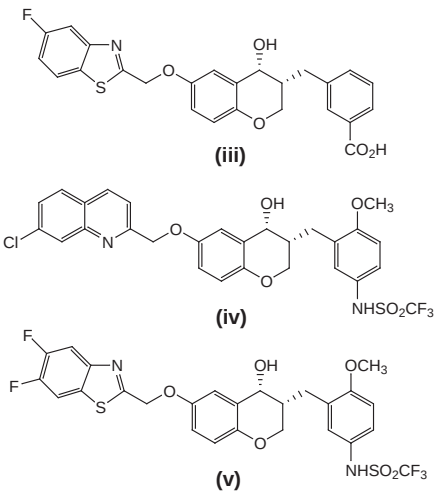
Cysteinyl LT_1-receptor antagonists

The cysteinyl leukotrienes (cysLT) have been implicated as key mediators in asthma through an action at the $cysLT_1$ receptor. Recent studies at Pfizer (Groton, CT, USA) have identified CP85958 (**iii**) as a potent $cysLT_1$-receptor antagonist. However, this agent has unacceptable liver toxicity in monkeys. Following analysis of the metabolic pathway, compounds have been synthesized that incorporate functional groups to increase potency, and are metabolically labile to enable metabolism by an alternative pathway[3].

These studies have led to the identification of CP199330 (**iv**) and CP199331 (**v**) $cysLT_1$-receptor antagonists, which



are equipotent with currently marketed $cysLT_1$-receptor antagonists, have good pharmacokinetic profiles in rats and monkeys, and are devoid of the liver toxicity observed with CP85958.

3 Chambers, R.J. *et al.* (1999) Discovery of CP-199,330 and CP-199,331: Two potent and orally efficacious cysteinyl LT_1 receptor antagonists devoid of liver toxicity. *Bioorg. Med. Chem. Lett.* 9, 2773–2778

Marine natural products as therapeutic agents

The marine environment provides a wealth of diverse chemical structures with biological activities. The increasing number of patents in this field in recent years provides an indication of the industrial growth of this field. A recent analysis of the patent literature provides a useful reference source for workers in this field[4].

This minireview focuses on the patent literature from 1996 to April 1999, during which time almost 100 patents have been issued in this field. The review covers the isolation and characterization of potential active agents from marine bacteria, marine algae, sponges, cnidaria, bryozoans, molluscs and tunicates. The paper also highlights the challenges of obtaining adequate quantities of these complex marine-derived metabolites for commercialization, emphasizing the importance and challenges of total chemical syntheses and the possible use of aquaculture and cell culture to provide strategies for marine natural product production. The author rightly highlights that the ultimate elucidation of the biosynthesis of these compounds might enable the use of biotechnology to develop recombinant systems for product manufacture.

4 Kerr, R.G. and Kerr, S.S. (1999) Marine natural products as therapeutic agents. *Exp. Opin. Ther. Patents* 9, 1207–1222

Combinatorial chemistry

Fourier-transform screening

Many different materials have been suggested as solid supports for combinatorial chemistry, but cotton threads have only occasionally been used. Using a one-dimensional support necessitates clever methods for the generation of a library, and a recent publication describes an ingenious method for both the synthesis and testing of a library[5].

To prepare this library, the cotton thread was wrapped around a cylinder of specified diameter, and zones marked on the side of the cylinder using wax lines. The cylinders could then be dipped into reagent solutions to attach various monomeric building blocks. After derivatizing the cotton with the first set of monomers, the cotton was unwound and rewound onto a cylinder of different diameter. In this way, subsequent steps of functionalization were staggered along the cotton thread with a different repeat frequency, thereby permitting the preparation of every monomer combination. A peptide library of the sequence Ac-X-X1-Pro-Gln-Phe-Ala-Ala-Ala-linker was constructed where X and X1 were chosen from seven and five alternatives, respectively. The compounds, designed to include the known streptavidin-binding motif, were screened for their ability to bind to fluorescein-conjugated streptavidin by passing the thread through a spectrometer cell using a modified audiotape cassette.

The variation of fluorescence along the thread, resulting from the differing peptide sequences bound along the cotton, gave a signal that could be Fourier-transformed to generate a library spectrum. The peaks in this spectrum represent the cylinder frequencies and their harmonics, with the magnitude of the signal indicating the significance of the activity averaged over the library. From this analysis, it was readily possible to discern the general features that were important for binding and helped to define trends in activity within the library.

