Multi-parameter Optimisation in Drug Discovery:
Quickly targeting compounds with a good balance of properties

Dr Matthew Segall

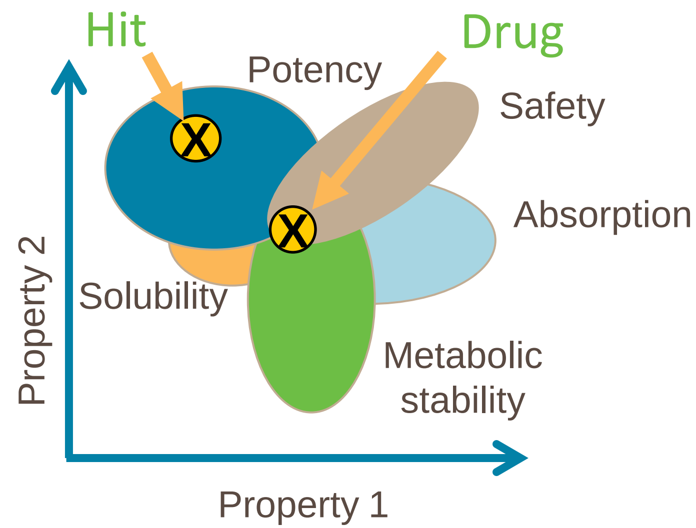
ELRIG Drug Discovery 2011, 7th September 2011

Overview

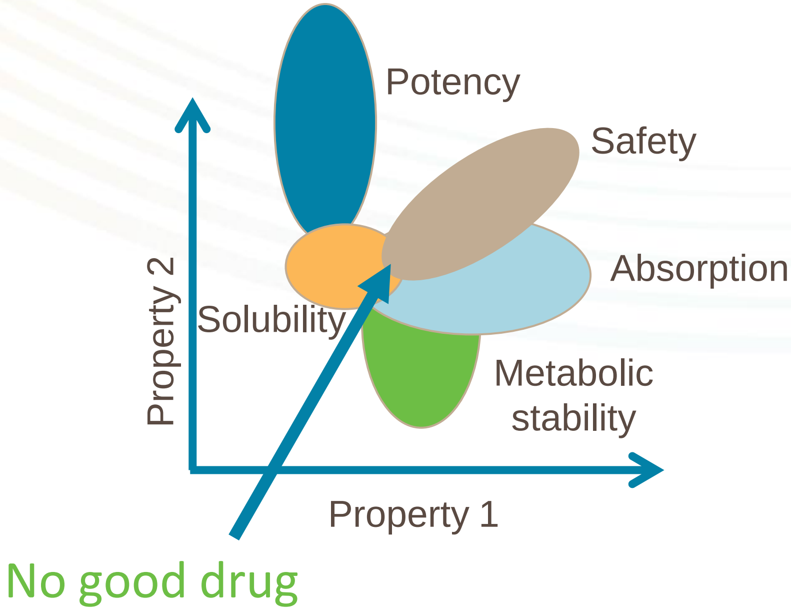
- Introduction: Balancing Properties in Drug Discovery
  - The challenges of multi-parameter optimisation (MPO)
  - Requirements for MPO in drug discovery
- Approaches for Multi-Parameter Optimisation
  - Rules-of-thumb
  - Filtering
  - Calculated metrics
  - Pareto optimisation
  - Desirability functions
  - Probabilistic scoring
- Balancing quality and diversity
- Case study
- Conclusion

The Objectives of Drug Discovery
Multi-parameter optimisation

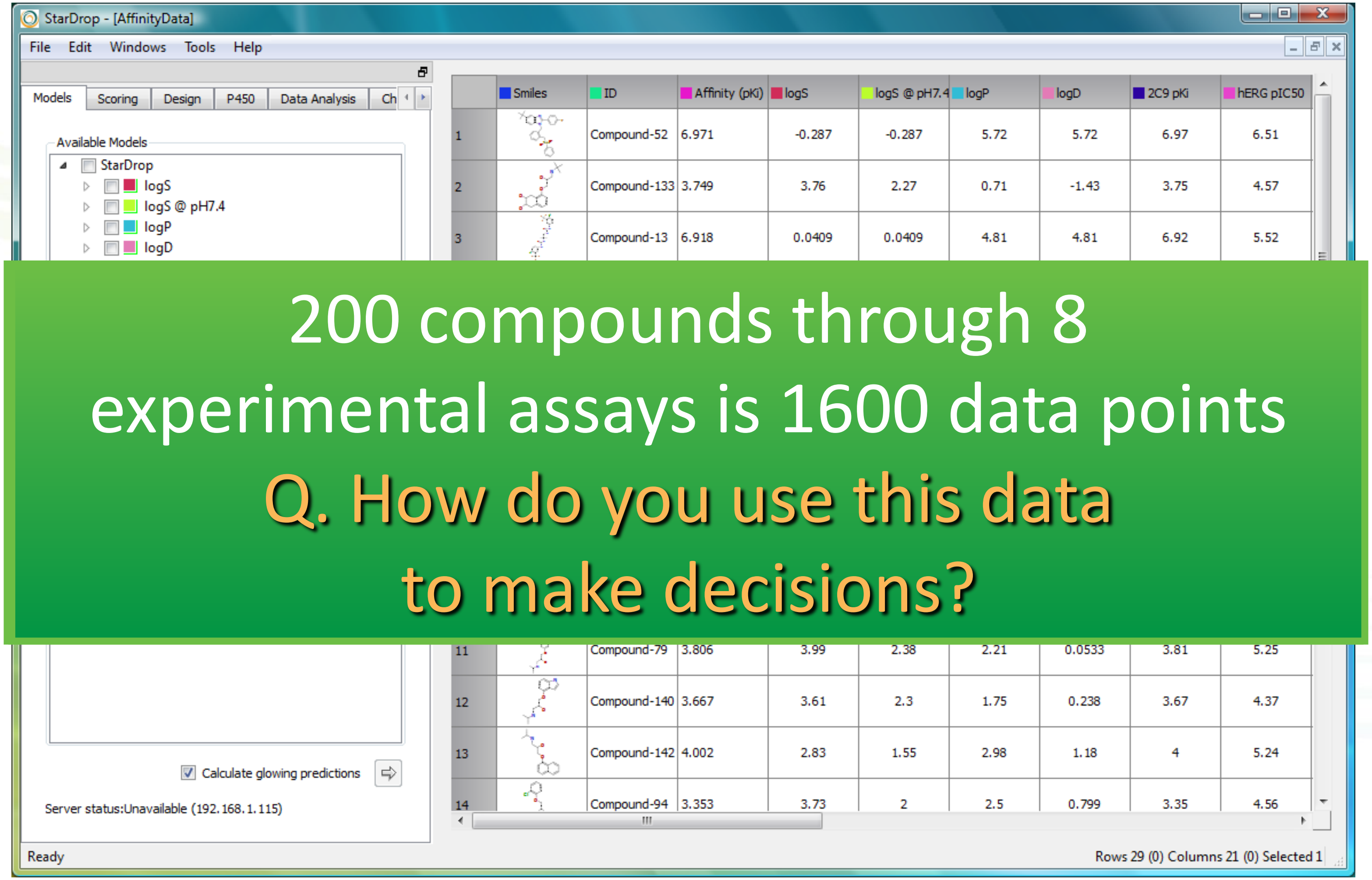
- Identify chemistries with an optimal **balance** of properties



- Quickly identify situations when such a balance is not possible
  - –Fail fast, fail cheap
  - –Only when **confident**



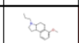
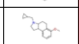
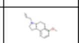
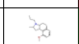
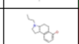
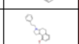
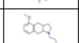
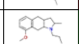
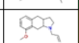
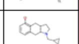
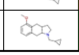
Challenge 1: Complexity of Data

