How does drug reach ‘site of action’?

- Target
- Administration
- Deaggregation/Dissolution
- Absorption
- Distribution
Absorbed drug enters liver via portal vein before reaching systemic circulation:

Drug continuously metabolized throughout systemic circulation:

Absorption in small intestine

Drug metabolism in liver
Drug disposition

Drug elimination is typically the most important factor limiting the pharmacological response of a drug.
ADMET

Progress of drug through human body

dose
soluble & stable
absorbed
not metabolized by liver
freely distributed
not further cleared
bioavailability
unbound volume of distribution
Importance of ADMET properties for drug design

Figure 1 | An analysis of the main reasons for attrition in drug development. In this analysis, published five years ago, half of all failures were attributed to poor pharmacokinetics (39%) and animal toxicity (11%). Such analyses clearly indicated that these two areas should be focused on as early as possible in the drug-discovery process (although it should be noted that the interpretation of such data is often hampered by the fact that compounds may have more than one flaw and, as the project was halted, these might not always have been identified). An even better approach would be to use predictive tools in the design phase of the synthesis of compounds and compound libraries.

ADMET

Levels of computational modeling:

- Solubility
- Absorption
- Metabolization
- Excretion

Bioavailability

physico-chemical properties

enzymatic reactions

transport processes

Model of overall process:

Disadvantage: simplified model → predictive power?

Advantage: simple and quick models

Model individual processes:

complex network of factors, not all processes known
extendable: the more knowledge, the more predictive power interpretable
Figure 3: An analysis of the crucial ADME processes for which predictive models are available or are being developed.
Solubility:

\[ \log S = \text{mol/l} \]

\[ S = \text{concentration of compound in saturated aqueous solution in equilibrium with stable crystalline form} \]

Typical range for drugs (≈85% of all drugs):

\[ -5 \leq \log S \leq -1 \]

\[ \log S > -1 : \text{very polar (e.g. sugar, peptides)} \]

→ active transport

“compromise between high aqueous solubility and acceptable membrane passage”
Methods using group/fragment contributions:

\[ \log S = c_0 + \sum_i c_i g_i \]

frequency of appearance in compound

R. Kühne, R.-U. Ebert, F. Kleint, G. Schmidt, G. Schüürmann, Group contribution methods to estimate water solubility of organic chemicals, Chemosphere 30 (1995) 2061–2077:

Dataset consists almost entirely of hydrocarbons, halocarbons, polychlorinated biphenyls (PCBs), and monofunctional organic molecules ⇒ not adequate fragment types for drug molecules


Dataset consists of 1168 organic chemicals that cover a great variety of chemical classes, including some complex drugs.
"as with any group contribution model, the calculation of the solubility of new compounds, which contain fragments not encountered in the model, may yield unanticipated errors"
Solubility

Problem of linearity:
If molecule has many hydrophilic groups, such as in sugars, or many hydrophobic groups, such as in alkane chains, their contribution to solubility tend to decrease as their number increase:

<table>
<thead>
<tr>
<th>name of compd</th>
<th>molecular structure</th>
<th>exptl logS (M/m³)</th>
<th>contribution of the last −CH₂− group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-heptane</td>
<td>CH₃(CH₂)₅CH₃</td>
<td>−1.57</td>
<td></td>
</tr>
<tr>
<td>n-octane</td>
<td>CH₃(CH₂)₆CH₃</td>
<td>−2.35</td>
<td>−0.78</td>
</tr>
<tr>
<td>n-nonane</td>
<td>CH₃(CH₂)₇CH₃</td>
<td>−3.00</td>
<td>−0.65</td>
</tr>
<tr>
<td>n-decane</td>
<td>CH₃(CH₂)₈CH₃</td>
<td>−3.64</td>
<td>−0.64</td>
</tr>
<tr>
<td>n-undecane</td>
<td>CH₃(CH₂)₉CH₃</td>
<td>−4.04</td>
<td>−0.4</td>
</tr>
<tr>
<td>n-dodecane</td>
<td>CH₃(CH₂)₁₀CH₃</td>
<td>−4.51</td>
<td>−0.47</td>
</tr>
<tr>
<td>n-tridecane</td>
<td>CH₃(CH₂)₁₁CH₃</td>
<td>−4.72</td>
<td>−0.21</td>
</tr>
<tr>
<td>n-tetradecane</td>
<td>CH₃(CH₂)₁₂CH₃</td>
<td>−4.95</td>
<td>−0.23</td>
</tr>
<tr>
<td>n-pentadecane</td>
<td>CH₃(CH₂)₁₃CH₃</td>
<td>−5.14</td>
<td>−0.19</td>
</tr>
<tr>
<td>n-hexadecane</td>
<td>CH₃(CH₂)₁₄CH₃</td>
<td>−5.27</td>
<td>−0.13</td>
</tr>
<tr>
<td>n-heptadecane</td>
<td>CH₃(CH₂)₁₅CH₃</td>
<td>−5.30</td>
<td>−0.03</td>
</tr>
</tbody>
</table>

