

Increasing the Coverage of Medicinal Chemistry-Relevant Space in Fragment Screening

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Making the discoveries that defeat cancer

Overview

- Fragments screening
- Understand medicinal chemistry space coverage in fragment screening
 - Substructure analysis
 - Chemical space analysis
- What should we screen?

Increasing the Coverage of Medicinal Chemistry-Relevant Space in Commercial Fragments Screening

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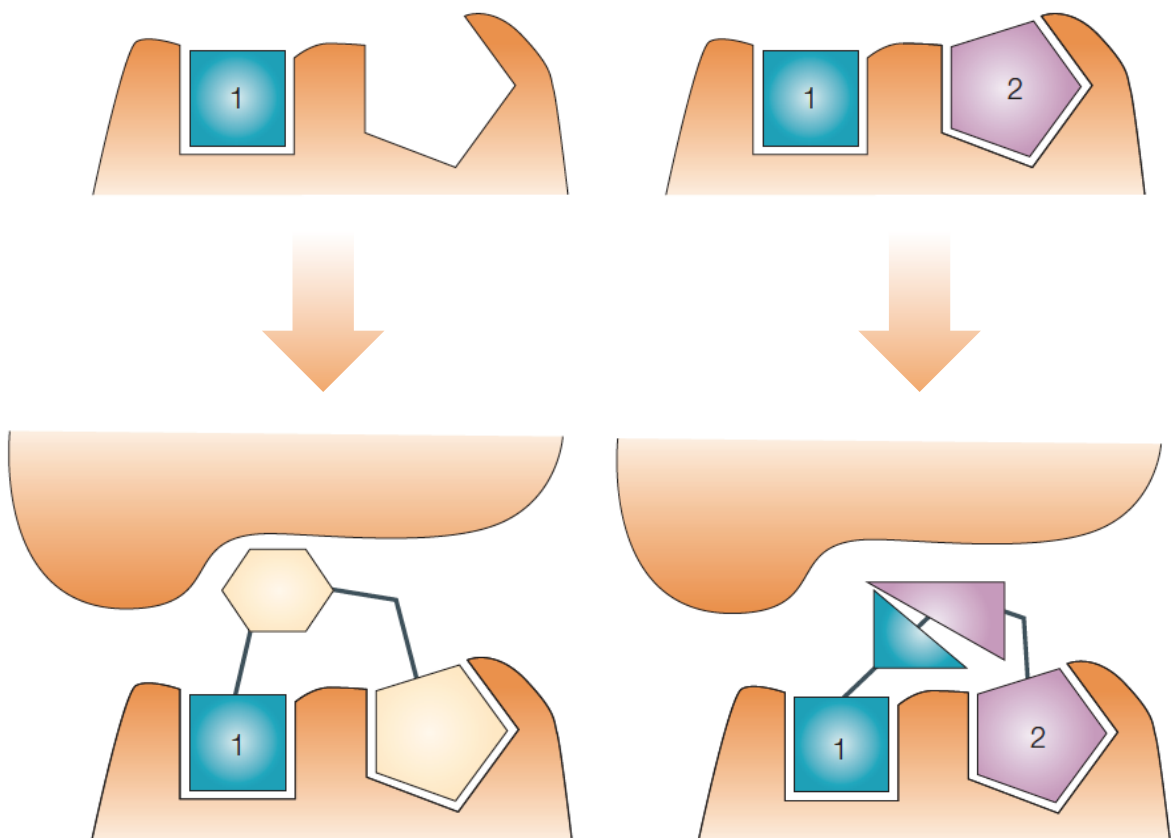
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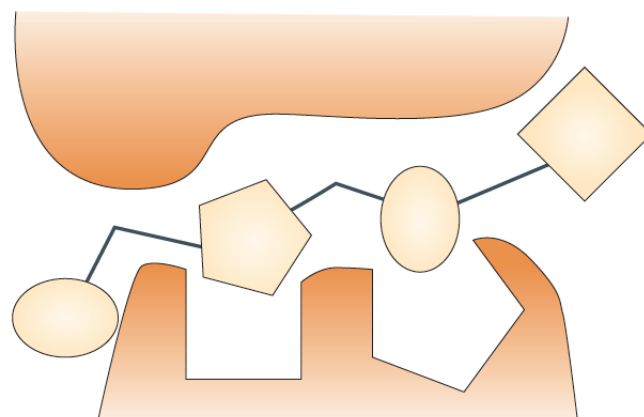
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Fragment screening

