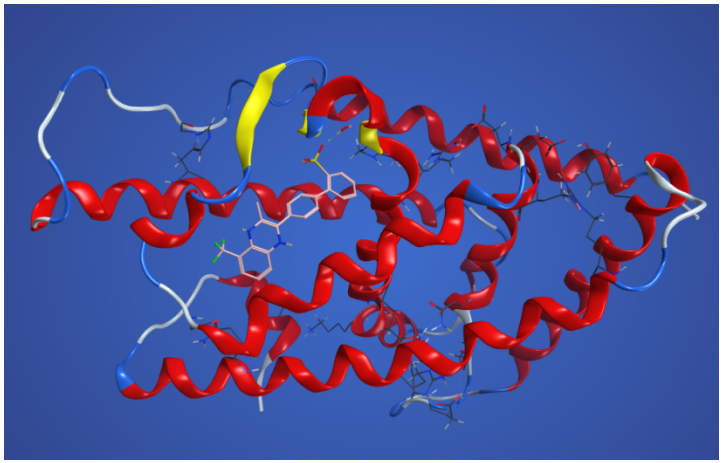
Specific Ligand-Residue Interactions that Lead to Liver X Receptor Isoform Selectivity

Susannah Davis and Kathryn Hardin

Background

Liver X Receptor (LXR)

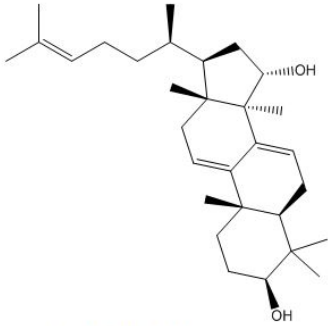
- Nuclear Receptor
- Ligand Activated
- Isoforms: Alpha and Beta



LXRβ Protein

Functions

- Cholesterol and fatty acid metabolism
- Glucose homeostasis
- Inflammation
- Neurological homeostasis



polycarpol

Background

Potential Applications

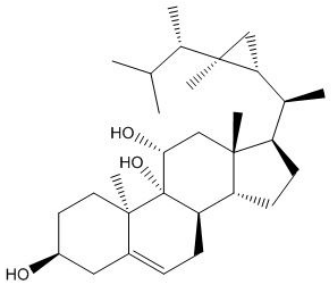
- Hormone-dependent cancer, atherosclerosis, and Alzheimer's disease

LXR-623

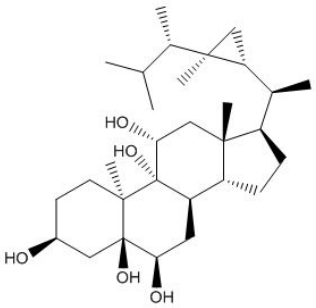
- Beta selective
- First to human clinical trials
- Attacked central nervous system

Isoform	Dominant Location	Effect on Cholesterol	Effect on Hepatic Triglyceride
Alpha	Liver, small intestine, macrophage	Lowers	Raises
Beta	Ubiquitous	Lowers	No effect

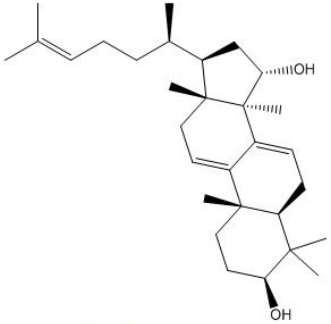
4 Ligands



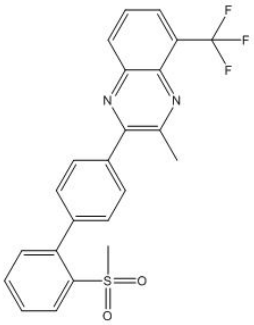
gorgost-5-ene-3β,9α,11α -triol
Non-isoform selective



gorgostane-3β,9α,5α, 6β, 11α-tetrol
LXRα isoform selective



polycarpol
LXRα isoform selective

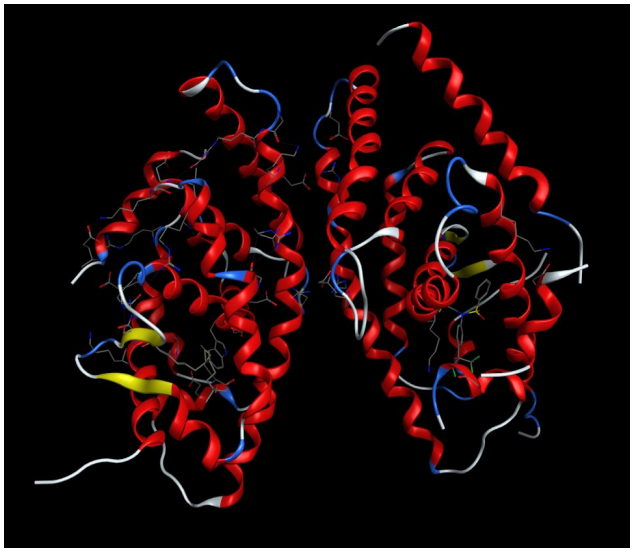


wye-672
LXRβ isoform selective

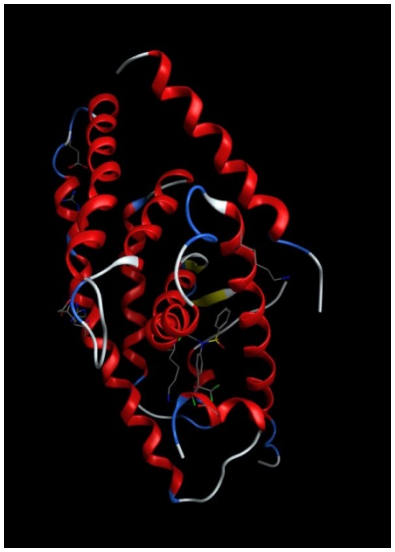
Homology Model

Tag	Chain	1 5 10
1UHL	1: 1UHL.A	GLU–MET–PRO–VAL–ASP–ARG–ILE–LEU–GLU–ALA–GLU–
	2: 1UHL.B	MET–SER–PRO–GLU–GLN–LEU–GLY–MET–ILE–GLU–LYS–
	3: 1UHL.C	HIS–LYS–ILE–LEU–HIS–ARG–LEU–LEU–GLN–ASP
	4: 1UHL.D	HIS–LYS–ILE–LEU–HIS–ARG–LEU–LEU–GLN–ASP
	5: 1UHL.A	MEI
	6: 1UHL.B	444
	7: 1UHL.A	HOH HOH HOH HOH HOH HOH HOH HOH HOH HOH HOH
	8: 1UHL.B	HOH

