

# Bioisosteres in Medicinal Chemistry

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# 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

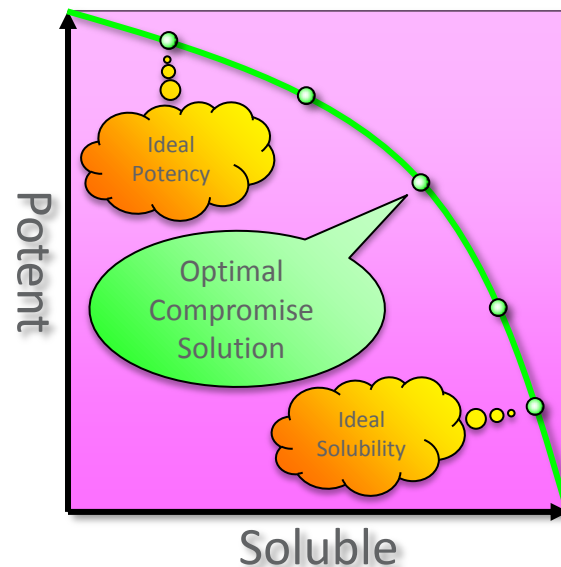
- Important to mimic **shape** and **function**

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**

# Irving Langmuir, 1919

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

## ISOMORPHISM, ISOSTERISM AND COVALENCE.

BY IRVING LANGMUIR.

Received June 30, 1919.



Irving Langmuir  
1881 – 1957

TABLE I.  
List of Isosteres.

Type.	
1.....	H <sup>-</sup> , He, Li <sup>+</sup>
2.....	O <sup>-</sup> , F <sup>-</sup> , Ne, Na <sup>+</sup> , Mg <sup>++</sup> , Al <sup>+++</sup>
3.....	S <sup>-</sup> , Cl <sup>-</sup> , A, K <sup>+</sup> , Ca <sup>++</sup>
4.....	Cu <sup>+</sup> , Zn <sup>++</sup>
5.....	Br <sup>-</sup> , Kr, Rb <sup>+</sup> , Sr <sup>++</sup>
6.....	Ag <sup>+</sup> , Cd <sup>++</sup>
7.....	I <sup>-</sup> , Xe, Cs <sup>+</sup> , Ba <sup>++</sup>
8.....	N <sub>2</sub> , CO, CN <sup>-</sup>
9.....	CH <sub>4</sub> , NH <sub>4</sub> <sup>+</sup>
10.....	CO <sub>2</sub> , N <sub>2</sub> O, N <sub>3</sub> <sup>-</sup> , CNO <sup>-</sup>
11.....	NO <sub>2</sub> <sup>-</sup> , CO <sub>3</sub> <sup>---</sup>
12.....	NO <sub>3</sub> <sup>-</sup> , O <sub>3</sub>
13.....	HF, OH <sup>-</sup>
14.....	ClO <sub>4</sub> <sup>-</sup> , SO <sub>4</sub> <sup>---</sup> , PO <sub>4</sub> <sup>---</sup>
15.....	ClO <sub>3</sub> <sup>-</sup> , SO <sub>3</sub> <sup>---</sup> , PO <sub>3</sub> <sup>---</sup>
16.....	SO <sub>2</sub> , PO <sub>2</sub> <sup>-</sup>
17.....	S <sub>2</sub> O <sub>8</sub> <sup>---</sup> , P <sub>2</sub> O <sub>8</sub> <sup>---</sup>
18.....	S <sub>2</sub> O <sub>3</sub> <sup>-</sup> , P <sub>2</sub> O <sub>3</sub> <sup>-</sup>
19.....	SiH <sub>4</sub> , PH <sub>4</sub> <sup>+</sup>
20.....	MnO <sub>4</sub> <sup>-</sup> , CrO <sub>4</sub> <sup>---</sup>
21.....	SeO <sub>4</sub> <sup>---</sup> , AsO <sub>4</sub> <sup>---</sup>



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.

# 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.”

## 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.

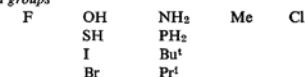
(A) A given molecular modification may allow some, but probably not all of the parameters (a)—(h) to be kept the same.

(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.

