

On the Origins of Three-Dimensionality in Drug-Like Molecules

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@nathanbroon

Where it all started...

Fragment-based hit identification: thinking in 3D

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The identification of high-quality hits during the early phases of drug discovery is essential if projects are to have a realistic chance of progressing into clinical development and delivering marketed drugs. As the pharmaceutical industry goes through unprecedented change, there are increasing opportunities to collaborate via pre-competitive networks to marshal multifunctional resources and knowledge to drive impactful, innovative science. The 3D Fragment Consortium is developing fragment-screening libraries with enhanced 3D characteristics and evaluating their effect on the quality of fragment-based hit identification (FBHI) projects.

Overview

- **Motivations for enhanced three-dimensionality**
- **Descriptors of three-dimensionality**
 - PMI: Principal Moments of Inertia
 - PBF: Plane of Best Fit
- **Three-dimensionality analyses of drug-like space**
 - Extant drug-like molecules
 - ‘Retrosynthetic’ analyses
 - Fragmentation analyses
 - Virtual libraries

Overview

SPECIAL FOCUS | Computational chemistry & computer-aided drug discovery – Part I

Research Article

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Future
**Medicinal
Chemistry**

On the origins of three-dimensionality in drug-like molecules

Aim: Many medicinal chemistry-relevant structures and core scaffolds tend toward geometric planarity, which hampers the optimization of physicochemical properties desirable in drug-like molecules. As challenging drug target classes emerge, the exploitation of molecular three-dimensionality in lead optimization is becoming increasingly important. While recent interest has emphasized the importance of enhanced three-dimensionality in molecular fragment designs, the extent to which this is required in core scaffolds remains unclear. **Materials & methods:** Three computational methods, Scaffold Tree deconstruction, Synthetic Disconnection Rules retrosynthetic deconstruction and virtual library enumeration, are applied, together with the descriptors plane of best fit and principal moments of inertia, to investigate the origins of three-dimensionality in drug-like molecules. **Conclusion:** This study informs on the stage at which molecular three-dimensionality should be considered in drug design.

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Michael Carter¹, N Yi Mok^{*,†}
& Nathan Brown^{*,‡}

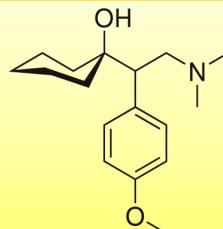
¹Cancer Research UK Cancer Therapeutics Unit, Division of Cancer Therapeutics, The Institute of Cancer Research, London, SM2 5NG, UK

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Structural Moieties Promoting 3D

Quaternary Centres



Effexor XR

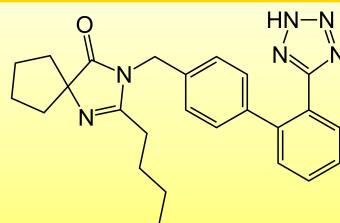
(Venlafaxine)

\$1,431 Million (19th)

ANTIDEPRESS. & MOOD STAB.

28/12/1993

Spiro Ring Systems



Avapro

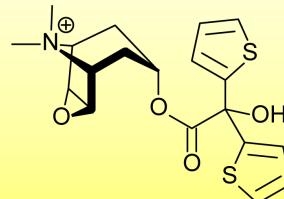
(Irbesartan)

\$370 Million (91st)

ANGIOTEN-II ANTAG, PLAIN

30/09/1997

Bridged Bicycles



Spiriva

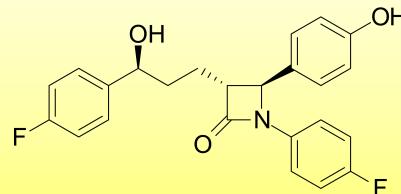
(Tiotropium)

\$1,594 Million (14th)

ANTICHOLINERGIC+B2-STIM

30/01/2004

Conformational Restriction



Zetia

(Ezetimibe)

\$986 Million (31st)

CHOEST.&TRIGLY. REGULATOR

25/10/2002

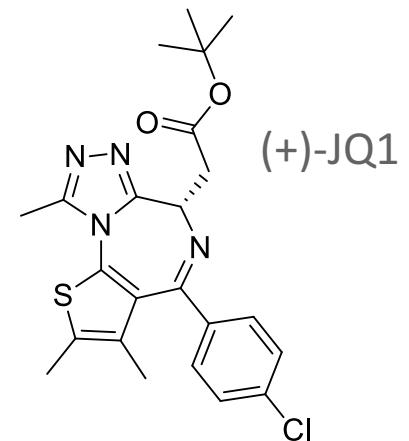
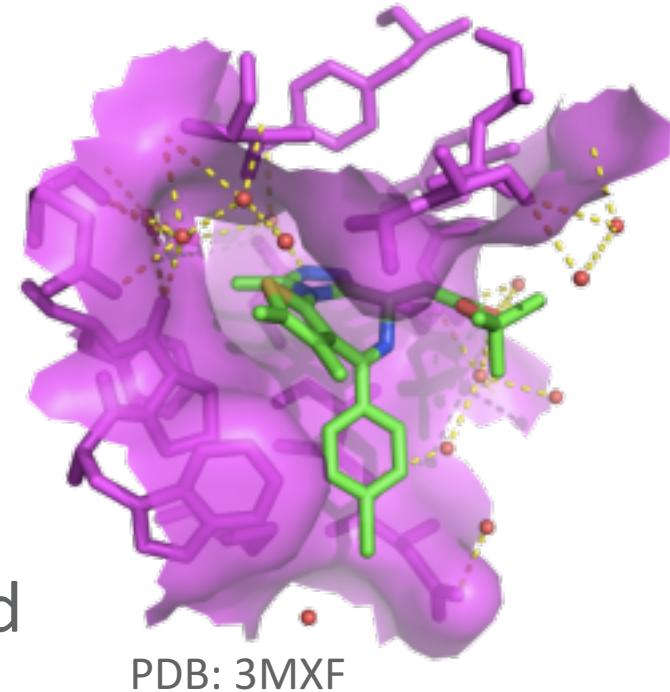
On The Origins of Three-Dimensionality

System	Fragment	Screening	ChEMBL	Vendor
Bridged	45	491	24,837	11,544
Spiro	33	908	9,074	26,108
<i>N</i>	2,465	85,931	440,055	2,440,878
<hr/>				
% Bridged	1.83%	0.57%	5.64%	0.47%
% Spiro	1.34%	1.06%	2.06%	1.07%

**There is Enhanced ‘Shape’ Diversity in
Exemplified Medicinal Chemistry Space**

Motivation: Three-Dimensional Molecules

- Mimicking natural products
 - Natural products frequently incorporate 3D scaffolds
- Improvement in properties
 - 3D shape often conveys improved aqueous solubility
- Addressing new and challenging drug targets
 - *e.g.* protein-protein interactions



Escape from Flatland...

6752 *J. Med. Chem.* 2009, 52, 6752–6756
DOI: 10.1021/jm901241e

Journal of
**Medicinal
Chemistry**
Article

Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success

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Wyeth Research, Chemical Sciences, ¹200 Cambridgepark Drive, Cambridge, Massachusetts 02140, ²401 North Middlestown Road, Pearl River, New York 10965, and ³1865 Ridge Road, Monmouth Junction, New Jersey 08854

