Promiscuity: Friend or Foe?

Jackie Macritchie, Vivienne Allen, Phillip Black, Paul Hinchliffe, Richard Hill, Michael Lipkin, María Palomero-Vázquez

Charles River Discovery, Chesterford Research Park, Saffron Walden CB10 1XL, UK; Jackie.Macritchie@crl.com

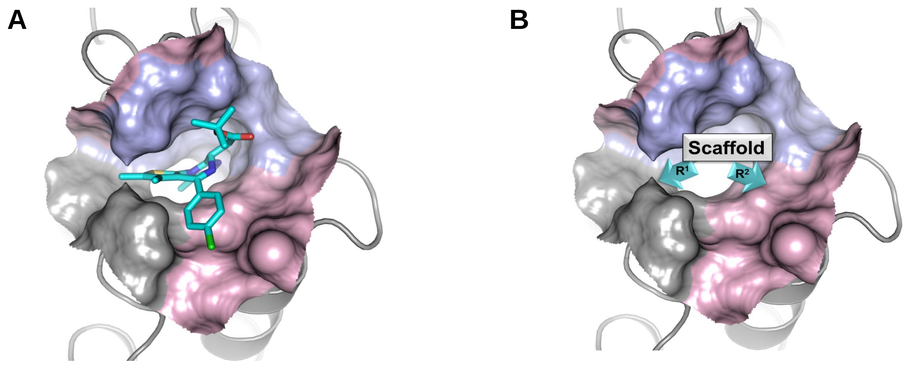
discovery from charles river

1 INTRODUCTION

Promiscuous or privileged motifs have been defined as "structures that are able to provide high affinity ligands to more than one type of receptor".[1] However, selectivity can be difficult to attain. We describe here our library design approach which targets the benefits of promiscuity, while minimising the frequently associated problems.

2 CHEMOGENOMIC DESIGN APPROACH

Our SoftFocus® library compounds are designed towards a family or related sub-class of proteins, rather than individual targets. The scaffold is designed to maintain the key interactions in regions which are conserved between family members, whilst careful monomer selection can provide selectivity between family members.



A) Analysis of target family

Key interactions and conserved regions identified (purple)

Variable regions shown in pink

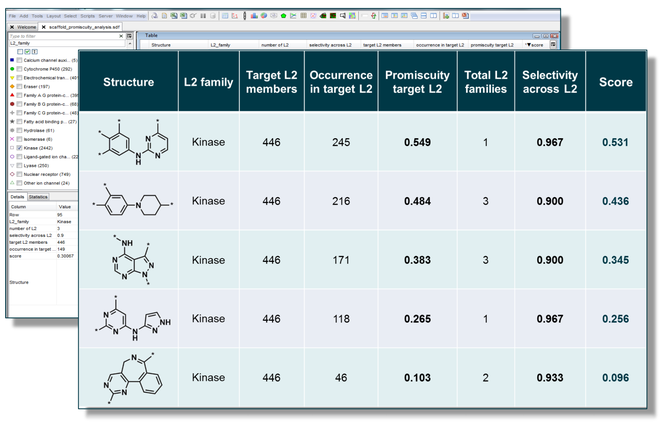
B) Library design

Key recognition features are incorporated within the scaffold

Monomers occupy the more variable regions (pink)

3 DATA MINING

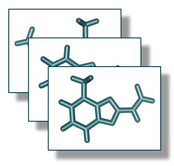
We have developed a new web-based tool for mining literature data in order to identify promiscuous scaffolds for use as starting points within our library design process.



Structure	L2 family	Target L2 members	Occurrence in target L2	Promiscuity target L2	Total L2 families	Selectivity across L2	Score
	Kinase	446	245	**0.549**	1	**0.967**	**0.531**
	Kinase	446	216	**0.484**	3	**0.900**	**0.436**
	Kinase	446	171	**0.383**	3	**0.900**	**0.345**
	Kinase	446	118	**0.265**	1	**0.967**	**0.256**
	Kinase	446	46	**0.103**	2	**0.933**	**0.096**

Scaffold hopping from frequently occurring motifs identifies new scaffolds

ROCS
Pharmacophore
Scaffold replacement



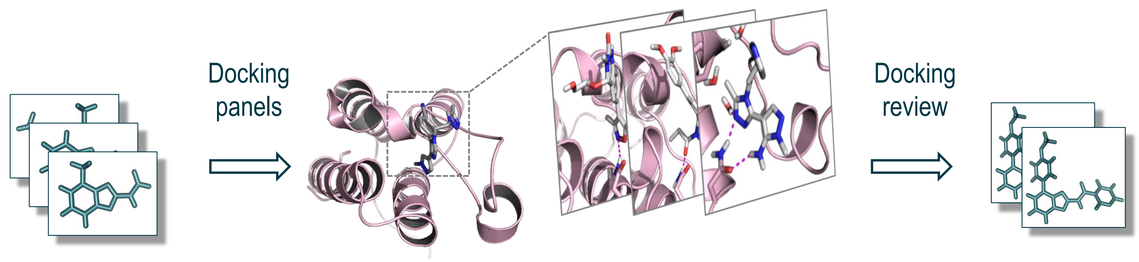
Sample output from target categorisation

- **Promiscuity target L2** = Occurrence in target L2 / Target L2 members Proportion of targets of interest with inhibitors containing the scaffold
- **Selectivity across L2** = 1- (Total L2 families / 30) [db has 30 L2 families]
- **Score** = Promiscuity target L2 * Selectivity across L2

4 SCAFFOLD ASSESSMENT

Individual scaffolds are assessed for suitability within the specified target class, typically *via* structure-based or ligand-based shape profiling approaches.

