Fragment hit prioritisation

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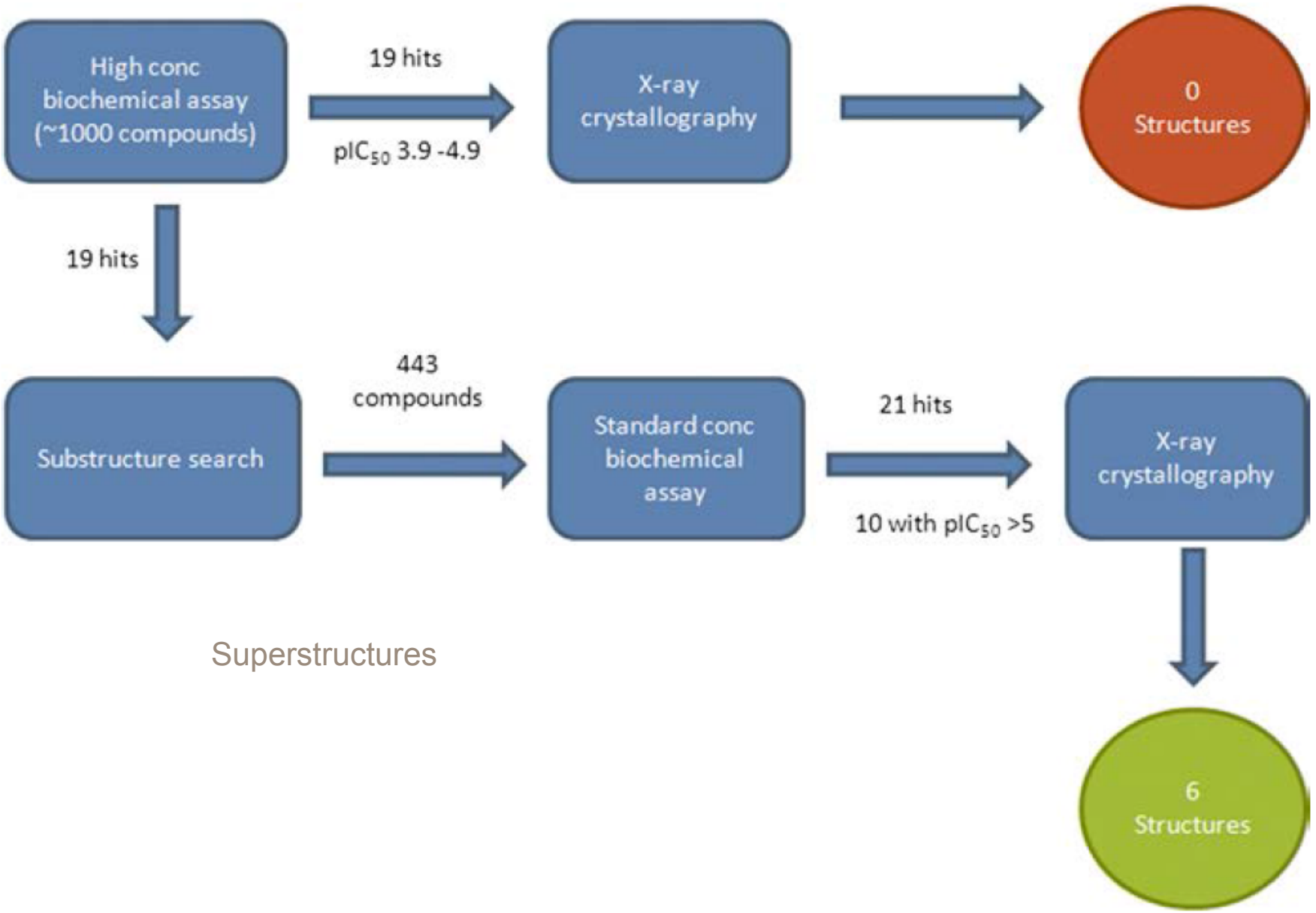
