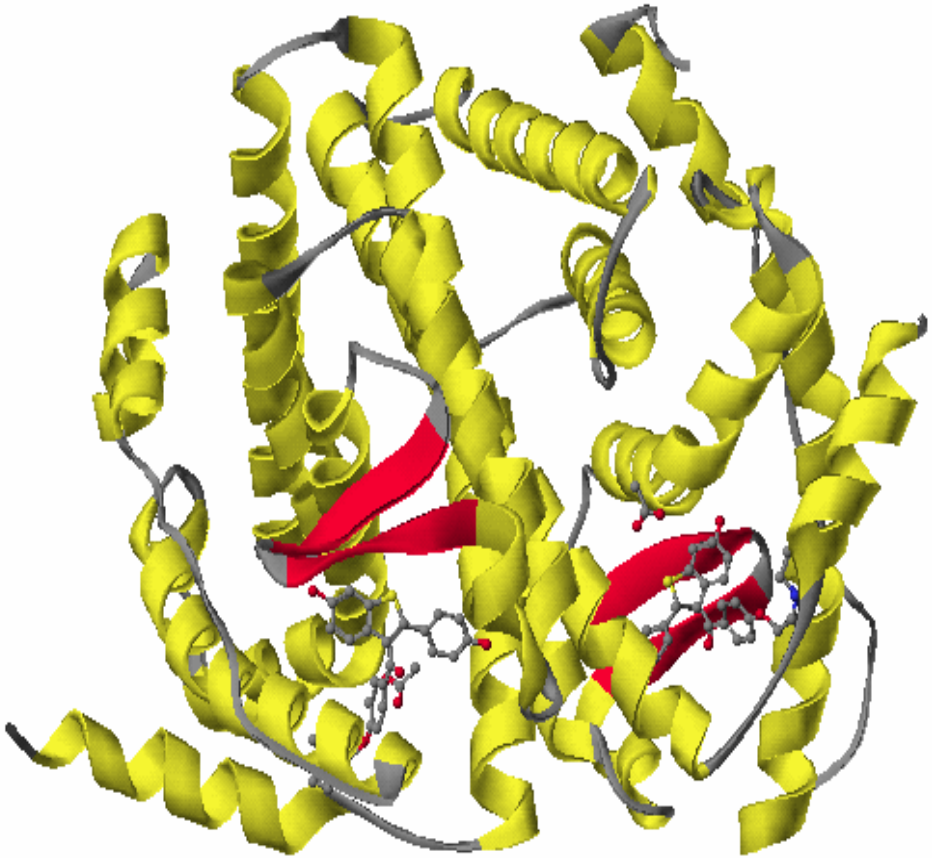
Selective Estrogen Receptor Modulators

Overview

Jelena Janjić, *Dipl.Pharm.*
Graduate student
Wipf group



SERMs lectures

- John Katzenellenbogen, *University of Illinois*, "Nuclear Hormone Receptors: Structure, Function, Ligands and Imaging"
- Jeff Dodge, *Lilly Research Laboratories*, "Discovery and Pharmacology of LY2066988: A Novel, Highly Potent SERM for the Treatment of Uterine Fibroids"
- Richard E. Mewshaw, *Wyeth Research*, "Exploiting New Scaffolds Toward the Discovery of ERß-Selective Ligands"

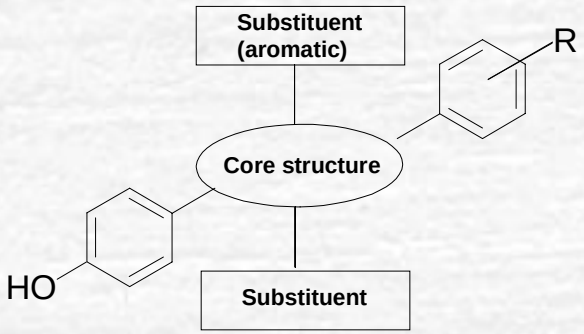
Nuclear receptors ERα vs. ERβ

- **Met 336 in the ERß LBD is a major factor determining the ERß selectivity of DPN**

