Molecular diversity and solid-phase synthesis

Two meetings, *Exploiting Molecular Diversity* and *Solid Phase Synthesis* were held back-to-back between January 29 and February 2, 1996, at the Hotel Del Coronado, San Diego, CA, USA.

Designing diverse libraries

The first-day session provided a forum for the direct comparison of three informatics solutions to 'perfectly diverse' libraries; approaches which in themselves are diverse. Dr S. Teig (CombiChem, San Diego, CA, USA) described the universal library of conformationally flexible, promiscuous molecules overlapping in pharmacophoric space, which relies on both positive and negative screening information to generate information, not leads. Iterative use of this information allows the scientist to narrow down rapidly on the correct hypotheses consistent with the data and thence to optimized libraries. Critically, Tanimoto distances were considered unreliable in obtaining high-quality information from the library. In contrast, Dr E.K. Davies (Chemical Design, Chipping Norton, UK) and Dr R. Cramer (Tripos, St Louis, MO, USA) rely on Tanimoto distances as a measure of diversity that generate one representative compound for each area of pharmacophoric space. Both of these latter approaches entail a lead explosion step (to offset the paucity of information obtained in the first library), which provides focused libraries of overlapping pharmacophores around a lead candidate before the optimization libraries are designed and constructed.

Dr T.L. Graybill (3-D Pharmaceuticals, Exton, PA, USA) described the Directed-Diversity method embodied in a far-reaching patent with claims to *de novo* design, combinatorial chemistry, automated synthesis, biological screening and SAR analysis in an iterative process, thereby claiming the very focus of many drug discovery programs within the pharmaceutical industry.

Dr S.A. Kauffman (Santa Fe Institute, NM, USA) tantalized the audience with a presentation on how to produce really high numbers of diverse compounds by using random chemistry and chemical reaction graphs where products are tagged by recovering the reaction pathways. With a rather different utility in mind, Dr K. Burgess (Texas A&M University, TX, USA) described multiparallel synthesis as a tool for the identification of catalysts for organic chemistry. Thus, high-throughput screening of catalysts that were arrayed as one catalyst and one compound per well was exemplified in the study of chiral C–H insertion and cyclopropanation catalysts.

Strategies for library generation

The second day saw a switch from the theoretical approach to library design to the more intuitive approach based on a wealth of medicinal and combinatorial chemistry experience displayed by scientists who have actually been successful. Dr J.J. Baldwin (Pharmacopeia, Princeton, NJ, USA) felt that if a lead was already available there is a need to be focused *not* diverse, although he agreed that diversity assessment of libraries used to discover leads will be increasingly important. He described europium-based assays for detecting binding to G protein-linked receptors that were shown to be equally sensitive and reproducible to the traditional radioligand binding assays, but much more convenient to operate. Dr A.L. Harris explained how the Ontogen group (Carlsbad, CA, USA) have developed an impressive high-speed solid-phase library synthesis and screening capability, although design was described as 'hopefully diverse'. Libraries ranging from β-lactams through imidazoles, oxazol and thiazoles to phosphinates had been evaluated in receptor- and enzyme-based assays relevant to cancer and inflammation. As a successful example of the approach, the advanced lead OC104-26 was highlighted as a reversing agent of P-glycoprotein and therefore useful in MDR chemotherapy.

In principle, mixture-based combinatorial libraries should be more successful than natural product extracts and broths, although the latter have a proven track record, because the structures of such mixtures are known, their chemistry can be controlled and the components are present in equimolar concentrations (Dr R.A. Houghten, Houghten Pharmaceuticals, San Diego, CA, USA). Whilst this remains to be proven, alkylated, reduced tetrapetides related to YYFP-NH_2 were described as nanomolar inhibitors selective for opioid μ receptors. Dr M.R. Pavia's (Sphinx Pharmaceuticals, Cambridge, MA, USA) description of the biphenyl motif as a representative universal scaffold caused some misunderstanding of the universal library approach introduced by CombiChem (Dr S.L. Teig and Dr P.L. Myers). Succinctly put, the difference between the two concepts is that the former is an elegant example of how to search for leads whilst the latter seeks only information on which hypotheses may be built for subsequent library design. Dr P.D. Cook (Isis Pharmaceuticals, Carlsbad, CA, USA) followed in the same vein by presenting the azacyclophanes which, having five positions for substitution, can rapidly access diverse mixtures, albeit with some control, as thought necessary.

