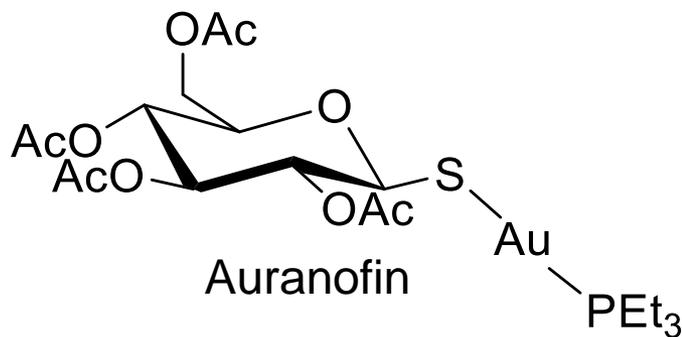


Metal-based Inhibitors of Enzymes

Auranofin: a serendipitous enzyme inhibitor

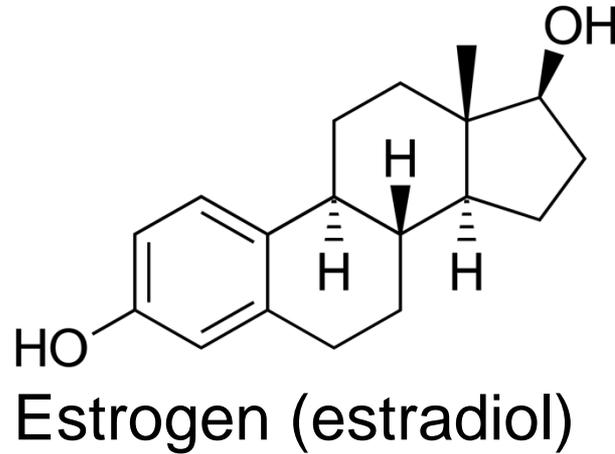
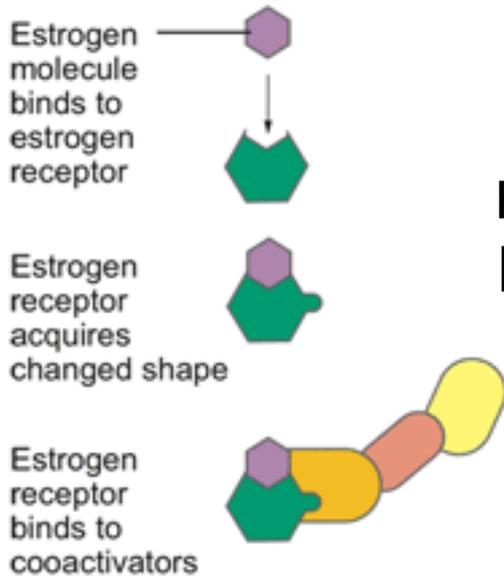


- Introduced in the late 1970s as oral substitute of gold anti-arthritic agents (developed on the wrong assumption that arthritis was caused by a bacterial infection).

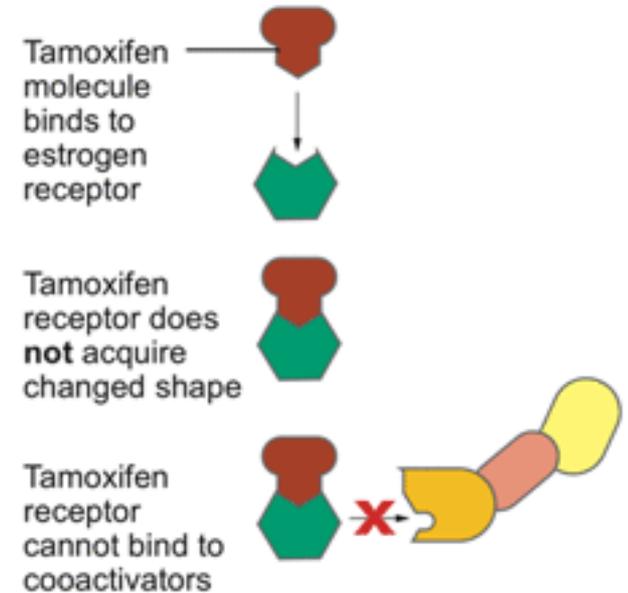
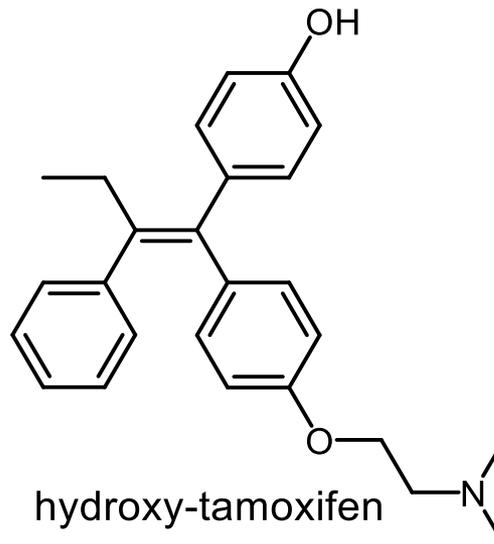
Aniparasitic action:

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

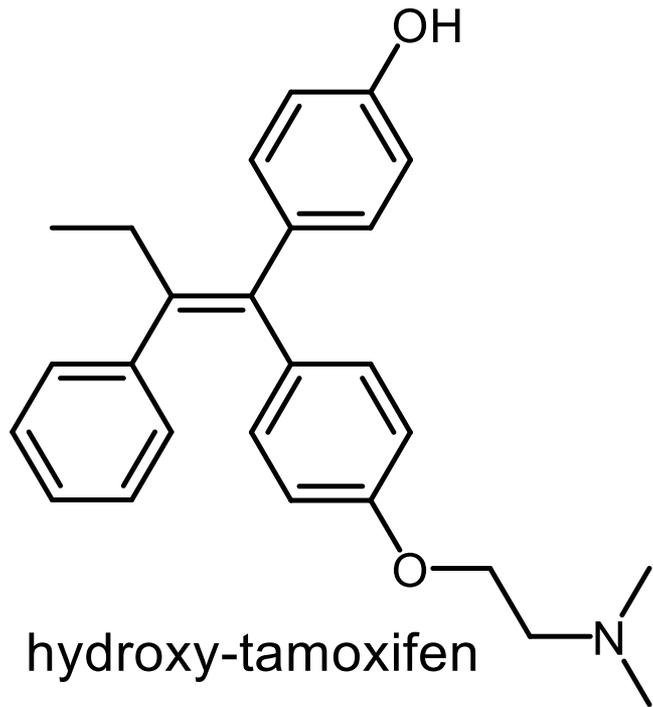
Inhibitors of the estrogen hormone receptor



Proliferation of cancer cells

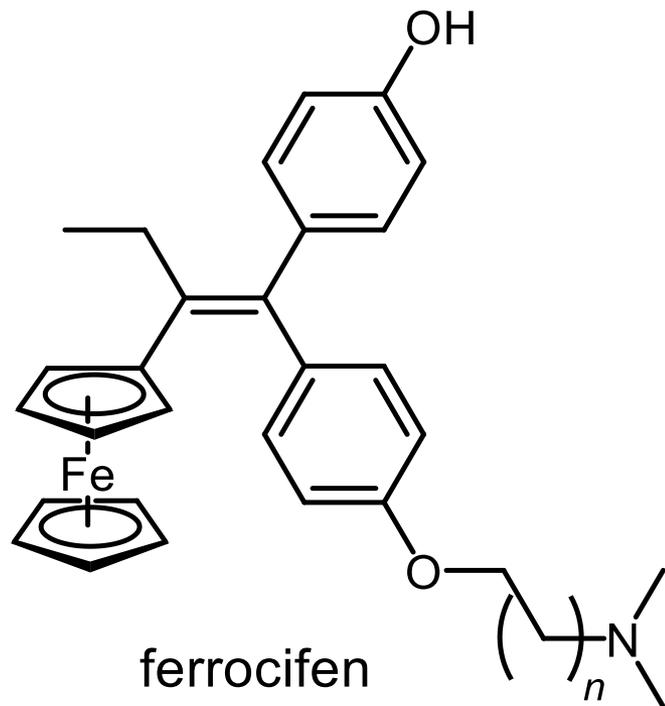
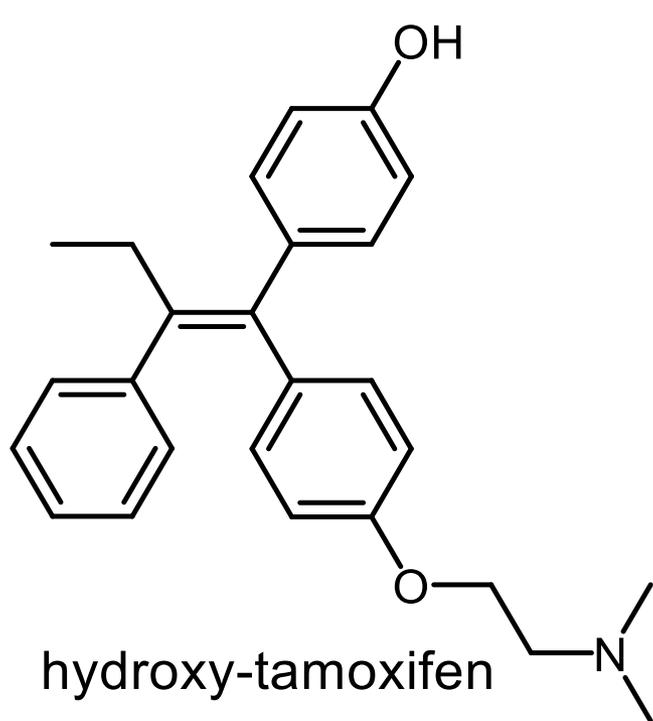