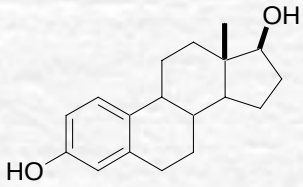
- 20–25 residues of the ER-LBDs in close contact with bound ligands

- **Leu-384 and Met-421 in ERα *vs.* Met-336 and Ile-373 in ERß**

Pharmacophore model

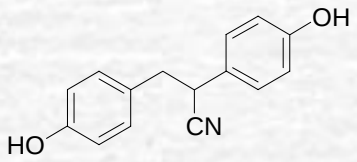


Estrogen Ligand Pharmacophore



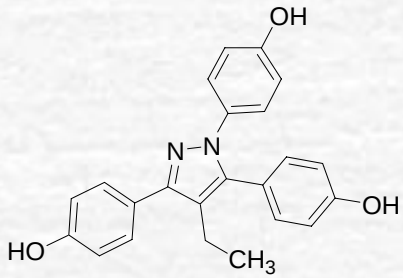
17β-Estradiol

ERα and ERβ



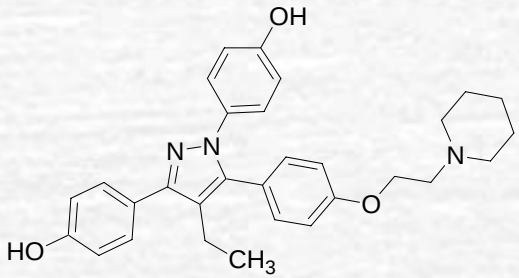
2,3-Bis-(4-hydroxy-phenyl)-propionitrile (DPN)

