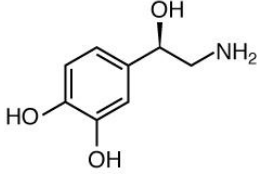
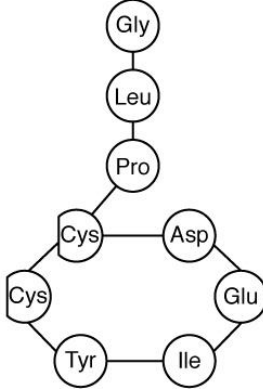
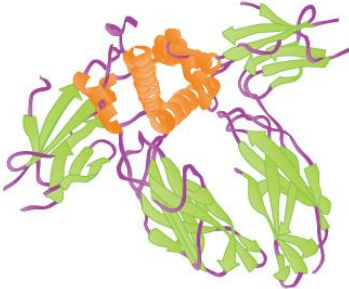
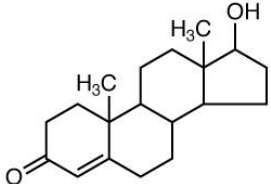
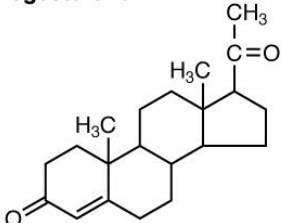


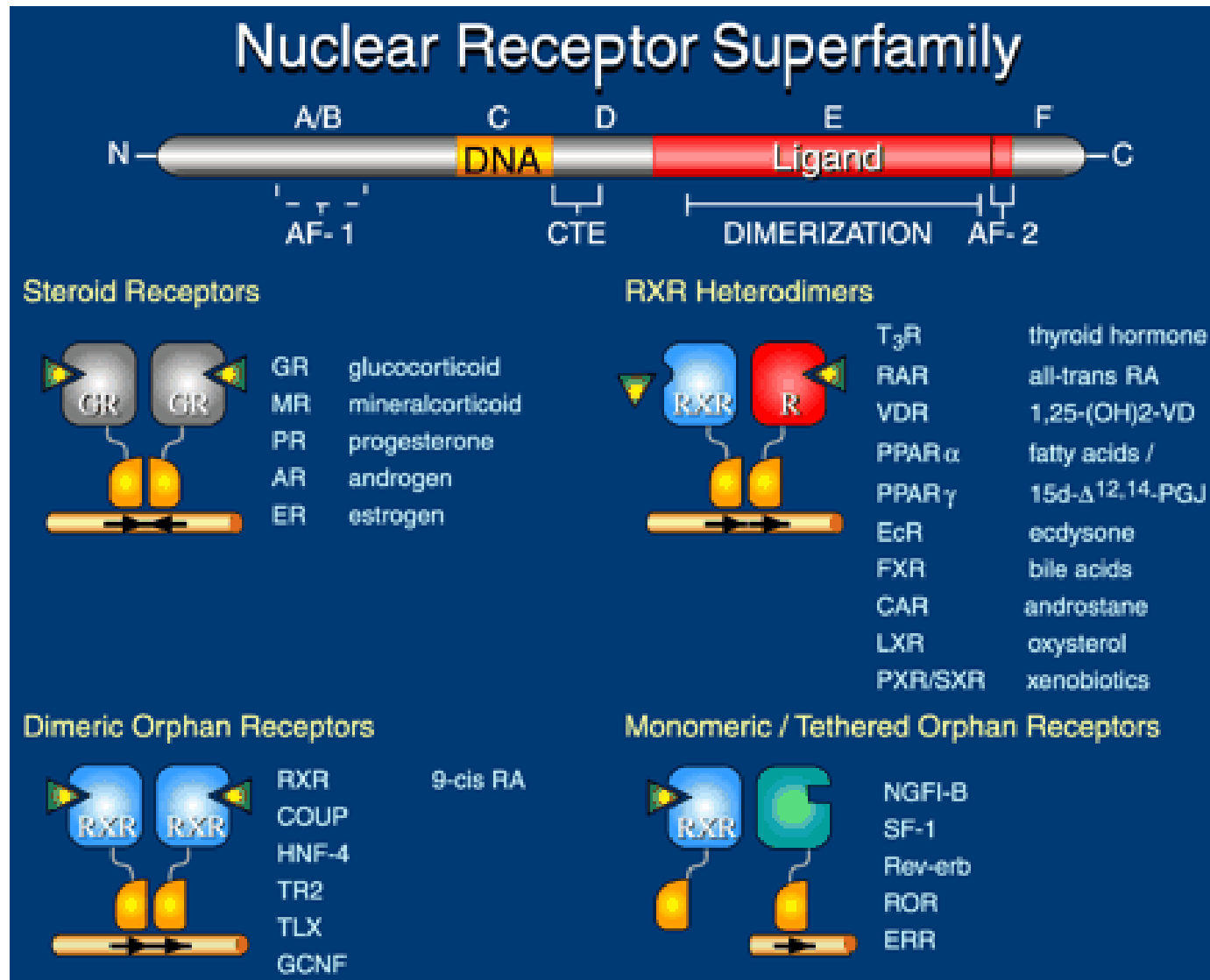
Chemical aspects of the cell

Chemicals that control cell signaling:
hormones

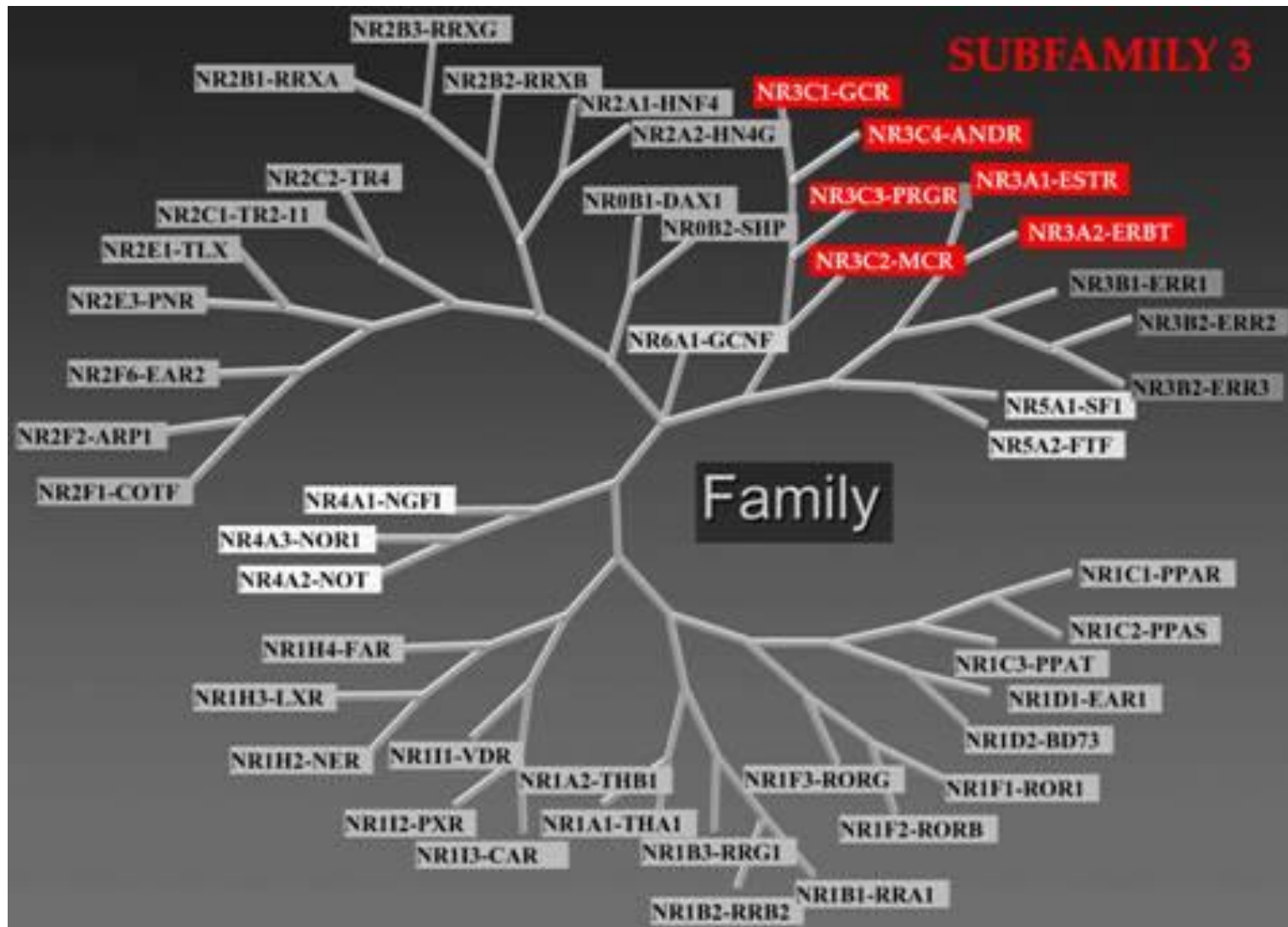
Hormone Class	Components	Example(s)
Amine Hormone	Amino acids with modified groups (e.g. norepinephrine's carboxyl group is replaced with a benzene ring)	Norepinephrine 
Peptide Hormone	Short chains of linked amino acids	Oxytocin 
Protein Hormone	Long chains of linked amino acids	Human Growth Hormone 
Steroid Hormones	Derived from the lipid cholesterol	<div> Testosterone  </div> <div> Progesterone  </div>