Fragment hits

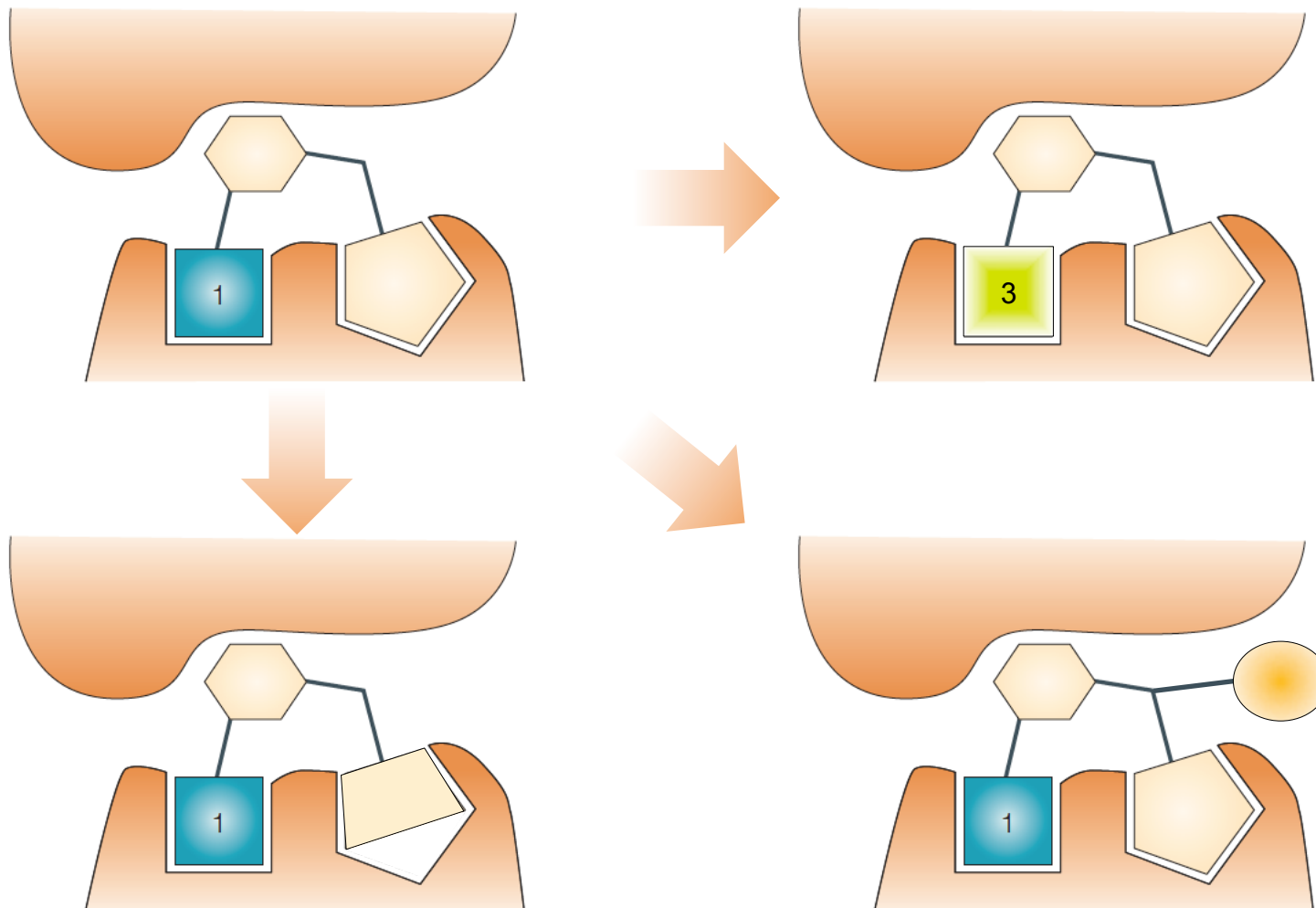


HTS hits

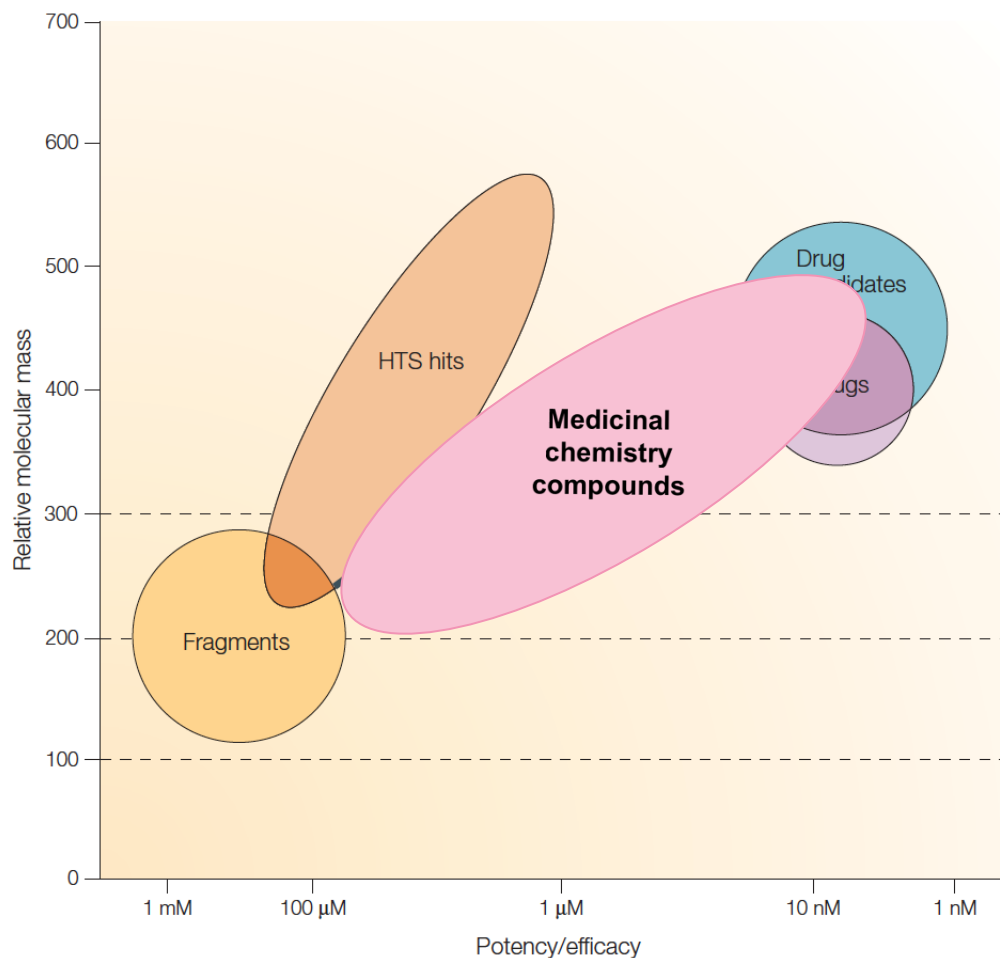


Fragment screening

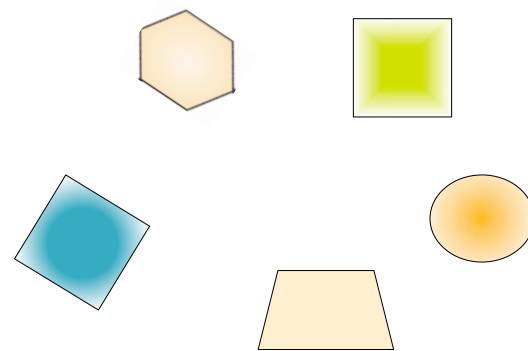
Fragments optimisation



Fragment screening



- Are fragment libraries covering the chemical space of medicinal chemistry compounds?
- Do fragment screens have the appropriate building blocks?



