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Confidently Targeting High Quality Hits from High-Throughput Screening

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Overview

- Goals of high-throughput screening (HTS) triage
- Mapping the chemical space of activity
- Understanding the activity landscape
- Targeting high quality hit series
- Conclusions

Goals of HTS Triage

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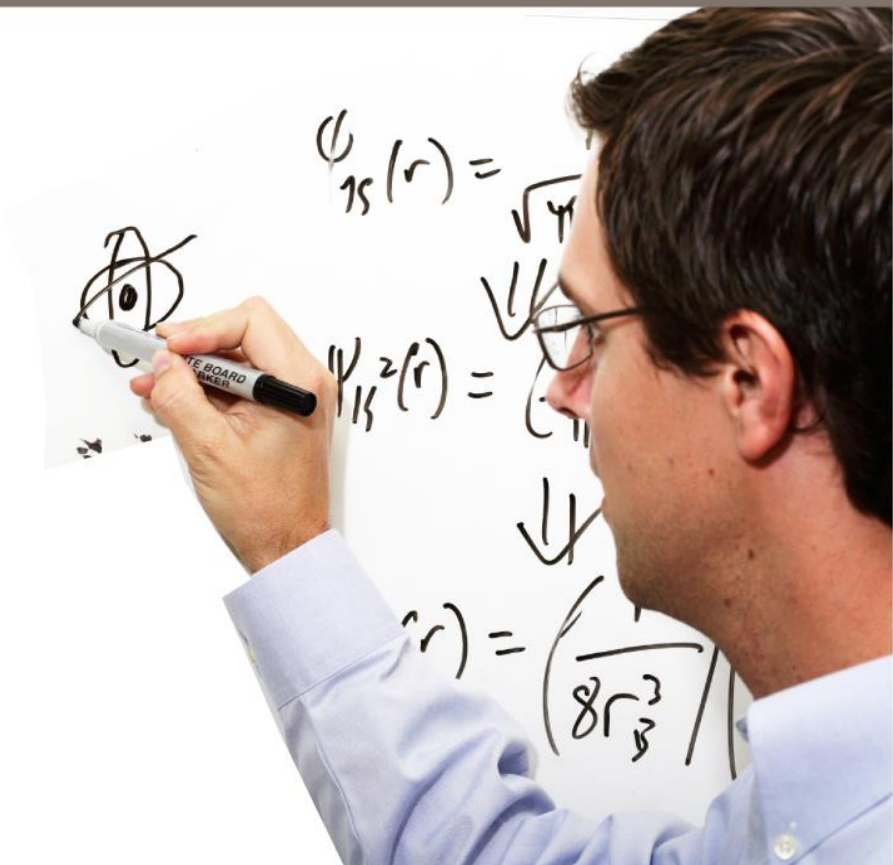

Goals of HTS triage

- One or more active series
  - Diversity is beneficial to provide backup series
- Good structure-activity relationships in series
  - Opportunities for optimisation
- High quality starting points for hit-to-lead
  - Appropriate physicochemical properties
  - Access to good absorption, distribution, metabolism and excretion (ADME) properties
  - Avoid frequent hitters (false positives) and high risk functionalities

Mapping the Chemical Space of Activity

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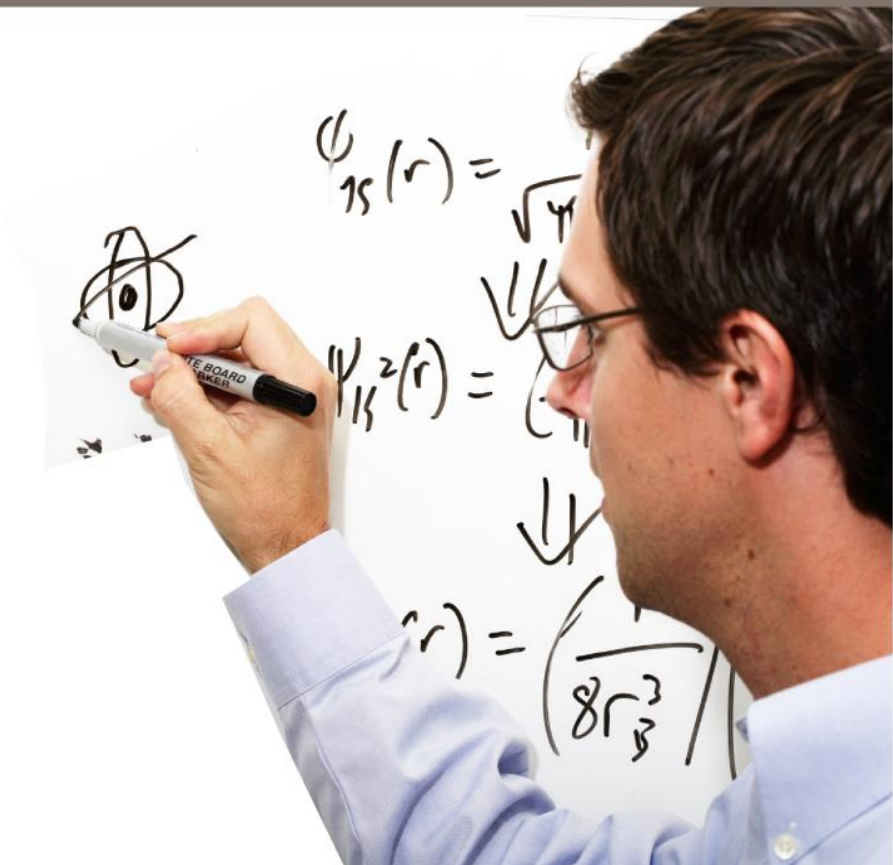
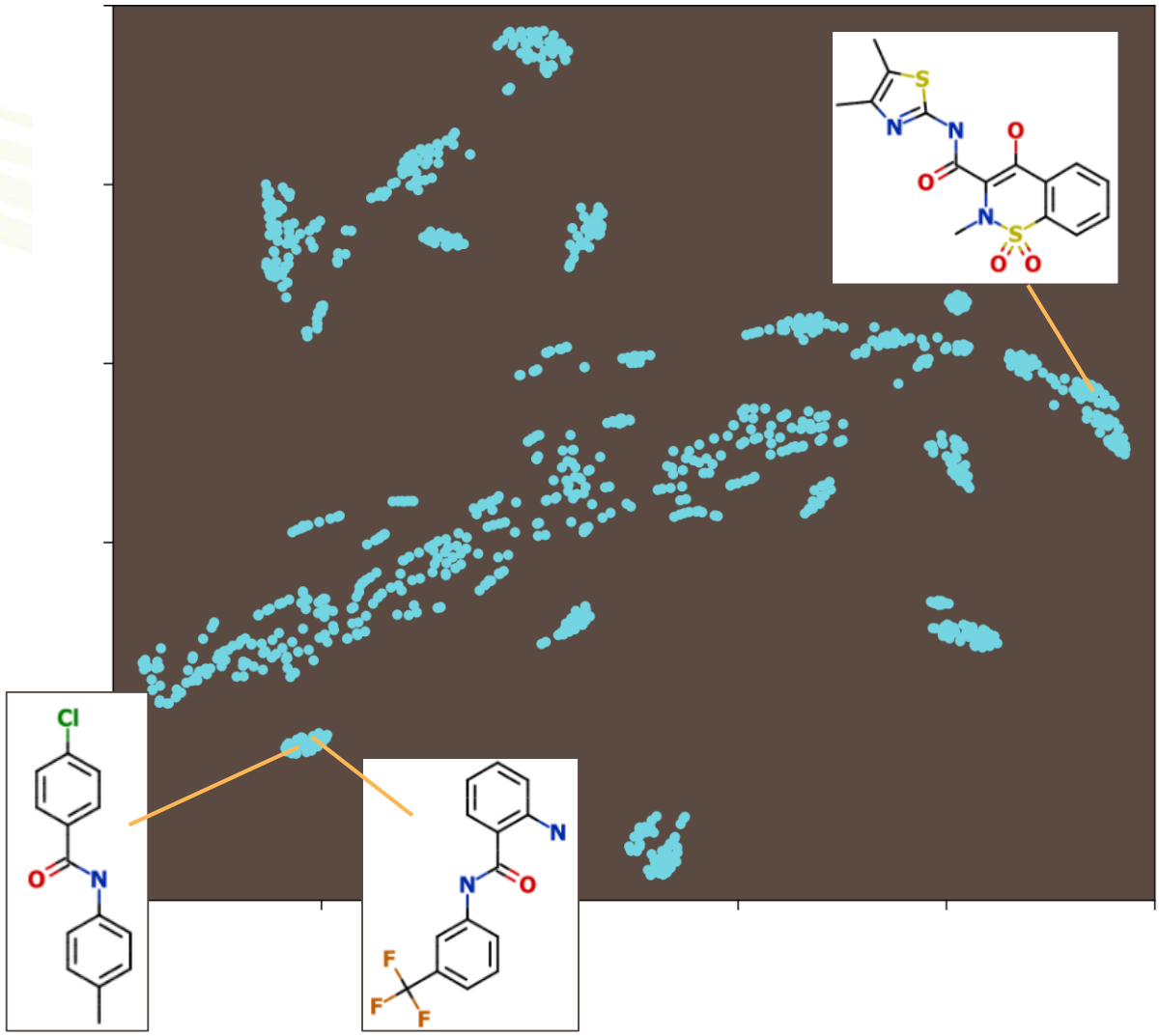
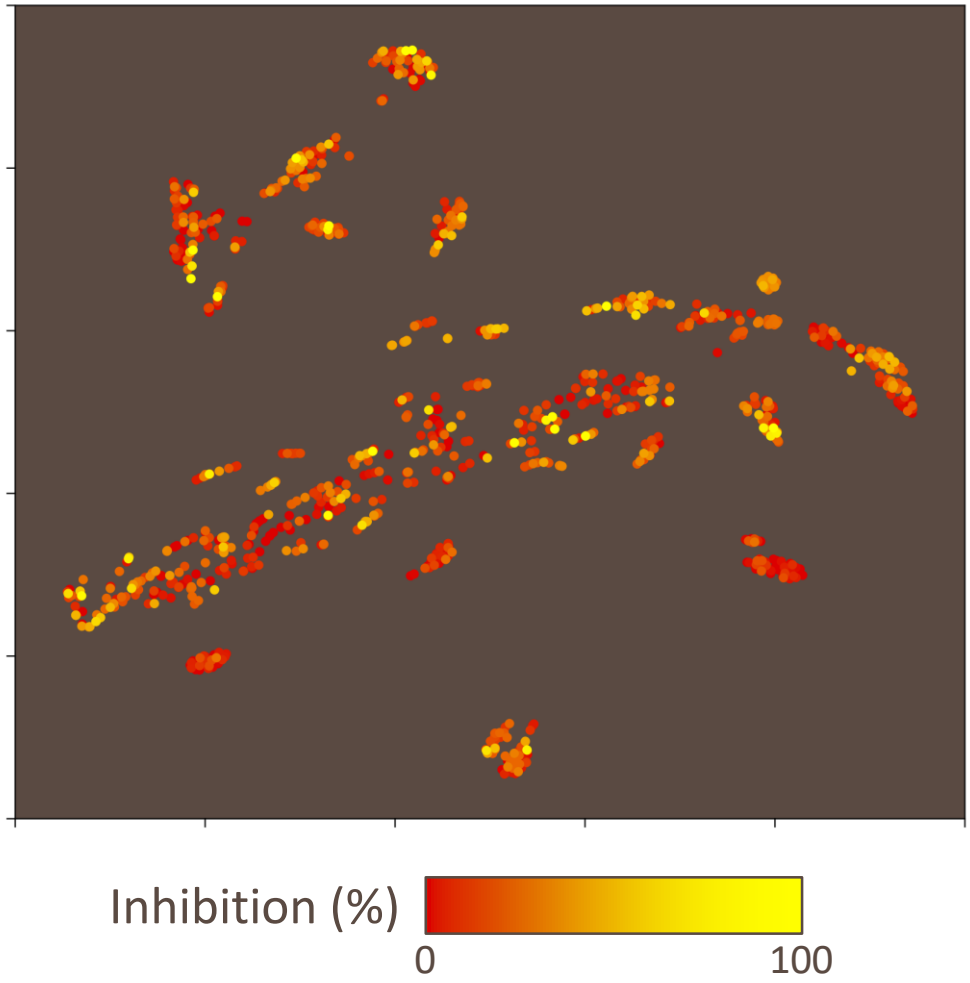
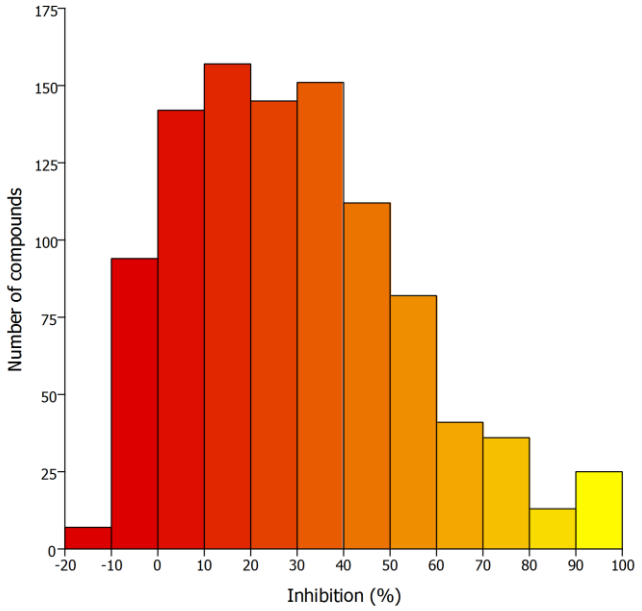