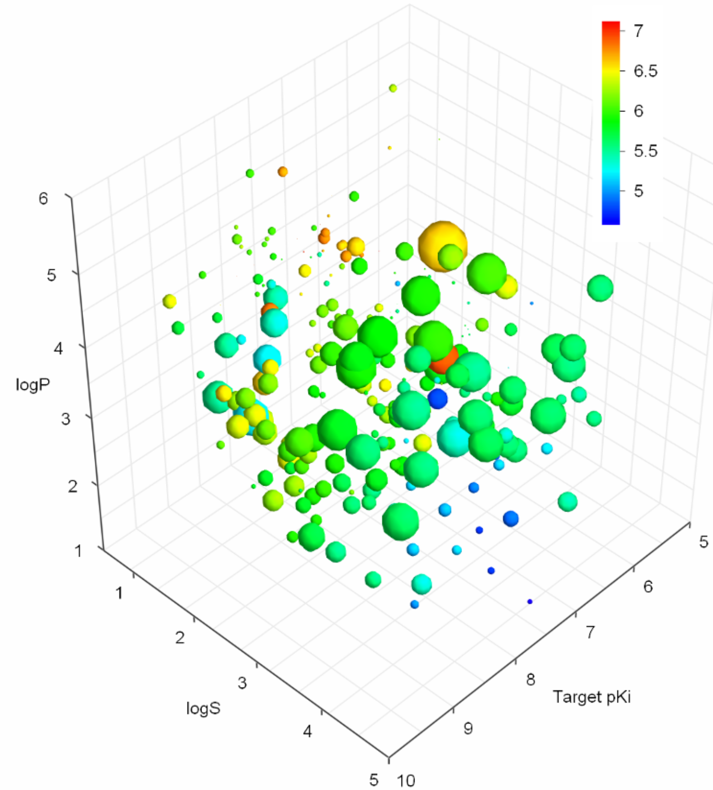


200 compounds through 8 experimental assays is 1600 data points

Q. How do you use this data to make decisions?

Visualisation is Important But Not Enough…*

MolName	Structure	pki 5HT1a affinity	logS	logP	2C9 pKi	hERG pIC50	log(BB)	BBB category	HIA category	P-gp category	2D6 affinity category	PPB category
S1-10		6	3.884	3.322	3.464	5.636	0.8671	+	+	no	medium	high
S1-11		6	3.697	3.44	3.485	5.72	0.7745	+	+	no	very high	high
S1-12		6.6	4.124	3.106	3.677	5.684	0.9036	+	+	no	medium	high
S1-13		9	3.659	3.844	3.558	5.65	0.8504	+	+	no	very high	high
S1-14		6	4.051	2.992	3.369	5.56	0.4056	+	+	no	high	high
S1-15		6.5	2.554	4.38	4.502	6.175	0.6534	+	+	yes	medium	high
S1-16		5.3	3.698	3.892	3.464	5.646	0.6799	+	+	no	medium	high
S1-18		7.96	3.444	4.34	3.558	5.647	0.6568	+	+	no	very high	high
S1-19		6.98	3.927	3.594	3.677	5.677	0.6858	+	+	no	medium	high
S1-20		7.16	3.721	3.487	3.391	5.639	0.2327	+	+	no	very high	high
S1-21		7.54	3.632	3.964	3.485	5.725	0.6016	+	+	no	very high	high



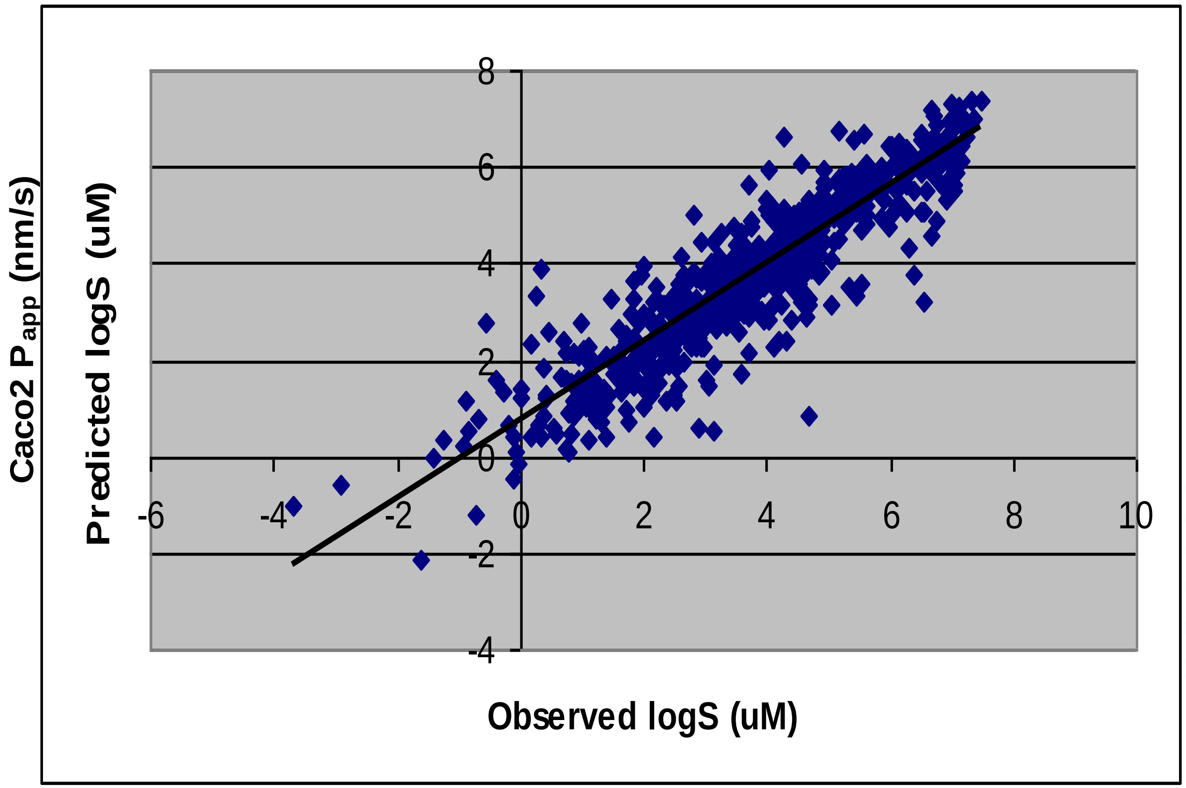
How can you make a confident decision by looking at these?

*Segall and Champness (2010) GEN, **30** (Sep 1) http://bit.ly/cSx4Tm

Challenge 2: Uncertainty in Data

Caco2 vs. Human Intestinal Absorption*

Predicted Solubility



R^2=0.81, RMSE=0.8 log units

* Irvine, *et al.* (1999) J. Pharm. Sci. **88**, p. 28

Requirements for MPO in Drug Discovery

- Interpretable
  - Easy to understand compound priority and how to improve compounds’ chances of success
- Flexibility
  - Define criteria depending on therapeutic objectives of project
- Weighting
  - Take into account relative importance of different endpoints to success of project
- Uncertainty
  - Take uncertainty into account, avoid missed opportunitites

Approaches for MPO in Drug Discovery

optibrium

Multi-Parameter Optimization: Identifying high quality compounds with a balance of properties
Curr. Pharm. Des. 2011 (submitted)
Download preprint from: www.optibrium.com/community

Approaches for MPO
Rules-of-Thumb

- The most famous – Lipinski's Rule-of-Five for oral absorption

logP<5	MW<500
HBD<5	HBA<10

- Many other have been proposed, e.g. Hughes *et al.** explored risk of adverse outcomes in *in vivo* toleration studies

logP<3	TPSA>75 Å^2

- Strengths:
  - Simplicity, ease of application and interpretation
- Caveats:
  - Rules tailored to specific objectives – lack of flexibility
  - Risk of too rigid application

* Hughes *et al.* Bioorg Med. Chem. Lett. (2008) **18** p. 4875

Rules of Thumb

- How predictive are rules-of-thumb?
  - E.g. Lipinski's RoF applied to 1191 marketed drugs

	RoF result	
	Pass (≤1 RoF Failure)	Fail (>1 RoF Failure)
Oral	709	59
Non-oral	333	90

Approaches for MPO
Filtering

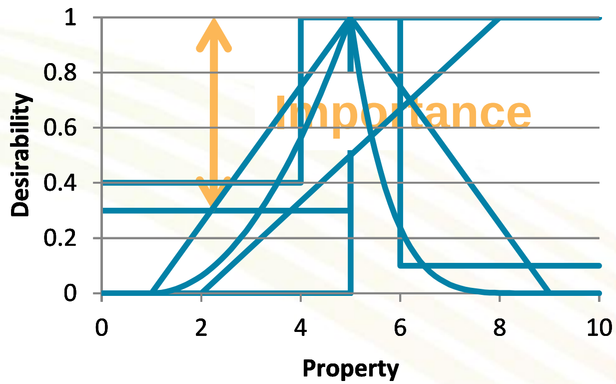
Potency

Absorpti

Metabolic Stability

Approaches for MPO
Desirability Functions*

- Relate property values to how ‘desirable’ the outcome



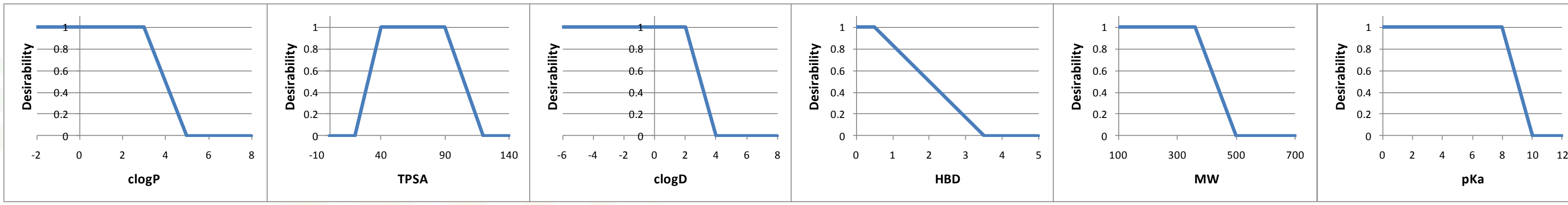
value: 5
(Derringer Function)

