Your Speakers

Peter Astles

Peter completed his Chemistry degree and Ph.D. at the University of Oxford before spending two years of postdoctoral research with Prof. Leo Paquette at the Ohio State University, USA. He joined Rhone-Poulenc Rorer, now Sanofi, in 1992 learning about medicinal chemistry and drug discovery while working on several asthma/ inflammation projects. In 2000, Peter moved to Eli Lilly, based at Windlesham in the UK, where he is a Group Leader in med chem and a project leader in the CNS therapeutic area focusing on Alzheimer's Disease and schizophrenia.

Darren McKerrecher

Darren obtained his Chemistry degree at Edinburgh, and completed his D.Phil with Richard Taylor at York. He joined Zeneca, now AstraZeneca, at Alderley Park in 1997. He has been involved in a number of projects with ADMET challenges, in disease areas as diverse as cancer, diabetes, obesity, asthma and COPD, and is co-author of more than 50 papers and patents.
From 2006-2008, Darren undertook a secondment in AZ Lund (Sweden), before returning to Alderley Park where he is now Associate Director of Medicinal Chemistry, Project Leader and responsible for chemistry outsourcing in the Oncology iMED.

Dr Ted (AH) Parton

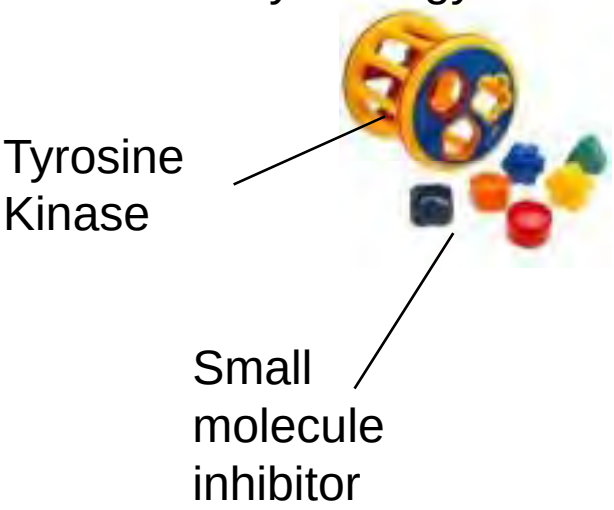
Ted studied Chemistry at Cambridge and gained a PhD in the analytical chemistry of insect pheromones at the University of Southampton. He began his career in pharmaceutical development in 1985 at Upjohn Laboratories in Crawley. In 1993, he moved to Celltech in Slough, acquired by UCB in 2004, where he is a Director in Pre-clinical PKPD and DMPK Project Support. He still enjoys talking with chemists and is delighted to be first author on a patent!

Molecular Interactions

Small molecules bind to protein targets through a combination of;

Sterics:

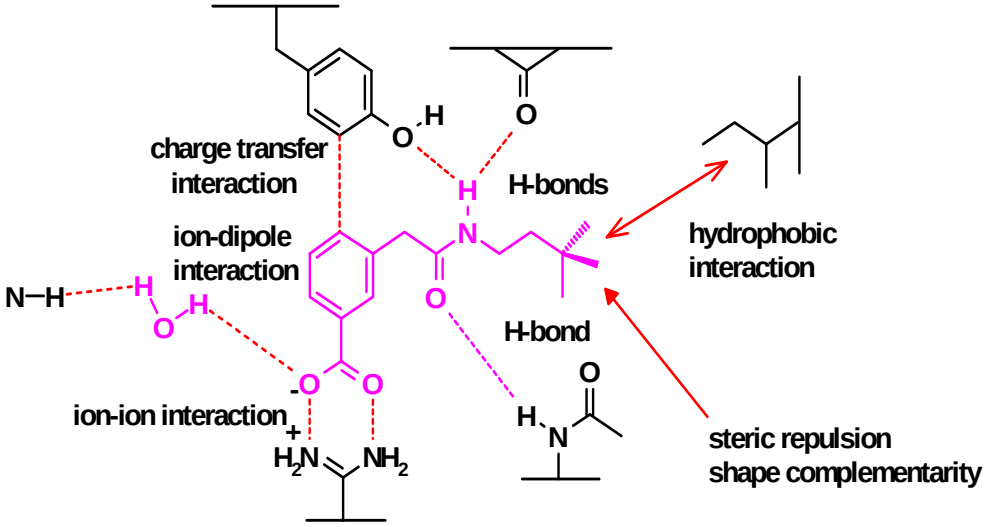
- Shape complementarity (vs natural substrate/ligand)
- Lock and key analogy



'How to make the shape of the key fit the lock?'

Electronics:

- Energetically favourable interactions



'How to maximise these binding interactions?'

Historically potency is not everything!

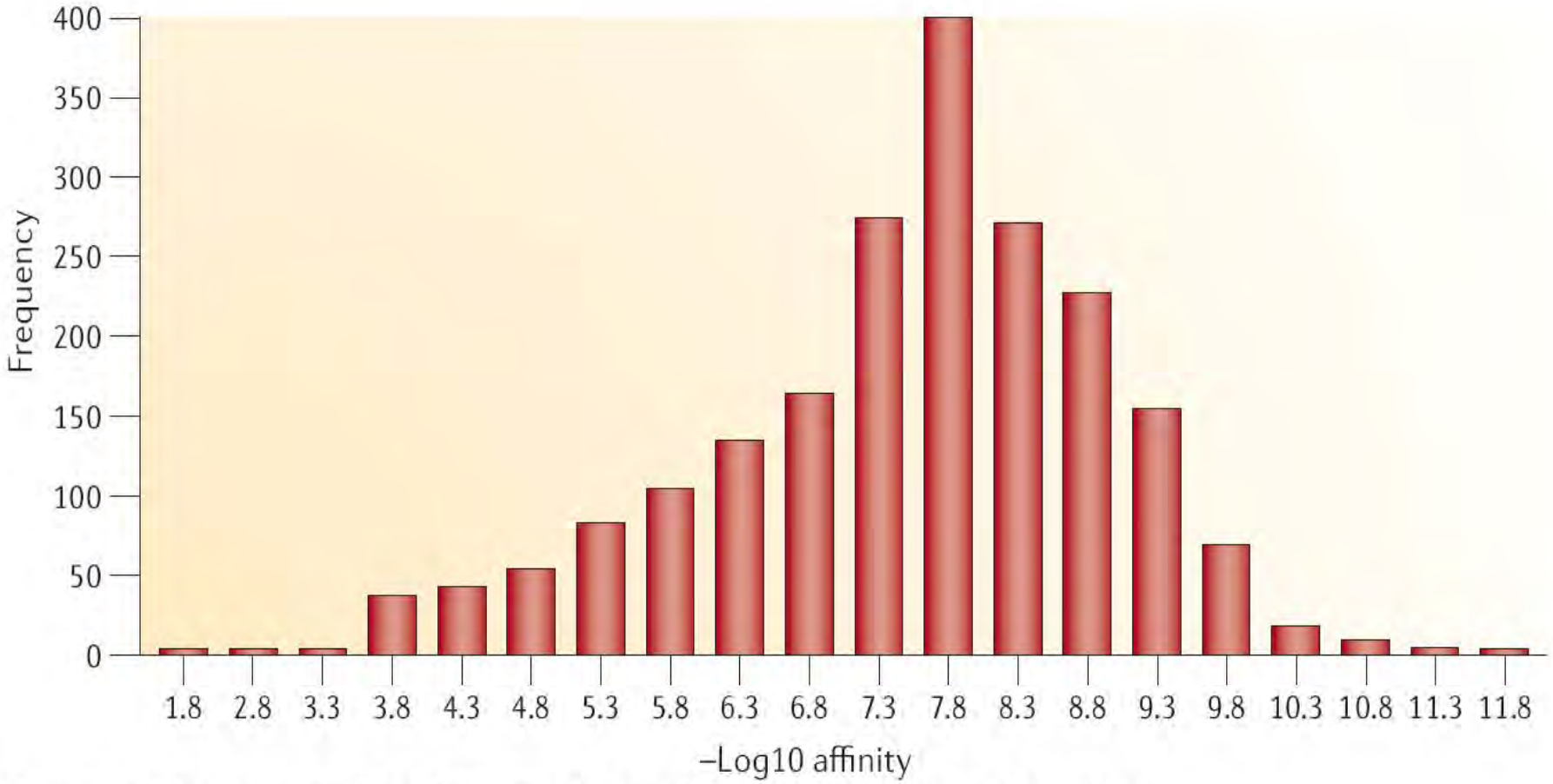


Figure 2 | **Frequency distribution for small-molecule drug potencies.**

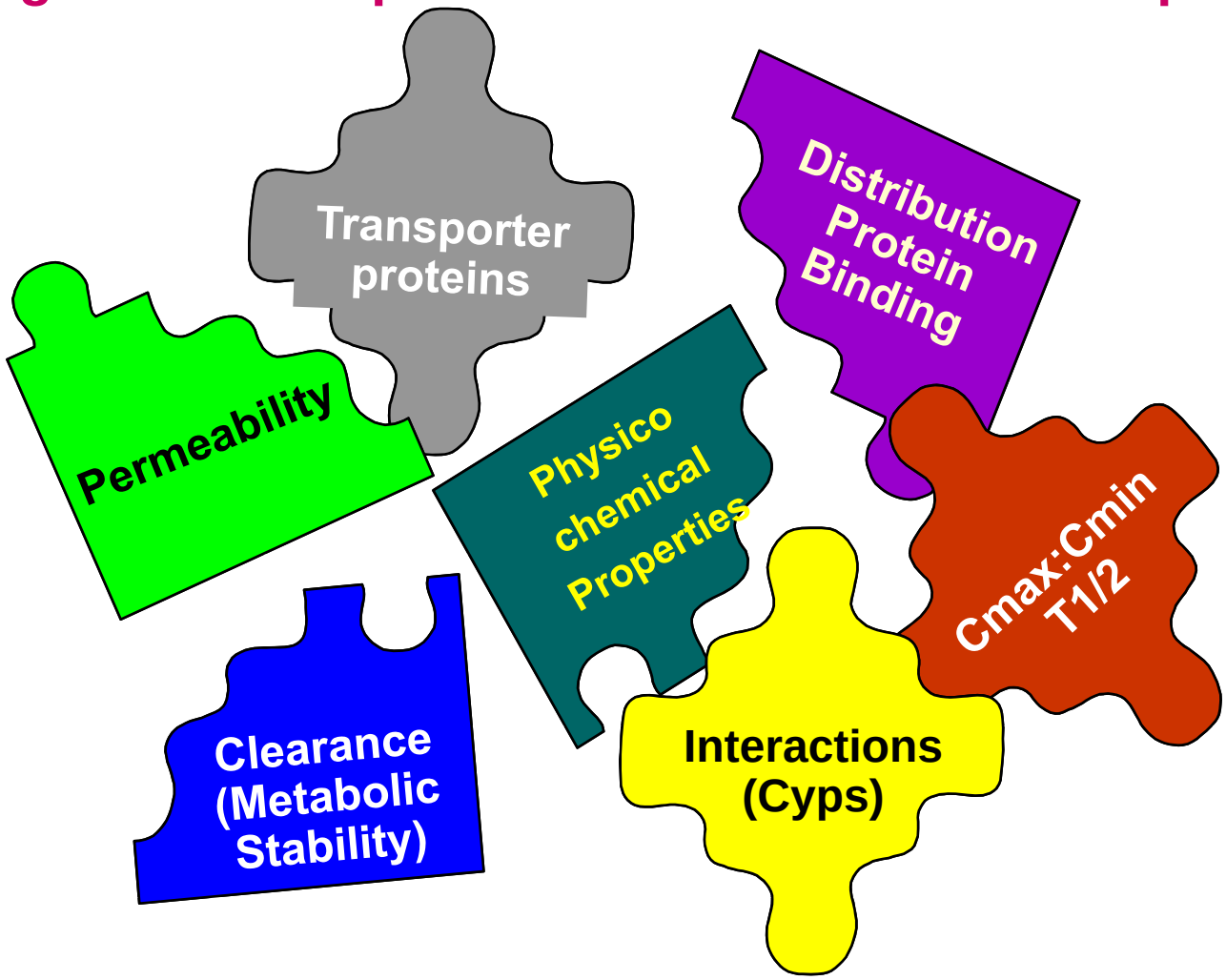
How many drug targets are there? Overington, John P.; Al-Lazikani, Bissan; Hopkins, Andrew L.
Nature Reviews Drug Discovery (2006), 5(12), 993-996

Pharmacokinetics, Physical & Pharmaceutical properties in Medicinal Chemistry

Potential drugs... or merely good ligands?