Example Screening Library



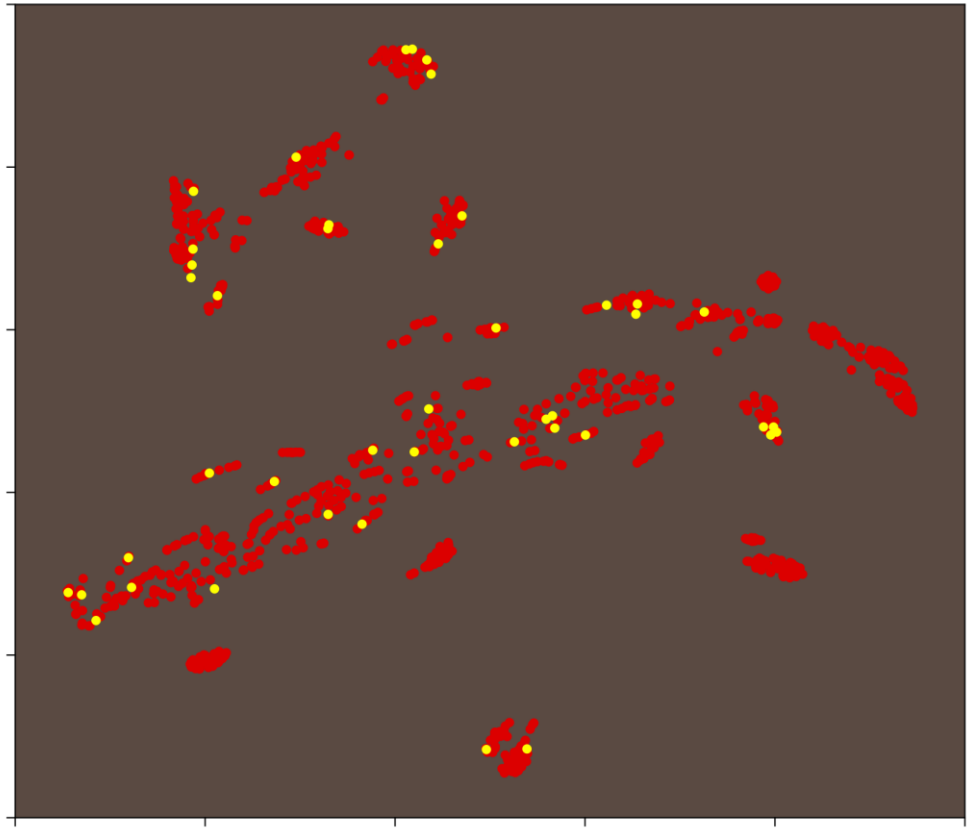
Distribution of Activity
Inhibition (%)

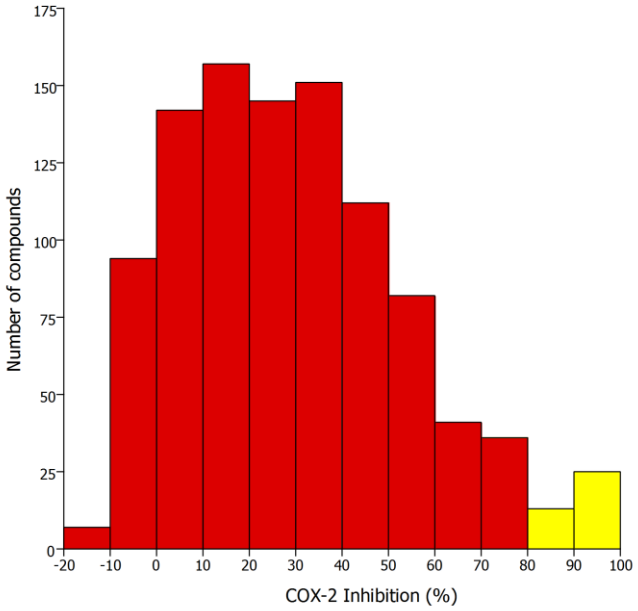




	Mean	Max	Min	SD
Inhibition (%)	31	100	-17	24

Identifying Hits





Hit (>80% Inhibition)

