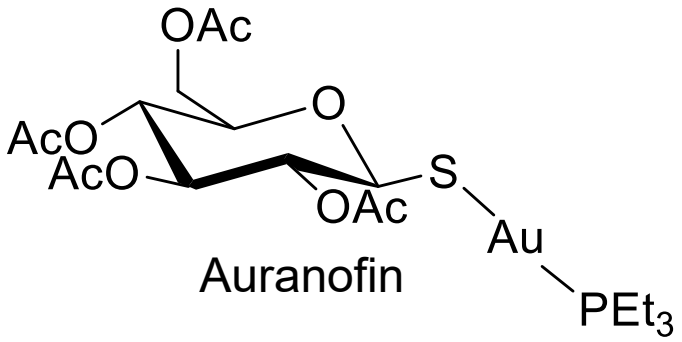
Structural compounds

Metal-based Inhibitors of Proteins and Enzymes

Auranofin: a serendipitous enzyme inhibitor

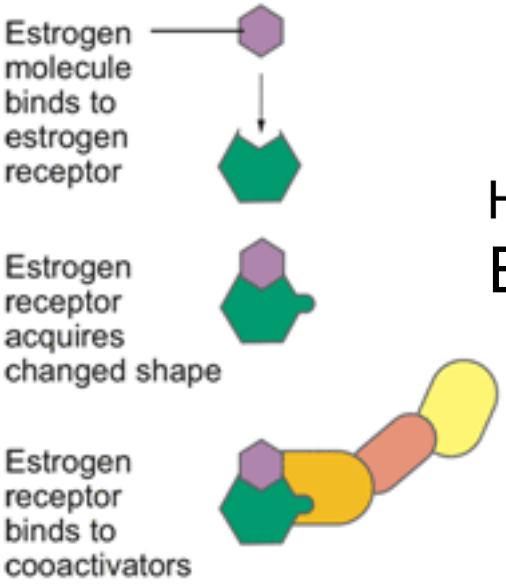


Auranofin

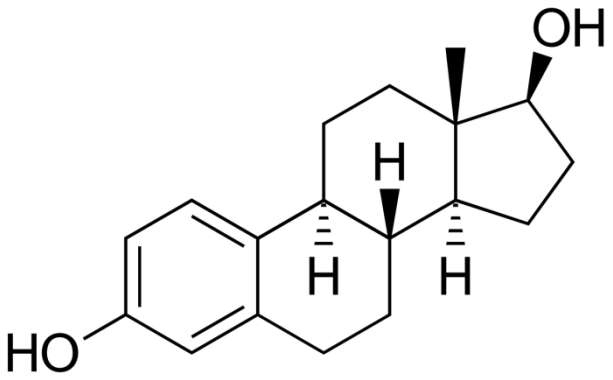
- Introduced in the late 1970s as oral substitute of gold anti-arthritic agents (developed on the wrong assumption that arthritis was caused by a bacterial infection).

Antiparasitic action (example of drug repurposing):
Au(I) from Auranofin strongly inhibits *in vitro* the seleno-cysteine enzymes *Thioredoxin reductase* and *Glutatione peroxidase*

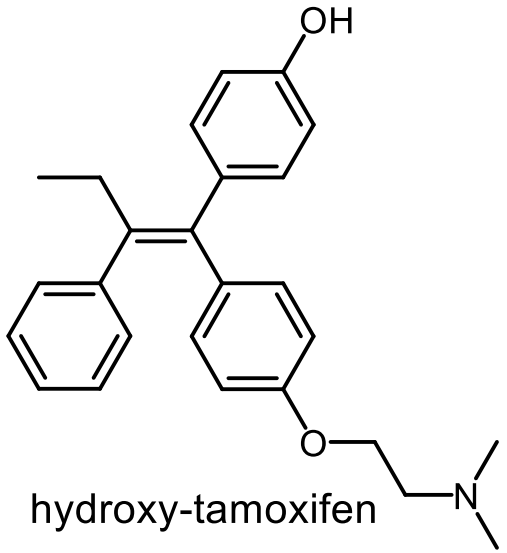
Inhibitors of the estrogen hormone receptor



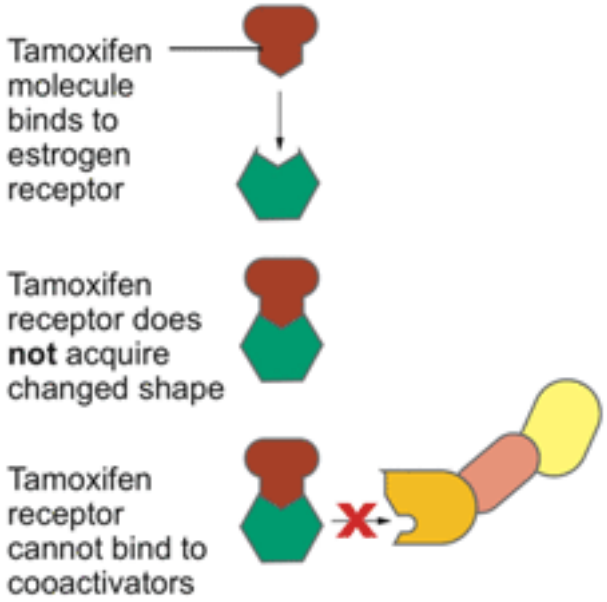
Proliferation of cancer cells



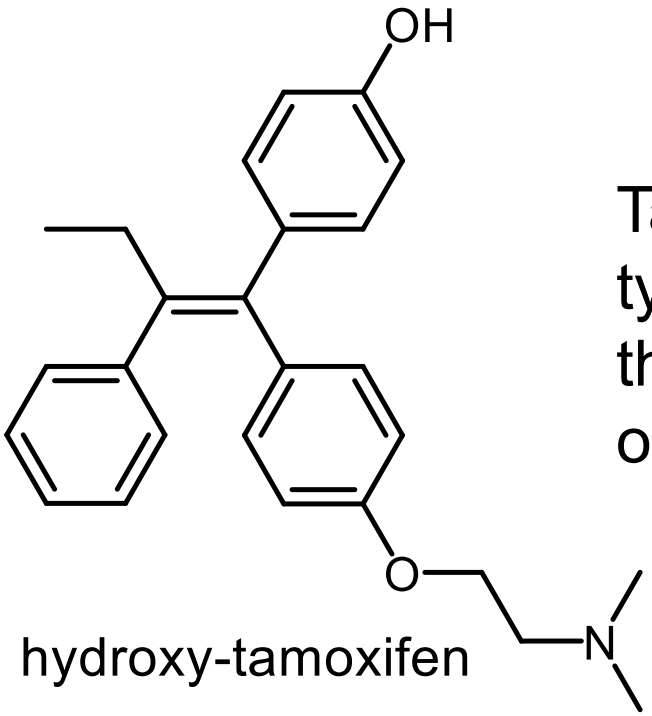
Estrogen (estradiol)



hydroxy-tamoxifen



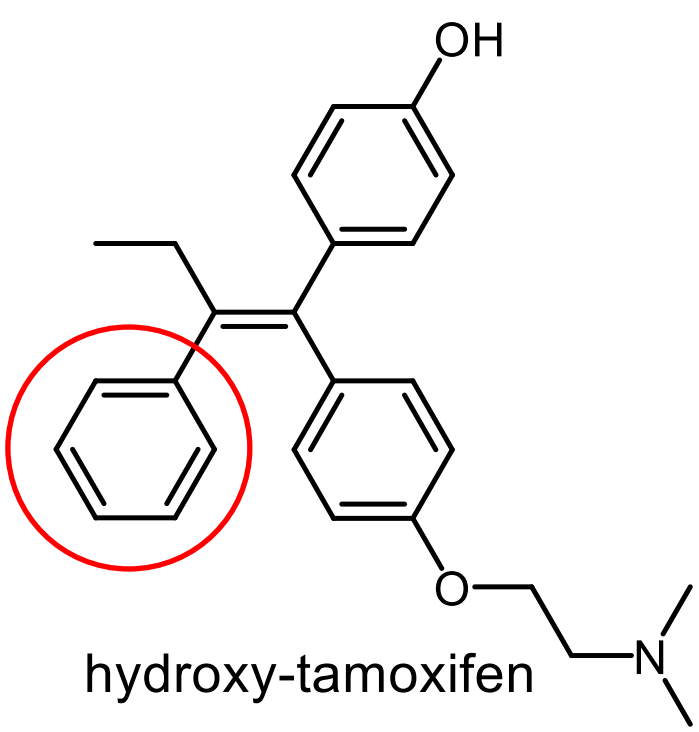
Inhibition of cancer cells



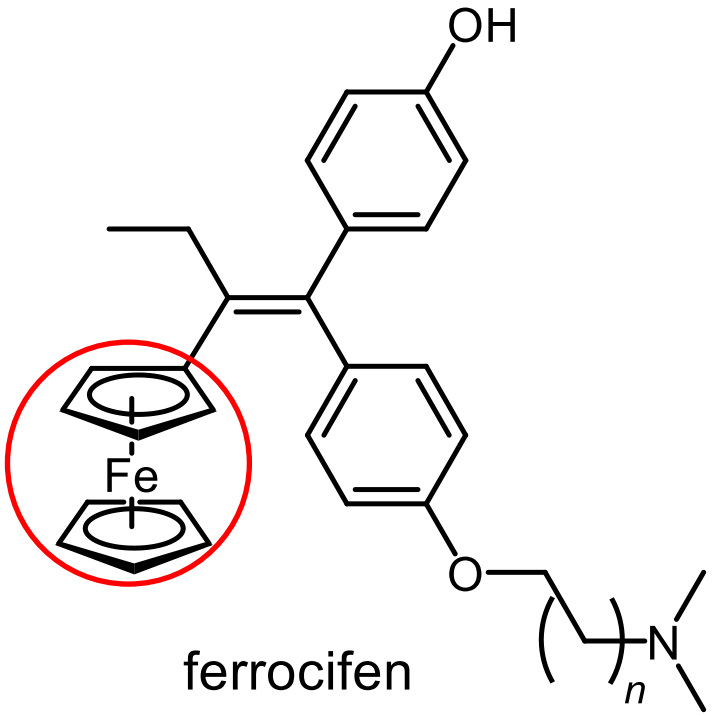
hydroxy-tamoxifen

Tamoxifen is active only against those types of breast cancer that overexpress the Estrogen Receptor α (ERα+, ca. 2/3 of total).

