

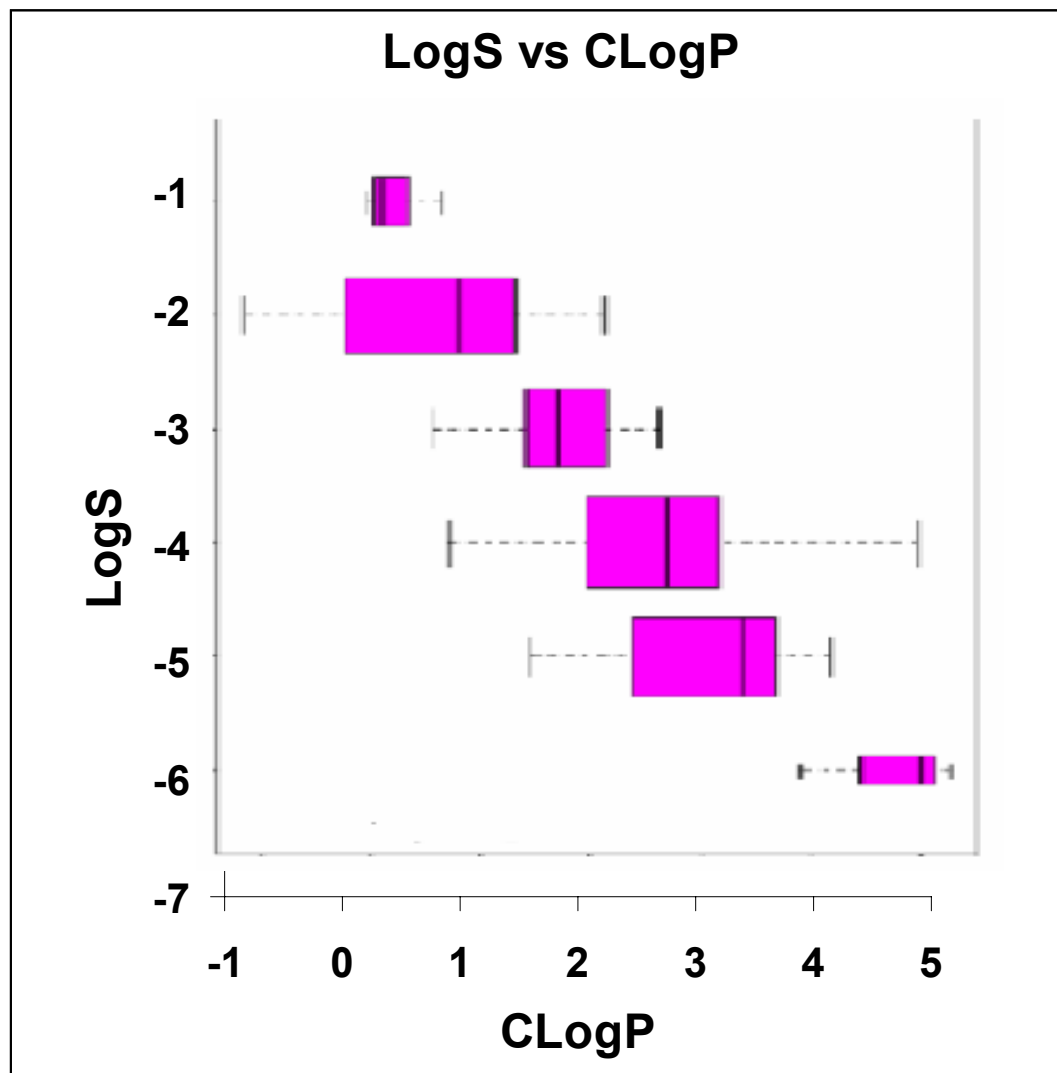
Relationships between Lipophilicity and Solubility