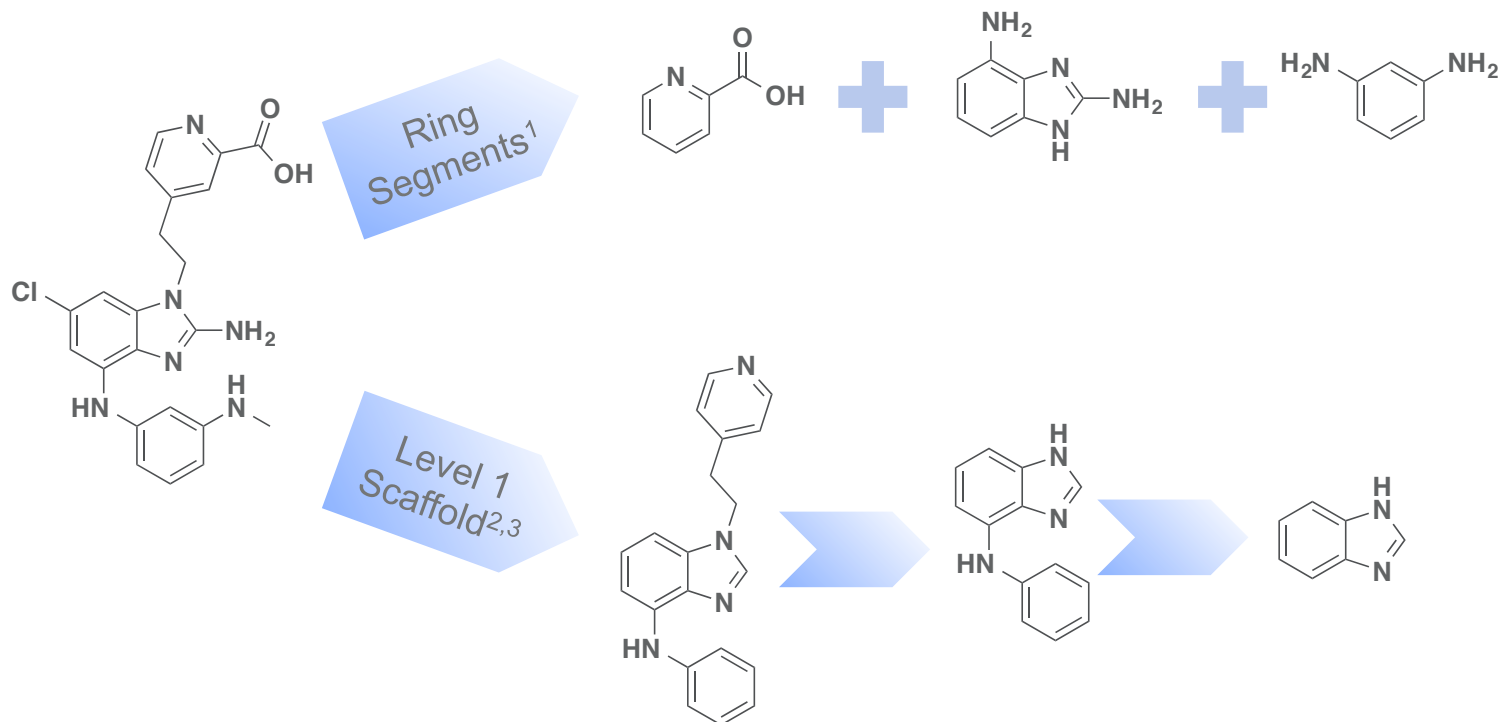


Analysis design

- Data sets
 - Medicinal chemistry compounds
 - Rule-of-three compliant fragments
- Substructure generation
- Compare substructures overlap
- Compare chemical space overlap

Substructure generation

- Two complementary methods
 - Rings containing functional groups relevant for molecular recognition
 - Molecular scaffold + linkers




¹Brenk *et al.* (2008) *ChemMedChem*, 3, 435.

²Schuffenhauer *et al.* (2007) *J. Chem. Inf. Model.*, 47, 47.

³Langdon *et al.* (2011) *J. Chem. Inf. Model.*, 51, 2174.

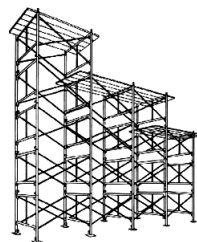
Data collection

- Medicinal chemistry compounds

1.01m (min. 1 ring)

v11

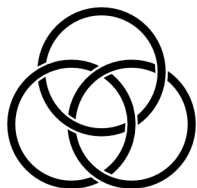
Substructures

99k



Filters

75k



Filters

27077
unique
substructures

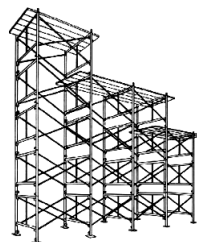
- Commercial fragments

224k


eMolecules

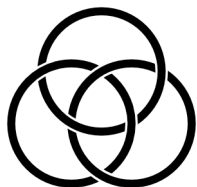
Substructures

77k



Filters

21k



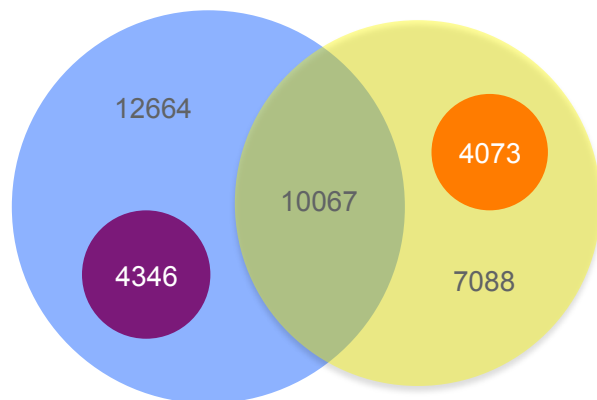
Filters

21228
unique
substructures

Substructures overlap

All ChEMBL

- EPFP7 fingerprint similarity (Tanimoto cut-off ≥ 0.85)¹
- >12k ChEMBL substructures not represented in commercial fragments