Solution: Transform equation:
\[
\log S^* = c_0 + \sum_i c_i g_i
\]
\[
\log S = F(\log S^*)
\]
Solubility

Using descriptors:

\[ \log S = \sum_i n_i d_i + c_0 \]

many descriptors \( d_i \) → select statistically relevant
or
define physico-chemically relevant descriptors


MC simulation of solute in water → 11 descriptors averaged over simulation → Regression with 5 terms

\[ \log S = 0.32 \text{ESXL} + 0.65 \text{HBAC} - 162 \text{HBAC} \cdot \text{HBDN}^{1/2} / \text{SASA} \\
+ 2.19 n_{\text{amine}} - 1.76 n_{\text{nitro}} + 1.18 \]

Good regression quality (\( q^2 = 0.87 \); \( n = 150 \)), but computationally slow
Solubility

Experimental accuracy:
- variations in crystal shape
- polymorphism
- crystal hydrate formation
- pH (esp. for ionizable compounds)
- temperature control for the solution
- concentration measurements

Range in literature data, 411 compounds
average standard dev. 0.58 log units

pesticide rotenone: \( \log S = -4.42 \) to \(-6.29\)
guanine: \( \log S = -1.86 \) to \(-3.58\)
Human intestinal absorption

Membrane permeation (epithelial transport):
Multiple processes have to be considered

- Passive paracellular diffusion
- Passive transcellular diffusion
- Active transport e.g. bile acids
- Drug metabolism e.g. P450 enzymes
- Efflux pumps e.g. P-glycoprotein
- Active transport e.g. bile acids
- Passive paracellular diffusion > Passive transcellular diffusion
Human intestinal absorption

Experimental data:

Data for physiological membrane: rare

⇒ Use of model systems:

- Parallel artificial membrane-permeability assay (PAMPA): only passive transport

- Caco-2 cells: includes transporters

- Regional jejunal perfusion system

⇒ Estimate effect of active transport
Membrane permeation

PSA most important individual descriptors

Sigmoidal relationship between %HIA (Caco-2 cells) and PSA

Pooper correlation
Reasons:
- more challenging data set (435 compounds)?
- consistent data? (multiple literature references)
Membrane permeation


Other important descriptors:

- $\log D_{pH=6.5}$
- Number of hydrogen bond donors and acceptors: $N_{HBD}$, $N_{HBA}$
- Number of rule of five violations (see next lecture): $N_{\text{rule-of-5}}$

$$\% HIA = 97.12 - 11.48 \cdot N_{\text{rule-of-5}}$$

$$- 8.99 \cdot S \left( 0.05 - \log D_{pH=6.5} \right)$$

$$- 0.15 \cdot S \left( TPSA - 49.41 \right)$$

$$+ 0.17 \cdot \left( \log D_{pH=6.5} \right)^2$$

$$+ 3.76 \cdot S \left( N_{HBD} - 7 \right)$$

$$r^2 = 0.76$$
logD

For ionizable compounds A:

$$\log P = \log \frac{[A]_{\text{octanol}}}{[A]_{\text{unionized water}}}$$

$$\log D = \log \frac{[A]_{\text{octanol}}}{[A]_{\text{unionized water}} + [A]_{\text{ionized water}}}$$

logD is pH dependent !!!