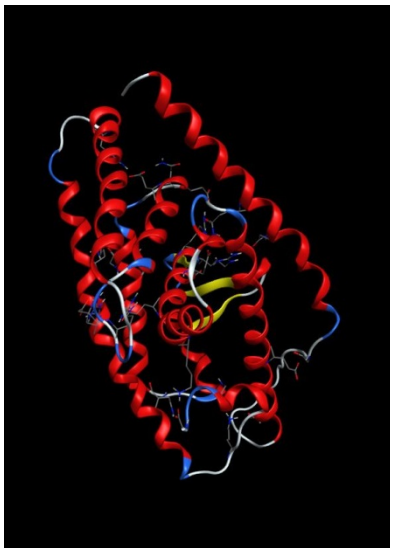
Tag	Chain	1 5 10
1UHL	1: 1UHL.B	MET–SER–PRO–GLU–GLN–LEU–GLY–MET–ILE–GLU–LYS–
	2: 1UHL.B	444
	3: 1UHL.B	HOH



Heterodimer

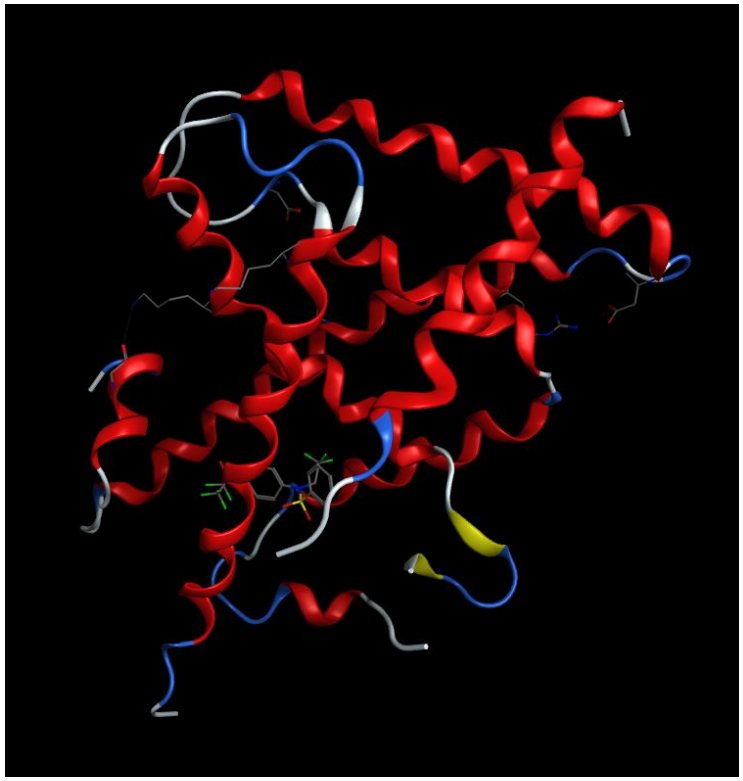


LXRα

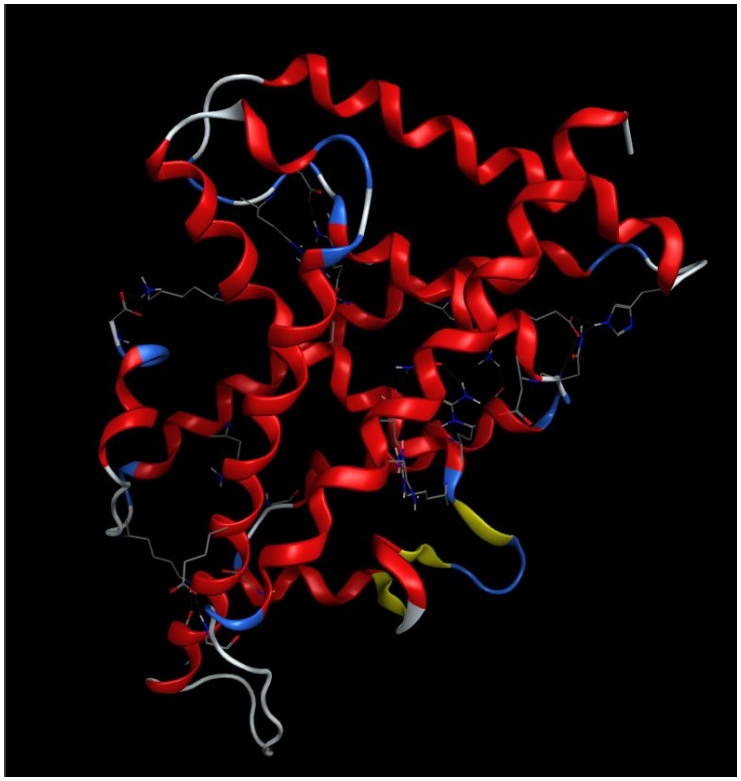


LXRα homology model

Homology Model

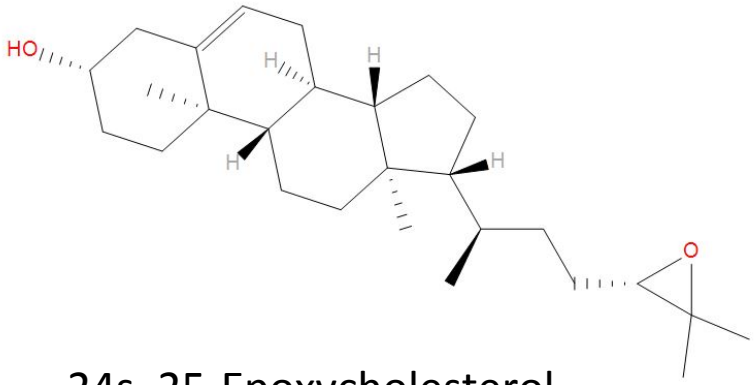


Before homology model

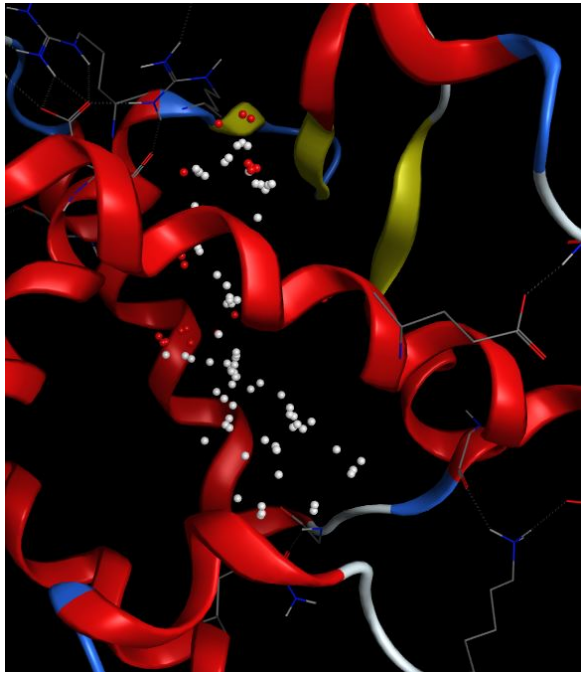


After homology model

Ligand Replacement



24s, 25-Epoxycholesterol



Procedure

Preparation

