Fragment-Based Screening, What can we learn from published hits?

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Fragment-Based Screening

- Fragment-based screening has become increasingly popular and has proven to be a viable alternative to high-throughput screening.
- Fragment space is smaller
  - A million compounds cover only a small fraction of the suggested 10^{60} Chemical Space, whilst 2000 compounds can probe much of the 10^{6} Fragment Space
- Hit rates for Fragment-based screening appear to be higher, typically 3-10%.
- Binding Efficiency for small molecules is likely to be higher.

Design of the Fragment Library

- Several approaches have been described in the design of fragment libraries. Most comply with the commonly accepted Astex "Rule-of-Three"
  - MW <300, H-bond donors/acceptors <=3, cLogP <3.
- Solubility is key requirement since screening carried out at higher concentrations
  - Often overlooked
- Rather than simply cull available molecules there have been recent attempts to design libraries based on known drugs, PDB ligands, natural products, or enhanced 3D structure.

What can we learn from known fragment hits?

- Compile database of published hits from fragment screens.
- Include:-
  - Screening technology
  - Target and Uniprot ID
  - Target type, using ChEMBL ontology
- Calculate
  - Physicochemical properties
  - LogP, LogD, PSA, HBA, HBD, RotB, pKa, shape descriptors, MR, HAC, fraction aromatic. (ChemAxon, MOE)
  - Functional groups (Checkmol)

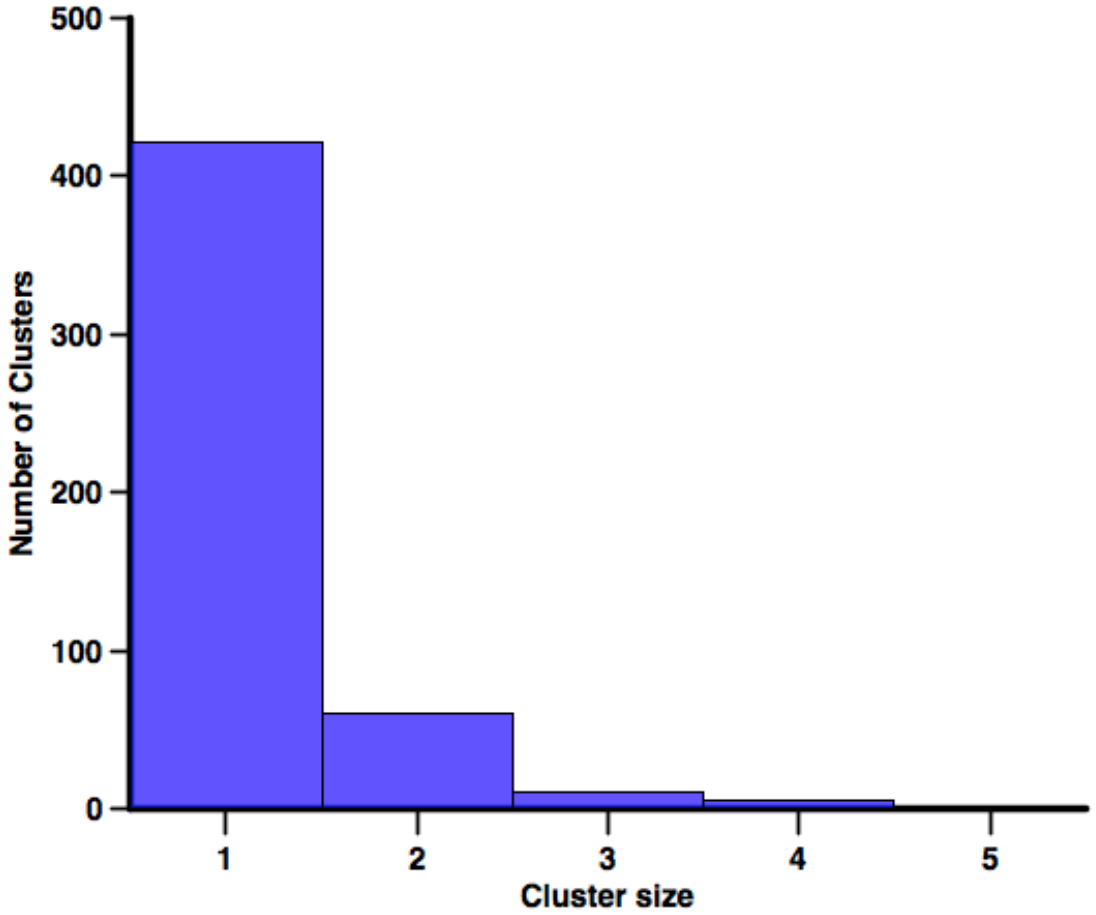
Current Status (4 November 2013)

- 165 Publications
- 620 Published hits
- 116 Different targets
- 19 Detection technologies

- Finding the data is getting more of a challenge, it seems as fragment screening becomes more mainstream it is often not mentioned in the title or abstract.

Diversity

- Clustered using MACCS fingerprints in MOE. Tanimoto 0.85
- Majority are singletons
- Diverse fragments for same target



Suppliers of hits

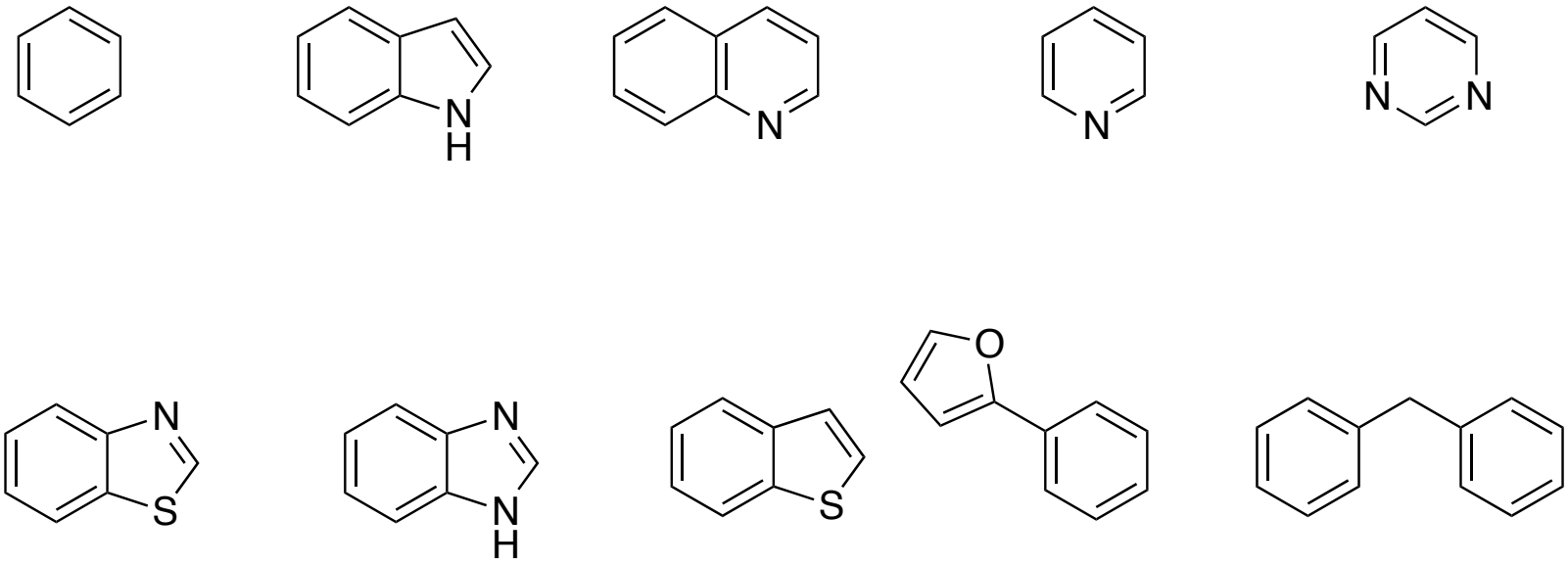
	PubFragAllData.mdb
MaybridgeAll.mdb	158
Maybridge_2500_Feb2013.mdb	96
LifeChemicals_frags.mdb	47
Otava.mdb	44
Specs.mdb	41
KeyOrganicsAll.mdb	37
Enamine_frags.mdb	37
Selcia_Frag_Library.mdb	30
Prestwick.mdb	29
Vitas.mdb	24
ChemDiv_Feb2013.mdb	19
ChemX.mdb	15
TimTec.mdb	13
Chembridge_frags_feb2013.mdb	9
KeyOrganicsBionetPrem.mdb	8
Enamine_Golden.mdb	4
LCZenobia.mdb	3
Asinex.mdb	3
3DFragConsortium.mdb	1
WuXi_frags_Feb2013.mdb	0
Pyxis.mdb	0
Infarmatik3D.mdb	0
Analyticon.mdb	0