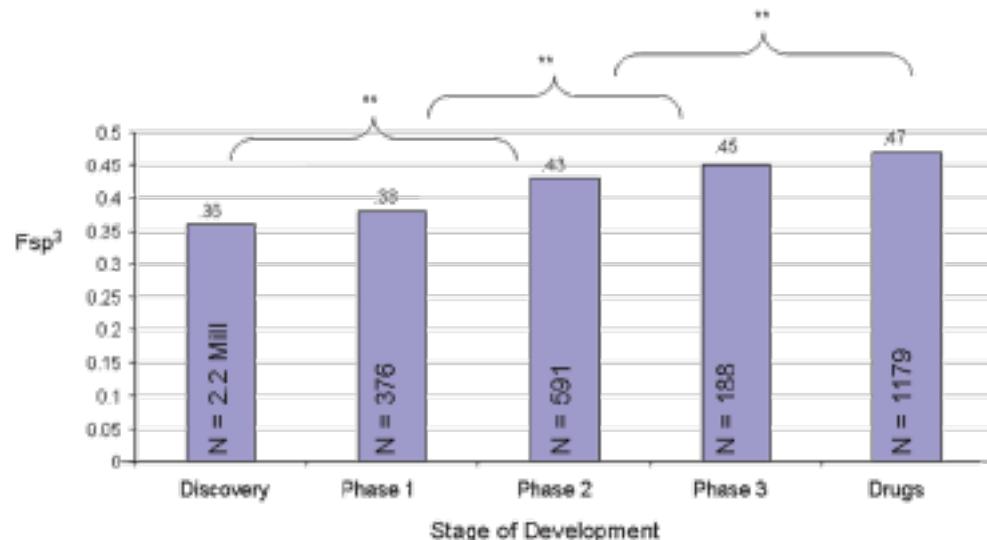
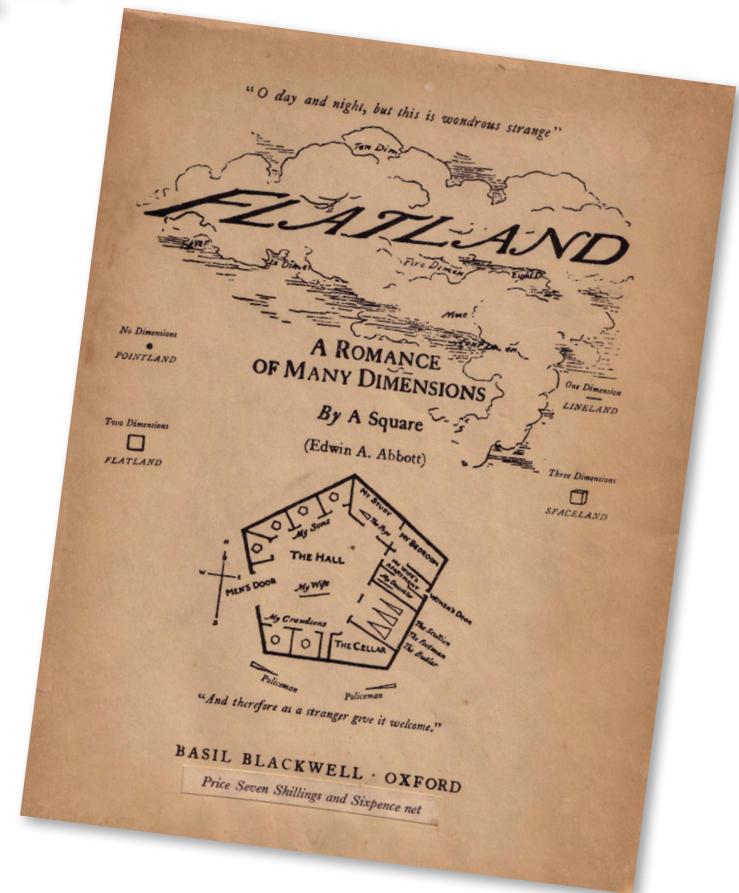
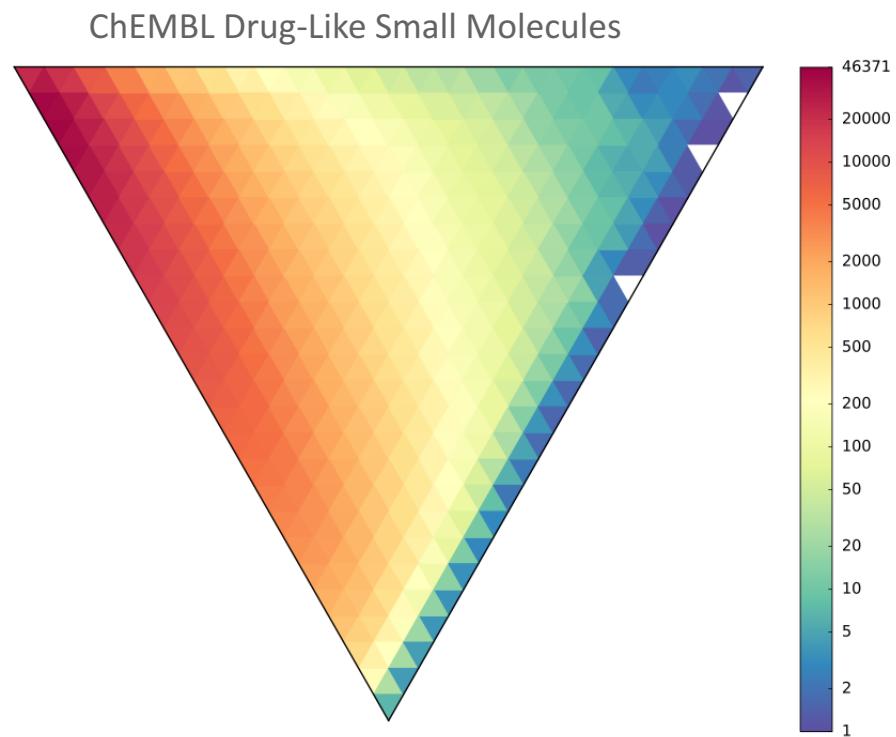
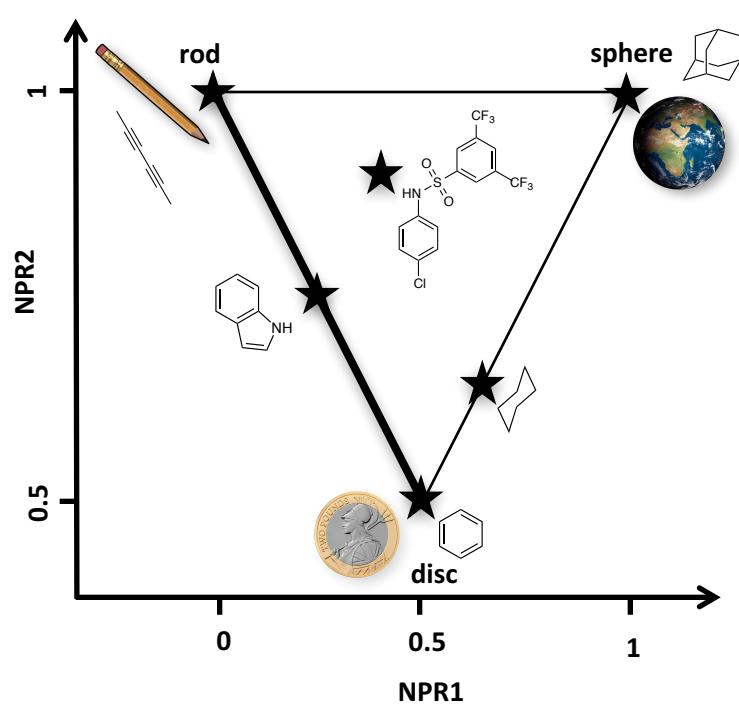


Figure 3. Mean Fsp³ for compounds in different stages of development. **P value < 0.001.

