Relationships between Lipophilicity and Solubility

Karl J. Box

Physical Chemistry Symposium

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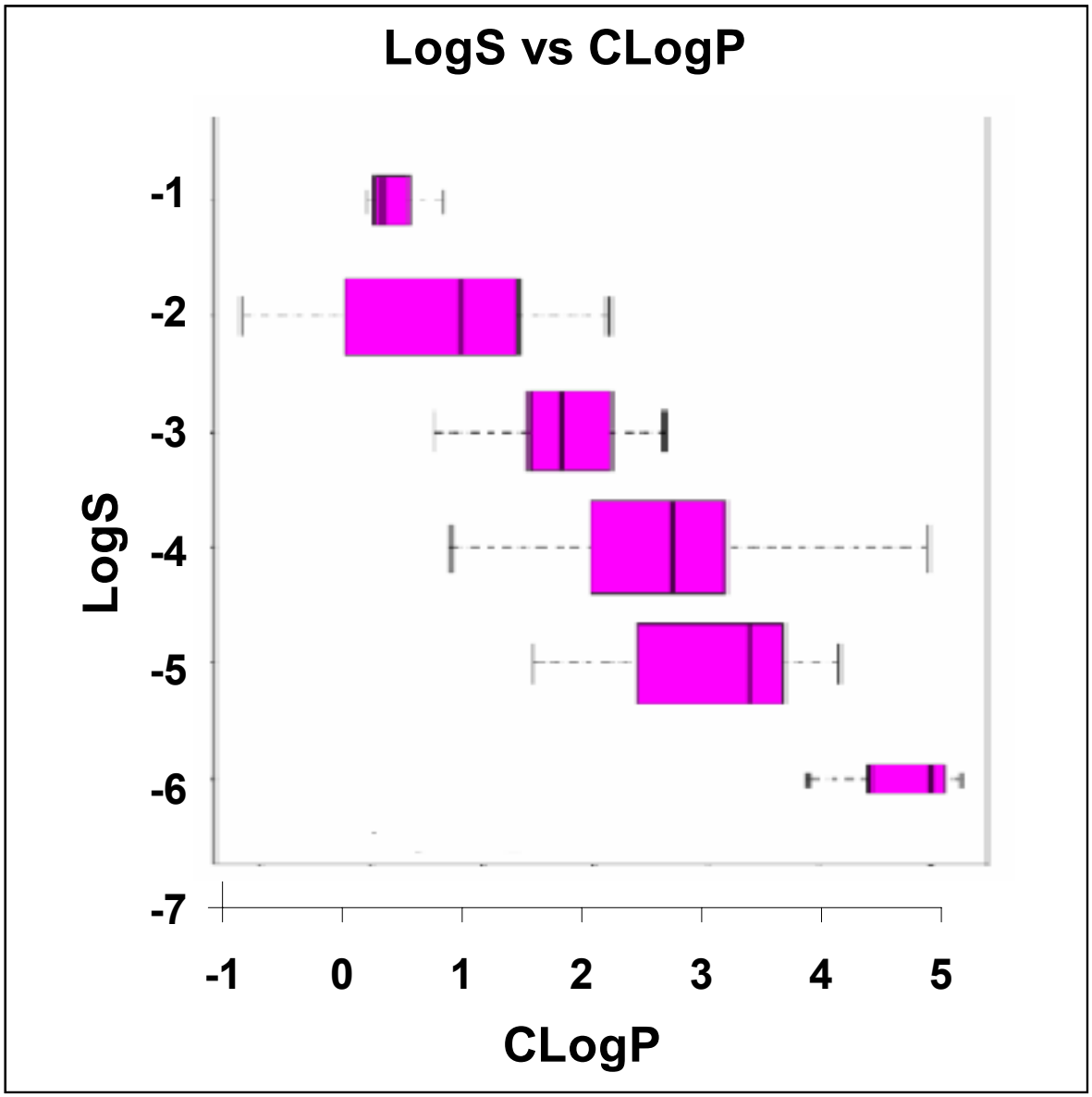
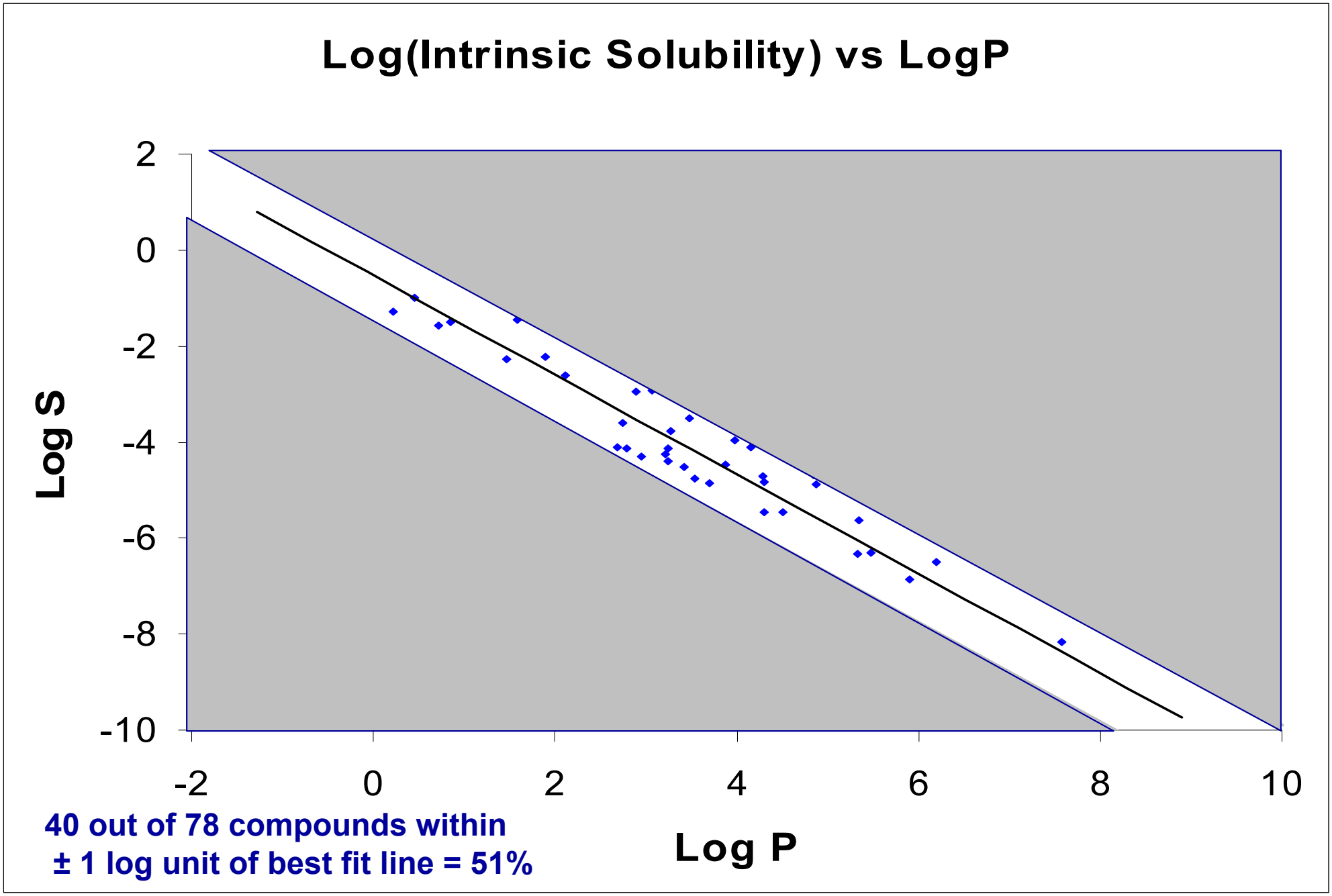
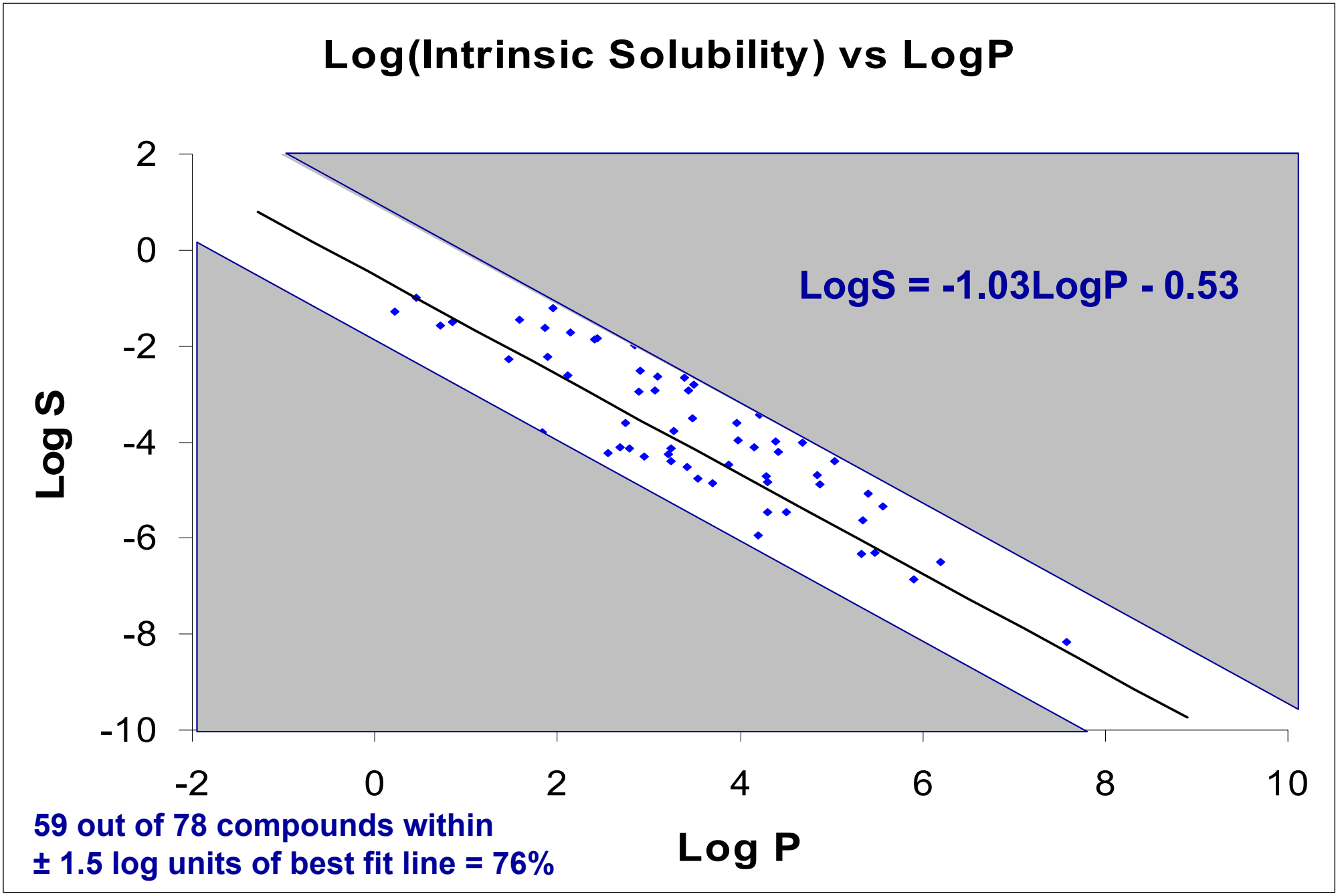
Sirius Analytical Instruments Limited



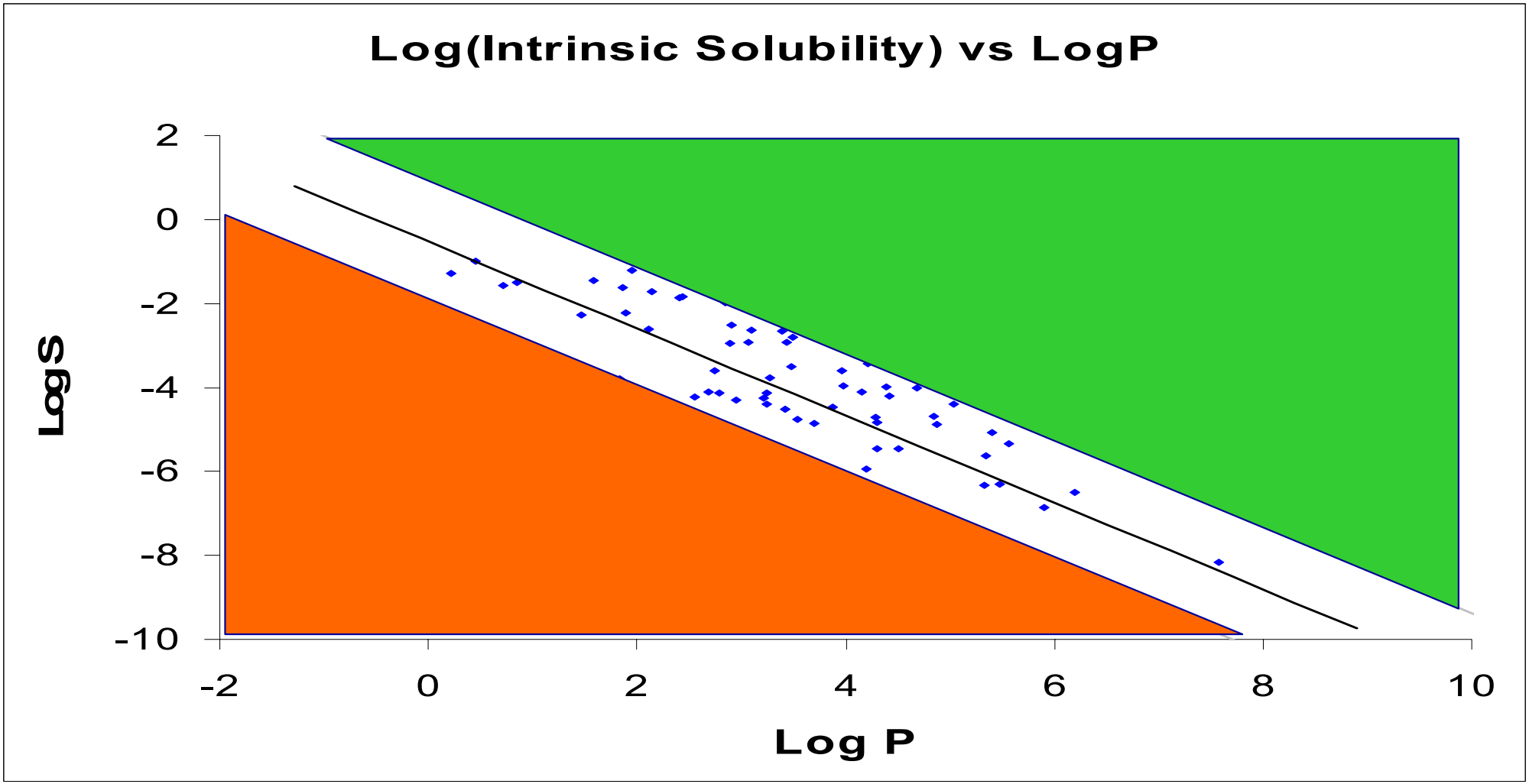
Presented by James Blake, Array BioPharma –
"Finding Drugs within Chemistry Space"

