Predictive Application of Bioisostere Transformations to Identify Novel, High Quality Compound Ideas

J. Chisholm,* J. Barnard†, J. Hayward†, M. Segall*, E. Champness*, C. Leeding,* H. Garcia,* I. Yusof*

* Optibrium Ltd., Cambridge, UK †Digital Chemistry Ltd., Sheffield, UK

Introduction

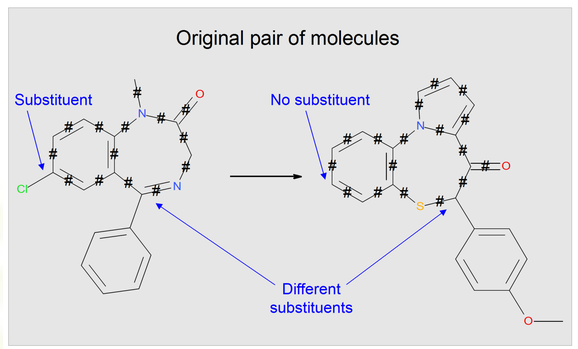
Bioisosteres are functional groups which have similar physical or chemical characteristics and hence similar biological effects. In this poster, we will describe how the relationships between bioisosteres may be encoded as molecular transformations and automatically applied to new compounds to generate novel compound structures that are likely to preserve the required biological activities. Furthermore, we will discuss how *in silico* models may be applied to prioritise the resulting compound ideas, by combining the predictions for multiple properties using a multi-parameter optimisation (MPO) method [1], to identify those that are most likely to achieve a required property profile. Finally, we will illustrate the application of these methods using retrospective examples from drug discovery.

Methods

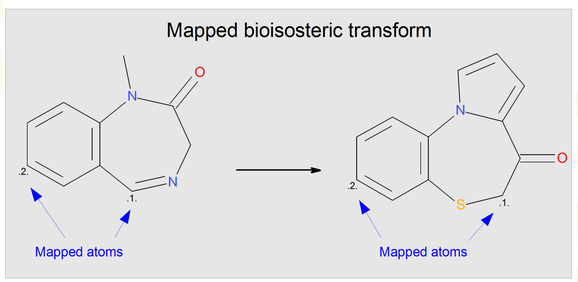
Generating Bioisosteric Transformations

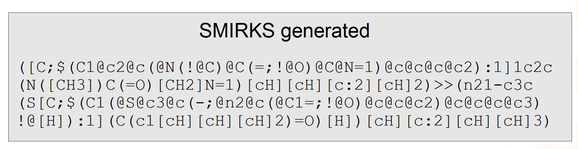
The BIOSTER database [2] is a compilation of 27,366 pairs of molecules with bioisosteric substructures, manually curated from the scientific literature.

Each BIOSTER record is in the form of a pseudo reaction, with a manually designated 'reaction centre', indicating the biosisosteric substructure (labelled with hash marks in the figure to the right).



A transformation was generated for each record, representing the atoms in the bioisosteric substructures in Daylight's SMIRKS notation[3] using a customised version of Digital Chemistry's MOLSMART program [4]. Of the 27,366 records in the latest version of the BIOSTER database, it is currently able to generate SMIRKS for 22,547 (82.4%).





The substituent groups around these substructures are not necessarily identical in both molecules. Therefore, equivalent substitution positions on the 'reactant' and 'product' sides were determined heuristically on the basis of:

- Chemical similarity of the substituent groups or substituted element types
- Spatial orientation of the substituent groups in the original BIOSTER diagrams
- Avoidance of valency violations

In bioisosteric replacement, the same atoms do not generally appear on both sides of the transformation. Therefore, in the SMIRKS, only the substitutable atoms are 'mapped'.