ERβ / ERα 100 x



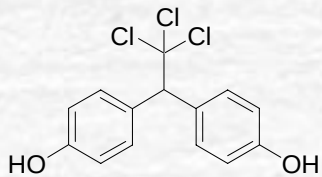
ethyl-pyrazole-triol agonist

ERα



ethyl-pyrazole-triol antagonist

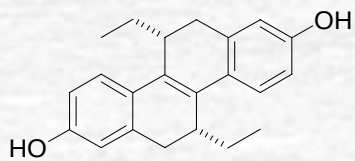
ERα



HPTE

ERα agonist

ERβ antagonist



THC

ERα agonist

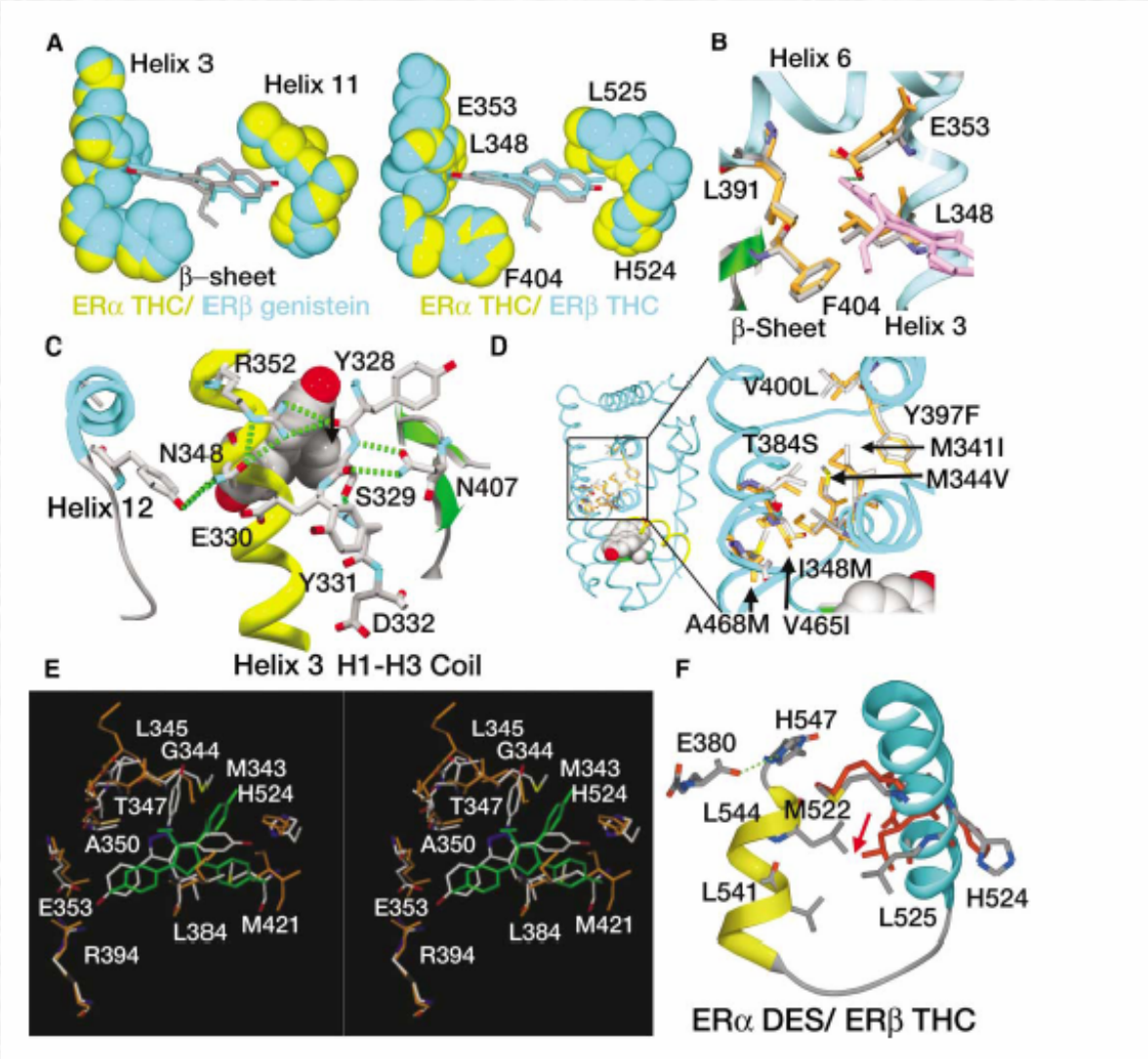
ERβ antagonist

Molecular Endocrinology 17 (2003): 247-258

Molecular Cell 2004, 13, 725–738

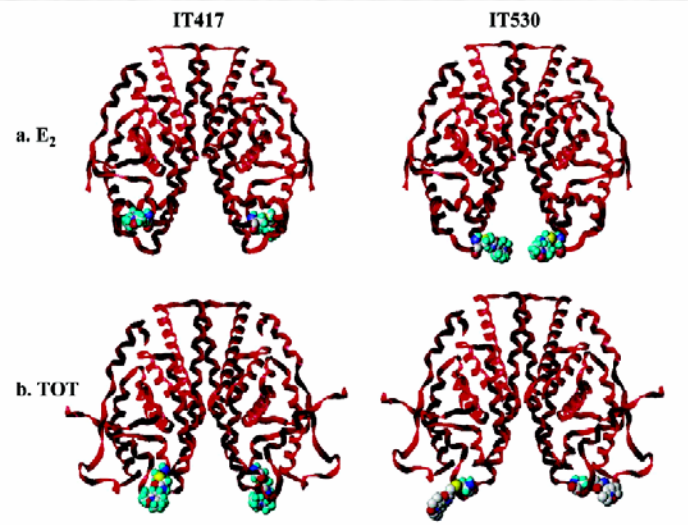
Molecular Cell 2004, 13, 317–327

Residues that Control Ligand Orientation



Molecular Cell 2004, 13, 317–327

Labeling methods to investigate ER-ligand interactions and coregulator recruitment