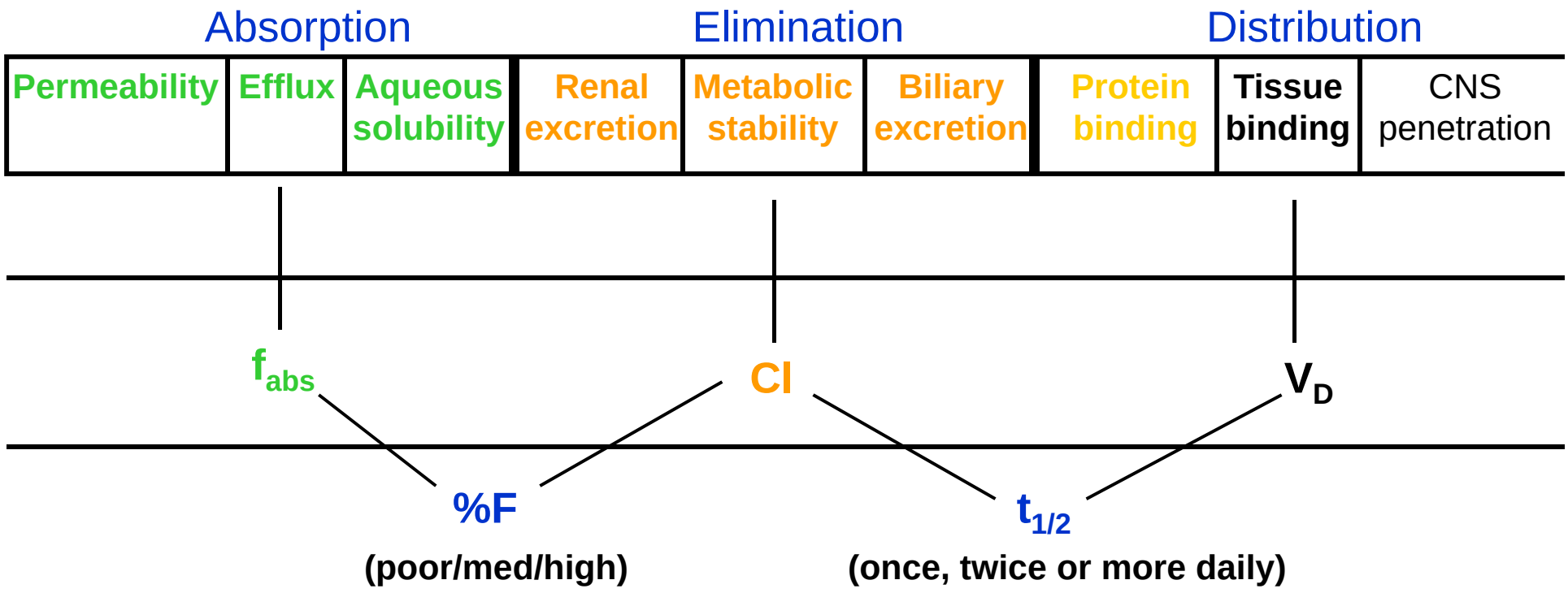
DMPK & Candidate Drugs

Candidate Drugs need good predicted human PK & minimal drug-drug interaction potential to have a chance of progress



Drug Design Criteria for Medicinal Chemists to be worried about

ADME Overview

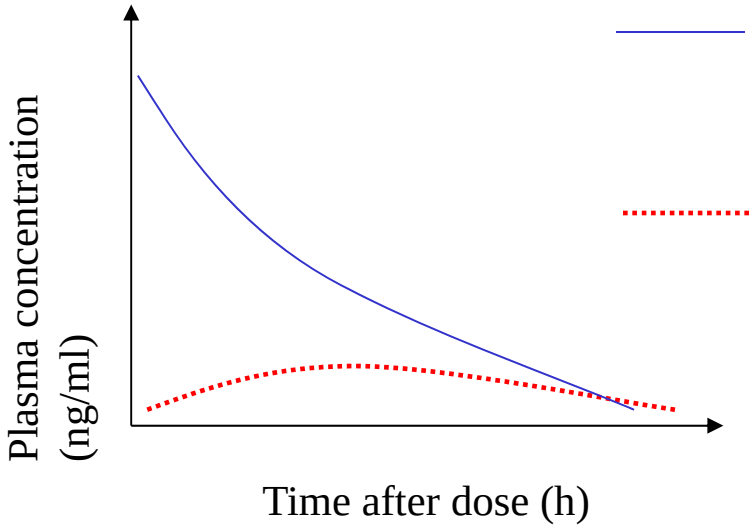


And once you've cracked all that, compounds can still be toxic!

Absorption

Absorption from an oral dose

How do you know you have a problem?



Compound A i.v. bolus injection 1 mg/kg

- **Good plasma exposure (area under curve AUC)**
- **Metabolic or other plasma clearance appears low**

Compound A oral dose (p.o.) 10 mg/kg

- **Low plasma exposure (AUC)**
- **Unchanged parent drug may appear in faeces**

Oral Bioavailability (F)

= fraction of the dose which makes it to the systemic circulation

(Combination of absorption & clearance)

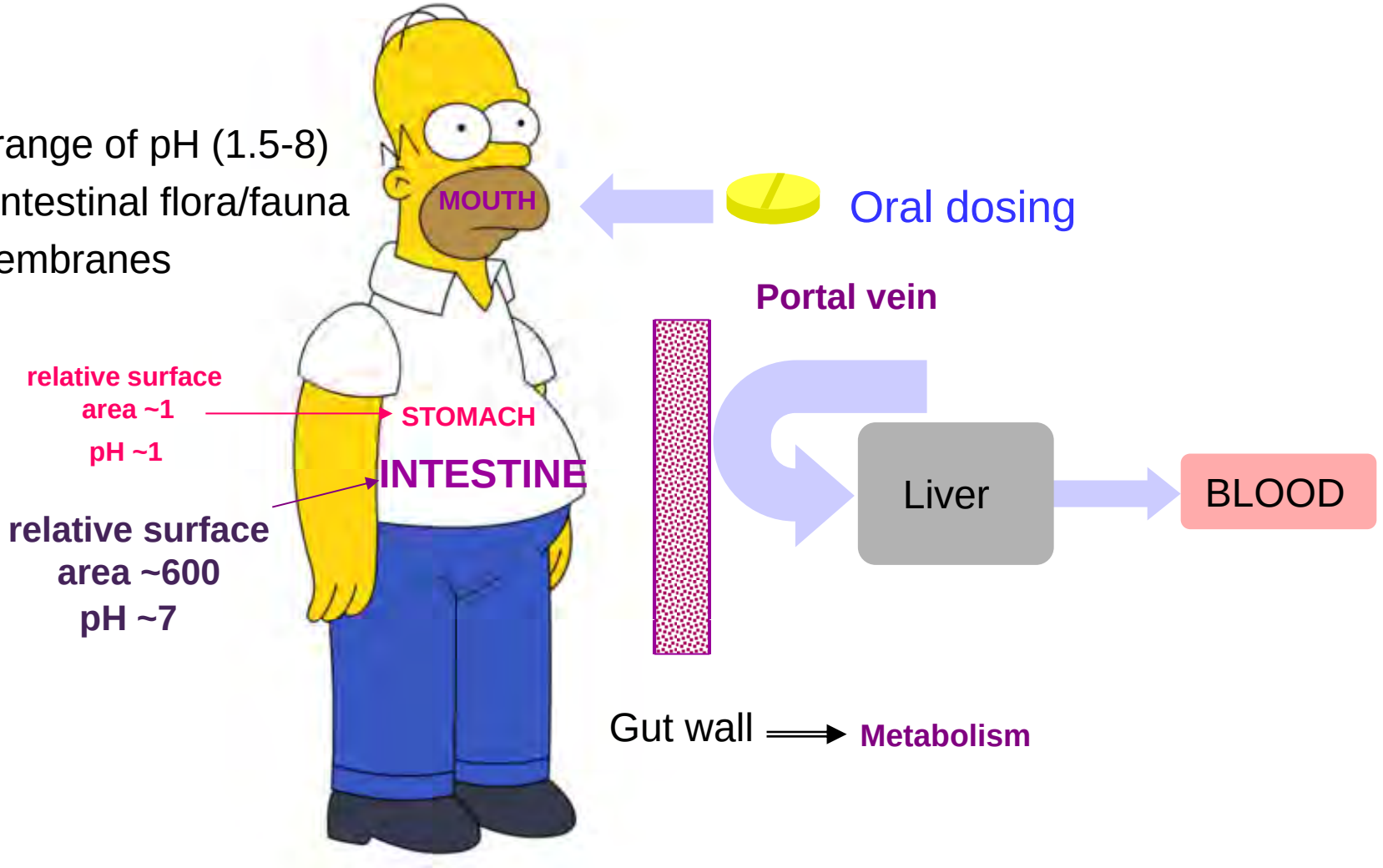
$$F\% = \frac{\text{AUC po / dose}}{\text{AUC iv / dose}} \times 100$$

Compound A has low oral bioavailability

Absorption

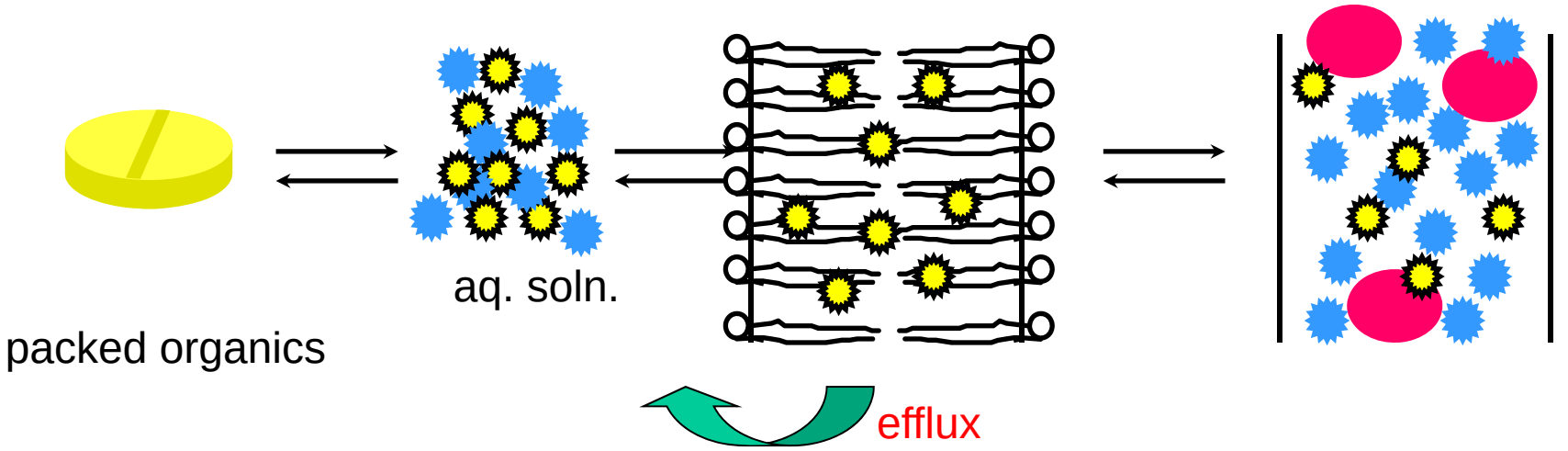
The process by which a drug moves from its site of administration to the systemic circulation

- dissolve
- survive range of pH (1.5-8)
- survive intestinal flora/fauna
- cross membranes



Adapted from a slide by Rhona Cox

Absorption – sources of the problem



dissolving in stomach/intestine
Surviving pH 1-7

crossing membranes (permeability)

- Solubility
- Instability
- Permeability
- Efflux

Absorption - Solubility

Solubility can be measured in a number of
different media: eg, water, (simulated gastric fluid) and
pH values: pH 7.4 (blood), pH 6.5 (small intestine – major site of absorption)

Typical assays for measuring solubility/ dissolution rate:

- "Traditional" solubility / dissolution measurements
  - **Thermodynamic** (equilibrium) measurements
  - values will depend on the crystalline form of the compound
  - caution with amorphous solids!
  - lower throughput

- High throughput turbidometric measurements
  - **Kinetic** measurement from DMSO solutions
  - for newly synthesised compounds
  - quick indication of low solubility

- Calculation/ Prediction from molecular structure
  - in house and commercial programs available

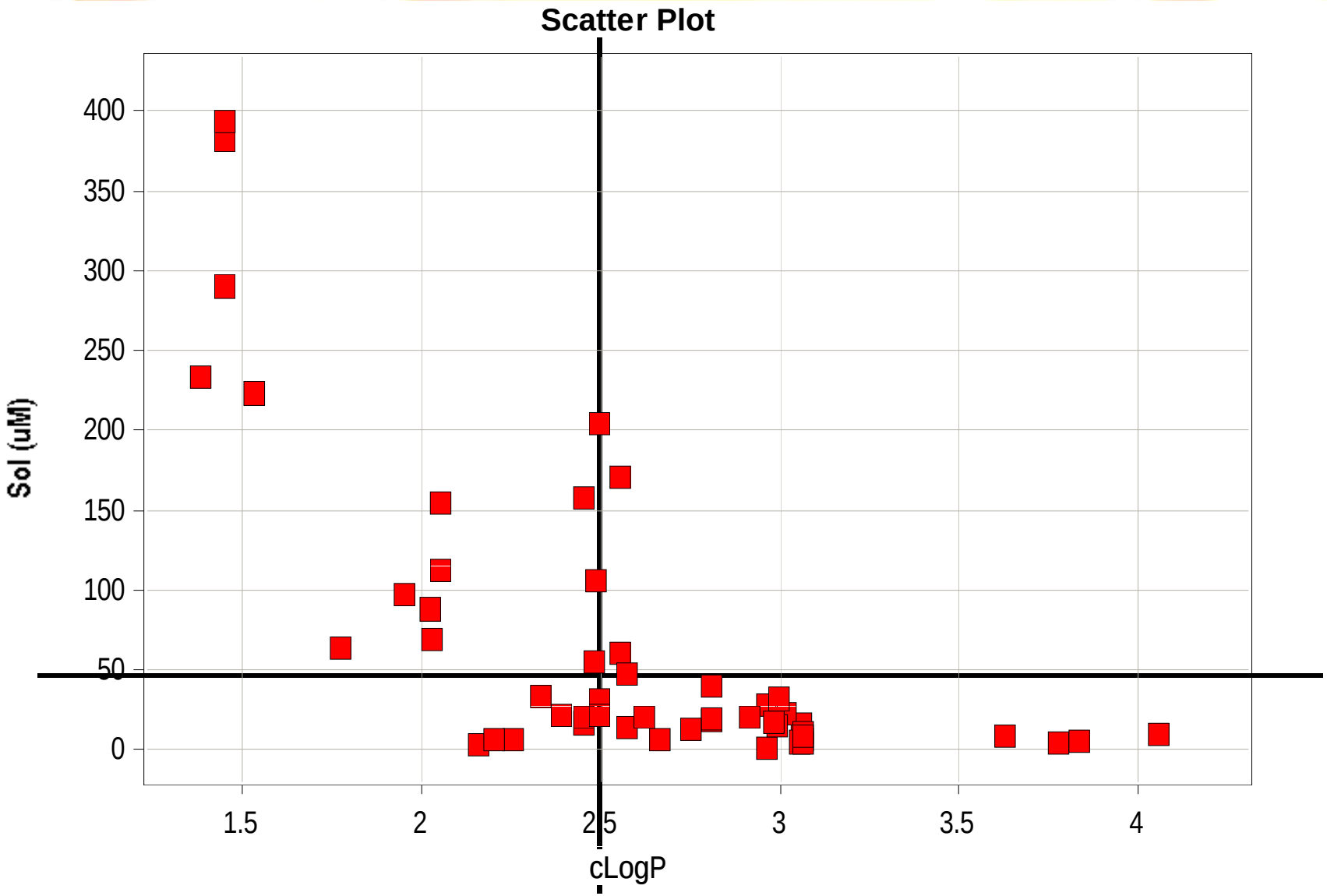
Caution! Need to be aware of differences between thermodynamic and kinetic solubility

Solubility is physical chemistry

What factors govern solubility?