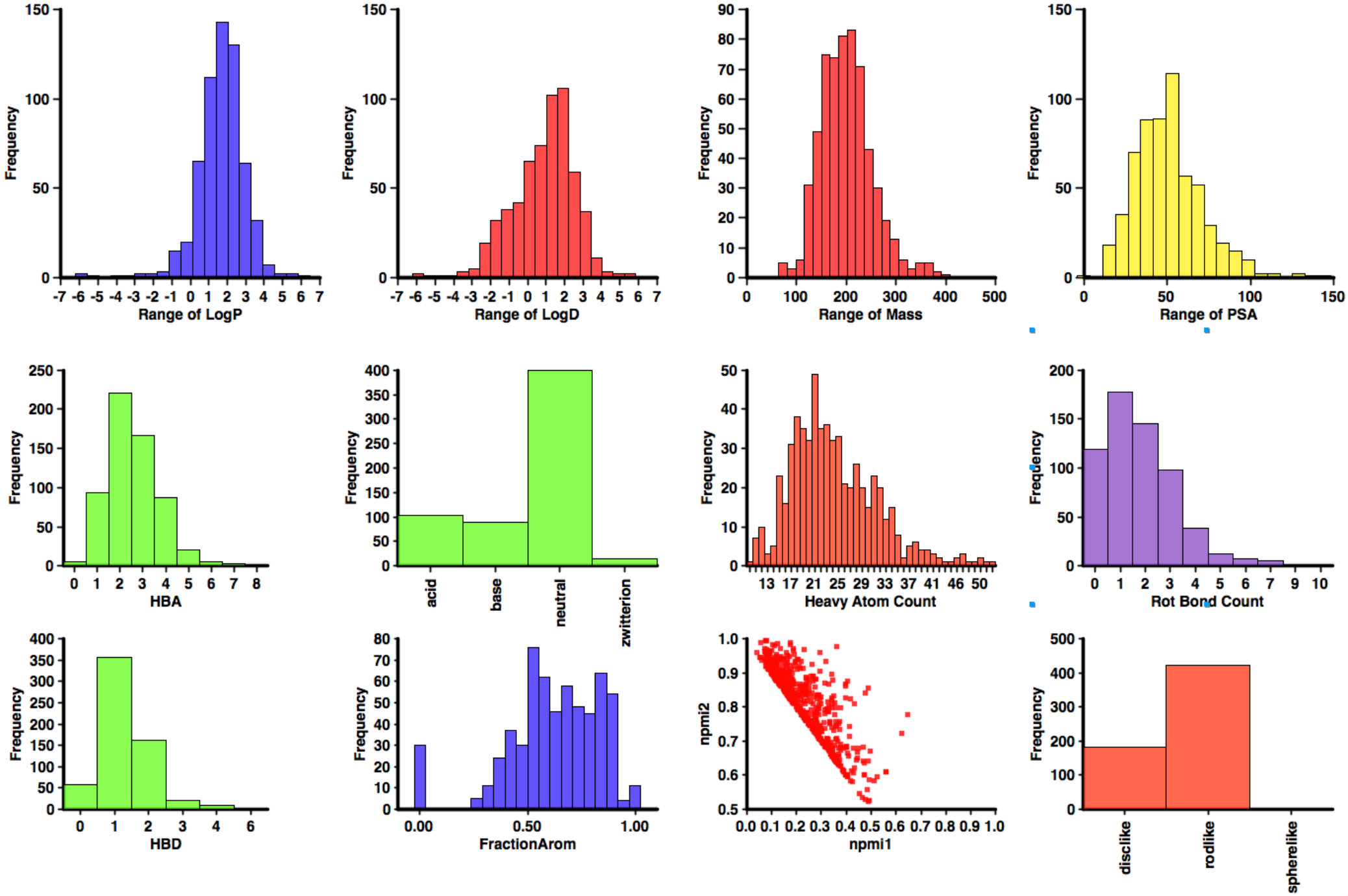
Maybridge are by far the most popular supplier
First major supplier to check solubility of fragments

Functional Group Analysis

- 590/620 contain an aromatic ring, 488 of which are heterocylic
- 131/620 contain an arylhalide
- 117 contain an acidic group, 103 a basic group
- 15 contain a nitro group
- 115 contain a hydroxy, 72 an ether
- 231 contain an amine, 120 “anilines”
- 76 amides, 29 esters, 15 ureas

