Combining Structure- and Ligand-Based Approaches to Model Receptor-Mediated Toxic Effects

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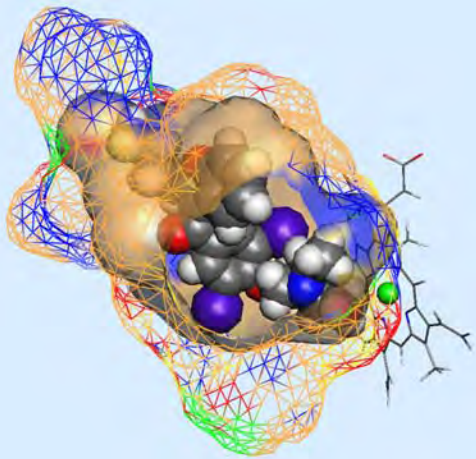

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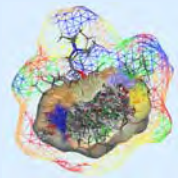
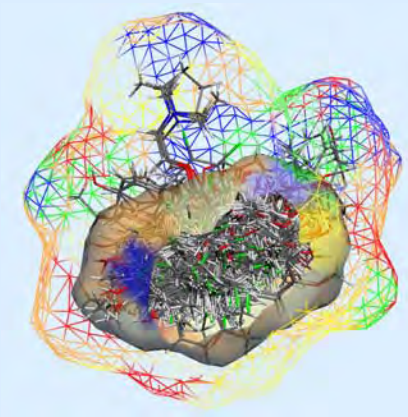


Overview

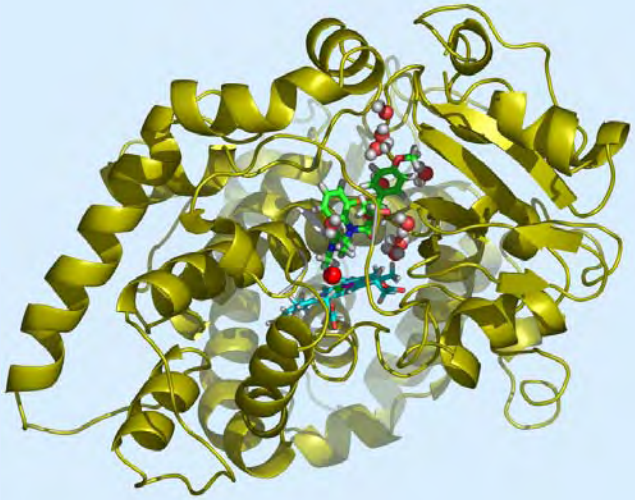


Introduction

Methodology

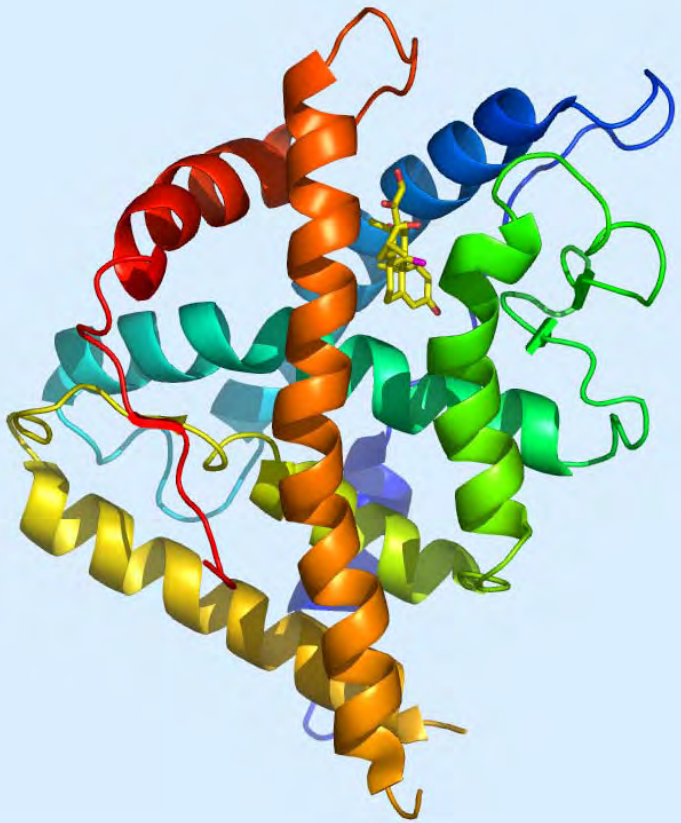
Applications

Current directions



Biological systems

Nuclear receptors



Cytochrome P450 enzymes

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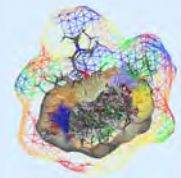
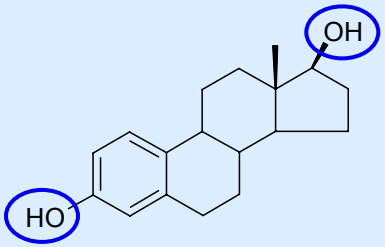
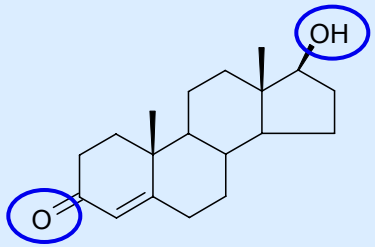


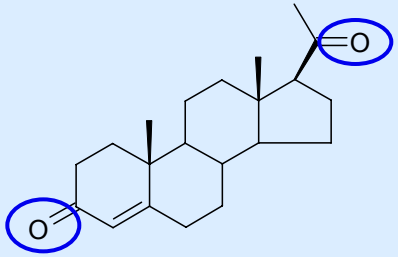
Endogenous ligands



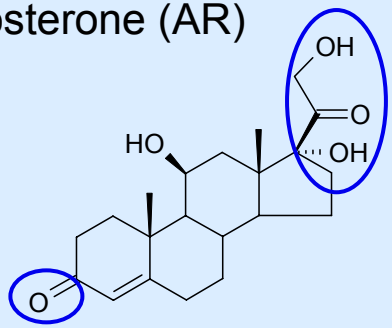
17-β estradiol (ER)



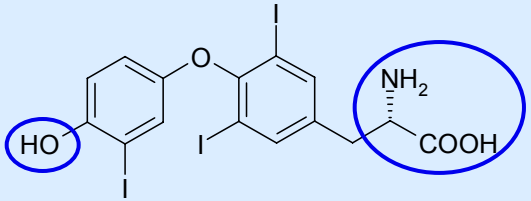
testosterone (AR)



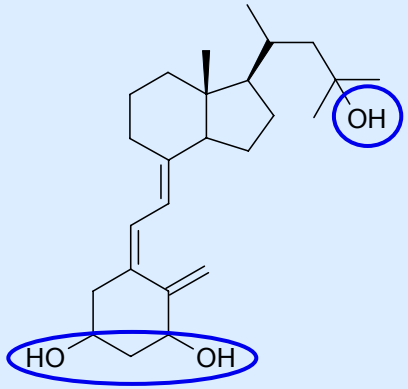
progesterone (PR)



cortisol (GR)



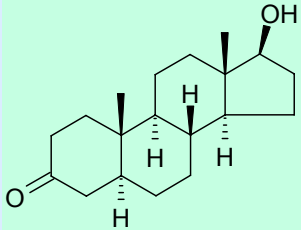
triiodothyronine (TR)



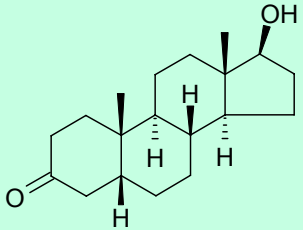
1,25-dihydroxy vitamin D_3 (VDR)

- small (volume = 250-350 Å^3)
- rigid
- highly hydrophobic
- polar groups predominantly at the ends

selective for very potent ligand molecules (nM):

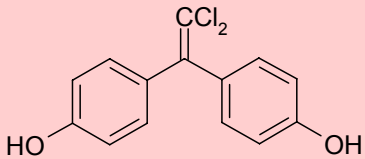


2.2 nM (AR)

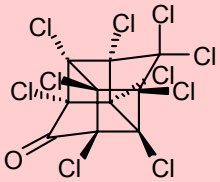


385 nM (AR)

not selective for moderate-binding ligand molecules (μM):



6 μM (AR)



11 μM (AR)

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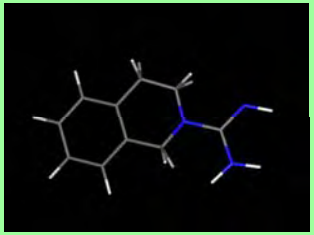
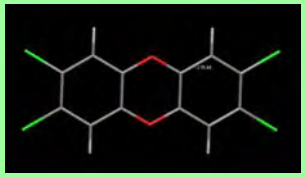
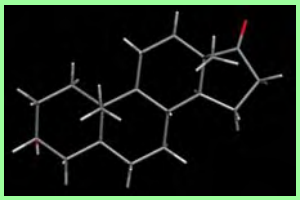
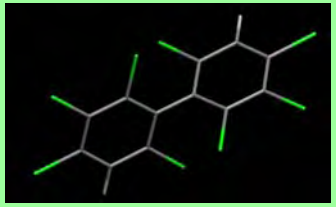
Receptor-mediated toxicity

Drugs/Chemicals

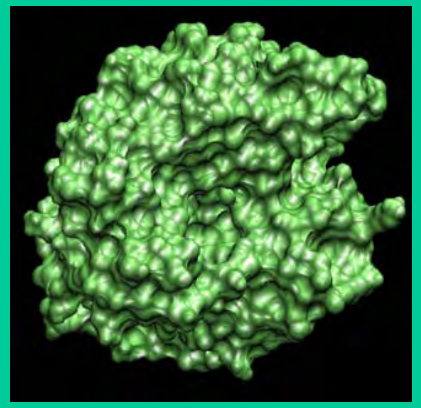








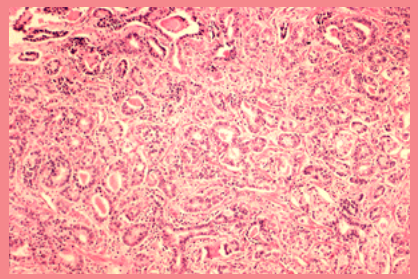
Binding



- Estrogen receptor
- Androgen receptor
- PPAR$_\gamma$
- Thyroid receptor
- …

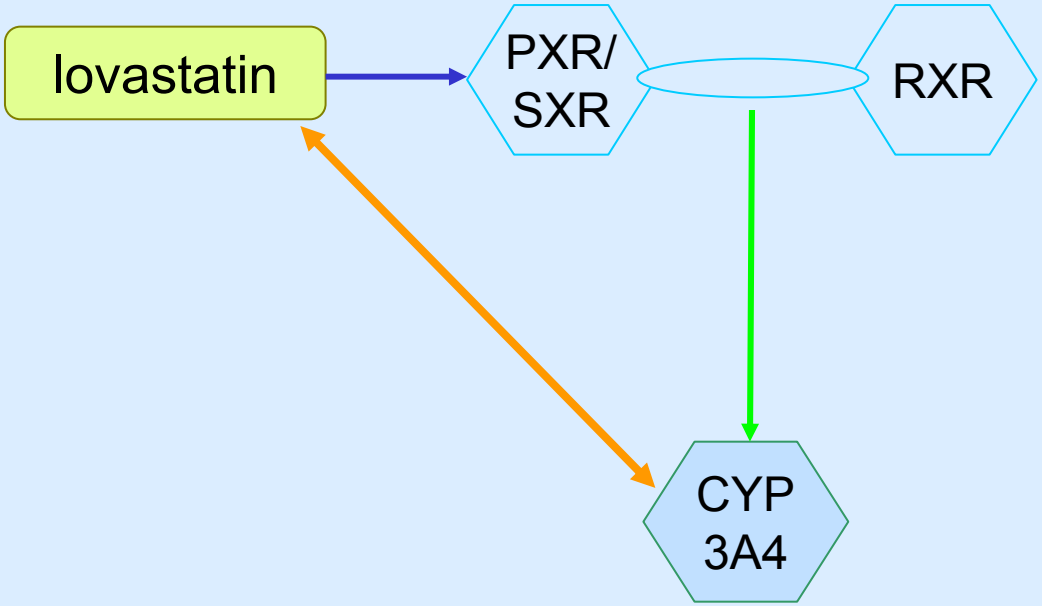
Transcription

Endocrine disruption

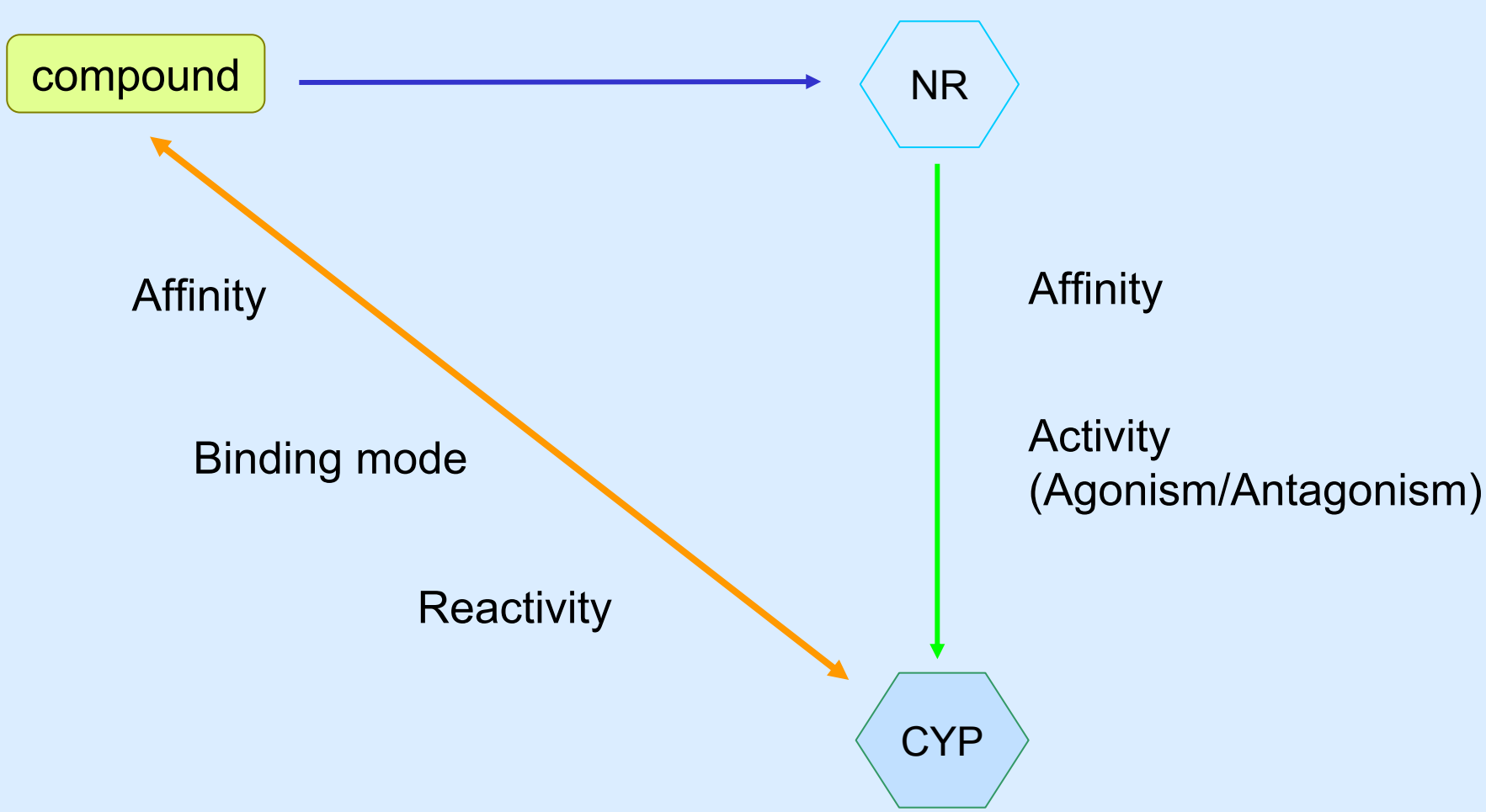


NR & P450

NR induce CYP genes



Specific factors



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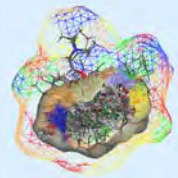
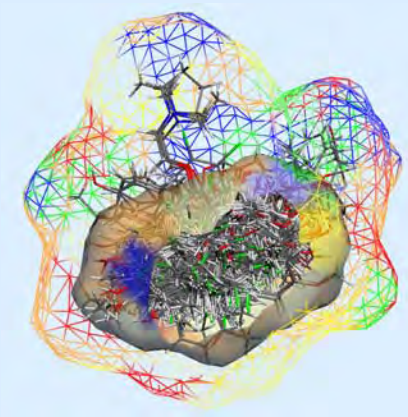


Overview



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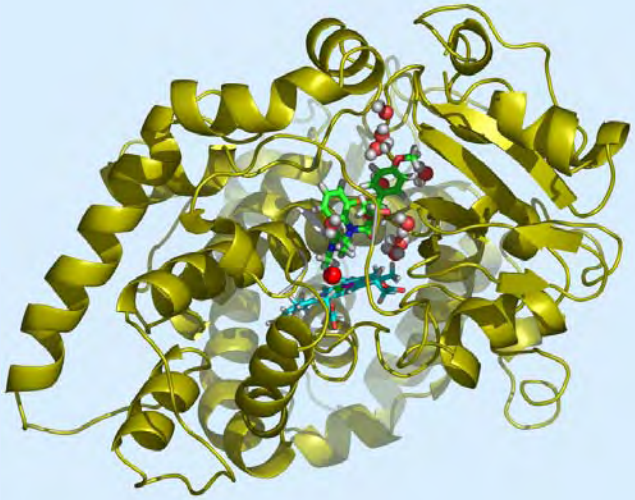
Current directions