Measured Solubility versus Measured Lipophilicity





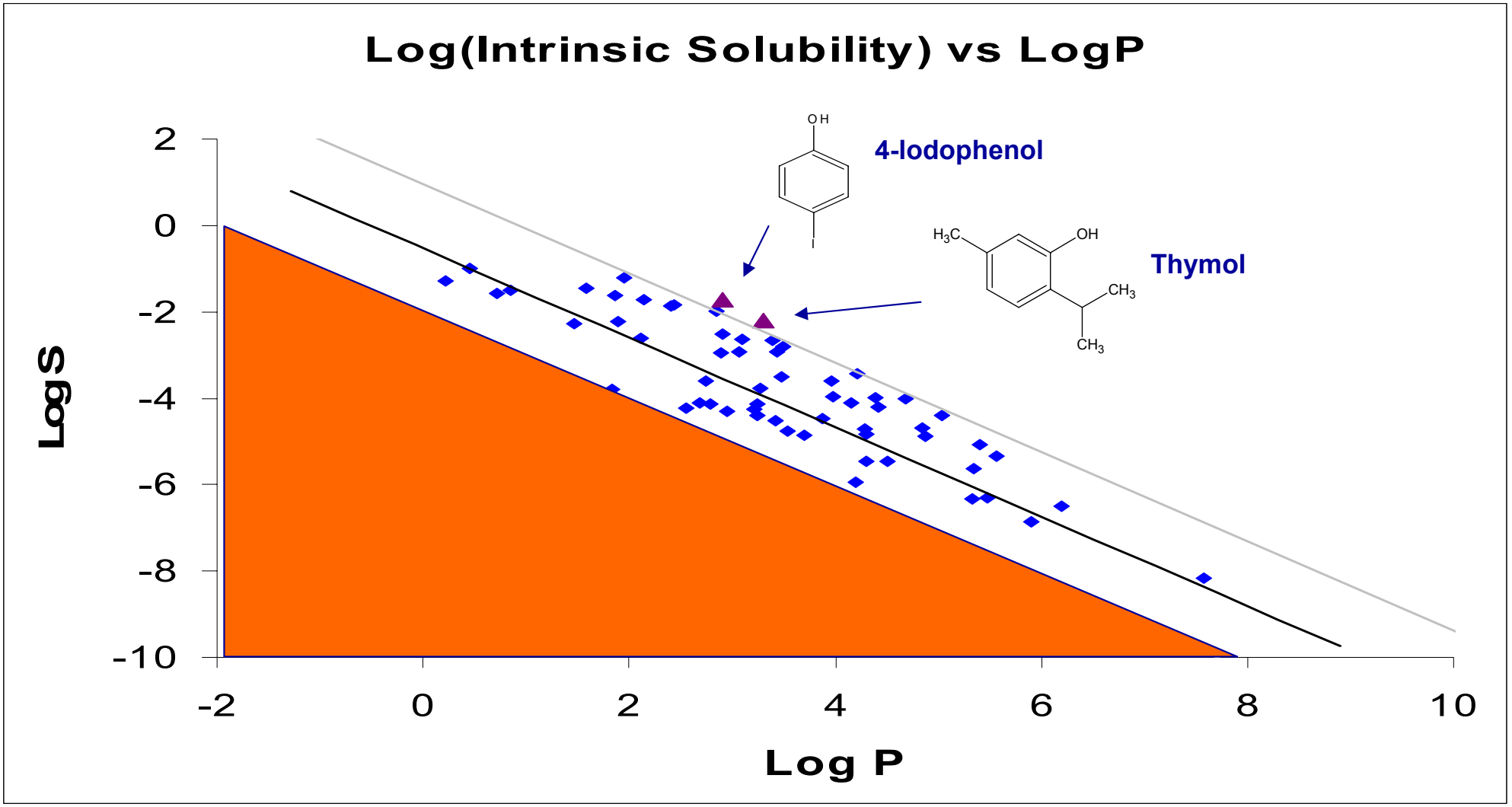
High and Low Solubility Regions



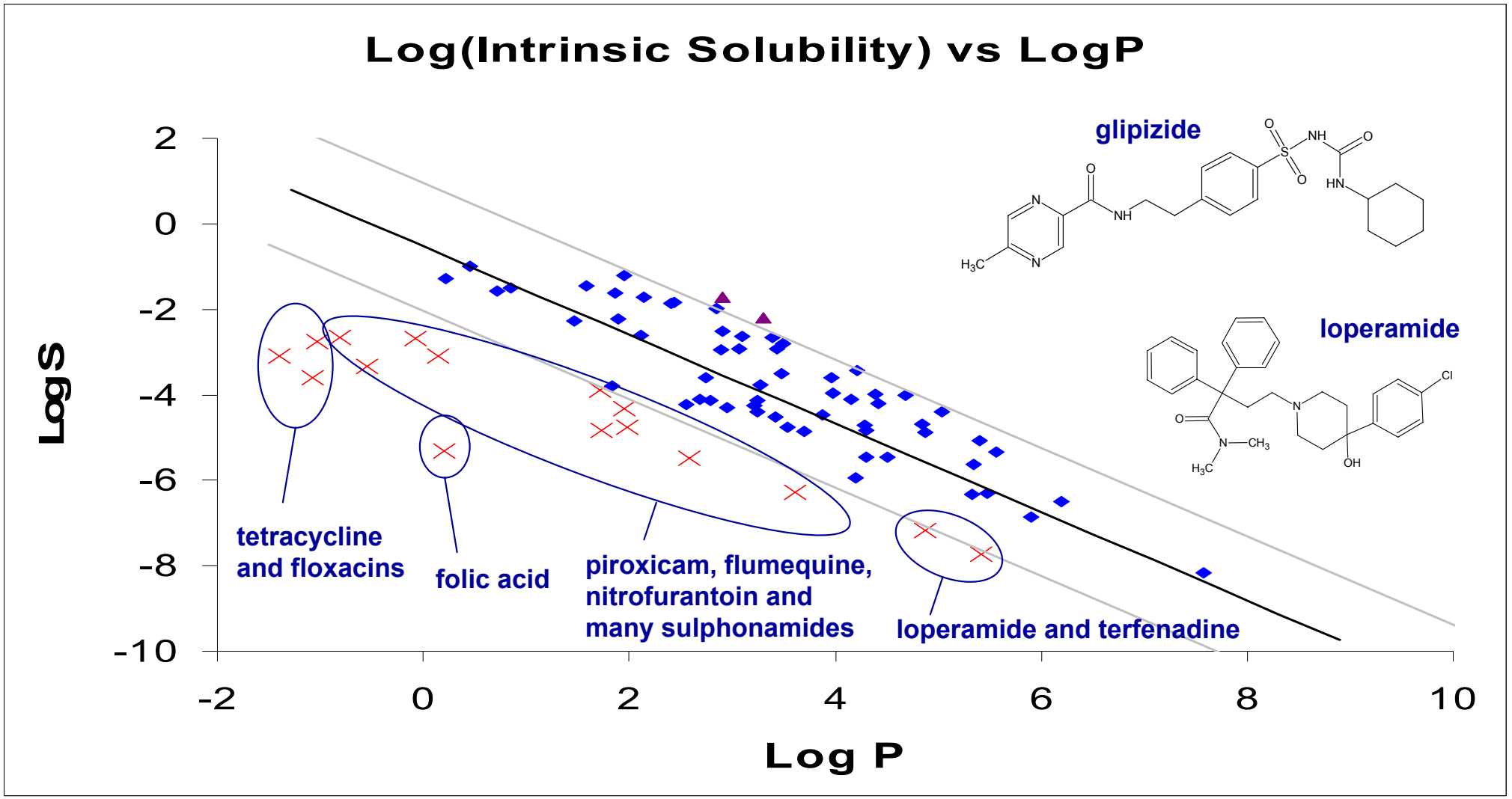
High solubility region for a given lipophilicity

What often happens ! Poor solubility region for a given lipophilicity

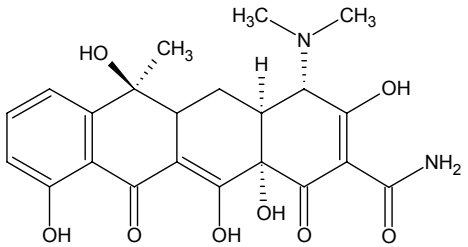
Compounds in High Solubility Region



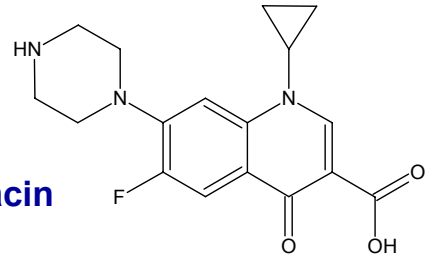
Poor solubility region for a given lipophilicity