Medicinal chemistry compounds

Commercial fragments

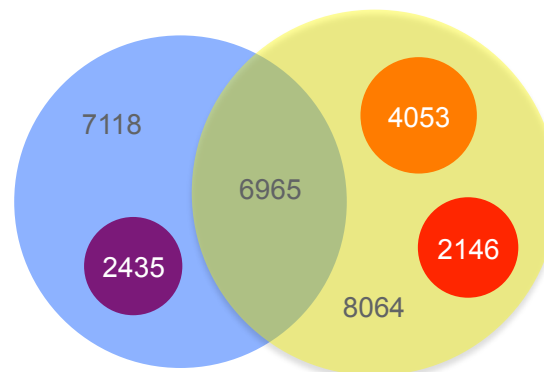
Similar to commercial fragments

Similar to medicinal chemistry compounds

Only appeared in non-active medicinal chemistry compounds

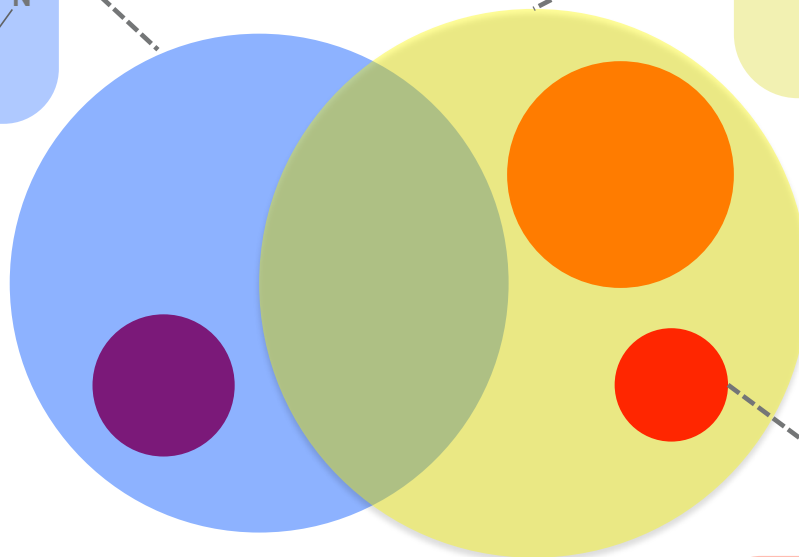
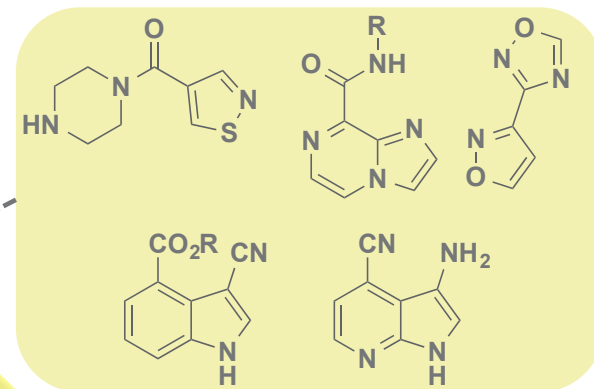
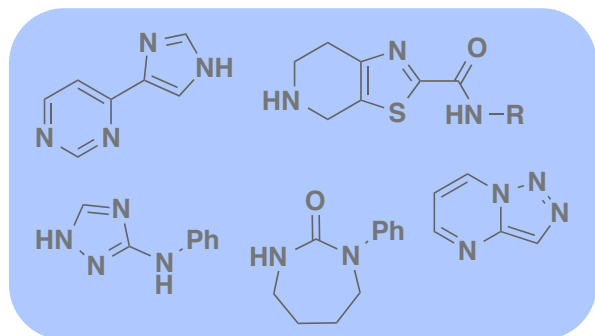
Bioactive ChEMBL

- Parent compounds have reported bioactivity (K_i , K_d , IC_{50} , EC_{50} , etc.) $\leq 10 \mu\text{M}$
- >2k commercial fragments present only in non-active parent ChEMBL compounds



¹Brown & Martin (1996) *J. Chem. Inf. Model.*, 36, 572.