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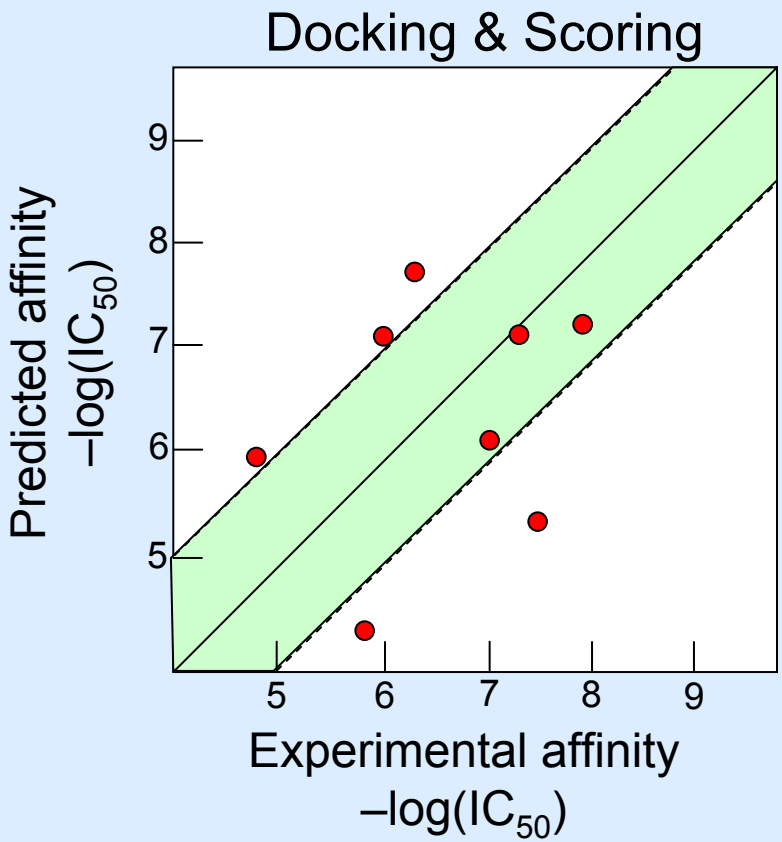
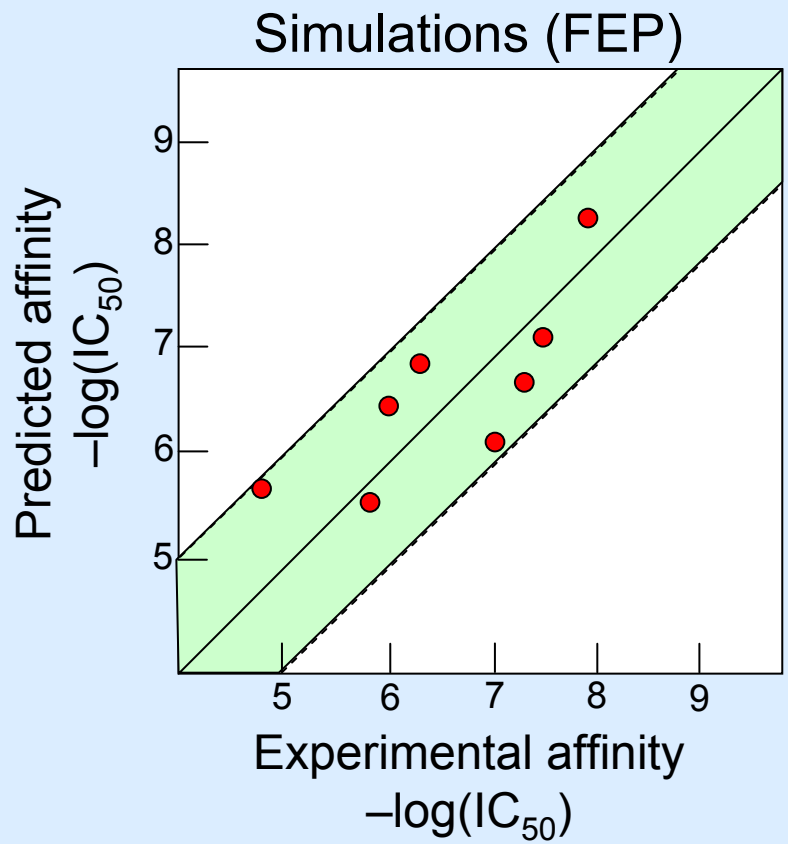
Prediction of binding affinities

BIG challenge: Predict binding affinities in reasonable amount of time

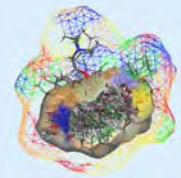




~1min

Computing time

1day - 1week



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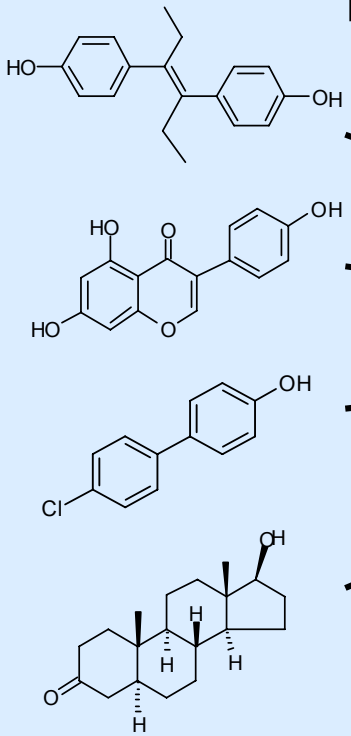
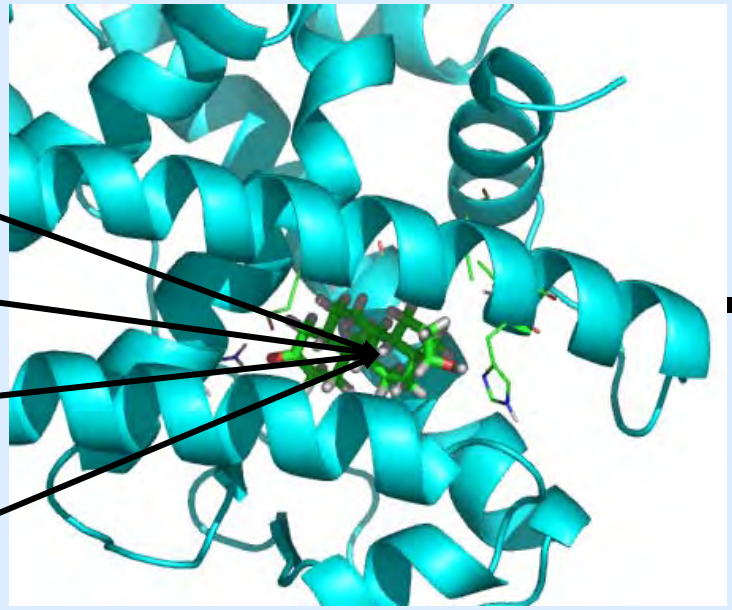
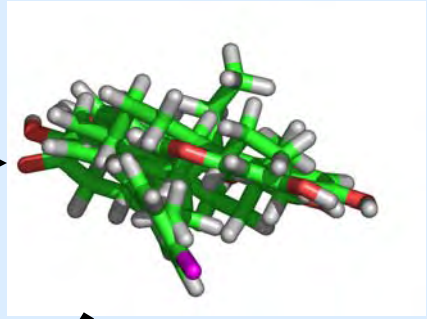
Quantification of binding affinities

Docking

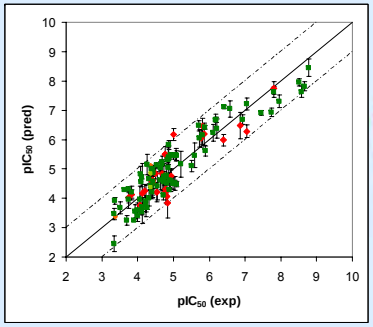


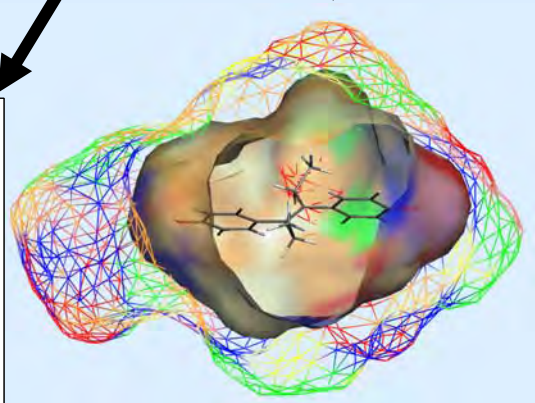


Binding modes



Protein modeling based on QSAR





Quantification

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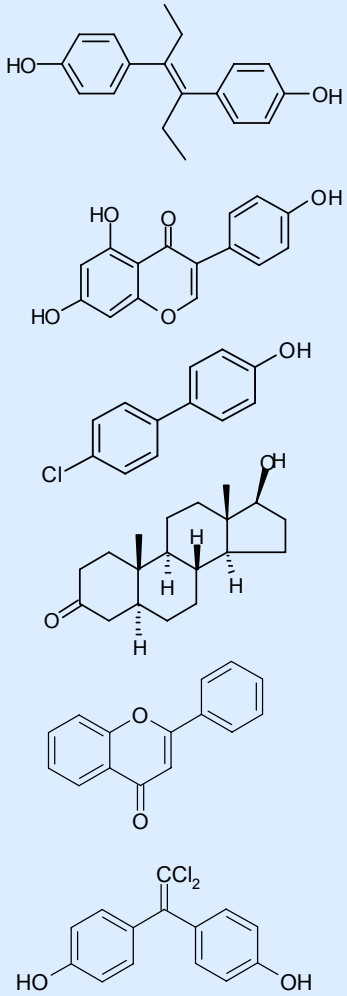
QSAR

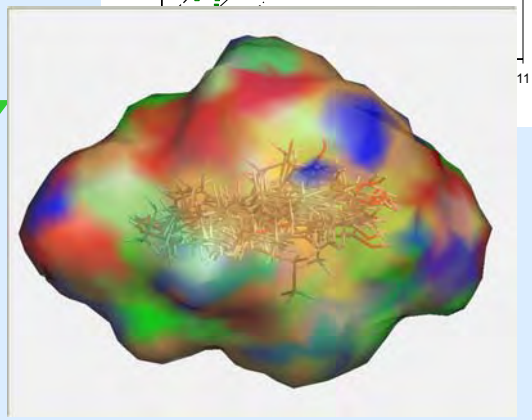


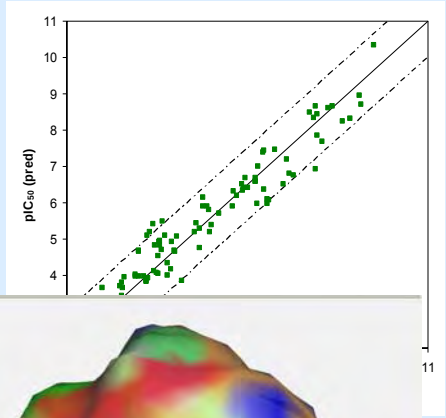
Training set

Test set

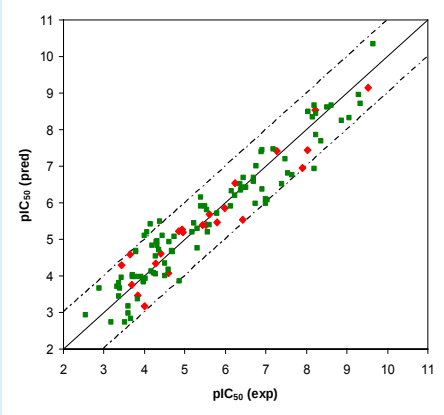
Alignment

Optimize model





Predict affinities



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Quantification of binding affinities

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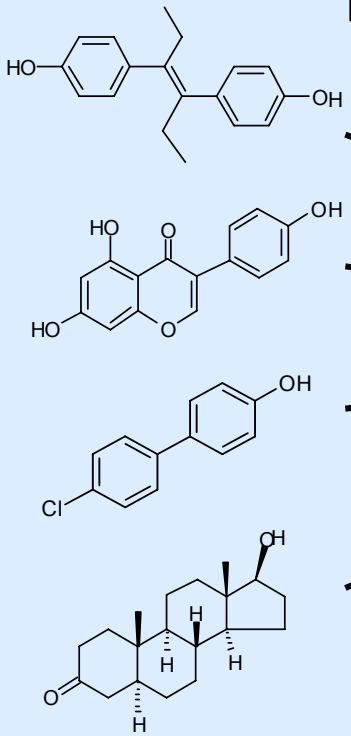
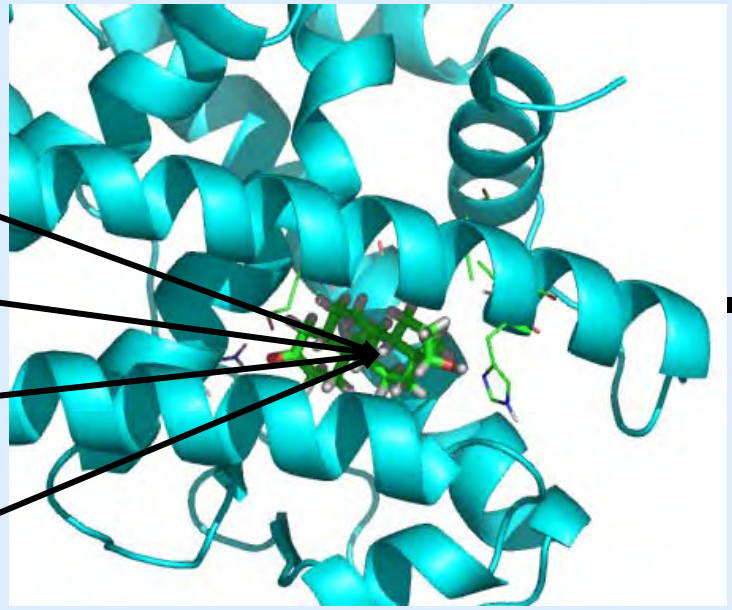
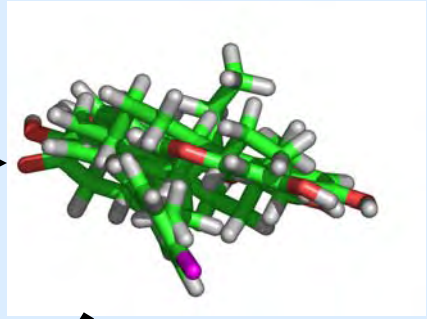




Binding modes



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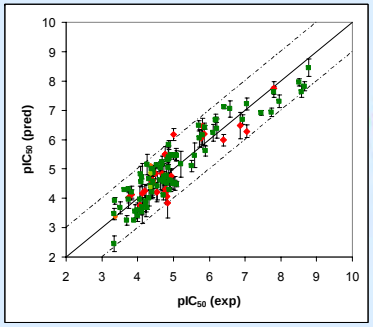

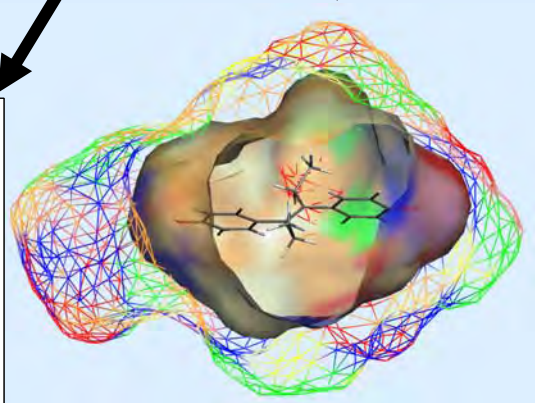

Quantification

Issues:
- No unique docking solution

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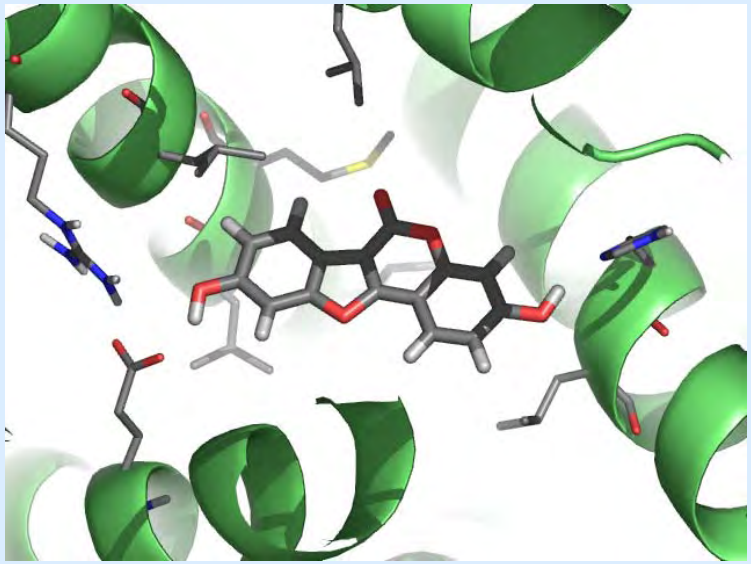
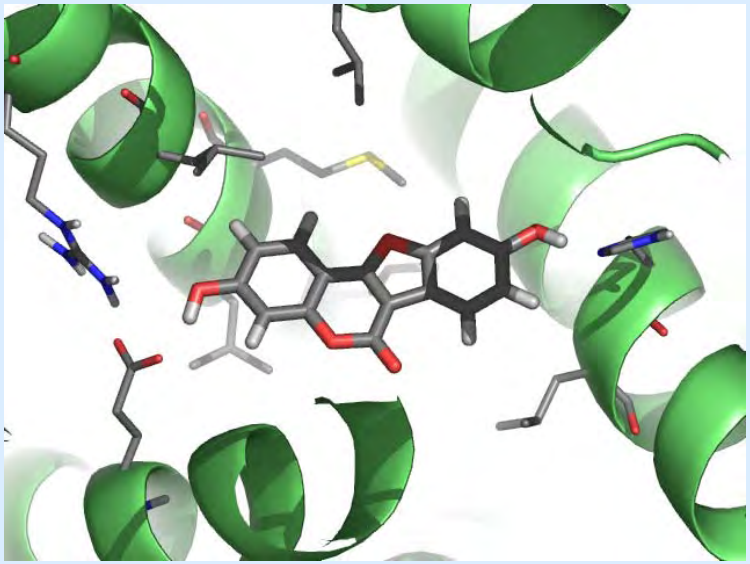
Bioactive conformation

