Physical Chemistry; A Medicinal Chemist's Perspective

Rob Young
Discovery Medicinal Chemistry,
Stevenage

Physical Chemistry; A Medicinal Chemist's Perspective

- What regard to medicinal chemists pay to physical properties of their molecules?
  - Current landscape of drug discovery molecules
- Size and Hydrophobicity: key physical measures
  - Zolmitriptan: an old but salient story
  - Predictive modelling
- Case Studies: Factor Xa programme
- Solubility
- Impact of pKa: iNOS programme
- Key Concepts for medicinal chemistry

Physical Chemistry to most Medicinal Chemists?

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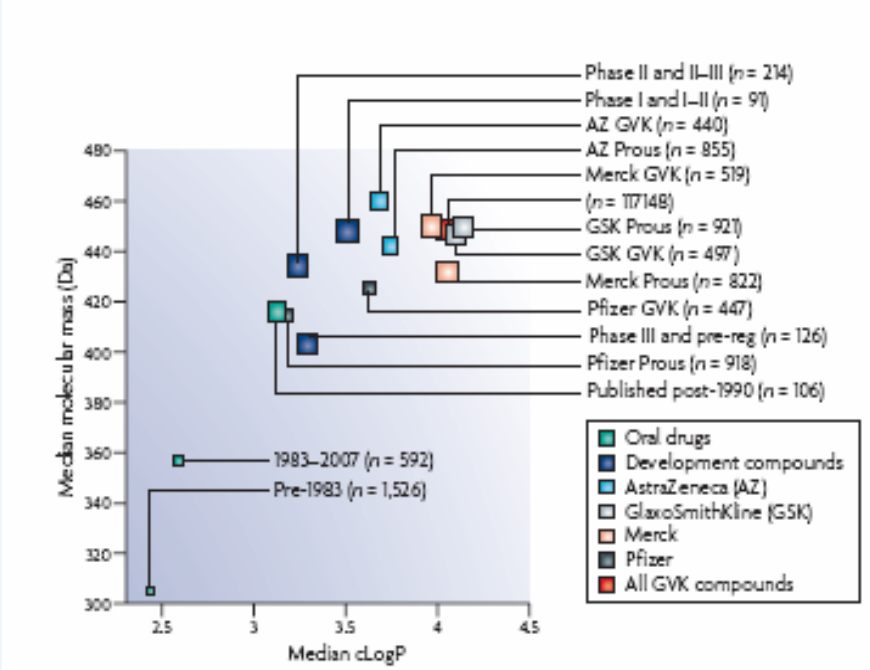
The influence of dark forces?

- Recent literature would suggest that the Med Chem community is not paying good attention to physical constraints
  - Hydrophobicity, Size and (by implication) Solubility…
- Trend towards bigger/more lipophilic molecules
  - Leeson & Springthorpe, *nature reviews* ***drug discovery*** **2007** *6* 881
    - Greater risks & attrition of such molecules
- Simple ADMET rules of thumb
  - Gleeson, *J Med Chem* 2008, 51(4), 817-834.
    - Highlights the implications of poor physical make-up

The Bigger Fatter Generation

- Analyses of trends in drug discovery highlight increase in the size and hydrophobicity of drug candidates
- L&S implicate resulting increased promiscuity in high attrition rate of compounds
- Even if average weight of drugs has increased, there is barely a shift in hydrophobicity



From Leeson & Springthorpe,
nature reviews ***drug discovery*** **2007** *6* 881

Have we seen this kind of analysis before?

- Profiling compounds using logD and cmr as a size surrogate
  - GI Absorption – Alan Hill c1989…
  - Work that led to the GSK logD/cmr absorption model

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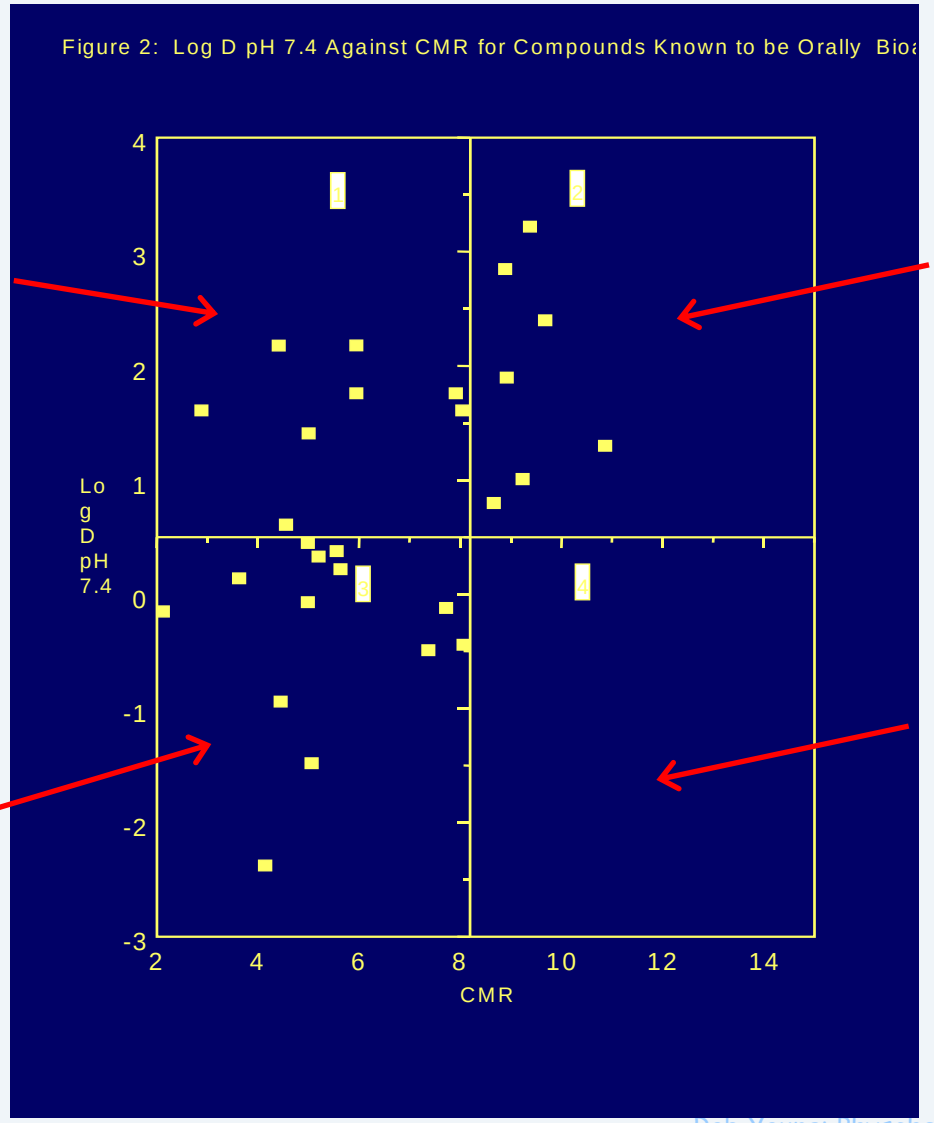
- Profiling compounds using logD and cmr as a size surrogate
  - GI Absorption – Alan Hill c1989…
  - Work that led to the GSK logD/cmr absorption model
- Considered the two main routes of absorption from GI tract:
  - Transcellular - hydrophobicity dependent
  - Paracellular - size dependent
- Properties chosen to model these processes:
  - logD pH 7.4
  - CMR (calculated molar refractivity)

4 box model for absorption

Bioavailable Compounds (Literature)

Either?



