(1997) *Nucleic Acids Res.* 25, 3164–3168].

The combination of these two technologies allows PCR reactions to be observed and optimized in real time within various microstructured glass, silicon or plastic reaction vessels. Each material shows a different influence on the performance of the PCR process in terms of thermal behaviour or surface effects. Finally, a procedure was proposed for parallel sequence-specific detection by PCR. A chip containing 48 microreaction chambers connected by a microstructured manifold is preloaded with the reagents and then filled in one shot with the sample. Positive wells (containing the sequence-specific primer) emit fluorescence and, hence, can be discriminated from wells without any signal.

Miniaturized analytical thermocyler

Allen Northrup of Cepheid (Santa Clara, CA, USA) presented a battery-driven, miniaturized thermocycler: the Miniature Analytical Thermal Cycler Instrument (MATCI). Northrup demonstrated the analytical potential of this instrument with quantitative detection of *Salmonella* and other bacteria, including an extraordinary detection accuracy across ten different strains, within 30 min.

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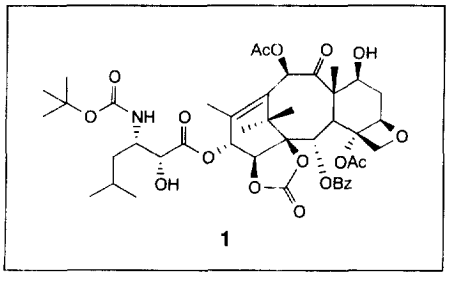
Drug discovery at IKCOC-7

The 7th International Kyoto Conference on New Aspects of Organic Chemistry (IKCOC-7) was held on 10–14 November 1997 and was attended by over 900 delegates. This brief report highlights work relevant to drug discovery that was presented at the meeting. Professor Iwao Ojima (Stony Brook State University of New York, NY, USA) presented his work on taxoid antitumor agents. A problem with taxol and taxotere therapy is multidrug resistance (MDR) caused by overproduction of P-glycoprotein. The Ojima group has identified a new taxoid (**1**, SBT101131) that is two orders of magnitude more active than taxol and taxotere in an apoptosis assay against MDR cells. This compound has been selected for development.

Ojima and coworkers have identified a common pharmacophore for taxol (**2**), the epothilones (**3**) and discodermolide (**4**). These three compounds appear to bind competitively to the same β-tubulin site. According to this pharmacophore, the thiazole group of the epothilones overlays with the benzamide of taxol, while the 16-membered ring of the epothilone overlays with the south and southwestern parts of taxol, which is in a conformation where the phenyl rings of the benzoyl group and the β-amino acid side-chain are relatively close together. This analysis may lead to the design of novel taxol and epothilone derivatives.



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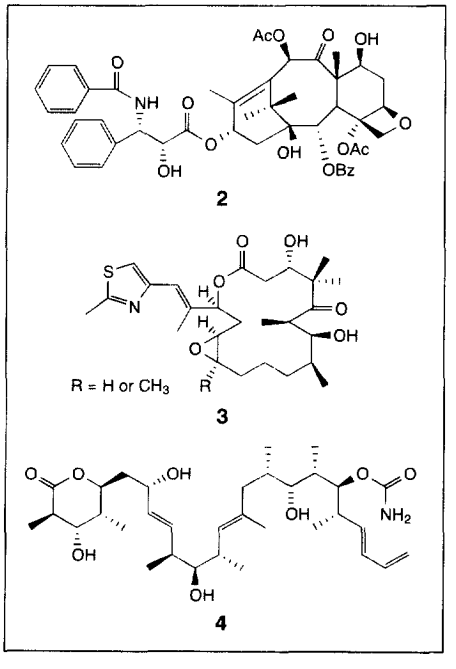

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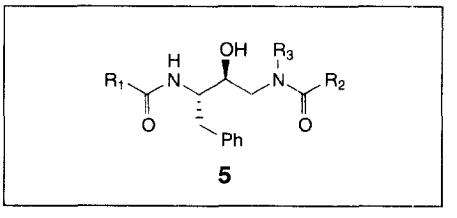

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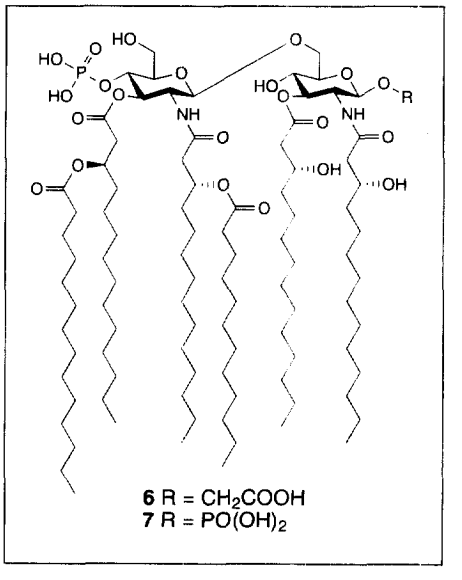

Combinatorial chemistry

As part of the conference, there was a mini-symposium on combinatorial

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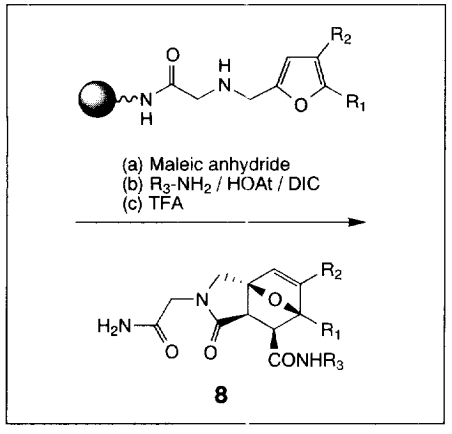