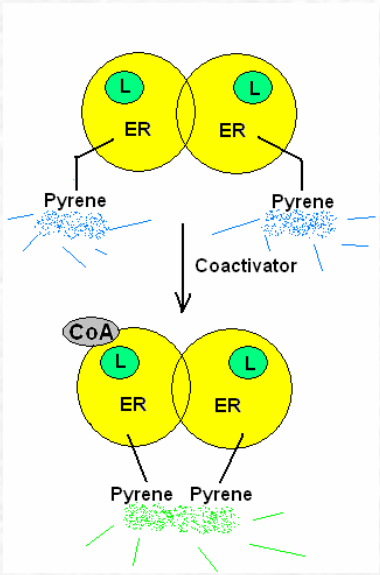
Biochemistry (2004), 43, 1891-1907

Pyrene – dual color emitting fluorophore
Monomer – blue
Excimer – green
Excimer/monomer 3 fold

Dynamics at C530 is ligand biocharacter dependent and C530 was labeled with pyrene to monitor coregulator recruitment

Dynamics at C530 is ligand biocharacter dependent
Dynamics at C417 is ligand biocharacter independent

Both labeled – fluorescence polarization monitoring of conformational changes.



John Katzenellenbogen, *Univ. of Illinois*

John Katzenellenbogen, *University of Illinois*

Tamoxifen challenge test

- FES image 1 – baseline – total uptake
- FES image 2 – non specific uptake
- ***Δ Specific uptake***

FES = (^{18}F)-estradiol

TAM (7-9 days)

↓

TAM continued

↓

Clinical outcome

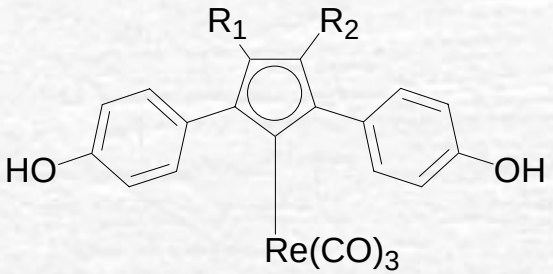
↓

PET imaging

- FDG image 1 – baseline metabolism
- FDG image 2 – stimulated metabolism
- ***Metabolic flare – clinical flare***

FDG = 2(^{18}F)-2-deoxyglucose

New imaging reagents:



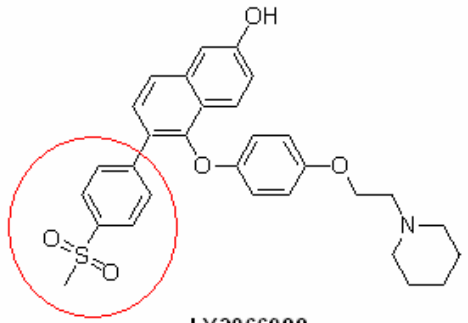
RBA at ERα - 23
RBA at ERβ - 13

Glucose image gave positive prediction: 91% for responders!

John Katzenellenbogen, *University of Illinois*

LY2066988 - Treatment of Uterine Fibroids

- Unterine leiomyomas (fibroids) – clinically apparent in 25% of women at reproductive age (25-44) - leading cause for hysterectomies (200,000 / year in US).
- Leiomyomas are estrogen dependent
- TAM in premenopausal women had no effect on fibroid size, but gave ovary hyperstimulation through inhibition of hormonal axis
- Lack of antagonist activity on axis was required
- Decrease brain/plasma exposure – SAR
- K_i = 0.47 nM (ERα) and 1.48 nM (ERβ)
- Ishikawa cells IC_{50} 10.7 nM
- MCF-7 cells IC_{50} 0.86 nM
- Decreases uterine wet weight by 51%
- Orally active



LY2066988

6-(4-methanesulfonyl-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenoxy)-naphtalen-2-ol