Karl J. Box

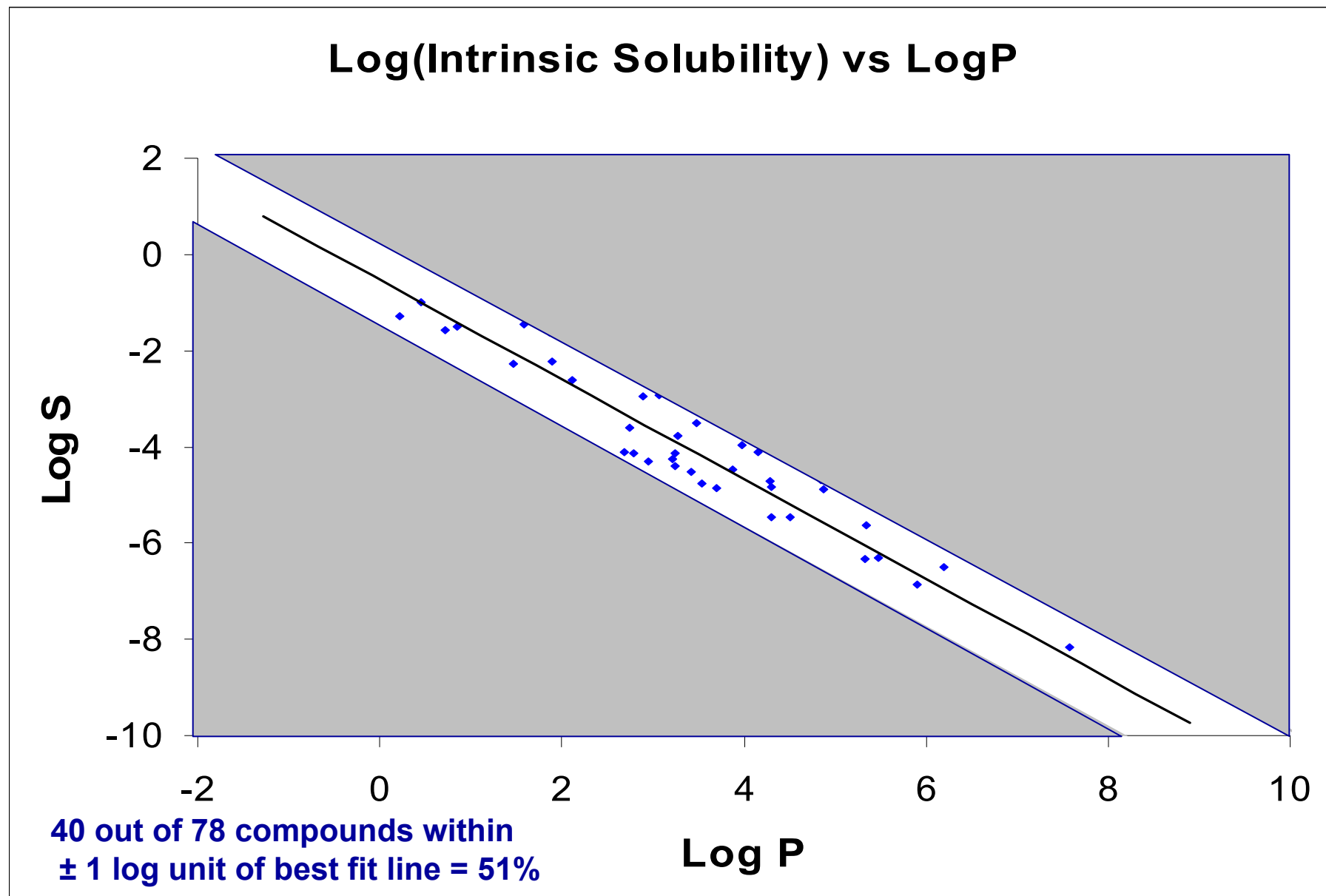
Physical Chemistry Symposium

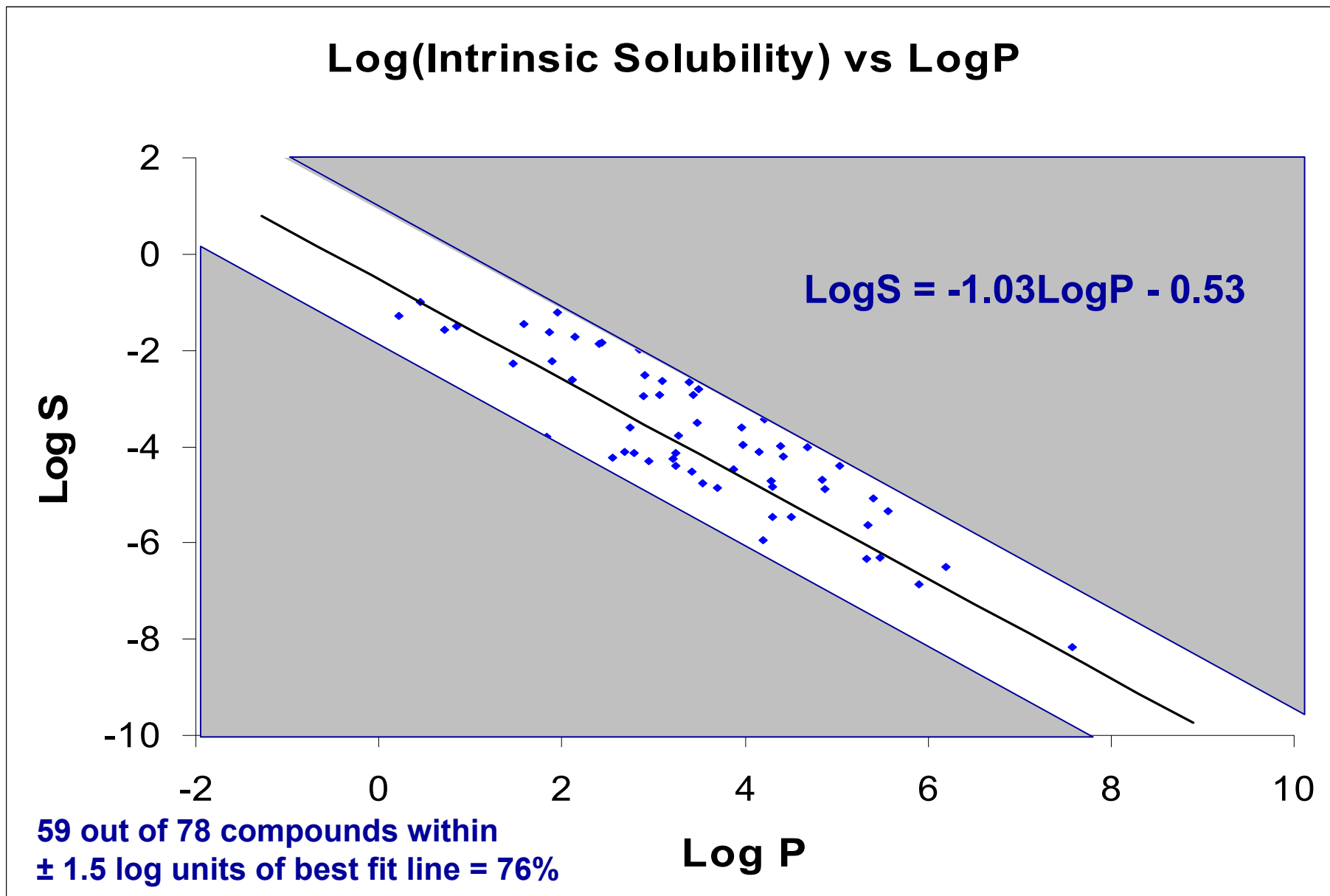
Nov 29th 2006

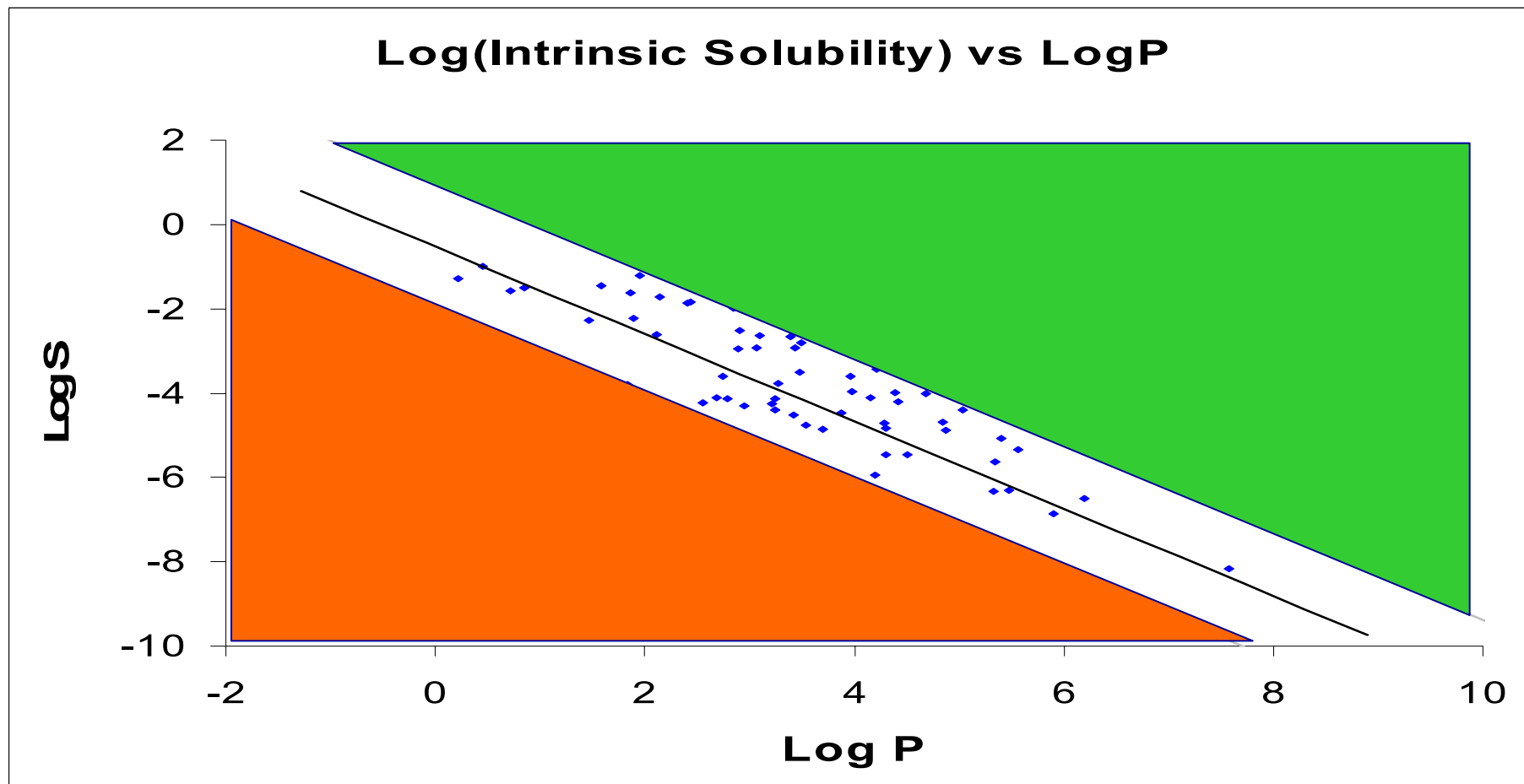
Sirius Analytical Instruments Limited



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

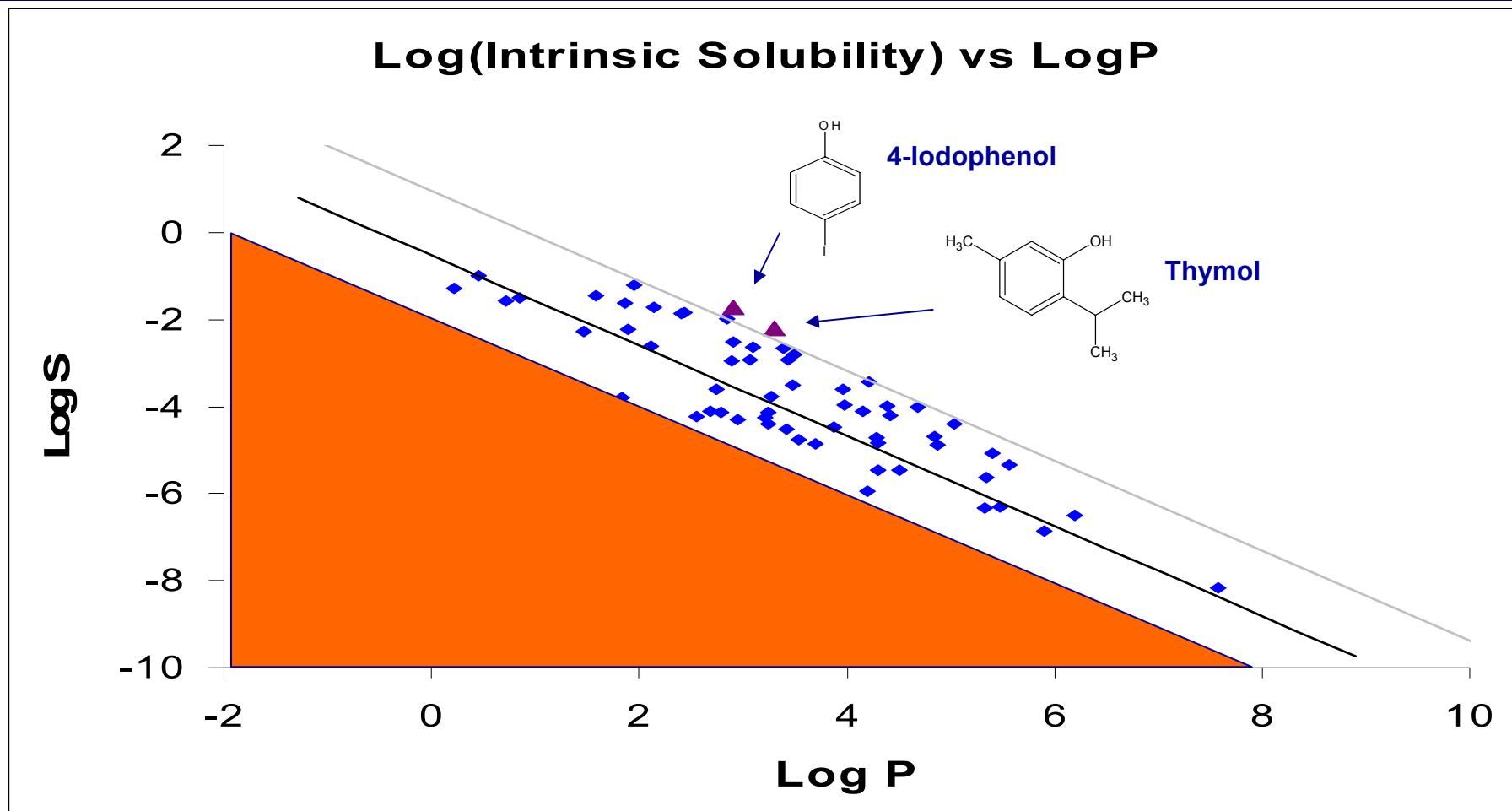




