oxygen species (ROS), which may exacerbate excitotoxicity by inhibiting EAA uptake. ROS are also formed by a number of other mechanisms following brain injury. Potent antioxidant molecules therefore have clear neuroprotective potential. Dr Jill Ann Panetta (Lilly, Indianapolis, IN, USA) illustrated this by describing the discovery of benzylamine LY 231617 (**8**), which inhibits Fe-induced lipid peroxidation and also diminishes $H_2O_2$-induced loss of cultured hippocampal cells and global ischaemia-induced loss of cells from the $CA_1$ region of the hippocampus.

### Prospects for the future

In his summing up, Dr Ian Cliffe (Cerebrus, Ascot, UK) emphasized the fact that the prospects for the development of effective treatments for severe brain injury appeared good, even though the issues involved were multifactorial and complex. Drugs that block the cascade of destruction associated with excitotoxic injury appear to have the greatest potential. Preclinical studies have already established the utility of NMDA and AMPA/kainate receptor antagonists in the treatment of acute brain injury, and a number of NMDA receptor antagonists (e.g. Cerestat) are now in clinical development for ischaemic stroke and severe head injury. It seems only a matter of time before an EAA-receptor antagonist with an acceptable side-effect profile is launched on the market. The likelihood of this occurring has been increased by the emergence of subsite-selective EAA-receptor antagonists. Prospects for effective therapy have been further enhanced by the discovery of inhibitors of excitotoxic processes downstream from EAA receptors and the development of neuroprotective antioxidants. Dr Cliffe concluded that, although the emergence of effective therapies for chronic neurodegenerative disorders (for example Alzheimer's disease, Parkinson's disease and motor neurone disease) appear to be somewhat further in the future, it is clear that the same approaches may provide treatments for both acute and chronic neurodegenerative disorders. Thus the prospects for effective neuroprotective therapies for chronic neurodegenerative disorders will be substantially improved by the introduction of well-tolerated neuroprotective drugs to treat acute brain injury.

*Alan M. Palmer and*
*Ian A. Cliffe*
*Cerebrus Ltd, Silwood Park,*
*Buckhurst Road*
*Ascot, Berkshire*
*UK SL5 7PN*

# Combinatorial chemistry and automation

In June, 150 international scientists, managers and decision makers from the pharmaceutical industry, research institutes and universities gathered in Geneva, Switzerland for IBC's *Third European Forum on Combinatorial Chemistry & Automation: Applications for Accelerated Drug Discovery.*

Combinatorial chemistry is probably one of the most actively expanding research areas within the pharmaceutical industry, and the application of combinatorial chemistry to facilitate and accelerate drug discovery has, from the beginning, been totally dominated by US scientists, despite the fact that some of the pioneering work underlying combinatorial chemistry had both Australian and European roots. An early (but often overlooked) European contribution to combinatorial chemistry came from Dr Pierre Chambon's group in Strasbourg on multi-oligonucleotide synthesis on cellulose discs[1]. At approximately the same time, Dr Mario Geysen and his Australian coworkers presented their work on multipeptide synthesis on pins[2]. Later, the group of Dr A. Furka in Hungary pioneered the 'split-and-mix' synthesis scheme[3,4].

The conference presented some of the celebrities of combinatorial synthesis as keynote speakers, including Drs Eric Martin and Jeff Jacobs (formerly Affymax Research Institute, CA, USA; both currently at Versicor, South San Fransisco, CA, USA) as well as Dr Wolfgang Rapp (Rapp Polymere, Tübingen, Germany), the inventor of the renowned and widely used TentaGel™. Thus, the scene was set for a successful conference – especially so because merging of the fields of automation and combinatorial chemistry remains one of the most important tasks for the successful implementation of high-throughput synthesis in the pharmaceutical industry.

### Single compounds

It is always difficult to select the highlights from such a meeting, but this report summarizes some of the new trends. One such trend is the tendency to favor single compounds, especially so in the major pharmaceutical industry. The fact that European pharmaceutical industry is picking up the concept of combinatorial synthesis was illustrated by Dr Gabriele Handke (Bayer AG, Leverkusen, Germany). She presented the solid-phase synthesis of a series of quinazolines, which is quite a common pharmacophore. The use of a relatively simple set-up enabled the synthesis of 96 different quinazolines as single compounds in 10–20 mg quantities over the course of two days. Another point that was brought up was the theme of diversity. Dr Handke took a rather pragmatic view, defining a chemical library as diverse if it would bind to or activate more than one biological target.