Drug development

Dr I. Chaiken (University of Pennsylvania, Philadelphia, PA, USA) opened the session on the third day with two dominant themes: (a) rational design is not a perfect art (mythical, indeed, in some people's eyes) and (b) while true diversity is present in biology, proteins tend to cluster into a small number of classes or 'superfamilies'. One possible direction for combinatorial chemistry in drug discovery is to match up the truly random with somewhat rational design in the hope of developing mimetics, agonists and antagonists, but this also affords the chance to learn about recognition mechanisms as well. The speakers followed this theme and used biological diversity techniques to examine protein folding, structure and molecular recognition. In an approach by Dr R.O. Fox (UTMBG, Galveston, TX, USA), phage display libraries of conformationally constrained disulfide-containing peptides were generated and panned for with a SEM-SH_3 domain in order to correlate the hydrogen bonding and peripheral interactions that determine orientation and stability of the

complex. Dr Chaiken's group examined the structural elements responsible for 4-helix bundle cytokine receptor recognition sites. Using libraries of coil–coil step loop mini proteins, they can mimic the coil–coil interactions of IL-5 and are now exploring the use of these libraries to search for small molecules that may bind to the helical portion or use the constrained loop to bind to other proteins. They expect to be able to predict a structure around a hit by point mutation and then predict a scaffold for further use in small molecule discovery efforts. If ways of antagonizing classes of proteins, such as 4-helix bundles, can be found, these classes of compounds might be used for recognition of other proteins in the family.

Applications for drug discovery

Dr M.C. Pirrung (Duke University, Durham, NC, USA) opened this session and emphasized the pragmatic strategies available to medicinal chemists for lead optimization and discovery. The presentations highlighted a new line of thinking for diversity generation stressing smaller, well defined libraries of individual compounds with Dr P.L. Myers (CombiChem), Dr A. Polinsky (Alanex Corporation, San Diego, CA, USA) and Dr G.T. Wang (Abbott Laboratories, IL, USA) describing libraries of discrete compounds for lead optimization and lead generation.

Perhaps the most intriguing discussion brought the participants full circle to the opening presentations – the debate on the size of libraries required for lead generation was reopened. Dr Myers initiated the dialogue by describing a universal informer library containing less than 10,000 reasonably flexible and feature-rich molecules. Needless to say, a lively discussion ensued in which it was debated which types of descriptors and which numbers are needed to completely explore pharmacophore space.

Automation for solid-phase synthesis

In the *Solid Phase Synthesis* conference, Dr G. Grethe (MDL Information Systems, San Leandro, CA, USA) described a solid-phase organic reaction database (SPORE) that will allow searches based on using information unique to solid-phase synthesis, such as polymer-used, linker, tagging-method and substrate-linkage chemistry. This enables the chemist to make a rapid assessment of synthetic strategy in the context of a rapidly expanding set of known solid-phase reactions, instead of having to translate from solution-phase reaction conditions.

On the analytical front, Dr K. Russell (Zeneca Pharmaceuticals, Wilmington, DE, USA) described a quantitative FT–IR method for analyzing resin-bound molecules. This relies on the C–D stretch of deuterium incorporated into the molecule of interest, as exemplified by determining the number of d_9-BOC-lysines incorporated into a target peptide but, of course, is limited to cases where deuterium incorporation is feasible. Dr C.M. Tarby (CombiChem) highlighted product isolation as one of the advantages of solid- over solution-phase chemistry. However, she then described two templates (hexahydroindolyl-5,6-dicarboxylic and iminodiacetic anhydrides) offering reactivity and functionality that permit solution chemistry without this disadvantage.

Heterocycles

Dr A.M.M. Mjalli (Ontogen Corporation) reviewed the high-yielding Ugi four-component reaction, which has given an array of nitrogen heterocyclic libraries of considerable biological relevance. For example, resin-bound isonitriles can be condensed with α-ketoaldehydes in the presence of an amine and a carboxylic acid to give an intermediate diamide that can be cyclized to imidazoles. A tetrahydroisoquinoline library can be constructed from resin-bound imines having two positions of diversity in condensation with homophthalic anhydride (Dr J. Kiely, Torrey Pines Institute for Molecular Studies, San Diego, CA, USA). The resulting unmasked carboxylic acid was further derivatized by coupling with amines to generate a library of 52 subsets, with each subset having 836 compounds. Perhaps the most adventurous chemistry was the synthesis of 18–26 macrocyclic ring targets formed by intramolecular Heck coupling of resin-bound acrylamides and aryl iodides (Dr J.R. Hauske, Versicor, Marlborough, MA, USA).

In summary, whilst a significant amount of new chemistry was reported, there were rather too many 'second showings' and, with the added inconvenience and repetition of yet another combinatorial meeting the previous week, conference fatigue was clearly evident.

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Swedish scientist honoured for Turbohaler

The University of Lund has awarded an honorary doctorate to Professor Kjell Wetterlin for his role in developing the Turbohaler inhalation system. The multidose dry powder inhaler is designed to deliver anti-asthma drugs, and it is operated by the patient's own effort during inhalation. Previous inhalers were difficult to use, and often only about 10% of the dose was actually delivered. Professor Wetterlin's own daughter is asthmatic and her experience prompted his work; she also took part in the early trials.

The Bricanyl® Turbohaler, delivering terbutaline, was launched in 1987 by Astra Parmaceuticals in Sweden. It was enthusiastically received, and the system is now licensed by health authorities in 40 countries around the world. The main advantages of the inhaler over previous devices are that it is much easier to use in very young and old patients alike, it is robust and the multidose capacity means that it can take up to 200 doses of a particular drug before needing reloading and it offers a high lung deposition and consequently lower doses can be used.

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