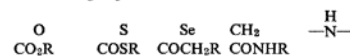
(C) From (A) and (B) it follows that what proves to be a good bioisosteric replacement in one series of compounds will not necessarily be useful in another.

Table 1

1) Univalent atoms and groups



2) Bivalent atoms and groups



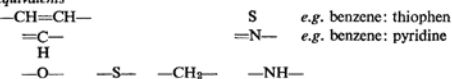
3) Trivalent atoms and groups



4) Quadrivalent atoms



5) Ring equivalents



- Size.
- Shape (bond angles, hybridization).
- Electronic distribution (polarizability, inductive effects, charge, dipoles).
- Lipid solubility.
- Water solubility.
- $pK_a$ .
- Chemical reactivity (including likelihood of metabolism).
- Hydrogen bonding capacity.

# 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.”**



# Exploration *versus* Exploitation



Mont Blanc

Matterhorn

Dufourspitze

**Exploration Enabled Through Introduction of 'Controlled Fuzziness' of Bioisosteric Transformations and Descriptors**



# Methods to Identify Bioisosteres

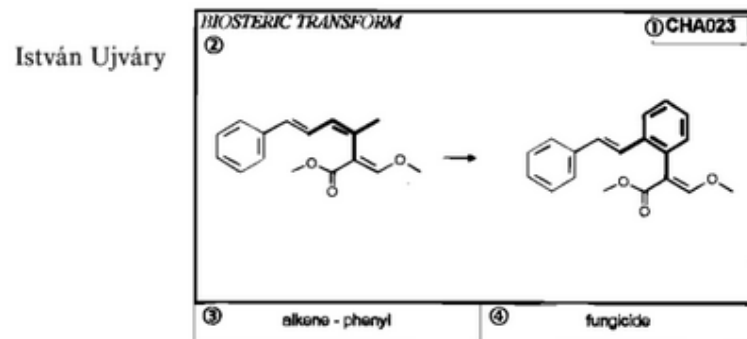
- **Databases**
  - BIoSTER
  - ChEMBL – Matched Molecular Pairs
  - Cambridge Structural Database (CSD) [**next talk**]
- **Descriptors**
  - Physicochemical properties
  - Molecular Topology
  - Molecular Shape
  - Protein Structure

# BIOSTER Database – István Ujváry

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- 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



**Fig. 1.** Typical data form of *BIOSTER* database with field types as follows: ① ID code; ② structures of the bioisosteric transformation (bioisosteric 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.

Bioisosteric 'transformation' PUR015

Activity 1 of 2 Tumor necrosis factor inhibitor

Fragments 1 of 2  
kxanthine - thioxanthine  
purine - thiazolopyrimidine

Citation(s) 1 of 2  
Cottam H B et al, J Med Chem, 38() p. 2, 1996  
Nagamatsu T et al, Heterocycles, 72() p. 573, 2007

Component No. 1 of 2

Molecule

Exact Mol Mol SSS

Fragment

Exact Frag Frag SSS

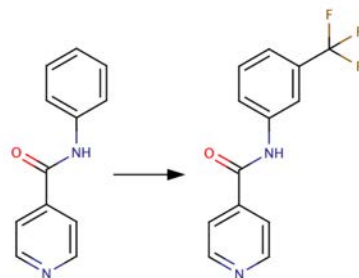
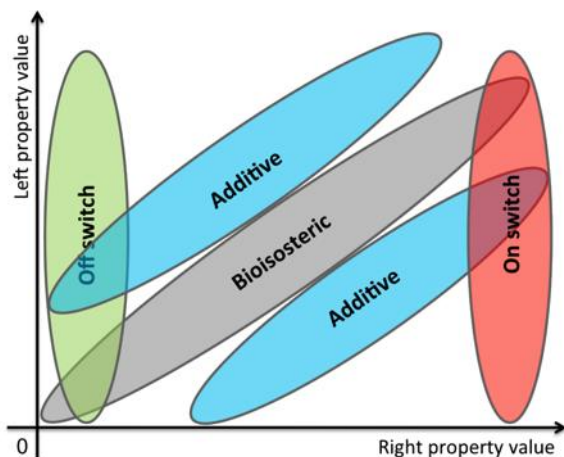
1. Ujváry, I. *BIOSTER: a database of structurally analogous compounds*. *Pesticide Science* **1997**, *51*, 92-95.
2. Distributed by Digital Chemistry: <http://www.digitalchemistry.co.uk>