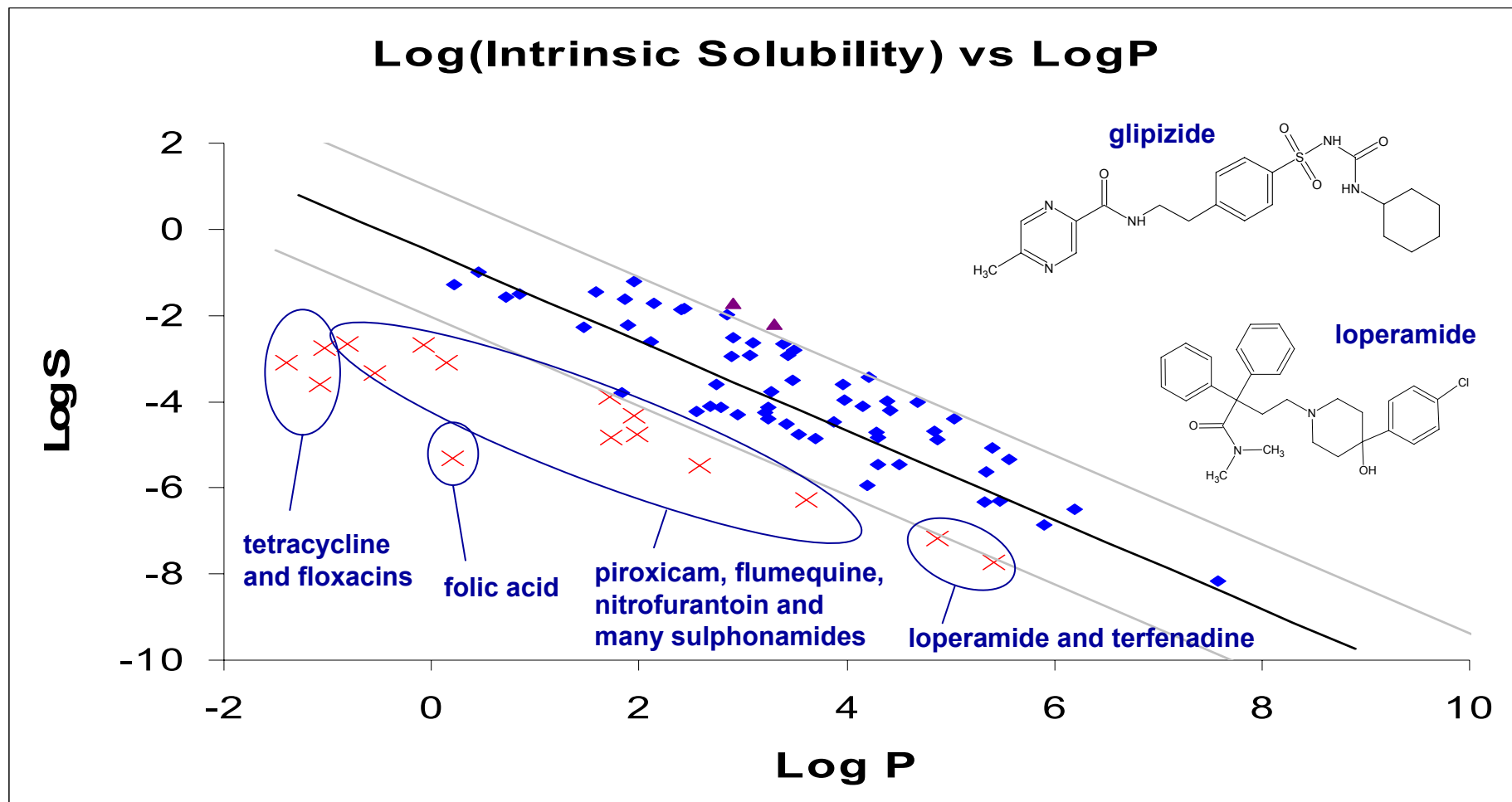


 High solubility region for a given lipophilicity

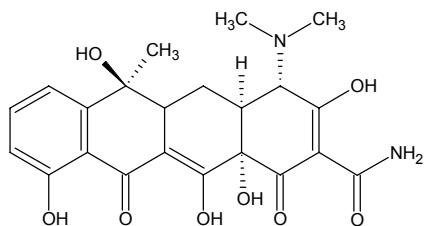
 What often happens ! Poor solubility region for a given lipophilicity



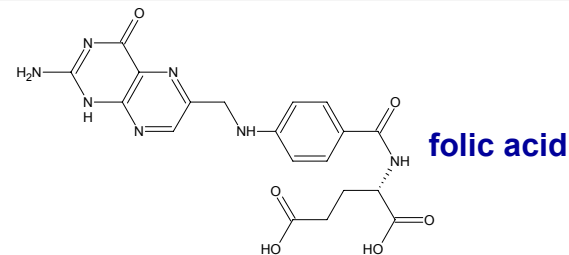
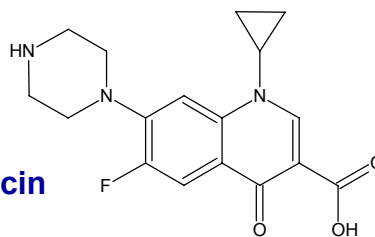
 Poor solubility region for a given lipophilicity