Miss

Understanding the Activity Landscape

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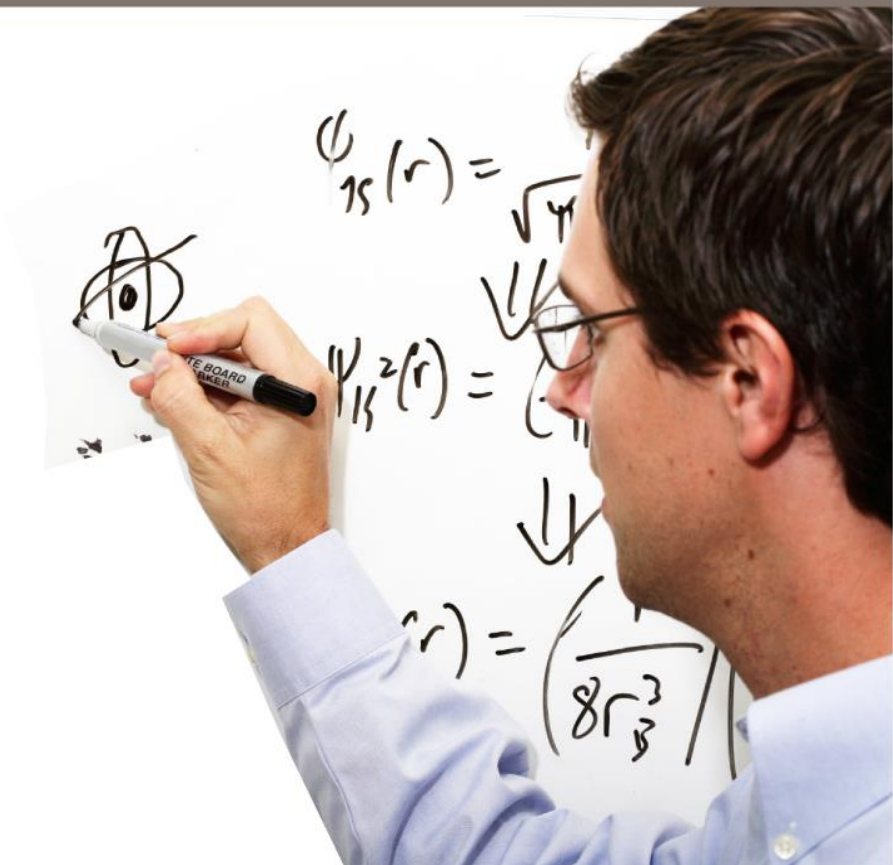
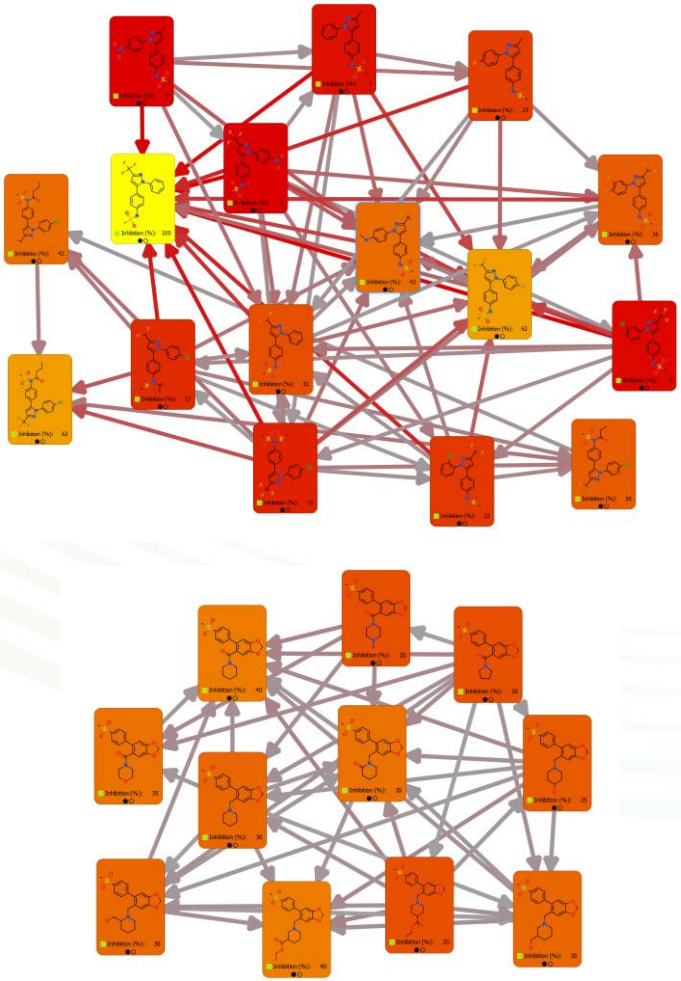
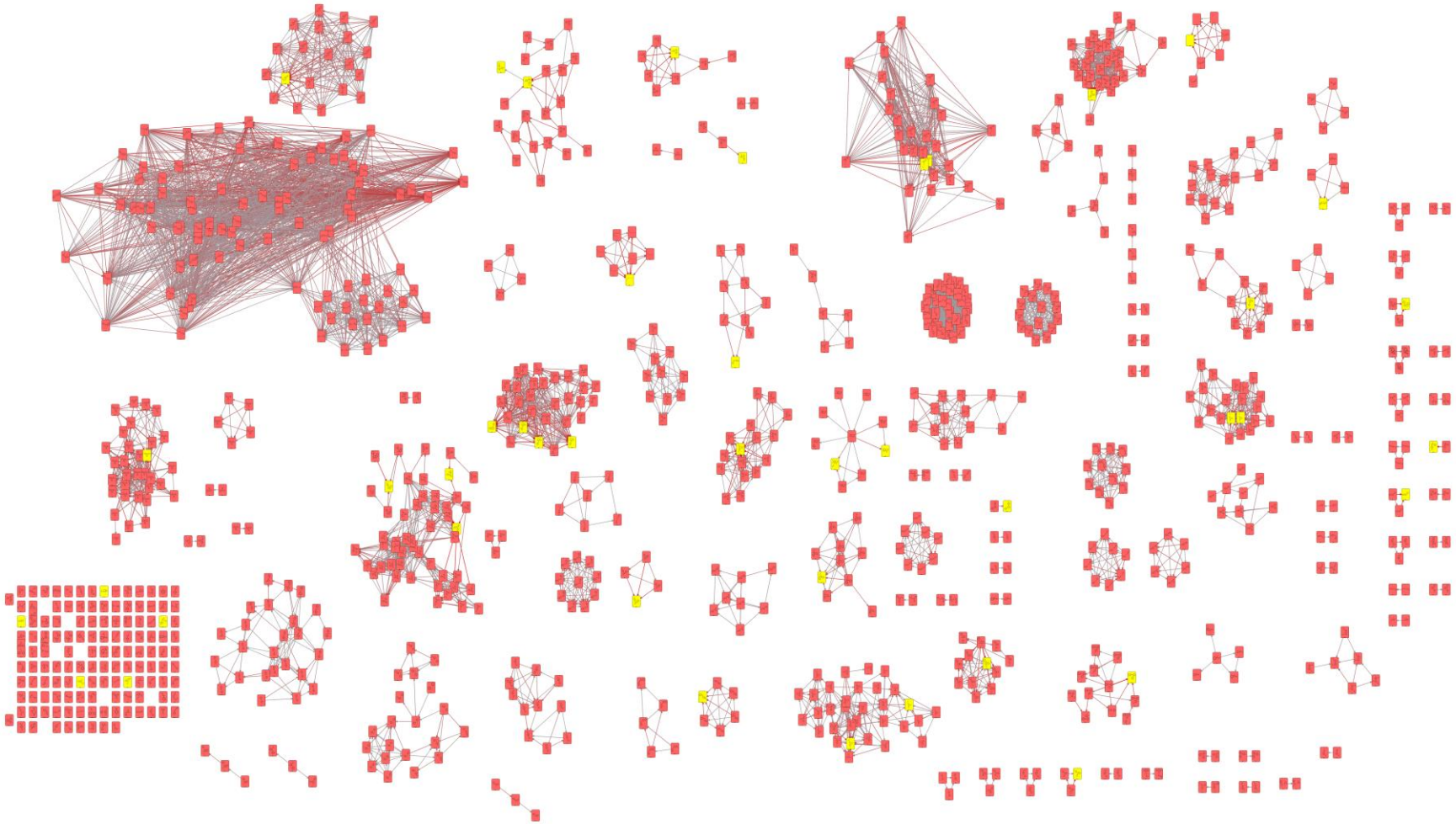


Activity Landscapes

- All-by-all comparison
  - Identify groups of ‘similar’ compounds
- ‘Rough’ regions
  - large changes in activity result from small changes in structure
  - Interesting SAR
- ‘Flat spots’
  - Limited opportunity for optimisation of activity
  - Opportunity to optimise different property without having negative impact on activity