To minimise the number of inappropriate or 'promiscuous' transforms generated:

- Substitution is permitted only where there is a substituent on at least one side of the 'reaction'
- Atoms are designated aliphatic or aromatic based on original molecules
- Bonds are designated as ring or chain based on the original molecules

Multi-parameter Optimisation

A high quality lead or drug candidate must achieve a balance of many, often conflicting properties, including potency, ADME and safety. Therefore, the compound ideas generated are prioritised using a probabilistic scoring algorithm that assesses the quality of a compound against the ideal property profile for the project, based on multiple predictions. An example profile is shown below, defining appropriate ADME properties for an orally dosed compound against a CNS target. This illustrates how a project can define the desired outcome for each property and the importance of each criterion to the overall project objective. In this way, the profile reflects the acceptable trade-offs between different properties. A score is calculated for each compound reflecting its likelihood of achieving the ideal property profile, taking into account the uncertainty in the individual property predictions [1].

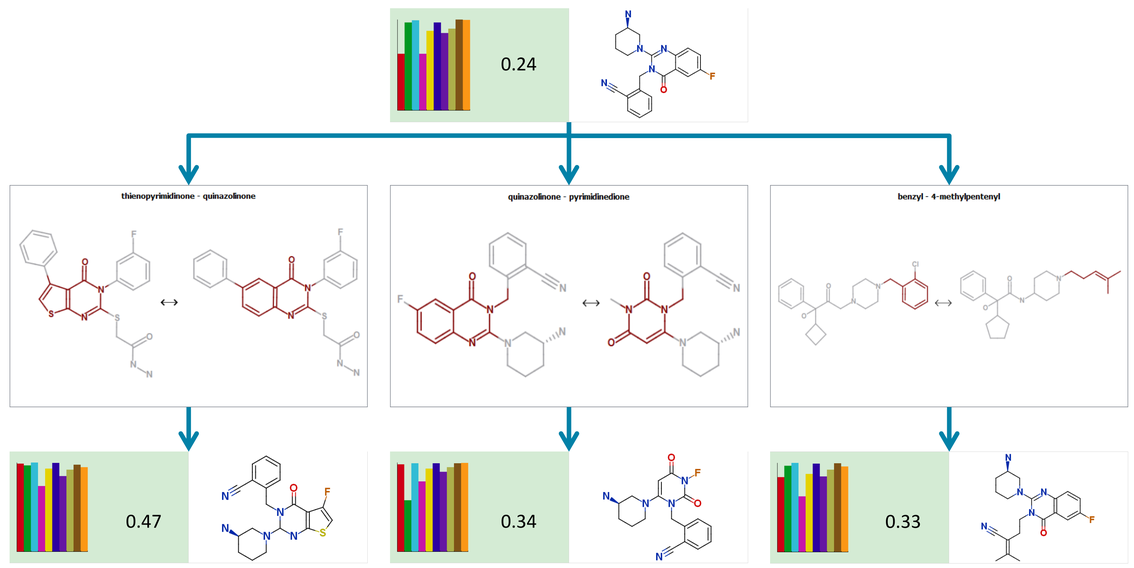
Profile	Desired Value	Importance
logS	> 1	
HIA category	+	
logP	0 -> 3.5	
hERG pIC50	⩽ 5	
2D6 affinity category	low medium	
2C9 pKi	⩽ 6	
P-gp category	no	
PPB90 category	low	
BBB category	-	
BBB log([brain]:[blood])	⩽ -0.5	

Examples

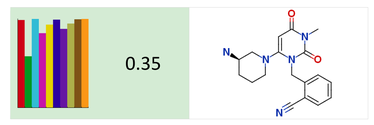
The bioisosteric transformations were applied using the Nova™ [5] module of Optibrium's StarDrop™ software platform [6] and the resulting compounds were automatically prioritised using StarDrop's predictive ADME models and probabilistic scoring algorithm.