- Combine multiple properties into ‘desirability index’
  - Additive: $$D = \frac{d_1(Y_1) + d_2(Y_2) + \cdots + d_n(Y_n)}{n}$$
  - Multiplicative: $$D = (d_1(Y_1) \times d_2(Y_2) \times \ldots \times d_n(Y_n))^{1/n}$$
- Strengths
  - Very flexible; Explicitly weight properties; Easy to interpret
- Caveats
  - No explicit consideration of uncertainty; Need to know criteria *a priori*

* Harrington EC. (1965) Ind. Qual. Control. **21** p. 494

Desirability Functions
CNS MPO*

clogP | TPSA | clogD | HBD | MW | pKa



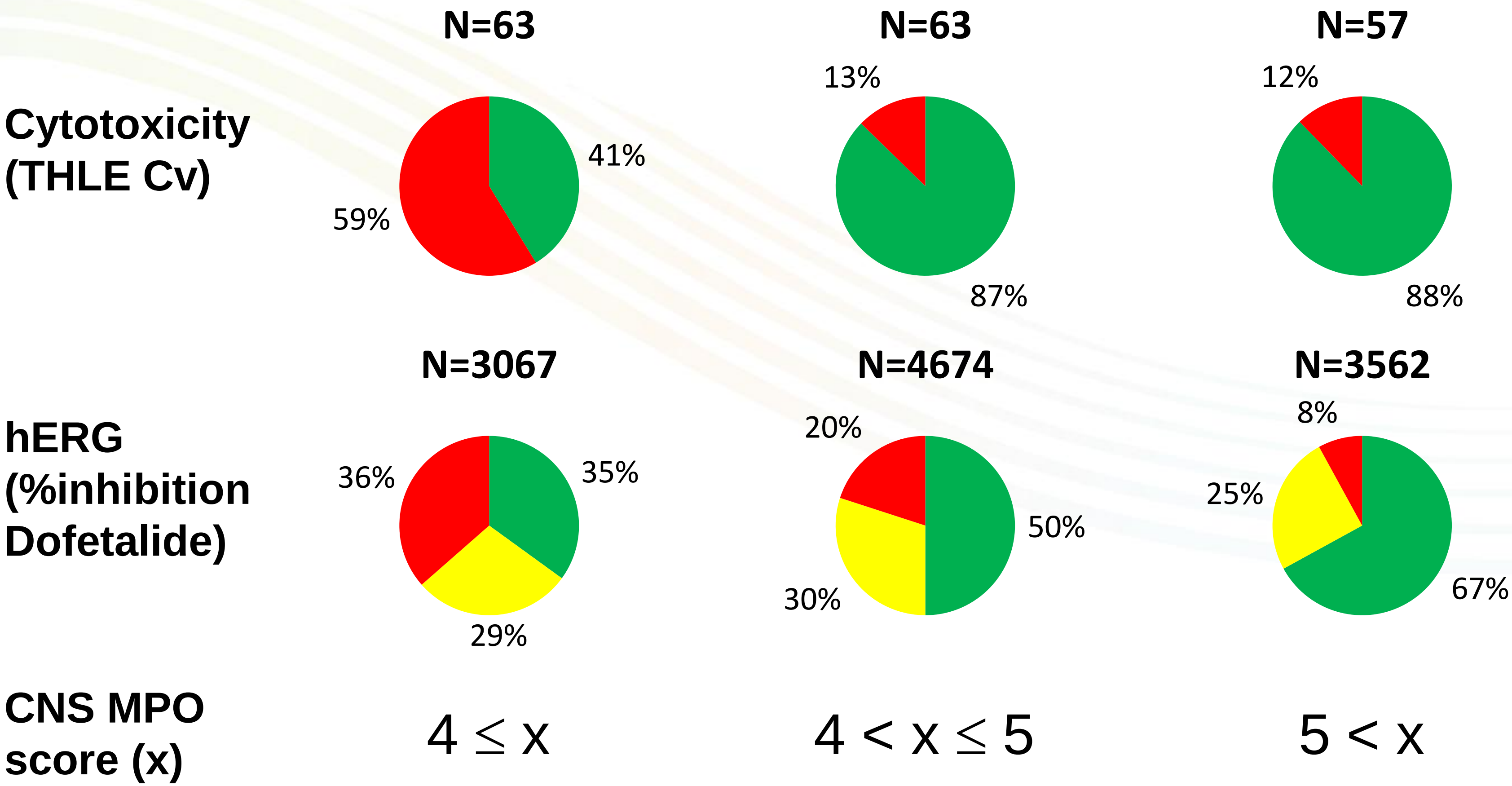
CNS MPO = sum of desirabilities for each parameter

- 74% of marketed CNS drugs achieved CNS MPO > 4 vs. 60% of Pfizer candidates
- Correlations observed between high CNS MPO score and good *in vitro* ADME properties, e.g. MDCK P_{app}, HLM stability, P-gp transport

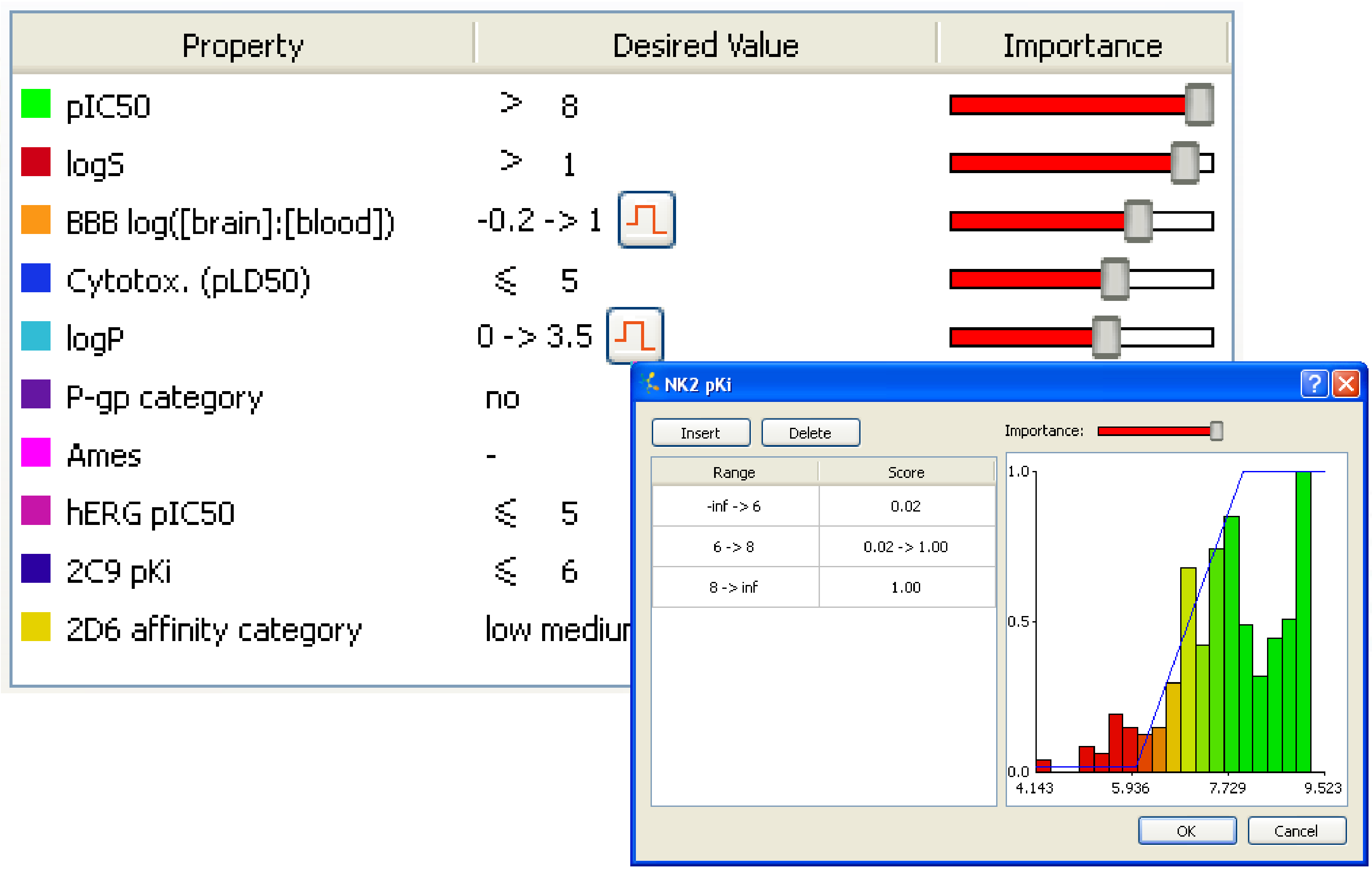
*Wagner *et al.* (2010) ACS Chem. Neurosci. **1** p. 435

Desirability Functions
CNS MPO and safety*

- CNS MPO score was also found to correlate with safely endpoints:



