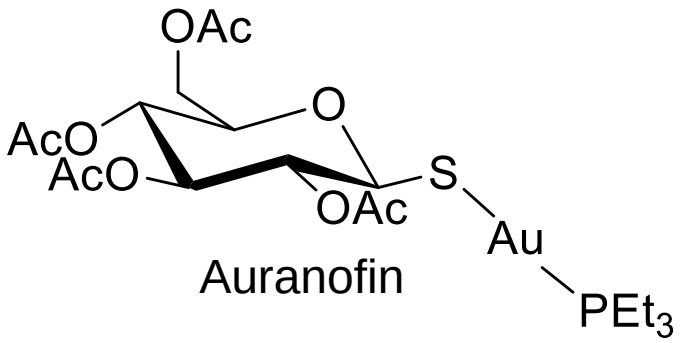
Metal-based Inhibitors of Enzymes

Auranofin: a serendipitous enzyme inhibitor

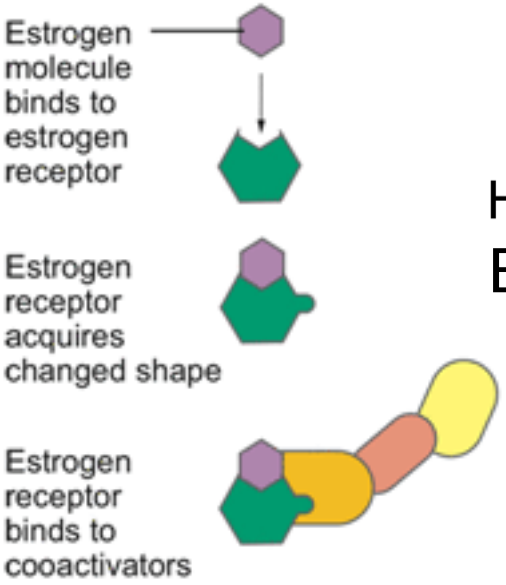


Auranofin

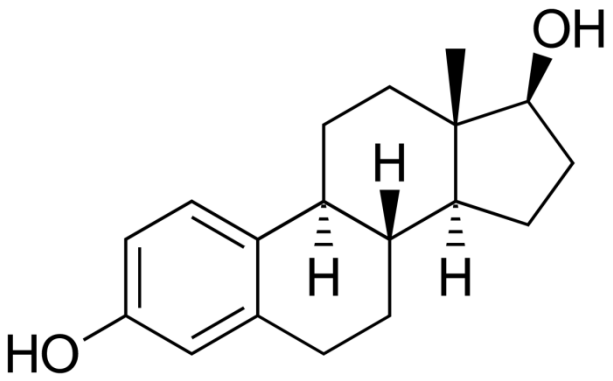
- Introduced in the late 1970s as oral substitute of gold anti-arthritic agents (developed on the wrong assumption that arthritis was caused by a bacterial infection).

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

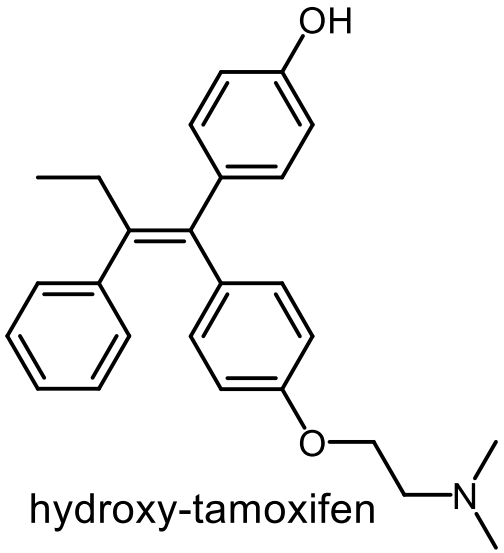
Inibitori dei recettori ormonali dell'estrogeno



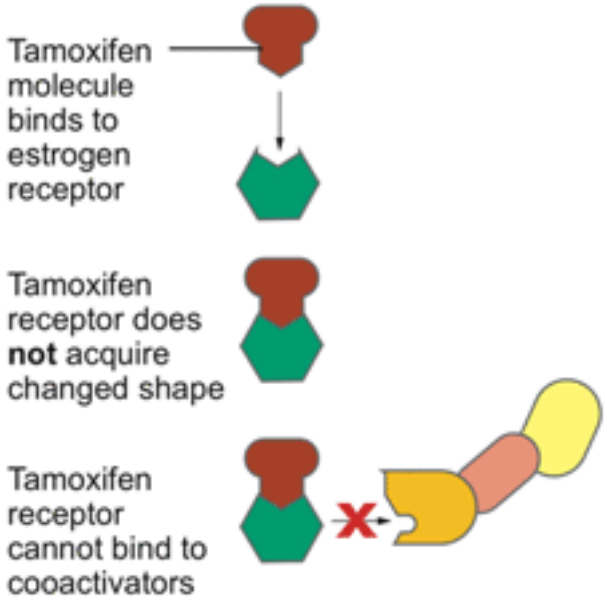
Proliferazione delle cellule tumorali



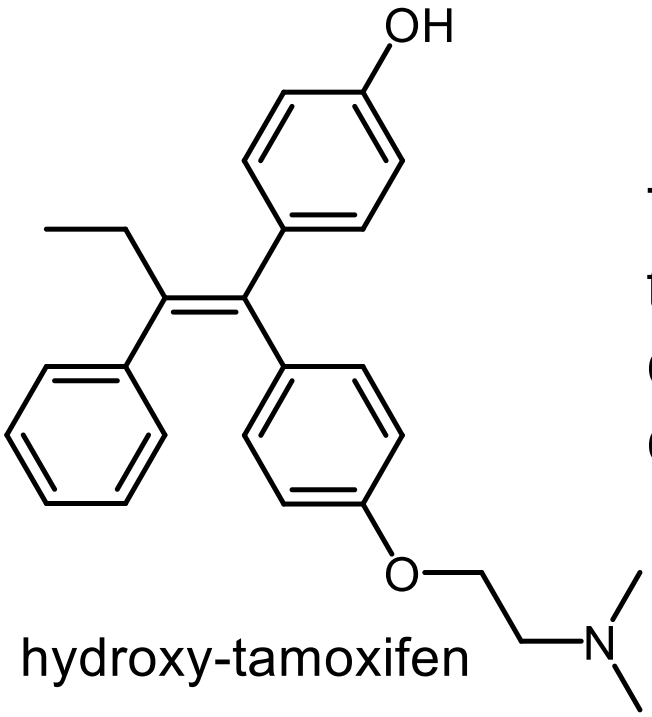
Estrogeno (estradiolo)