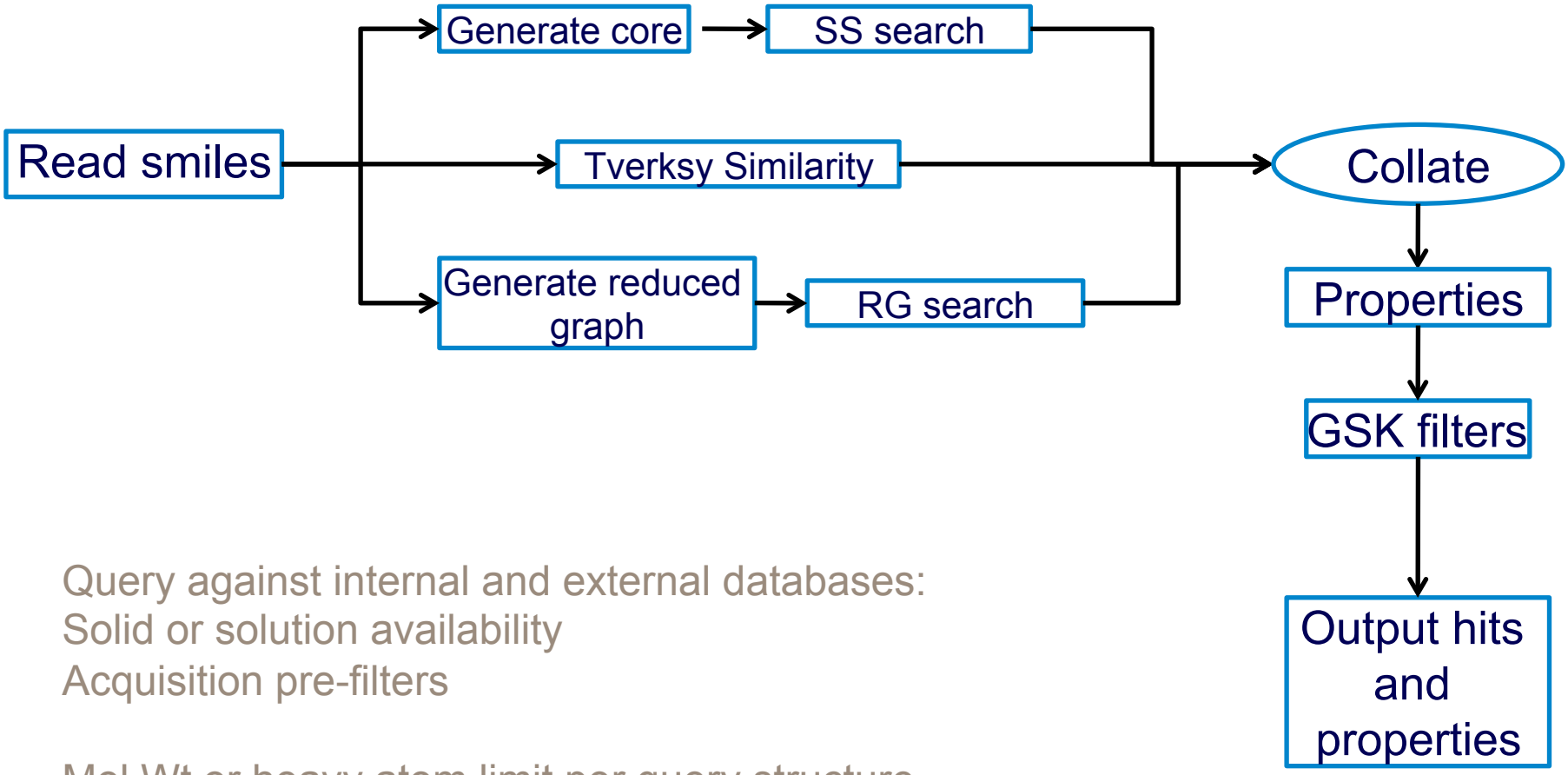
Analogue Searching increases X-ray Success