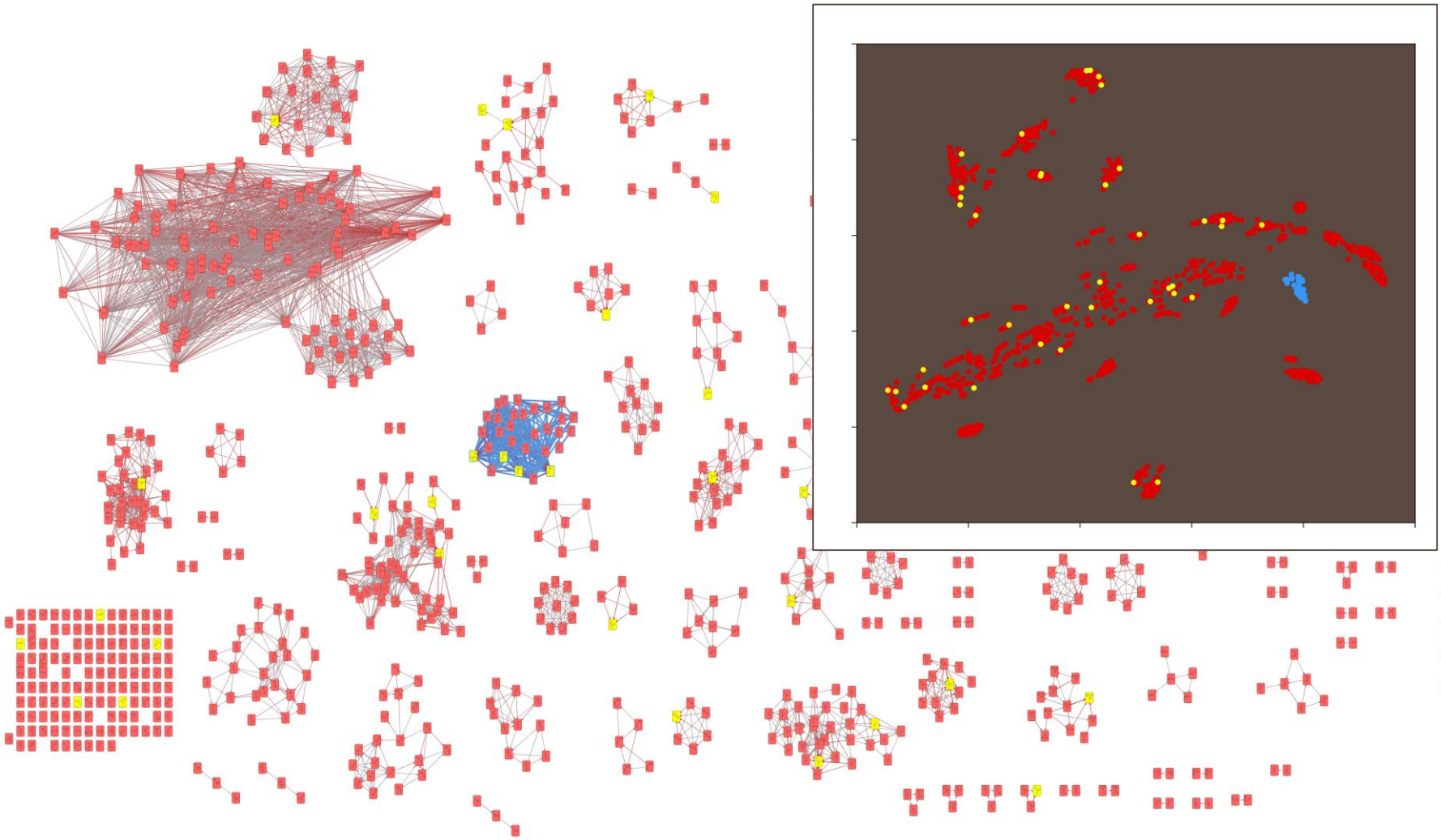


Identifying Regions with Interesting SAR



Hit (>80% Inhibition) Miss Tanimoto similarity > 0.8 →

Identifying Regions with Interesting SAR



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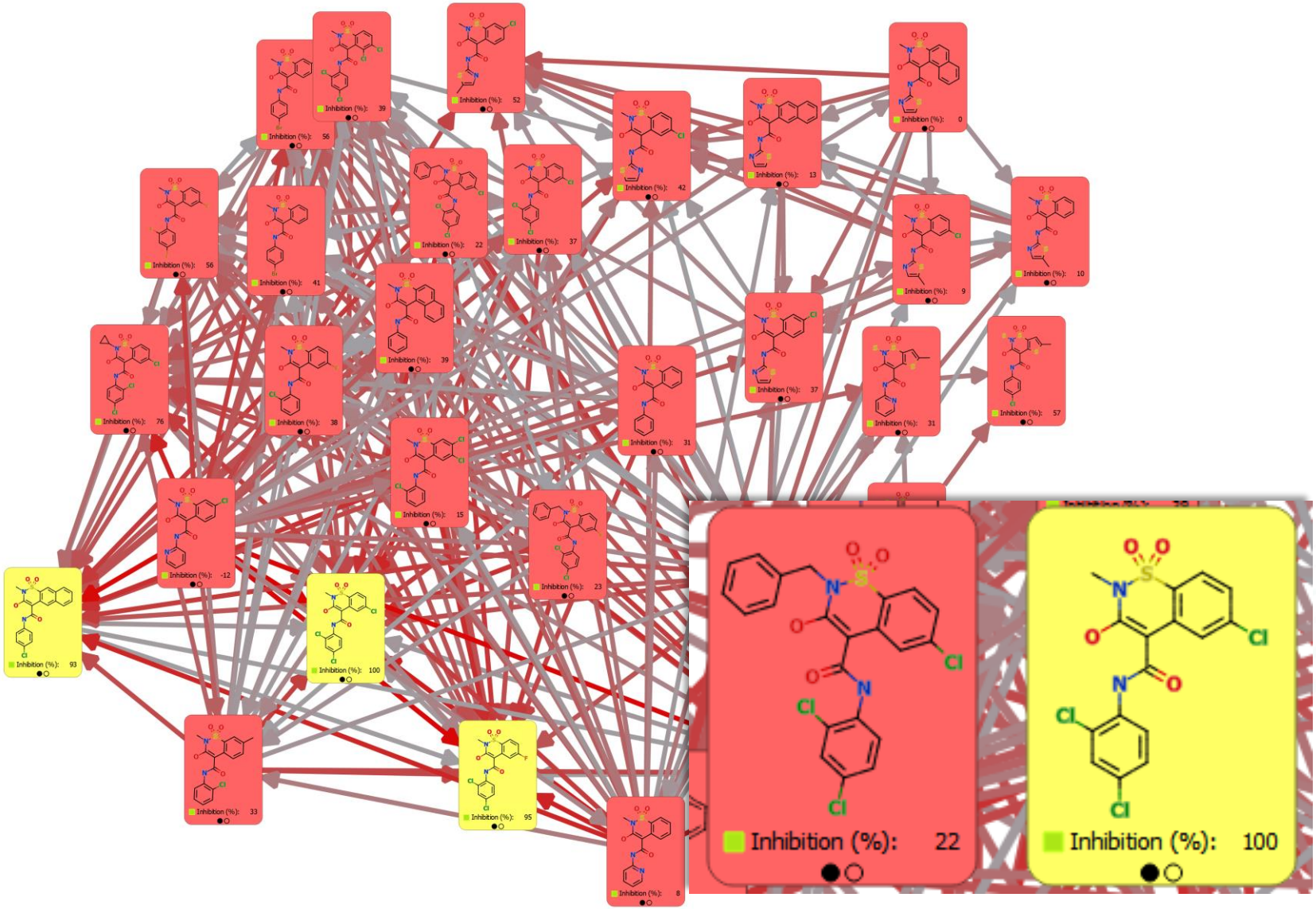
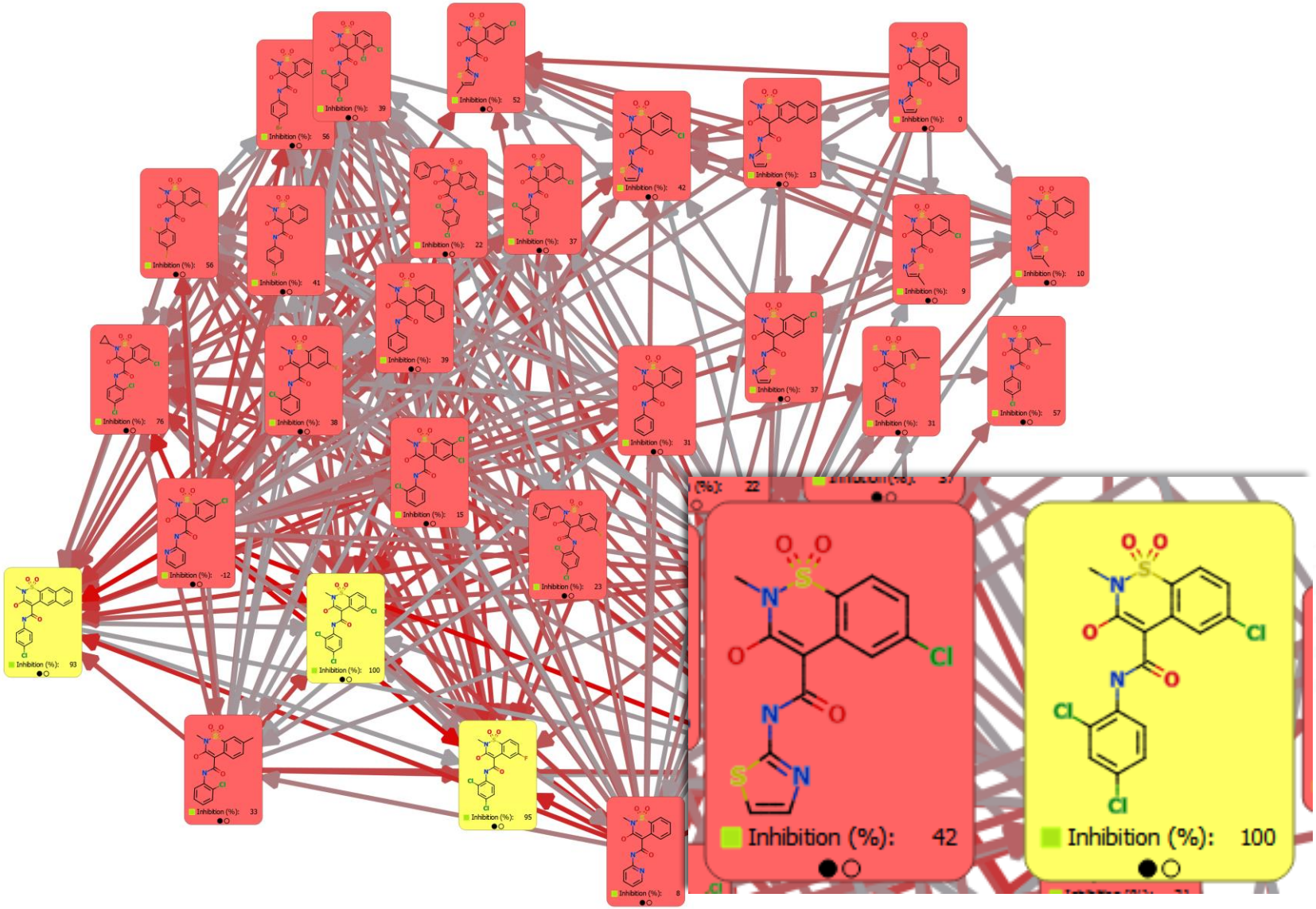


M.D. Segall *et al.* (2015) Drug Discov. Today **20**(9) pp. 1093-1103

Identifying Regions with Interesting SAR



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Targeting High Quality Hit Series

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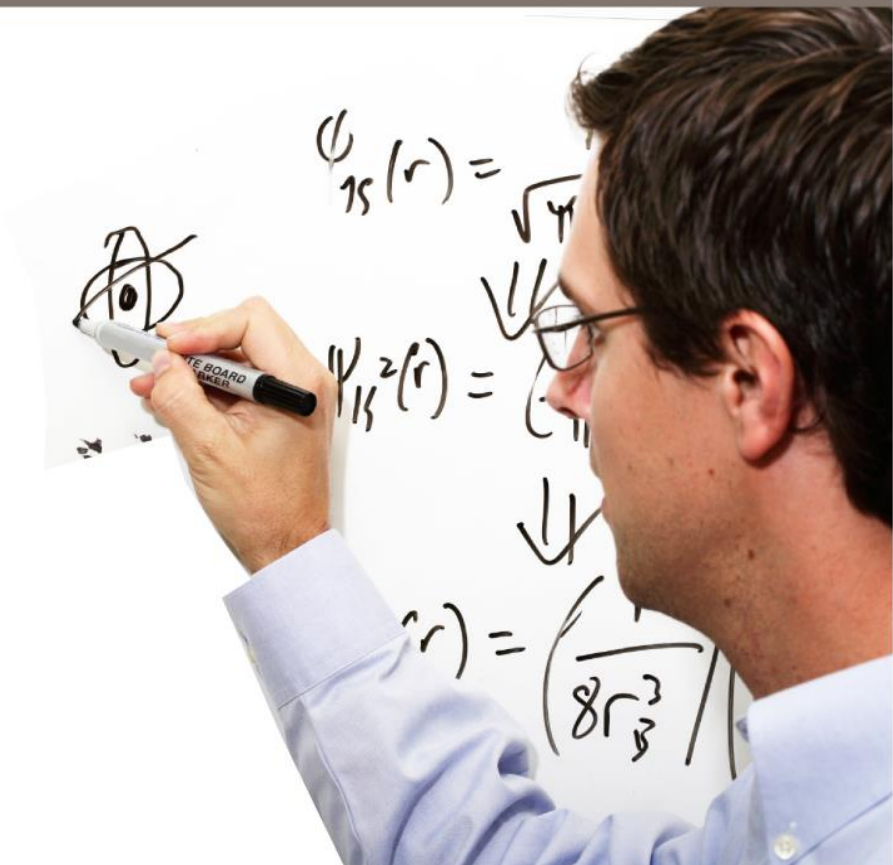


What Does "High Quality" Mean?

