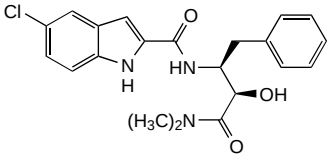
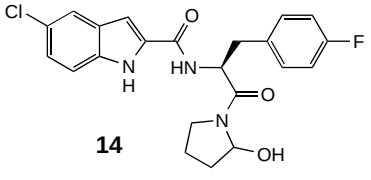
from both elevated gluconeogenesis and glycogenolysis has encouraged various workers to consider the inhibition of glycogen phosphorylase, which releases glucose-1-phosphate units from glycogen, as an alternative strategy for plasma glucose control.

Workers from Pfizer (Groton, CT, USA) have recently reported the synthesis and evaluation of two series of indole-2-carboxamides derived from **13**, as an orally active glycogen phosphorylase inhibitor originally identified by high-throughput screening against recombinant human liver glycogen phosphorylase *a* [Hoover, D.J. *et al. J. Med. Chem.* (1998) 41, 2934–2938].



13

From these series CP320626 (**14**) was identified and shown to produce oral activity at 10 mg kg^{-1} in diabetic *ob/ob* mice. These compounds will provide useful tools for the further evaluation of glycogenolysis in both normal and disease states in order to elucidate whether glycogen phosphorylase is a useful therapeutic target for the treatment of type 2 diabetes.

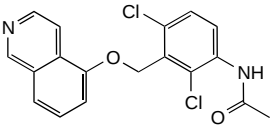


14

Anti-*Helicobacter pylori* agent

Helicobacter pylori has been associated with a variety of gastric disorders and particularly gastric ulcers. Although treatment of *H. pylori* infections with antibiotics would seem attractive, clinical evidence has shown that effective eradication can only be achieved using double- or triple-therapy regimens using a combination of broad-spectrum antibiotics and H_2-antagonists or proton-pump inhibitors. This problem has led to the need to develop novel alternative agents suitable for single-therapy treatment.

Yoshida, Y. and coworkers have recently reported the synthesis and anti-*H. pylori* activity of a novel series of benzyloxyisoquinoline derivatives [*Bioorg. Med. Chem. Lett.* (1998) 8, 1897–1902]. Following *in vitro* optimization studies, the group identified FR180102 (**15**) as a novel highly potent anti-*H. pylori* agent that showed no activity against a series of common Gram-positive and Gram-negative bacteria.



15

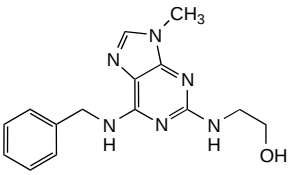
Combinatorial chemistry

Kinase inhibitor libraries

A recent paper from the Schultz group at Berkeley reports on the culmination of a long-standing interest in kinase inhibitor libraries [Gray, N.S. *et al. Science* (1998) 281, 533–538]. Cyclin-dependent kinases (CDKs) play a pivotal role in the timing of cell division, and inappropriate functioning of these enzymes is characteristic of several cancers. Consequently, inhibition of CDKs is a possible target for therapeutic intervention. Following the known activity of the purine olomucine (**1**), several libraries of compounds were prepared with the intention of selectively binding to the kinase ATP-binding site.

Solid-phase synthesis of 2,6,9-trisubstituted purines was achieved through nucleophilic displacements of halogens in the 2- and 6-positions and Mitsunobu chemistry in the 9 position. The most potent analogues, such as purvalanol B (**2**) were discovered to possess 3- and 4-substituted anilines or benzylamines in the 6-position.

The structural basis for the activity of these compounds was explored by determining the crystal structure of the



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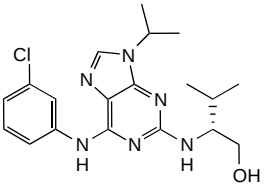

2

human CDK2–purvalanol B complex. It was found that the purine ring is rotated relative to the position of the adenine ring of ATP, and that the C-2 side chain fits into the ribose-binding pocket. The N-6 aniline substituent points towards a region not occupied in the CDK2–ATP complex and the 4-position of the aniline ring is subsequently highly tolerant of various substituents making it a good site for structural modifications that could tune the physicochemical properties.

Sensor arrays

Several groups have investigated the development of 'electronic noses', but recently a paper described a new sensor methodology that allows analyte identification in solution [Lavigne, J.J. *et al. J. Am. Chem. Soc.* (1998) 120, 6429–6430]. This first step towards an 'electronic tongue' uses derivatized resin beads and has the potential to be extended through combinatorial chemistry.

