construct and found this leads to elevated levels of ET and hypertension. They also created lesions in rat carotid artery using balloon angioplasty, and observed that injection with ET worsened these lesions (i.e. more neointima developed). Two weeks after the angioplasty, the expression of both ET_A and ET_B receptors was found to have increased by 40%. Treatment with ET antagonist SB209670 [**5**; $K_i(ET_A)$ = 0.2 nM, $K_i(ET_B)$ = 18 nM] reduced the neointimal growth[7]. Both magnetic resonance imaging (MRI) of the rat carotid artery and histological studies indicated 45% inhibition of neointima formation.

The meeting closed with a discussion of endothelin in the clinical area by Dr David J. Webb (University of Edinburgh, UK). Dr Webb's group studied the effects of the administration of ET_A receptor antagonist BQ123 and combined $ET_{A/B}$ receptor antagonist TAK044 directly into the forearm in healthy volunteers. Both drugs were found to cause forearm vasodilation. TAK044 was also administered systemically, which resulted in a reduction in vascular resistance and blood pressure lowering[8]. However, an increase in heart rate and stroke volume partially offset the effect on systemic vascular resistance. These studies show that ET is important for the maintenance of basal vascular tone in man. Using the forearm technique, Dr Webb and coworkers also showed that endothelin antagonists cause additional vasodilation in heart failure patients who are receiving treatment with an ACE inhibitor and diuretic. This result should encourage studies into the benefit of ET antagonist/ACE inhibitor combination therapy.

The Society for Medicines Research is organizing a meeting in April 1997 on *New Frontiers in the Treatment of Epilepsy*. A one-day meeting entitled *Pain and Analgesia* is scheduled for July. For more information contact Barbara Cavilla, tel: +44 171 581 8333, fax: +44 171 823 9409.

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Race to displace Taxol

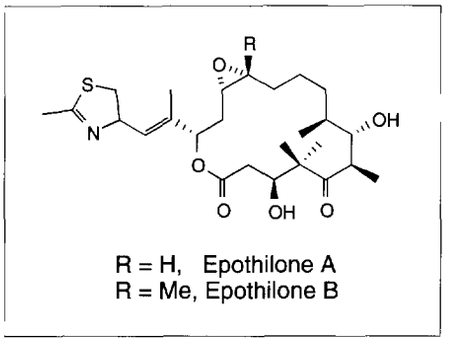
The race is over between three independent groups of chemists who spent much of last year trying to find ways to make the novel anticancer antifungal agents, the epothilones. These compounds promise to take the anticancer crown from Taxol in the next few years.

The epothilones were discovered in a bacterial brew in the 1980s by natural product chemist Gerhard Höfle (National Biotechnology Research Institute, Braunschweig, Germany). He found that they had powerful effects on runaway cell division *in vitro*. Further research showed that the epothilones' mode of action is very similar to that of Taxol (paclitaxel) and Taxotere (docetaxel), the major new anticancer agents derived from extracts of yew tree bark and needles. These compounds affect the microtubules that are assembled and disassembled during normal cell division.

In vitro tests on standard US National Cancer Institute cancer cell lines for breast and colon tumours showed the epothilones to be even more potent than paclitaxel in spite of their simpler structures. The epothilones have two properties that may make them more attractive as drugs than paclitaxel. First, the epothilones are slightly soluble in water (the solubility of paclitaxel is very poor), which should facilitate formulation. Second, and more important, they have shown high *in vitro* efficacy against certain drug-resistant cancer cells, a problem that is plaguing the clinical development of paclitaxel.

In July 1996, Höfle and his team established the exact structure of the epothilones using X-ray crystallography and effectively fired the starting gun in the race to find a synthetic route to the compounds.

First past the publication post was a team led by organic chemist Professor



R = H, Epothilone A
R = Me, Epothilone B

Samuel Danishefsky (Sloan-Kettering Institute for Cancer Research, New York, USA) and his colleagues at Columbia University [*Angew. Chem. Int. Ed. Engl.* (1996) 35, 2801–2803] with Professor K.C. Nicolaou of the Scripps Research Institute (La Jolla, CA, USA) a very close second [*Angew. Chem. Int. Ed. Engl.* (1997) 36 (1/2), 166–168]. Nicolaou and his team were winners in the race to synthesize paclitaxel itself in 1994. Dr Dieter Schinzer (Technical University of Braunschweig, Germany) will probably be third with his team's version of the synthetic epothilones.

