

A Better Way to Understand the Activity, Toxicity and IP Risks of Drug Candidates

The challenge of accurately predicting which in-licensing drug candidates will successfully progress all the way through Phase III and on to market is significant. Complex factors including efficacy, ADMET¹, IP position, cost effectiveness, potential value, competition and fit with the corporate portfolio have to be evaluated and business critical decisions made, usually very quickly. One of the best ways to evaluate the likely activity and the scale of the ADMET, safety and IP risks is to look for information about molecules that share similar activities and properties (such compounds are known as bioisosteres). Unfortunately this is considerably more difficult in practice than it should be.

One of the biggest obstructions is simply finding all of the molecules in the literature, in competitor's programmes, commercial databases or even in your own corporate collection that might share the same biological properties. This is because almost all of the tools that we routinely use to search for similar molecules have a fundamental flaw – they use the similarity of the 2D structures of molecules as a direct proxy for the similarity of their properties. The notion is that if two compounds look the same in 2D, they will behave the same. Whilst this is convenient for computer searching, this approach is demonstrably inaccurate and does not give us the right results.

The lack of accuracy in our search tools has profound consequences. We may miss ideal candidates, even those that we have developed, simply because they 'look' (in 2D) too dissimilar to share the same activity. As well as missing potential opportunities, we may end up paying unnecessarily to acquire activities that we already own or miss the fact that bioisosteres have known ADME, toxicity or efficacy issues in a clinical setting, increasing the risk associated with a candidate. We may also fail to protect our own compounds effectively, and find that a competitor puts a bioisostere on market with just enough structural difference to overcome our 2D based Markush patents².

Understanding Activity and Properties

The activity of compounds is known to be independent of 2D molecular structure. It has been realised since the early days of drug discovery that molecules with very different 2D structures can elicit the same biological action. At the same time, small changes even in a single chemical substituent (e.g. a methyl to ethyl group switch) can cause massive shifts in the activity and toxicity of molecules even though their 2D structures remain very similar. The 2D structure is therefore often a poor indicator of the likely biological activity and properties of a molecule.

With a little thought this is obvious - a protein target does not 'see' the atoms and bonds of a drug (its 2D structure) nicely drawn in a manner convenient for chemists and computers, but instead interacts with the electron cloud around the molecule and the physicochemical properties that the compound presents on its surface. Until recently it has been too difficult to evaluate those properties accurately and quickly enough to use them in finding bioisosteres. This has now changed with the advent of new Field-based methods.

Field Based Molecular Comparison

Instead of relying on 2D structure, Field based methods use the surface properties around molecules to assess their likely activity and properties, regardless of structural similarity. Four molecular Fields are used to

¹ *Absorption, Distribution, Metabolism, Excretion and Toxicity – drug properties*

² *Patents which protect not only a specific molecule or complex substance, but also a larger group of related products, acting as a ring fence to the most important one.*

describe the electrostatic (positive and negative), steric (shape) and hydrophobic ('fat-loving') properties on the surface of a compound, which are the main contributors to molecular interactions between drugs and their protein targets. The most important regions on the Fields are then substituted with a Field Point. As shown in Figure 1, Field Points provide a highly condensed but accurate representation of the nature, size and location of the critical properties required for binding and instigating a specific therapeutic effect.

The pattern of Field Points contains no structural information and in fact many different structures could potentially generate a similar pattern. Crucially, any molecule that can present that same configuration of Field Points is likely to have the same biological activity. By finding molecules with similar Field patterns to a candidate we wish to evaluate we can find a lot of potentially valuable information, and even possibly an alternate candidate.

The anti-inflammatory example below shows the results of using a Field based search system. The search for molecules matching the steroidal natural ligand identified 23 bioisosteres with 4 distinct chemical scaffolds each with nM- μ M activity. The molecular weight range of the resulting bioisosteres was 300-450, and included no steroids, no toxic flags or outstanding ADME impediments, and all structures showed activity in cell based assays. Patents protecting a number of structures very similar to these results were subsequently filed by other companies.

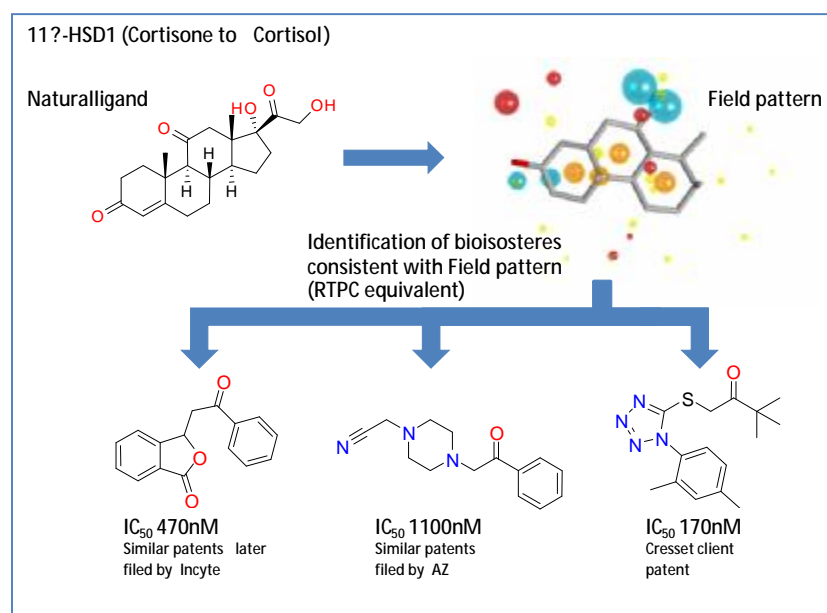


Figure 1. The Generation and use of Field patterns to identify structurally diverse active chemistry from a natural ligand

Choosing and Protecting the Right Molecules

When choosing a new in-licensing candidate it is very useful to understand all of the diverse chemical scaffolds that will display the specific activity and to find the empirical data that are available on those compounds. By using Field-based methods to search all of the available databases, internal and commercial, for information relating to bioisosteres we can quickly build up a detailed picture of the likely ADME, toxicity and efficacy profile of the candidate which we can then use to inform our decisions about its suitability for in-licensing.

To then protect all of our candidates, whether sourced internally or externally, the question becomes, how many different Markush structures are needed to cover the important bioisosteres that are predicted for a given activity? By covering each of these different chemical scaffolds, the development of closely related 'me-too' products can be blocked leading to stronger patent portfolios and potentially extending the period of market exclusivity for new medicines.

Field-based methods offer new tools to help gain a deeper and more rapid understanding of the risks associated with in-licensing candidates as well as potentially identifying new opportunities. They offer a wide range of potential advantages to in-licensing, IP, safety and R&D scientists throughout pharma and biotech.

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