hydroxy-tamoxifen



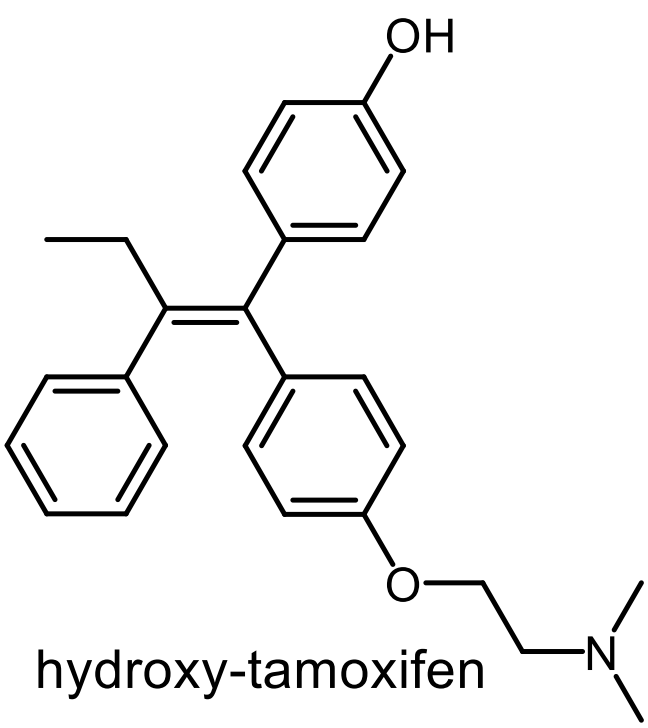
Inibizione delle cellule tumorali



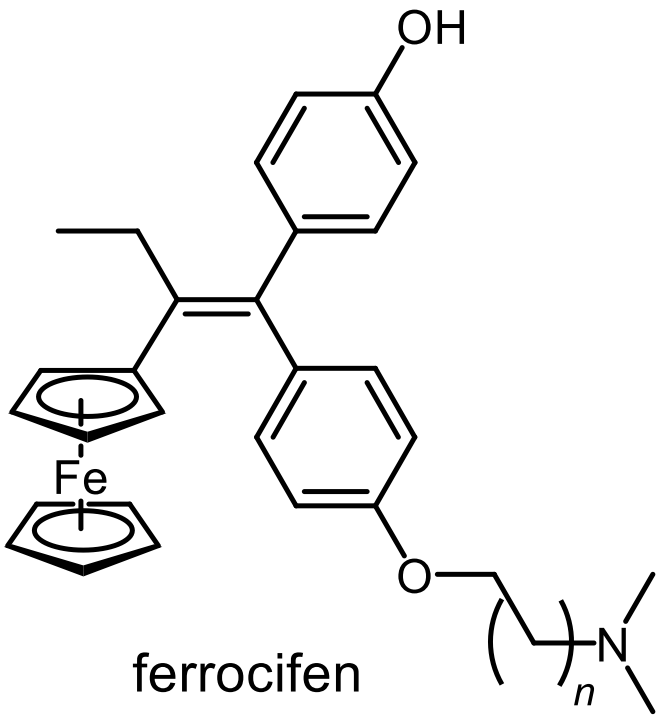
hydroxy-tamoxifen

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

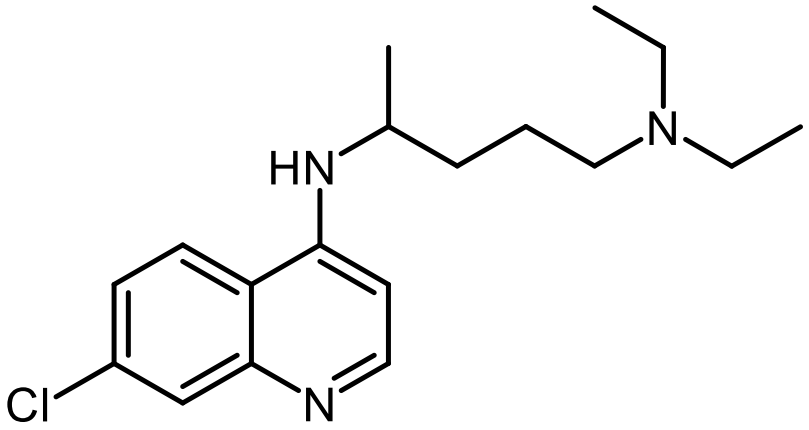


hydroxy-tamoxifen

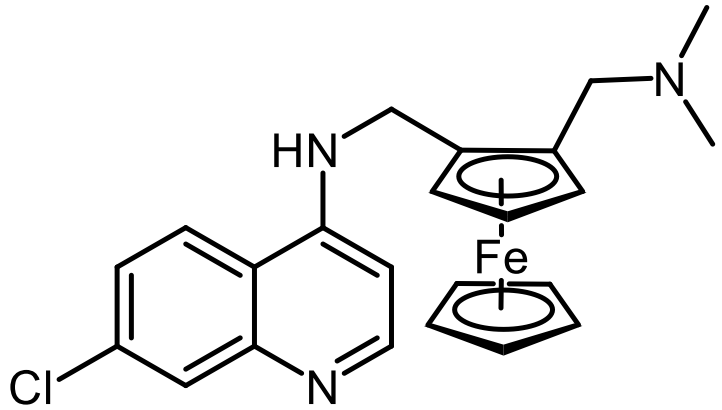


ferrocifen

Bio-isosteric replacement applied to antimalarial drugs



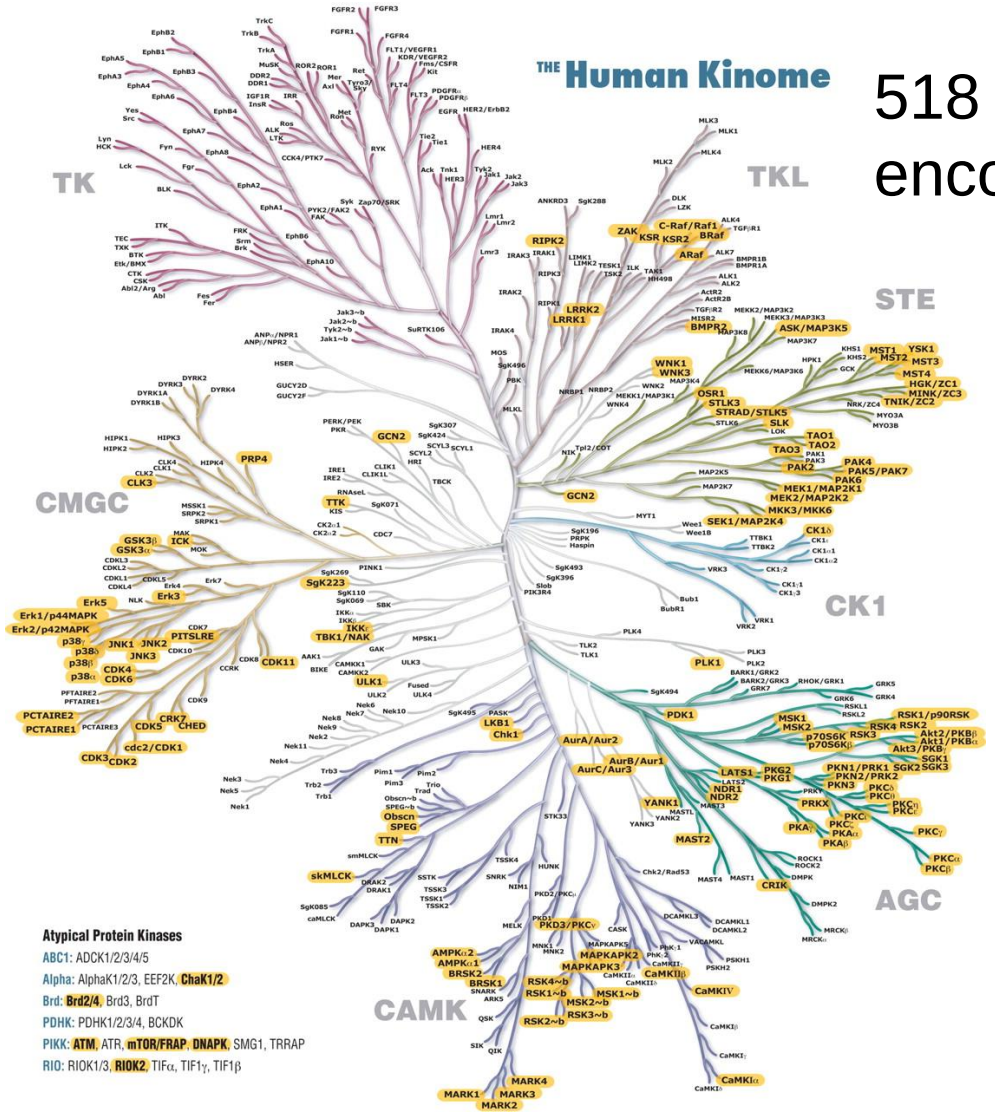
chloroquine



ferroquine

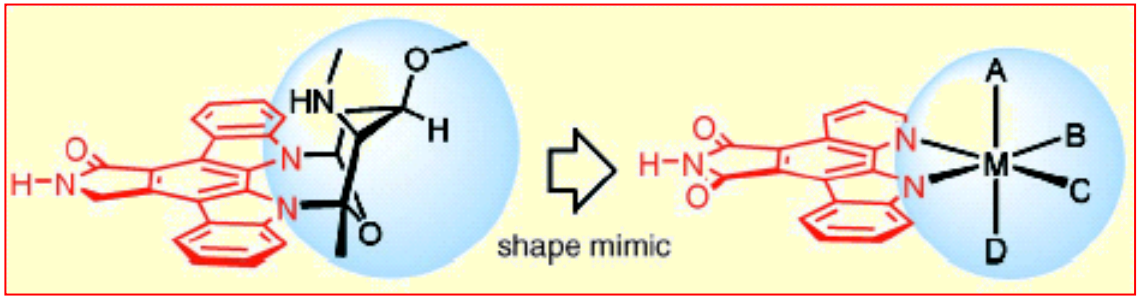
- Ferroquine is the ferrocenyl analogue of chloroquine, an established antimalarial drug.
- Ferroquine is active also against chloroquine-resistant strains and is due to enter clinical phase III trials.

Protein Kinase inhibitors



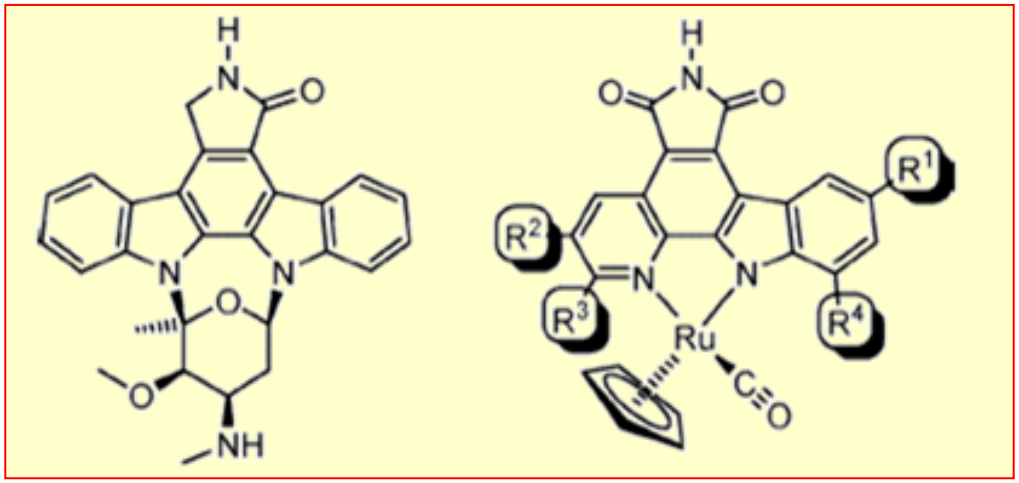
518 different kinases are encoded in the human genome

