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Bioisosteres in Medicinal Chemistry

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In Silico Medicinal Chemistry, Cancer Research UK Cancer Therapeutics Unit
Division of Cancer Therapeutics
The Institute of Cancer Research

SCI Molecular Interactions in Drug Discovery, Cambridge, UK
Thursday 21st March 2013

Making the discoveries that defeat cancer

What is a Bioisostere?

Bioisosteres

- Structural moieties with broadly similar shape and function
- Function should be biological but modulate other properties
- **Bioisosteric replacement**: replacement of functional groups

Molecular Scaffolds

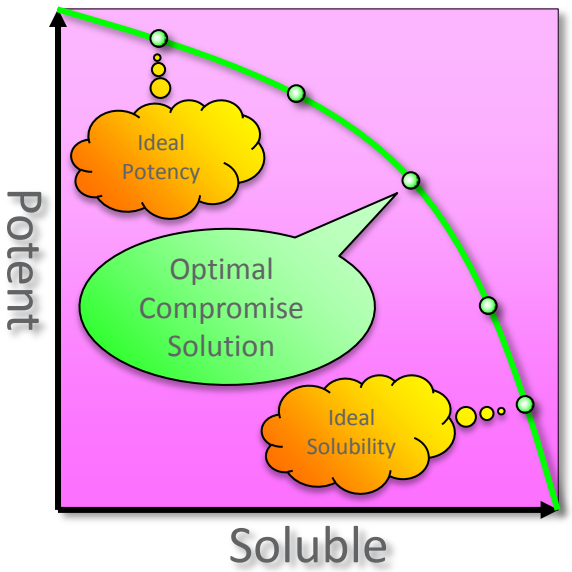
- Subset of bioisosterism
- Identification of the core functional or structural element
- **Scaffold hopping**: replacement of core element

The ***molecular interactions*** must be maintained

- Important to mimic **shape** and **function**

1. Papadatos, G.; Brown, N. *In Silico* Applications of Bioisosterism in Contemporary Medicinal Chemistry Practice. *Wiley Interdisciplinary Reviews: Computational Molecular Science* **2013**, *in press*.
2. Langdon, S. R.; Ertl, P.; Brown, N. Bioisosteric Replacement and Scaffold Hopping in Lead Generation and Optimization. *Mol. Inf.* **2010**, *29*, 366-385.

Why Bioisosteres?



Many properties can be modulated with appropriate bioisosteres:

- Improved selectivity
- Fewer side effects
- Decreased toxicity
- Improved pharmacokinetics: solubility/hydrophobicity
- Increased metabolic stability
- Simplified synthetic routes
- Patented lead compounds

Drug Design is Inherently a Multiobjective Optimisation Problem

1. Nicolaou, C. A.; Brown, N. Multi-objective optimization methods in drug design. *Drug Discovery Today: Technol.* **2013**, *in press*.

Irving Langmuir, 1919

Irving Langmuir
1881 – 1957

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE GENERAL ELECTRIC COMPANY.]

ISOMORPHISM, ISOSTERISM AND COVALENCE.

BY IRVING LANGMUIR.

Received June 30, 1919.

TABLE I.
List of Isosteres.

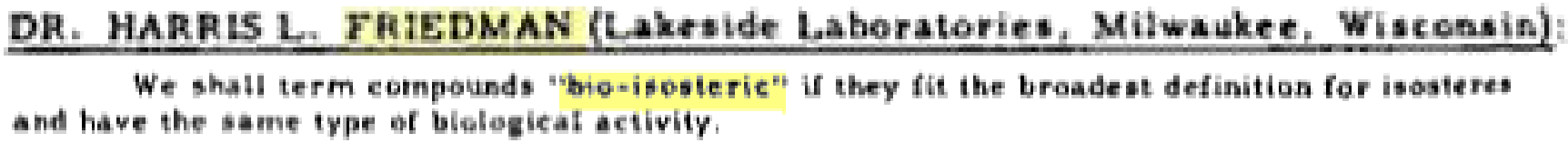
Type.	
1	H^-, He, Li^+
2	O^{--}, F^-, Ne, Na^+, Mg^{++}, Al^{+++}
3	S^{--}, Cl^-, A, K^+, Ca^{++}
4	Cu^+, Zn^{++}
5	Br^-, Kr, Rb^+, Sr^{++}
6	Ag^+, Cd^{++}
7	I^-, Xe, Cs^+, Ba^{++}
8	N_2, CO, CN^-
9	CH_4, NH_4^+
10	CO_2, N_2O, N_3^-, CNO^-
11	NO_3^-, CO_3^{--}
12	NO_2^-, O_3
13	HF, OH^-
14	ClO_4^-, SO_4^{--}, PO_4^{---}
15	ClO_3^-, SO_3^{--}, PO_3^{---}
16	SO_3, PO_3^-
17	$S_2O_6^{--}$, $P_2O_6^{----}$
18	$S_2O_7^{--}$, $P_2O_7^{----}$
19	SiH_4, PH_4^+
20	MnO_4^-, CrO_4^{--}
21	SeO_4^{--}, AsO_4^{---}

The octet theory of valence indicates that if compounds having the same number of atoms have also the same total number of electrons, the electrons may arrange themselves in the same manner. In this case the compounds or groups of atoms are said to be isosteric. Such compounds should show remarkable similarity in physical properties, that is, in those properties which do not involve a separation of the atoms in the molecule.

1. Langmuir, I. Isomorphism, Isosterism and Covalence. *J. Am. Chem. Soc.* **1919**, *41*, 1543-1559.

Harris L. Friedman, 1951

- Friedman first coined the term bio-isosteric in 1951:



DR. HARRIS L. FRIEDMAN (Lakeside Laboratories, Milwaukee, Wisconsin):

We shall term compounds "bio-isosteric" if they fit the broadest definition for isosteres and have the same type of biological activity.

- "We shall term compounds "bio-isosteric" if they fit the broadest definition for isosteres and have the same type of biological activity."

1. Friedman, H. L. Influence of isosteric replacements upon biological activity. In: *First Symposium on Chemical-biological Correlation*, May 26-27, 1950, NAS-NRS Publication No. 206, Washington, D.C., pp. 295-362, **1951**.

Craig W. Thornber, 1979

Isosterism and Molecular Modification in Drug Design

By C. W. Thornber
IMPERIAL CHEMICAL INDUSTRIES LIMITED, PHARMACEUTICALS DIVISION, MERESIDE, ALDERLEY PARK, MACCLESFIELD, CHESHIRE, SK10 4TG

The element of a molecule being modified may have one or more of the following roles.