Inhibition of cancer cells



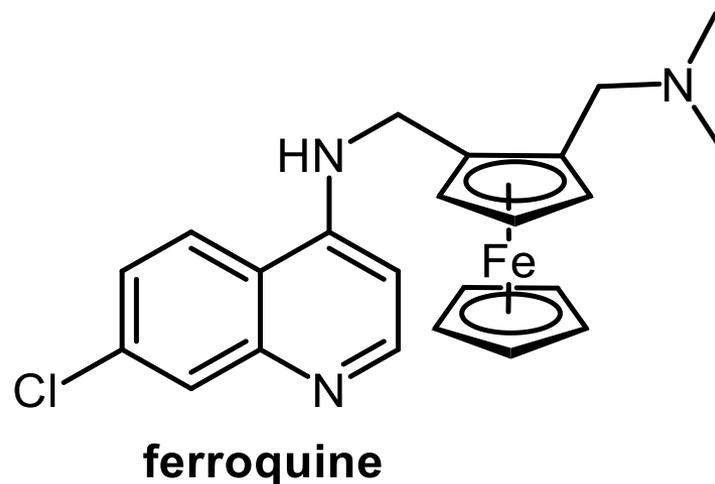
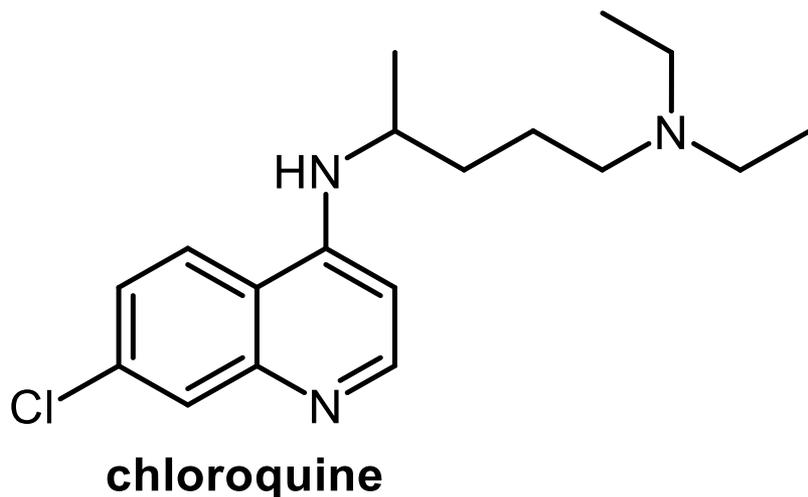
Tamoxifen is active only against those type of breast cancer that overexpress the Estrogen Receptor α ($ER\alpha+$, ca. 2/3 of total).

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



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



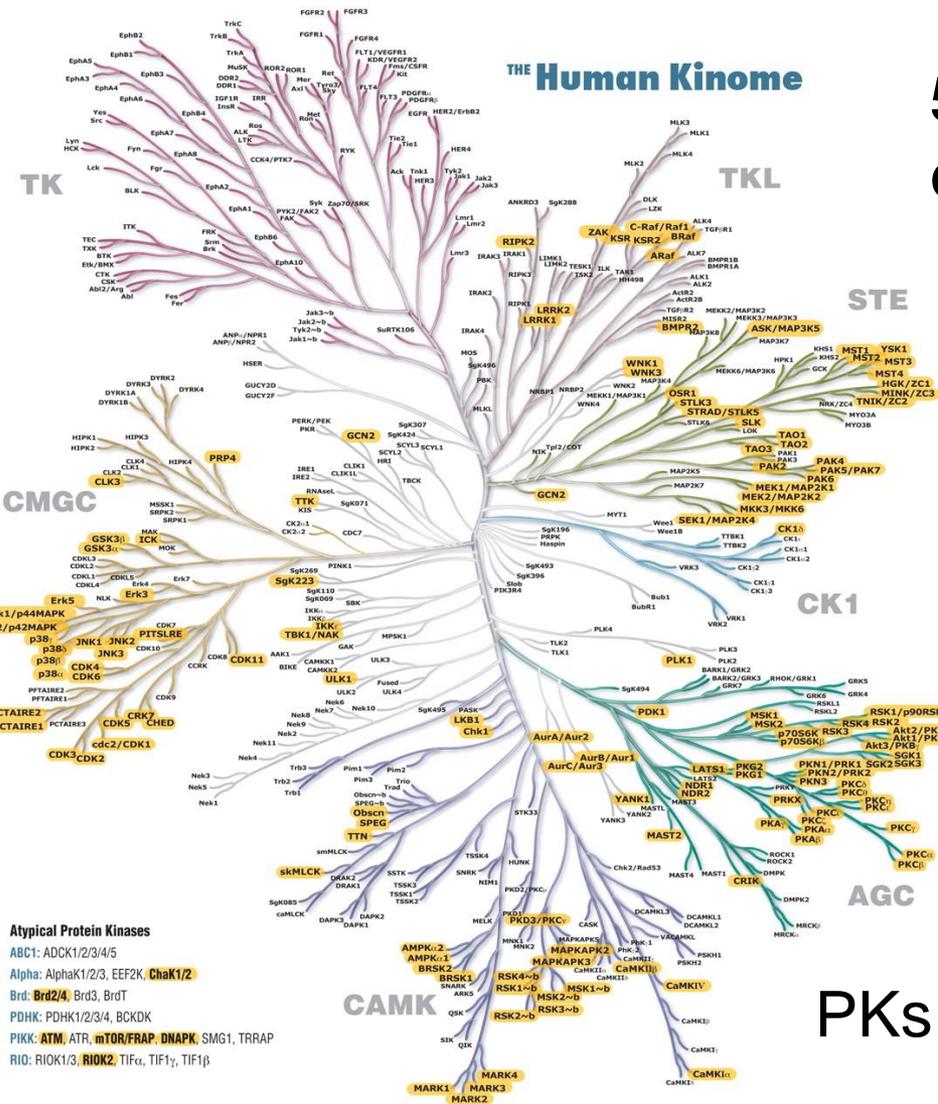
- Ferroquine is the ferrocenyl analogue of chloroquine, an established antimalarial drug.
- Ferroquine is active also against chloroquine-resistant strains and is due to enter clinical phase III trials.

Inhibitors of Protein Kinases (PKs)

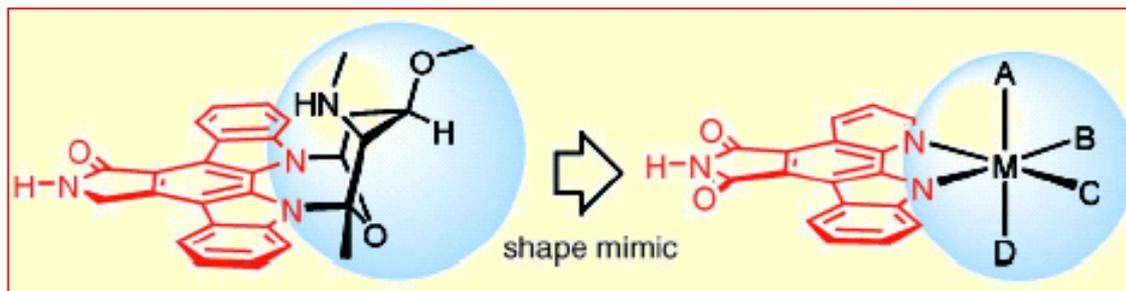
538 different protein kinases are encoded in the human genome