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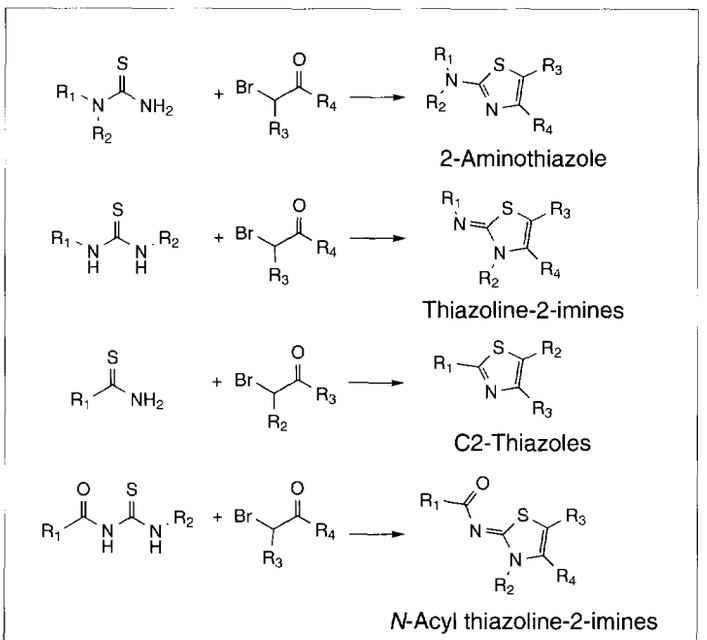
1359-6446/96/$15.00

Dr Harold Meyers reviewed the efforts of Sphinx Pharmaceuticals (Durham, NC, USA). He caused excitement during the conclusive part of his talk, when he mentioned that his group had identified a CNS clinical candidate in one year from initiation of combinatorial chemistry to clinic. This point elicited many questions for the discussion panel. Dr Meyers explained that in this example, they were dealing with a pre-existing lead and the combinatorial synthesis of approximately 500 compounds. Like many others in this field, Sphinx focuses on libraries of single, small organic compounds.




*Thiazole templates synthesized by high-throughput solution-phase methodology.*

## Solution-phase synthesis

Another trend in modern combinatorial chemistry is the investigation of the potential of high-throughput solution-phase synthesis. Dr Steve Watson (GlaxoWellcome, Stevenage, UK) presented some very impressive results from his work. He gave examples of four different thiazole templates (see figure), the 2-aminothiazoles, thiazoline-2-imines, C2-substituted thiazoles and *N*-acyl-thiazoline-2-imines, some of which are relatively abundant pharmacophoric groups. Moreover, an impressive number of single compounds was obtained in the 25 mmol scale. For example, 11,520 different thiazoline-2-imines were synthesized from 12 isothiocyanates, 12 α-haloketones and 80 amines, resulting in an apparently very diverse collection of compounds with a variety of lipophilic, H-bonding, acidic and basic substituents.

## New polymeric supports and analytical techniques

New developments in polymeric supports and analytical techniques are always welcome in combinatorial chemistry, and both were very well illustrated by Dr Wolfgang Rapp. He focused on the use of new, larger beads that allow nondestructive analysis of single beads. Very impressive microanalytical techniques have been developed for monitoring reactions during solid-phase synthesis, such as FT-IR equipped with an attenuated total reflection (ATR) unit, photo-acoustic resonance spectroscopy, single-bead magic angle spinning (MAS) NMR and single-bead $^{13}C$ NMR of $^{13}C$-enriched samples, as well as FT-ion-cyclotron resonance spectroscopy (ICR) for precise and very accurate analysis of compounds cleaved from the resin.

Dr Benoît Déprez (Pasteur Institute, Paris, France) presented another example of a solution-phase library involving the synthesis by microwave irradiation of pyradazinediones[5]. Dr John Nielsen (Danish Technical University, Lyngby, Denmark) described the implementation of convergent solid-phase syntheses to generate combinatorial libraries inspired by natural products. The solid-phase synthesis of an actinomycin-D analogue[6] and the synthesis of a small balanol library were presented as two examples to illustrate that relatively complex natural products can serve as structural templates for combinatorial synthesis.