Superstructures

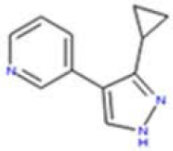
FindAnalogues



Query against internal and external databases:
Solid or solution availability
Acquisition pre-filters

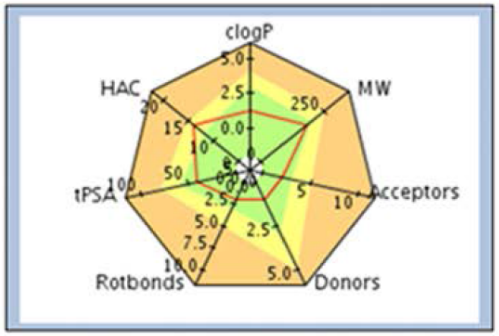
Mol Wt or heavy atom limit per query structure
Total hits per sub-query (most similar or lowest mol wt)

Multi parameter decision making

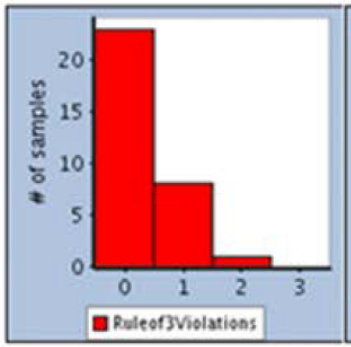


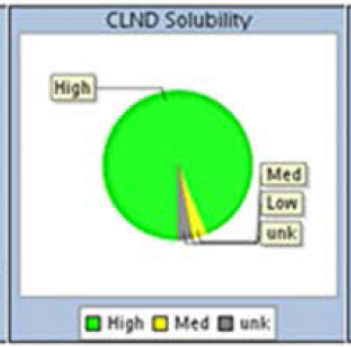
Calculated Properties	
Regno	
mw	185.23
clogP	1.2
tPSA	41.57
NumHeavy	14
Acceptors	2
Donors	1
Rotbonds	2

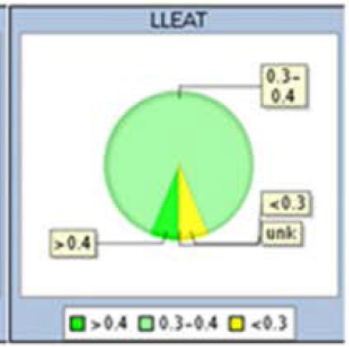
Measured Properties	
Regno	
HPGDS pIC50	4.8
LigEff	0.47
LigEffAT	0.46
CLND_sol	>=391 uM
CHROM_LOGD_PH74	1.6
HSA_PCT_BIND	84.2
AGP_PCT_BIND	53.0