## Matched Molecular Pairs as a Medicinal Chemistry Tool<sup>†</sup>

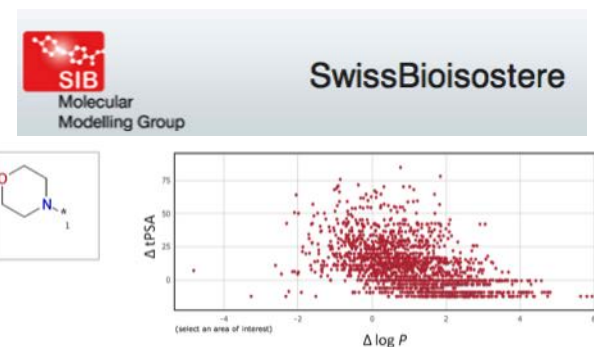
### Miniperspective

Ed Griffen,<sup>†</sup> Andrew G. Leach,<sup>\*,§</sup> Graeme R. Robb,<sup>§</sup> and Daniel J. Warner<sup>||</sup>

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



MMP Transformation:  
H >> CF<sub>3</sub>



Showing 1 to 20 of 1,784 entries  
Show (20) entries

Replacement	Activity Frequency	Score	# Better	# Equal	# Worse	Δ log P	Δ IPSA	Δ HW	R group distance
	837	0.84	305	436	116	0.44	-9.23	-42.04	8.36
	823	0.87	353	386	84	1.49	-9.23	-1.97	8.24
	666	0.86	266	322	78	0.97	-9.23	-16	7.4
	653	0.84	209	362	82	-0.06	-5.99	13.04	5.31
	539	0.73	196	208	135	0.44	-12.45	-85.1	10.92

1. Kenny, P. W.; Sadowski, J. *Structure Modification in Chemical Databases*. In: *Cheminformatics 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

**Substituent Bioisosteric Search**

- draw substructure or spacer for which you want to find analogs and mark group's attachment point(s) by the -R label(s)
- choose search criteria from the menu
- start search by pressing the [Identify Bioisosters] button

**Consider properties:**

- electronic
- hydrophobic
- steric
- hydrogen bonds

**Identify Bioisosters**

**Substituent Bioisosteric Search - Results**

100.0	91.0	90.5	86.0
85.5	85.4	84.7	83.8
83.4	83.2	83.2	83.2
82.8	81.4	81.3	81.3

Peter Ertl

## Molecular Topology

**0010-4-1100-6-0100-6**

**Similog**

**CATS**

**CATS3D**

**SURFCATS**

**Hopfen**

radius

atoms

N		
O		
C		

## Molecular Shape

**ROCS**

**USR**

optical isomerism descriptor =  $[c - (a \times b)]^{1/2}$

**Cresset**

## Protein Structure

**James Mills**



# Three-Dimensionality in Molecules

## Mimicking natural products

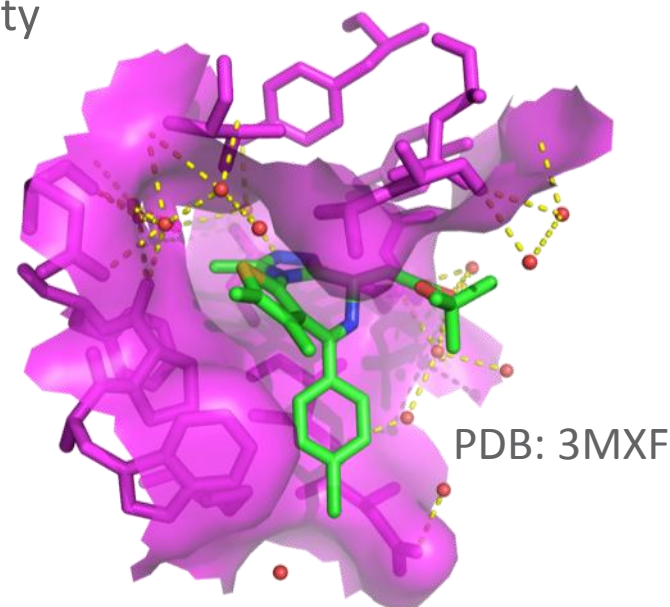
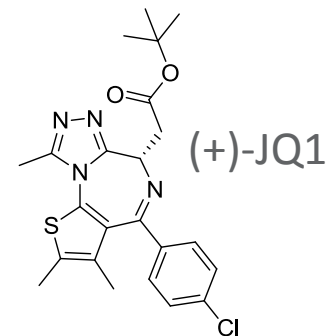
- Natural products frequently incorporate 3D scaffolds