(i) *Structural*. If the moiety has a structural role in holding other functionalities in a particular geometry, parameters such as size and bond angle will be important. The moiety may be buried deep in the molecule and have little contact with the external medium.

(ii) *Receptor interactions*. If the moiety to be replaced is concerned with a specific interaction with a receptor or enzyme its size, shape, electronic properties, pK_a, chemical reactivity, and hydrogen bonding will be the important parameters.

(iii) *Pharmacokinetics*. The moiety to be replaced may be necessary for the absorption, transport, and excretion of the compound. In this case lipophilicity, hydrophilicity, hydrogen bonding, and pK_a are likely to be important.

(iv) *Metabolism*. The moiety may be involved in blocking or aiding metabolism. In this case chemical reactivity will be an important parameter. For example chloro and methyl substituents on a benzene ring may be interchangeable for certain purposes but the toluene derivative can be metabolized to a benzoic acid and may therefore have a shorter half-life or unexpected side effects.

(A) A given molecular modification may allow some, but probably not all of the parameters (*a*)—(*h*) to be kept the same.

(B) Whether the same or a different biological activity results from the replacement will be governed by the role(s) which that moiety fulfils in the molecule and whether parameters affecting that role have been disturbed.

(C) From (A) and (B) it follows that what proves to be a good bioisosteric replacement in one series of compounds will not necessarily be useful in another.

Table 1

1) *Univalent atoms and groups*

F, OH, SH, I, Br, NH_2, PH_2, Bu^t, Pr^i, Me, Cl

2) *Bivalent atoms and groups*

O, CO_2R, S, COSR, Se, $COCH_2R$, CH_2, CONHR, H—N—

3) *Tervalent atoms and groups*

—N=, —P=, —CH=, —As=

4) *Quadrivalent atoms*

—C—, —Si—

5) *Ring equivalents*

—CH=CH—, =C—H, S, =N— *e.g.* benzene: thiophen; *e.g.* benzene: pyridine

—O—, —S—, $—CH_2—$, —NH—

(*a*) Size.

(*b*) Shape (bond angles, hybridization).

(*c*) Electronic distribution (polarizability, inductive effects, charge, dipoles).

(*d*) Lipid solubility.

(*e*) Water solubility.

(*f*) pK_a.

(*g*) Chemical reactivity (including likelihood of metabolism).

(*h*) Hydrogen bonding capacity.

1. Thornber, C. W. Isosterism and molecular modification in drug design. *Progress in Drug Research* **1979**, *37*, 563-580.

Exploration *versus* Exploitation

Exploration

"... includes things captured by terms such as search, variation, risk taking, experimentation, play, flexibility, discovery, innovation."

All Exploration: "...the costs of experimentation without any of its benefits." Undeveloped ideas, little distinctive competence."

Exploitation

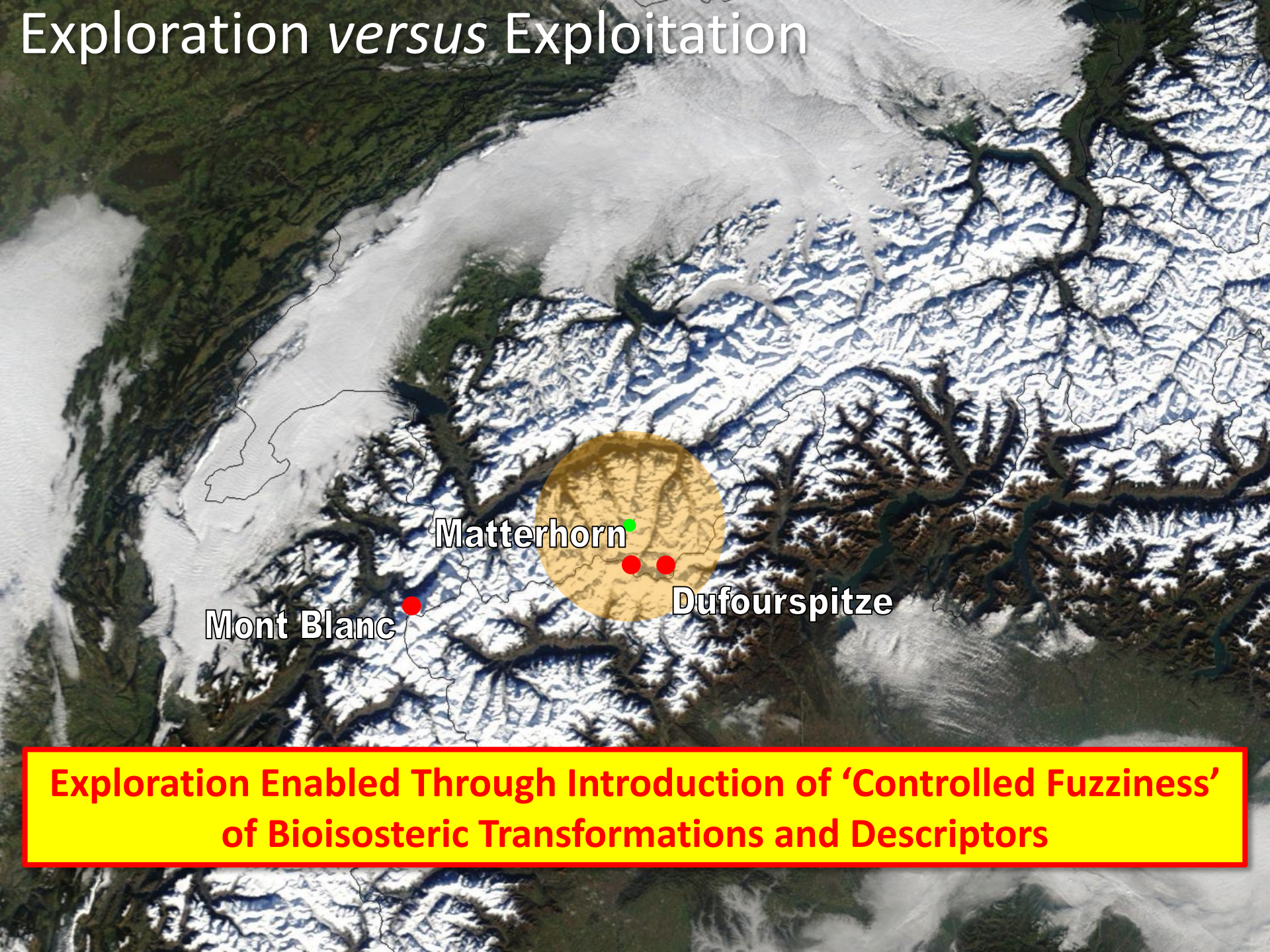
"... includes such things as refinement, choice, production, efficiency, selection, implementation, execution."