Likely transcellular

Likely paracellular

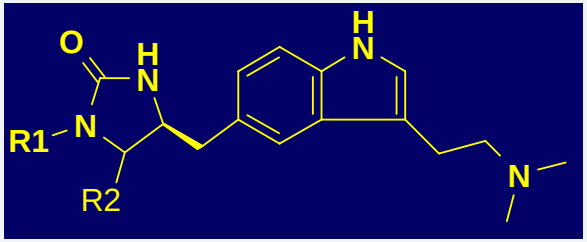
Likely poor

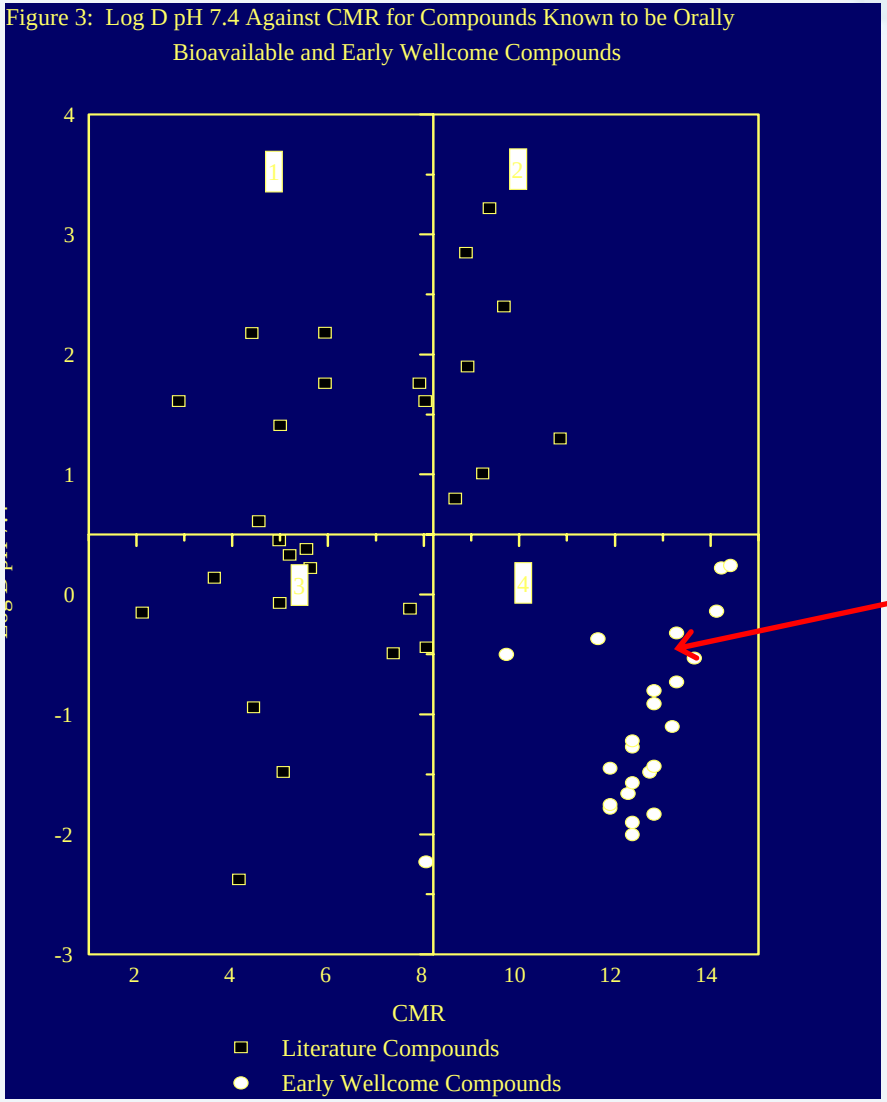
Project data

Modelling Early Wellcome Compounds

A.P.Hill et al,

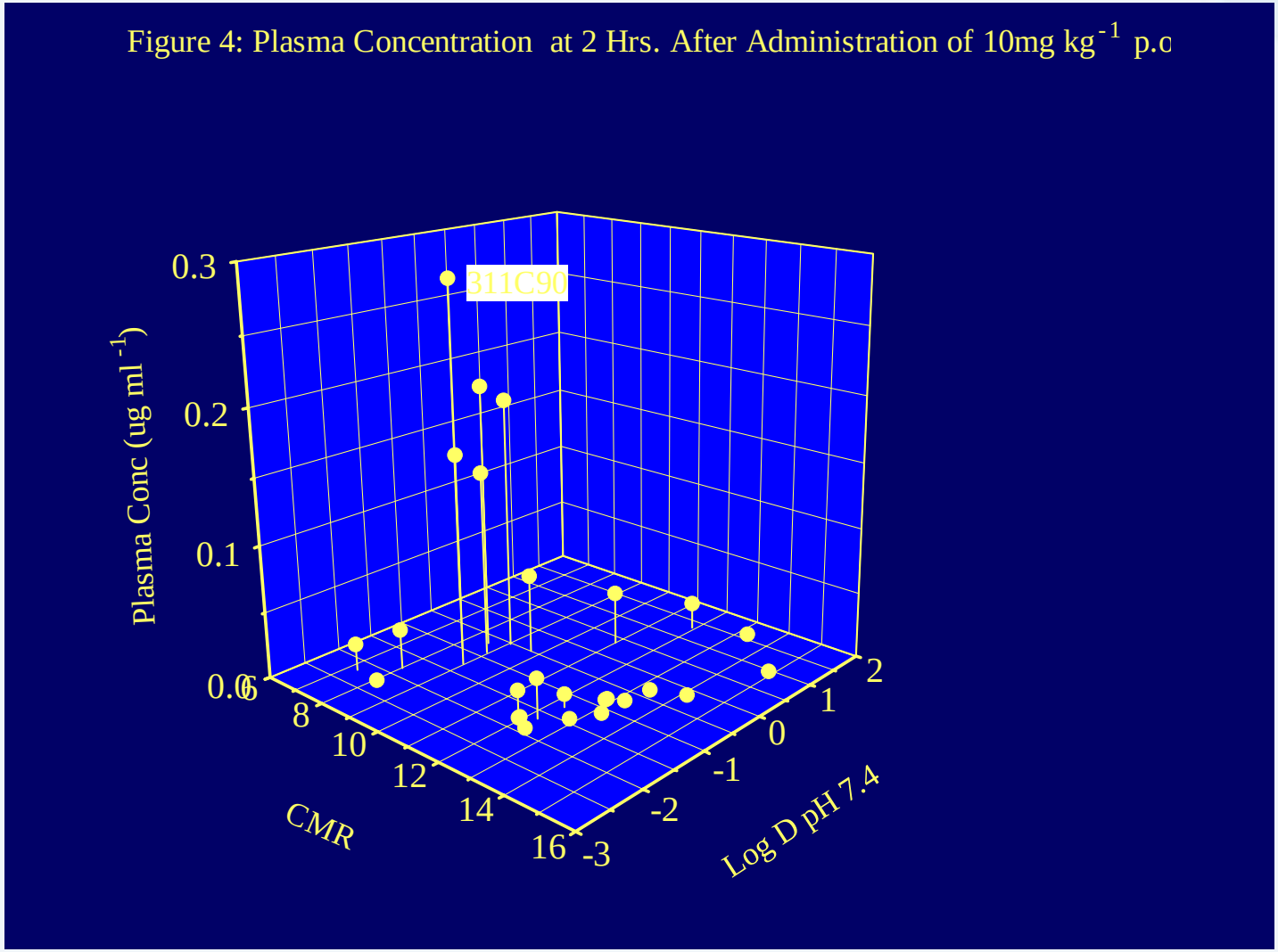
Headache 1994, 34, 308.



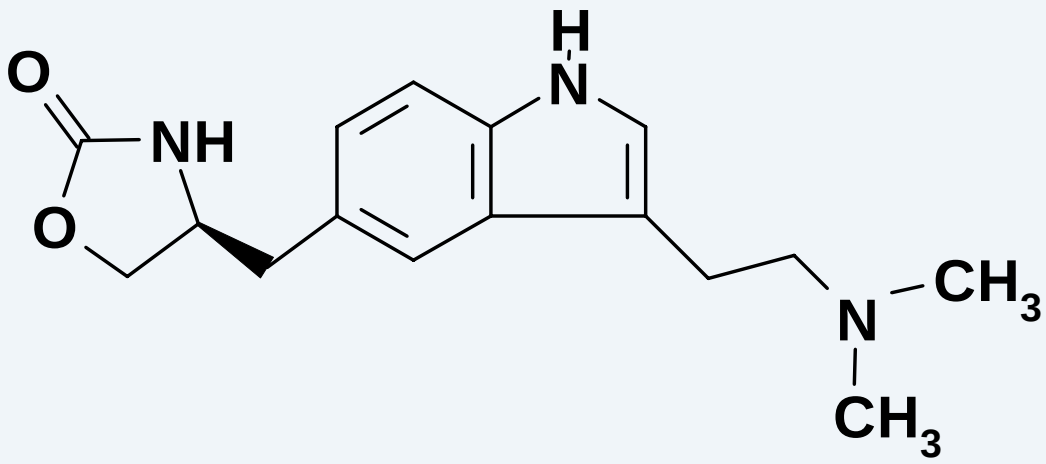


Likely poor

Plasma levels vs PC properties: new series



The Final compound - *zolmitriptan*



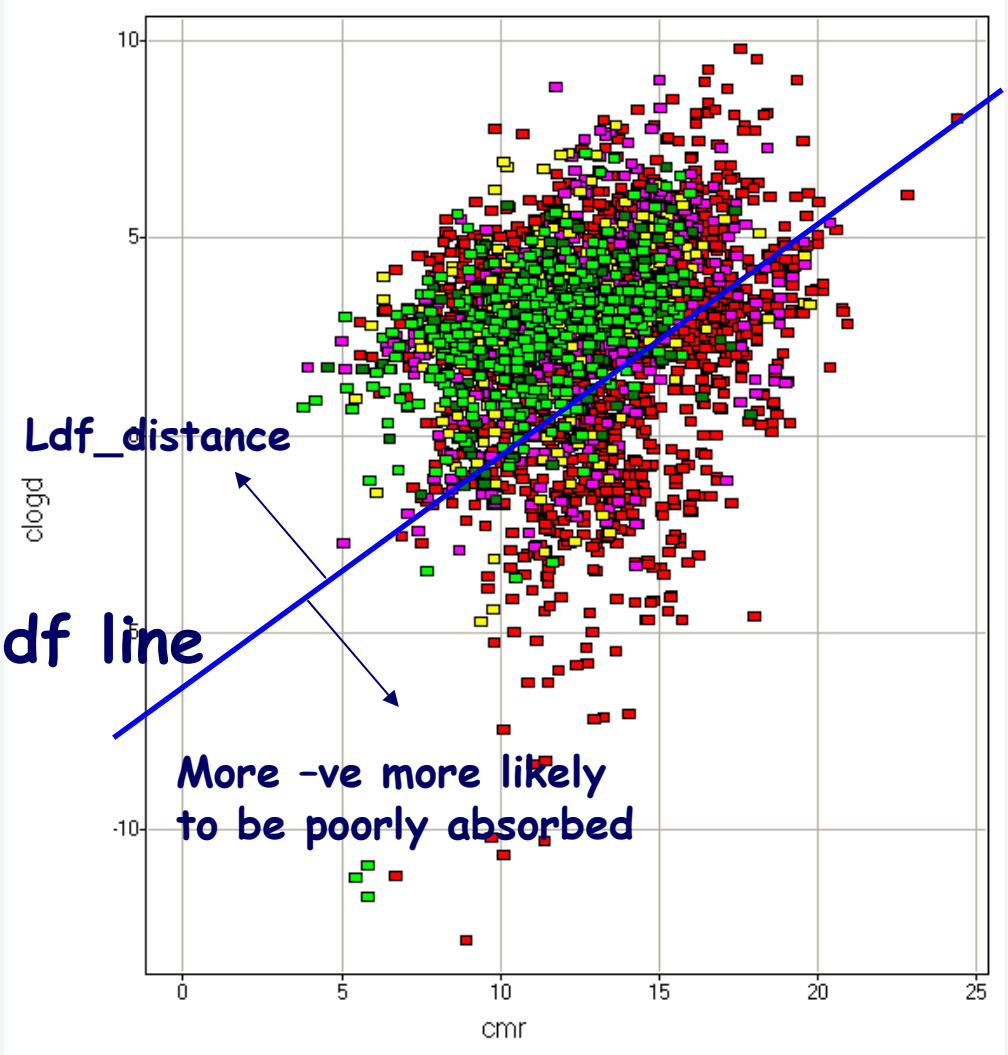
311C90

(*S*)-4[[3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl]methyl]-2-oxazolidinone

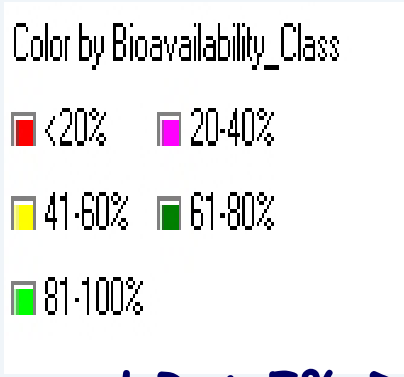
Log $D_{pH\ 7.4}$ = -1.00 CMR = 8.27

J. Med. Chem. **1995**, *38(18)*, 3566-3580.

ADAMANTIS Permeation Model



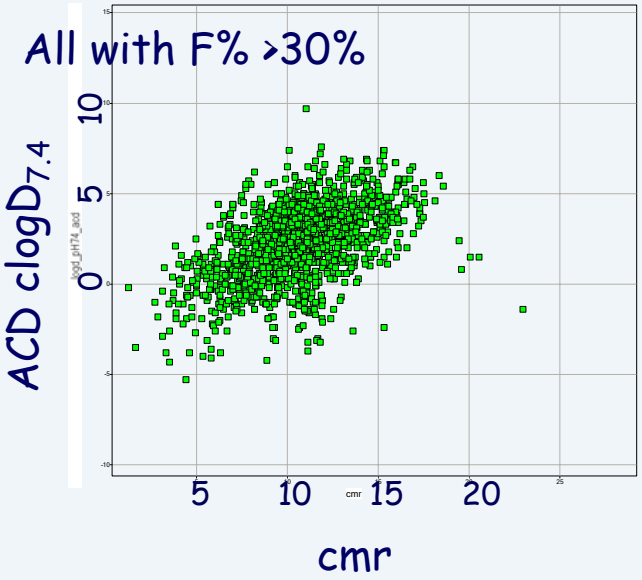
- Compounds below line likely to have poor absorption
- Low F% above the line: probably due to high first pass metabolism