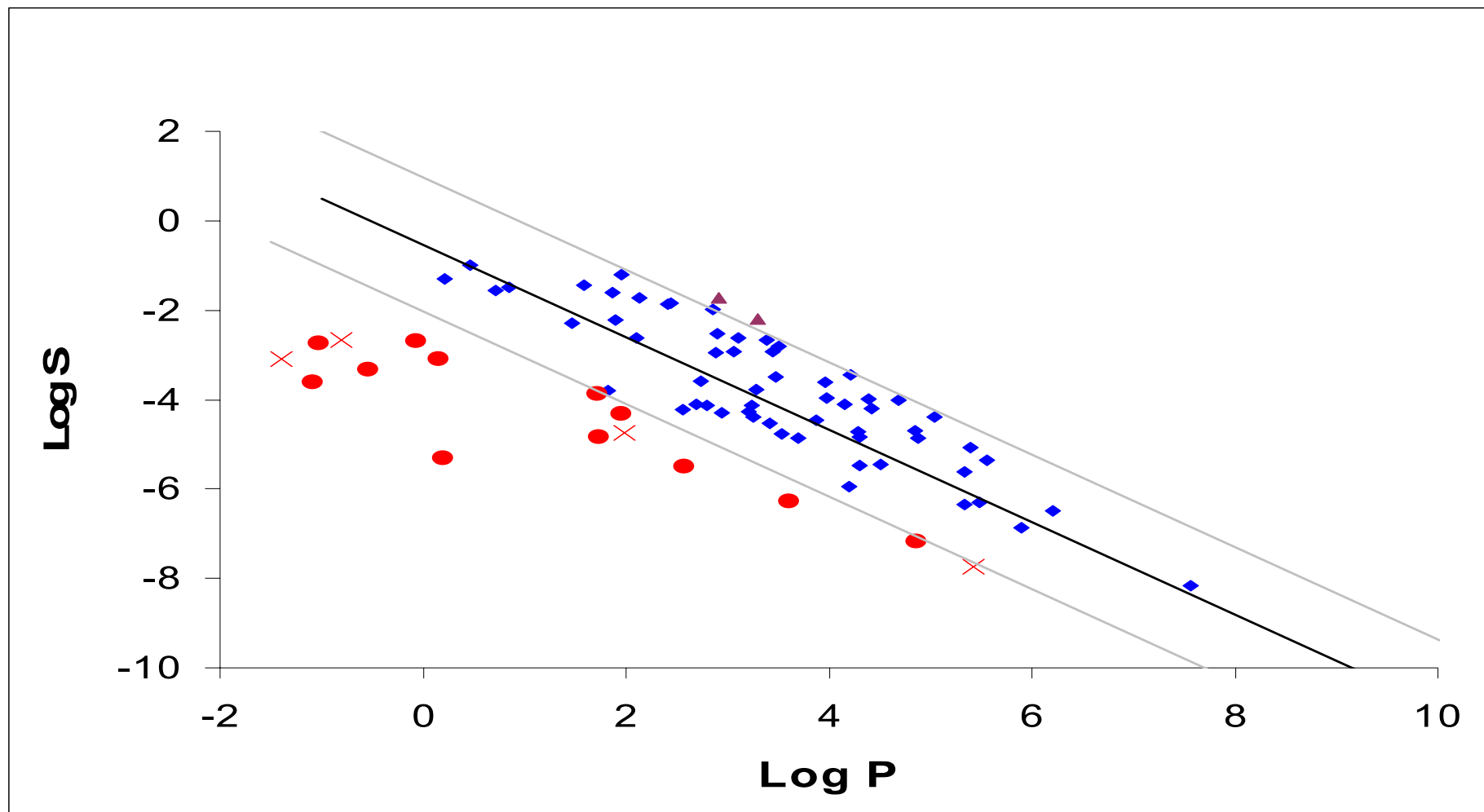


tetracycline

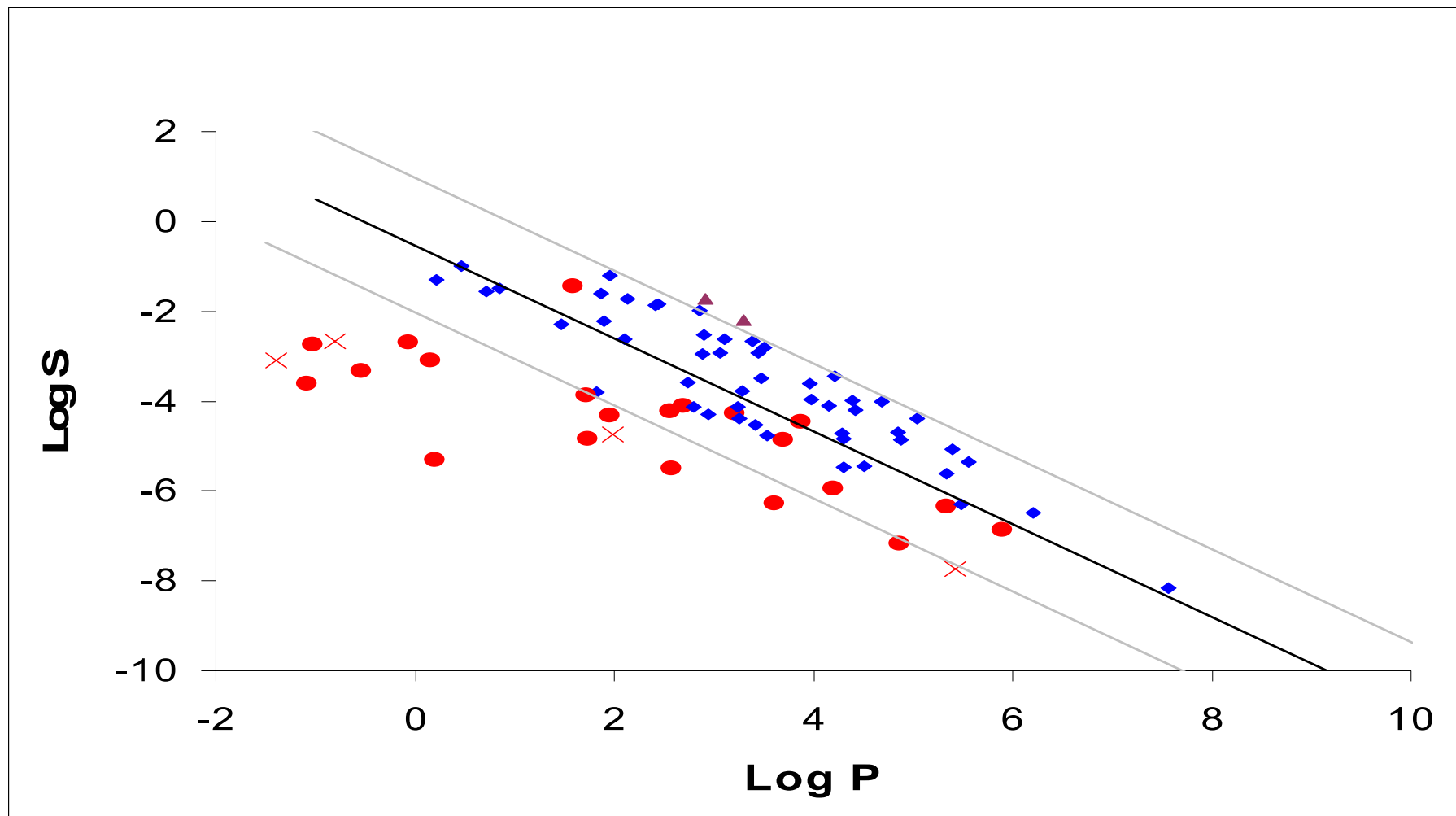


ciprofloxacin

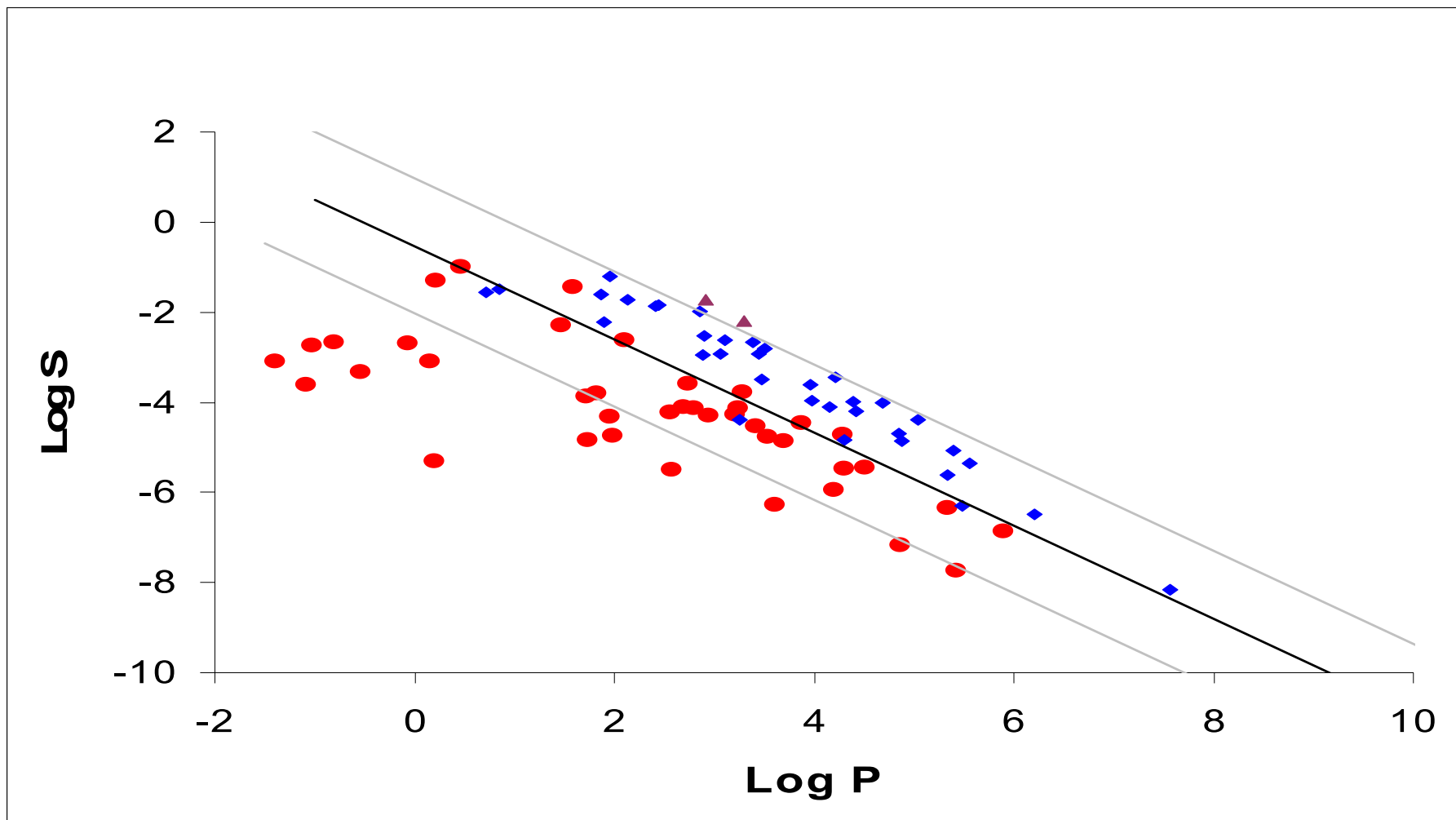




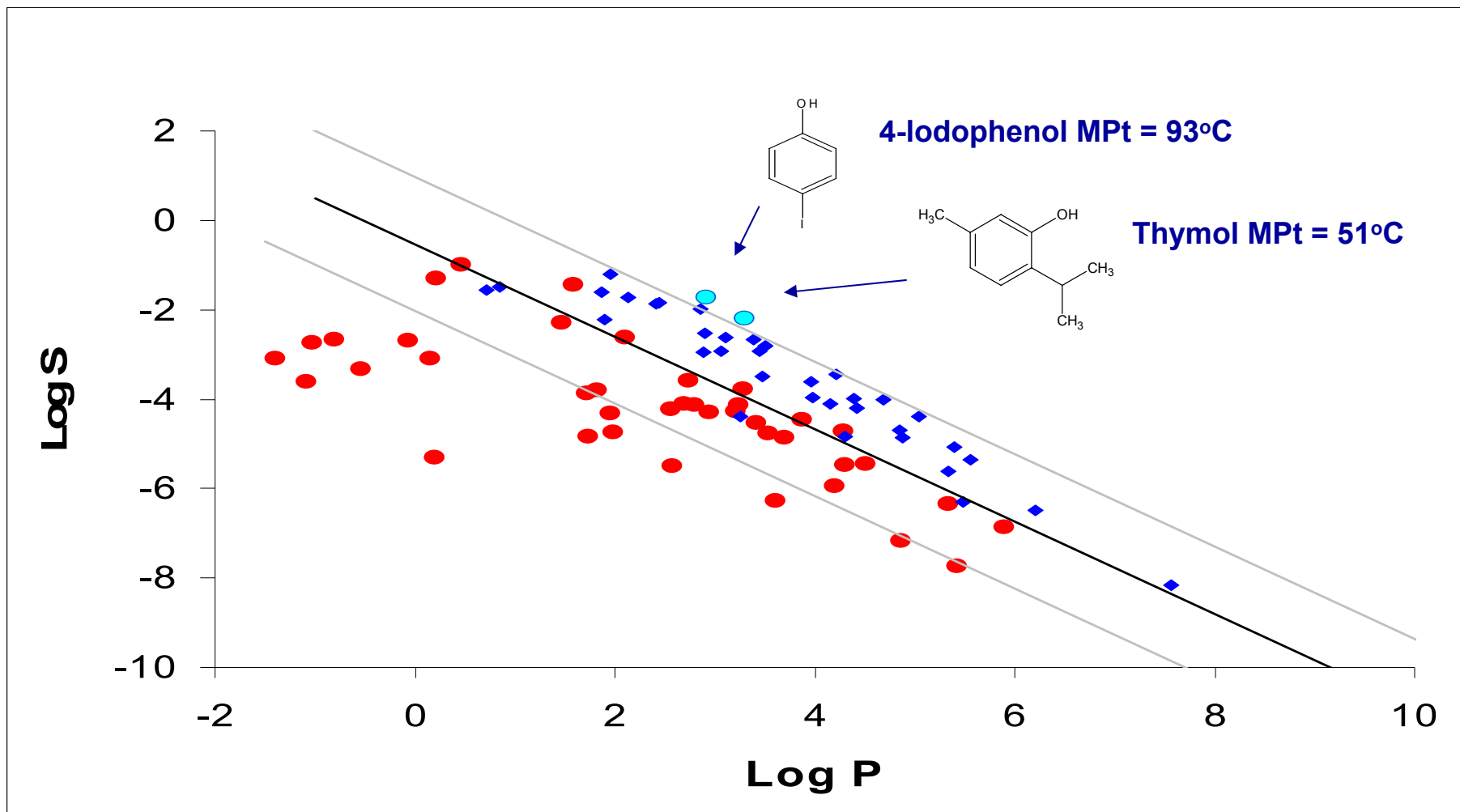
● Compounds with MPts > 200°C

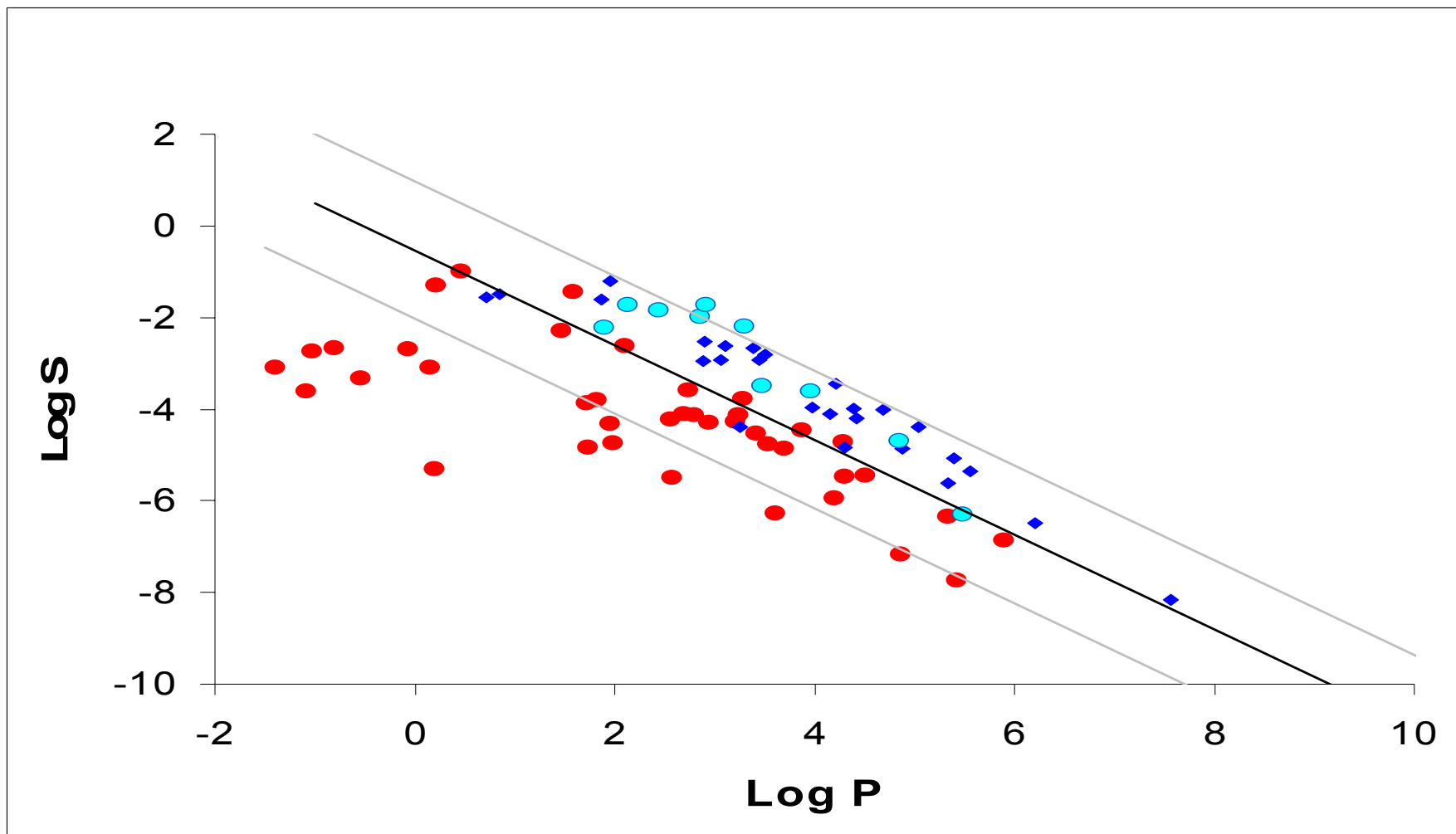


● All Compounds with MPts > 200°C

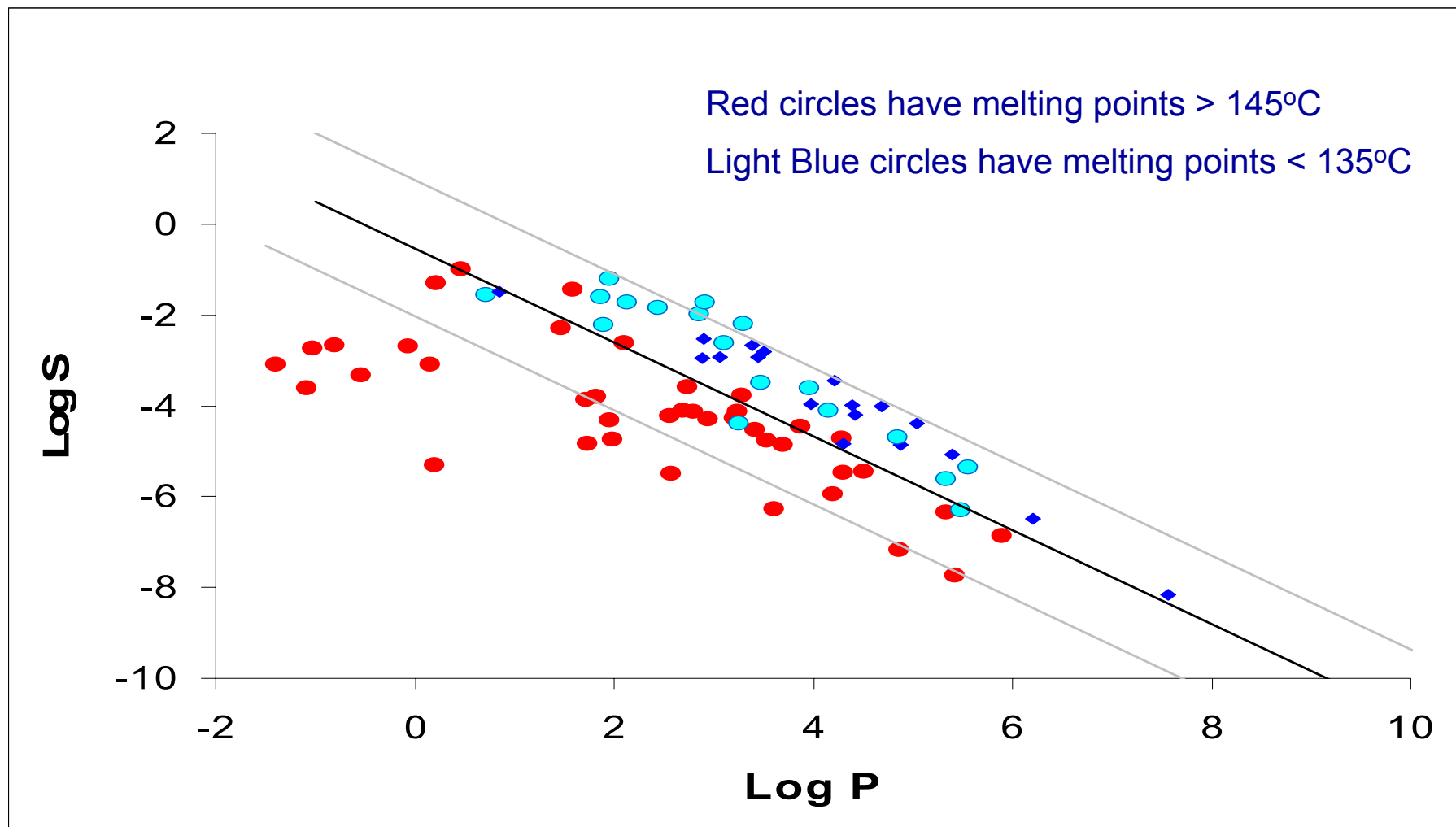


● Compounds with MPts > 145°C





 Compounds with MPts < 100°C