Structure-based evaluation



Novel ideas

Wide coverage of phylogenetic tree ensures applicability across the family

Enumerated scaffolds

Ligand-based evaluation

Filter by shape into ligand sub-sets

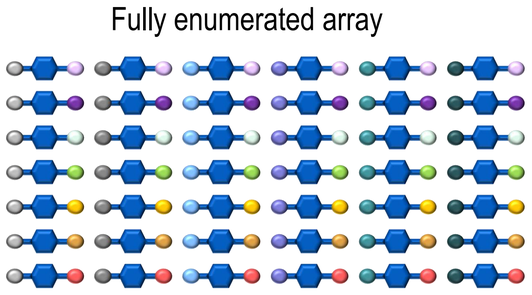
Identify common scaffold features

Biased monomer selection towards target class

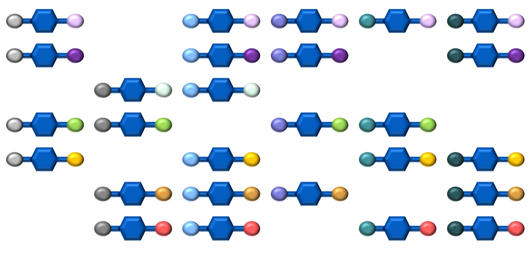
5 LIBRARY ENUMERATION

Our proprietary library enumeration tool enables us to optimise both structural diversity and physicochemical properties simultaneously before the final synthesis stage.

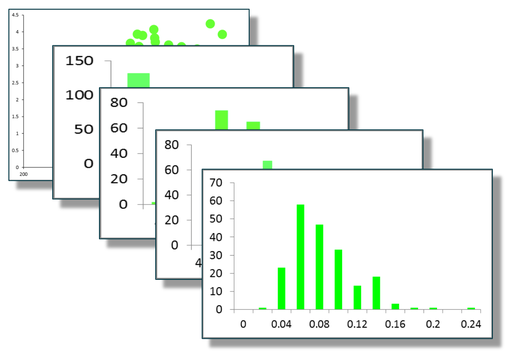
Fully enumerated array



Filtering based on physicochemical properties



Property and shape profiles



cLogP, MW, HBA, HBD, TPSA and shape

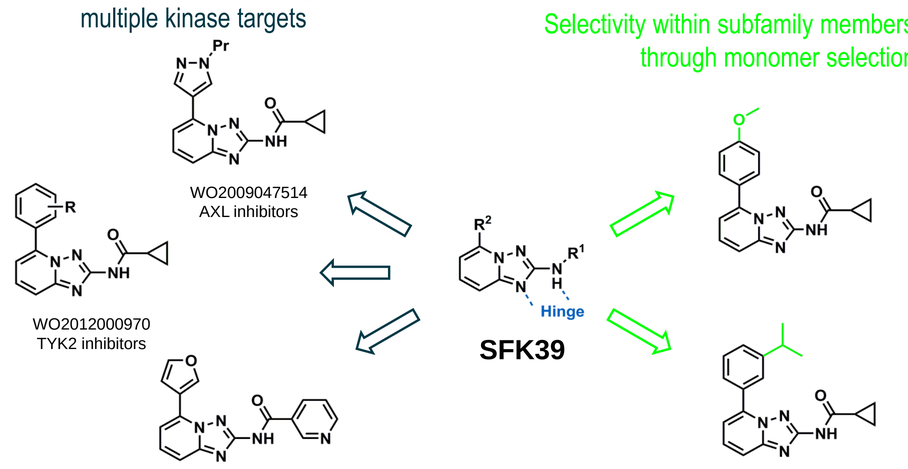
Sparse matrix optimises library profile

Design review ensures full coverage of the target class

6 LITERATURE EXAMPLES

Library compounds active against multiple kinase targets

Selectivity within subfamily members achieved through monomer selection



Galapagos (RA)
J. Med. Chem. **2014**, 57, 9323

hJAK1 IC_{50} = 70 nM
hJAK2 2 x

GLPG0634 from this series is currently in Phase 2B for RA

Genentech (oncology)
Bioorg. Med. Chem. Lett. **2013** 23, 5014

hJAK2 IC_{50} = 80 nM
hJAK1 3.8 x

7 CONCLUSIONS

We have shown how a single scaffold can have activity across a range of family members. Selectivity can then be achieved through strategic monomer selection. This demonstrates the potential benefits of promiscuity within a target family, particularly from a library design perspective.

charles river

[1] Evans, B. E. *et al. J. Med. Chem.* **1988**, *31*, 2235-2246.