Selective protein kinase inhibitors

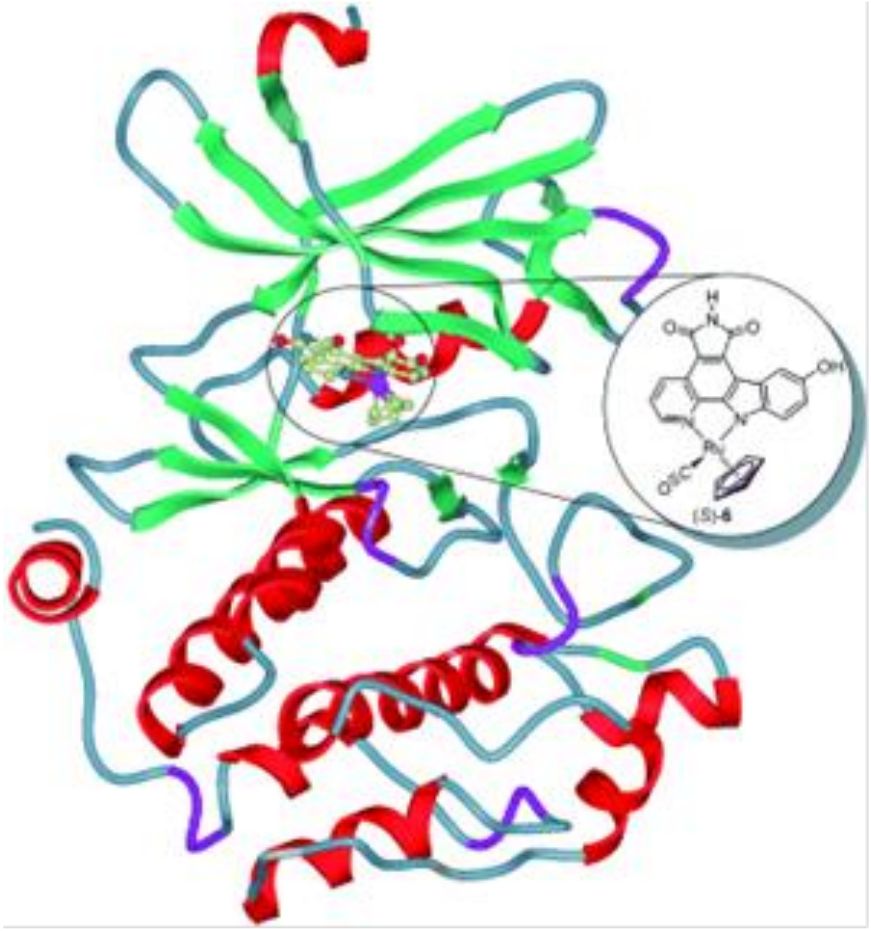


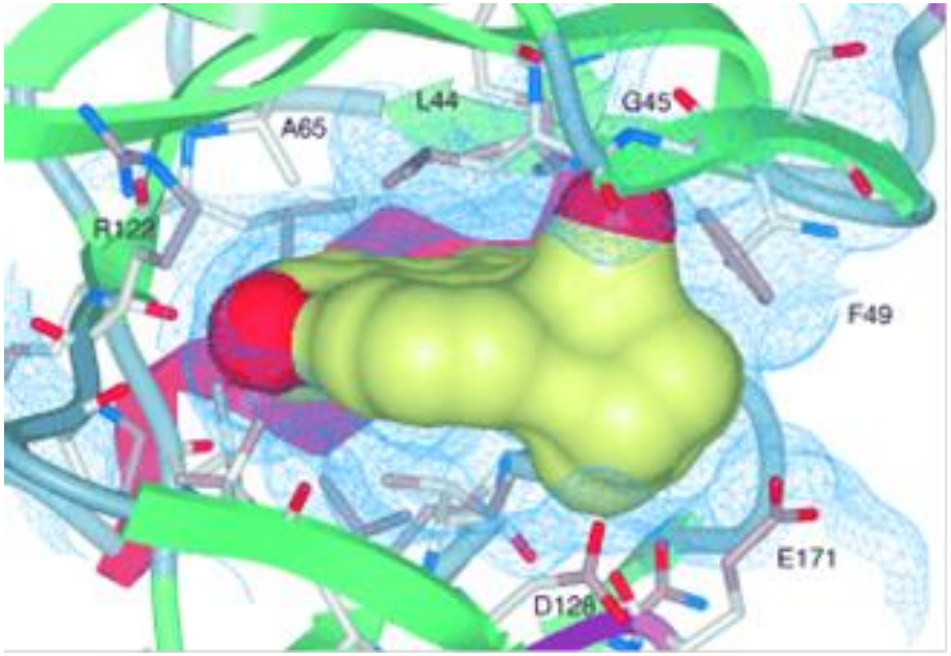
Staurosporine, unselective protein kinase inhibitor (ATP binding site)

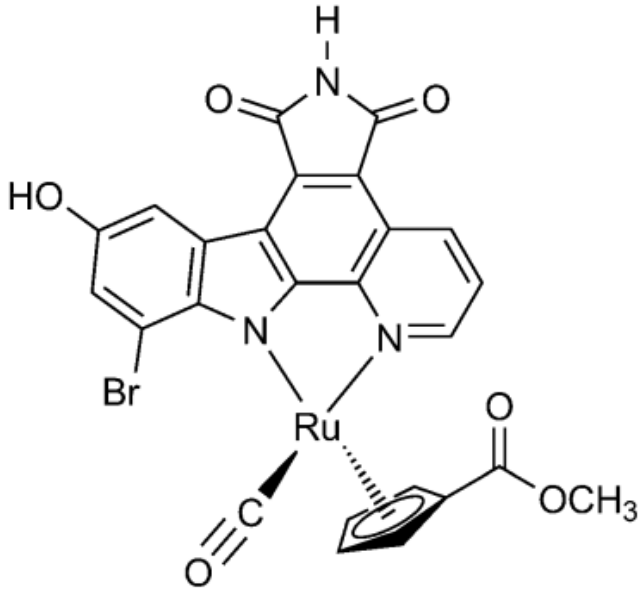
- Great structural variety (geometry)
- Stereochemistry far more diverse than organic compounds
- Rational ligand design



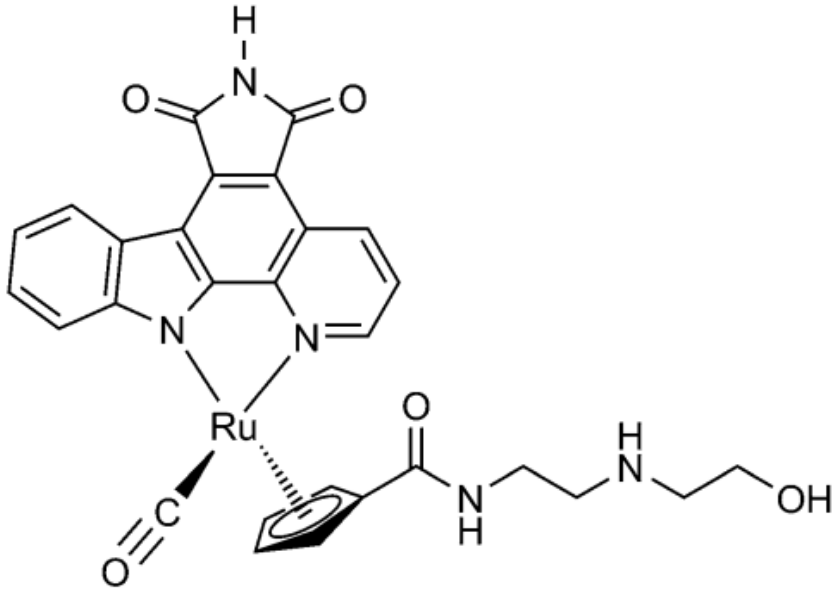
The binding of an organometallic ruthenium inhibitor to the ATP binding site of protein kinase Pim-1