"Brick Dust or Greaseballs"*:*
J. Med. Chem. **2007,** *50,* 5858-5862

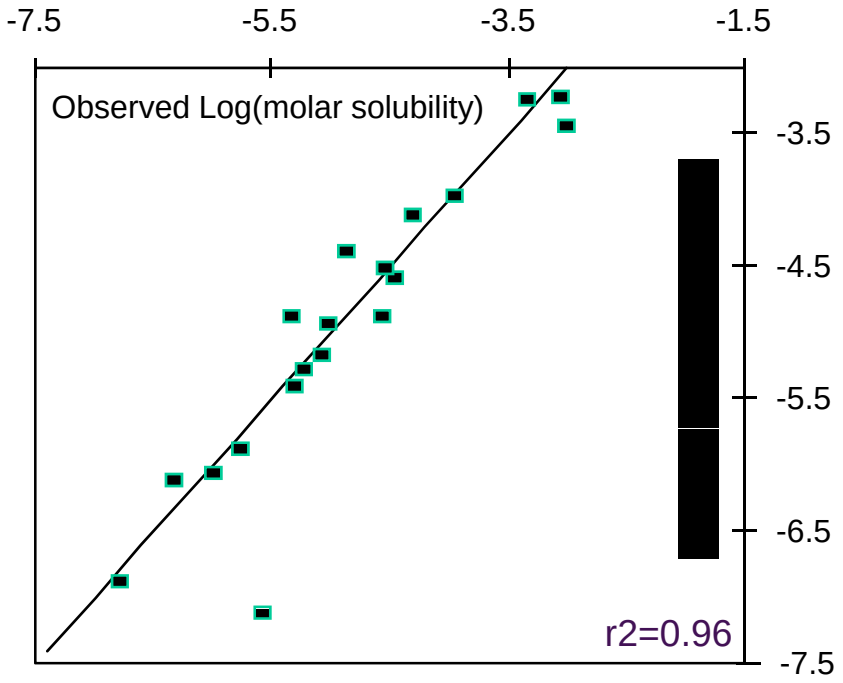
Solubility vs ClogP



Series needs clogP <2.5 for solubility >50µM (~0.025mg/ml)

Predicted vs Observed Aqueous Solubility

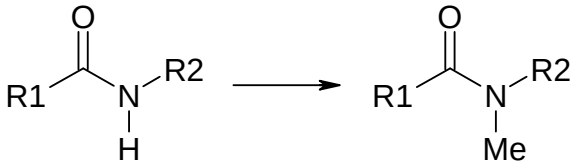
Series of Lipoxygenase Inhibitors:



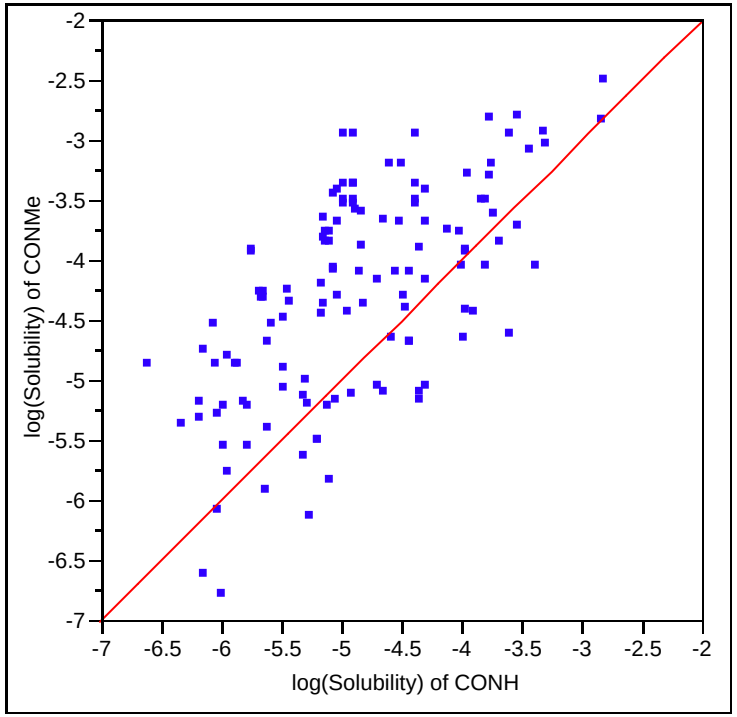
$$\log S = -1.16 \times \log P - 0.018 \times Mpt + 0.93$$

- Mpt reflects energy required to break crystal lattice
- LogP reflects energy required for solute to enter aqueous phase
- Lowering melting point and logP increases solubility

Example: Methylation of amides

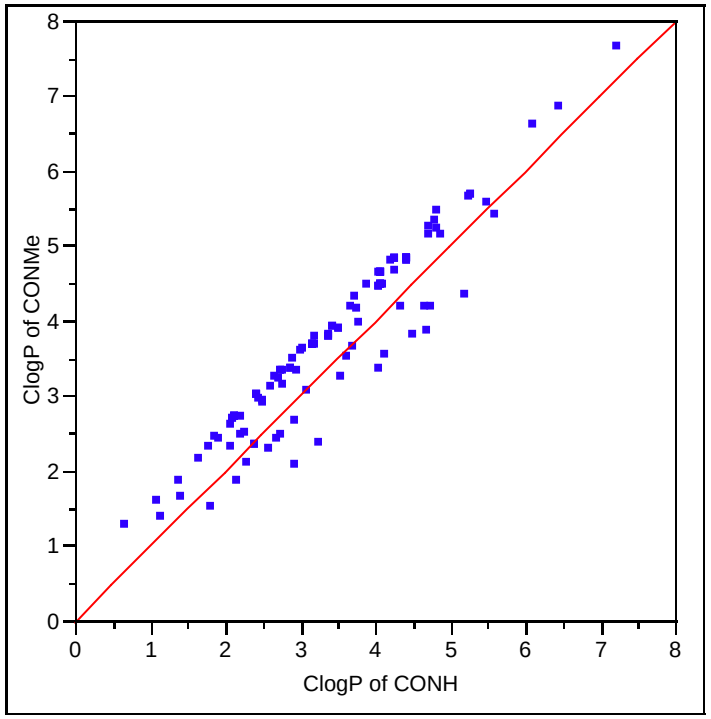


Survey of whole company database of solubility



Mean change = +0.61
For 77% of cases, CONMe is more soluble than CONH

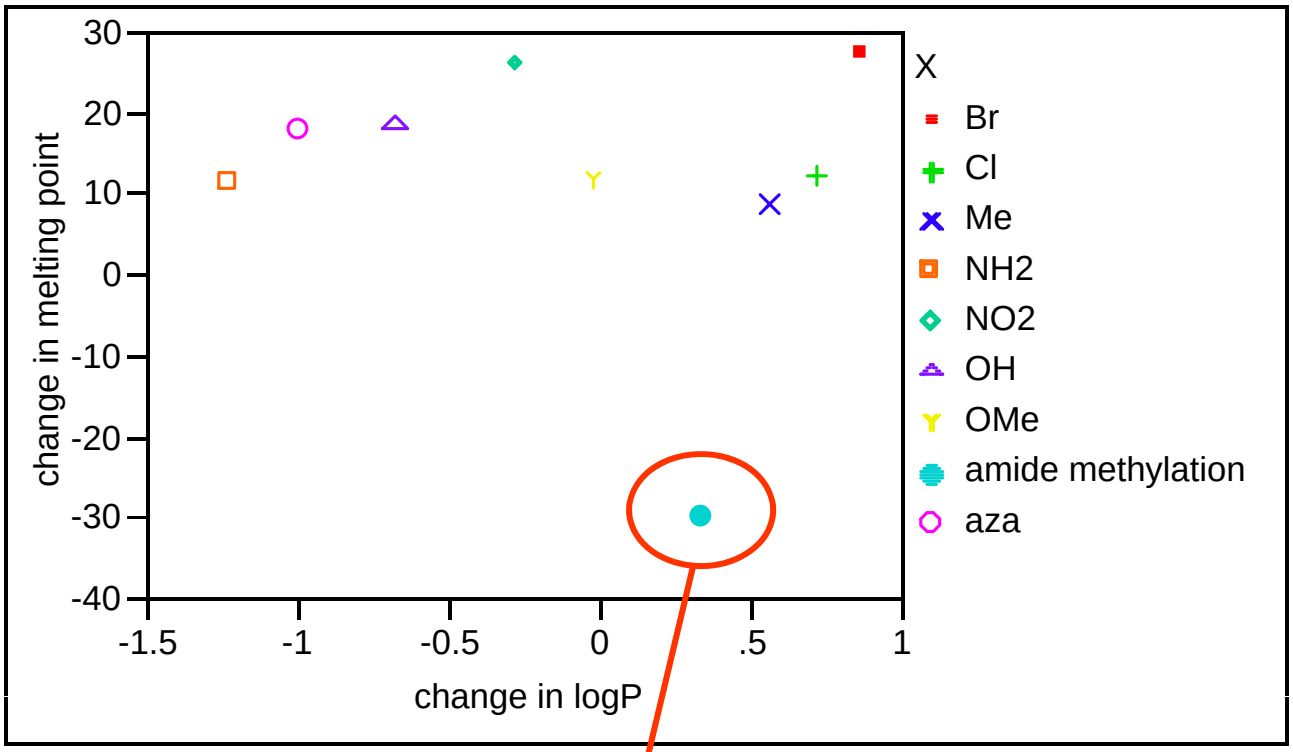
Not lipophilicity driven



Mean change = +0.34
For 82% of cases, CONMe is more lipophilic than CONH

Thanks to: Andrew Leach, AstraZeneca Alderley Park

The solid state & melting points



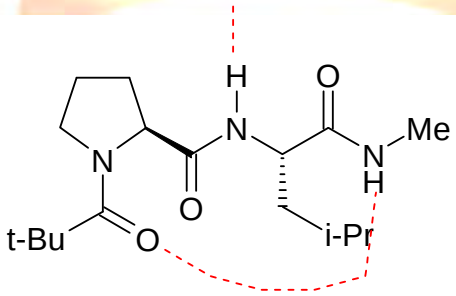
Average change in logP and MPt for matched pairs (data from Beilstein)

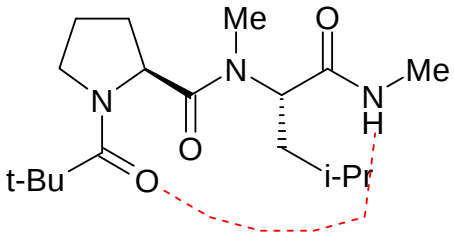
CONMe has higher average logP **lower average melting point** than CONH

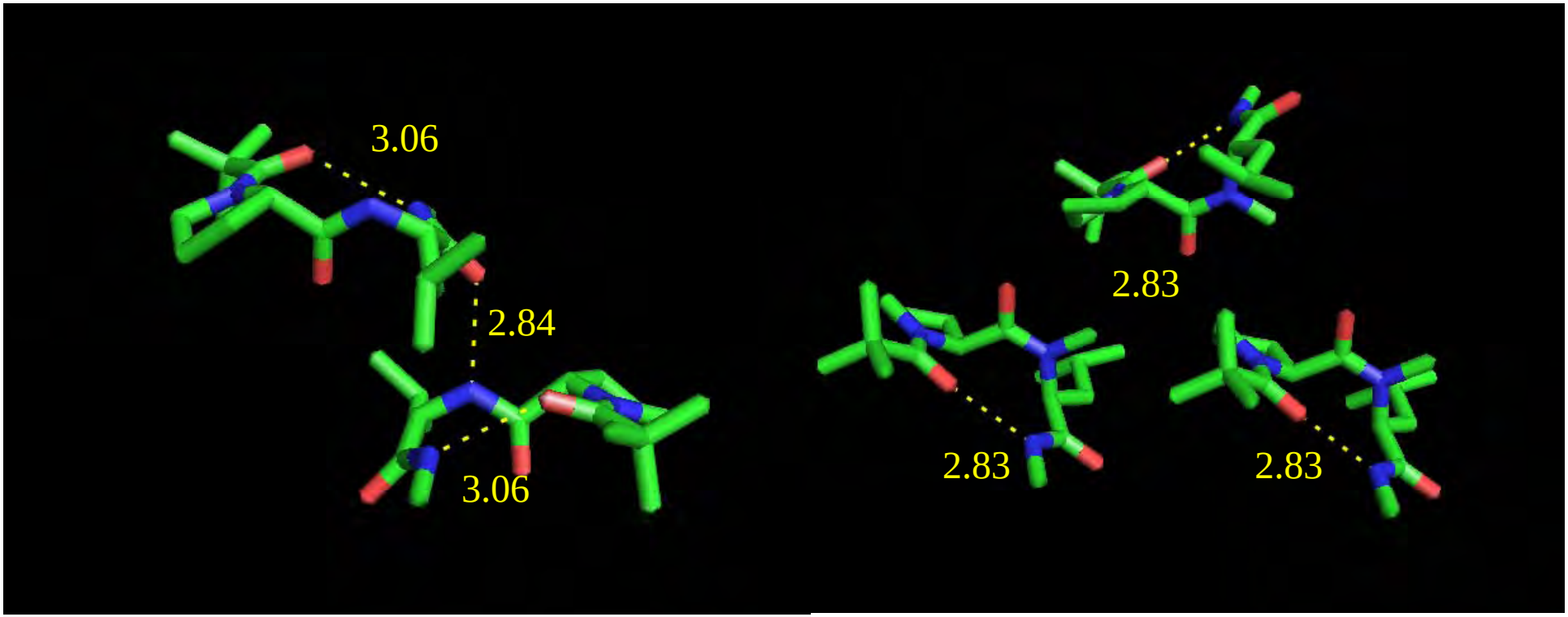
Thanks to: Andrew Leach, AstraZeneca Alderley Park

Journal of Medicinal Chemistry (2006), 49(23), 6672-6682

The solid state & melting points



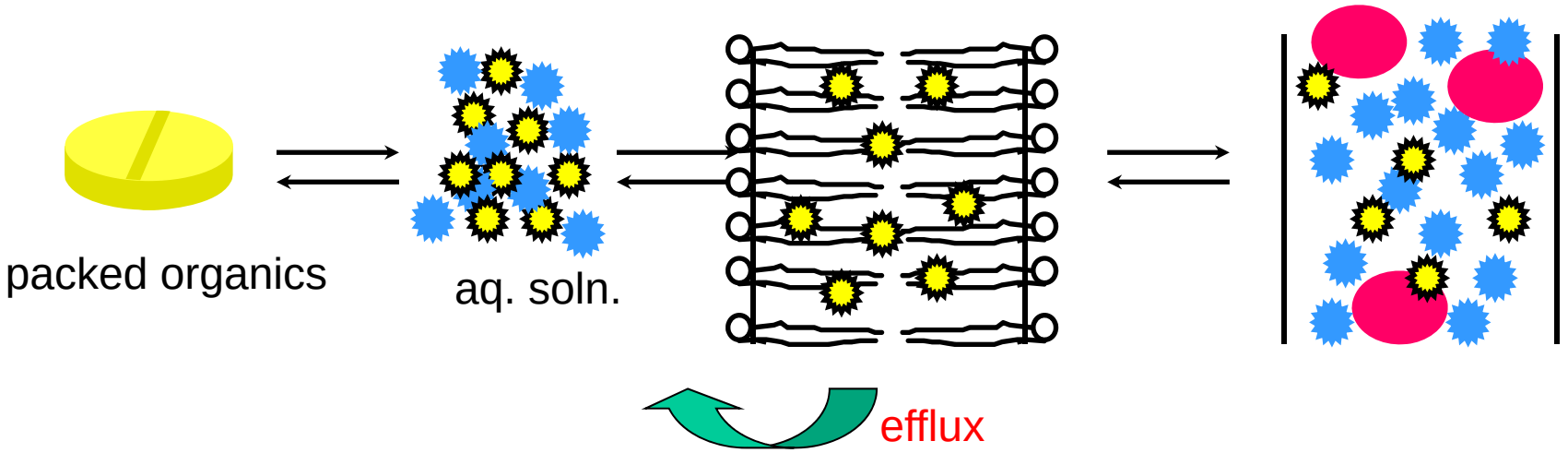




Introduction of CONMe eliminates intermolecular H-bonding:
lowers lattice energy, lowers melting point & increases solubility