All Exploitation: "Locked-in to suboptimal equilibria (local maxima). Can't adapt to changing circumstances."

Feedback to exploitation occurs much more quickly. Increasing returns can lead to lock-in at a suboptimal equilibrium.
"...these tendencies to increase exploitation and reduce exploration make adaptive processes potentially self-destructive."

1. March, J. G. Exploration and Exploitation in Organizational Learning. *Org. Sci.* **1991**, *2*, 71-87.

Exploration *versus* Exploitation



Exploration Enabled Through Introduction of ‘Controlled Fuzziness’ of Bioisosteric Transformations and Descriptors

Methods to Identify Bioisosteres

- **Databases**
  - BIOSTER
  - ChEMBL – Matched Molecular Pairs
  - Cambridge Structural Database (CSD) **[next talk]**

- **Descriptors**
  - Physicochemical properties
  - Molecular Topology
  - Molecular Shape
  - Protein Structure

1. Papadatos, G.; Brown, N. *In Silico* Applications of Bioisosterism in Contemporary Medicinal Chemistry Practice. *Wiley Interdisciplinary Reviews: Computational Molecular Science* **2013**, *in press*.

BIOSTER Database – István Ujváry

- Database of ~26,000 bioisosteric transformations
- Bio-analogous pairs mined from the literature:
  - Systematic abstracting since 1970
- Compound pairs represented as hypothetical reactions
  - ‘bioisosteric transformations’
  - Compatible with most reaction-searching software

BIOSTER—A Database of Structurally Analogous Compounds

István Ujváry

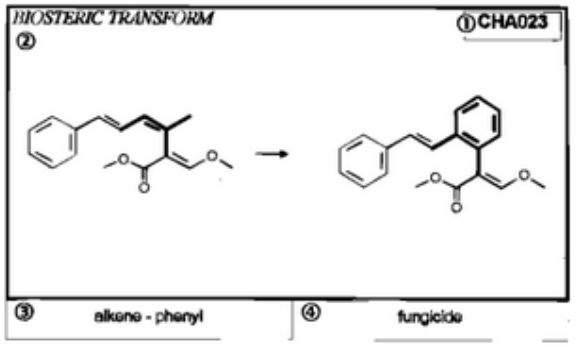
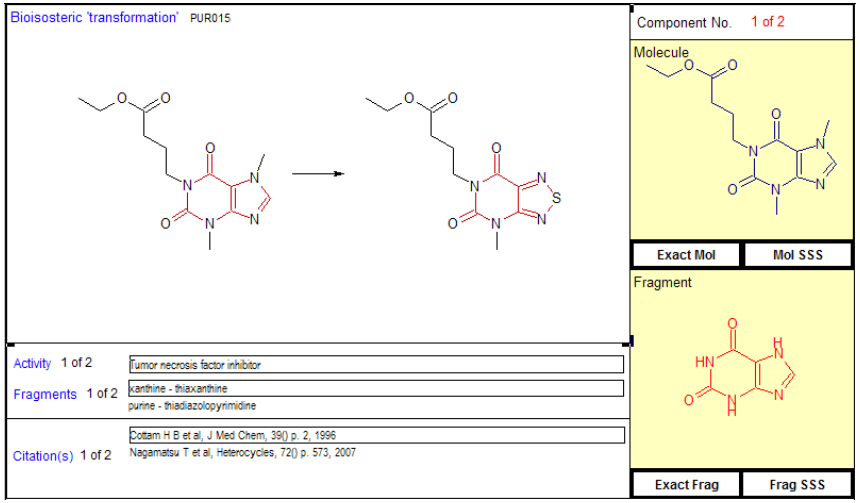


Fig. 1. Typical data form of *BIOSTER* database with field types as follows: ① ID code; ② structures of the biosteric transformation (biosteric fragments in the analogues are highlighted); ③ chemical fragment types relevant to transformation; ④ biological activity type related to the structures shown; ⑤ key references.



1. Ujváry, I. BIOSTER: a database of structurally analogous compounds. *Pesticide Science* **1997**, *51*, 92-95.
2. Distributed by Digital Chemistry: http://www.digitalchemistry.co.uk

Matched Molecular Pairs

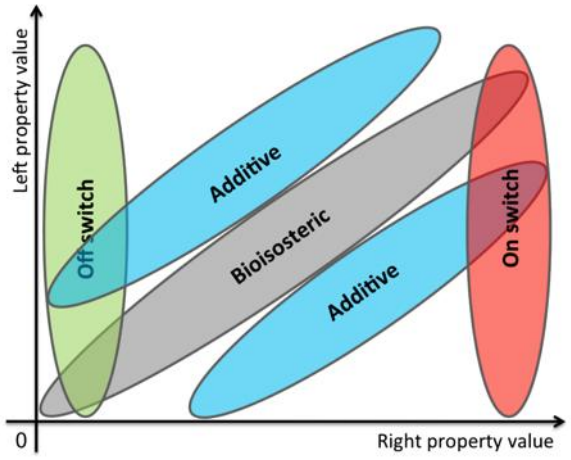
Journal of Medicinal Chemistry
PERSPECTIVE
pubs.acs.org/jmc

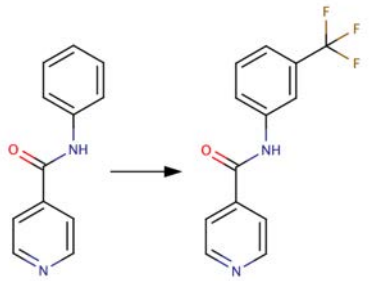
Matched Molecular Pairs as a Medicinal Chemistry Tool[†]