GSK-3 inhibitor
IC_{50} ~ 0.5 nM



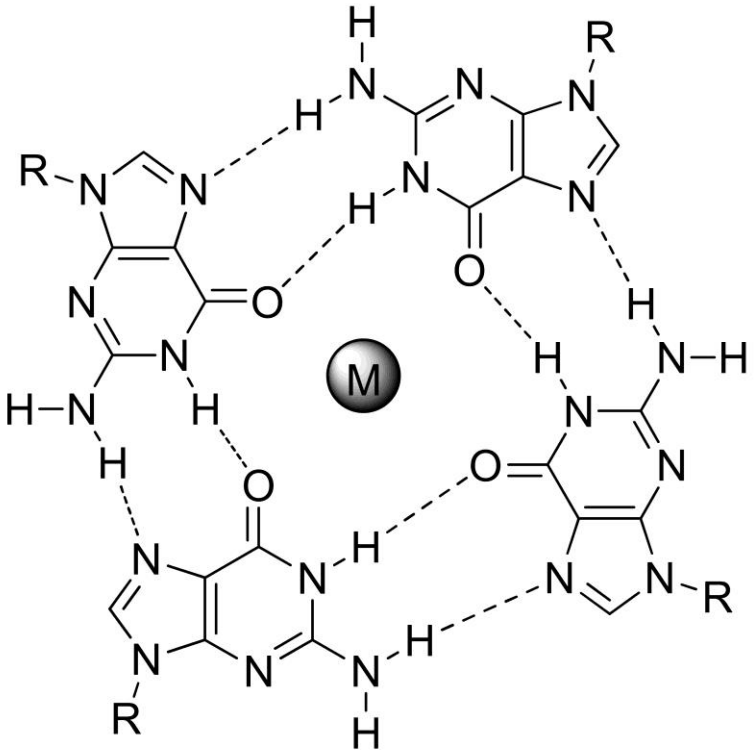
Pim1 inhibitor
IC_{50} ~ 2 nM

Commercially available

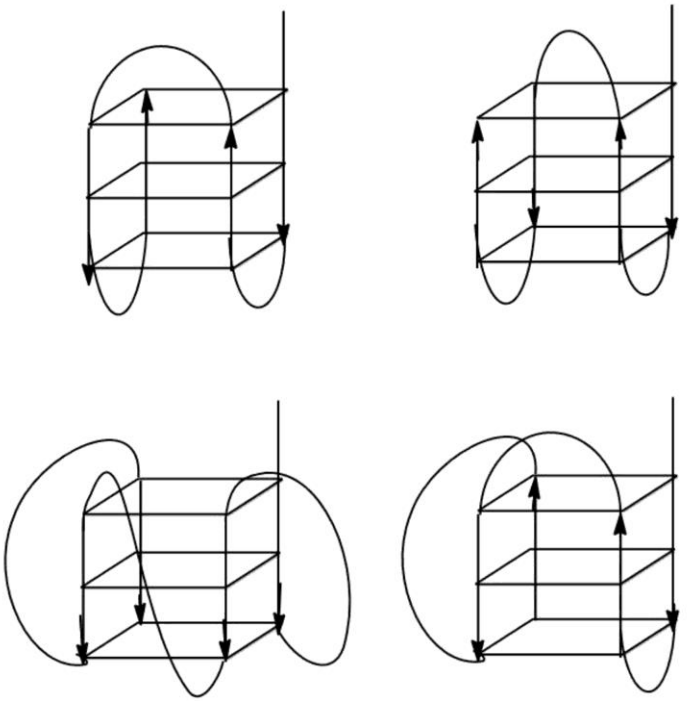
Telomeri

i telomeri sono regioni del DNA situate alla fine dei cromosomi e formate da un singolo filamento composto da sequenze ripetitive d(TTAGGG) con funzione protettiva

G quartet



G quadruplexes



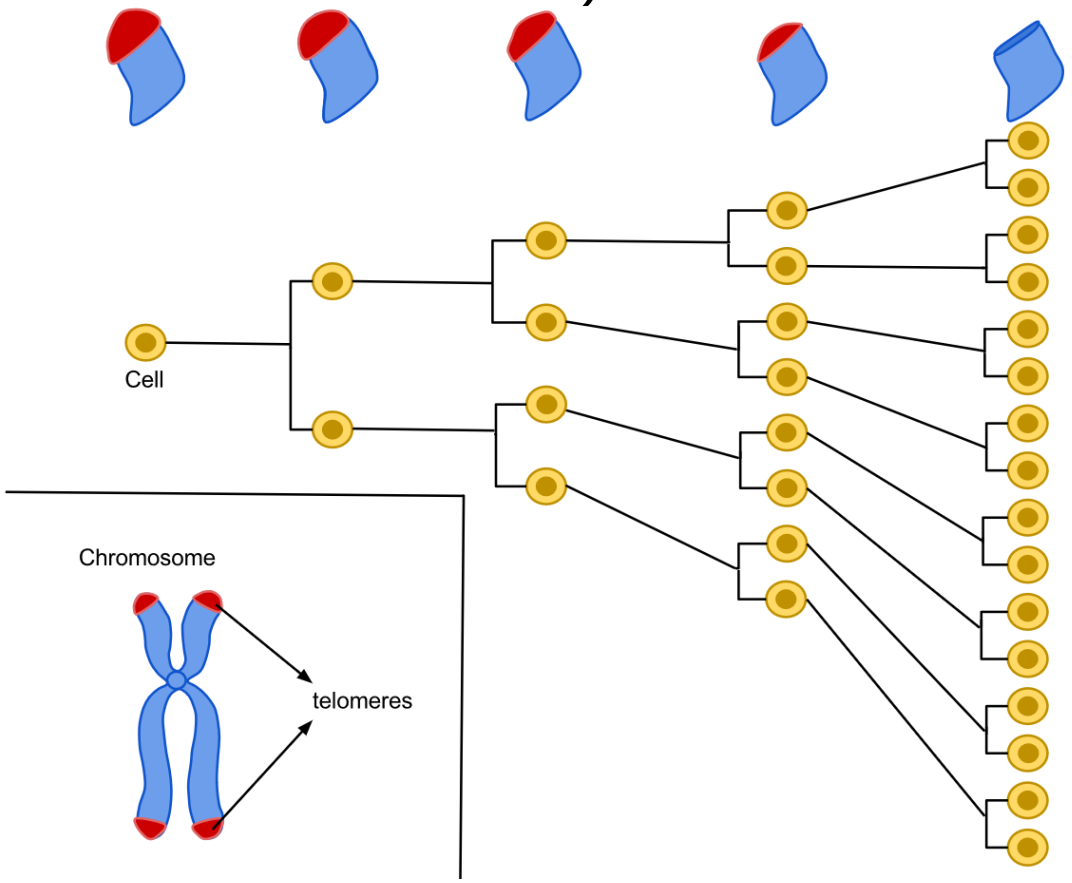
Le sequenze ricche di guanine del telomero si autoassemblano a formare i G-quartets ed essi formano poi i G-quadruplexes.

Telomeri = orologio biologico delle cellule

(in assenza della telomerasi)

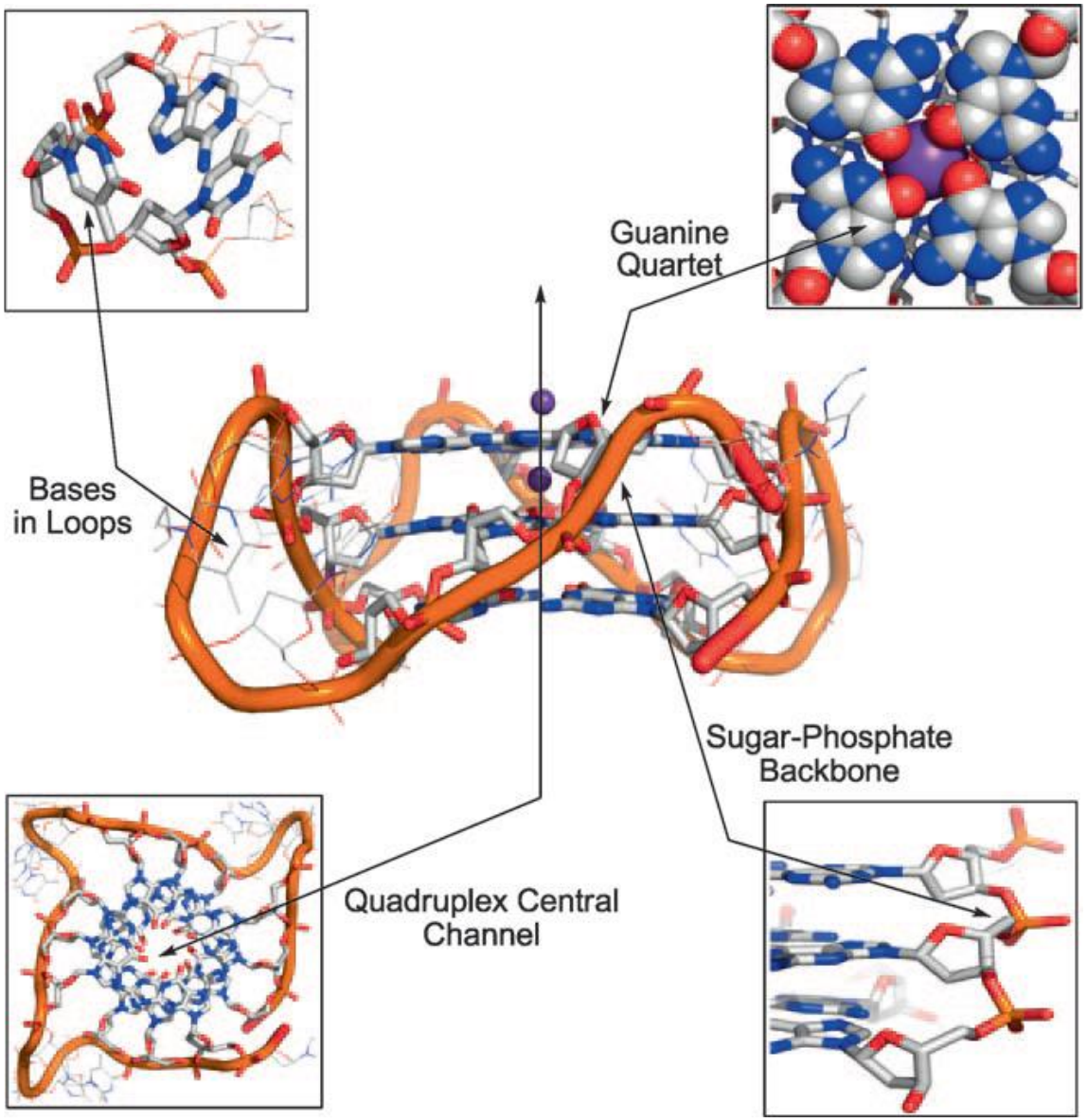
The Hayflick limit

(ca. 50 divisioni cellulari, poi apoptosi)