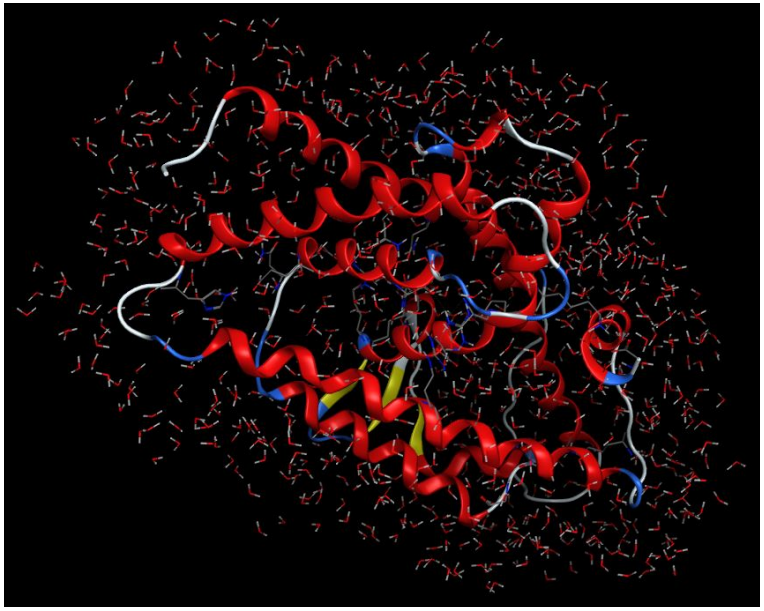
- Protonate
- Solvate

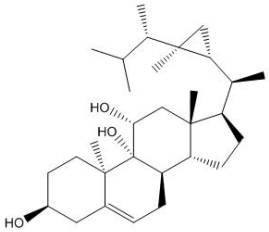
Dock

- Induced fit protocol
- Dummy atoms as the site
- Layer solvent of margin 4.0 Å

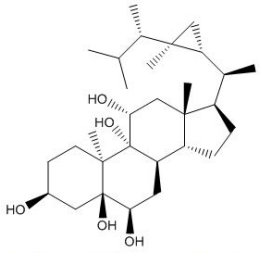
Minimization

- Pose selection





gorgost-5-ene-3β,9α,11α -triol
Non-isoform selective



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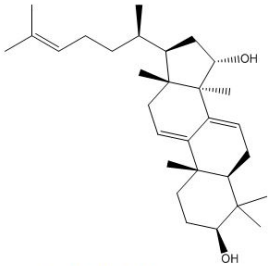
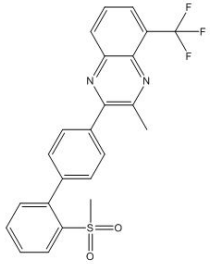
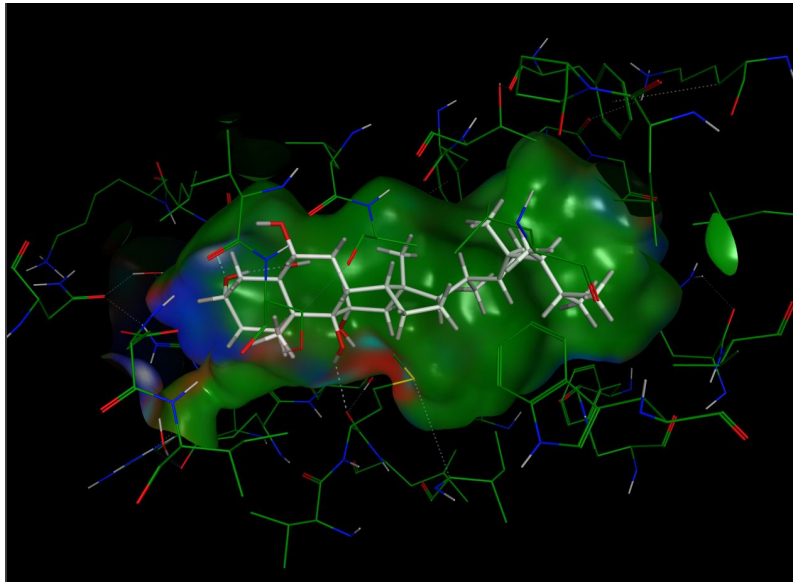