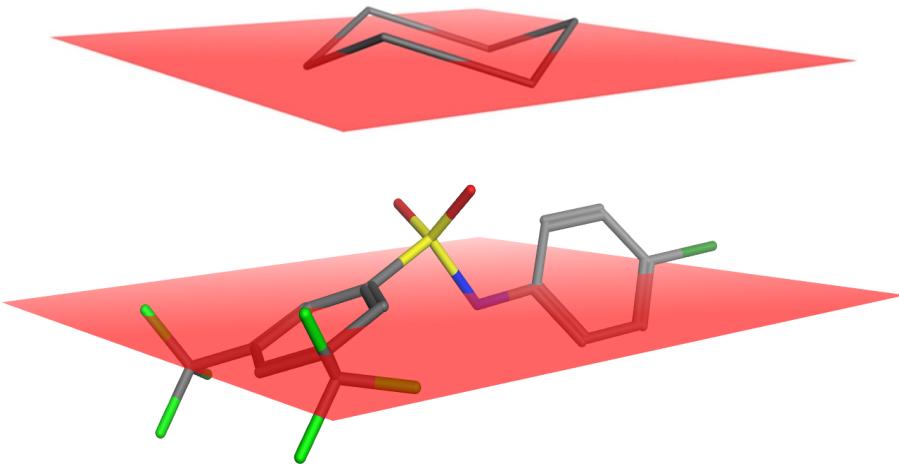


Principal Moments of Inertia (PMI)

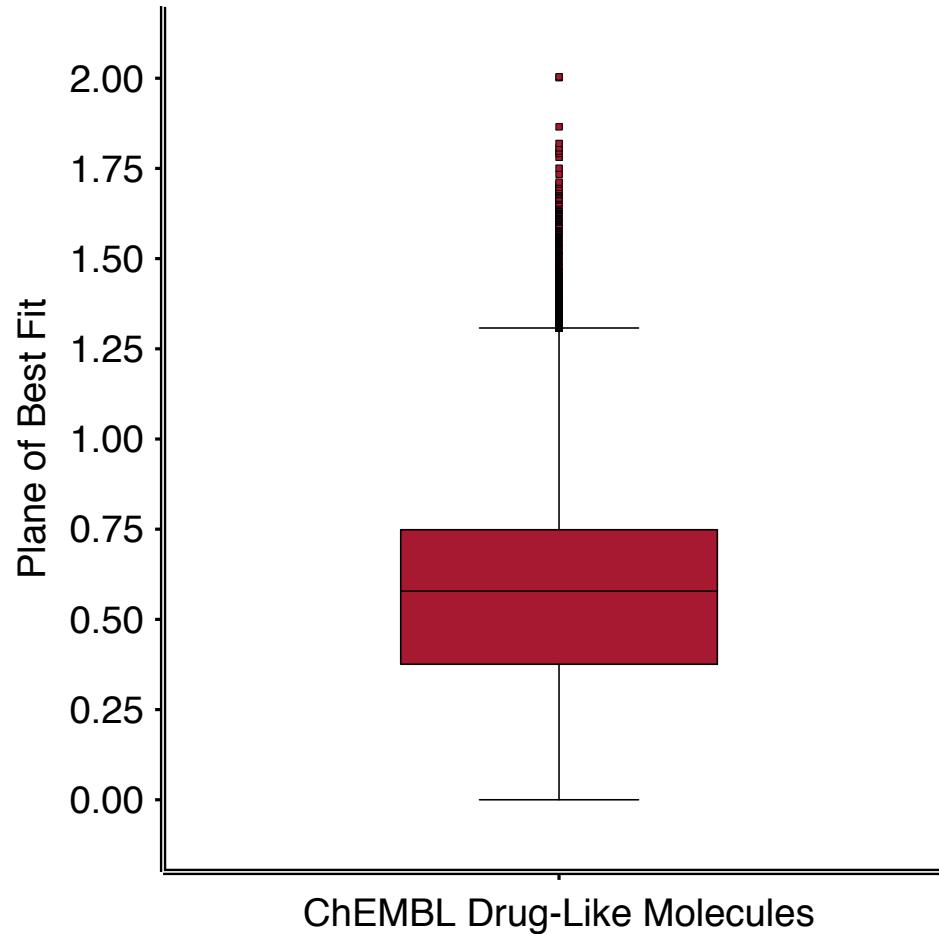


Intuitive in Presentation
Size Independent

Plane of Best Fit (PBF)

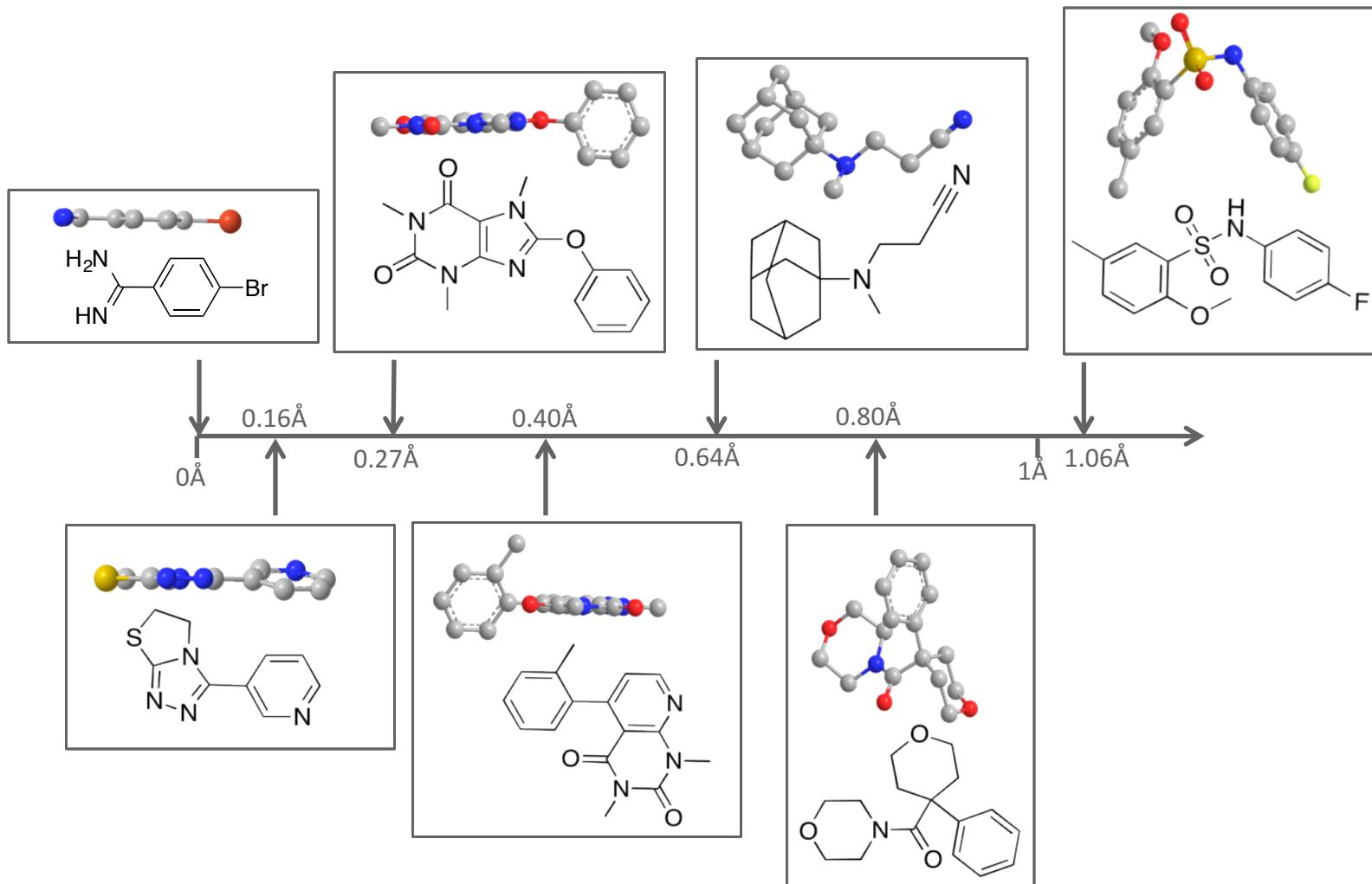


Simple in Concept
Size Dependency
Unbound Descriptor



1. Meyers, J.; Carter, M.; Mok, N. Y.; Brown, N. On The Origins of Three-Dimensionality in Drug-Like Molecules. *Future Med. Chem.* **2016**, 8(14), 1753-1767.
2. Firth, N. C.; Brown, N.; Blagg, J. Plane of Best Fit: A Novel Method to Characterize the Three-Dimensionality of Molecules. *J. Chem. Inf. Model.* **2012**, 52, 2516-2525.