Values of particular interest:

logD$_{6.5}$ as pH=6.5 in small intestine (main location for absorption)

logD$_{7.4}$ as pH=7.4 in blood serum and in liver
Analysis of 2245 compounds entering phase II clinical testing

→ **Lipinski’s Rule-of-five:**

Poor absorption is more likely if more than one of the following criteria is violated:

A. Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)

B. Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms)

C. A molecular weight under 500 daltons

D. An octanol-water partition coefficient logP of less than 5

Percentage of violations (always ≤10% for combination of two criteria):

A.+B.: 10%
A.+C.: 7%
B.+C.: 4%
C.+D.: 1%
ADMET

1. Stability
2. Solubility
3. Passive transport
4. Active transport
5. Metabolization

Absorption
Distribution
Metabolization
Excretion

Bioavailability


\[
\text{Bioavailability} = \frac{\text{dose reaching systemic circulation}}{\text{orally administered dose}}
\]

Dataset: 232 drugs:
- Multiple literature sources
- 130 bases, 58 neutral, 44 acids
- excluded drugs: prodrugs, unstable compounds (nitroglycerine), zwitterions at physiological pH, quaternary ammonium compounds.
- 37 drugs in class 1, 54 in class 2, 63 in class 3, 78 in class 4

<table>
<thead>
<tr>
<th>Table 1. Bioavailability Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>rating</td>
</tr>
<tr>
<td>bioavailability (%)</td>
</tr>
</tbody>
</table>

Classification QSAR:
- **Score**
  - <2
  - 2-3
  - 3-4
  - >4
- **Class**
  - 1
  - 2
  - 3
  - 4
Bioavailability

\[ S(X) = \sum w_i s_i \quad (8) \]

<table>
<thead>
<tr>
<th>descriptors ( s_i )</th>
<th>weight ( w_i )</th>
<th>CI(^a)</th>
<th>( n^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \log D_{6.5} )</td>
<td>-0.027</td>
<td>0.05</td>
<td>232</td>
</tr>
<tr>
<td>( \log D_{6.5} )^2</td>
<td>-0.046</td>
<td>0.25</td>
<td>232</td>
</tr>
<tr>
<td>( \Delta \log D (\log D_{6.5} - \log D_{7.4}) )</td>
<td>0.370</td>
<td>0.23</td>
<td>232</td>
</tr>
<tr>
<td>phenolic OH(^c) (excluding di-ortho-subst)</td>
<td>-1.032</td>
<td>0.45</td>
<td>22</td>
</tr>
<tr>
<td>( \text{SO}_2\text{NH}_2 )</td>
<td>-1.014</td>
<td>0.17</td>
<td>7</td>
</tr>
<tr>
<td>alcoholic OH (excluding tert-OH)(^d)</td>
<td>-0.177</td>
<td>0.09</td>
<td>59</td>
</tr>
<tr>
<td>hydrolysis: esters, ( \beta )-lactams, alkyl carbonates</td>
<td>-1.074</td>
<td>0.37</td>
<td>24</td>
</tr>
<tr>
<td>aromatic ( p )-hydroxylation(^f)</td>
<td>-0.599</td>
<td>0.26</td>
<td>33</td>
</tr>
<tr>
<td>ArCH(( R^g ) (excluding di-ortho subst Ar)</td>
<td>-0.235</td>
<td>0.12</td>
<td>47</td>
</tr>
<tr>
<td>allylic oxidation (C-C=C)(^h)</td>
<td>-0.201</td>
<td>0.09</td>
<td>13</td>
</tr>
<tr>
<td>tert-acyclic amine (no ring heteroatoms)(^i)</td>
<td>-0.340</td>
<td>0.10</td>
<td>24</td>
</tr>
<tr>
<td>XCCNR (R = Me, Et; X = N,O, Ar, C=C(^j)</td>
<td>-0.410</td>
<td>0.15</td>
<td>28</td>
</tr>
<tr>
<td>readily oxidized moieties: thiols, dihydropyridines</td>
<td>-1.137</td>
<td>0.24</td>
<td>11</td>
</tr>
<tr>
<td>ketones(^k)</td>
<td>-0.493</td>
<td>0.10</td>
<td>15</td>
</tr>
<tr>
<td>( \text{NO}_2 ) on a benzene ring (excluding ortho subst)</td>
<td>-0.148</td>
<td>0.03</td>
<td>7</td>
</tr>
<tr>
<td>( \text{ArNH}_2, \text{ArNHNH}_2, \text{ArCONHNH}_2, \text{ArC(=NH)NH}_2 ) as ( p_K_a ) value(^l)</td>
<td>-0.034</td>
<td>0.04</td>
<td>16</td>
</tr>
<tr>
<td>HOCCNH tert-alkyl, HOCCN&lt; (cyclic rings)</td>
<td>0.210</td>
<td>0.05</td>
<td>16</td>
</tr>
<tr>
<td>benzodiazepine (with no additional fused rings)</td>
<td>0.231</td>
<td>0.05</td>
<td>10</td>
</tr>
<tr>
<td>constant</td>
<td>4.358</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: Contribution index = weight*standard deviation in descriptor among dataset
\( n \): Total number of usage of descriptor
Bioavailability