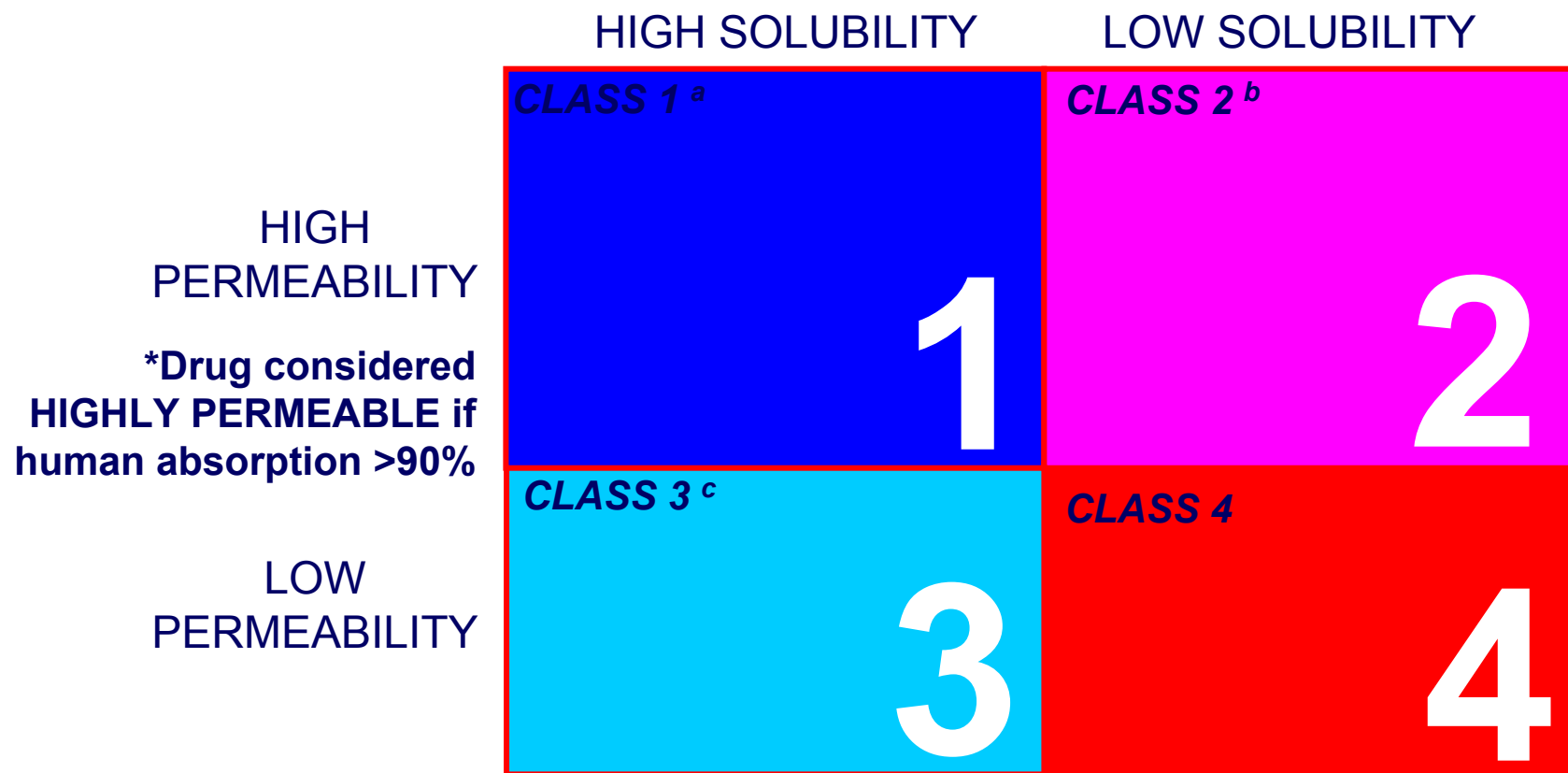


 Compounds with MPts < 135°C

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%**

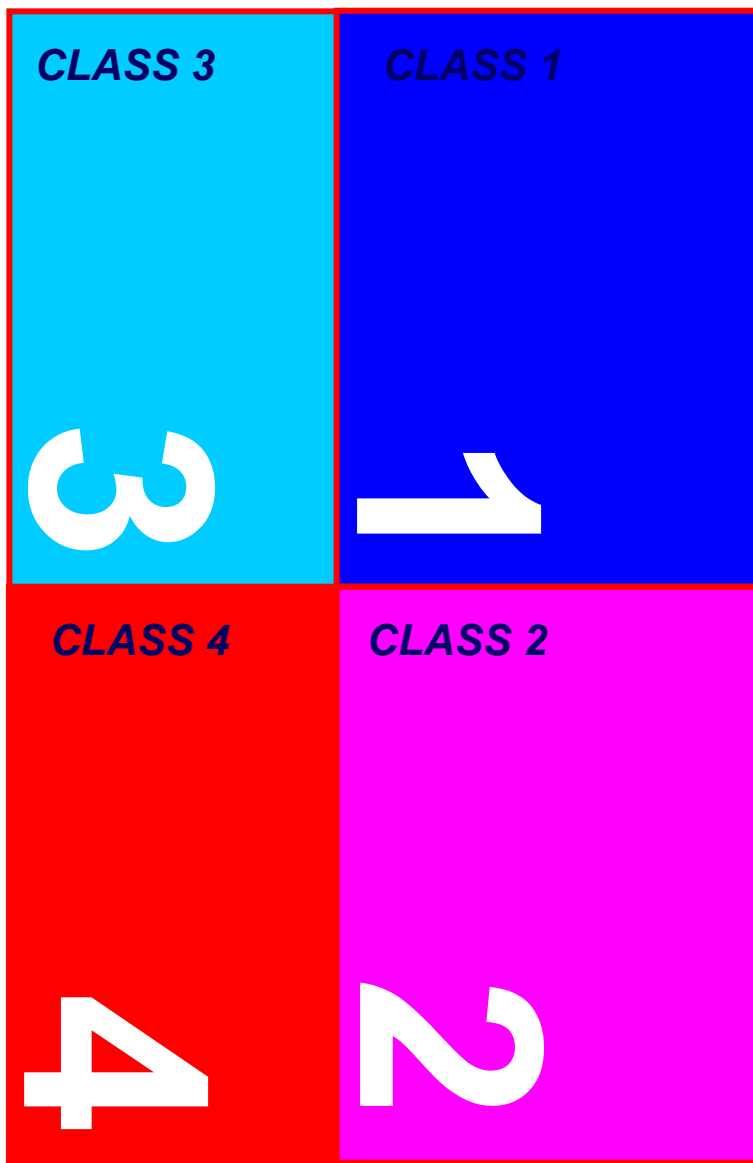
- ^a RATE OF DISSOLUTION limits *in vivo* absorption
- ^b SOLUBILITY limits absorption flux
- ^c PERMEABILITY is rate determining

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

Biopharmaceutics Classification System (BCS)

