

Integrating Process and Discovery Chemistry to Design out Problems at an Earlier Stage, Speeding up Drug Discovery

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Executive Summary

Reducing time-to-market is the holy grail of drug development, benefitting pharmaceutical companies and patients.

Over time, companies have created highly specialised teams, each working towards a specific goal before handing their result onto the next phase of the process. However, this has led to a tendency to work in silos. If each silo had a better understanding of the next stage requirements, it could enable potential issues to be addressed earlier and speed up the overall process.

Examining the drug discovery process suggests there is an opportunity to reduce time-to-market at the intersection between the discovery and development phases. Both are primarily handled by synthetic chemists, but working at different scales and under different pressures.

In our experience, increasing the overlap between these teams offers significant benefits. This paper discusses the benefits of using development chemists' techniques during the discovery phase. This can pay dividends in designing out potential problems before candidate compounds move to the development phase. We use this approach in our own discovery and development work and have found that it can significantly speed up the drug discovery process.



Introduction

Time saved at an early stage pays dividends later

Taking new drugs from concept to market typically takes some 10-15 years and, according to research from the London School of Economics carried out among US biopharmaceutical companies, costs an average of almost \$1 billion for each new drug.

Clearly, any way of working that could potentially speed up the process by even a few months or increase its efficiency would be welcome.

Examining the development process suggests that the best opportunity is at the late discovery and early development stages. Once a candidate compound reaches clinical trials, the process necessarily follows a tightly prescribed pattern and any scope for condensing the timeline is significantly reduced.

Both discovery and early development stages are primarily synthetic chemistry, although each group of chemists is working at very different scales: typically creating 10-50mg of product during discovery, and beginning with hundreds of grams for early development. The chemists in each team will have similar skills and be working towards the same ultimate goal. However, the way many organisations work creates barriers between the teams. They operate in separate labs, often separate buildings; they develop different approaches; and, importantly, work under different pressures, which has given each team a narrow view of their role and what success looks like.

There are a range of issues that regularly emerge when compounds with the desired activity move from discovery to development. If some of these could be designed out at an earlier stage, the overall timescale could be condensed. It is much cheaper and quicker to solve problems in the lab than at a pilot stage or in the plant.

This approach is often taken by some contract research organisation (CROs), using a combined discovery and development offer to speed up early stages for their pharmaceutical clients.

In the rest of this paper we will discuss how this could be done by using the skills typically employed by development chemists at the later stages of drug discovery, and using desk analysis to design out problems before candidate compounds move to larger scale synthesis. This requires an understanding of best practice process chemistry, facilitated by analytical tools such as transformation maps.

Traditional discovery chemist focus on desired activity

A development chemist – or medicinal chemist – is focused on identifying compounds with the required biochemical activity. They will design, synthesise and purify thousands of compounds in a single campaign, creating small libraries of related chemicals and using screening cascades to establish which structure has the desired activity, and the relationships between different properties. They need a strong understanding of biology to achieve the desired therapeutic effect while considering drug metabolism and pharmacokinetic (DPMK) liabilities.

A discovery chemist will use techniques such as computational modelling to generate new ideas for synthesis and a toolbox of reliable reactions, such as amide bond formation (amidation). Speed is of the essence. Once they identify strong candidates, typically made in small quantities, purified by chromatography, and then structurally characterised before biological testing, the compounds then enter the development phase.