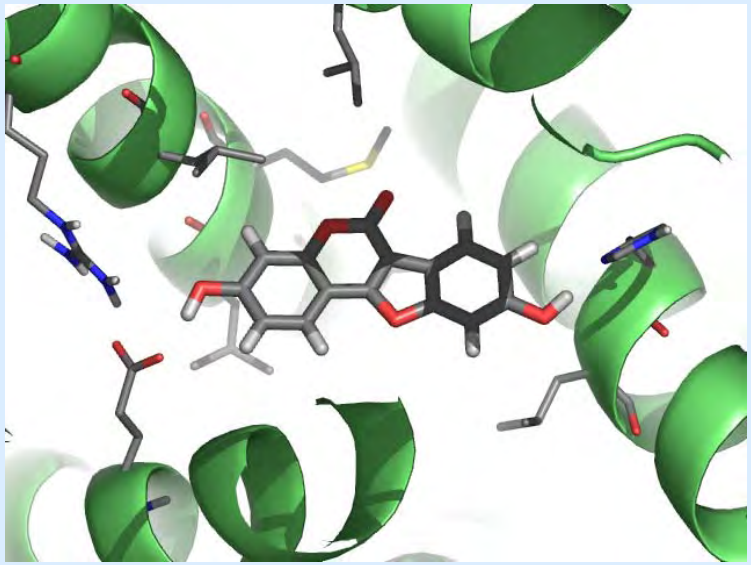


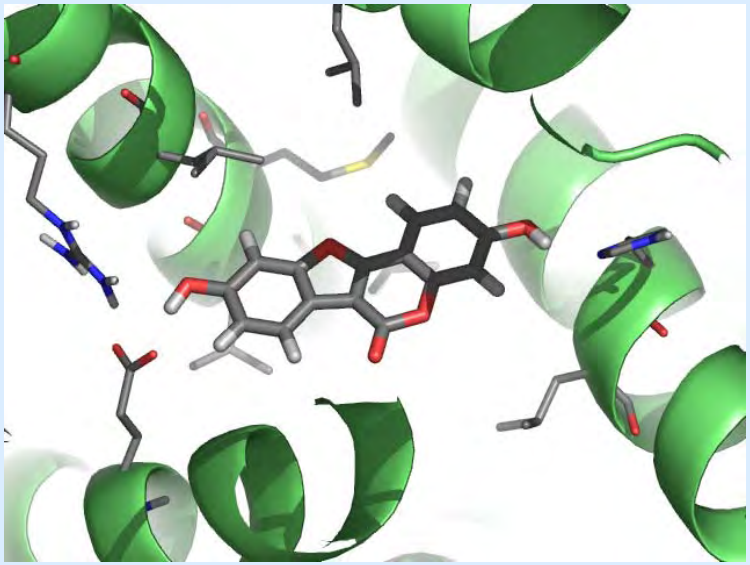
Coumestrol

binding to the

estrogen receptor







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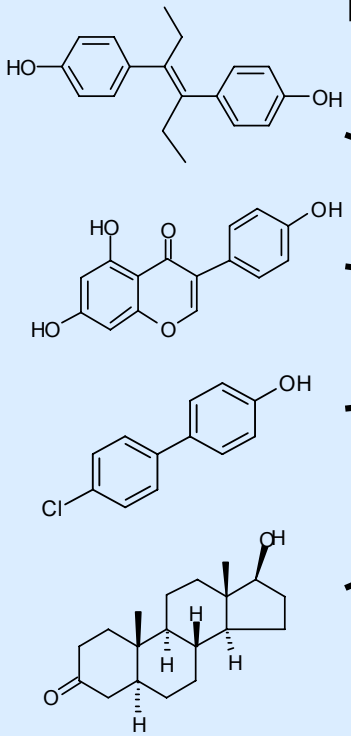
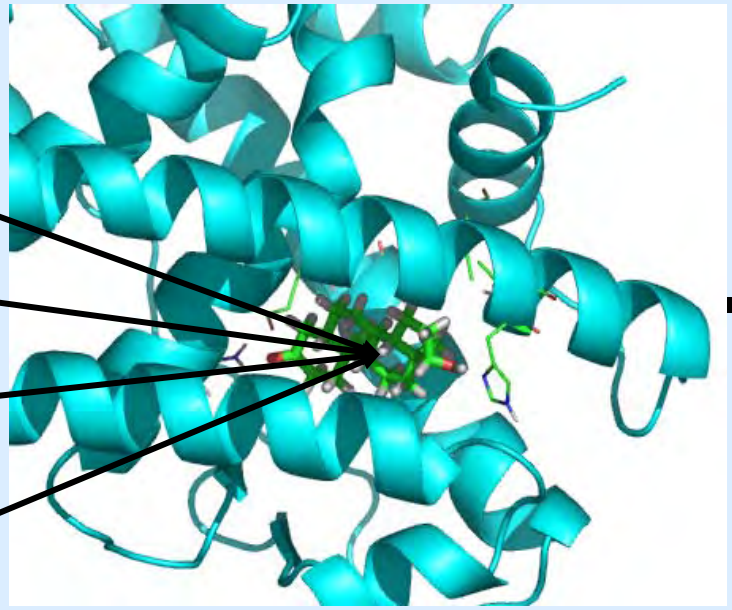
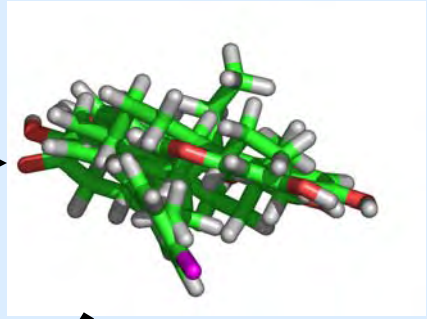
Quantification of binding affinities

Docking





Binding modes



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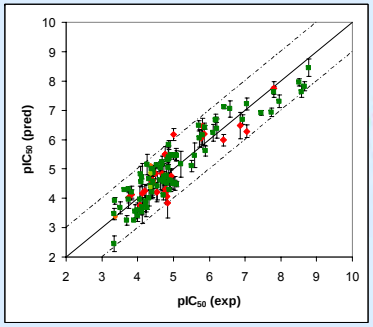
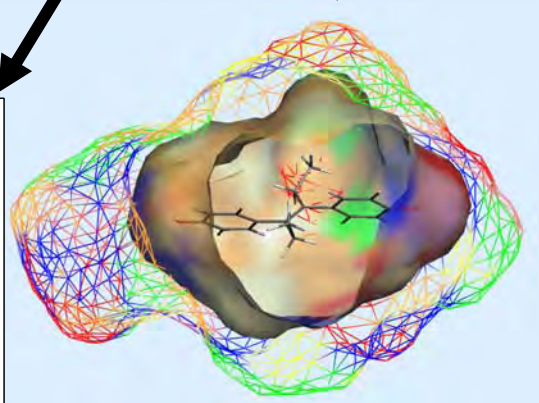
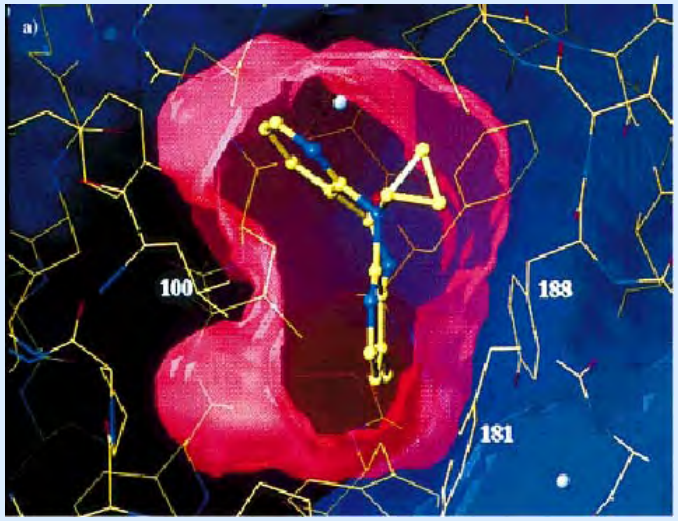




Quantification

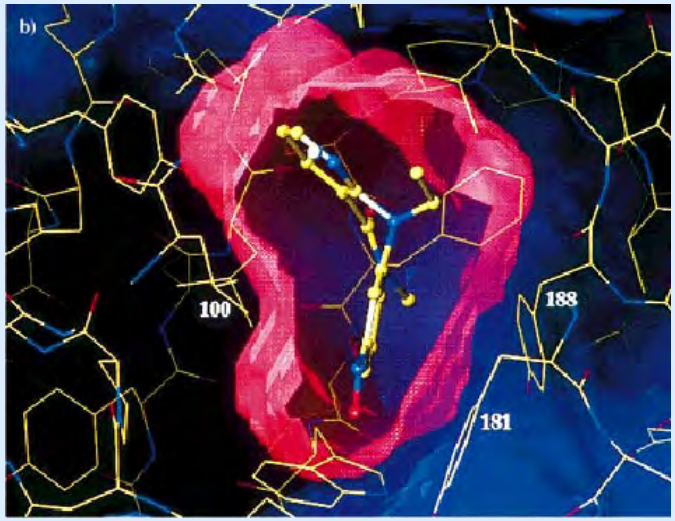
Issues:
- No unique docking solution
- Induced protein fit

Induced fit

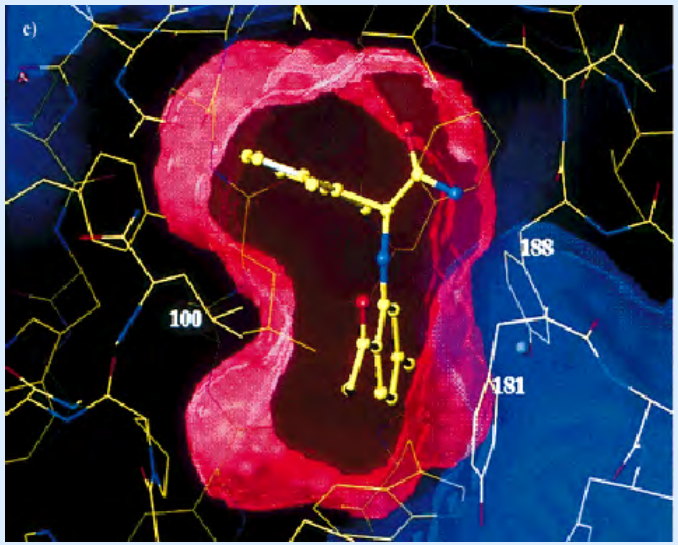


HIV-1 RT with

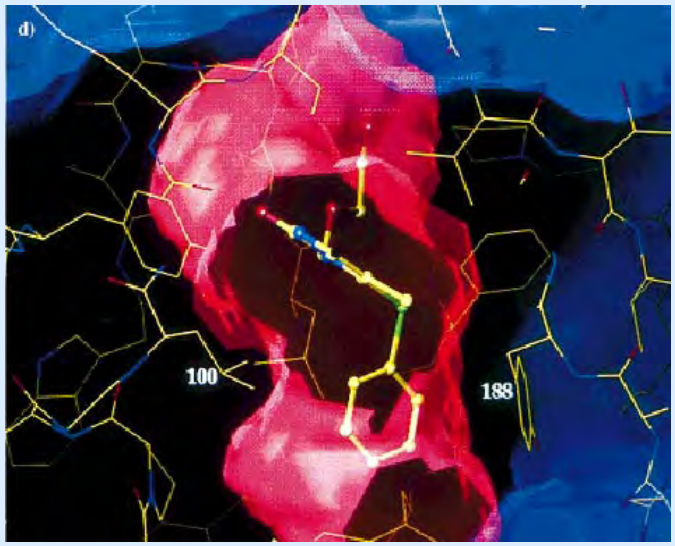
nevirapine



1051U91



AAP



HEPT

Davis, A.M.; Teague, S.J. *Angew. Chem. Int. Ed.* **1999**, *38*, 736-749.

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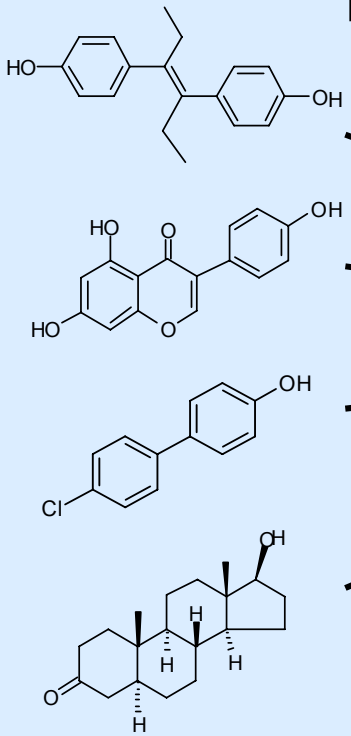
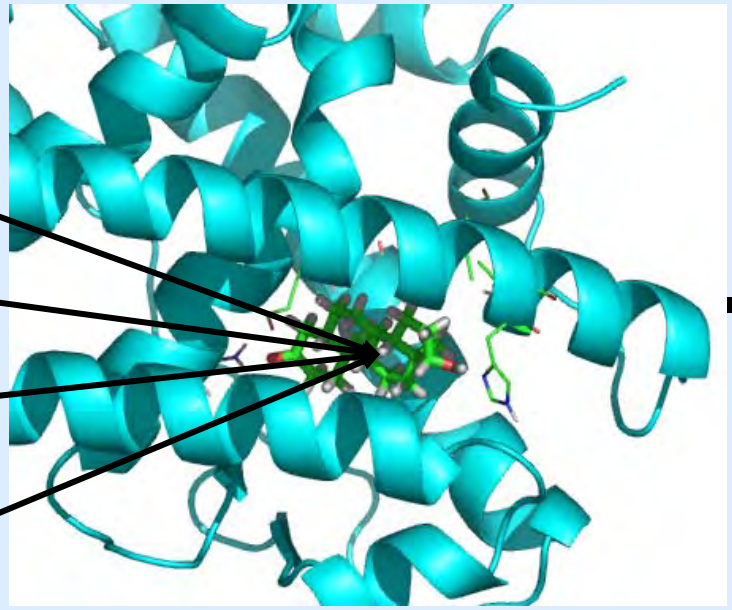
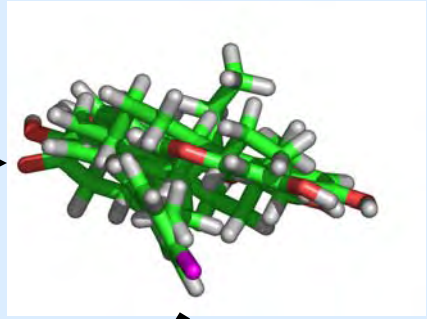
Quantification of binding affinities

Docking

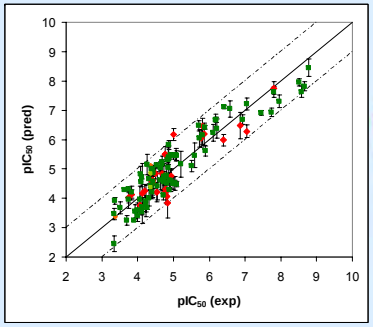


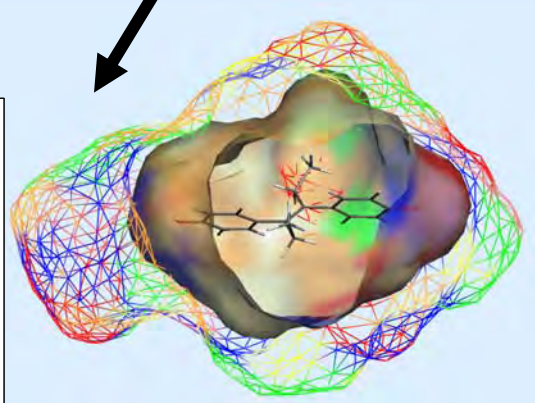


Binding modes



QSAR

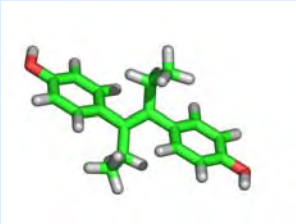


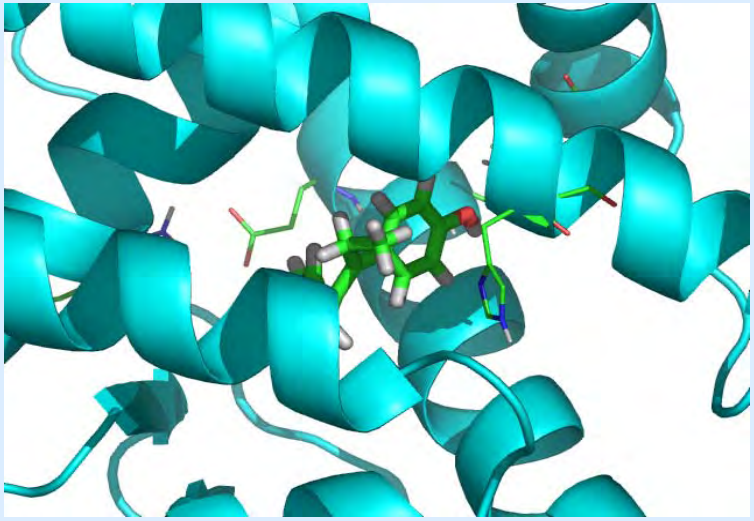


Quantification

Issues:
- No unique docking solution
- Induced protein fit

Flexible docking





1. Autodock ligand to binding site
2. Monte Carlo search (flexible minimization & dynamic solvation)
3. Identify new binding mode