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

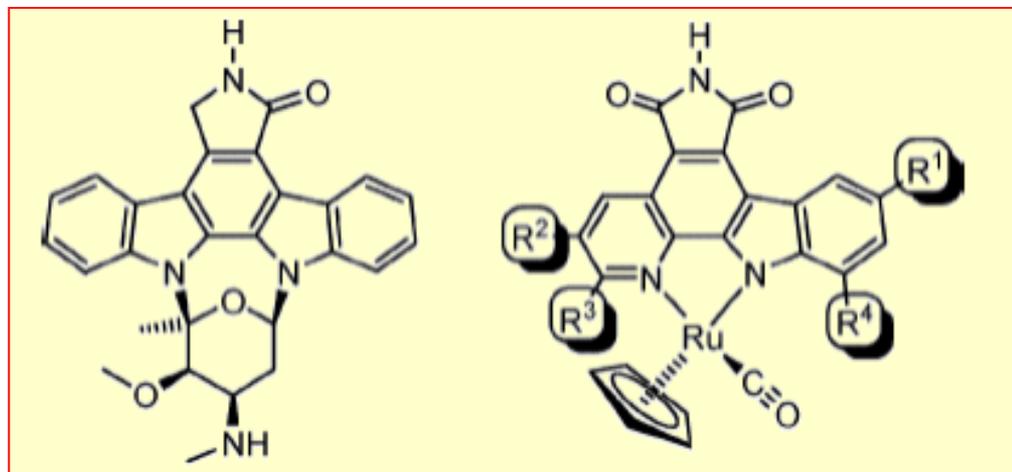


Selective protein kinase inhibitors

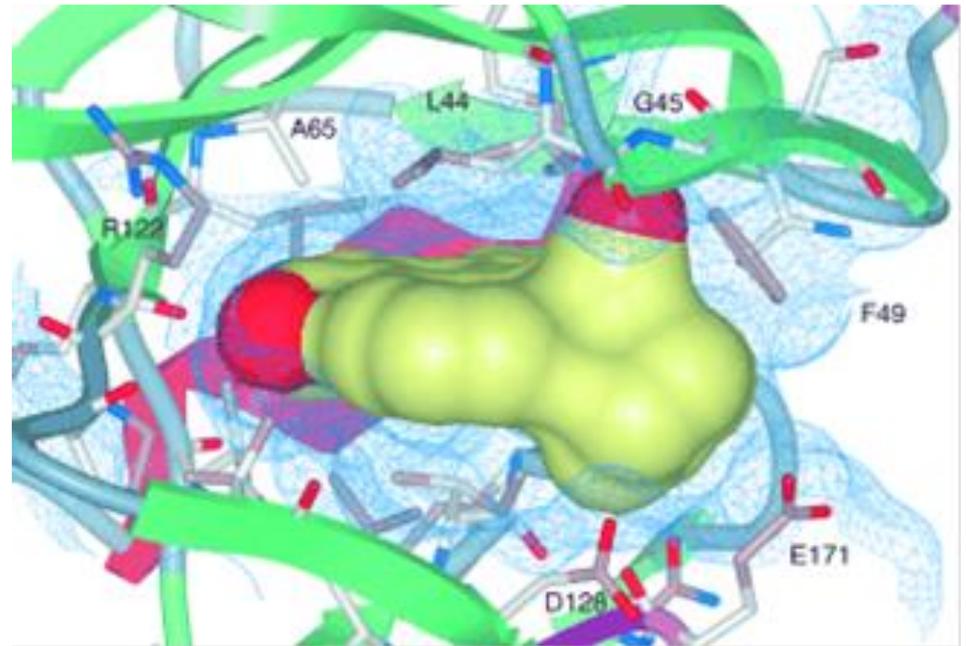
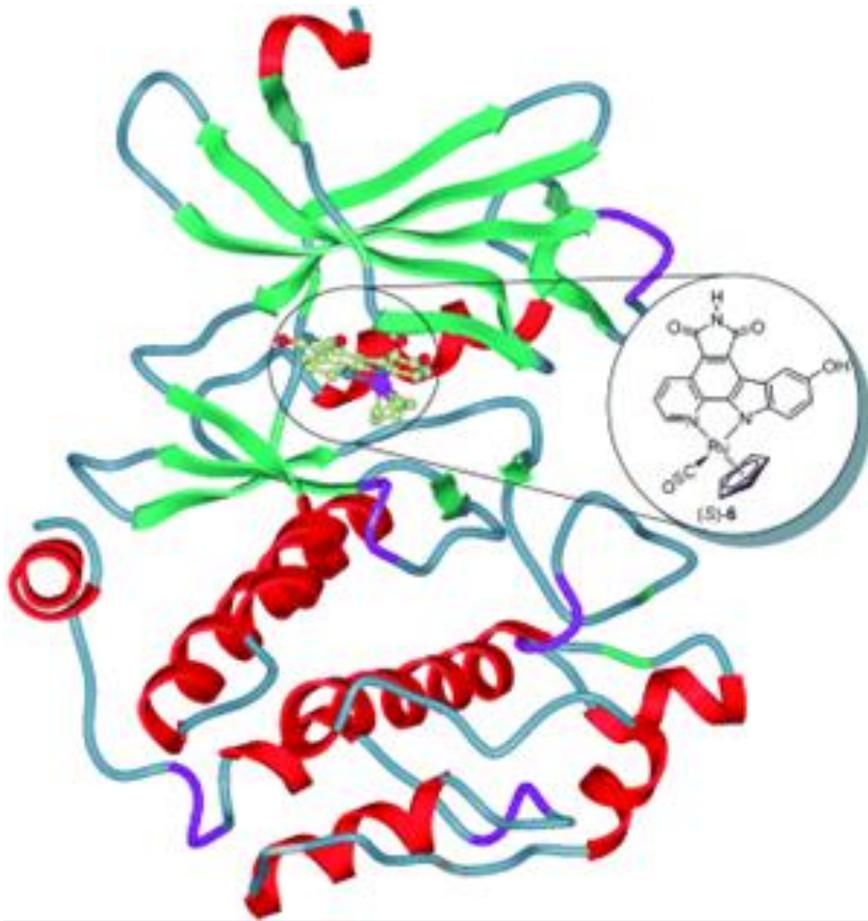


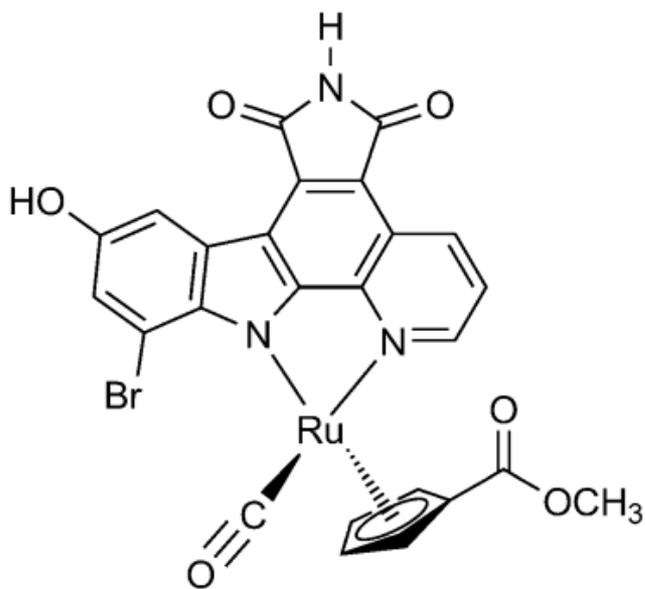
Staurosporine, unselective protein kinase inhibitor (ATP binding site)

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

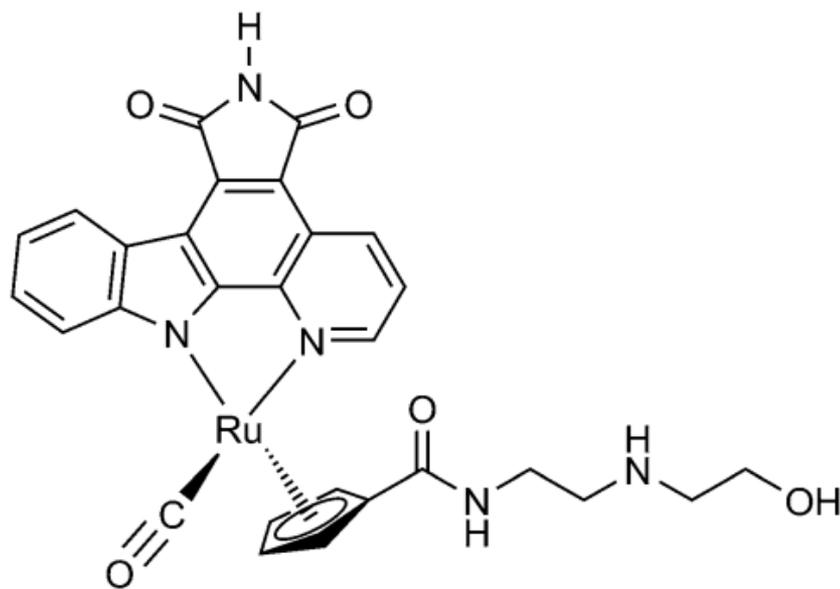


The binding of an organometallic ruthenium inhibitor to the ATP binding site of protein kinase Pim-1