Types of hormones

Classification of NR



Classification of NR



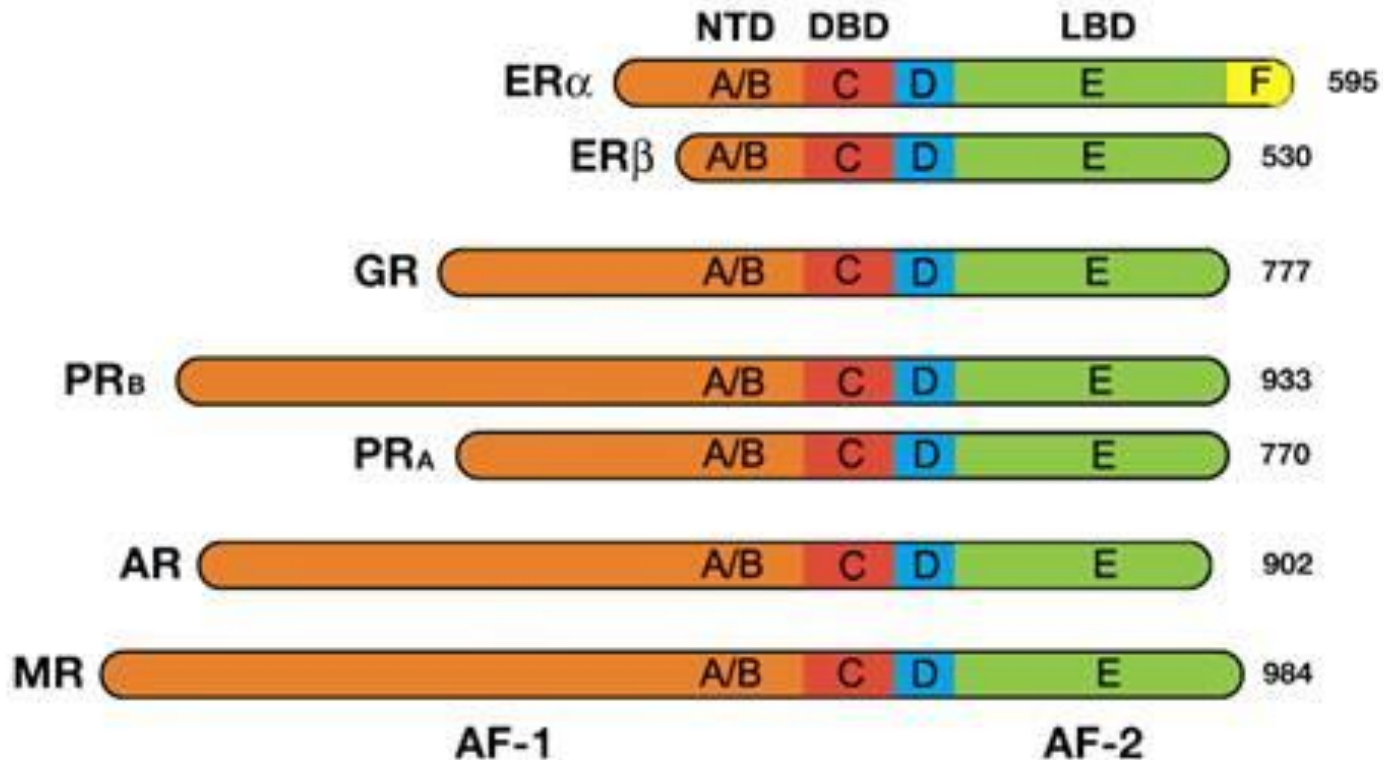
Structural aspects

- **Composition:**



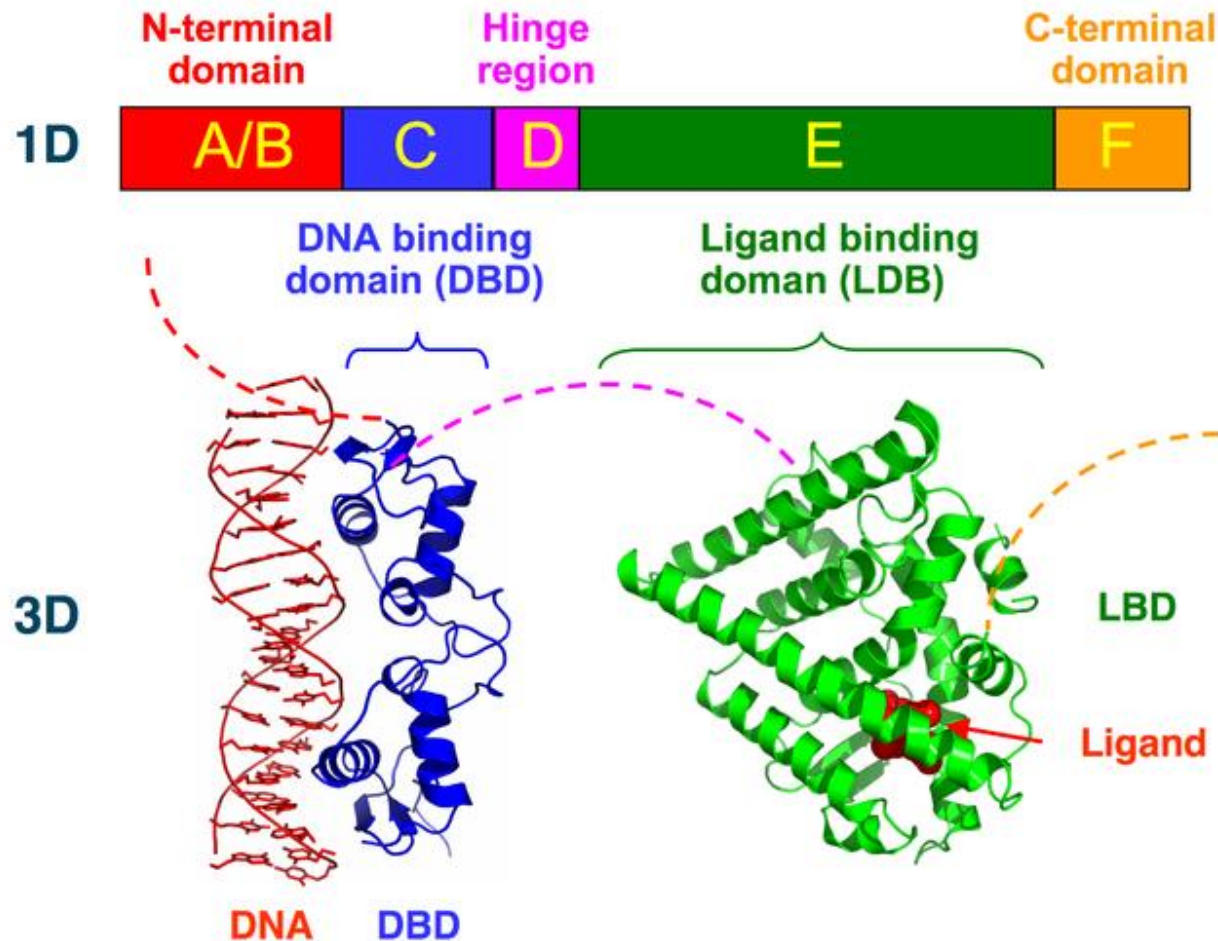
- **Domains:**

N-terminus (left) to C-terminus (right). NTD = N-terminal domain, DBD = DNA binding domain. LBD = ligand binding domain. AF = activation function.