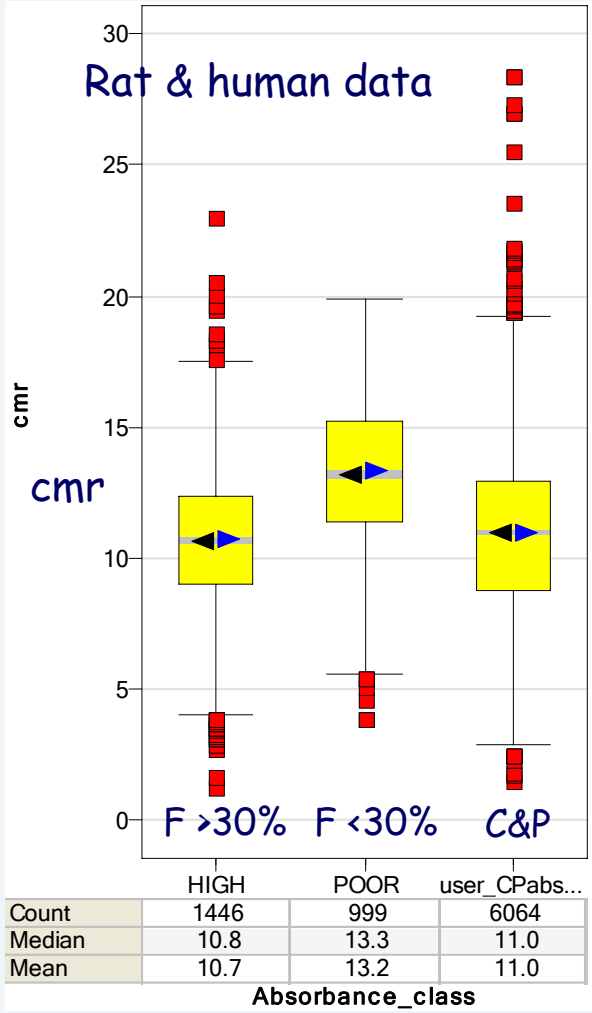


Measured Rat F% Data

N.B. This figure was more predictive of good F% than Caco data in "Clop"

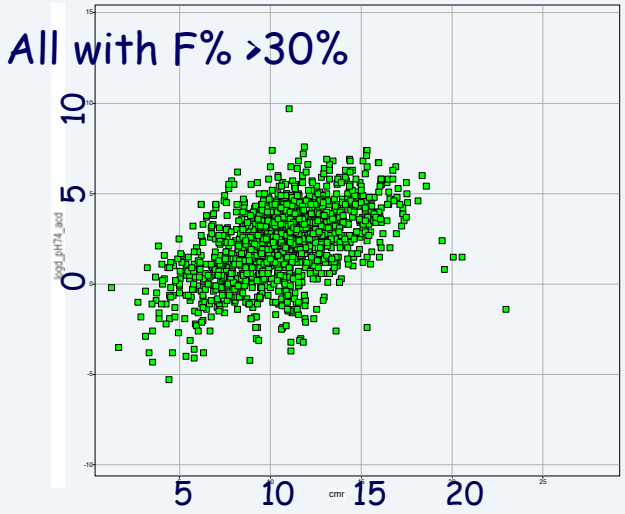
Size and logD – for orally bioavailable molecules

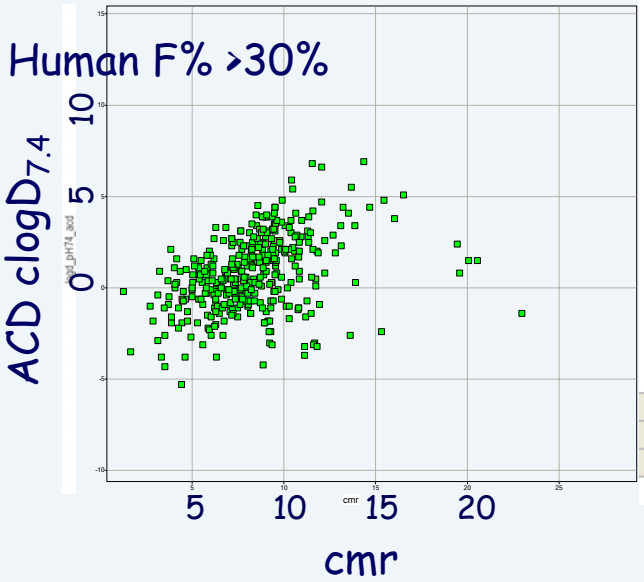


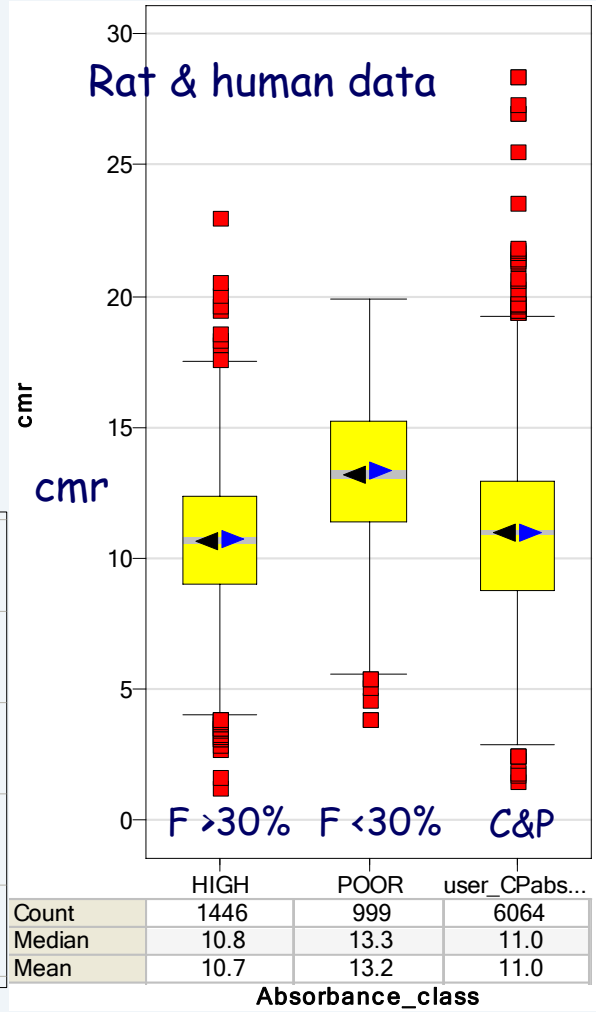


C&P = Screening set being profiled

Size and logD – for orally bioavailable molecules

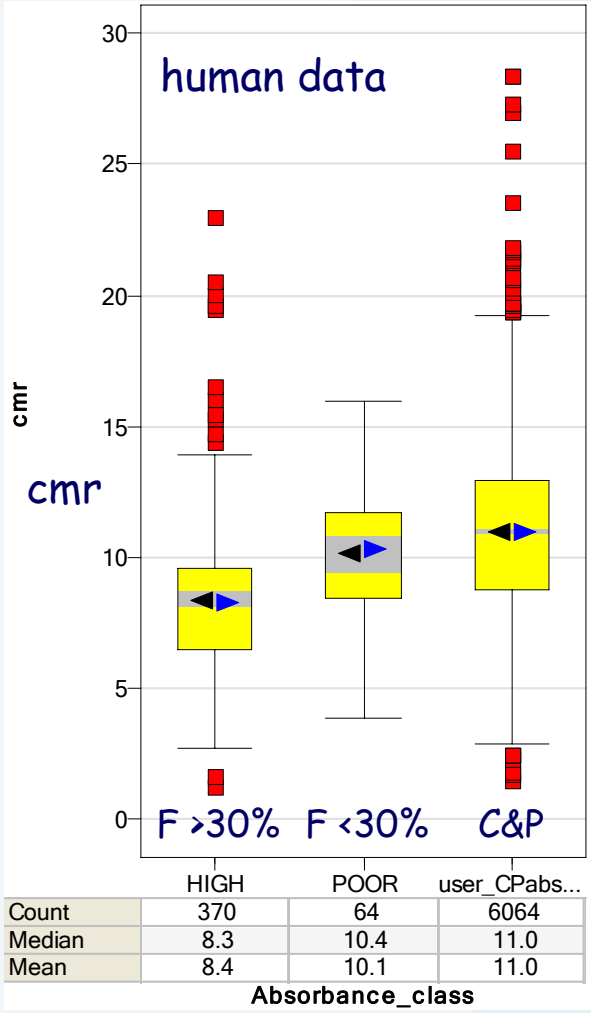






	HIGH	POOR	user_CPabs...
Count	1446	999	6064
Median	10.8	13.3	11.0
Mean	10.7	13.2	11.0

Absorbance_class



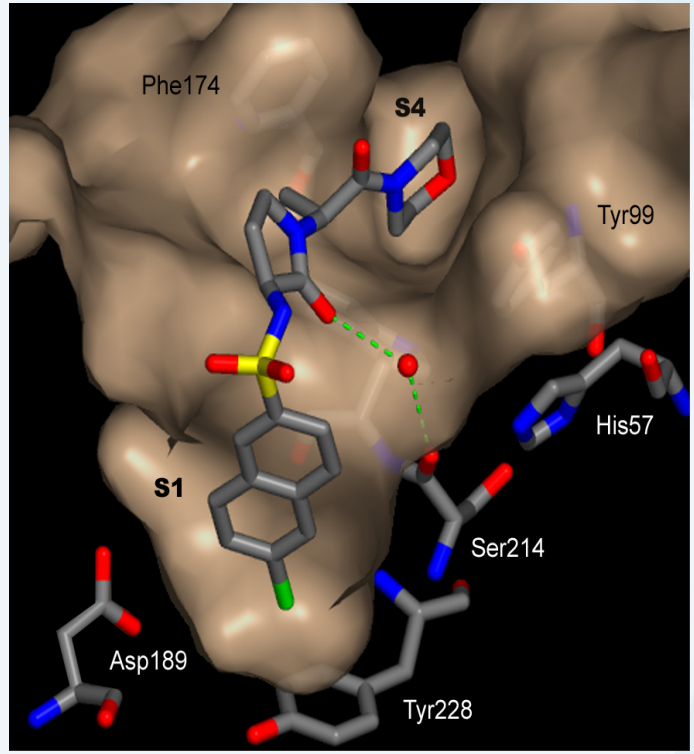
	HIGH	POOR	user_CPabs...
Count	370	64	6064
Median	8.3	10.4	11.0
Mean	8.4	10.1	11.0

Absorbance_class

Human (Oral) Mean clogD$_{7.4}$ = 0.8

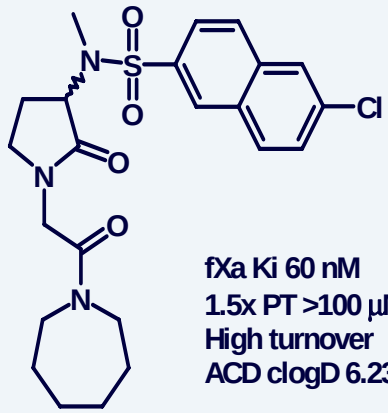
Factor Xa as a target for oral therapy

- Pivotal role in coagulation cascade
  - Prothrombin to thrombin cleavage
- Trypsin-like serine protease
  - Recognises basic AA in S1
- Many potent, basic, inhibitors reported
  - Poor oral DMPK profile
- Our goal: oral therapy (uid?)
  - Predictable/reliable DMPK profile
    - Good absorption, low metabolism; minimise risk of drug interactions
  - Avoid highly basic compounds