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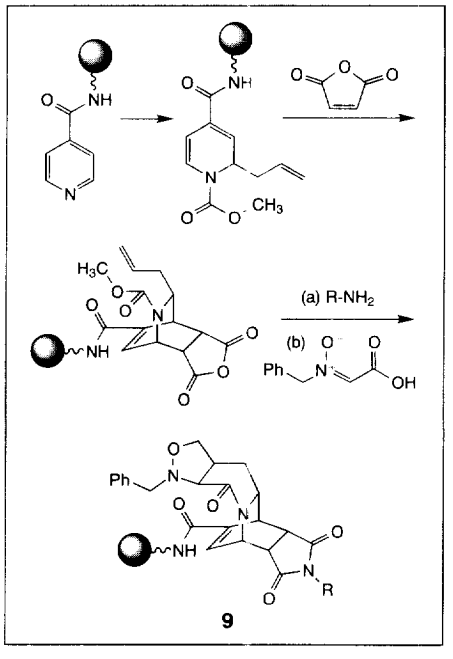

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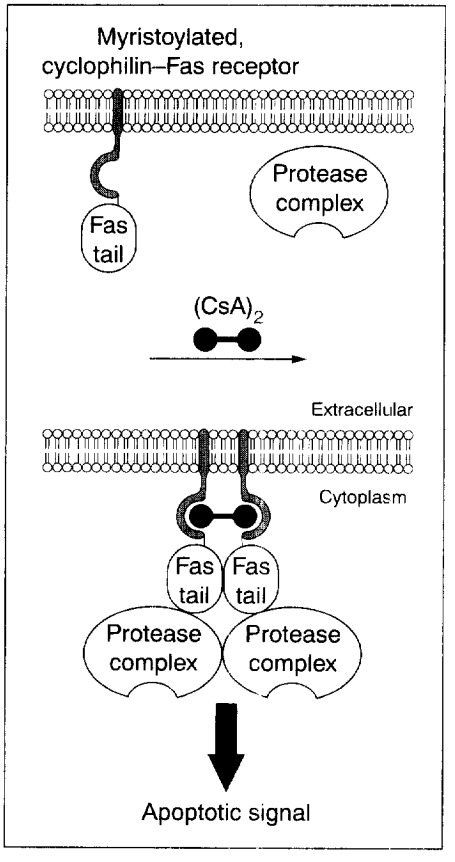
chemistry. Professor Jonathan Ellman (University of California, Berkeley, CA, USA) gave an impressive account of the preparation of libraries of cathepsin D inhibitors. Low nanomolar inhibitors of this aspartyl protease were identified from the screening of focused libraries based on the hydroxyethylamine pharmacophore (**5**).

Professor Koichi Fukase (Osaka University, Osaka, Japan) described research towards the solid-phase synthesis of lipid A analogues (e.g. **6**). Lipid A (**7**) is a chemical entity responsible for the biological activity of lipopolysaccharide (LPS), a cell-surface glycoconjugate of Gram-negative bacteria, which induces various endotoxic activities, such as pyrogenicity and lethal toxicity.

Dr Kumar Paulvannan of Affymax (Santa Clara, CA, USA) described the solid-phase synthesis of hydroisoindole derivatives (**8**) using an intramolecular Diels-Alder reaction strategy.

Dr Sheila de Witt described the progress being made by Orchid Biocomputers (Princeton, NJ, USA) towards their goal of producing an instrument capable of performing 10,000 parallel reactions simultaneously. To date, a 144-well synthesis chip has been constructed. The well size of 1 μl can accommodate three solid-phase beads. The chip incorporates microfabricated components for valving and pumping fluids. The electrokinetic pumping has been validated for the common organic solvents used in organic synthesis.

The final plenary lecture was given by Professor Stuart Schreiber (Howard Hughes Medical Institute, Harvard University, Cambridge, MA, USA) and was entitled 'discovery of ligands for use in chemical genetics'. Schreiber argues that there is an equivalency of ligands and mutations because they can both inactivate or activate proteins. In an elegant series of experiments, Schreiber's group has prepared dimeric structures capable of binding two proteins simultaneously. These so-called 'dimerizers' bring the two proteins into close proximity (ensuring a high effective molarity), which results in activation of one of the proteins by increased reaction rates. For example, a dimer of cyclosporin A (CsA) induces apoptosis in T cells transfected with a recombinant cyclophilin–Fas receptor (see diagram).



Human genome project for organic synthesis

Schreiber concluded his presentation on chemical genetics with a 'Kyoto Proposal' for a 'human genome project for organic synthesis' to discover a small-molecule partner for every gene product. Schreiber's group have started to approach this task of high-throughput, cell-permeable ligand discovery by developing methods of split-and-pool solid-phase combinatorial synthesis. An example of a synthetic procedure to give 'natural-product-like' heterocyclic compounds (**9**) was presented.

The chemistry is performed using a photo-labile linker and the Clark Still electron-capture gas chromatography (ECGC)-detectable tag-encoding methodology. The assays are performed in nanodroplets. Engineered yeast cells and beads are arrayed into small wells (etched by photolithography) on a plate using a process akin to spray painting. Light is shone on the plate to release the compounds, ligand binding is sensed by growth of the engineered yeast cells, and active beads are removed for tag decoding. It will be interesting to see how the community of synthetic chemists responds to this call for a 'human genome project for organic synthesis'.

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