polycarpol
LXRα isoform selective

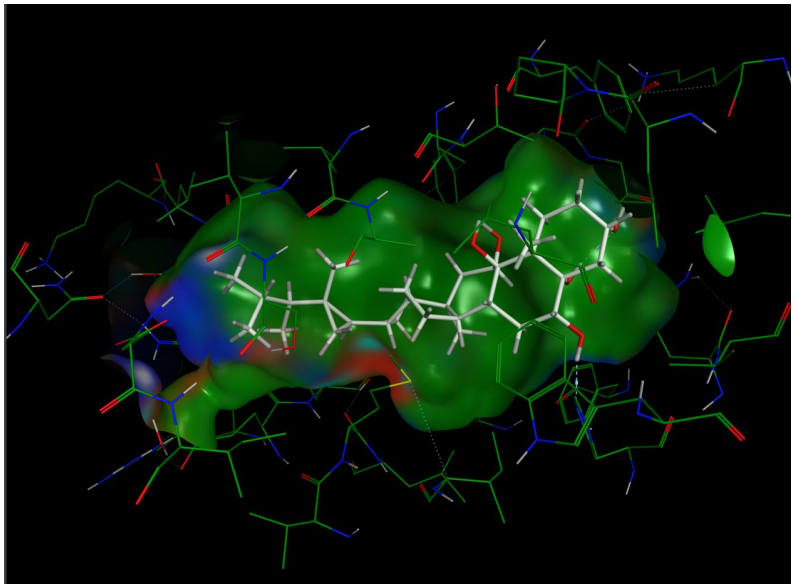


wye-672
LXRβ isoform selective

Pose Selection

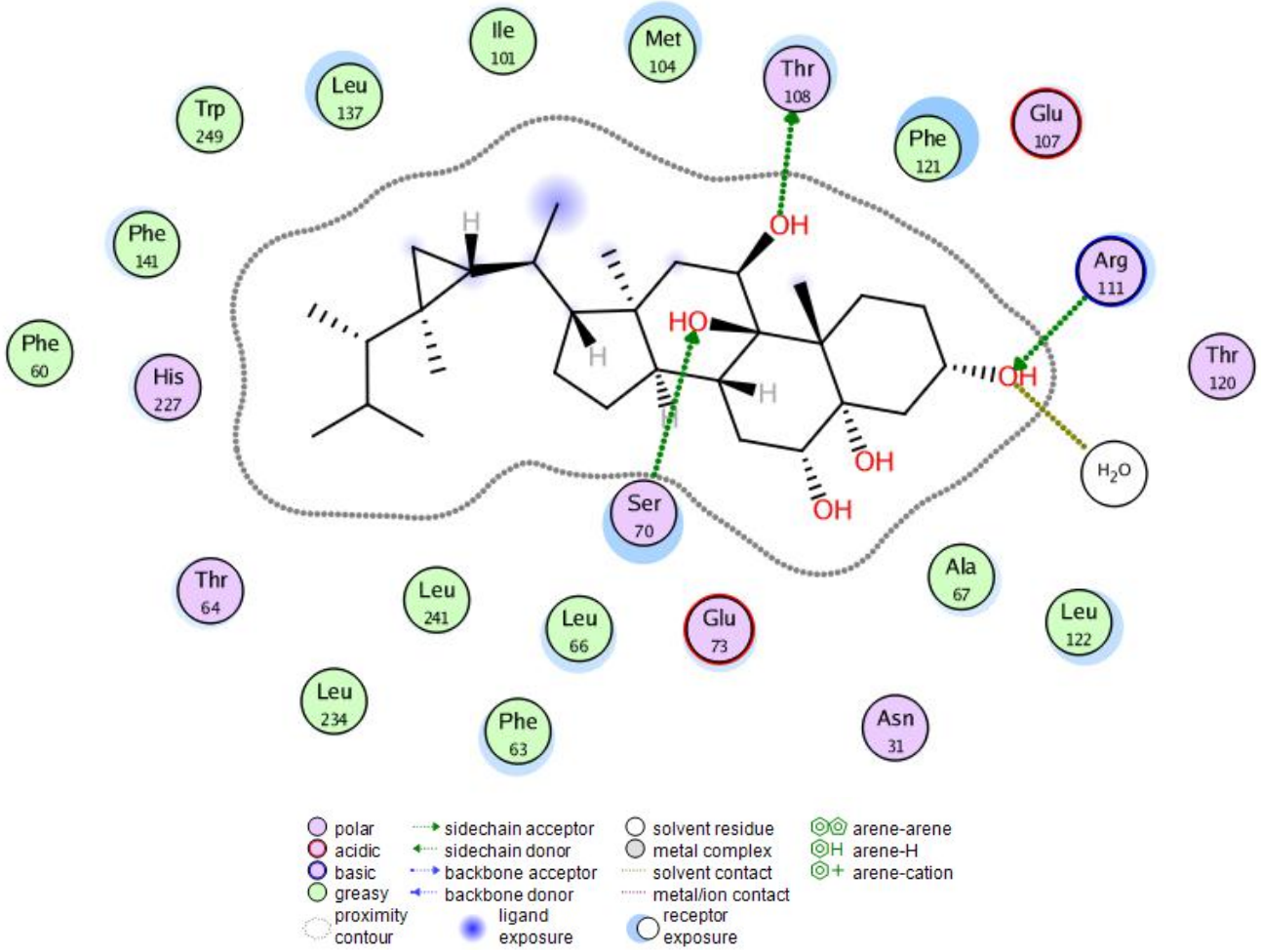


Correct

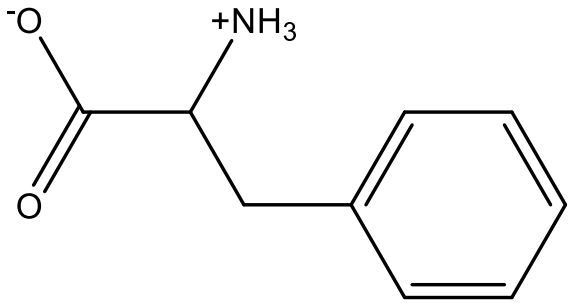


Incorrect

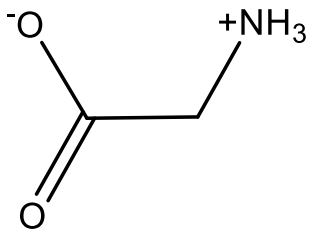
