Field-Based Technology in the Evaluation of In-Licensing Candidates

By Steve Gardner and Andy Vinter at Cresset Group

By identifying similar molecules in terms of their likely activities and properties, rather than their 2D structural similarity, Field-based methods offer a way of rapidly assessing the activity, safety and IP landscape of in-licensing candidates.

In the current drug discovery process, accurately predicting which in-licensing candidates will successfully progress through the clinical trials process and on to market is critical to a company's commercial success. It is of course also highly complex and challenging. A range of factors including efficacy, absorption, metabolism and distribution (ADME) properties, safety, intellectual property (IP) position, cost-effectiveness, potential market value, competition and fit with the corporate portfolio have to be evaluated and, considering all of these, business-critical decisions have to be made rapidly. This complexity and the need for speed creates the potential to overlook key information and for decisions to be made without a full understanding of all of the relevant risks associated with the various in-licensing candidates. This may have significant financial consequences in terms of wasted licensing fees and development effort.

A rapid and effective way to elucidate the likely activities of a compound, and any ADME, toxicity and IP risks, is to look for information already known about molecules that share similar activities and properties (so-called bioisosteres). By looking up the known properties of all of the bioisosteres for a given activity, we can get a rapid sense of the types of chemical scaffolds that exhibit the specific activity, and also understand whether a particular scaffold consistently presents problematic toxicity or ADME issues.

Although simple in principle, this approach is complicated by the fact that it is hard to spot a genuine bioisostere. Many have different 2D structures that no medicinal chemist could confidently predict would be active at the target of interest, and compounds that are similar in 2D structure may in fact have quite different biological activities and properties. Even good bioisosteres with very similar activities and properties do not necessarily look remotely like the compound that is being offered. An example of this is the diversity of the 2D structures of the HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs), as shown in Figure 1.

Unfortunately, almost all of the tools that are available to identify similar molecules have a fundamental flaw – they evaluate how alike molecules are in terms of their 2D structural similarity, rather than in terms of their likely activities and properties. While this is convenient for computer searching, we know from long experience of examples such as the NNRTIs that this approach is limited and does not give us the right results. These inaccurate search tools can have profound consequences. Not knowing that potential bioisosteres already exist may cause a company to miss opportunities, or end up paying unnecessarily to acquire activities that it already owned. Worse still for the commitment of corporate resources, a company may miss the fact that an in-licensing candidate is very likely to have known ADME, toxicity or efficacy issues in a clinical setting, increasing its associated risk of failing further down the line.