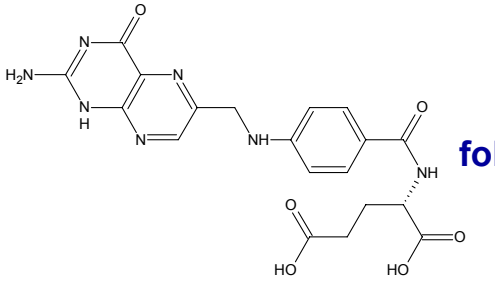


tetracycline



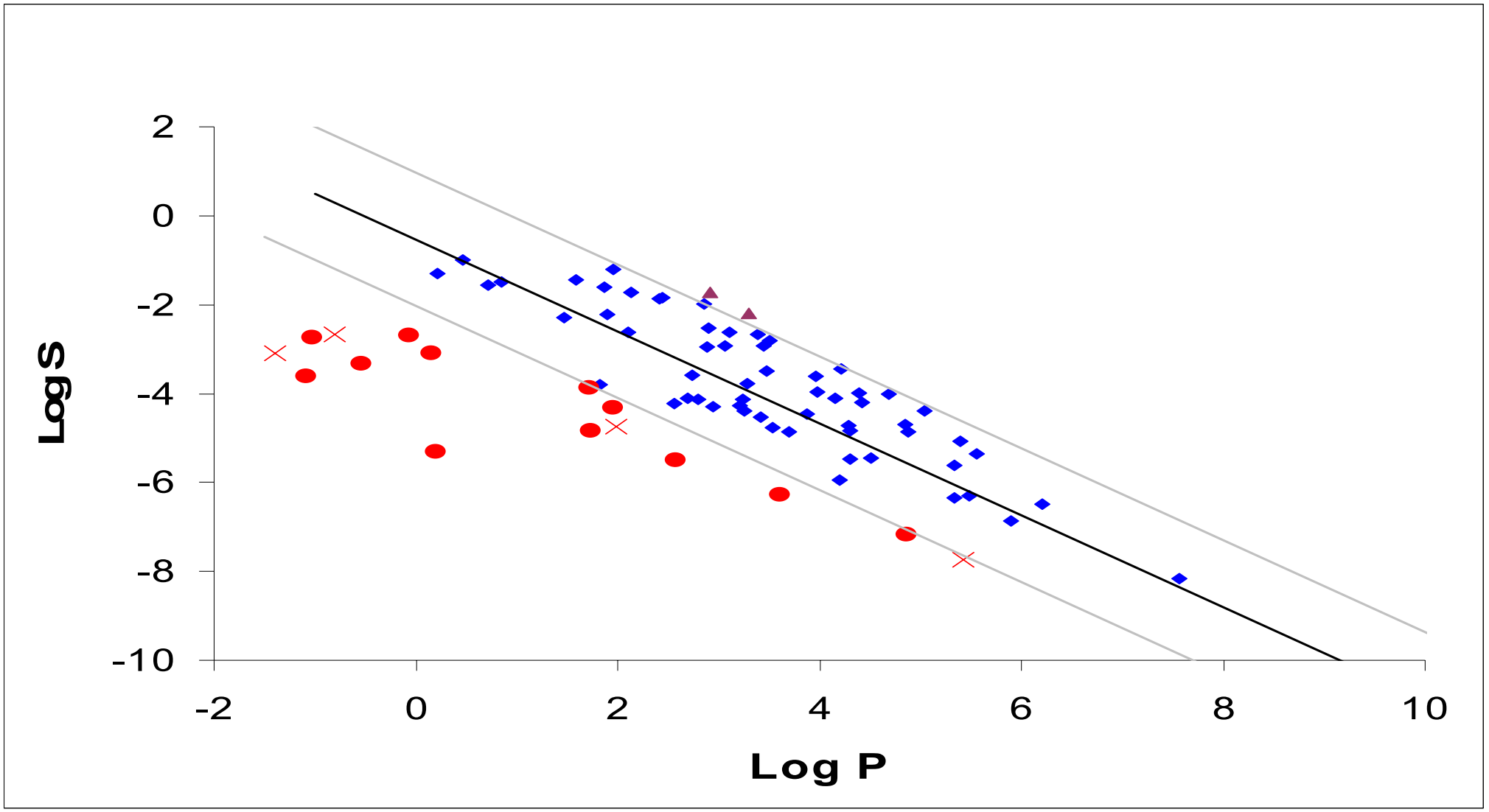
ciprofloxacin





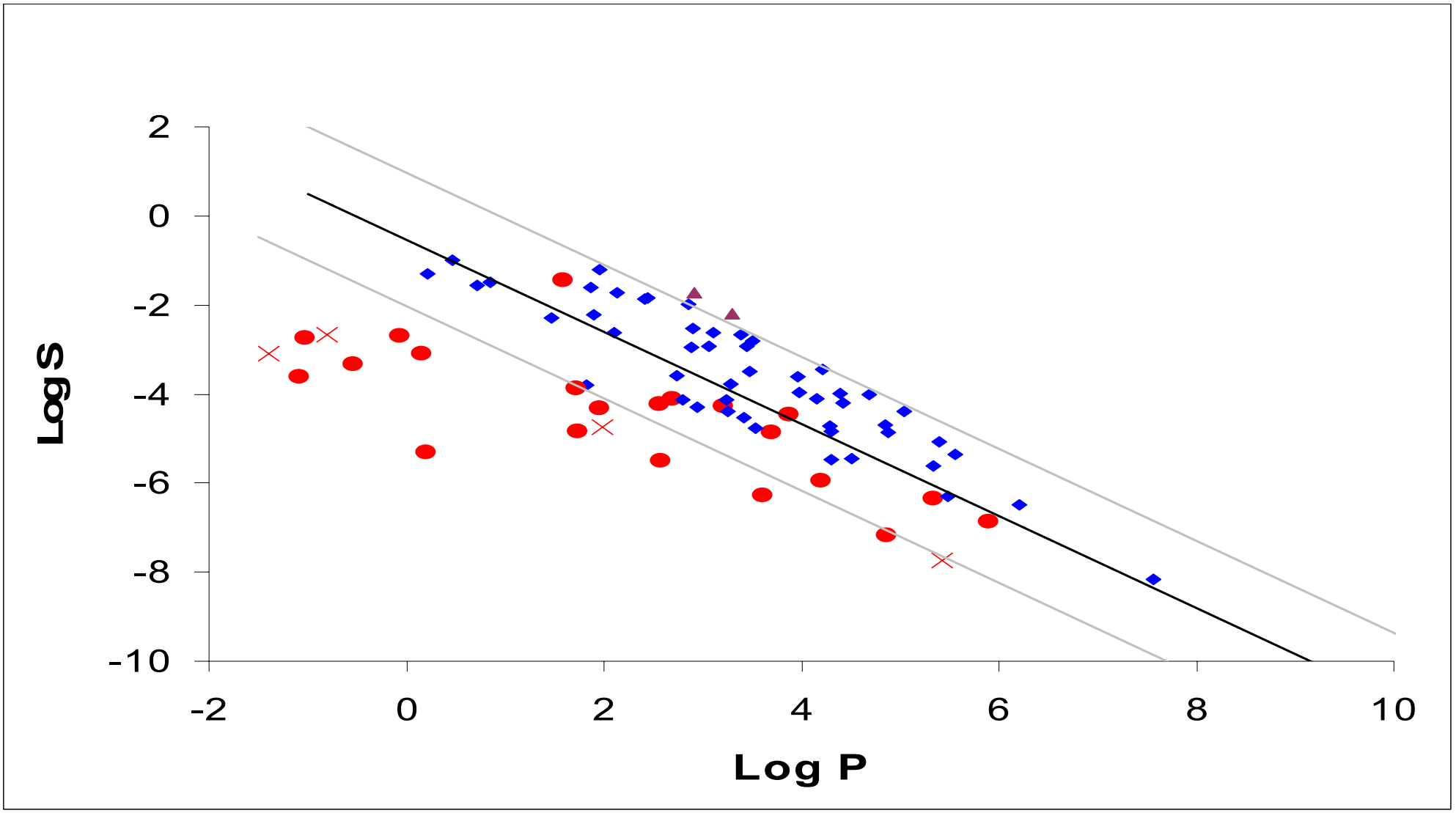
folic acid

Low Solubility Compounds with High Melting Points



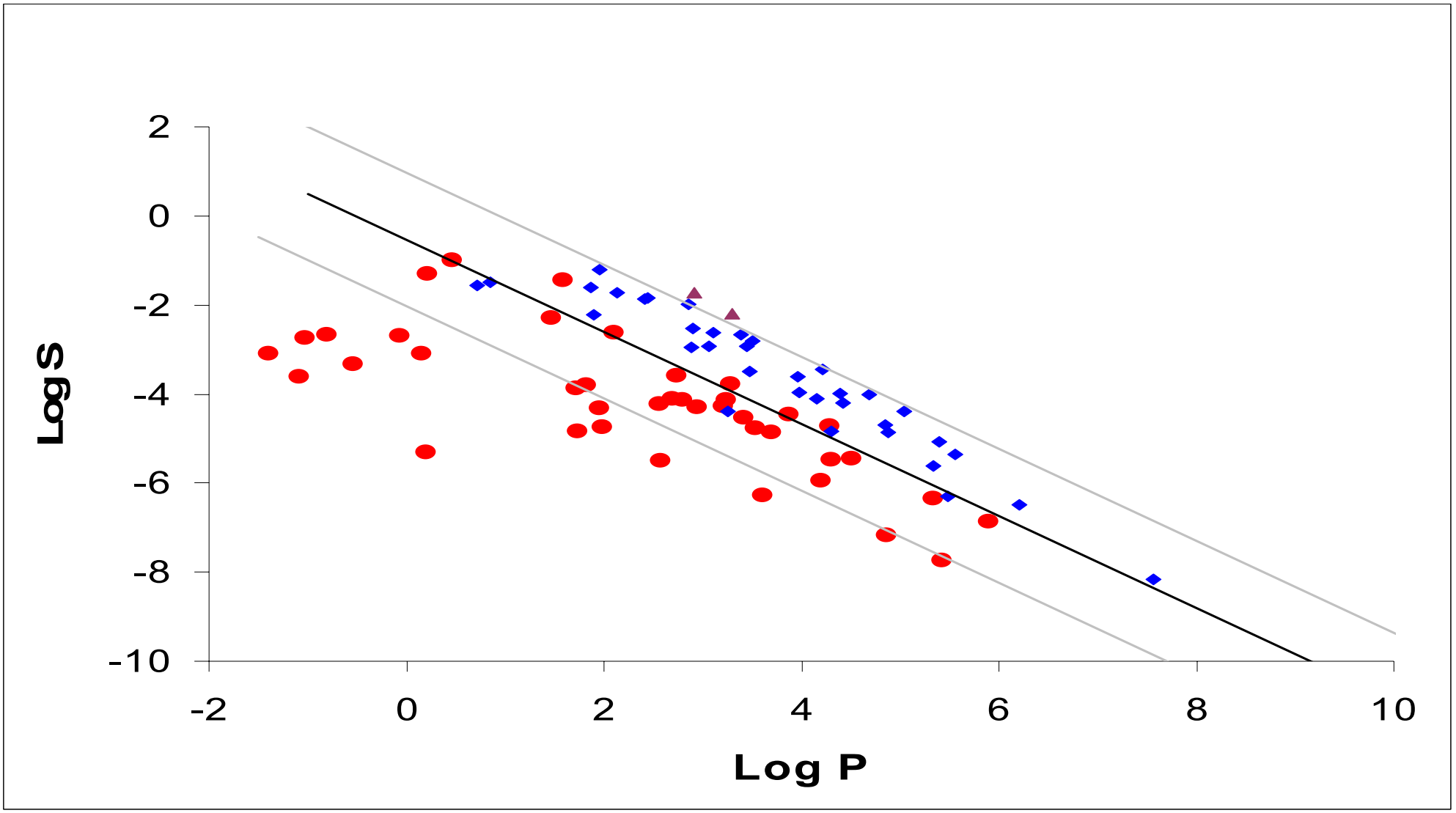
Compounds with MPts > 200°C

All Compounds with High Melting Points



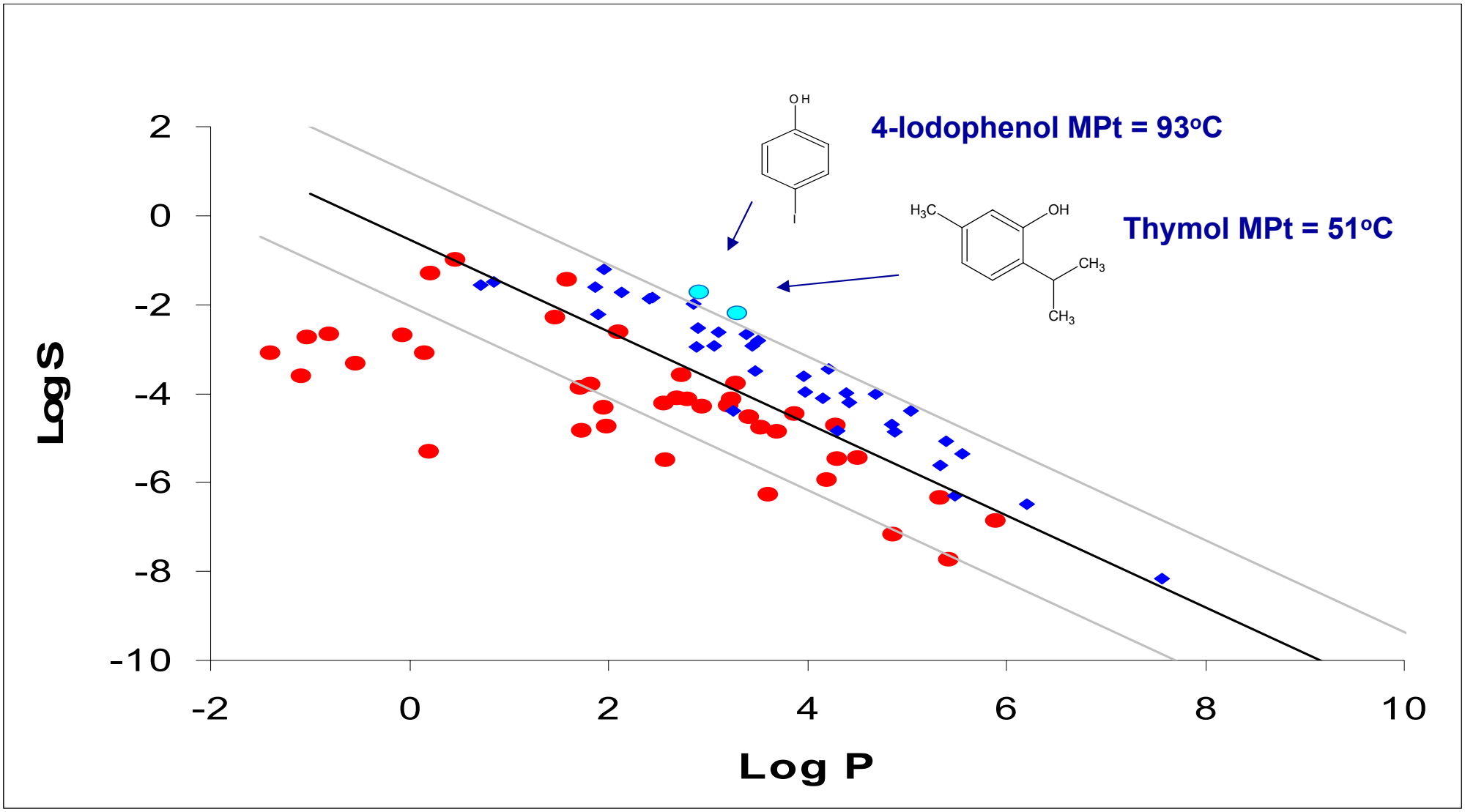
All Compounds with MPts > 200°C

Relationship with Melting Points

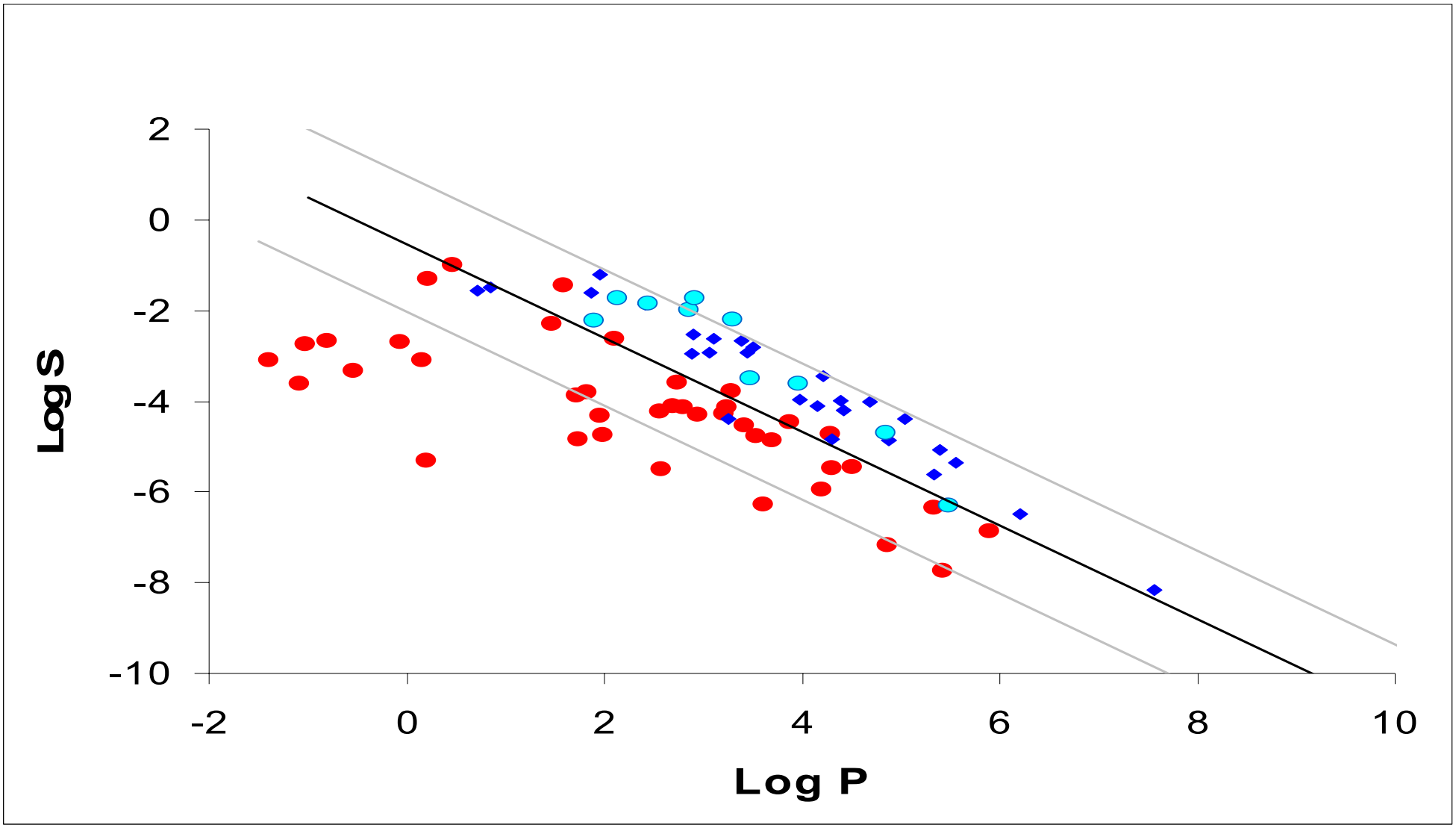


Compounds with MPts > 145°C

Compounds in High Solubility Region with low Melting Points

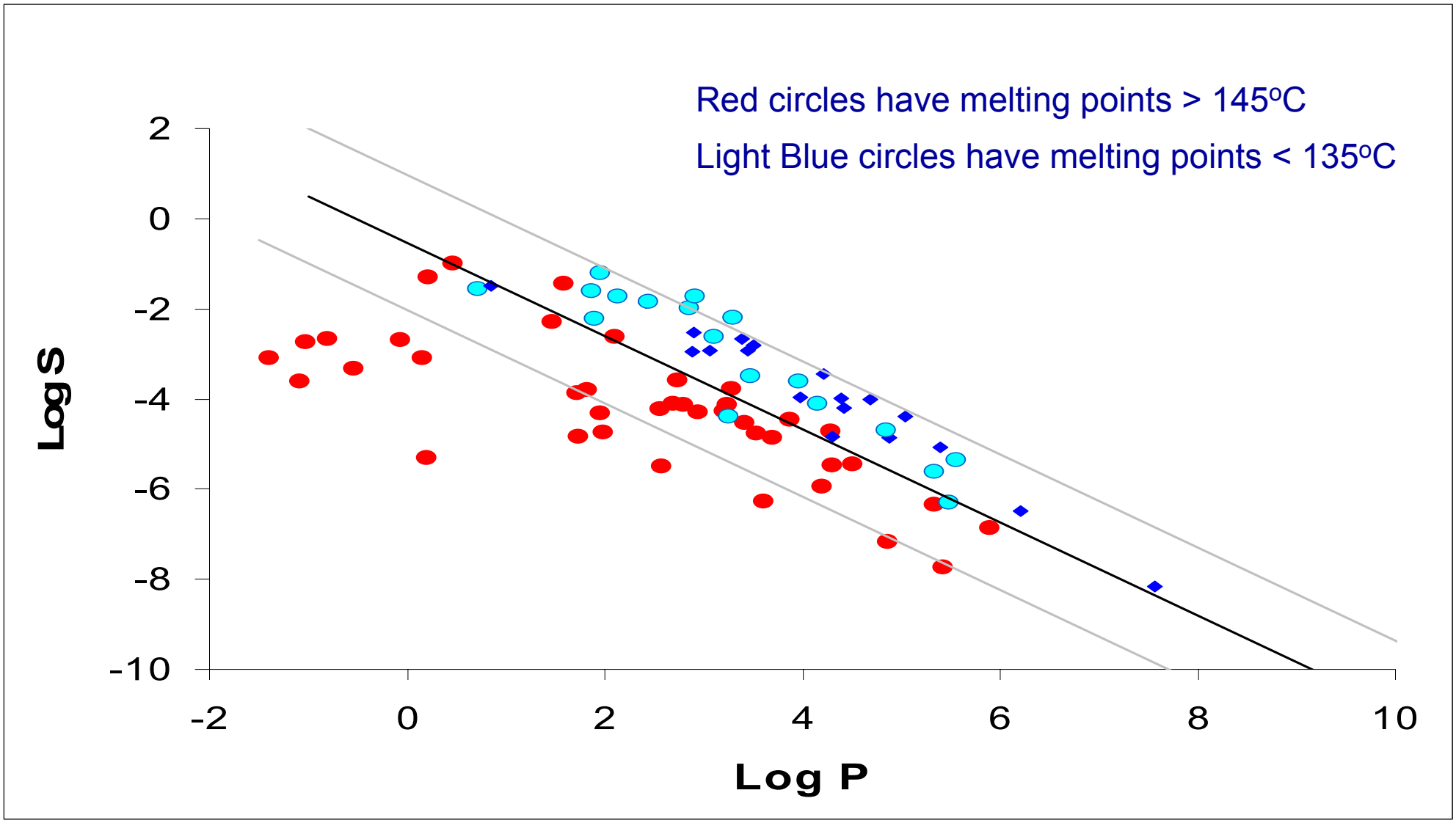


All Compounds with low Melting Points