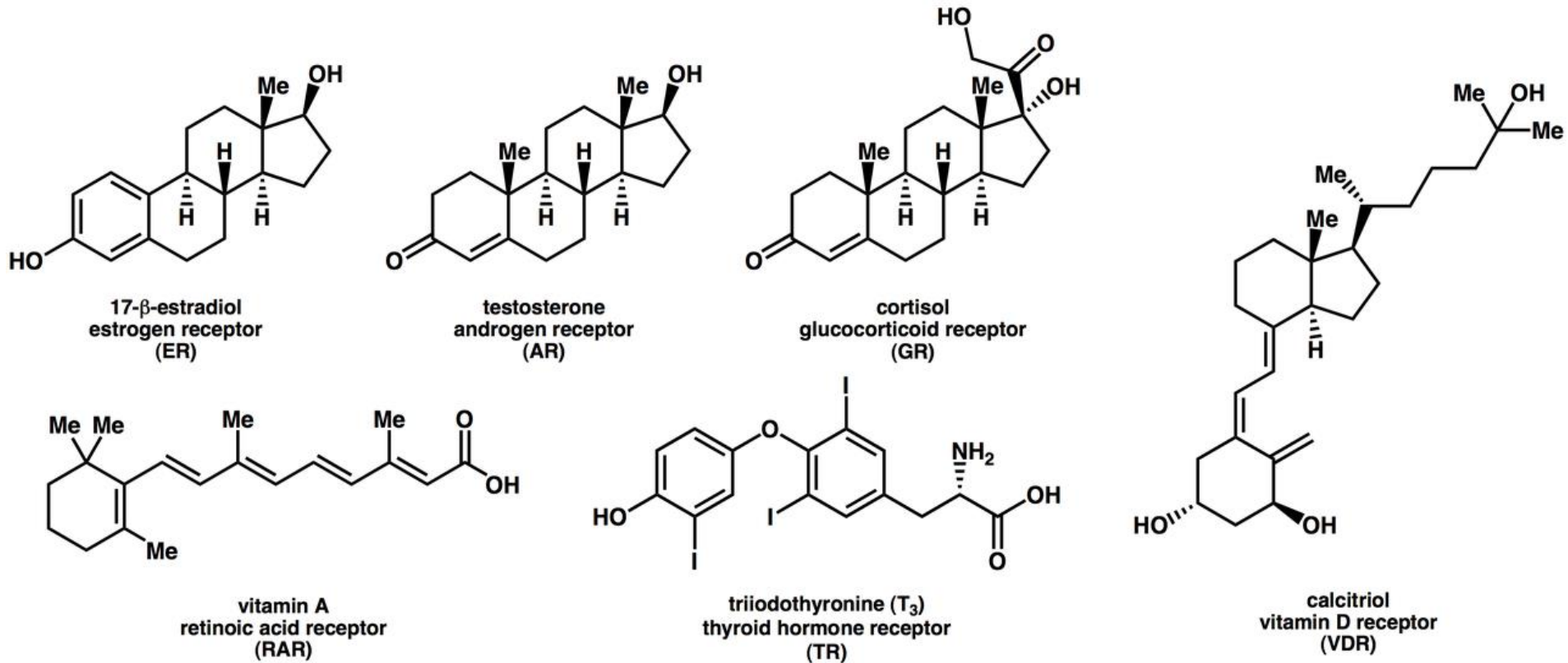


Structural aspects

Structural Organization of Nuclear Receptors



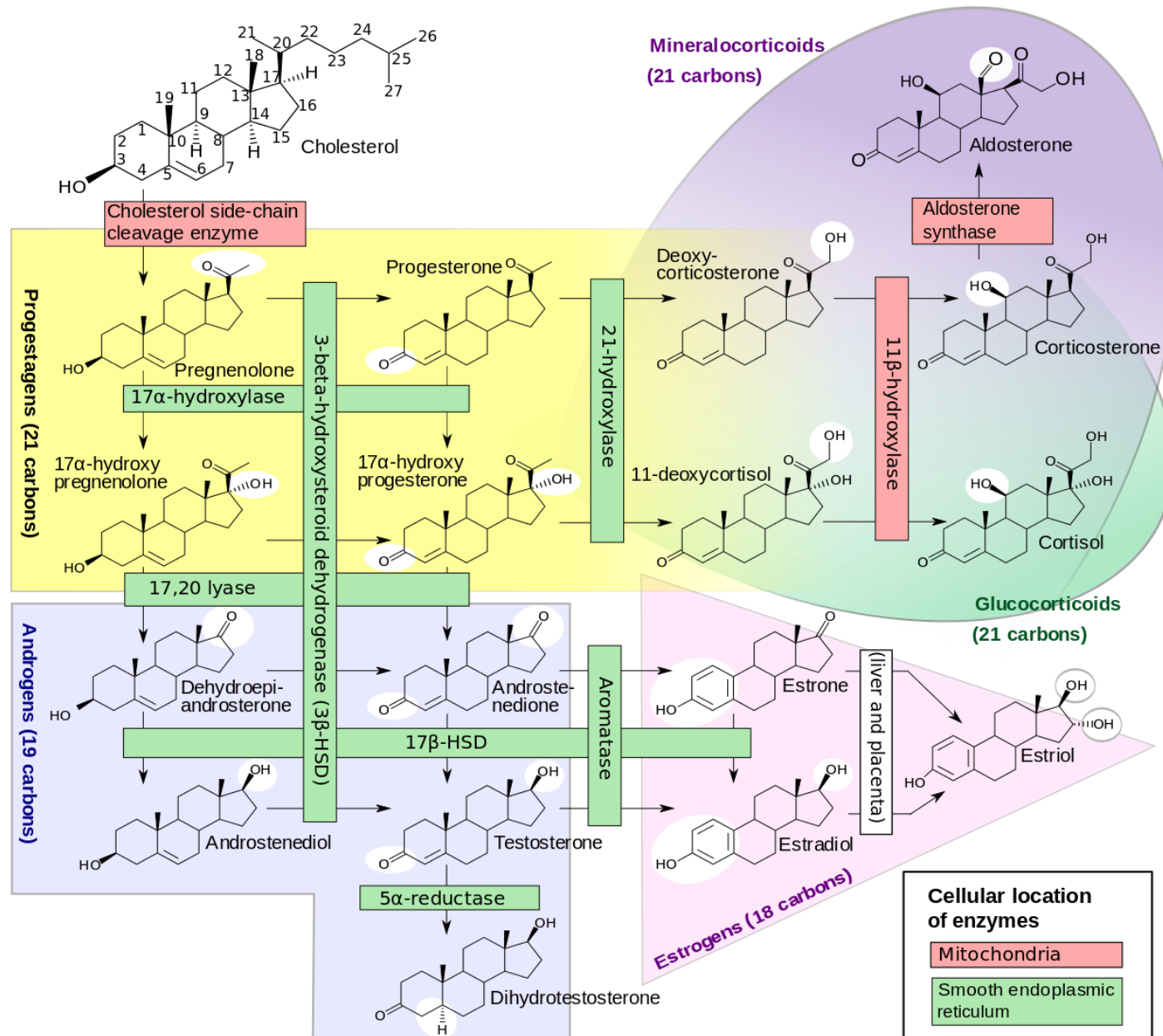
Some nuclear receptor binders



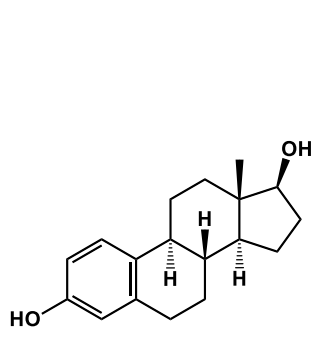
Steroid hormones: example (1)

- **Nuclear receptors (ER, GPER)**
 - **Estrogen receptor (ER) – 2 subtypes: ER α , ER β**
 - Importance for breast and endometrial cancer
 - Bone density, cardiovascular diseases, among others
 - **GPCR with estrogenic activity: GPER**
 - New type of receptor that estradiol interacts with
 - Physiological aspects under study