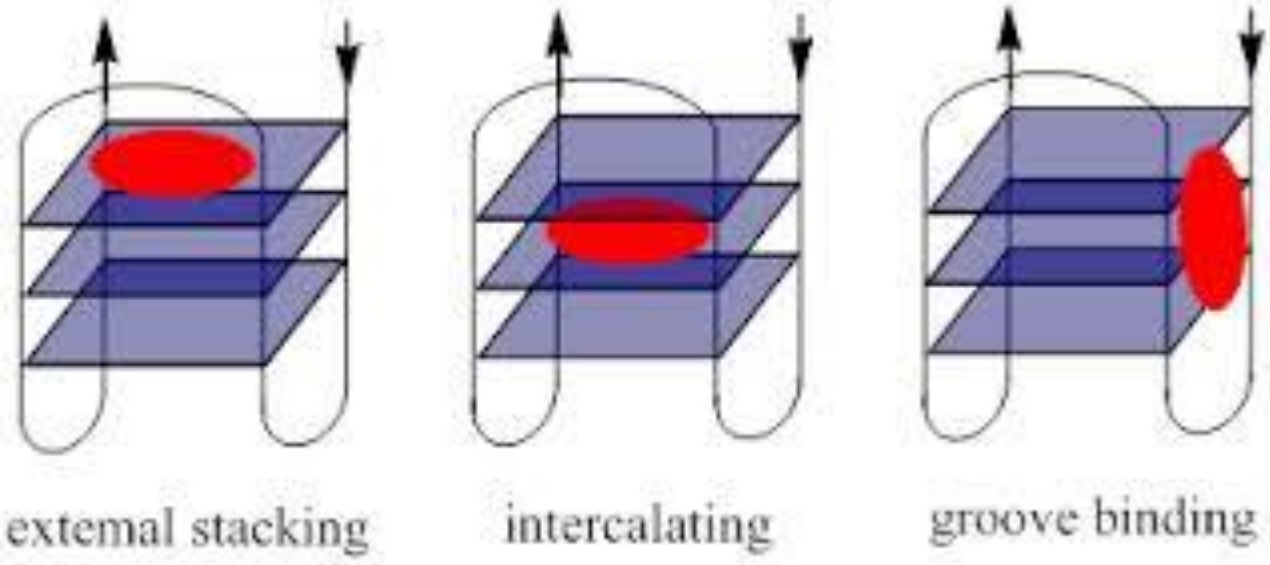


La telomerasi, sovra-espressa nelle cellule tumorali (normalmente assente nelle cellule somatiche, cioè differenziate), ha la funzione di aggiungere unità esameriche d(TTAGGG) alla parte 3′-terminale del telomero di DNA, mantenendone inalterata la lunghezza (rendendole immortali)

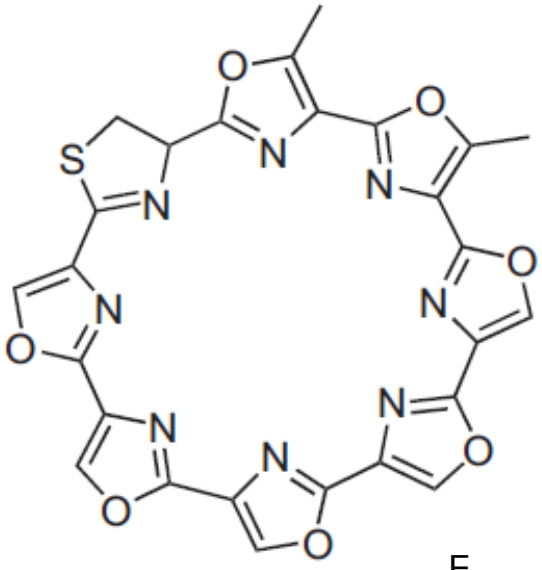
Potenziali siti di binding dei *G-quadruplex*



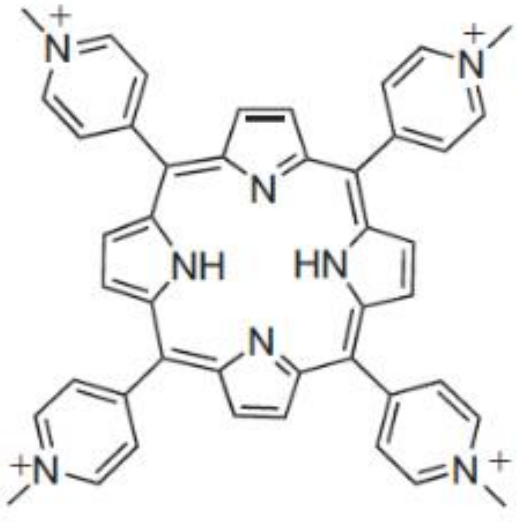
G-quadruplex stabilization for telomerase inhibition



