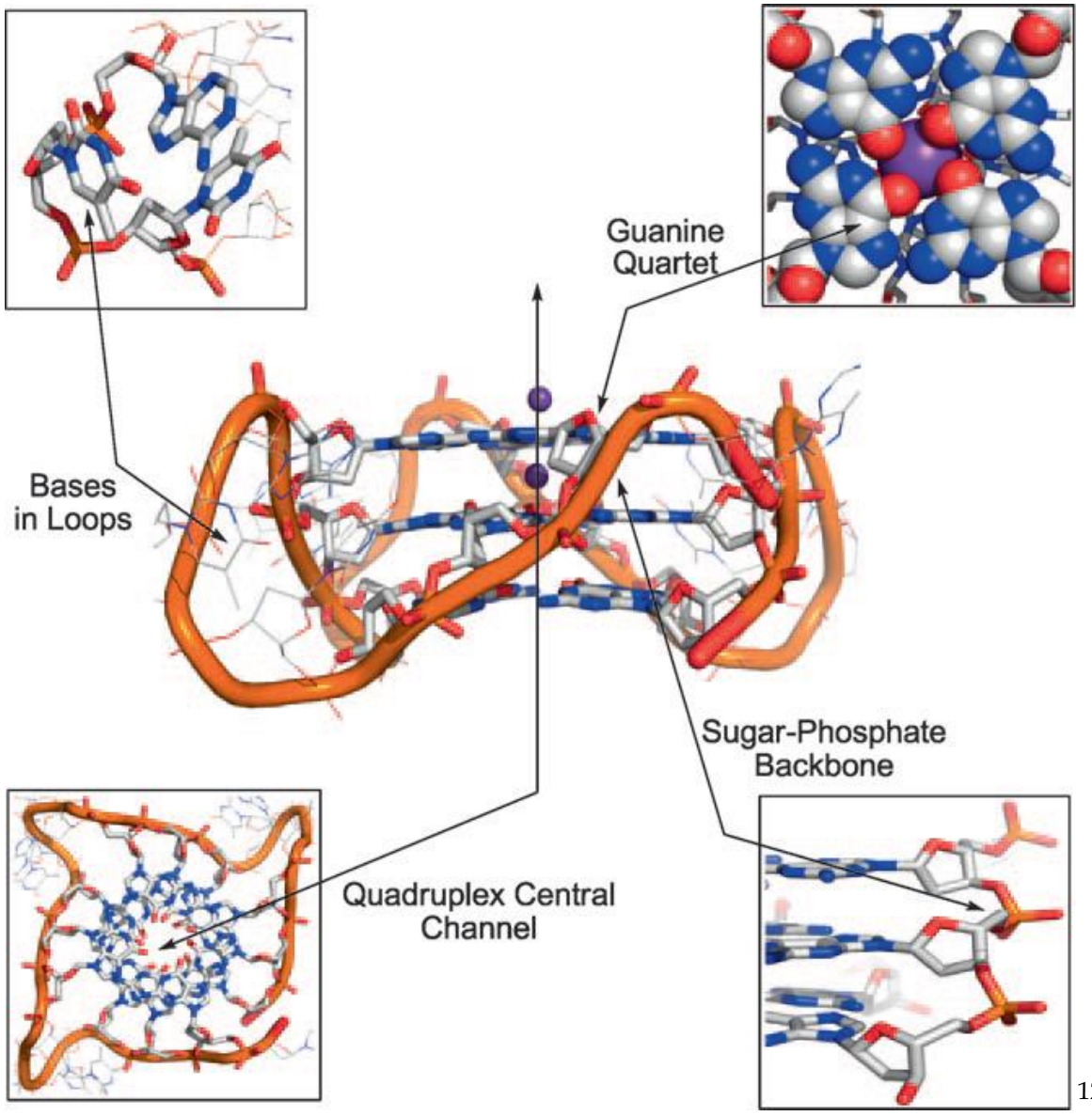
G quadruplexes



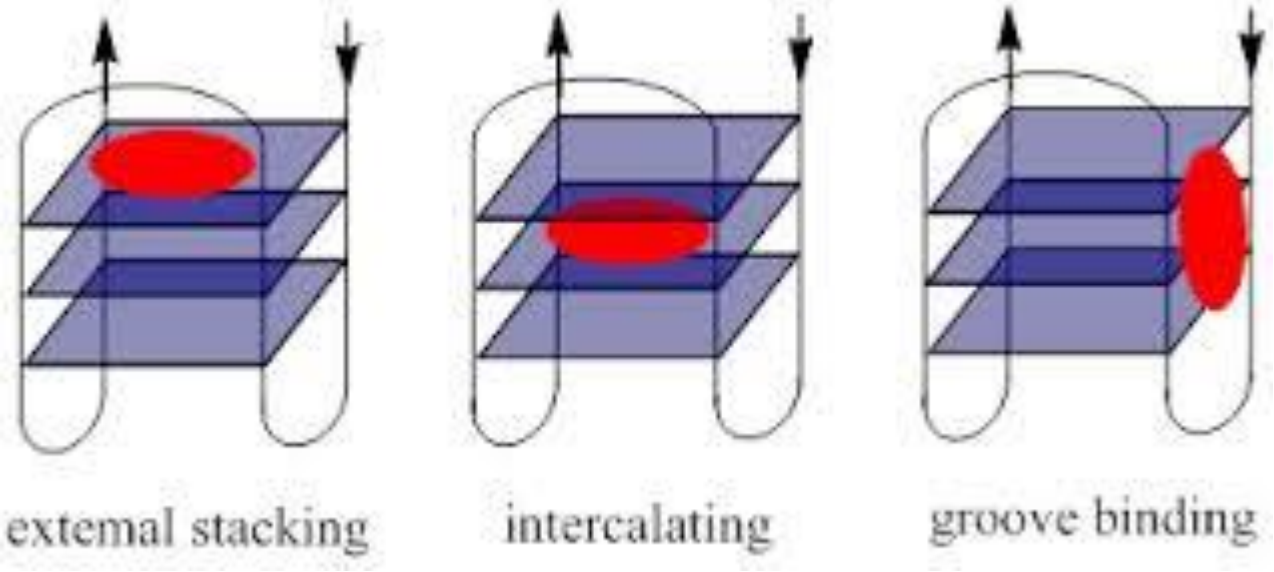
d(TTAGGG) sequences

The Hayflick limit

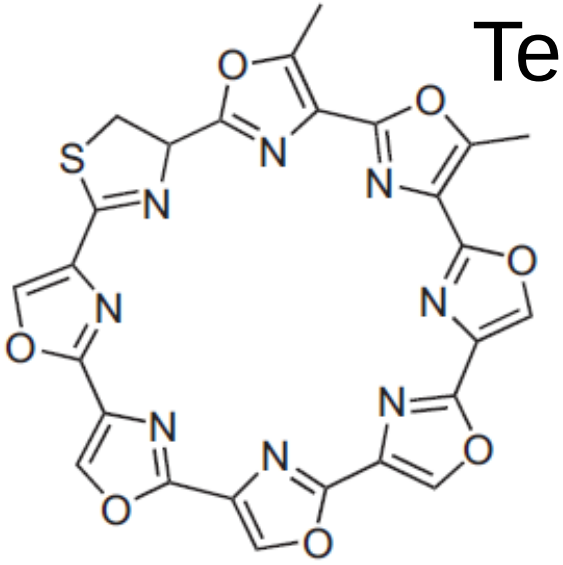



Guanine
Quartet
Bases
in Loops
Sugar-Phosphate
Backbone
Quadruplex Central
Channel