Miniperspective

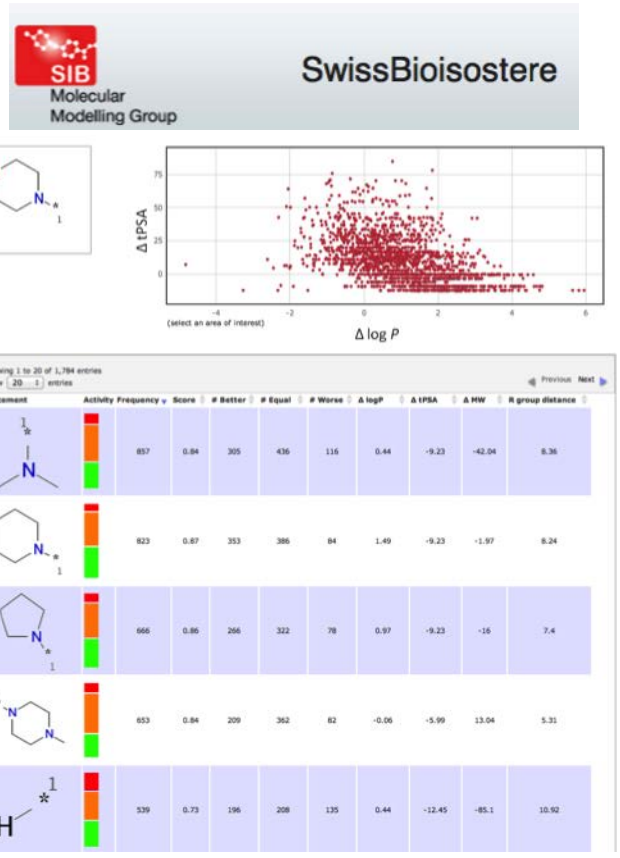
Ed Griffen,[†] Andrew G. Leach,[*,§] Graeme R. Robb,[§] and Daniel J. Warner[∥]

- Identification of molecules that differ in only one position
  - Can suggest structural changes to modulate biological or physicochemical properties





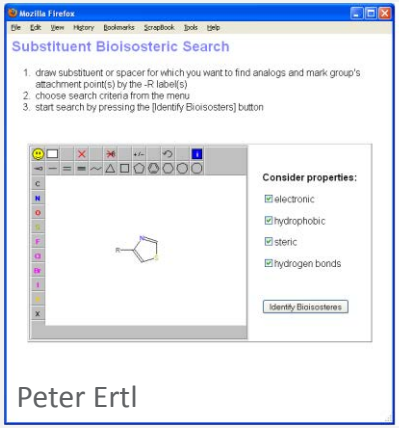
MMP Transformation:
H>>CF_3

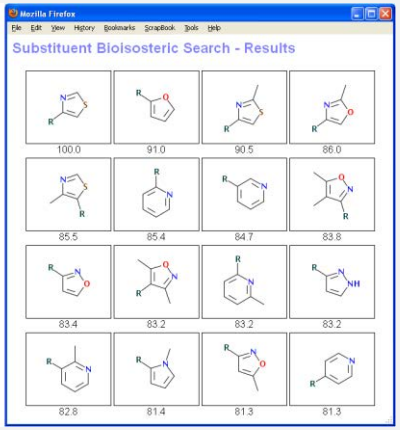


1. Kenny, P. W.; Sadowski, J. Structure Modification in Chemical Databases. In: *Chemoinformatics in Drug Discovery* (Ed. Oprea, T. T.). Wiley-VCH **2004**.
2. Griffen, E.; Leach A. G.; Robb, G. R.; Warner, D. J. Matched Molecular Pairs as a Medicinal Chemistry Tool. *J. Med. Chem.* **2011**, *54*, 7739-7750.
3. Wirth, M.; Zoete, V.; Michielin, O.; Sauer, W. SwissBioisostere: a database of molecular replacements for ligand design. *Nucleic Acids Research* **2012**, doi: 10.1093/nar/gks1059.: http://www.swissbioisostere.ch:8080/SwissBioisostere/