Ligand Interactions



Procedure



Phe - phenylalanine

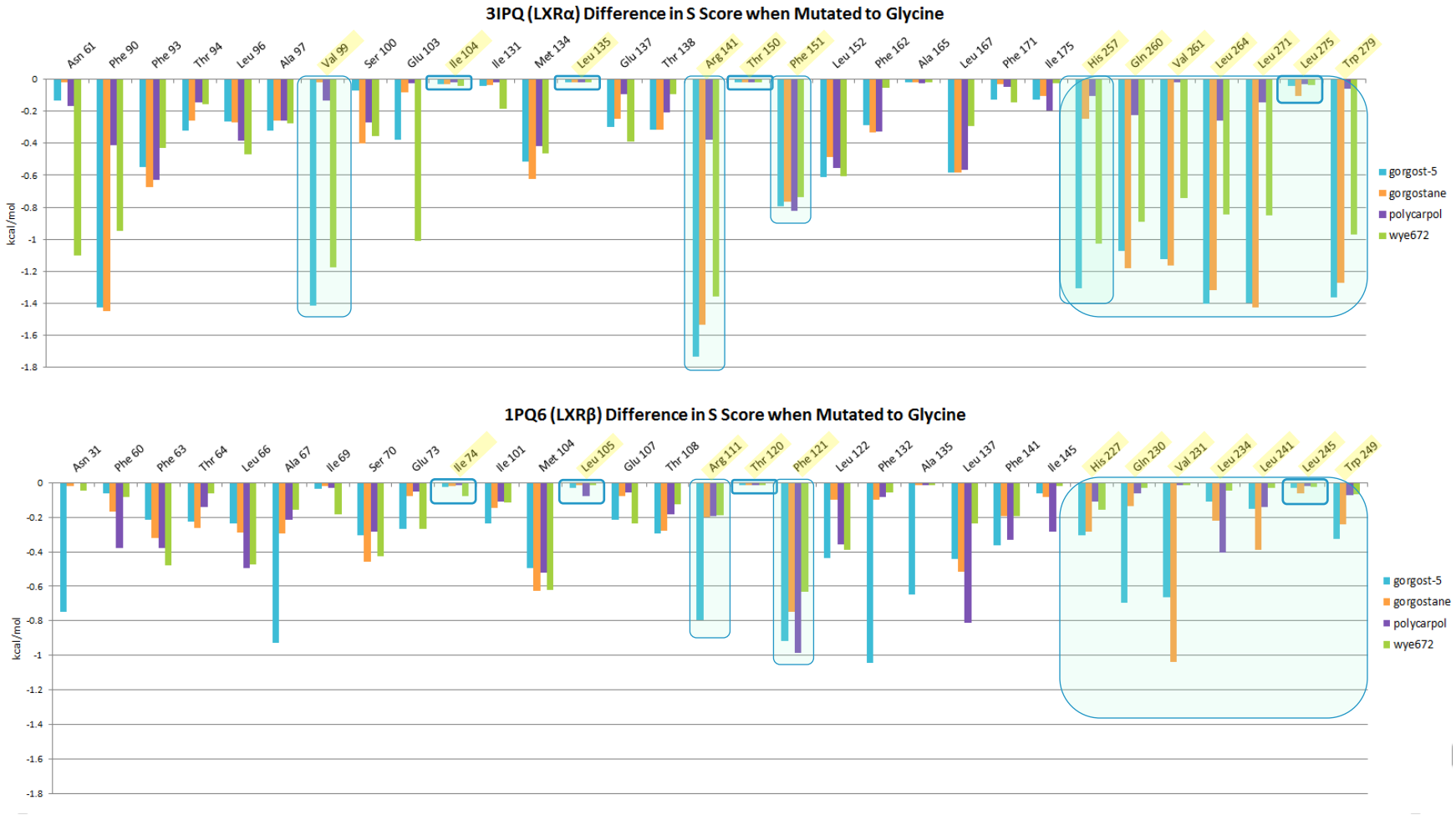


Gly - Glycine

Ligand	Base S score	Thr 150	Arg 141
Gorgost-5	-13.019	-13.019	-11.286
Gorgostane	-12.561	-12.556	-11.028
Polycarpol	-10.937	-10.931	-10.558
Wye-672	-11.159	-11.156	-9.801