Compounds with MPts < 100°C

Relationship with Melting Points



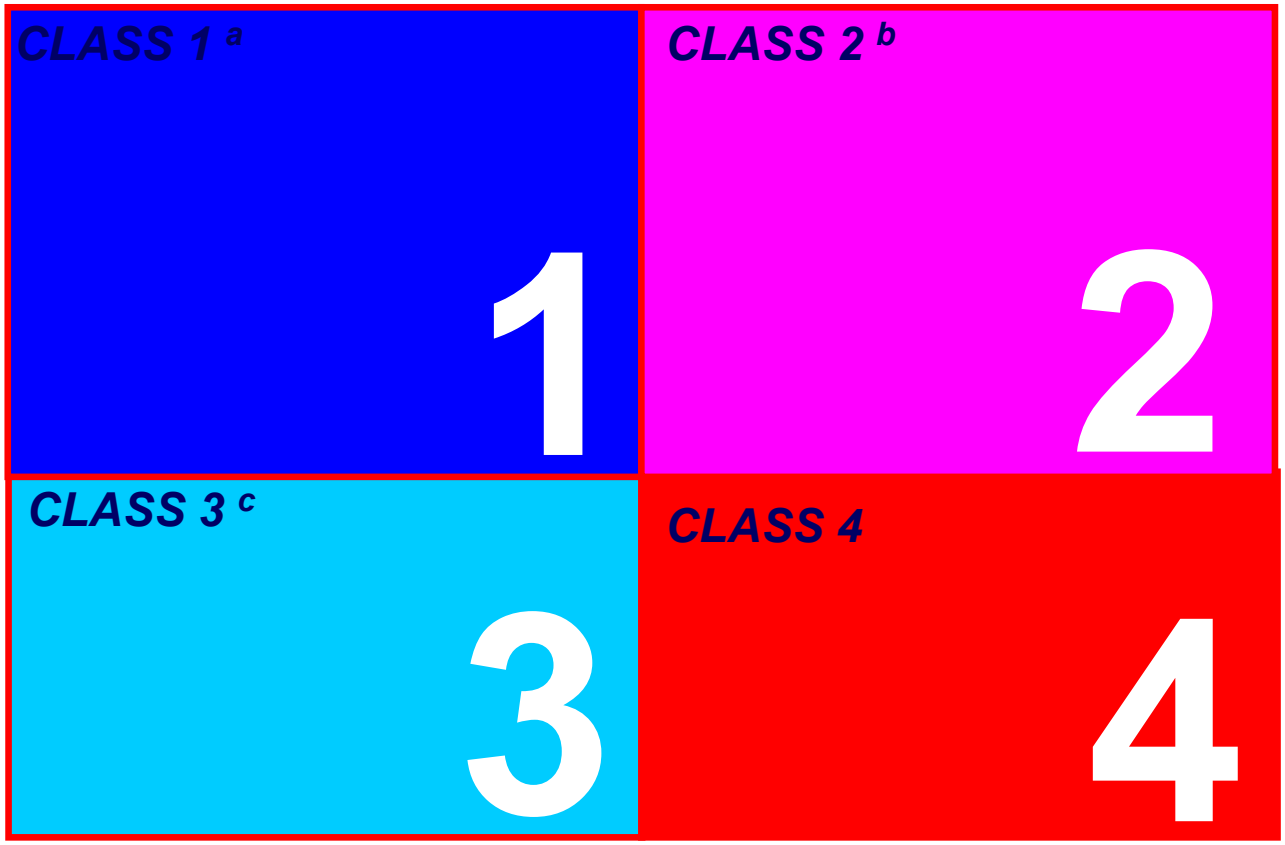
Compounds with MPts < 135°C

But what is left? Do compounds shown as ◆ have MPts between 135 – 145°C?

Biopharmaceutics Classification System (BCS)

***Drug considered HIGHLY SOLUBLE if the highest dose remains in aqueous solution between pH 1 - 8**

***Drug considered HIGHLY PERMEABLE if human absorption >90%**

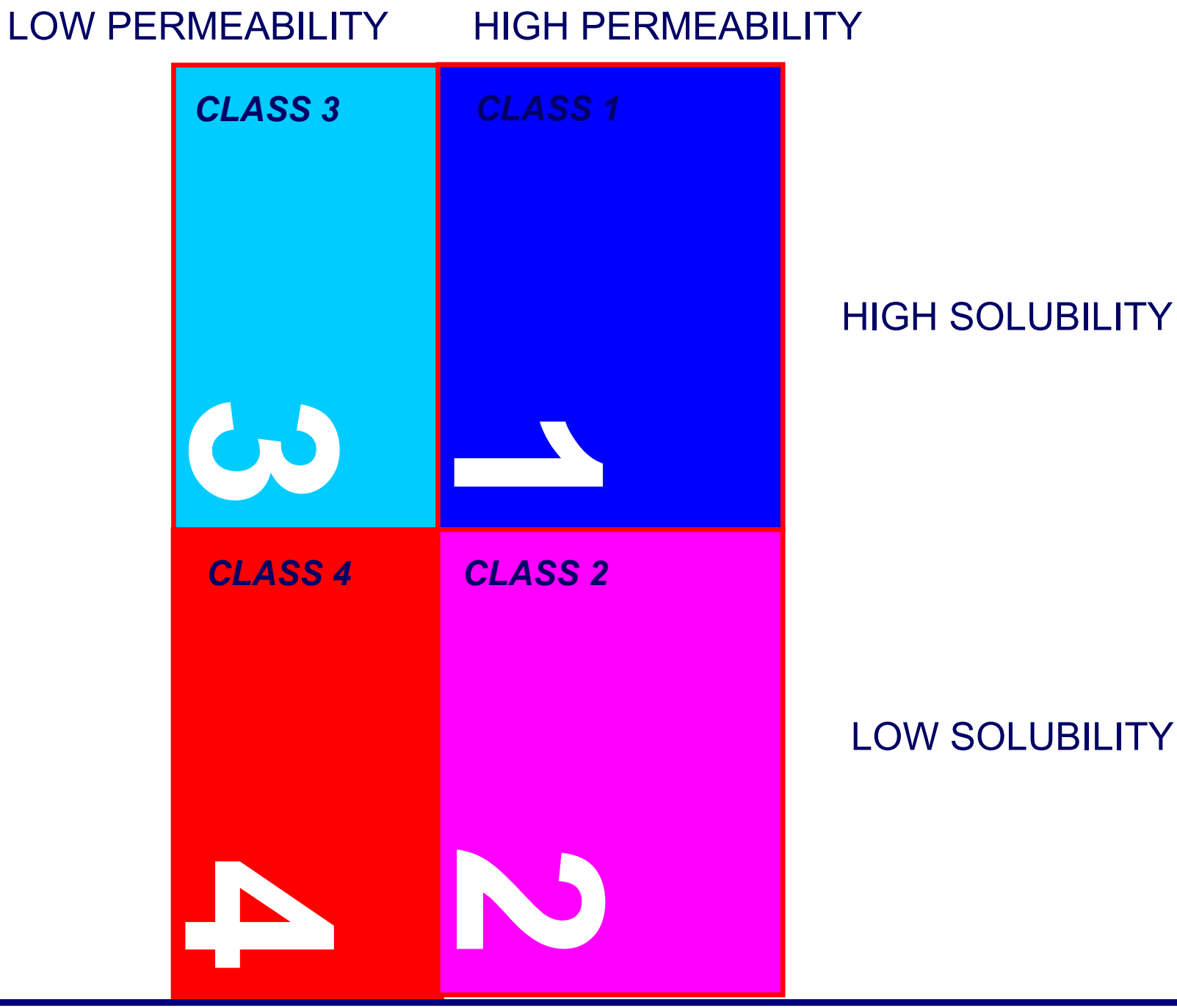


[a] **RATE OF DISSOLUTION limits *in vivo* absorption**
[b] **SOLUBILITY limits absorption flux**
[c] **PERMEABILITY is rate determining**

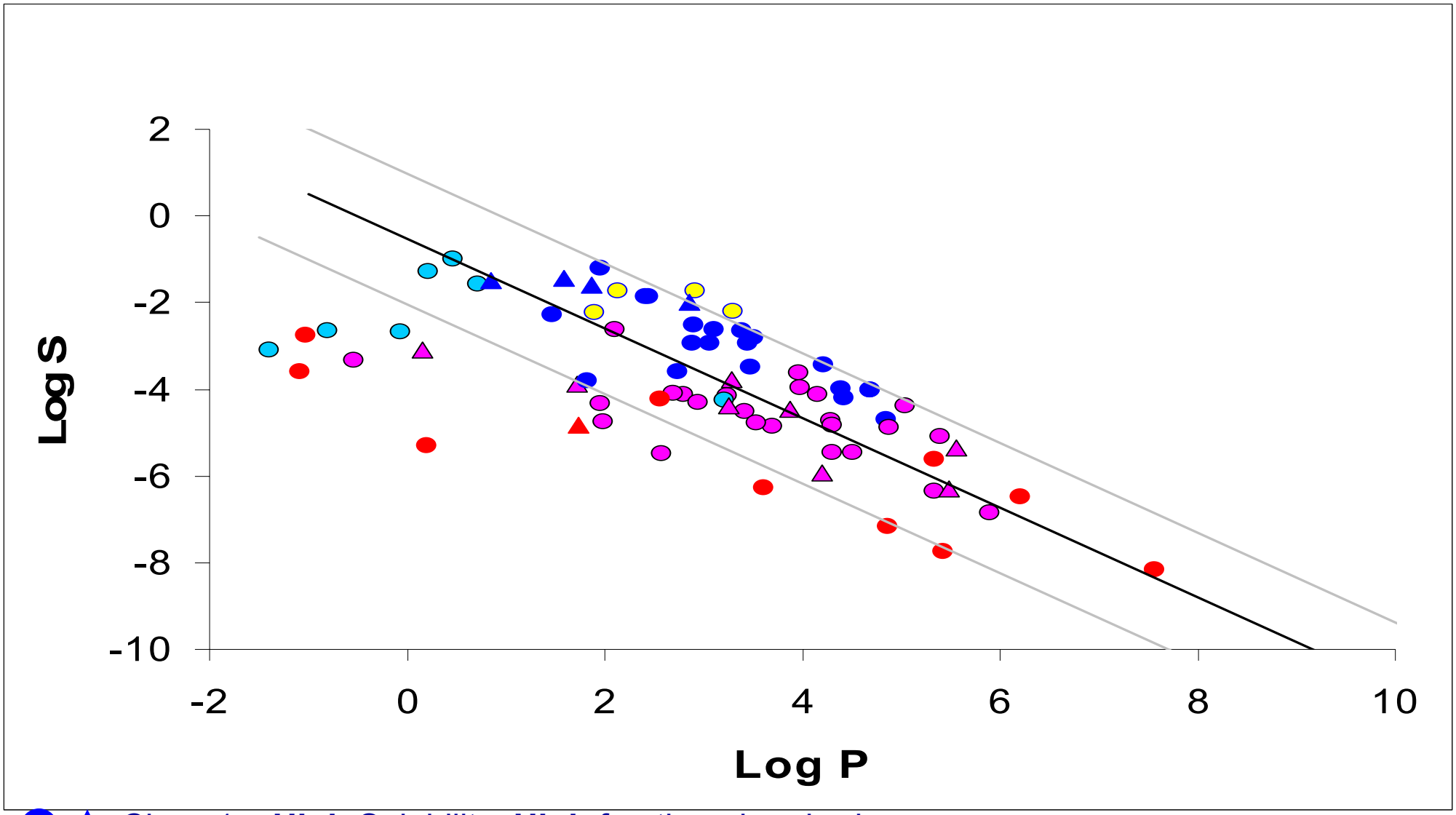
*** www.fda.gov/cder/guidance/3618fnl.pdf**