Major contributions:

• parabolic dependency on logD

<table>
<thead>
<tr>
<th>bioavailability class</th>
<th>log $D_{6.5}$ range</th>
<th>% compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>-2.0 to 3.0</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>-2.0 to 3.0</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>-2.0 to 3.0</td>
<td>81</td>
</tr>
<tr>
<td>1</td>
<td>-2.0 to 3.0</td>
<td>65</td>
</tr>
</tbody>
</table>

• acids generally have better bioavailability characteristics than bases: $\log D_{6.5} - \log D_{7.4}$

Possible reason:

– acids higher percentage neutral at pH=6.5 than at pH=7.4

– neutral form higher permeability through intestine membrane (pH=6.5)

– charged form usually metabolically more stable (less affinity to P450 enzymes)
Bioavailability

• metabolically labile functional groups reduce bioavailability
e.g. aromatic hydroxylation, \( \text{tert} \)-amine hydroxylation

Results:

• Classification accuracy for training set (232 compounds): 71\% (97\% to within one class)
• Classification accuracy for test set (40): 60\% (95\%)

General:

• Dataset based on existing drugs
→ Applications to leads or drug candidates?
• Accurate direct prediction of bioavailability with a single QSAR model is difficult
Metabolization

Bioavailability → Dose → Absorption → Metabolism → Bioavailability

Bioavailability → Dose → Absorption → Metabolism → Bioavailability

CH₃

oxidation

reduction

hydrolysis

COOH

conjugation

reactions

O=N-CH(COOH)
Metabolization

Metabolizing enzymes:
- cytochromes P450  
- esterases  
- epoxide hydrolase  
- dihydropyrimidine dehydrogenase  
- glutathione S-transferases  
- N-acetyltransferases  
- sulfotransferases  
- thiopurine methyltransferase  
- glucuronosyltransferases  
- …

in humans: 17+ families with 50+ isoforms
Electronic factor

Postulated rebound mechanism for carbon hydroxylation reaction:

\[ \text{Singh, S.B. J. Med. Chem. 2003, 46, 1330:} \]

Metabolic liability can be estimated by

- Quantum chemical calculations of hydrogen abstraction energies
- Solvent exposure >8Å² (i.e. atom has to be accessible to catalytic heme group)
Electronic factor

Amiodarone

Diazepam

Tamoxifen

Midazolam

predicted

experimental

predicted

predicted
Regioselective metabolism

Experimental results:

Topography of protein binding site and steric hindrance of the access to the catalytic heme group are important factors for predicting drug metabolism.
Regioselective metabolism

CYP3A4

CYP2D6
Factors determining metabolic rate

Orientation towards reactive center

Binding affinity towards enzyme

Intrinsic reactivity and steric accessibility of chemical group in close proximity to the catalytic center
Structure-based approaches

Used methods:

- Docking: Functional groups close to catalytic center $\rightarrow$ Potential for metabolization
- Simulations to calculate free energies (e.g. MMPBSA, LIE) $\rightarrow$ Strength of interaction

Challenges:

- Multiple binding modes are in agreement with experiment:
- Protein flexibility
SMARTCyp: Concept

Atom Reactivity Library

A. Calculate Quantum Chemical Reference Energies
Calculate transition state energies using density functional theory

B. Define SMARTS Rules
Group calculations by fragments and calculate average energies

SMARTCyp

1. Assign Energies By SMARTS matching

<table>
<thead>
<tr>
<th>Atom</th>
<th>SMARTS</th>
<th>Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><a href="=O">CX3H1</a>[#6]</td>
<td>40.2</td>
</tr>
<tr>
<td>2</td>
<td>[CX4][N]</td>
<td>39.8</td>
</tr>
<tr>
<td>3</td>
<td>[N^3][H1,H2]</td>
<td>54.1</td>
</tr>
</tbody>
</table>