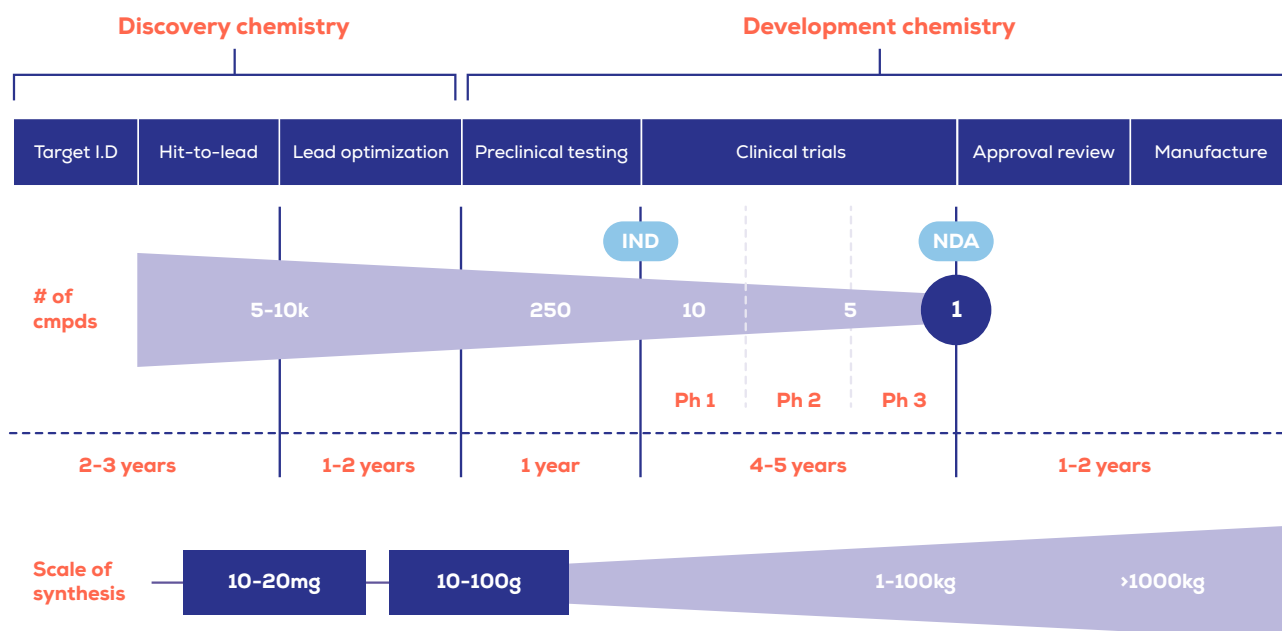


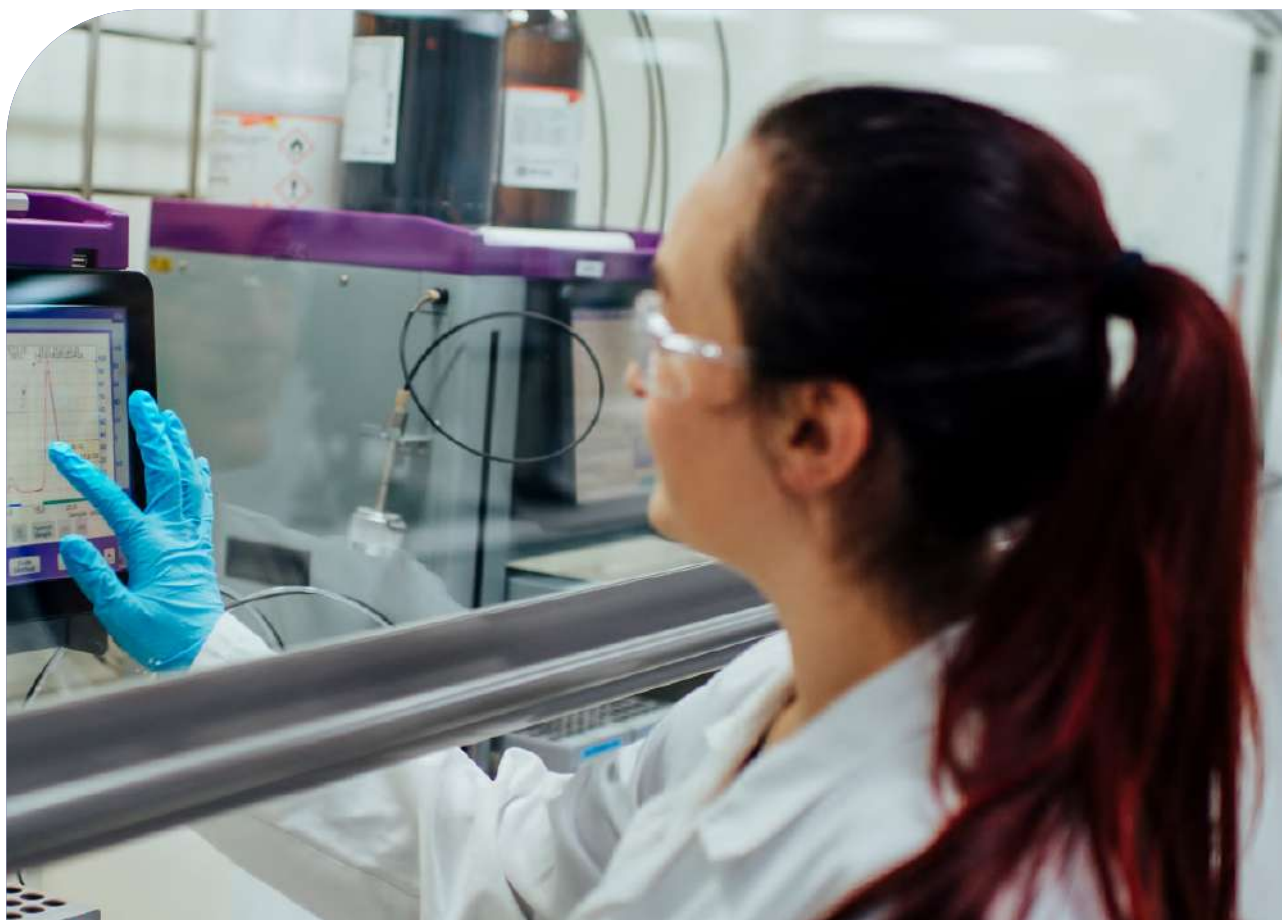
Figure 1: The traditional drug discovery process

Development chemists look for efficient, low cost and robust syntheses

The development chemist is focused on yield, cost of goods and reliability. Their aim is to design a robust, highly efficient and cost-effective route to synthesising the candidate compounds in larger quantities, ready for transfer to pilot plants and beyond. When taking on the candidates selected by the discovery chemist, the most pressing need for the development chemist is the rapid synthesis of hundreds of grams of Active Pharmaceutical Ingredient (API). They need this to fuel the pre-clinical development work, such as determination of a suitable solid form and carrying out in depth absorption, distribution, metabolism, excretion toxicity (ADMET) studies and animal toxicology studies. Typically they will begin by scaling up the discovery chemistry route. They will then identify and carry out the development work that is necessary before the process is suitable to move on to a pilot plant.

Whereas the discovery chemist will be happy with a ten percent yield, the development chemist requires a much higher figure. Obtaining this requires a detailed mechanistic understanding of each stage in the synthesis and the rate processes driving the reactions, so they can design out unwanted materials and minimise the number of purification steps, which become costly and time consuming at scale.

How much better would it be, and how much time could potentially be saved, if the discovery route was closer to an acceptable development route?