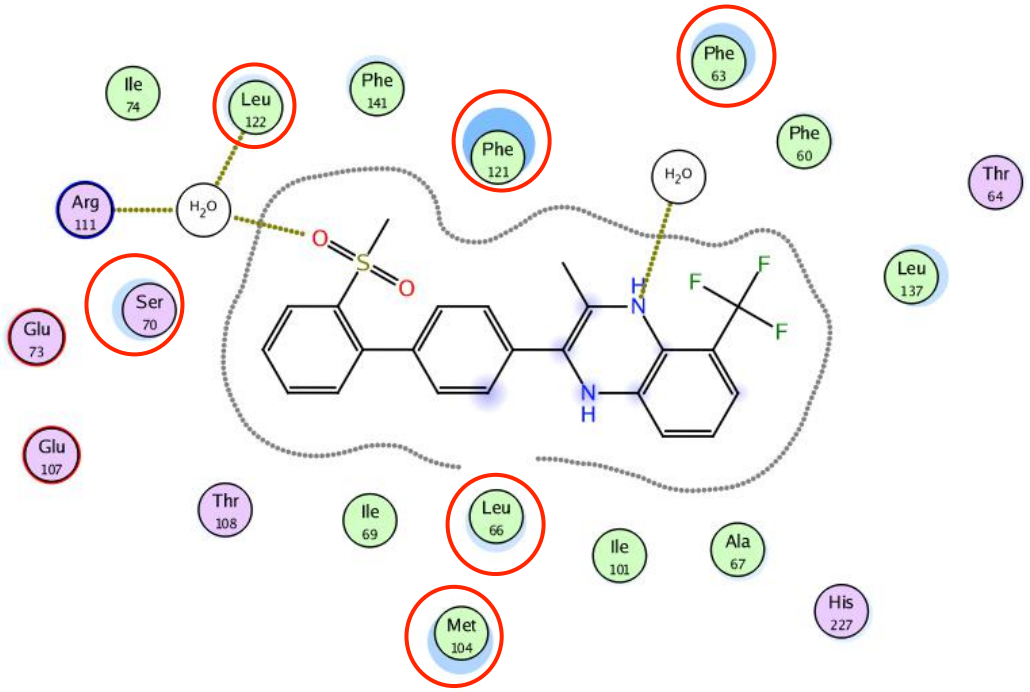
Glycine Scan

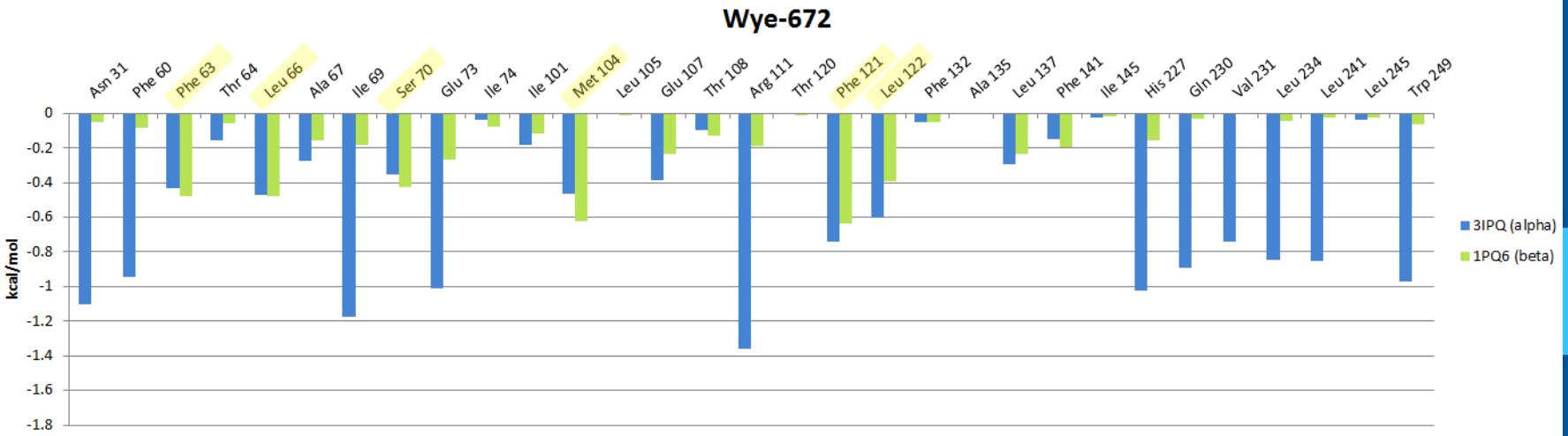
Results



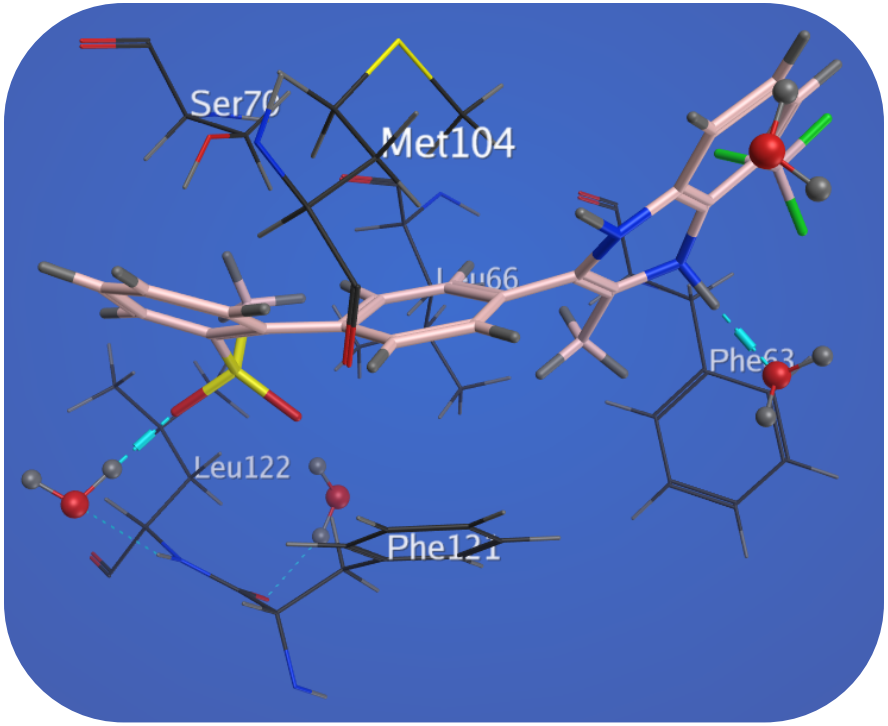
Results

Amino Acid	Difference
Phe 121	-0.6341
Met 104	-0.62322
Phe 63	-0.47719
Leu 66	-0.47576
Ser 70	-0.4263
Leu 122	-0.39017