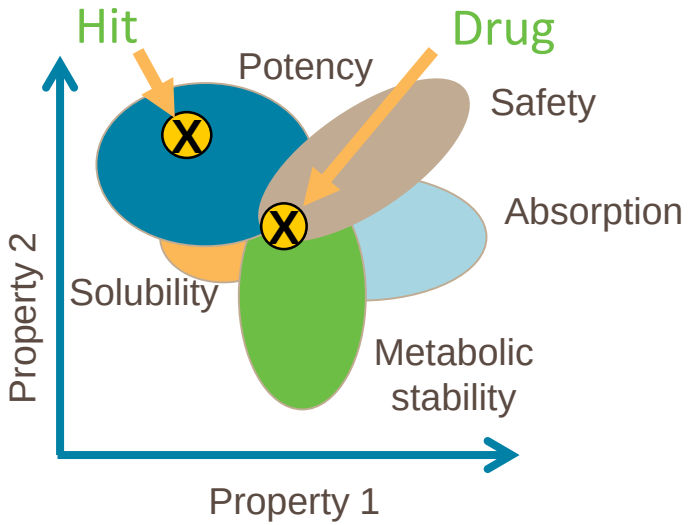
- Low molecular weight?
  - More room for optimisation
- Low logP?
  - Better opportunity for optimisation
  - Reduce risk of off-target effects
  - Better chance of good solubility/permeability
- Avoid pan-assay interference compounds (PAINS)*?
  - Maybe promiscuous binders
  - Undesirable functionalities
- Appropriate ADME properties
  - Depends on project's therapeutic objectives

*Baell and Holloway, J. Med. Chem. 2010 **53**(7) pp. 2719-2740

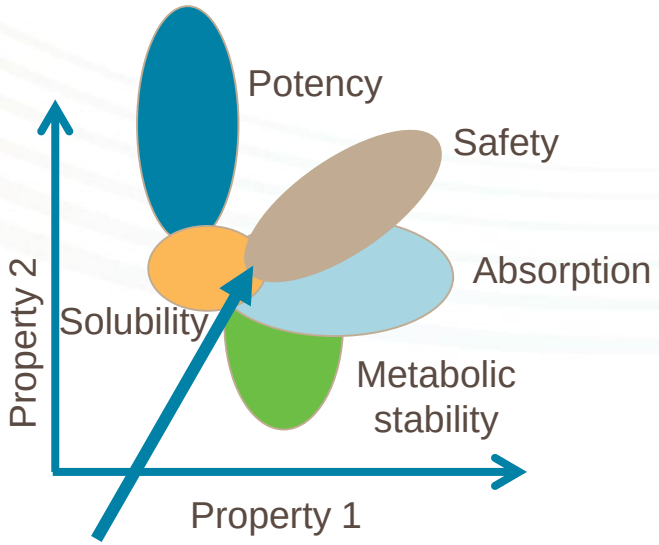
Guiding Decisions in Compound Optimisation

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**
  - –Avoid **missed opportunities**

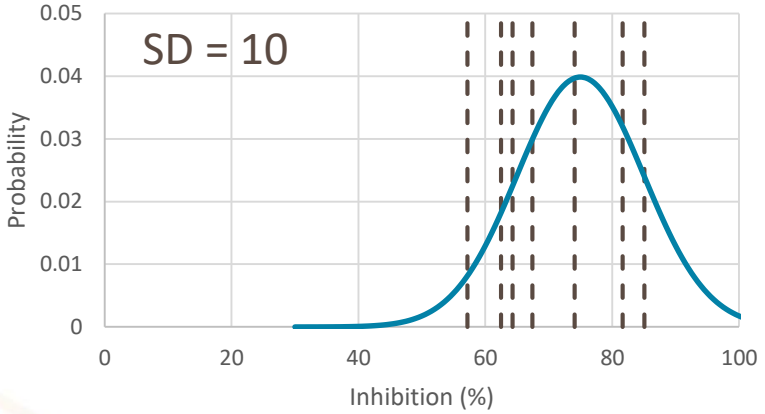


No good drug

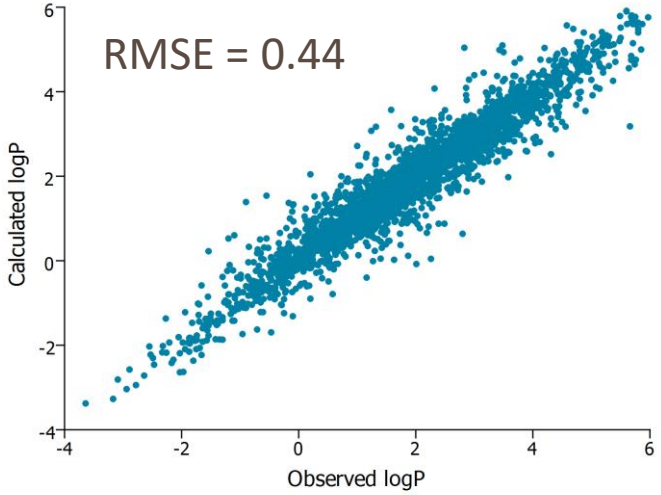
Filtering

Sources of Uncertainty

- Experimental variability



- Statistical uncertainty, e.g. logP



- Relevance, e.g. PAINS*
  - Many compounds with PAINS alerts are not frequent hitters
  - Several successful drugs contain PAINS alerts

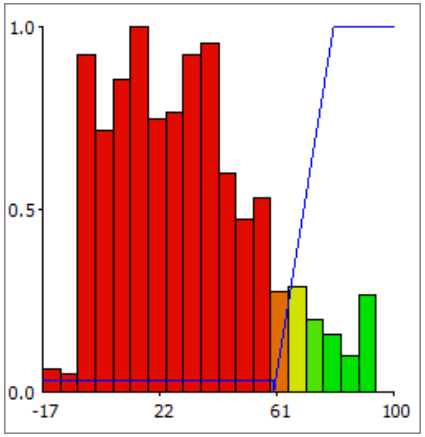
*Capuzzi *et al.* JCIM DOI: 10.1021/acs.jcim.6b00465

Probabilistic Scoring
Scoring Profile

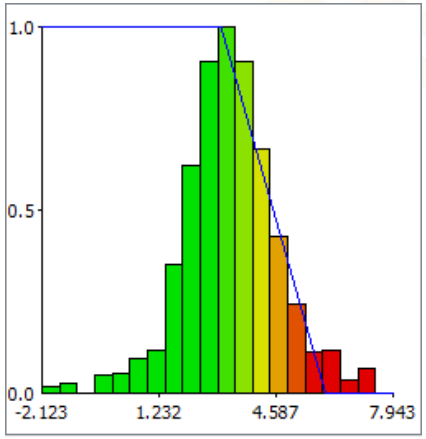
Property	Desired Value	Importance
Inhibition (%)	80 -> inf	
logP	-inf -> 3	
MW	-inf -> 300	
PAINS count	0	

Desirability Functions

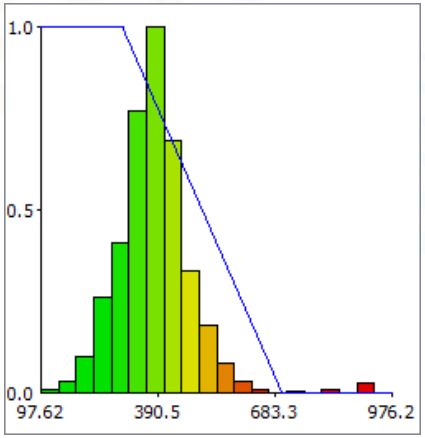
Inhibition (%)