PCT Int. Appl. (2004), WO 2004009086

Jeff Dodge, *Lilly Research Laboratories*

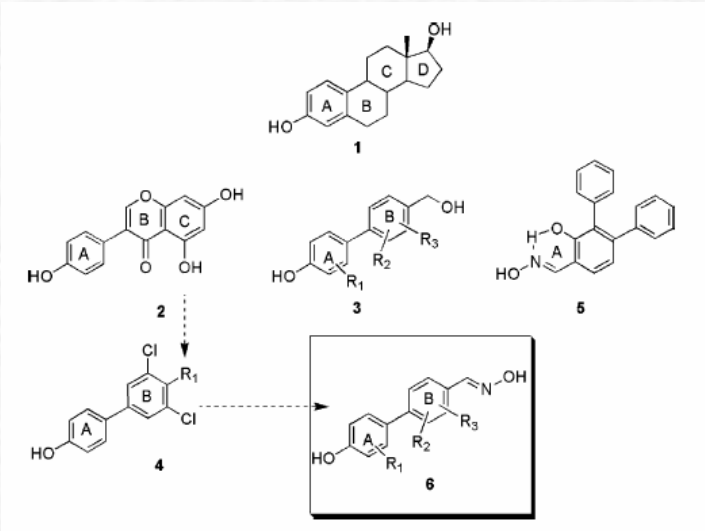
Selective ERβ Ligands

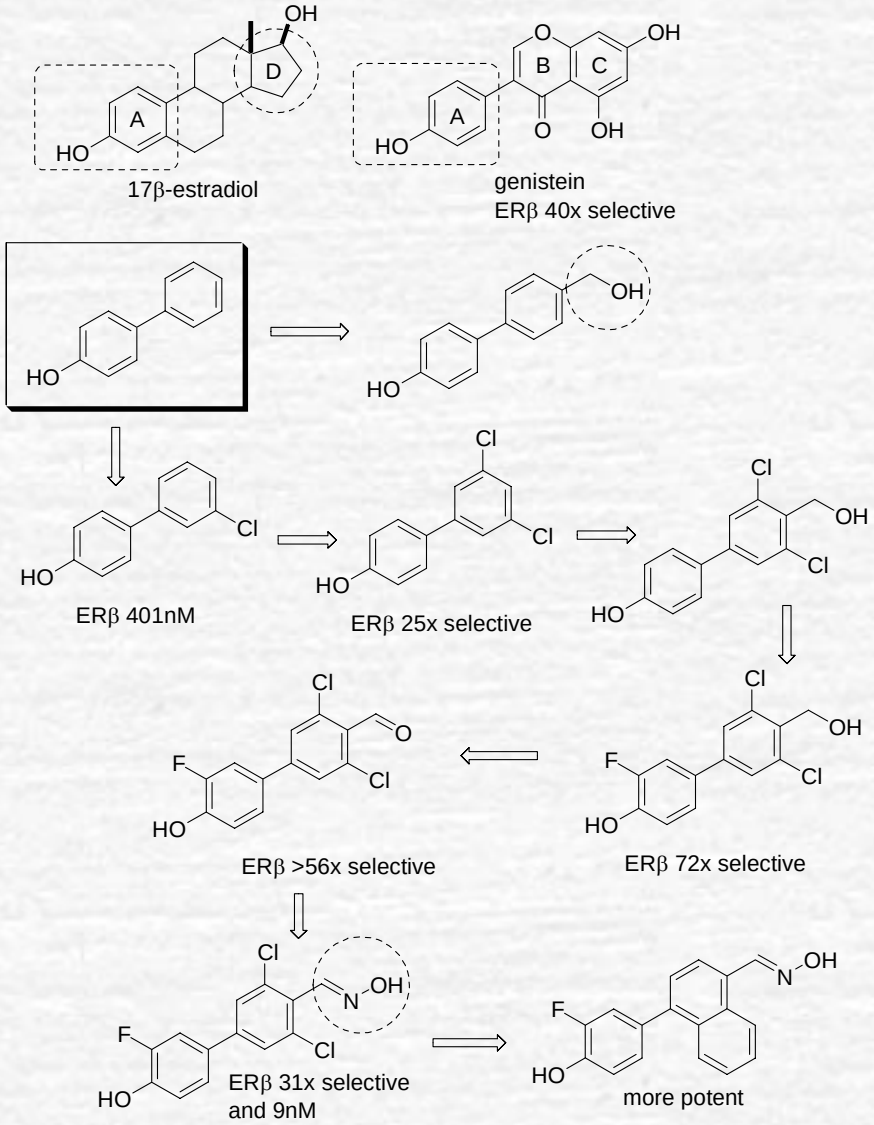
- ERß is expressed in bone, colon, endothelial cells, bladder, and areas of the brain important for cognition
- ERß-selective ligand would be the third generation selective ER modulator.
- Such a compound would be expected to retain a number of features of traditional hormone therapy [*e.g.* alleviation of vasomotor instability (hot flushes) and prevention of osteoporosis]
- Lack the stimulatory effect on the uterus and possibly the breast.
- ERß high expression in ovarian granulosa cells suggested that an ERß ligand might be a contraceptive agent.