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



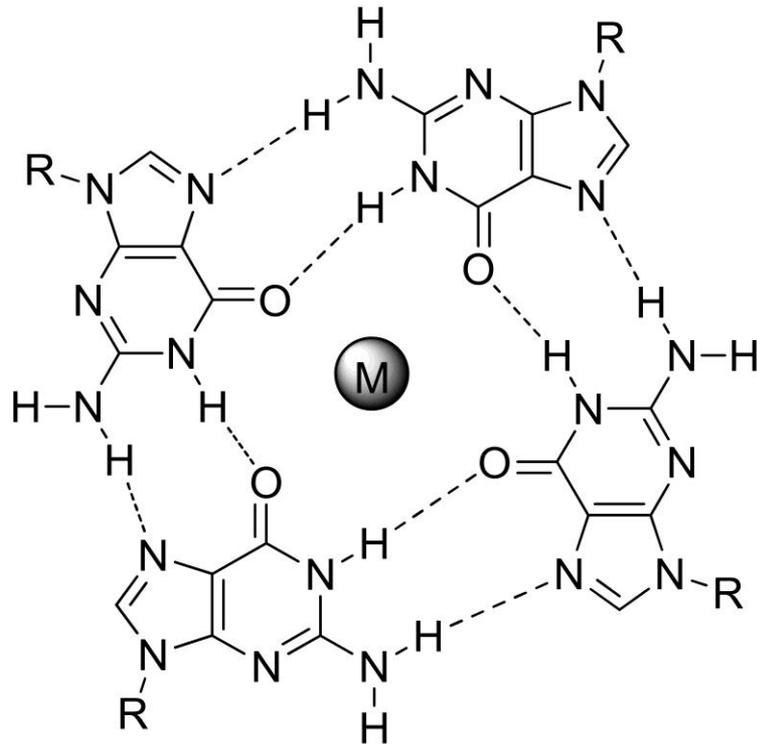
Pim1 inhibitor
 $IC_{50} \sim 2 \text{ nM}$

Commercially available as specific PK inhibitors

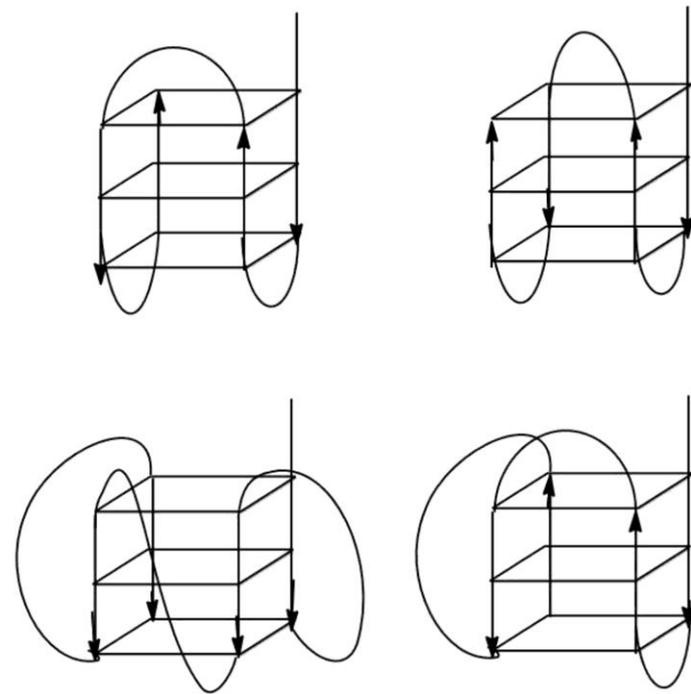
Telomers and telomerase inhibitors

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

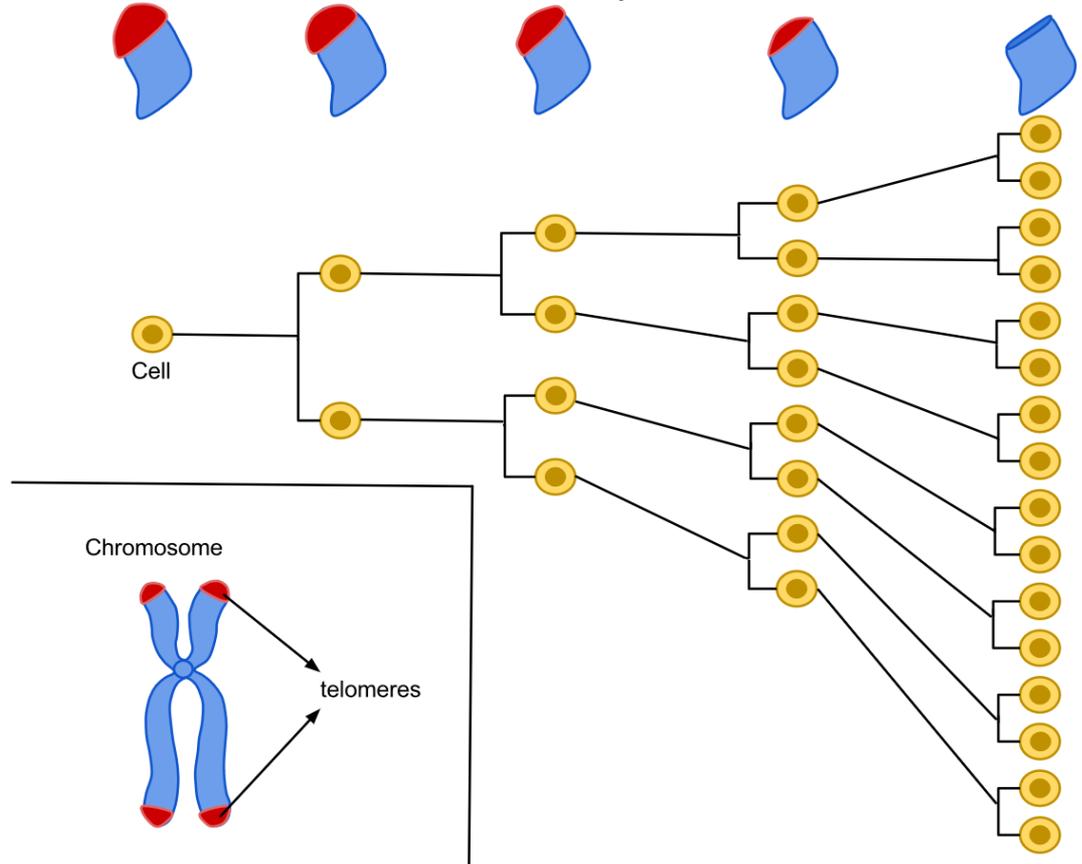


The guanine-rich sequences of the telomer self-assemble through H-bonds into G-quartets which, in turn, form G-quadruplexes.

Telomers = cell biological clock

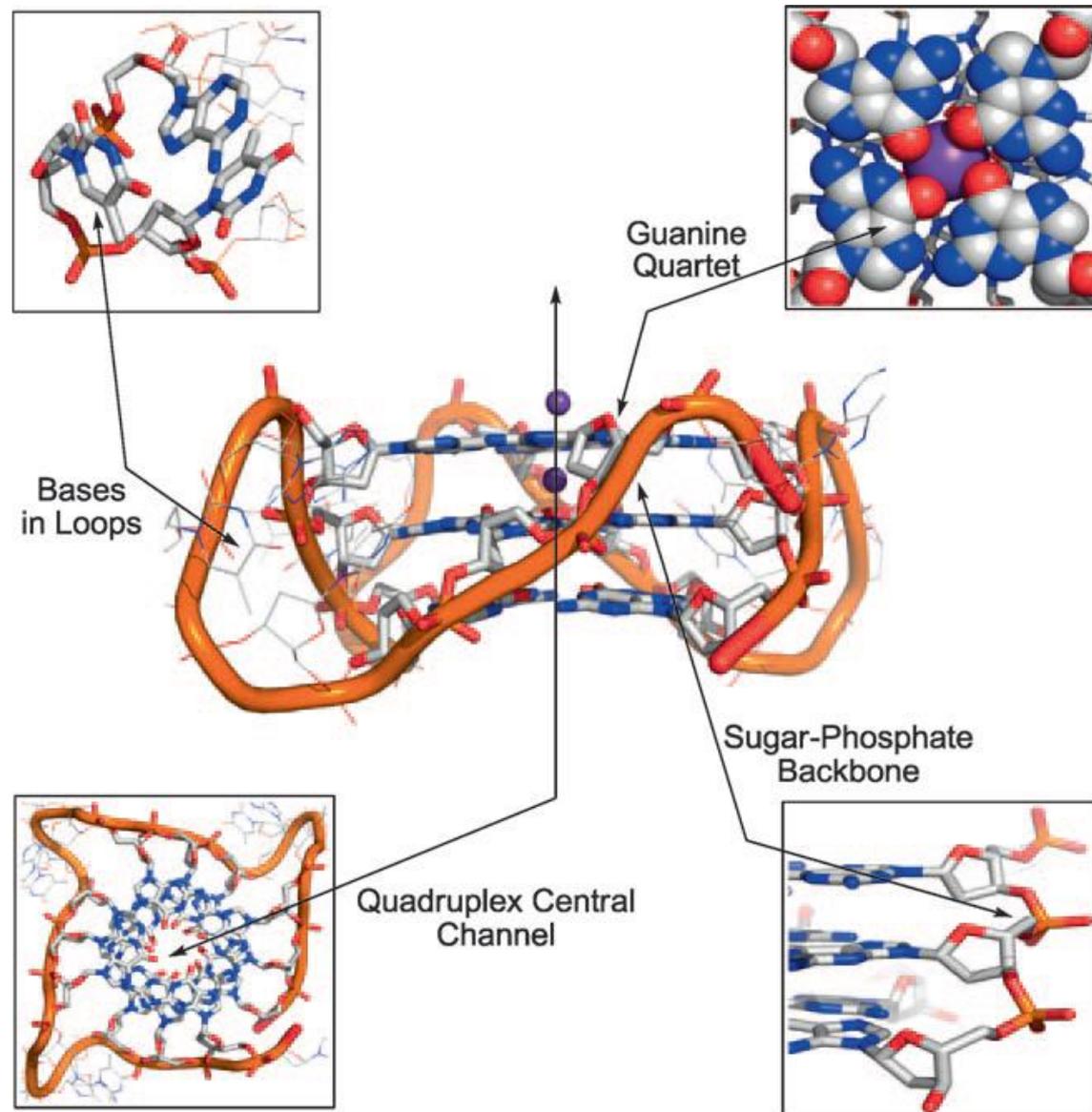
(in the absence of telomerase)