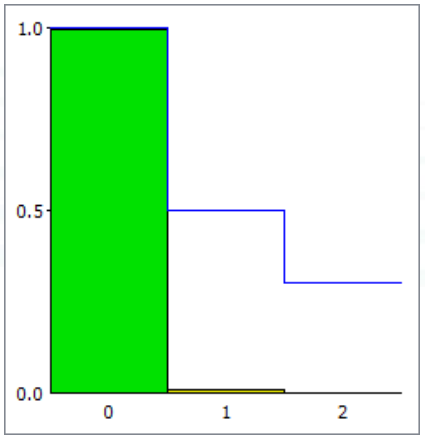
logP



MW



PAINS count



Probabilistic Scoring

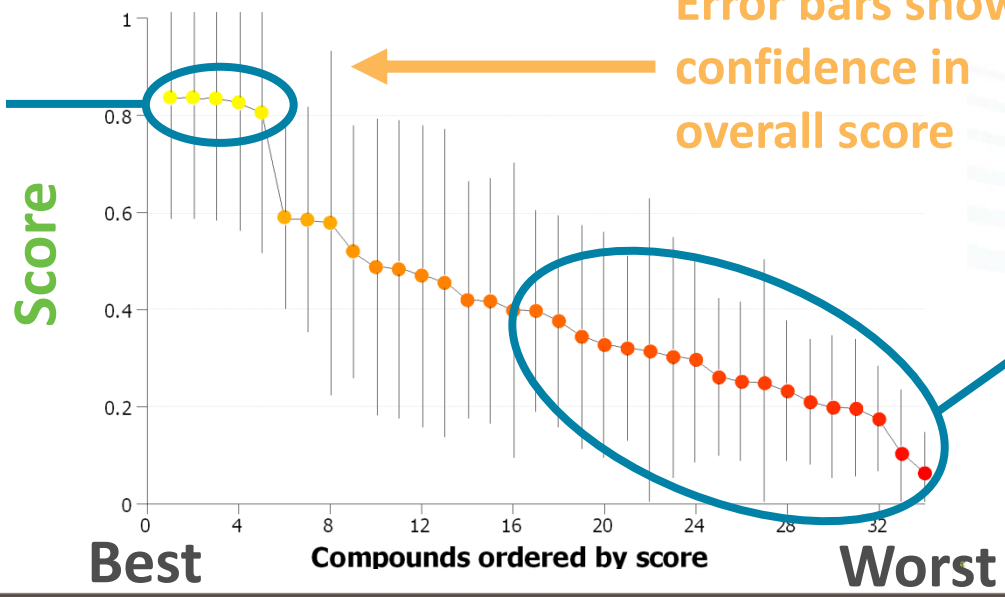
- **Property data**
  - Experimental or predicted
- **Criteria for success**
  - Relative importance
- **Uncertainties in data**
  - Experimental or statistical

- **Score (Likelihood of Success)**
- **Confidence in score**

Data do not separate these as error bars overlap

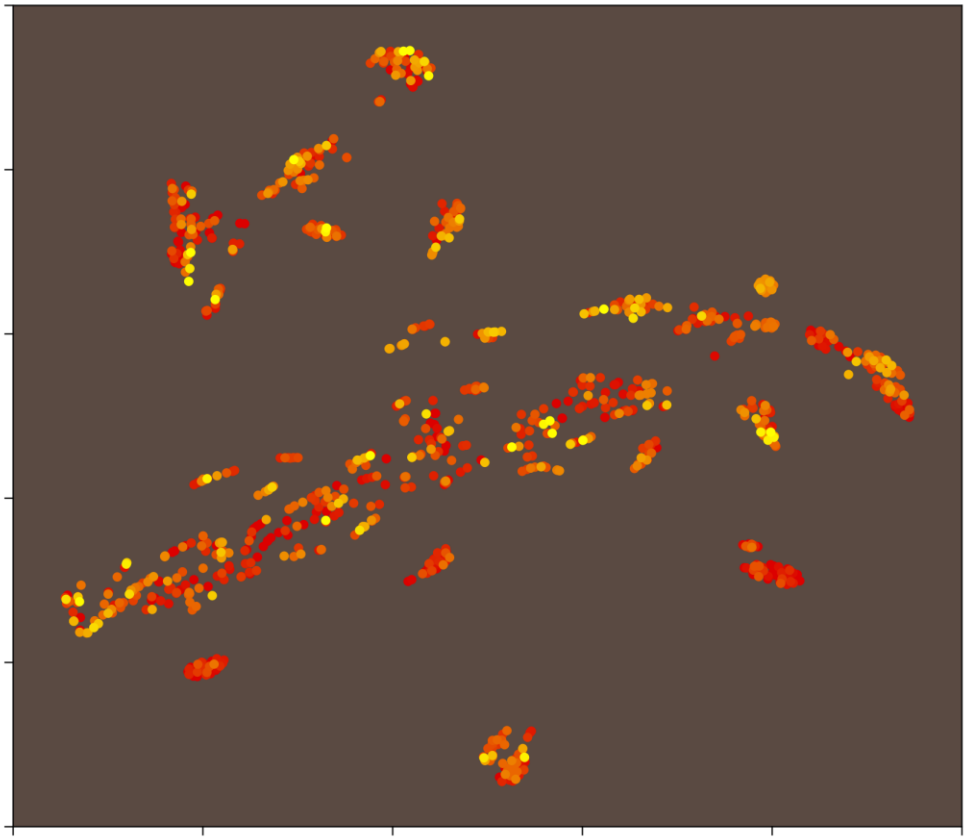
Error bars show confidence in overall score

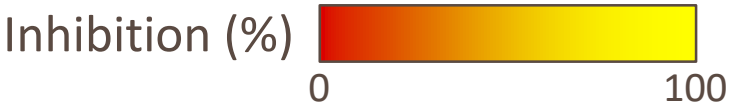
Bottom 50% may be rejected with confidence



M.D. Segall (2012) Curr. Pharm. Des. **18**(9) pp. 1292-1310

Mapping Activity vs Score





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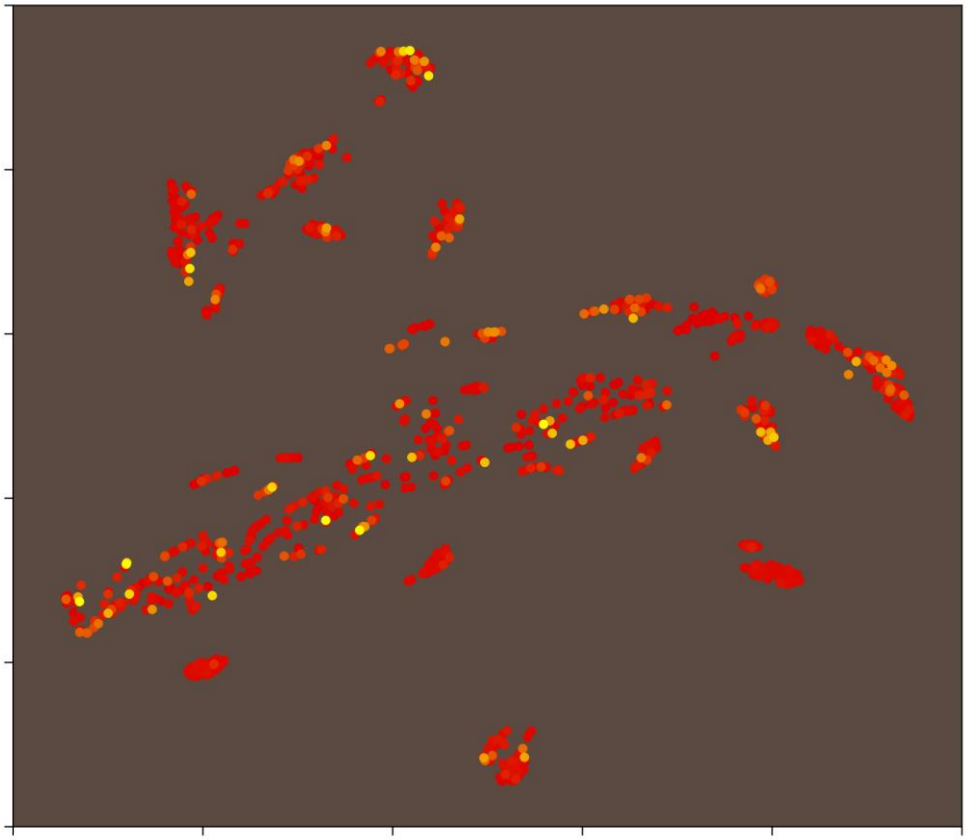
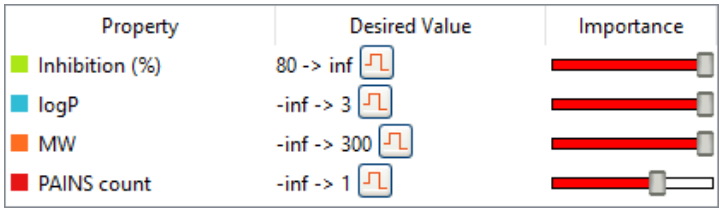
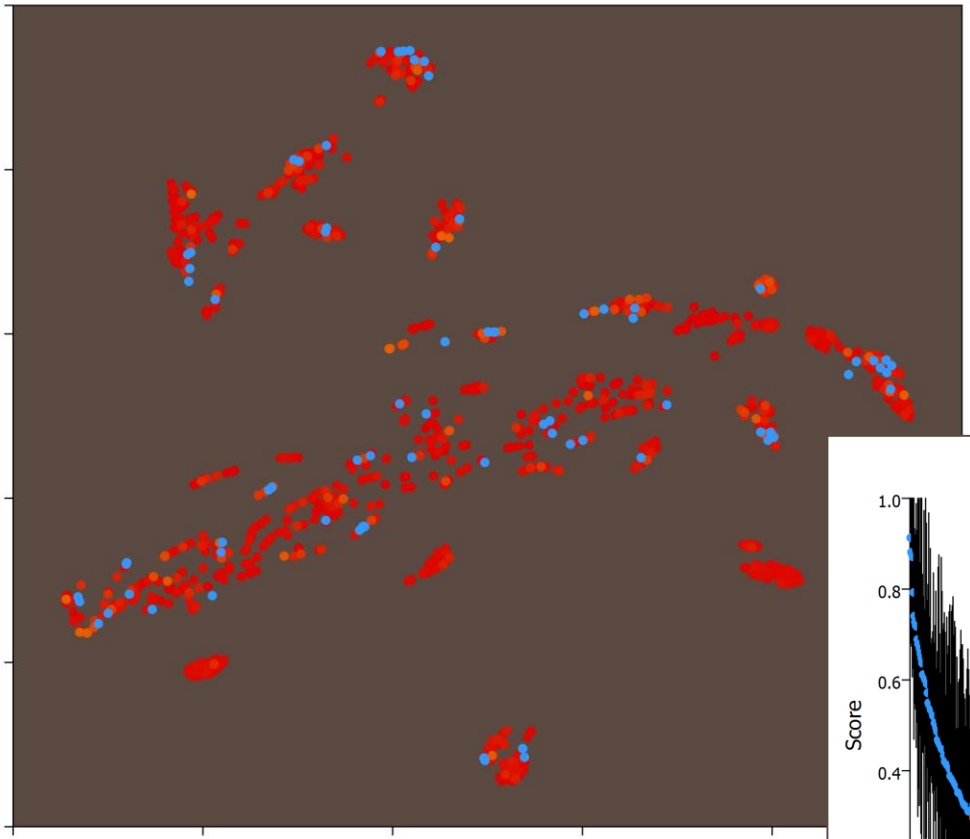
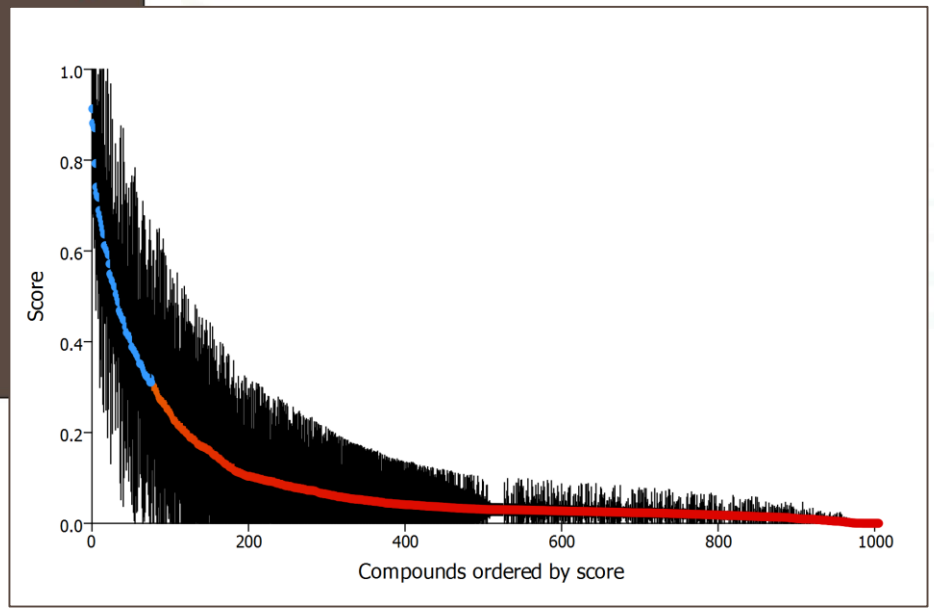