Endocrinology 2003, 144, 4241-4249

Selective ERβ Ligands

- The role of ERβ is still being unraveled.
- ERβ is widely expressed, but is not the dominant ER in the uterus. There is much optimism about ERβ as a drug target.
- Genistein is selective for ERβ (9.7nM) over ERα (395nM)

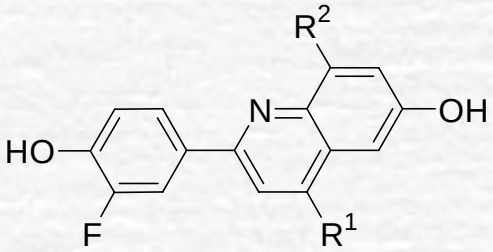




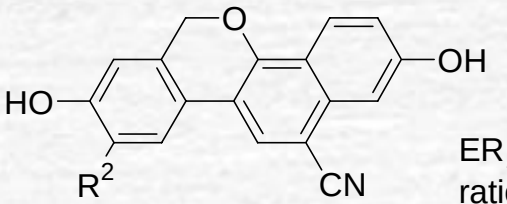
Bioorganic & Medicinal Chemistry 12 (2004) 2553–2570

Richard Mewshaw, *Wyeth Research*

Most selective

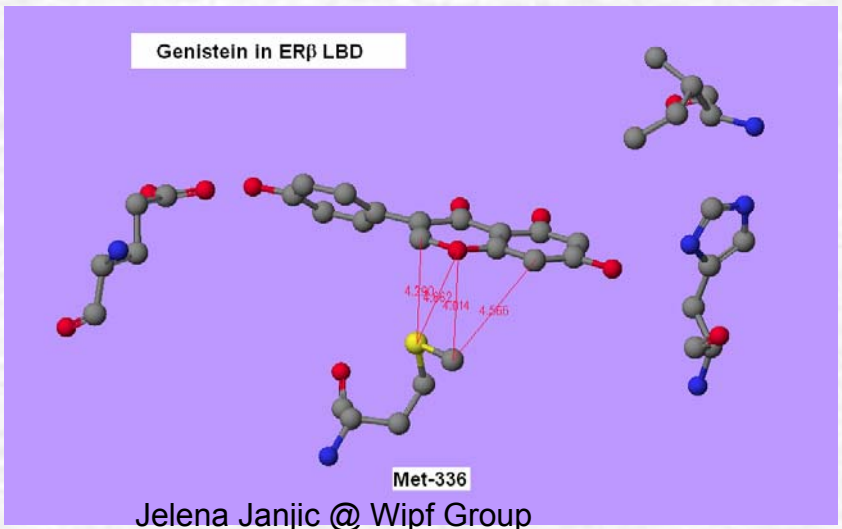


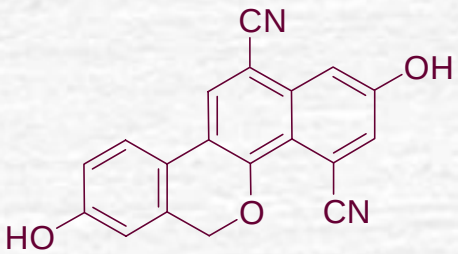
R_1	R_2	ERβ nM	ERβ/ERα ratio
CN	H	23	46
H	CN	17	32
Cl	H	5.3	46
CCH	H	32	107
Cl	CN	1.2	98



ERβ/ERα ratio 53

bulky group - selectivity drops!