Bioisosteric Similarity Methods

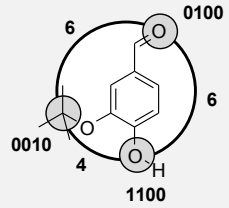
Physicochemical Properties





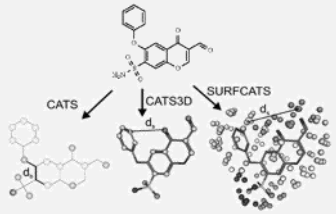
Peter Ertl

Molecular Topology

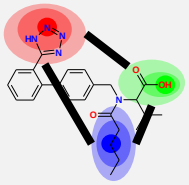


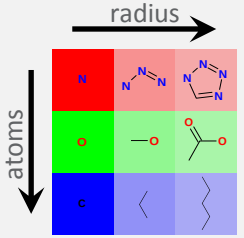
0010-4-1100-6-0100-6

Similog



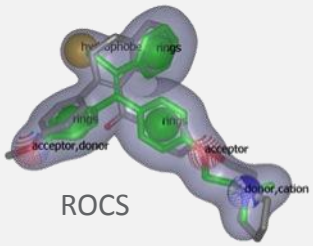
CATS



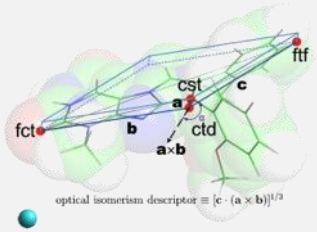


Hopfen

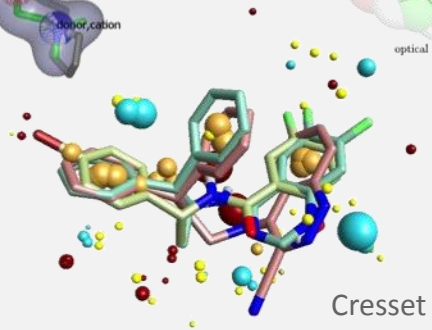
Molecular Shape



ROCS

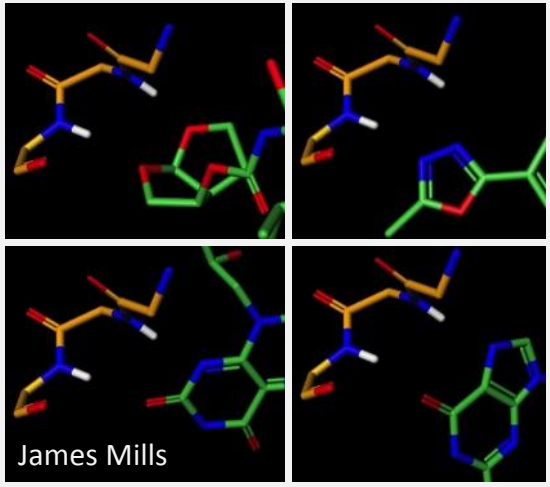


USR



Cresset

Protein Structure

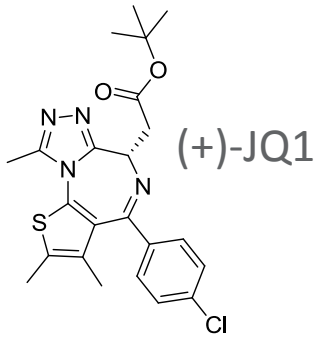


James Mills

Three-Dimensionality in Molecules

Mimicking natural products

- Natural products frequently incorporate 3D scaffolds



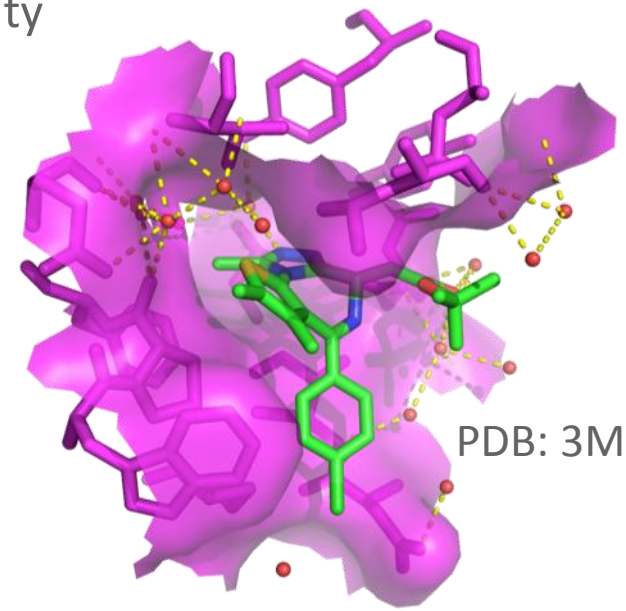
(+)-JQ1

Improvement in properties

- 3D shape often conveys improved aqueous solubility

Addressing new and challenging drug targets

- *e.g.* protein-protein interactions



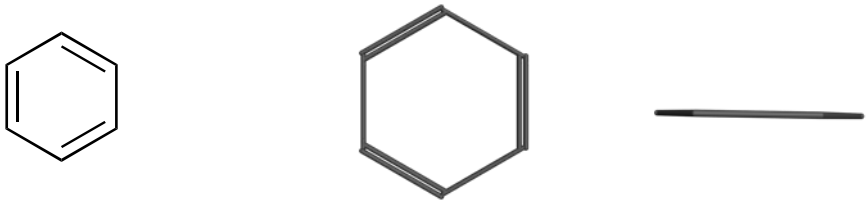
PDB: 3MXF

1. Fry, D. C. Protein–protein interactions as targets for small molecule drug discovery. *Curr. Protein Pept. Sci.* **2008**, *9*, 240-247.

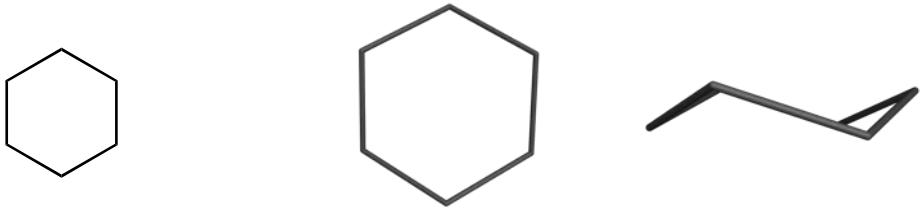
Definitions of Dimension

- A molecule is one dimensional (1D) if the centers of mass of the heavy atoms lie in a straight line.

- A molecule is two dimensional (2D) if the centers of mass of the heavy atoms lie in a plane.



- A molecule is 3D if it is not 2D.

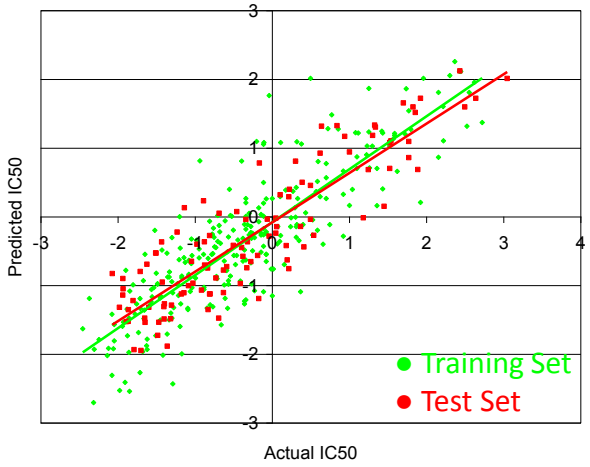


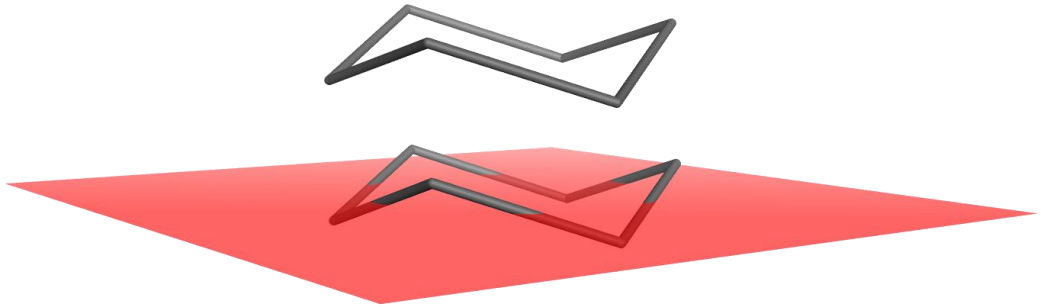
- This gives us the set of definitions needed in order to begin quantifying the property of 3D.[1]

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.

Plane of Best Fit

- Use the definitions given to **quantify** 3D character of a conformation.
- Describe a conformation of a molecule (3 or more heavy atoms) with a plane of best fit, using a least squares method.