Thanks to: Andrew Leach, AstraZeneca Alderley Park

Absorption – sources of the problem



dissolving in stomach/intestine
Surviving pH 1-7

crossing membranes (permeability)

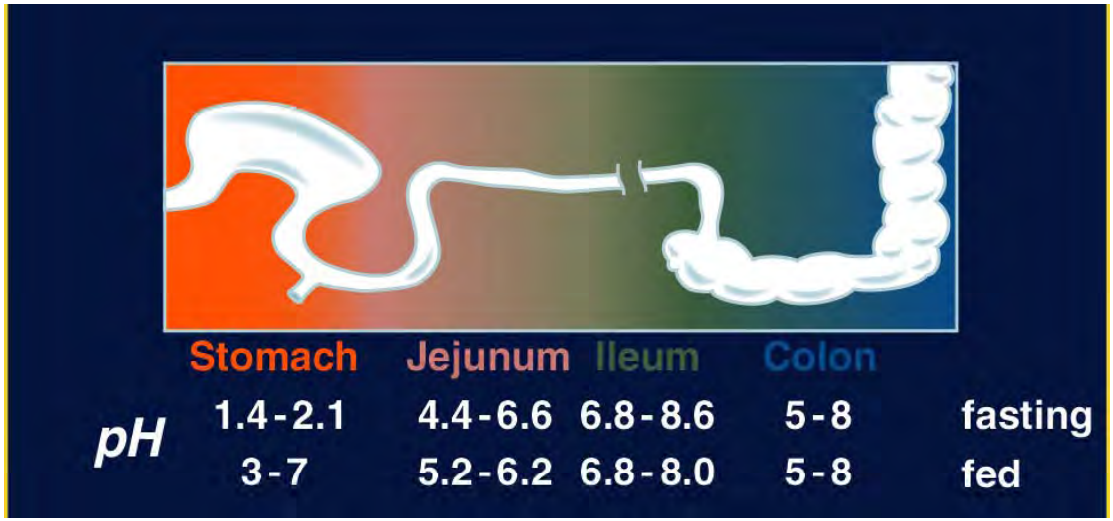
- Solubility
- Instability
- Permeability
- Efflux

→ Measure stability in GI fluids/range of pHs

Absorption: pH ranges and GI stability

Compounds administered orally will encounter:

- A pH range from 1 to 8 in the GI tract
- Digestive and bacterial enzymes



note effect of feeding!

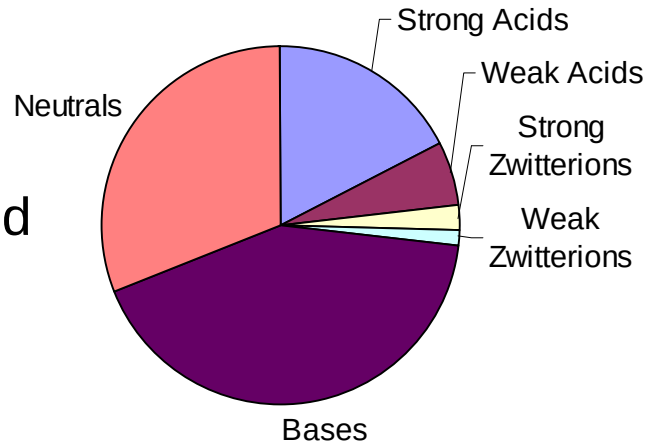
Compounds may be unstable to acid pH range (1-3)

- measure stability over time as a measure of pH

Compounds may be unstable to lipases, peptidases, esterases etc

- use gastric fluid ex vivo or purified enzymes

Why is pKa important ?



When pH = pKa, 50% charged & 50% uncharged

Many marketed drugs are acids or bases

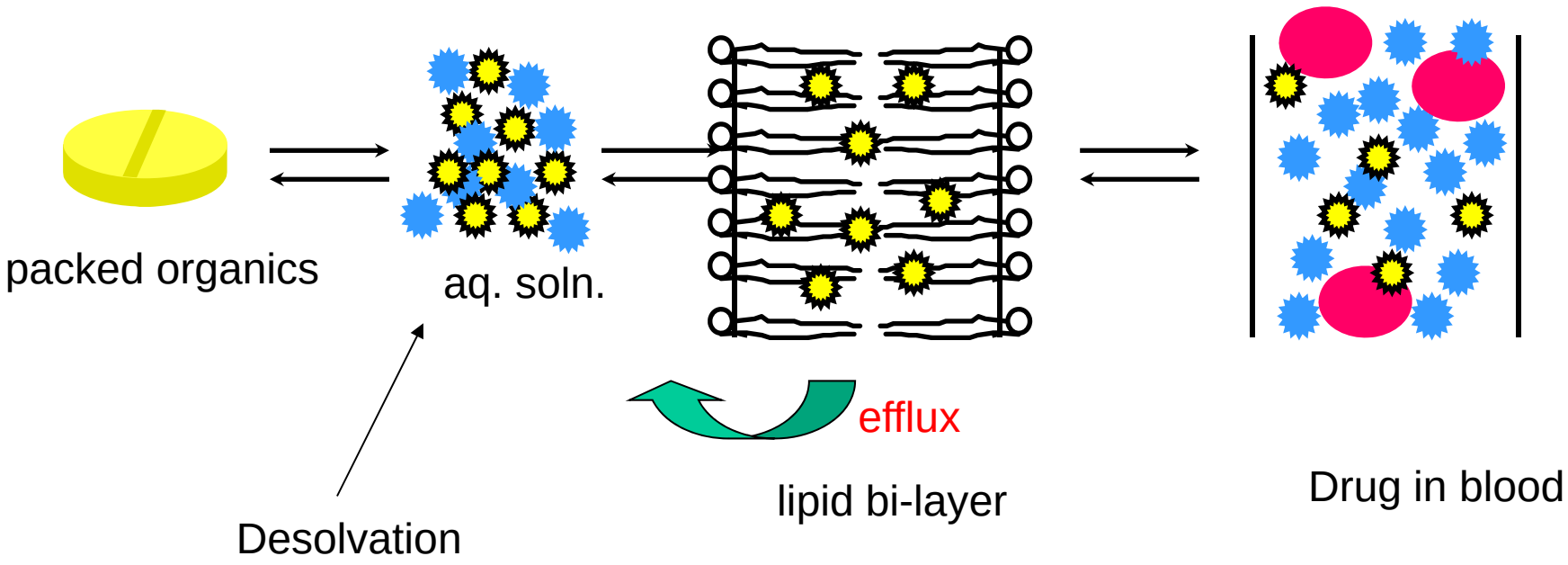
Acids, bases and neutrals have very different ADMET properties:

- Adding ionizable groups can enhance solubility (pH dependent)

but...

- Ionized species pass through lipid membranes at a much lower rate than neutrals

Absorption – sources of the problem



crossing membranes (permeability)

- Solubility
- Instability
- Permeability
- Efflux

Permeability is also physical chemistry

What factors govern permeability?

Lipinski Rule of 5

• Poor permeability is more likely when:

- Mol Weight > 500
- LogP > 5
- > 5 H- bond donors (eg OH, NH)
- The sum of N and O atoms > 10

Adv. Drug Delivery Rev. 1997, 23, 4-25
J. Pharm. Toxicol. Methods 2000, 44 235-249

• Since Lipinski's data set relates to marketed drugs, and
• Lead optimisation often involves increasing complexity,
• The concepts of 'lead-like' parameters and 'ligand efficiency' have arisen:

"Astex Rule of 3" for optimal lead compounds:

- Mol Weight < 300
- LogP < 3
- No. donors < 3
- No. acceptors < 3

See: Congreve et al: *J. Med. Chem*., **2008**, 51, 3661 (excellent recent review) & *DDT,* **2003**, 8, 876 (Rule of 3)
Teague et al: *Angewandte Chemie, International Edition* **1999**, 38, 3743 (lead-like)

Larger molecules need more lipophilicity to permeate membranes.

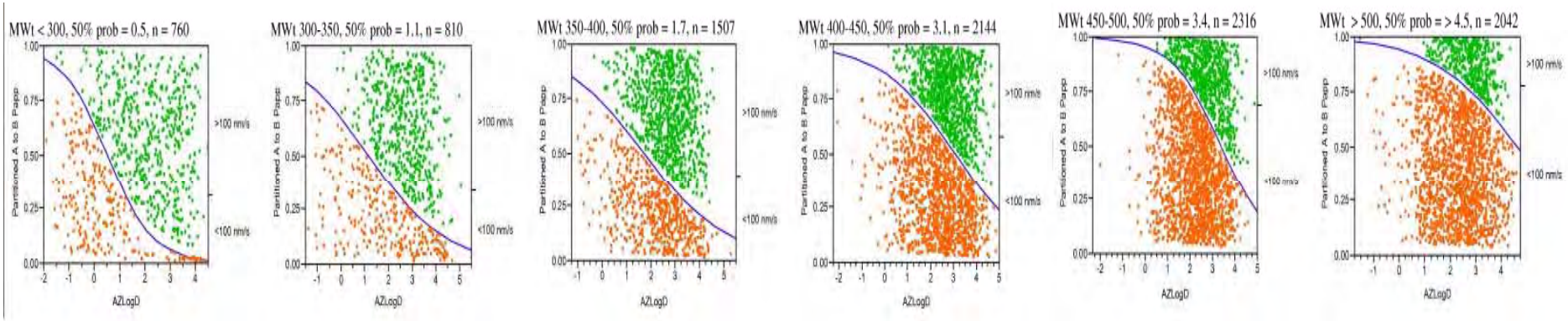
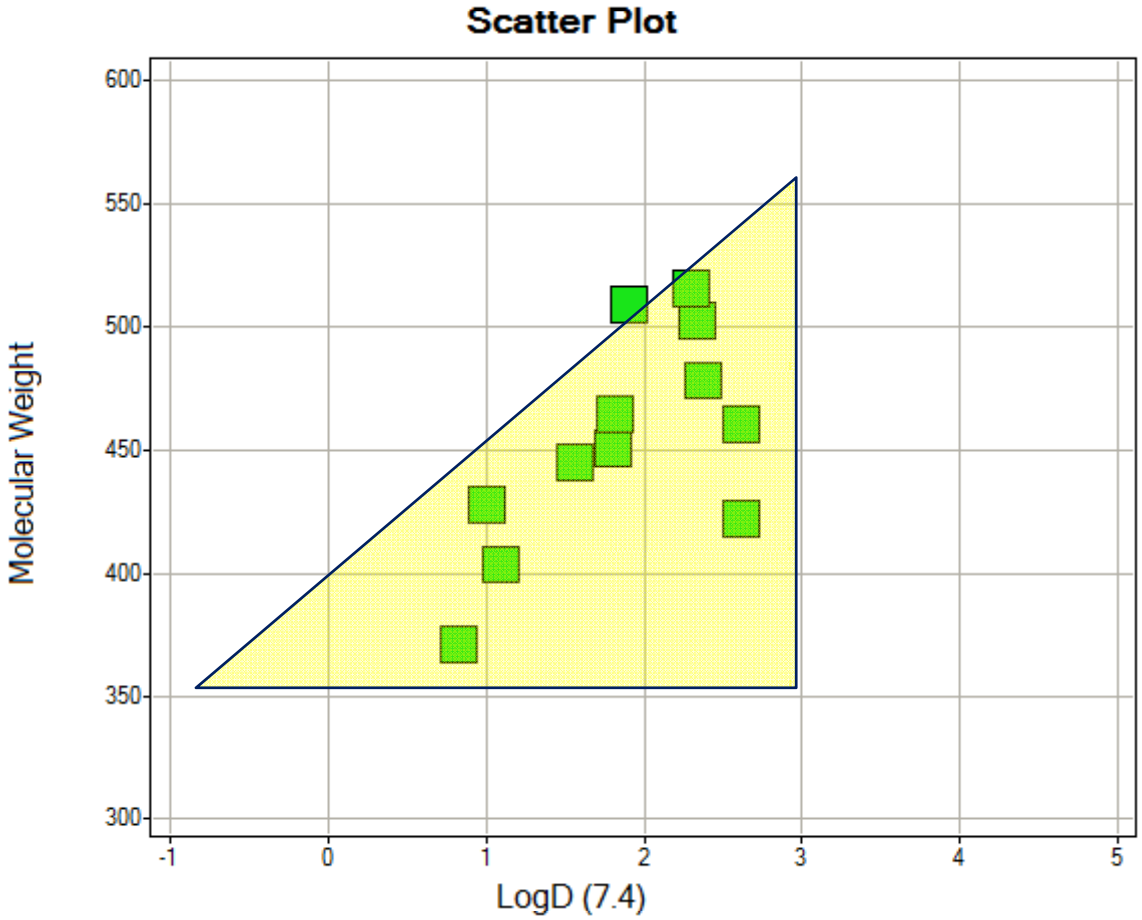


Table 2
Permeability rules defining *AZlog D* limits required to achieve >50% chance of high permeability for a given molecular weight band

Molecular weight	*AZlog D*
<300	>0.5
300–350	>1.1
350–400	>1.7
400–450	>3.1
450–500	>3.4
>500	>4.5

- Defining optimum lipophilicity and MW ranges for drug candidates – MW dependent logD limits based on permeability. Waring, *Bioorg. Med. Chem. Lett.*, 2009, *19*, 2844
- Lipophilicity in drug discovery. Waring. Expert Opin Drug Discov. (2010) 5(3) 235

Optimal Window & Development Compounds



- Development compounds often lie within optimal window – ‘Golden Triangle’
- More polar compounds allowed by lower MWt
- Does this lead to increased chance of success?