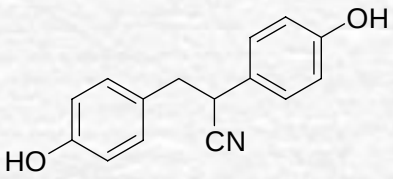


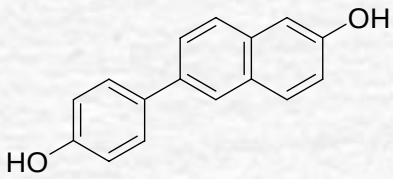


Took advantage of 2 orientations of Genistein

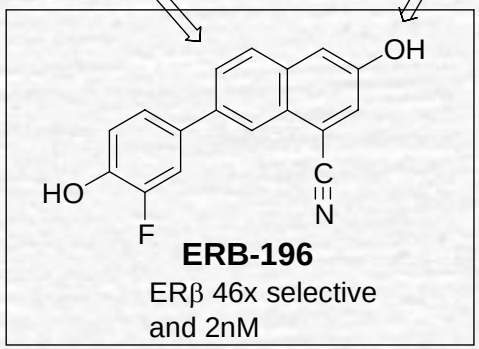
ERβ/ERα ratio 132 and ERβ 3nM

ERβ selective ligand – preclinical - inflammation



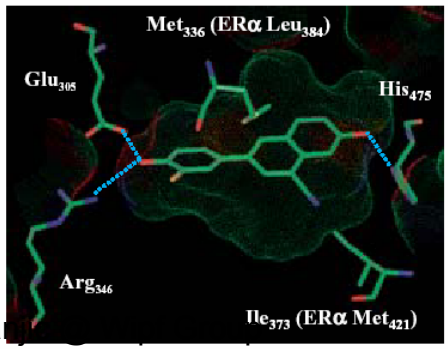


2,3-Bis-(4-hydroxy-phenyl)-propionitrile
(DPN)
ERβ / ERα 100 x

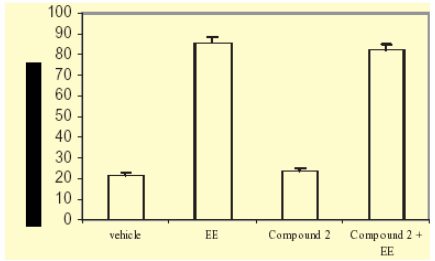


ERB-196
ERβ 46x selective
and 2nM

X-ray of Compound **2** Co-crystallized with ER_β

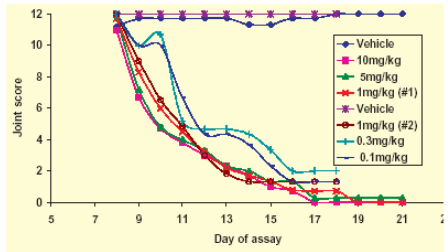


ER_β Compounds Are Not Uterotrophic



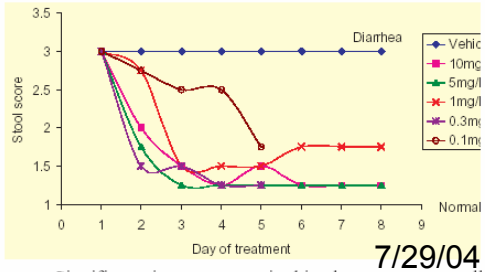
EE = 0.06mg/rat
Compound **2** = 2mg/rat

Compound 2 reduces joint swelling in Lewis rat adjuvant-induced arthritis



Synovitis and Mankin histology scores significantly reduced at doses ≥0.3mg/kg; Haptoglobin levels reduced ~70% with 1 and 0.3mg/kg dose

Compound **2** Normalizes Stool Character in HLA B27 rat



Significant improvement in histology scores at all doses
Minimum fully efficacious dose (both endpoints) = 0.3mg/kg

Richard Mewshaw, *Wyeth Research*

Lipinski rules rule!