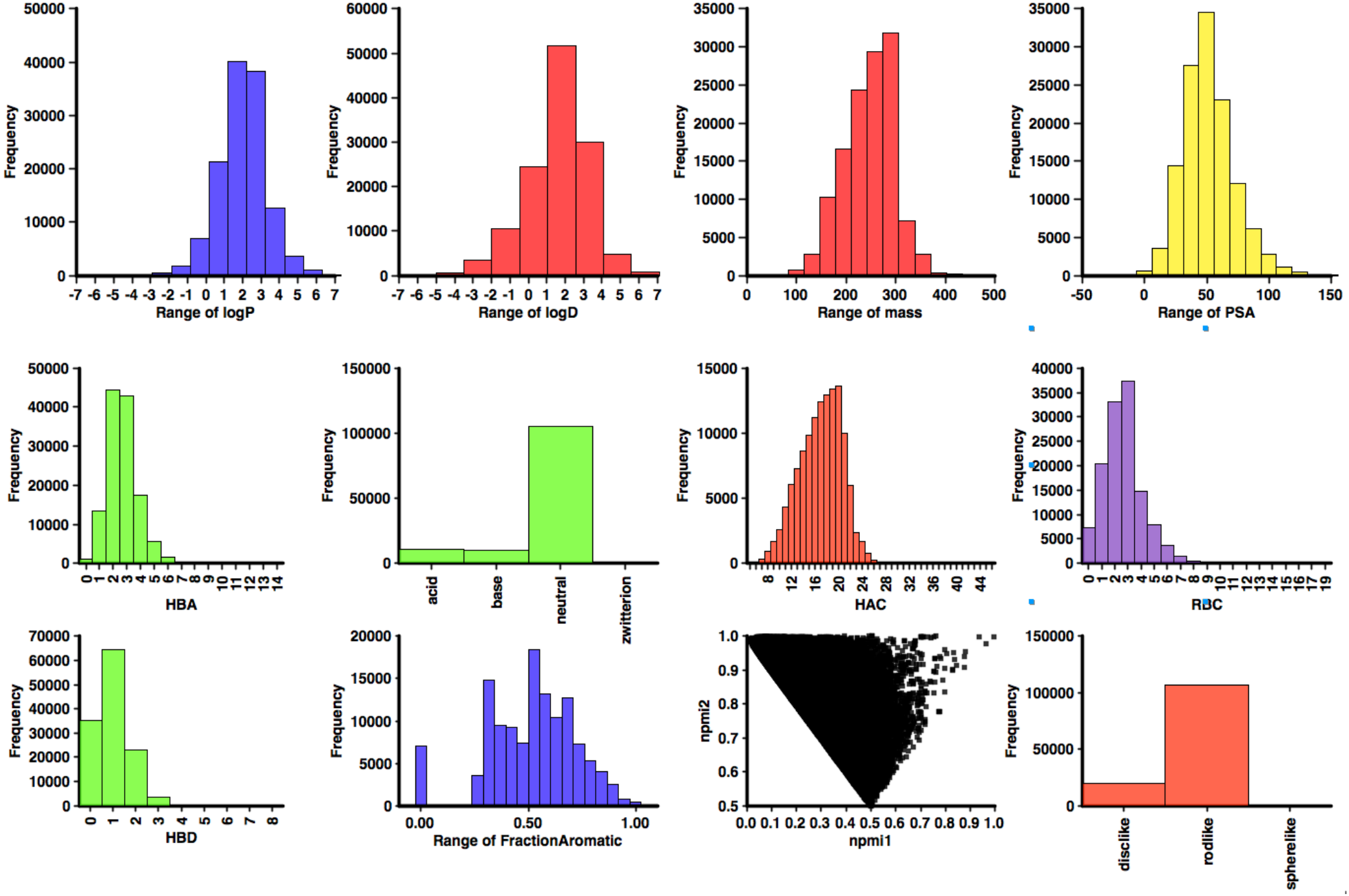
Most common scaffolds



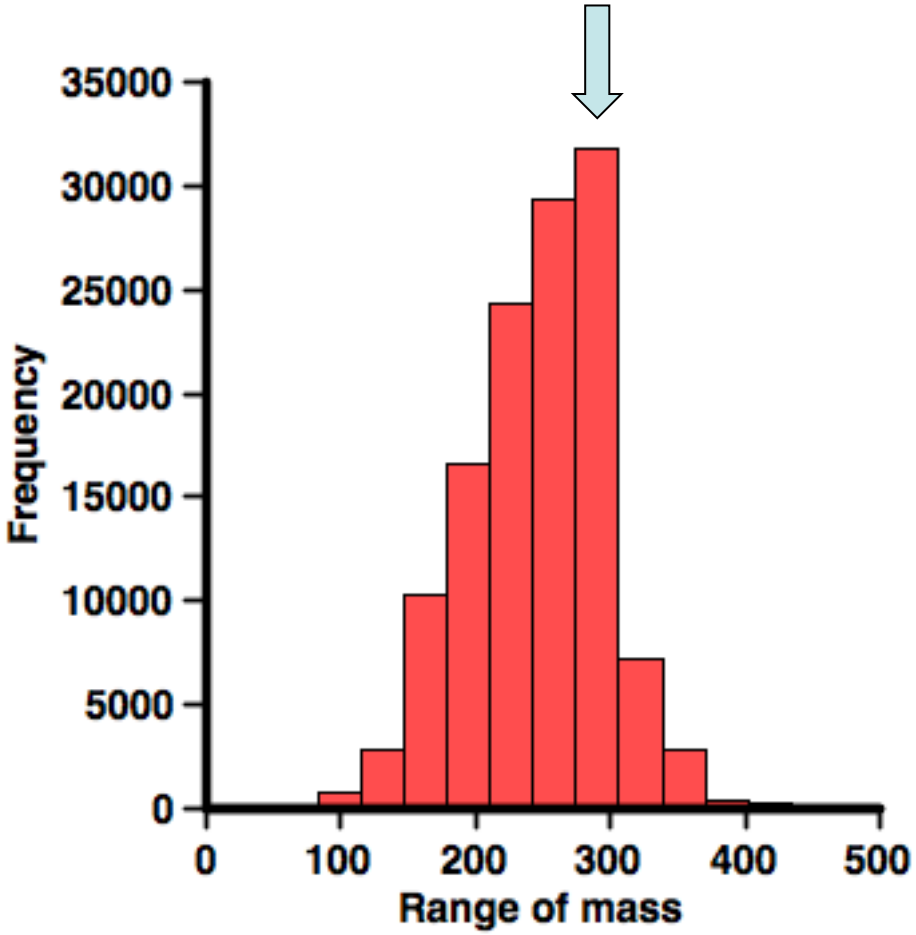

Frequency
Range of LogP
Range of LogD
Range of Mass
Range of PSA
HBA
acid
base
neutral
zwitterion
Heavy Atom Count
Rot Bond Count
HBD
FractionArom
npmi2
npmi1
disclike
rodlike
spherelike

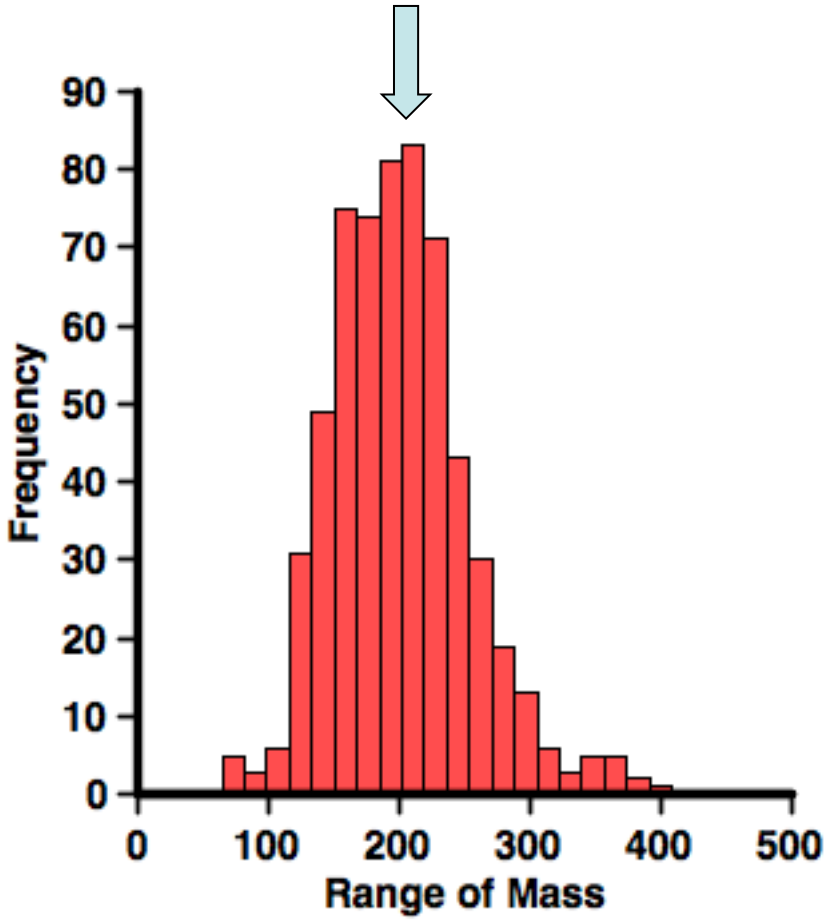
You can only test what is available

- Some papers describe the source of the screening compounds, many do not.
- Looking at the hits we can make a guess at the likely source of the screening collection used.
- Use same tools to calculate profile of putative screening compounds.