## Automation systems

During the last keynote lecture, Dr Jeff Jacobs provided the audience with an elaborate overview of the automated systems available for the synthesis of combinatorial libraries, ranging from advanced robotics systems to more simple, and even home-made, systems. This lecture was followed by some more detailed description of actual systems. First, Dr Burt Goodman (Amgen, Boulder, CO, USA) illustrated Amgen's very impressive, but expensive, commitment to automated combinatorial synthesis. This lecture was followed by examples from vendors represented by Dr Mark Peterson (Advanced ChemTech, Louisville, KY, USA), Dr Joel Martin (Argonaut Technologies, San Francisco, CA, USA) and Dr Dave Juranus (Tecan, Research Triangle Park, NC, USA). Dr Peter Myers (Combichem, La Jolla, CA, USA) introduced the CombiSyn machine, which will be available later this year. They showed that a healthy number of choices is available at the moment, and with probably more to come.

Finally, the many valuable contributions by Dr David Brown (GlaxoWellcome, Stevenage, UK) throughout the meeting should be emphasized. Dr Brown highlighted the trend in the field of combinatorial chemistry to move from larger libraries, including mixtures, towards smaller and more focused libraries of single (or few) compounds. He emphasized the value of decentralization of the application of combinatorial synthesis; instead of forming a central department for combinatorial synthesis, modular automated workstations, equipment for parallel synthesis, parallel purification and analysis can be accessed by many different individuals throughout the organization. Finally, from the very beginning of combinatorial chemistry, solid-phase synthesis has been an essential part of the

process. However, he suggested that in future we will have to consider the potential of high-throughput solution-phase synthesis as a serious alternative, especially when solid-phase chemistry cannot be applied or when larger quantities are necessary.

This very successful conference provided helpful advice for beginners and experts. Some very useful conclusions concerning important issues such as sample sizes, mixtures versus single compounds, diversity and solution-phase versus solid-phase synthesis were drawn, and the gap between combinatorial chemistry and automation was successfully filled.

*John Nielsen*
*Department of Organic Chemistry*
*Building 201*
*The Technical University of Denmark*
*DK–2800 Lyngby, Denmark*

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# Book review

**Emerging Drugs: The Prospect for Improved Medicines** edited by W.C. Bowman, J.D. Fitzgerald and J.B. Taylor, Ashley Publications, 1996. £295 (435 pages) ISSN 1361 9195

*Emerging Drugs* is the first of a series of annual executive briefings on topics of current research in the pharmaceutical industry. The editors have solicited 19 review articles from experts in the field. The reviews cover a diverse range of subjects across most major therapeutic areas with particular emphasis on those relating to common diseases. Topics vary from established areas of medicinal chemistry, such as COX-2 inhibitors, to more embryonic subjects such as transcription factors and prospects for developing selective antagonists. The book seeks to undertake an assessment of the degree of innovation and the associated relative risk in each area of research.

Each chapter adopts a similar format with a brief overall summary and a précis of medical need, scientific rationale and competition. An assessment of the success and value of the research area is also included. The information is provided in a concise, readable form that allows the non-expert reader to rapidly assimilate the critical issues associated with a particular therapeutic approach. The text is supplemented with a number of very useful tables, particularly those relating to the competitive environment. These tables contain the structure and development status of lead compounds together with the relevant sources of data and patent priority information.

In each of the reviews a valiant attempt is made to assess the balance of effort and success in the research areas covered, but the criterion used to judge success (number of published patent applications) is somewhat arbitrary when the topics vary so widely. Indeed, some of the chapters cover multiple targets and this inevitably results in oversimplified generic conclusions. Sufficient detail is included, however, for the target audience to be able to make their own judgements as to the value of these data.

Sections on potential development issues and editorial analyses of potential advantages and disadvantages of each approach give a balanced and useful view. In most chapters the references are subdivided into 'very helpful' and 'essential' reading. Brief summaries of the most important references have also been provided. These are all valuable features.

The indices have been thoughtfully subdivided to allow searches by therapy (including an interesting pun on therapeutic index!), author and company. Unfortunately, a number of typographical errors could limit the usefulness of these sections. However, in general these errors do not tarnish the quality of the information provided in the main body of the work.

Overall, this book should make an important addition to the company library, because much of the information presented here is normally difficult to find in a collated form. Readers from any discipline within the drug-hunting industry will certainly find it a valuable 'first port of call' for background information.

The second volume of *Emerging Drugs* is due for publication in January 1997.

*Chris Hill and Phil Jones*
*Roche Research Centre*
*Welwyn Garden City, UK AL7 3AY*