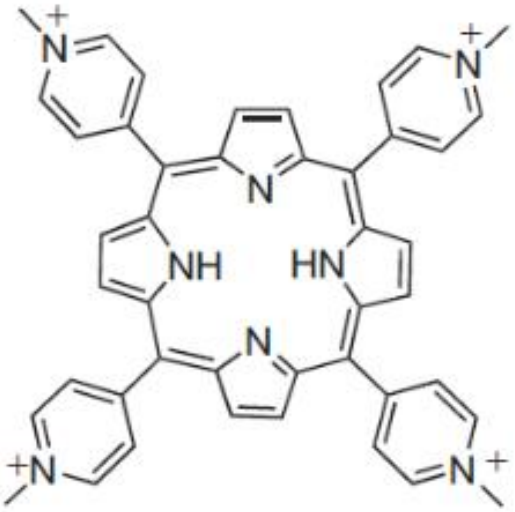
G-quadruplex stabilization



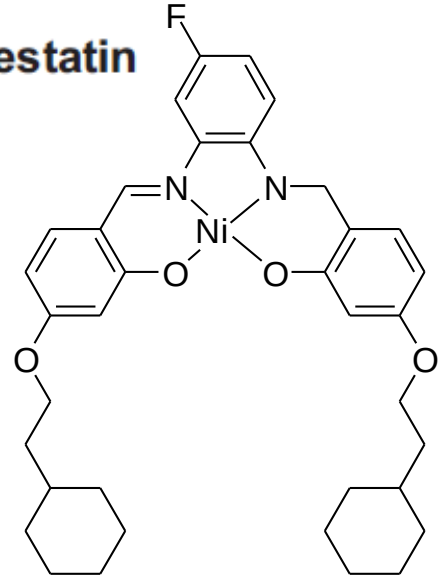
Telomerase Inhibitors

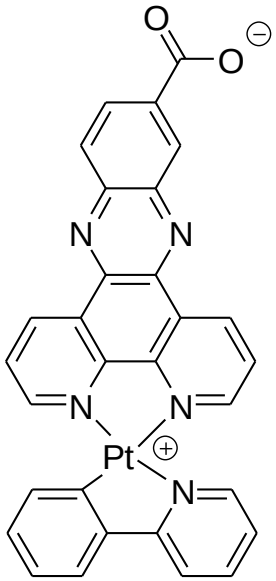


π stacking on G quartets

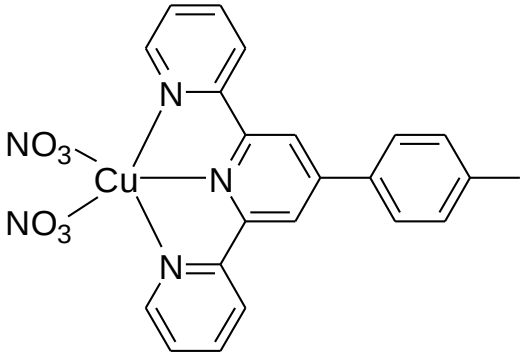


Telomestatin



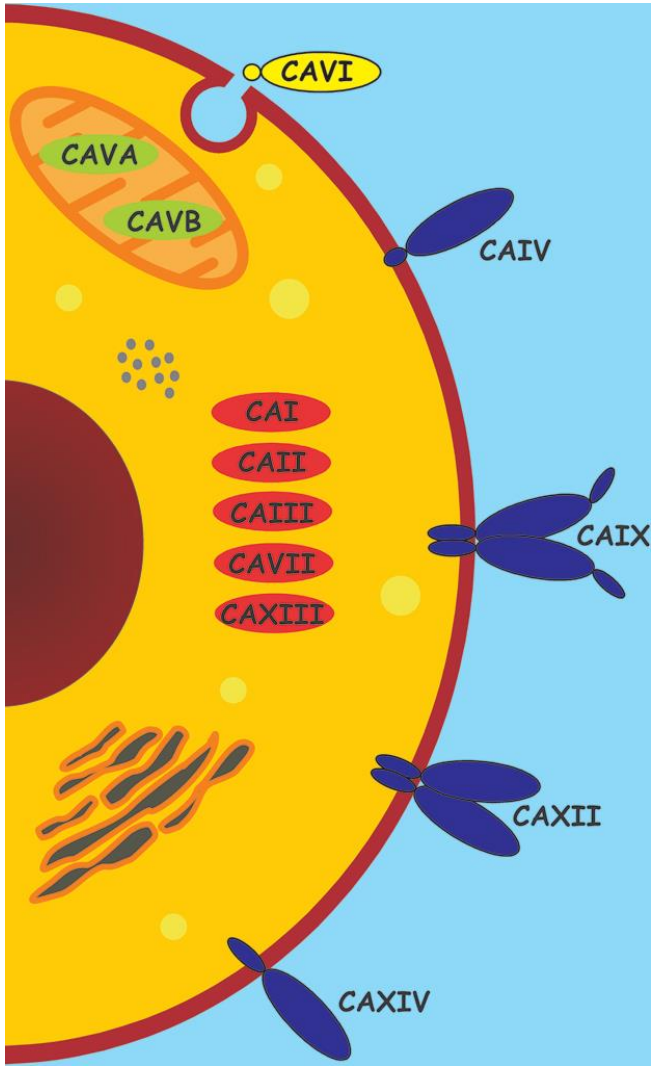


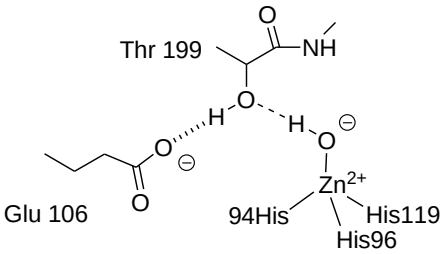
TmPyP4



Metal-based Inhibitors of Metallo-Enzymes

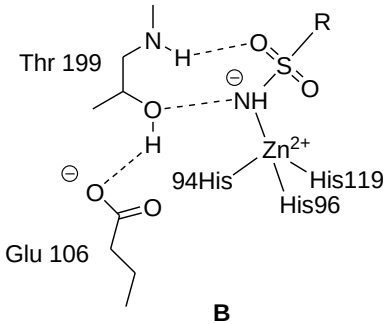
Human Carbonic Anhydrase (hCA) inhibitors





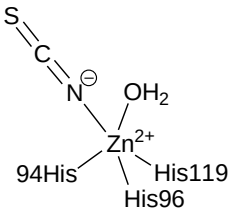
A

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



B

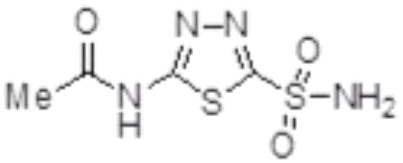
Tetrahedral adduct (sulfonamide)



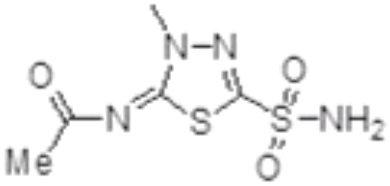
C

Trigonal-bipyramidal adduct (thiocyanate)

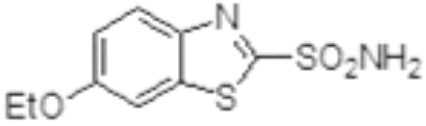
Sulfonamides as CA inhibitors



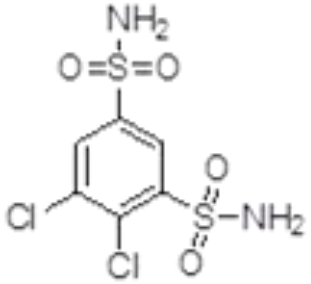
Acetazolamide (AAZ)



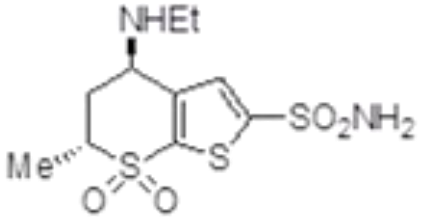
Methazolamide (MZA)



