Getting the ADME Properties Right Through Property-Based Design

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Overview

• Early assessment - HT ADME
• Experimental molecular properties
• In silico molecular properties
• Prediction of absorption, bioavailability, metabolism, PK (Vd, ppb)
• Drug-like properties & property-based design
Absorption (physicochemistry)

Distribution

Metabolism, tox (enzymes)

Clearance

Elimination, Half-life

DOSE in MAN
Early ADME assessment
Early ADME studies

• In silico drug-like properties
• Absorption potential (permeability, Caco-2/MDCK)
• Physicochemical profile (solubility, lipophilicity)
• In vitro metabolism
  • Rate of metabolism (microsomes, hepatocytes)
  • Involvement of enzymes using cDNAs, Supermix
  • Potential for drug-drug interactions
    (fluorescent probe inhibition assays)

Key: performant analytics
Experimental molecular properties: Automation & HT
HT solubility

Laser nephelometry (96/384 plates)
HT ppb: equilibrium dialysis
Drug-drug interactions

Fluorescent probes for CYP inhibition

- CEC (CYP1A2, CYP2C19)
- 7-MFC (CYP2C9)
- AMMC (CYP2D6)
- 7-BFC (CYP3A4)
- 7-BQ (CYP3A4)
- DBF (CYP3A4)
Experimental molecular properties

Solubility
  Turbidimetric, pH-metric, nephelometric

Lipophilicity
  Log D (shake plate, pH-metric)

Permeability
  IAM,, liposomes, biosensors, artificial membranes (PAMPA, filter IAM)

H-bonding
  Δlog P

pKa
  Potentiometric, UV
Physicochemistry and absorption

Permeability of renin inhibitors

Would there be life on earth without log D?
Components of log P/log D

\[ \log D = a V - \Lambda \]

Lipophilicity =

Hydrophobicity – polarity = size – H-bonding

Components:
- Non-polar
- Polar
In silico molecular properties
In silico molecular properties

molecular structure

Experimental data → Calculated properties

Handbook of Molecular Descriptors, Todeschini and Consonni, Wiley-VCH (2000), 667 pages!!
In silico issues

- Solubility
  - not very accurate for poor solubility compounds
- Lipophilicity
  - errors in log P and pKa; and in current log D programs
  - other measures than log Doct/water?
- Hydrogen bonding
  - various options (PSA, HYBOT); select best?
- Molecular size/shape
  - various options (MW, MR, A, V); select best?
Prediction of ADME properties
Estimation of absorption

- In vivo
  (rat, dog, rabbit)
- In vitro systems
  (Caco-2, MDCK, Ussing)
- Physicochemical approaches
- Computational (in silico)
Effect of MW

Single-pass rat perfusion model
Influence of lipophilicity and MW on permeability

GI absorption

Yee, S., Pharm. Res. 14 (1997) 763-766
Prediction of oral absorption using polar surface area (PSA)

Clark, 1999; Palm et al, 1996, 1998
Absorption optimisation

- Solubility
- Size
- H-bonding
- pKa
- P-gp efflux
- Gut wall metabolism
- CYP3A4
- Lipophilicity
  - log D / log P
Predictive computational absorption models

Single descriptor (sigmoidal)
- \( \log D \)
- \( \Delta \log P, \text{PSA} \)

Multiple descriptors (MLR, PLS, PCA, CA)
- MolSurf (Norinder)
- VolSurf (Cruciani)
- AbSolv (Abraham)
- Mixed approaches (e.g. Lennernas)
Prediction of A% with Abraham descriptors

A% = 92 + 2.94E + 4.10S + 21.7A - 21.1B

r² = 0.74; r²cv = 0.72; n = 169; s = 14; F = 93

Simulation of absorption

GastroPlus (Simulations Plus)
Transporters

Ayrton and Morgan, Xenobiotica 2001

Intestinal efflux
- P-gp
- OCT1
- MRP2
- MRP1
- OATP3
- NTCP

Biliary excretion
- P-gp
- MDR3
- MRP2
- sPGP

Hepatic uptake
- OATP2
- OCT1
- OATP8
- NTCP
- OATP-B
- OAT2
- OAT3

Brain transport
- P-gp
- OAT3
- MRP1
- MRP5
- OATP1

Renal secretion
- OAT1
- OAT3
- OCT1
- OCT2
- OATP

Renal secretion
- P-gp
- MRP1
P-gp SAR

P-gp binding

H-bonding

large lipophilic basic

log D
In silico prediction of bioavailability

QSAR model based on

• $\log D_{6.5}$, $(\log D_{6.5})^2$
• $\Delta \log D (= \log D_{6.5} - \log D_{7.4})$
• presence of metabolising functional groups (currently 15 defined)

In silico prediction of bioavailability

- 591 compounds
- 85 descriptors
- MLR
- recursive partitioning
- $r^2 = 0.71$; $q^2 = 0.63$

Graphical prediction of bioavailability

How will we predict absorption/bioavailability in the future?

In silico ADME, e-ADME

- QSPR, QSAR, QSBR
- $A\% \text{ or } F\% = f (\text{structural, phys chem properties})$

efflux
active transport
metabolism

passive diffusion
(permeability)
In silico metabolism

- Predictive databases
- **Molecular modelling**
  - Pharmacophore
  - Protein (CYPs, others)
- QSAR
  - Neural networks
  - Decision trees
- Expert systems

The lab species of the future
P450 modelling

CYP2D6 model

CYP3A4 inhibitor models

Ketoconazole fitted in CYP3A4 inhibitor Catalyst model. Hydrophobic areas (cyan) Hydrogen bond acceptor features (green).

Estimation of PK from physchem
Unbound volume of distribution

Plasma protein binding

What is needed next?

- HT physicochemistry screens
- HT permeability screens
- Good P-gp efflux data (P-gp SAR)
- Understanding of role of P-gp and CYP3A4
- Other transporters?
- Measures and prediction of CYP3A4 metabolism
- More human absorption data (currently ca 300 cpds)
- Larger bioavailability database (currently ca 600 cpds)
Drug-like properties
&
Property-based design
Structure-based design

Uses the crystal structure of the target (here thrombin)
Property-based design

Rule-of-5

Poor absorption is likely when:

- > 5 H-bond donors
- > 10 H-bond acceptors
- MW > 500
- log P > 5

Blood-brain barrier

Van de Waterbeemd et al., J. Drug Target. 6 (1998) 151-165
## Design properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Lead-like</th>
<th>Drug-like</th>
<th>CNS-like</th>
</tr>
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<tbody>
<tr>
<td>MW</td>
<td>&lt;350-450</td>
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<td>CLOGP</td>
<td>&lt;3.5-4.5</td>
<td>&lt;5</td>
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<td>log D</td>
<td>-1 to 4</td>
<td>-1 to 3</td>
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<td>PSA</td>
<td>&lt;120-140</td>
<td>&lt;60-90 A²</td>
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<tr>
<td>HA</td>
<td>&lt;10</td>
<td></td>
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</tbody>
</table>
In silico approaches (e-ADME)

In vivo & in vitro data → Databases → Robust models → Prediction

Internet? → In silico data
Thanks