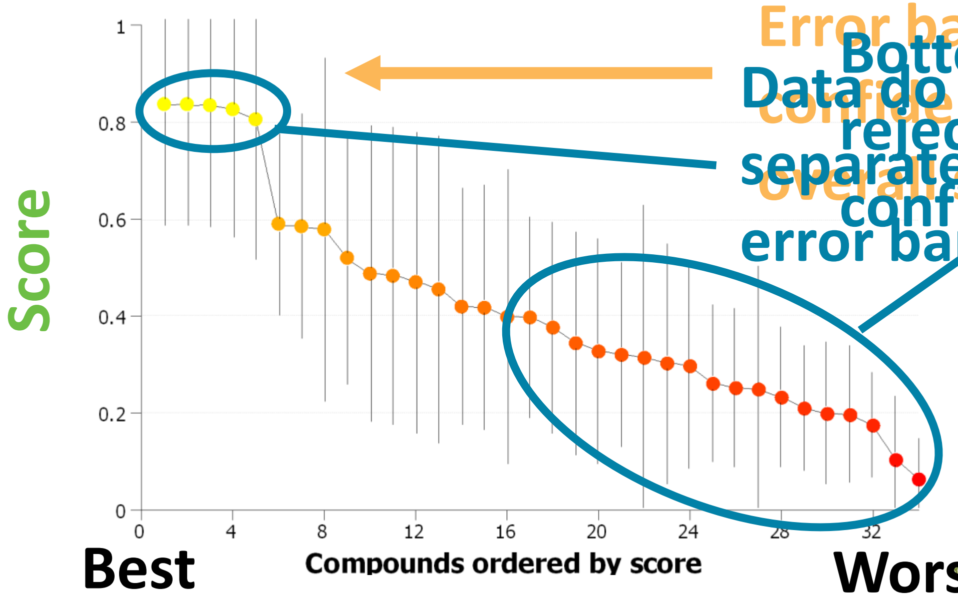
Approaches for MPO
Probabilistic Scoring* – Scoring Profile



Probabilistic Scoring*

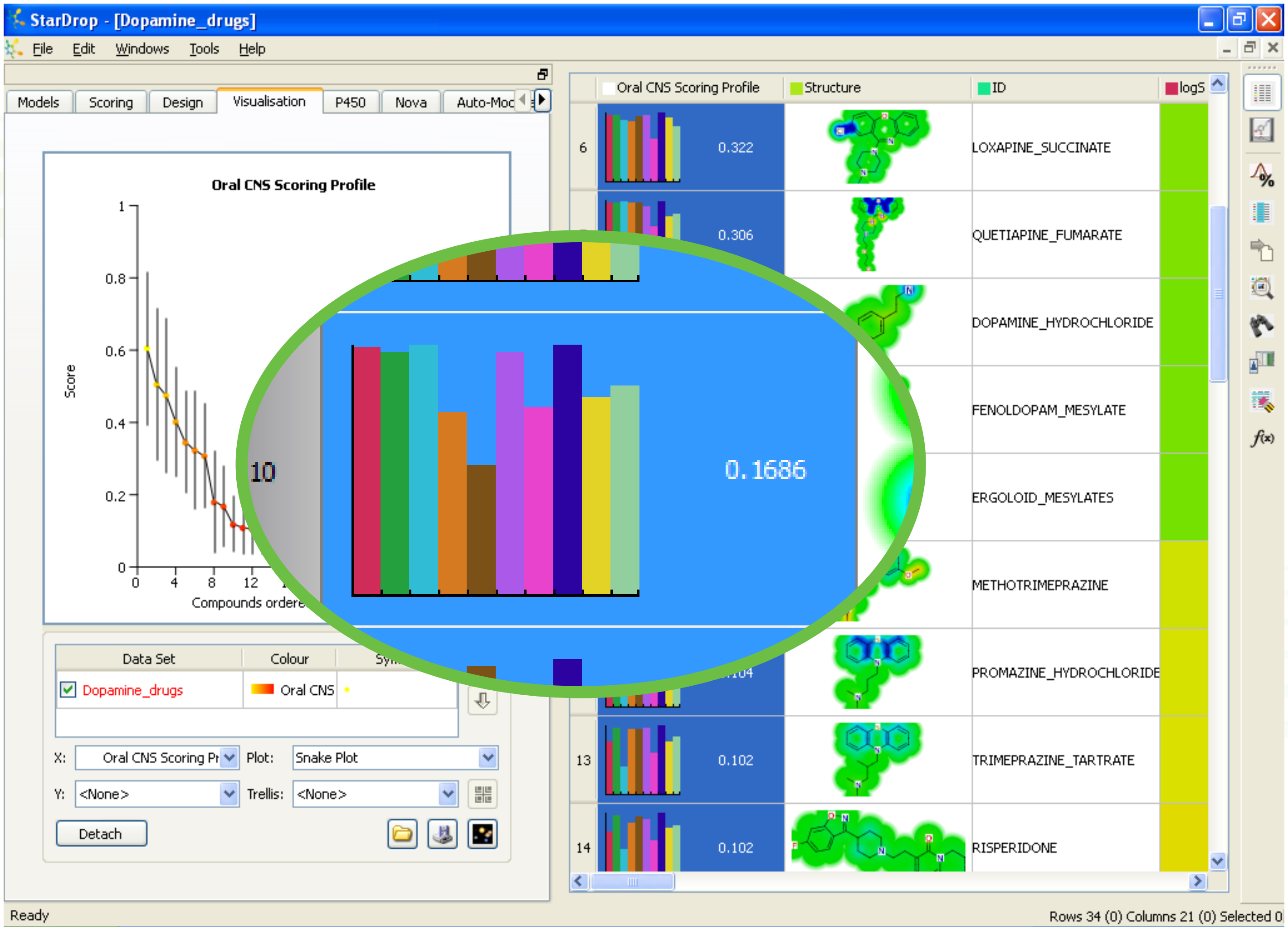
- **Property data**
  - Experimental or predicted
- **Criteria for success**
  - Relative importance
- **Uncertainties in data**
  - Experimental or statistical