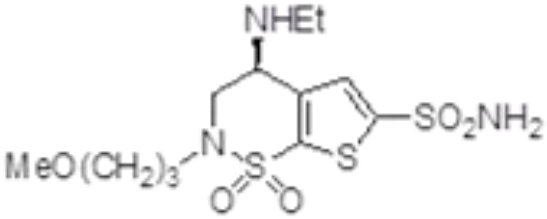
Ethoxzolamide (EZA)



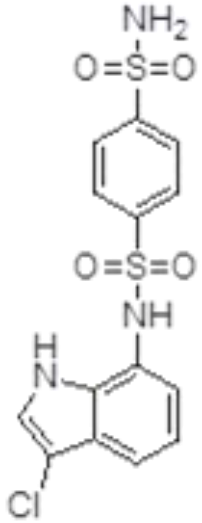
Dichlorophenamide (DCP)



Dorzolamide (DZA)

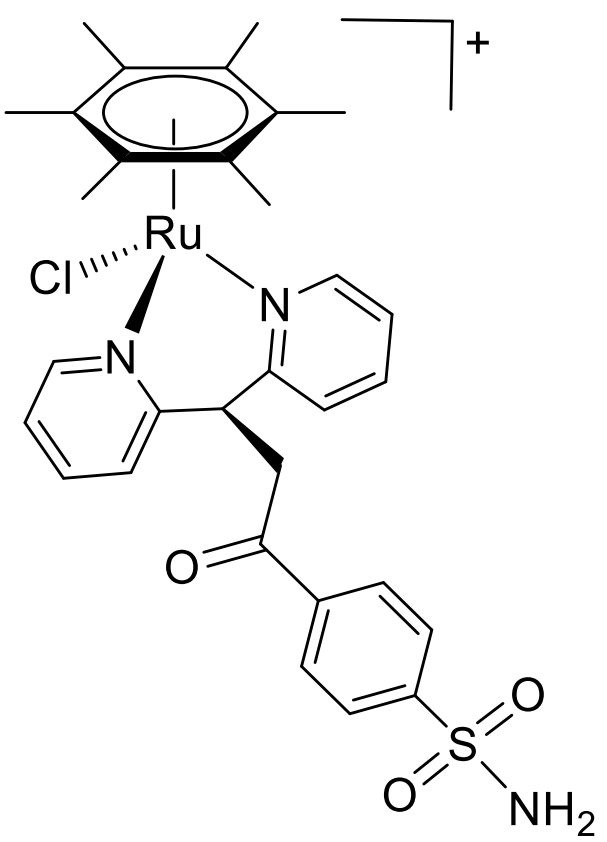


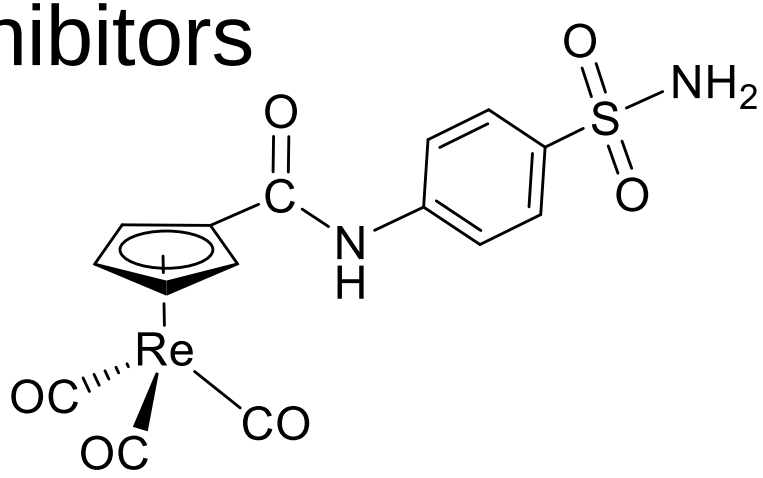
Brinzolamide (BRZ)

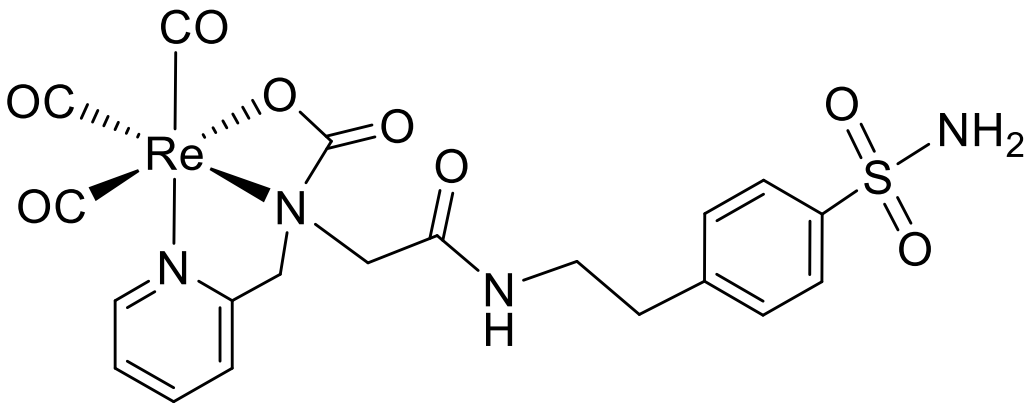


Indisulam (IND)