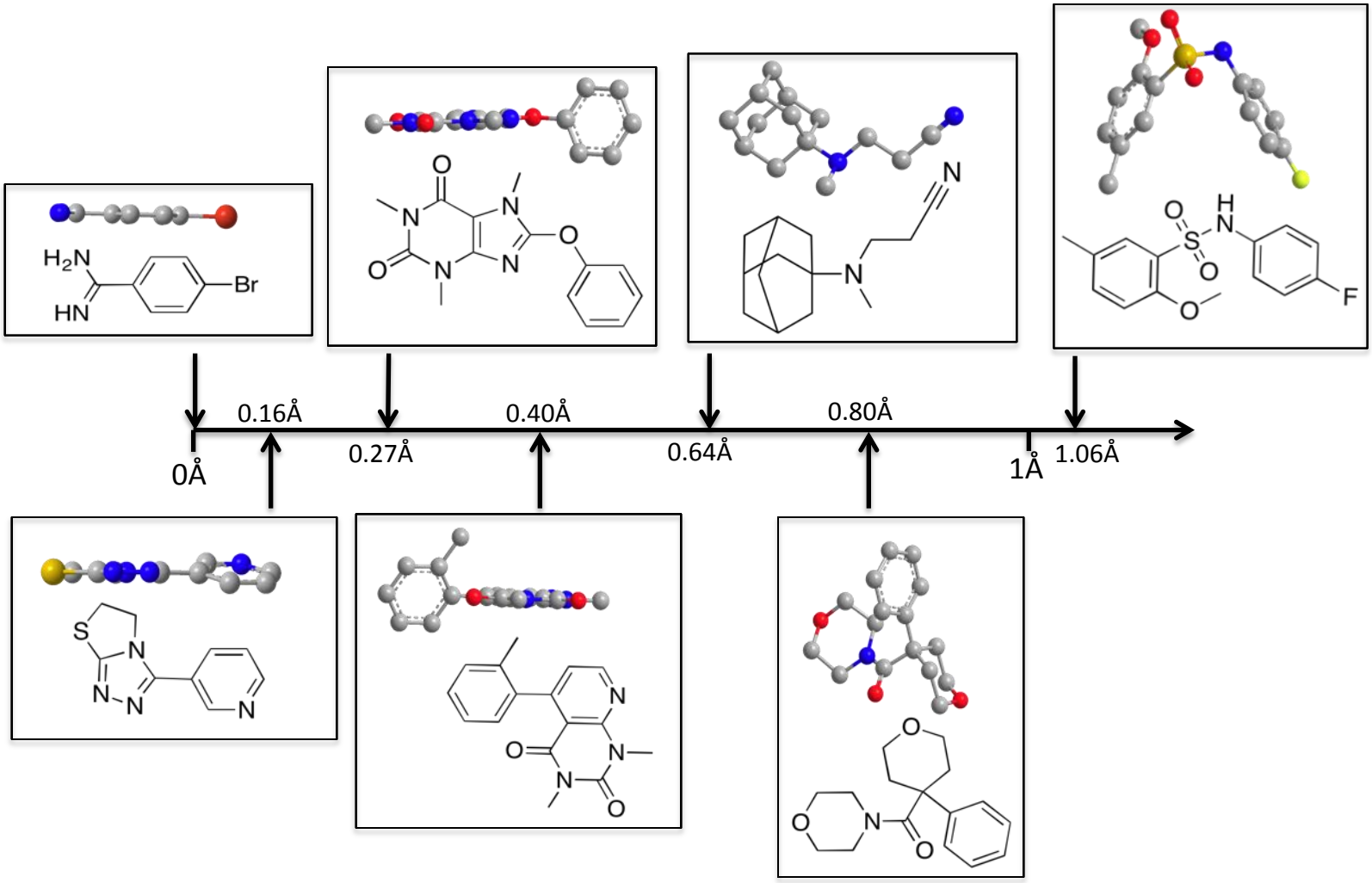




- This is used to give the distance in ångströms from each of the heavy atoms to the plane of best fit. The final output of this method is given by the mean of these distances.[1]

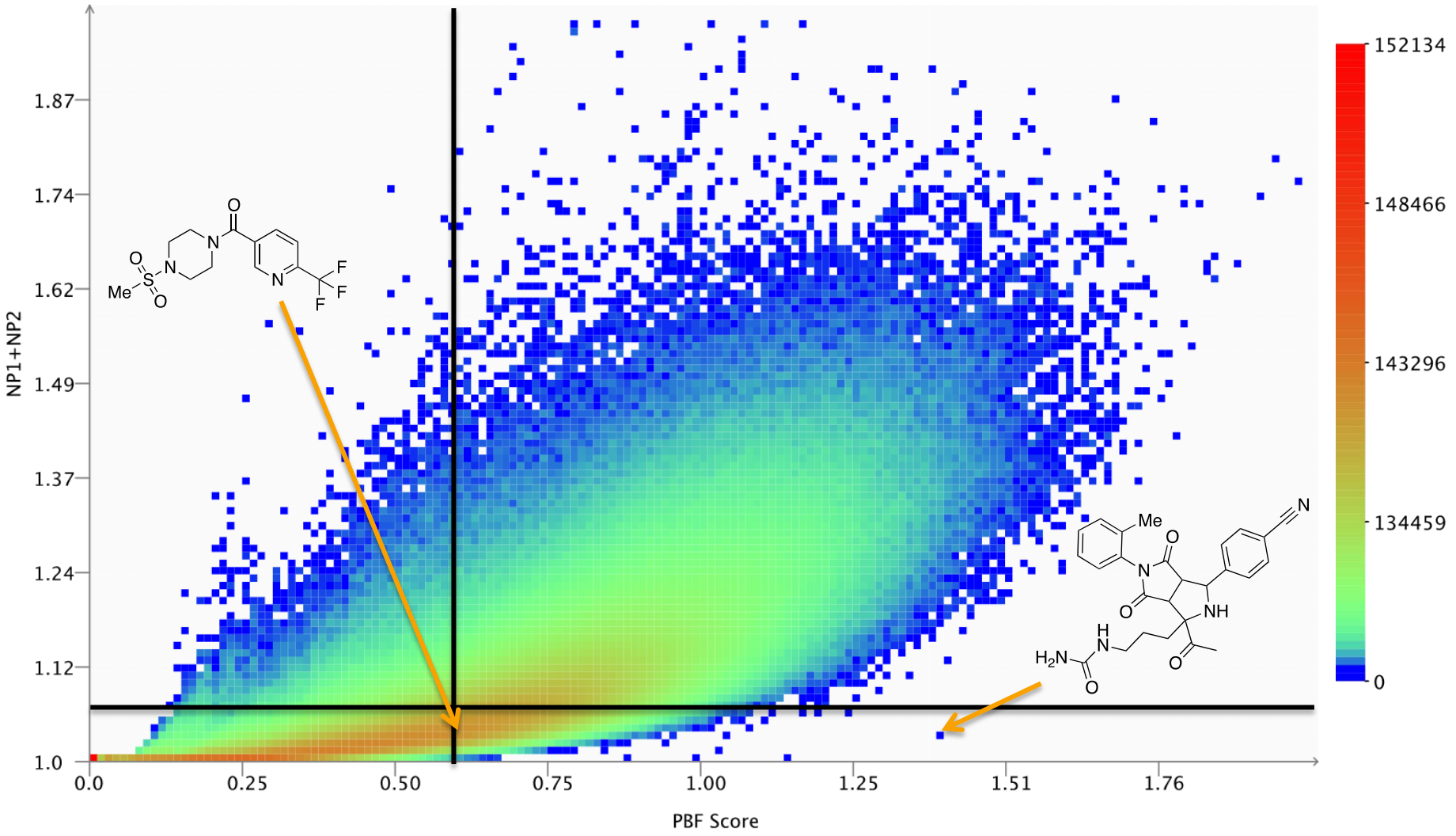
1. Firth, N. C.; Brown, N.; Blagg, J. Plane of Best Fit: A Novel Method to Characterize the Three-Dimensionality of Molecules. *J. Chem. Inf. Model.* **2012**, *52*, 2516-2525.