2. Compute Accessibility Descriptor

\[ A_i = \frac{\text{Maxbonds}_i}{\text{Maxbonds}_\text{all}} \]

\[ A_1 = \frac{2}{3} = 0.67 \]
\[ A_2 = \frac{2}{3} = 0.67 \]
\[ A_3 = \frac{3}{3} = 1.00 \]

3. Compute Score and Rank Atoms

Score, \( S_i = E_i - 8A_i \)
Lowest score gets rank 1

\[ S_1 = 40.2 - 8 \times 0.67 = 34.84 \]
\[ S_2 = 39.8 - 8 \times 0.67 = 34.44 \]
\[ S_3 = 54.1 - 8 \times 1.00 = 46.10 \]

Ensemble docking

Decouple protein from ligand conformational search:

Docking to ensemble of protein structures

Ensemble of protein conformations

MD simulations
Is protein flexibility important?

Combine docking to MD ensemble of CYP2C9 structure with reactivity prediction using SMARTCyp:

\[
CS = R_i + \gamma S_i
\]

Docking score

Reactivity

Weighting factor (optimized)

Accuracy of predicting experimentally known site of metabolism:

<table>
<thead>
<tr>
<th></th>
<th>Random</th>
<th>SMARTCyp Alone</th>
<th>Vina (Ensemble)</th>
<th>Vina + SMARTCyp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top-1</td>
<td>12%</td>
<td>42%</td>
<td>38%</td>
<td>51%</td>
</tr>
<tr>
<td>Top-2</td>
<td>24%</td>
<td>58%</td>
<td>52%</td>
<td>75%</td>
</tr>
<tr>
<td>Top-3</td>
<td>38%</td>
<td>67%</td>
<td>64%</td>
<td>84%</td>
</tr>
<tr>
<td>% docked</td>
<td></td>
<td></td>
<td></td>
<td>96%</td>
</tr>
</tbody>
</table>
Quantification of binding affinities

Docking → Binding modes

QSAR

Quantification

Graph showing pIC\(_{50}\) (exp) vs. pIC\(_{50}\) (pred)

Chemical structures showing different functional groups.
Application to SoM prediction

Standard 3D-QSAR/nD-QSAR:
• Train binding-site model for reproducing binding affinity
• Raptor:
  \[ Q_{\text{score}} = \Delta G \]

Modified QSAR approach:
• Train binding-site model for reproducing SoM data, i.e. differentiate between active poses (‘correct SoM in vicinity of heme’) and decoy poses (‘incorrect SoM in vicinity of heme’)
• Raptor:
  \[ Q_{\text{score}} = \Delta G + 0.1 \cdot S_{\text{SMARTCyp}} \]
Raptor model
Docking + reactivity + QSAR

Combine docking to MD ensemble of CYP2C9 structure with reactivity prediction using SMARTCyp and QSAR modeling:

Accuracy of predicting experimentally known site of metabolism:

<table>
<thead>
<tr>
<th></th>
<th>SMARTCyp Alone</th>
<th>Vina (Ensemble)</th>
<th>Vina (Ensemble)+SMARTCyp</th>
<th>Vina (Ensemble)+SMARTCyp+QSAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top-1</td>
<td>42%</td>
<td>38%</td>
<td>51%</td>
<td>89%</td>
</tr>
<tr>
<td>Top-2</td>
<td>58%</td>
<td>52%</td>
<td>75%</td>
<td>93%</td>
</tr>
<tr>
<td>Top-3</td>
<td>67%</td>
<td>64%</td>
<td>84%</td>
<td>96%</td>
</tr>
<tr>
<td>% docked</td>
<td>96%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Only few individual factors are currently modeled:

**Drug binding to human serum albumin**
- human serum albumin comprises about half of the blood serum protein
- drug can bind to human serum albumin → influences half-life and bioactive dose of drug
- most computational approaches are QSAR simulations trying to predict the affinity of drugs towards human serum albumin

**CNS active drug passing through the blood-brain barrier (BBB)**
- mostly QSAR approaches correlating BBB permeability with drug structure
- many processes such as active transport are not well characterized
Toxicity

Drug

- Carcinogenicity & Mutagenicity
- hERG binding
- Hepatotoxicity
- Drug-drug interactions
- Endocrine disruption
Principal QSAR approaches