Frequency
Range of logP
Range of logD
Range of mass
Range of PSA
HBA
acid
base
neutral
zwitterion
HAC
RBC
HBD
Range of FractionAromatic
npmi2
npmi1
disclike
rodlike
spherelike

Comparison of Molecular Weight

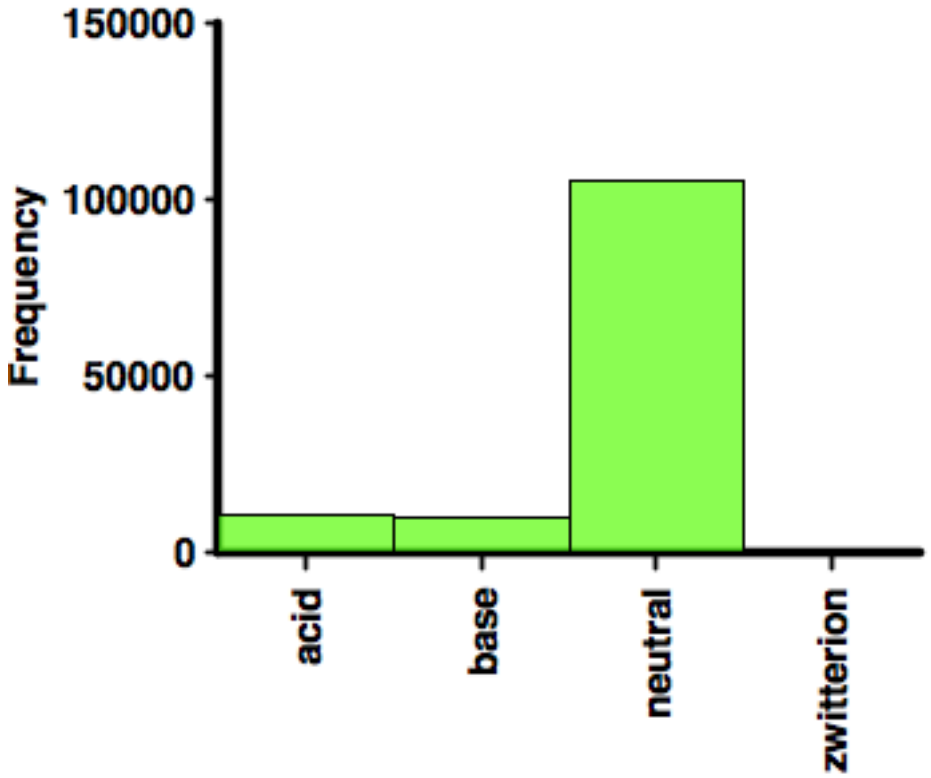




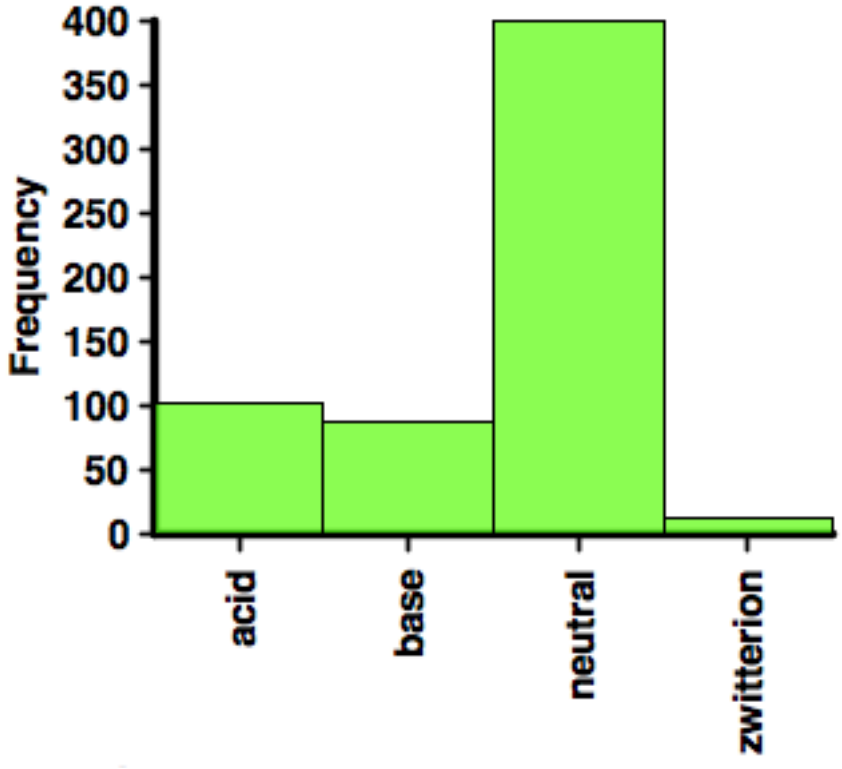
"Screening Collection"

Hits

Comparison of ionisation

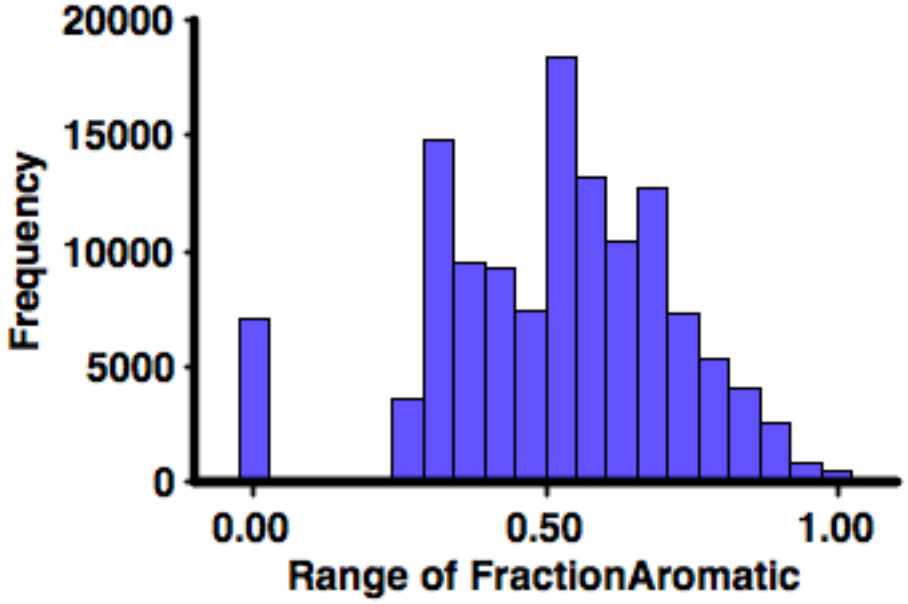


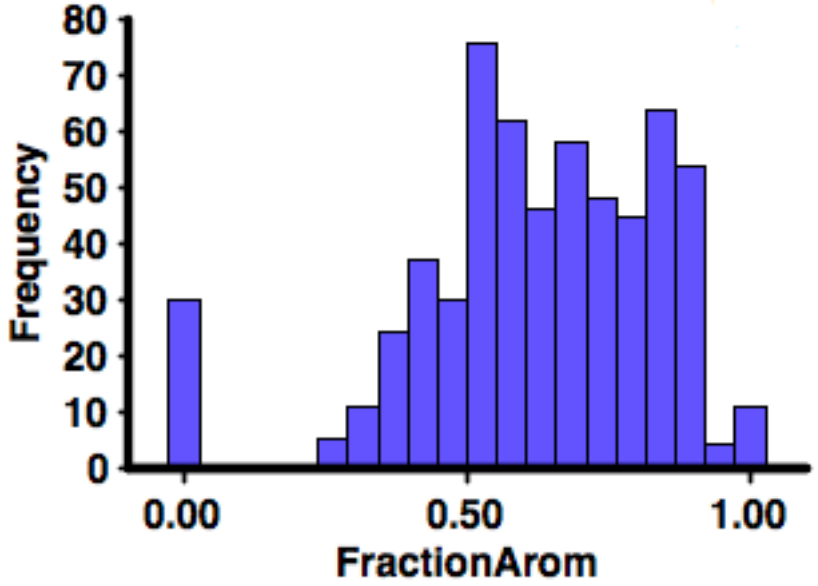
“Screening Collection”