Telomerase Inhibitors

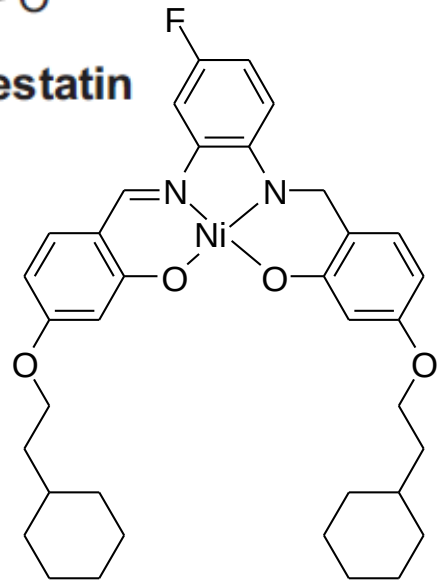


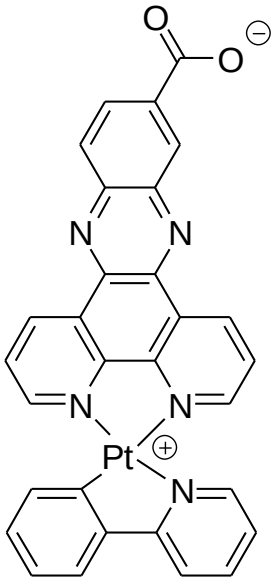
π stacking on G quartets

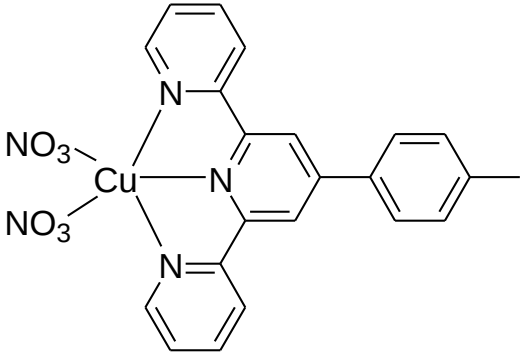


TmPyP4

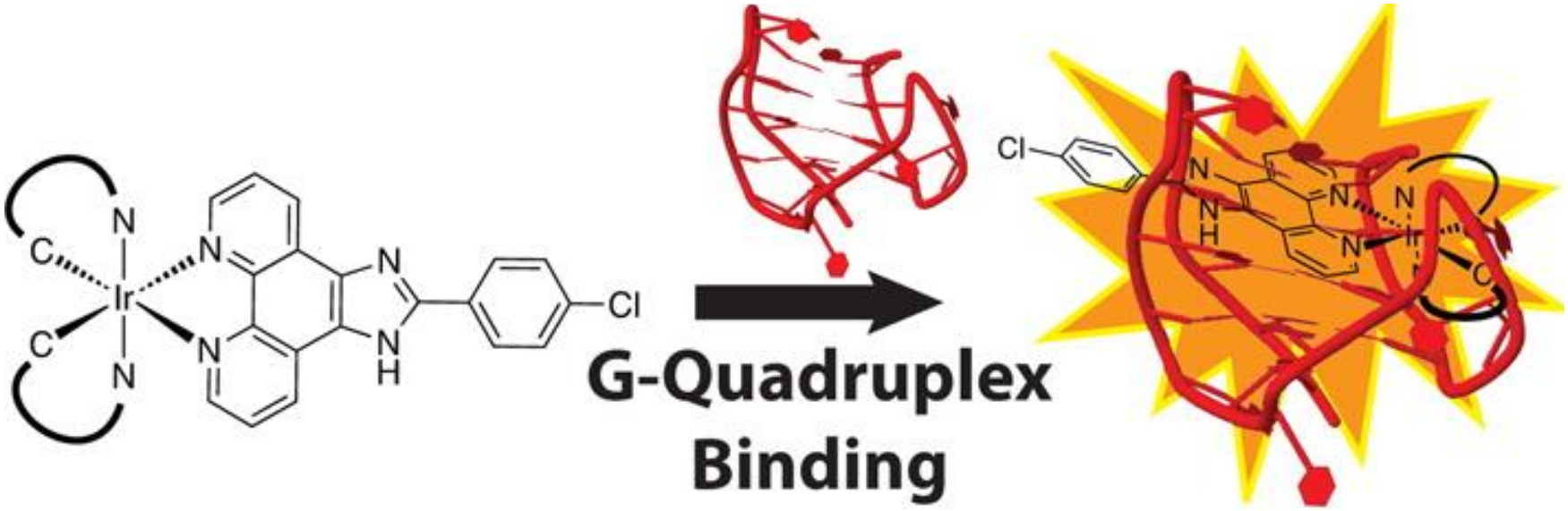
Telomestatin





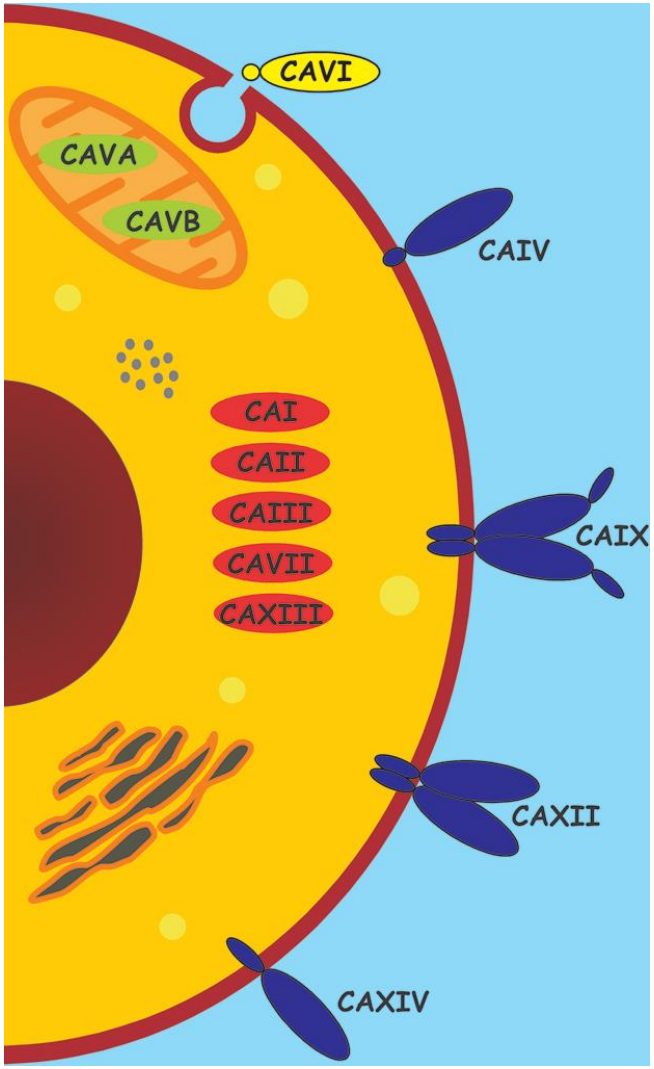


G-quadruplex sensing



Metal-based Inhibitors of Metallo-Enzymes

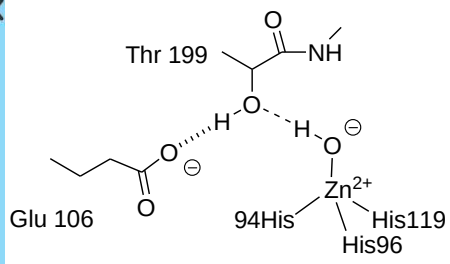
Human Carbonic Anhydrase (hCA) inhibitors



Isoforme di CA

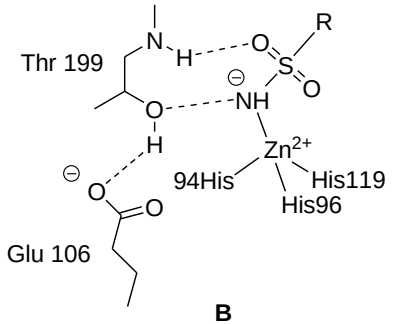
Patologie che sovra-esprimono CA: glaucoma, epilessia e disordini neuro-muscolari, obesità, osteoporosi, morbo di Alzheimer, numerosi tipi di tumori…

sulfonamidi anioni coordinanti



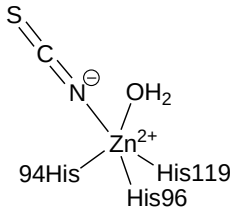
A

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



B

Tetrahedral adduct (sulfonamide)



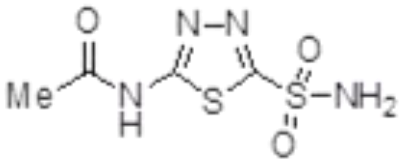
C

Trigonal-bipyramidal adduct (thiocyanate)

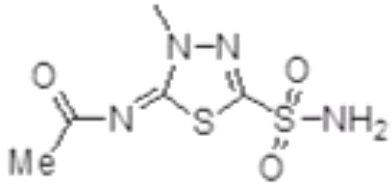
$$H_2O + CO_2 \rightleftharpoons HCO_3^- + H^+$$

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

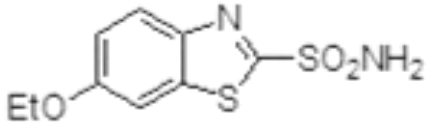
Sulfonamides as CA inhibitors



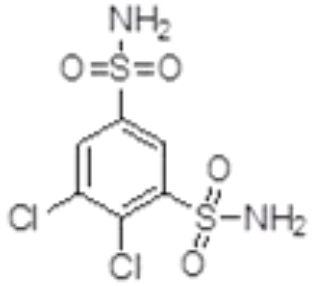
Acetazolamide (AAZ)



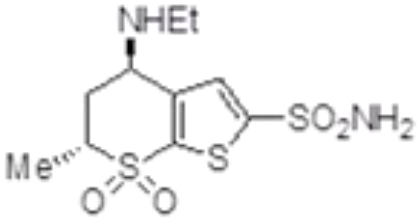
Methazolamide (MZA)



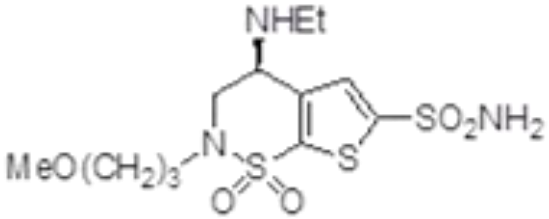
Ethoxzolamide (EZA)



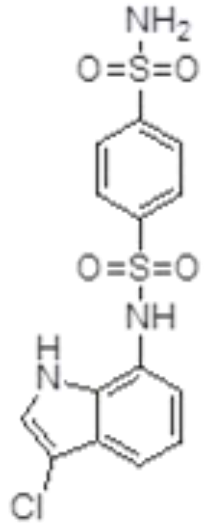
Dichlorophenamide (DCP)



Dorzolamide (DZA)

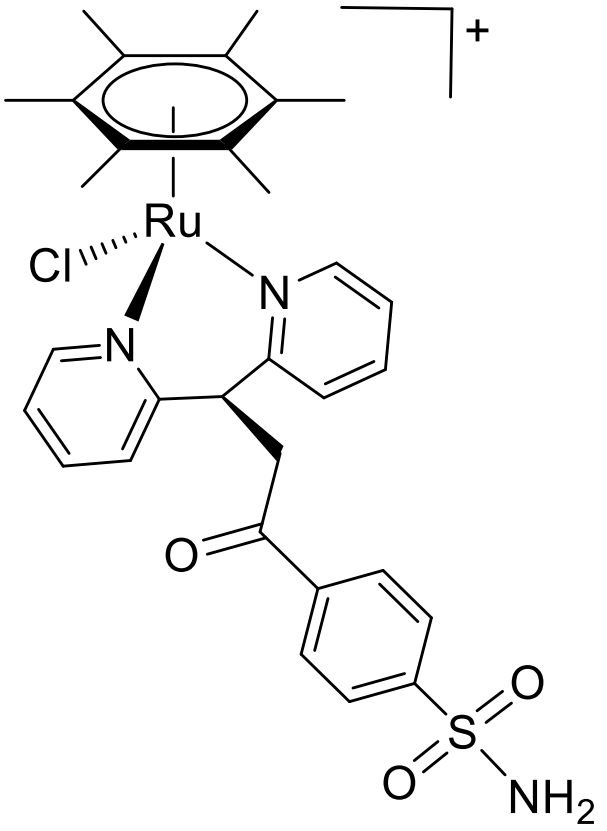


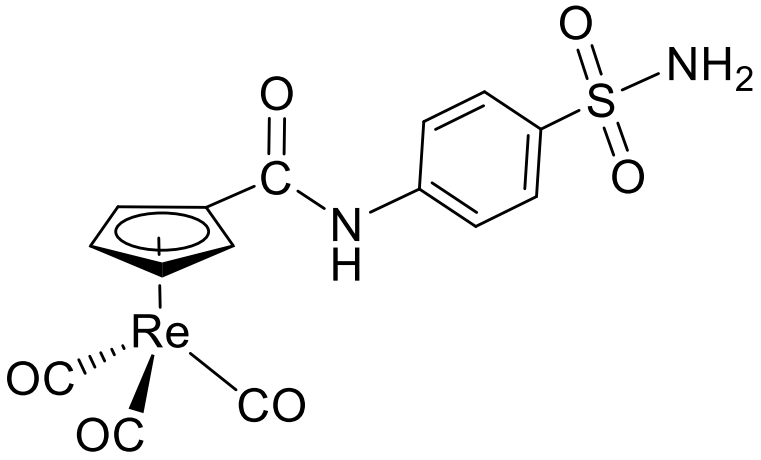
Brinzolamide (BRZ)