Complex molecular basis

- Homologous-series based QSAR

Problems:
- Confined to interpolation within the series
- Difficult to determine if a specific substance is within that series
- Problematic when overlap of series

Clear defined molecular mechanism

- QSAR based on common mechanism of toxic action

Advantage:
- Possible to predict different chemical classes

Problem:
- Mechanism has to be known and understood
Expert systems

Knowledge-based expert systems:
Rules defined by human experts

If secondary amine, then potential for carcinogenicity
If aromatic amine, then potential for carcinogenicity
If 4-aminoaryl-sulfonamide, then potential for thyroid-toxicity
Expert systems

In vivo genotoxicity (DEREK, 306 compounds; 30 toxic)

Expert systems

Possible Reason (same is true for general QSAR):
The underlying biochemical processes are much more complicated.

Mutation → Binding ← Transport → Stability
Mutation → Activation ← Stability
Mutation → Deactivation ← Stability
Mutation → Carcinogenicity
Mutation → Excretion
Receptor-mediated toxicity

Chemicals

Binding

Signal Transduction

Estrogen receptor
Androgen receptor
Ah receptor
…

Induced Dysfunction
Endocrine disruption

Pesticides:

- DDT
- Chlordecone
- ...

Estrogen receptor

**Estrogenic effect**
e.g. for chlordecone: Decreased sperm motility, abnormal sperm

Androgen receptor

**Anti-androgenic effect**
e.g. abnormalities in male sex development

Endocrine disruption

PVC materials → house dust

food packaging

cosmetics, parfums

…

Phthalates:

Diethylhexylphthalate (DEHP)

Butylbenzylphthalate (BBP)

Dibutylphthalate (DBP)

Estrogenic effect
e.g. abnormal sperm

Anti-androgenic effect
e.g. abnormalities in male sex development

e.g. Soto, A.M. et. al Environ. Health. Persp. 103 (1995), 113-122;
Receptor-mediated toxicity

Quantitative Prediction of Binding Affinity

Toxicity
Dose dependency

QSAR

Dose dependency

Quantitative Prediction of Binding Affinity

Toxicity classes (0-4)

pK\(_{\text{Binding}}\) (Ah receptor)

Toxicity

Dose dependency

Quantitative Prediction of Binding Affinity

Toxicity classes (0-4)

pK\(_{\text{Binding}}\) (Ah receptor)
Androgen receptor

119 compounds
6 substance classes

- steroids
- phytoestrogens
- phenols
- DES and related compounds
- diphenylmethanes
- organochlorines
Androgen receptor

\[ r^2 = 0.867 \]

\[ p^2 = 0.754 \]

Androgen receptor

polychlorinated biphenyls

3,4-diphenyltetrahydrofuran

Hepatotoxicity

75% of blood coming to the liver arrives directly from gastrointestinal organs which bring drugs in concentrated form.

Different possible factors:

• Activation of drugs by P450 enzymes to reactive species, e.g. acetaminophen in high doses
• Inducing P450 enzymes → too many active metabolites that cannot be conjugated
• Inhibiting P450 enzymes → accumulation of drug
• ….

Computational approaches:

• QSAR for predicting binding to transcription factors inducing P450 genes
• QSAR for predicting binding affinities to P450 enzymes
Drug-drug interactions

CYP3A4 mediated drug-drug interactions:

midazolam + clotrimazole

• Midazolam is a substrate for CYP3A4, and its metabolism is inhibited by clotrimazole, a potent inhibitor of CYP3A4.

Clotrimazole

Midazolam metabolites
hERG binding

- Human ether-á-go-go related gene expresses potassium ion channel that plays a central role in timing the return to the resting state (repolarization) of the cell membrane of heart muscle cells during the cardiac action potential.
- Inhibition by drugs can lead to arrhythmic heart beat and finally to sudden death.
- Several drugs (e.g. anti-arrhythmics, anti-psychotic agents, certain antibiotics) are known to bind to hERG.
- Preclinical studies on hERG binding are nowadays standard.

Computational approaches:
- QSAR to predict affinity towards hERG.
- Pharmacophore models to characterize binding to hERG.
hERG binding


Analysis of existing binders + homology modeling → pharmacophore model

- **cation-pi interaction** with Tyr625
- **pi-pi interaction** with Phe656
- **pi-pi interaction** with 12.5 Å