Amidon, G L. Lennernas, H. Shah, V P. Crison, J R. Pharm. Res. 1995, (12(3)) pp 413-420

Biopharmaceutics Classification System (BCS)



LogP vs LogS and the BCS



Class 1 – **High** Solubility, **High** fraction absorbed

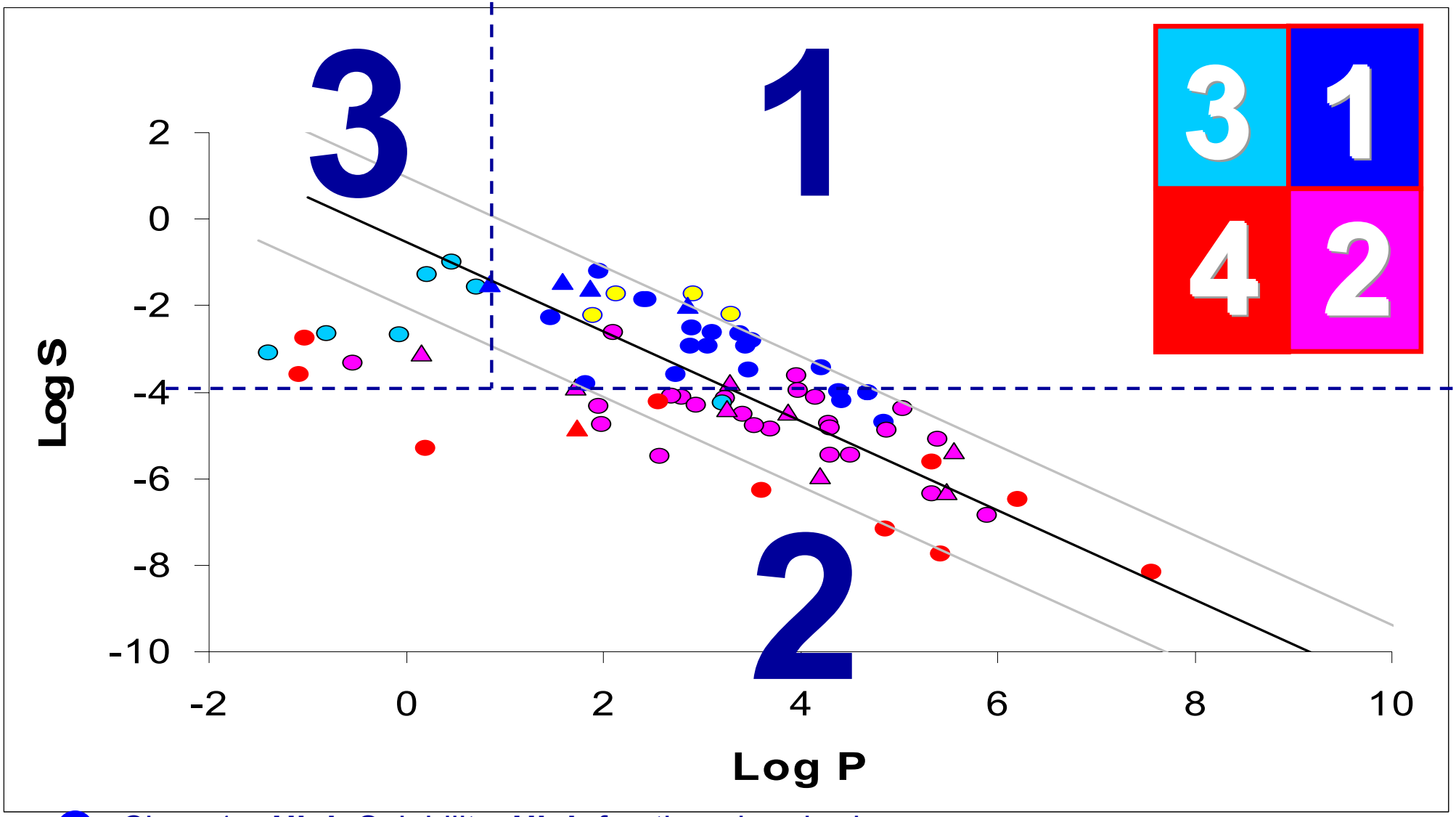
Class 2 – **Low** Solubility, **High** fraction absorbed

Class 3 – **High** Solubility, **Low** fraction absorbed

Class 4 – **Low** Solubility, **Low** fraction absorbed

Not known (includes topical anesthetics)

LogP vs LogS and the BCS



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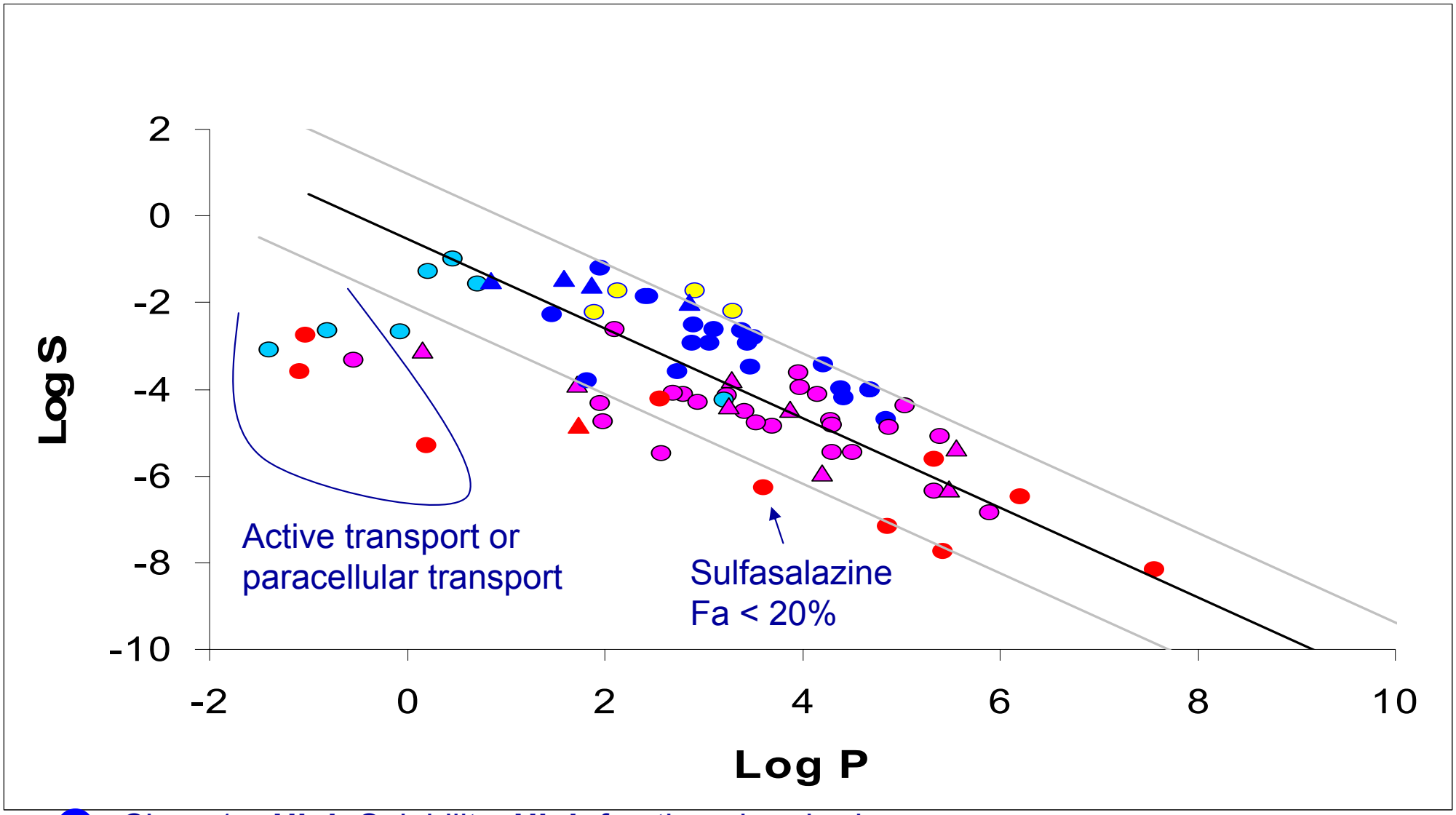
4?

Actively transported and paracellularly transported compounds



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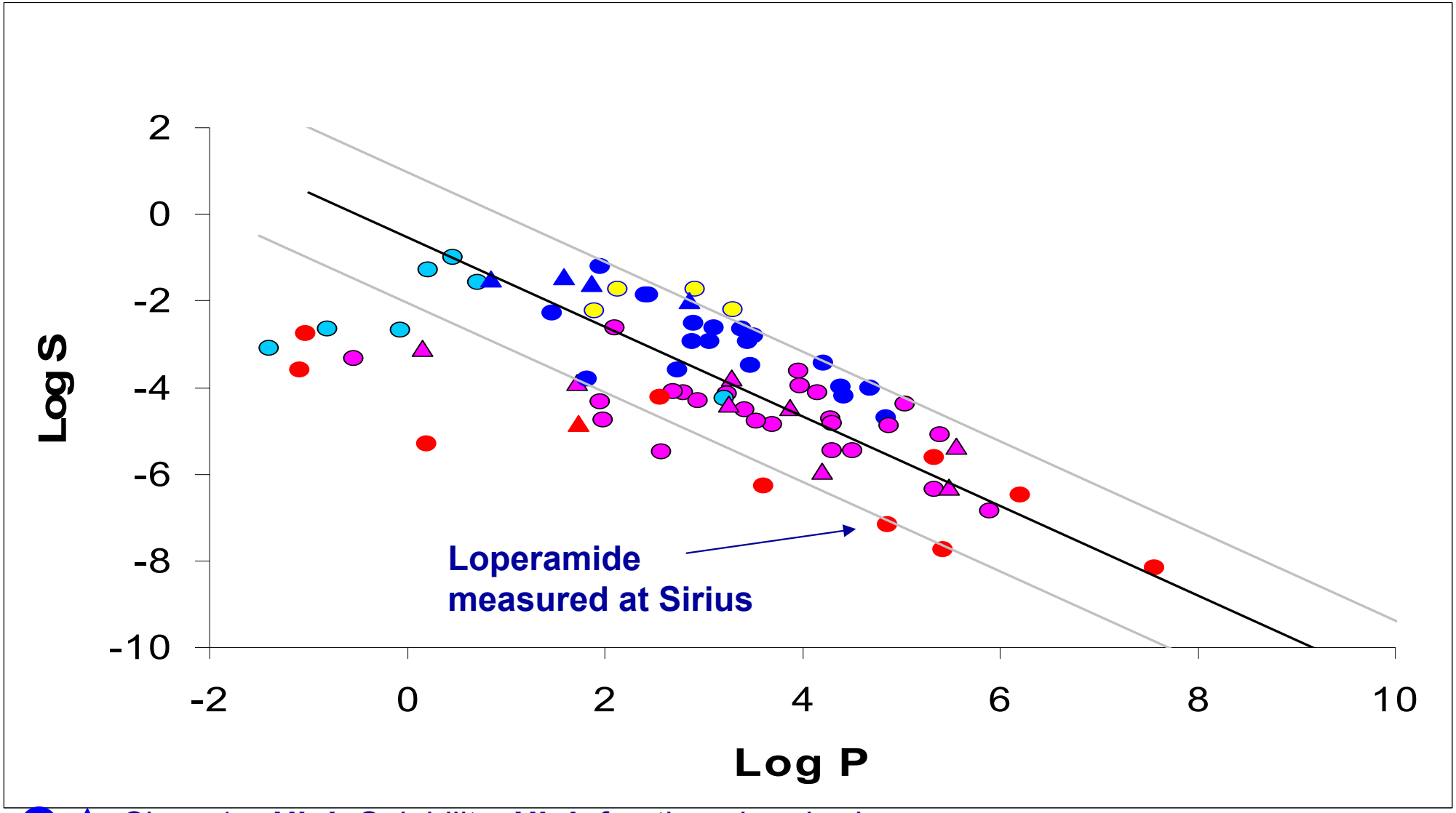
Marketed drugs. All compounds >20% fraction absorbed except one.

Problems with reported literature values



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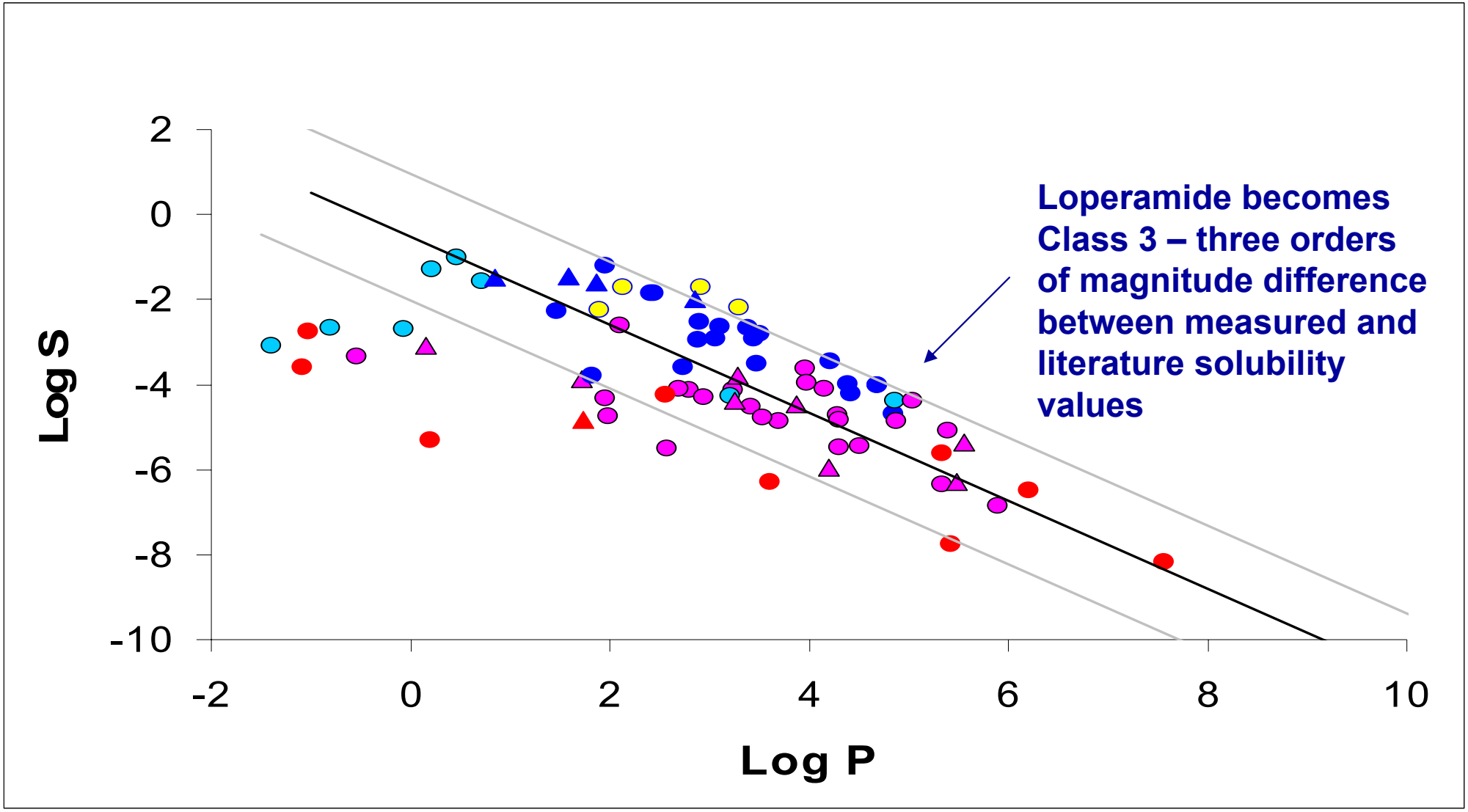