Substructures overlap



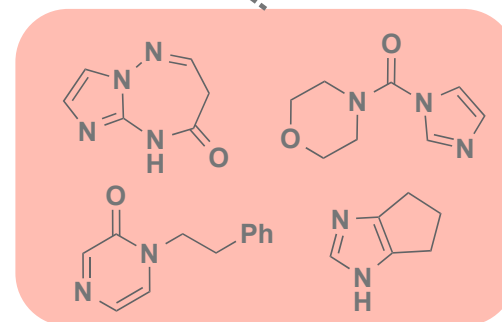
Medicinal chemistry compounds

Commercial fragments

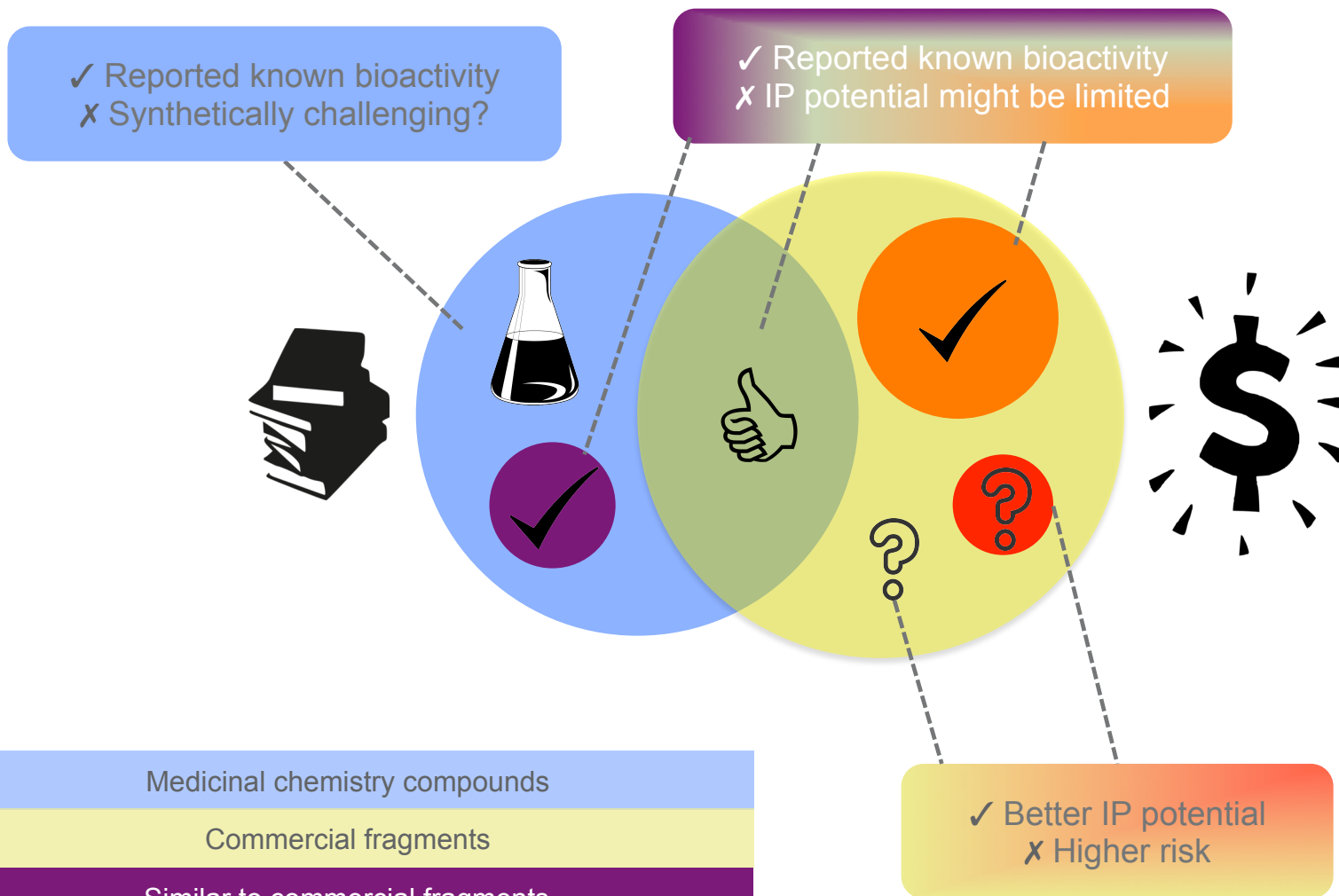
Similar to commercial fragments

Similar to medicinal chemistry compounds

Only appeared in non-active medicinal chemistry compounds



Substructures overlap



Medicinal chemistry compounds

Commercial fragments

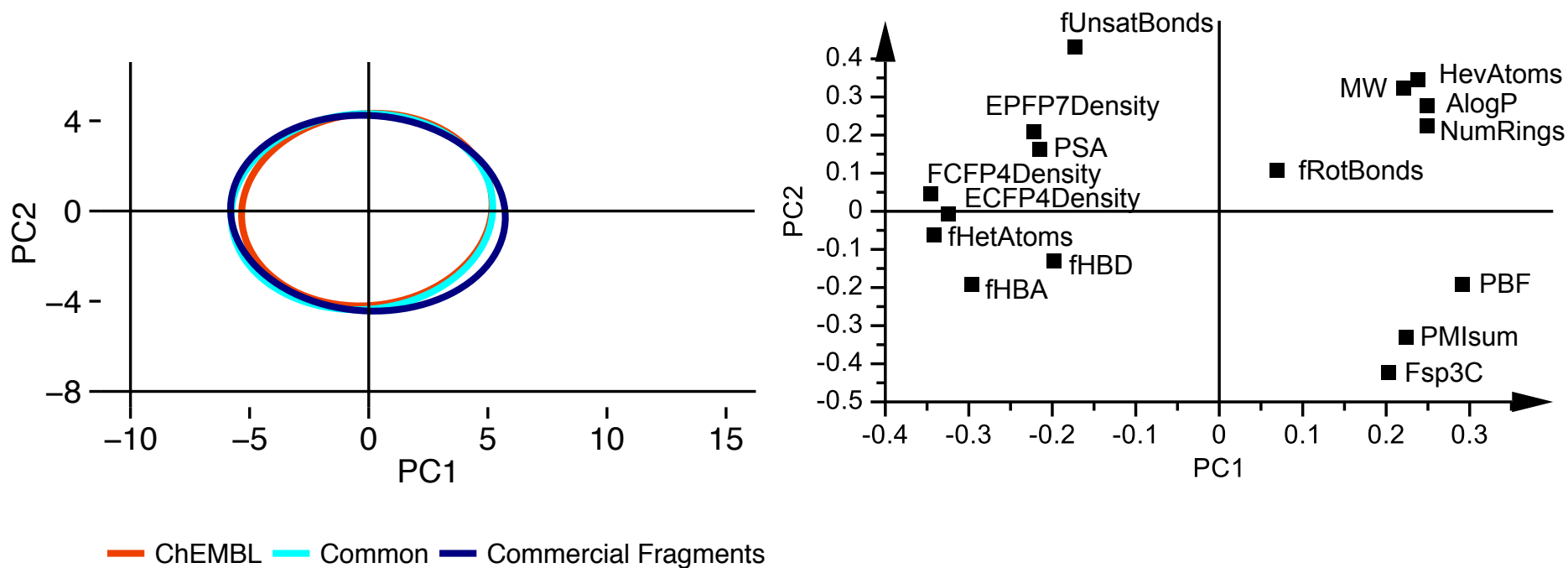
Similar to commercial fragments

Similar to medicinal chemistry compounds

Only appeared in non-active medicinal chemistry compounds