The Hayflick limit
(ca. 50 cellular divisions,
followed by apoptosis)

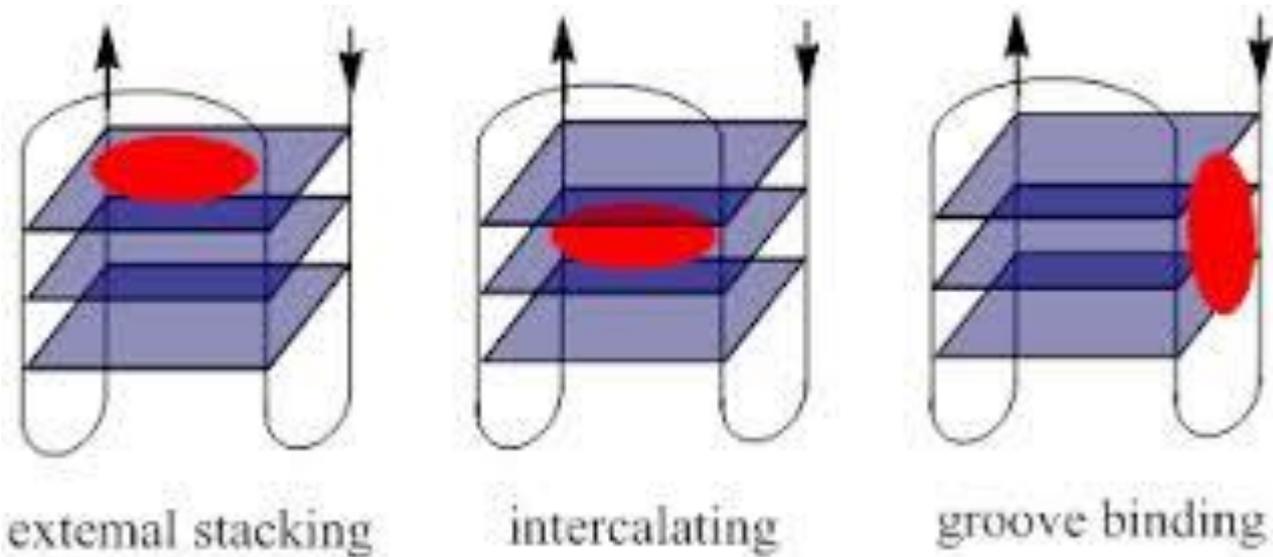


Telomerase is a protein with DNA-polymerase activity, over-expressed in most cancer cells (normally absent in somatic, i.e., differentiated, cells). It has the function of adding hexameric d(TTAGGG) units to the 3'-terminal part of the DNA telomere, keeping its length unchanged (making them **immortal**)

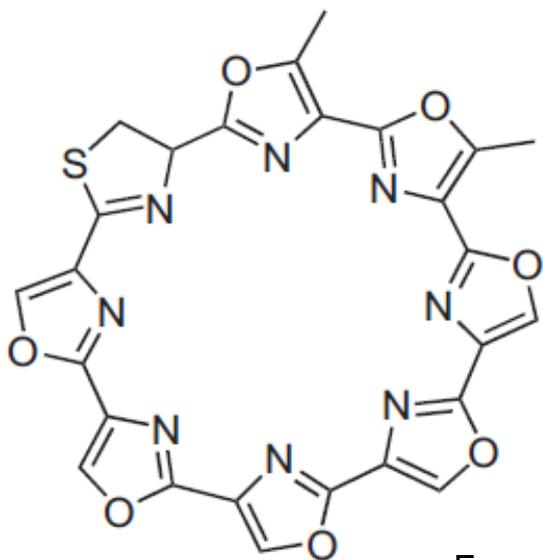
Potential binding sites in a *G-quadruplex*



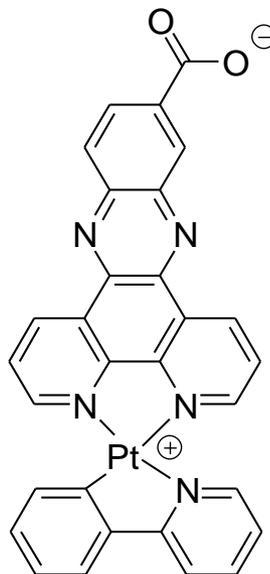
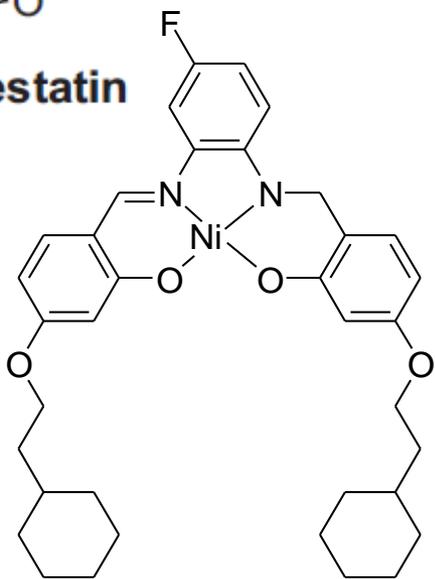
G-quadruplex stabilization for telomerase inhibition