Polyethylene glycol-polystyrene beads were derivatized with several different indicator molecules and were placed into micromachined wells in Si/SiN wafers. These beads represented the 'taste buds' and their response to analytes in solution, including pH, calcium and cerium ions, was monitored by charge-coupled devices recording red, green and blue transmitted light intensities. Using such an array, the simultaneous detection of several analytes is possible and the development of further detectors through combinatorial methods offers more sophisticated recognition protocols.

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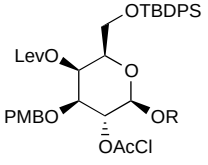
Oligosaccharide libraries

This column has frequently featured approaches to oligosaccharide libraries, mainly because these products are important pharmacological agents, but also because the synthesis of oligosaccharides poses significant problems. A recent paper from The Scripps Research Institute describes a useful orthogonal protection strategy that extends the accessibility of oligosaccharide libraries made in solution [Wong C-H. *et al. J. Am. Chem. Soc.* (1998) 120, 7137–7138].

The key advance described in this paper is an effective orthogonal protection–deprotection strategy that allows



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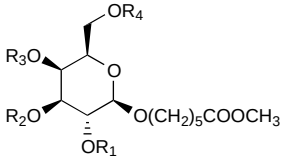

4

the sequential removal of four different protecting groups from a core building block (**3**). Each of the four hydroxyls is protected by a different group: chloroacetyl (ClAc), *p*-methoxybenzyl (PMB), levulinyl (Lev), and *t*-butyldiphenylsilyl (TBDPS) selectively removed by sodium bicarbonate, trifluoroacetic acid, hydrazine and hydrogen fluoride-pyridine, respectively. After each deprotection the hydroxyl revealed can be coupled with a choice of seven glycosyl donors to generate 56 disaccharides, 1176 trisaccharides and, ultimately, 38,416 pentasaccharides.

This strategy has been used to prepare 45 protected oligosaccharides (**4**) in multimilligram amounts. Work is in progress to increase the number of compounds synthesized and screen for compounds that bind to lectins and antibodies.

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Emerging molecular targets

Caspase-8: an initiator of Fas-mediated apoptosis

Apoptosis – programmed cell death – is responsible for most cell deaths observed during embryogenesis, metamorphosis and normal tissue turnover. During apoptosis, protein-degrading enzymes known as caspases are activated and cleave critical cellular substrates leading to the ultimate death of the cell. The caspases are produced as inactive precursors that must themselves be activated by other caspases, so there is a cascade of cleavage and activation to induce apoptosis. In the immune system, the Fas molecule is a key inducer of the apoptotic process.

A recent paper by a group from Harvard Medical School describes an investigation into a human T-cell line variant found to be resistant to Fas-induced apoptosis [Juo, P. *et al. Curr. Biol.* (1998) 8, 1001–1008]. Examination of the cells for all the molecules known to be involved in Fas-induced apoptosis showed that the variant lacked the expression of caspase-8 but that all the other proteins were found to be present at normal levels. The group also showed that reintroduction of caspase-8 into these cells restored their sensitivity to Fas-mediated apoptosis. This implicates caspase-8 as the key enzyme responsible for the initiation of apoptosis in Fas-triggered cell death.

As malfunctions in the Fas system are involved in a variety of diseases, caspase-8 inhibitors or activators may have therapeutic potential for the correction of Fas-pathway defects.

Lymphoid sulphotransferase

During the inflammatory process, lymphocytes migrate from the bloodstream into the tissues by adhering to the endothelial cells lining specialized blood vessels. The process of adhesion is mediated through the binding of L-selectin on the surface of the lymphocytes to glycoproteins on the endothelial cell surface. Previous studies have shown that L-selectin binding requires sulphation of the endothelial surface glycoproteins but, until now, the identity of the sulphotransferase enzyme responsible for this process has been unknown.

Bertozzi's group has recently reported the identification of an enzyme specific to lymphoid tissue that can sulphate synthetic glycoprotein analogues, and suggest that this enzyme may be responsible for sulphation of glycoproteins recognized by L-selectin [Bowman, K.G. *et al. Chem. Biol.* (1998) 5, 447–460]. In addition to providing an insight into the mechanism of lymphocyte homing, the identification of this enzyme may lead to useful therapeutic agents for inflammatory control.

Andrew Lloyd

Bioinformatics

Integrated approach to bioinformatics

The tremendous pace of biomedical science is leading to an 'information explosion', an increased dependency on computers and an absolute need for effective and efficient use of bioinformatics. Bioinformatics is essential for the management and analysis of biological information and serves to eliminate *ad hoc* planning, enable informed decision-making, provide relevant information and mobilize all available biological information to take the discovery process forward and produce commercially viable products and patents. Consequently, up-to-date and rapid access to the right information (computer databases) and the right analytical tools (computer programs)

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