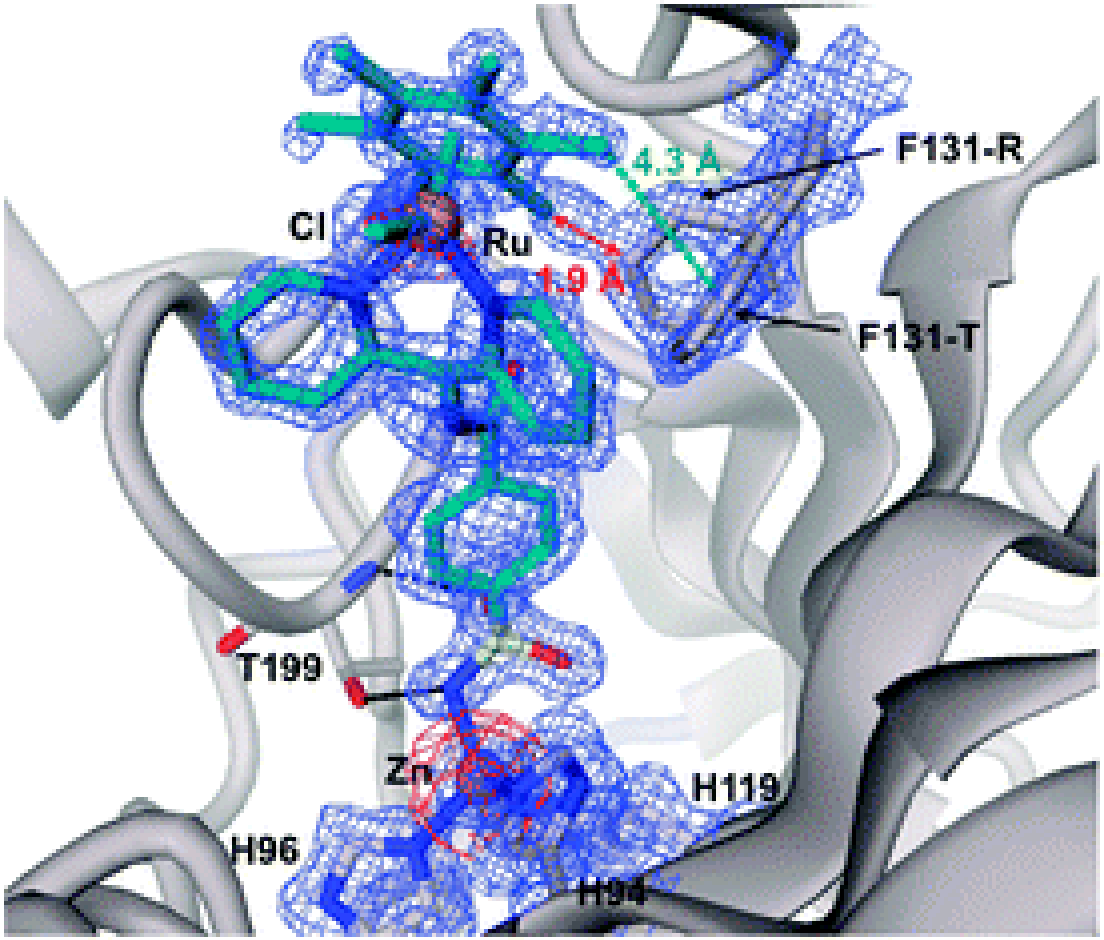
Inert organometallic compounds as hCA inhibitors