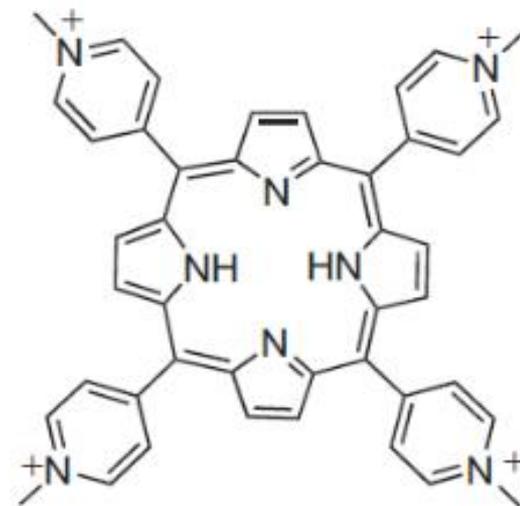
Telomerase Inhibitors



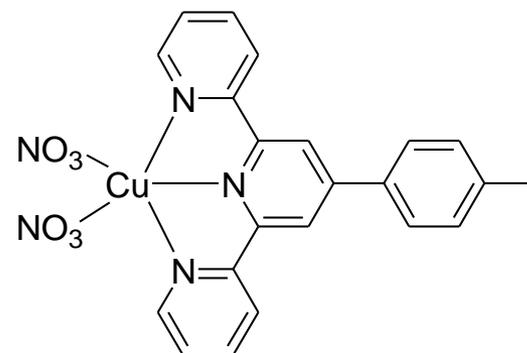
Telomestatin



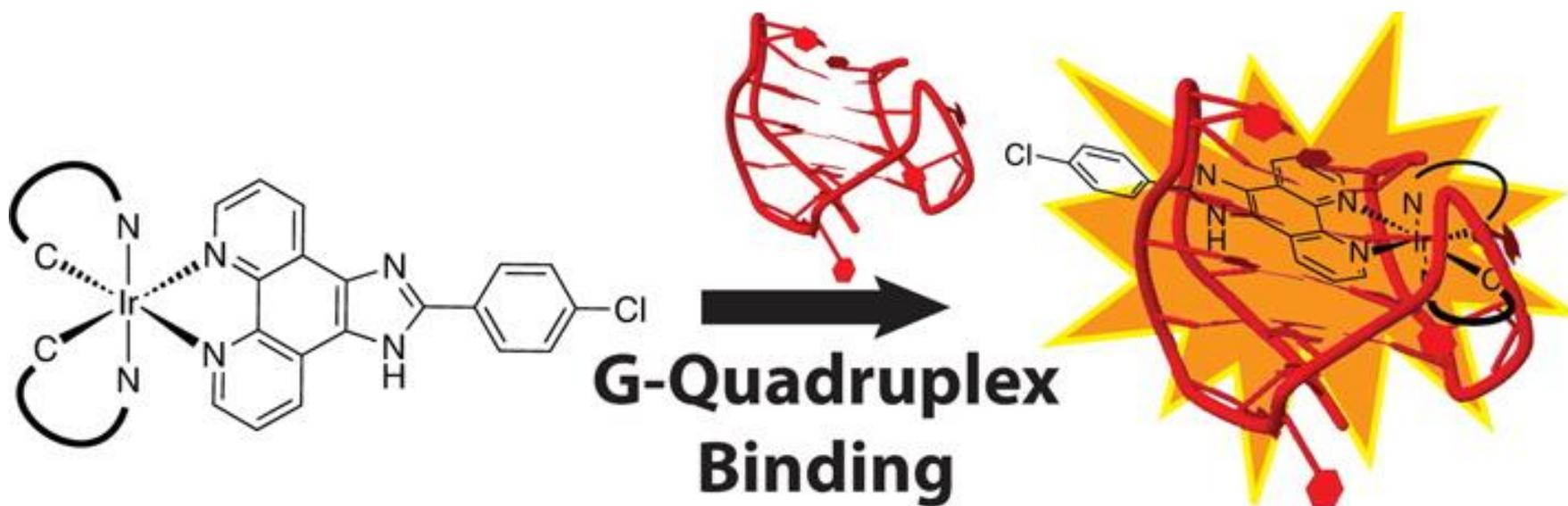
π stacking on G quartets

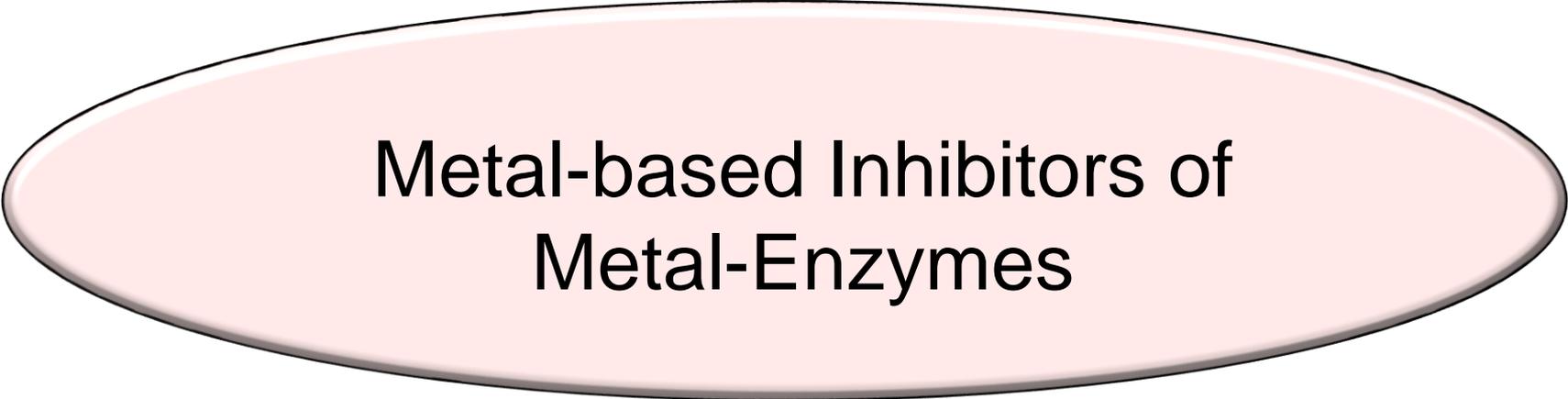


TmPyP4



G-quadruplex sensing

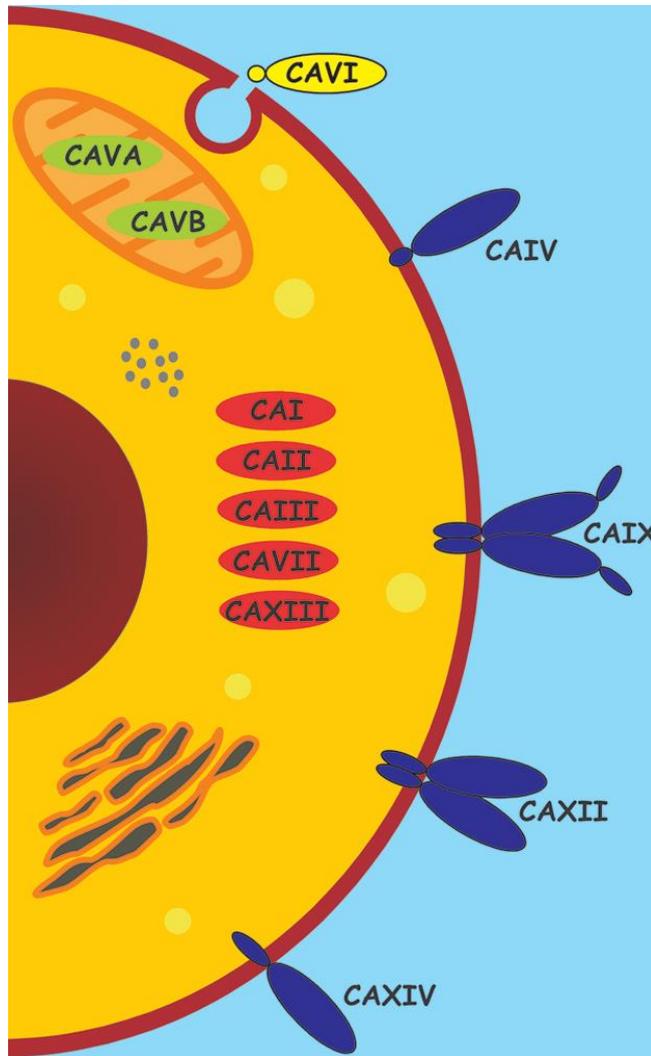




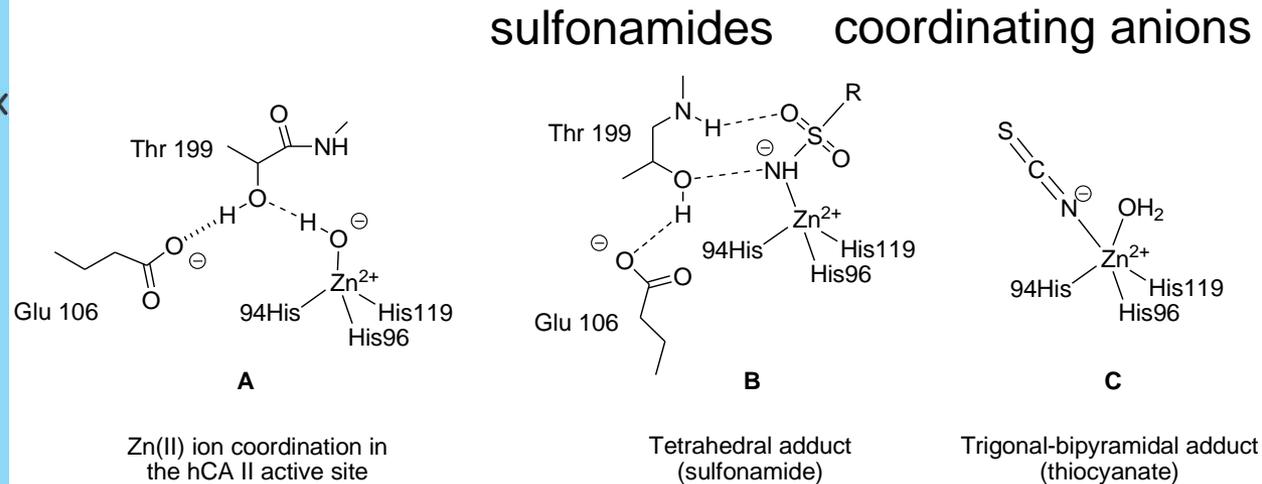
Metal-based Inhibitors of
Metal-Enzymes

Human Carbonic Anhydrase (hCA) inhibitors

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



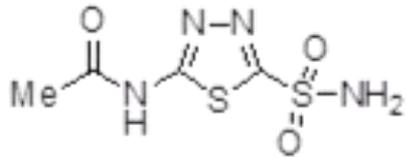
Isoforms of CA



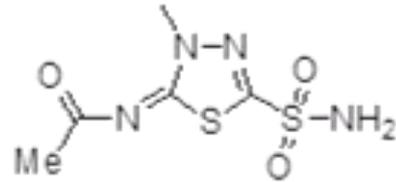
$$k \approx 10^{-1} \text{ s}^{-1} \rightarrow 10^6 \text{ s}^{-1}$$