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



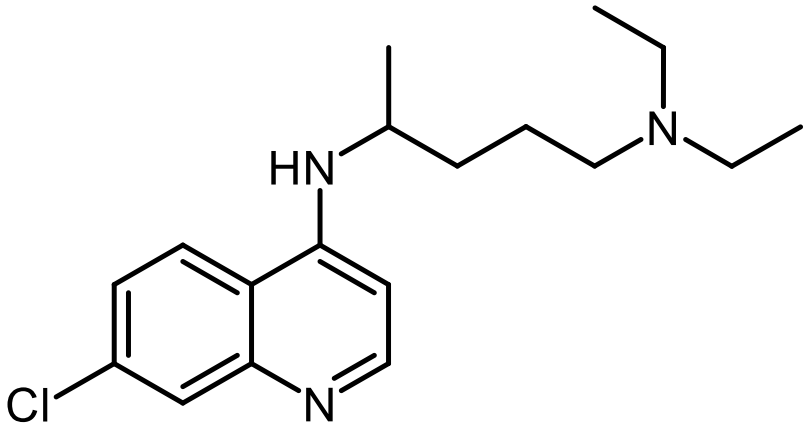
hydroxy-tamoxifen



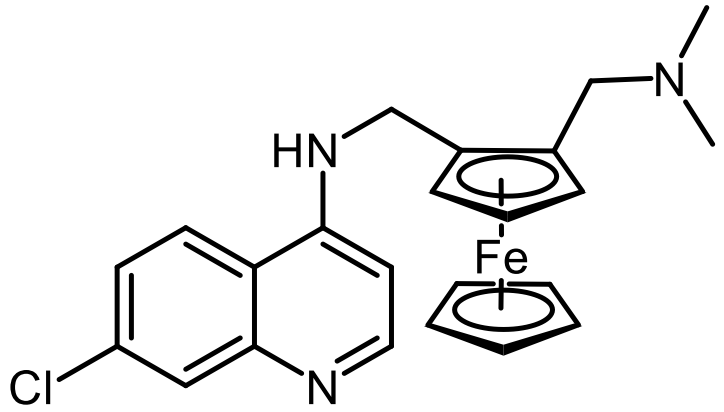
ferrocifen

Ferrocene is very stable, does not alter the charge of the molecule, typically does not introduce toxicity, and is very lipophilic. Ferrocifen showed activity also against tumors that became resistant to tamoxifen.

Bio-isosteric replacement applied to antimalarial drugs



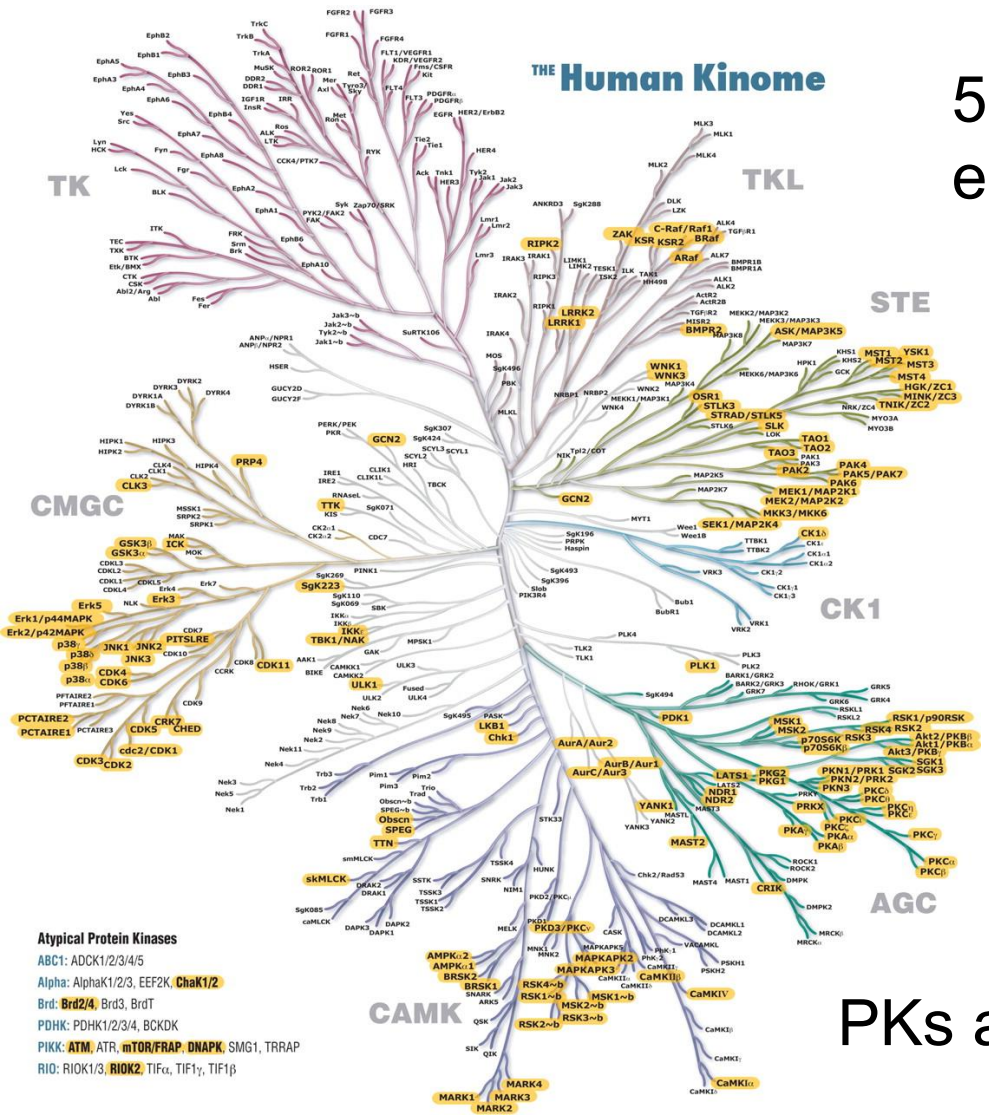
chloroquine



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.

Inhibitors of Protein Kinases (PKs)



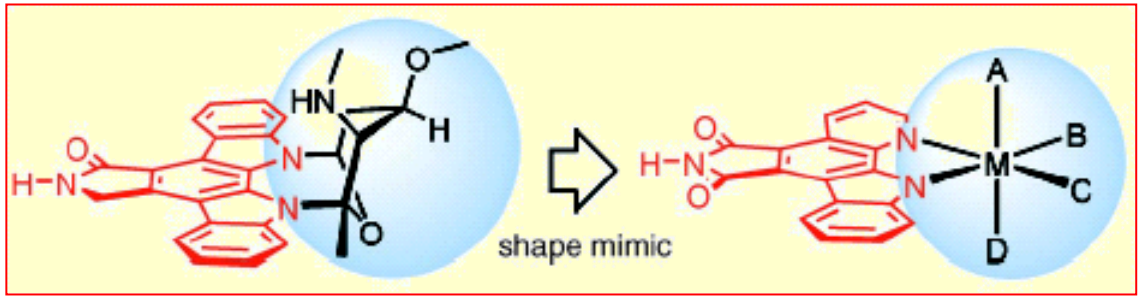
538 different protein kinases are encoded in the human genome

Protein kinases are *enzymes that regulate cell growth and proliferation* by phosphorylating target proteins in response to specific signals.

All PKs have a well conserved **ATP binding site**.