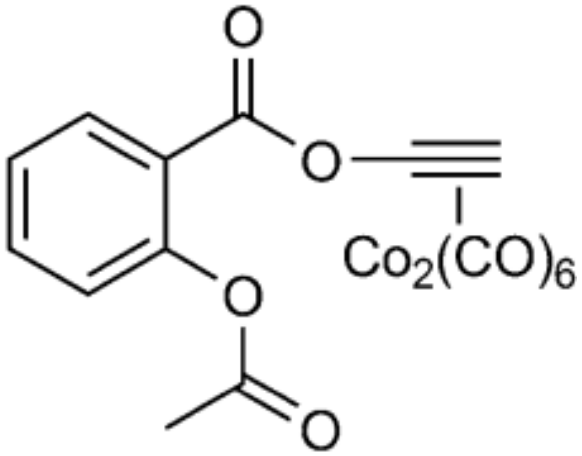




Ru-arene piano-stool complex @ hCA II



COX inhibitors

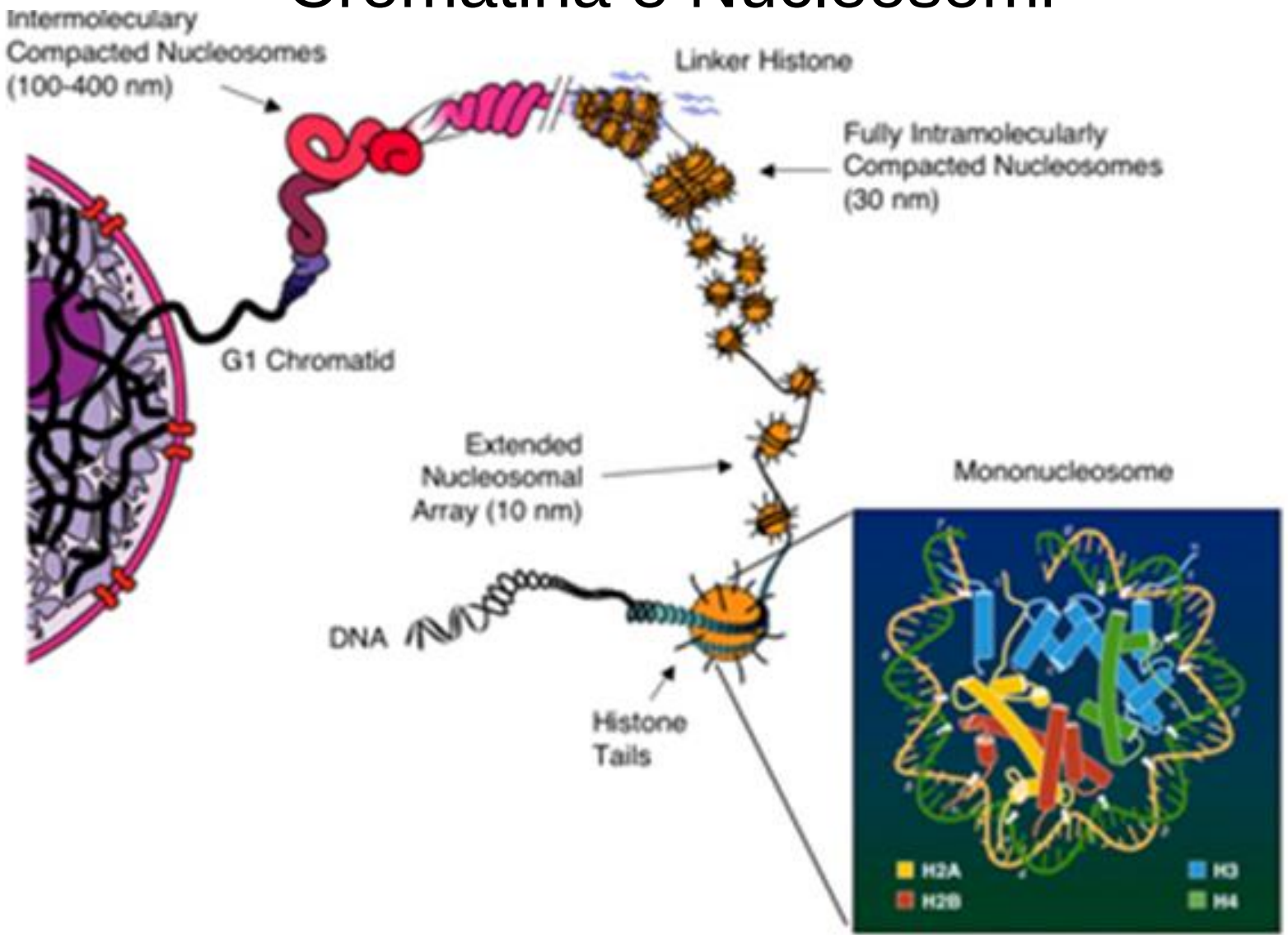


Co-ASS

Alkyne hexacarbonyldicobalt ($Co_2(CO)_6$) species

Powerful inhibitor of cyclooxygenases 1 and 2 (COX-1 and COX-2), the main target enzymes of NSAIDs (non-steroidal anti-inflammatory drugs)