Examples of PBF Score



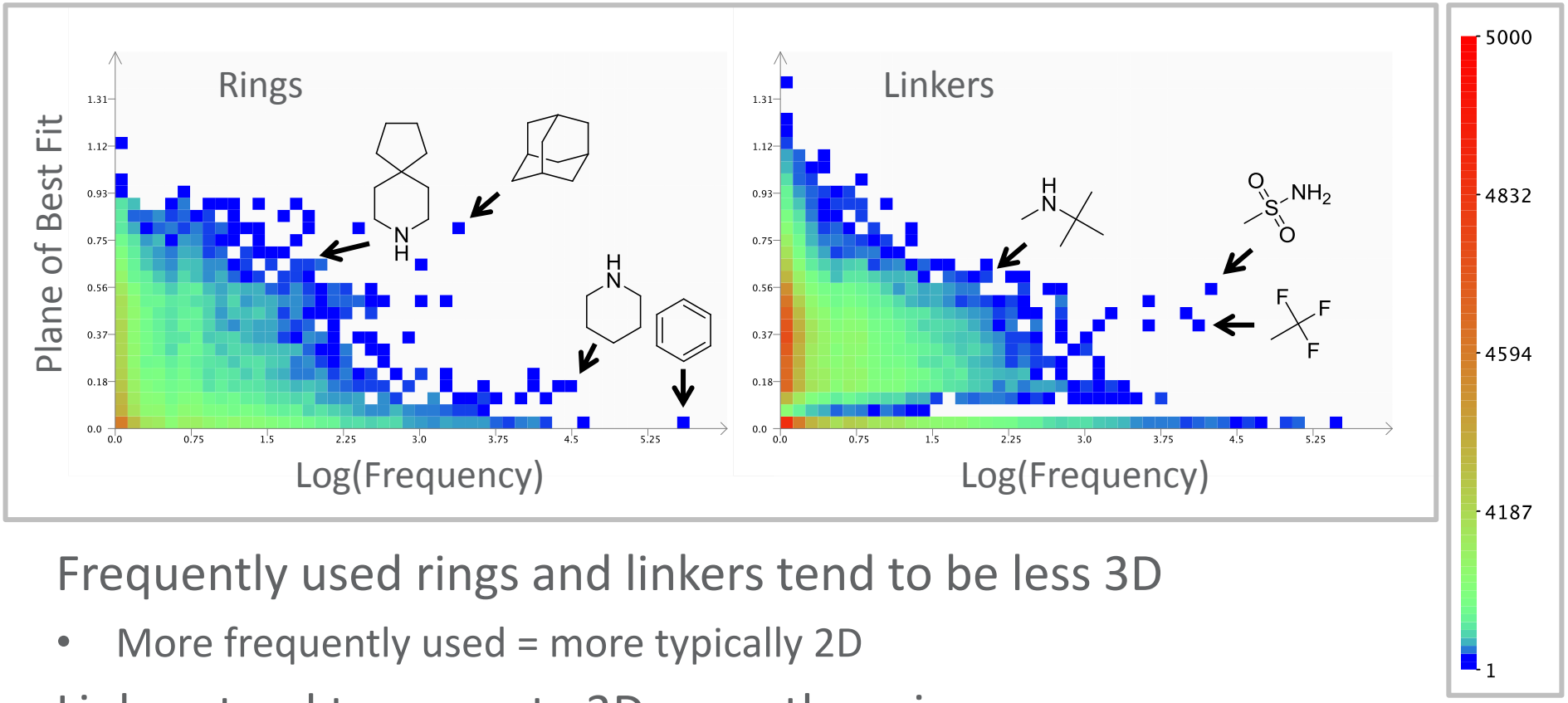
1. Firth, N. C.; Brown, N.; Blagg, J. Plane of Best Fit: A Novel Method to Characterize the Three-Dimensionality of Molecules. *J. Chem. Inf. Model.* **2012**, *52*, 2516-2525.

Where Can We Use Plane of Best Fit



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.