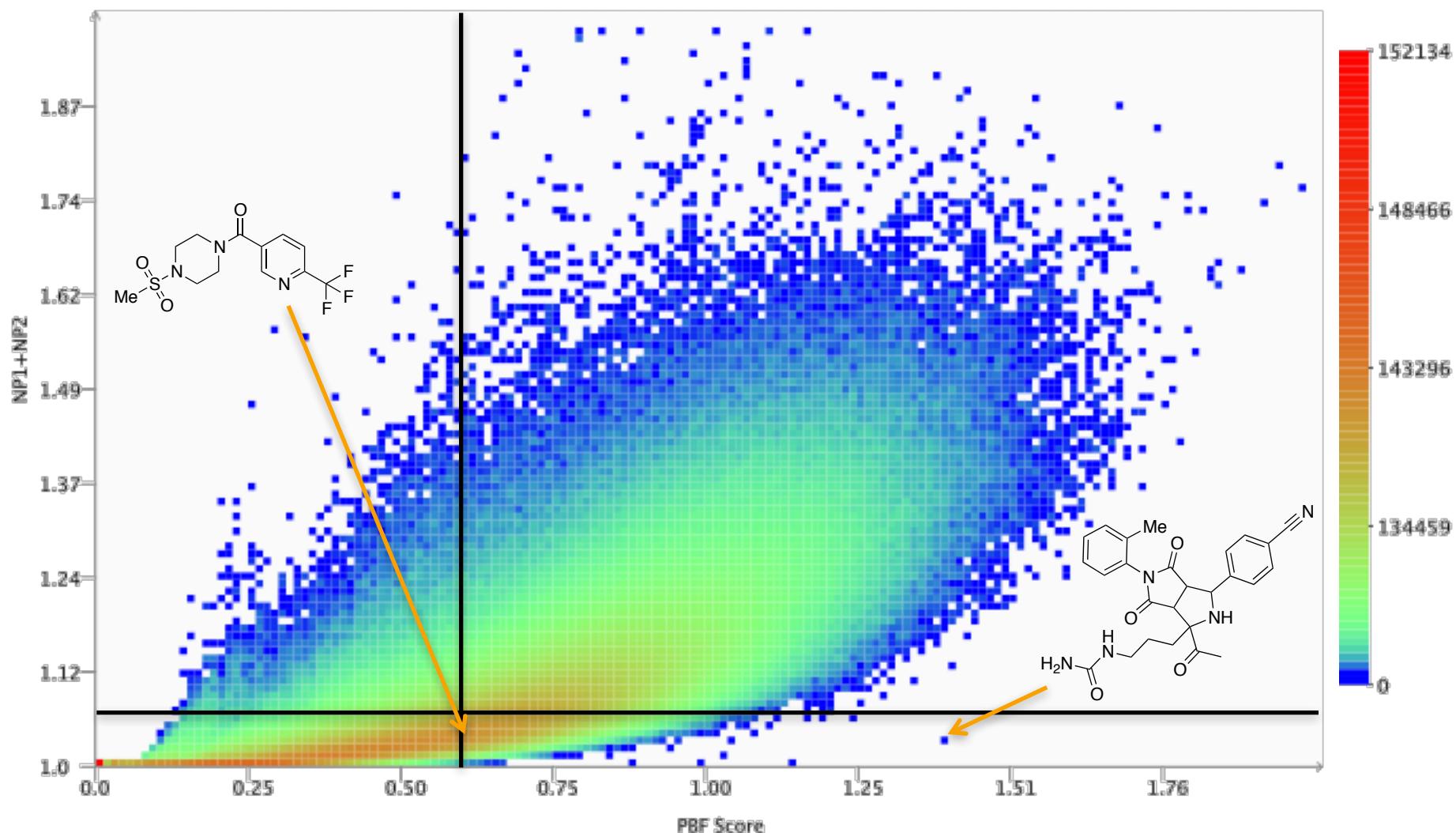
Plane of Best Fit



- Firth, N. C.; Brown, N.; Blagg, J. Plane of Best Fit: A Novel Method to Characterize the Three-Dimensionality of Molecules. *J. Chem. Inf. Model.* **2012**, 52, 2516-2525.

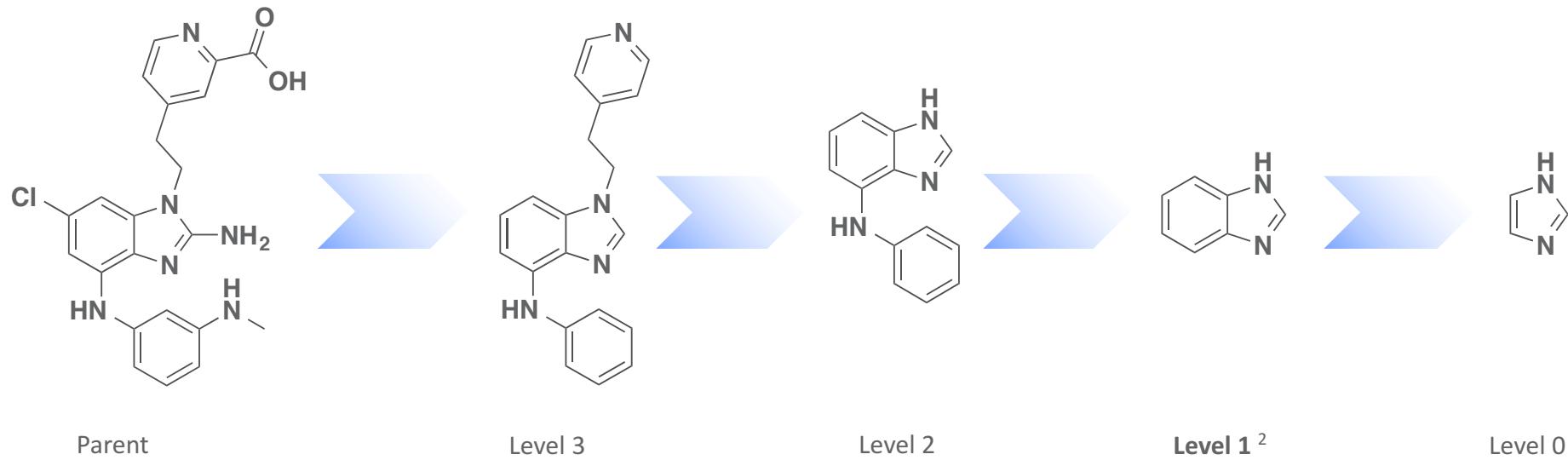
PMI & PBF – Perfect Partners

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1. Firth, N. C.; Brown, N.; Blagg, J. Plane of Best Fit: A Novel Method to Characterize the Three-Dimensionality of Molecules. *J. Chem. Inf. Model.* **2012**, *52*, 2516-2525.