- Score (Likelihood of Success)
- Confidence in score

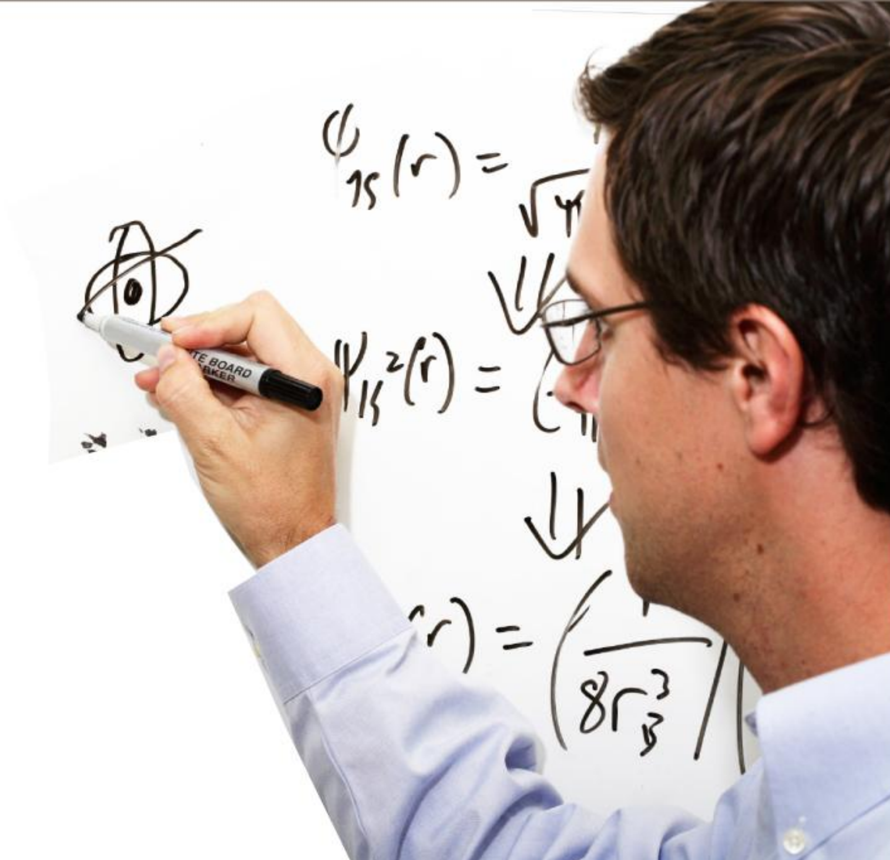


* Segall *et al.* (2009) Chem. & Biodiv. **6** p. 2144

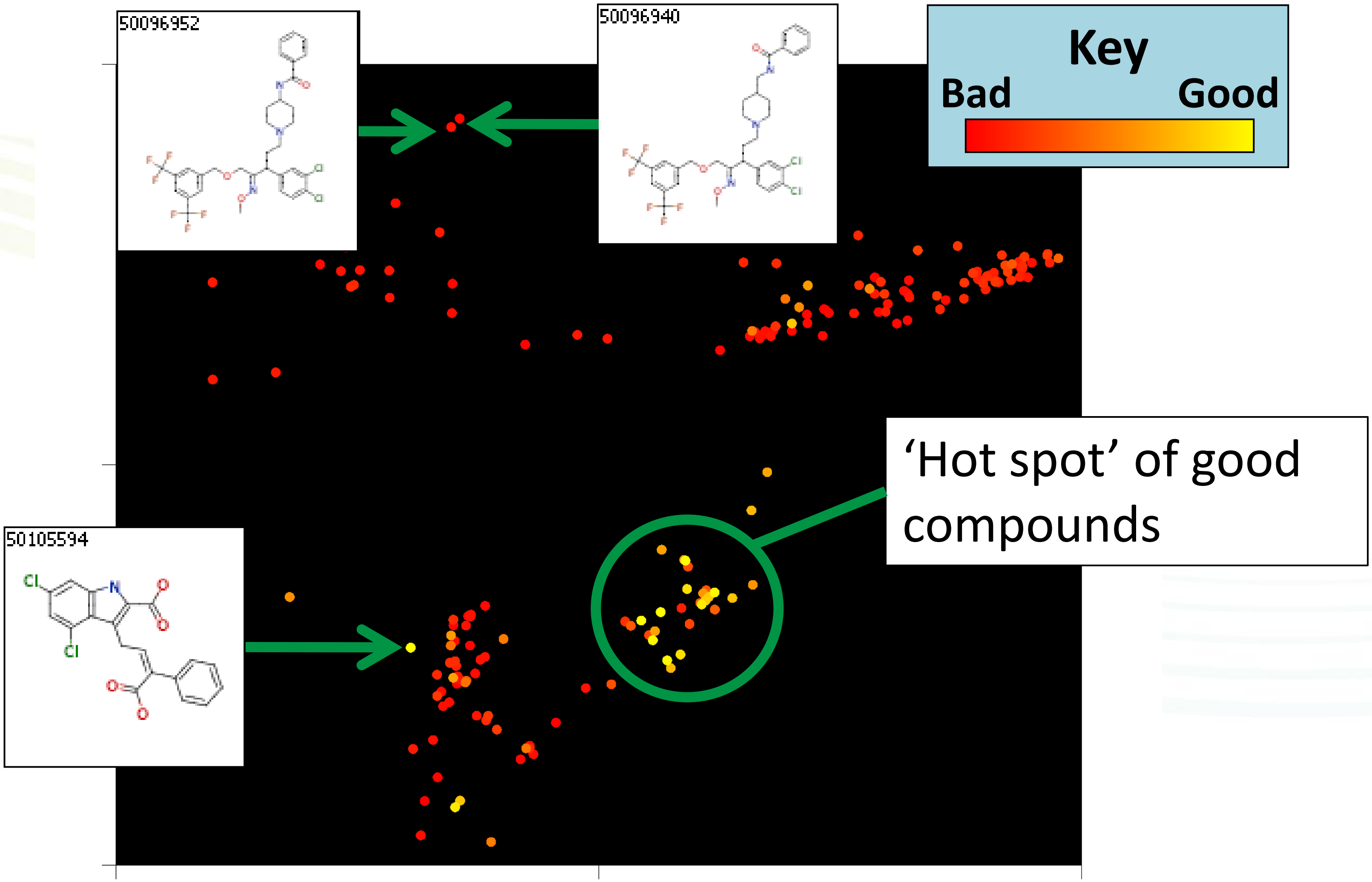
Provide Feedback on Influence of Properties
Guide redesign to improve chance of success