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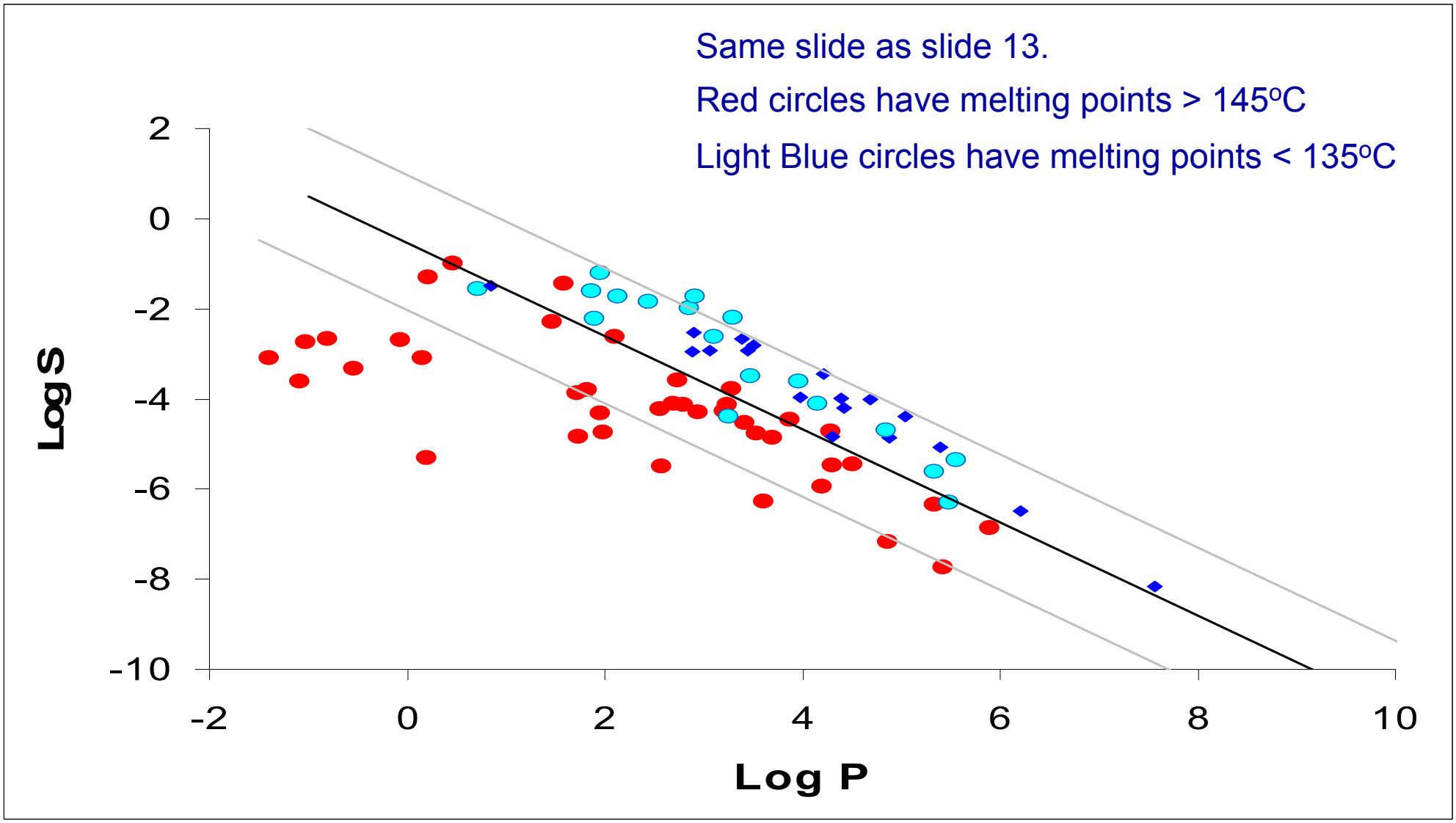
Not known (includes topical anesthetics)

Now let's return to the compounds with missing melting points

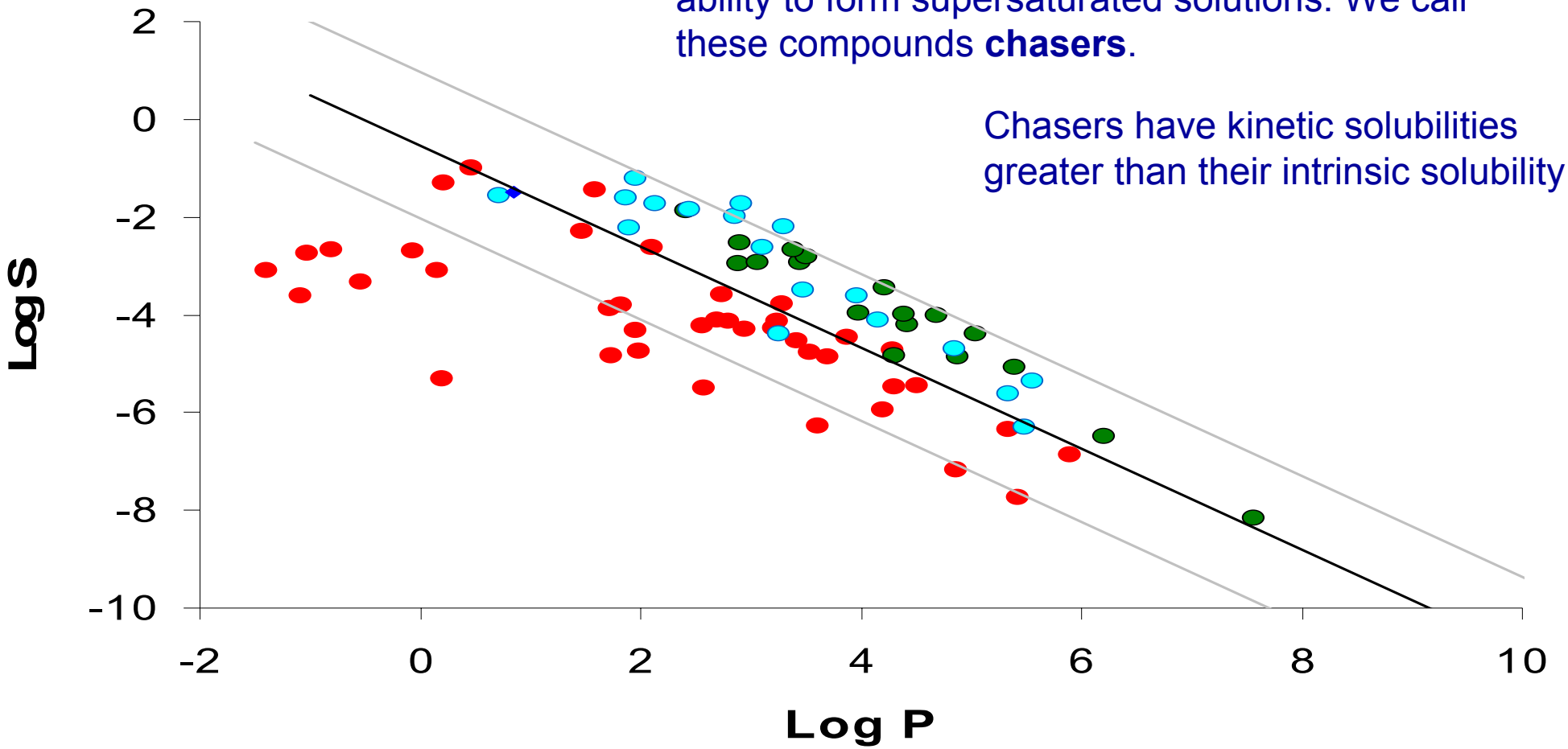


But what is left? Do compounds shown as ◆ have MPts between 135 – 145°C?

The missing compounds can not form supersaturated solutions

All other compounds not marked in green have the ability to form supersaturated solutions. We call these compounds **chasers**.

Chasers have kinetic solubilities greater than their intrinsic solubility.

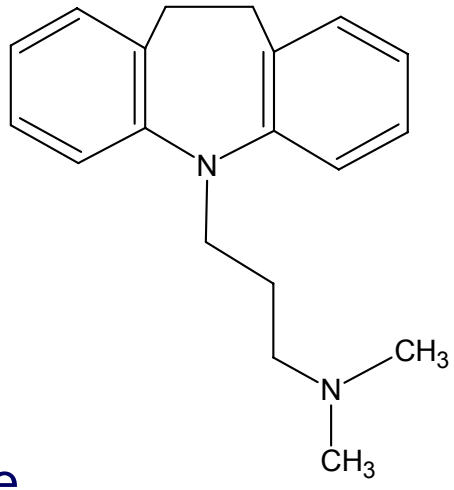


- These compounds cannot form supersaturated solutions. When the pH is right, they fall out of solution immediately the solubility limit is exceeded. We call these compounds **Non-Chasers**. The kinetic solubility and Intrinsic solubility of non-chasers is equal.

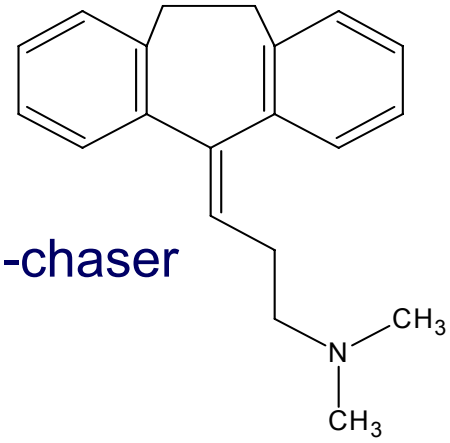
Can we predict whether a sample is a non-chaser?

Imipramine

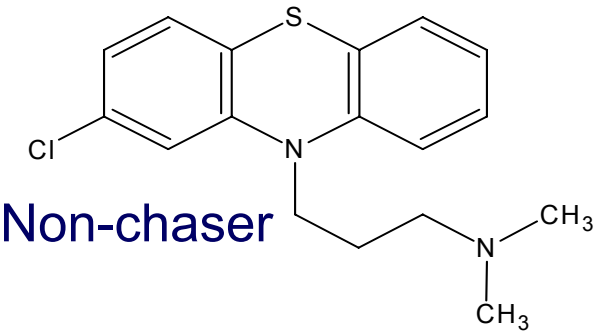
Non-chaser



Amitryptyline

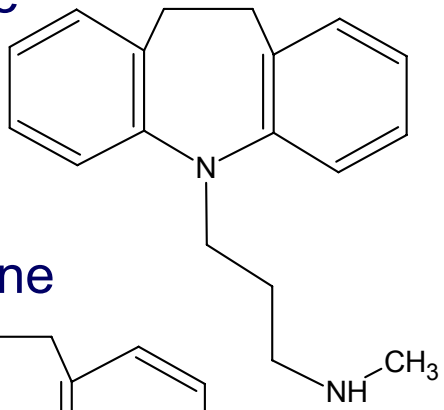


Chlorpromazine

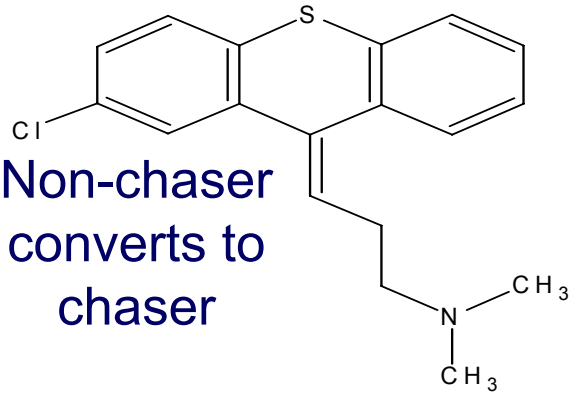


Desipramine

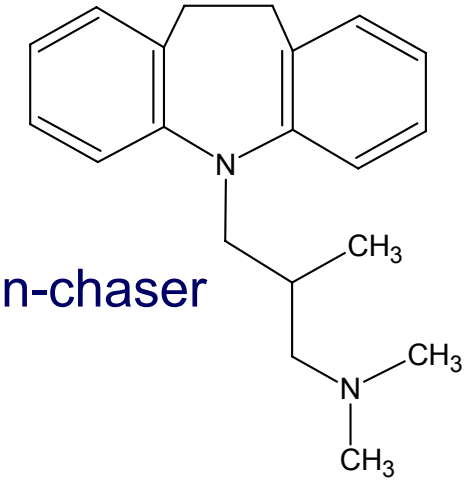
Non-chaser



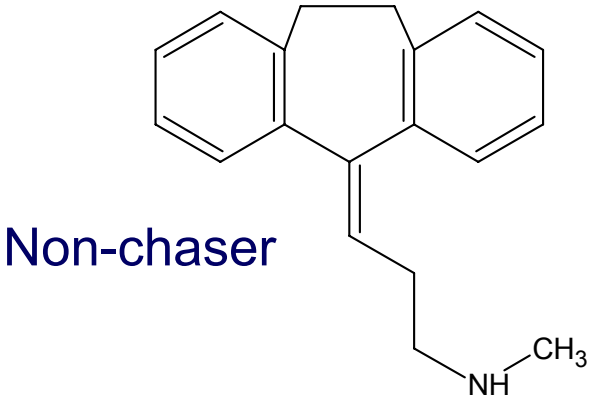
Chlorprothixene



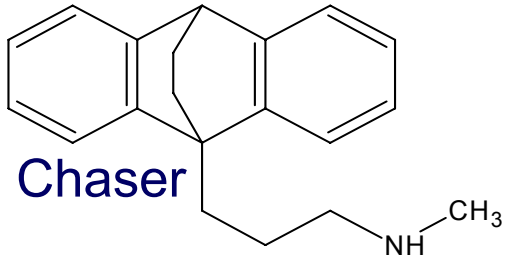
Trimipramine



Nortriptyline



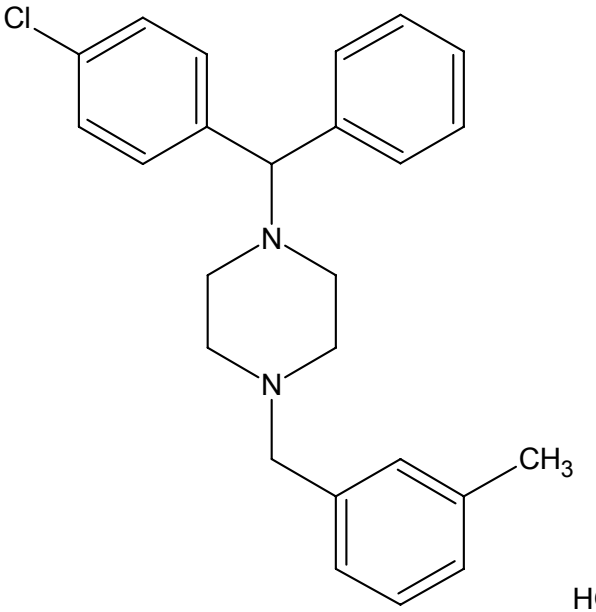
Maprotiline



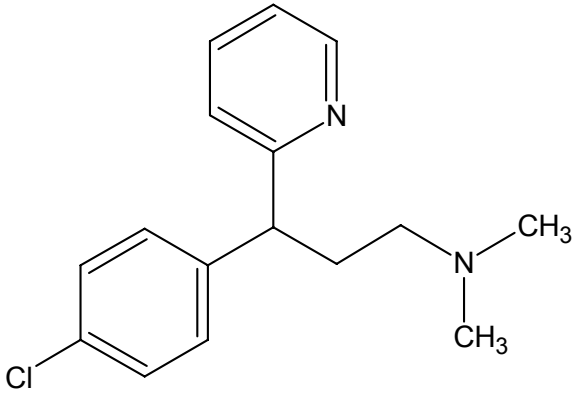
Secondary and tertiary amines with logP > 4.