Scaffold Tree Fragmentation

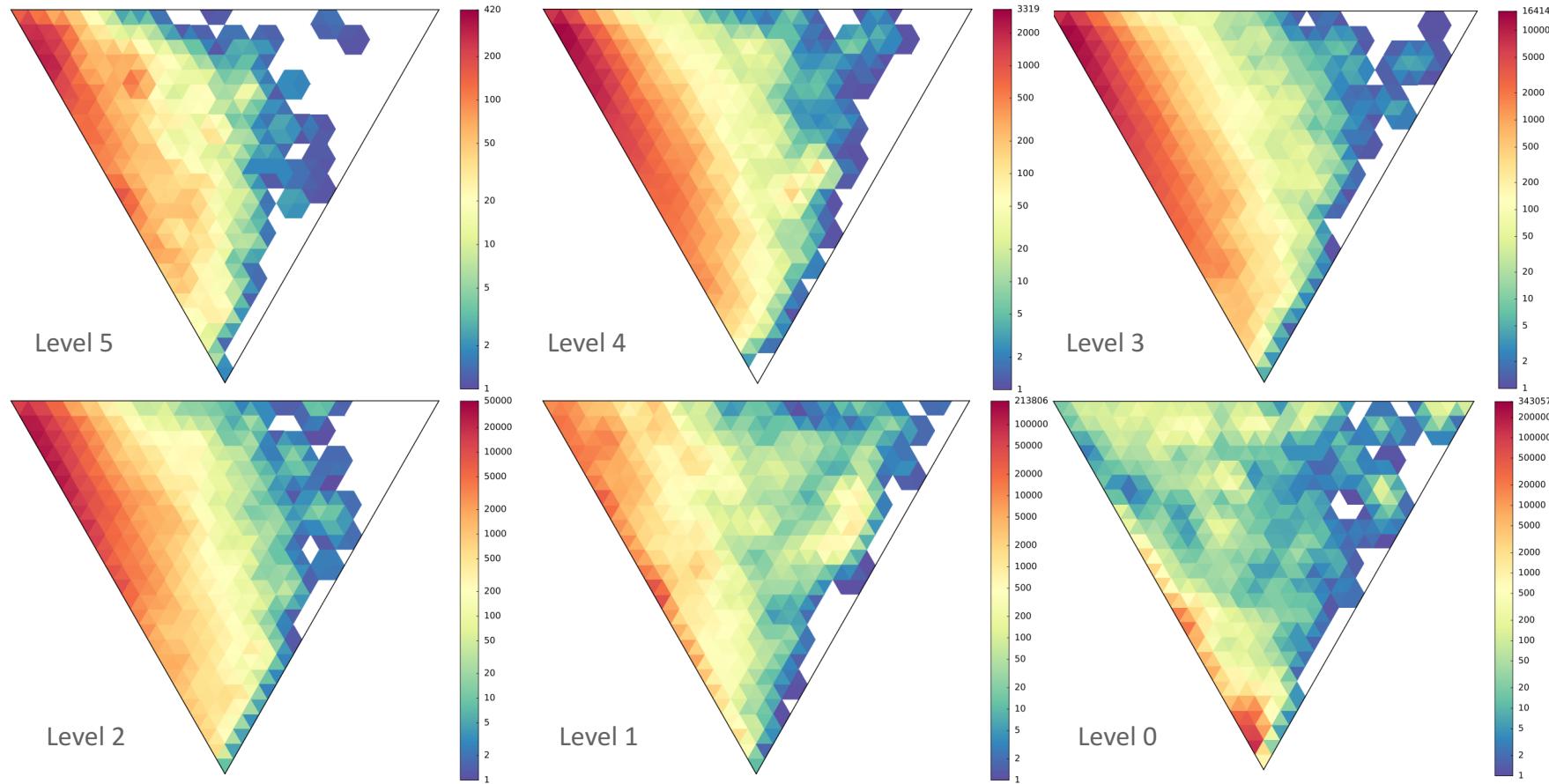


Simple & Intuitive Rules
Mimics Chemist Thinking
Systematic Evaluation

1. Schuffenhauer, A.; Ertl, P.; Roggo, S.; Wetzel, S.; Koch, M. A.; Waldmann, H. The Scaffold Tree – Visualization of the Scaffold Universe by Hierarchical Classification. *J. Chem. Inf. Model.* **2007**, *47*, 47-58.
2. Langdon, S. R.; Brown, N.; Blagg, J. Scaffold Diversity of Exemplified Medicinal Chemistry Space. *J. Chem. Inf. Model.* **2012**, *51*, 2174-2185.

PMI: Scaffold Tree Analysis of ChEMBL

Return to Flatland...

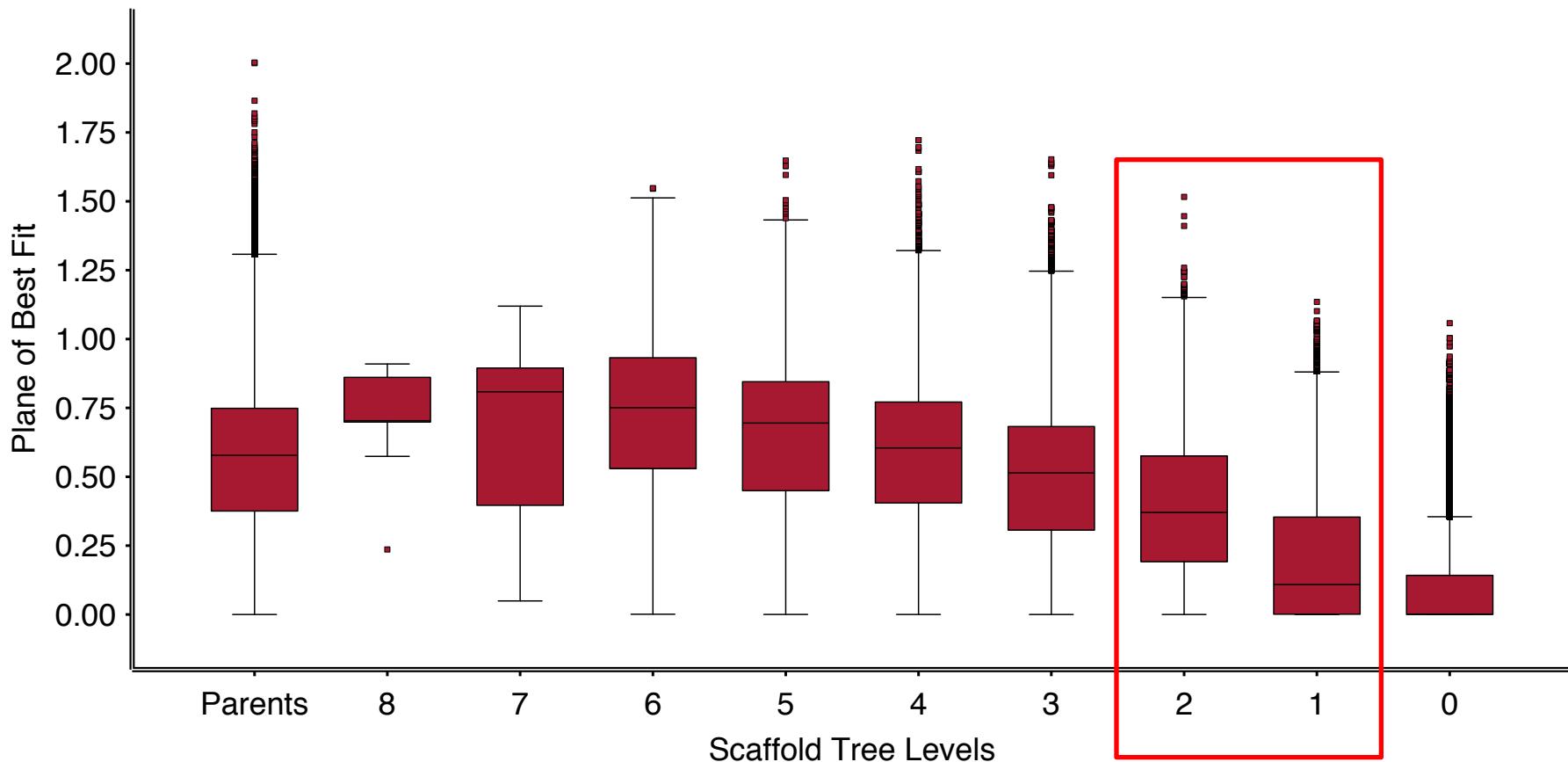


Medicinal Chemistry Relevant Scaffolds Tend Towards Planarity

PBF: Scaffold Tree Analysis of ChEMBL

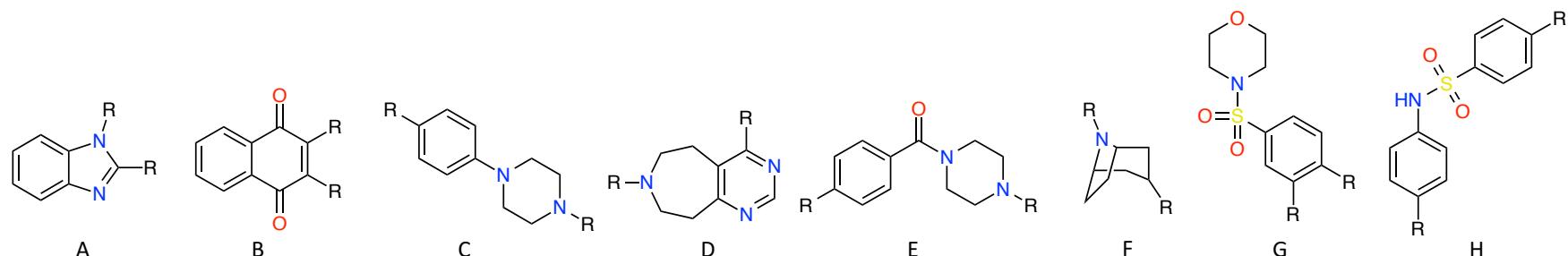
Return to Flatland...