Balancing Quality and Diversity

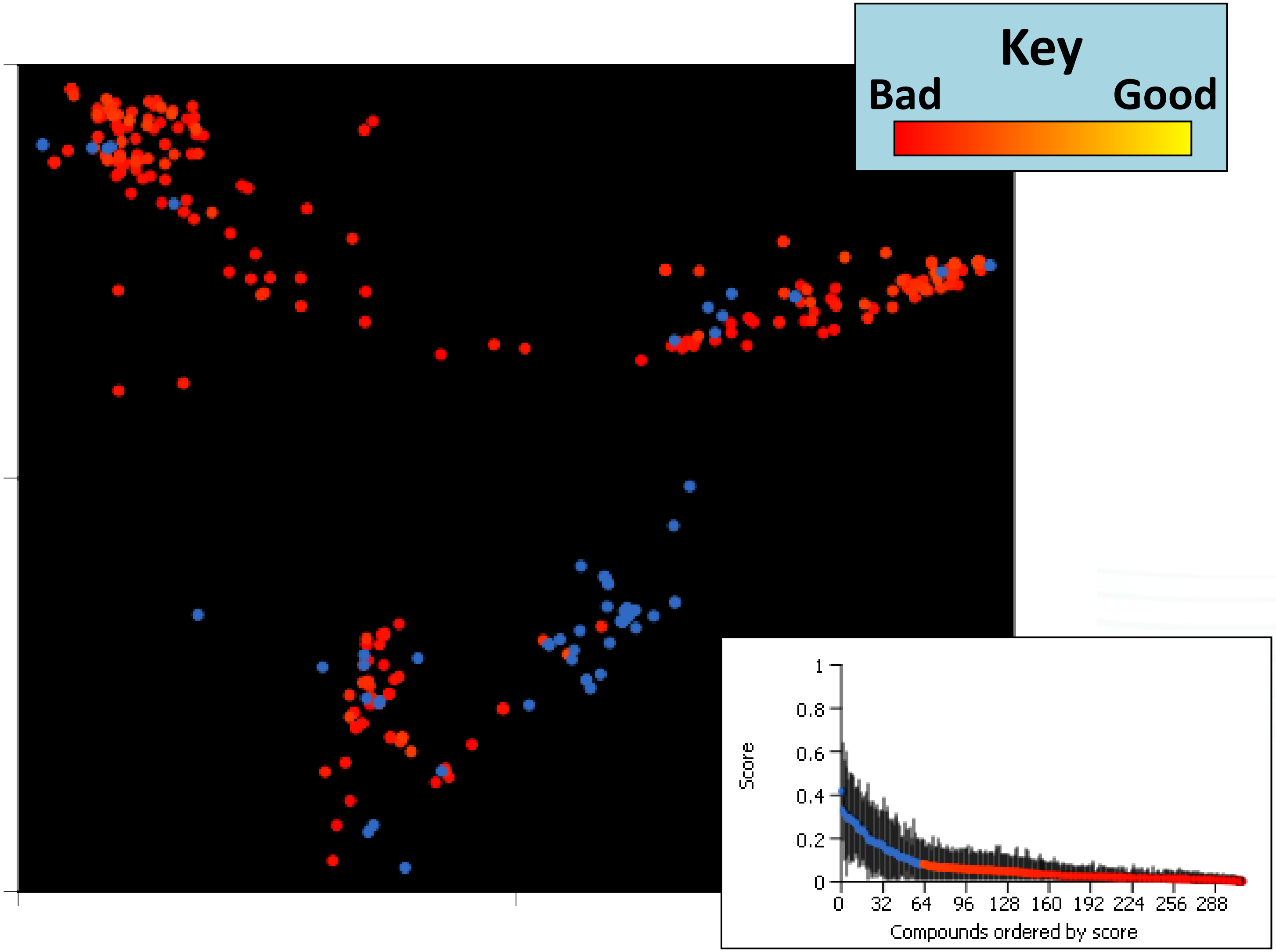


Visualising 'Chemical Space'
Exploring trends across chemical diversity

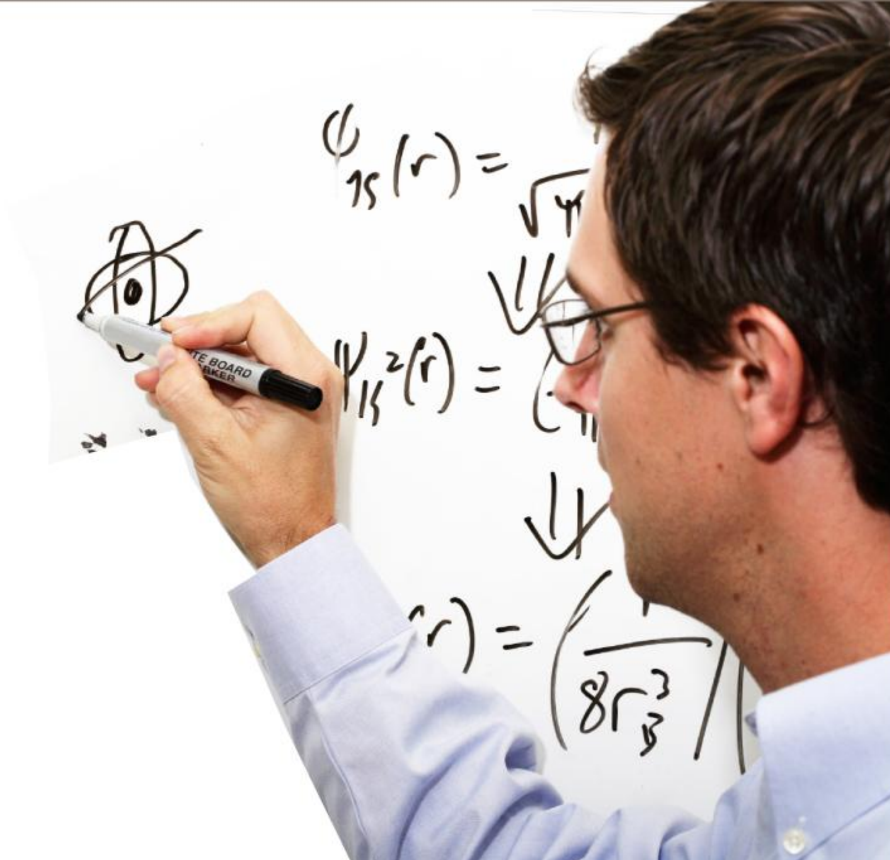


Balance Quality Against Diversity

Mitigating risk



Case Study
Rapid Focus in Lead Optimisation

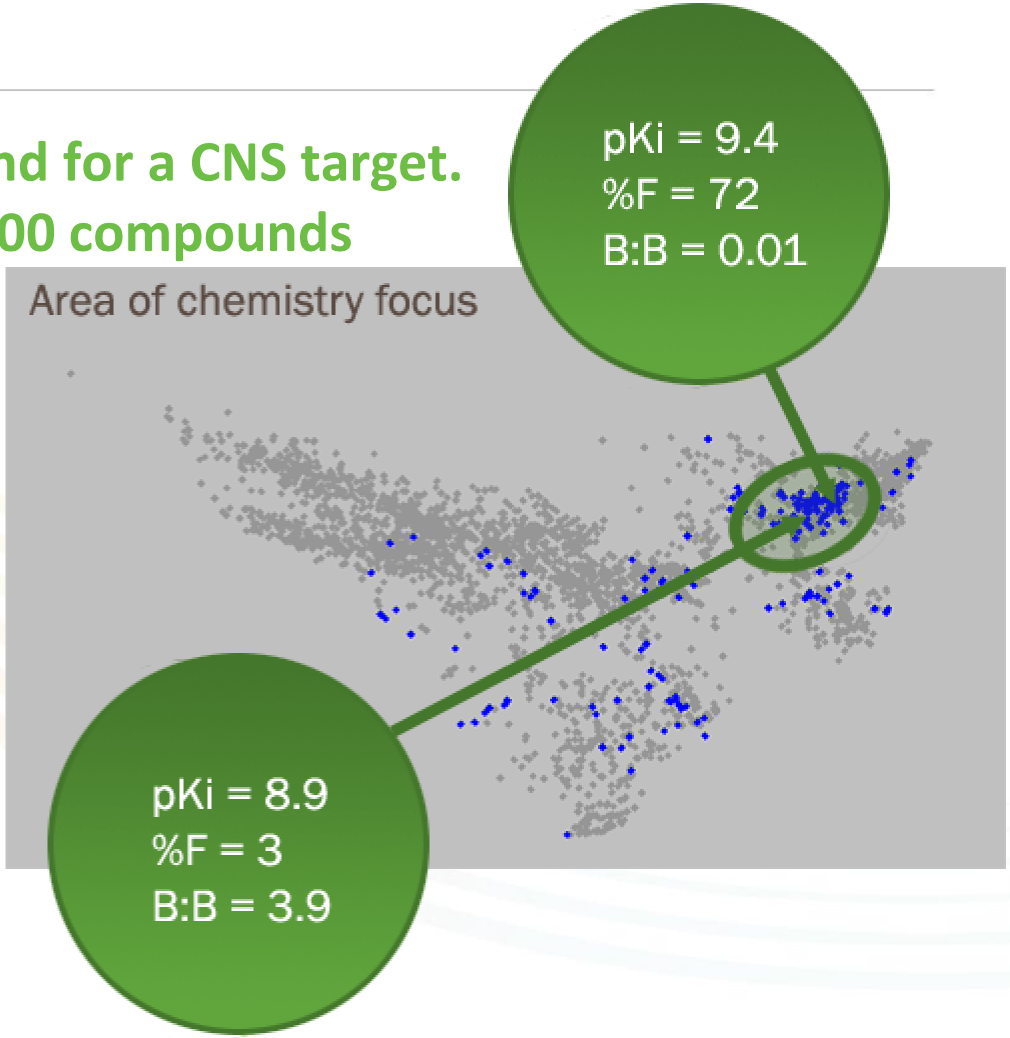


Challenge

Identify orally active compound for a CNS target.
Project 'chemical space' of 3100 compounds

Summary of original project progress

- Focus biased towards one area of chemistry space



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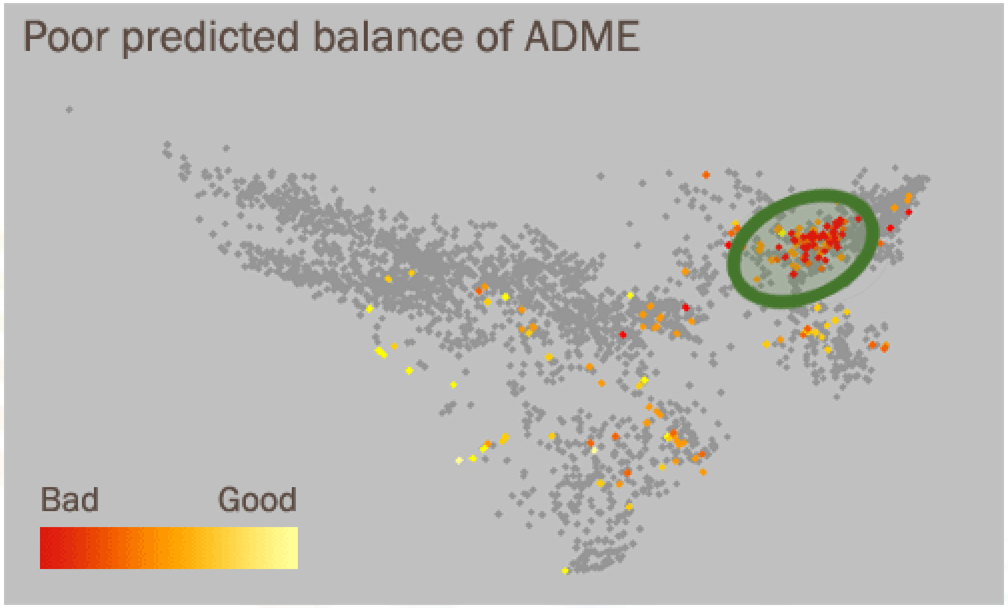


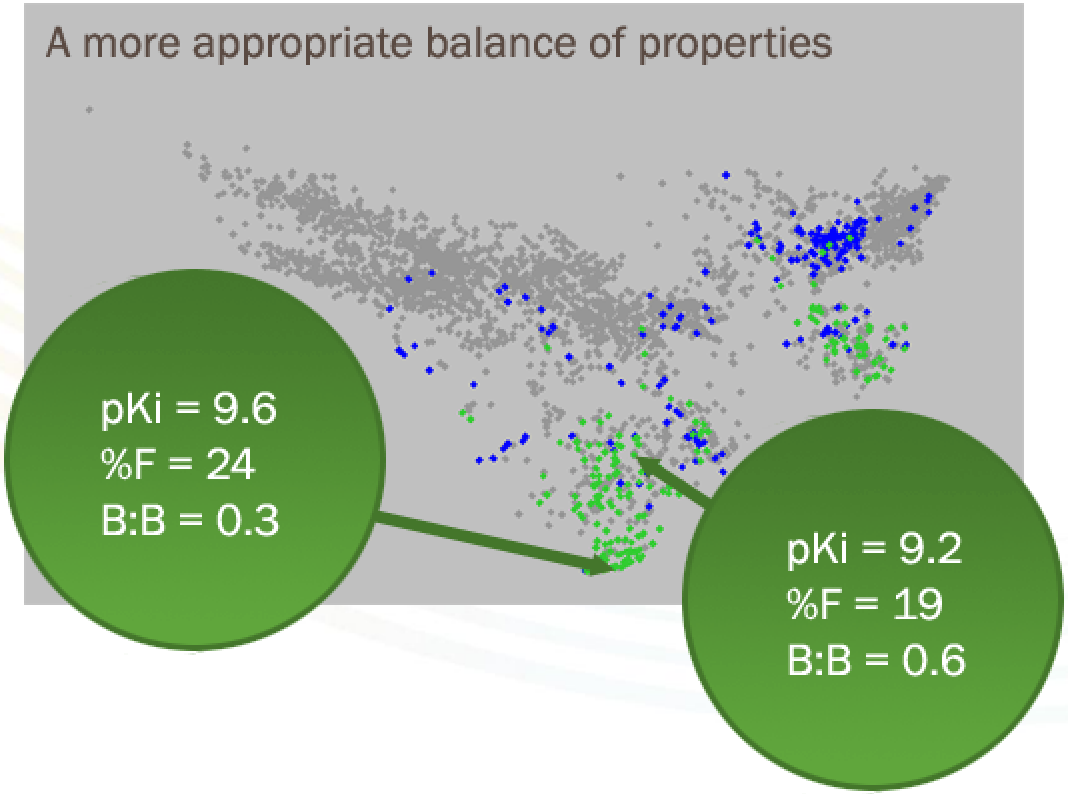
Summary of original project progress

- Focus biased towards one area of chemistry space
- Poor ADME properties

Property	Desired Value	Importance
logS	> 1	
HIA category	+	
BBB log([brain]:[blood])	> -0.5	
logP	⩽ 3.5	
2D6 affinity category	low medium	
2C9 pKi	⩽ 6	
P-gp category	no	