 Similar structures, but maprotiline contains a -CH_2-CH_2- bridge.

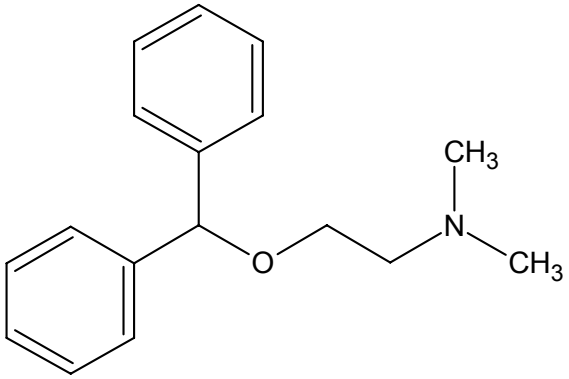
Meclizine

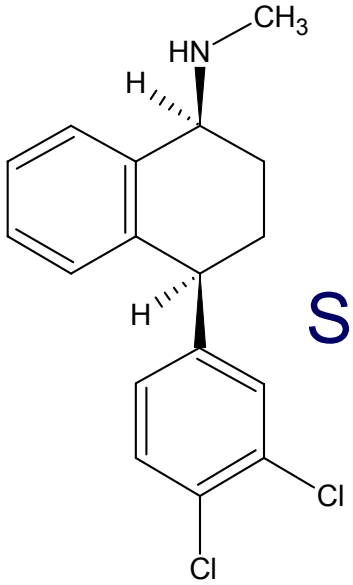


Chlorpheniramine

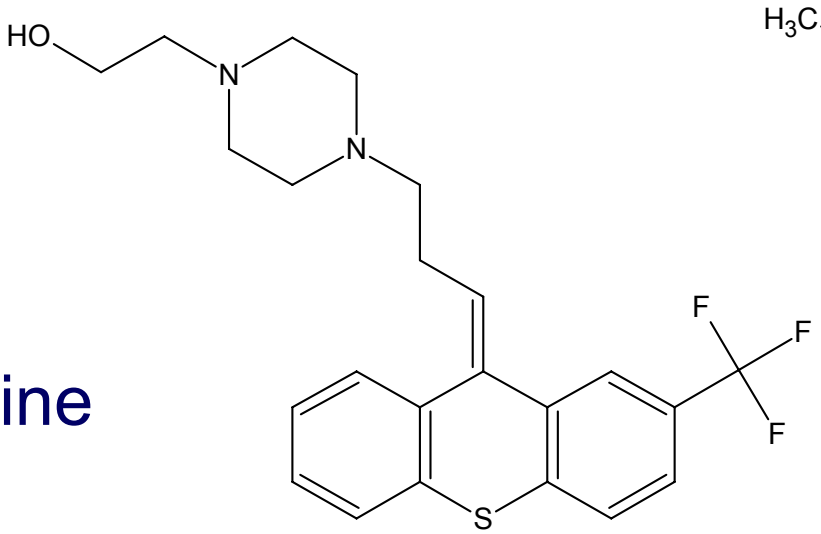


Diphenhydramine

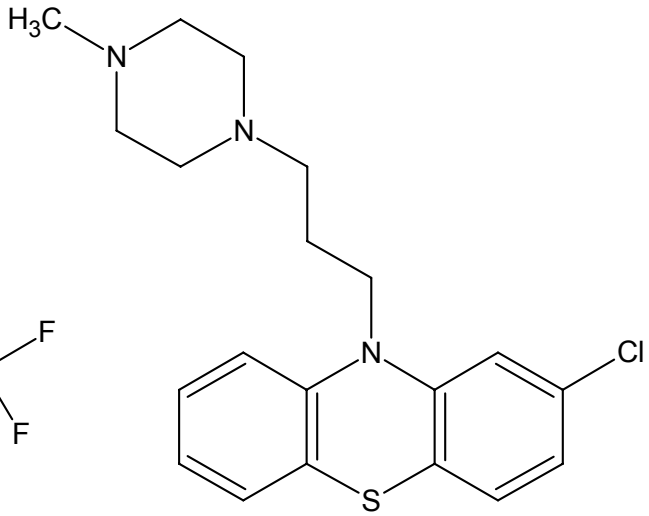




Sertraline

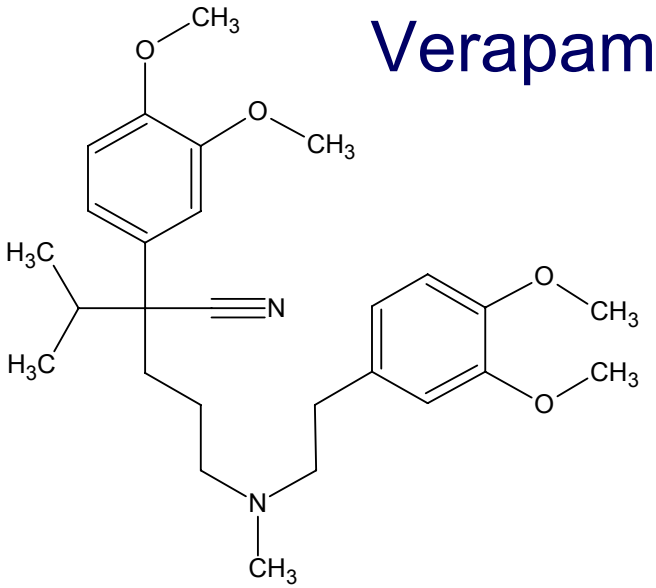


Flupenthixol

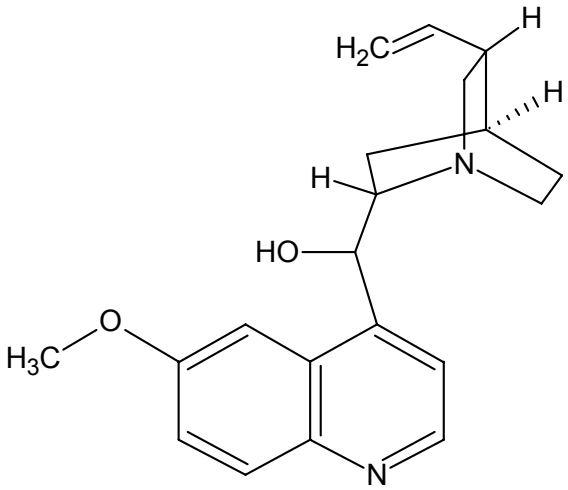


Prochlorperazine

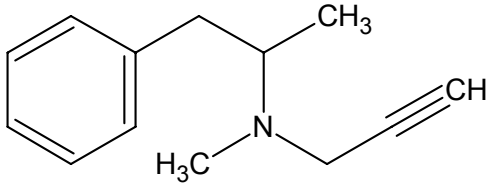
More non-chasers……



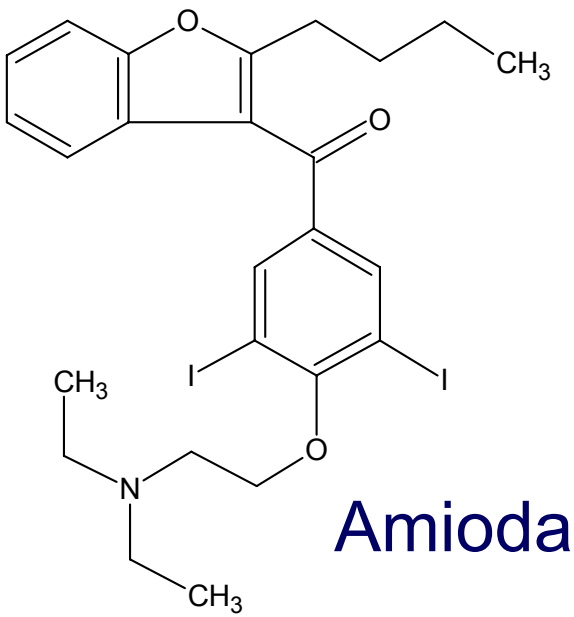
Verapamil



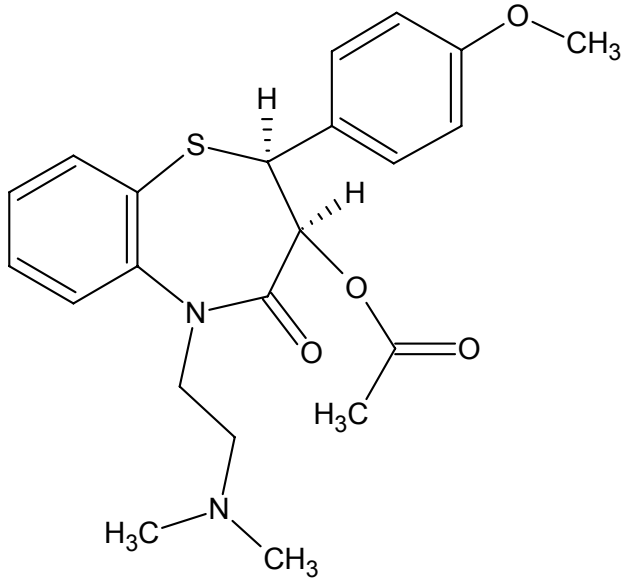
Quinine



Deprenyl

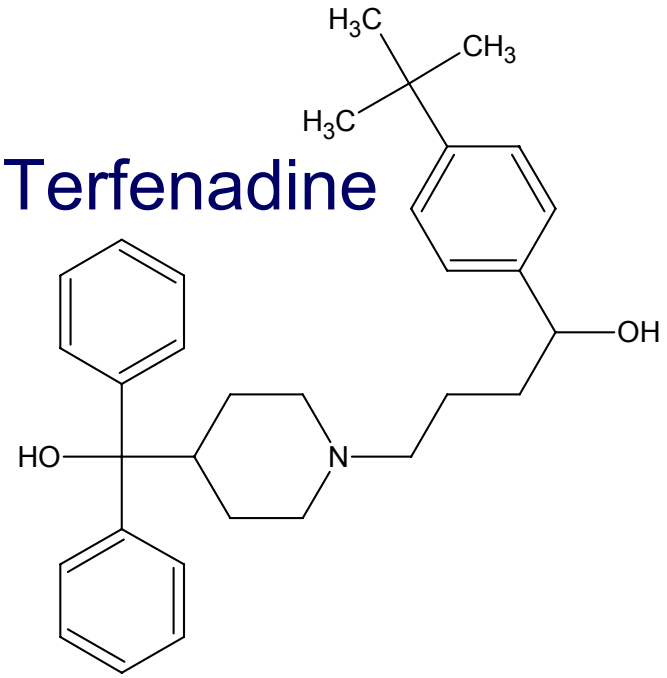


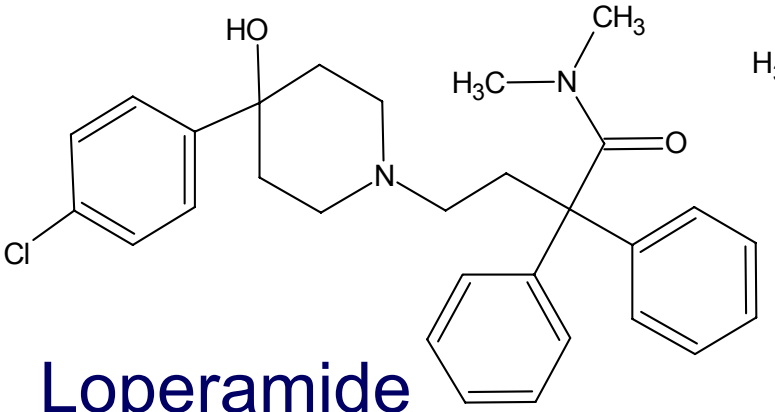
Amiodarone



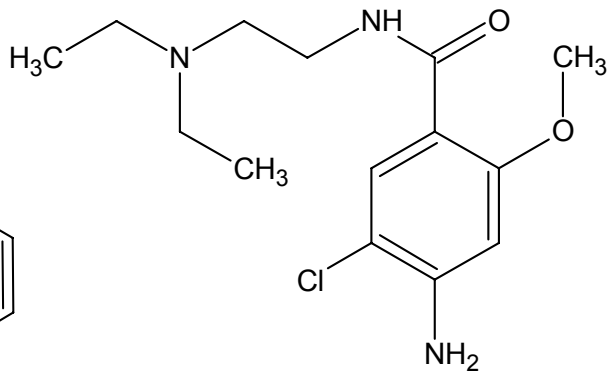
Diltiazem

Terfenadine

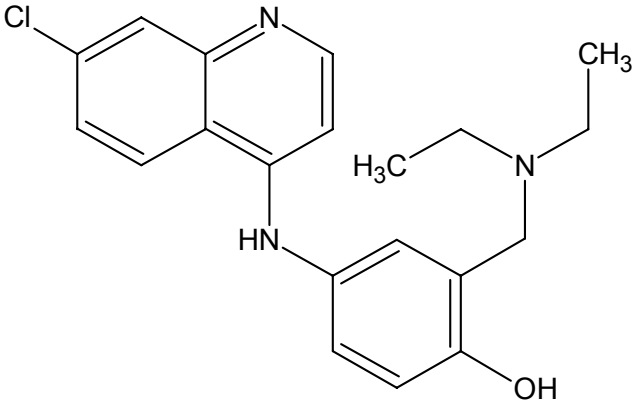




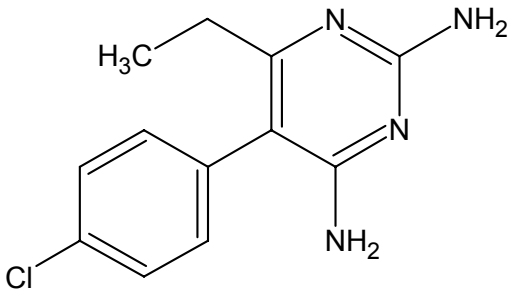
Loperamide



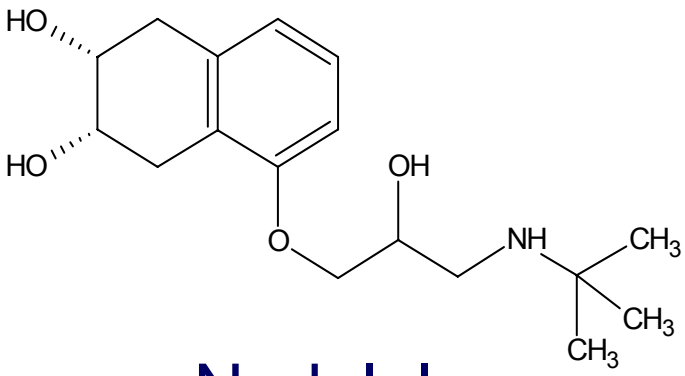
Metoclopramide



Amodiaquin



Pyrimethamine



Nadolol

References – chasers and non-chasers

- First paper, introducing the concept of chasing equilibrium
  - Stuart, M. Box, K. Chasing equilibrium: measuring the intrinsic solubility of weak acids and bases. Anal. Chem. **2005**, 77(4), 983-990
- Second paper, collaborative research to validate method and introduce concept of non-chasers
  - Box, K J. Völgyi, G. Baka, E. Stuart, M. Takács-Novák, K. Comer, J E A. Equilibrium vs. kinetic measurements of aqueous solubility, and the ability of compounds to supersaturate in solution - a validation study. J. Pharm. Sci. **2006**, 95, 1298-1307.

Non-chasers

- While the similarities between some non-chasing structures are obvious, we don't yet have strict rules for predicting non-chasing from structure.
- Since introducing CheqSol in March 2004, we have found only a few non-chasing acids, but about 20% of bases have been non-chasers.
- Supersaturation impacts on drug bioavailability and must be considered during formulation and manufacturing.
- Some attempts at predicting non-chasing compounds are shown in the following slides.

Possible implications of chasing vs. non-chasing

- The propensity of a compound to supersaturate and remain so for a reasonable time might have implications in drug adsorption
- For example, a weak base might dissolve fully in the stomach but precipitate on entering the high pH environment of the upper intestinal tract. A better understanding of this would enable better adsorption models to be constructed.
- Do non-chasers fall out of solution as amorphous material whereas chasers produce crystalline precipitate?
- Amorphous materials are amenable to solid state dispersion nanoparticle delivery methods.
- Conversely, do the non-chasers have some kind of structured or ordered solution phase (liquid crystals, micelles, aggregates) that prevents supersaturation?
- Is it possible to formulate supersaturated solutions that stay in solution long enough such that absorption is enhanced?
- Conversely, if a compound is administered in supersaturated solution, could it crash out of solution with unpleasant side effects?

Correlating non-chasing with melting point

- Melting point
  - Many non-chasers have low melting points *