Cromatina e Nucleosomi



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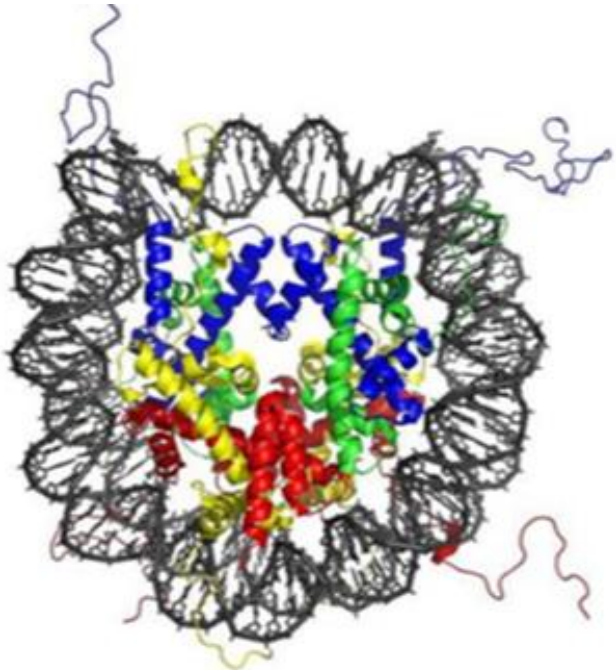