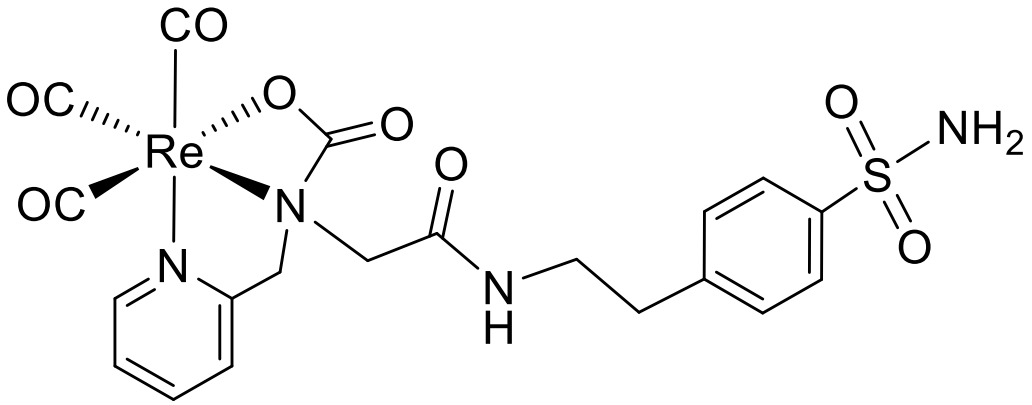


Indisulam (IND)

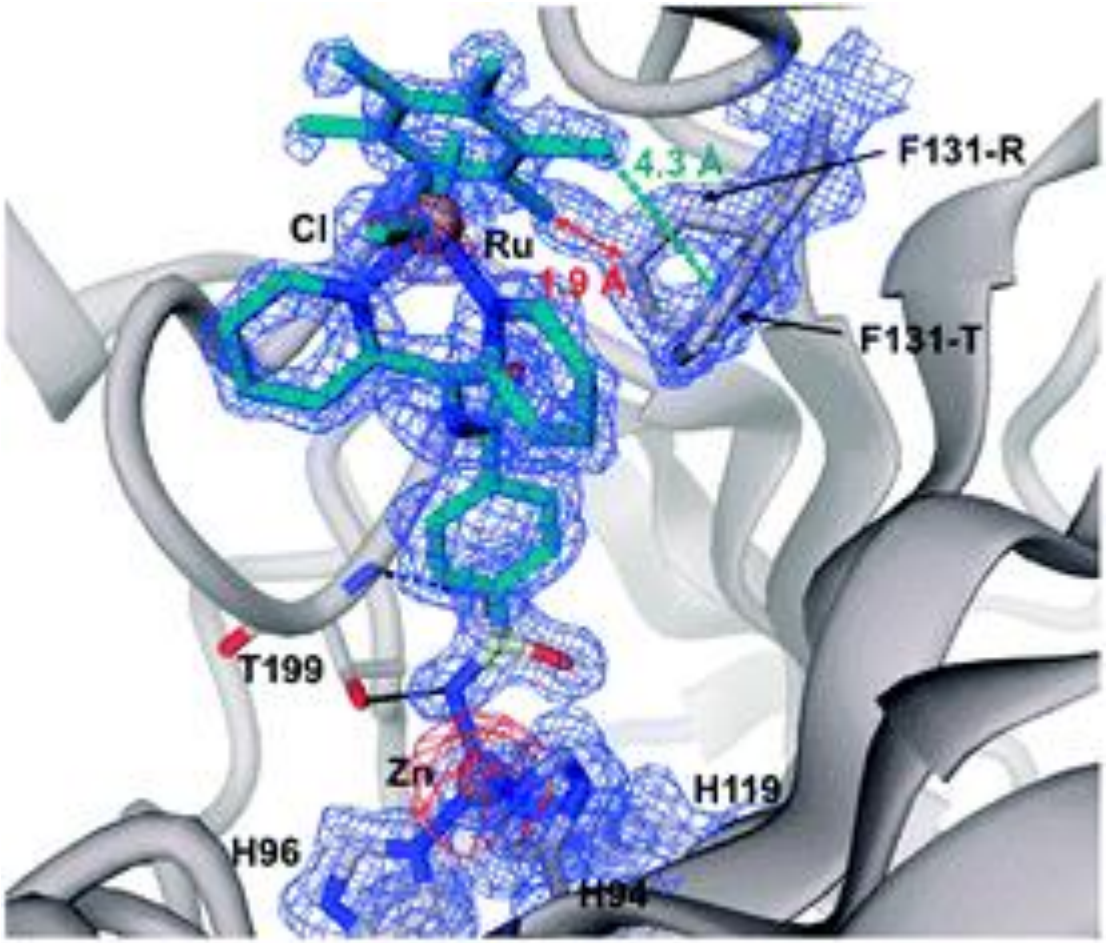
Inert organometallic compounds as hCA inhibitors