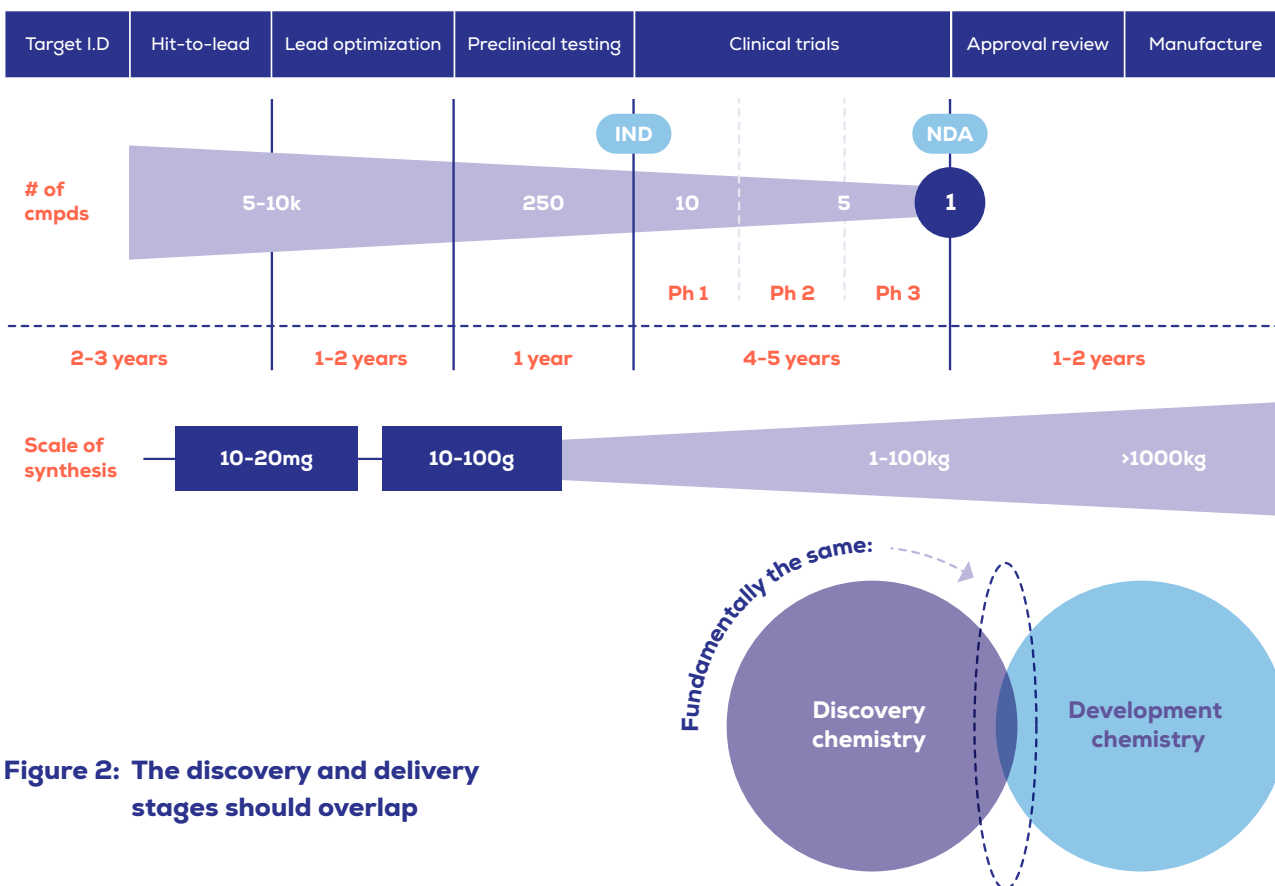
The challenges of scaling up

As every development chemist knows, a process that works well in the lab does not always scale easily. For example, take a heat generating (exothermic) reaction. In a 100ml flask, the heat will be quickly dissipated, as there is a high surface to volume ratio, and the flask can be cooled effectively in an ice bath. Thus the heat is of limited concern to the discovery chemist. However, in a 100 litre flask, the amount of heat generated is much larger and the smaller surface to volume ratio means a different method of cooling is required – a problem for the development chemist to solve.

Side products are another common issue. In the lab, analysis may show the presence of multiple products, but this is considered acceptable provided the yield of the desired product is sufficient for initial screening. However, while purification using a process such as column chromatography is straightforward in the lab, it is much more time-consuming and expensive on a larger scale, so development chemists will put significant time and effort into finding ways to minimise or eliminate unwanted products.