Chemical space overlap

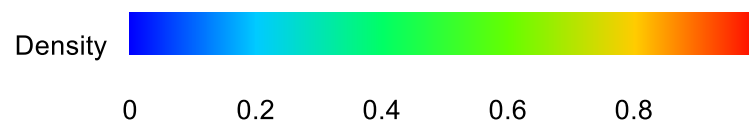
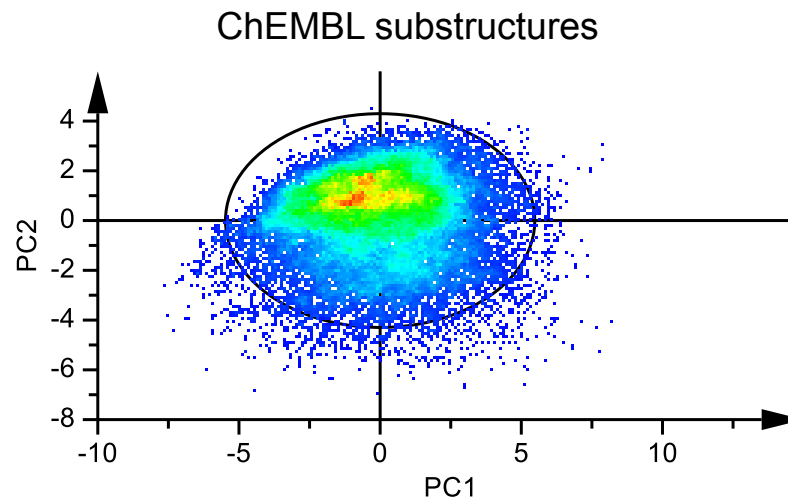
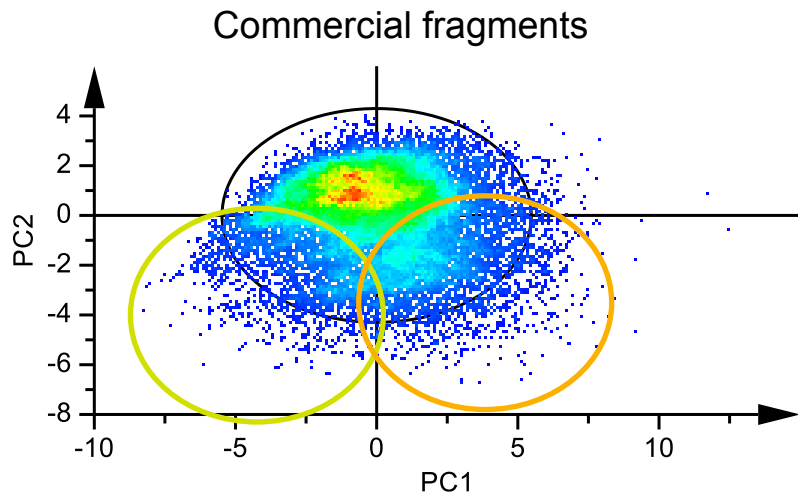
- Substructures distribution occupy similar chemical space



Complexity	Size
Polarity	3-dimensionality

Chemical space distribution

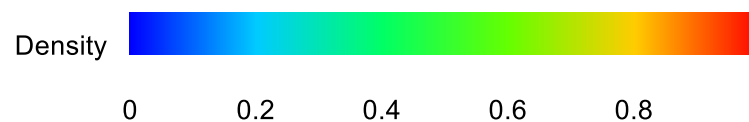
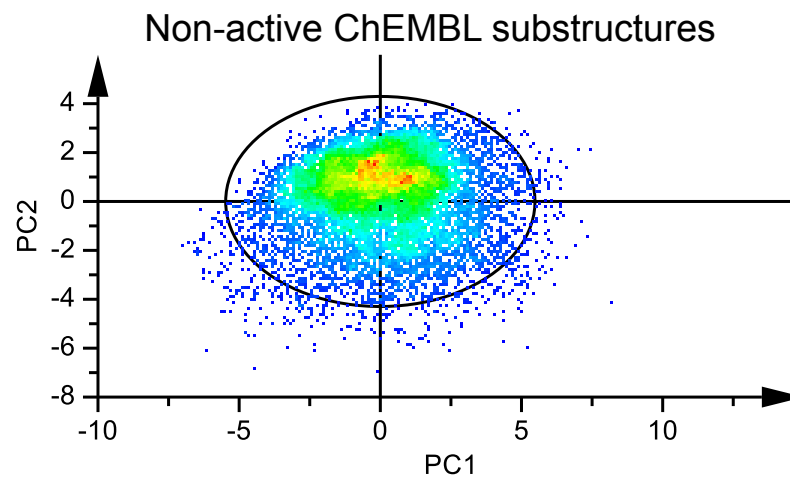
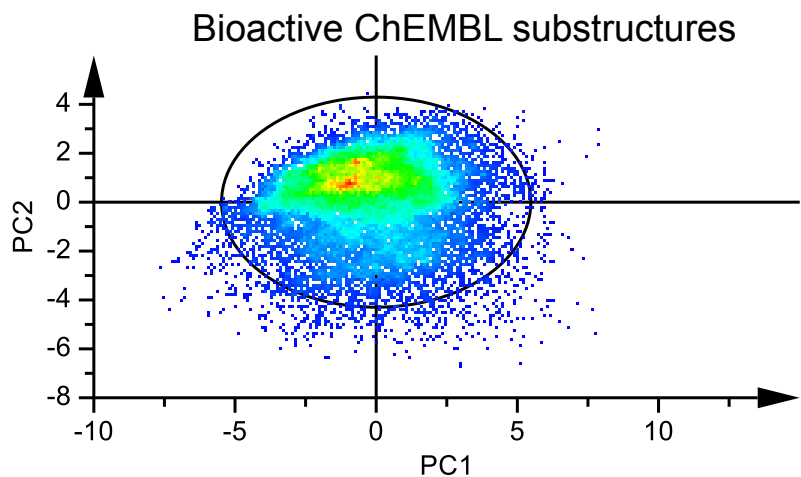
- Lowest representation in polar substructures (quadrant 3)
- 3D substructures not extensively exemplified (quadrant 2)