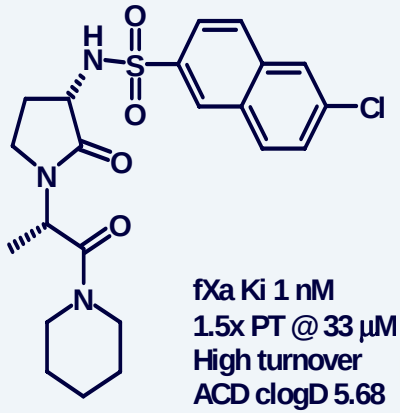


Factor Xa "Hit to Lead" work: early days

- Racemic Azepine-amide from exploratory array chemistry
- Changing Gly to Ala linker gave increased potency
- 3*S*-Stereochemistry preferred for pyrrolidinone substituent
- Numerous Ala-cyclic amides highly potent vs fXa
- BUT – poor translation into anticoagulant activity (PT assay) & high in vitro metabolic turnover



fXa Ki 60 nM
1.5x PT >100 µM
High turnover
ACD clogD 6.23

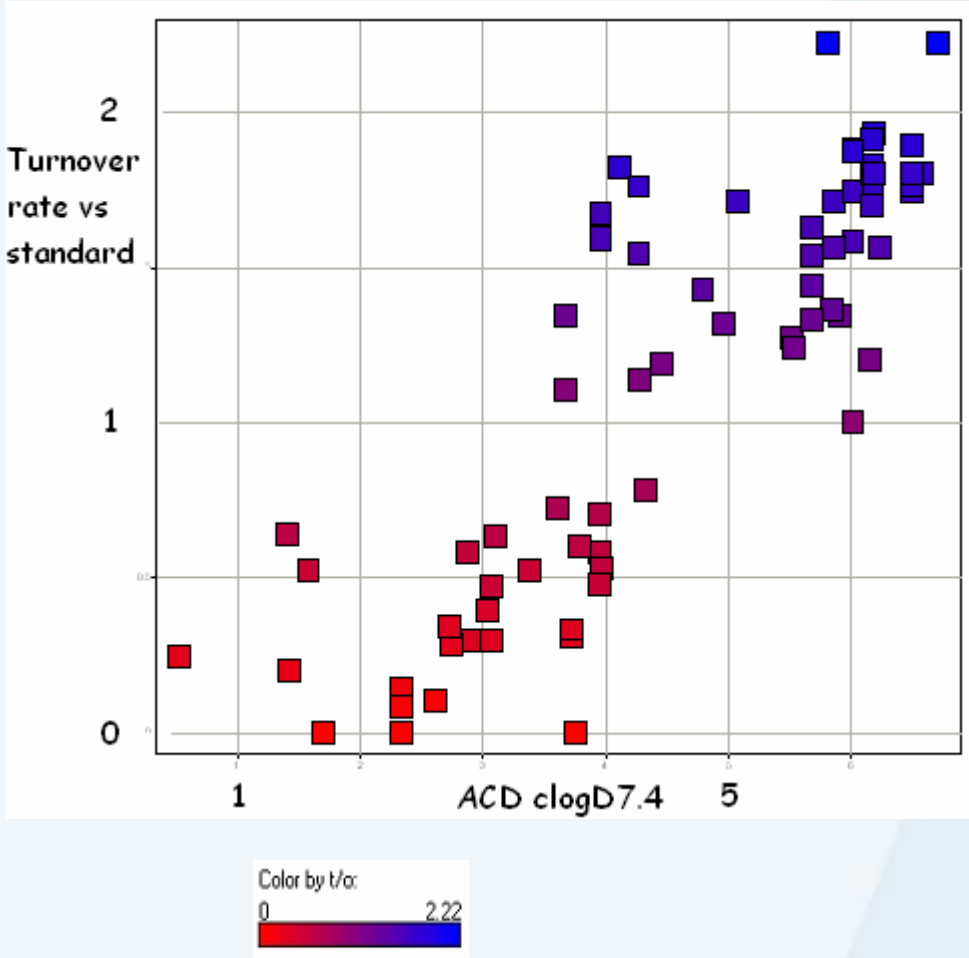


fXa Ki 1 nM
1.5x PT @ 33 µM
High turnover
ACD clogD 5.68

BMCL, **2006**, *16*, 3784

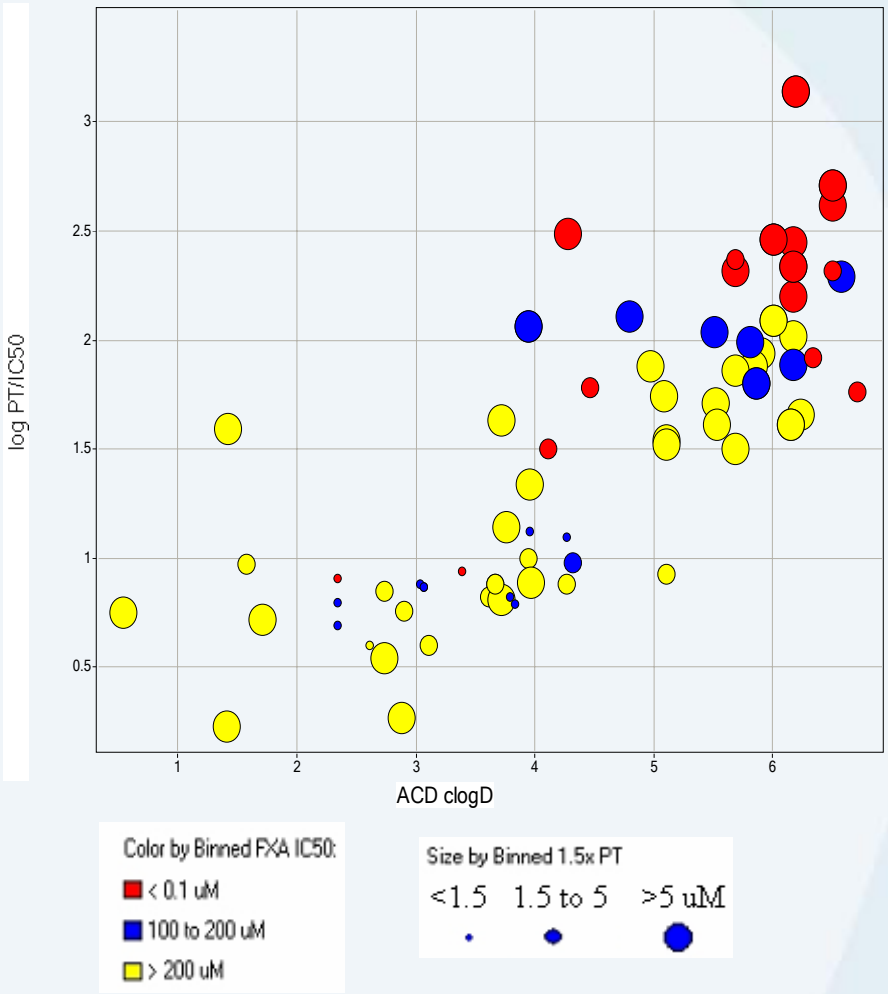
Impact of hydrophobicity on metabolism

- Part of a broad data review
- Analysis clearly showed benefit of reduced hydrophobicity on lowering metabolism
  - From HT microsome assay; relative turnover vs verapamil
- Established ACDlog$D_{7.4}$ as best hydrophobicity predictor
  - Correlation: mlogD/CHI & experimental observations



Impact of hydrophobicity: Anticoagulant activity

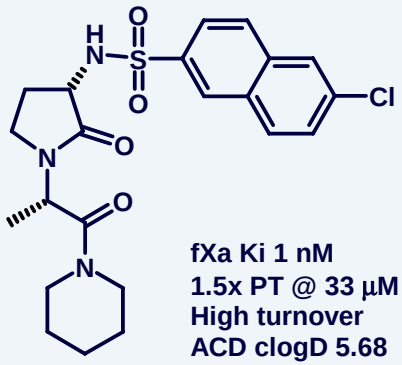
- Most active compounds generally the most hydrophobic
  - A common trend…
- Very few anywhere near target levels for anticoagulant activity
- Clear that potency translated into better anticoagulant effect with more hydrophilic molecules
- Compound design: ACDclogD$_{7.4}$ < 4



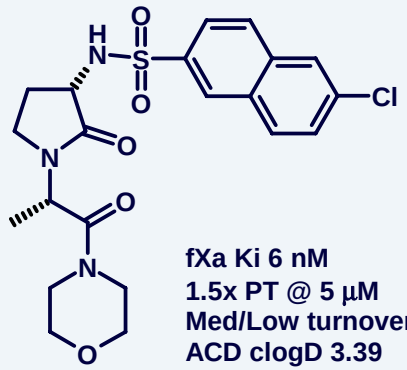
N.B. data from older assays

FXa Lead Optimisation: first candidate

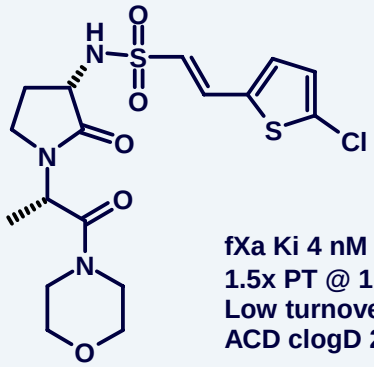
- Piperidine to morpholine switch reduced fXa potency
- BUT enhanced anticoagulant activity (as predicted) as logD reduced
  - Turnover also reduced
- Further reductions in hydrophobicity through variation of sulphonamide
- Gave overall profile appropriate for further progression with *bid* dosing
  - Active in Rat Venous Thrombosis model (EC_{50} 2.1 μM)
    - No bleeding liability



fXa Ki 1 nM
1.5x PT @ 33 μM
High turnover
ACD clogD 5.68



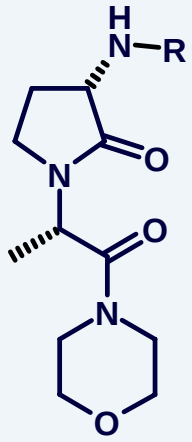
fXa Ki 6 nM
1.5x PT @ 5 μM
Med/Low turnover
ACD clogD 3.39