Hits

Comparison of Aromaticity

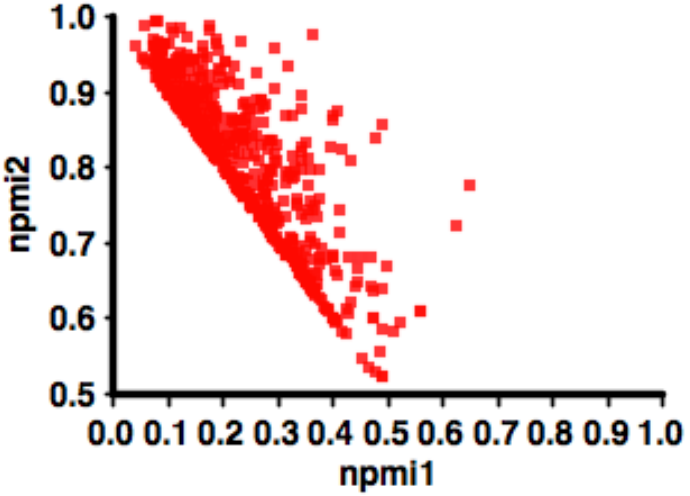


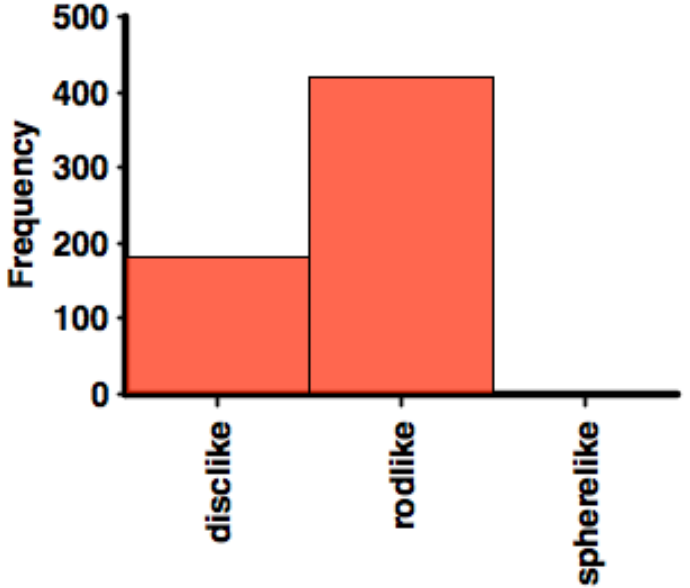


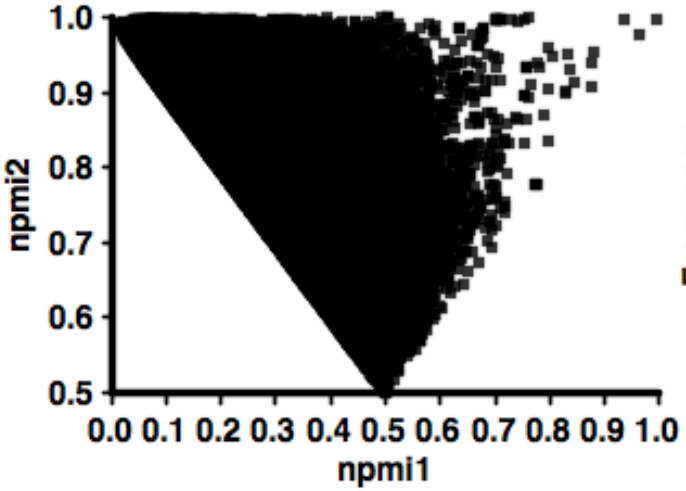
"Screening Collection"

