Assessing the Estrogenic Mechanisms Driving Cancer: Binding Affinity Calculations of ER-Paraben Complexes

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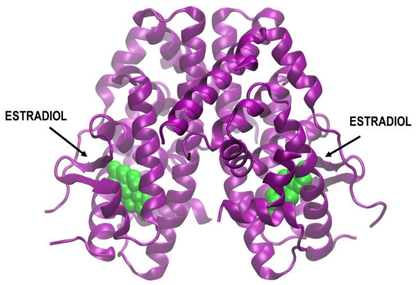
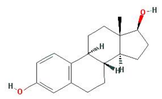
Introduction

- 70% of mammary tumors are related to the overexpression of the **estrogen receptor-α (ER)**.
- This type of cancer is known as **ER+**.
- ER binds to molecules known as **estrogens**.

How is estrogen related to cancer?

- Estrogens are steroid molecules that promote cell growth and division.
- **Estradiol** is the most prevalent form of estrogen in our lifecycle.
- Estrogens bind to the ER and promote the expression and repression of genes involved in cell growth and division.





17-β-ESTRADIOL

- **ER+ cancer** is treated with compounds that block the interactions of estrogen with the ER receptor.

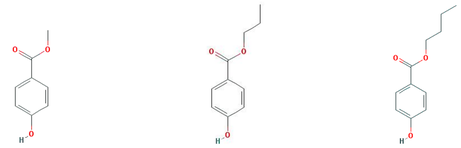
What are parabens?

- Xenoestrogens are synthetic compounds that exhibit estrogen-like behavior.
- One group of xenoestrogens that act as antibacterial preservatives are known as **parabens**.
- Parabens in food, cosmetics and beauty products have drawn mainstream scrutiny.

- Evidence demonstrates that parabens can regulate similar genes as estradiol and cause proliferation of breast cancer cells in vitro.
- Unlike naturally occurring parabens in foods that are metabolized when ingested, parabens in cosmetics bypass the metabolic process and enter the bloodstream and organs intact.

What structural data exists for ER-paraben binding?

- Minimal structural data exists for ER-paraben complexes. Only two PDB structures exist but they contain a mutation.



METHYLPARABEN PROPYLPARABEN BUTYLPARABEN

- Structure/activity study by Blair et al identified several important trends with the binding of parabens:
  1) Phenyl ring and hydroxyl group are necessary for binding.
  2) Lengthening alkyl chain increases affinity.
- Limited modeling work has been done to explain the binding mechanism of these compounds.

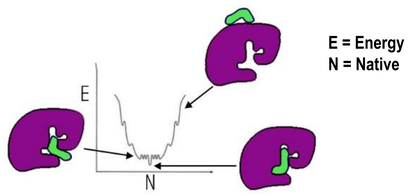
Question

- How do parabens bind to the ER and affect the downstream signaling processes involved in the estrogenic response related to the development of cancer?

Hypotheses

- The interactions driving binding of a paraben will be similar to estradiol.
- Hydrogen bonds interactions will be formed between the hydroxyl group of the paraben and the ARG394 and GLU353 amino acids in the ER.
- Hydrophobic packing will occur between the benzene ring of the paraben and PHE404.

Method



Conformational Coordinates

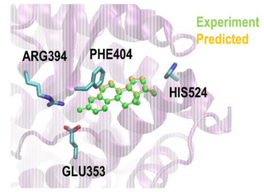
- AutoDock Vina predicted the **binding affinity** and **most favorable binding pose** of different ligands in the ER binding pocket.
- Binding pose takes into account the (1) **orientation** of the ligand in the protein binding pocket and the (2) **conformation** of the ligand.
- Binding affinity takes into account the strength of binding. The binding affinity is expressed as a free energy ($\Delta G°_b$). Strong binders have a more **negative** affinity.
- Docking was performed on a rigid protein structure (PDB: 1GWR).

Results

Can AutoDock Vina predict the experimental binding pose of estradiol in the ER binding pocket?

$\Delta G°_{calc}$ (kcal/mol)	$\Delta G°_{exp}$ (kcal/mol)
-10.9	-11.8

The experimental binding free energy and pose have been predicted accurately by AutoDock Vina.

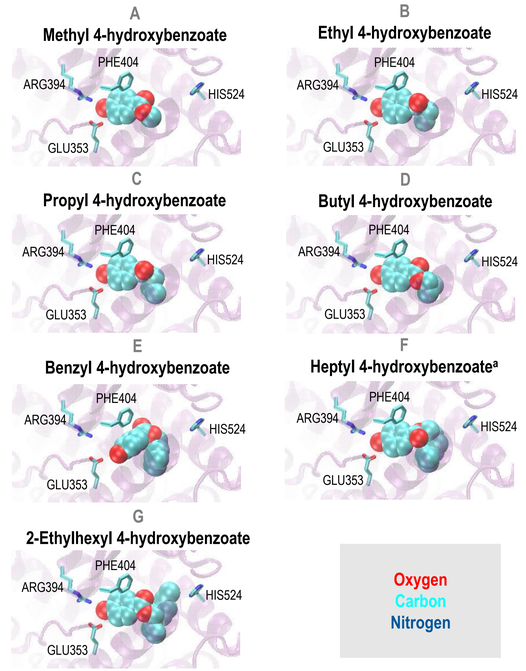


How do parabens bind to the ER binding pocket?

Paraben	$\Delta G°_{calc}$ (kcal/mol)	$\Delta G°_{exp}$ (kcal/mol)
A	--5.7	-4.7
B	--6.0	-5.0
C	--6.3	-5.0
D	--6.6	-5.2
E	--7.8	-5.9
F	--7.0	-6.5
G	--7.4	-6.9

Average Absolute Error (kcal/mol)	Correlation Coefficient
1.11	0.80

The calculated binding free energies are similar to the experimental binding free energies.



Conclusions

- AutoDock Vina can accurately predict the binding free energy and native pose of ligands to the ER based on the estradiol docking experiment.
- The binding free energy calculations were in reasonable agreement based on the average absolute error and correlation coefficient.
- The binding poses are predicted reasonably well despite the variation in the hydrophobic tail relative to the experimental models.
- An induced fit approach may improve the structural prediction of paraben binding poses in the ER binding cavity.
- Future work will focus on developing these models that we obtained from docking calculations.

References

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