Sulfonamide drugs as CA inhibitors

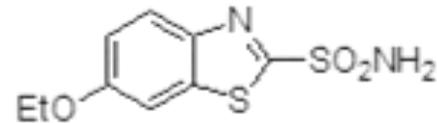
(diuretics, anti-glaucoma and anti-epileptic agents)



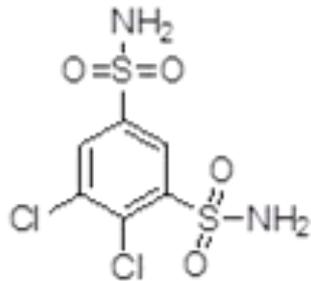
Acetazolamide (AAZ)



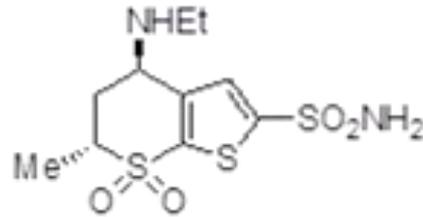
Methazolamide (MZA)



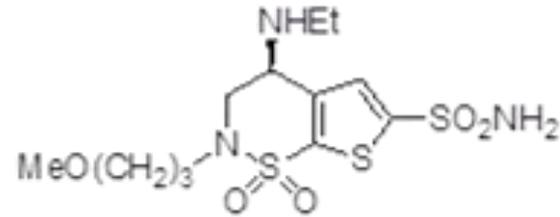
Ethoxzolamide (EZA)



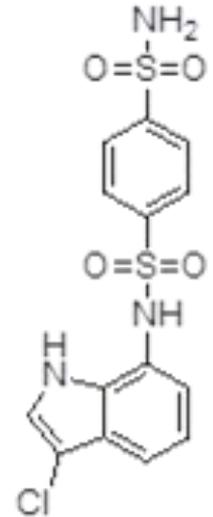
Dichlorophenamide (DCP)



Dorzolamide (DZA)

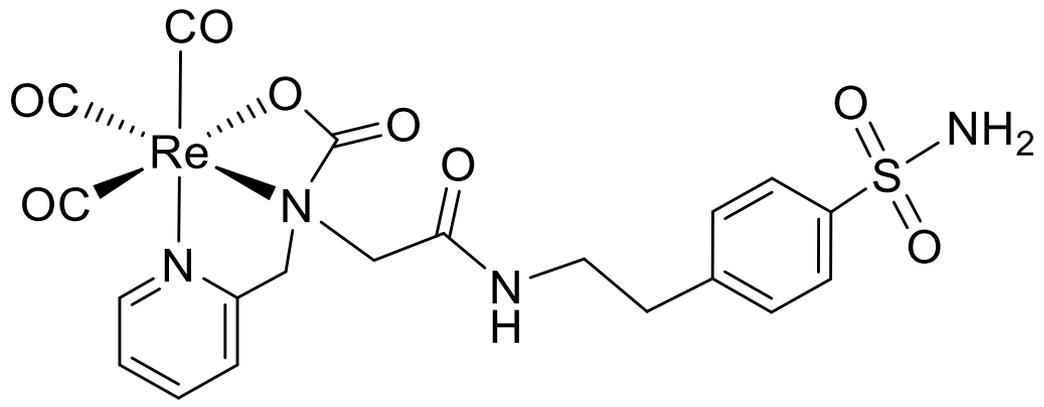
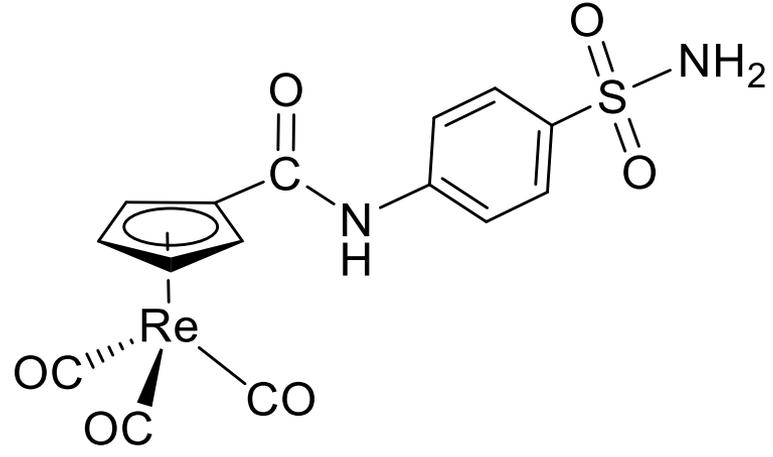
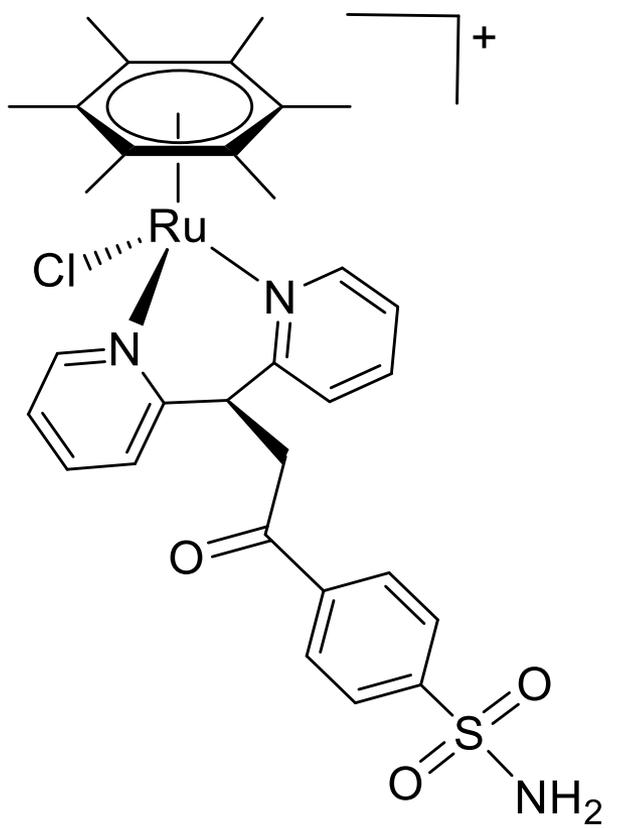


Brinzolamide (BRZ)

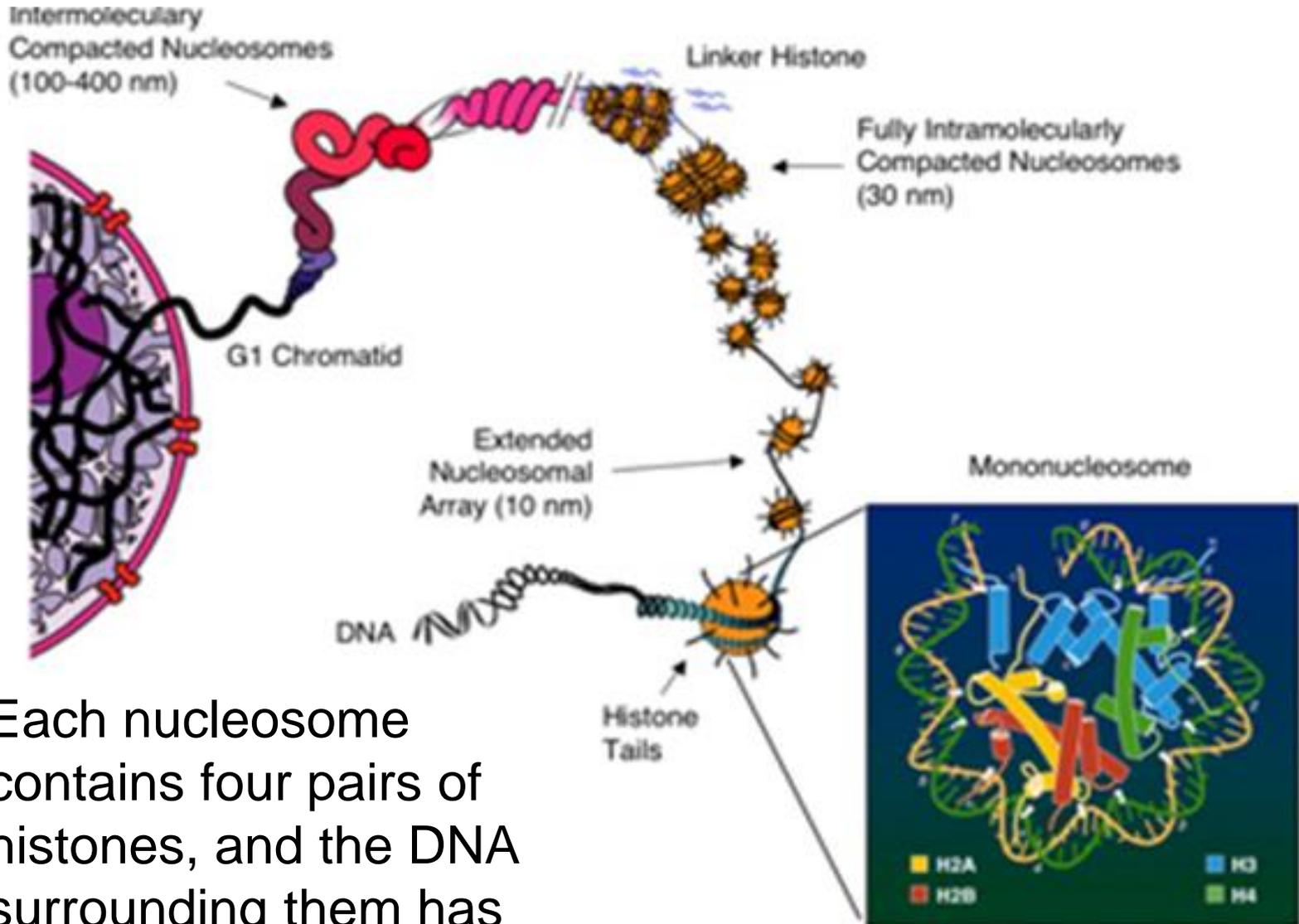


Indisulam (IND)