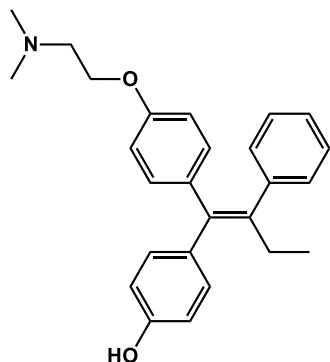
Biosynthesis of hormones



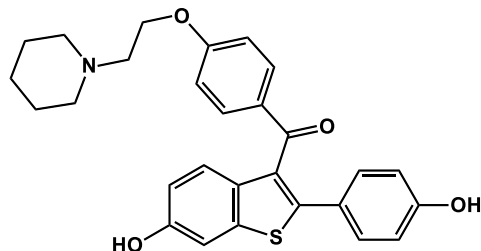
Hormone and inhibitors



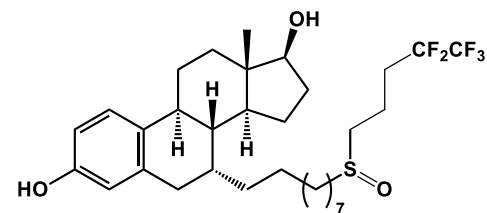
**17β-estradiol
(E₂)**



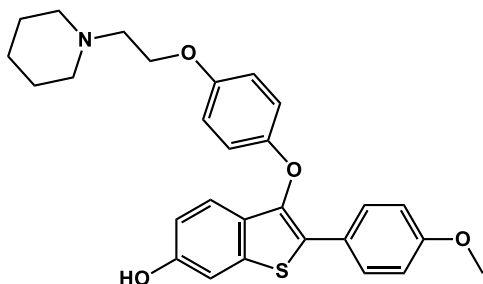
**4-hydroxytamoxifen
(4-OHTMX)**



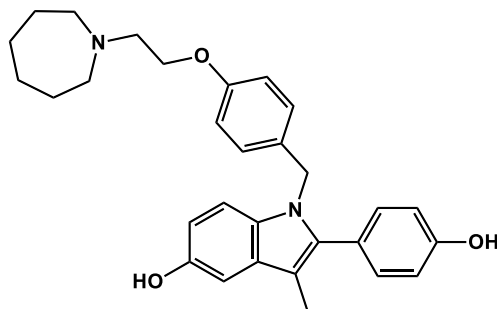
**raloxifene
(RAL)**



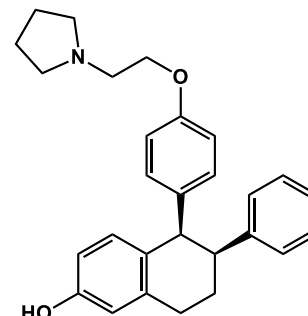
**ICI182780
(Fulvestrant)**



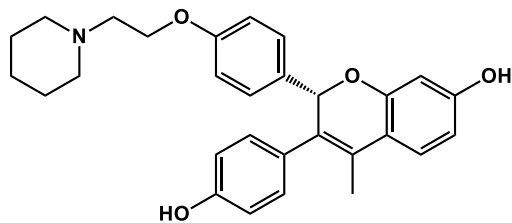
Arzoxifene



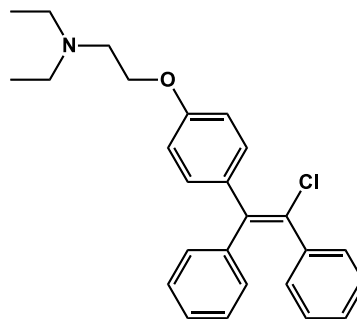
Bazedoxifene



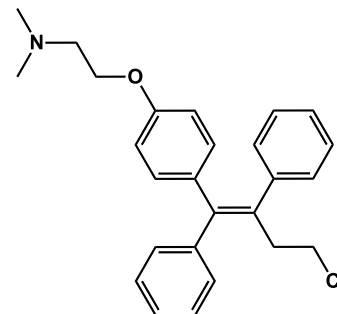
Lasofoxifene



Acolbifene



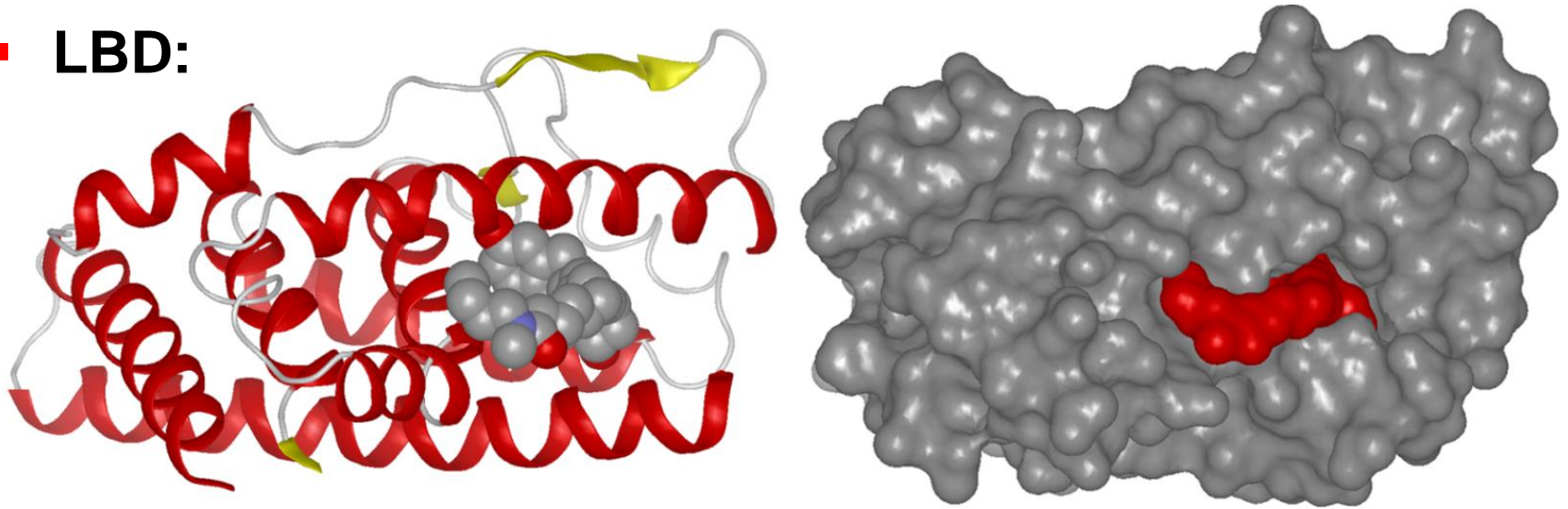
Clomifene



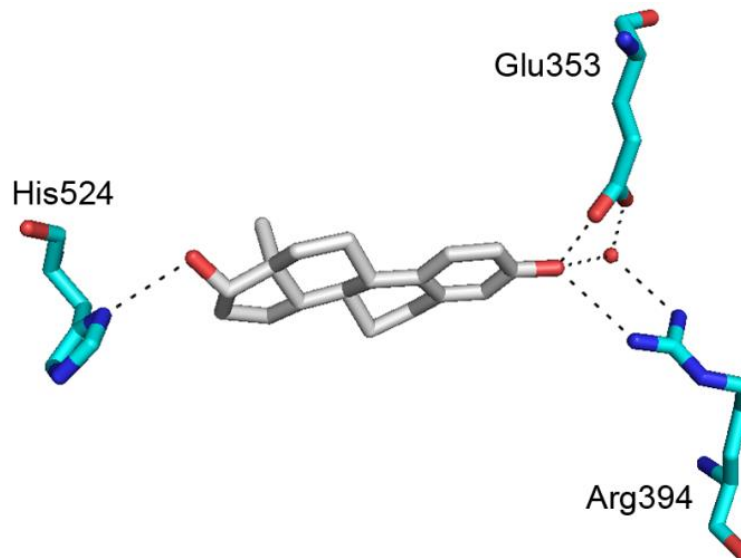
Toremifene

E₂ binding with the ER α

- **LBD:**

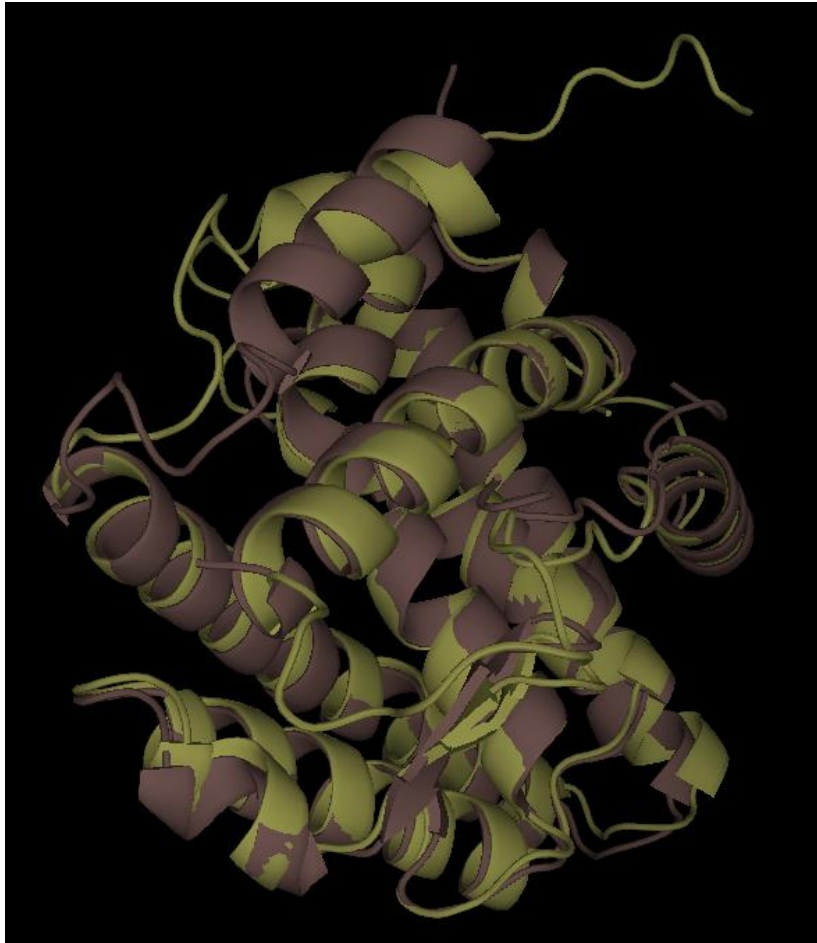


estradiol-ER α (1GWR)