Other considerations include cost and availability of materials. A discovery chemist may use an expensive or less common reagent to synthesise the desired candidate compounds. For instance, specialist ligands used for Pd-catalysed reactions. However, only around five percent of reagents are suitable for use in large scale manufacture, so their development colleagues will have to find a way of making the synthesis work effectively using a much more limited and affordable repertoire.

All these and many more challenges are solved every day during drug discovery. However, moving from a linear process to one with more overlap between discovery and development stages (Figure 2) could smooth this transition and reduce the amount of redesign needed.



Designing Syntheses with an Understanding of Development

A development approach i.e. considering the key requirements of process chemistry as well as biochemical activity could be incorporated at all stages of discovery; from making libraries of compounds to fine-tuning the synthesis once a series with the required activity and no undesired characteristics have been identified. Although this will reduce potential problems later, it may slightly increase the length of the discovery stage. Taking this approach means managing customer expectations and explaining why a slightly longer discovery time does not mean that the project is behind schedule, as this time and more should be recovered later. Key development challenges that should be considered at the discovery phase are:

1. Is the process feasible on a larger scale

As mentioned earlier, some aspects of a process developed in the lab can be difficult to scale up. If discovery chemists are supported to consider these when fine-tuning their synthesis, whether through tailored training, co-locating teams to create shared understanding or involving development chemists in discussions and brainstorming sessions, such issues can be identified much earlier.

Closer working relationships could mean development chemists can suggest less expensive or easier to handle reagents with similar reactivity which would perform well on a larger scale. These can then be tested for performance using range-finding experiments in the lab. Taking this a stage further, restricting the use of certain solvents in the lab that do not work well at scale would avoid the need to replace them at a later stage.

An early review between discovery and development teams may generate further ideas and options for discovery, leading to alternative and perhaps even more effective reactions. A feedback loop between discovery and development at this stage could offer significant benefits.

Development chemists can also highlight factors which only become significant when working on a larger scale, such as heat generated. Using their knowledge of previous developments, they may be able to suggest alternative routes to the same conclusion, such as carrying out the stages of a synthesis in a different order.

2. Designing out unwanted side-products.

Few chemical reactions are as simple as $A+B=C$. They involve a number of steps, generating many compounds along the way as well as the desired product. By obtaining a detailed mechanistic understanding of each step, and the factors influencing it, synthetic chemists can optimise the reaction to favour the desired products and design out unwanted side products rather than have to remove them later. Transformation maps provide a critical tool for this analysis (Figure 2).

They show the different pathways and the factors influencing them, enabling synthetic chemists to consider the impact of changing one element on a specific step and hence the ultimate result. For example, would a more reactive solvent or different coupling agent at step two improve or reduce the ratio of wanted and unwanted products at the end of the reaction?

Transformation maps will also help understanding of other issues. For example, unwanted products may be formed via the rearrangement of an intermediate or its reaction with the starting material or another side product. Understanding what is happening may enable chemists to find a solution through synthesis, simplifying purification and eliminating the need for chromatography. This approach is typically introduced at the development stage, but adopting it during the final stages of discovery would help to validate results and reduce rework. It can be carried out on paper, then tested in the lab.