5 Schwabacher, A.W. *et al.* (1999) Fourier transform combinatorial chemistry. *J. Am. Chem. Soc.* 121, 8669–8670

Erm methyltransferase inhibitors

Significant resistance to the macrolide–lincosamide–streptogramin (MLS)-type antibiotics in pathogenic bacteria stems from the bacteria's ability to selectively methylate ribosomal RNA near to, or within, the macrocycle binding site. The enzymes responsible for this

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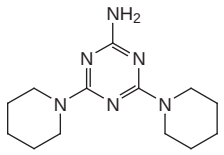
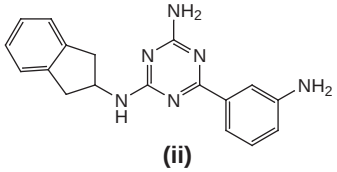
methylation are the erythromycin-resistance methylase (Erm)-family of methyltransferases, and inhibition of these enzymes sensitizes MLS-resistant bacteria to macrolide antibiotics.



(i)



(ii)

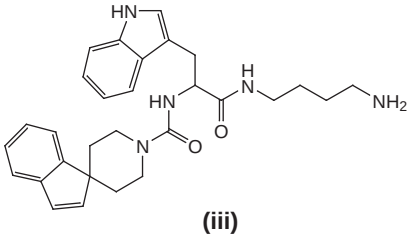
In the search for novel and selective inhibitors of ErmAM methyltransferase using structure–activity relationship studies (SAR) by NMR, several small organic molecules have been found[6]. In particular, compound (**i**) was discovered to have a K_i of 75 μM. Solution-phase parallel synthesis was then employed to independently optimize the piperidine substituents, resulting in compounds, such as (**ii**), that have low micromolar affinity for the ErmAM methyltransferase. Because of their non-nucleoside structure, they are potentially selective inhibitors of Erm methyltransferase that could be given in combination with a broad-spectrum macrolide antibiotic.

6 Hajduk, P.J. *et al.* (1999) Novel inhibitors of Erm methyltransferases from NMR and parallel synthesis. *J. Med. Chem.* 42, 3852–3859

Somatostatin-receptor ligands

Somatostatin, a ubiquitous tetradecapeptide, is involved in a range of different biological functions including modulation of the secretion of growth hormone, insulin, glucagon and gastric acid. Five different human somatostatin receptors have been cloned and characterized, offering the potential for the design of novel and selective non-peptide ligands.

To find such ligands, database searching techniques have been used to screen the Merck-compound sample collection using the modelled conformation of a known potent cyclic peptide mimetic of somatostatin[7]. Of the 75 compounds selected, L264930 (**iii**) was selected as a high-affinity ligand suitable for combinatorial optimization.



(iii)

The compound can readily be considered to comprise three parts, and a mix-and-split solid-phase synthetic protocol was used to prepare an expected 131,670 compounds in 79 mixtures of 1330 or 2660 products. A semi-automated procedure was used for the screening of the library in a 96-well plate format. Following deconvolution, several potent ligands selective for the somatostatin receptor subtypes (K_i = 50 pM to 200 nM) were discovered.

7 Berk, S.C. *et al.* (1999) A combinatorial approach toward the discovery of non-peptide, subtype-selective somatostatin receptor ligands. *J. Comb. Chem.* 1, 388–396

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High-throughput screening

Rapid fluorescent-based reporter-gene assays for HTS of platinum-based cytotoxic agents

Although cisplatin and carboplatin are widely used in chemotherapy, many tumours are resistant to these compounds. This has led to an interest in rapidly screening combinatorial libraries of cisplatin analogues to assess their potential use as antitumour agents. Two high-throughput fluorescent-based reporter-gene assays have recently been described that might offer a means of screening cisplatin analogues and related compounds for antitumor activity[8].

One reporter-gene assay used HeLa Tet-On cells that were transfected with the doxycycline-inducible enhanced green fluorescent protein (GFP) gene. A highly inducible, low background clone was isolated and used to evaluate the effects of cisplatin, cisplatin analogues and other cytotoxic stress enhancers on GFP expression. Cisplatin and other *cis*-disubstituted platinum complexes inhibited GFP expression whilst alternative forms of cytotoxic stress stimulated GFP transcription. The other reporter-gene assay used the hydrolysis of the fluorescent cephalosporin substrate CCF2 to monitor β-lactamase expression in Jurkat cells. Using this assay, cisplatin was found to inhibit the β-lactamase expression whereas $[Pt(NH_3)_2Cl_2]$ and $K_2(PtCl_4)$ were not.

As these assays provide results more rapidly than conventional cytotoxicity assays, they might offer a means, in conjunction with combinatorial chemistry, of accelerating the discovery of novel anticancer agents.

8 Sandman, K. *et al.* (1999) Rapid fluorescence-based reporter-gene assays to evaluate the cytotoxicity and antitumor drug potential of platinum complexes. *Chem. Biol.* 6, 541–551

Andrew Lloyd

New safer non-steroidal anti-inflammatory drugs?

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely

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