N best solutions → 4D data set

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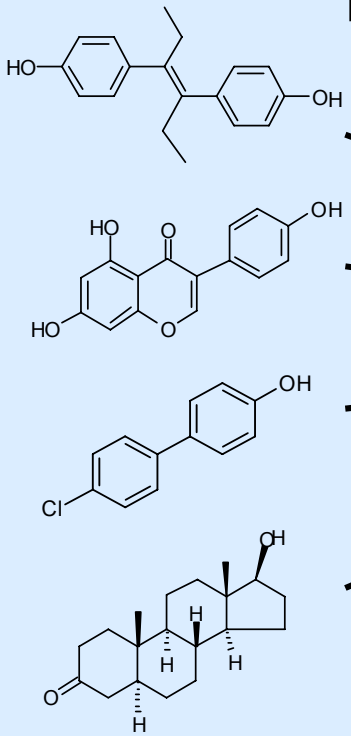
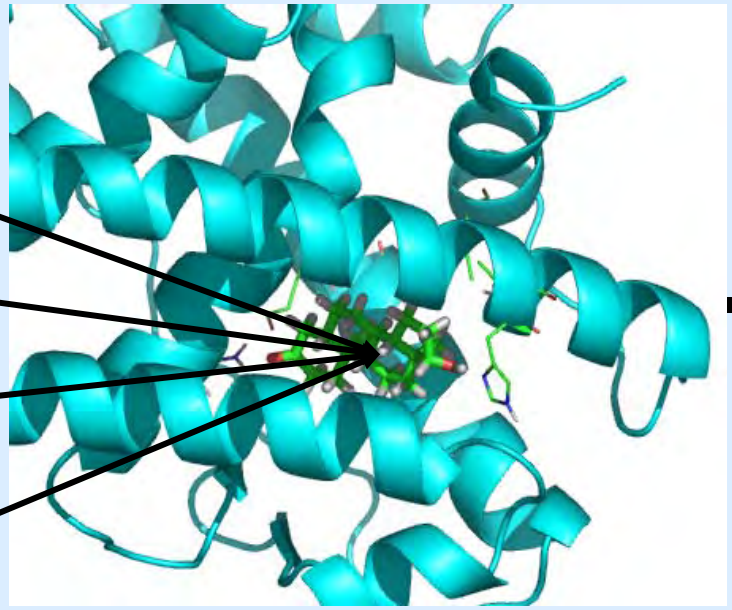
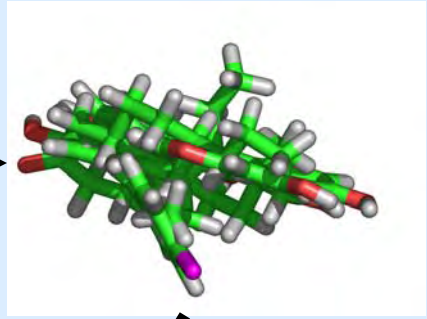
Quantification of binding affinities

Docking

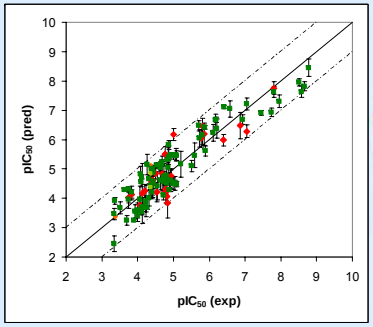


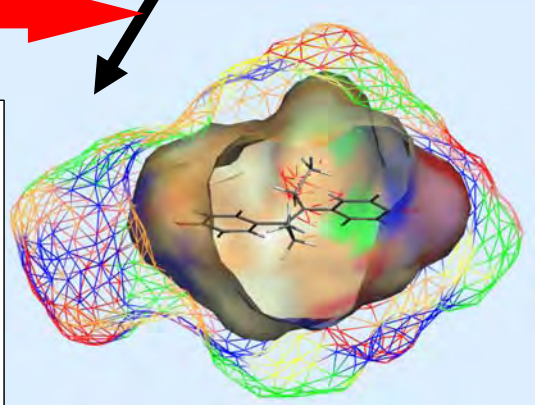


Binding modes



QSAR





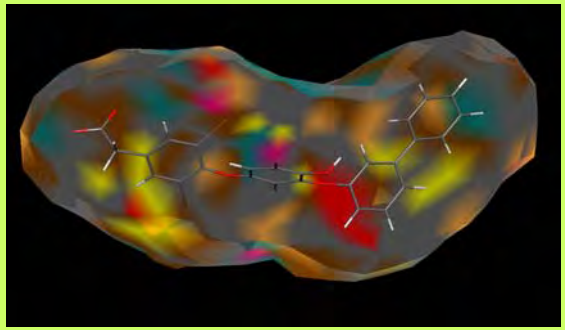
Quantification

Issues:
- No unique docking solution
- Induced protein fit

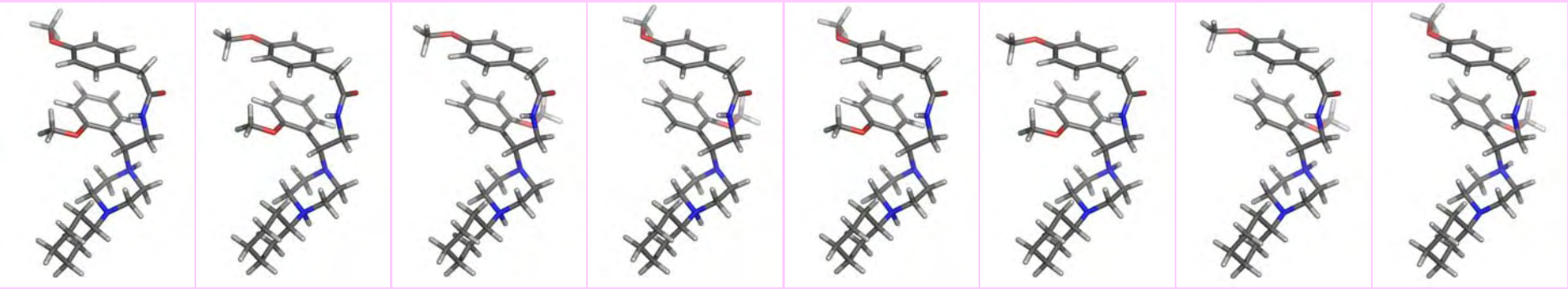
Quasar

3D-QSAR: Simulation based on 3D structures

5D-QSAR: Ensemble of induced-fit scenarios



4D-QSAR: Representation by an ensemble of conformations

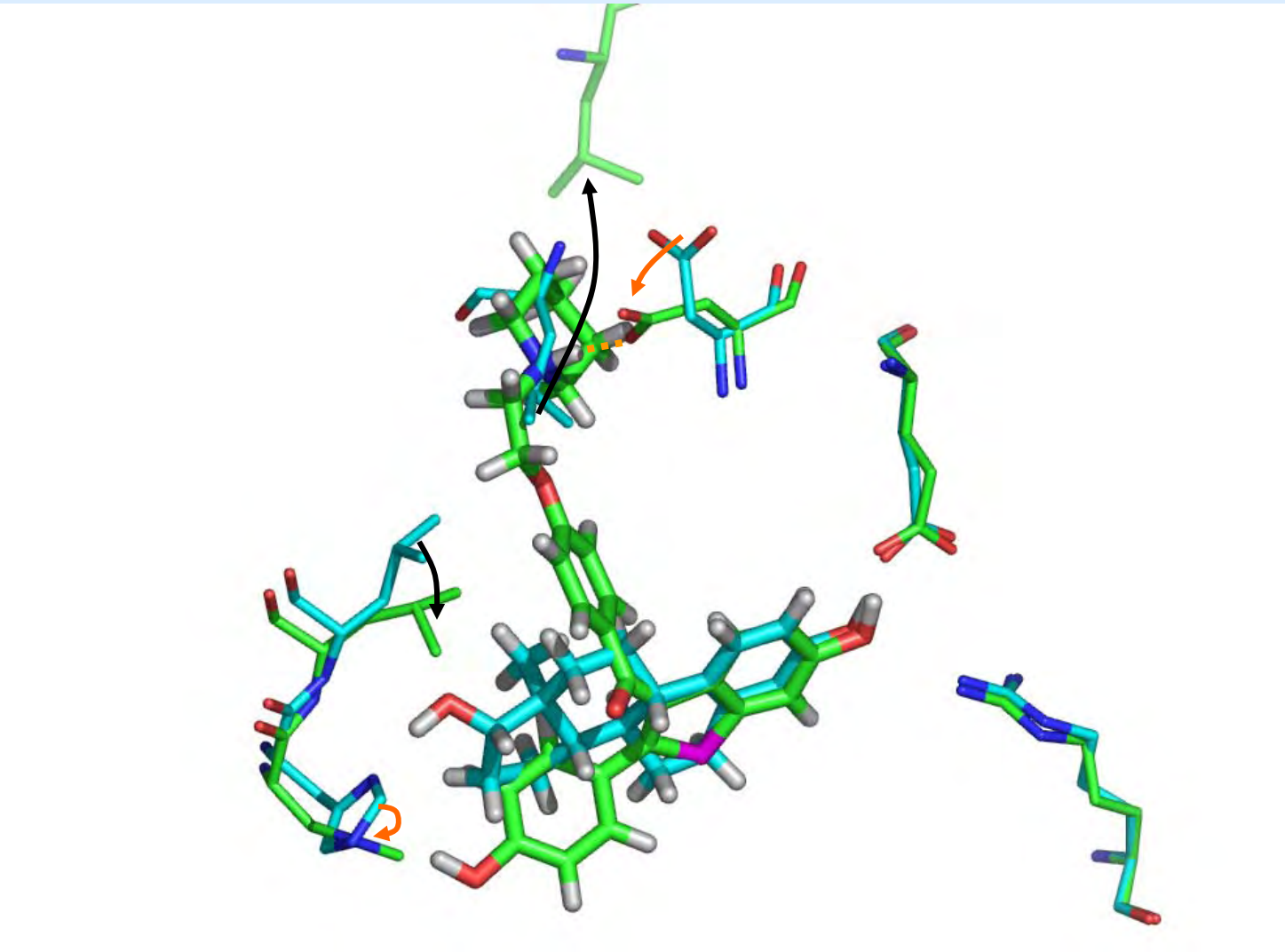


Scoring function based on a directional force field and explicit desolvation: $\Delta G = \Delta E_{\text{force field}} - \Delta G_{\text{solvation}} - T\Delta S - \Delta G_{\text{induced fit}}$

Vedani, A.; Dobler, M.; Lill, M.A. *J. Med. Chem.* **48**, 2005**,** 3700-3703.

Induced fit

Estrogen receptor

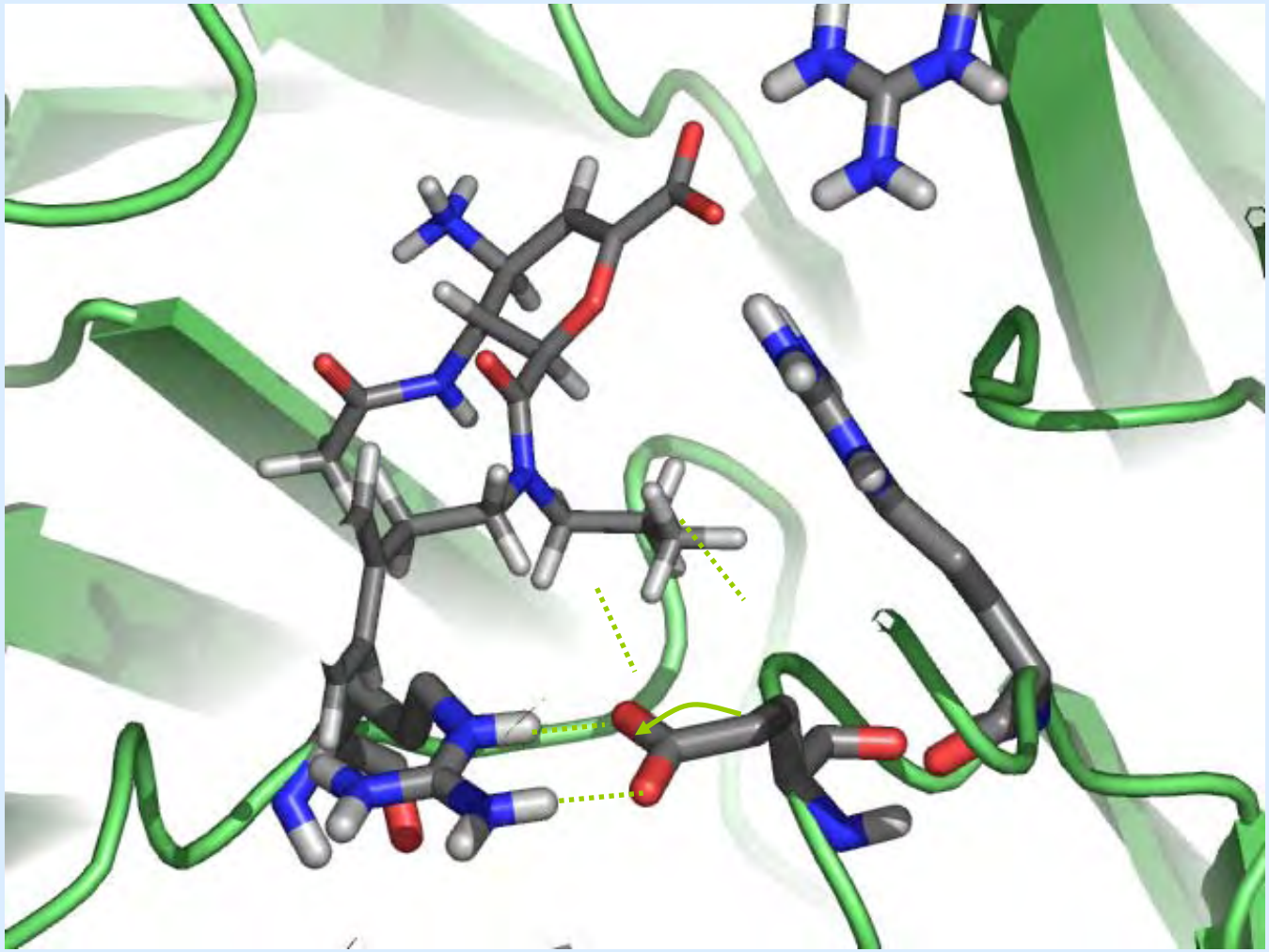


17β-estradiol

Raloxifene

Induced fit

Neuraminidase

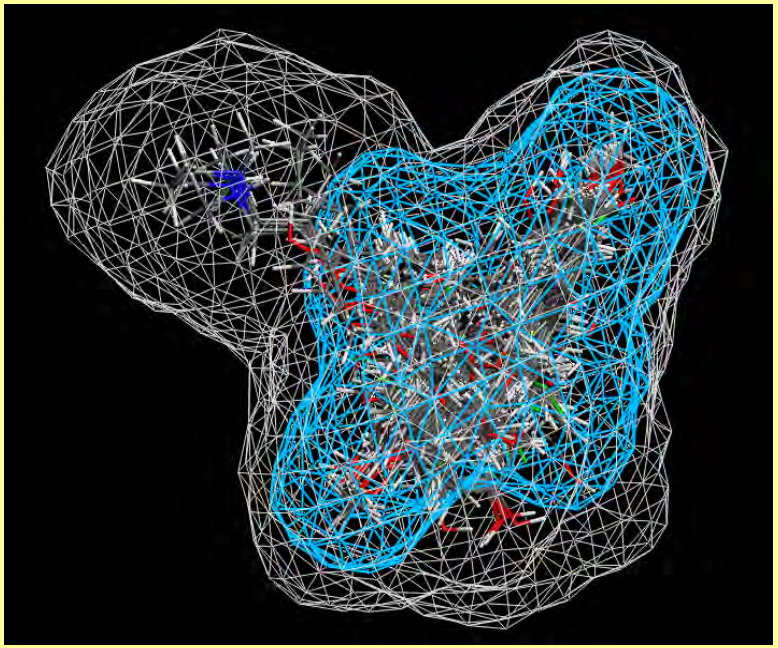


Zanamavir

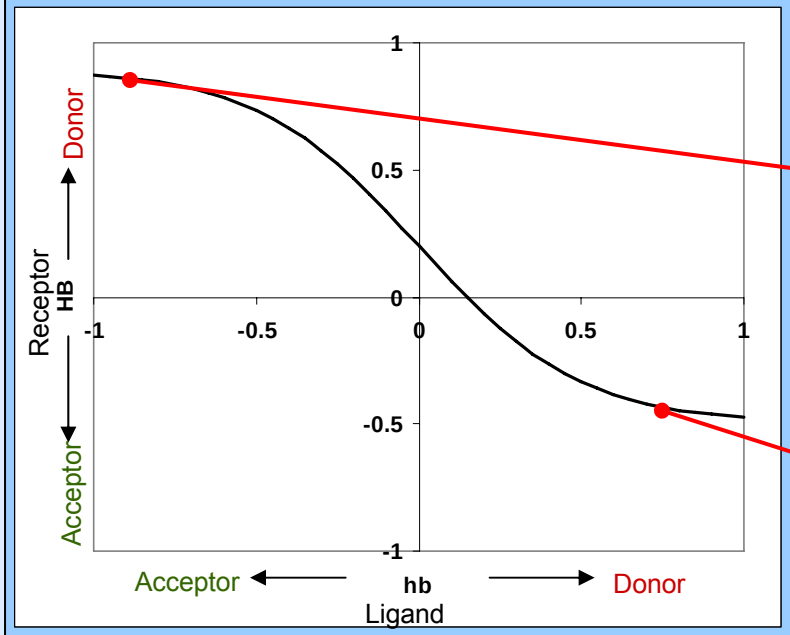
2-dihydropyran-phenethyl-propyl-carboxamide (2-PPC)

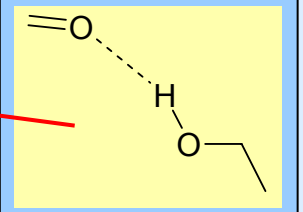
Raptor

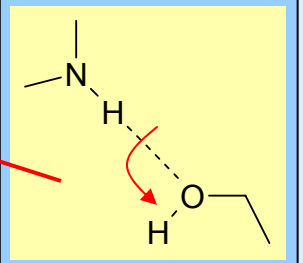
Dual-shell representation



Adaptation due to ligand properties







$$HB_{\alpha} = \left(HBA_{\alpha}^{0} - HBD_{\alpha}^{0}\right) \frac{1}{1+\exp\left(\delta_{hb,\alpha}\left(hb_{\alpha} - \omega_{hb,\alpha}\right)\right)} + HBD_{\alpha}^{0}$$

Lill, M.A.; Vedani, A.; Dobler, M. *J. Med. Chem.* **2004**, *47*, 6174-6186.

