We have now made the first 500 examples of what we estimate to be some 10,000 or more heterocyclic reactive intermediates and we are continuing to build what will eventually become a comprehensive chemically and structurally diverse collection of heterocyclic building blocks.

Library design frequently involves in-silico diversity analysis so it is essential that all the building blocks are available since the non-availability of just one intermediate necessitates starting the analysis again from scratch. In order to ensure continuous off the shelf 100% availability the compounds are prepacked under argon in 250mg and 1g amounts. Technological advances in the drug discovery process over the last 25 years have shifted the chemical rate determining step. Medicinal chemists need rapidly to build focussed libraries from readily available structurally diverse building blocks.

Maybridge have recognised this need and are producing a diverse range of heterocyclic reactive intermediates aimed at the drug discovery chemist. Visit www.maybridge.com to learn more about the benefits of Maybridge’s science.

References

4 Calculated by Oxford Molecular using the Chem-X definition of a pharmacophore
5 Defined as a triplet of any combination of hydrogen bond donors, hydrogen bond acceptors, aromatic ring centres and positive nitrogen atoms.

Maybridge plc is a leading producer of organic compounds used in High Throughput Screening and Lead Generation, and Combinatorial Chemistry and Lead Optimisation. The Maybridge Screening collection consists of over 56,000 organic diverse drug-like compounds, produced by innovative synthetic techniques, often unique to Maybridge. The CombiChem unit produces compounds for combinatorial chemistry applications in the lead optimisation process. Maybridge also offers a unique range of Reactive Intermediates, building blocks specifically designed for lead optimisation and diverse library generation. The Maybridge Research Unit - MRU - gives customers the opportunity to benefit from Maybridge’s expertise in the fields of lead generation and lead optimisation, and is uniquely placed to help customers exploit hits that are generated from the Maybridge Screening collection. These projects are tailored according to the customer’s requirements and expectations, and are typically based on FTE contracts involving template or scaffold design and the production of focussed libraries around specific intermediates, for the hit-to-lead optimisation stage of drug discovery programmes.

During the last 25 years almost every part of the drug discovery process has undergone radical change.

Technologies that would have seemed like science fiction in 1977 have become commonplace. For instance, the latest high throughput screening methodologies can handle 500,000 compounds a day and using robotics and combinatorial techniques chemists can now synthesise single libraries that contain more compounds than existed in the total chemical literature of 1977.

The human genome has been sequenced and advances and advances in molecular biology and in our understanding of biological processes continue to suggest new approaches to the treatment of the many untreated and inadequately treated diseases that still afflict mankind. These advances are reflected by the investment in pharmaceutical R&D which has more than doubled since 1990.

Despite all of these apparently positive changes, the rate of introduction of new medicines has stalled. There are no doubt a number of reasons for this unhappy situation some of which involve chemistry strategy. These include the naive idea prevalent in the early 90s that successful drug research was a numbers game and that the number of hits obtained would be directly proportional to the number of compounds screened. There was at that time a lack of appreciation of the importance of diversity and of the fact that diversity in a collection of molecules requires amongst other things diversity in the chemistries used for their synthesis. The quality of a hit molecule in terms of its molecular weight, lipophilicity, aqueous solubility etc was also largely ignored and it is only recently that these factors have been fully recognised in the literature and acknowledged in the research laboratory. There is also no doubt that regulatory authorities have become increasingly demanding and that clinical trials have become ever more costly and perhaps as a result companies have become more risk averse. It would also seem to be difficult for the very large research organisations that are currently in vogue to maintain the thrusting innovation seen in many smaller teams with output per worker appearing to decrease with increasing size. Whatever the reasons for the disappointing situation it is clear that despite all of the scientific advances drug discovery remains a challenging, expensive and risky business.