Challenge

Identify orally active compound for a CNS target.
Project 'chemical space' of 3100 compounds

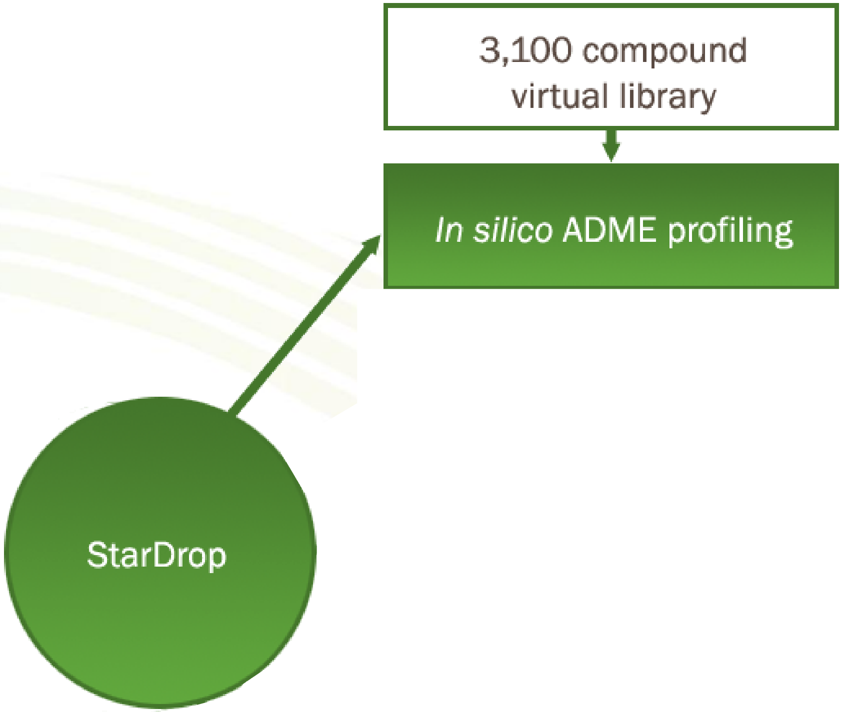


Summary of original project progress

- Focus biased towards one area of chemistry space
- Poor ADME properties
- Follow-up chemistry exploration
- Nowhere obvious to go next!

Cost so far: >**3000** compounds synthesised, **400** compounds tested *in vitro* and **70** compounds tested *in vivo*

StarDrop Process
Select 25 compounds for *in vivo* testing



StarDrop Process
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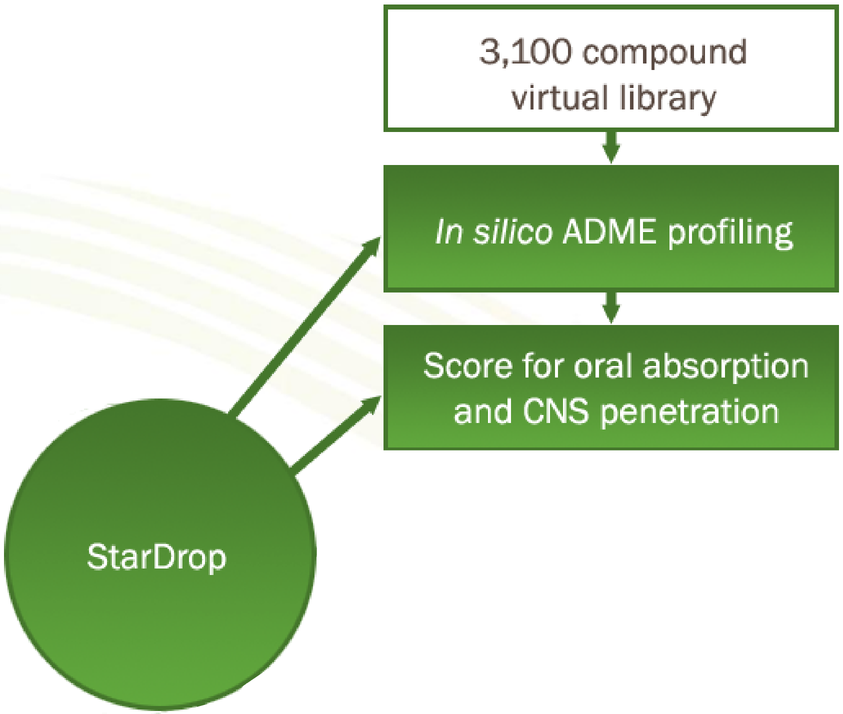
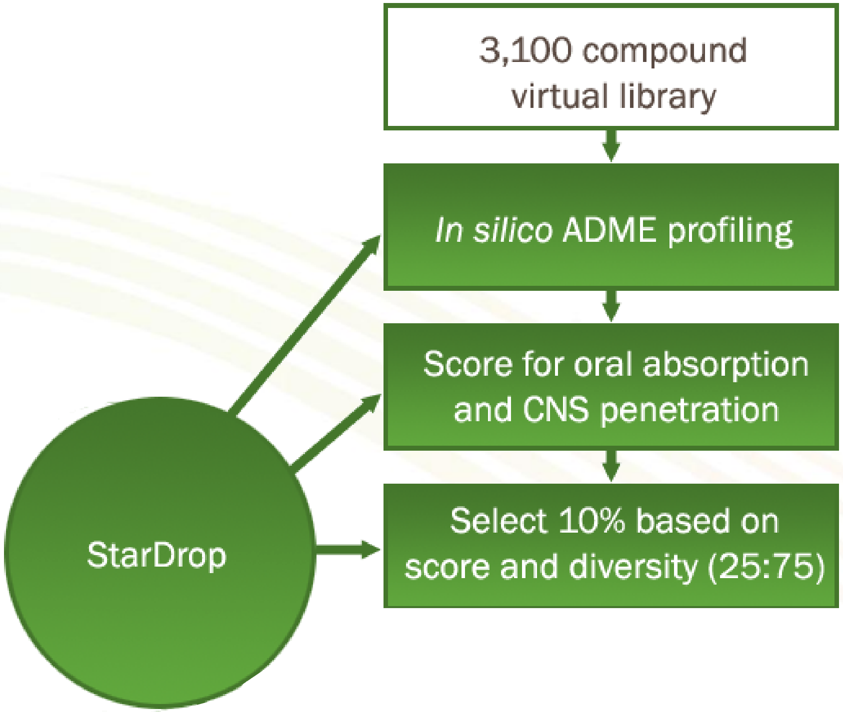


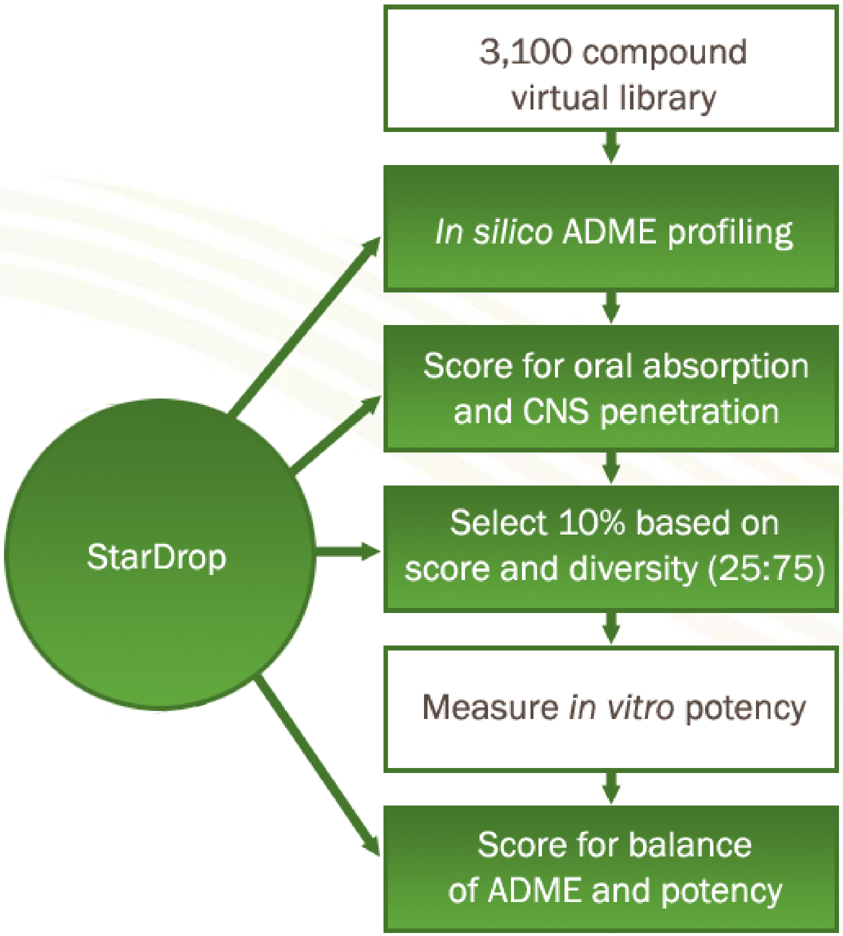
Property	Desired Value	Importance
logS	> 1	
HIA category	+	
BBB log([brain]:[blood])	> -0.5	
logP	≤ 3.5	
2D6 affinity category	low medium	
2C9 pKi	≤ 6	
P-gp category	no	