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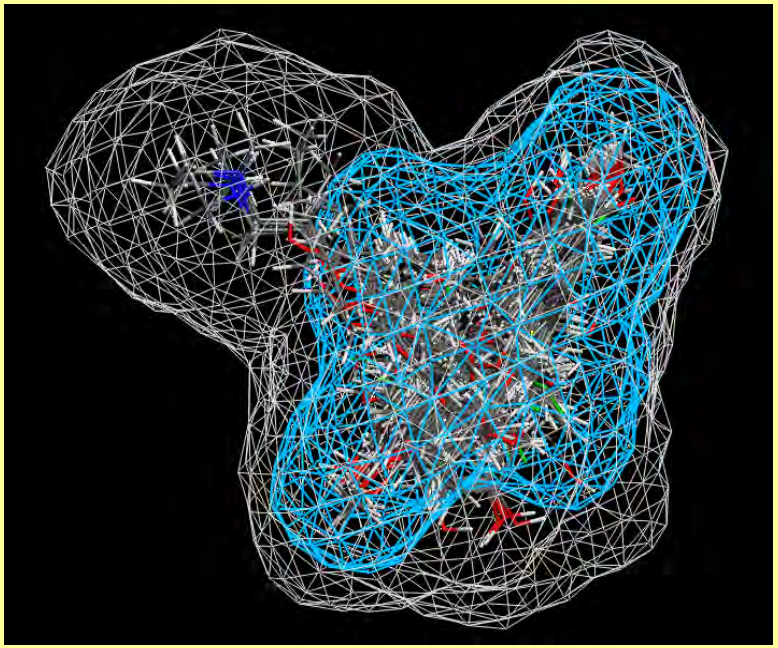
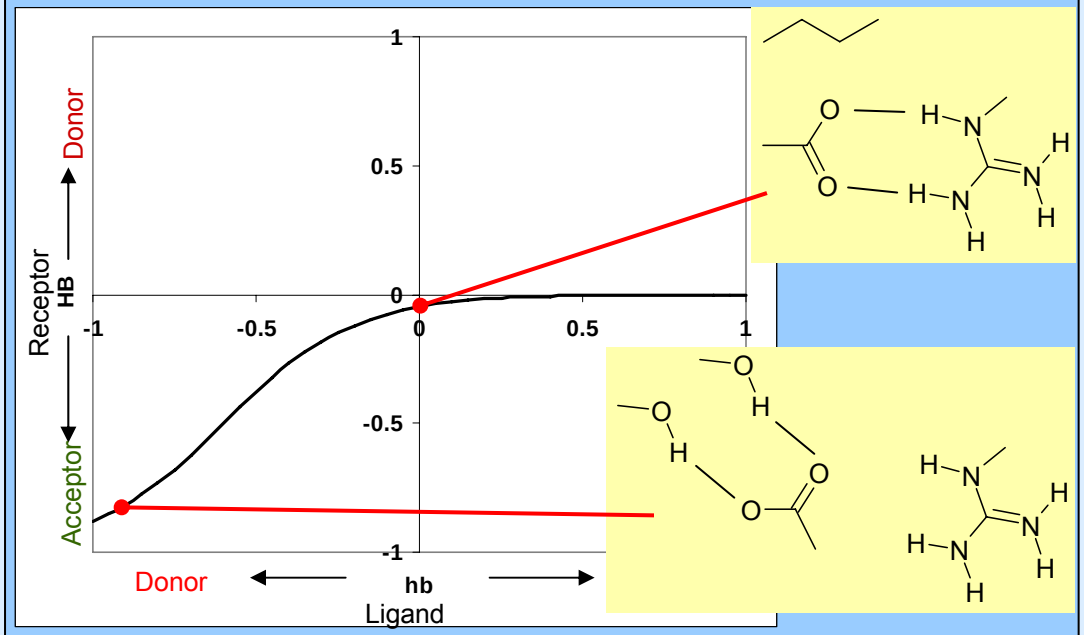
Raptor

Dual-shell representation



Adaptation due to ligand properties



$$HB_\alpha = \left(HBA_\alpha^0 - HBD_\alpha^0\right) \frac{1}{1+\exp\left(\delta_{hb,\alpha}\left(hb_\alpha - \omega_{hb,\alpha}\right)\right)} + HBD_\alpha^0$$

Scoring function based on hydrophobicity and hydrogen bonding

$$\Delta G = \Delta G_{\text{const}} + \Delta G_{\text{HPhob}} + \Delta G_{\text{HBond}} - \Delta G_{\text{induced fit}} - T\Delta S$$

Lill, M.A.; Vedani, A.; Dobler, M. *J. Med. Chem.* **2004**, *47*, 6174-6186.

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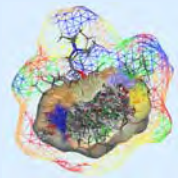
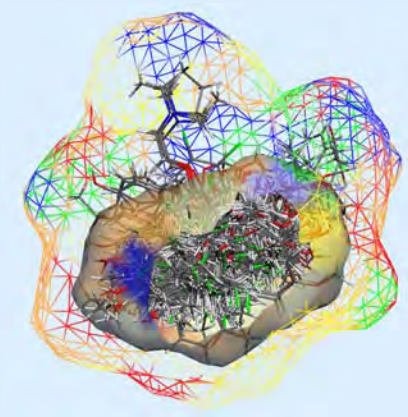


Overview

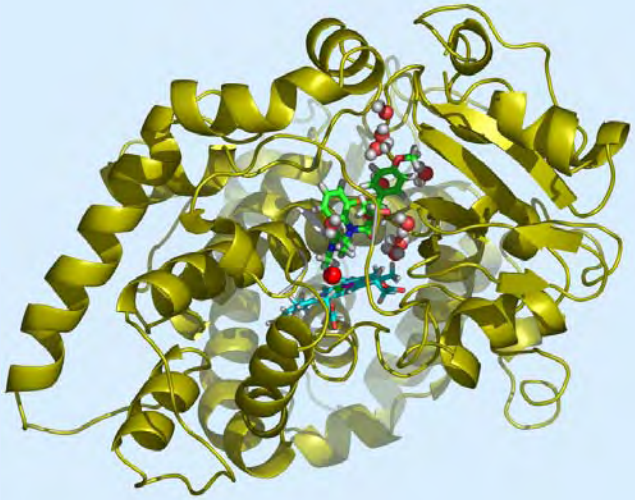


Introduction

Methodology

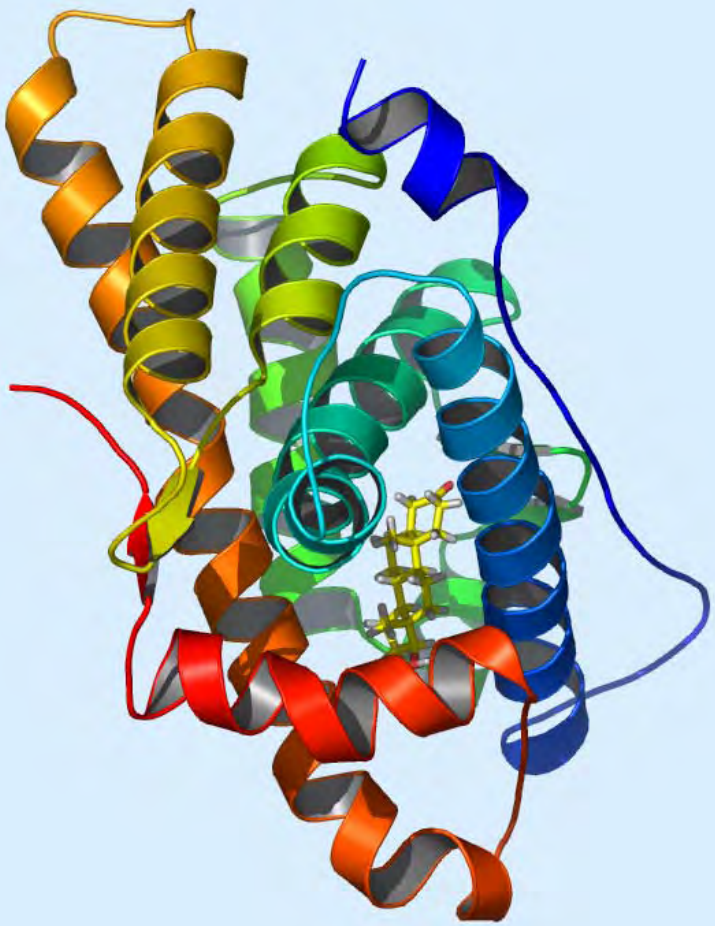
Applications

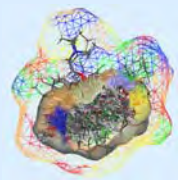
Current directions



Applications

Nuclear receptors
- Estrogen receptors
- Androgen receptor
- Thyroid receptors





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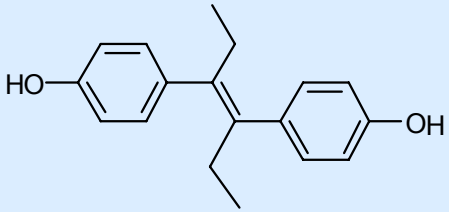
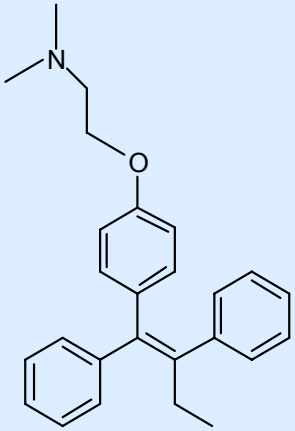
Estrogen receptor