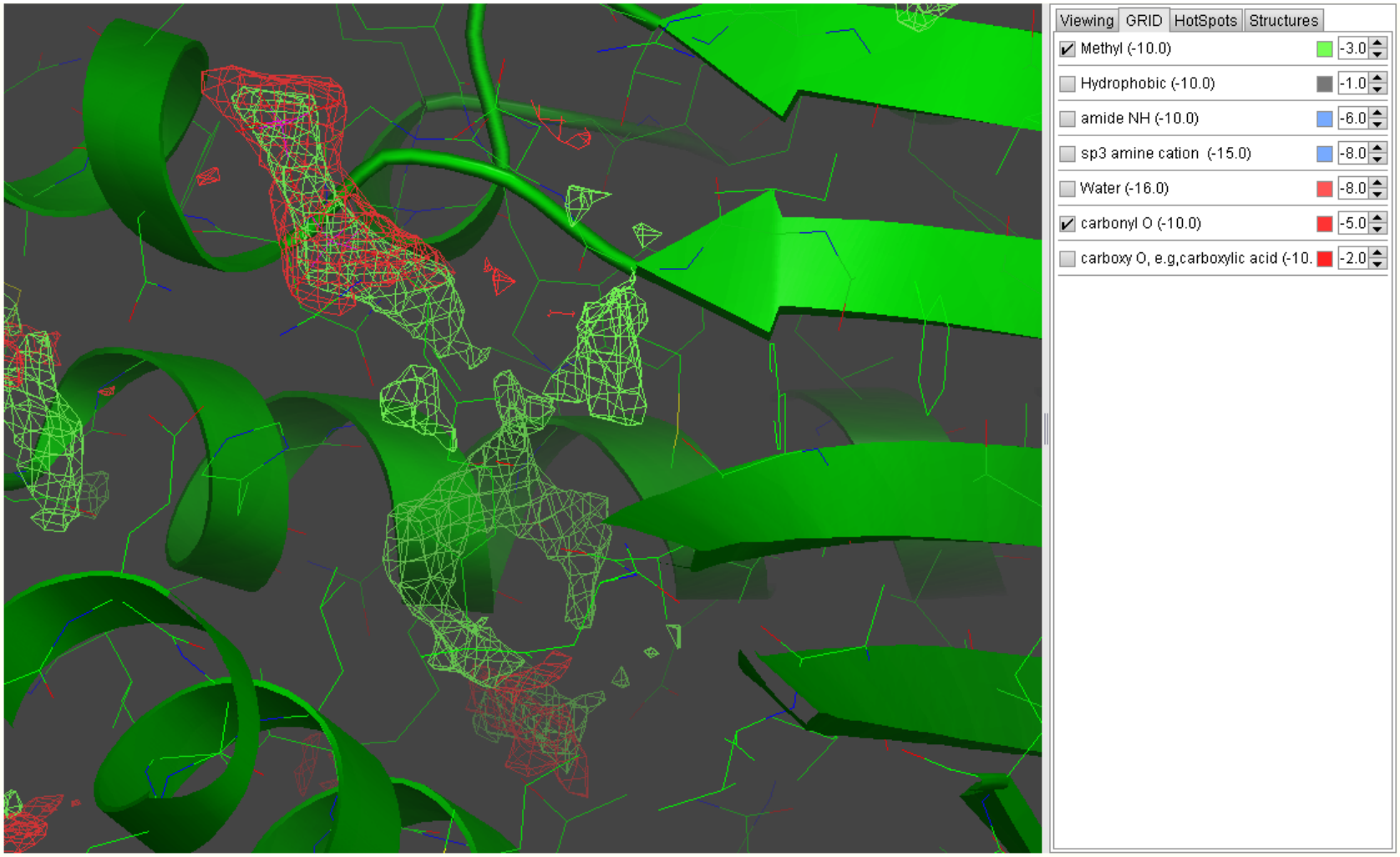
Summary Comments					
Properties of Validated Hit Series	Current data pIC50	LE	LLEAT	Does the series hit the criteria	Comments
LE between 0.3 & 4.3					
Best in cluster					
Clear X-ray binding mode					
Astex rule of 3					
Synthetic tractability					
Expectation that elaborated molecules will be patentable					
Off target effects					
EXP					
Stability data					







Active site mapping (eg GRID)



Hit prioritisation

- Hit validation? (active in orthogonal assays)
- Judge the series not the hit
- Generate as much data as possible to inform decisions
- Potency a consideration, but not the primary factor
- Consider potential for growth
  - Growth vectors
  - Known structures/SAR
  - Hot spotting tools
- Synthetic tractability
- Chemical stability
- Not worried about selectivity at this point

Fragment to Lead

- Collect all screening data before committing to work on a series
- Screen available analogues to generate SAR before starting chemistry
- Core optimisation (most LE starting point)
- Grow slowly
- Monitor properties (use of LE, LLE, etc.)
- Use of structure based design to drive chemistry plans
- Growing and hybridisation preferred to linking fragments
- Avoid flat highly aromatic compounds

Was my change “worthwhile”?

- Required potency change to maintain LLE_{AT} for common aromatic substituents