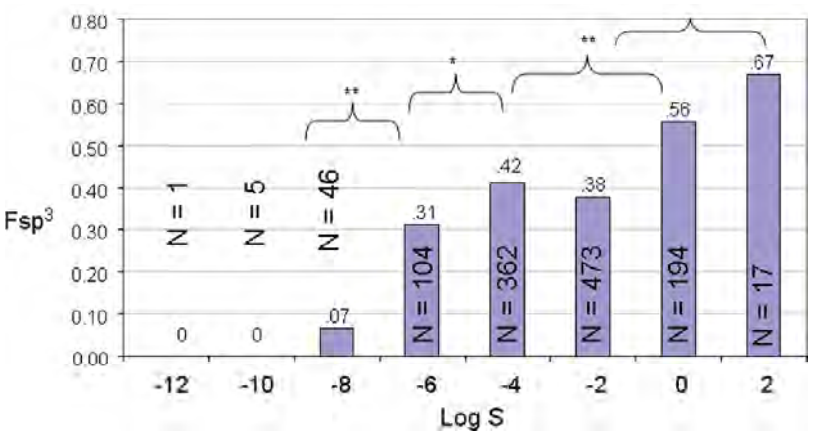
See also: Johnson, T.; Dress, K.R.; Edwards, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5560

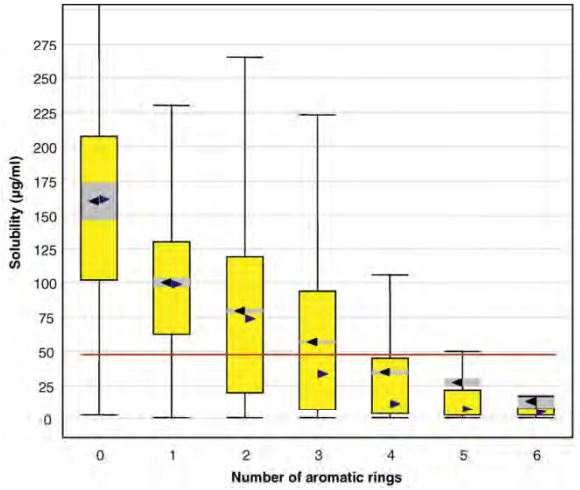
Impact of Molecular Shape / Complexity

- Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success (Lovering, Wyeth)

J. Med. Chem. 2009, 52, 6752–6756

- A simple & interpretable measure of the complexity of molecules is carbon bond saturation, as defined by Fraction sp^3 (Fsp^3) where: $Fsp^3 = (\text{number of } sp^3 \text{ hybridized carbons}/\text{total carbon count})$
- Significant enrichment of increased saturation as compounds progress through clinical testing:
- Fsp^3 correlates with improved solubility (& reduced Mpt):





- The impact of aromatic ring count on compound developability – are too many aromatic rings a liability in drug design? (Ritchie & Macdonald, GSK)

Drug Discov. Today 2009, 14, 1011-1020

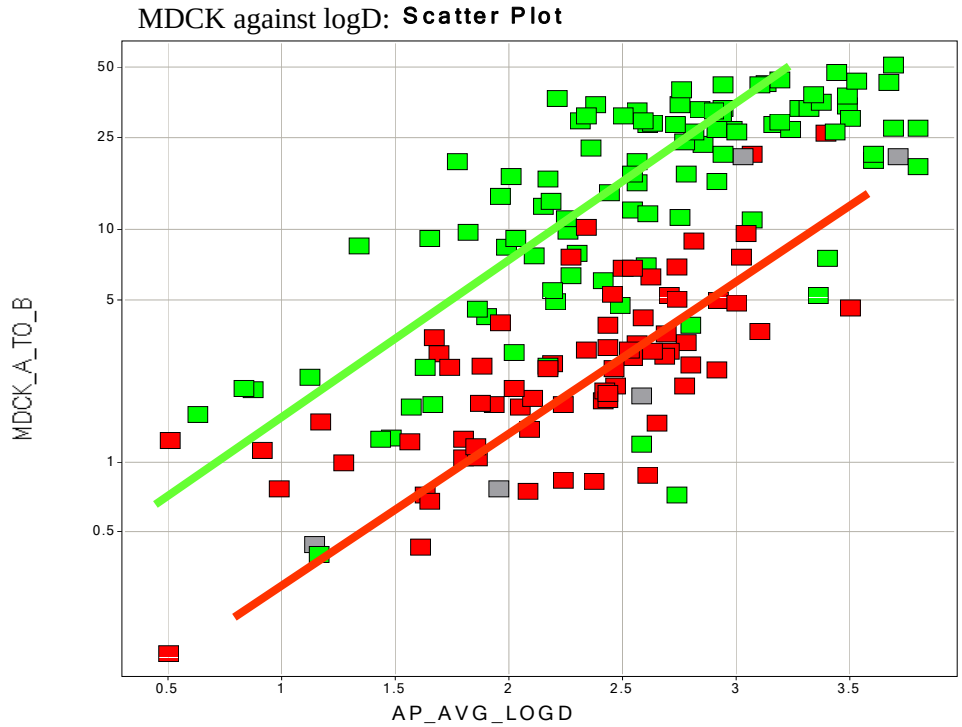
  - As aromatic ring count increases:
    - Lipophilicity increases
    - Solubility decreases (even when clogP remains constant)
    - Protein binding, Cyp inhibition & hERG liability increase (later...)
  - >3 Ar rings correlates with poorer compound developability & increased risk of attrition in development

- Molecular flexibility (# of rotatable bonds) has also been shown to correlate with oral bioavailability (*Veber, GSK)*

J. Med. Chem. 2002, 45, 2615

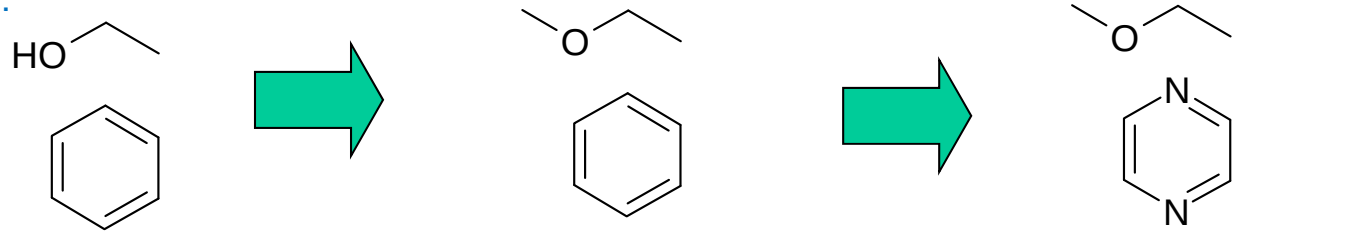
H-bonding & Permeability

Minimising number of H-bond donors is a good strategy to improve permeability:



1 donor green,
2 donors red,
>2 grey

Structural changes:

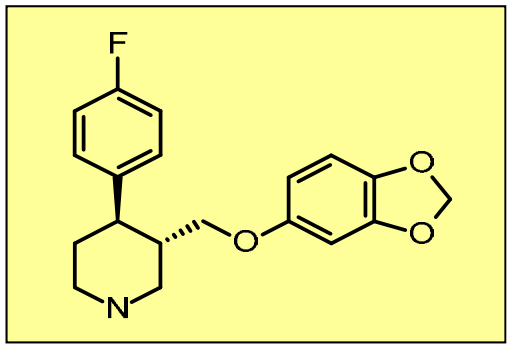


Removal of donor improves permeability but increases logD outside target range

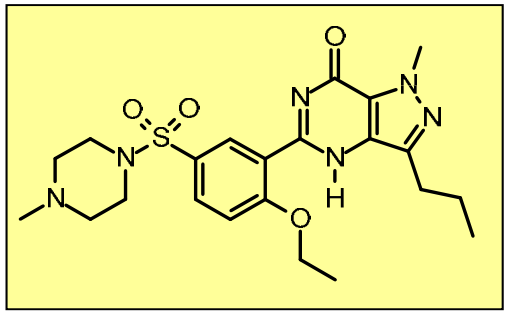
logD increase can be offset by introducing heteroatoms

Polar Surface Area (PSA)

The Polar Surface Area (PSA) of a molecule is defined as the area of a molecule's van der Waal's surface that arises from O or N atoms, or hydrogen atoms attached to O or N atoms.

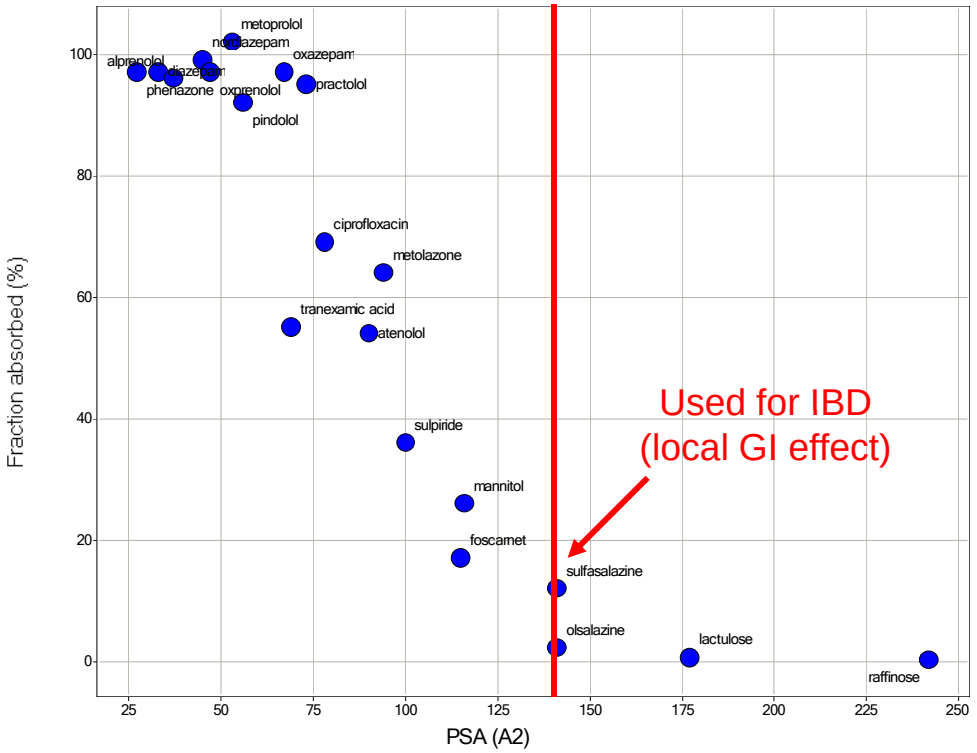


Paroxetine 39A^2



Sildenafil 109A^2

Human intestinal permeability v PSA



Veber reported that best probability of good oral bioavailability if PSA < 140 A^2

J. Med. Chem. 2002, 45, 2615

Maximum Absorbable Dose (MAD)

MAD (mg) = S x Ka x SIWV x SITT

Pharmaceutical Research, Vol. 13,1996,1795-1798

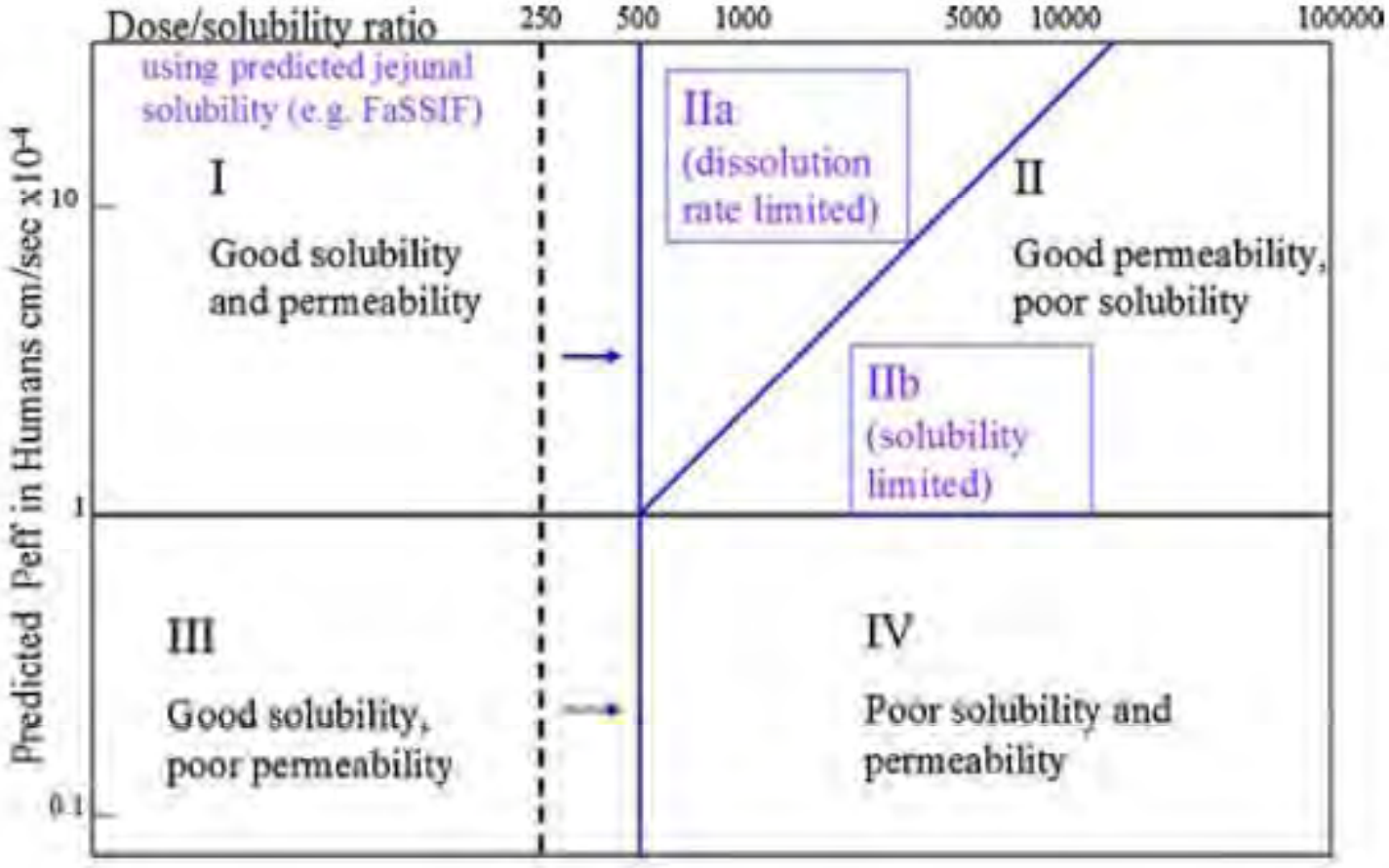
S = solubility (mg/ml) at pH 6.5
Ka = intestinal absorption rate constant (min^{-1})
(derived from rat intestinal perfusion expt - similar to man)
SIWV = small intestine water volume ~ 250 ml for man
SITT = small intestine transit time ~ 270 min (4.5h) for man

MAD = quantity absorbed if the small intestine were saturated with drug for 4.5h
(eg, dose 10g/kg to saturate small intestine, how much of the dose will be absorbed)

Impact of MAD:
Take two compounds with projected human dose of 70 mg

Compound	Ka	Solubility	MAD
Cmpd A	0.001 min^{-1}	5 mg/ml	337 mg
Cmpd B	0.03 min^{-1}	0.001 mg/ml	2 mg

Developability Classification System

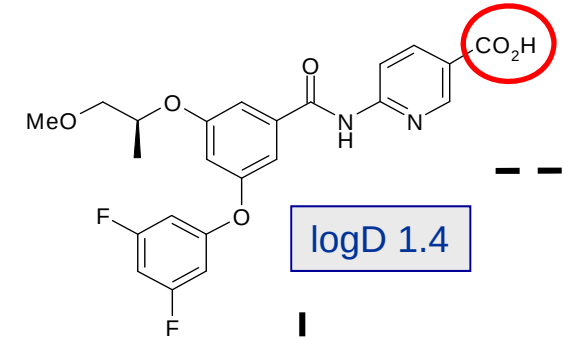


Compounds in class IIb take on average twice as long (ie 2 years longer) to fail in development.