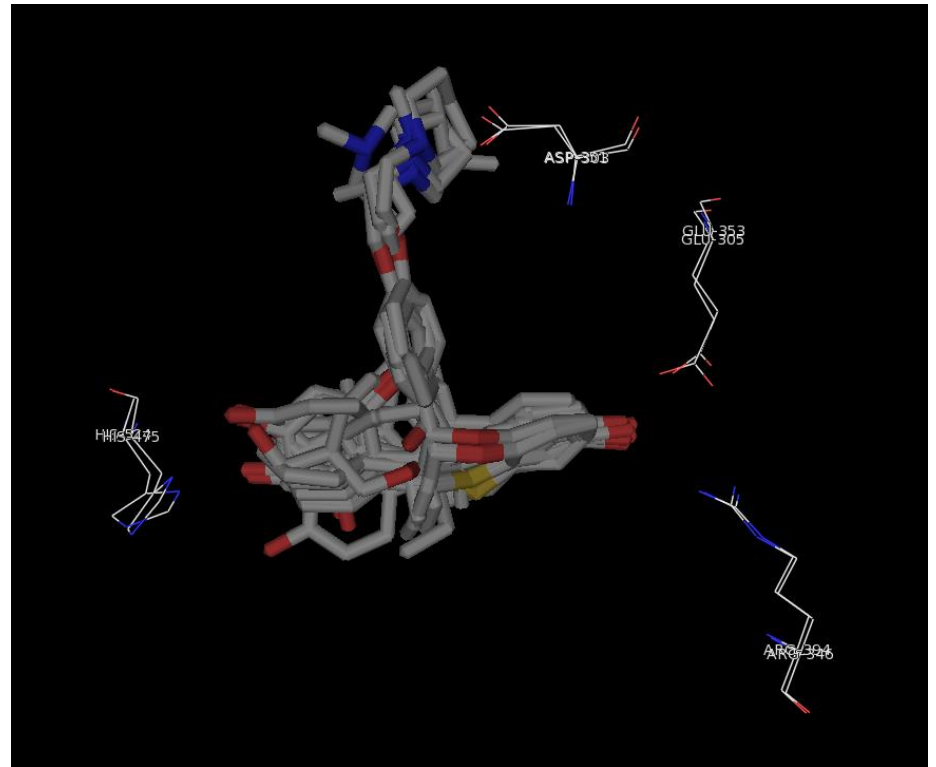


Superposition of ER α and ER β

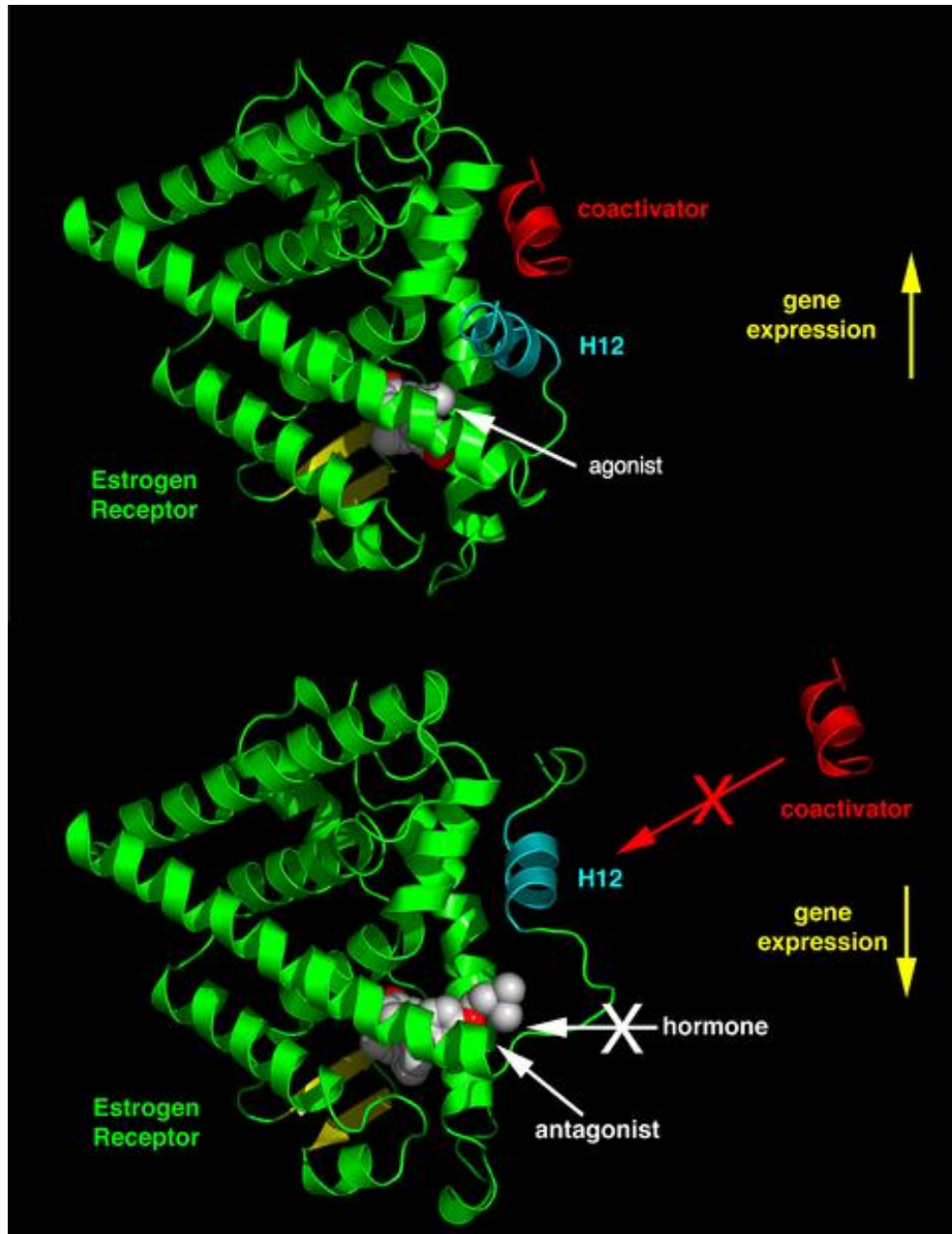
Superposition of 2 structures
(ER α yellow)



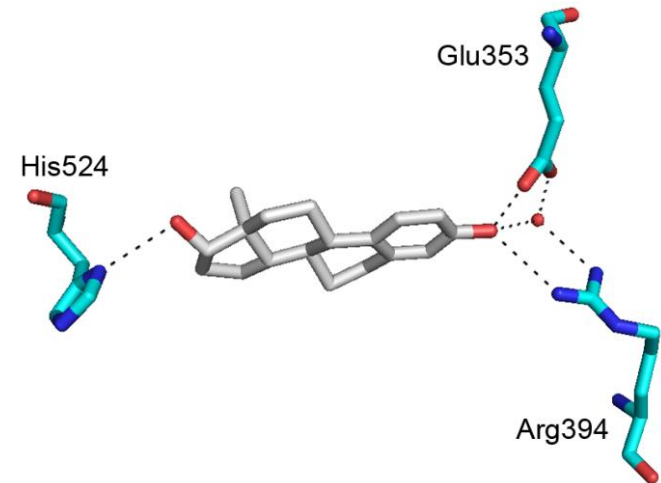
Ligand positioning after the
superposition of many structures