## Improvement in properties

- 3D shape often conveys improved aqueous solubility

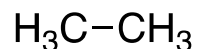
## Addressing new and challenging drug targets

- *e.g.* protein-protein interactions

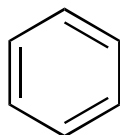


# Definitions of Dimension

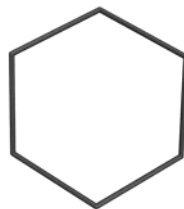
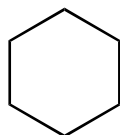
- A molecule is one dimensional (1D) if the centers of mass of the heavy atoms lie in a straight line.



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



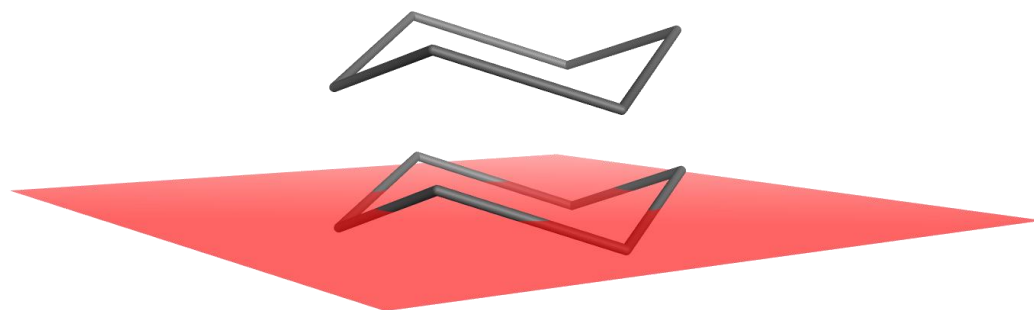
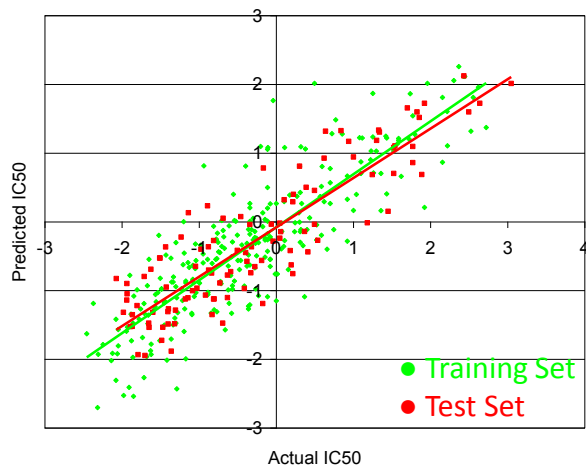
- A molecule is 3D if it is not 2D.



- This gives us the set of definitions needed in order to begin quantifying the property of 3D.<sup>1</sup>