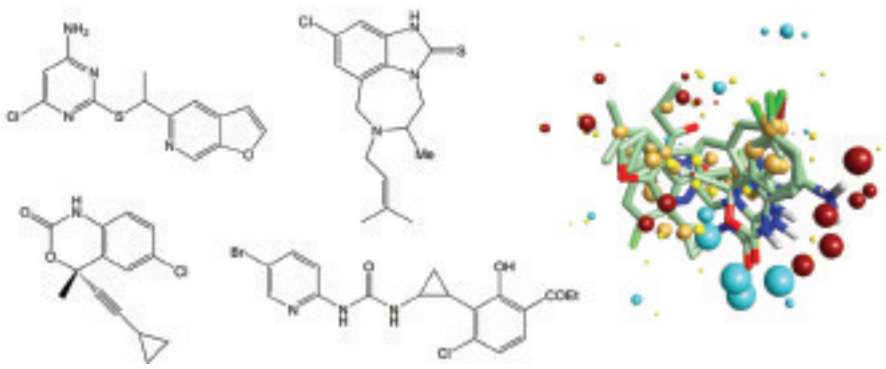
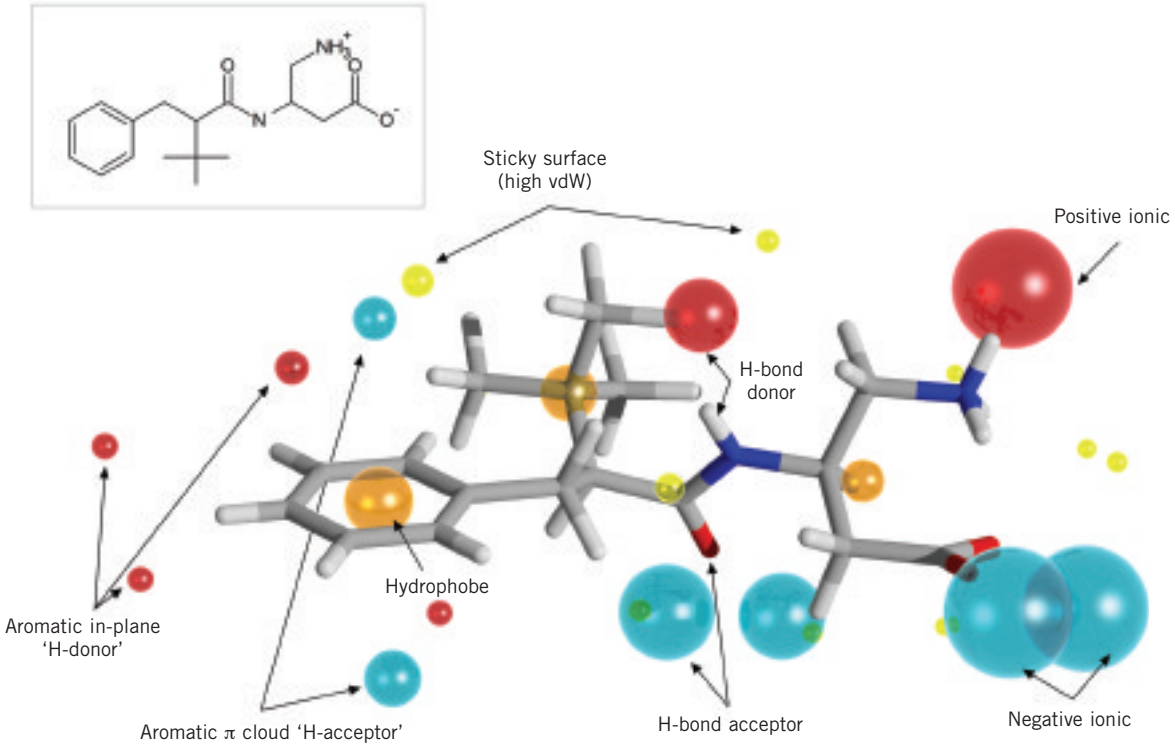


Figure 1: 2D structural diversity of the HIV NNRTIs contrasts with strong Field similarity when structures are overlaid



We may fail to identify ideal candidates simply because they 'look' too different (in 2D). In Figure 1, for example, there is no obvious reason to believe that the 2D structures shown on the left of the figure have any relationship to each other as they have no 2D chemical similarity of any note. The right hand side of the figure, however, begins to offer some hope. It is clear that we are able to generate a clear consensus of the position and size of the spheres around the two molecules, and that this does reflect their shared activity. These spheres are known as Field points, and they provide a much more accurate way of finding bioisosteres.

USING FIELDS TO IDENTIFY BIOISOSTERES

Rather than 2D structure similarity, Field-based methods use the surface properties around molecules to assess their likely activity and properties. Four molecular Fields are used to describe the electrostatic (positive and negative), steric (shape) and hydrophobic ('fat-loving') properties on the surface of a compound in its bioactive conformation. These are the main contributors to molecular interactions between drugs and their protein targets.

Until recently, it has been too difficult to evaluate these properties accurately and quickly enough for them to be of use in making rapid decisions. This has now changed with the advent of new Field-based methods that can compare molecules very efficiently. To simplify an entire Field around a molecule, the most important regions of a Field are replaced by Field points, as shown on the right hand side of Figure 1, using advanced methods that have been extensively validated (1,2).