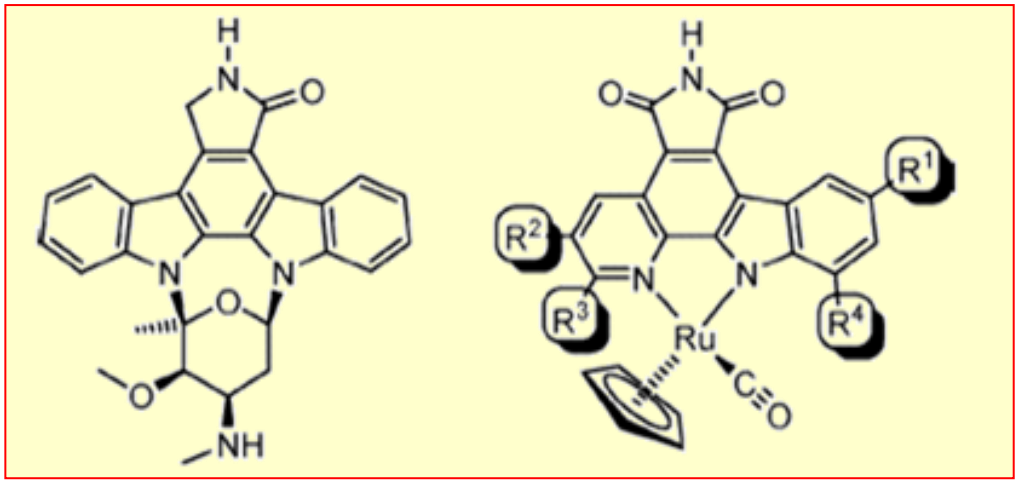
PKs are important therapeutic targets

Selective protein kinase inhibitors

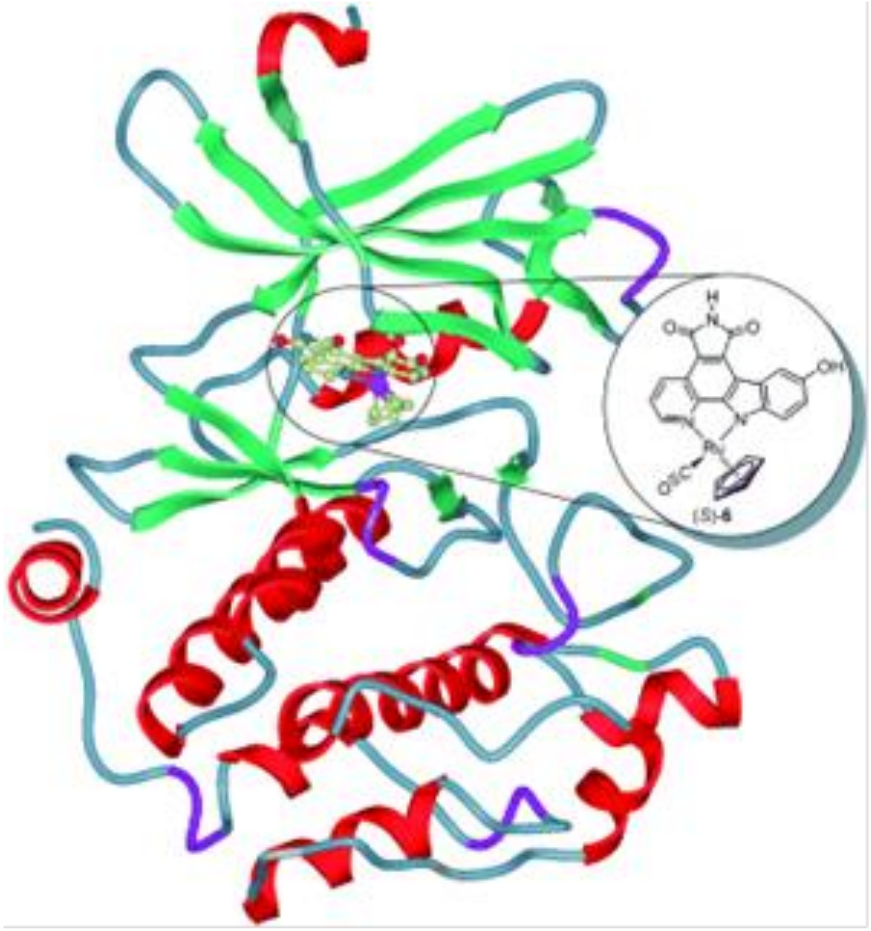


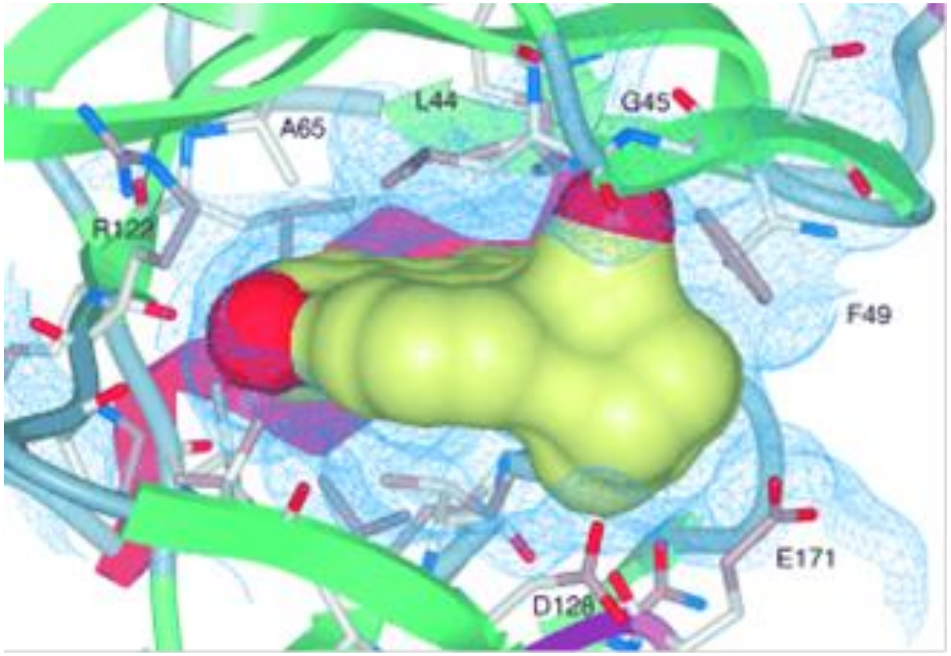
Staurosporine, unselective protein kinase inhibitor (ATP binding site)

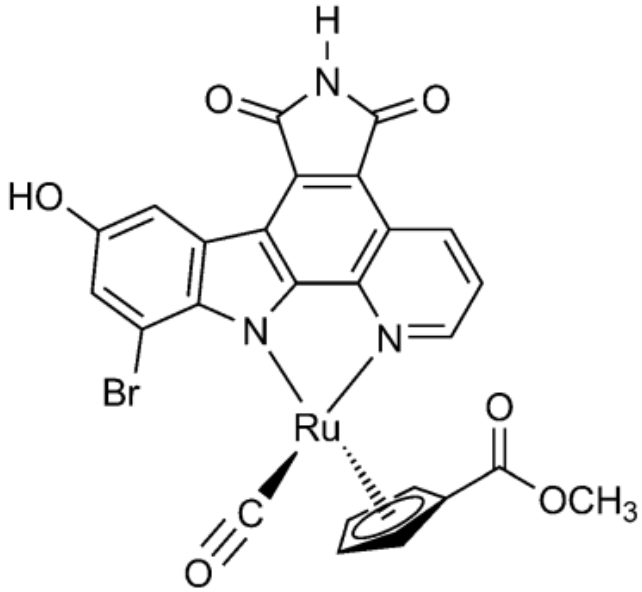
- Great structural variety (geometry)
- Stereochemistry far more diverse than organic compounds
- Modular synthesis
- Rational ligand design
- Stability
- Moderate toxicity



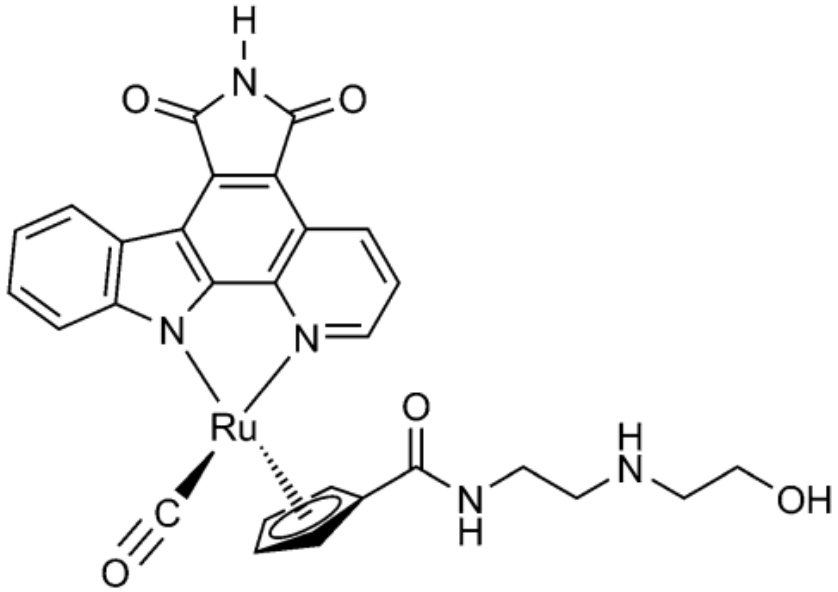
The binding of an organometallic ruthenium inhibitor to the ATP binding site of protein kinase Pim-1