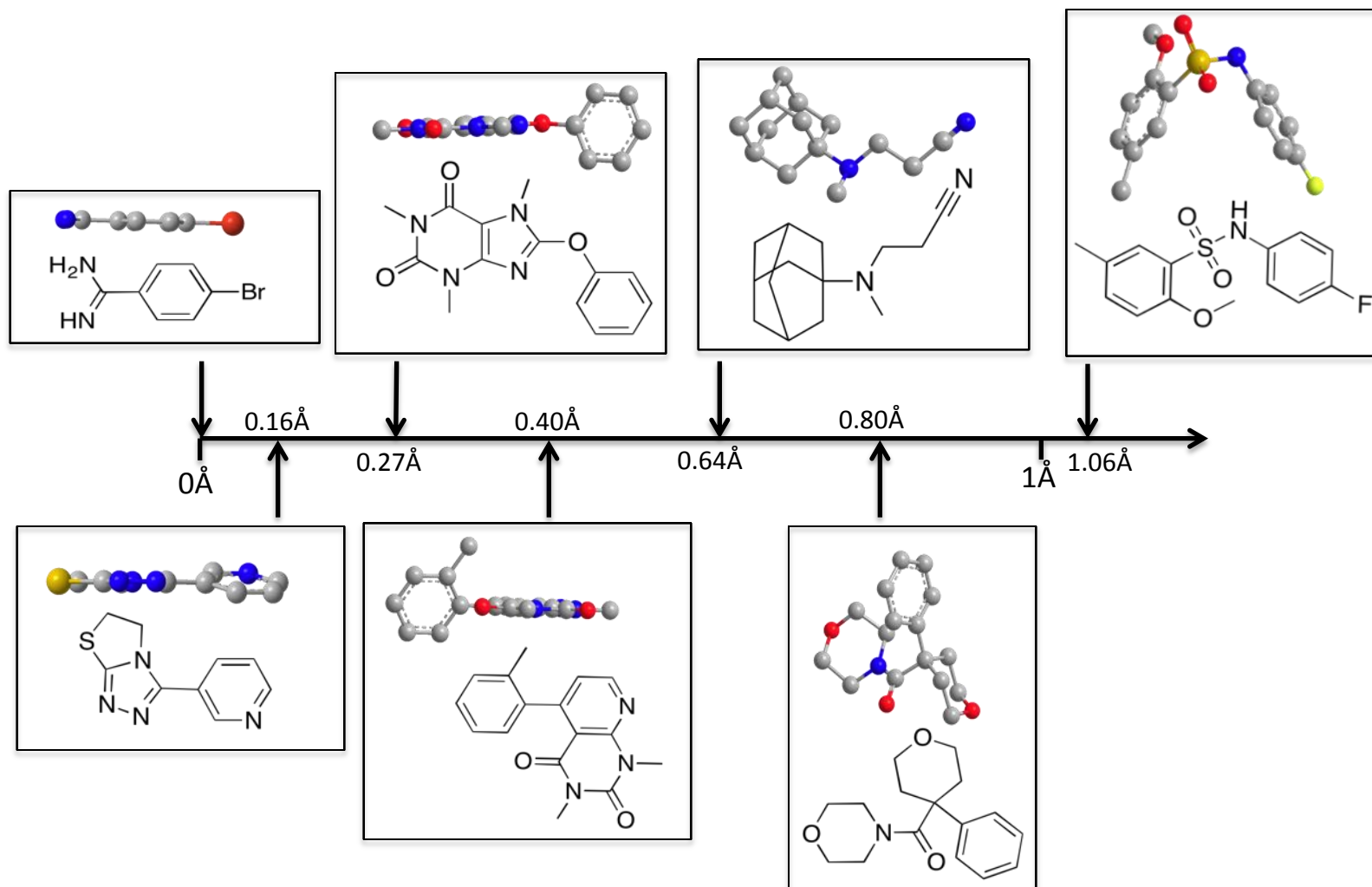
# Plane of Best Fit

- 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.<sup>1</sup>

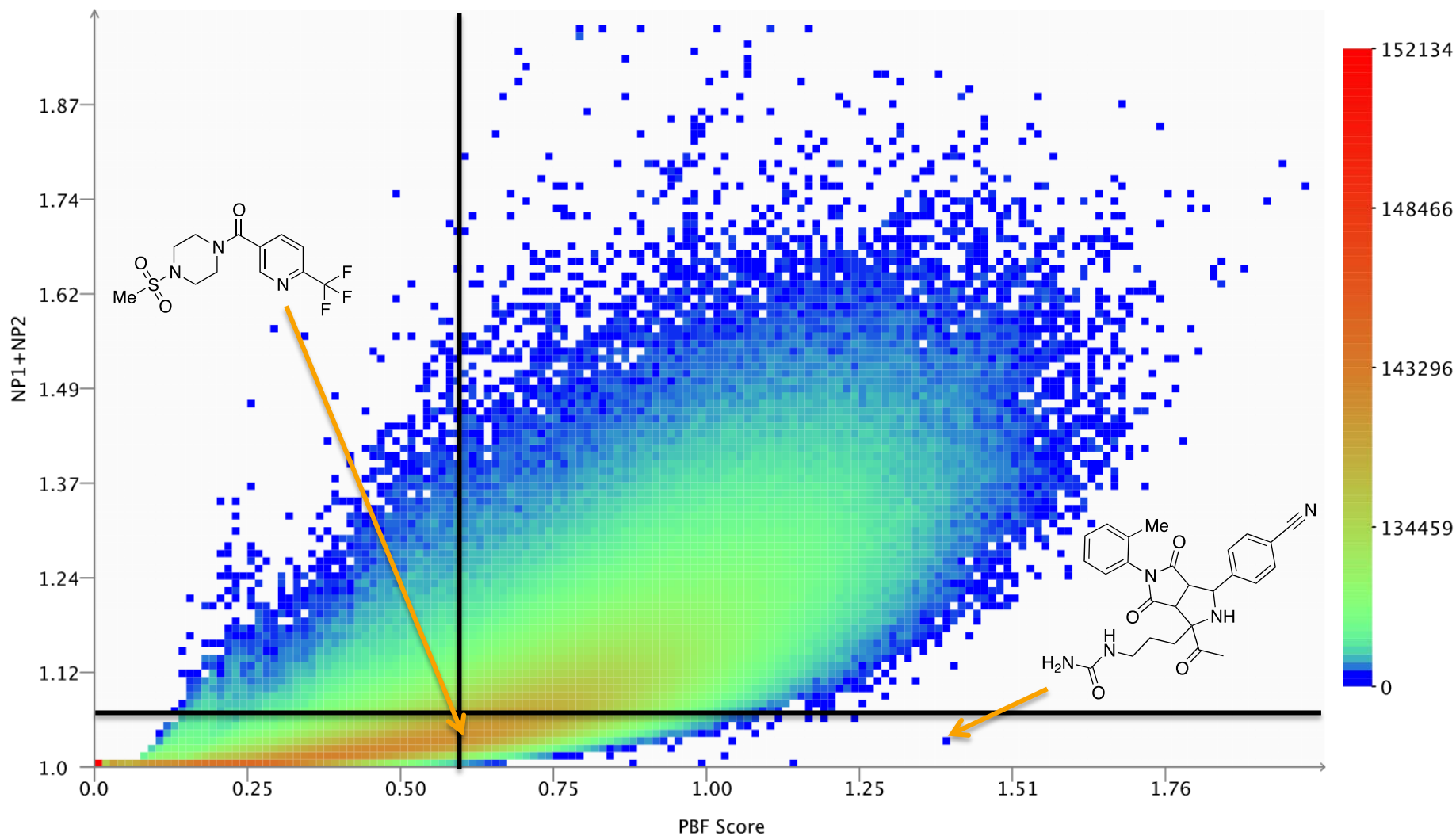
# Examples of PBF Score





# Where Can We Use Plane of Best Fit

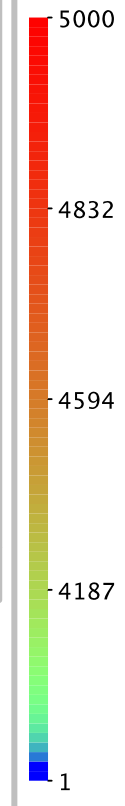