Features of Wye-672



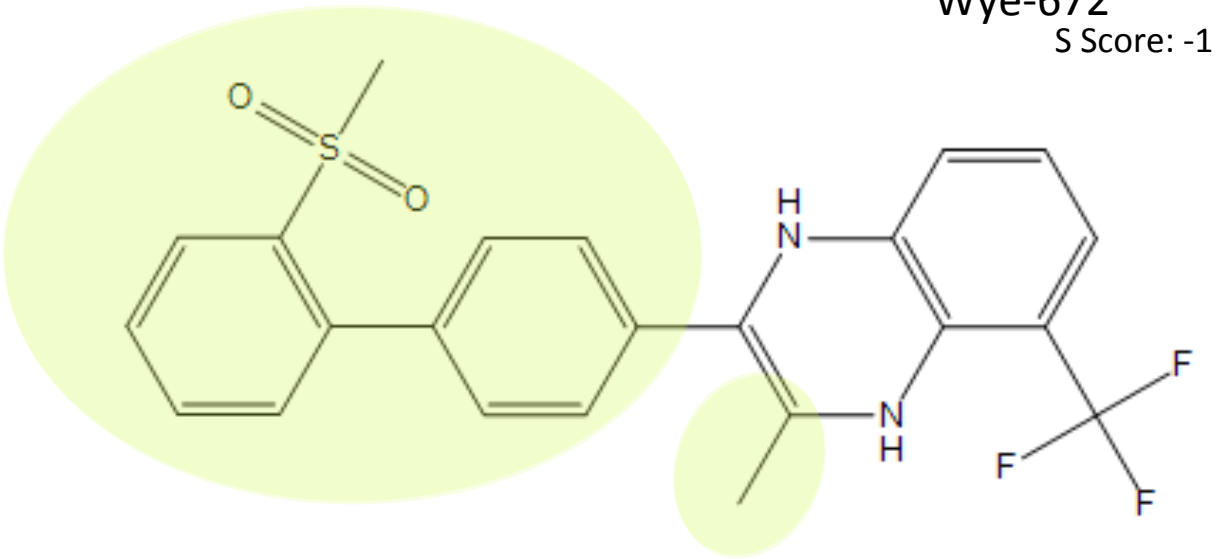
Amino Acid	Interaction
Phe 121	pi-pi
Met 104	hydrophobic
Phe 63	pi-methyl; hydrophobic
Leu 66	hydrophobic
Ser 70	pi-OH
Leu 122	H-bond bridged by H_2O

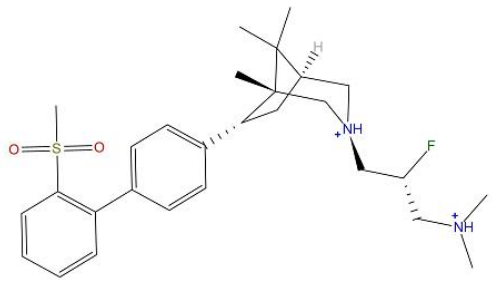
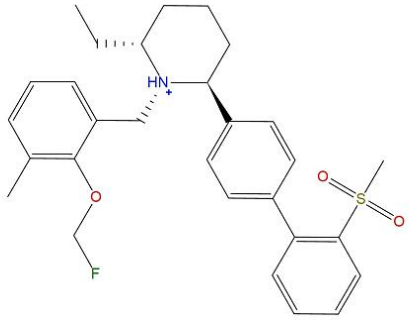
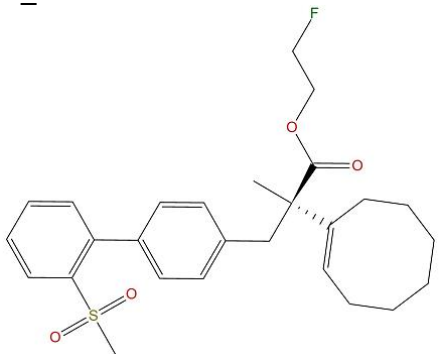
Scaffold Replacement