15

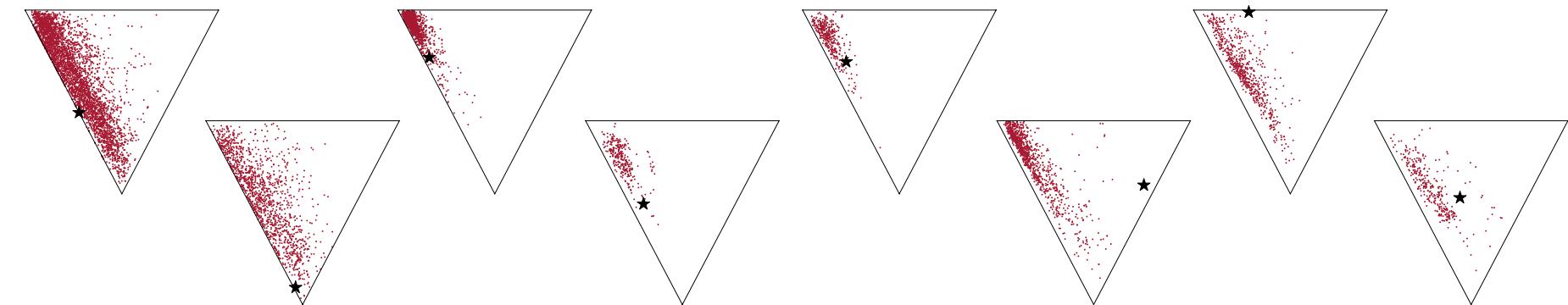


Medicinal Chemistry Relevant Scaffolds Tend Towards Planarity

Scaffolds versus ChEMBL Parents

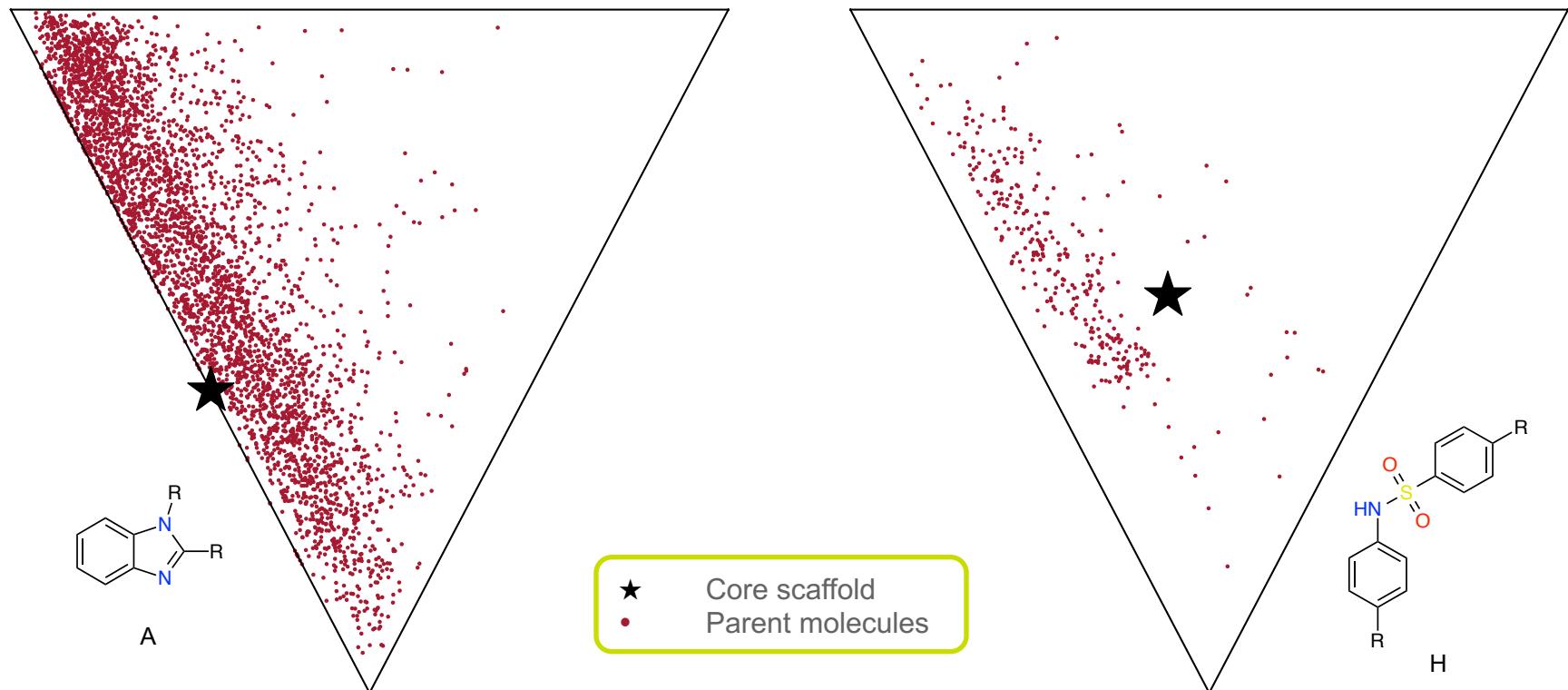


Increasing PBF



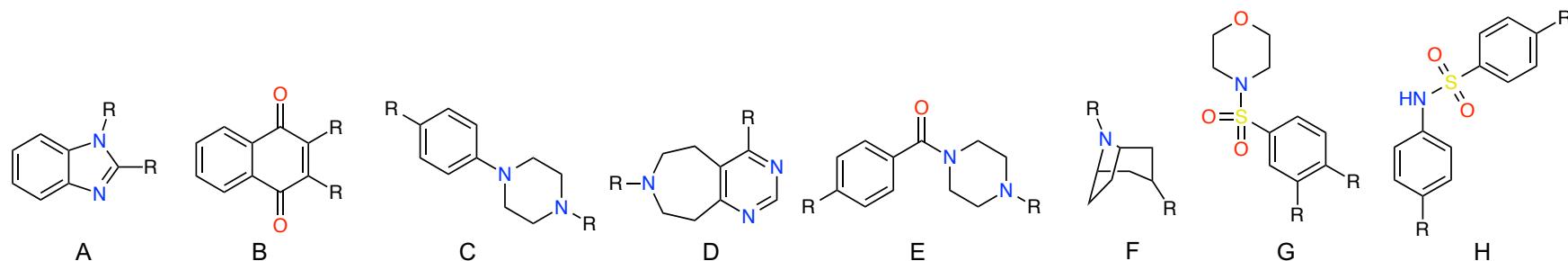
★ Core scaffold
● Parent molecules

Scaffolds versus ChEMBL Parents

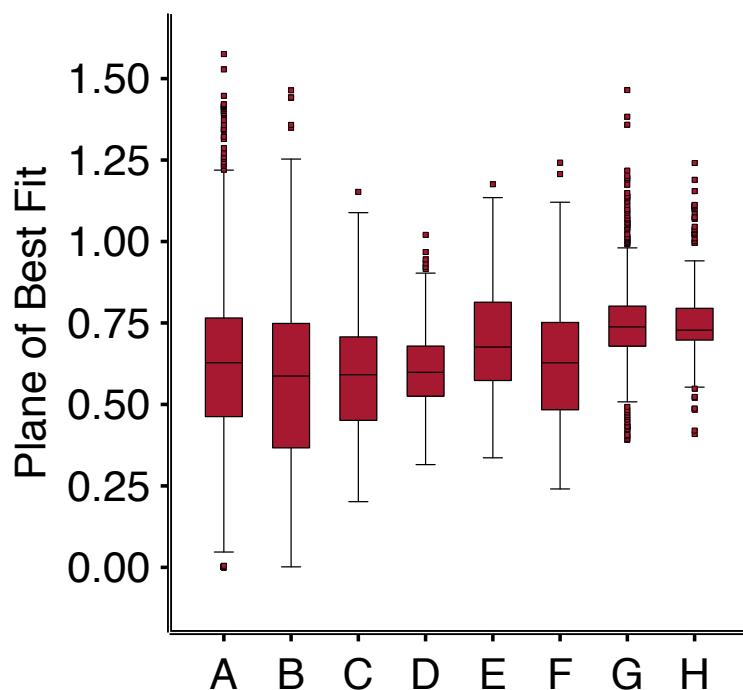