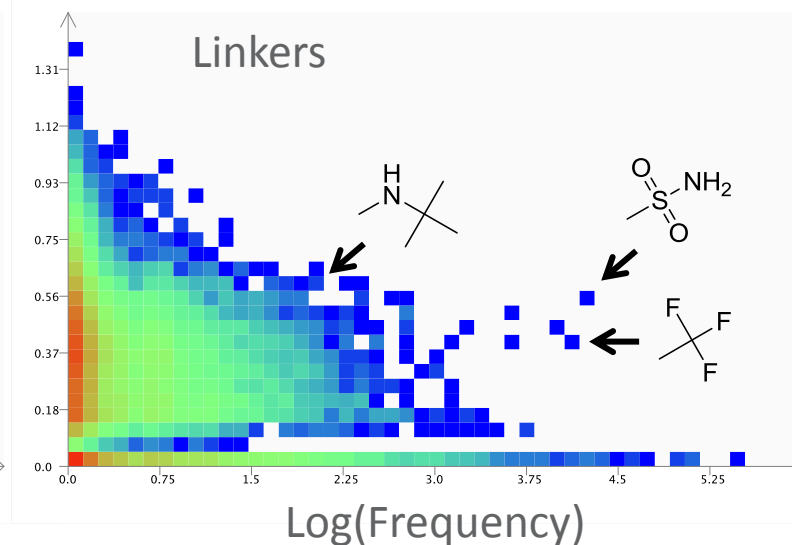
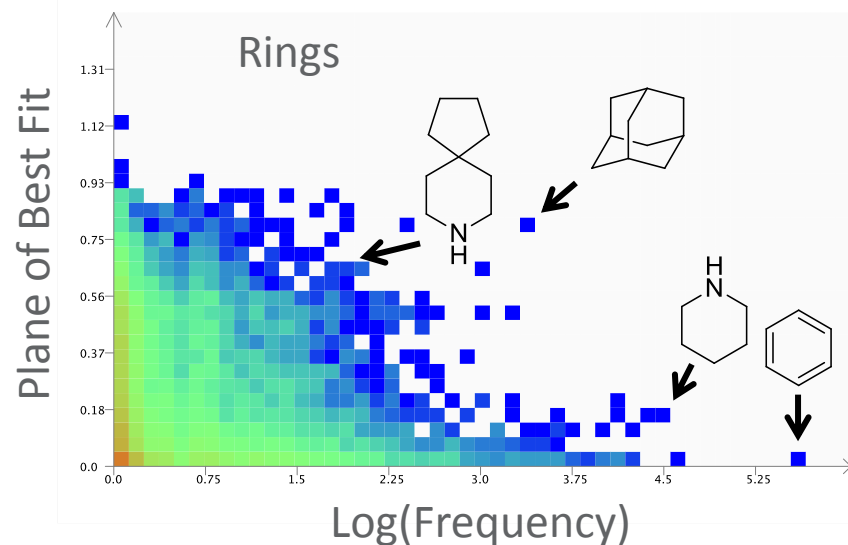
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1. Firth, N. C.; Brown, N.; Blagg, J. [Plane of Best Fit: A Novel Method to Characterize the