beneficial if DNA is to be synthesized on a much smaller scale. Performing DNA synthesis in Orchid's chips in such a large array (10,368 wells) would be much more flexible than the complex photolithography used in the construction of other DNA chips.

### Biosensor applications

Orchid's device can also be used with intact cells. In fact, Orchid is working with DARPA (Defense Advanced Research Projects Agency, USA) to create biological-threat detection systems (biosensors to detect biological warfare agents). Taking this to extremes, the potential to grow cells such as neurons compartmentalized in wells and interconnected via the channels could in fact form the foundation for biocomputers. Perhaps one day, we will be using *n*th generation devices to grow 'real' neural nets used to replace damaged brain cells or even for 'upgrading' ourselves. But, enough of the science fiction.

With respect to future collaborations, Pfost divulges that they have had more than 60 meetings with major companies. Because of the great interest Orchid has attracted, the company is building a consortium for high-throughput screening, and they hope it will drive new standards through collaboration with instrumentation companies.

A device such as Orchid's 'credit card' is likely to cause a shift from the use of standard microplates to small high-density integrated systems for many applications. However, the device has yet to be tested to establish whether it can outperform its microplate ancestors, but it will not be long before the old and new formats find their niches in the modern day drug discovery laboratory.

*Martin Leach*

# Peptidomimetics and small molecule design

In March, *Peptidomimetics and Small Molecule Design*, a conference on the discovery and development of small-molecule drugs, was organized by IBC for the fourth year. The meeting, held in Philadelphia this time, consisted of a two-day conference with a further one-day workshop on combinatorial approaches to small-molecule design. It had a broad perspective with respected speakers from both industry and academia. Topics ranged from aspects of the investigation of protein–protein interactions to the synthesis of peptidomimetics on an industrial scale.

### Protein–protein interactions

The conference was opened by Dr Nigel Beeley (Amylin Pharmaceuticals, San Diego, CA, USA), who discussed how small nonpeptide molecules that imitate proteins can be identified. One approach is to focus on the protein's binding motif. The surface area of the binding motif, which is the area that needs to be mimicked, is often of the size of a small molecule. Calmodulin, leptin and amylin are examples of proteins for which this approach works.

Amylin is co-secreted with insulin, controls the release of glucose from the stomach, and is important in the regulation of the blood sugar level. It is predicted to bind as a loop-helix-turn, and alanine scan data suggest that six non-contiguous amino acids are involved in receptor binding, two of which appear to trigger agonism. Screening of a 30,000-compound database identified four structurally distinct nonpeptide antagonist leads. With the aid of the binding model the antagonist leads are being modified in a combinatorial fashion to develop agonists with oral bioavailability.

A method for determining helix–helix interactions in the absence of an X-ray structure was presented by Dr Weislaw Kazmierski (Glaxo Wellcome, Research Triangle Park, NC, USA). He described a disulphide trapping approach in which covalent bonds are formed between cysteine residues on the helices, thus identifying which faces come together upon dimerization (Figure 1). This technique provides useful information for the design of small molecules that interfere with dimerization. Such molecules have therapeutic potential in a variety of disease states. For example, the gp41 protein of HIV (which serves as the transmembrane anchor for the receptor-binding protein gp120) functions as a dimer. Disruption of its dimerization process should lead to disruption of the virus–host binding process.

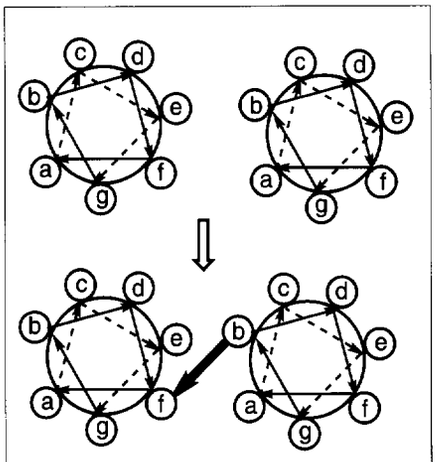


***Figure 1.*** *Dimerization of helices by the formation of a covalent bond between residues b and f.*

### Designed peptidomimetics

Prof. Victor Hruby (University of Arizona, Tucson, AZ, USA) described his approach to *de novo* design of stable, bioavailable ligands for G-protein-coupled receptors. The endogenous ligands for these receptors are unsuitable for examining biological function, or as drugs, because of their instability and lack of selectivity. Hruby's working hypothesis is that because the receptors are known to have considerable conformational homology,