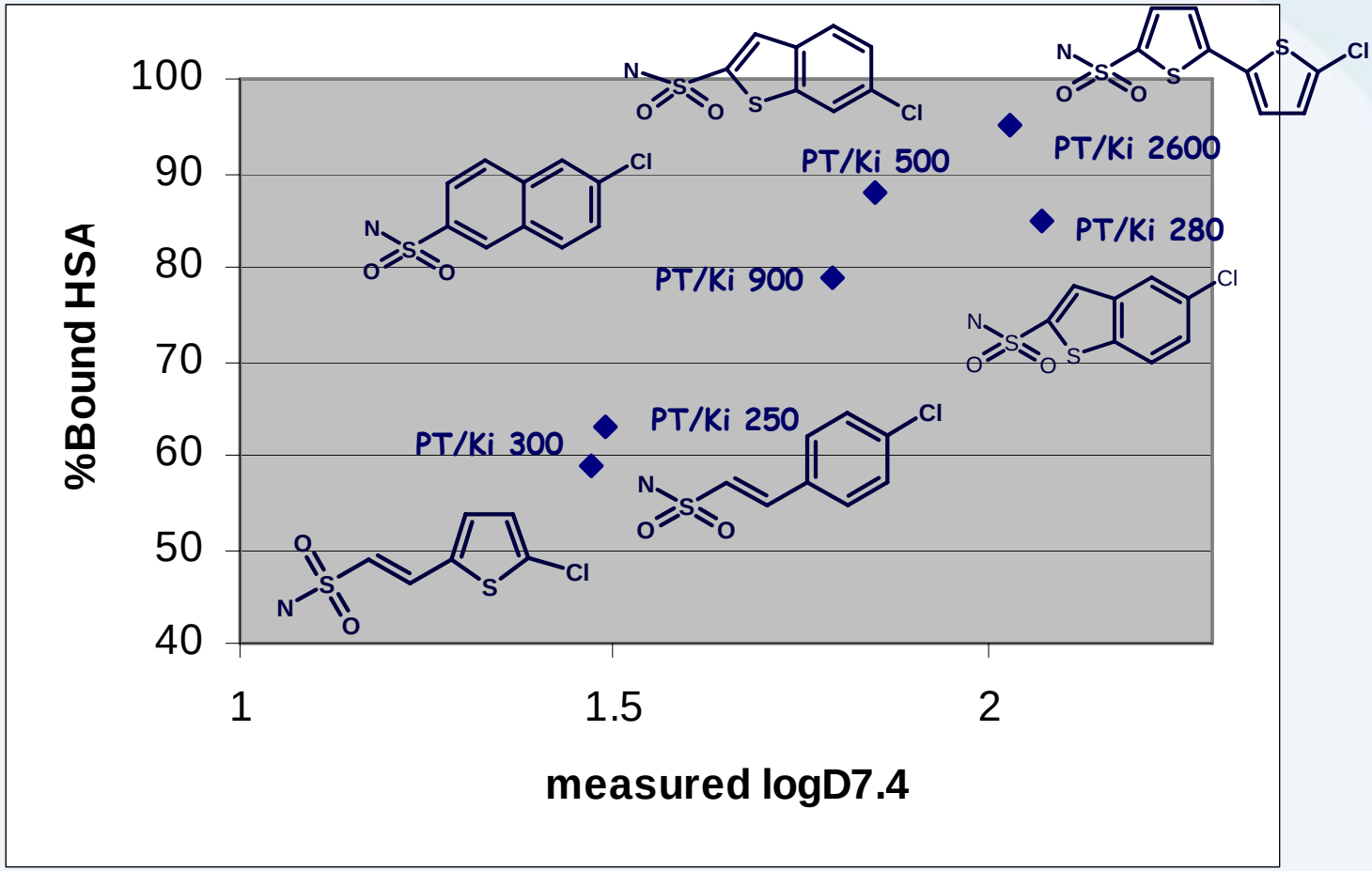


fXa Ki 4 nM
1.5x PT @ 1.2 μM
Low turnover
ACD clogD 2.67

J Med Chem, **2007**, *50*, 1546

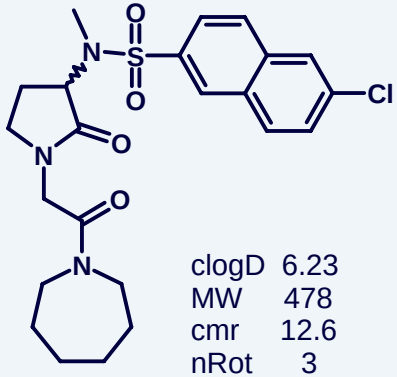
Plasma Protein Binding and logD



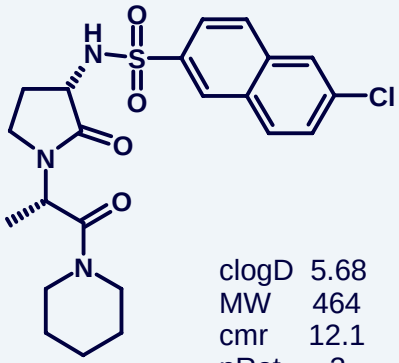


- Reducing logD had tangible effect on PPB, which was a likely influence on anticoagulant activity.

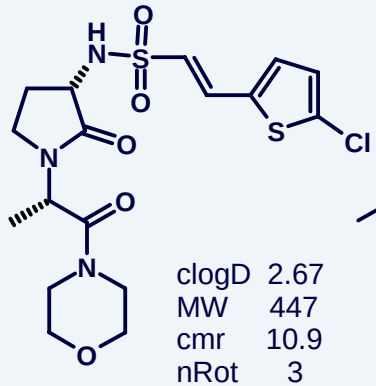
Molecular evolution towards a second candidate



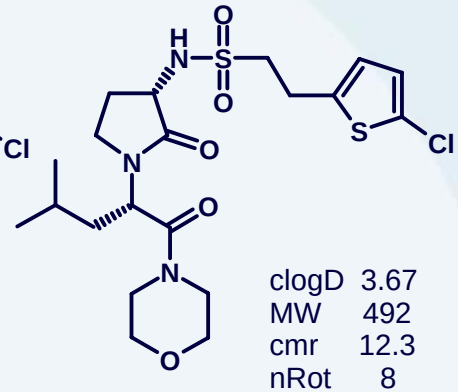
clogD	6.23
MW	478
cmr	12.6
nRot	3



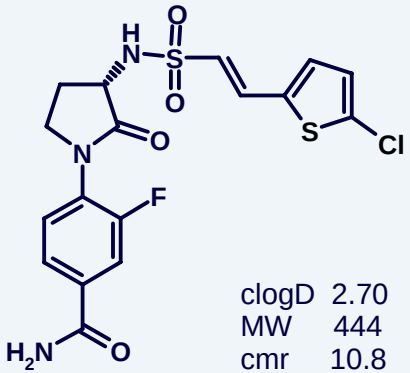
clogD	5.68
MW	464
cmr	12.1
nRot	3



clogD	2.67
MW	447
cmr	10.9
nRot	3



clogD	3.67
MW	492
cmr	12.3
nRot	8



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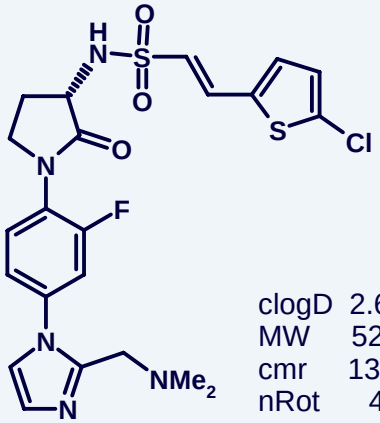

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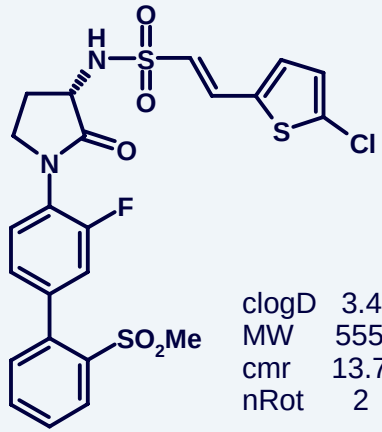
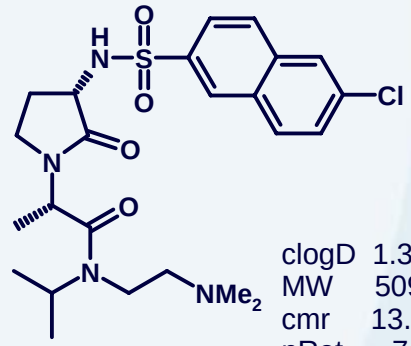
MW	524
cmr	13.3
nRot	4



clogD	3.42
MW	555
cmr	13.7
nRot	2

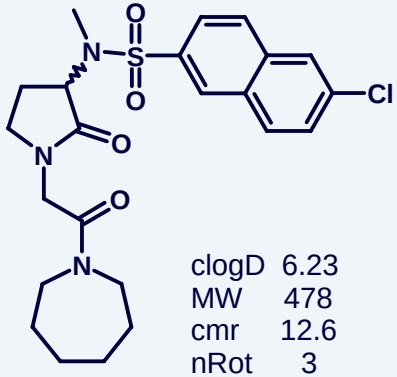


clogD	1.30
MW	509
cmr	13.6
nRot	7

- Highlighting key drivers of structure-property relationships

BMCL, **2007**, *17*, 2927
BMCL, **2006**, *16*, 5953
BMCL, **2008**, *18*, 23 & 28

Molecular evolution towards a second candidate



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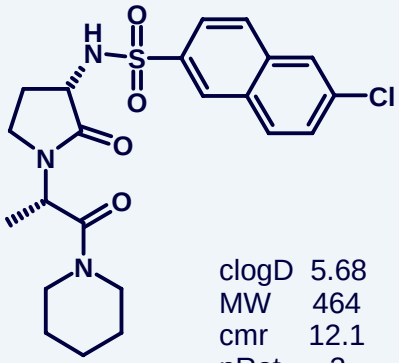

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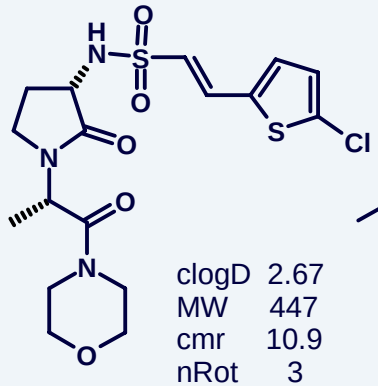

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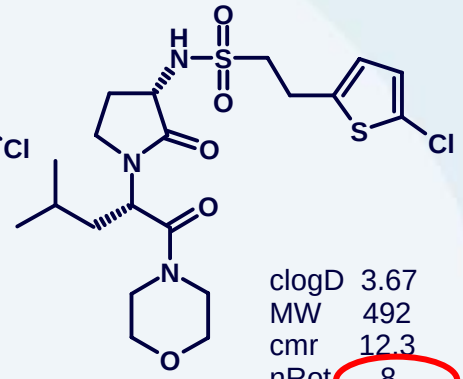

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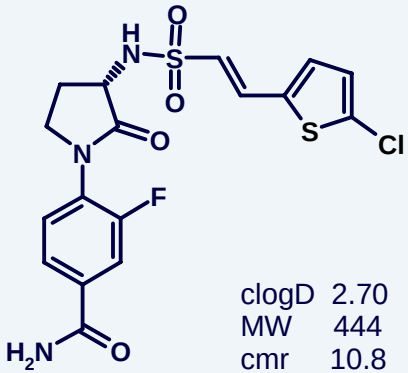

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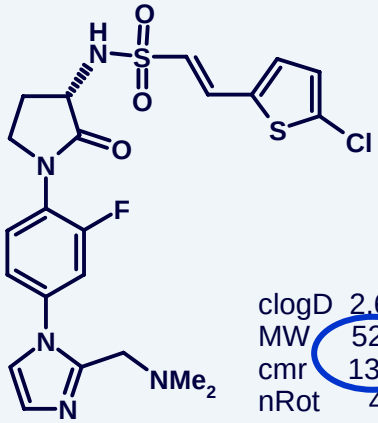

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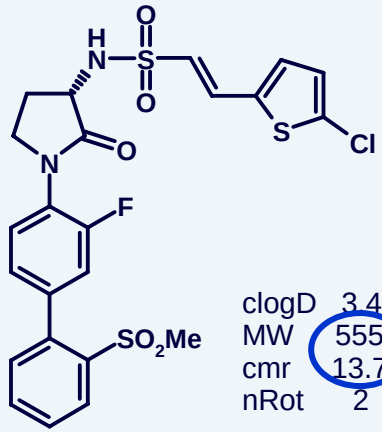

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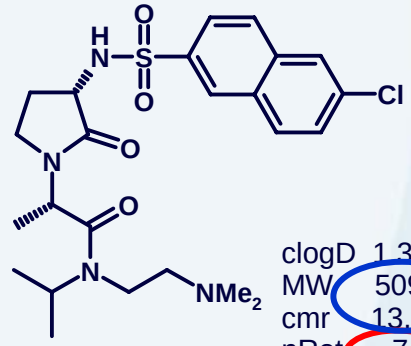

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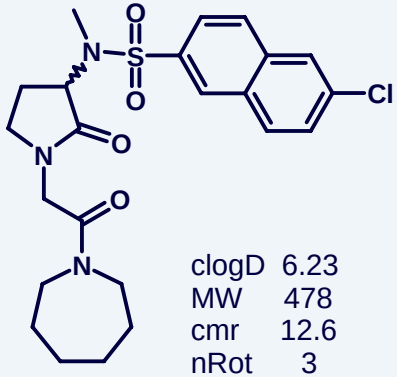