Return to Flatland



Frequently used rings and linkers tend to be less 3D

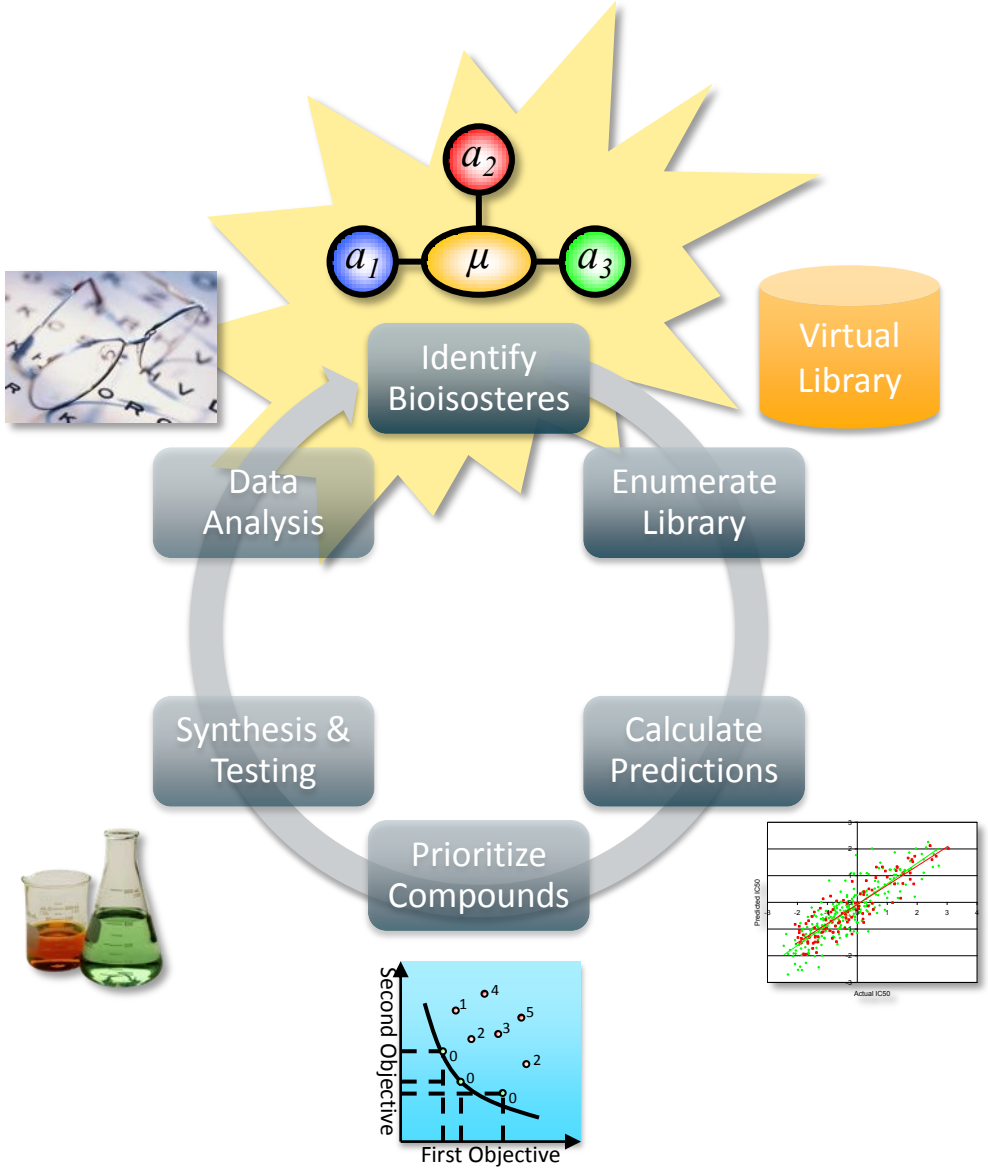
- More frequently used = more typically 2D

Linkers tend to promote 3D more than rings

Tendency to Promote 3D Connecting 2D Moieties in 3D Ways

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.

How Are Bioisosteres Used in Practice?



1. Brown, N. (Ed.) *Bioisosteres in Medicinal Chemistry*. Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, **2012**.
2. Nicolaou, C. A.; Brown, N. Multi-objective optimization methods in drug design. *Drug Discovery Today: Technol.* **2013**, *in press*.

Conclusions

Bioisosterism has seen more than a century of innovation

- Remains a difficult concept to define accurately, however…
- Databases of bioisosteric transforms routinely available
- Molecular descriptors allow for the exploration and validation of structurally disparate replacements

Exemplified medicinal chemistry space covers

- Flat things connected together in a 3D way
  - Bridges, spiro and quaternary centres, conformational restriction

Acknowledgements

In Silico Medicinal Chemistry

- Dr Fabio Broccatelli
- **Nick Firth**
- Sarah Langdon
- Dr Yi Mok
- Lewis Vidler

Medicinal Chemistry

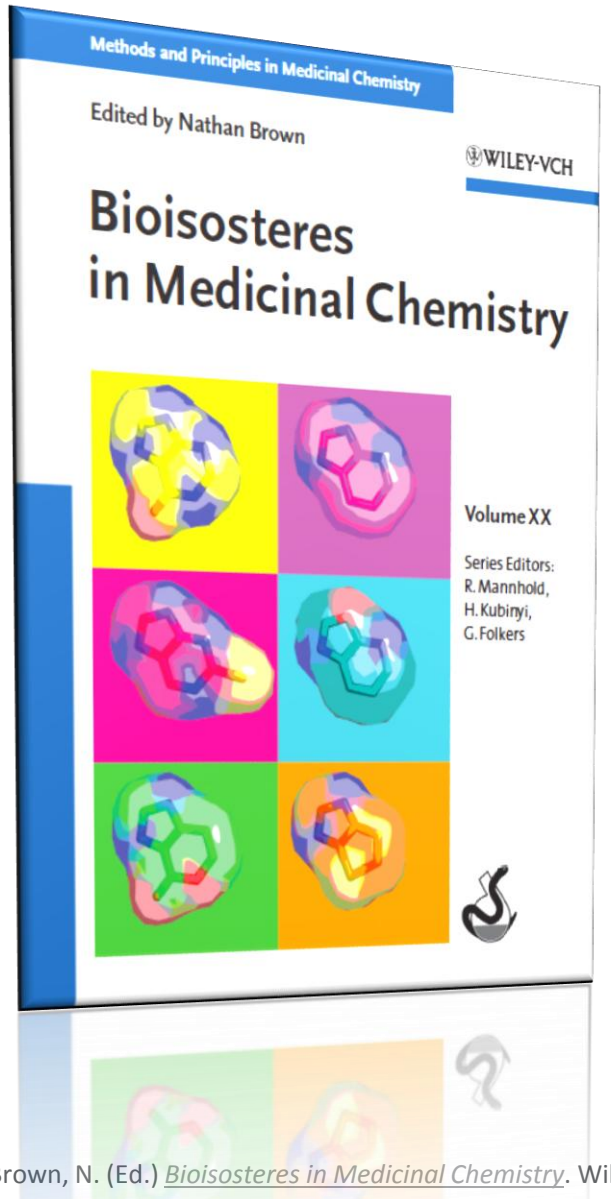
- **Prof. Julian Blagg**

CANCER RESEARCH UK

ICR The Institute of Cancer Research

Cancer Research UK Grant No. C309/A8274

Bioisosteres in Medicinal Chemistry



Contributions include:

- Principles
  - History, Classical Bioisosteres, Consequences
- Data Mining
  - BIOSTER, CCDC, ChEMBL
- Methods
  - Physicochemical, Topology, Shape, Protein
- Case Studies
  - Drug Guru, NPY-Y5 antagonists
- Perspectives

Abbott, BMS, CCDC, Digital Chemistry, EBI, Eli Lilly, ETH-Zurich, GSK, ICR, Novartis, Pfizer, Uni. Manchester, Uni. Sheffield

1. Brown, N. (Ed.) *Bioisosteres in Medicinal Chemistry*. Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, **2012**.