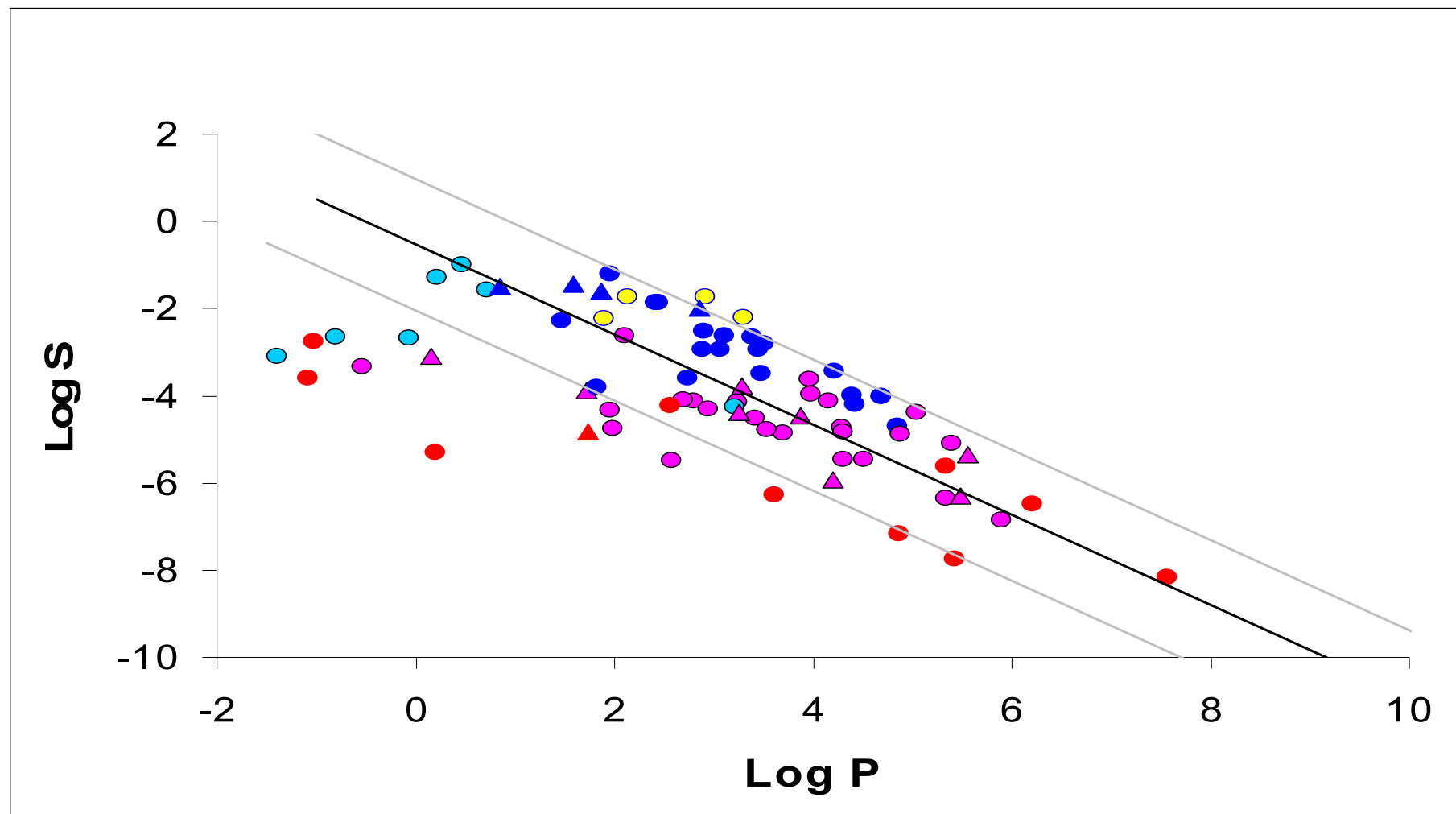
LOW PERMEABILITY

HIGH PERMEABILITY



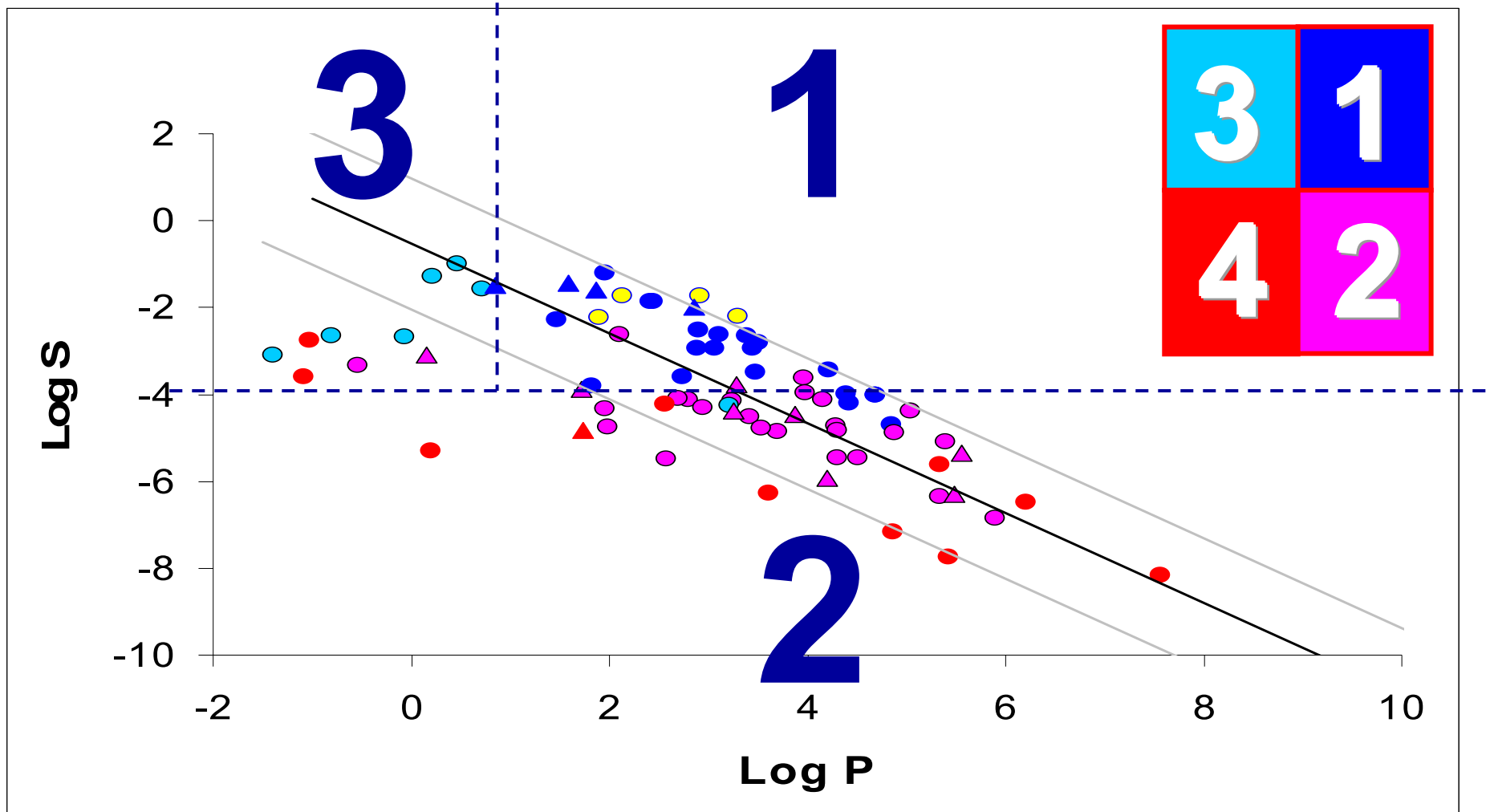
HIGH SOLUBILITY

LOW SOLUBILITY



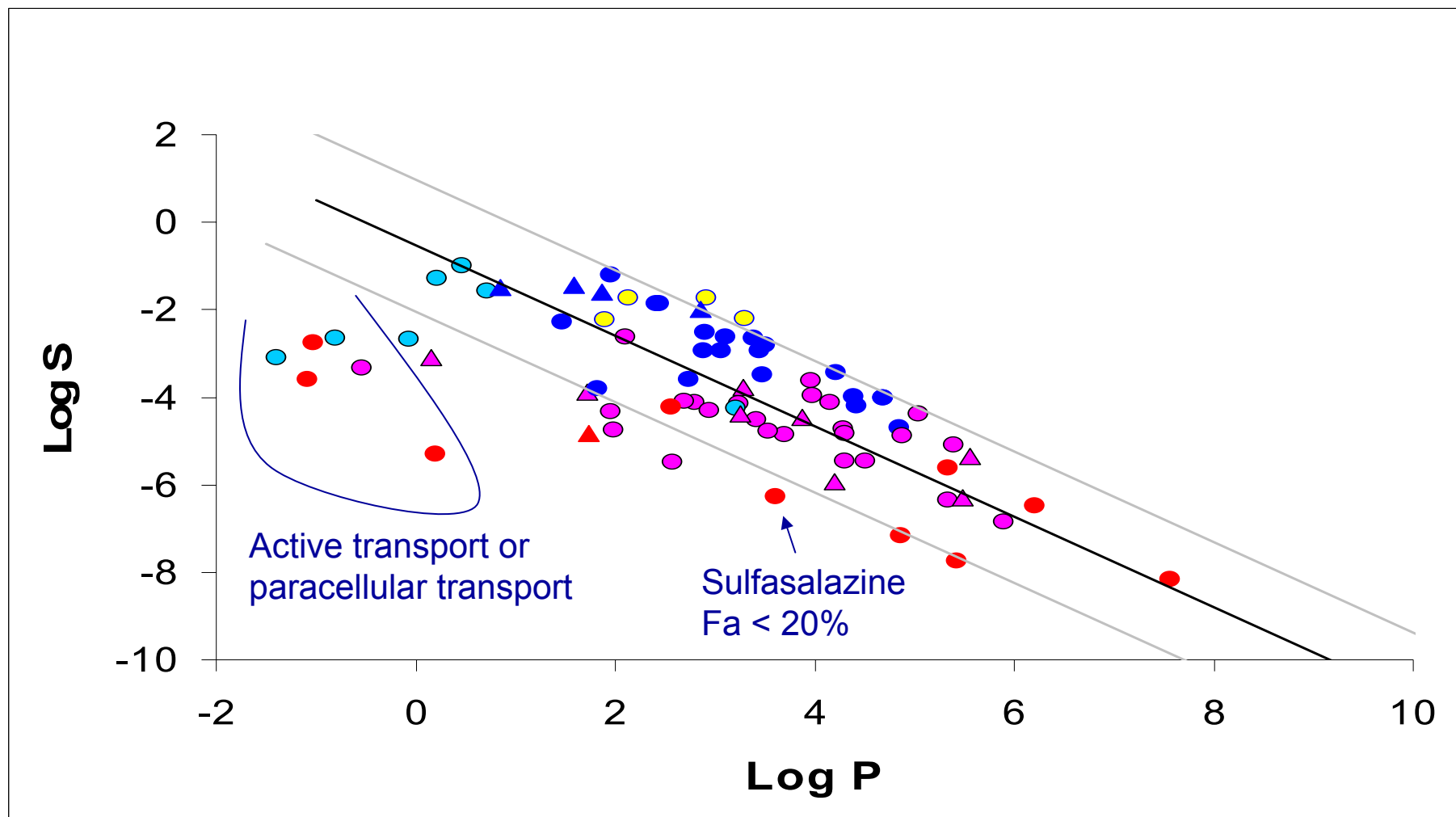
- ▲ Class 1 – **High** Solubility, **High** fraction absorbed
- ▲ Class 2 – **Low** Solubility, **High** fraction absorbed
- ▲ Class 3 – **High** Solubility, **Low** fraction absorbed
- ▲ Class 4 – **Low** Solubility, **Low** fraction absorbed

● Not known (includes topical anesthetics)



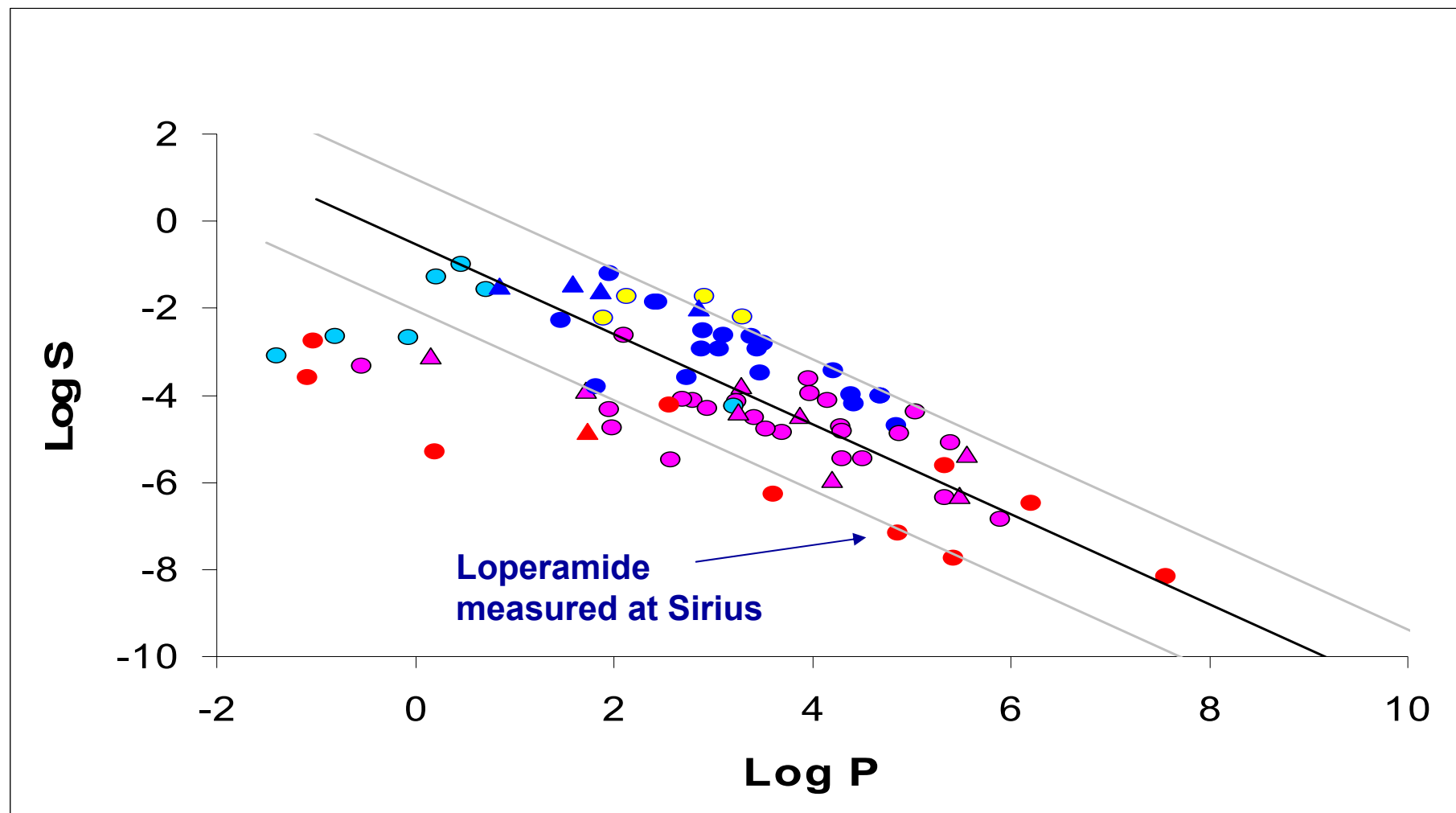
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- Class 4 – **Low** Solubility, **Low** fraction absorbed

4?



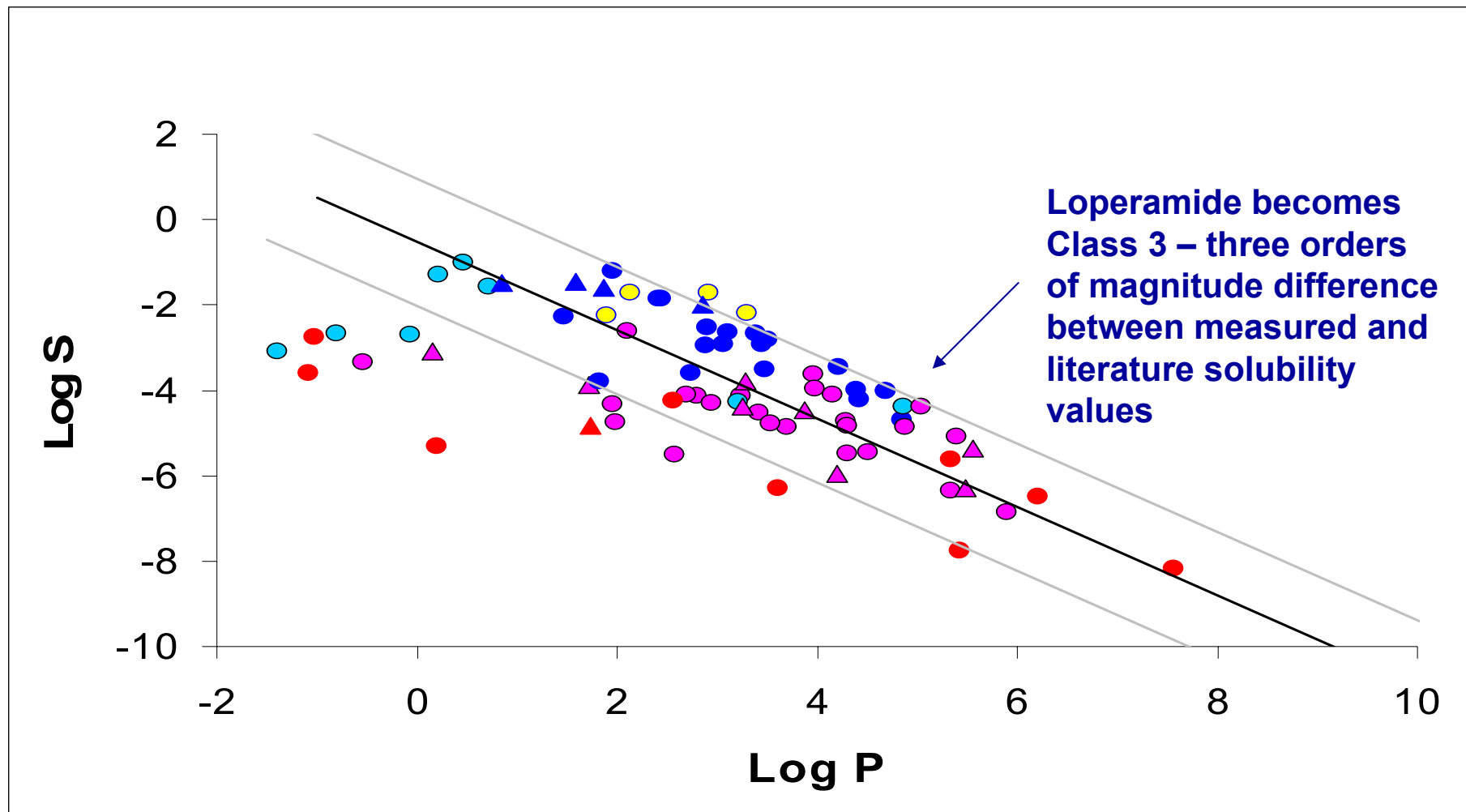
- Class 1 – **High** Solubility, **High** fraction absorbed
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- Class 4 – **Low** Solubility, **Low** fraction absorbed

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



- ▲ Class 1 – **High** Solubility, **High** fraction absorbed
- ▲ Class 2 – **Low** Solubility, **High** fraction absorbed
- ▲ Class 3 – **High** Solubility, **Low** fraction absorbed
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● Not known (includes topical anesthetics)