116 substances

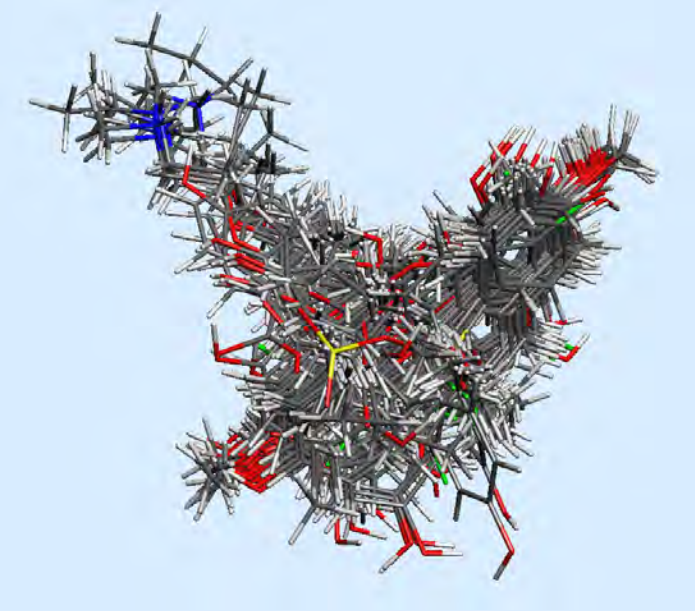
8 substance classes

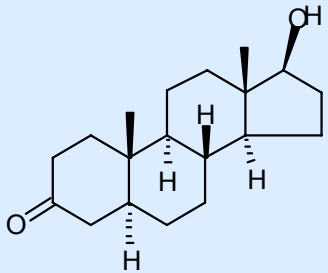


DES and related compounds

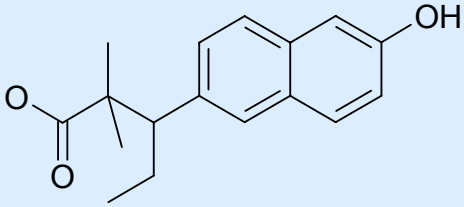


antiestrogens

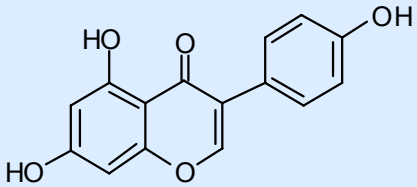




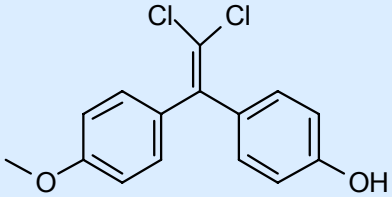
steroids



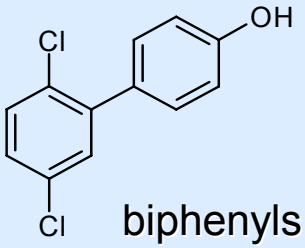
α-α-dimethyl-b-ethyl allenolic acid



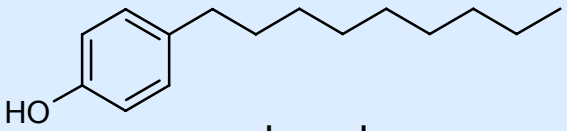
phytoestrogens



diphenylmethanes

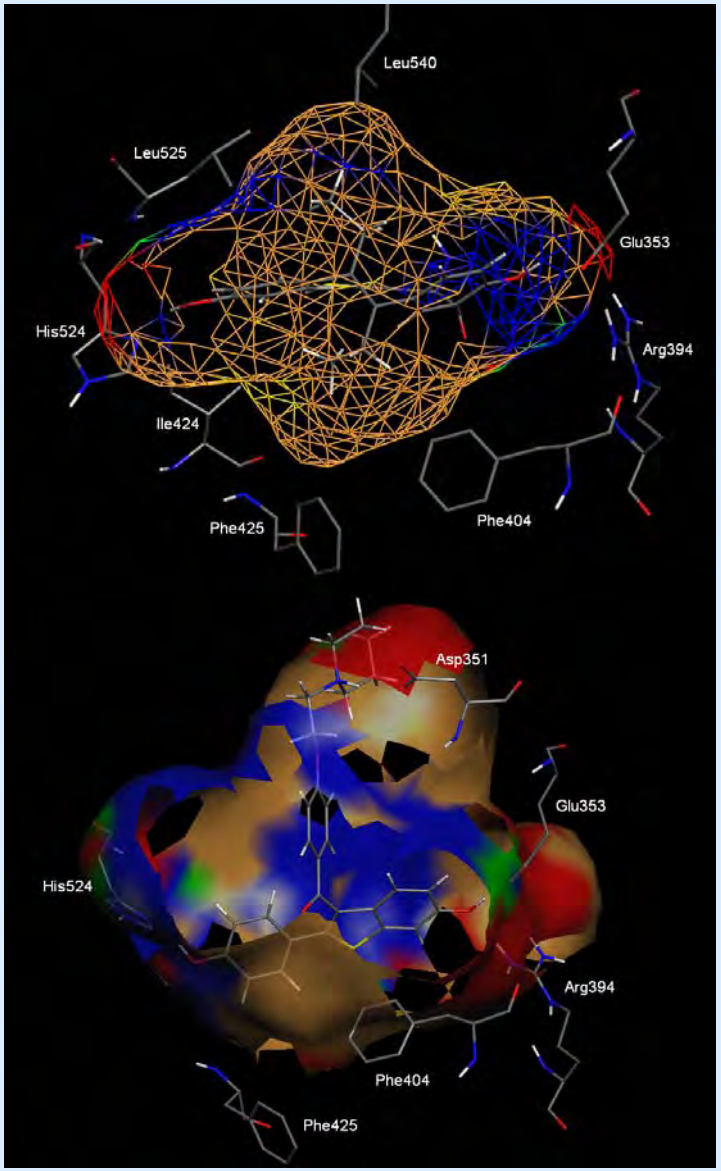


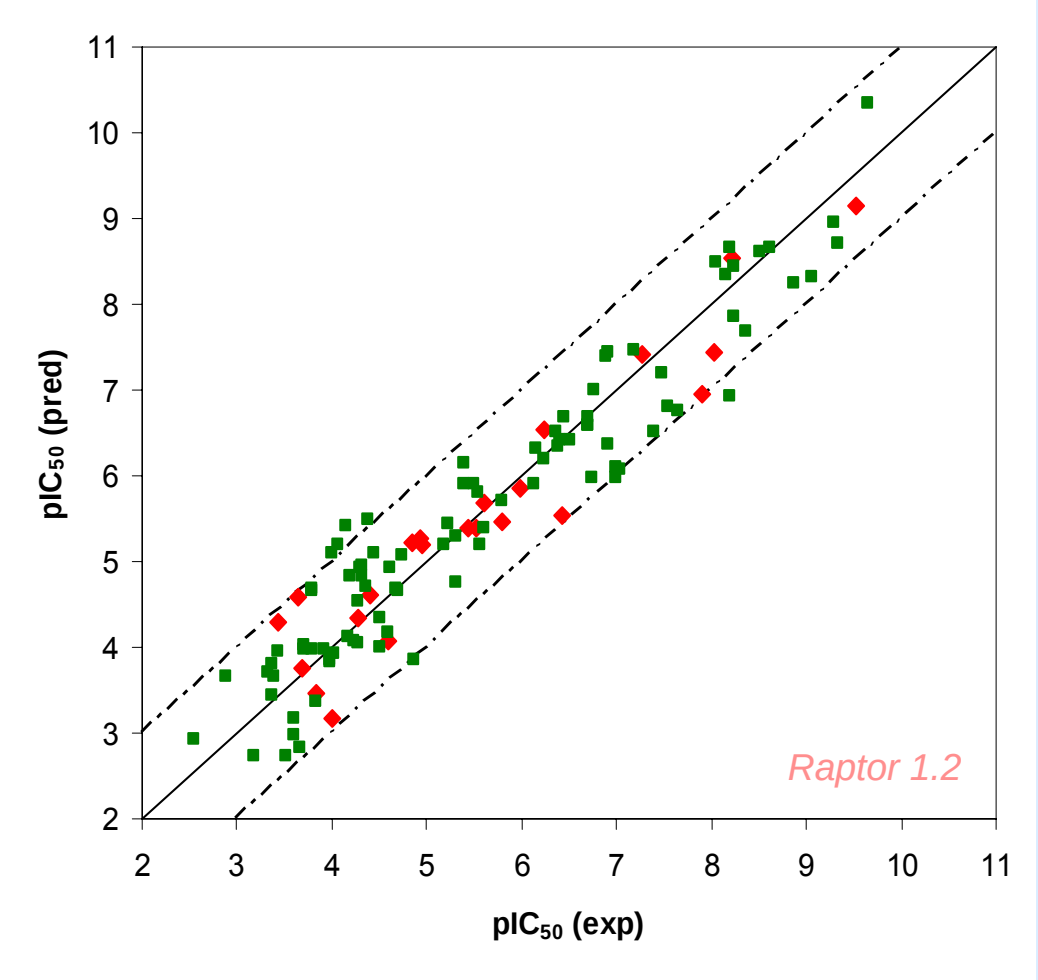
biphenyls



phenols

Estrogen receptor



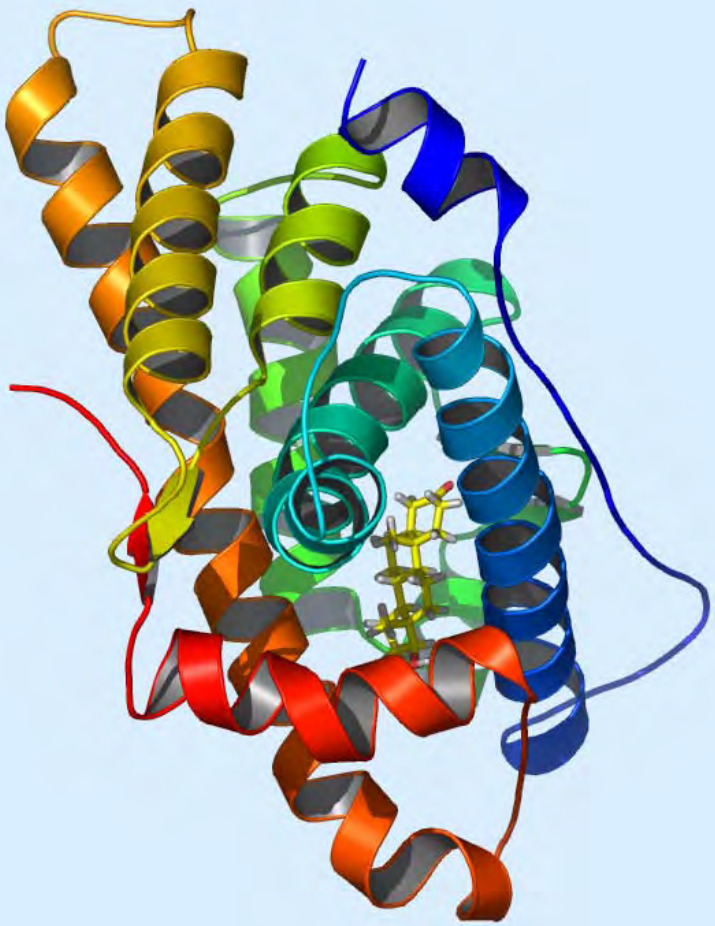


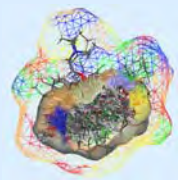
q^2 = 0.908 p^2 = 0.907

Lill, M.A.; Vedani, A.; Dobler, M. *J. Med. Chem.* **2004**, *47*, 6174-6186.

Applications

Nuclear receptors
- Estrogen receptors
- Androgen receptor
- Thyroid receptors





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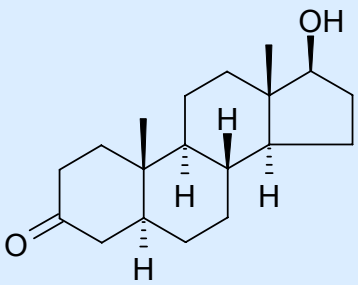
Androgen receptor

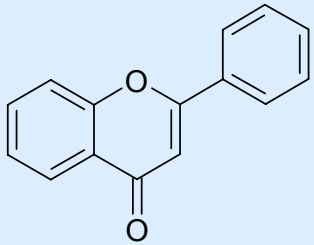
119 compounds

6 substance classes

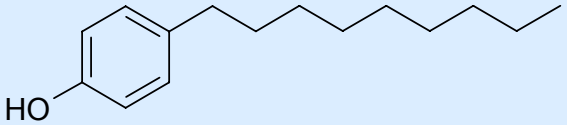
steroids



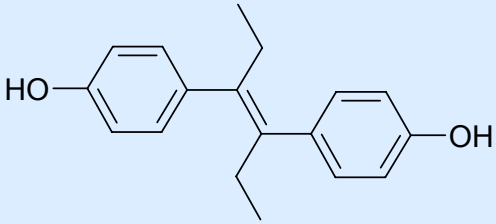
phytoestrogens



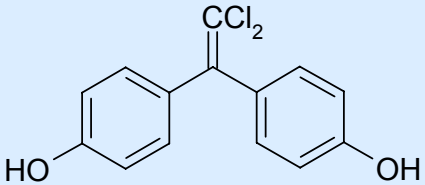
phenols



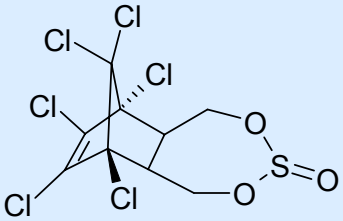
DES and related compounds

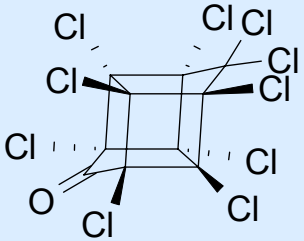


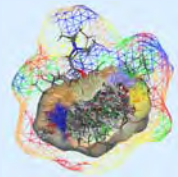
diphenylmethanes



organochlorines







Androgen receptor

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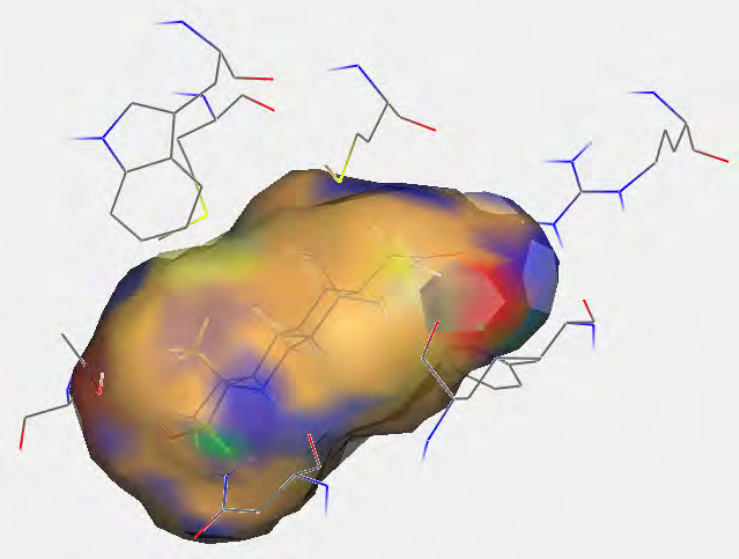
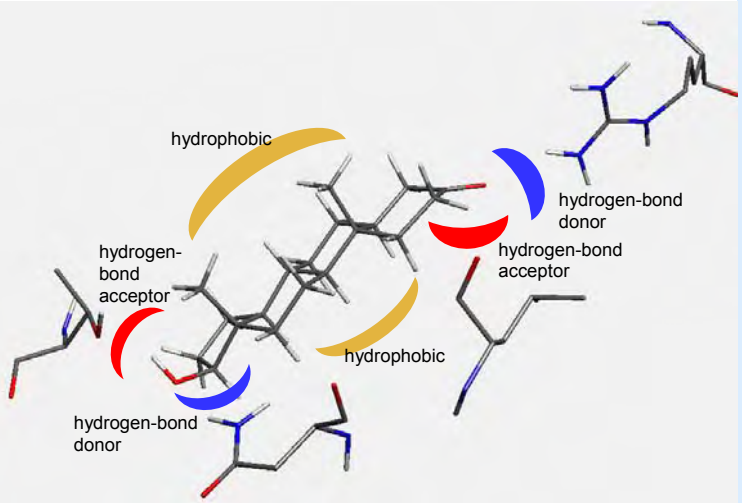
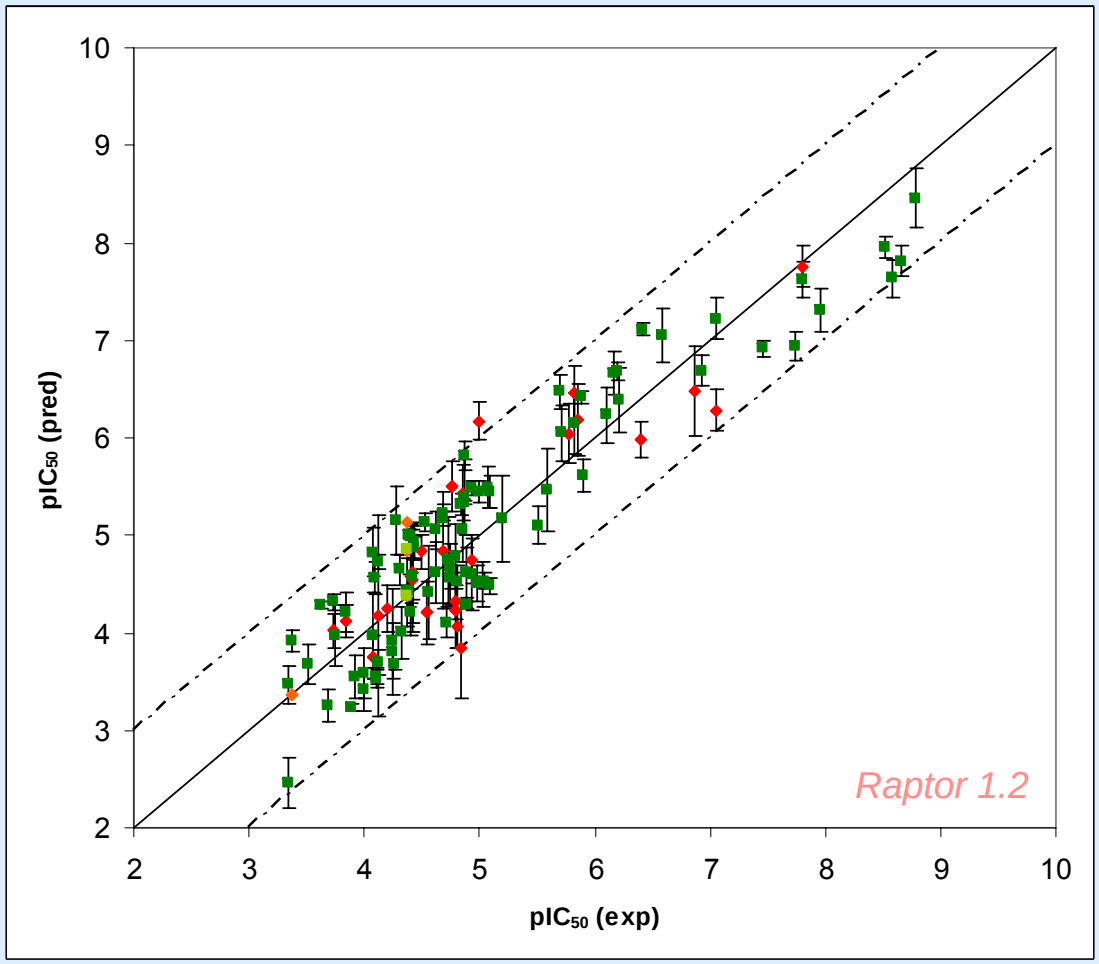
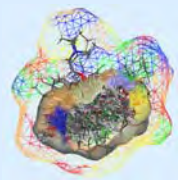






$q^2 = 0.858$ $p^2 = 0.792$

Lill, M.A.; Winiger, F.; Vedani, A.; Ernst, B. *J. Med. Chem.* **2005**, *48*, 5666-5674.



Androgen receptor

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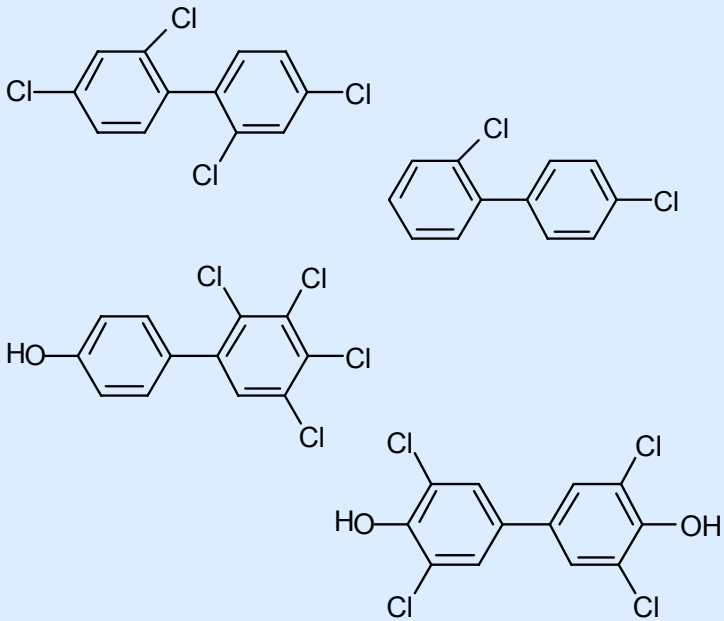
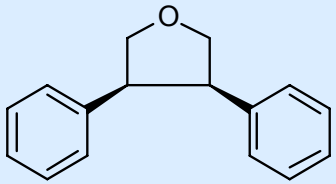
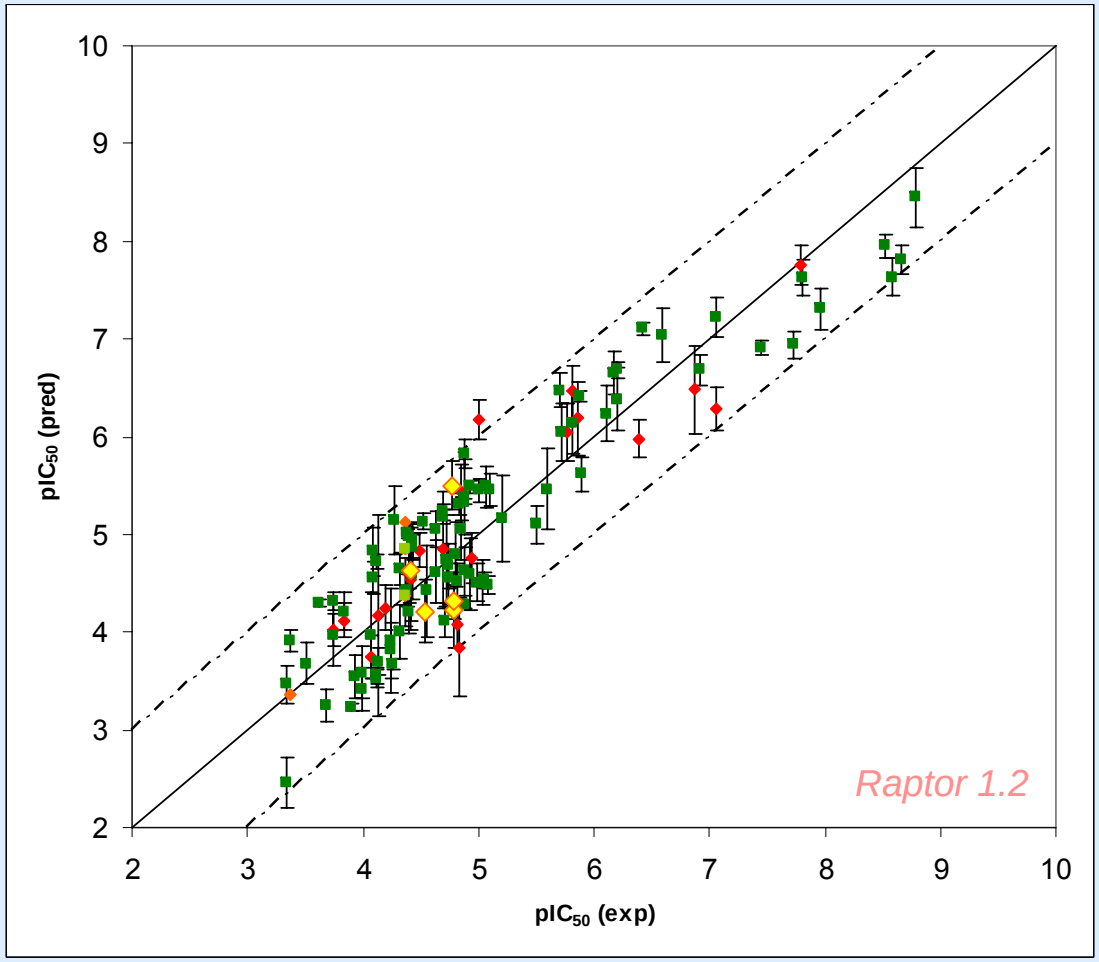
polychlorinated biphenyls