GSK-3 inhibitor
IC_{50} ~ 0.5 nM



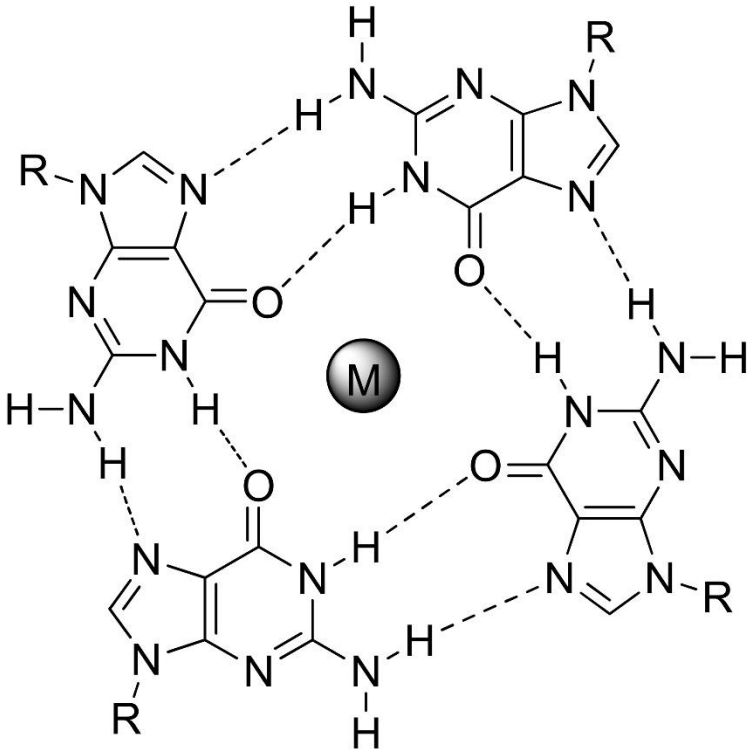
Pim1 inhibitor
IC_{50} ~ 2 nM

Commercially available as specific PK inhibitors

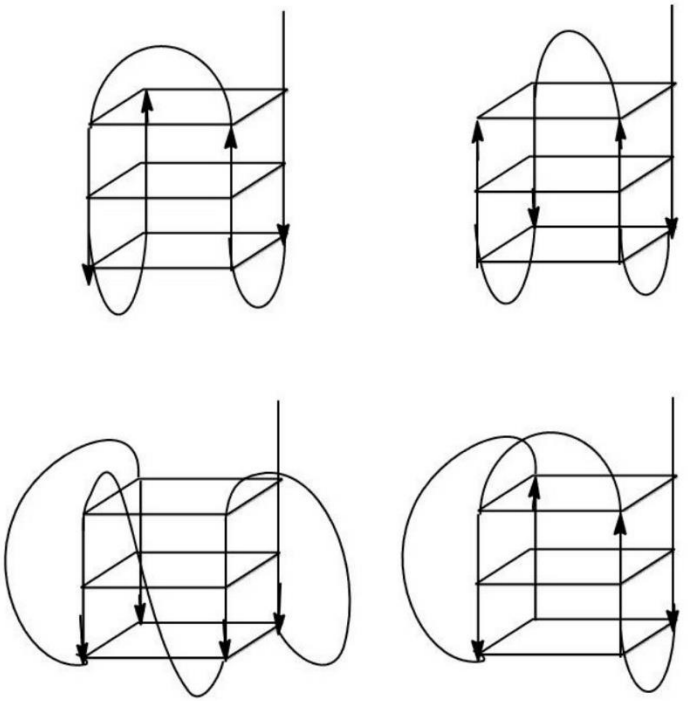
Telomers and telomerase inhibitors

Telomers are DNA regions located at the end of the chromosomes and made of a single filament with a protective function. Telomers contain repeating d(TTAGGG) sequences

G quartet



G quadruplexes polymorphs



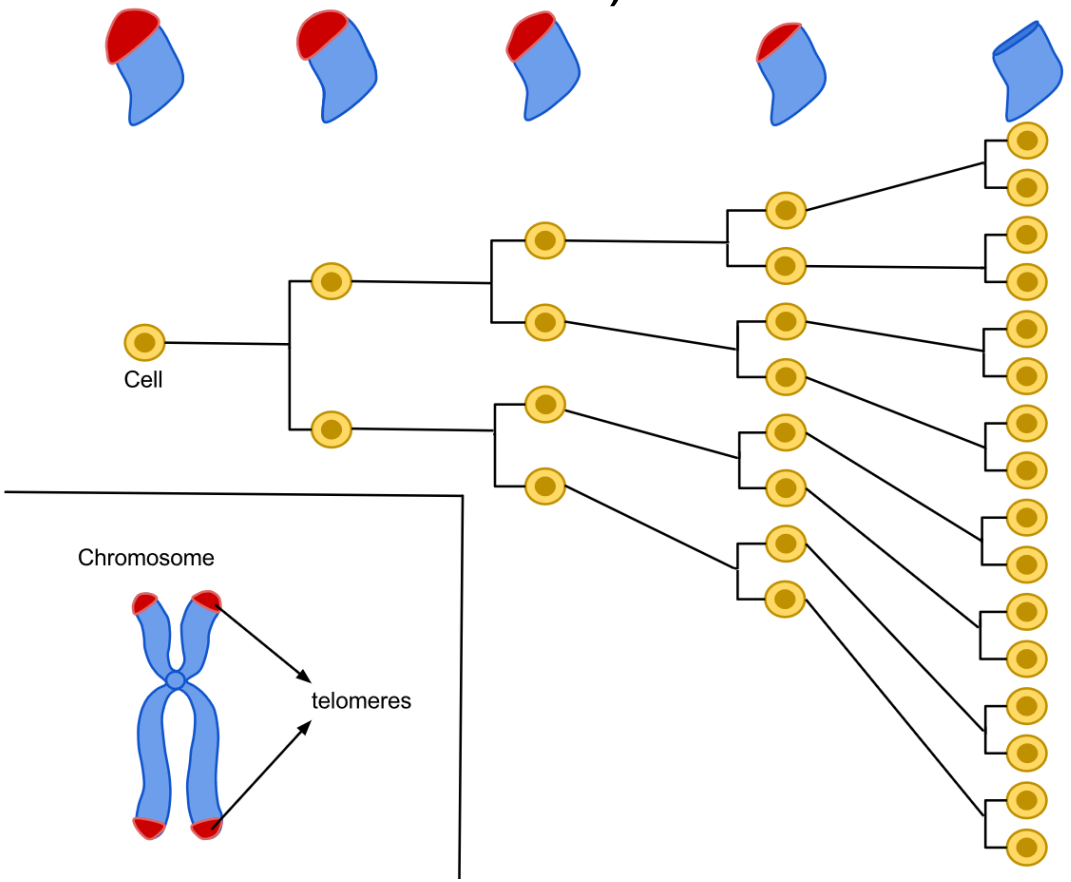
The guanine-rich sequences of the telomer self-assembly through H-bonds into G-quartets which, in turn, form G-quadruplexes.

Telomers = cell biological clock

(in the absence of telomerase)

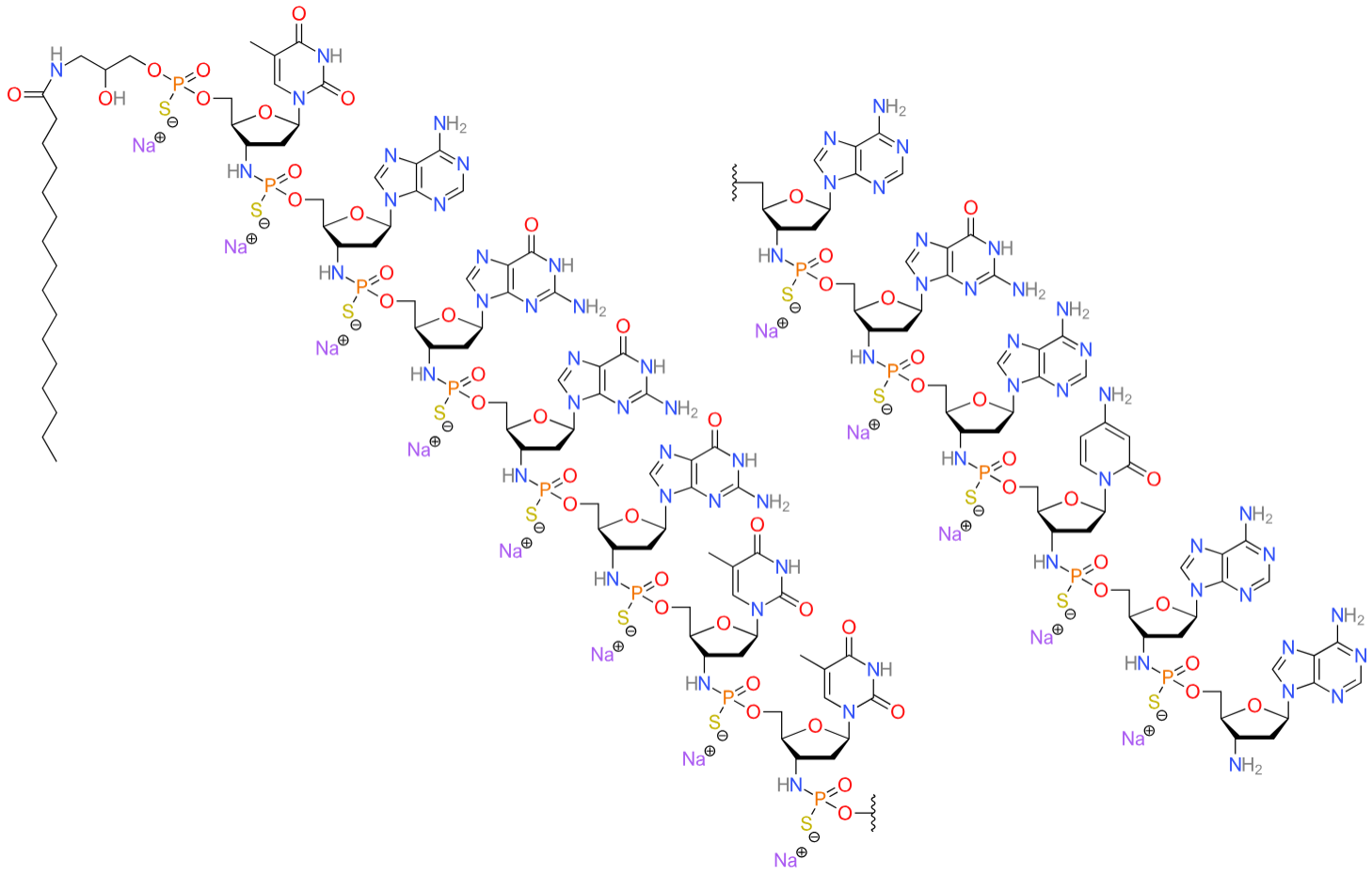
The Hayflick limit

(ca. 50 cellular divisions, followed by apoptosis)