Three-Dimensionality of Molecules](#). *J. Chem. Inf. Model.* **2012**, *52*, 2516-2525.

# Return to Flatland

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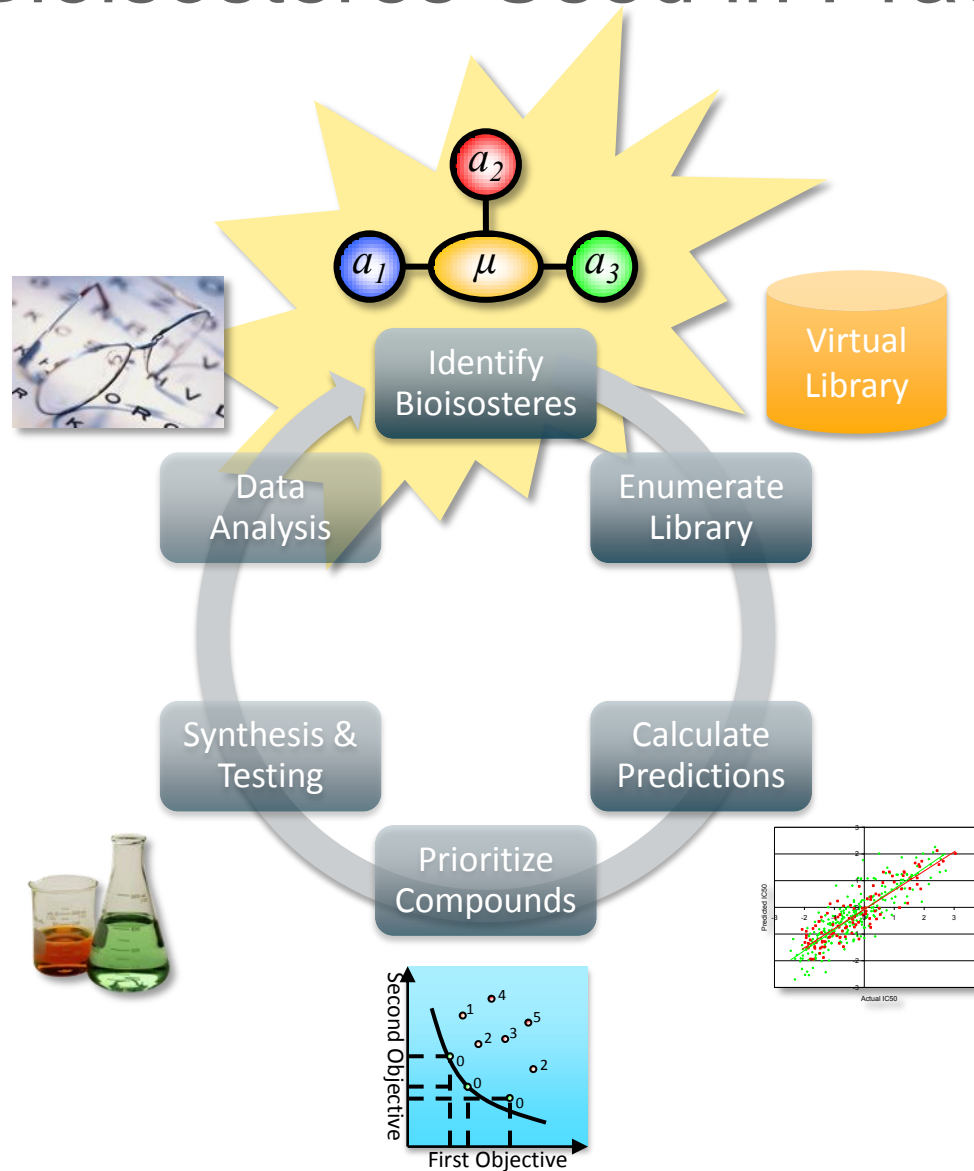
Frequently used rings and linkers tend to be less 3D