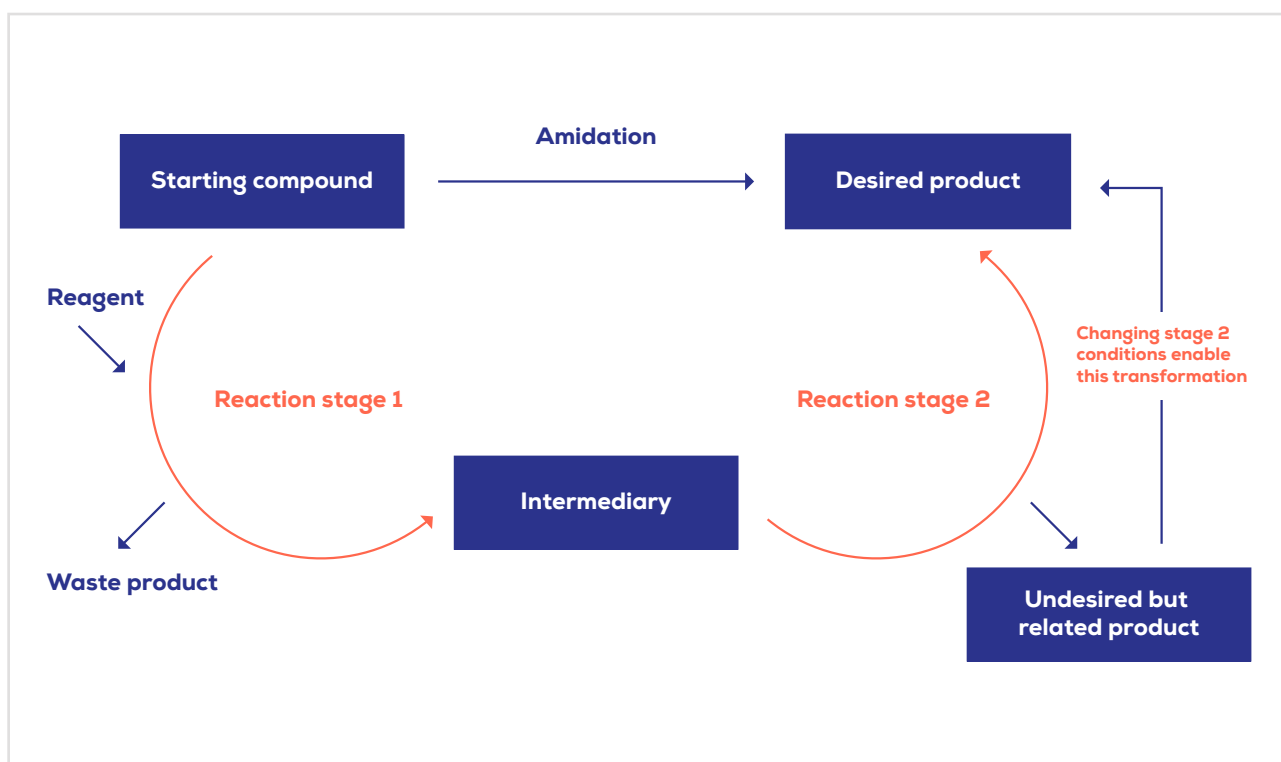


Figure 3: Schematic transformation map

3. Evaluating side pathways for potential benefits

The transformation map approach can also be used to review side pathways and consider if undesirable products can be transformed into desirable ones, rather than having to be taken out at a later stage. A relatively small change in conditions or reactivity of a key reagent may be all that is needed to transform a problematic compound into its much more desirable relative, significantly increasing yield and reducing the need for purification.

4. Taking a holistic view of all reactions.

A transformation map approach is critical to maximising efficiency. Without a thorough mechanistic understanding of each stage of the reaction, the synthetic chemist may miss a potential opportunity to make a small change that will change the balance of a rate process in favour of the desired result. This type of analysis helps them spot both opportunities and potential challenges at an earlier stage. Many problems can be designed out by a combination of paper analysis and lab work, reducing time required later in the development process.

Examples: using transformation maps to improve yield

In a real example, an amidation process continued to generate a low yield, regardless of the acid used – a result accepted by the original discovery team. After examining the transformation map and considering evidence from carrying out familiarisation work, the synthetic chemist realised that the problem was due to the relative reactivity of the incoming aniline. Further research led them to an award winning amidation reaction documented by a team in New Brunswick, Canada. By applying the principles set out in this paper, they were able to achieve a significant improvement in yield.