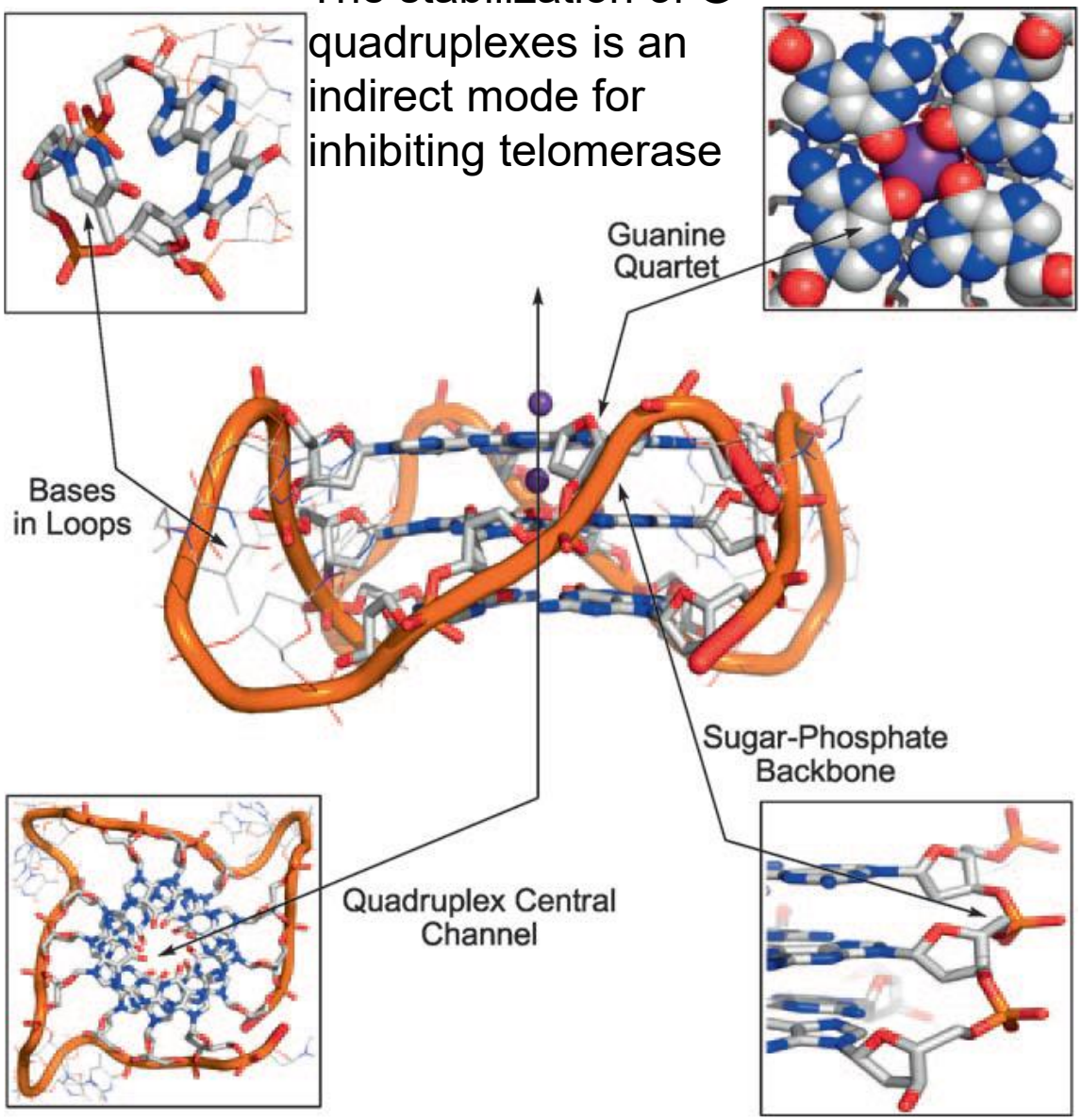
Telomerase is a ribonucleo-protein with **DNA-polymerase** activity, over-expressed in most cancer cells (normally absent in somatic, i.e., differentiated, cells). It has the function of adding hexameric d(TTAGGG) units to the 3′-terminal part of the DNA telomere, keeping its length unchanged (making them **immortal**)

Imetelstat (Rytelo): a telomerase inhibitor

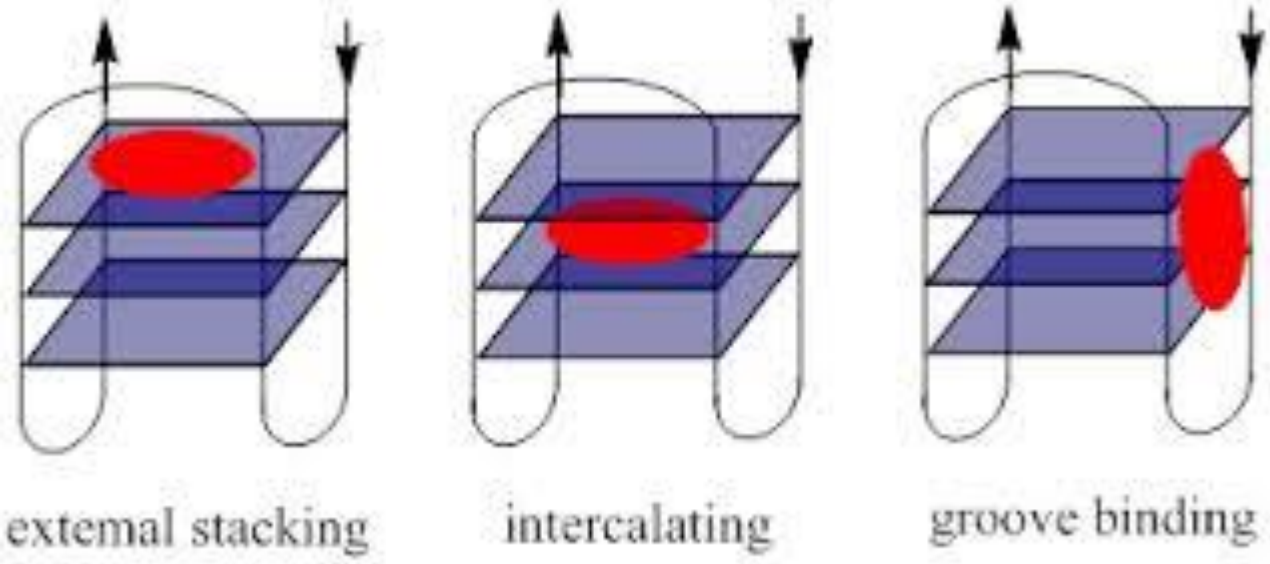


Potential binding sites in a *G-quadruplex*

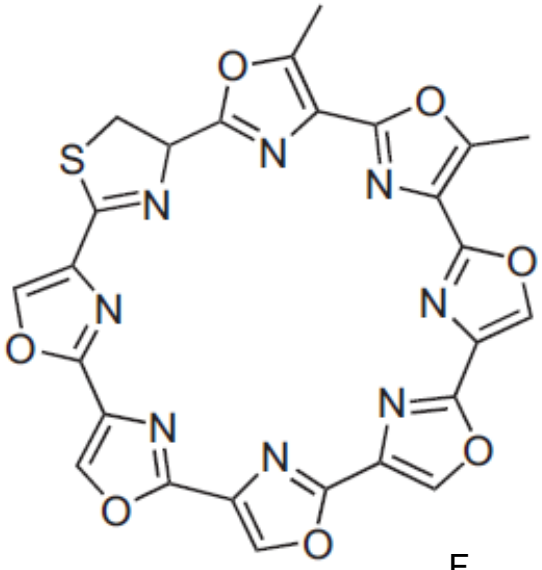
The stabilization of G-quadruplexes is an indirect mode for inhibiting telomerase