As shown in Figure 2, 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. They also provide considerable insight into why the molecule is able to have the effect that it does. Once generated, the pattern of Field points is independent of the molecular structure and is, in effect, an information-rich activity pharmacophore. Any

Figure 2: Understanding the properties and activity of a compound using Fields

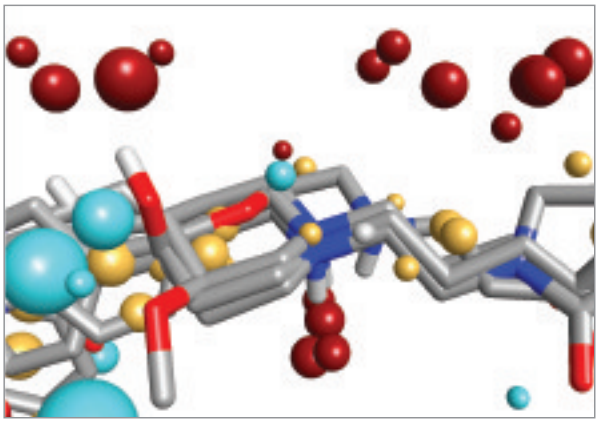


Figure 3: Partial Field template describing cardiac safety liability at the hERG channel

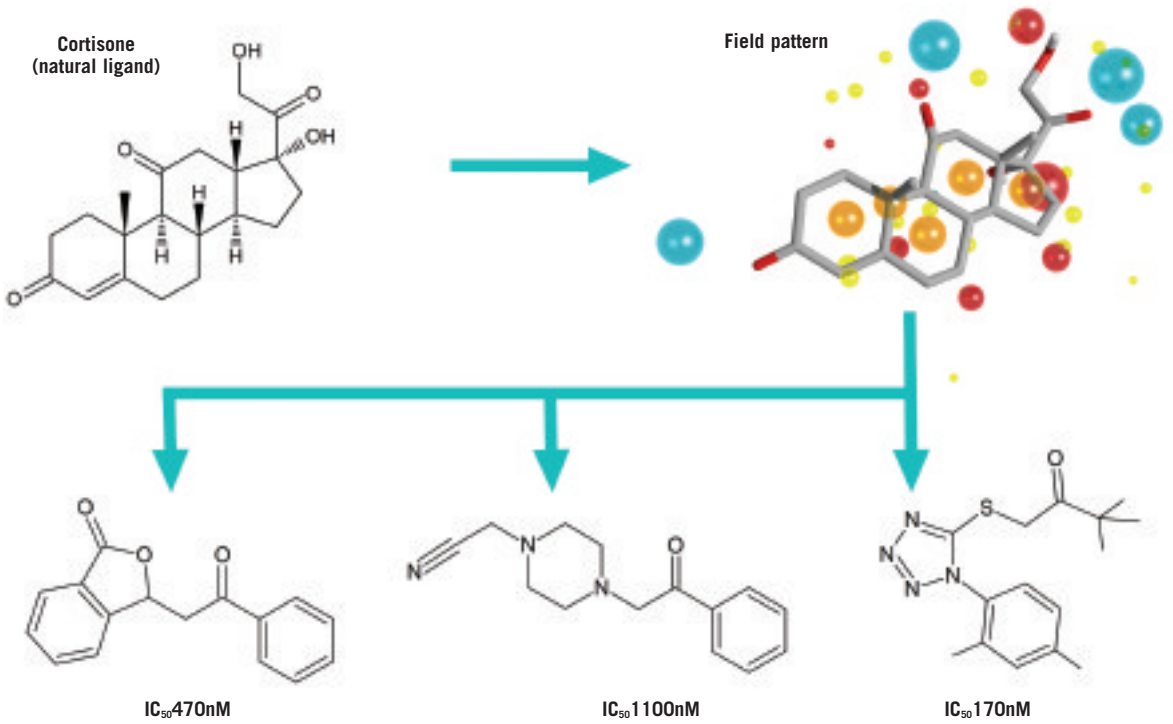


Figure 4: The generation and use of Field patterns to identify structurally diverse active chemistry from a natural ligand

molecule that can present that same configuration of Field points is likely to have the same biological activity and properties. We can now search, not by 2D structure but using Field patterns, to find molecules that have similar Field patterns to a candidate that we wish to evaluate. An example of the results of such a search is shown in Figure 4.