1359-6446/97/$17.00. PII: S1359-6446(97)01062-3

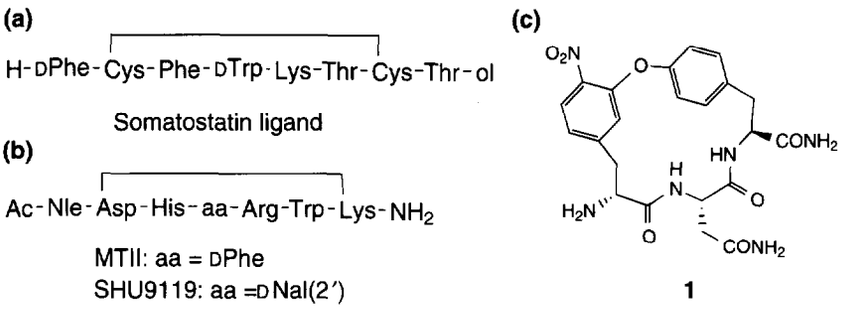


***Figure 2.*** *(a) Cyclic somatostatin ligand that was converted into (b) melanocortin agonist MTII and antagonist SHU9119. (c) Cyclic tripeptide containing a biaryl linkage.*

selective ligands may also share conformational similarity. He described how his group converted a cyclic somatostatin ligand into potent (sub-nanomolar $EC_{50}$), cyclic melanocortin agonists (e.g. MTII) and antagonists (e.g. SHU9119), with little or no binding at the somatostatin receptor (Figure 2). The melanocortins have a variety of functions including pigmentation control, adrenal and cardiovascular functions and control of feeding behaviour. The approach may be general, as success had previously been achieved in deriving selective μ-opioid receptor ligands from the same somatostatin template.

Cyclic peptidomimetic templates were also the topic of Dr Kevin Burgess' (Texas A&M University, College Station, TX, USA) presentation. He described his group's method of forming endocyclic biaryl ether bonds on a solid support. Tripeptides were synthesized containing a tyrosine, silylated on the phenolic hydroxyl, and an N-terminal *ortho*-fluoronitrophenyl derivative. Desilylation of the tyrosine hydroxyl using fluoride with concomitant nucleophilic substitution (SNAr reaction) led to cyclic peptides containing a biaryl ether linkage (**1**; Figure 2). This approach is being extended to other nucleophiles, and towards the preparation of cyclic peptidomimetic combinatorial libraries and analogues of vancomycin.

## Mimetics on an industrial scale

Peptidomimetics are not just academic fare, but have made it to market. Dr James Tien (Abbott Laboratories, Abbott Park, IL, USA) described Abbott's efforts to overcome the process development challenges of preparing the complex structure of ritonavir (**2**; Figure 3) on a 100-kilogram scale. Most impressive was the four-step preparation of the core structure (**3**), which contains three chiral centres in close proximity, in over 96% diastereomeric excess (Figure 3). The original sequence developed for small-scale synthesis used vanadium chemistry, gave relatively low diastereoselectivity, was longer and had relatively low thoughput.

## Peptidomimetics and combinatorial chemistry

When the key amino acids required for binding a ligand to its receptor are not contiguous, how can a small nonpeptide ligand be designed? Dr Philippe Bovy (Synthelabo Recherche, France) addressed this challenge using interleukin 1 (IL-1) as an example. IL-1 contains four amino acids, which are separated in the primary sequence and are clustered together in space as a result of the tertiary structure of the protein. Screening of a phage display library identified the tetrapeptide Trp-Gln-Pro-Tyr as a small peptide antagonist lead. Replacing the proline with a nonpeptide bifunctional scaffold facilitated construction. The glutamine piperazinyl scaffold (**4**) was anchored to the resin via the glutamine side chain with the two amines orthogonally protected