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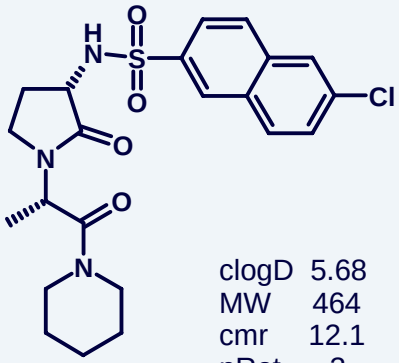

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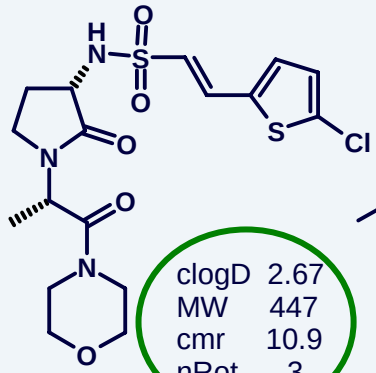

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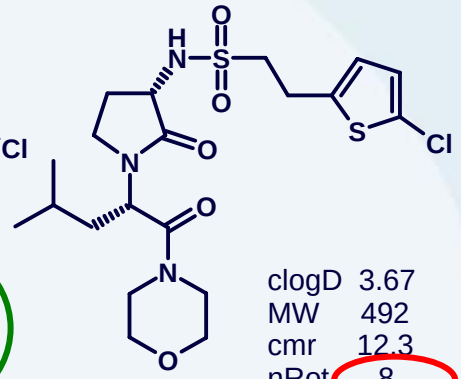

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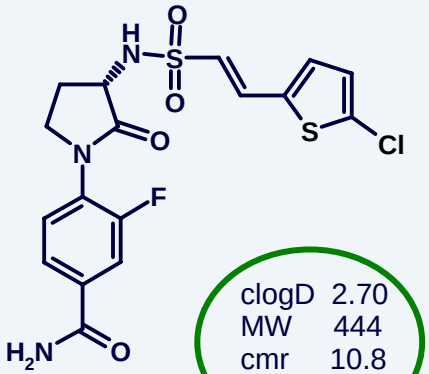
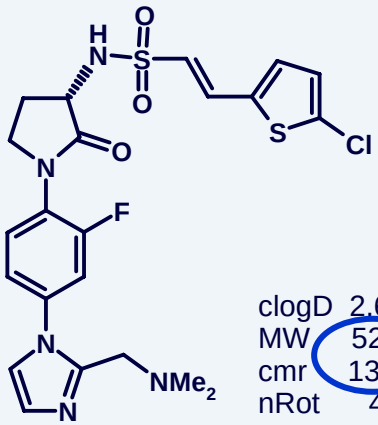
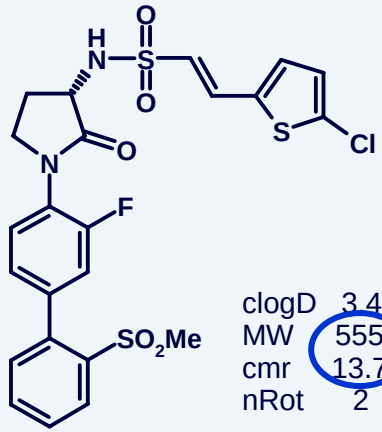
cmr 12.3
nRot 8



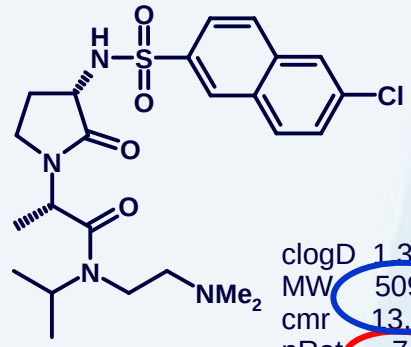
clogD 2.70
MW 444
cmr 10.8
nRot 2



clogD 2.69
MW 524
cmr 13.3
nRot 4



clogD 3.42
MW 555
cmr 13.7
nRot 2

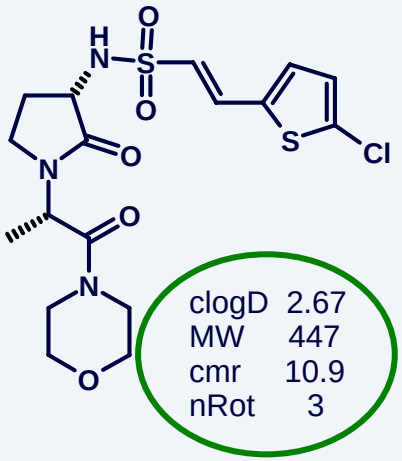


clogD 1.30
MW 509
cmr 13.6
nRot 7

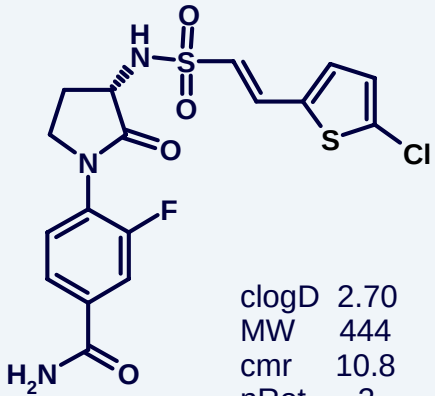
- Highlighting key drivers of structure-property relationships

BMCL, **2007**, *17*, 2927
BMCL, **2006**, *16*, 5953
BMCL, **2008**, *18*, 23 & 28

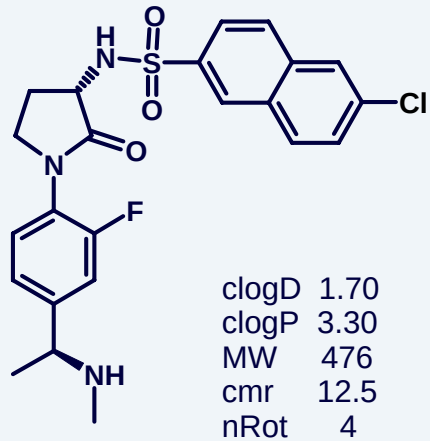
Fine tuning the process for a second candidate



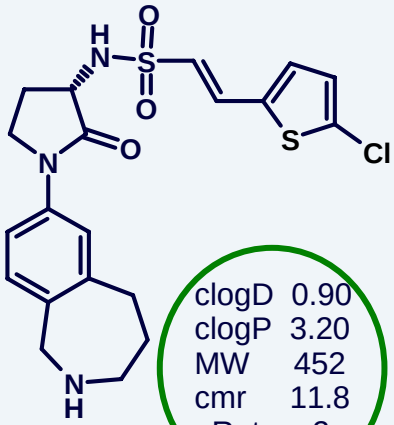
clogD	2.67
MW	447
cmr	10.9
nRot	3



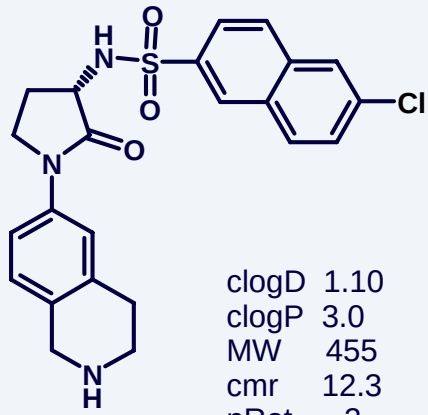
clogD	2.70
MW	444
cmr	10.8
nRot	2



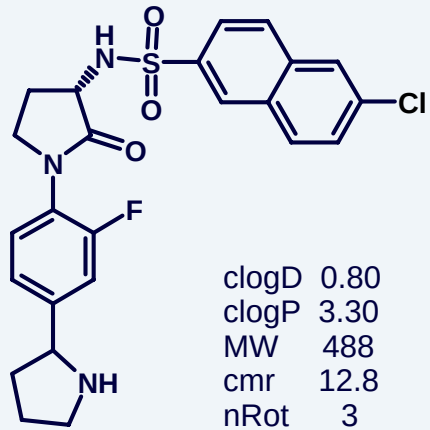
clogD	1.70
clogP	3.30
MW	476
cmr	12.5
nRot	4



clogD	0.90
clogP	3.20
MW	452
cmr	11.8
nRot	2



clogD	1.10
clogP	3.0
MW	455
cmr	12.3
nRot	2



clogD	0.80
clogP	3.30
MW	488
cmr	12.8
nRot	3

- Leeson review. Post 1990, oral drugs median values: clogP 3.2, MW 420

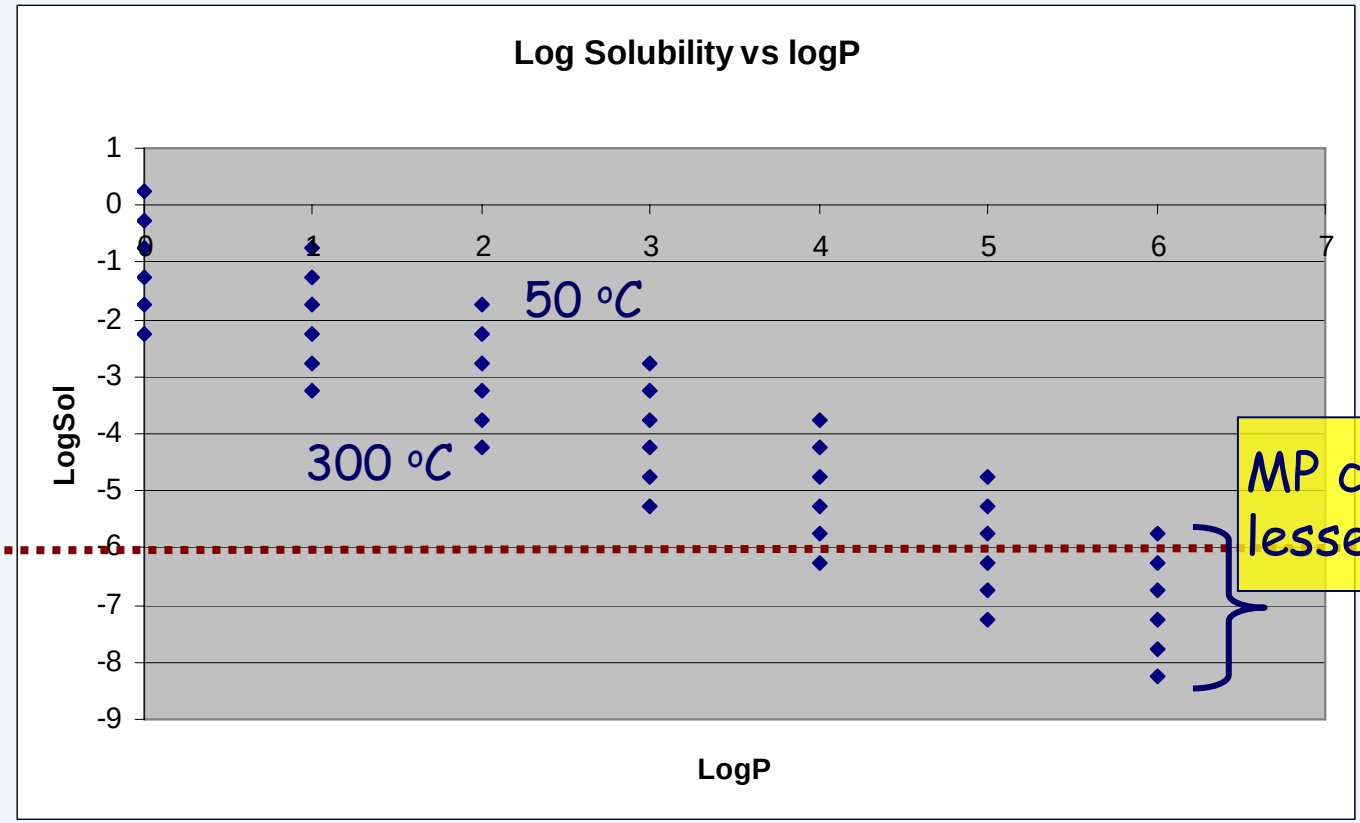
Solubility: Yalkowsky Equation

- Log Sol = 0.5 -0.01(MP-25) – LogP
  - *J.Chem. Inf. Comput. Sci.* **2001**, *41*, 354
- Log of Solubility (Molar)
  - MP = Melting Point (Celsius)
  - LogP = log(Partition coefficient, Oct:H_2O)