G-quadruplex stabilization for telomerase inhibition

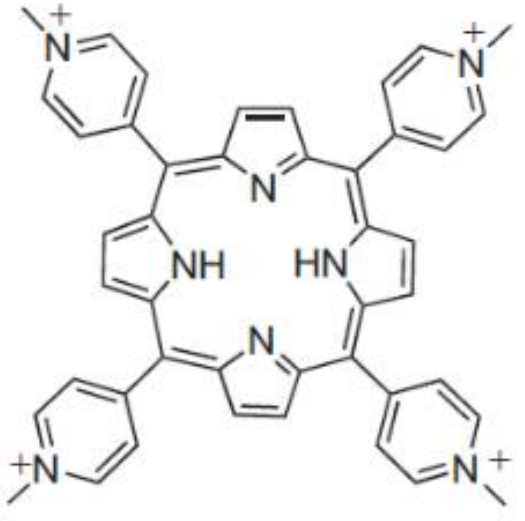


Telomerase Inhibitors

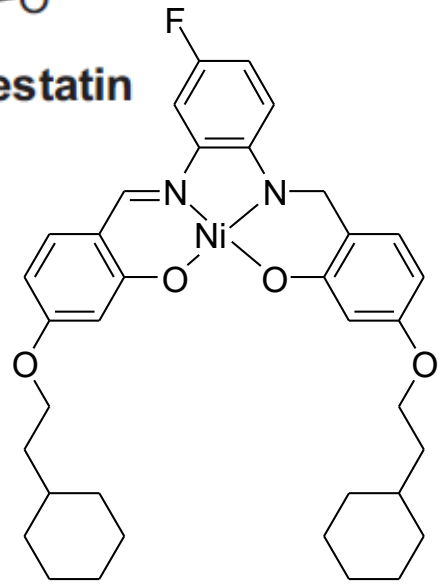


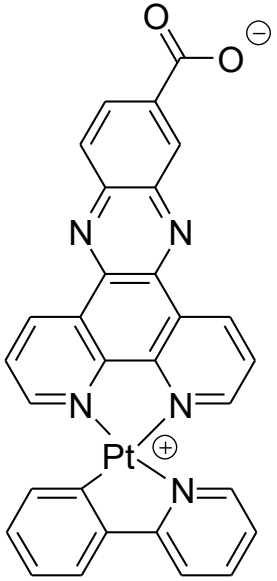
Telomestatin

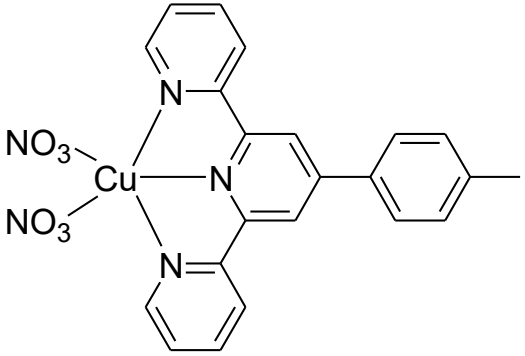
π stacking on G quartets



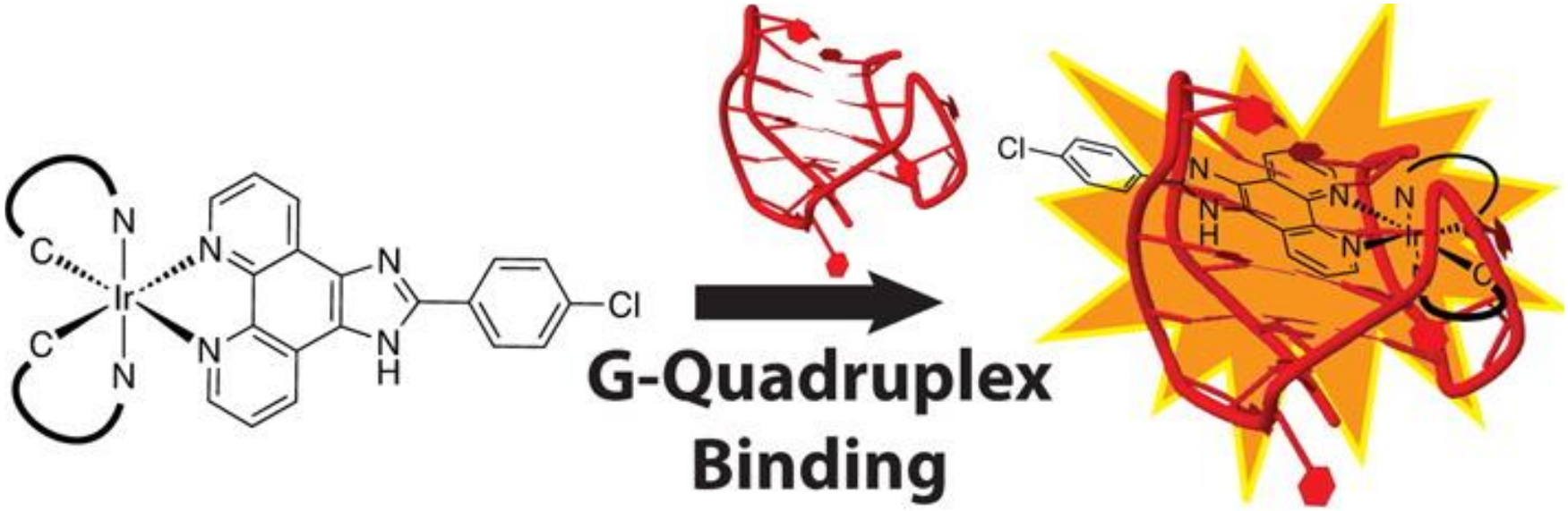
TmPyP4





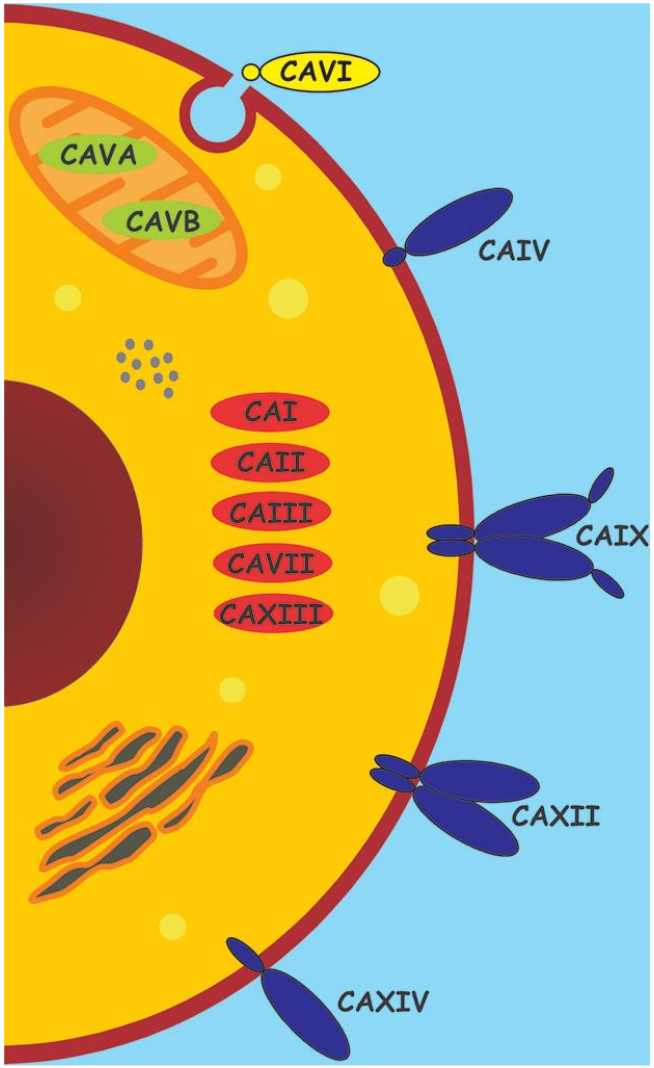


G-quadruplex sensing



Metal-based Inhibitors of Metal-Enzymes

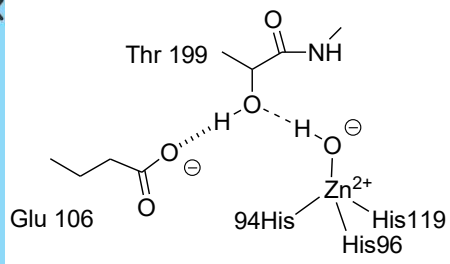
Human Carbonic Anhydrase (hCA) inhibitors



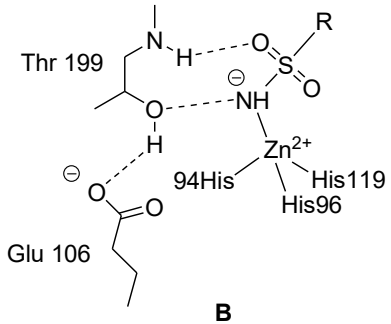
Isoforms of hCA

Diseases that over-express CA: glaucoma, epilepsy and neuro-muscular disorders, obesity, osteoporosis, Alzheimer's disease, numerous types of cancer…

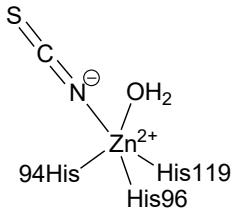
sulfonamides coordinating anions



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



Tetrahedral adduct (sulfonamide)

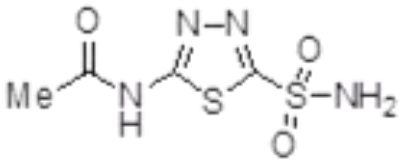


Trigonal-bipyramidal adduct (thiocyanate)

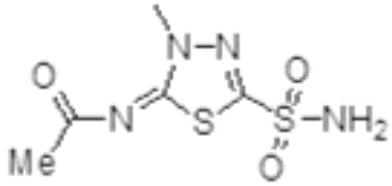
$$H_2O + CO_2 \rightleftharpoons HCO_3^- + H^+$$

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

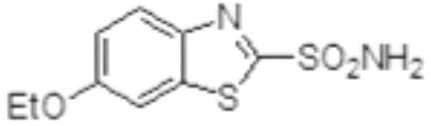
Sulfonamide drugs as CA inhibitors
(diuretics, anti-glaucoma and anti-epileptic agents)



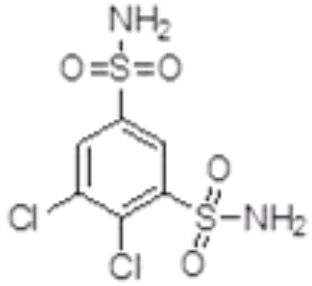
Acetazolamide (AAZ)



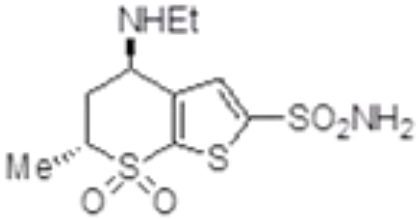
Methazolamide (MZA)



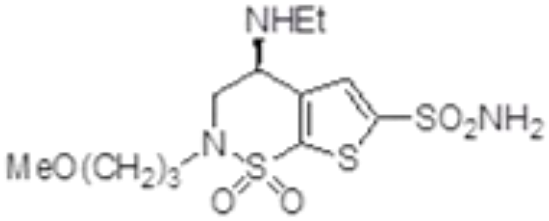
Ethoxzolamide (EZA)