Anti-Diabetic: DPP IV Inhibitor

The BIOSTER transformations were applied to the lead compound from the project that resulted in the discovery of the DPP IV inhibitor Alogliptin [7]. This resulted in the generation of 230 compounds that were prioritised against the scoring profile shown at the bottom of the left column. Some illustrative results are shown below:



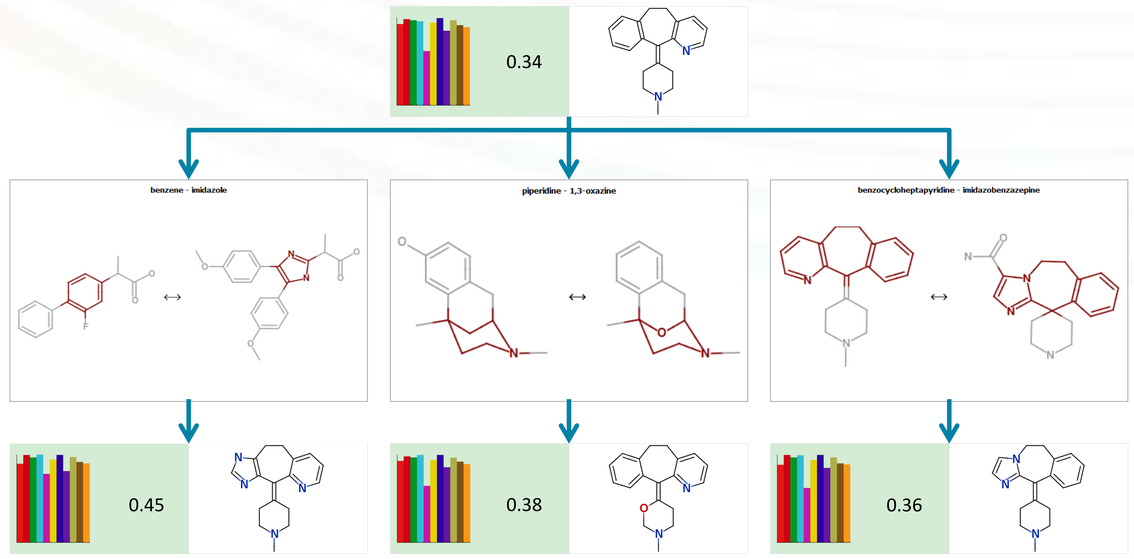
The product shown in the centre above is a close analogue of Alogliptin (right):



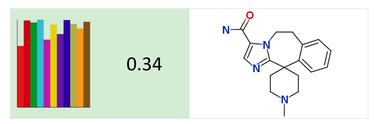
Antihistamine: Histamine H1 Receptor Antagonist

Application of the BIOSTER transformations to the antihistamine drug Azatadine yielded a total of 89 compounds that were prioritized against the profile shown to the right, including pK_i against the Histamine H1 receptor, predicted using a QSAR model. Some illustrative results are shown below:

Profile	Desired Value	Importance
Histamine H1 receptor Ki...	> 7.5	
logS	> 1	
HIA category	+	
logP	0 -> 3.5	
hERG pIC50	⩽ 5	
2D6 affinity category	low medium	
P-gp category	no	
2C9 pKi	⩽ 6	
PPB90 category	low	
BBB log([brain]:[blood])	⩽ -0.5	
BBB category	-	



The product on the right above represents the core replacement that led to the candidate compound Hivenyl™ (right) [8]:



Conclusion

A large, high quality database of precedented bioisosteric transformations, combined with a platform for their rapid application and prioritisation of the resulting compounds, provides a rich source of synthetically feasible strategies for compound optimisation. Potential applications in drug discovery include exploration of opportunities for lead hopping, generation of backup series and patent protection.

References

[1] M.D. Segall, Curr. Pharm. Des. (2012) **18**(9) pp. 1292—1310
[2] BIOSTER: A Database of Bioisosteres and Bioanalogues. I. Ujváry and J. Hayward, in Bioisosteres in Medicinal Chemistry, N. Brown, ed. (2012) ISBN 978-3-527-33015-7
[3] Daylight Theory Manual, www.daylight.com/dayhtml/doc/theory/theory.smirks.html
[4] http://www.digitalchemistry.co.uk/prod_chemicalquery.html
[5] M. Segall *et al.* J. Chem. Inf. Model. (2011) **51**(11) pp. 2967-2976
[6] http://www.optibrium.com/stardrop
[7] J. Feng *et al.* J. Med. Chem. (2007) **50**(10) pp. 2297-2300
[8] F. Janssens *et al.* J. Med. Chem. (2005) **48**(6) pp. 2154-2166