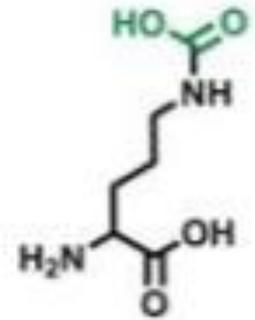
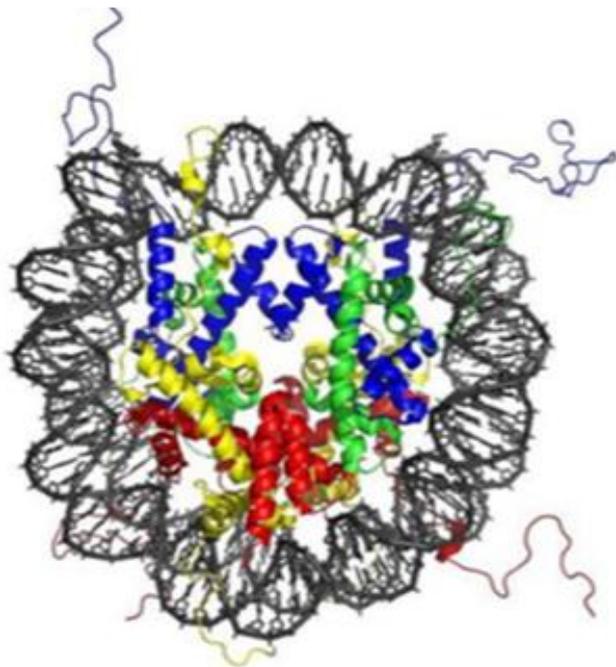
Inert organometallic compounds as hCA inhibitors



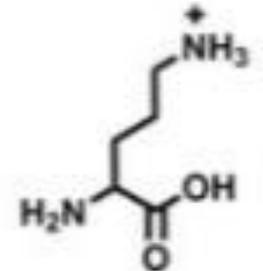
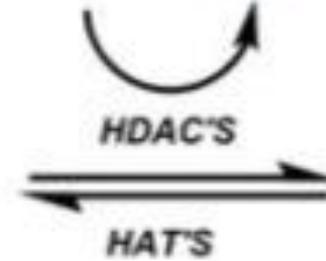
Chromatine, Nucleosomes and Histones



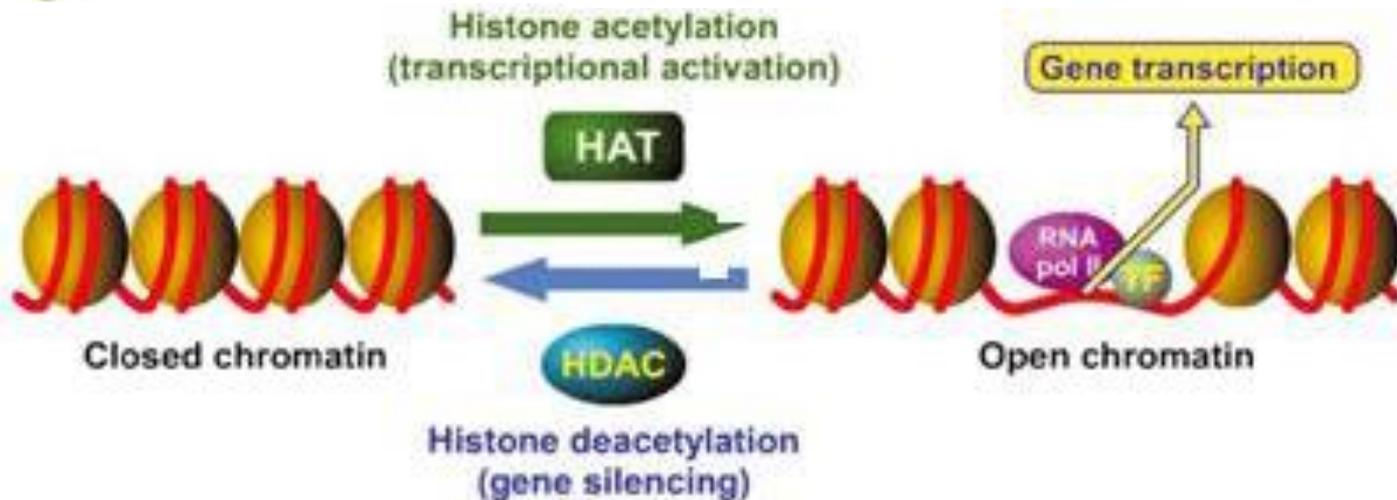
Each nucleosome contains four pairs of histones, and the DNA surrounding them has 145-147 base pairs



acetylated lysine residue



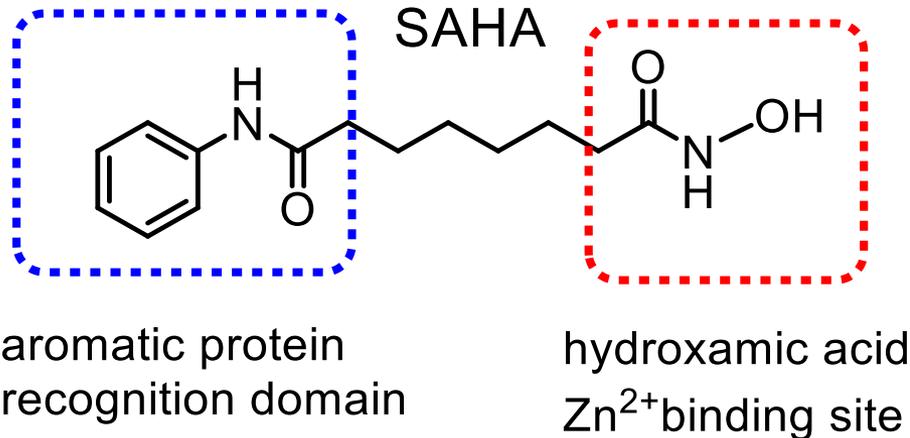
protonated lysine residue



HAT and HDA enzymes are potential pharmacological targets

HDAC Inhibitors (HDACi) as anticancer agents

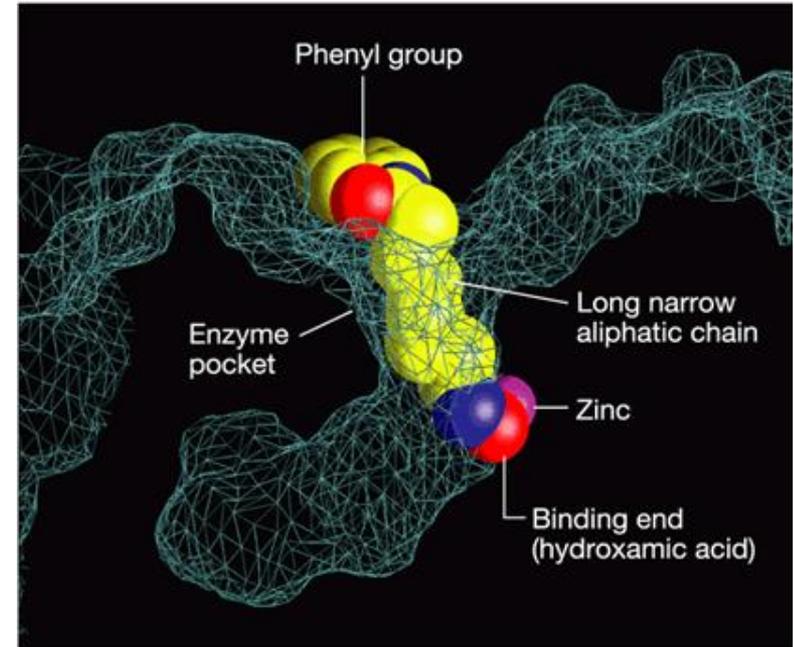
Some HDACi's can reactivate gene expression and inhibit the growth and survival of cancer cells at non-toxic concentrations



Zolinza®

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

epigenetic modulation



Metal-based HDAC Inhibitors