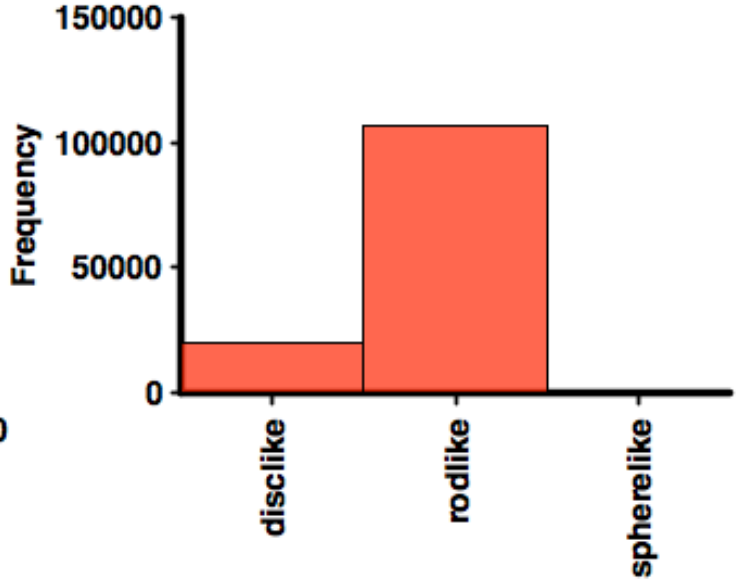
Hits

Comparison of Shape





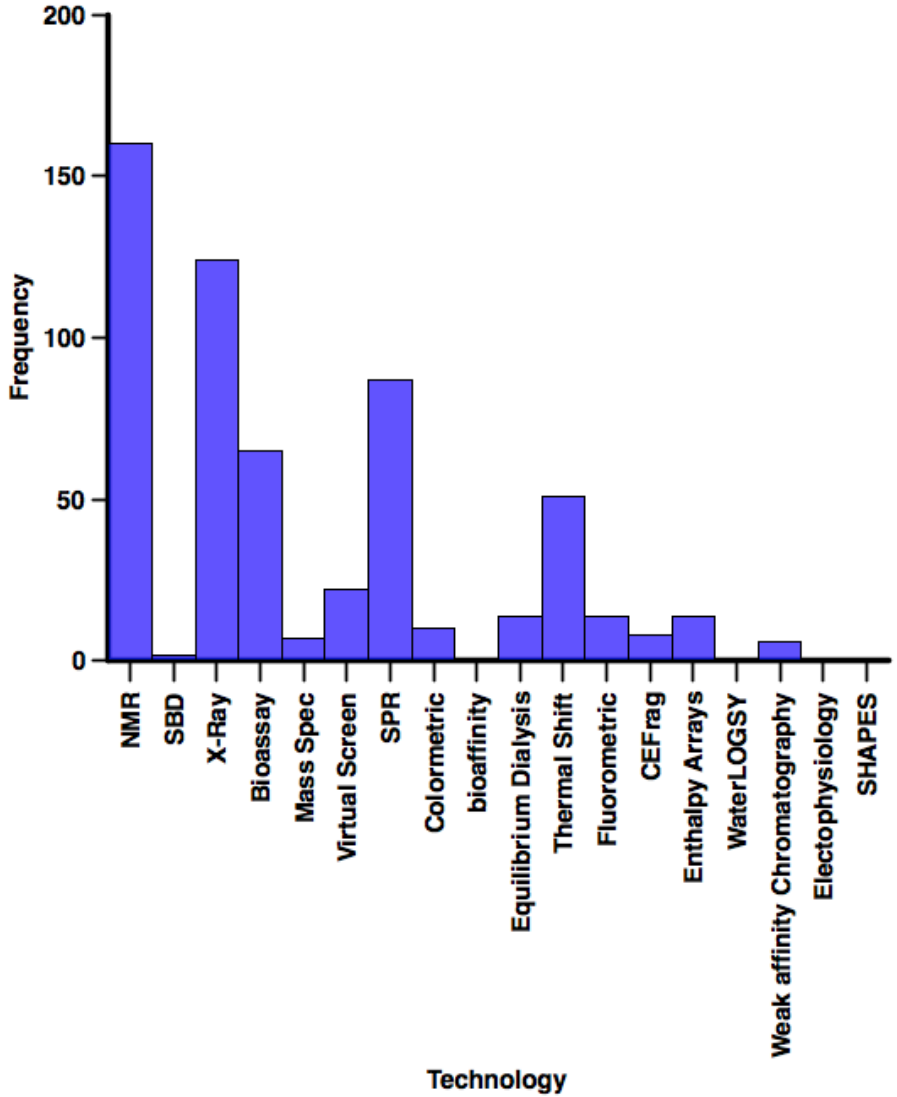


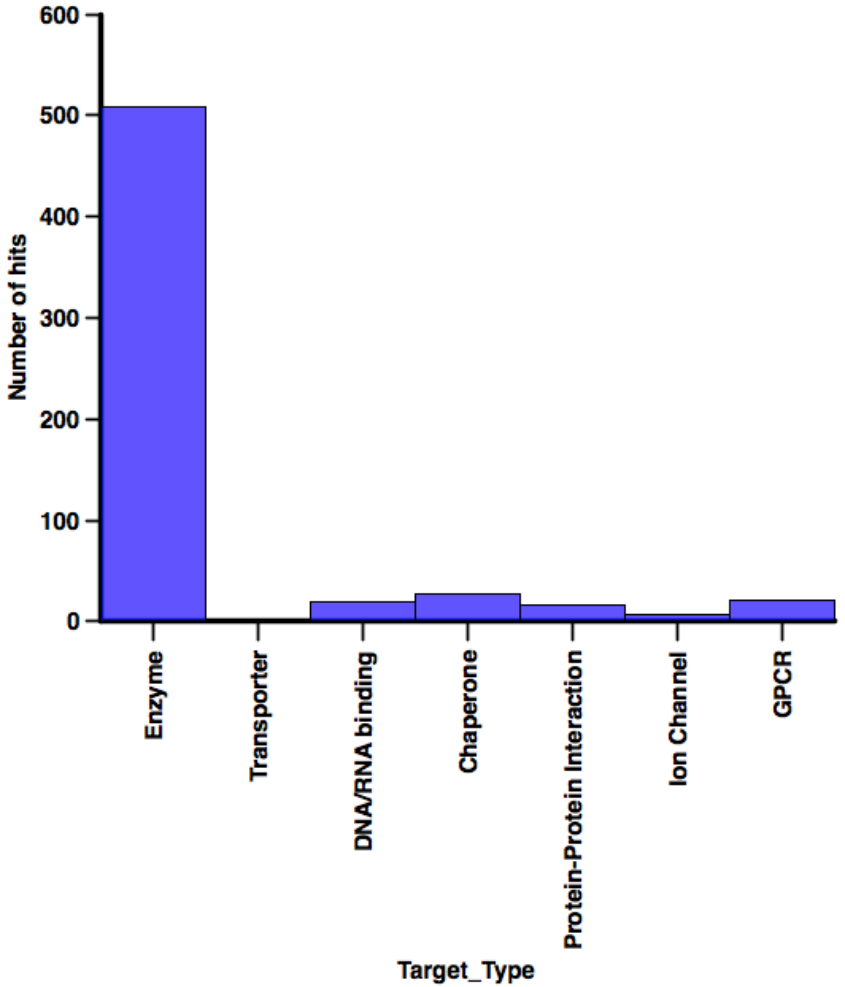


Conclusions

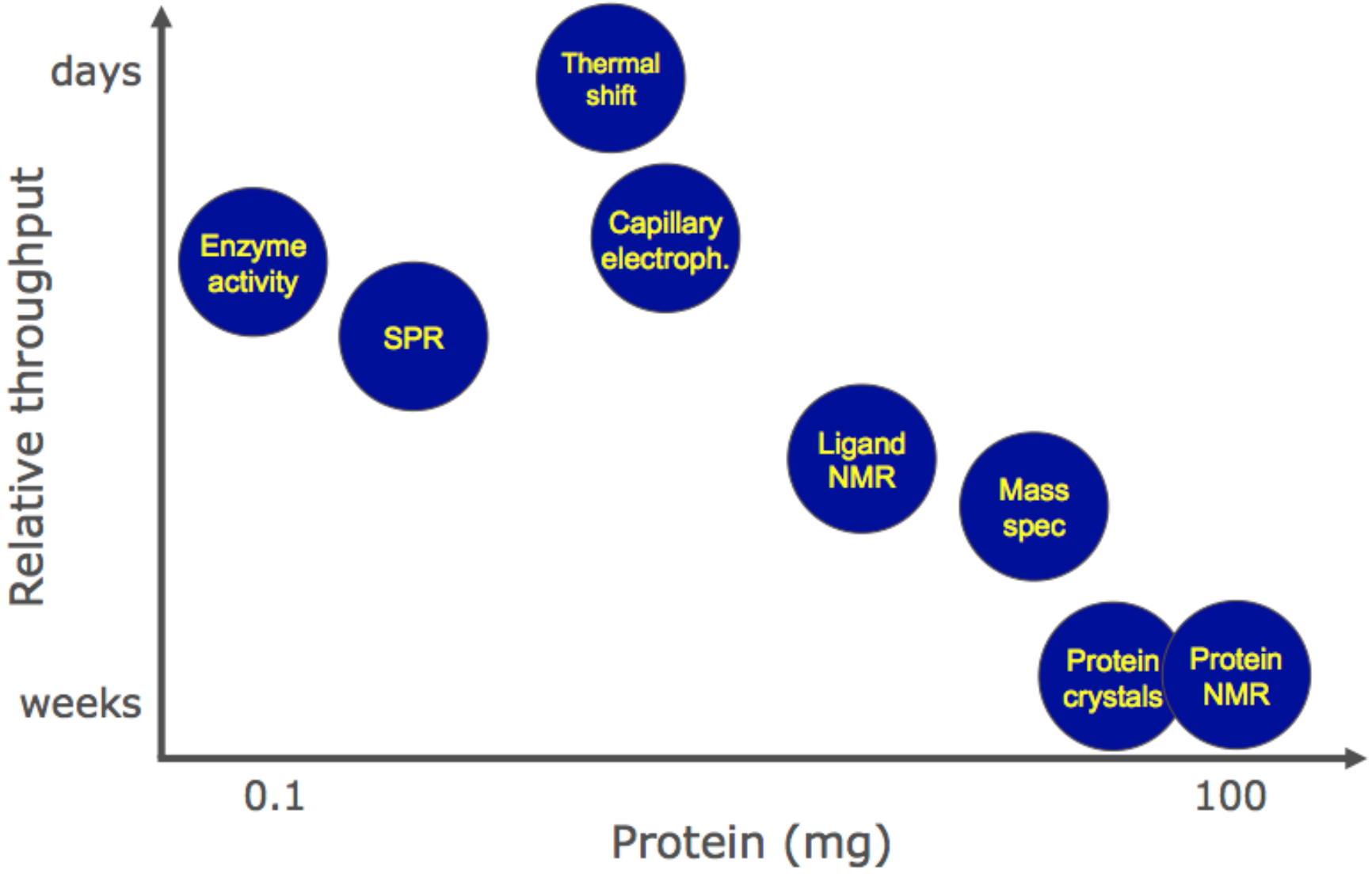
- Published fragments are lower molecular weight
- They contain a greater proportion of ionisable groups
- They contain a greater proportion of aromatics rings
- They contain a greater proportion of “disc-like” shaped molecules
- The role of increased 3D shape is unproven.