Complexity	Size
Polarity	3-dimensionality

Chemical space distribution

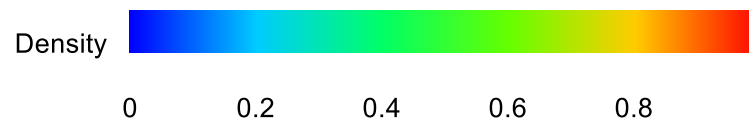
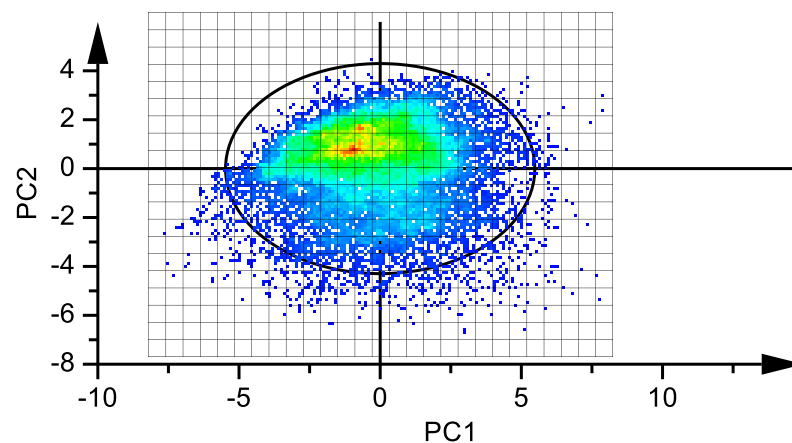
- Similar uneven distributions observed