StarDrop Process
Select 25 compounds for *in vivo* testing



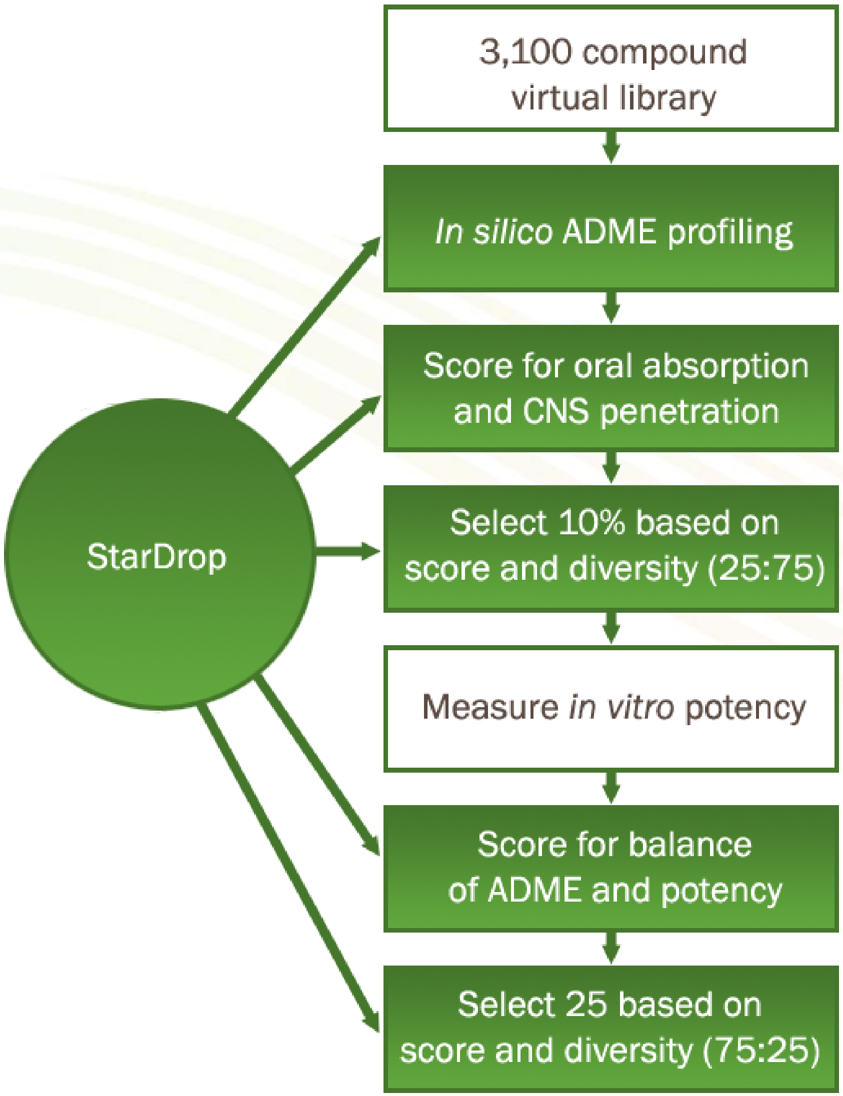
StarDrop Process

Select 25 compounds for *in vivo* testing



Property	Desired Value	Importance
Potency (pKi)	> 8	
logS	> 1	
HIA category	+	
BBB log([brain]:[blood])	> -0.5	
logP	≤ 3.5	
2D6 affinity category	low medium	
2C9 pKi	≤ 6	
P-gp category	no	

StarDrop Process
Select 25 compounds for *in vivo* testing

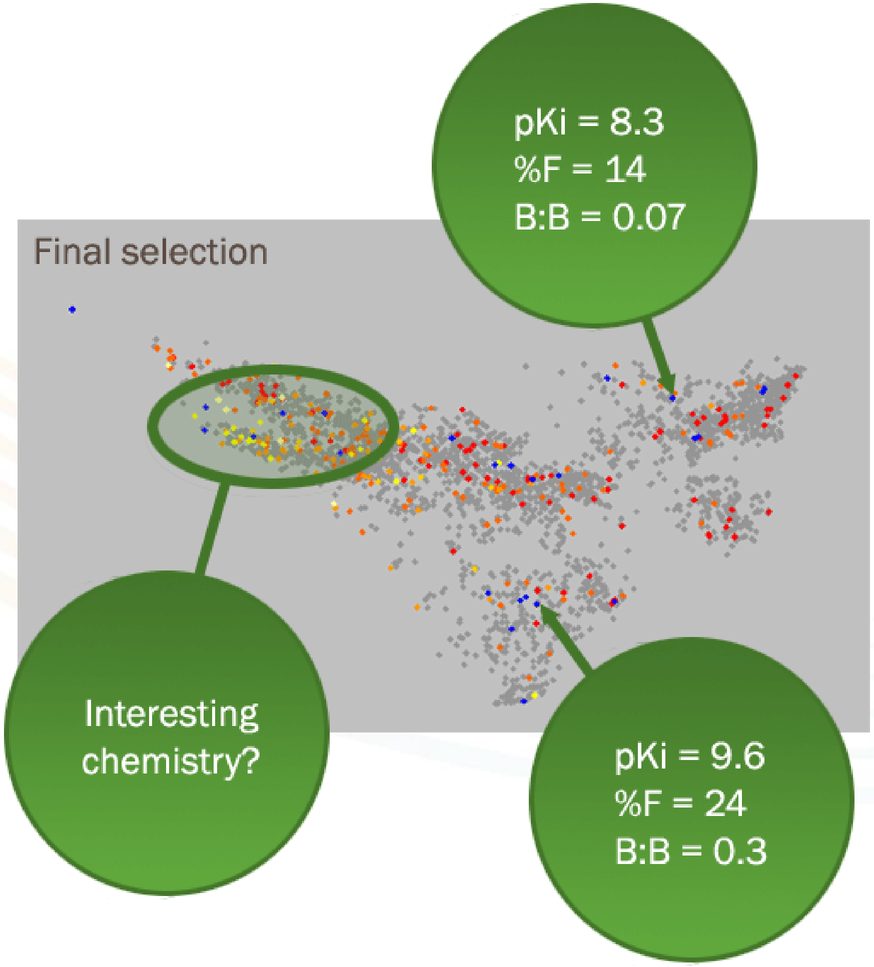


Results

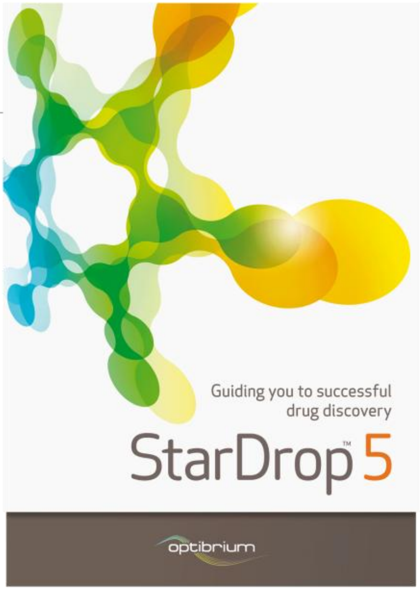
Successfully selected same key compounds identified by the project but with:

- **90%** fewer compounds synthesised
- **90%** less potency screening
- **70%** less *in vivo* testing

In addition, identified a new area of chemistry with good potential!



Conclusions



- In drug discovery, we must make confident decisions on complex multi-dimensional data
  - Uncertainty in all data
- Requirements for MPO in Drug Discovery
  - Interpretable
  - Flexible
  - Weighting
  - Uncertainty
- Detailed review (submitted to Curr. Pharm. Des.)
  - **Multi-Parameter Optimization: Identifying high quality compounds with a balance of properties**
  - **www.optibrium.com/community**
  - **matt.segall@optibrium.com**

Acknowledgements

- StarDrop group past and present, including:
  - Ed Champness
  - Chris Leeding
  - Iskander Yusof
  - James Chisholm
  - Olga Obrezanova
  - Alan Beresford
  - Dawn Yates
  - Dan Hawksley
  - Joelle Gola
  - Brett Saunders
  - Simon Lister
  - Mike Tarbit