Time is expended on having to do very expensive human studies to only discover that the compound can not be progressed because of, for instance, lack of efficacy due to lack of exposure of compound to target. This would have been found out earlier in animal studies if the compound had better properties that could have enabled more effective earlier decision studies.

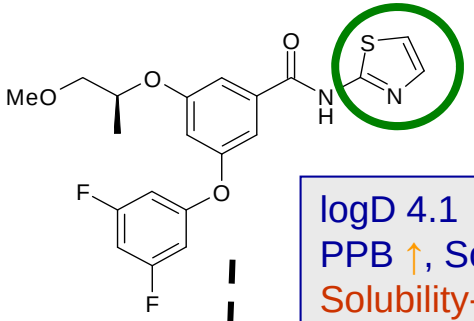
The developability classification system: Application of biopharmaceutics concepts to formulation development
James M. Butler, Jennifer B. Dressman· Journal of Pharmaceutical Sciences, 99(12),4940–4954, 2010

Balancing Solubility & Permeability



logD 1.4

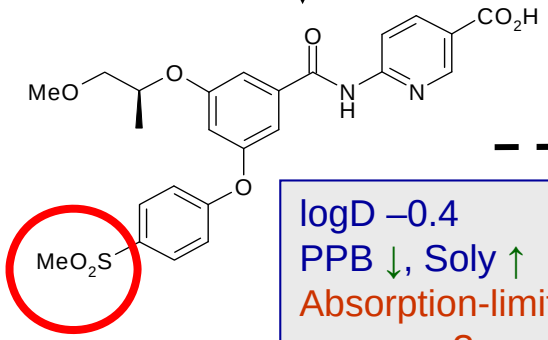
Want to remove acid functionality



logD 4.1
PPB ↑, Soly ↓
Solubility-limited exposure?

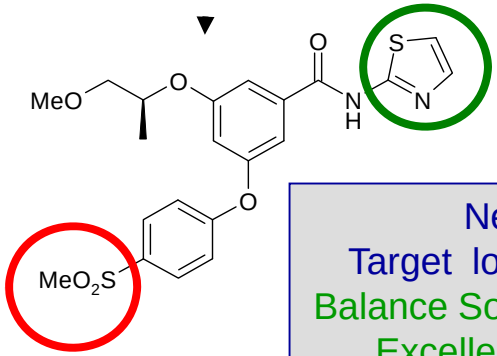
Sought to increase solubility

Combine



logD –0.4
PPB ↓, Soly ↑
Absorption-limited exposure?

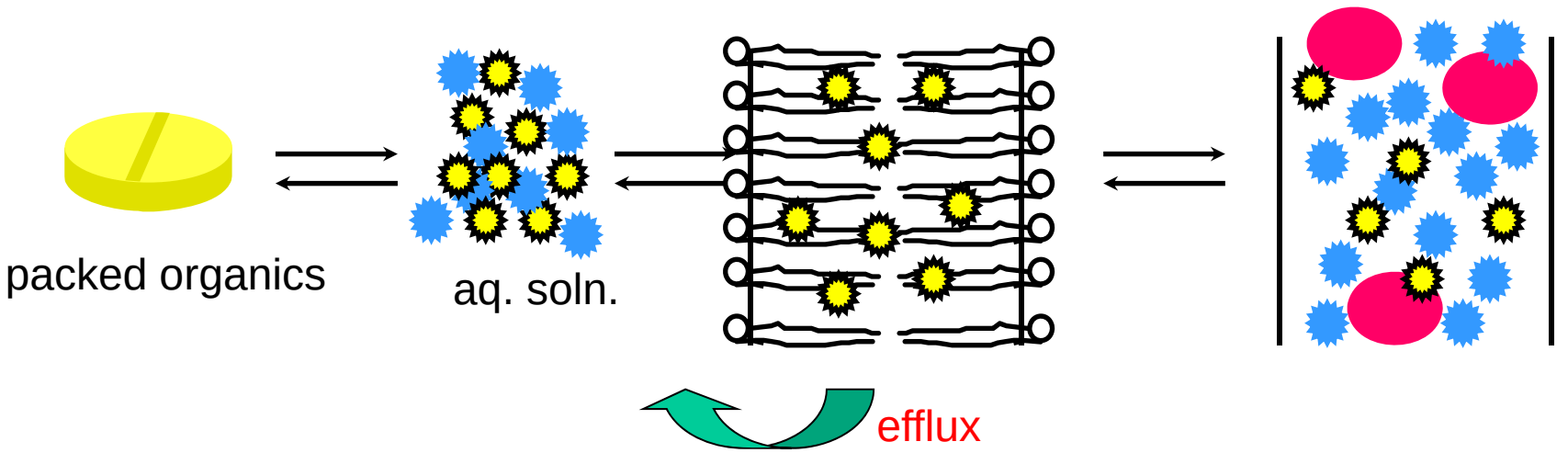
Combine



Neutrals
Target logD range 2-3
Balance Soly & Absorption
Excellent exposure

Example of need to balance permeability & solubility to optimise in vivo exposure

Absorption – sources of the problem



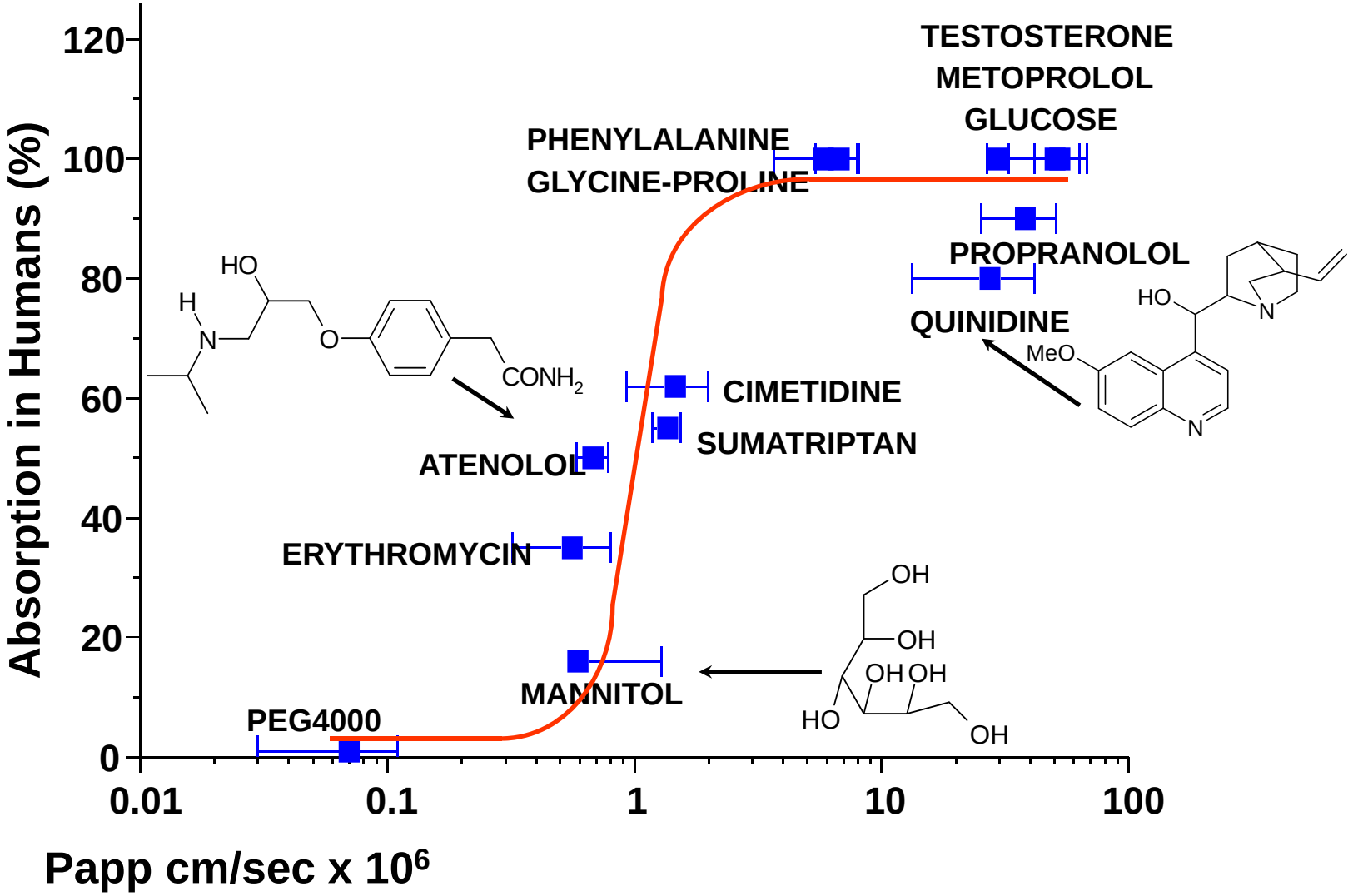
dissolving in stomach/intestine
Surviving pH 1-7

crossing membranes (permeability)

- Solubility
- Instability
- Permeability
- Efflux

Active Transport

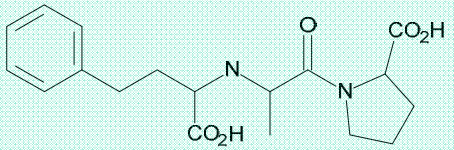
Caco-2 Model of Absorption



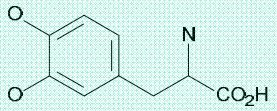
Uptake Transporters

- Uptake transporters enhance the absorption of drug molecules from the intestine (*Current Drug Metabolism 2004, 5, 109-124*)
- They may also enhance the distribution of drugs into certain organs such as the brain and into hepatocytes to enable metabolic or biliary clearance
- In contrast to passive diffusion, active transport can be saturated
  - Finite number of transporter protein molecules on cell

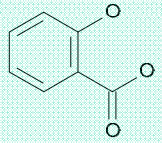
- Examples of uptake transporters and their substrates
  - Oligopeptide transporters PEPT1, PEPT2 - enalapril



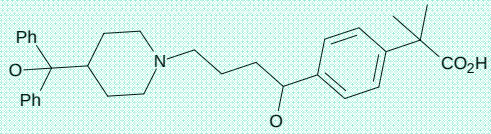
  - Large neutral amino acid transporter (LAT1) - L-dopa



  - Monocarboxylic acid transporter (MCT1) – salicylic acid



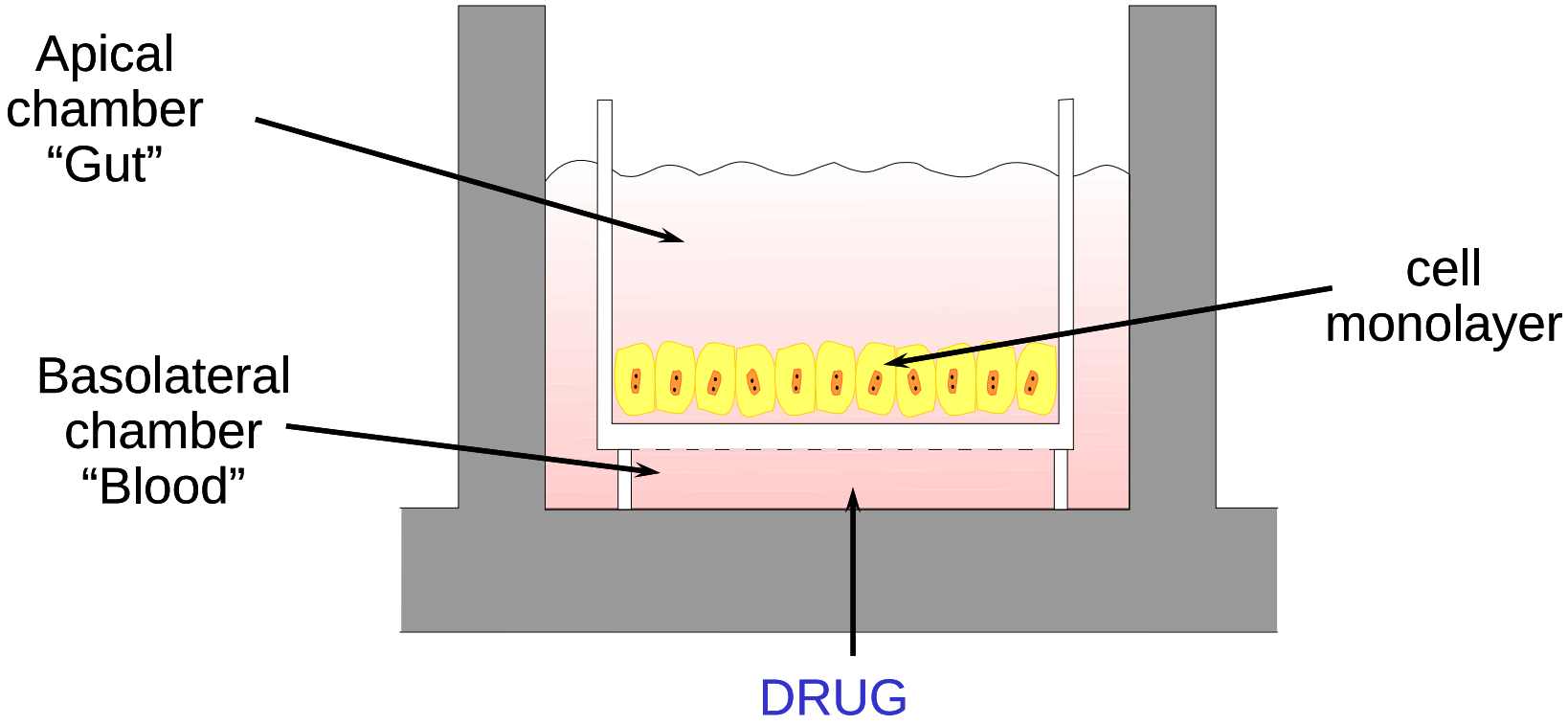
  - Organic anion transporters (OATP1B1, OATP1B3) – Fexofenadine
    - Other substrates – statins, Angiotensin II antagonists