Compound Selection

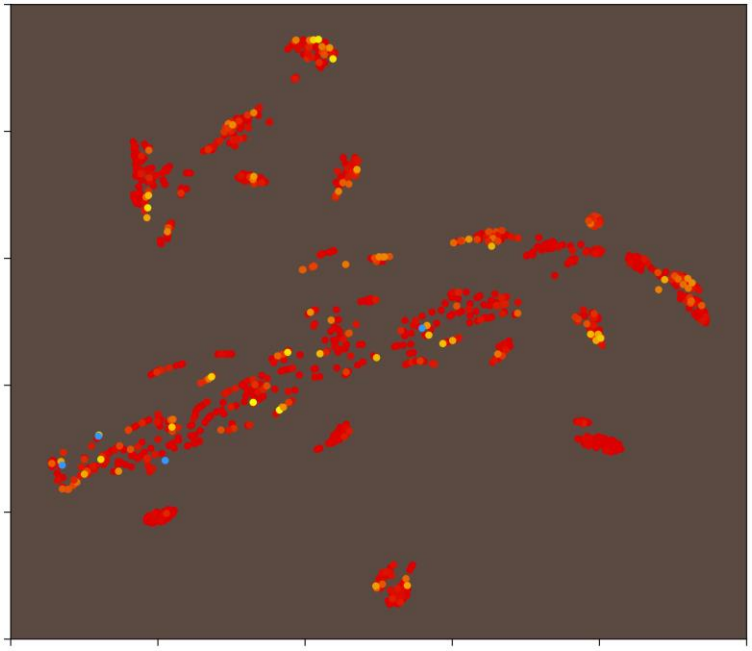


Property	Desired Value	Importance
Inhibition (%)	80 -> inf	
logP	-inf -> 3	
MW	-inf -> 300	
PAINS count	-inf -> 1	



Comparison with Filters

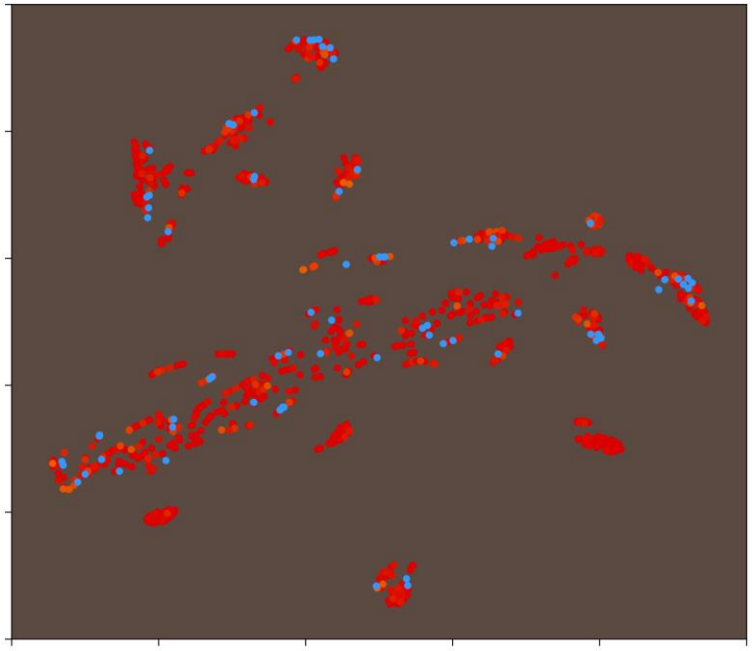
Filtered Compounds



Inhibition (%) > 80
MW < 300
logP < 3
No PAINS hits

} Only 4 compounds!

Scoring Selection



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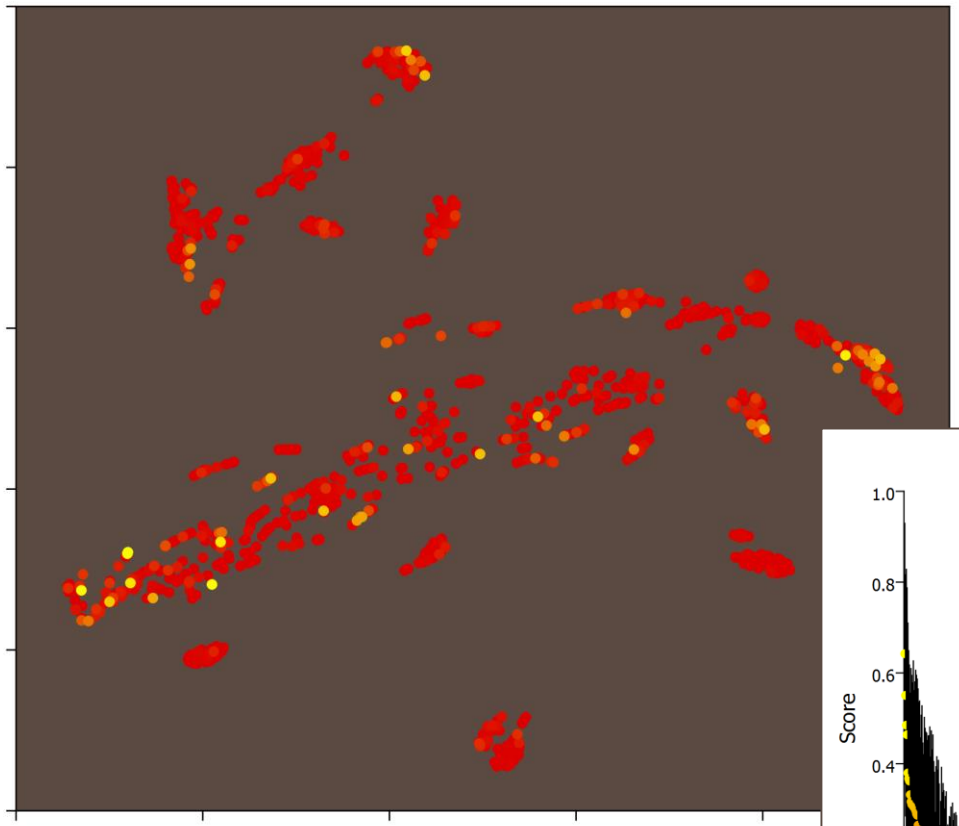
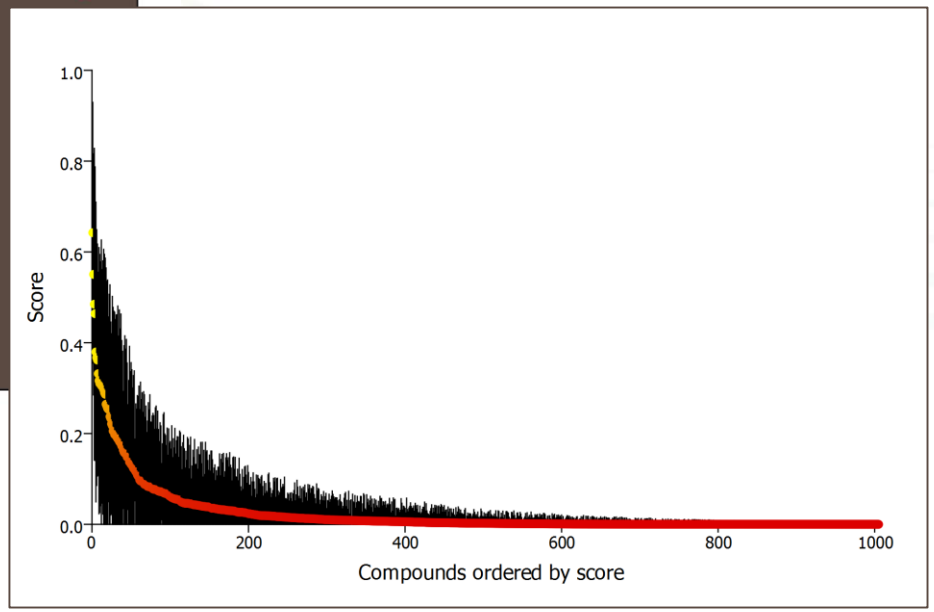
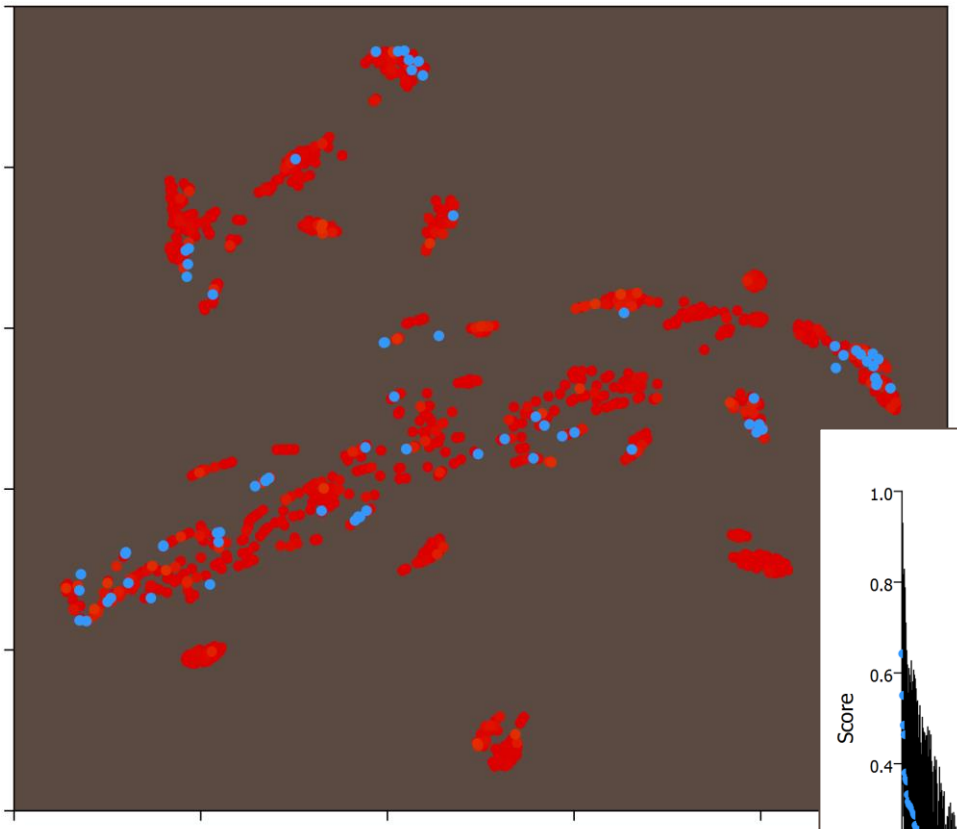
ADME and Potency Profile