Modulation of Three-Dimensionality Easier with Planar Scaffolds

Scaffold *versus* ChEMBL Parent Molecules



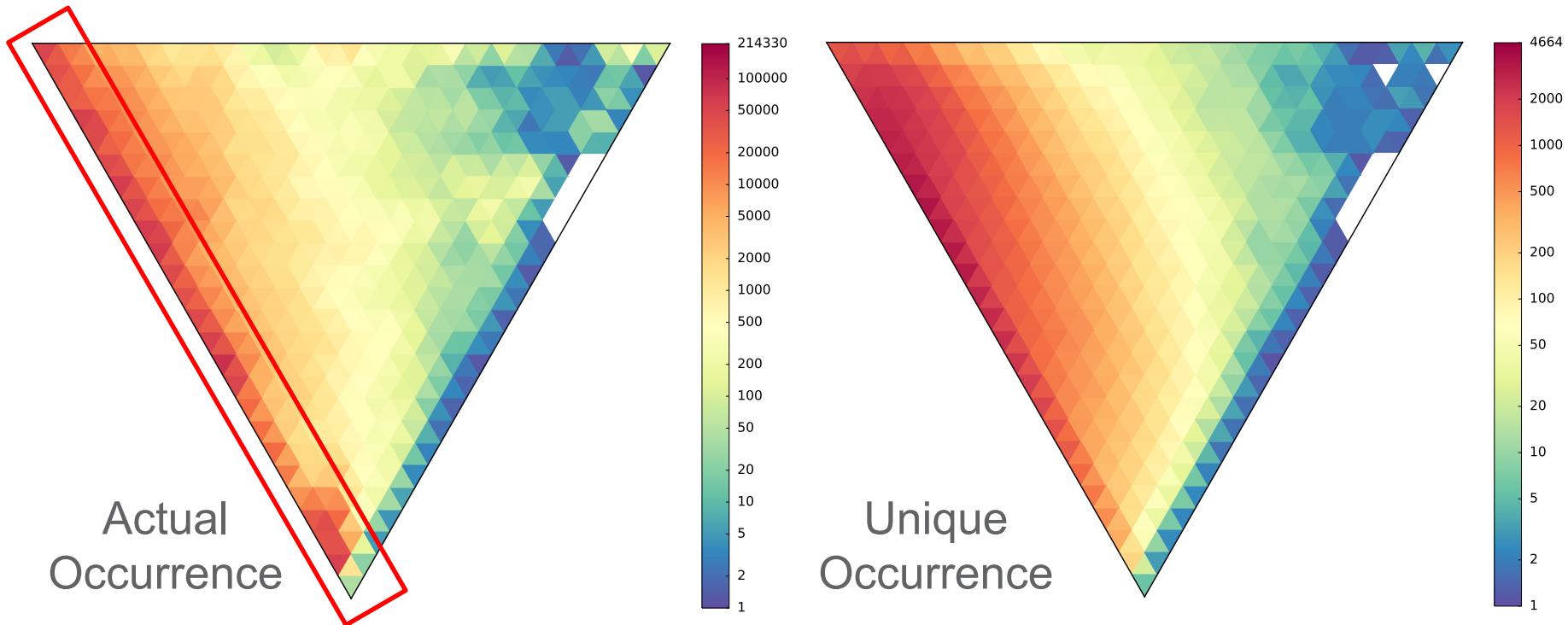
Increasing PBF



More Three-Dimensional Scaffolds Do Not Necessarily Translate into More Three-Dimensional Structures

SynDiR – Synthetic Disconnection Rules

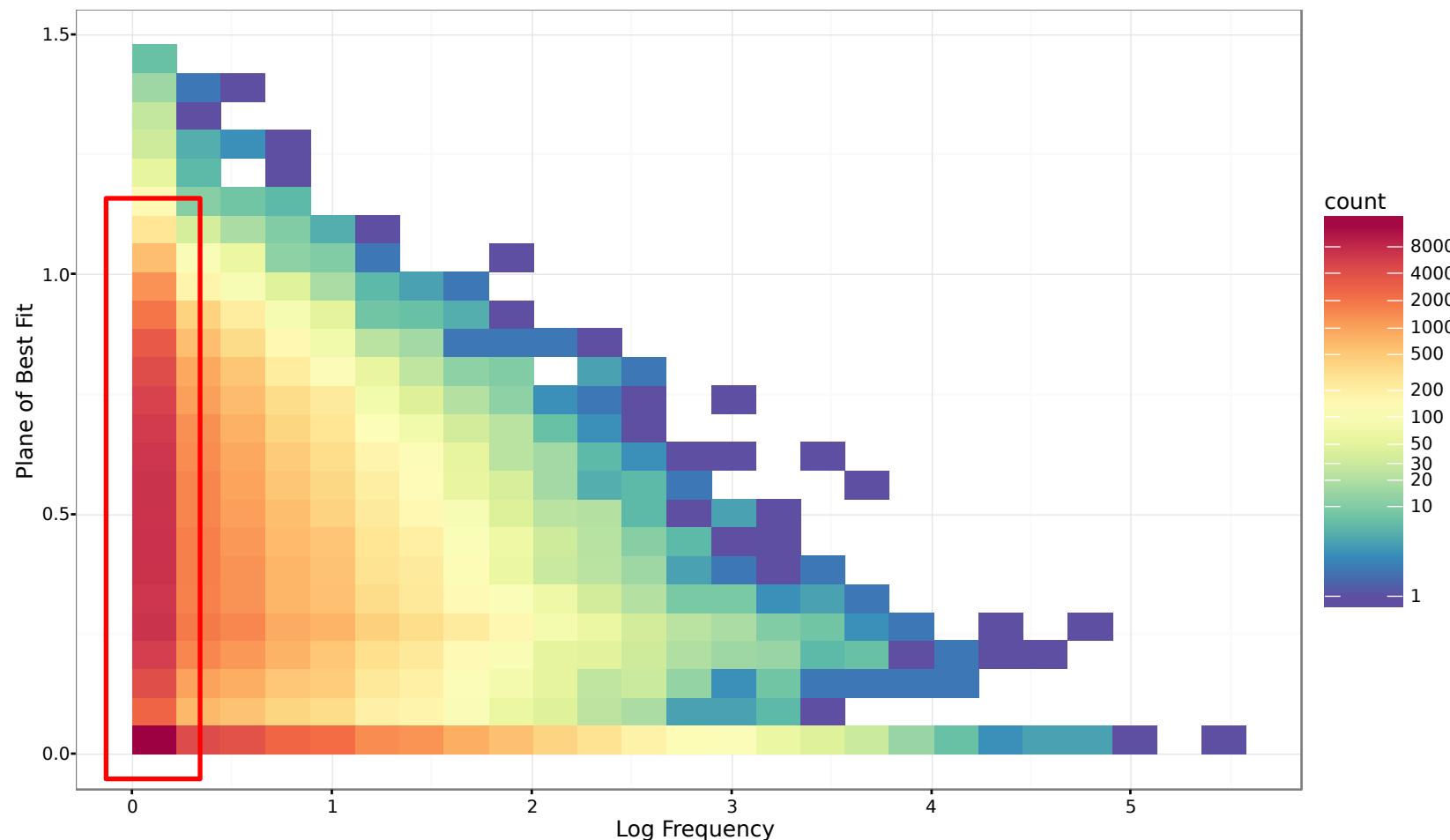
- New retrosynthetic fragmentation scheme published in 2015