Detection technology and target type

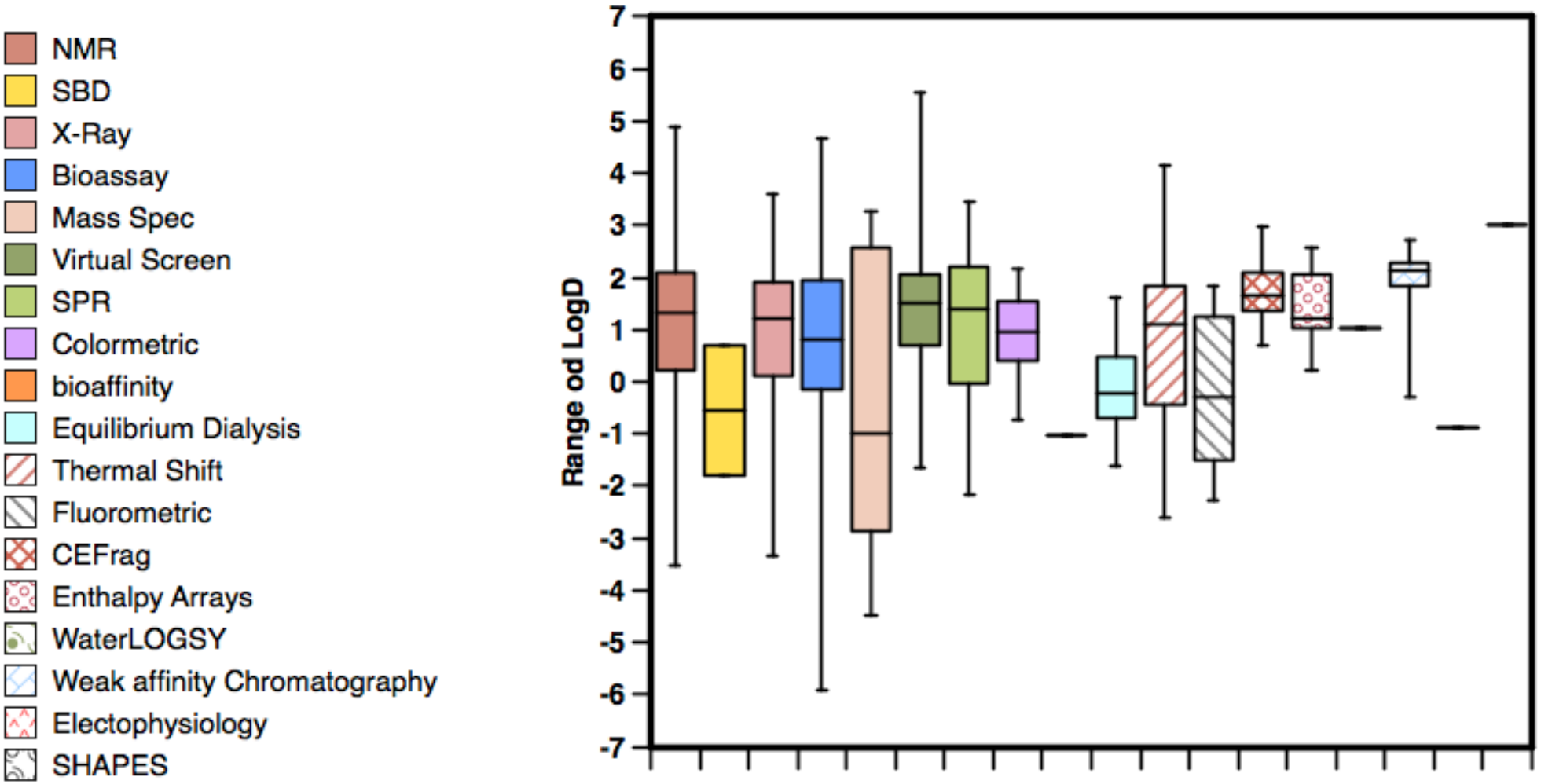




Choice of technology



Detection Technology



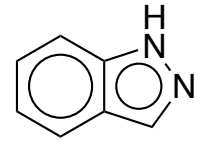
Detection Technology

- Evidence from literature that different technologies can identify hits for a single target.
- No evidence that detection technology influences the physiochemical properties of the hits identified.
  - Some technologies (e.g. SPR) are thought to have a higher false positive rate.

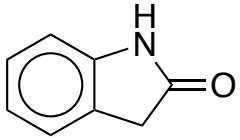
Multiple targets

- Over 80 fragment hits have been shown to be active against multiple targets.
- Whilst a few are active against similar targets (e.g. kinases), many are active against seemingly unrelated proteins.

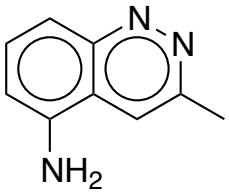
Fragments active against multiple targets



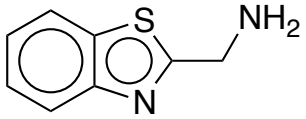
CDK2
DNA Gyrase



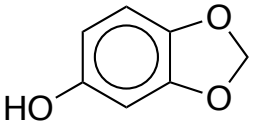
Inositol-3-phosphate synthase
DNA Gyrase



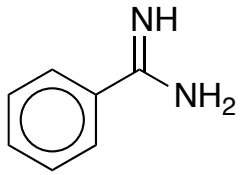
Inositol-3-phosphate synthase
thymidylate synthase



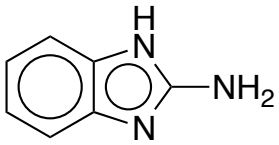
Inositol-3-phosphate synthase
ASIC3



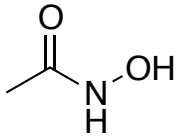
Inositol-3-phosphate synthase
HIV Integrase



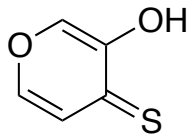
Factor Xa
Urokinase
Tryptase
Thrombin



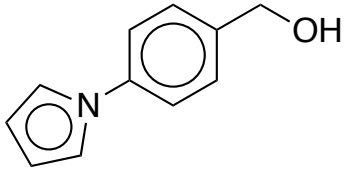
phenylethanolamine N-methyltransferase
Urokinase
Tryptase



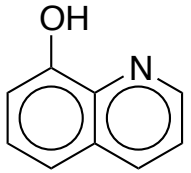
MMP-2
anthrax lethal factor
tyrosinase
Stromelysin