Solubility: Yalkowsky Equation

- Log Sol = 0.5 -0.01(MP-25) – LogP
  - *J.Chem. Inf. Comput. Sci.* **2001**, *41*, 354
- Log of Solubility (Molar)
  - MP = Melting Point (Celsius)
  - LogP = log(Partition coefficient, Oct:H_2O)
- How can the implications of this be visualised?
  - Simple means of understanding what it tells us!
- Used Excel to input MP 50 to 300 °C with LogP values of 0 to 7 in following graphs…

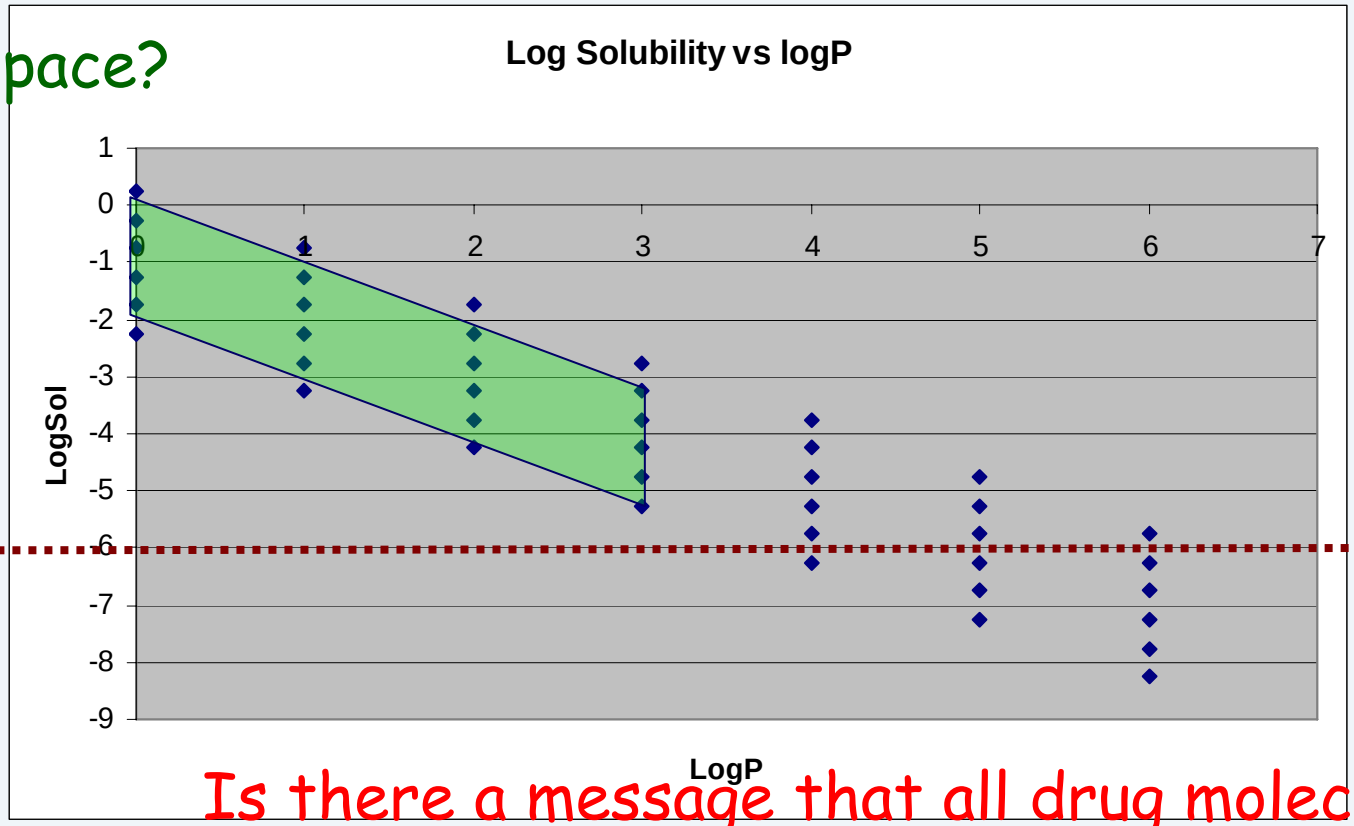
Calculated Solubility vs LogP



At a given logP, points are MP = 50 to 300

If average drug has clogP <3…

Drug Space?



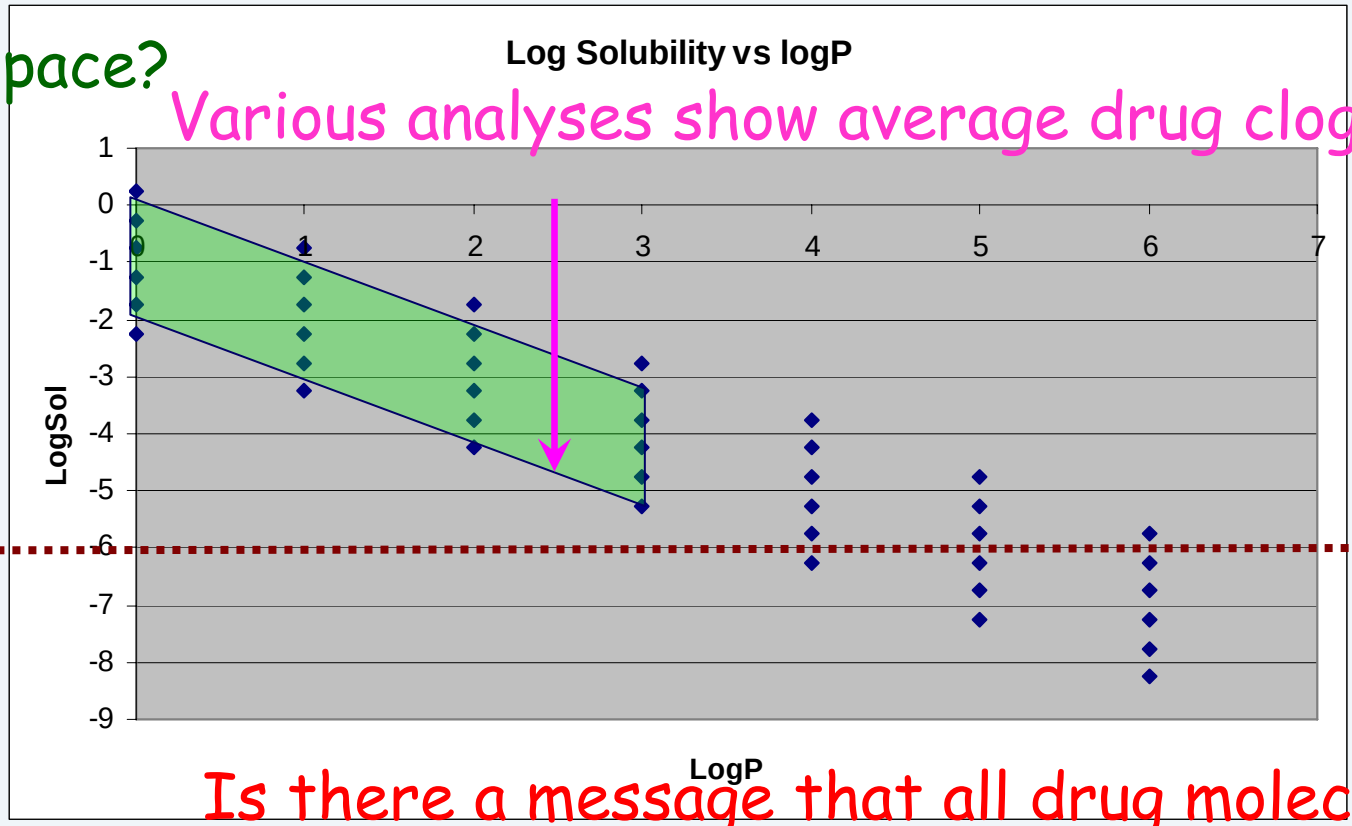
1 μM

Is there a message that all drug molecules should at least have >10 μM solubility?

If average drug has clogP <3…

Drug Space?

Various analyses show average drug clogP is ~2.5



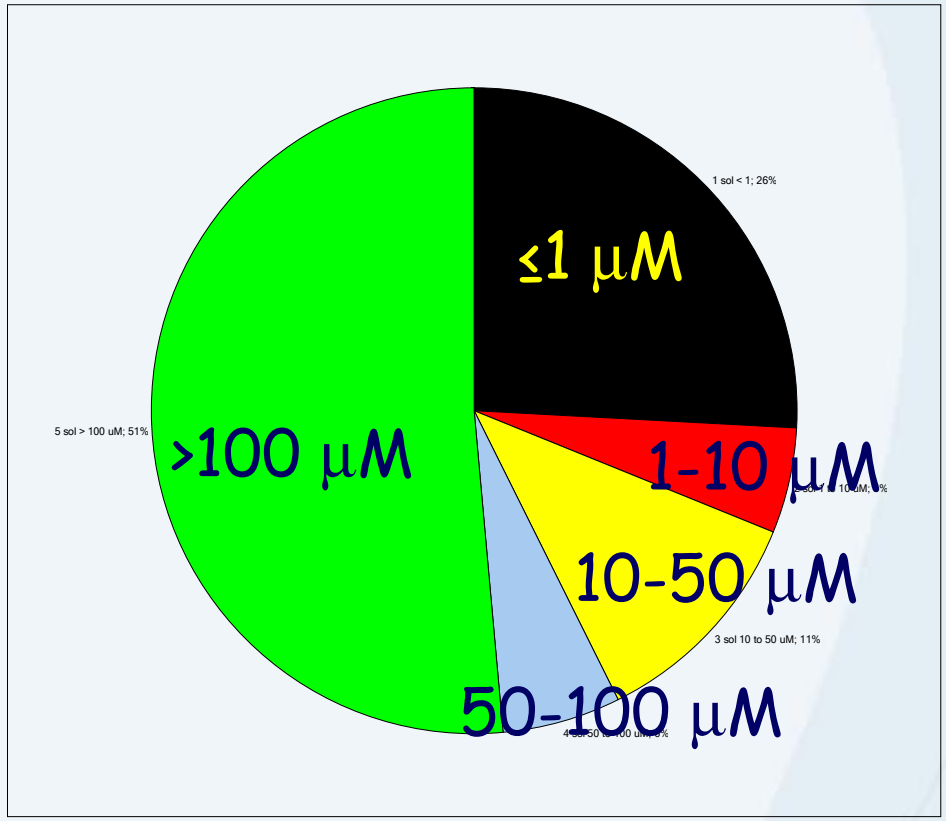
1 μM

Is there a message that all drug molecules should at least have >10 μM solubility?