Procedure

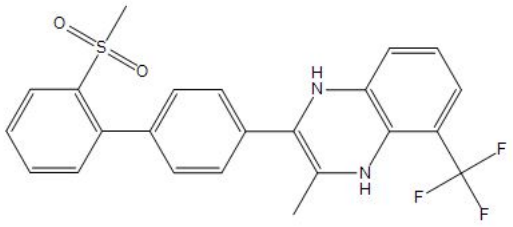
Wye-672

S Score: -11.031

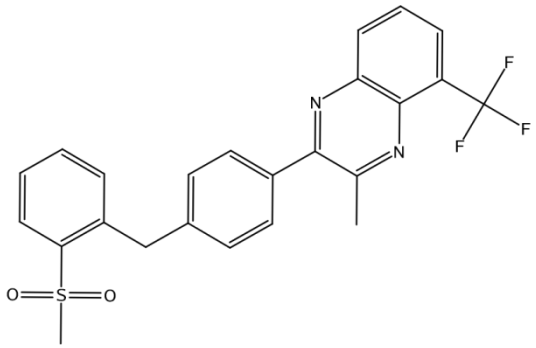


Results	m_46 	m_10 	m_5 
S score (kcal/mol)	-11.829	-11.695	-11.204

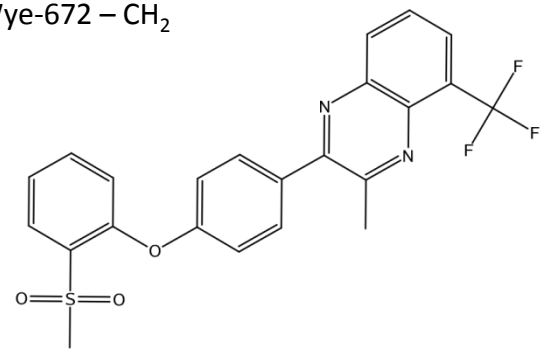
Alterations for Synthesis



Wye-672 – no change



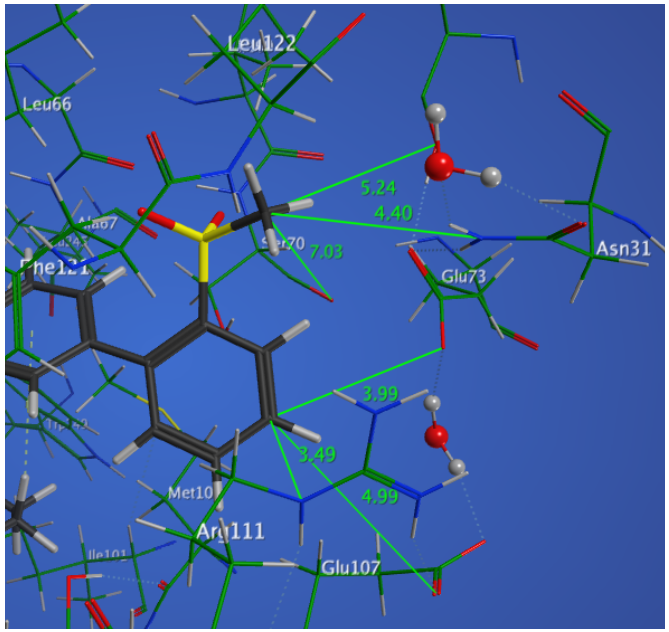
Wye-672 – CH_2

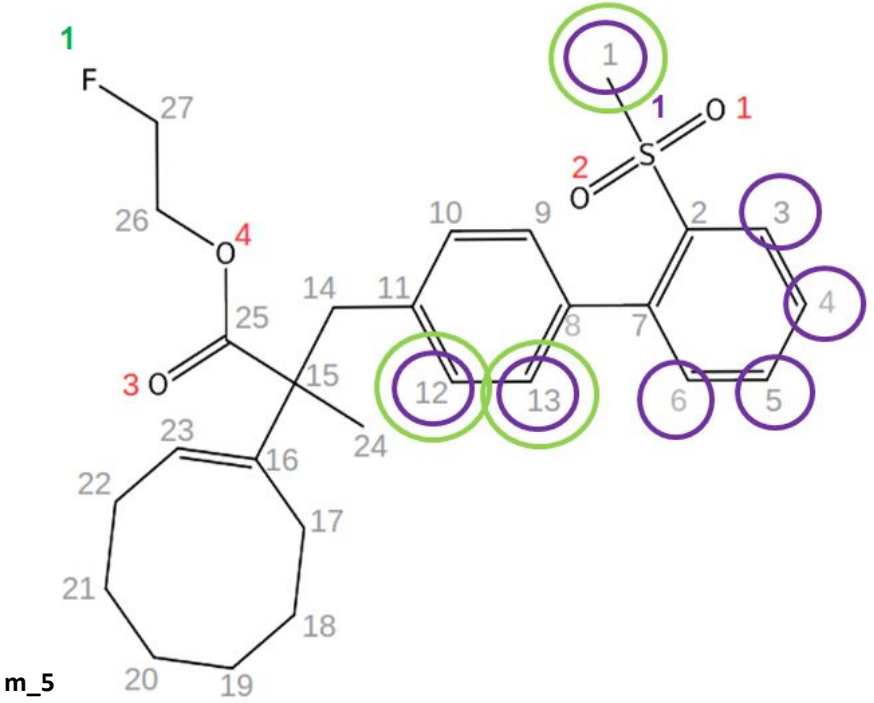


Wye-672 – O

Ligand	Original S score (kcal/mol)	-CH_2 S score (kcal/mol)	-O S score (kcal/mol)
wye-672	-9.974	-10.357	-10.333
m_10	-11.621	-12.418	-11.798
m_5	-11.210	-11.962	-11.543
m_46	-11.836	-11.661	-11.497
m_21	-10.022	-10.702	-10.426

Substituent Groups





Possible Substituents

- **Greasy** – methyl
- **Polar** – hydroxyl, amine

Future Work

- Evaluate scaffold replacement results for viability as LXRβ selective ligands using YASARA (Yet Another Scientific Artificial Reality Application).
- Perform glycine scanning and scaffold replacement using other beta selective ligands.
- Corroborate results by repeating procedure with alternate starting crystal structures for LXRα and LXRβ.
- Perform molecular dynamics simulation to obtain snapshots for further analysis.
- Synthesize developed structures

Acknowledgement

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- National Institute of Health

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- Xavier Chemistry Department

References

1. Viennois E, Mouzat K, Dufour J, Morel L, Lobaccaro JM, Baron S. Selective liver X receptor modulators (SLiMs): what use in human health? Mol Cell Endocrinol. 2011;351(2):129-41.

2. Matsuda, Takayuki, Ayumu Okuda, Yuichiro Watanabe, Tohru Miura, Hidefumi Ozawa, Ayako Tosaka, Koichi Yamazaki, Yuki Yamaguchi, Sayaka Kurobuchi, Minoru Koura, and Kimiyuki Shibuya. "Design and Discovery of 2-oxochromene Derivatives as Liver X Receptor β-selective Agonists." *Bioorganic & Medicinal Chemistry Letters* 25.6 (2015): 1274-278. Web.