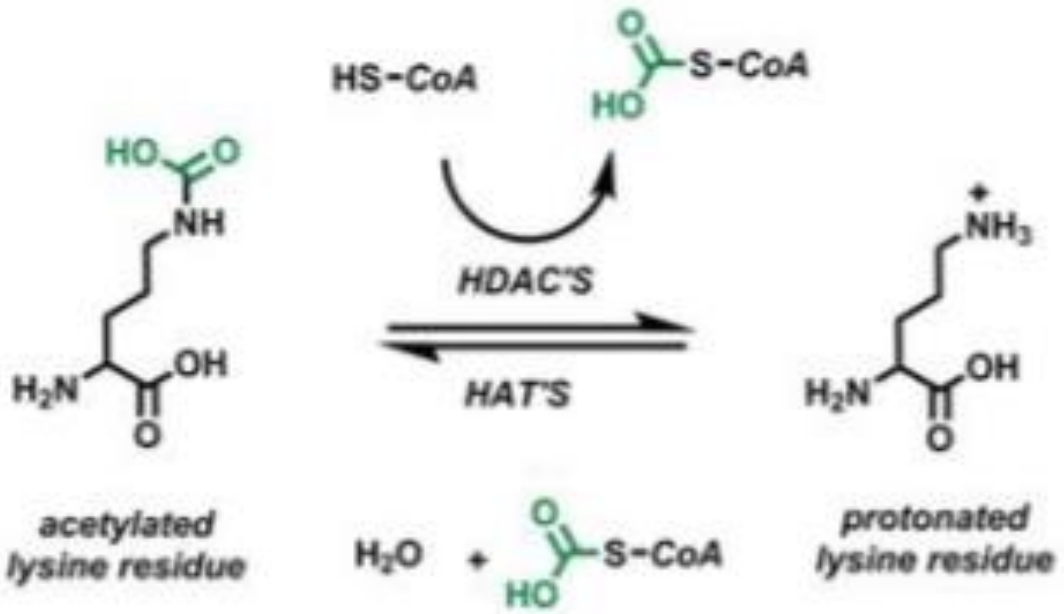
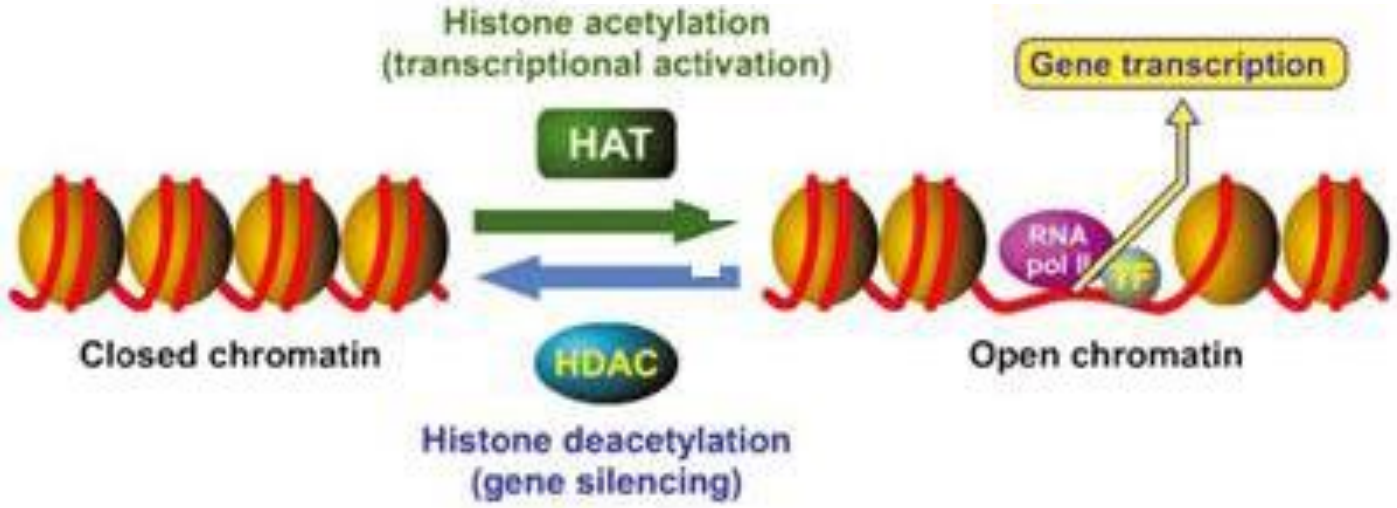
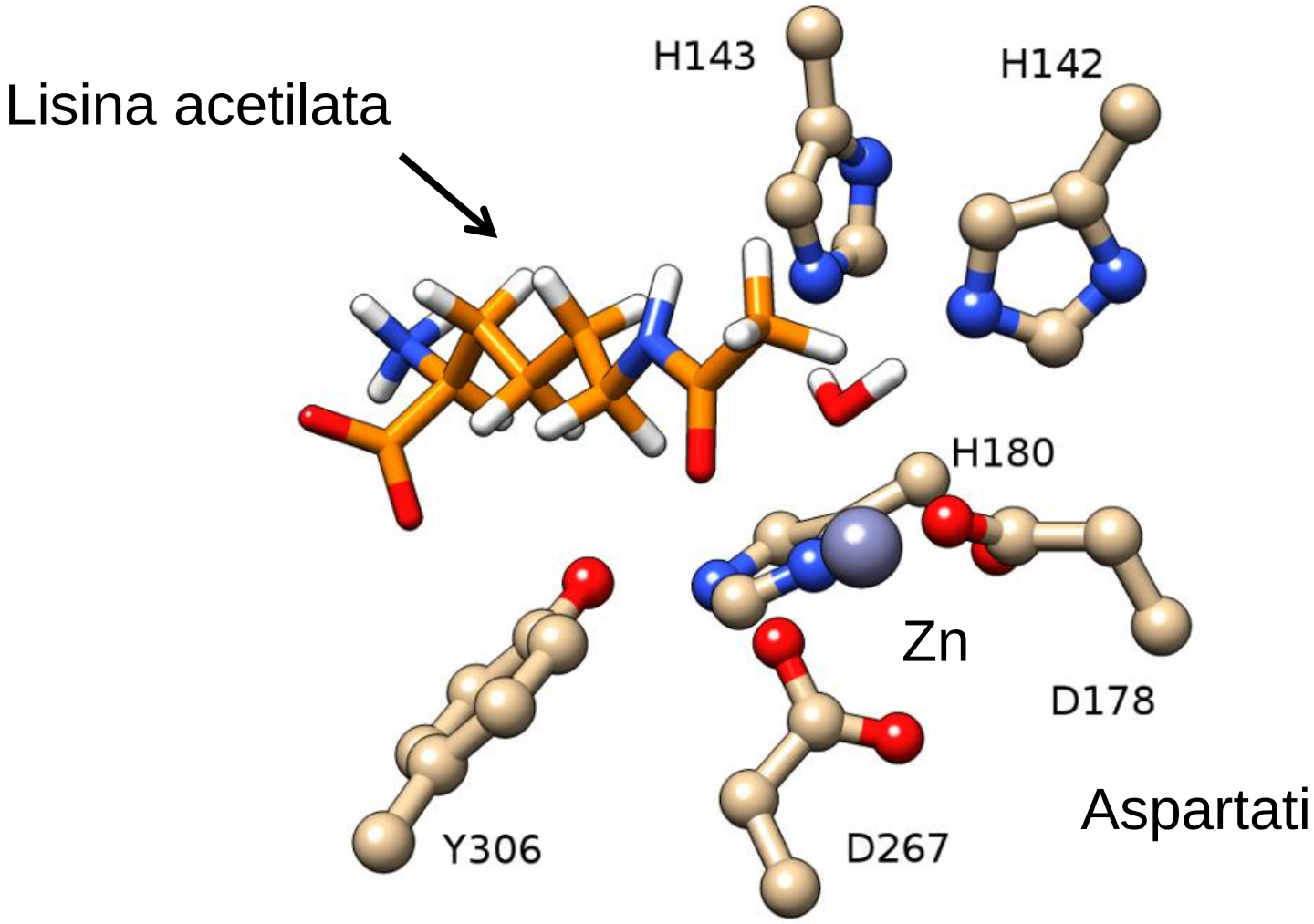