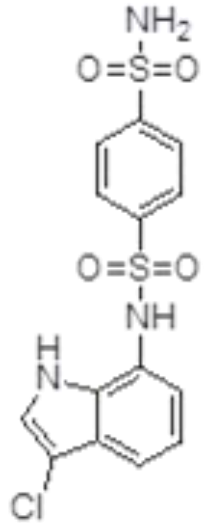
Dichlorophenamide (DCP)



Dorzolamide (DZA)

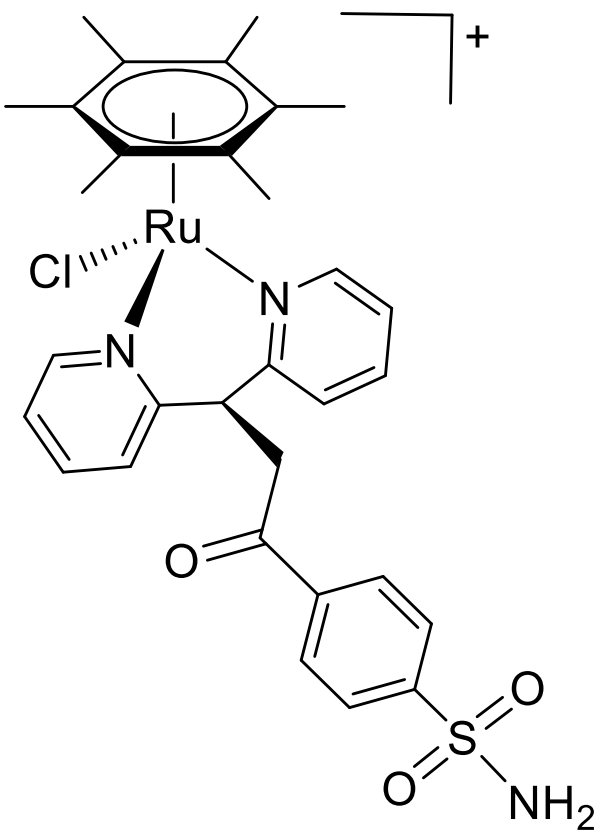


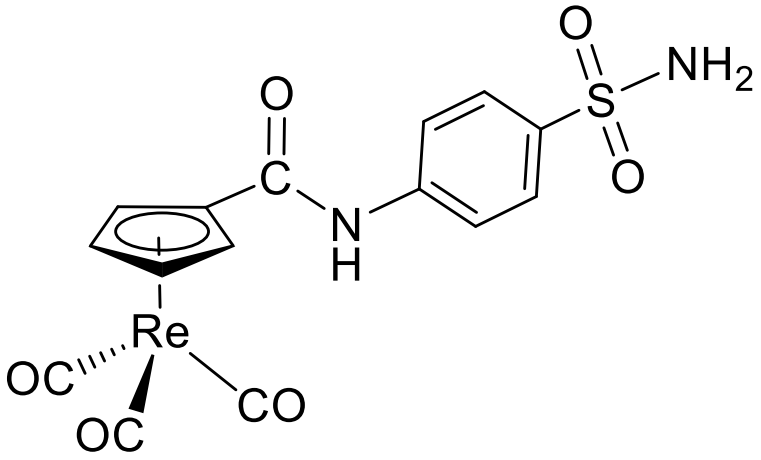
Brinzolamide (BRZ)

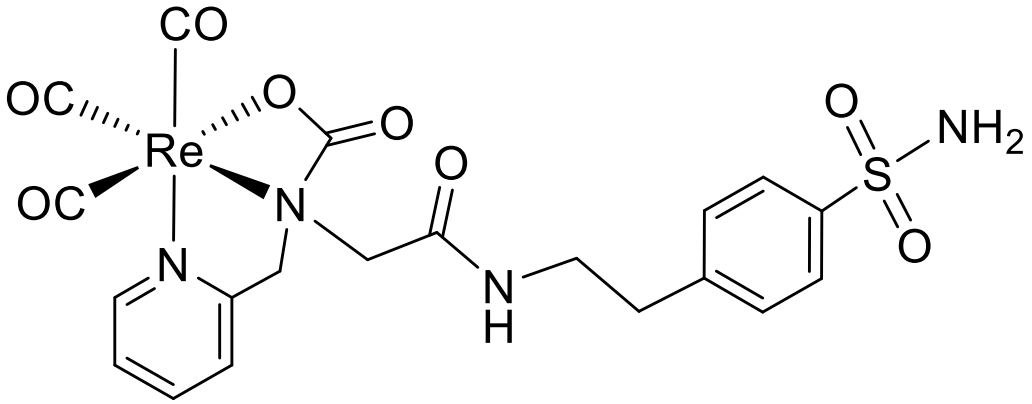


Indisulam (IND)

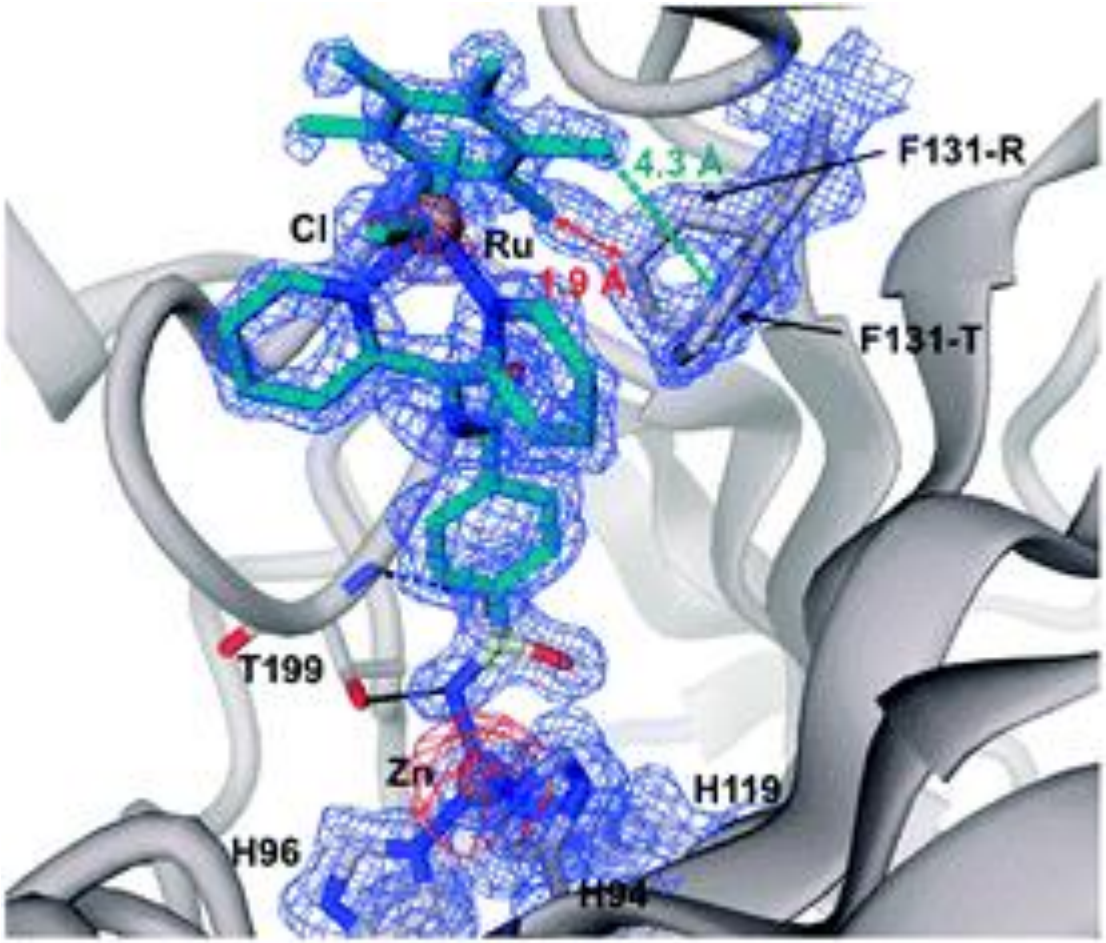
Inert organometallic compounds as hCA inhibitors