Efflux (P-glycoprotein, P-gp, MDR-1)

- Efflux transporters on the intestinal lumen (apical) oppose the absorption of certain drug molecules
- Mainly a function of a transporter in the cell membrane called P-glycoprotein. Abundant in “protective cells – BBB, intestine, liver, kidney
- Some compounds are a substrate for P-gp
  - Enter the cell by passive diffusion, some of the compound is transported back into the intestinal lumen.
  - No clear SAR but common features emerging
- Some compounds inhibit P-gp
  - An inhibitor (eg verapamil) will increase the absorption of P-gp substrates
- Other efflux transporters exist eg BCRP, MRP2 which effect drug disposition

Caco-2 cells - Transport Experiment (efflux measurement)

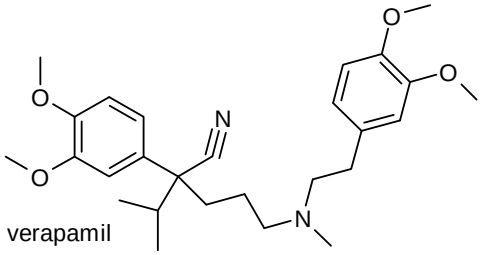


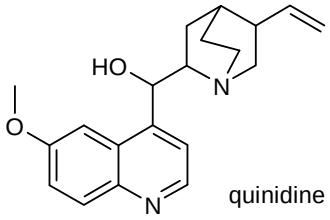
If Papp B-A > A-B then efflux may be operating

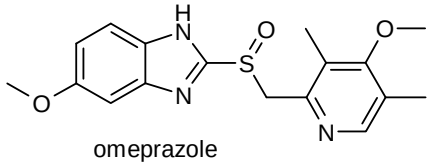
General Characteristics of P-glycoprotein Substrates

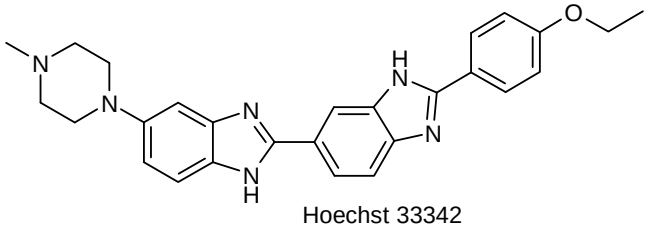
- Lipophilic often with multiple aromatic rings
- High Mol Wt (>400) (increased probability for points of interaction)
- Ampiphilic often with weak cationic group present
- Electronegative groups contributing dipole moment
- 1-3 H-bond acceptors (N, 0) and/or 1-2 H-bond donors (NH, OH)
  - Alkoxy and Carbonyl are frequent functionalities

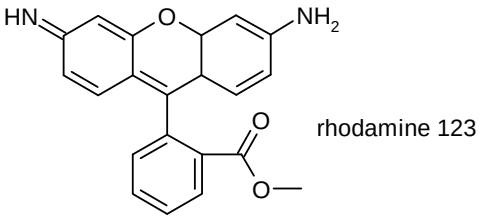
- **As membrane passive diffusion increases, P-gp pump efficiency decreases**
- Review – T.J. Raub, Molecular Pharmaceutics, 2006, 3(1), 3-25.





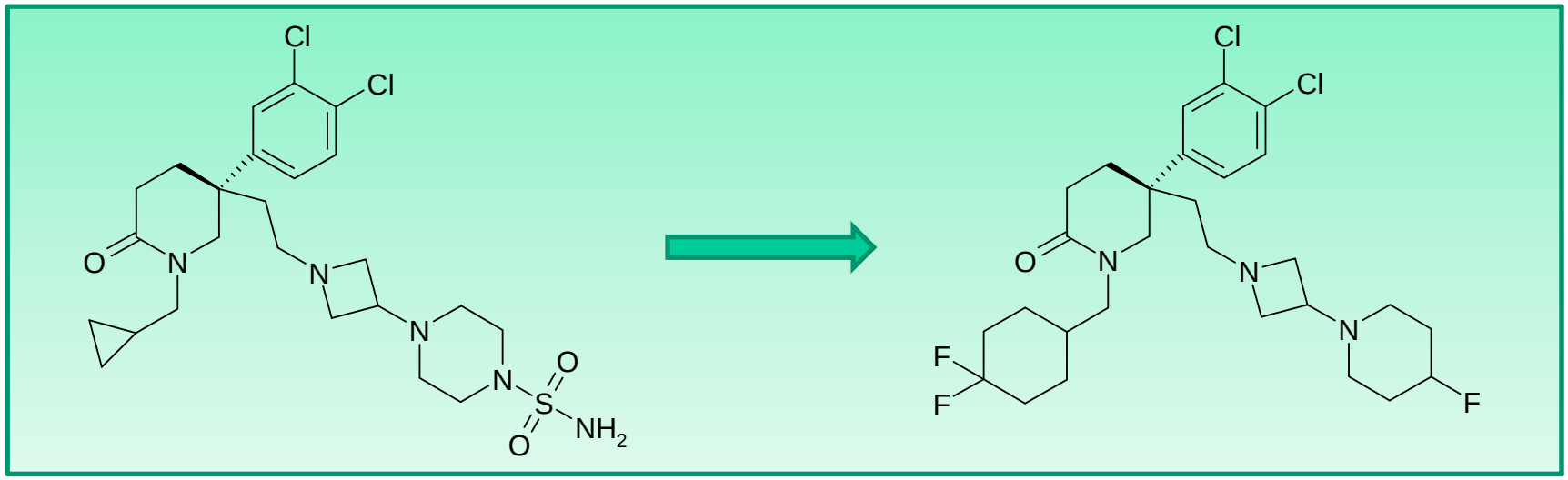






Pfizer NK2 Antagonists

Journal of Medicinal Chemistry (2002),45(24),5365-5377.



UK-224,671
NK2 pIC_{50} = 8.4

clogP = 2.2
Mol weight = 545
PSA = 98 A^2, HBD = 2

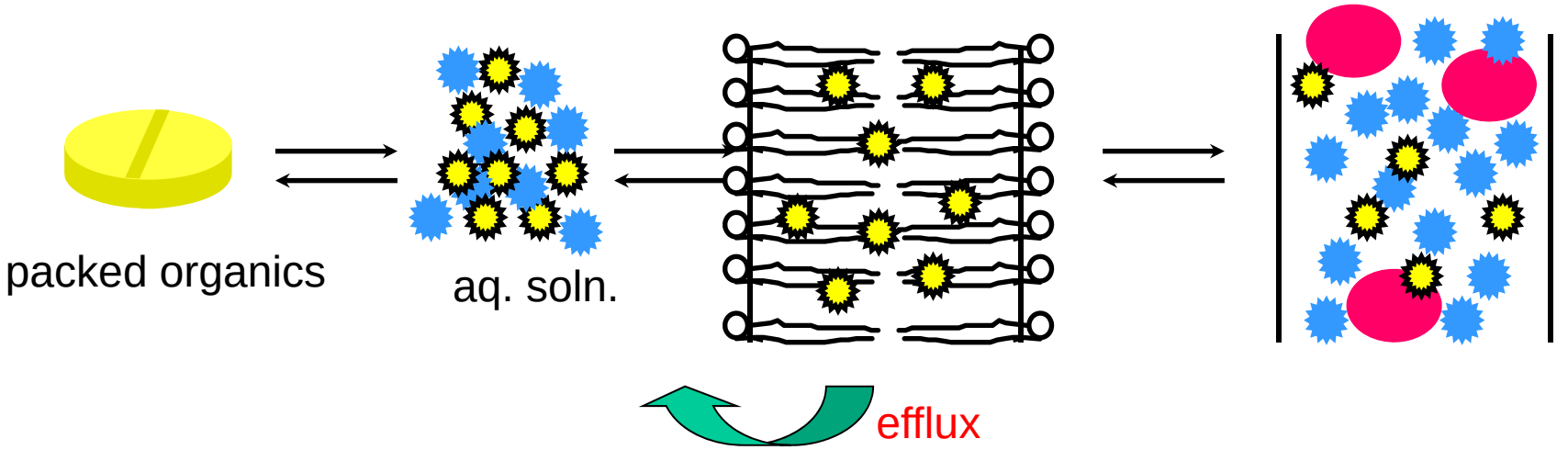
Caco-2 %/h A-B/B-A = 1/18
Rat %F < 20
P-gp KO mice > 20%

UK-290,795
NK2 pIC_{50} = 9.4

clogP = 4.1
Mol weight = 561
PSA = 27 A^2, HBD = 0

Caco-2 %/h A-B/B-A = >35/>35
Rat %F > 80

Absorption – sources of the problem

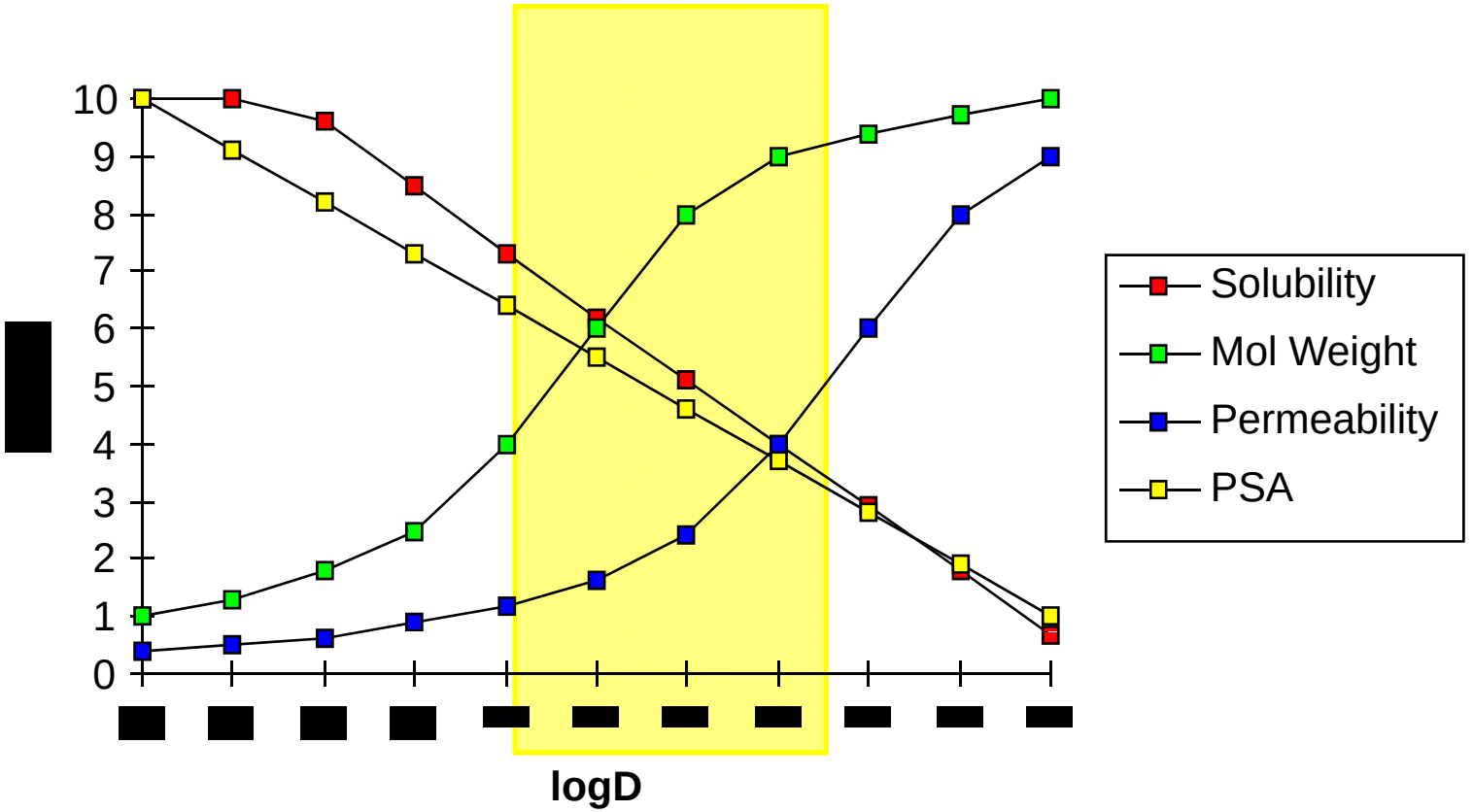


Dissolving in stomach/intestine
Stable pH 1-7

Crossing membranes (permeability)

- Solubility
- Instability
- Permeability
- Efflux

logD vs physicochemical parameters



Over-simplification and series-dependent, but can be a useful working guide to chemistry

eg see Smith et al, *Med. Research Rev*. 1996, 16, 243-266

In Summary..what *you* can do:

- Poor absorption may be due to :

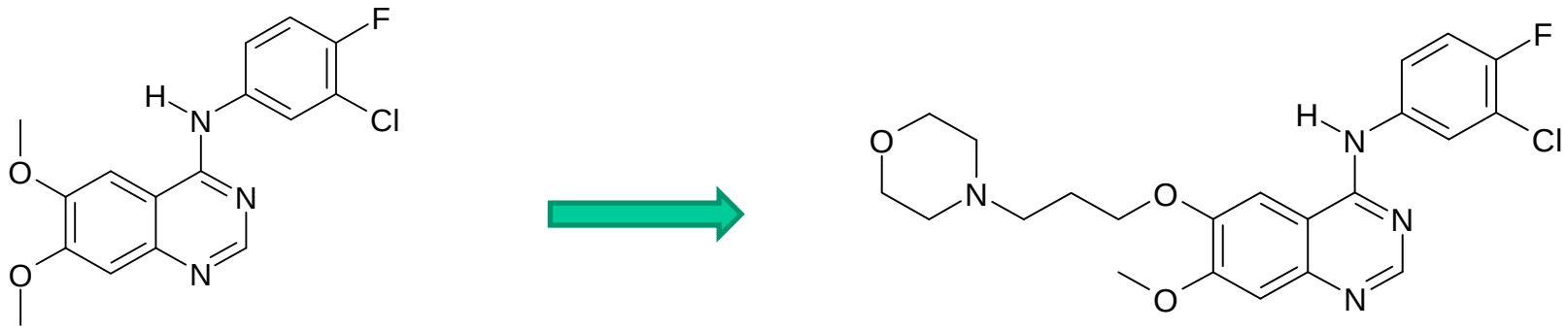
- Poor solubility
  - Reduce lipophilicity/ add polar/ ionizable groups
  - Reduce melting point (by reducing symmetry, planarity)