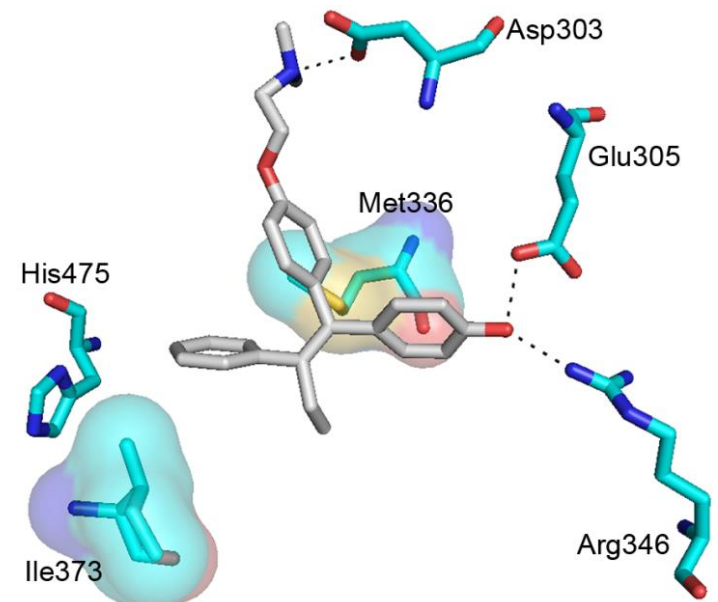
Modulation of the ER



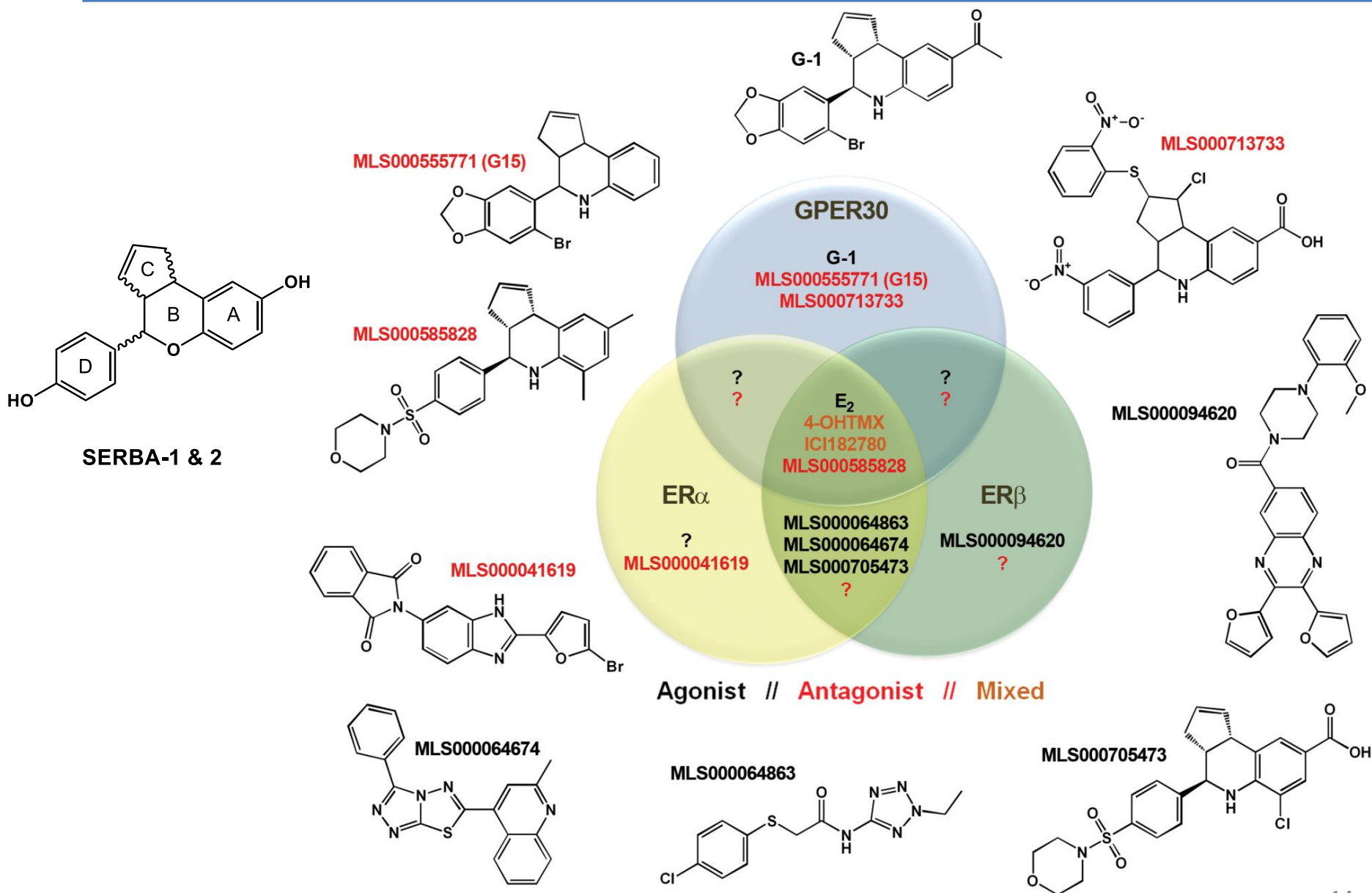
estradiol-ER α (1GWR)



4-hydroxytamoxiphen-ER β (2FSZ)

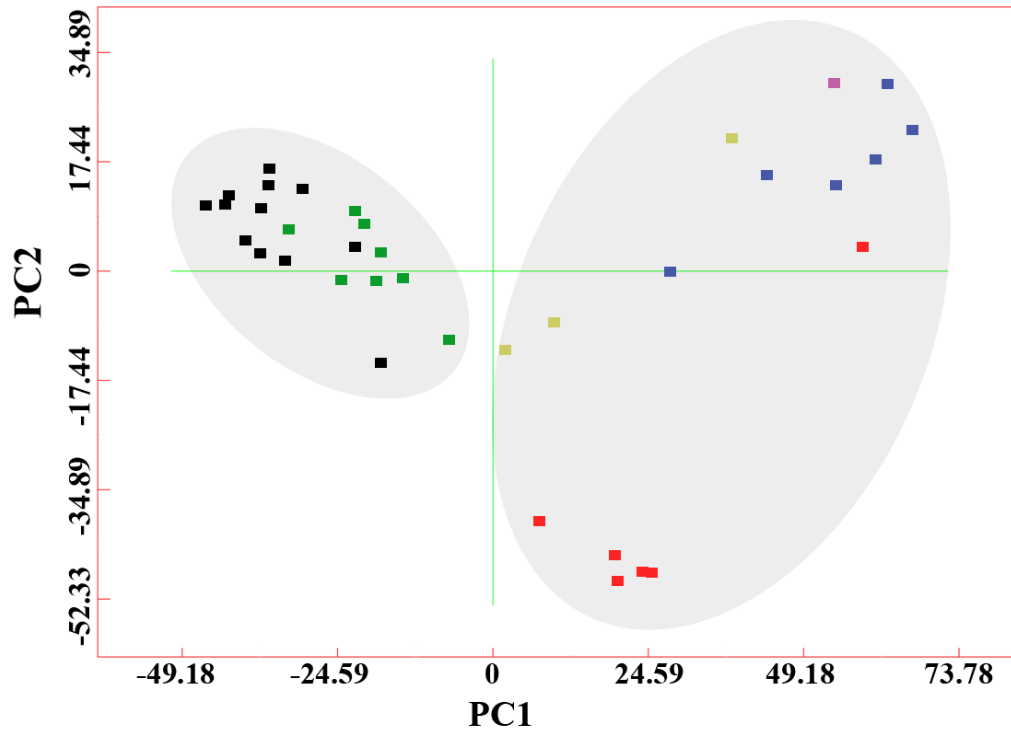
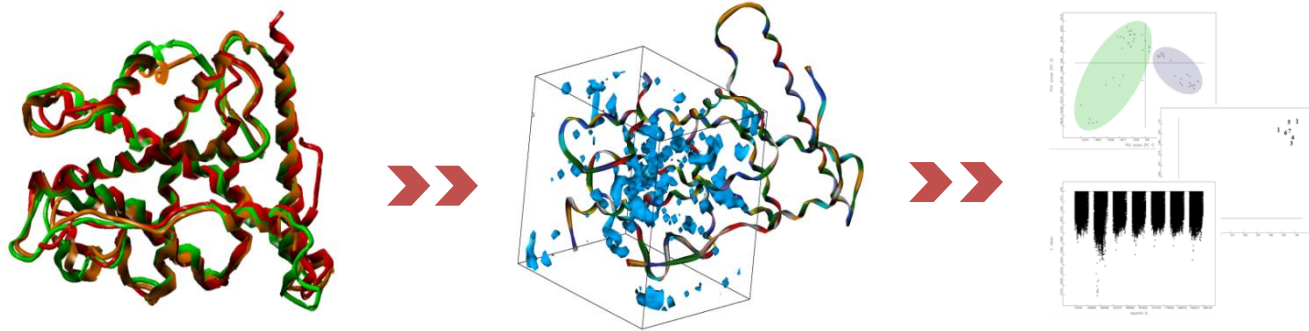