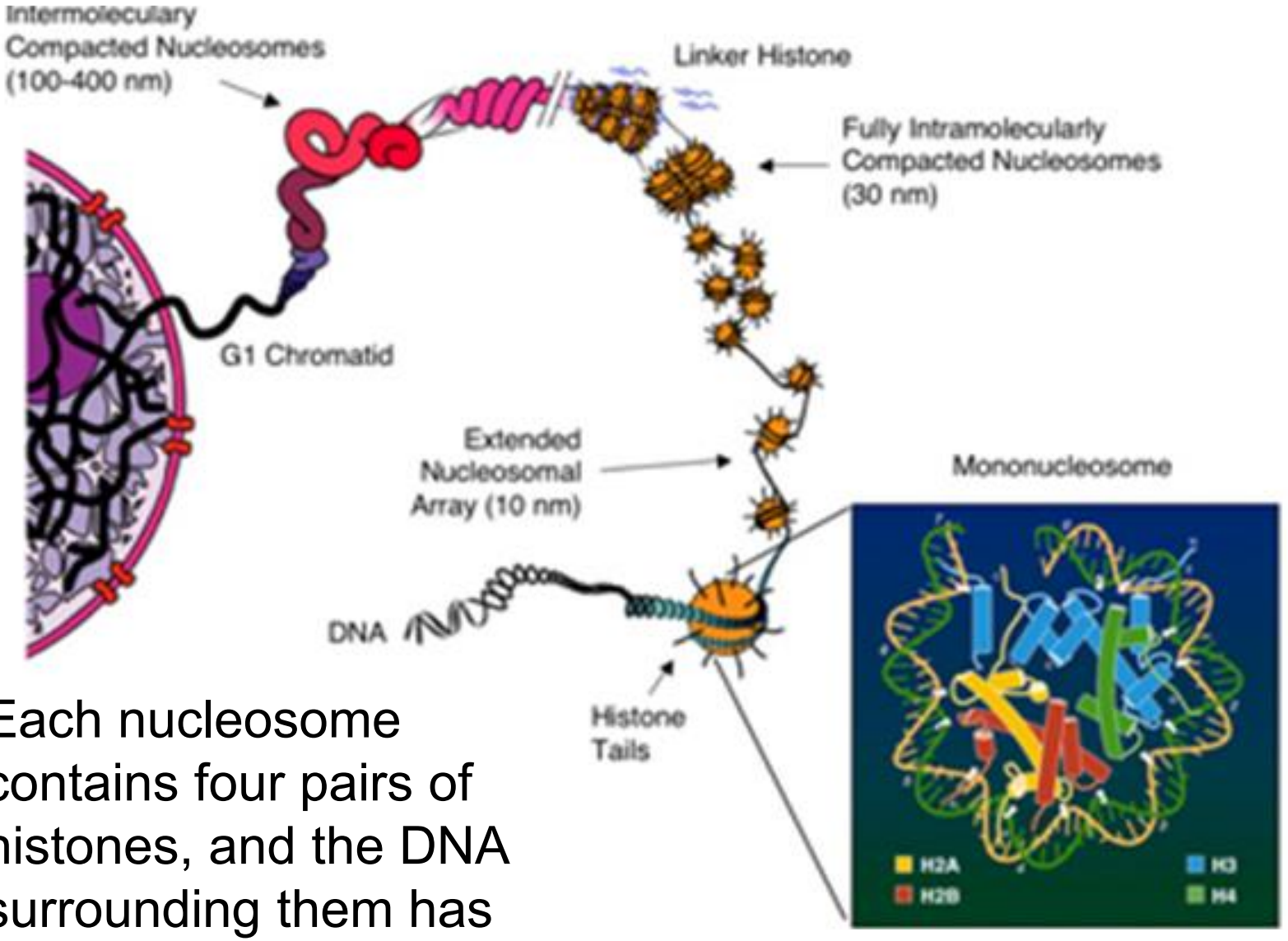




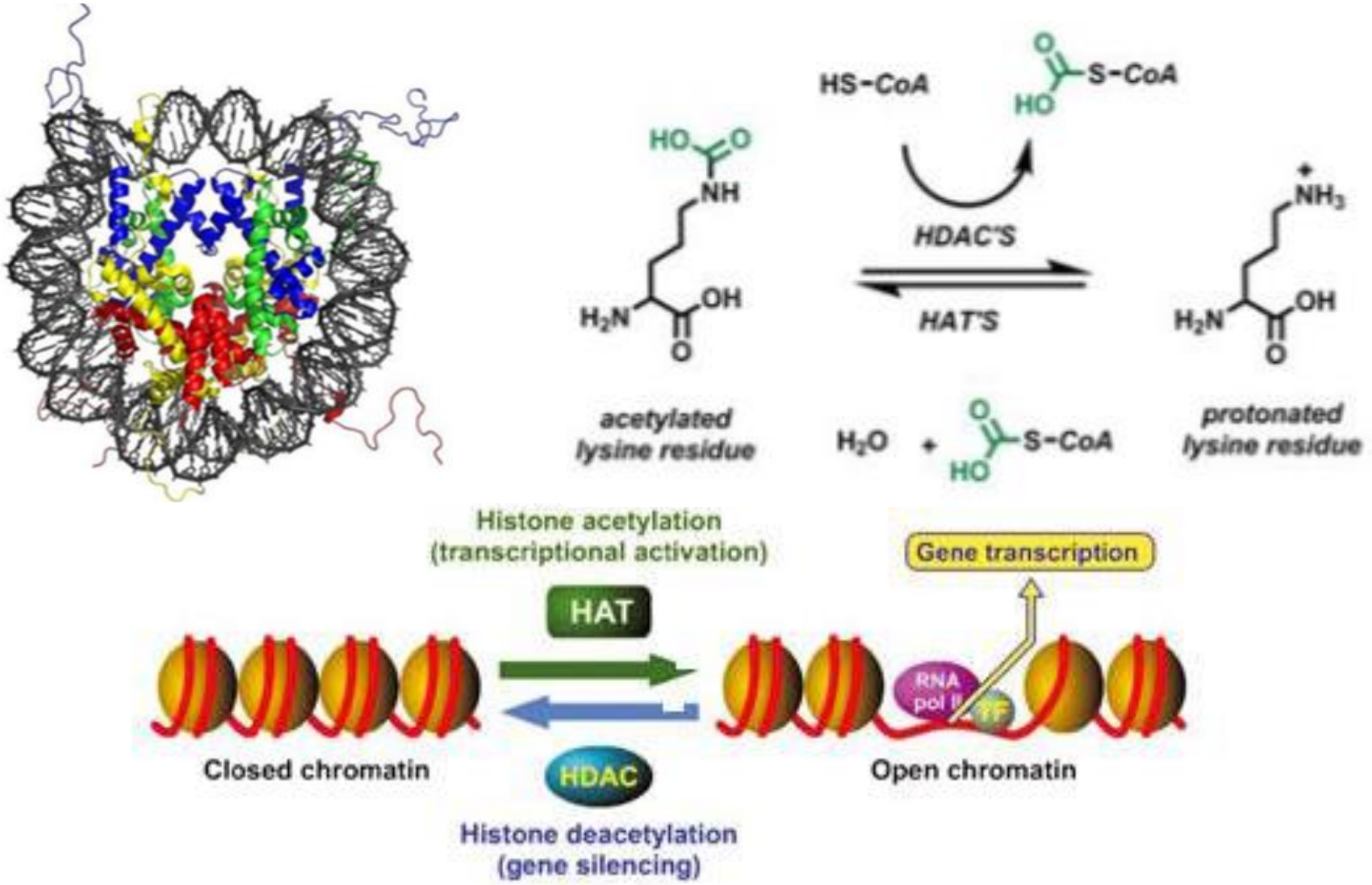
Ru-arene piano-stool complex @ hCA II



Chromatine, Nucleosomes and Histones



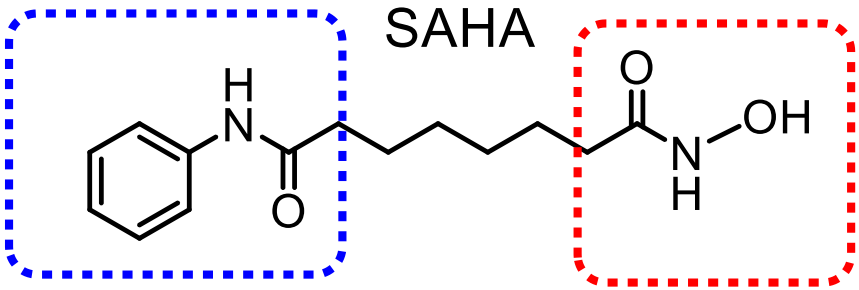
Each nucleosome contains four pairs of histones, and the DNA surrounding them has 145-147 base pairs



HAT and HDA enzymes are potential pharmacological targets

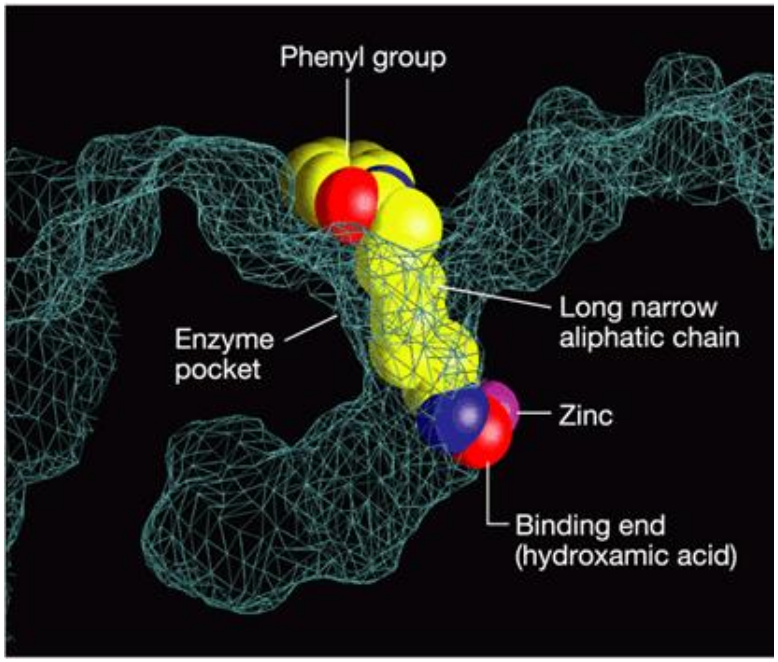
HDAC Inhibitors (HDACi) as anticancer agents

Some HDACi's can reactivate gene expression and inhibit the growth and survival of cancer cells at non-toxic concentrations



aromatic protein recognition domain

hydroxamic acid Zn^{2+}binding site



Zolinza®

FDA approval in 2006, treatment of *cutaneous T-cell lymphoma*

epigenetic modulation

Metal-based HDAC Inhibitors