- More frequently used = more typically 2D

Linkers tend to promote 3D more than rings

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

# 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.

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

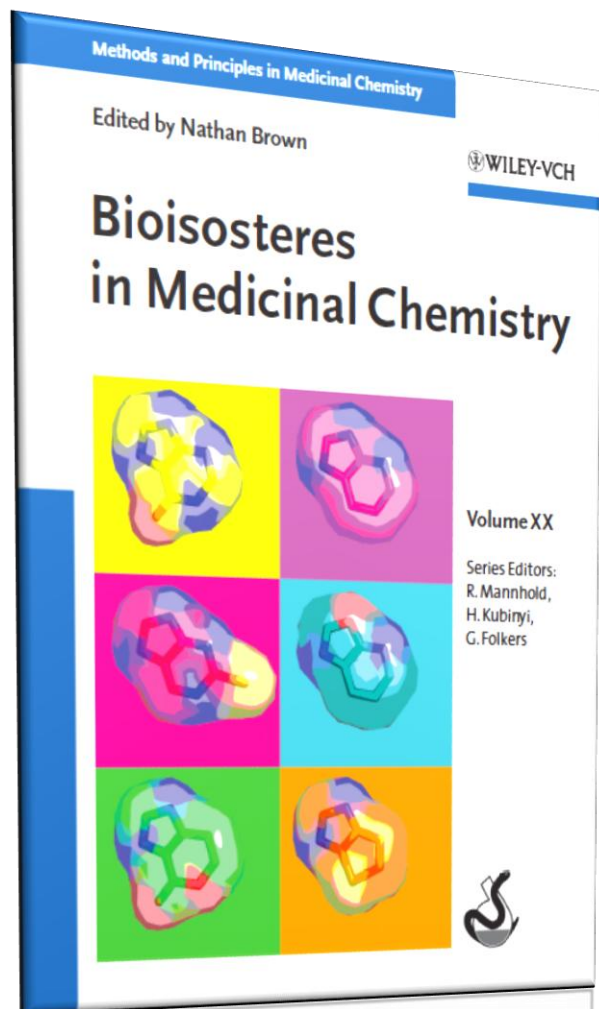
- Dr Fabio Broccatelli
- **Nick Firth**
- Sarah Langdon
- Dr Yi Mok
- Lewis Vidler

## Medicinal Chemistry

- **Prof. Julian Blagg**



Cancer Research UK Grant No. C309/A8274



## 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