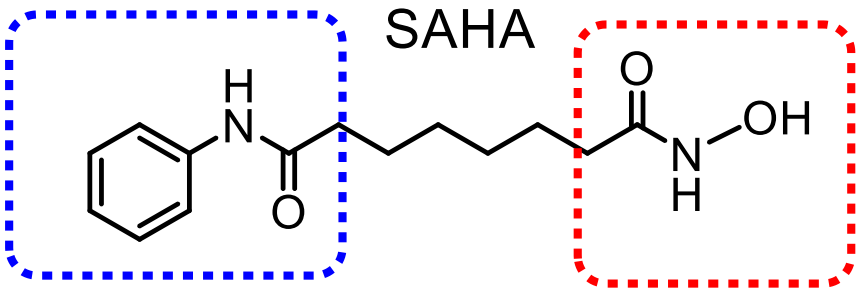




HDAC8 active site

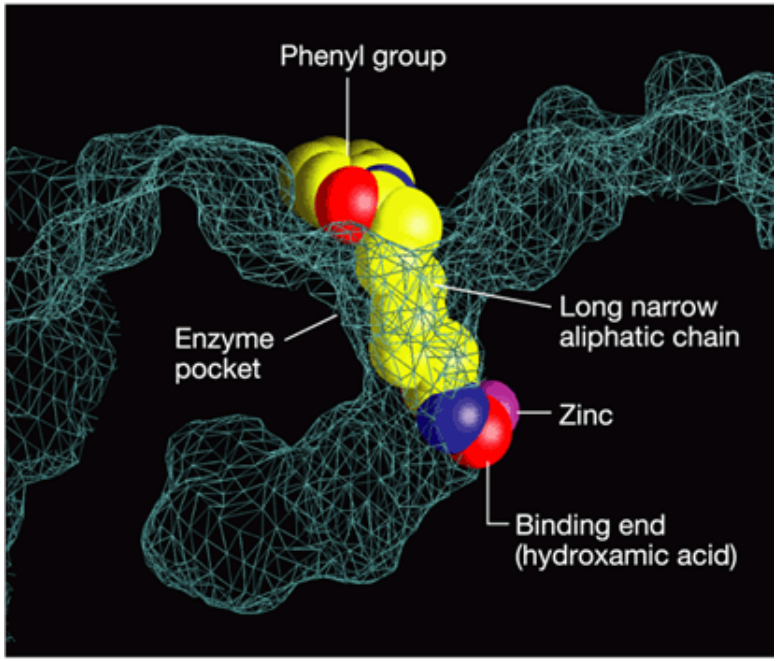


HDAC Inhibitors (HDACi) anticancer agents



aromatic protein recognition domain

hydroxamic acid Zn^{2+}binding site



Zolinza®

Treatment of *cutaneous T-cell lymphoma*

Metal-based HDAC Inhibitors