Selectivity for ER and GPER



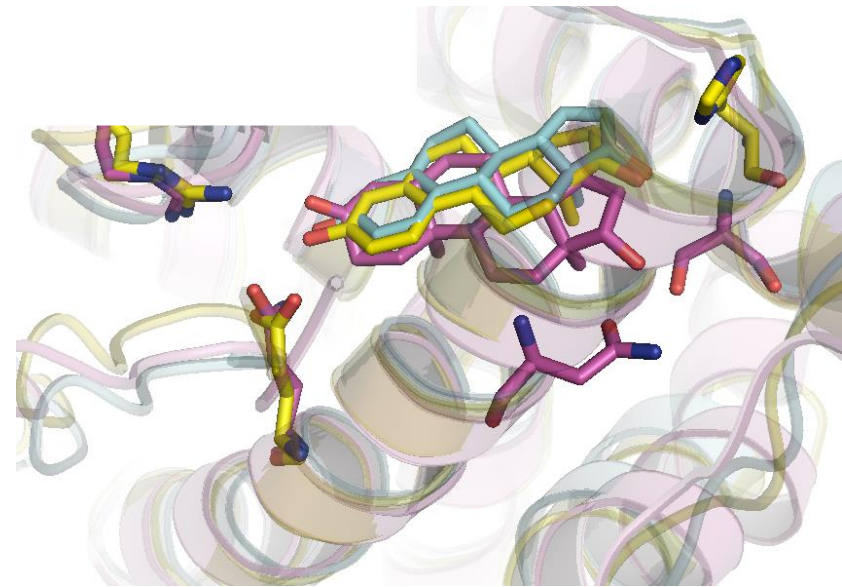
Selectivity against other NR3 class receptors

- ER, ERR, AR, PR, MR, GR



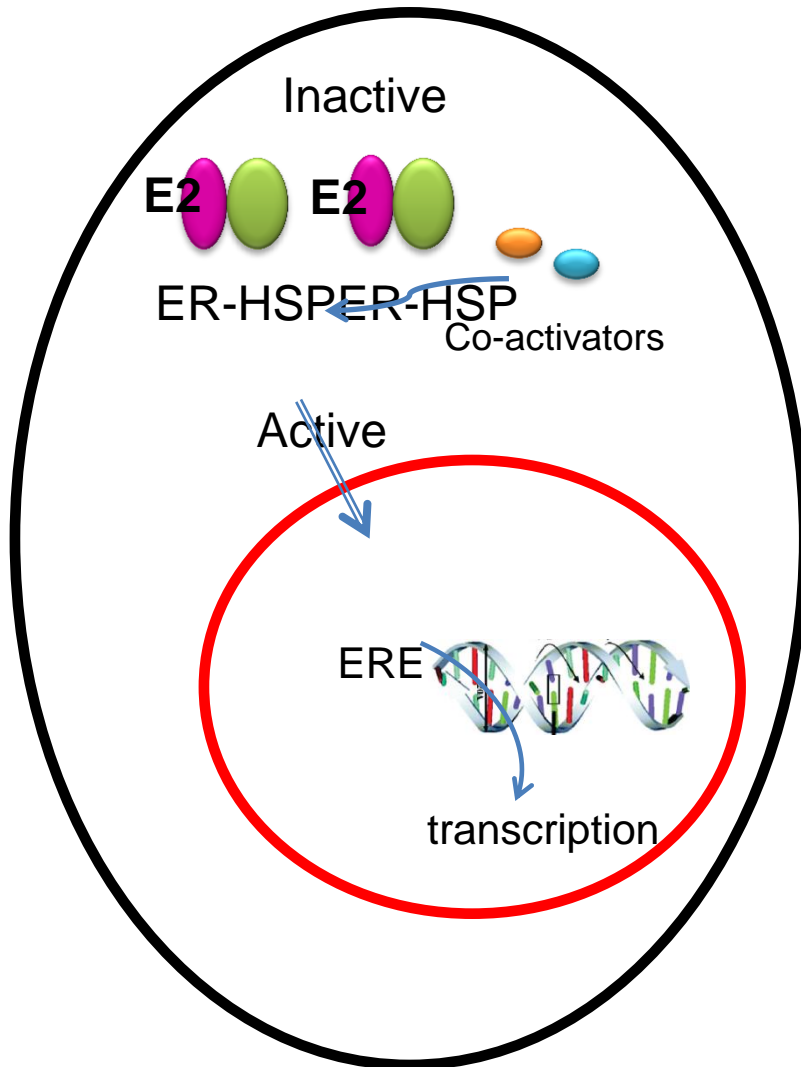
Colors: ERa, ERb, GR, MR, PR, AR

ER α , ER β and AR

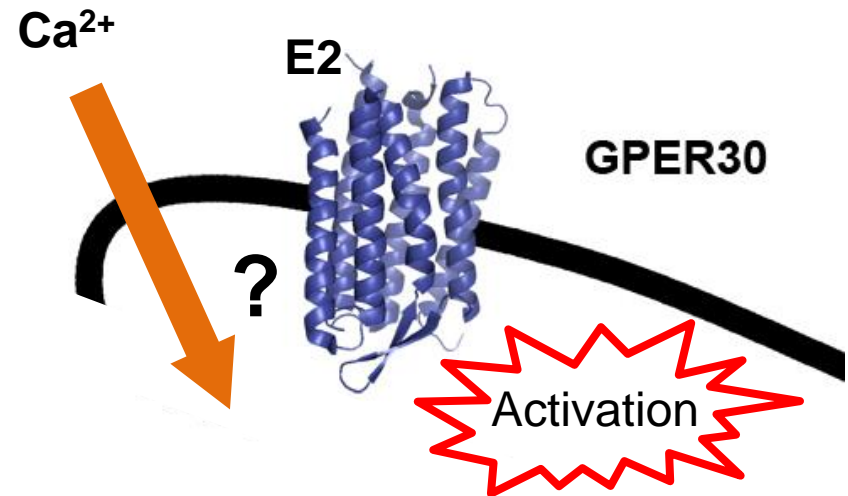


Differences between mechanisms

Genomic Mechanism (slow)

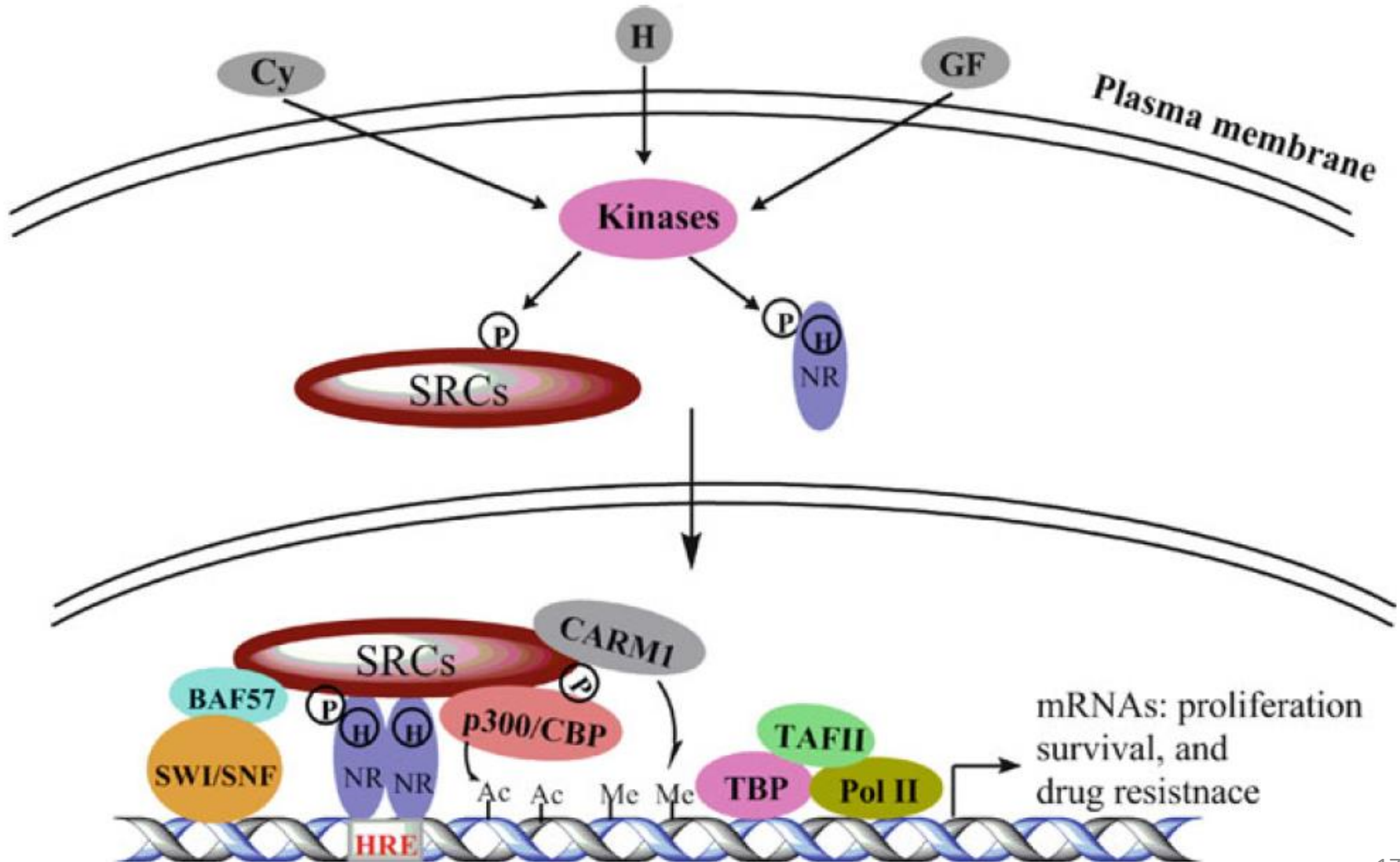


Non-genomic mechanism (fast)