3,4-diphenyltetrahydrofuran

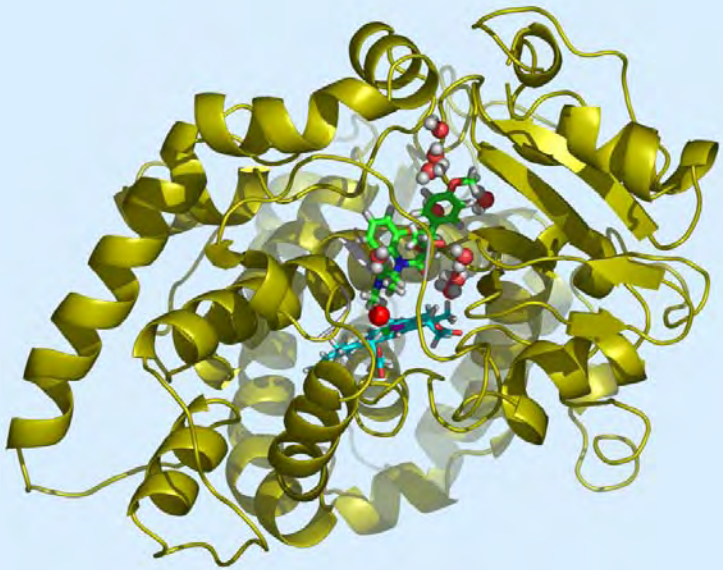


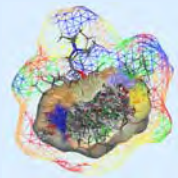


Lill, M.A.; Winiger, F.; Vedani, A.; Ernst, B. *J. Med. Chem.* **2005**, *48*, 5666-5674.

Applications

Cytochrome P450
- CYP 3A4





Cytochrome P450 3A4

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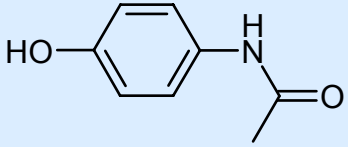

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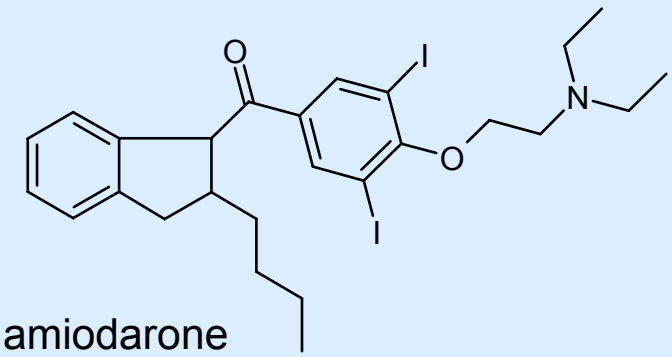
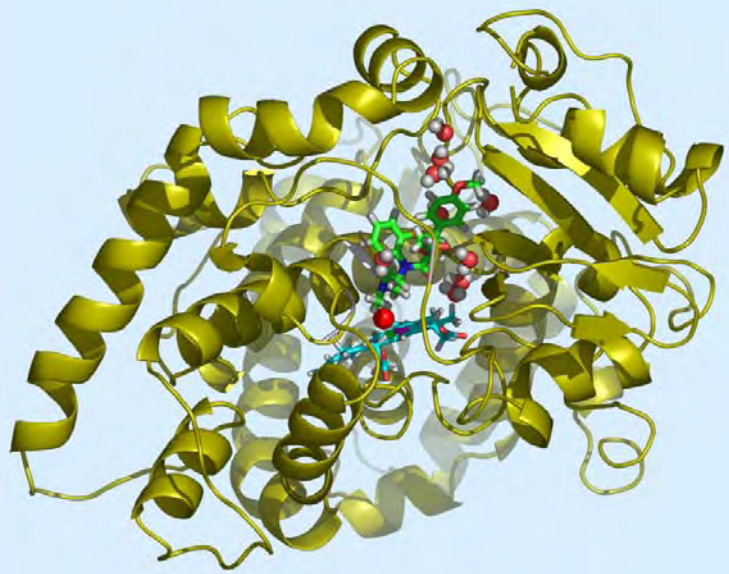
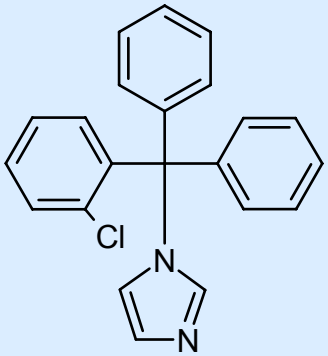
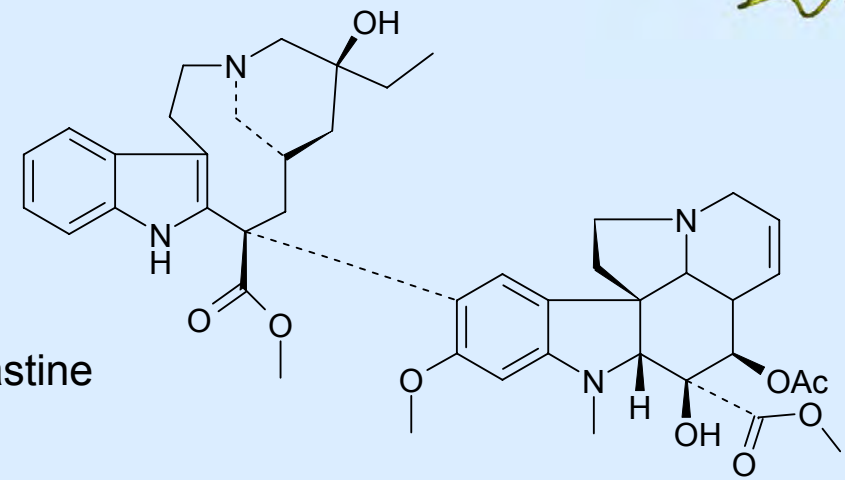


amiodarone

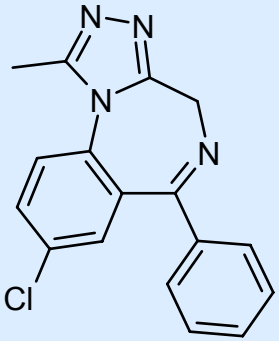




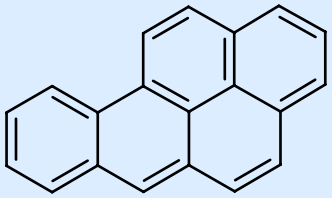
clotrimazole



vinblastine



alprazolam



benzo(a)pyrene

Cytochrome P450 3A4

Automated Docking
- protein & ligand flexibility
- ‘on-the-fly’ solvation

↓

Binding modes

↙ ↘

Metabolites

Quantification of binding affinities using multi-dimensional QSAR

↓

Drug-drug interaction

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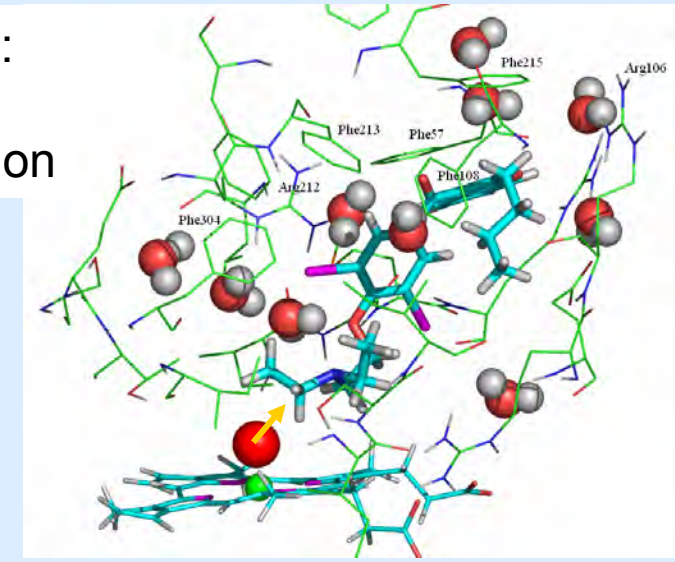
Cytochrome P450 3A4

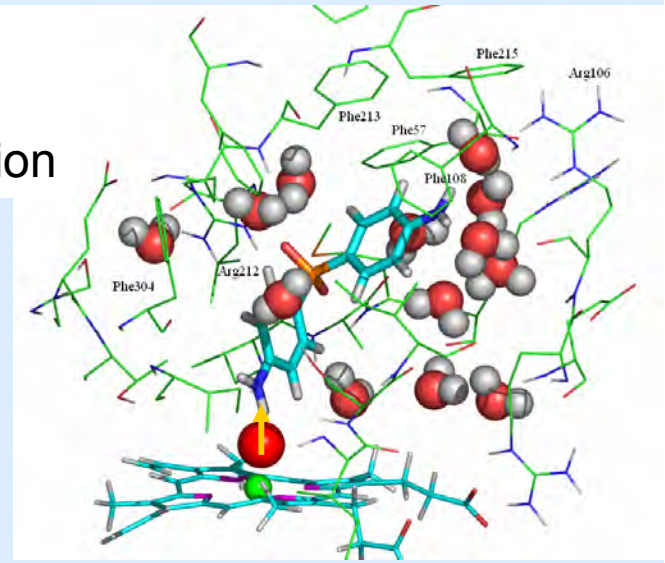
amiodarone:

N-deethylation



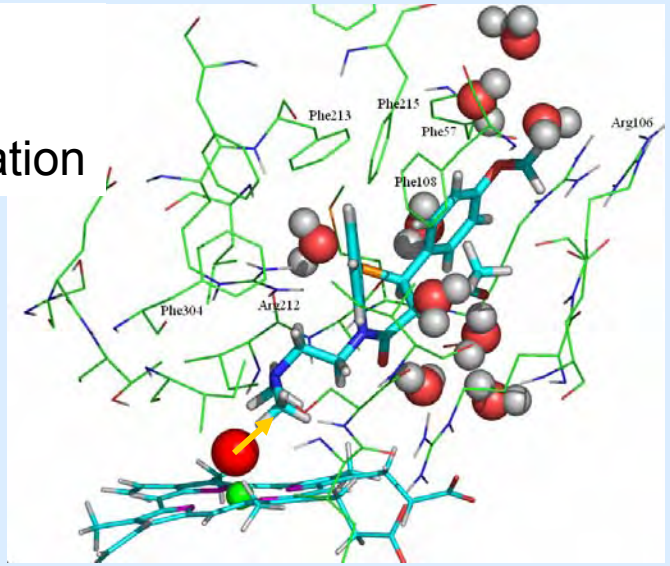
dapsone:

N-hydroxylation



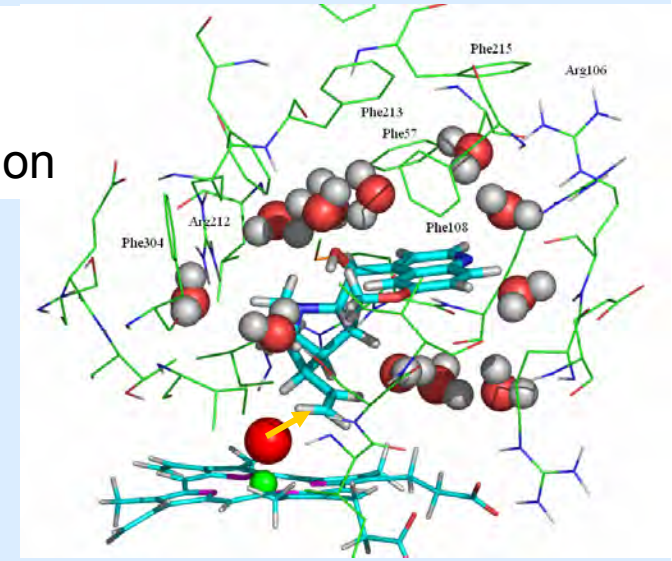
diltiazem:

N-demethylation



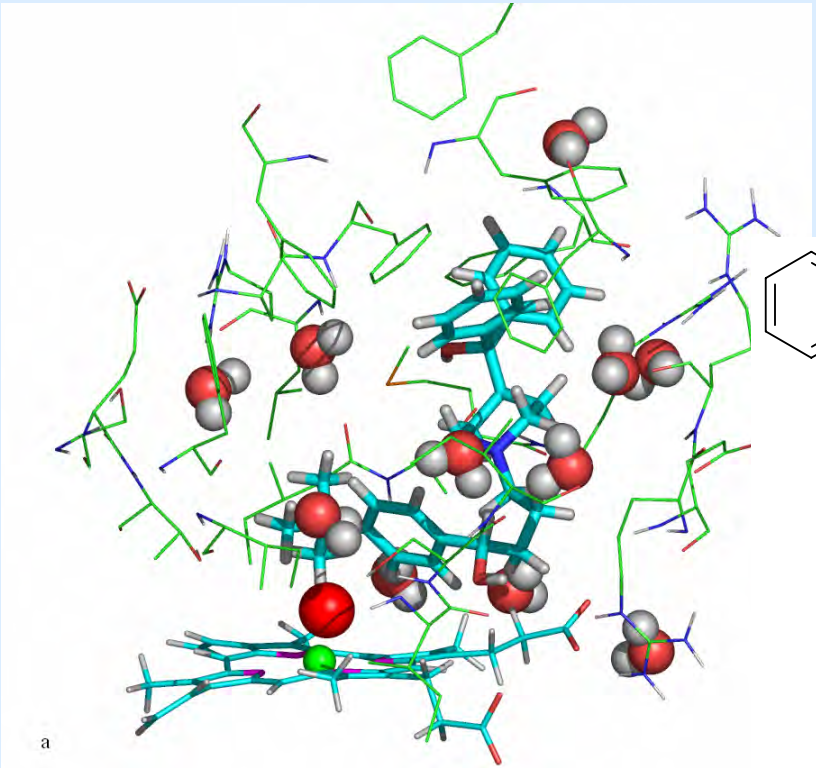
quinine:

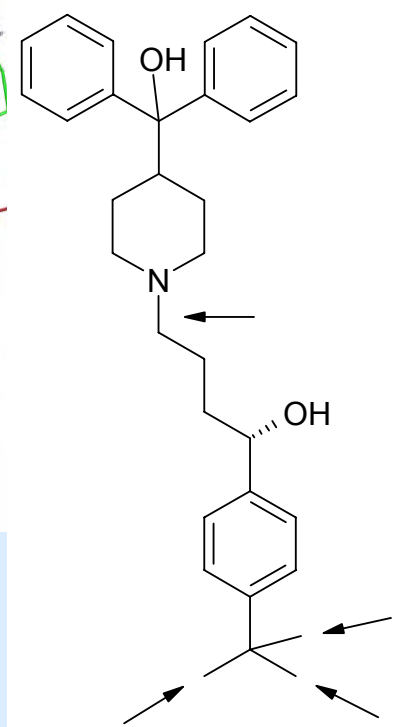
3-hydroxylation

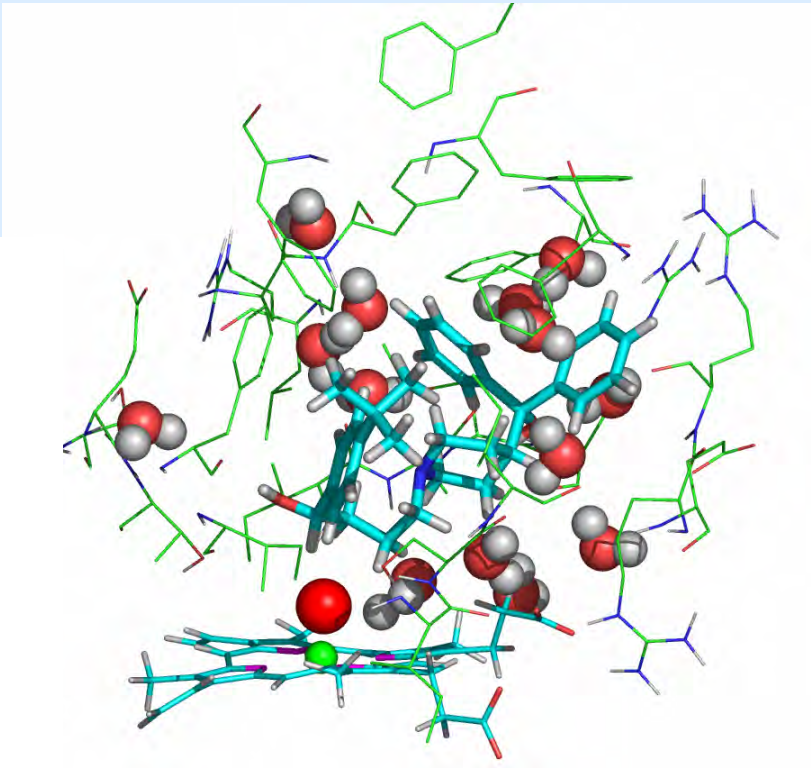


Cytochrome P450 3A4

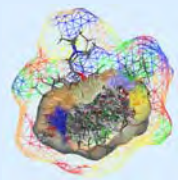
Different binding modes







terfenadine



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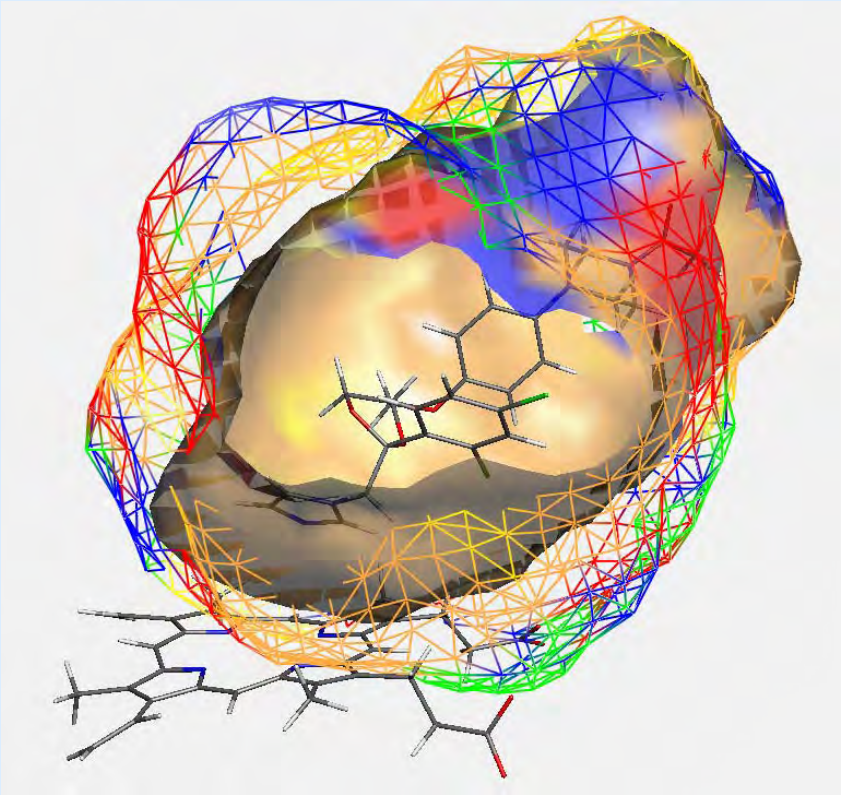
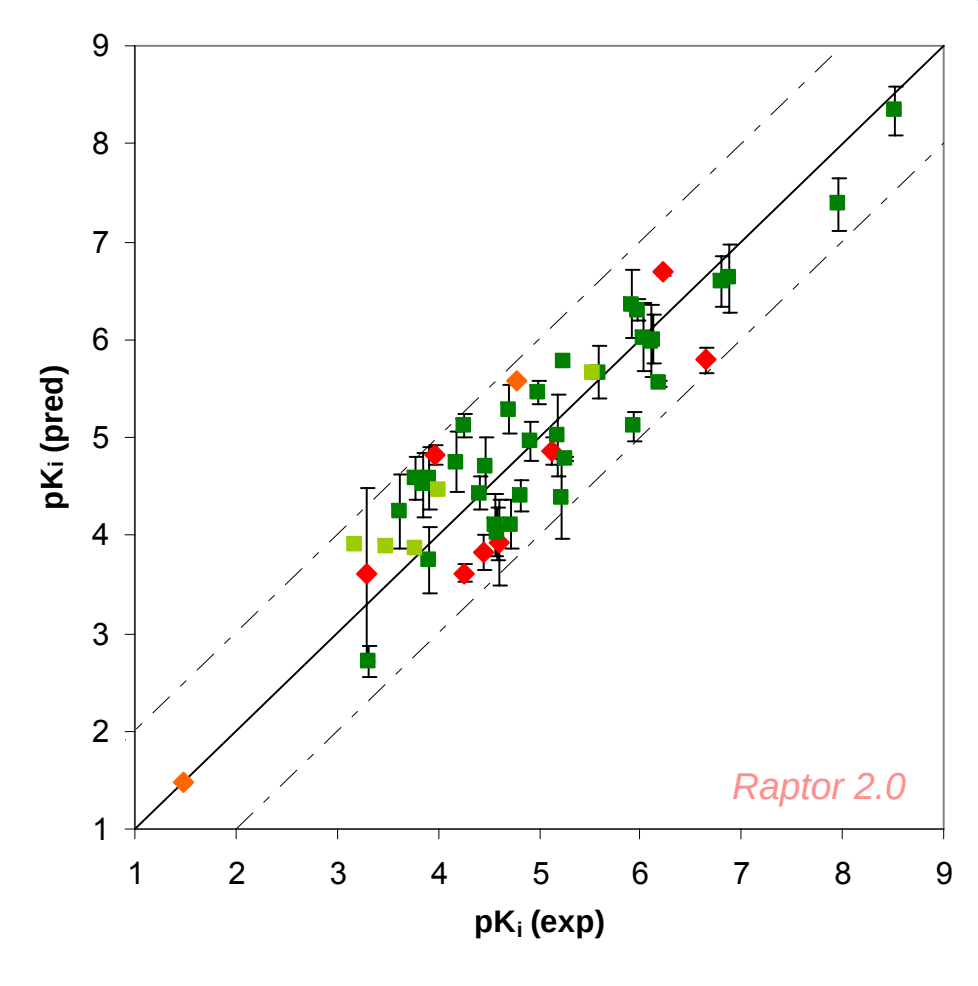
Cytochrome P450 3A4

48 compounds
(192 representations)



q^2 = 0.825 p^2 = 0.659



Lill, M.A.; Dobler, M.; Vedani, A. *ChemMedChem* **2006**, *1*, 73-81.

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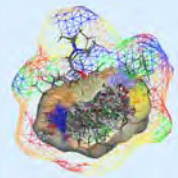
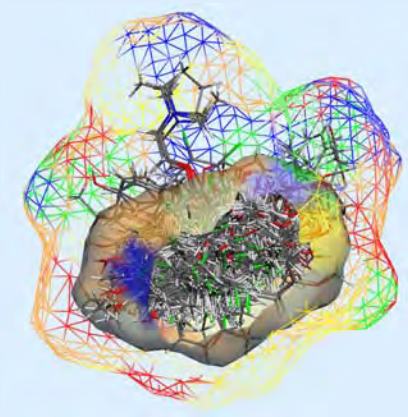


Overview

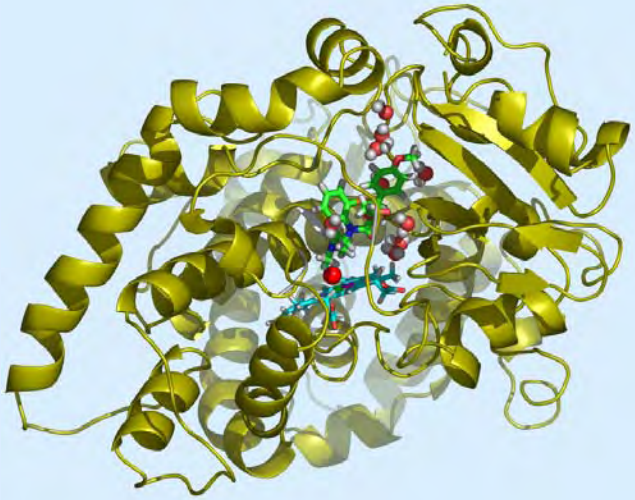


Introduction

Methodology

Applications

Current directions

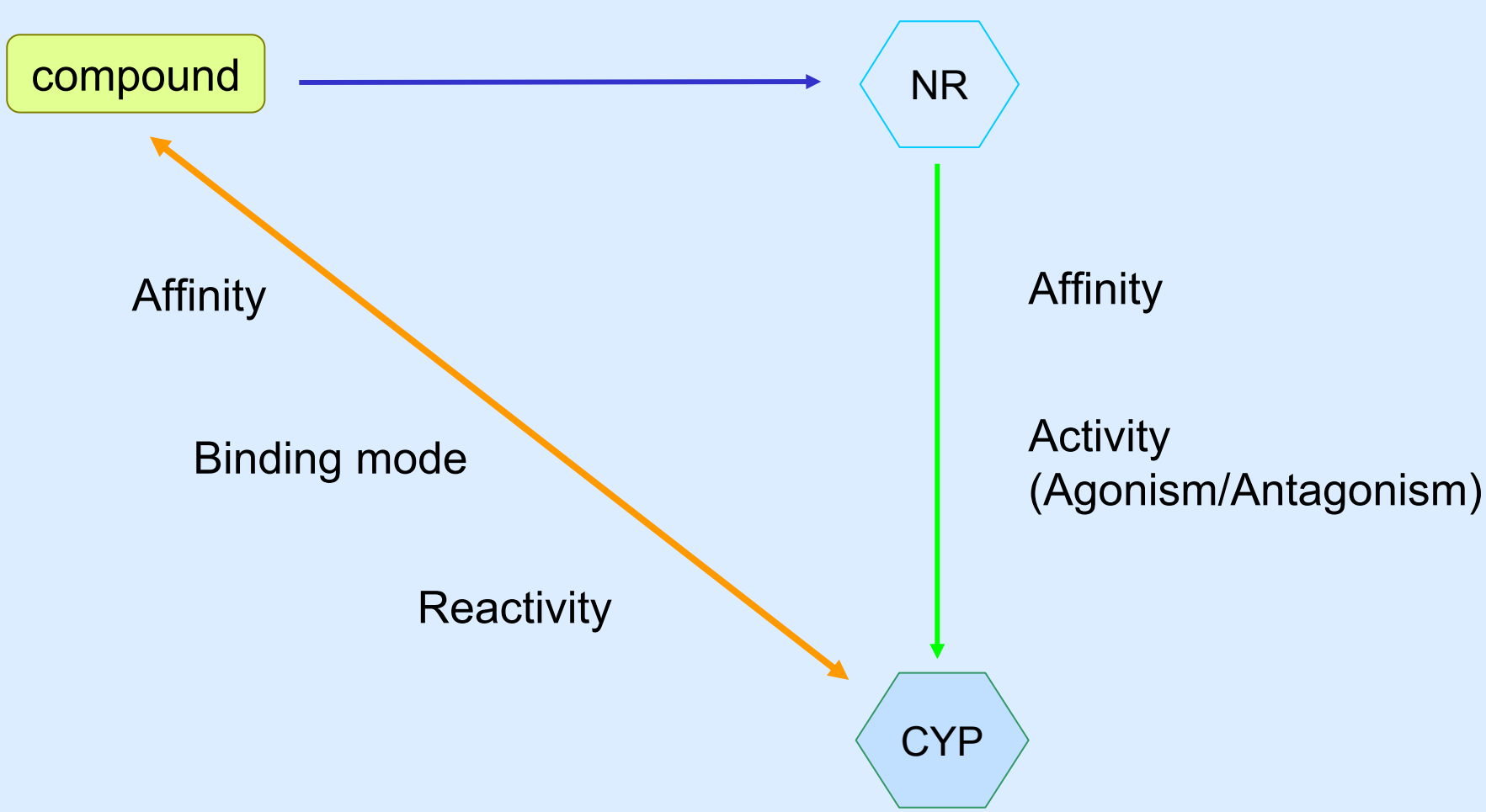


Current directions

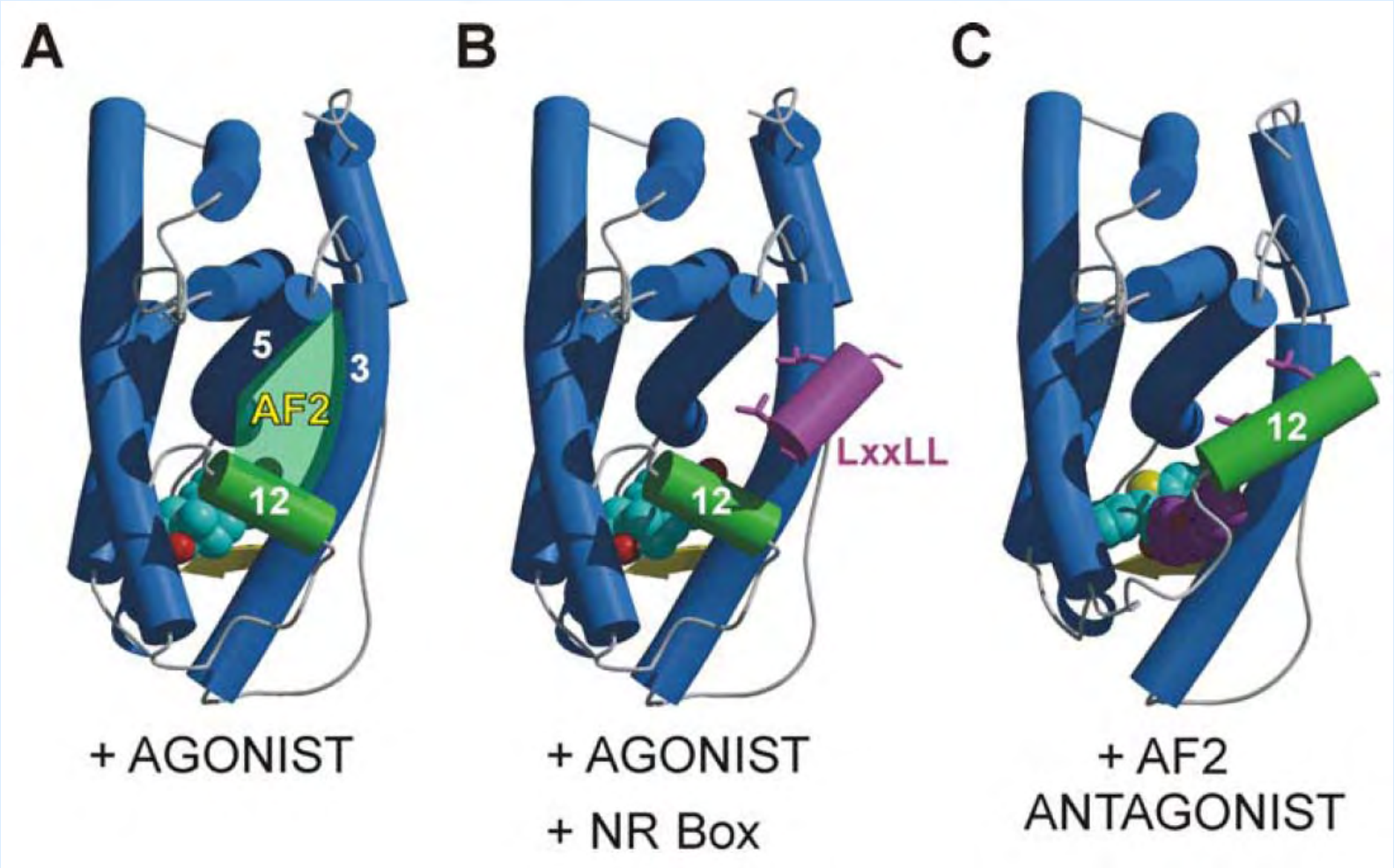
Current limitations and research directions

- Flexibility during docking limited to side-chain motion

Specific factors



Agonism/Antagonism

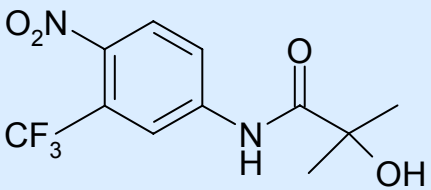


Pike, A.C.W. *Best Pract. Res. Clin. Endocrinol. Metab .* **2006**, *20*, 1-14.

Agonism/Antagonism

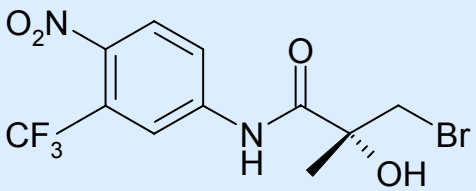
Androgen receptor

hydroxyflutamide



antagonist

R-3



agonist

Acknowledgements

Department of Medicinal Chemistry
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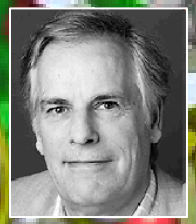
Angelo Vedani

Beat Ernst


Max Dobler

Fabienne Winiger

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