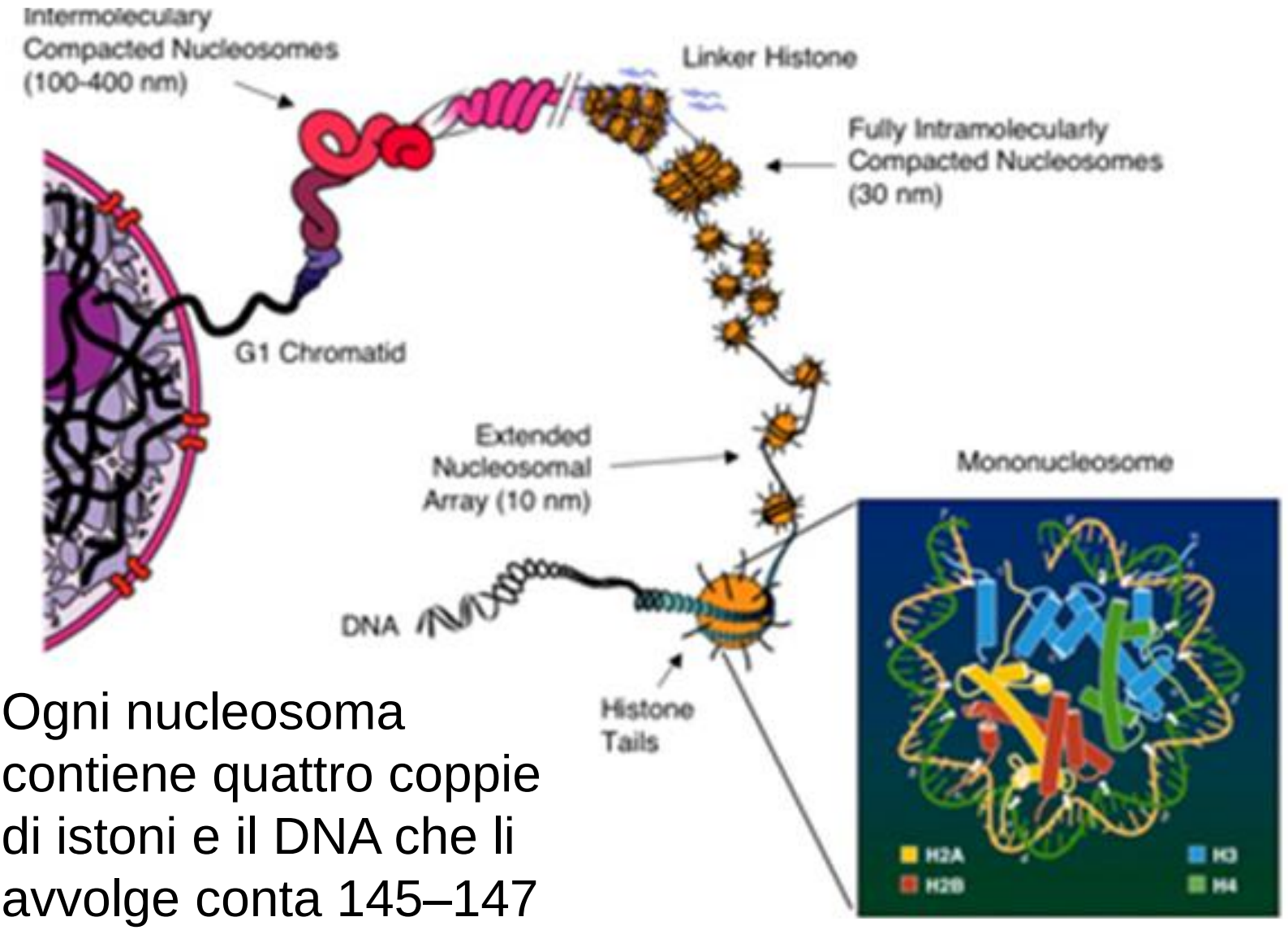




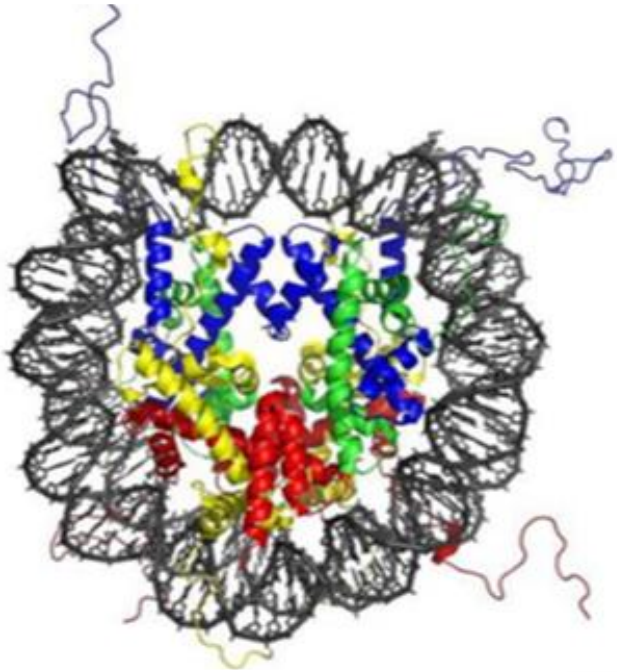
Ru-arene piano-stool complex @ hCA II

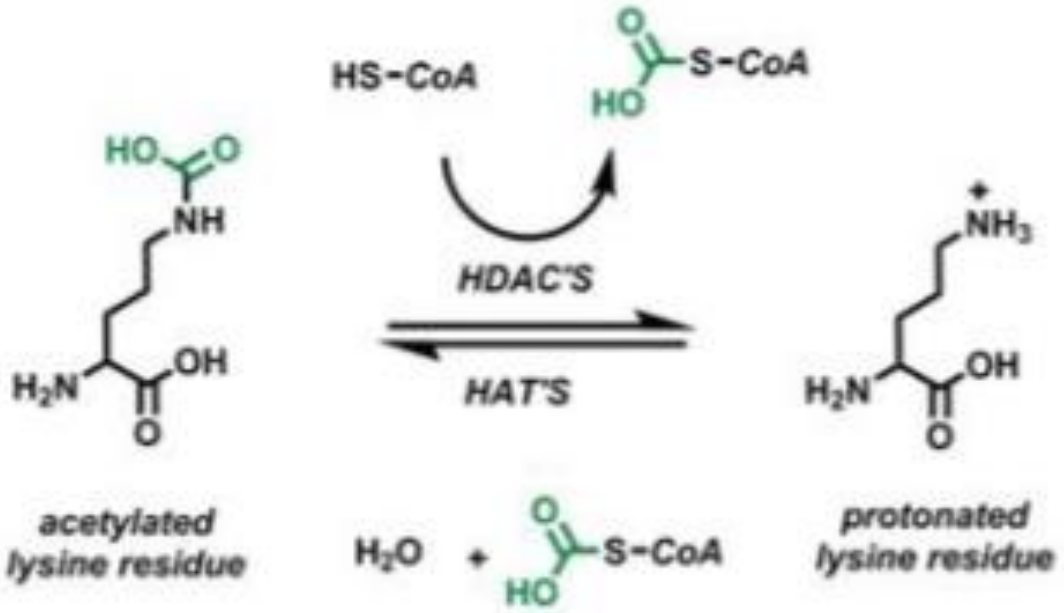


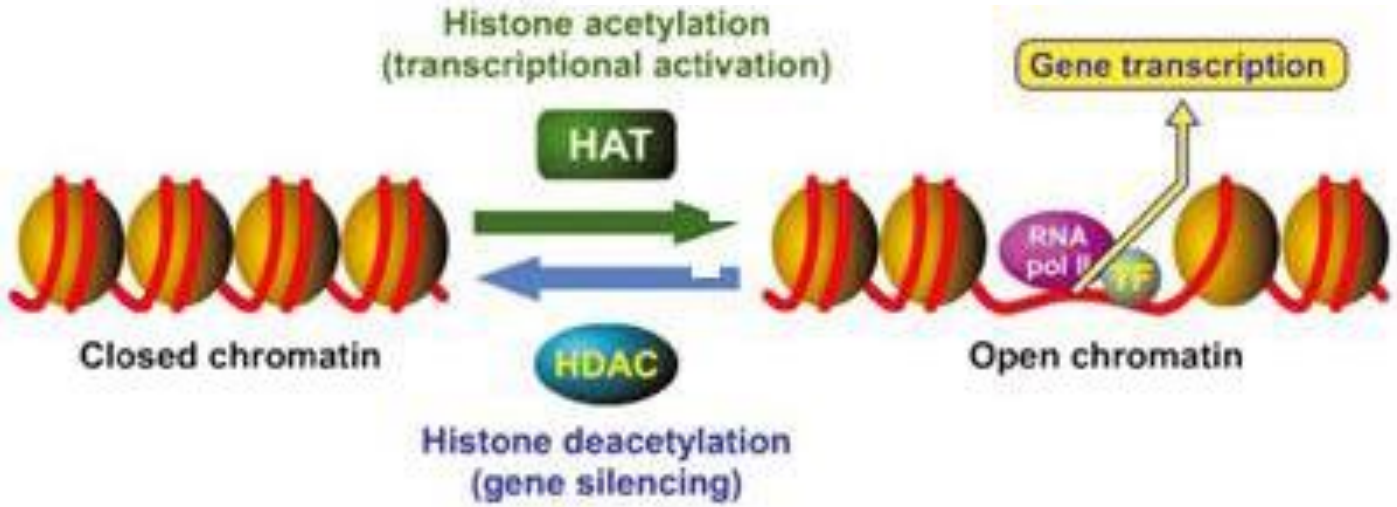
Cromatina, Nucleosomi e Istoni



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

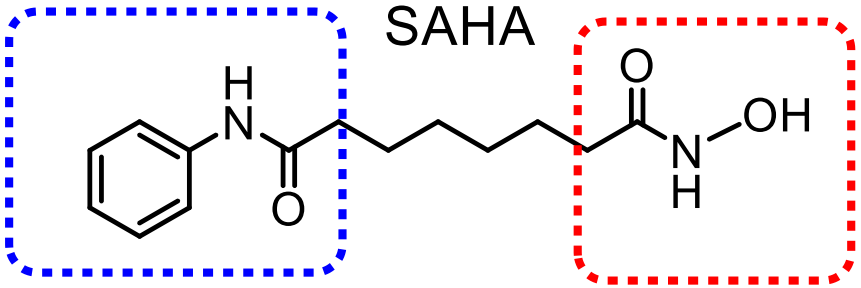



HS-CoA
S-CoA
HO
HDAC'S
HAT'S
NH
OH
H_2N
O
NH_3
acetylated
lysine residue
H_2O
protonated
lysine residue


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

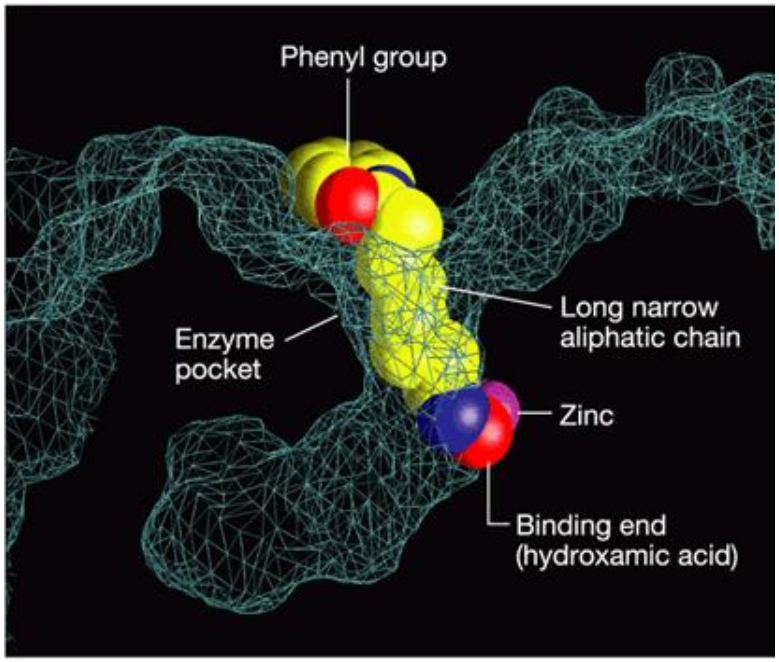
HDAC Inhibitors (HDACi) as anticancer agents

Alcuni HDACi possono riattivare l'espressione di geni e inibire la crescita e la sopravvivenza di cellule tumorali a concentrazioni non-tossiche



aromatic protein recognition domain

hydroxamic acid Zn^{2+}binding site



Zolinza®

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

modulazione epigenetica

Metal-based HDAC Inhibitors