  - According to the Merck Index the free forms of Chlorpheniramine, Verapamil, Imipramine and Chlorpromazine are oils. The free form of nortryptyline is structurally similar to Imipramine and may also be an oil. Do non-chasers precipitate as an oily phase which cannot change into crystals?
  - Quinine forms crystals with a M.pt of 177ºC, but it forms a trihydrate with a very low M.pt of 57ºC. Does it come out of solution as a fluid droplet which does not further crystallise?

* With thanks to Rod Kittlety, AstraZeneca, Alderley Park, Macclesfield, UK

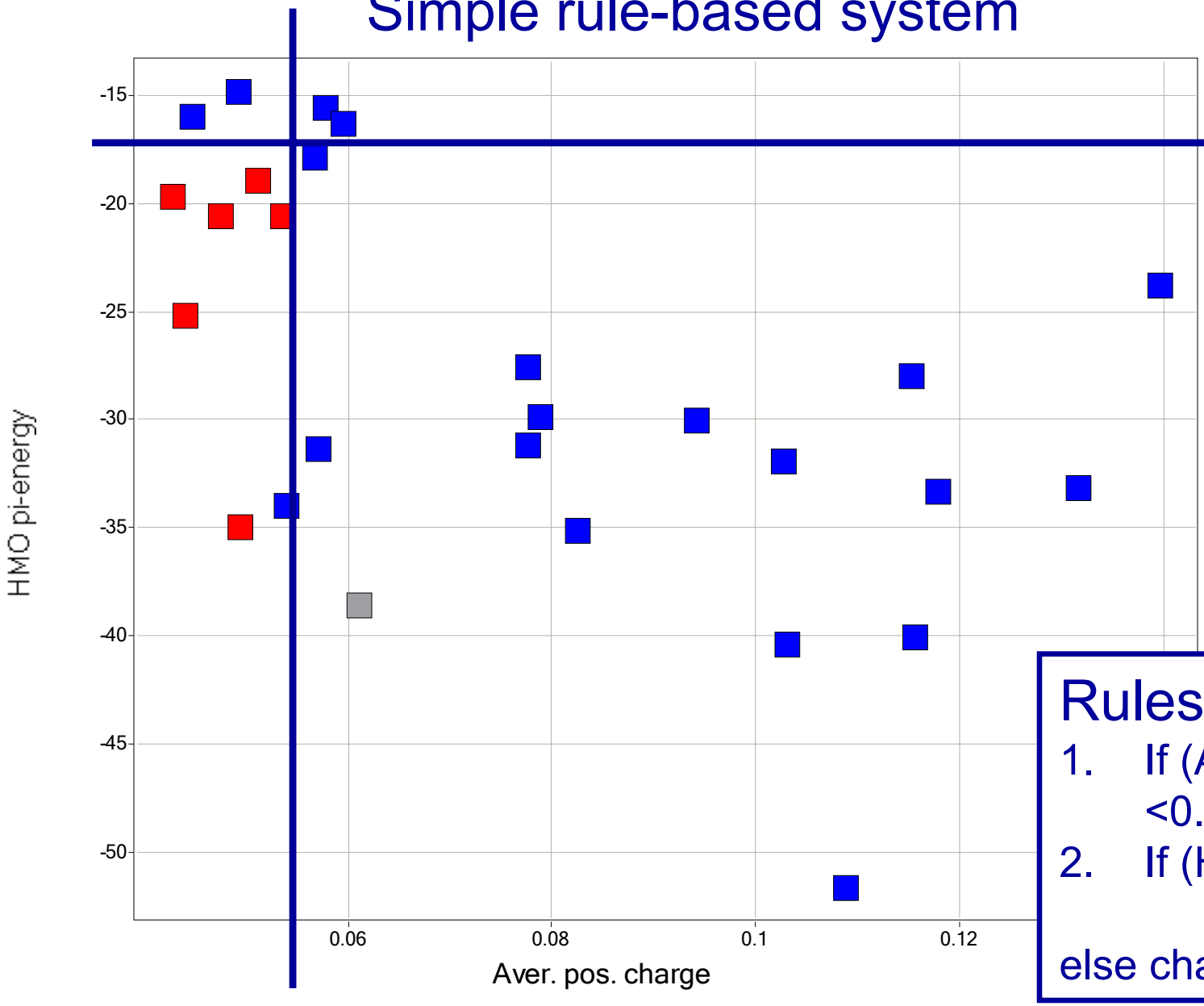
Correlating non-chasing with number of H-bond donors

Compound	No. of H-Bond Donors	No. of H-Bond Acceptors	Total Polar Surface Area	No. of rotatable bonds
Amiodarone	0	4	42.7	11
Amitriptyline	0	1	3.2	3
Chlorpheniramine	0	2	16.1	5
Chlorpromazine	0	2	31.8	4
Deprenyl	0	1	3.2	5
Desipramine	1	2	15.3	4
Diltiazem	0	6	84.4	7
Diphenhydramine	0	2	12.5	6
Flupenthixol	1	3	52.0	6
Imipramine	0	2	6.5	4
Meclizine	0	2	6.5	5
Nortriptyline	1	1	12.0	3
Prochlorperazine	0	3	35.0	4
Quinine	1	4	45.6	4
Sertraline	1	1	12.0	2
Trimipramine	0	2	6.5	4
Verapamil	0	6	64.0	14

All weak bases with zero or one H-Bond Donor only

Correlating non-chasing with SELMA descriptors *

Simple rule-based system



Blue = chaser
Red = non-chaser

PLS-analysis of Astra (SELMA) set of chemical descriptors shows that polarisation properties of the molecules e.g. that they are amphiphiles (with surfactant properties) causes non-chasing.

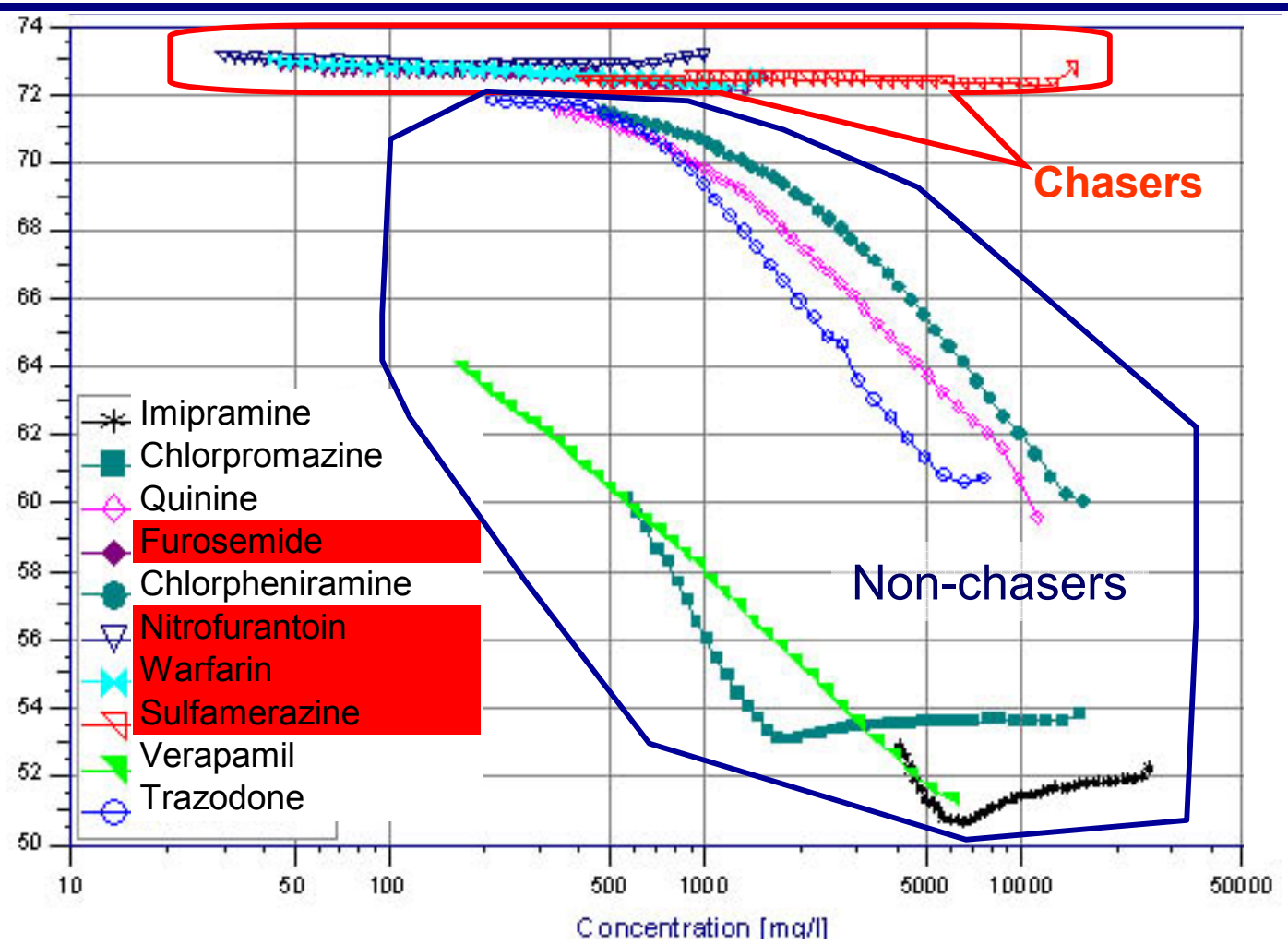
Rules:

1. If (Aver. pos. charge <0.054), non-chaser
2. If (HMO pi-energy<-17), non-chaser

else chaser

* With thanks to Olle Stålberg, AstraZeneca, Södertälje, Sweden

Correlating non-chasing with surface activity



4 mL of dissolved sample was diluted 30 fold over 35 to 40 steps with 0.15M KCl. At each increment, the surface tension of the sample was measured using Kruss K100 tensiometer (above), with roughened Pt probe of known geometry.

- The surface tension of chasers and non-chasers is noticeably different
- For non-chasers, the surface-active properties lead to the formation of thermo-dynamically stable structures in solution that don't lead to supersaturated solutions.

Data from poster co-authored with Bernd Riebesehl and other scientists from Eli Lilly and presented at AAPS 2005. Poster can be downloaded from Sirius web site.

Summary

- Generally, the higher the lipophilicity the lower the solubility
- High melting points often lead to lower than expected solubility. Conversely, low melting points often lead to higher than expected solubility.
- Non-chasers often have higher solubilities than would be expected from logP alone.

- **Accurate measured solubility and lipophilicity give good guidance for pinpointing the BCS category.**

Further reading:

A Provisional Biopharmaceutical Classification of the Top 200 Oral Drug Products in the United States, Great Britain, Spain, and Japan.

Takagi, T.; Ramachandran, C.; Bermejo, M.; Yamashita, S.; Yu, L. X.; Amidon, G. L. *Molecular Pharmaceutics;* **(Article); 2006**; ASAP Article; DOI: 10.1021/mp0600182