2004 Medicinal Chemistry Award

Dr. Chris Lipinski, recently retired from the Pfizer Global Research and Development Groton Laboratories, has been selected as the recipient of the 2004 Division of Medicinal Chemistry Award of the ACS Division of Medicinal Chemistry. The award will be presented at the 2004 National Medicinal Chemistry Symposium to be held at the University of Wisconsin, Madison, during June 27 – July 1, 2004. The award is given biennially in even-numbered years to a scientist whose research has directly or indirectly had a significant effect on Medicinal Chemistry.

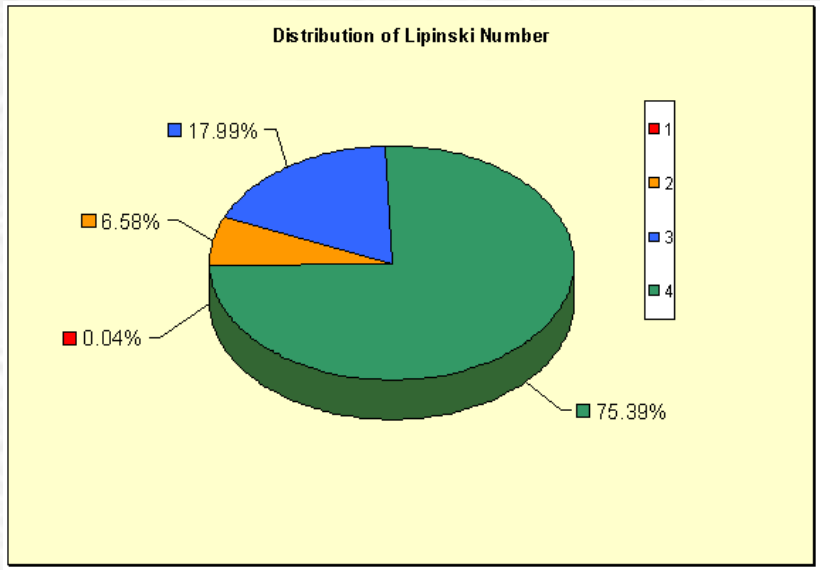
http://www.union.wisc.edu/conferenceservices/chemistry/award.html

Dr. Chris Lipinski

THE SIGMA-ALDRICH LIBRARY OF RARE CHEMICALS (SALOR)

The database [containing the L and R products] provides extra data such as cLogP, the number of H-Bond Donors, Acceptors and Rotational Bonds as well as number of Lipinski rules satisfied. The total number of structures in this database is **94,426 (35,943 L compounds and 58,483 R compounds**).

Lipinski rules of five	Number of satisfied rules	Percentage of compounds
H-bond donors <= 5	1	0.04 %
H-bond acceptors <= 10	2	6.58 %
Log P <= 5	3	17.99 %
Mol. Weight <= 500	4	75.39 %



http://cds.dl.ac.uk/cds/datasets/orgchem/isis/salor.html

Dr. Lipinski quotes from his award acceptance presentation at NMCS 2004

- Drug screening – "garbage in ⇒ garbage out"
- Never pursue a series that is not drug-like!

- Combinatorial chemistry – most significant chemistry experiment in last 40 years
- Improvements:

1. Correct identity by MS
2. Automated purification ⇒ 80-90% purity
3. Design for better ADME
4. SP synthesis improved
5. Smaller more targeted libraries
6. Lead like libraries

Dr. Lipinski quotes from his award acceptance presentation at NMCS 2004

- Mono vs polypharmacology
- Mechanistic vs phenotypic screening
- > 50% of new drugs are biologicals
- Only 13 out of 24 new targets are combichem-like
- To rethink the target assumption!

- ***Screen against the phenotype and then look for mechanism***
- ***No one really knows the exact concentration of combichem compounds in DMSO in HTS screens***
- ***Tox testing – 80-90% purity good enough?!***

Thanks
Questions?