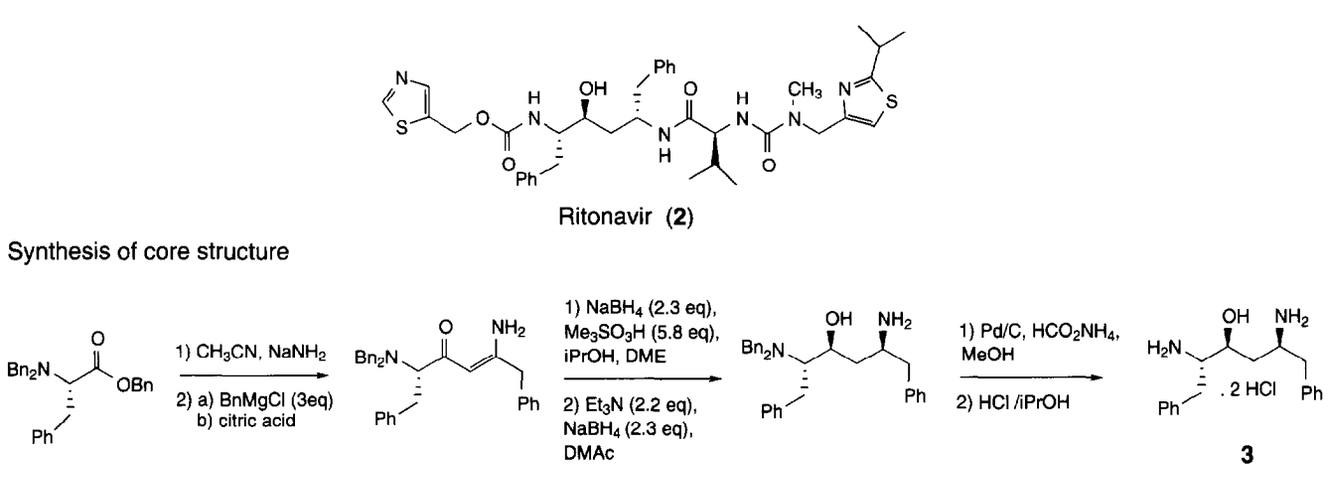


***Figure 3.*** *Hundred-kilogram scale synthesis of the core structure (**3**) of ritonavir (**2**).*

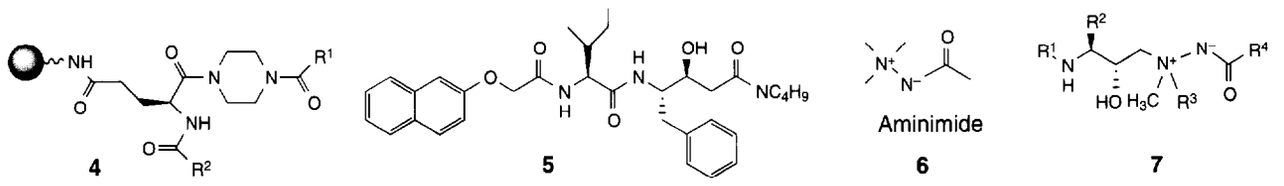


***Figure 4.*** *Synthelabo's glutamine piperazinyl scaffold anchored to a solid-phase support via the glutamine side chain (**4**); Pharmacopeia's plasmepsin I inhibitor (**5**); general structure of aminimides (**6**) and ArQule's aminimide library (**7**).*

(Figure 4). Functionalization of the amines gave a library of 1,296 compounds after cleavage, from which nonpeptide IL-1 antagonists with sub-micromolar activity were identified.

A related combinatorial approach was described by Dr Hitesh Patel (Pharmacopeia, Princeton, NJ, USA) for identifying selective inhibitors of the aspartic proteases cathepsin D and the plasmepsins. Aspartic protease inhibitors usually contain a transition state mimetic core consisting of a secondary hydroxyl group β to a residue that binds in the S1-pocket of the protease. The hydroxyl group displaces the water molecule required for amide hydrolysis from the enzyme's active site. The invariant hydroxyl was linked to the resin using a photolabile linker and the amine and carboxyl termini functionalized by reacting with acids, aldehydes or amines to give a 20,000-compound library. Deconvolution was aided by the use of tagging methodology, and useful leads were identified especially for plasmepsin I. Compound **5** (Figure 4) exhibited low nanomolar inhibition of plasmepsin I with 100-fold selectivity over plasmepsin II and 10,000-fold selectivity over cathepsin D.

An unusual class of compounds that have found success as peptidomimetics are the aminimides of general structure **6** (Figure 4). Dr Steven Gallion (ArQule, Medford, MA, USA) described the synthesis of aminimide libraries (**7**) for the inhibition of HIV protease and elastase. The hydroxyaminimides for HIV protease inhibition were synthesized by a one-pot acylation of a substituted hydrazine and ring opening of an epoxide. Aminimides have potential as future drugs; they exhibit oral bioavailability, low toxicity and are present in known pharmaceuticals, such as besulpamide.

The above report can only hope to give a flavour of the conference. My apologies to those speakers whose presentations have not been reviewed.

*Steven Langston*
*Peptide Therapeutics*
*321 Cambridge Science Park*
*Milton Road*
*Cambridge, UK CB4 4WG*
*fax: +44 1223 423111*
*e-mail: stevelangston@peptide.co.uk*

# Natural products drug discovery – new technologies and approaches

A two-day meeting entitled *Natural Products Drug Discovery: new technologies to increase speed and efficiency* was held in San Diego (CA, USA) on 17 and 18 March 1997. The purpose of this meeting, organized by IBC, was to discuss how natural products research within the pharmaceutical industry could continue to become more efficient and innovative in order to maintain its position as a valuable source of drug leads. One of the three sessions, 'New Technologies to Expedite Discovery', addressed this core issue, with the remaining two discussing 'New Drugs from Natural Products', and 'Biodiversity and Supply'. There was a very useful post-conference workshop, which addressed the 'interfacing' of combinatorial and natural product technologies. This report summarizes some of the key points of interest that were discussed at the conference and the workshop.

## New technologies to expedite discovery

The rate-limiting step in natural products screening programs has traditionally been the isolation and characterization of bioactive metabolites from relatively crude and uncharacterized natural extracts. Intensive efforts have been made to increase efficiency here; indeed some companies have opted to 'prefractionate' such complex source extracts to provide purer samples that can be more rapidly characterized following the detection of activity in a screen.

Dr Ines Chicarelli-Robinson (Xenova, Slough, UK) presented Xenova's initiative to generate pure compounds for screening. The process comprises an initial HPLC/UV/MS analysis of a crude plant or microbial fermentation-broth extract. After searching the appropriate

  1359-6446/97/$17.00. PII: S1359-6446(97)01060-X 