D039 | Addressing Toxicity Risk when Designing and Selecting Compounds in Early Drug Discovery

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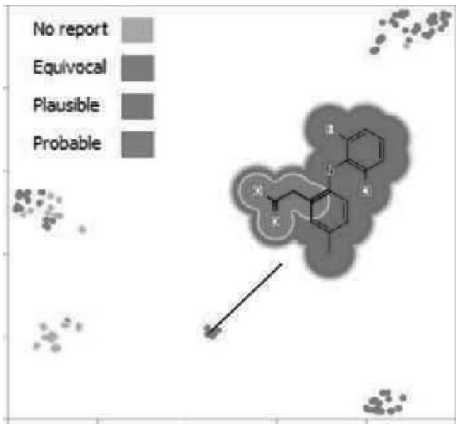
It has been estimated that toxicity accounts for approximately 30 % of expensive, late stage failures in development. Therefore, identifying and prioritising chemistries with a lower risk of toxicity, as early as possible in the drug discovery process, would help to address the high attrition rate in pharmaceutical R&D. We will describe how expert knowledge-based prediction of toxicity can alert chemists if their proposed compounds are likely to have an increased risk of causing toxicity, based on precedence for similar compounds where experimental data are available. However, an alert for potential should be given appropriate weight in the selection of compounds. It is important to balance potential opportunities against the risk of late stage failures caused by toxicity; an alert may not be sufficient reason to 'kill' a compound or chemical series. If a series achieves good outcomes for other requirements, it may be appropriate to progress selected compounds and generate experimental data to confirm or refute a prediction of potential toxicity. We will discuss how multi-parameter optimisation approaches can be used to balance the potential for toxicity with other properties required in a high quality candidate drug, such as potency and appropriate absorption, distribution, metabolism and elimination (ADME). Furthermore, it may be possible to modify a compound to reduce its likelihood of toxicity and we will describe how information on the region of a compound that triggers a toxicity alert can be interactively visualised to guide this redesign.



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D040 | Visualising Structured Compound Data in an Unstructured Way

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When we view compound data sets, we almost always find ourselves looking at a 'chemical spreadsheet' or 'form views' of compounds in a long list. However, compounds have much more complex relationships that cannot be captured in a single, sequential order. We will describe an alternative approach to visualising sets of compounds and their associated data that enables more complex relationships to be captured and manipulated in a highly interactive way. The user can impose their own, arbitrary structure on their data, guided by their individual perspective. Alternatively, algorithms can be used to initialise the view to draw out interesting patterns or features. Example applications include quickly triaging results from high-throughput screening to quickly identify high-quality hit series; investigating structure–activity relationships using molecular matched pair analysis or by identifying activity cliffs; and tracking the flow of ideas through the course of a project.

D041 | Investigation of Ligand Binding Mode at 5-HT_6R with the Use of Bioisosterism

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One of the most recently identified serotonin receptor subtypes, the 5-HT_6 receptor,[1,2] localized practically only in the brain,[3] is a very promising target for different new psychotropic drugs. These receptors are supposed to be responsible mainly for motor control, memory and learning and its ligands can be used to treat cognitive impairments[4–6] or as antiobesity drugs.[7,8] So far, several thousands of ligands have been synthesized, and their structural diversity makes consensus binding mode very difficult to define.

Isosterism is the most common technique used by medicinal chemists to design and synthesize new series of compounds. An isosteric replacement can change compound activity, bioavailability, pharmacokinetics and metabolism. If isosteric replacement doesn't

substantially change biological properties of a substance, it is called bioisosteric replacement. Besides altering compound properties, bioisosterism can be used to get insight into interactions of ligand with the receptor. By carefully planning isosteric replacements it is possible to probe certain regions of receptor binding pocket.

With the use of specialized software (PypelinePilot, vBrood) a group of dozens of thousands of isosteres were generated. All of them were screened with virtual screening protocol and compounds to synthesize were chosen individually from those that met all the requirements of VS protocol. As a result a group of substances was synthesized together with their isosteres. By combining ligands affinity towards 5-HT_6R, their crystal structures and molecular modelling, a detailed explanation of ligand–5-HT_6R interactions is proposed.

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D042 | Finding Interesting Fragments

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A common task in the early stages of a drug discovery programme involves the analysis of large small-molecule datasets to derive relevant hit series that can be used for subsequent testing. Usually such datasets contain up to 10^6 molecules, which makes this an especially difficult procedure as structural commonalties and similarities between molecules need to be explored. Common approaches make use of generating molecular scaffolds, structural fingerprints or maximal common substructures (MCSS) of the aforementioned datasets. However, such approaches can be computationally demanding and therefore unfeasible for large datasets.

We present a novel approach for deriving frequently occurring fragments from small-molecule datasets. Our new approach is based on a two-step workflow: a clustering step, and an MCSS-generation step. The clustering step serves as a pre-grouping stage where molecules are grouped into clusters. For this, a very fast k-Means clustering algorithm is based on structural fingerprints and can handle large sets of molecules in very little time. In the second stage of the workflow, MCSS fragments are generated per cluster and then de-duplicated across all clusters. Lastly, our new approach enables the automatic ranking of the found MCSS-based fragments according to accumulated properties (e.g., average activity, IC_{50}, …) from the original molecules where the fragment is contained. This makes it possible to quickly identify those groups of molecules that are likely to exhibit for example higher activity towards a biological target of interest than others. The workflow is implemented by Dotmatics' Vortex making it easy to combine the results with various data visualisation tools, such as scatterplots and other similar graphical methods.

D043 | Novel Androgen Receptor Antagonists Identified by Virtual Screening

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Androgen receptor (AR) signaling is known to regulate the development and progression of malignant prostate cancer cells, and thus it has been recognized as an important target in prostate cancer treatment. AR antagonists such as bicalutamide and cyproterone acetate are commonly used to treat androgen-dependent disorders. However, long-term treatment with bicalutamide induces resistance by turning into agonist due to the development of a T877A point mutation of AR. In addition, a mutant type AR containing two mutations (L701H and T877A) was isolated from the androgen-independent human prostate cancer cell lines. The purpose of this study is to discover novel AR antagonists effective against both wild type and mutant AR.

Two AR receptors including wild type (PDB ID: 3B68) and mutant type (PDB ID:1GS4) were used for Surflex-Dock docking screening. Ligand binding affinity was computed taking into account Surflex-Dock score and CSCORE. Based on docking scores and analysis of