- Poor permeability
  - Increase lipophilicity
  - Decrease polar surface area/H-bonding
  - Decrease mol weight

- Efflux
  - Increase passive permeability to reduce impact of efflux

Worked examples…

Solubility of Iressa



EGF - RTK IC_{50} 0.009 μM

Stim. Cell Growth IC_{50} 0.08 μM

Solubility at pH 7 7.2 μM

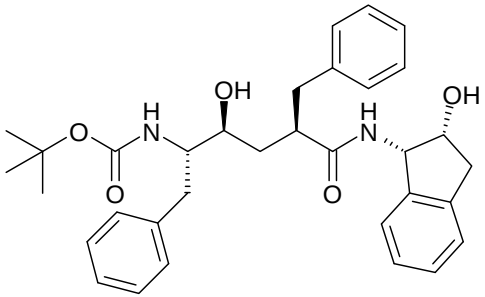
Solubility at pH 7 (phosphate) 3.7 μM

Solubility at pH 3 (phosphate) 2.2 mM

Solubility at pH 1 (HCl) 48 mM

Solubility and oral absorption

HIV protease inhibitors (J. Med. Chem. 1994, 37, 3443-3451)



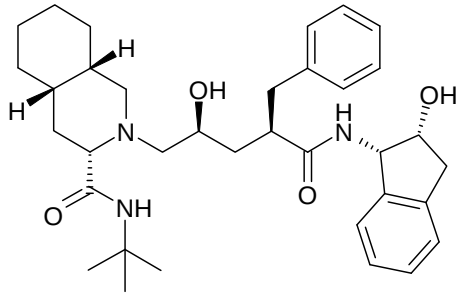
I

IC_{50} = 0.3nM

No oral bioavailability in dog

Solubility (pH 7.4) < 0.001 mg/ml

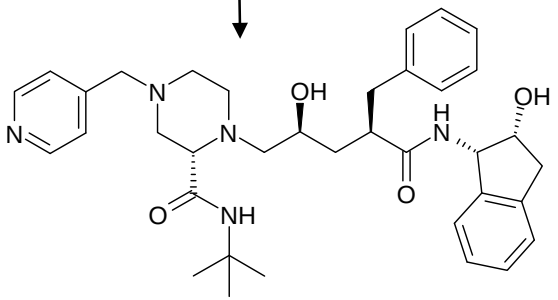
clogP = 5



II

IC_{50} = 7.8 nM

15% oral bioavailability in dog



III

IC_{50} = 0.3 nM

Solubility (pH 7.4) = 0.07 mg/ml

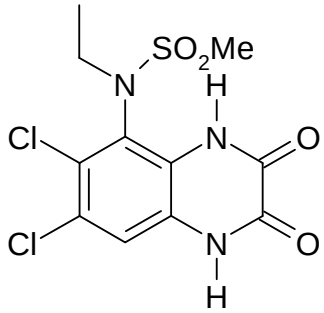
70% oral bioavailability in dog

clogP = 2.8

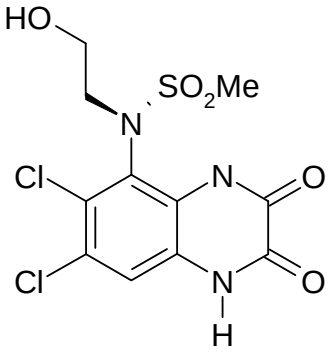
Indinavir – marketed for HIV infection

- **Incorporation of solubilising groups (weakly basic amine, pyridine) and lowering logP increases oral absorption**

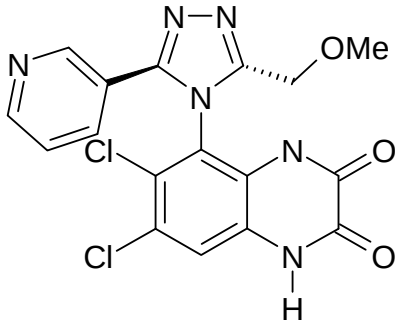
Pfizer Glycine Antagonists



Increase solubility by reducing lipophilicity



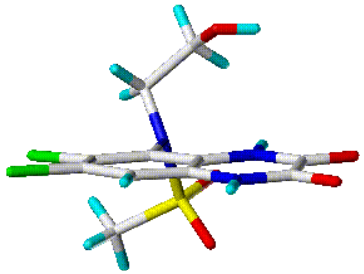
Increase solubility by decreasing lattice energy

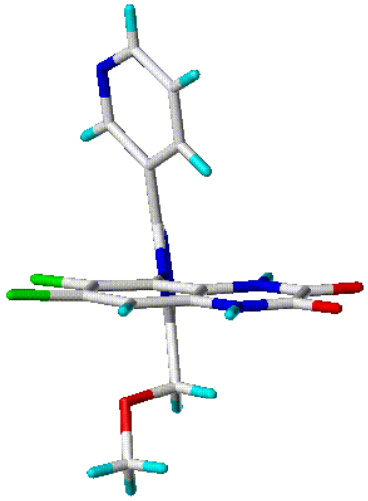


Potency 20nM
Solubility <1mg/ml

Potency 3nM
Solubility 5-30mg/ml

Potency 2.6nM
Solubility >30mg/ml

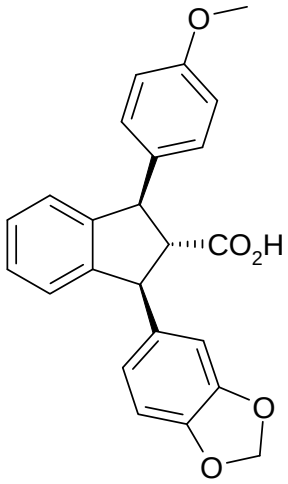




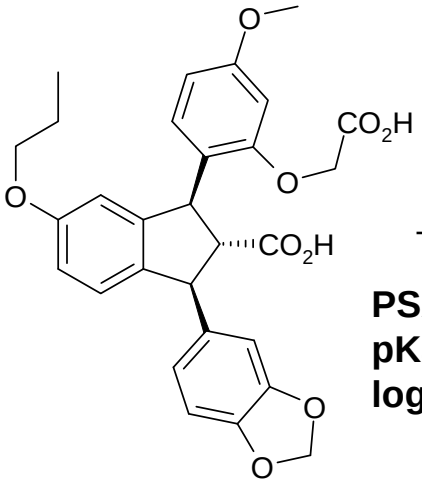
(thanks to Alan Stobie)

Intestinal permeability and oral absorption

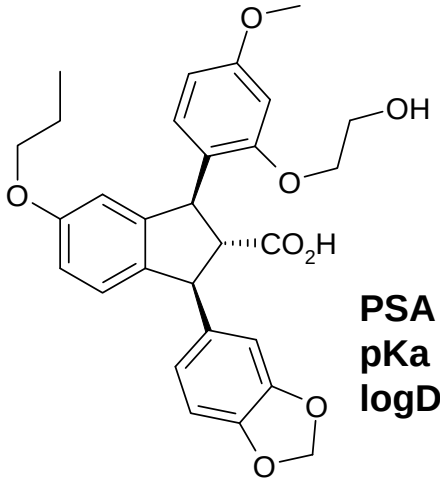
Endothelin (ET) A receptor antagonists (J. Med. Chem. 1994, 37, 1553-1557)



PSA = 75
pKa = 4.1
$logD_{7.4}$ = 2.2



PSA = 141
pKa = 3.1, 4.1
$logD_{7.4}$ = 0.4



PSA = 130
pKa = 4.1
$logD_{7.4}$ = 1.8

Lead
Ki ET_A = 43 nM
Caco-2 cell permeability
Papp = 0.17 cm/hr

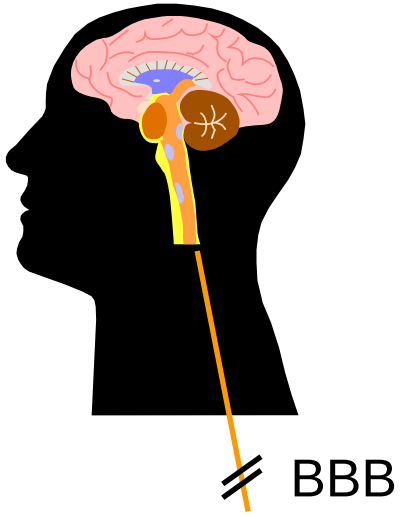
SB 209670
Ki ET_A = 0.4 nM
Papp = 0.0075 cm/hr
< 5% bioavailable (rat)

SB 217242
Ki ET_A = 1.1 nM
Papp = 0.2 cm/hr
66% bioavailable

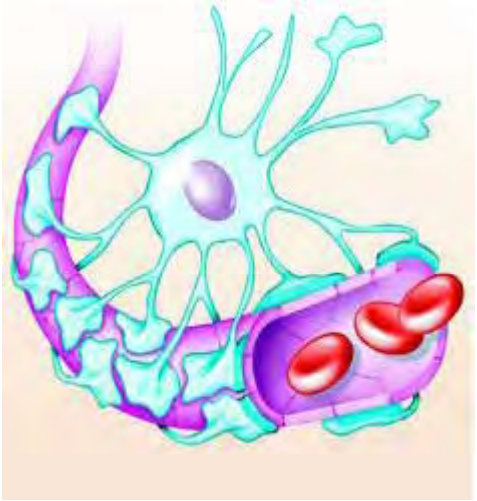
- **Caco-2 cell assay used to identify issue with SB 209670 – low intestinal permeability and rapidly identify non acidic sides chains with improved permeability**

Distribution

And you thought getting from the gut to the blood was a challenge…



Distribution to Site of Action
Blood Brain Barrier and CNS Penetration



What is the BBB?

- Blood Brain Barrier is the interface between blood vessels and brain cells
- Protective lipid membrane with tight cellular junctions
- Polar, hydrophilic molecules are prevented from entering CNS
    - Active transport does operate eg for peptides, amino acids, glucose, fatty acids
- Efflux pumps (eg P-gp) acts to keep “foreign” drug molecules out of CNS
- BBB has some metabolic capacity
- Main route of CNS drug penetration is by passive diffusion

Blood Brain Barrier Penetration

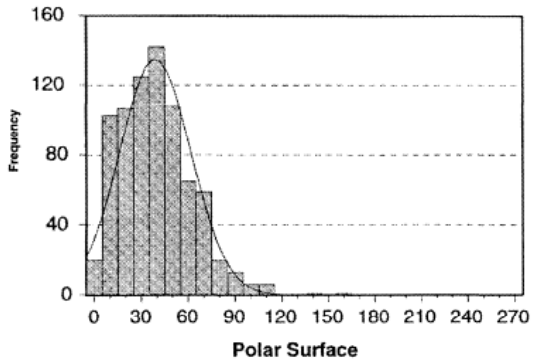
Features of CNS drugs

- **Mol Weight < 400**

- **logP/ logD 2 – 4 (optimum ~ 2)**

Strong correlation of logD and passive permeability to BBB penetration

- **PSA < 60-90 Å2**



PSA range for 776 oral CNS drugs that reached phase 2 efficacy studies

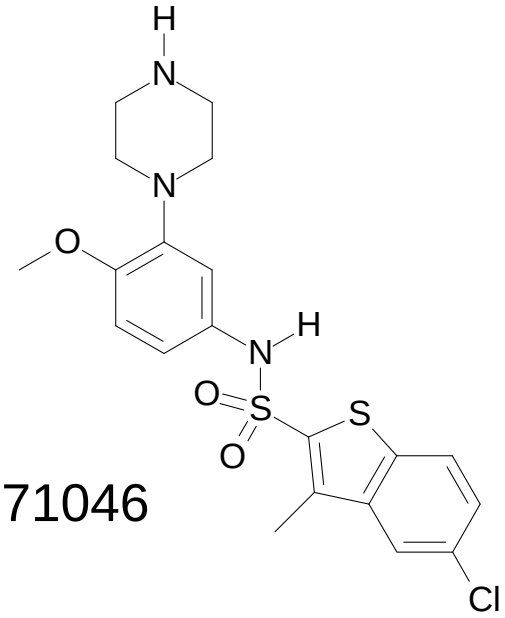
- **pKa - optimum pKa range is 7.5 – 10.5**

- **H-bond donors 0 - 1**

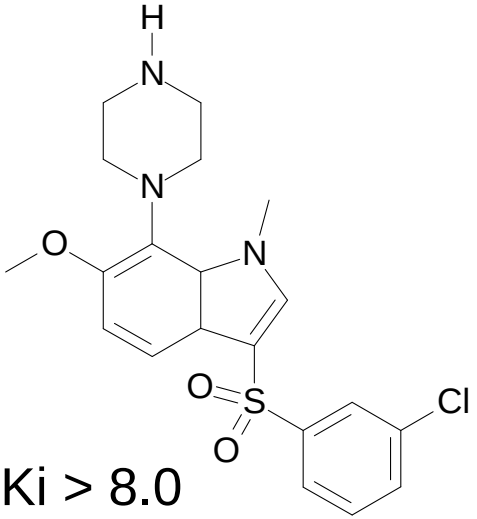
- **Few CNS drugs are P-gp substrates - harder to achieve saturating concentrations in plasma.**

Journal of Medicinal Chemistry, 2006, 49, 26, 7559

5-HT6 Antagonists



SB-271046

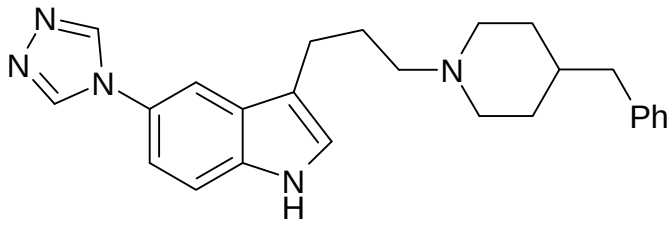


5-HT6 pKi > 8.0

MW	**452**	**390**
clogP	**4.1**	**3.0**
clogD	**3.6**	**1.4**
PSA (A^2)	**71**	**54**
HBD	**2**	**1**
Brain / Plasma	**0.05**	**2.6**

Brain Teaser – 5-HT_{1D} Receptor Agonists

(J. Med. Chem. 1999, 42 2087 – 2104)



1

Compound	5-HT1D Ki	pKa	cLogD	Concentration in rat plasma HPV sampling 0.5h after 3 mg/kg p.o.
1	0.3 nM	9.7	2.5	25 ng/ ml

Compound 1 is a potent 5-HT_{1D} agonist but is poorly absorbed orally

Basic Nitrogen is important to activity

What is a possible barrier to absorption?

What strategies would you use to attempt to improve oral absorption?

HPV = hepatic portal vein