Perhaps even >50 μM?

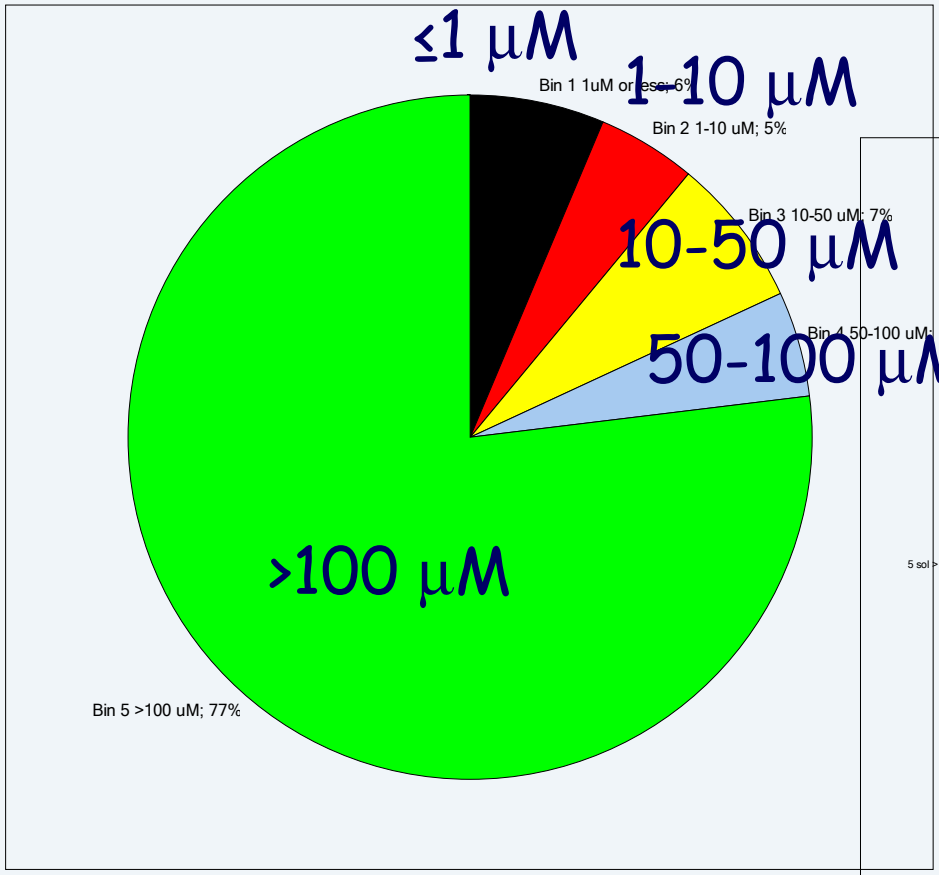
Impact on solubility of keeping logD in check

- Distribution of GSK measured solubility in ~2001 - 2005
  - Timeframe of fXa project
- Stevenage assay
  - From 10mM DMSO stock; 5% final [DMSO]
  - HPLC area comparison
- Is >50 μM a good solubility target for a drug?

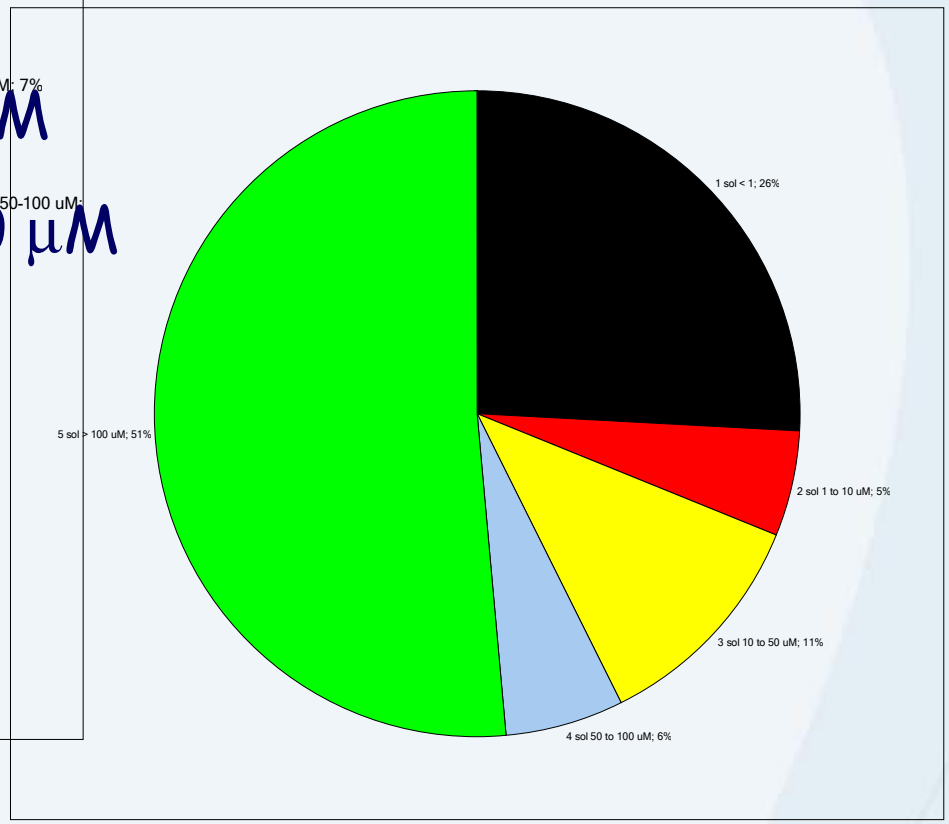


Impact on solubility of keeping logD in check

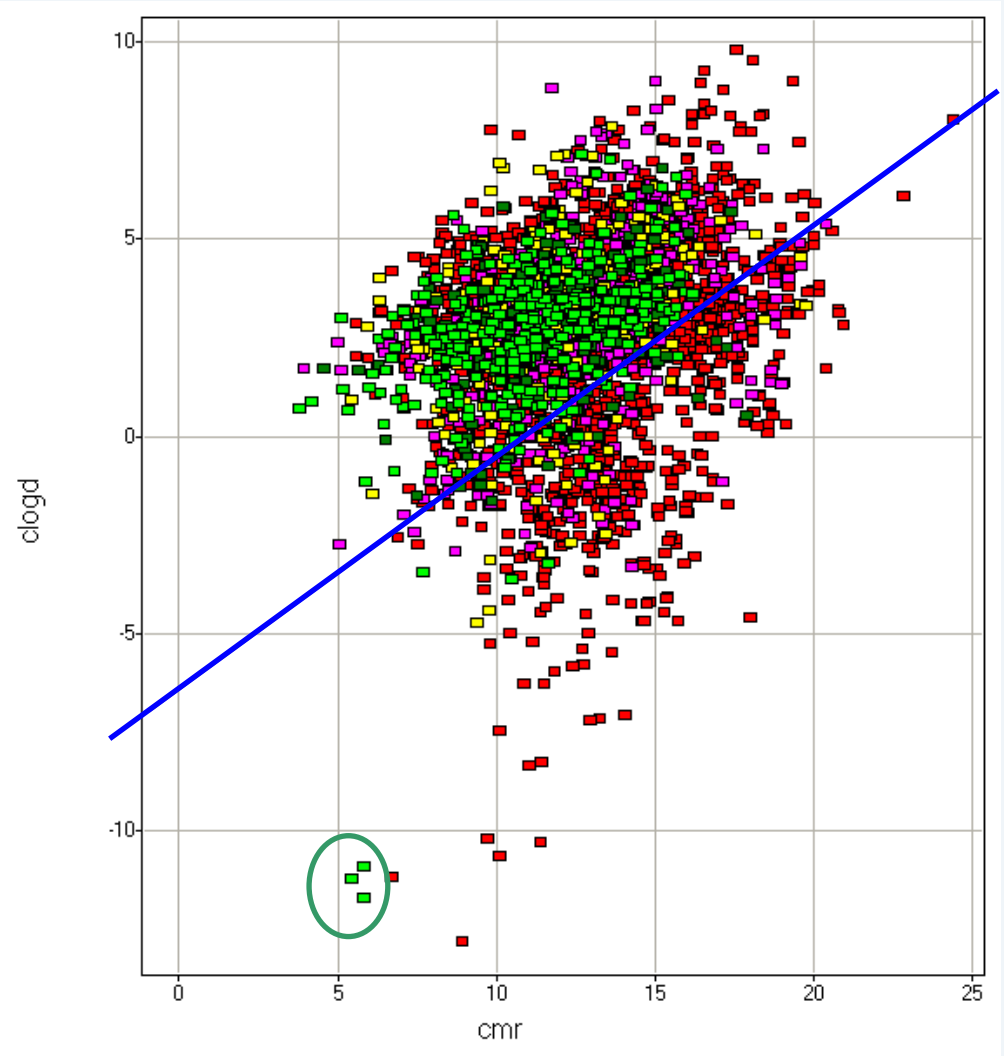
- Factor Xa programme



- Representative GSK set

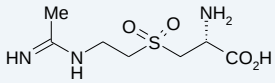
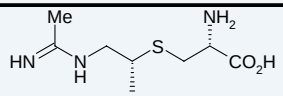
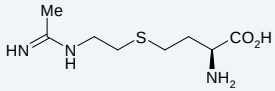
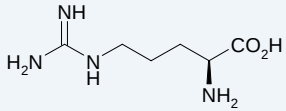


Working with Mother Nature



- Responsibility taken for the outliers in this graph!
- iNOS programme: Mimics of L-Arg

Importance of pKa values

Compound	Structure	Rat		pKa		
		F (%)	$t_{1/2}$ (h)	acid	amine	amidine
Cys sulphone		<5	0.6	1.6	7.1	11.0
Cys sulphide		100	~ 2	2.0	8.4	11.4
hCys sulphide		100	4.3	2.1	8.9	11.4
Arginine		-	-	1.9	9.0	12.5

- Half-life and F% in the series showed importance of ionization of the molecules; compounds shown to be actively transported

To summarise; for the enlightened ones?

Are these key concepts in Medicinal Chemistry?

- Structure Property Relationships are more important than Structure Activity Relationships in Lead Optimisation
- Recognising the value and impact of physical measurements and predictions in compound profiling and design
  - Having a proper understanding of the meaning, implications and impact of parameters such as logP, $logD_{pH}$, pKa, solubility, PPB
    - AND knowing how to modulate them
- Use this physical knowledge to Hypothesise, Measure, Model, then Predict an expedient way forward in a lead optimisation programme?

Above all…

- Good drug molecules: a balance of size, weight and, particularly, lipophilicity

Acknowledgements

- Physical Chemistry
  - Alan Hill
  - Klara Valko; Pat McDonough; Chris Bevan; Shenaz Nunhuck
- In Silico Modelling
  - Sandeep Modi, Anne Hersey, Chris Luscombe
- Alan Hill, Alan Robertson 311C programme team members
- Nigel Watson and very many in the Factor Xa Project team
- Richard Knowles and very many in the iNOS project team

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- Nigel Watson and very many in the Factor Xa Project team
- Richard Knowles and very many in the iNOS project team

Remember:

- Physical Chemists are very much our allies…

Better caricature of a Physical Chemist