and the strength of London's biotechnology base. It shows how far the network has come in just two years and we will be running the conference again in December 2002.

We are also increasing our efforts overseas in looking for new partners for our London companies and researchers. In 2001, we spent a week in Germany meeting with European biotech and support companies and are planning two further trips to Germany with the inward investment arm of London First, to meet not only potential partners but companies who might locate in London. We already host inward missions from the USA, Canada, Japan and Europe, and we envisage this work increasing, along with undertaking increased overseas missions ourselves. We will also continue to run small investor meetings, where London biotechnology companies present to a mix of venture capitalists and business angels.

If the sector continues to grow at the current rate, there could be ~100 biotech companies located in London in the next two years or so – a significant cluster for the UK. Supporting these companies in helping them find funding, accommodation and new partners will continue to be our goal, providing practical help for the biotechnology community in London.

The *Discussion Forum* provides a medium for airing your views on any issues related to the pharmaceutical industry and obtaining feedback and discussion on these views from others in the field. You can discuss issues that get you hot under the collar, practical problems at the bench, recently published literature, or just something bizarre or humorous that you wish to share. Publication of letters in this section is subject to editorial discretion and company-promotional letters will be rejected immediately. Furthermore, the views provided are those of the authors and are not intended to represent the views of the companies they work for. Moreover, these views do not reflect those of Elsevier, *Drug Discovery Today* or its editorial team. Please submit all letters to Rebecca Lawrence, News & Features Editor, *Drug Discovery Today*, e-mail: Rebecca.Lawrence@drugdiscoverytoday.com

Dynamite approach to delicate complex scaffolds

When Alfred Nobel invented dynamite, he essentially managed to meet two contradicting needs. A useful explosive needs to be safe to store and handle but concurrently highly dynamic and absolutely destructive when required. The famous solution to this problem could be compared to the development of the safety-catch principle for solid-phase peptide synthesis by George W. Kenner in 1971 [1].

The strategic integration of synthesis and purification is now widely recognized as a prominent advantage of the use of polymeric supports or other solubility-control auxiliaries in organic synthesis [2]. Yet, the mild and selective removal of products from these temporarily attached solubility-modifying groups is an important prerequisite for the successful construction of complex molecules in multistep synthesis sequences. Therefore, an anchor group in polymer-supported organic synthesis should be stable under a wide range of reaction conditions and be able to withstand attack by nucleophiles or protons. Simultaneously, the linker must allow mild cleavage conditions at the end of a given synthetic sequence, to neither destroy valuable product nor to lose material by incomplete removal from the support used.

Kenner solved this problem most elegantly. The growing peptide chain was attached to a sulfonamide anchor via an acyl sulfonamide functionality. The resulting immobilization is robust to treatment with strong bases or acids. The deprotonation of the acidic construct leads to an effective protection against nucleophilic attack, superior but mechanistically comparable to the stability of the phosphate backbone of oligonucleotides. At the end of a peptide synthesis sequence, alkylation of acylated primary sulfonamides yields *N*-alkylated derivatives that lack the ability to release a proton and thus can be cleaved by nucleophiles under mild conditions. In cases where the product synthesized does not enable activation by alkylation without being alkylated itself, alternative procedures, such as a Mitsunobu protocol, have been suggested [3].

However, the yields obtained for peptide synthesis using the Kenner linker together with racemization problems did not lead to a successful career of this concept in peptide synthesis. There are, however, niches for this construct in the synthesis of cyclic peptides, in chemical ligation strategies or as surprisingly selective *N*-acylating polymeric reagents [4].

A remarkably elegant refinement of the safety-catch principle can be achieved when the activation step is not

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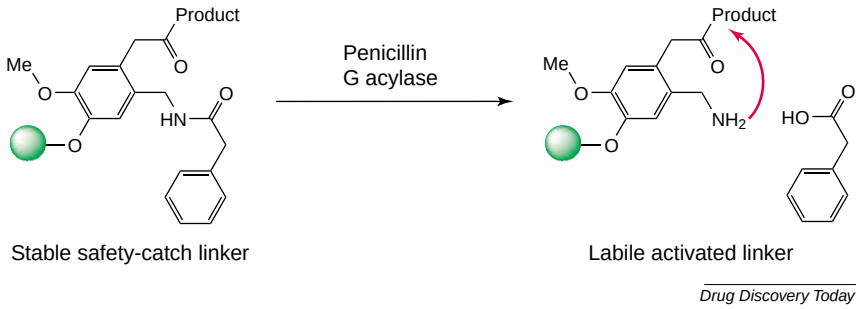

Figure 1. After enzymatic cleavage, the resulting labile activated linker is susceptible to intramolecular nucleophilic attack (red arrow) resulting in product release (not shown).

performed by using reactive chemicals, such as alkylating agents, but by instead resorting to mild and highly selective natural tools: enzymes. As was demonstrated by Grether and Waldmann recently, the penicillin-G-acylase-mediated cleavage of an amino group and subsequent lactam formation led to mild and selective cleavage of a safety-catch linker construct (Fig. 1) [5]. Using the combination of the safety-catch and enzyme-cleavable linker concepts, only one functional group of the anchor has to be transformed, which is much easier to achieve than enzymatic cleavage of the actual linkage.

Waldmann's group thus opened the way for the future synthesis of delicate, complex scaffolds bearing many different functional groups: natural products. This seems highly desirable, because natural-product-like molecules are progressively regarded as biologically validated drug leads.

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Don't underestimate the power of VS

Despite the rapid expansion of HTS throughout the pharmaceutical industry, virtual screening (VS) technology continues to play an important role in the lead discovery process. Indeed, as both technologies continue to mature, significant synergies are beginning to develop between them [1]. Schneider and Böhm provided a nice overview of VS techniques in a recent edition of *Drug Discovery Today* [2]. The review covered a wide range of topics from simple library filtering through to structure-based fast docking and *de novo* design methods.

An excellent example of the successful use of VS technology was conducted by Böhm *et al.* [3], which detailed the discovery of multiple inhibitor chemotypes for DNA gyrase using structure-based screening. These studies are particularly interesting because data is included for both lead discovery and lead optimization. It is also worth noting that a random screen undertaken by the same research facility produced no leads, thus highlighting the value-added potential that VS techniques can bring to a screening campaign.

One of the techniques used to good effect in this example was the application of pharmacophore constraints. These are included in the review but their potential use bears further emphasis. The authors touch on the problem of false positives in screening campaigns. The two major reasons for this in VS are insufficient configuration and conformation sampling and the use of simplistic scoring functions. Pharmacophore constraints provide a useful tool for mitigating both effects, by creating a significant drop in the number of binding modes a ligand can adopt, thus producing a subsequent reduction in the sampling undertaken.

Pharmacophores also force the presence of essential interactions (e.g. hydrogen bonds and salt bridges) in a given binding mode. This lessens the impact of the inability of many scoring functions to distinguish between hydrogen bond and salt-bridge strengths. There is also a more practical element to pharmacophore use. Baxter and colleagues presented a nice example of VS success for a search targeted at the estrogen receptor (http://www.lib.uchicago.edu/cinf/220nm/slides/220nm16/220nm16.pdf). In this presentation, the need for post-screen analysis and filtering criteria were emphasized. Pharmacophore constraints permit the user to build criteria for binding up-front, thus saving much time in post-screen hit evaluation.

The authors also touch on the recent progress in computing processing unit power available. With the advent of distributed computing, this is perhaps the single most important event to greet

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