However, they also noted the presence of a major impurity. Although tempted to use column chromatography to eliminate this, it would have sacrificed almost half the yield. By reviewing the transformation map again, the synthetic chemist was able to change conditions so that the impurity was transformed into the required product. This eliminated the problem without the need for purification.

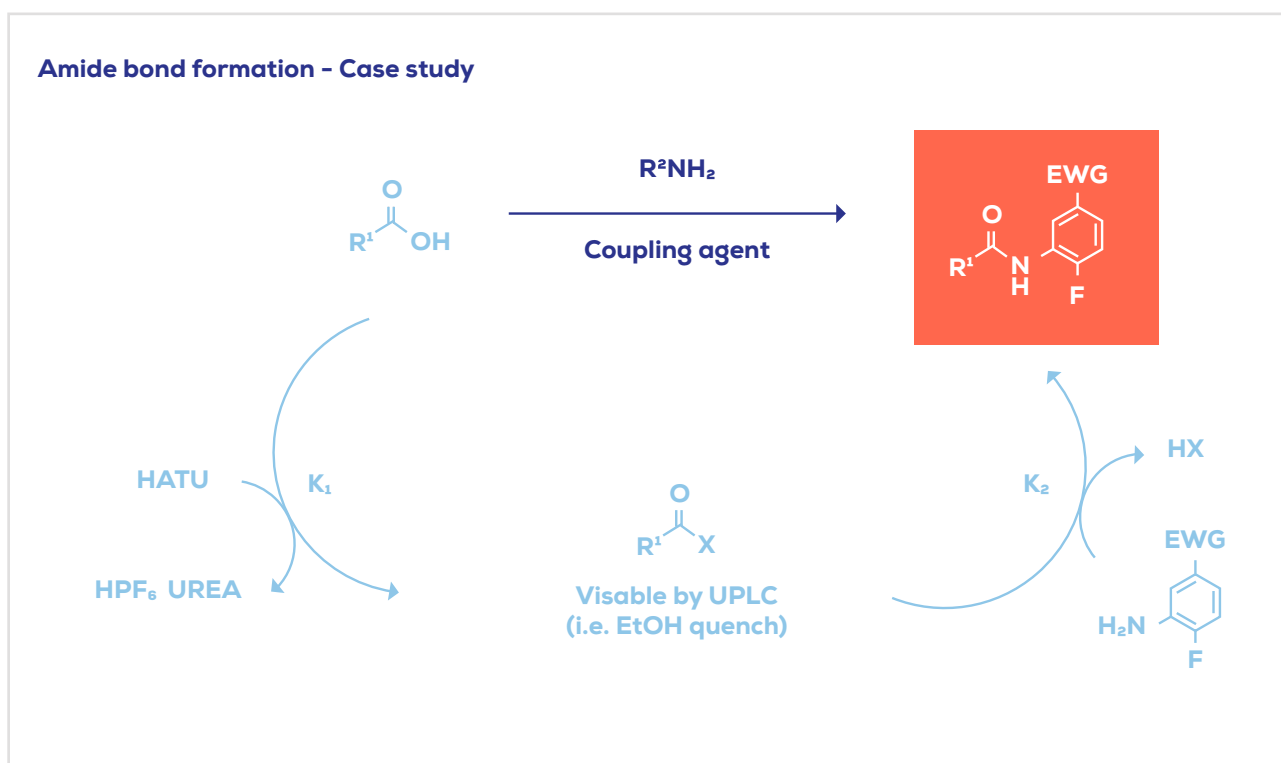


Figure 4: Amide bond formation case study

Conclusion

Over time, the drug discovery process has evolved to create specialised teams working in silos. In particular, discovery and development chemists are working towards different aims and under different pressures, although they have the same core synthetic skills. By taking a development approach to the later stages of discovery, or using a combined discovery and development such as that provided by a third party such as a CRO, many potential problems can be designed out in the lab rather than at a later stage. This will save time and effort and ultimately help to bring drugs to market more quickly.



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