One of the few things that has not changed is that the majority of medicines are still small synthetic organic molecules and that a high proportion of them contain a heterocyclic ring. It is interesting to speculate as to why so many bio-active molecules are heterocycles. One possible
explanation is that heterocyclic rings have hydrogen bond donors and acceptors in a semi-rigid framework and they can therefore present a diverse array of pharmacophores. Some experimental support for this view was obtained when the Maybridge screening collection, which is heterocyclic based and contains 57,000 members, was analysed to see how many of the 400,000 theoretical pharmacophores expressed by the compounds in the World Drug Index it contained. It was found that some 348,000 (87%) of them are present in the collection. This surprisingly high pharmacophoric diversity is almost certainly a reflection of the heterocyclic focus of this particular library.

As technological advances overcome the traditional rate limiting steps in the drug discovery pathway so new factors become the choke points. Thus the actual synthesis of a focussed library of say 500 compounds has become a trivial exercise provided that the necessary building blocks are available. However if the building blocks are not available and have to be synthesised then the construction of even a small library may become far from trivial. Discussions with colleagues in the pharmaceutical industry confirmed that the lack of commercially available building blocks is a choke point in the chemical side of the drug discovery process. In many instances, of course, the required intermediates will be specific to a particular project and at Maybridge we frequently synthesise such bespoke molecules for our pharmaceutical customers.

It seemed to us that the range of commercially available heterocyclic reactive intermediates was very limited and a review of the area confirmed our suspicions that this important field is poorly served. At Maybridge we resolved therefore to produce a comprehensive collection of these molecules specifically designed to help the drug discovery process.

Such a collection needs to provide chemical as well as structural diversity. Thus the user chemists need to be able to employ a good proportion of the available bond forming reactions in order to incorporate the heterocyclic fragment into the target molecule. In order to provide this synthetic diversity we chose twelve of the most widely used electrophilic and nucleophilic groups and these are shown in table 1. For each heterocyclic system as many of the twelve groups as is synthetically and commercially feasible will be made.

<table>
<thead>
<tr>
<th>Table 1 - Reactive groups chosen for chemical diversity</th>
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<tr>
<td>CO₂H</td>
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<td>COCl</td>
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<td>SO₂Cl</td>
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<td>CHO</td>
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<td>CH₂Br</td>
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Having defined the chemical diversity of the collection we must now decide on the elements of structural diversity. If we take the isoxazole ring as an example (Figure 1) then there are three possible regio-isomers since the reactive group (R) can be attached to carbon 3, 4 or 5. In fact the carbon atom at position 5 is the most reactive followed by 3 and 4. Thus to make the 3-substituted isomer it may be necessary to block position 5 whilst to make the 4-substituted isomer it may be necessary to block both positions 3 and 5. When it is necessary to block a position we decided only to use methyl groups. This minimal substitution simplifies the interpretation of structure activity relationships.

For medicinal chemists both the pharmacophoric and pharmacokinetic profiles of a molecule are important. A compound’s pharmacophoric profile determines its ability to interact with the receptor once it reaches it and helps to define a drugs receptor specificity. A pharmacophore may be defined, for example, as a triplet of any combination of hydrogen bond acceptors, hydrogen bond donors, aromatic ring centres and positive nitrogen atoms. Thus the parent heterocycle substituted with a phenyl ring (1) or with a second aromatic or saturated heterocyclic ring (2) (Figure 2) will also be of interest since such compounds present further pharmacophoric diversity. For each of these systems there are six regio-isomers. Similarly compounds of type 3, with nine possible regio-isomers and of type 4 with five regio-isomers will further add to structural diversity.

The pharmacokinetic profile of a molecule determines its success in reaching its target receptor when administered by the preferred dosing route. The most important parameters are aqueous solubility, lipophilicity, molecular weight and hydrogen bond donor and acceptor capabilities. The preferred values for the latter four properties as determined by an analysis of The World Drug Index form the basis of Lipinski’s “rule of five”.

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**Figure 1** - Isoxazole regio-isomers

**Figure 2** - Isoxazoles-expansion of pharmacophore diversity

**Figure 3** - Isoxazoles as template molecules