Complexity	Size
Polarity	3-dimensionality

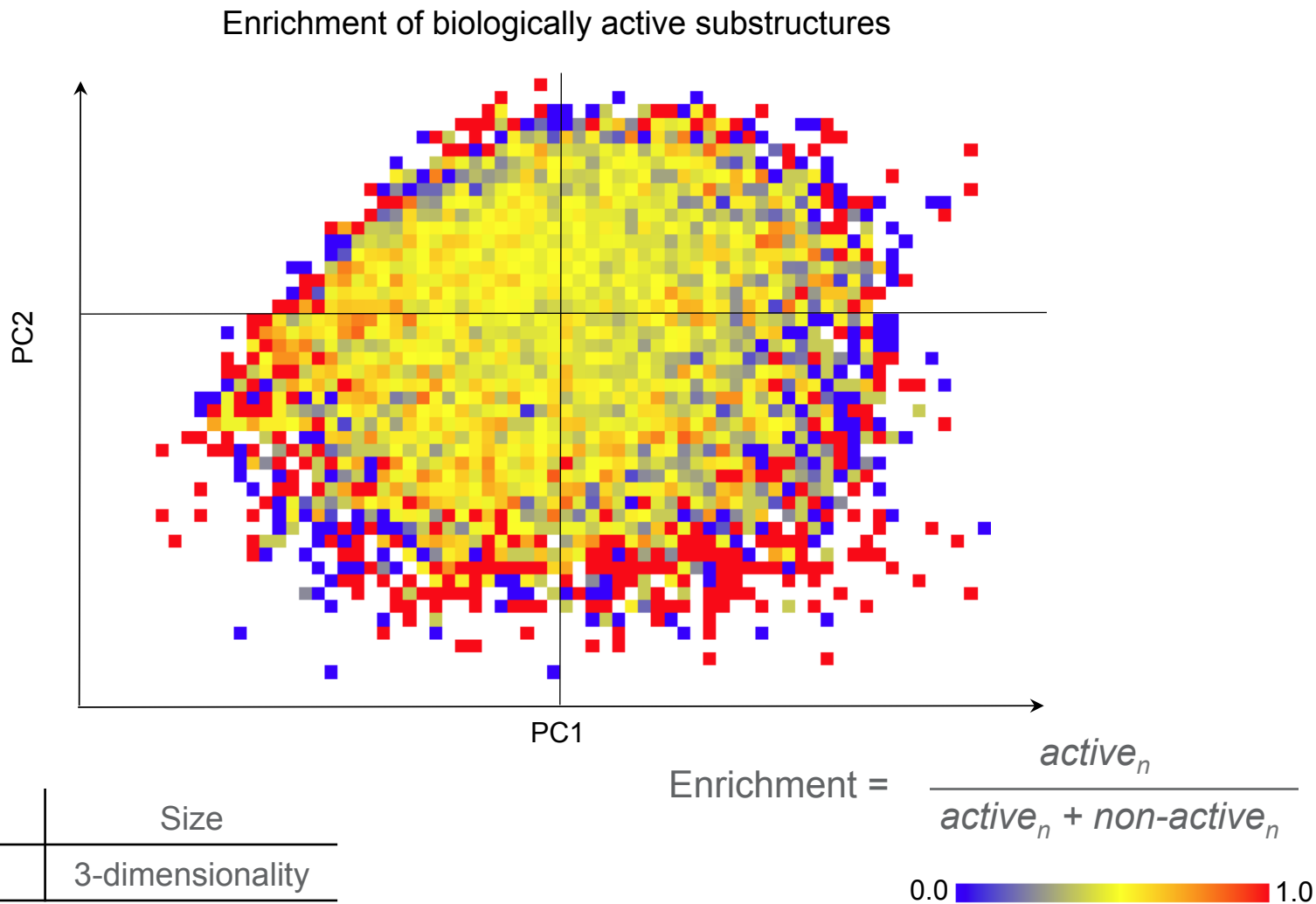
Chemical space distribution

- Similar uneven distributions observed



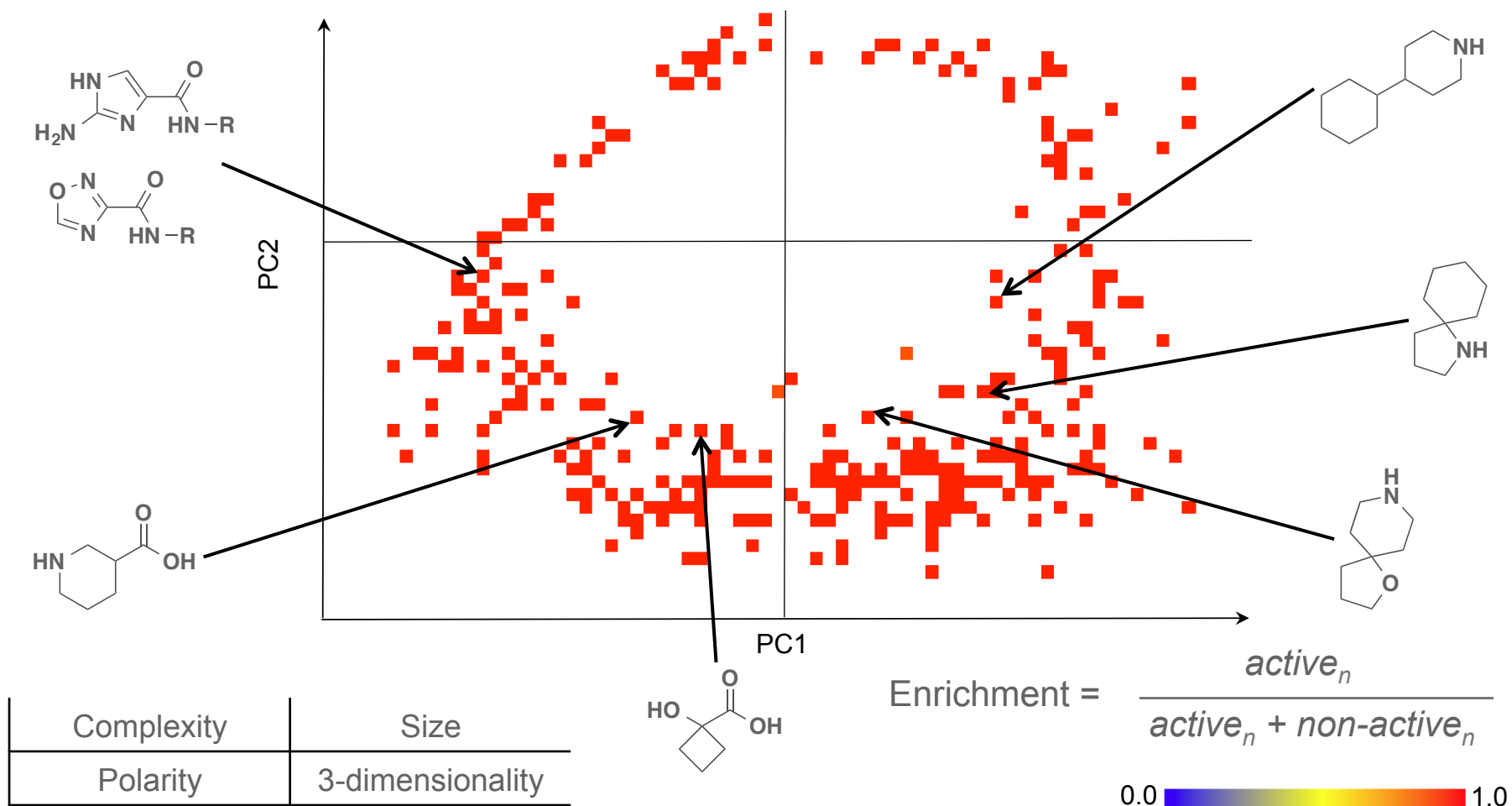
Complexity	Size
Polarity	3-dimensionality

Chemical space density



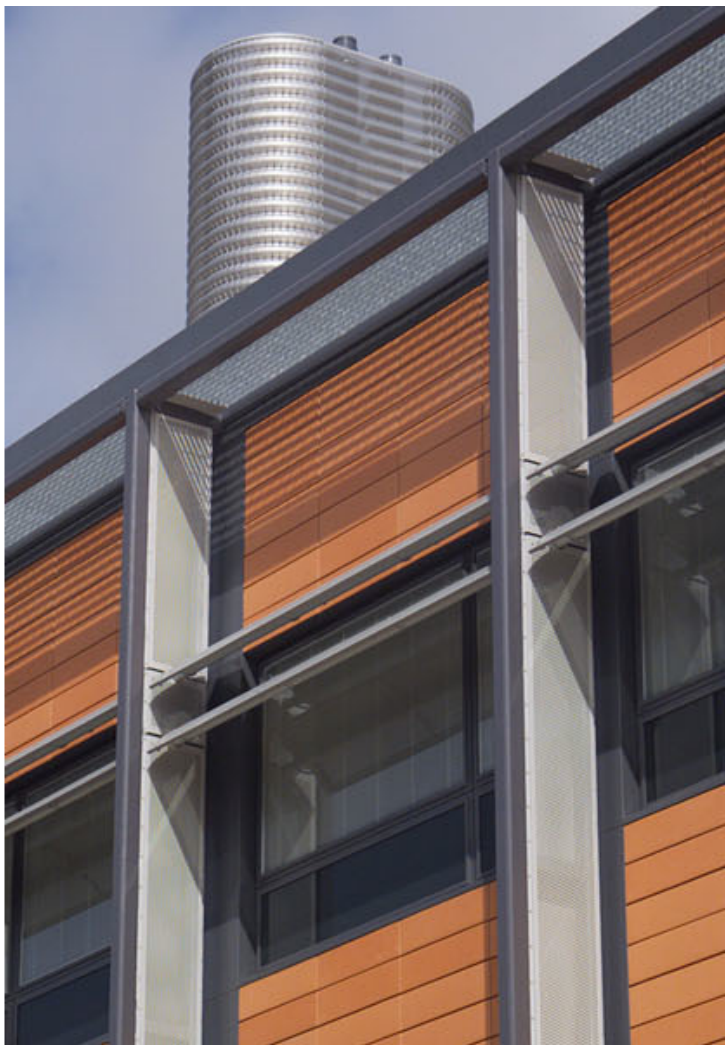
Chemical space density

- Highest enrichment observed for many polar and/or 3D substructures (NB Population of these enriched cells rather low)



Summary

- Low overlap between medicinal chemistry output & commercial fragments
- Choose relevant fragments
 - Literature precedence *vs* risk
 - Library size
 - Targets of interest
- Sample polar and/or 3-dimensional substructures
 - Enhance chemical space sampling relevant to medicinal chemistry output
 - Understand realistic enrichment of these substructures for bioactive compounds within chemical space



in silico Medicinal Chemistry

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