MMP-2
anthrax lethal factor
tyrosinase

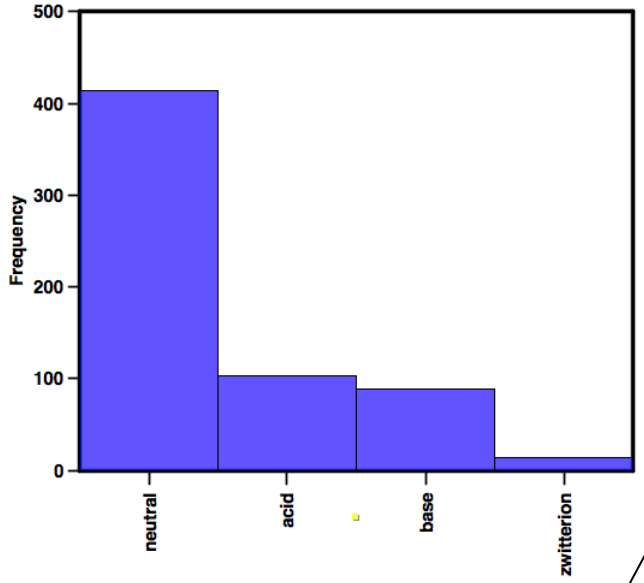


Inositol-3-phosphate synthase
Trypanosoma brucei Choline Kinase



HIV-1 Integrase-Lens Epithelium-Derived Growth Factor/p75 (IN-LEDGF/p75) Interaction
MMP-2

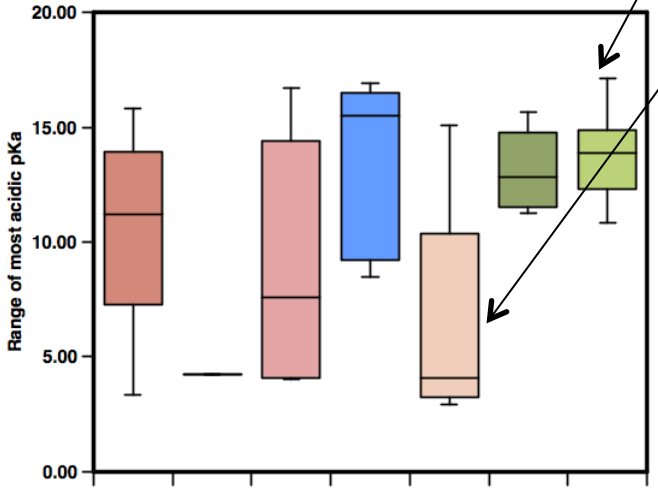
Effect of pKa and Target Type

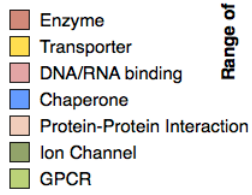


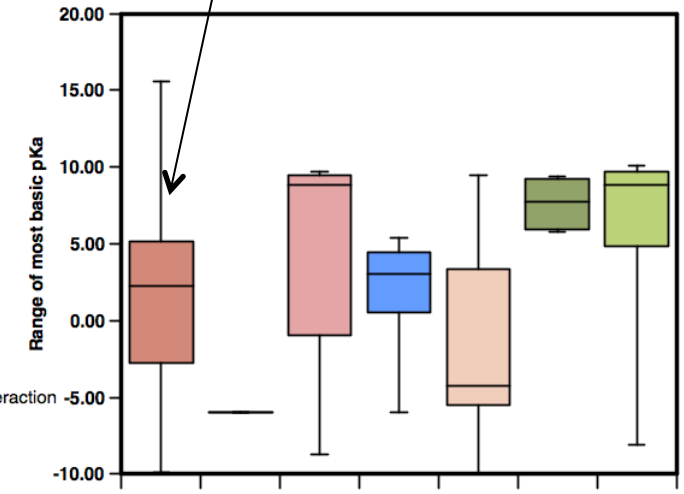
Ion Channel and GPCR no acids but number of basic

PPI mainly acids

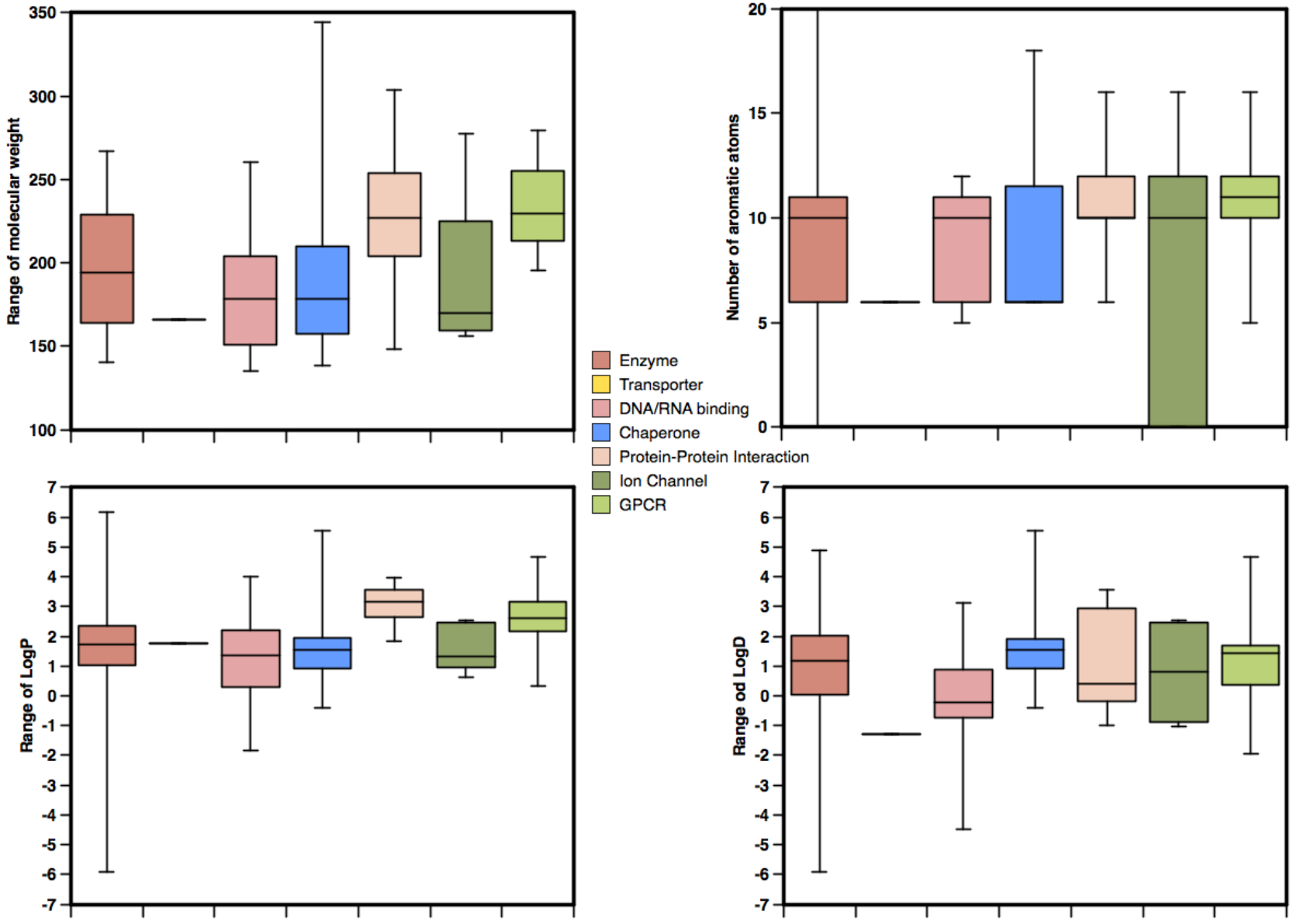
Enzymes mainly neutral







Target type physicochemical properties



Conclusions

- Fragment screening hits tend to be lower molecular weight, contain aromatic rings and ionizable groups.
- Some targets (GPCR, Ion channels, PPI) select for specific physicochemical properties
- Detection technology does not appear to influence properties of hits identified.

Ongoing work..

- This work is part of an ongoing collaboration with Cheminformatics groups at University of Cambridge and The Institute of Cancer Research, London

  - Zehner et al. Structural and physicochemical property trends of screening hits from a diverse fragment library. Manuscript in preparation.