Because of the simpler structures of the epothilones, the synthetic routes are shorter. Synthesizing epothilone analogues may therefore be a lot simpler, with less waste and better yields, and may circumvent the need for complex biotechnologial routes. The generation of analogues will provide new candidates and help to illuminate the way in which paclitaxel and the epothilones block the disassembly of microtubules during cell division.

Danishefsky's synthesis involves building the basic skeleton of the compounds in a linear form from much simpler starting materials and then using an aldol condensation to 'stitch' the two ends together to make a ring. According to Danishefsky, the synthesis provides workable amounts of material for further experimentation and also allows analogues to be made quickly that are simply not available from bacterial brews.

Nicolaou and his team, again, started with simple materials, but they built up three fragments of the epothilone molecules and then locked them together to form the ring, rather like piecing together a molecular jigsaw. Nicolaou believes that his route too will allow a whole library of analogues to be made, which will hopefully include examples suitable for clinical development. He is confident that 'A practical [production scale] synthesis for epothilone, or an analogue of it, is a very real possibility'.

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Book review

Cost-Effective Strategies for Automated and Accelerated High-Throughput Screening edited by K. Emory and J. Schlegel, IBC, 1996. $795 (comm.)/$495 (acad.) (over 400 pages)

A relatively new spin-off of commercial conferences, which are rapidly increasing in number, is to sell the conference proceedings. These books are often prepared from audio recordings of each presentation, edited, then updated by the speaker with new information, figures and references. The documents may benefit scientists unable to attend the meeting and may also allow staff to access selected information from a meeting in a more comprehensive manner than is possible by reading an attendee's notes or trip report. Unlike the hard-copy documents usually provided at the meeting, the figures and tables in the proceedings book are of high quality and follow in a logical order.

This book is an example of such a document and is based on a conference of the same name organized by IBC in June 1995. It focuses on new assay and detection technologies, strategies for optimizing sample handling and approaches to automating HTS assays. The chapters are organized to give a brief background and clear examples so the reader has an appreciation of the state-of-the-art on each topic. Most of the chapters conclude with questions and answers transcribed from the original meeting.

Six of the 16 chapters are devoted to hardware companies describing their robotics and detector systems. Another six chapters are overviews supplied by emerging pharmaceutical companies giving examples of their strategies for identification of novel molecules. The remaining four chapters are divided equally between academic programs for lead identification and approaches taken by established pharmaceutical companies.

In order for an expensive book like this to be worthwhile, it is critical that several factors be addressed. First, the material must be timely. Second, it must be in sufficient detail to allow the reader to assess the relevance of the topic to their own research projects. Third, the material should not be so simplistic that it insults the intelligence of readers.

Several of the chapters meet these criteria. The chapters describing new homogeneous assays, luminescence assays and fluorescence techniques give a good overview with detailed examples. Similarly, the two chapters by authors at established pharmaceutical companies provide good background information on sample mixing strategies and setting up an assay for identification of Ras inhibitors. Regretfully, not a single chapter gives specific examples of how the strategies yielded an efficacious molecule, and many chapters are strongly biased towards the authors' points of view. In order for the less experienced reader to make a knowledgeable conclusion, however, a balanced approach should be presented.

In conclusion, I believe that this type of document represents yet another attempt to capitalize on science, and that the book suffers from being expensive, largely outdated and somewhat biased. There are much better ways for a scientist to gain insight into new areas – for example, many presenters who take the time to prepare hard copies of slides for the on-site meeting booklet would be willing to mail a copy to interested colleagues. Similarly, manufacturers of hardware and software products are more than happy to provide their scientific literature. Finally, it does seem oxymoronic that a book with 'cost-effective' in the title is so expensive and that not a single chapter (except the introduction) even mentions how this process can save money.

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