EVALUATING THE POTENTIAL DEVELOPMENT LIABILITIES OF A CANDIDATE

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

A number of commercial databases, such as Thomson Reuters Integrity or World Drug Index, provide detailed information on the known pharmacology, mechanism of action, adverse events, physicochemical and ADME properties of compounds. By identifying a complete set of bioisosteres in these and other internal databases, all of their known properties can be correlated to reveal potential development issues with the compound going forward.

As well as generating templates for a desired protein target activity, Field-based tools can help to build templates that can identify the safety liabilities of a compound. In the example shown in Figure 3, a series of compounds known to exhibit cardiac toxicity (via interactions with the hERG channel) have been overlaid in their bioactive conformations and their Field patterns compared. There is a consensus Field pattern (shown above the molecules in Figure 3, page 39) that is highly indicative of cardiac toxicity.

Interestingly, this Field pattern is usually observed only as part of the overall Field pattern for the compounds that are known to show cardiac toxicity. While there may well be other chemistry (and related Field patterns) in other regions of a molecule's structure, the possession of this small pattern is sufficient to mark the compound as having a potential liability. If necessary, this can be quickly tested to validate the prediction. Comparison of in-licensing candidates against libraries of such templates for specific toxicities, off-target interactions and ADME properties can be used to further understand the likely issues that might be expected with a particular candidate compound.

CHOOSING & PROTECTING THE RIGHT MOLECULES

Once a candidate is selected, it must then be protected. The inventor will of course transfer some patents as part of the deal, but can they be relied upon to offer full protection for the candidate and avoid fast-followers eroding market exclusivity? Once again, the fundamental protection offered for the compound – the Markush structure specified in the patent – is based on the 2D structure of the compound. It will cover one chemical scaffold only with a combinatorial set of R-group substituents. This is often insufficient, and there are many examples of fast-follower structures being developed (often deliberately) to avoid the specific Markush pattern laid out in the patent.

Because the kinds of Field-based tools described above can discover each of the bioisosteric chemical scaffolds active at a given target and allow them all to be protected, they can be used to mitigate the development of closely related 'me-too' products. This leads to stronger patent portfolios and potentially extends the period of market exclusivity for new medicines.

An example of the use of Field-based searching to inform patenting strategies in the anti-inflammatory space is shown in Figure 4. In this case, the search was for molecules matching the steroidal natural ligand, although this could easily have used an in-licensing candidate as the search structure instead. The search in the example identified 23 bioisosteres with four distinct chemical scaffolds, each with nM-μM activity. The molecular weight range of the resulting bioisosteres was 300 to 450, and included no steroids, no toxic flags or outstanding ADME impediments, and all structures showed activity in cell-based assays. Three of the most active compounds are shown in the figure, illustrating the diversity of chemotypes that Field-based tools are designed to find. It can be seen that these structures bear little resemblance either to each other or to the natural ligands of the enzyme (3).

At the time, the tetrazole chemotype (rightmost result) was pursued and patents based on this scaffold were filed. Independent patent filings were subsequently submitted for the benzfuranones and piperazines by other drug discovery companies. Had the client chosen to pursue and protect all of these specific chemotypes, they would have been able to create a stronger patent position and licensing opportunities around the 11βHSD-1 activity. To do so, they would have had to create three specific Markush structures, each covering one of the chemical scaffolds of interest. These filings would protect all of the relevant chemistry (and very few inactive compounds). Aside from making it easier to examine these patents, this would also make it harder for fast-followers to patent-bust and create new partnering opportunities for the series that the inventor chose not pursue.

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CONCLUSION

Field-based methods offer a new way to gain deeper and more rapid understanding of the risks associated with in-licensing candidates than existing 2D-based tools can hope to provide. They may also help to identify new opportunities for existing compounds as activity against a given target is evaluated, and provide ways to increase the strength of the protection for all new compounds – whether developed internally or externally.

References

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