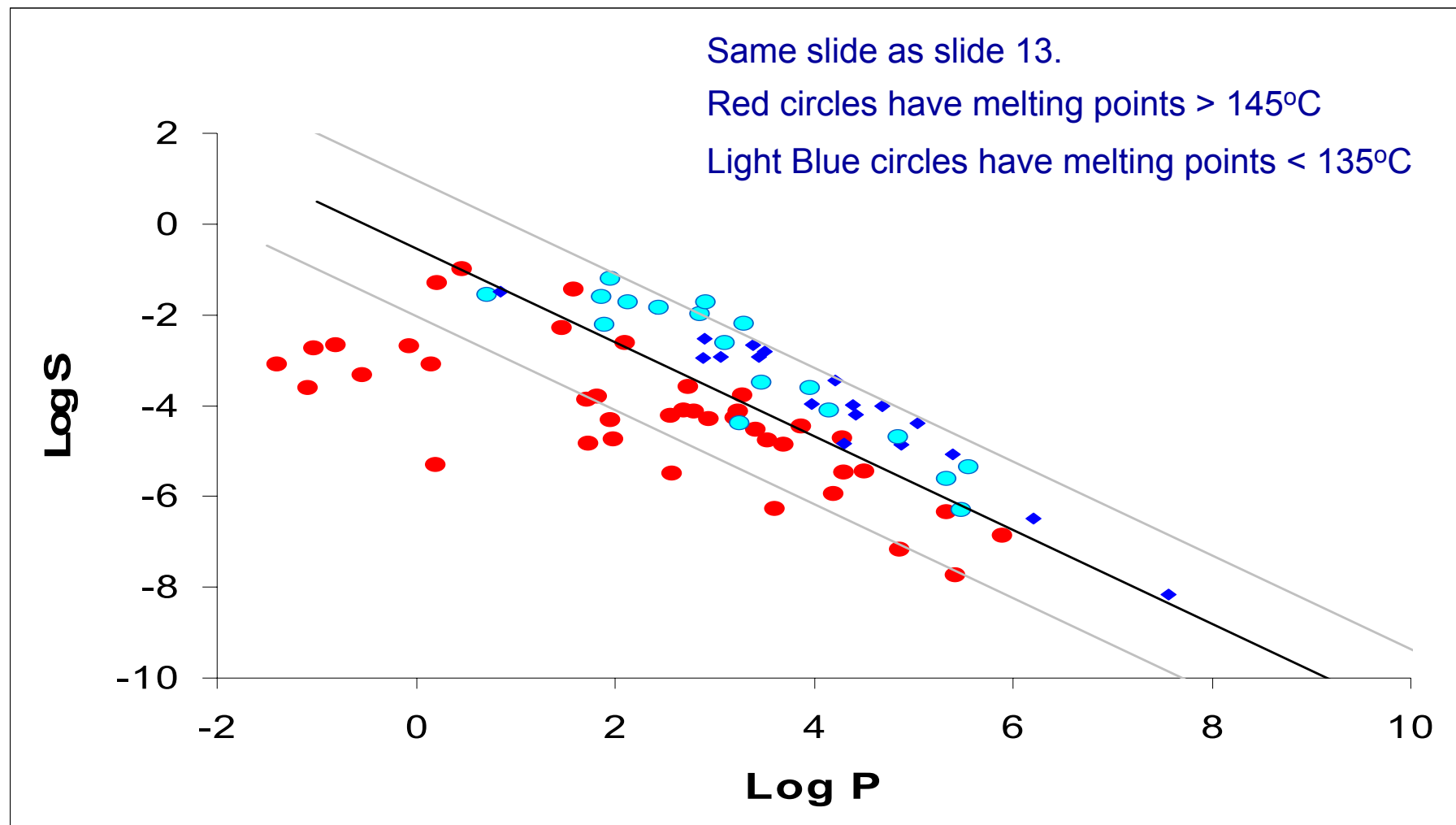


Loperamide becomes Class 3 – three orders of magnitude difference between measured and literature solubility values

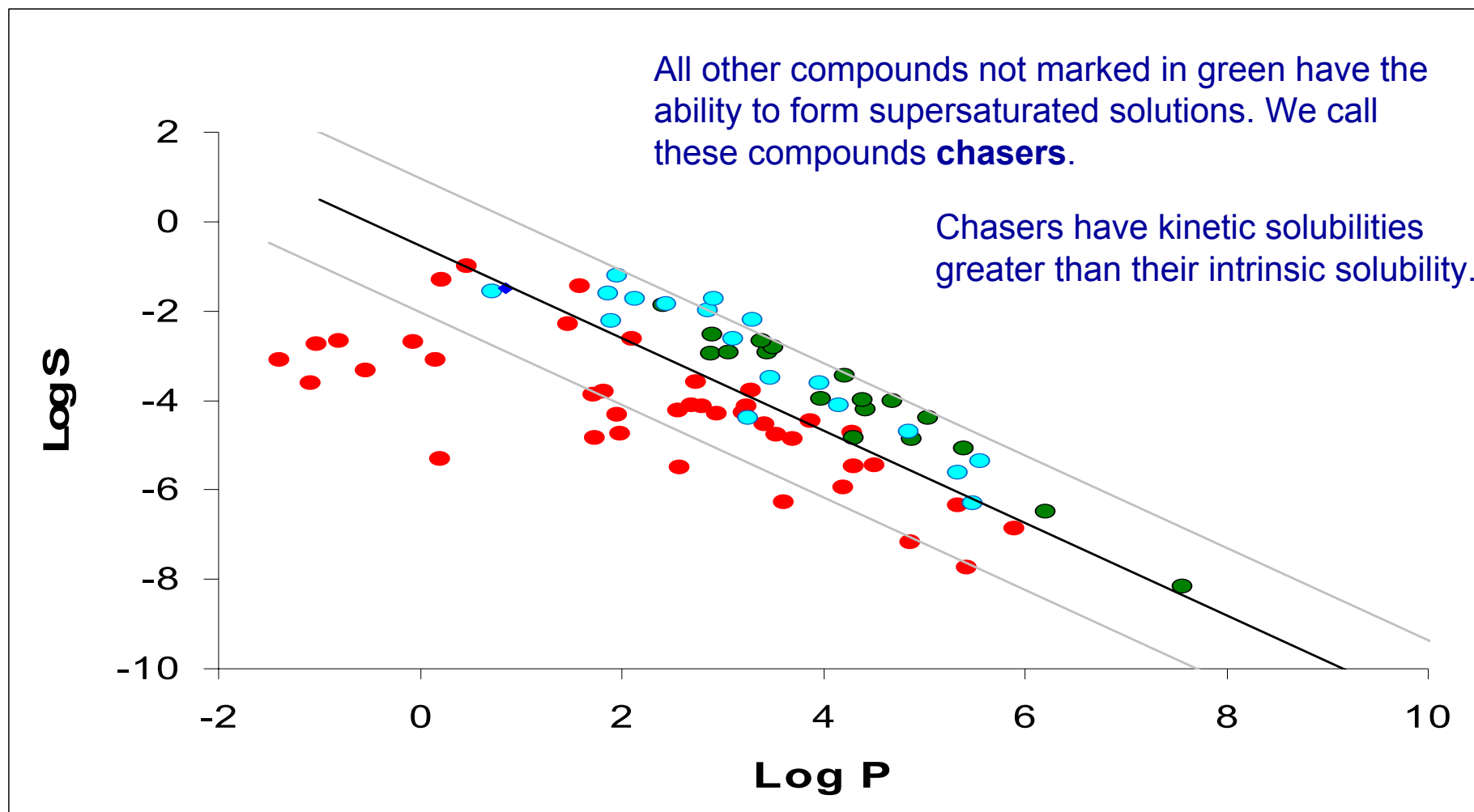
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- ▲ Class 3 – **High** Solubility, **Low** fraction absorbed
- ▲ Class 4 – **Low** Solubility, **Low** fraction absorbed

● Not known (includes topical anesthetics)

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



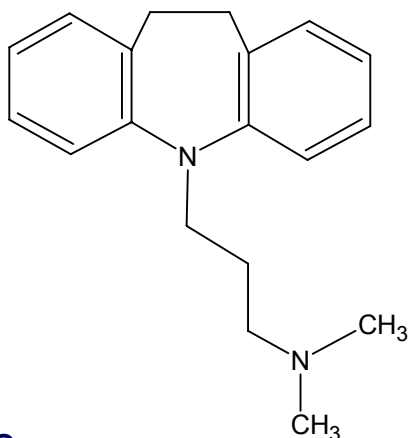
But what is left? Do compounds shown as \blacklozenge have MPts between $135 - 145^{\circ}\text{C}$?



- 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.

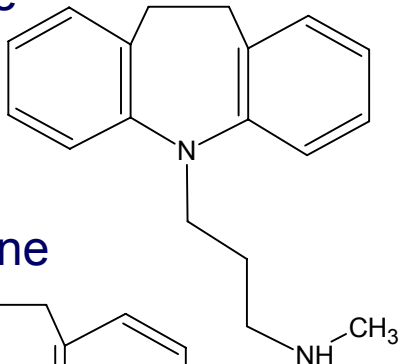
Can we predict whether a sample is a non-chaser?

Imipramine



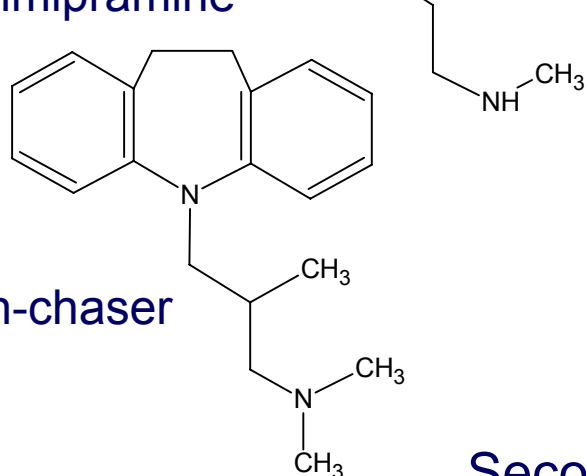
Non-chaser

Desipramine



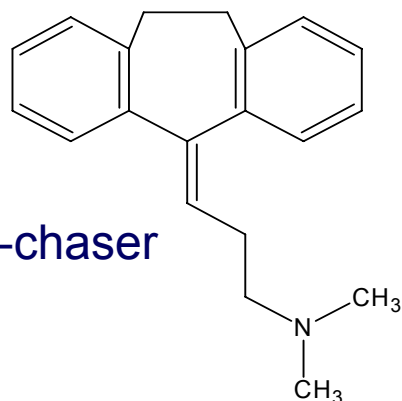
Non-chaser

Trimipramine



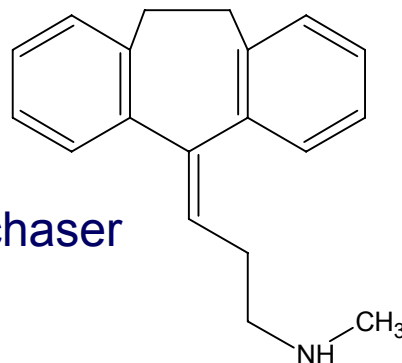
Non-chaser

Amitriptyline



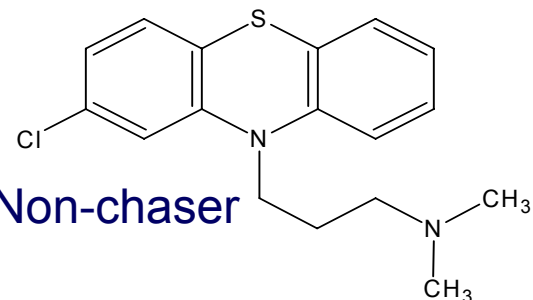
Non-chaser

Nortriptyline



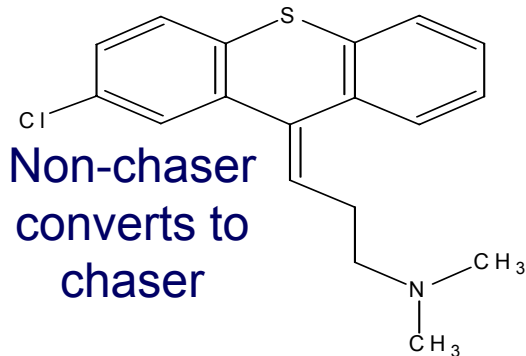
Non-chaser

Chlorpromazine



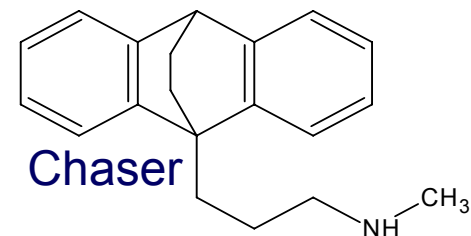
Non-chaser

Chlorprothixene



Non-chaser
converts to
chaser

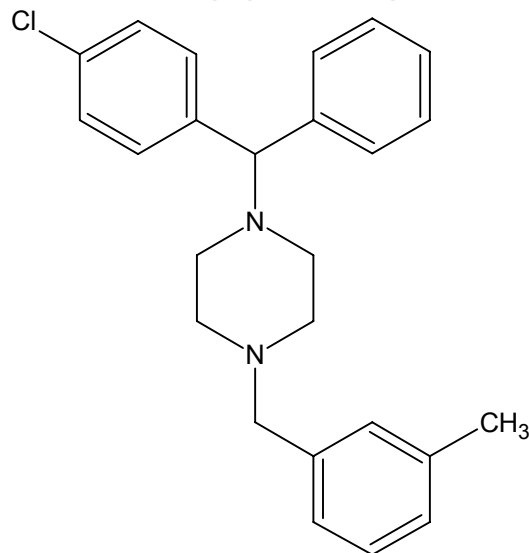
Maprotiline



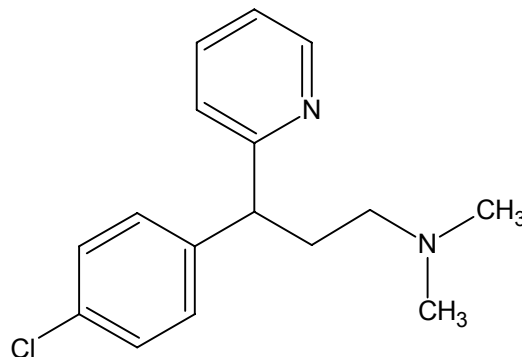
Chaser

Secondary and tertiary amines with $\log P > 4$.