**Most Substructures Tend Towards Planarity
Three-Dimensionality may Originate from Planar Moieties**

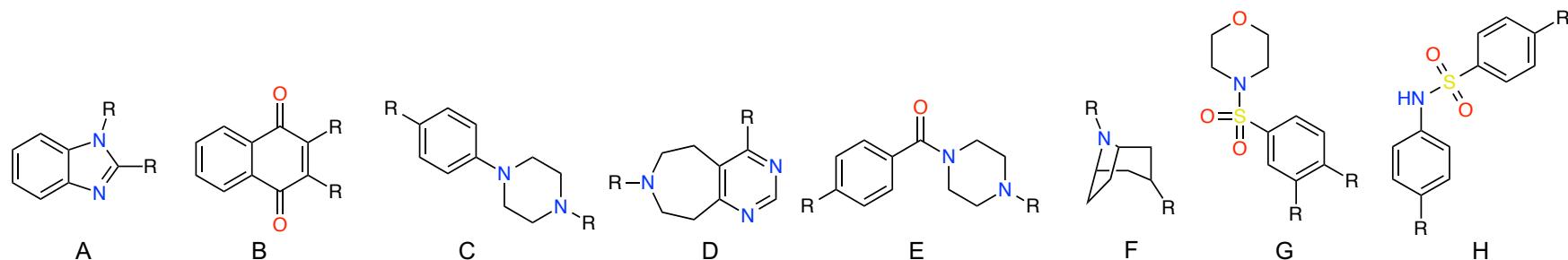
1. Firth, N. C.; Atrash, B.; Brown, N.; Blagg, J. MOARF, an Integrated Workflow for Multiobjective Optimization: Implementation, Synthesis, and Biological Evaluation. *J. Chem. Inf. Model.* **2015**, 55(6), 1169-1180.

SynDiR Analysis

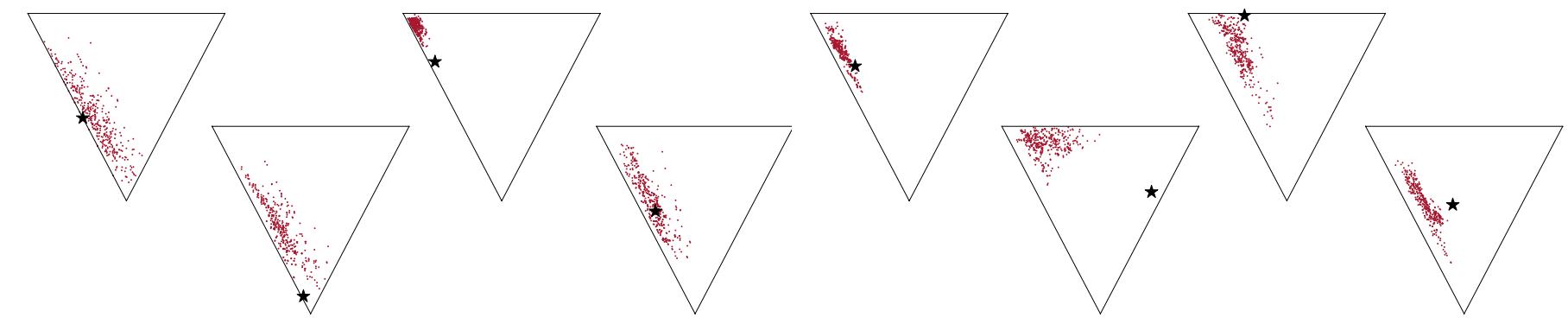


**Most Substructures Tend Towards Planarity
Three-Dimensionality may Originate from Planar Moieties**

Scaffold *versus* Enumerated Libraries



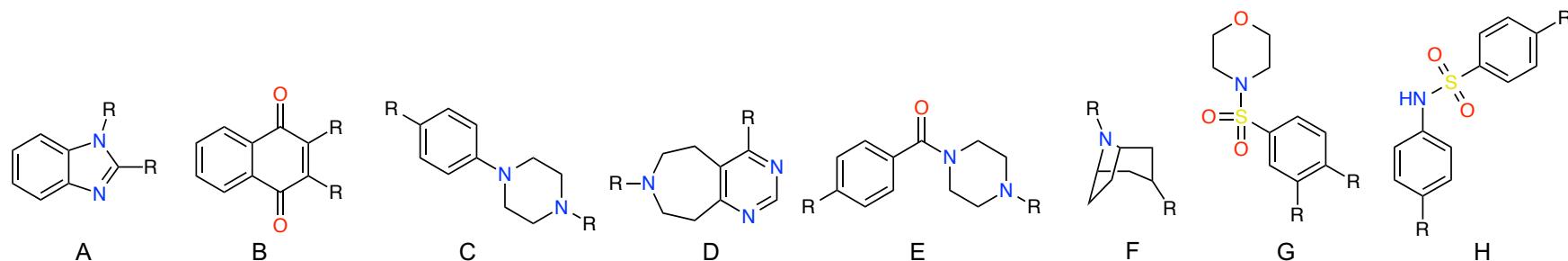
Increasing PBF



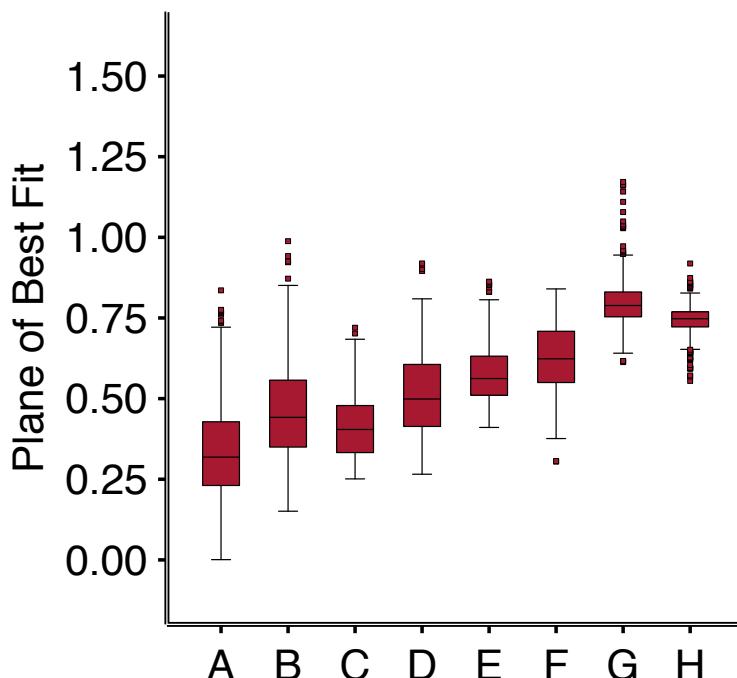
★ Core scaffold
• Enumerated library

Medicinal Chemistry Relevant Scaffolds Tend Towards Planarity

Scaffold *versus* Enumerated Libraries



Increasing PBF



Greater Increase in
Three-Dimensionality
when Starting from
Flatter Scaffolds

Summary & Conclusions

- **Presented approaches to analysing three-dimensionality**
 - Exemplified medicinal chemistry space
 - Paring back structures to scaffolds
 - Fragmenting into constituent substructures
 - Enumerating virtual libraries
- **When and where can we enrich three-dimensionality?**
 - Constituent substructures are relatively planar
 - Medicinal chemistry scaffolds are typically flat
 - Three-dimensionality can be modulated in design
 - We do not need inherent 3D in scaffolds & groups

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RESEARCH
UK



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Medicinal Chemistry

- Julian Blagg



The Conformer Problem...

...with apologies to Greg!

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...with apologies to Greg!



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...with apologies to Greg!