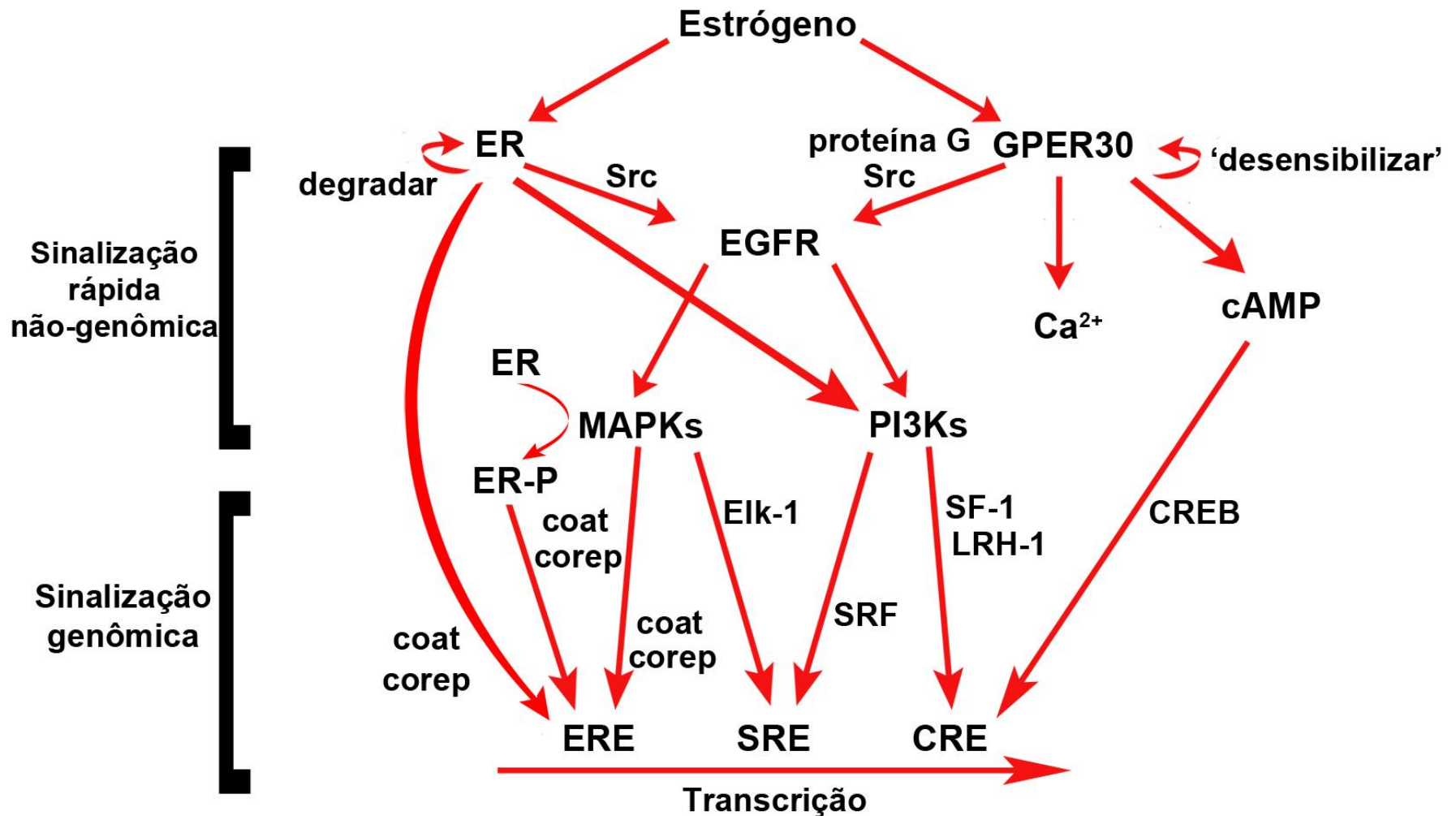


Genomic mechanism

SRCs-mediated hormone signaling and the cross-talk with growth factor and cytokine signals in regulating NR target gene expression.

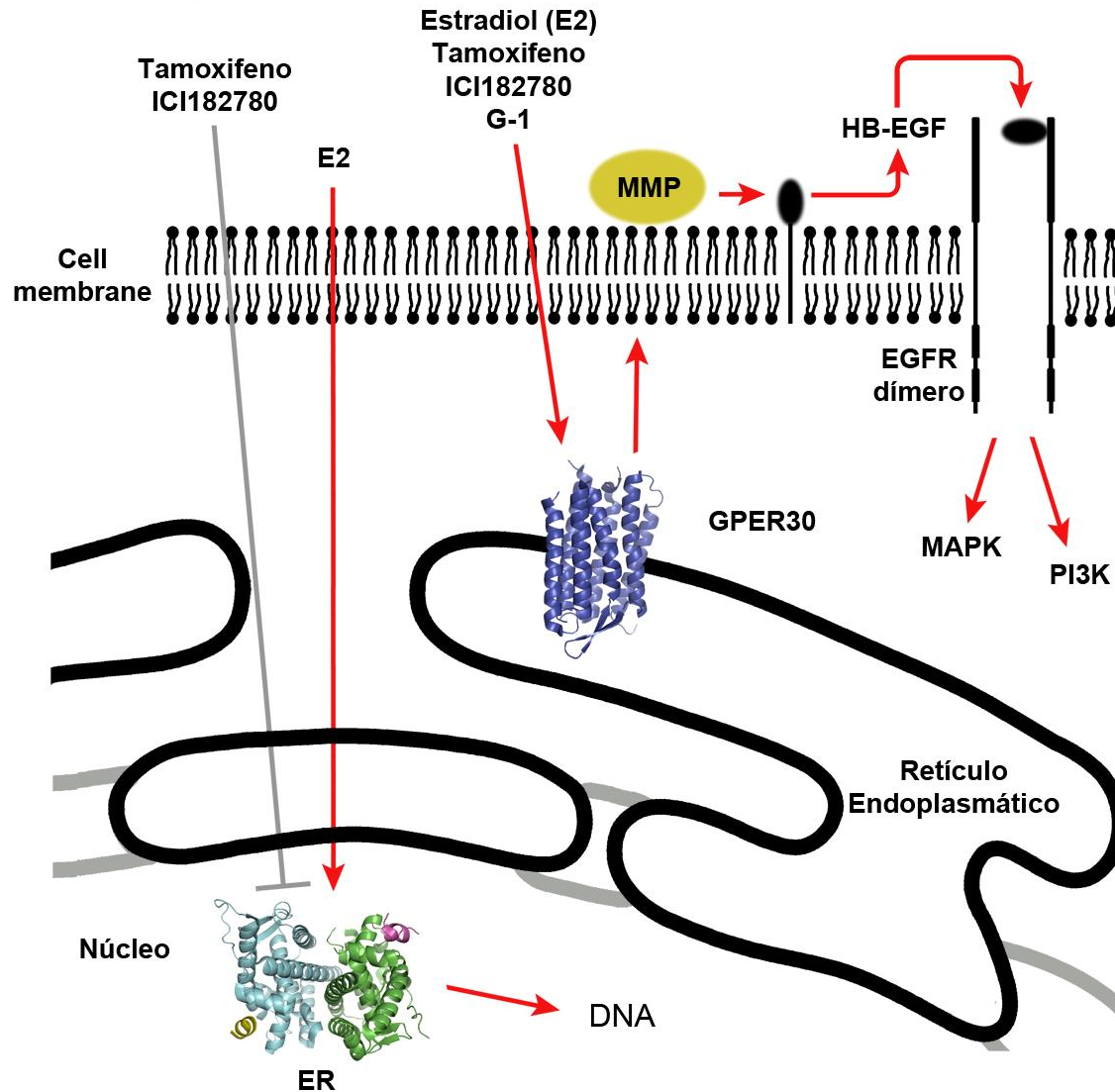


Cell signaling



Prossnitz, E.R. et al.
Annu. Rev. Physiol. **2008**, 70, 165-190.

Cell signaling (2)



Prossnitz, E.R. et al.
TRENDS Pharmacol. Sci. 2008, 29, 116-123.