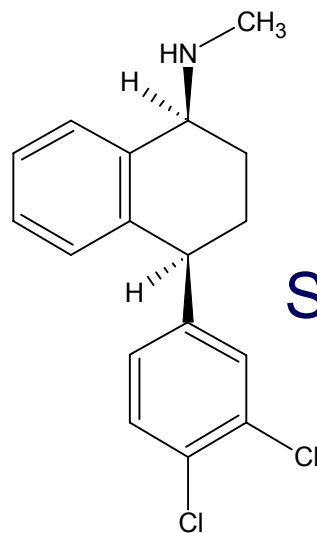
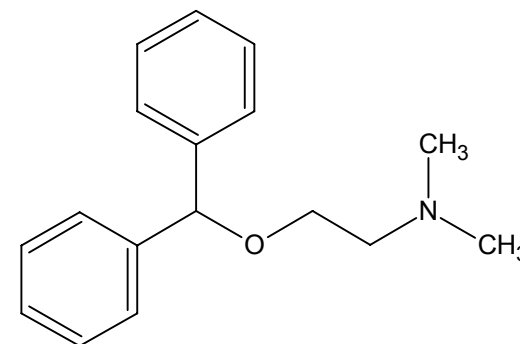
Meclizine



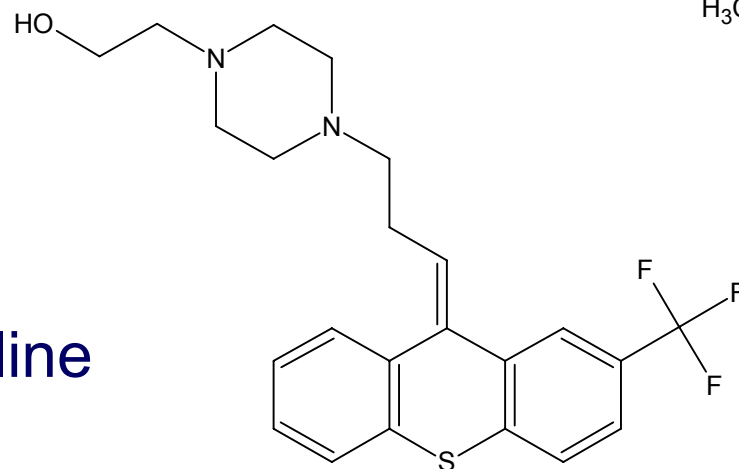
Chlorpheniramine



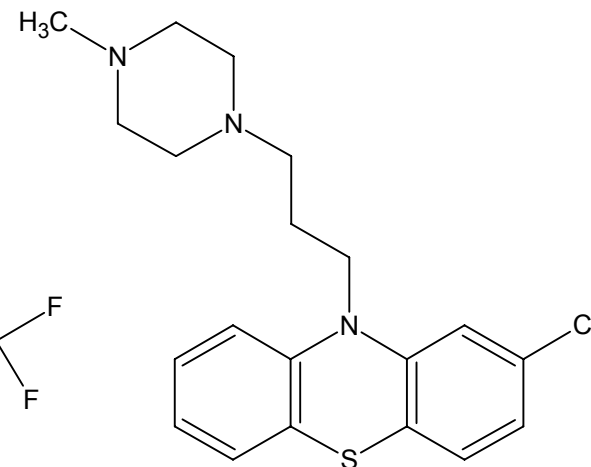
Diphenhydramine



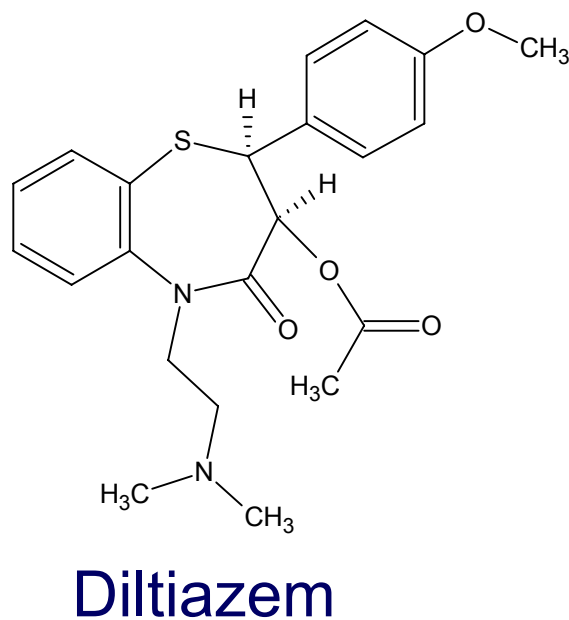
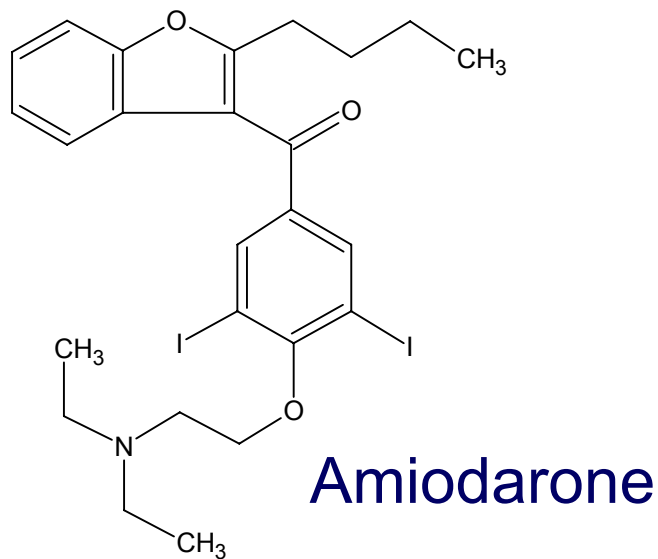
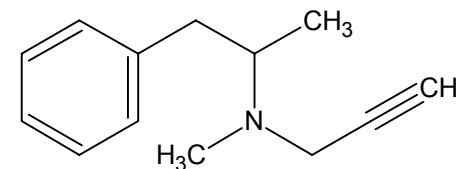
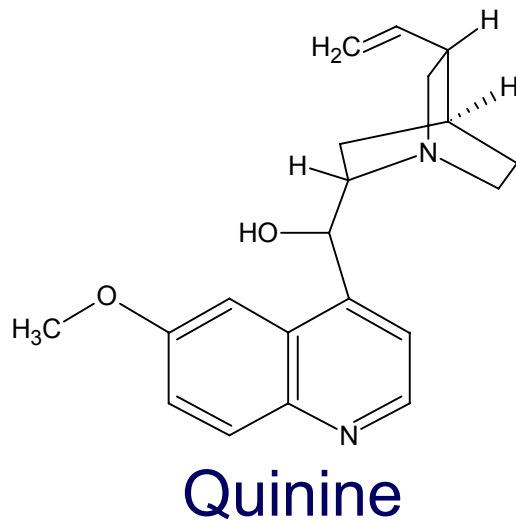
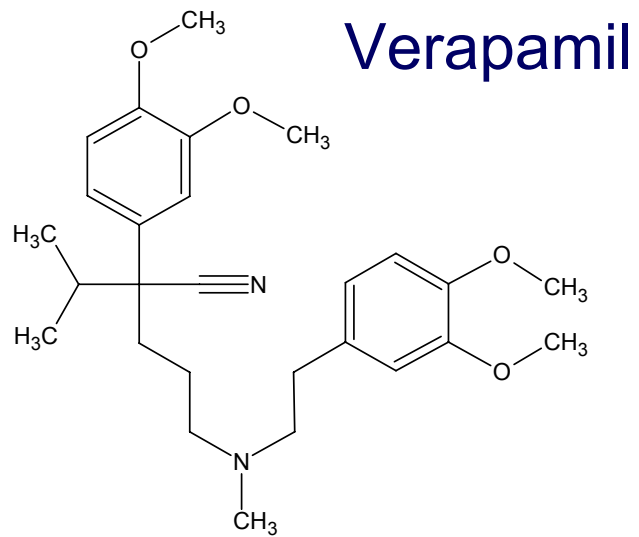
Sertraline



Flupenthixol



Prochlorperazine



✦ 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.



- ✦ 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.

- ✦ 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?

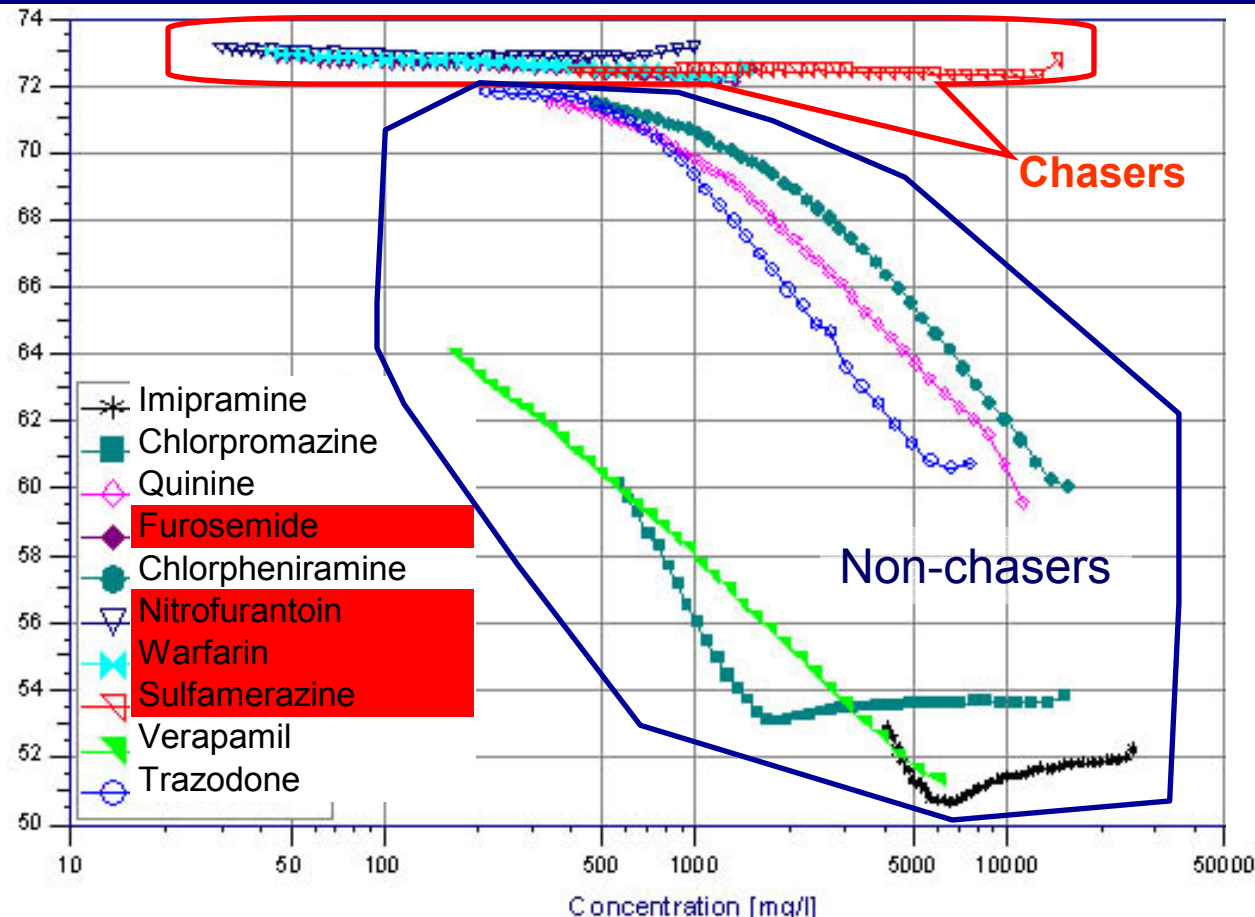
✦ Melting point

- 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 nortryptiline 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 177°C, but it forms a trihydrate with a very low M.pt of 57°C. 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



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 thermodynamically 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.

- ✦ 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