Property	Desired Value	Importance
Inhibition (%)	80 -> inf	
logS	> 1	
HIA category	+	
logP	0 -> 3.5	
hERG pIC50	⩽ 5	
2D6 affinity category	low medium	
2C9 pKi	⩽ 6	
P-gp category	no	
PPB90 category	low	
BBB category	-	
BBB log([brain]:[blood])	⩽ -0.5	



ADME and Potency Profile Selection



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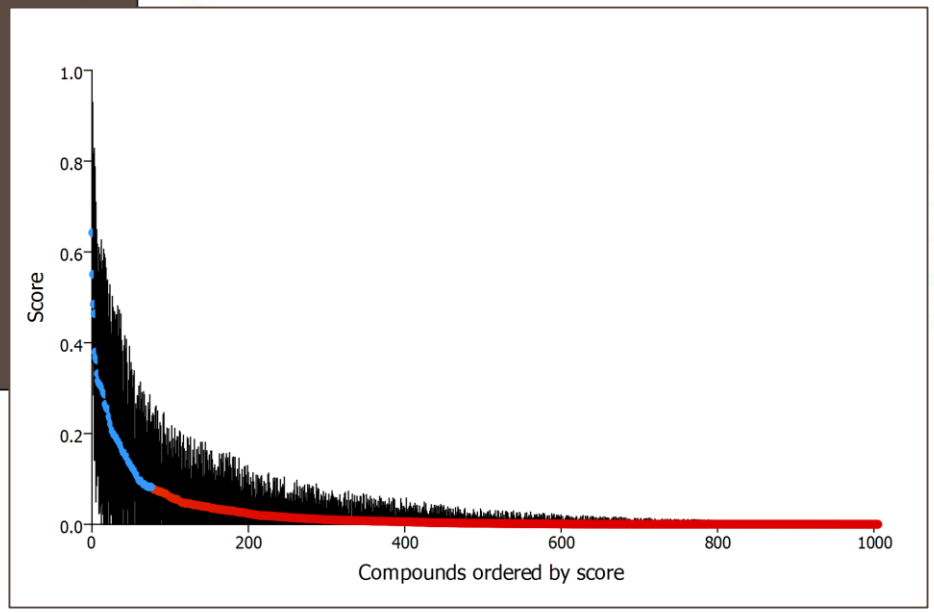
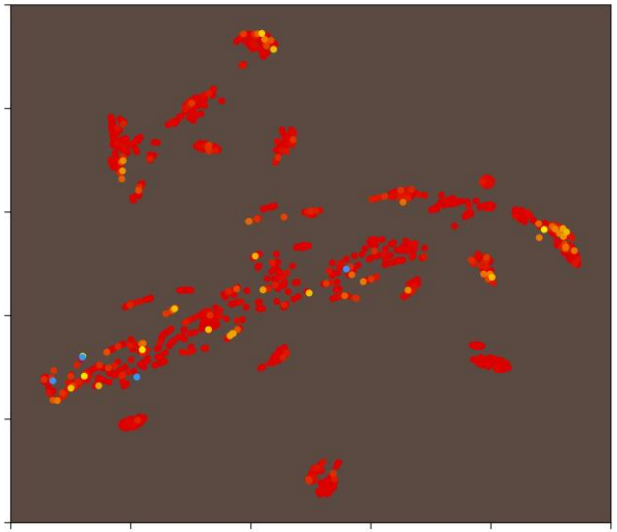


Comparing Selection Strategies

Filtered Compounds



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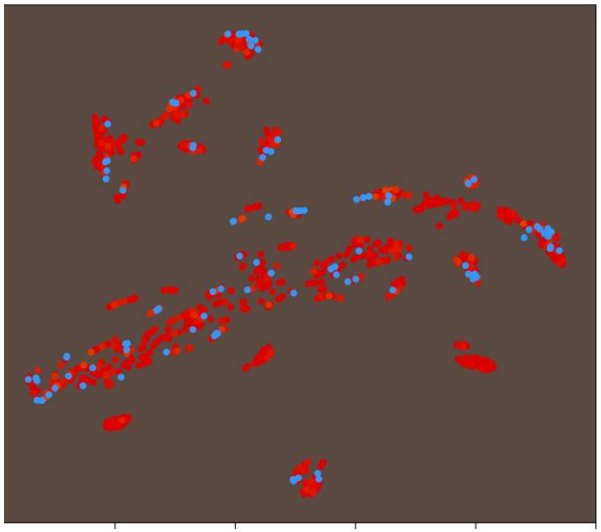
Simple Profile



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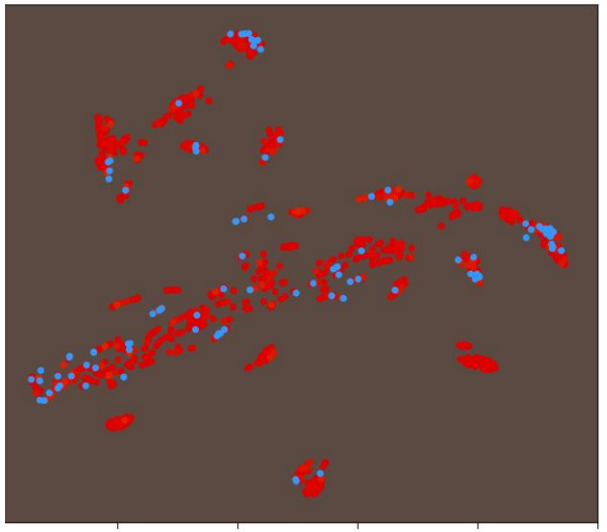
ADME + Potency Profile



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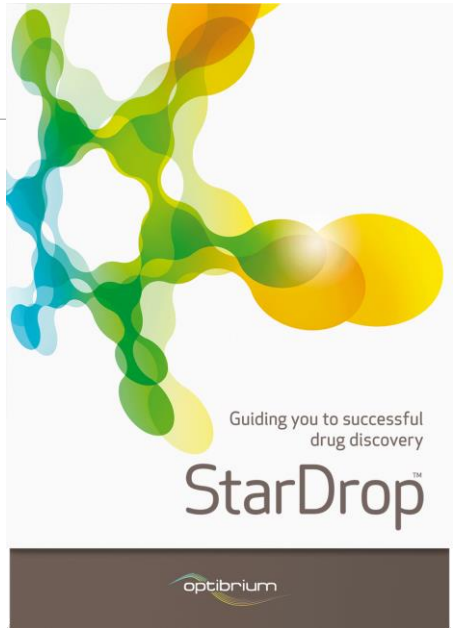
Conclusions



- When prioritising compounds/series from HTS, we should consider:
  - Activity
  - SAR of active series
  - Quality of hits
  - Novelty
- In assessing quality:
  - Be careful of 'hard' filters
  - Optimise the *balance* of properties appropriate for your project
  - Consider the uncertainties in your data – avoid missed opportunities
- Publications can be downloaded from www.optibrium.com/community
- For more information, please visit Booth #1420, go to www.optibrium.com/stardrop or contact info@optibrium.com

Acknowledgements

Colleagues at Optibrium, including:

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- Coran Hoskin
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- Aishling Cooke